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 - 05
Enolate alkylation of carboxylic acid derivatives
Lecture - 23
Meyer's bicyclic lactam based enolate alkylation

So, welcome back everyone. So, in particularly this lecture which will be supposed to be lecture 23 under module 5, we will be trying to have another alkylation strategy of carboxylic acid derivative and this is named as Meyer's bicyclic lactam based enolate alkylation the same Meyer's who was already we talked about the Meyer's oxazoline

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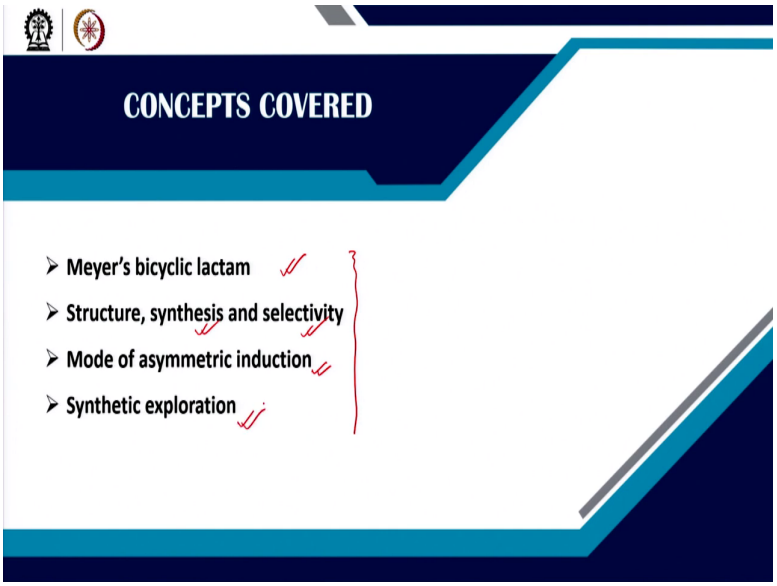

The main content of this particular lecture will be structural information of bicyclic lactam, its synthesis and its selectivity and mainly we will talking about mode of asymmetric induction how enantioselective construction of new carbon-carbon bond has been created and its synthetic exploration will be trying to discuss.

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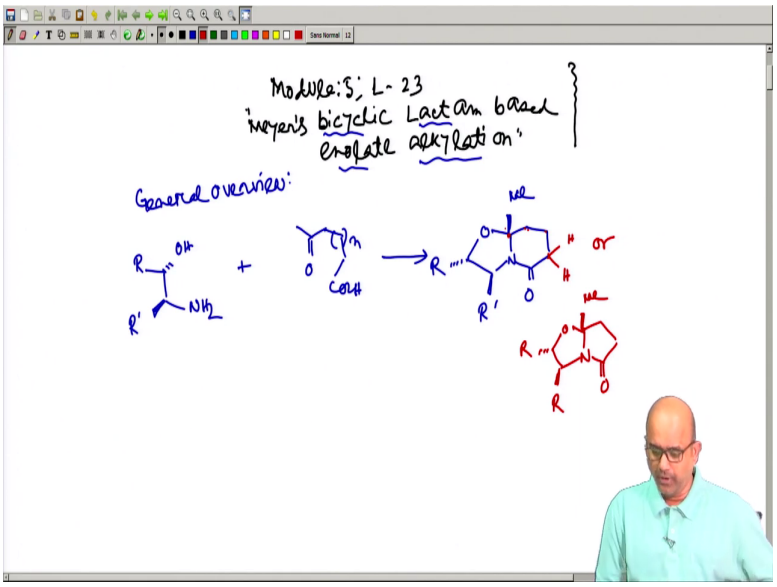

So, in this module we are mainly going to discuss about a new auxiliary based alkylation which is named as Meyer's bicyclic lactam based enolate alkylation. And as you can see the name is bicyclic lactam. So, definitely its structure is basically features on a bicyclic lactam.

Now we will try to give you a very general overview of such bicyclic lactam and how this compounds are synthesized. Usually such compounds are synthesized from corresponding keto acid……. this keto acid and this keto acids are you can usually you can prepare in the lab very easily.

And then you condense this compounds with corresponding amino alcohol which usually we have prepared in the earlier cases like Evans oxazolidinone through a simple reduction pathway. Now see this amino alcohol with the keto acid you can basically condense. Now once you condense you will actually get a bicyclic lactam structure of this and then ok and you have a methyl here. Now if you see how this compounds are forming? This compound is simple basically a dehydration reaction.

