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 - 24
Meyer's bicyclic lactam based alkylation

Welcome back everyone. So, today in this module 5, in continuation with our lecture, today we will be having lecture 24 and mainly we are discussing Meyer's bicyclic lactam based alkylation and its different features.

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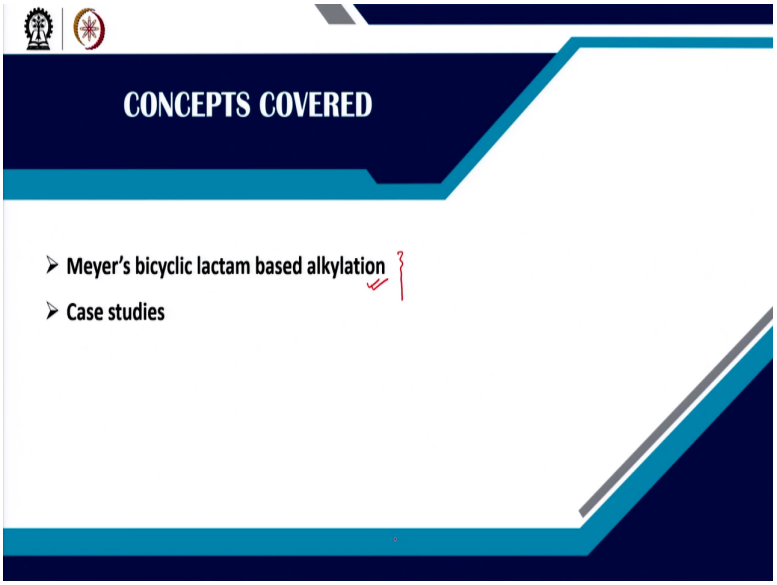

The main content of today's lecture, will be basically like last classes lecture, we will be talking about several features of Meyers bicyclic lactam based alkylation, the initial part which we have discussed the origin of asymmetric induction, we will be mainly focusing on several applications and case studies ok.

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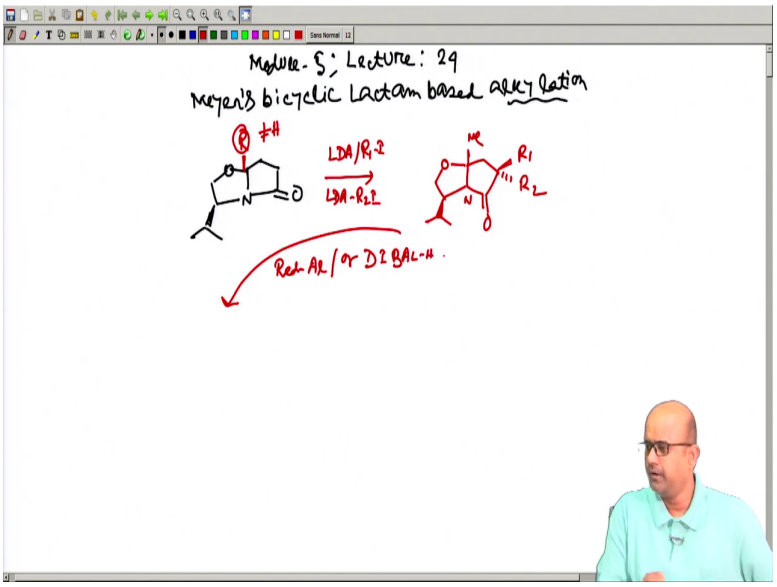

So, today we will be mainly focusing on this Meyers bicyclic lactam based alkylation, and as we discussed earlier, the alkylation can easily be done on this 5 member or 6-member lactam and actually this lactam you can easily prepare from the corresponding amino alcohol, and the keto acid; we also explain to you that this alkyl group is a must in the compound, it should be alkyl group it should not be hydrogen. So, that basically gives you a different selectivity.

Now, how can synthetically manipulate it such compounds. Now let us say you do the successive round of alkylation with LDA first you with one electrophile and second you do with the other electrophile; the mode of asymmetric induction you can already create now let us say you this R is a methyl group. So, you are having a methyl here, there is a N, and then this 5-member lactam is here and. So, you basically do have a R1 and R2 and then this part your auxiliary part which is coming from the amino alcohol.

Now, how you can synthetically manipulate it. In the last class we talked that, you can basically do a reductive cleavage as well as a hydrolytic cleavage or a nucleophile assisted cleavage. So, let us see first you do a reductive cleavage. So, you can just treat this compound with Red Al or Dibal-H which is a selective and mild hydride source.

