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 - 26
Few problem solving from Meyer's oxazoline/bicyclic lactam based alkylation

So, today we will be basically we are talking about lecture 26, which is the last lecture of this module 5. And mainly today we will be discussing few problem and its solution based on this Meyer's oxazoline and Meyer's bicyclic lactam as well as probably Gleason's thioglycolate based lactam.

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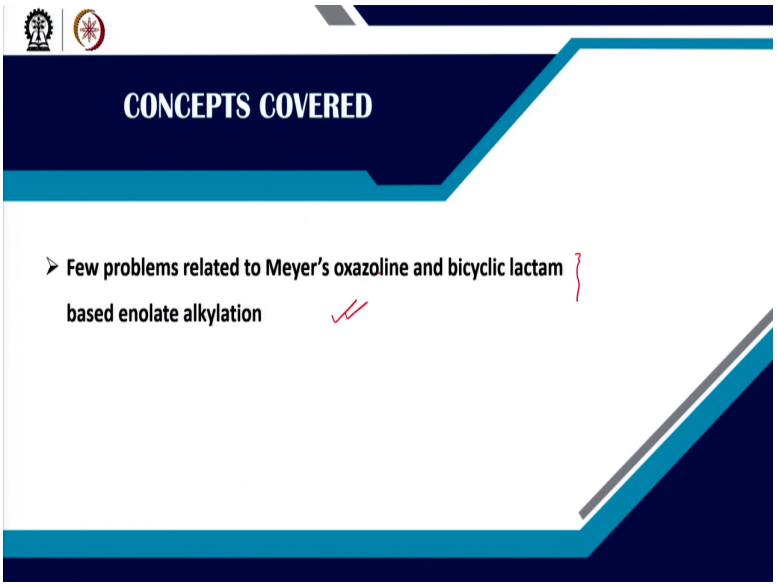

Concept we are going to cover today is basically the problem solving approach for different auxiliaries, mainly oxazoline as well as bicyclic lactam based enolate alkylation.

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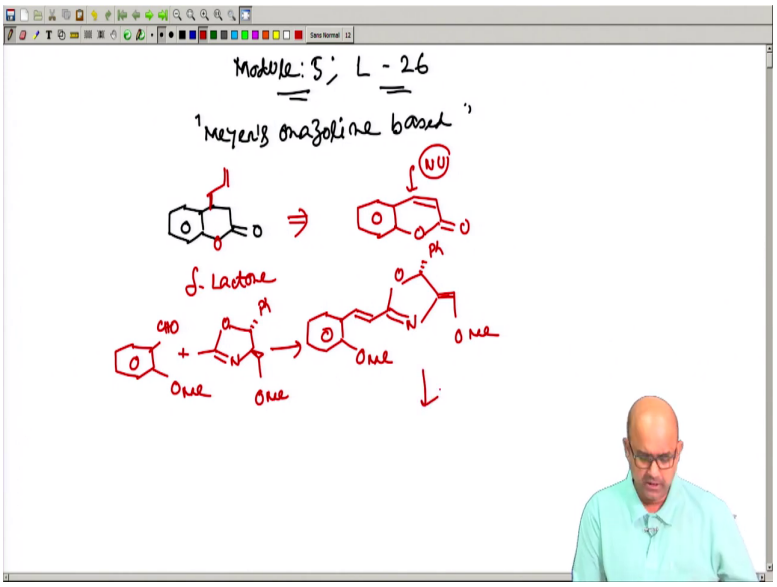

So, today we will be going to discuss some of the problems associated with Meyer's oxazoline and Meyer's bicyclic lactum. So, let us first start with the Meyer's oxazoline based enolate alkylation. We have already discussed that Meyer's oxazoline can be regarded as a d2 as well as a3 acceptor. Now, similar kind of problems we have already talked in the class in the earlier version, but let be bit specific with some substitution pattern.

First we will try to give you this kind of example which is a delta lactone and if you see it very carefully; we are if you now try to do a retro, it can be thought in a way, we can say that if you try to put an alpha beta unsaturated part, so this will be your acceptor part and you can add a nucleophile here. Now, what does it mean? It means that this nucleophile will be coming to this acceptor and then you can later on this O group; means the protected phenolic group you can deprotect and after oxazoline removal, you can close the ring.

