Principles and Applications of Enolate Alkylation: A Unique Strategy for Construction of C-C (sp3-sp3) bonds in asymmetric fashion

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Module - 06
Several methods for alkylation of amino acids derived enolates
Lecture - 30
Tricycloiminolactone as chiral glycine equivalents

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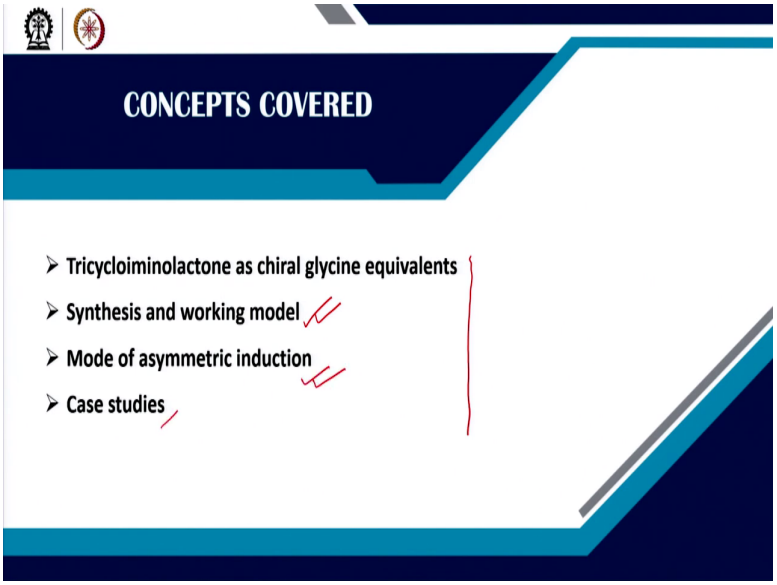

So, in this lecture, which is lecture no. 30; we will be mainly talking about Tricycloiminolactone as chiral glycine enolate equivalents and in today's lecture the main concept which we will be covering how this tricycloiminolactone can be used as a chiral glycine equivalent, how they can be synthesized, their working model and the mainly the mode of asymmetric induction, how new strategies for synthesis of new molecules can be created and few case studies.

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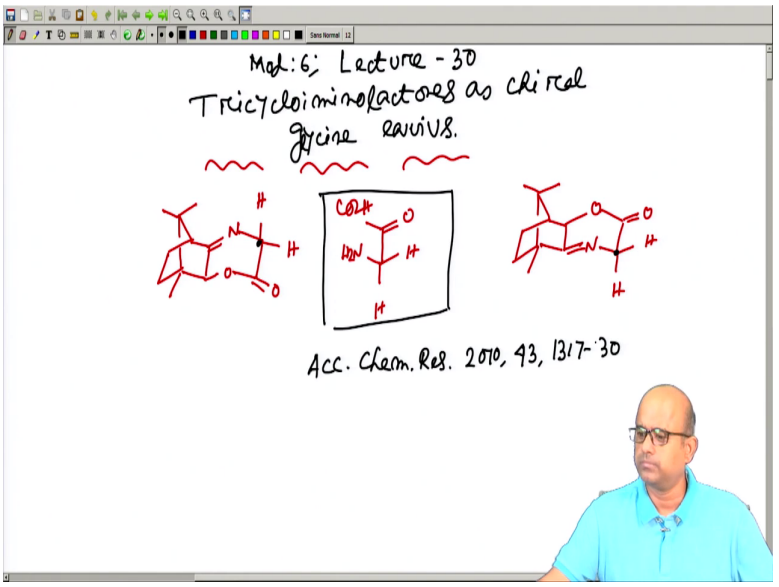

So, today in this lecture, lecture 30 we will be talking about tricycloiminolactones as chiral glycine equivalent. Probably I have given you a brief introduction of this chiral glycine equivalents based on tricycloiminolactone in the last class. And let me again draw the basic structural features of this tricycloiminolactone, these are usually camphor derived tricycloiminolactone, which can easily be prepared thorugh these compounds and are not commercially available.