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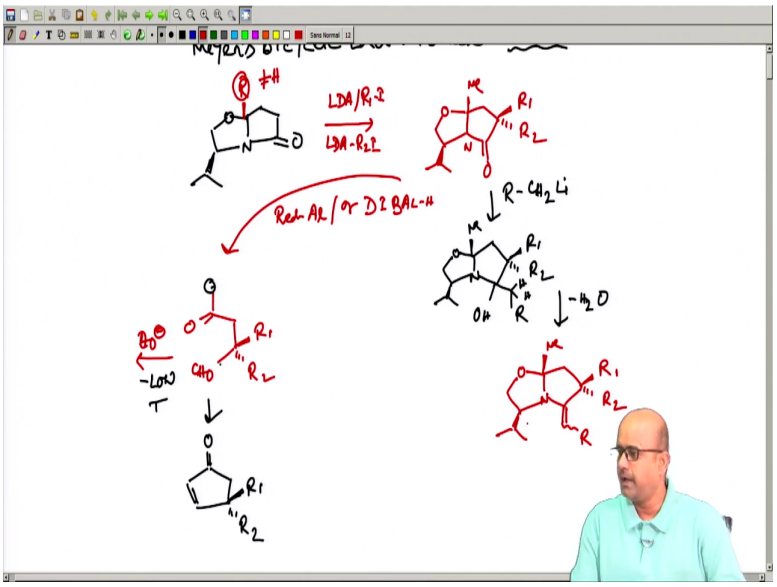

Now, the moment you do it, you can actually get corresponding Me CO and then you will find this, this you will get this quaternary stereo centre, as it is R1, R2 and CHO. The mechanism we have explained first you get the alcohol that basically cleaves and give you this keto aldehyde.

Now, this keto aldehyde is very simple if you try to do a sodium methoxide treatment, what it will give it? It will normally give you a enolate at this position. Now this is a very important factor you can actually generate an enolate at low temperature means low temperature.

So, a kinetic enolate means this enolate you can generate and you can close it. So, 1, 2, 3, 4, 5, this aldehyde is your electrophile. Now the moment you do it, what product you will get? You will actually get a substituted cyclo pentenone of this structural features R1 and R2 ok. There is also other features of this reaction.

Now, here let us say, you take this compound and react with a alkyl lithium of this structure RCH2Li. So, if you do this kind of reaction. So, this initially this alkyl lithium probably will give you OH, CH2R and then you have this remaining part is your R1 and R2, you have your methyl which is remain intact ok. So, this you might get at the beginning.

Now, this compound might not be that much stable. So, you can easily a get a water elimination, from this hydrogen, and what it will lead to you, this is very unique feature; this

compound will then lead to a methyl, and then, this, this it eventually gives you this kind of olefin with this feature. This is R1 and R , the rest of the part of the molecule.

Now, this compound will react in a different way ok.

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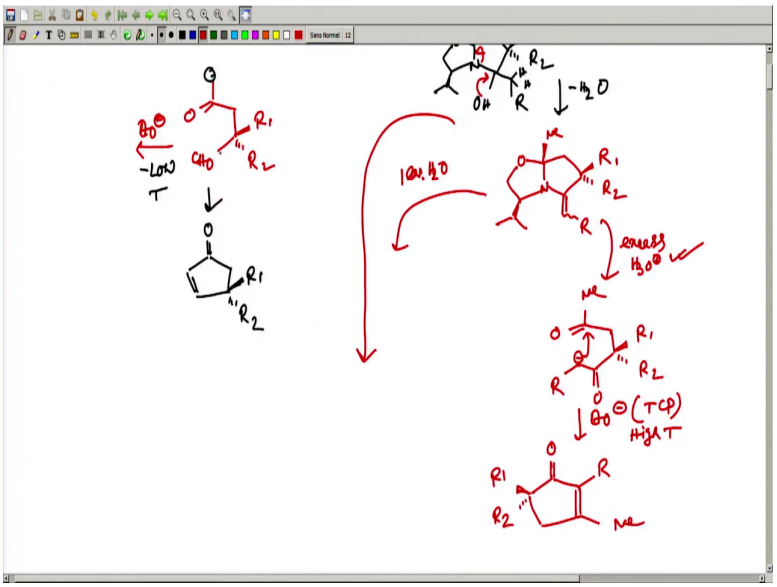

Now, take this compound and you treat in two different condition, in first case you react this compound with one equivalent of water and in other case you react with excess of water means say H_3O^+. If you treat this compound with excess amount of excess amount of water. So, means you are having a plenty of water in the reaction medium and at the very beginning, you will get a hydrolysis of this compound, which will now give you Me CO CH2 your this stereo centre R1 and R2 and then you will have CO CH2R.