So, let me first take what oxazoline you are going to use for here. So, OMe just phenolic OH……. I have protected ok and then you use as an a3 acceptor; so this, this N, this, this. Now, see this allyl should be above. So, phenyl here should be below and this CH2 OMe should be this. So, you just take the required enantiopure Parke-Davis alcohol. Now, how you can make this compound? This was probably you can also make it; just take this OMe and take the corresponding CHO and react with the this acidic…… acid derived oxazoline through an aldol dehydration pathway. So, this should be pretty simple. Now, once you get this compound, next you can think that, ok.

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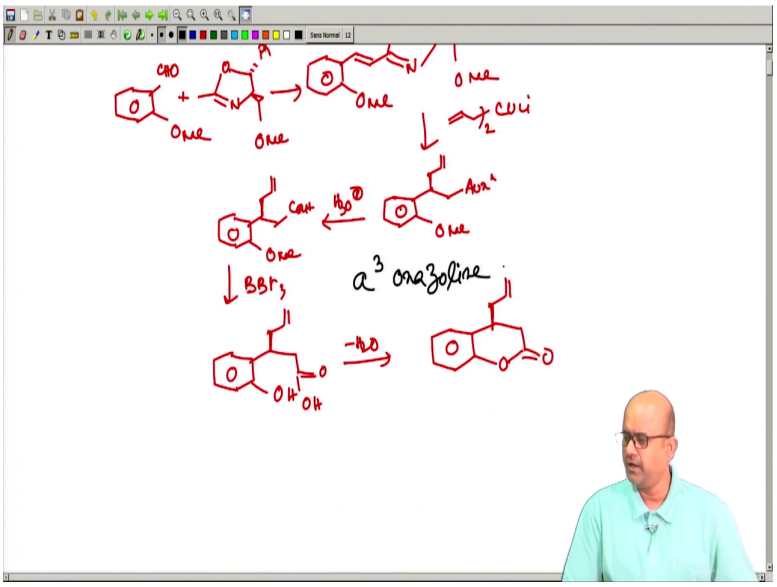

Now, if you try to use an allyl copper lithium as a nucleophile; so you can eventually complete the synthesis just by taking this OMe and here your allyl will be coming ok, then you have this entire part this and here will be your oxazoline I write Aux. Now, this can be hydrolyzed by simple aqueous workup treatment, across workup and what you are going to get; you get this OMe, this allyl will be beta and you have this CH2 CO2H.

Rest is very simple, you just remove the OH…..OMe methoxy group through BBr3 treatment and you get a phenolic OH; this is your allylic part and CH2 H, you close the ring by simple dehydration just heating it and now you can get the corresponding delta lactone. So, such things can be very easily created and you can eventually have an enantiopure delta lactone based on your choice. And here what strategy we use? We actually used the a3 oxazoline; a3 means you have accepted oxazoline and you try to use a nucleophile as your counterpart, this actually is not based on the enolate alkylation.

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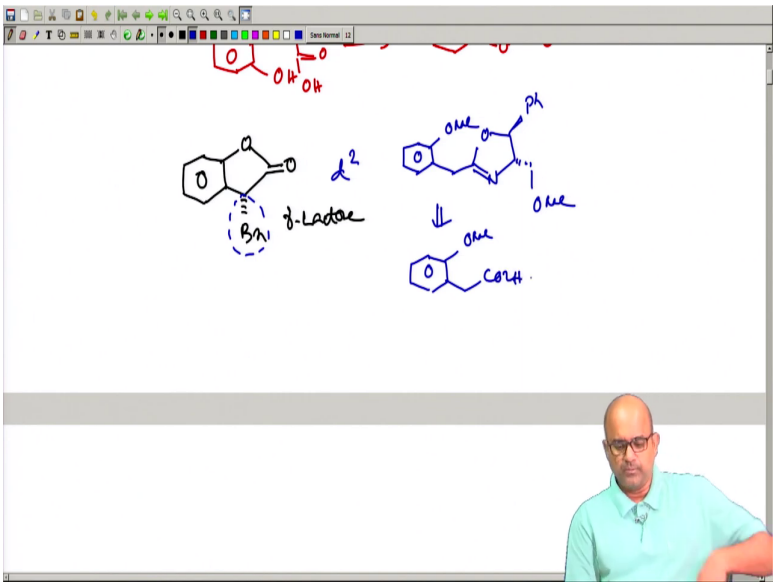

Now, fine net next problem, which will be a similar kind of problem; but now we will be giving you a benzyl group and then this lactone. This is a gamma lactone, a five-member lactone and here you can think that this will be your d2 part, d2 oxazoline and this benzyl group will be your electrophile.