And you can check the structural features, this compound does have a chiral glycine part in their structure either this left hand side structure or the right hand side structure which I am now drawing both can serve as a chiral glycine equivalent. The basic differences between both the structures, if you can see the only difference is the connectivity ok.

In one case the imine was on this carbon and this oxygen was here in another case the oxygen was just change the position. Actually, in reality these two compounds are basically will give you enantiomeric product after the alkylation. So, this is the glycine part which you are trying to visualize in both the cases ok. And this particular thing and this particular thing are basically enantiotopic usually you can see the plane of symmetry is going through that.

Now as we discussed this result was reported by a Chinese group and they have nicely reviewed the entire research in Accounts of Chemical Research journal which was published in 2010 and this is the page number. Now, let us go to the inner thing that how this compounds have been synthesized.

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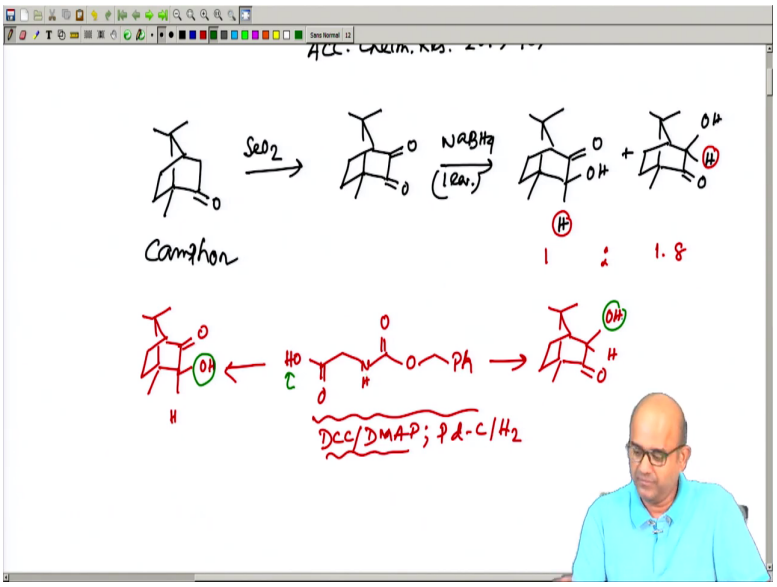

Initially what is happening? You first start with the parent compound which is the camphor, camphor is our parent compound. So, you start with this compound ok and then you just do a SeO2, mediated alpha oxidation for this camphor derived compound and then get the corresponding 1,2 diketone this and this.

Now, this diketone if you react with one equivalent of sodium borohydride one equivalent both the carbonyl group will be reduced in a sequential manner, one after one normally you know one equivalent means, you get one hydride comes here in another case one hydride comes here.

So, basically you get both the carbonyl reduced, but you will get two different compounds. So, one case this carbon will remain intact and you get this alcohol and in another case you get the other alcohol. You get this carbonyl was intact you get the OH you get the hydride.

In the selectivity pattern was pretty important. In most in both the cases you have seen that the hydride attacks from the endo face because, the exo face seems to be blocked by this bridged dimethyl group and the relative ratio for both this compound are kind of 1 is to 2, 1 is to 1.8. And these two compounds you can separate because they are diastereomers; and once you separate these two compounds your main journey was you take both the compounds.

So, let me now take the first compound means the Camphor part is here this the ketone this h and OH and in this case we will take the other compound which is this, this, this, this carbonyl I just try to explain that how you can make the tricycloiminolactone. Now both the compound was reacted with a glycine derivative a suitably protected glycine derivative a CBZ protected glycine derivative OCH to Ph.

Now, glycine having a free carboxylic acid and you have a free hydroxyl group in both the compound. So, this is selectively reacted, this is selectively reacted ok and what are the reagents and conditions DCC/ DMAP, which basically give you the acid and alcohol coupling and the moment you do the DCC/ DMAP reaction then followed by you treat with palladium charcoal /hydrogen.