So, it is basically nothing but just first you add a water molecule here, and then you cleave it, then this part is going to be cleaved, and you can get this compound. Now once you get this ketone, you can now basically control, if you treat with EtO minus and we can basically assume that which way you want to generate your carbanion.

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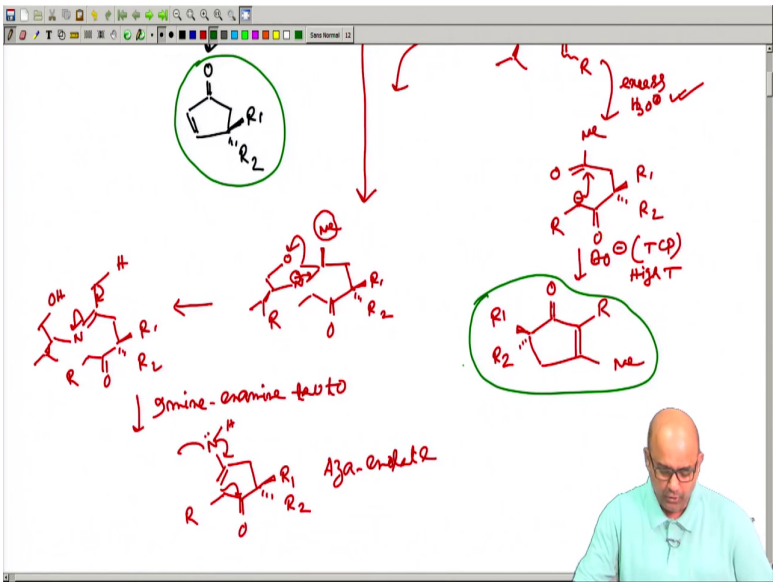

So, let us say for this compound, if you try to synthetically manipulate with EtO minus, you get this ketone you get this, this, this, this; now I will explain how this is going to be going to be happening. So, your this is R1, this is your R2 ok and then you get this is R this is methyl.

So, it means that, this CH2 part, this CH2 part you are actually generating the enolate or carbanion. So, this will attack here. Now this means, you are basically generating kind of a TCP enolate. So, TCP enolate means, you usually do this reaction at the high temperature not so high, but the high temperature. So, initial case you can get this compound, you can get this compound ok. Now this if you can easily create, that will give you a one equivalent of water ok.

Now, let us say you if you are having an excess sorry if you have excess water you can do this one, if you have one equivalent of water what potentially it can leave it to you. Now after initial addition of this product, you are actually here ok. After initial addition. Now I will try to draw a separate intermediate from this. So, with this the usual opens up in this way.

So, that basically means that one equivalent of Grignard or lithium first cleaves. So, it cleaves, what it gives, it gives you a CO, it gives you a CH2R and then, it gives you a here is a R1, here is a R2, then it gives you a CH2 ok. And then this methyl will be something like here ok. The entire ring is not open, you have an oxygen and you have a now a NH, NH means after opening of this nitrogen and then you can see this will be the remaining structure.

Now, this ketone, or if you one would like to prefer the way, it can have something like this, that it get a N minus, you do not do the protonation. So, this you have to need to be very much careful. So, you just write a N minus. So, this N minus; because now there is no excess water. Only one equivalent of water we have given ok. Now this N minus, this N minus can now actually, further assist you to open up this entire thing. So, the now it will be opening up through a different pathway.

Now, you are having a methyl means a CH2 H; and now this is C double bond N becomes a C double bond N ok. Now you are having this isopropyl group, as it is and rest of the part is OH fine. The right hand side, it remains CH2 it remains R1, R2, CO, CH2 R. So, this cleavage is very important. You need to be bit careful. Now, this compound is what? This compound is usually, if you take this compound, this is basically an imine kind of thing ok. Now this imine seems to undergo imine enamine Tautomerism.

So, you can write this is an imine enamine tautomerization; and the moment it undergoes this tautomerization what you will get you will actually then get a compound, this part is fine CO, CH2 R, then your this all carbon quaternary centre is there R2 and then C CH2 C ok, and then you just write the part means your double bond ok; and then your the rest of the compound part. So, this imine and enamine.

Now, what is this this this compound is an enamine, but it also an Aza enolate. So, means that this methyl thing, we have now created a selective enolate generation. Now this was absolutely this enolate was already generated ok. So, now the imine enamine tautomerization means this is a nucleophile. So, this will attack to the electrophile now ok.