So, let me try to proceed further for the forward synthesis; you have a O-methoxy means, the phenolic hydroxy group has been protected and then here you take the oxazoline part, right. And as you can see the benzyl group has to be in alpha, so phenyl has to be beta; if you take this alcohol and this you can easily prepare by taking this corresponding OMe…….. C H2 CO2H. The moment you have this oxazoline, what next you can do?

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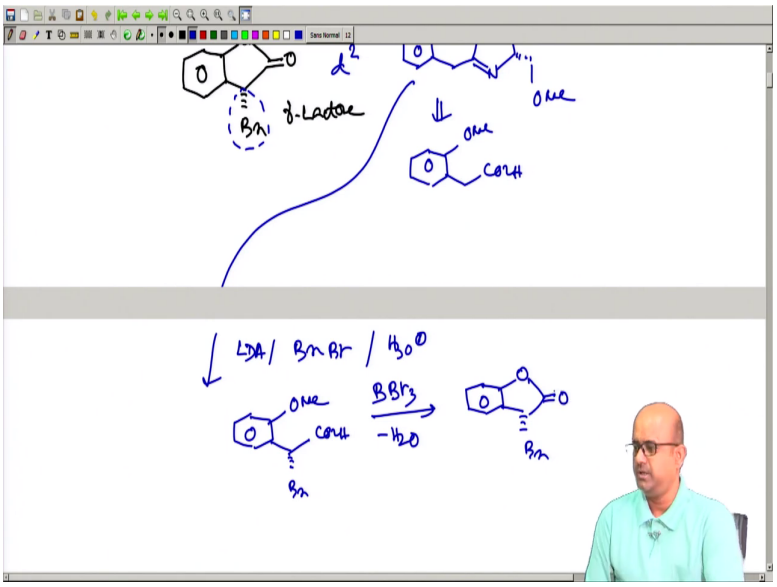

To take this oxazoline, come to the next slide or next paper and then you can see that this oxazoline after the alkylation is I just keep it here; alkylation means you treat a base LDA and benzyl bromide, ok. So, then definitely you are going to get this OMe and then you do a hydrolytic cleavage of the oxazoline. So, OMe, then your benzyl is there and you have a CO2H, so d2 oxazoline. Then you just remove this OMe group by BBr3 treatment and followed by lactonization.

Now, you can see this compound in an enantiopure form can be created very easily.

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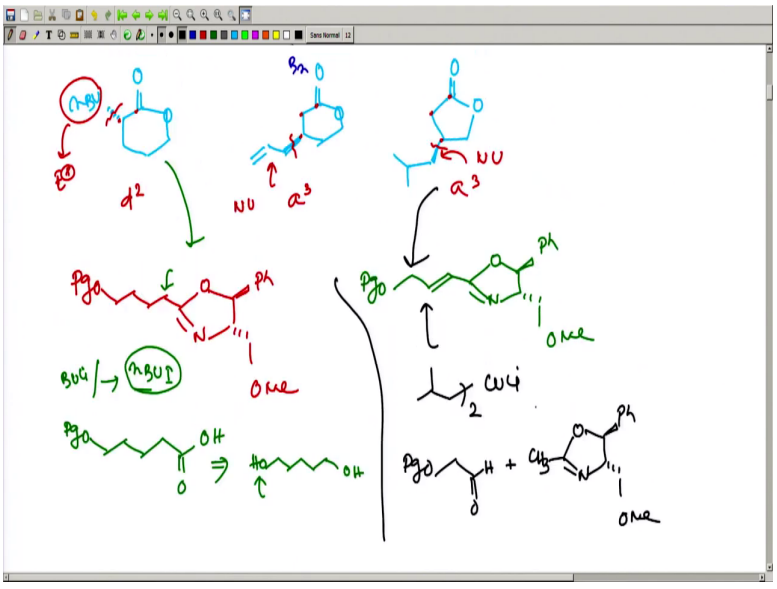

A rapid analysis for other such compounds, let me draw three compounds; these are again lactone, but all are aliphatic lactones. So, I put this as a COO; I put a n-butyl group here, here we I put O and here I put a allyl group here and just I for a change of practice, I took a another five member lactone, because the concept was already discussed.

Now, see the first case you need a d2 oxazoline fine, because you have a one and two; second case definitely you can write down is a3, because you need one, two, three here also one, two, three, so a3. So, things should be pretty much doable, you should not have any particular problem; but if you wanted to have a specific thing or just I can write the what are the steps you can use it.