You actually react this initially you form this cyclic acetyl type of compound and then corresponding amine group will react with this carboxylic acid then you get this bicyclic lactam. In this bicyclic lactam the basic features you have this 2 hydrogen which seems to be acidic. Now it could be a 5 member, it could be a 6 member. So, you depending on the number of n on the carbon atom you can eventually have a five membered bicyclic lactam something like this and rest of the portion will remain as it is. So, this keto acid gamma keto

acid or delta keto acid you basically require. Now you can just count the number. So, Me this Me CO CH2 CH2 CH2 CO2H. So, basically this is alpha, beta, gamma, delta; delta keto acid that will give you a delta lactam gamma keto acid that will give you gamma lactam.

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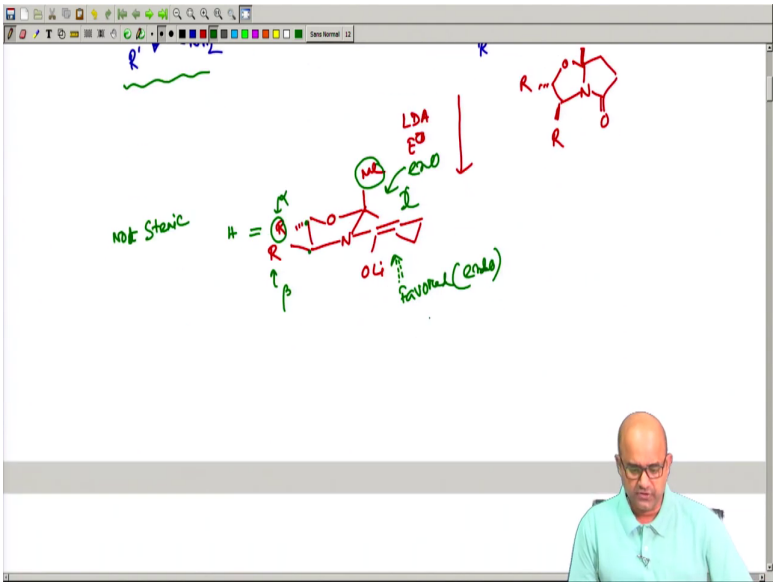

Now, once you prepare this lactam next is you actually take any of this five member or six-member lactam treat with base LDA and react with an electrophile and if you assume a six-member thing. So, initially let me draw the after hydrogen abstraction you get a six member enolate which is basically half chair conformation and this is your OLi metal. There will be absolutely no chelation, but chelation is not happening as you do not have a chelating group, but the ring size or ring conformation will have a major predictive role in these cases.

So, you definitely have a enolate…….. flat enolate now you can see that there are main two governing factors this angular methyl it can only adopt always a beta orientation because there is no other option it can take and this two center is mainly governed by this auxiliary part. Now if R and R prime if this seems to be the beta and this seems to be the alpha they are basically contradictory to each other.

So, in most of the cases this R seems to be hydrogen. So, that does not give you any steric not steric or no steric. So, in this case the hydrogen does not give you any steric fine. Now this R is beta methyl is beta. So, it is expected that if you are you always find that the electrophile will definitely approach from the alpha face, it's a usual assumption and this approach is basically the below face.

So, I say endo approach and X ……..way approach the top face approach seems to be not preferred mainly due to the steric crowding.

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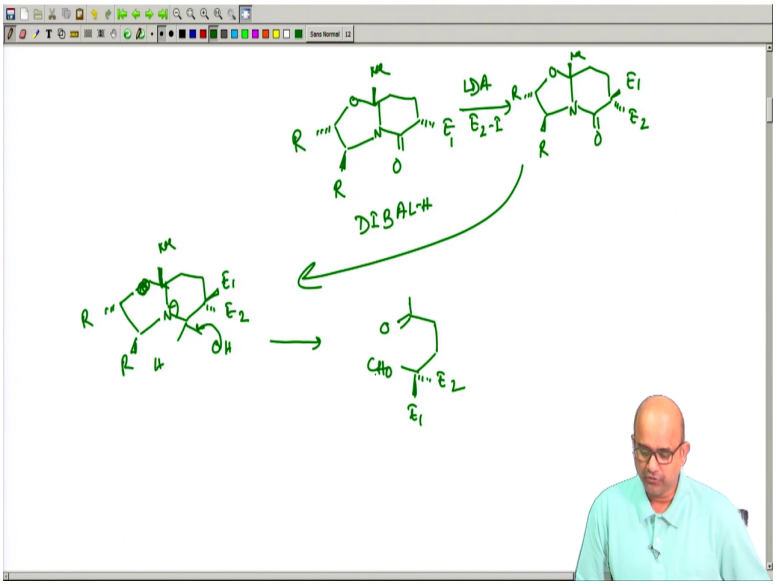

So, the moment you do this reaction what basically you will be now having? You have N you just write a six-member thing you get an electrophile carbon electrophile bond and then you have this part just write the remaining thing the methyl is always there you can do a second round of alkylation. So, this is E1.