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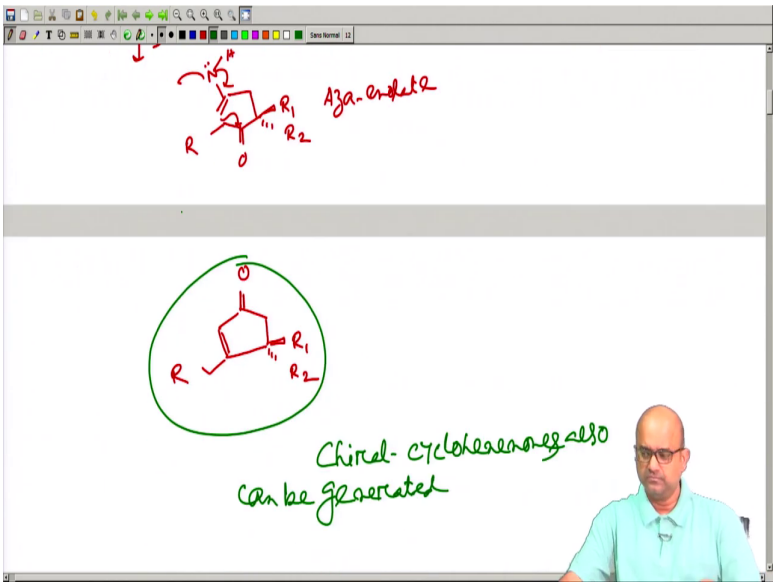

In the moment, it will attack to the electrophile, you will eventually we will see that now you will get the compound, after the hydrolysis CH2 your this R1 and R2 this. So, now, you will be getting the double bond here CH2 R.

So, now see is a very pretty. So, all different kind of compounds you are able to get. So, let me scroll little bit. So, at the very beginning, we get a 4, 4 di substituted cycloalkenone, you can also get a compound something like this; with excess water. And if you having a one equivalent of water, you can actually get this kind of aldol dehydration product. So, these things seem to be quite interesting and all different substituted cyclo pentenone, as well as cyclohexenone, you can actually create by using this method ok.

The same way, we created the cyclo pentenone, we can also create chiral cyclohexenone; if you just take the corresponding gamma lactam, and then do the alkylation, cyclohexenone also can be generated. Just follow the basic reaction pathway, and once you follow the basic reaction pathway, it will be quite clear to you the most interesting part is this one equivalent thing, you can be using an imine enamine tautomerization to selectively forcing that this methyl will lose is its hydrogen to generate the enolate.

So, once this enolate is been generated, you get the corresponding attack to this electrophilic carbonyl come group and then the aldol dehydration ok.

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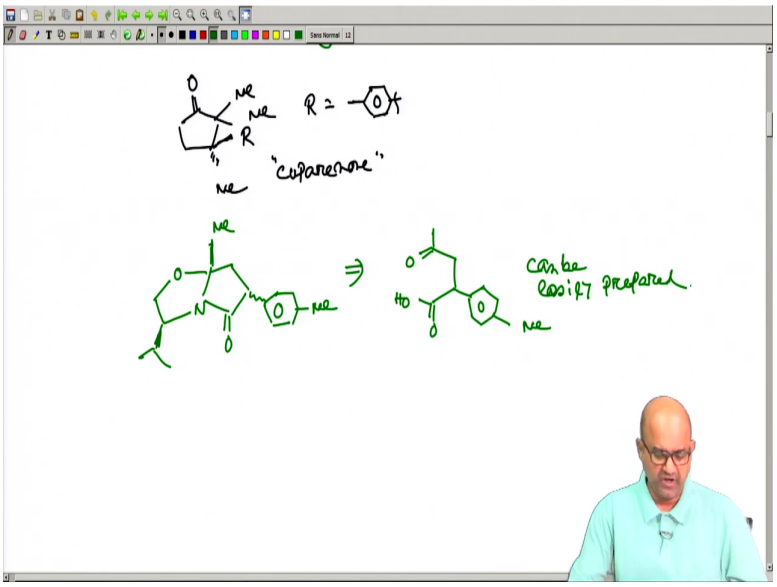

Now, let me try to give you some of the synthetic exploration of such method. This particular compound was a natural product which is a very important natural product, basically sesquiterpene and this sesquiterpene, this one where R is a para tolyl group means, you are having a methyl group here ok. Now this compound whose name is cuparenone, cuparenone was a plant secondary metabolite sesquiterpene.

Now, this compound was usually prepared by Meyers bicyclic lactam things, you can see that this is a usually content to cyclo pentenone framework. So, let me directly go to the bicyclic lactam which we need to make first, this nitrogen as a 5-member ring. So, you basically need a gamma lactam and this this ok and this part is this, this, this. Now here, this tolyl group was initially chosen at the very beginning, because this group as an electrophile you cannot add.

Now, what keto acid you then require. So, you need Me CO CH2 CH2 and then COOH with a para tolyl at this end. This compound you can easily prepare; this can be easily prepared. I guess you can easily prepare this compound, routine synthetic procedure. Now once you have this compound, you just condense with the corresponding amino alcohol fine.