So, first case there will be 3 CH2 part in between. So, it will be PgO means a protecting group and this will be your electrophile n-butyl part; n butyl would be your electrophile. So, just you can write it, it is your electrophile; this will be your nucleophile definitely and this will be your nucleophile, the bond connection you can initially do it. So, PgO fine, then you can see initial unit one, two, three, four; a four carbon based oxazoline. So, if you can state wise write the oxazoline, that will be your first part, ok.

Now, what you need to do? You first need to create a carbon carbon bond here ok through opposite attack of this phenyl. So, what could be electrophiles? n-butyl iodide, this could be simple. Now, how you can create this oxazoline? That we already talked about, you take PgO; means a protecting group one, two, three.

So, you need a carboxylic acid something like this. And how you can create this? This is basically one two three, four five, one five pentanediol; if you take one five pentanediol, means this one five pentanediol you can do a monoprotection here, then oxidizing this carboxyl alcohol group to its carboxylic acid by zones oxidation.

And then you can make this oxazoline, you treat with a base like LDA or butyl lithium also often used for this oxazoline based thing and then you do this carbon carbon bond formation, rest should be simple to all of you. Now, this one, this one seems to be the a 3. So, a 3 means now we need to draw the a 3, so this will be this one. So, a 3 means it will be having an alpha beta unsaturated Michael type of acceptor, ok. So, let me first draw this a3.

And so, similarly now you can find that this will be a nucleophilic addition to this group and what could be your potential alkyl nucleophile agent; particularly sorry this is basically we

are talking about, I am just we are talking about actually this problem, the third one ok, because you need a isobutyl group. So, you can just write isobutyl copper lithium, fine. Now, do the Michael addition followed by OPg cleavage and this compound I am sure all of you can make how this compound can be made.

This compound can be made quite easily if you try to take this PgO; let us see you need one, two, three. So, basically you need this PgO…….. C H2CHO ok and then react with this simple oxazoline in a aldol pathway to the dehydration and then. So, this CH2 is this, this is the another carbon, this is another carbon and the second one which seems to be the again a simple I guess.

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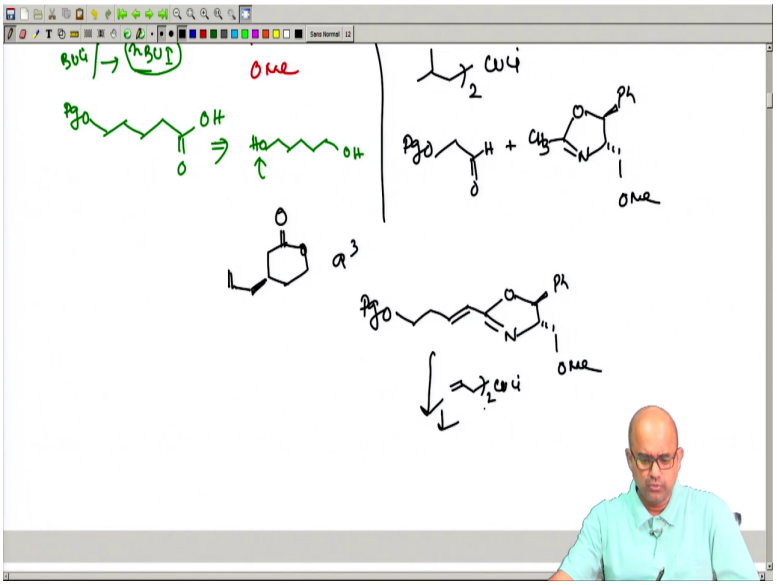

If you take the delta lactone, you can see this is usually having this allyl part. So, this is again a3, this will be again a simple thing. So, just you draw the correct one carbon extra. So, this Michael precursor or the oxazoline needs to be drawn carefully.

Now, be careful about choosing the correct oxazoline; because the moment you choose the oxazoline, that will dictate that which phase your enolate will be alkylated or the nucleophile will approach. In this case you need an allyl thing. So, just simple take the allyl copper lithium, CuLi and rest will be as it is. So, this as a simple way you can actually the do this synthesis.