If you use the second round of alkylation LDA, E2-I the next the electrophile the second electrophile will again attack from the endo face and what it will give it? It will usually give you a carbon E2 bond in the below and E1 will be now above. Now such compound you can easily synthetically manipulate you take this compound and you can just actually do a mild reductive cleavage with Dibal-H all RedAl what this compound is going to give it to you the mild reduction which will be happening will give you a first a reduction through hydride transfer here ok.

And then I am sorry this will be the O this is O, you have two different group R and R prime. Now this does not stay for long and that basically we will open up the aminol part. So, and then the moment it will open up it will undergo further cleavage and that ketone per the Me C double bond O will be released from this part and then here you can see CH2 CH2 ……..2 CH2 then this.

And here you are having this quaternary center E2 and this will be your CHO. So, you basically get a keto aldehyde. Now this keto aldehyde you can synthetically manipulate through different synthetic transformations which will be discussing little bit later on. So, Meyer's bicyclic lactam this is the main feature of such reaction.

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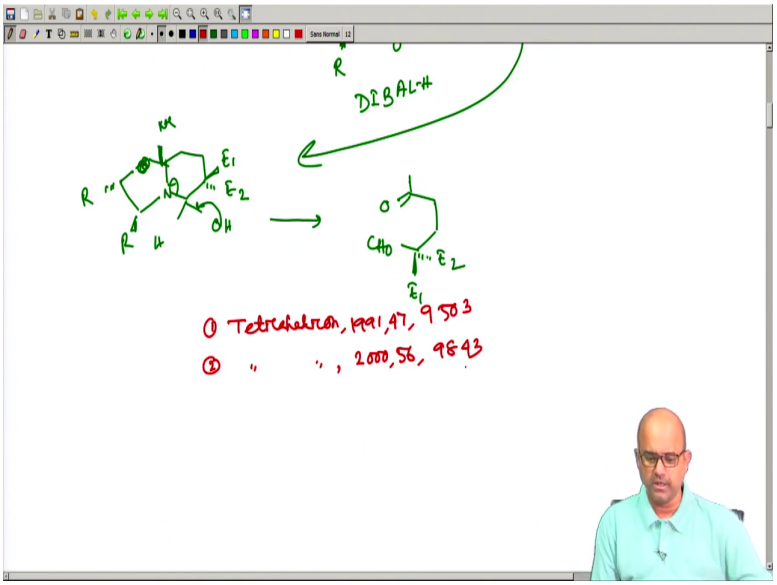

Now, there are two nice reviews where from you can get the basic idea of Meyer's bicyclic lactam, they have been published in Tetrahedral, in 1991, 47 is the volume page number is 9503. There is another review which also published in same journal in 2000, volume is 56 and page number is 9843. So, these two references will give you a detailed analysis now let me try to give you a different angle of this Meyer's bicyclic lactam.

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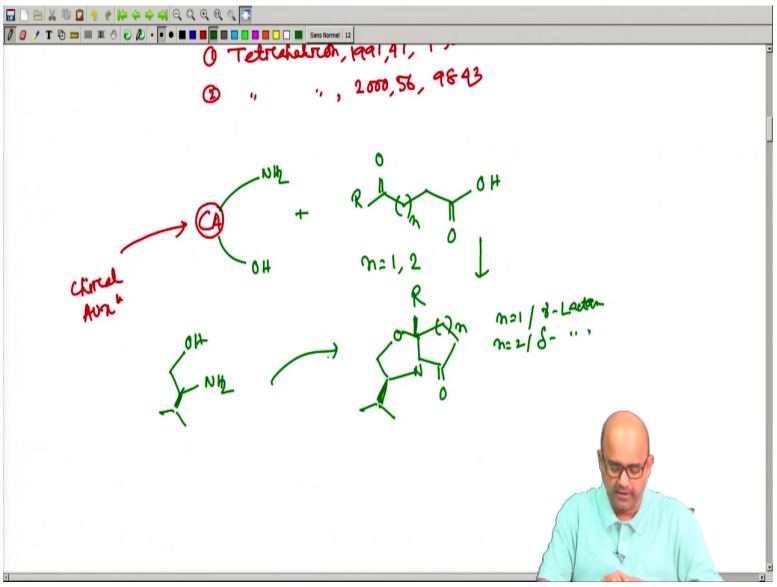

Now, Meyer's bicyclic lactam what we do we first use a CA. This CA actually stands for a chiral auxiliary. Now what is this chiral auxiliary? This chiral auxiliary is coming from the amino alcohol part. Now, this in the CA part, one part is having an amino group, one part is having a hydroxyl group ok.