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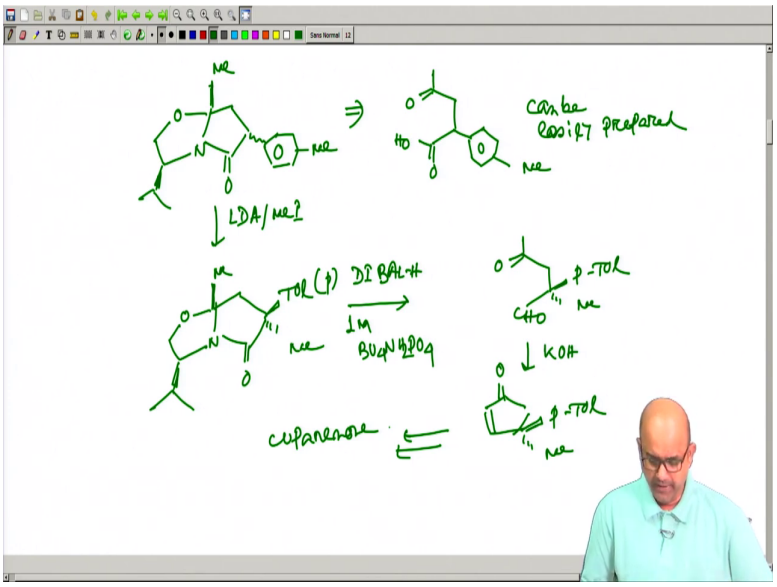

You get the corresponding bicyclic lactam and next your alkylation. So, basically you need to add LDA and methyl iodide. So, then you get N C double bond O your tolyl will be now above para tolyl, methyl will be below ok. This ring junction is methyl you have O, you have this.

So, everything is quite similar now, and what you know you basically now do a reductive cleavage; with Dibal-H and actually in this case the next step you are using a buffer solution of one molar a which is a very specific buffer tetra N butyl ammonium phosphate buffer. So, this buffer will actually act as a base as well as aqueous workup. And then what you will get? You get Me CO this, this you have a para tolyl, you have a methyl and you have a CHO.

Now, rest is simple, you can just do aldol dehydration by treating with potassium hydroxide and see you can eventually get the 4, 4 di substituted cyclo pentenone. From this to cuparenone seems to be a routine pathway and you can eventually try to make this. So, you can see that a simple target molecule can be effectively generated. I try to give you some more application, probably I can just try to give you that the target structure.

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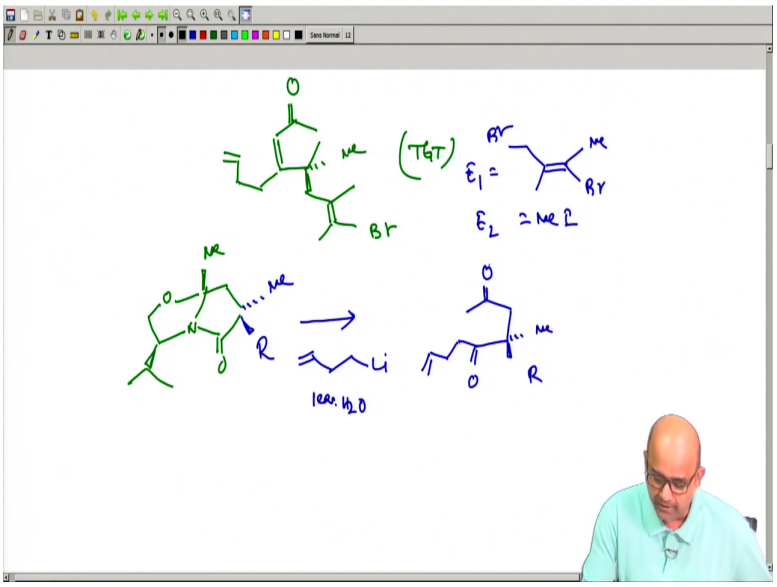

And I will ask you how you can prepare this compound with the help of this was another interesting compound again an intermediate for a natural product.

Now, here, if you see this compound falls in a different class. Now go back to the reaction pathway which we have discussed earlier, in the cleavage one. Now see, this is the part we are talking about. So, this kind of cyclo pentenone, now we are asking ok. That mean is that, you can eventually once your alkylation is done, you try to cleave it with an alkyl lithium with a controlled aqueous hydrolytic condition. So, let me take this as a target molecule, I do not do it a detail analysis, I will just try to draw the, so methyl this is your angular methyl, you need a 5-member ring.