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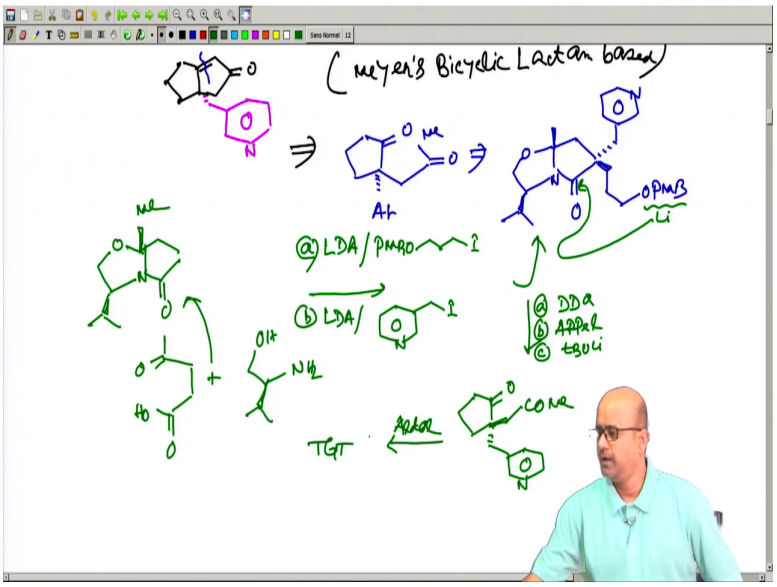

Now, in the assignment or next let me try to give you a one bicyclic lactam based problem solving and this problem seems to be kind of a not difficult, but just you need to practice it.

This is a pyridine thing, we use a different color pen, ok. So, then you have this sorry, this is becoming a bit yeah a cyclopentenone and this part also you have this thing ok and this is the fuse ring. So, for sake of simplicity, let me remove this part; I will draw it again plus this pen sometimes yeah this fine and then you have an alpha beta unsaturated thing. Now, this we will be trying to apply the Meyer's bicyclic lactam based method.

Now, if you can check it, it seems that here you need this CH2 pyridinyl group. So, this could be one of the electrophile obviously, and the other electrophile; other electrophile will be definitely this particular three carbon unit this, this and this and definitely you need to have an intramolecular version of this thing. Now, let me do the retro fast, if you have. So, first you disconnect here. So, this will be your ketone CH2CO and methyl; I put this group as a Ar, this can be done by simple aldol dehydration, ok.

Now, this how we can create? Now, we will be trying to draw the Meyer's bicyclic lactam. So, it will be a cyclo pentanol based thing, it will be gamma lactam. Now, see your pyridine part. So, as this is below. So, I will try to put the pyridine part on the below your nitrogen. And this part if you try to take an intramolecular nucleophilic atom; there are three carbons one, two, three and put a protecting group as a OPMB. The idea was this protecting group

will be next converted to lithium and this lithium then will attack to this carbonyl and it will give you a cleavage of the auxiliary.

So, let me now proceed to the entire synthesis. So, take the simple lactam whose structure; now this lactam you can definitely make by corresponding keto acid, which actually you can prepare by MeCO CH2 CH2 CO2H plus your valenol, the enantiopure valinol which is the auxiliary part. So, this will give you the lactam, fine. Now, you need to do a two successive round of alkylation; as the pyridine group is below, so first LDA and then the protecting group PMBO three carbon I the first one.

Second is your another round of alkylation LDA and then this, this, ok. So, that actually give you to this compound. Now, with this compound in hand, what you are trying to do? You have to remove the PMB group, which can be easily done by DDQ; I guess most of you know it, the free alcohol can be converted to corresponding iodo by Appel reaction and the iodo can be exchanged with tertiary butyl lithium to give you lithium, ok.

The moment you give get the lithium, you are almost close to the synthesis; you get this as a ketone and this part will be untouched, which is your pyridine part. And this part your CH2CON, you do the aldol dehydration; you simply do the aldol dehydration to get the target molecule. So, such problem if it comes, you can easily do it and I guess that can be quite easily doable.

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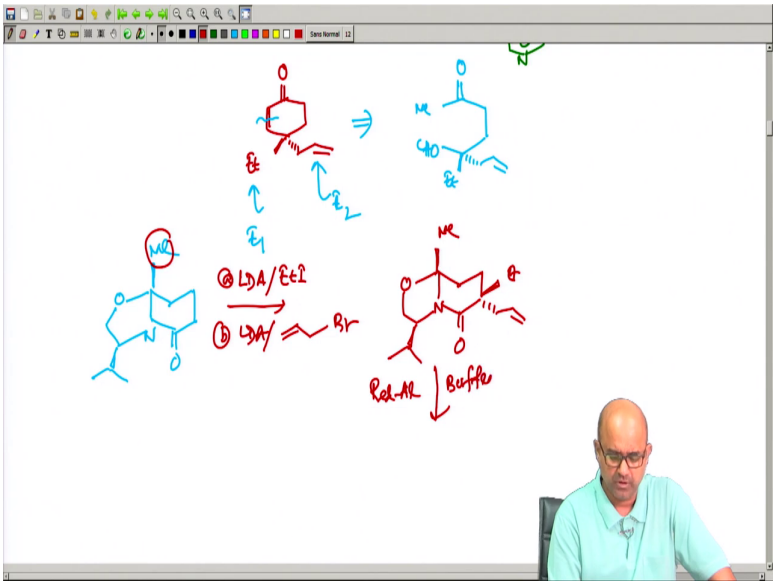