Now this is going to be coupled with R…. C double bond O and as I am saying you can have different kind of different kind of acids gamma keto acids or delta keto acid OH ok. So, this is alpha yeah this is alpha beta gamma. So, gamma keto acid and this is another. So, you just write a n.

So, n equal to 1 or n equal to 2. Now for after this reaction it is a simple dehydration reaction if you are trying to get the auxiliary whose structure will be just now we have drawn earlier. So, you have a n you have a C double bond O now here you put a this ok and you have a R here and you can put a n here. So, if n is 1, n is 1 this is a gamma lactam, if n is 2 that is a delta lactam.

Now, in this chiral part usually this seems to be an always an isopropyl group because you can easily prepare such isopropyl based amino alcohol from the valine. See this amino alcohol can lead you to this compound ok there are other amino acids also you can choose, but this seems to be quite interesting and; obviously, other amino acid based auxiliary also you can use it let us say you can write an another auxiliary.

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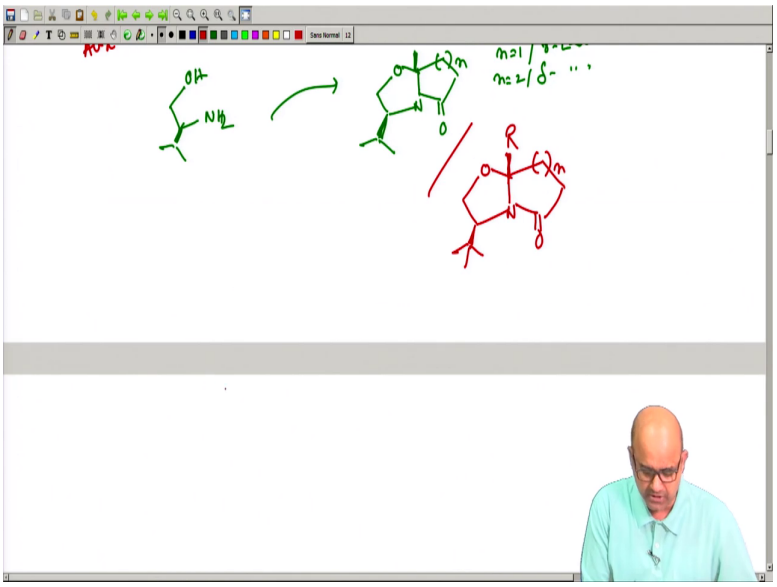

Whose structure is more or less similar you have a N C O, this part is almost similar and here is oxygen, there is a tertiary butyl. So, this kind of amino acid. Now the key structural features for such bicyclic lactam was pretty important.

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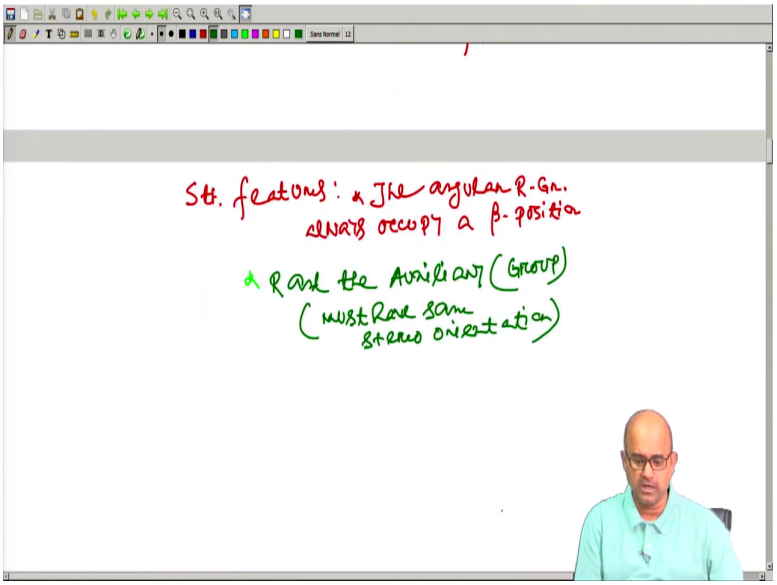

So, initially let me try to talk about the structural features just keep the one of the structure as it is. Now main structural features the angular R group the angular R group which is a very crucial position angular R group always occupies a beta position because you will not get

anything it is always above the plane. This is a bicyclic ring fused together. So, this has to be a beta ok if these are and this chiral auxiliary hanging group.

So, this is number 1 point and number 2 point is this R and the auxiliary the group the group which present in the auxiliary if they are in the same studio orientation that is usually preferred because they give you a double asymmetric induction or double control. So, R and the group in the auxiliary must have usually must have same stereo orientation means both should be above or both should be below ok. Now there are few other features which we might be considering here.