So, basically you need a gamma lactam and this and then this is your oxygen, this part; and you just try to write this as this, this entire group you can write as a R. So, second the both the electrophiles will be your there will be two, 2 electrophile. So, first electrophile E1 will be your the CH2 Br and then you have your methyl, then you have this Br and methyl anti and E2 is your methyl iodide ok.

Now, see the E2 goes down. So, this is up. So, fine. Once you have this compound, what next you are going to do it. Now you treat with a simple alkyl lithium, as I said, now this alkyl lithium means, you take this 1, 2. So, 1, 2, 3, 4. So, 1, 3 butenyl lithium. So, this could be your could be your potentially alkylating agent ok. And then, you treat with one equivalent of

water. By similar mechanism, what will be now getting you will eventually after this cleavage, you get this R and here, you get a CO ok. And this will be your this, this, this.

Now, remember, this is not obtaining as a ketone, but what you will get? This will be obtaining as an enamine.

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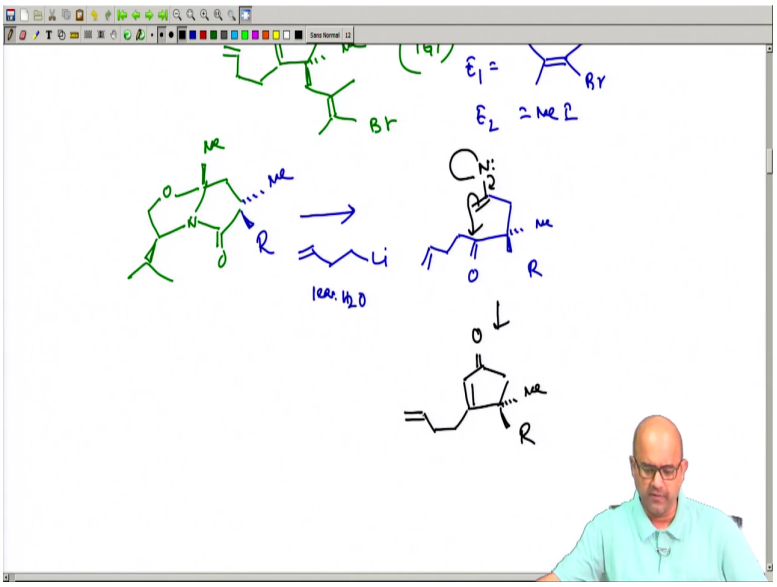

So, you are eventually let me write the correct structure, of this this portion; and you will actually, so this part is very crucial, you get this kind of compound. So, this part is all the remaining functionality. So, this as I enolate or enamine, will be now, coming as a nucleophile partner and you will attack it here ok. And then, you will get your target molecule. So, this was a very crucial step, in the entire synthesis. You need to be bit careful. So, this is your R, I am not going to write it the entire structure of this R and see you get this compound.

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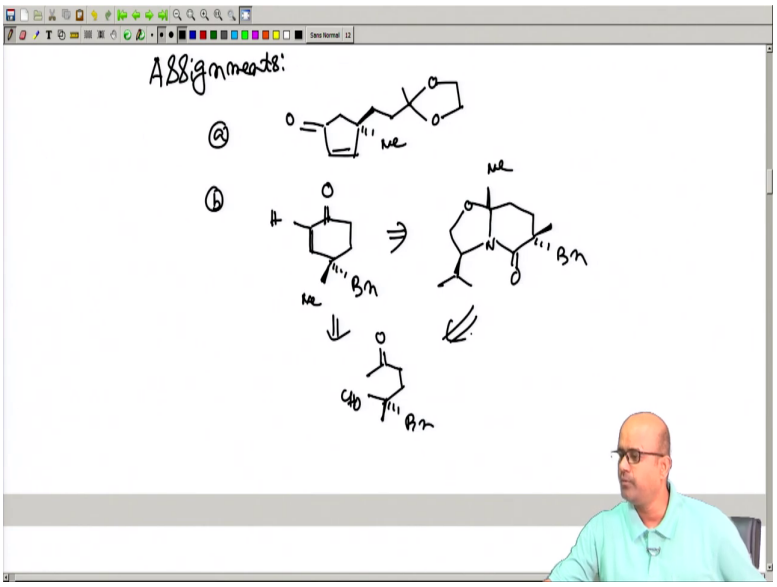

So, this will be a potential target which you are going to get. Now there if other target molecules, which I may give you as an assignment and I am sure you can eventually try to apply the similar principle, how you can access those compounds. So, let me try to write some of the simple assignment 1, you have this, this looks to me very simple, because we have talked about this kind of compound, just I have given you a little bit of extra functional group, you just need to do. So, you can use the this as a target.

