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 - 25
Meyer's bicyclic lactams, Gleason's bicyclic thioglycolate lactam based systems

Welcome back everyone. So, today we will be talking about module 5 and lecture 25. So, in this particular lecture we will be talking about remaining portion of the Meyer's bicyclic lactam, few extra case studies and then we will talk about another bicyclic lactam which is recently developed by Professor Gleason.

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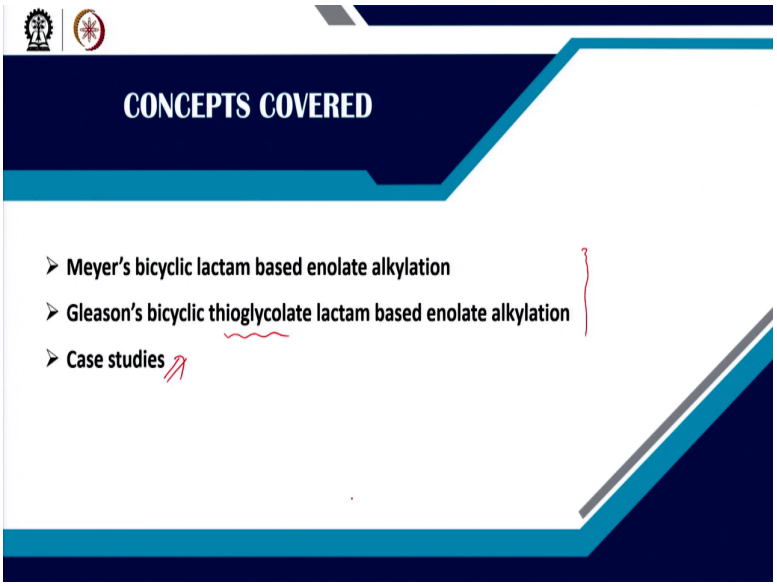

So, it is named as bicyclic thioglycolate lactam and a few examples of that lactam. And, the main topic which we are going to cover today, this remaining part of the bicyclic lactam based alkylation. And, we also talk about this Gleason's bicyclic thioglycolate lactam and few of its application, some case studies based on both the lactams.

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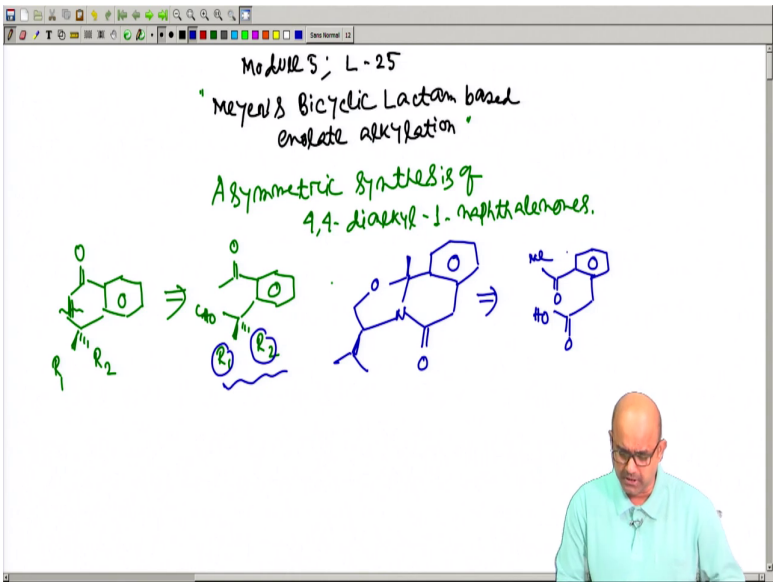

So, in this lecture we will be talking about some synthetic exploration of Meyer's bicyclic lactam based enolate alkylation. And, the very beginning we will talk about asymmetric synthesis of an enantiopure cyclohexenone derivative, but those cyclohexenones are containing a naphthalene part. So, these are this composition named as 4, 4 dialkyl 1 naphthalenes.