Now, first what happened? This free OH react with this carboxylic acid group this free O H reacts with this carboxylic acid group fine and then after that you have a palladium charcoal hydrogen, which basically debenzylate these things and carbon dioxide removal and deprotection you get the free amine. Now this free amine will condense with this corresponding carbonyl to get the corresponding imine.

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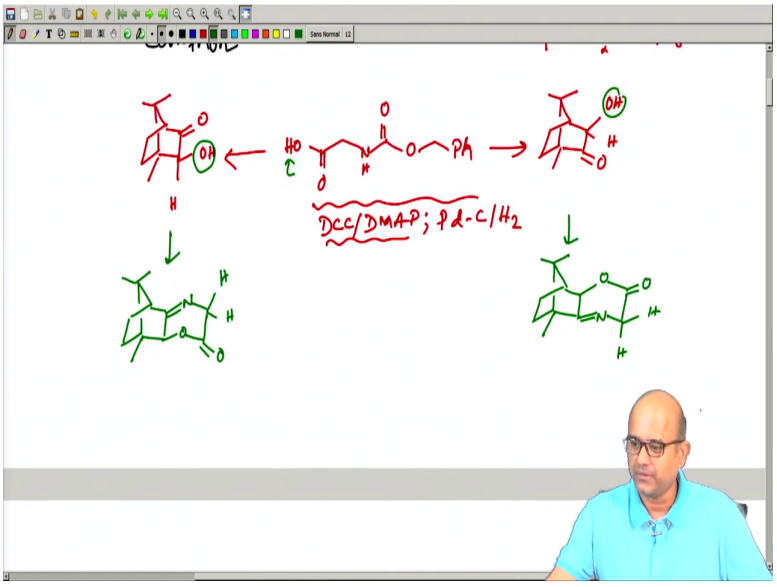

Now, let me draw the product, which we are going to get from the first case. So, this is there and now here you have this oxygen fine you have this glycine CO. Now here you have a carbonyl which is reacting with the imine. So, the imine part now comes it here this, this. So, the glycine 2 hydrogen are here fine.

And in this case what you are going to get? You get the opposite connectivity you get this, this, this, this here you now get the imine this N ok. So, you basically synthesize both the 2 tricycloiminolactone there are other methods also you can eventually get it, but for the time being just try to remember both the 2 tricycloiminolactone. Now once you have this tricycloiminolactone what next you can think about.

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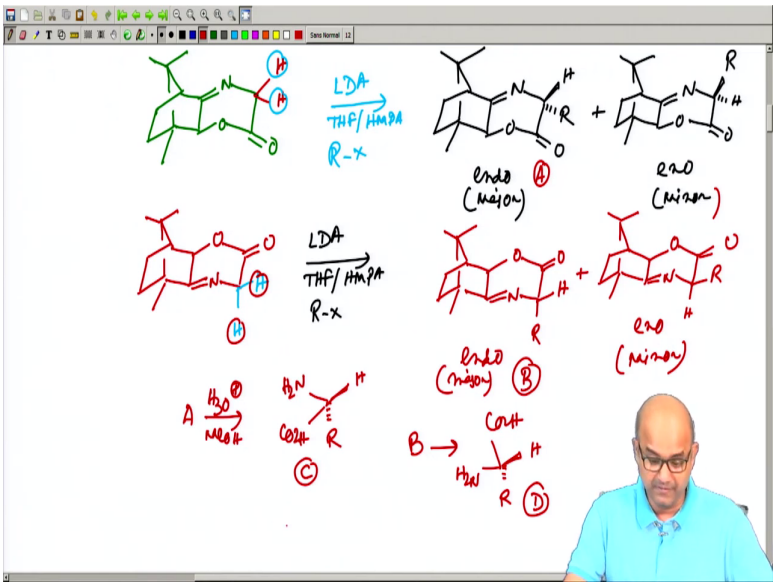

So, now we will write both the tricycloiminolactone one after another. So, first tricycloiminolactone if you can write it this, this, this the carbonyl and you have this 2 hydrogen……. 2 hydrogen. The second one you can write in the similar way everything remains same just you change the connectivity ok.