Let next switch over to another simple problem, which again based on Meyer's bicyclic lactam based methodology and which is also a 4,4 di alkylated cyclohexenone. And similar compound we have discussed earlier when we talked about the general features of the Meyer's bicyclic lactam.

Now, if you see the particular this problem, you can see that this is one electrophile, electrophile 1; this could be the second electrophile. So, the retro will be very much similar you take CO, will put methyl this, this and then your methyl, sorry ethyl and then this part is your allyl and here will be your CHO.

So, initial…… this bond disconnection is approached, fine. So, take this bond as your main disconnection target; first let me draw the parent bicyclic lactam. As this is a six-member thing; so definitely a delta lactam will be the main precursor ok and then you have this.

You need to have two electrophiles and you see allyl is below; so this allyl needs to be added in the second, ok. So, first is a, it is a LDA ethyl iodide; b is LDA which is your allyl bromide or allyl iodide. Now, after this alkylation, definitely you are going to create this all carbon quaternary stereo center; ethyl is above, your allyl is below, you have an angular methyl here, you have this and this chiral auxiliary part which comes from the valinol, ok.

Now, next will be very simple again; the cleavage will be a reductive cleavage the Red- Al with the buffer, which we already used earlier.

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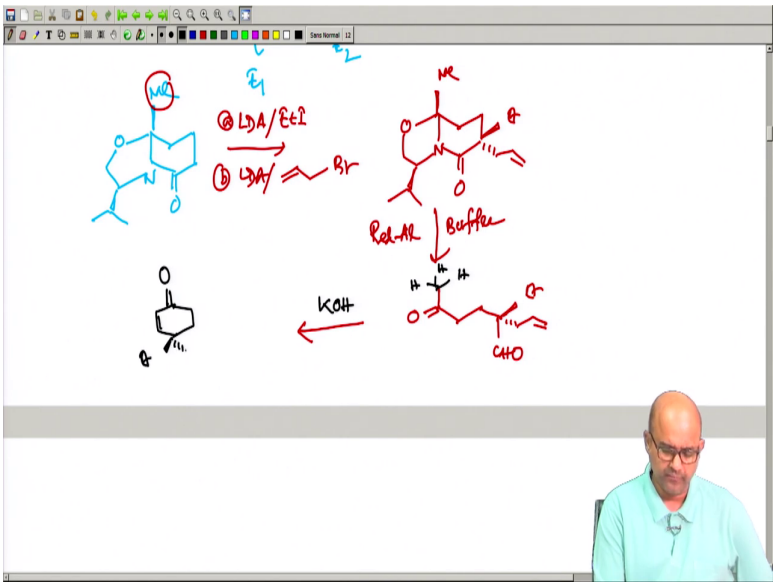

And now if you see what we are going to get here, you actually get methyl, you get CO you get CH2, CH2, CH2, ok. And then you put your ethyl, your allyl part and you get a CHO. Now, this compound you just do a kinetic deprotonation, because you need to do an abstraction of hydrogen from this methyl, ok.

So, take a low temperature kinetic deprotonation, usually just trying to do a potassium hydroxide also can give it to you and then your aldol reaction will take place. The moment you have this aldol reaction, you get this; you have your ethyl, you have your allyl. Let me try to give you some another work which also seems to be kind of interesting; this particular work was very interesting; I mean let me draw some other structure.