Let me draw its structure and then we will do the retro part and how bicyclic lactam is helpful to give or to allow you to access such molecules. There is a double bond here and then you can see this is a R1 and this is a R2. This is the, now you can easily see that this is basically nothing but an extended form of 4, 4 di alkylated cyclohexanone derivative. So, only addition is the phenyl ring which is present in the compound.

So, you can easily think about doing an aldol dehydration by disconnecting this bond R1 R2 and CHO. So, what are going to plan that this R1 and R2 is coming from two successive round of asymmetric enolate alkylation. Now, let me draw what could be the possible bicyclic lactam, as it is 6-member thing definitely you have to draw a delta lactam.

Now, as this compound already contained a naphthalene ring. So, probably this could be the proper bicyclic lactam which you need ok. Now, how this lactam can be prepared? You can eventually try to get this compound by corresponding keto acid CH2 CO2H and this part is your CO and methyl. So, this aromatic precursor based keto acid if you have, you prepare the corresponding delta lactam. And, then you can easily do the LDA. First will be your R1-I and

second another round of alkylation with R2-I. As 2 is below so, you can add R2 at the second part ok.

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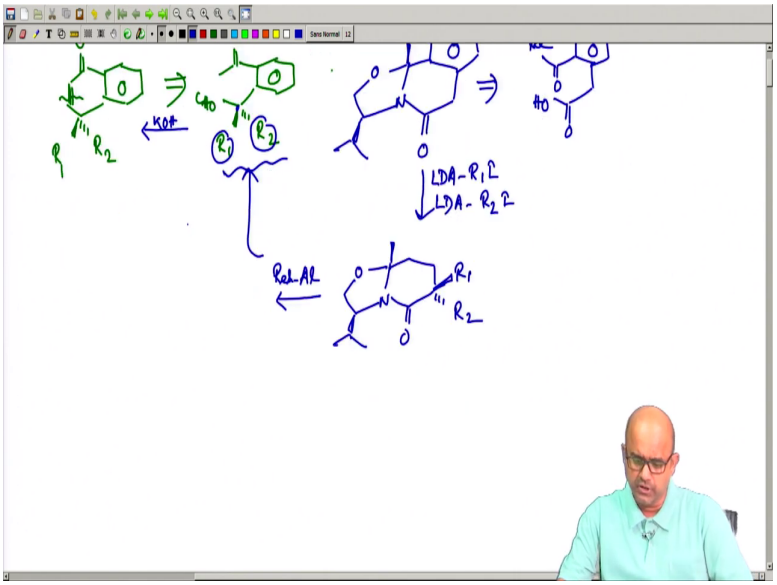

So, after this alkylation your all carbon quaternary centre will be created, if both R1 and R2 are carbon containing group then you will be having this fine. The reductive cleavage will serve the purpose. So, you can definitely do the radar based cleavage. And so, the moment you try to give the radar based cleavage, it will actually lead you this compound.

This compound is what? The corresponding keto aldehyde where you did the double alkylation through Meyer's bicyclic electron based pathway. And, you do the intramolecular aldol dehydration by simply treating with potassium hydroxide, you can get your corresponding product with excellent stereo control.

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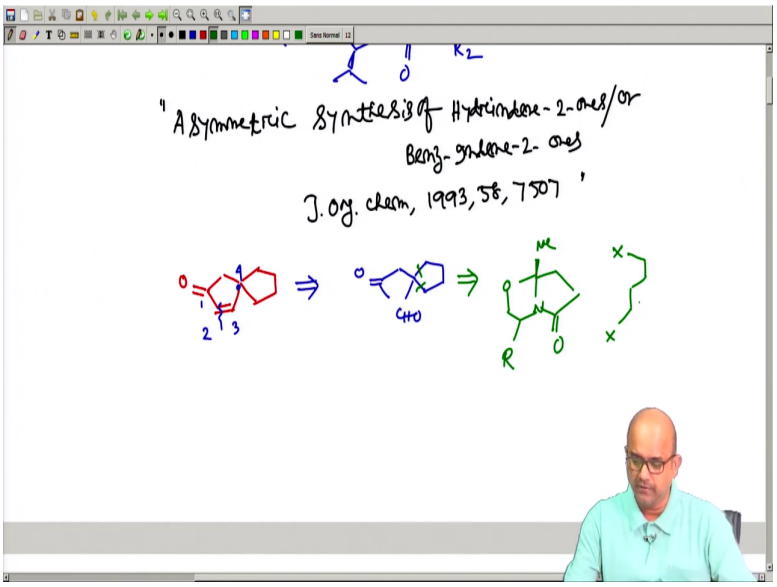

We will next switch over to few other application, over the first one; I mean we will try to give you a title for those molecules that asymmetric synthesis of these compounds are basically named as hydrindane, indene based compound hydrindane 2 ones or benz indenones……. benz indene 2 ones.