So, now we have this 2 hydrogen. So, now, first case let us take the first case you treat this compound with LDA one equivalent and base was used THF and HMPA a coordinating solvent and then you react with a R-X, an electrophile. Now definitely first the hydrogen will be abstracted any one of the hydrogen you get the mono enolate. Now incoming electrophile will be coming from the endo phase because exo face is blocked by the bridged dimethyl group.

So, now you can write the product distribution. So, this thing you have this N you write everything as the parent structure the ketone and you will definitely get now you can write hydrogen and this R will be below fine and if you want to write the major product and minor

product. So, first product is the major one, the second one will be the minor product. So, minor product also you can write this, this and R will be this hydrogen will be below.

So, this definitely will be the endo product because endo alkylation and this will be the exo, this will be the major this will be the minor, fine ok. Now second case of the similar so, LDA same condition TFH/ HMPA and then you react with R-X. Now everything seems to be similar. So, you just try to do it this oxygen and this N.

Now, here also these two hydrogens are the enolizable hydrogen. So, definitely once you abstract it the electrophile attack will be the endo one ok. Endo means the R will be below this is the hydrogen. So, you will be having the endo which seems to be the major one definitely and the minor one you can just try to follow the similar drawing you have the exo one which will be the minor one this is also can be like R and hydrogen.

So, this will be the exo …….this will be the minor one. Now once you do this thing you can eventually now hydrolyze this to after the reaction alkylation is over you have to basically hydrolyze ok. Now here the catch is the first case and the second case if you now try to take the compound ……A let us say this is compound A and this is compound B. So, compound A if you now just keep the structure compound A you just hydrolyze the thing a normal hydrolysis was done by H_3O^+ methanol / methanolic H_3O^+.

So, you can just write the structure the R seems to be below I will just keep it right this R this is we just keep it everything same H this H2N and CO2H. So, this you get from compound A. Compound B also if you just do the hydrolysis you will get similar thing you get R here you get hydrogen. So, I did not write the ketone part let me do it and then the amine will be here and this is your CO2H.

Now, compound 1 means, let me write this is C and this is D the amino acid. Now these two compounds these two compounds are what these two compounds are actually enantiomer you can just try to analyze because the relative orientation of CO2H and NH 2 are just opposite.

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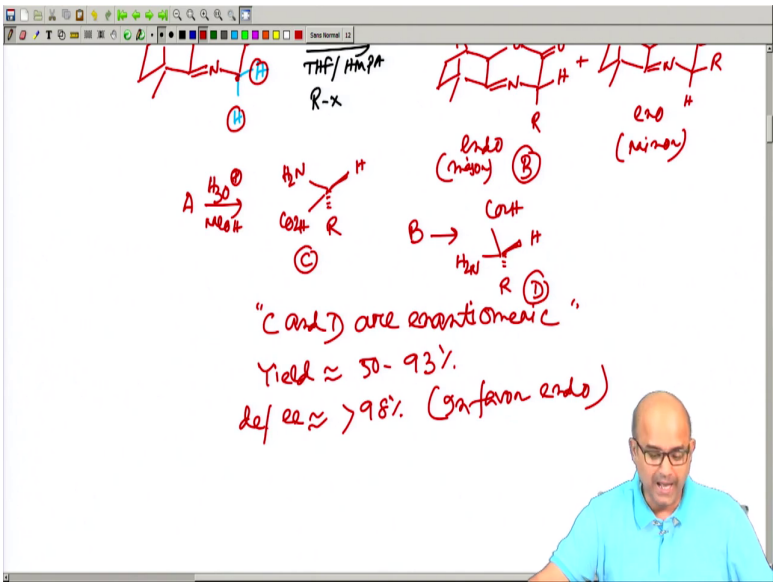

So, C and D this is the main beauty of this thing. So, C and D are enantiomeric. So, actually by using 2 tricycloiminolactone you can eventually get both the enantiomer. So, you start with this or you start with this, you start with this and you start with this, the first case you get 1 enantiomer second case you get 1 enantiomer.