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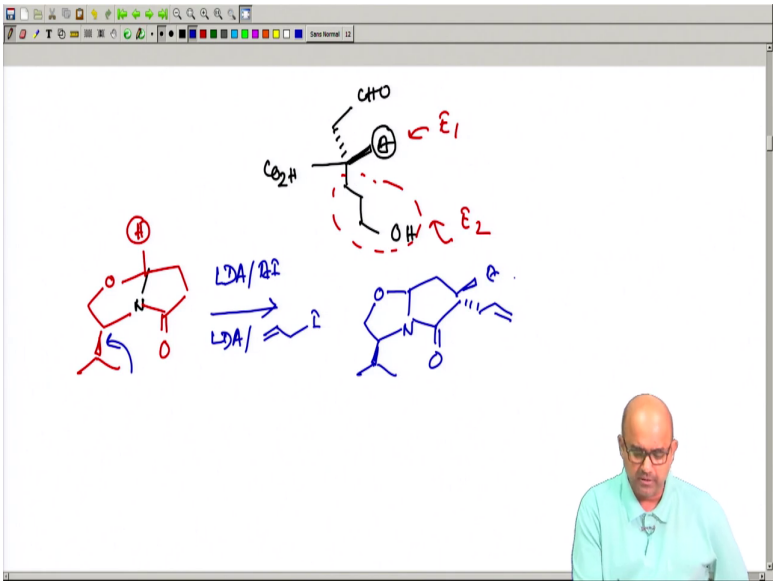

A all carbon quaternary is a Et, there is a CO2H and this could be a CHO; actually this was taken from literature references, which actually if you make this compound and then this, this is a potential intermediate for a natural product total synthesis.

Now, this compound can easily be, I mean prepared by using this Meyer's bicycle lactam based methodology, will directly go to the working mode of principle. So, let us first; you are not initially very difficult to visualize that how you can do it. Now, you can think that this e t, e t will be your one electrophile and this CH2, CH2, CH2 OH could be your another electrophile.

So, this you need to be take care; this is one electrophile and this will be another electrophile. This will be coming after this hydraulic cleavage of this lactam and this CH2, CHO it may come from if you are taking a gamma keto aldehyde, not the corresponding gamma keto acid.

Now, let me try to take a compound which is structurally having this. Now, to have an aldehyde here, you basically need a hydrogen here. And if you remember the earlier case we told that such compounds might not give a good selectivity; but in few cases only for due to this group, this compound give you a better endo selectivity, this is one of the example.

We need to have few reaction conditions as I am trying to, you need first LDA with ethyl iodide and then the second one how you can visualize this, I will try to take a LDA with allyl iodide, allyl is a three carbon precursor, ok.

So, you will now be going to get this, this, your ethyl, your allyl and this part is your O. Now, this allyl can be constructed through a three carbon unit primary alcohol just by hydroboration, ok.

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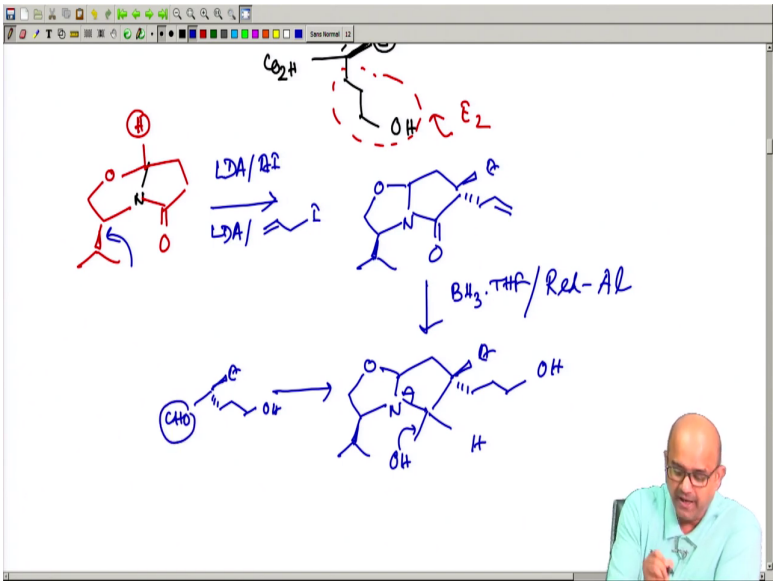

And actually you can simply do a hydroboration; the moment you do a hydroboration BH3.THF, even BH3.THF can also reduce the lactam, but low temperature hydroboration will not keep the lactam part and actually you get N C double bond OEt CH2 OH, ok.

Now, keeping the borane THF as a reducing agent also; because we know borane THF can reduce the lactam. Now, how the reaction takes place? Just now I said that borane THF might

not react, but take this as an another alternative. So, it will be OH and H. Now, remaining part all are there.

Now, definitely now this can cleave you and this can cleave means, from this part you get a CHO and this part also you can get a get a CHO, so that probably bit of difficulties from this way. But if you are not using let us say not using borane THF; so first you use borane THF and then you use your RedAl compound, RedAl which is already known.