Now, this is see this is basically nothing, 1, 2, 3, 4, 4, 4 di alkylated cyclo pentenone. This seems to be easily you can achieve and for 6 member, as we have not done anything, you can eventually try to write or try to take as a normal assignment or problem and you can just try to put a group methyl and a benzyl. Now this seems to be quite easily doable, for the compound B, though we have not done it, but compound B, you can easily write the first N, and then is a gamma lactam is a 6 membered thing and O. So, what parent lactam you want, you can eventually write.

Now, see there is a methyl, there is a benzyl. So, if you now cleave this compound in a reductive way, what actually you need? You need a methyl, you need a benzyl, you need a CHO, then CH2, CH2, CH2 CO methyl; which you can easily get it from here by aldol dehydration. So, such things should not be a problem for all of you.

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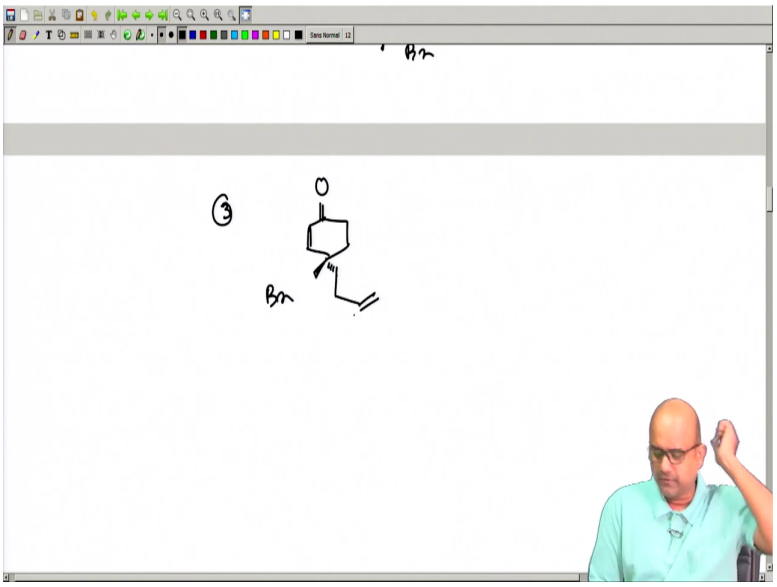

And we also can give you some of the extra assignment, which you might feel doing for some extra practice, let give you some one of the interesting compound which is a typical I will just write a benzyl part and this part, I will just write a CH2 CH2 allyl; I mean this kind of thing.

So, these are the simple way you can eventually try to do it.

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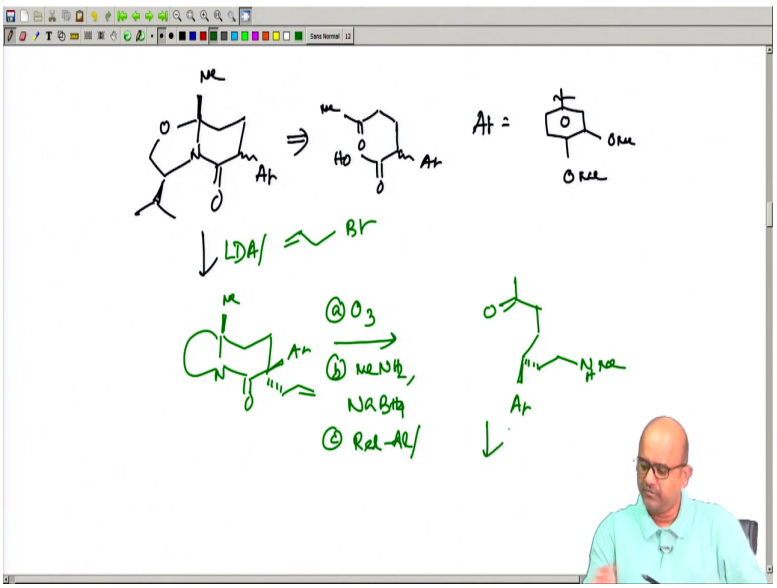

And let me do a very quick synthesis of a natural product, which was named as mesembrine, I will go very quickly, because this is based on a 6-member structure which we have not done earlier. So, I just write the structure in this way ok.

And this portion already having an aryl group, ok. Now this aryl group means that, you can easily make this compound, where from Ar it is a COH CH2 CH2. So, there will be two CH2 and then you have a CO Me. So, this compound can be easily being made and this Ar whose structure is basically nothing, it is a 3, 4 di methoxy structure ok.

So, now take this compound as a lead and then you what you do? You actually treat with LDA, followed by allyl bromide the moment you do it, you can get the methyl, the nitrogen CO, these things. So, aryl will be above this allyl will be down, this part I do not write anything ok.