So, we are saying that these methylene groups are usually enantiotopic normally in the camphor based case. So, this was usually done pretty nicely, the yield…… normal yield for such reaction is 50 to 93 percent for depending on different substrates and ee or de usually is pretty high greater than 98 percent in favor of always endo always you get the endo diastereomer.

So, that could be the de. So, this was pretty nicely documented thing and once you can do a mono alkylation you can subsequently do a dialkylation also let us give you an example for dialkylation.

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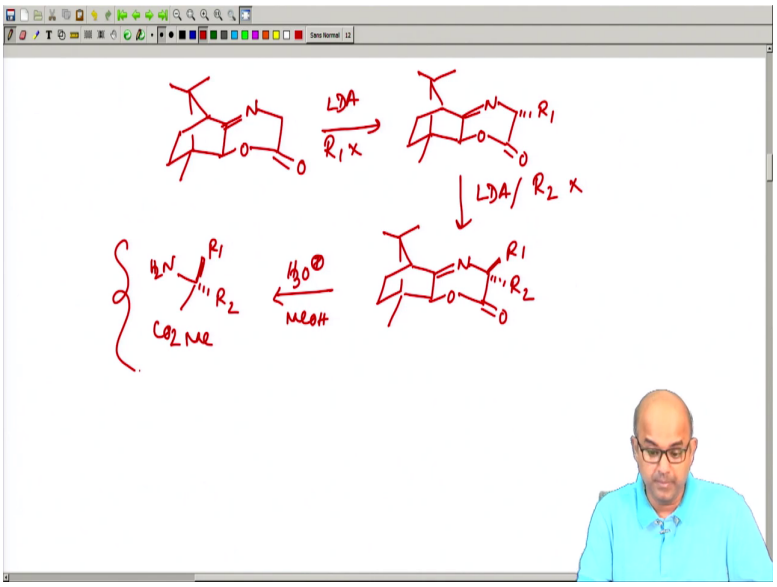

And this dialkylation can be similarly performed. So, this and then you have this N this oxygen as it is you can take any of this auxiliary let me take this auxiliary and then you first take LDA, R1X this we all know just like the similar thing the endo adduct will be the major adduct CO you will get the R1 fine take the same compound and then again LDA followed by R2X.

Now, the second electrophile will be next approaching from the endo. So, this will be. So, R2 will be now below and R1 will be above and then you just do the basic hydrolysis H_3O^+ in methanol treatment. So, what you will get you get the R1; R2 below this is your H2N and this will be your CO2Me. So, what you get? You get the dialkylated glycine derivative. So, such dialkylated glycine derivative we can easily prepare.

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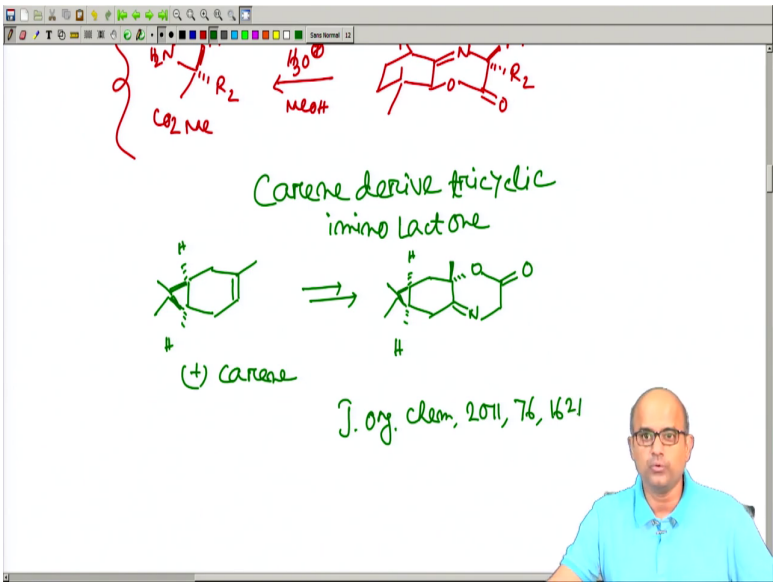

Now, next once the camphor derived thing is done the same group the same group also explored a similar kind of another tricycloiminolactone which you can now call as a carene derived tricyclic amino imino lactone. Now earlier it was camphor derived now it is carene derived, carene is a terpene a monoterpene.