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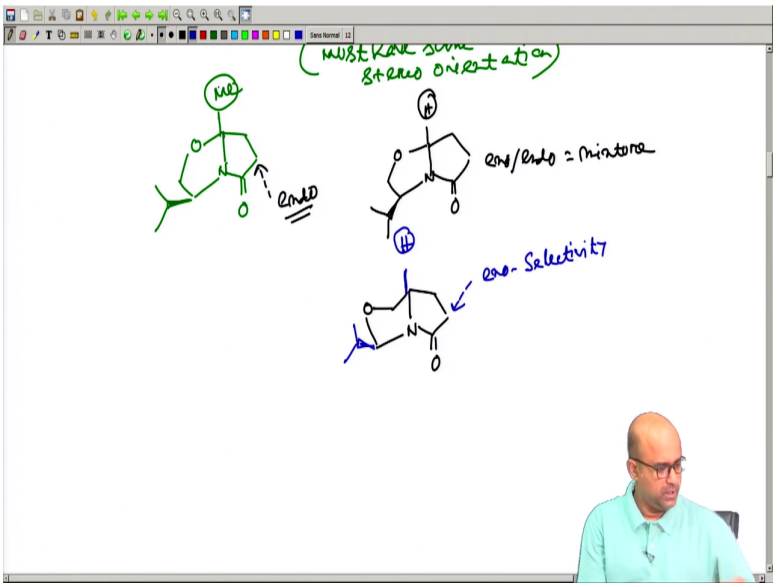

Let me try to give you some other auxiliary and such auxiliary the drawing was pretty important and usually it has been found that this auxiliaries kind of give you a commendable or predictable alkylation selectivity.

Now, see the first auxiliary like just now we talked about. In this case this is beta this is beta ok. So, alkylation usually prefers to below mode or the endo mode now fine. Now let us say there are some auxiliaries whereas I said the angular group is very important in some cases you might have a hydrogen at the angular position. So, if you have a hydrogen at the angular position that is a real tough thing ok.

And if you try to have a hydrogen here that compound is eventually do not give a good selectivity. So, exo endo you get a mixture. So, that basically gives you idea that this should

be a non hydrogenic group in the parent molecule now here. So, means that this group steric parameter is pretty much important ok this group steric parameter is pretty much important.

Now, other compound similarly if you keep a hydrogen in the ring I mean hydrogen in the angular position and then take a compound something like this where the oxygen is a little bit apart from the original position ok. Now this compound is crucial this compound is having a hydrogen here now this compound gives you a exo selectivity in the alkylation.

So, there is a different factor which might be responsible for endo selectivity as well as exo selectivity. Now why this compound gives exo selectivity? Actually if you check the ring carefully the bicyclic ring around this pivotal bond are basically tilted towards down ok. Tilted toward downs mean that basically makes the bottom face much more sealed. So, top face or exo selectivity is much more preferred.

But so, Meyer's I mean Professor Meyer's always try to avoid those confusion and he always prefers a alkyl group at this ring junction and that gives you a nice or predictable control……. which usually we prefer. Now once you prepare this Meyer's bicyclic lactam how this bicyclic lactam synthetically you can manipulate? We have just now told you couple of things let us say you have a Meyer's bicyclic lactam.

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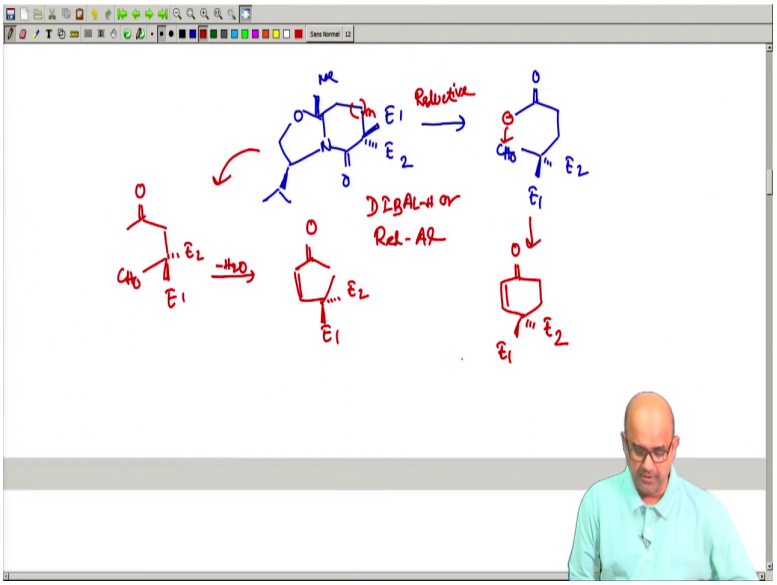

Let me first draw the six members structure ok and you have already created double alkylation. So, two successive carbon electrophile bond has been created and then you have a

methyl here, you have an oxygen and you have this group here ok just now we said you can do a reductive cleavage.