Now, here the remaining part of the synthesis was a little bit of different, but you can just try to write what was exactly happening; you just do a ozonolysis kind of cleavage here to get an aldehyde and then this aldehyde was reacted with MeNH2; methyl amine and then treat with a sodium borohydride. So, then ……..and then, you cleave with your RedAl part, with the buffer.

Now, see what we get you get methyl CO, this, this, this. You have your aryl and this group is now basically converted to CH2 CH2, CH2 CH2 NH Me.

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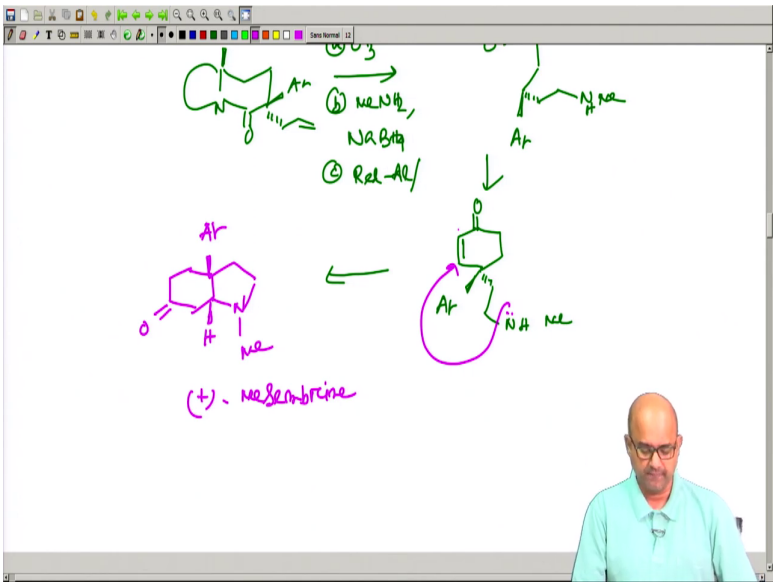

You do the aldol dehydration as simple, the moment you do the aldol dehydration, what we will get? You get actually this. So, this is Ar and then you get the CH2 CH2 NH Me.

Now, the idea was next, this nitrogen lone pair act as a nucleophile in the subsequent Michael reaction …….intramolecular Michael reaction. And then finally, you will eventually get a compound whose structure is this N methyl and this part is your aryl group. So, this compound name is mesembrine, and this is an enantiomer of mesembrene plus mesembraene it is an alkaloid, naturally occurring alkaloid, which have been synthesized by using this Meyers bicyclic lactam based methodology.

So, you can easily see that this kind of Michael addition took place and you get this compound. So, ok in the subsequent section, we will be discussing couple of more synthetic application of Meyer's bicyclic lactam based enolate alkylation.

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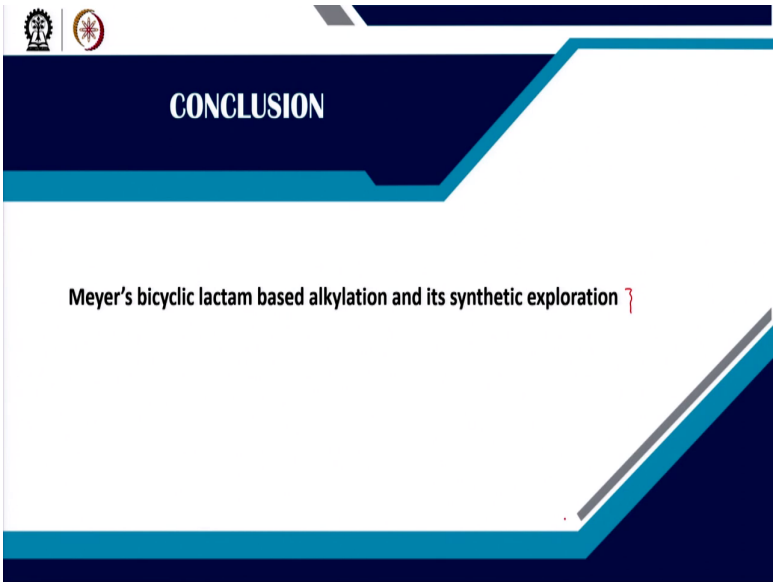

So, in the concluding remarks, we can say that Meyer's bicyclic lactam based alkylation.

It is a very useful synthetic strategy, for creating all carbon quaternary stereo centres as well as a mono alkylated product; in a selective fashion. And moreover the synthesized compounds which you can get after alkylation, mainly can be synthetically manipulated to various intermediates which we will find in its application in the natural product total synthesis. So, we will see you in the subsequent lectures.

Thank you have a good time.