So, the structure of carene seems to be interesting it is basically having a six membered structure with a double bond here and this part it is having a cyclo propane ring with 2 gem dimethyl. So, the enantiopure carene this is a naturally occurring terpene molecule and this compound is a plus carene. Now how they do this reaction? They basically convert this carene to this corresponding tricycloiminolactone we will explain how they make this compound just I am trying to give you the basic initial part.

So, this and then they do a similar kind of mechanism they actually get this tricycloiminolactone. Now this part is the cyclopropane thing ok. So, this is the carene derived tricyclic imino lactone this is 1, this is 2, this is 3 and this work also reported by the same Chinese group in a JOC paper in 2011. So, this these works are relatively recent work and now how they prepare this carene derived tricycloiminolactone will be next discussing.

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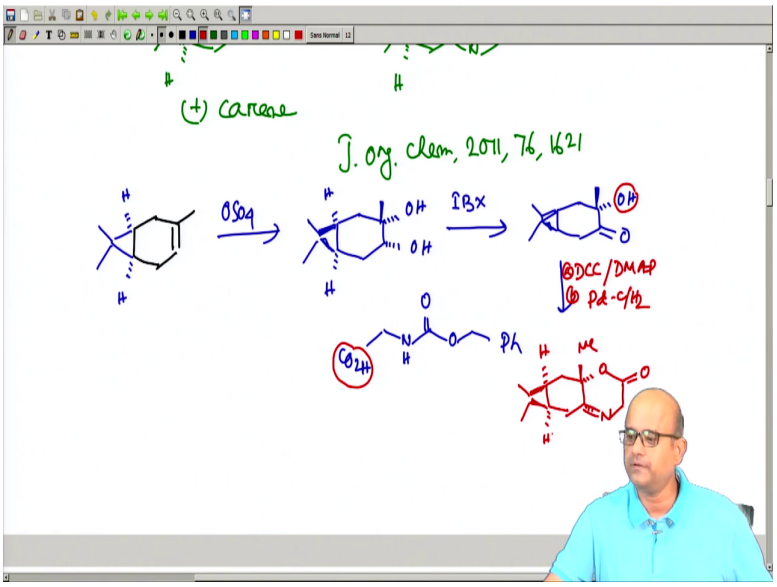

So, first you take the carene which you can get it from the commercial supplier. So, you have this I will just try to write the bridged bicyclic thing, I mean the cyclopropane thing this cyclopropane is above. So, that is why I put the hydrogen above and below this is the carene part ok. So, first they react with osmium tetroxide do the dihydroxylation.

Now, definitely as the cyclopropane is above. So, substrate directed dihydroxylation will be taking place and cis di-oxidation; the OH will be below OH will be below as cyclopropane is above ok fine. You get this compound first. Now this is a tertiary alcohol this is secondary alcohol. So, what we do a simple a hypervalent iodine mediated oxidation which is iodoxybenzoic acid.

Now, this secondary alcohol will be oxidized, this will be oxidized and remaining or will be there cyclopropane this ok. Now this compound in a similar fashion earlier what we have seen? You take the corresponding this glycine derivative earlier what we have shown to you that you take this glycine suitably protected glycine derivative with a CBZ protected NH COO CH2Ph and then you take this corresponding CO2H.

Now, this carboxylic acid this carboxylic acid will react with here then. So, first you do a DCC /DMAP coupling number 1. Number 2 your palladium charcoal hydrogen. So, palladium charcoal hydrogen the moment you do it that basically debenzylate the CBZ group the CBZ group will debenzylate and then it will be simple this ketone with amine

condensation. So, what we are going to get? You basically we will be now getting the chiral glycine derivative.