So, the moment you do a reductive cleavage it will six member ring. So, see what you can get? You can basically get a CO Me then CH2 CH2 CH2. So, you have a E1 and E2 and you have a CHO. Now see the moment you have a keto aldehyde you can you are you are basically expecting couple of extra reaction to be covered. So, basically you can do a simple aldol type of reaction.

So, you can generate a minus here and you can do an aldol type of reaction. So, that basically gives you a six-member ring ok. Similarly, if you have a one carbon less here means a five-member thing in that cases also you can get Me CO CH2 CH2…….. 1 carbon less. So, here you created the E2 and E1 and then you get a CHO. Now this compound also you can actually close the ring by simple aldol dehydration.

You can just apply a normal deprotonation followed by aldol. So, in this case what you will get? You can basically get a cyclo pentenone type of structure and you can see you can actually get a 1, 2, 3, 4. 4 4 di alkyl electro cyclopentenone and in this case what you can get you can actually get a six-member thing you can actually get this kind of compound.

Now, this cleavage usually is a reductive cleavage you usually treat the after this alkylation was done a pretty mild reducing agent like Dibal-H or RedAl was used ok and in addition this compounds once you try to do it you can do it do a reductive cleavage you can also cleave it in a different way different way means there are other ways. So, this is simple reductive cleavage which you which can give you as a keto aldehyde.

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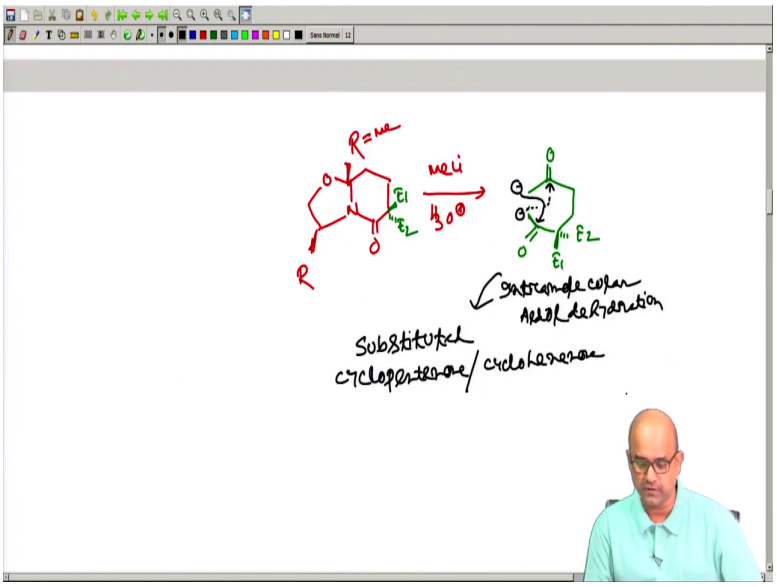

Now, let us say you want to try to do in a different way different way means other way. So, you can simply write N, your parent lactam it could be a six member could be a five member depending on your choice. Now initially without doing the reductive cleavage now if you try to use a methyl lithium kind of thing or a nucleophilic based image. Now methyl lithium is a pretty good nucleophile.

So, what it can do? It can basically react first here and then after that methyl lithium if you treat with H_3O^+. So, this amide you will be having a CO Me now if this R could be a methyl you now see what compound you can get. So, this is CO its a methyl on the top part CH2 CH2 this part your alkylation was done at the very beginning. So, after 2 …….CH2 CH2 CH2. So, now, here you get E1 you get E2.

Now, in this point you get a CO and methyl. So, now, here also you can actually try to do a selective kind of alkylation or aldol reaction. If you see if you are specifically able to generate a carbonyl either from this or from this. So, if you generate a carbonyl here you can attack on here ok then it will give you 1, 2, 3, 4, 5, 6 and then you can generate a carbonyl here and you can do a reaction here.

It can basically give you again 1, 2, 3, 4, 5, 6. So, in both the cases a substituted cyclohexenone can be generated by controlling the mode of attack through 2 different carbonyl. So, intra molecular aldol dehydration can be possible. So, same thing you can do a

six members things or a five-member thing. So, what you will be getting? You are basically getting a substitute state cyclo pentenone or cyclohexenone.

Now, such thing you can easily do it ok. Now let me before we come to a conclusion we will try to go the synthetic exploration for this comp this bicyclic lactam through different ways at the beginning we will explore that a different way that how you can mate simple 3, 3 di alkylated dihydronaphthalene.