So, first borane THF followed by RedAl; the moment you keep the RedAl, you will basically get a CHO here. So, now, you can check. So, if you try to get a RedAl, you get et CH2 CH2 OH CHO; but there is a question mark, we need a carboxylic acid here. So, RedAl also cannot solve the purpose; that is why I categorically drawn the RedAl, but RedAl cannot serve the purpose. So, what probably is best done, you just take this compound and do the hydroboration; the moment you do the hydroboration, you just keep the compound as it is as a lactam, ok.

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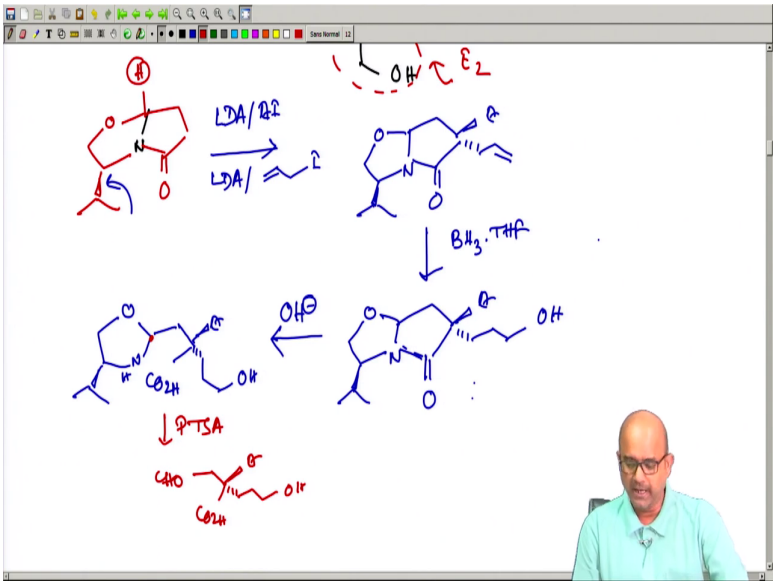

And this lactam will probably you can just do a hydrolysis by sample treating with a base sample treating with a base. So, what next, your everything is done and this part your left hand part will give you the carboxylic acid; you just treat with a OH minus and this part once it clips, it will give you carboxylic acid and then N H. So, let me write ethyl CH2 CH2 OH, you get your carboxylic acid CO2H and then this CH2 this ok; then you have this O, you have it NH this part.

Now, this is normally, this carbon is now the aldehyde thing which is basically protected. So, you can simply do an aqueous hydrolysis by PTSA and then that will give you the corresponding target molecule; C O2H, here is your Et, there is your CH2 CH2 OH and CH2 CHO. So, systematically this way you can clear or you can achieve different target molecules based on the required pathway.

I hope this serves the purpose and actually the problem solving approach, mainly we discussed couple of problems; there might be some problems which I did not discuss, but I will try to give some assignments during the course work and you can just go through it.

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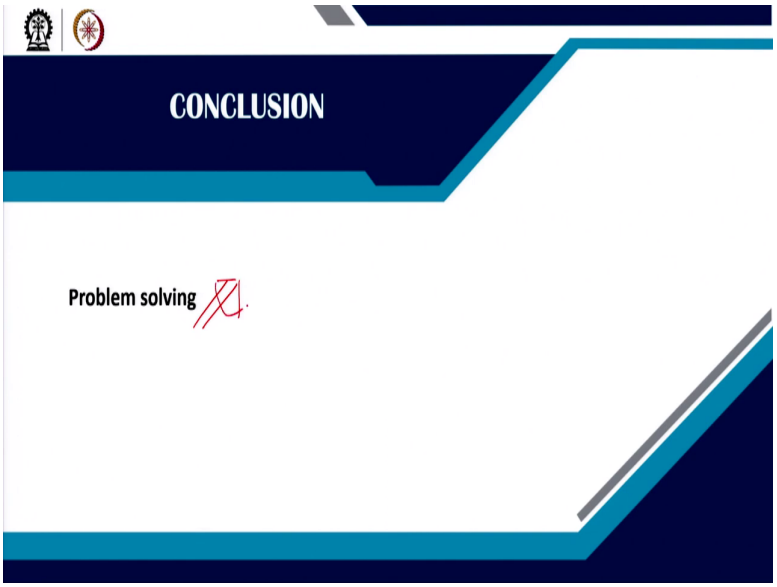

Conclusion, there is basically as I said, we have discussed couple of problems which give you an idea that such systems are very important in the field of asymmetric synthesis, mainly when you want to use specific enolates and then alkylate this enolates with those auxiliaries. So, we can continue our discussion in the next week; till then.

Thank you, have a good time.