So, write the stereochemistry properly this methyl, this O is below and then you have this is the C O this and then here you are having this imine part. So, we can write double bond N this. So, this is the chiral glycine derivative and then the cyclopropane part is here this, this. So, once you have this thing this is in principle very similar to the earlier carene derived imino lactone.

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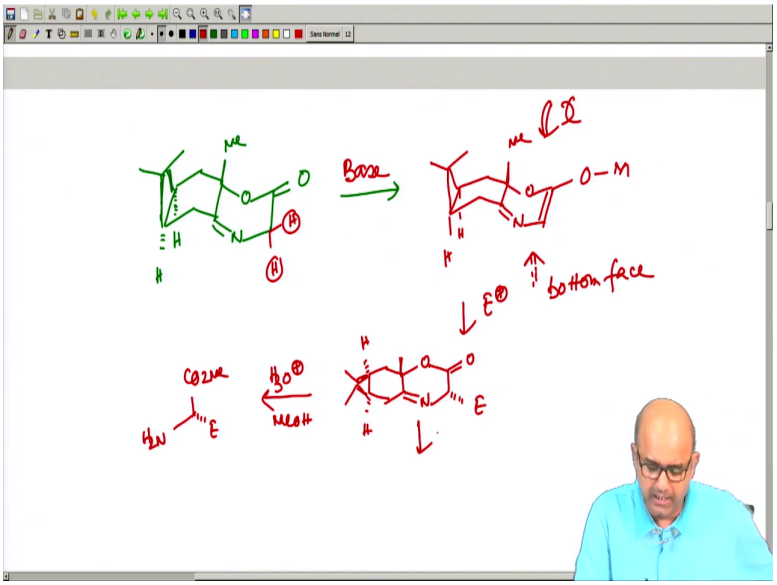

Now, we can try to draw the structure in a different way. So, let me try to put the cyclohexane in this way and this is the cyclohexane part ok. This methyl is above. So, you can write this methyl then this oxygen here, this and this double bond N then you have this kind of structure and this and this CH cyclopropane part. Now this structural drawing there is a you can easily think of that why we did it because as this cyclopropane is above and this is basically a rigid bicyclic structure.

So, this could be the most stable confirmation of the starting compound. Now the moment you do it you can eventually have an idea that in the earlier carene case sorry, the camphor case the bridged bicyclic ring bridged bridge gem dimethyl actually controls the incoming electrophile…… the steric course of the reaction.

Now, here in this case this bridged dimethyl of the cyclopropane actually controls it. So, first your base treatment, which basically gives you the deprotonation so, you can eventually write the structure, let me write the cyclopropane part you have this hydrogen below for this thing and then this part will be little bit below because this methyl is above this is the original structure. The oxygen and then this any one of this hydrogen will be abstracted ok.

So, then you have this and this you can just write O metal if you use a metal containing base. Now you can easily see that the electrophile definitely the attack of the electrophile from the top phase will be hindered mainly due to this methyl group, but the electrophile will be approaching from the bottom face. So, bottom face or alpha face…… the electrophile approach will be much more preferred.

So, similarly in the earlier case we see have seen that endo attack is preferred because the exo face is blocked by this the bridged dimethyl group. Now see once you have these thing you can easily try to explain the how the incoming electrophile will be approaching. So, we can now straight forward go to the two dimensional drawing this is the methyl, this is your oxygen, this is the nitrogen part the imine ok the CO and the electrophile if you write E plus this will be E ok and this is the cyclopropane part this, this.

So, conceptually this is very similar with the carene sorry the camphor derived tricycloiminolactone. So, carene and camphor both are similar and they have a similar kind of a steric course of the reaction now if you can do it a double alkylation or if you prefer not to do double alkylation you can just do the hydrolysis at this point. So, you can get the corresponding E you get a CO2 Me and you get the H2N.