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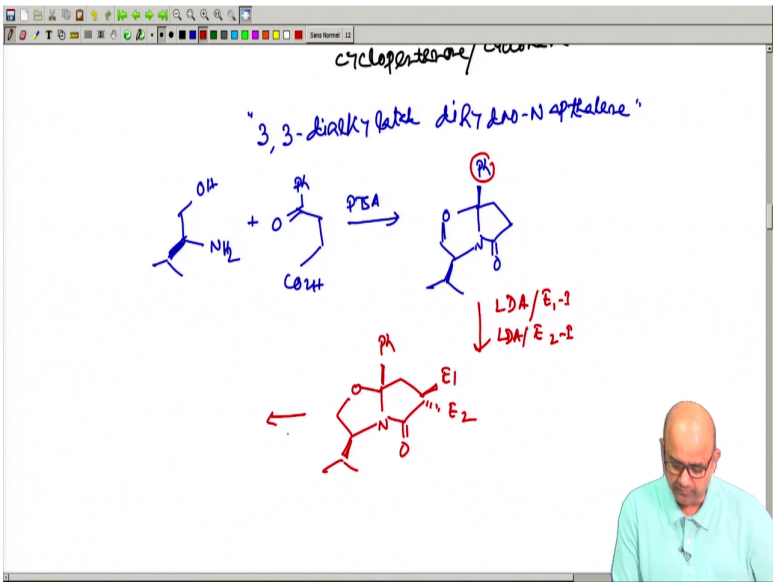

Now, you must be must be surprised that sir was initially talking about cyclopentenone and cyclohexanone suddenly he came to dihydronaphthalene.

Anyway we will be coming to each and every target molecule in a subsequent way now in this case this was a really nice application. So, what is go going to be done here? First you actually take this corresponding valinol with a this yeah this structure the keto acid which you going to take its a phenyl ketoacid. So, Ph CO CH2 CH2 CO2H and you just reflux this two compounds in a dehydrating condition with para-toluene sulfonic acid.

So, first you get this Ph O, this is the N, this is your you get a gamma lactam and this is your sorry the structure was a little bit wrong fine you get this compound ok. Now phenyl as well as this isopropyl seems to be the opposite. Now what you do? You do a successive round of alkylation ok? So, LDA first E1 iodide, second round of LDA…… E2 iodide. So, now, by doing this thing what it will get? You get Ph.

You get N you get C double bond O. So, first this E1 will be above E is below because E2 is added later on you can change the sequence also fine.

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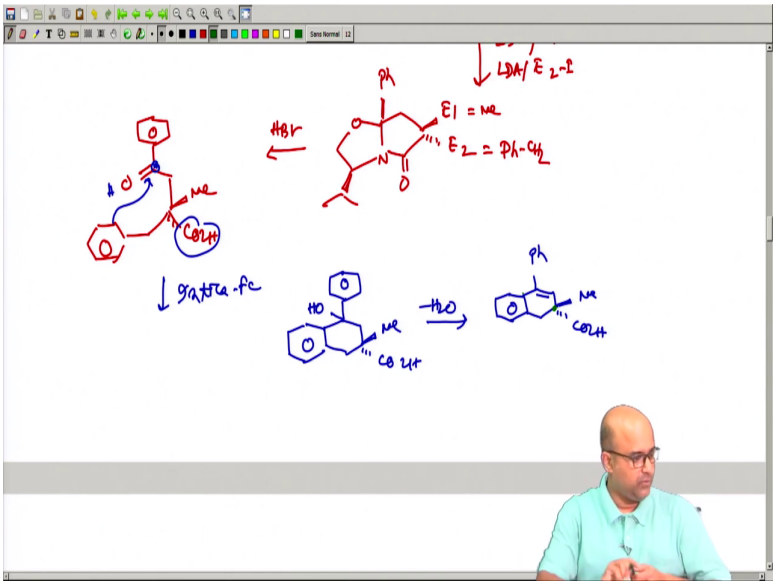

Now, this compound you just treat with a simple acid. Now simple acid means you are basically trying to removing the lactam. So, this part is phenyl CHO means ketone after hydrolysis, then here you have your methyl you have a I am just coming to it why I have written this one.

Now, assume E1 is a methyl and E2 is a benzyl Ph CH2. Now this benzyl is this carboxylic acid is coming from the lactam cleavage this carboxylic acid coming from the lactam cleavage. Now see this compound you have HBr in the reaction medium. So, basically this gives you a protonator form this is electrophile. So, intra molecular Friedel-Crafts now can take part intra molecular Friedel-Crafts with this benzyl group as the aromatic precursor. So, what we will now get? You get Ph you have a just let me finish the drawing then we will explain.

So, here you have a OH and here you have a methyl you have a CO2 H see. So, this is going to undergo the (Refer Time: 29:07) reaction. Now a simple dehydration reaction and what you will get? You basically get the alkylated naphthalene derivative. So, this is the compound which you can get now such compounds are very easily you can prepare with the help of Meyer's bicycling lactam based anode alkylation. So, this stereo center we have created.

And we do a intra molecular Friedel-Crafts reaction and this was a quite nice reaction to explore in the very beginning part. Now I will try to give you a home assignment based on this particular problem.

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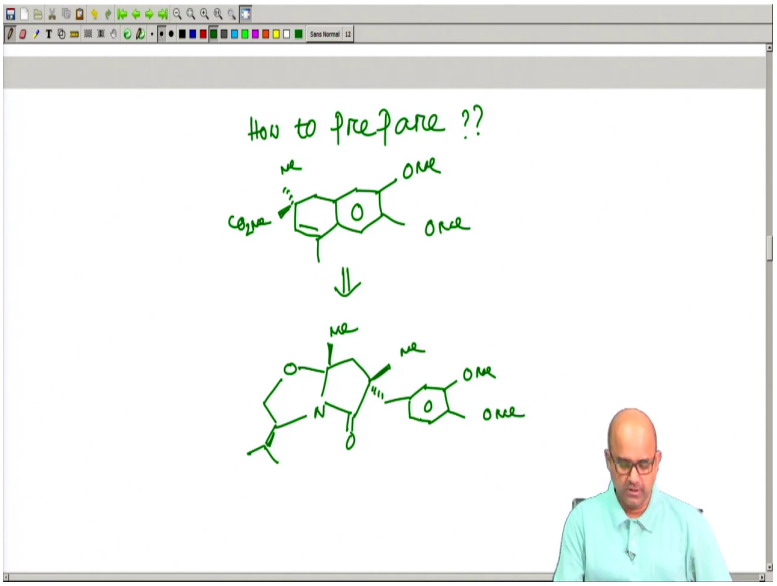

So, let me give you assignment how to prepare this compound just let me finish the structure we have a dimethoxy here, O methoxy you have this you have a methyl here.

Here you have a Me and you have a CO2 Me. This more or less very simple seems to be and what exactly you can try to think about if you try to use this compound as a target molecule by mass bisecting lactam. So, let me first draw the particular lactam which you might be needing. So, you need a methyl because earlier compound you have a methyl now here is a methyl ok.

And then you have a nitrogen, you have a C double bond O this. Now see here is a missile and another is your benzyl part which will undergo (Refer Time: 31:06) reaction. So, you can just write methyl and this benzyl will be this and then you can write the three four dimethoxy. So, this will be your two successive electrophile one is this methyl another is three four diameter methoxy benzyl bromide and rest part will be as it is. So, if you take this bicyclic lactam and do the intra molecular friedel craft you will be able to make such molecule with the help of Meyer's bicyclic lactam based alkylation.

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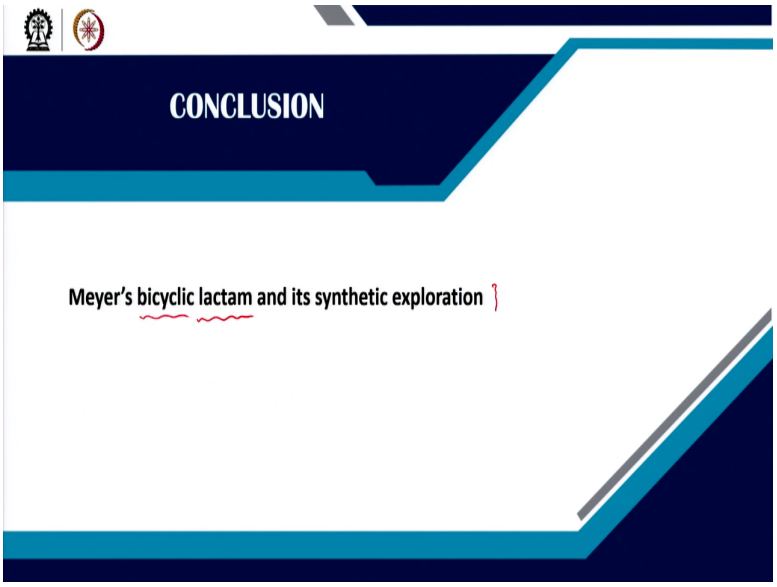

So, as a concluding remark we can say that Meyer's bicyclic lactam which seems to be a pretty important synthetic method for creating a series of or different enantiopure chiral starting materials for various purposes and this particular bicyclic lactam gives you a purely cyclic stereo control in the enolate alkylation. We will be discussing its several features in the subsequent lecture till then.

Thank you.