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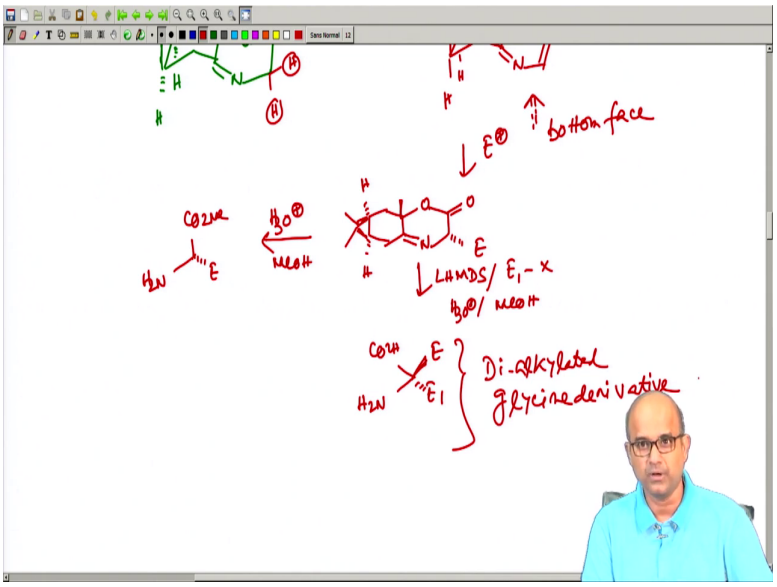

But if you prefer to do a double alkylation that also you can do and usually you can do it also you can take this compound treat with a base and second round of electrophile with E1-X followed by H_3O^+ and methanolic hydrolysis. In this case you have to identify that E1 the second electrophile will be the below. So, you can just write E1 will be below and the first electrophile will be above you have your CO2H you have your H2N.

So, Di-alkylated glycine derivative you can actually get. So, this part is mainly focused on the chiral glycine derivative and different kind of chiral glycine derivative can be prepared, where a glycine is fused in the chiral component and then you can selectively I mean you can remove the protons, you can generate the enolate and the steric course of the reaction will be mainly governed by the preexisting stereo center in those molecules.

Earlier we have seen you can control through chiral relay, but in all those chiral glycine derivative a preexisting stereo center which will control like this tricycloiminolactone carene derived or the camphor derived or your Williams oxygen zone or any other chiral glycine template almost all are principle is similar just the structural part is little bit different.

Just by seeing the structural part you can have a predictive behavior that from, which face of the enolate the electrophile is approaching. We will discuss more things in the amino acid alkylation in the subsequent lecture.

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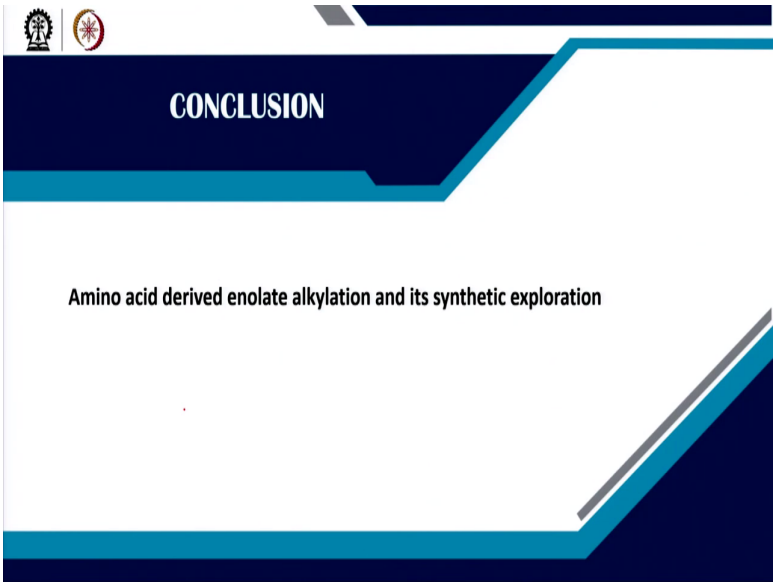

So, finally, we can say that this tricycloiminolactone based enolate alkylation is a potentially good tool. And this chiral glycine equivalent is very useful tool for making mono alkylated glycine as well as dialkylated glycine in enantiopure fashion.

Thank you and we will see you in subsequent lectures.