And, the application part was reported in a JOC paper, Journal of Organic Chemistry by Professor Meyer's group which was published in 1993. The page number is 7507. Now, before we go to the hydrindane and other compounds, in this particular paper they also described a Spiro cycle compound which could be potentially can also be accessed by this Meyer's bicyclic lactam based alkylation.

Now, this kind of bicyclic cyclo alkanones of this structure can easily be prepared. Now, if you check it this compound eventually falls in the class of your 1, 2, 3, 4. So, 4 4 dialkylated cyclopentanone. So, you can easily prepare just do the retro, the right hand side cyclo-pentane ring or cyclohexane depending on your choice, you can keep it as it is. This bond you are going to be cleaved. So, you can put a CHO and you can put a CO CH3.

Remember this centre is not stereogenic definitely, I mean as both the groups are same on the, but we are not talking about the chirality or optically active spiral molecules. So, is a non-stereogenic centre we assume and then you have to have this kind of thing. So, it means that these two carbon will be successively created by alkylation.

Now, what could be the potential alkyl letting agent? So, let me first draw the bicyclic lactam structure. You have this nitrogen; this will be 1 carbon more. So, I just need to remove these things this and then this ok. Here you put a R group. Now, if you take a dielectrophile means say X and the 4 carbon containing electrophile. So, there will be CH2 CH2 CH2 CH2 ok. So, 1 2 3 4. So, if you take this kind of electrophile, your job will be quite easily achievable.

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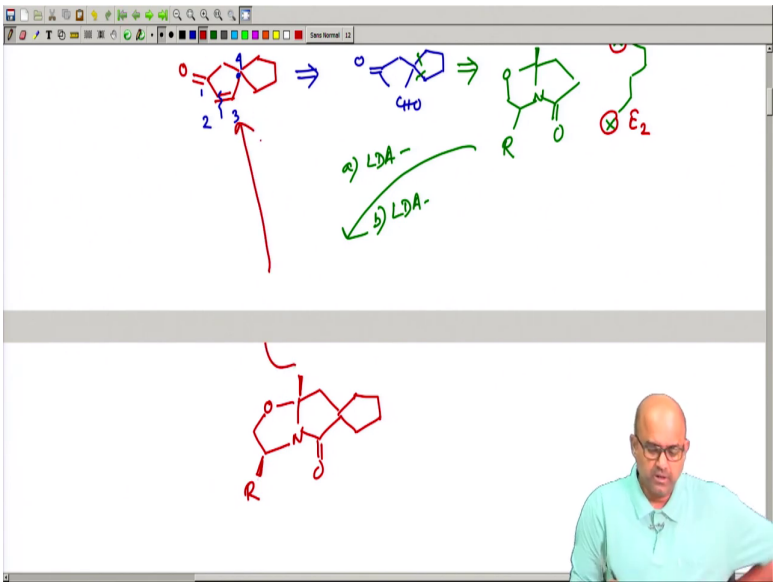

So, you take this lactam and do a successive round of electrophilic alkylation. So, first with this and then second also with this. Now, you can eventually write that this X act as a first electrophile, as it is symmetric. So, this is acts as second electrophile. And, then you can get the corresponding compound. And, then what could be the structure of the corresponding compound?

The compound will be methyl, your N, CO. Here you get the spiro cycle connectivity and then rest of the part is this part ok. Now, do the reductive cleavage and you can come to this part. Anyway, this is one of the nice way to explain it. Now, we will be talking about particular this hydrindane 2 molecule which we have initially started.

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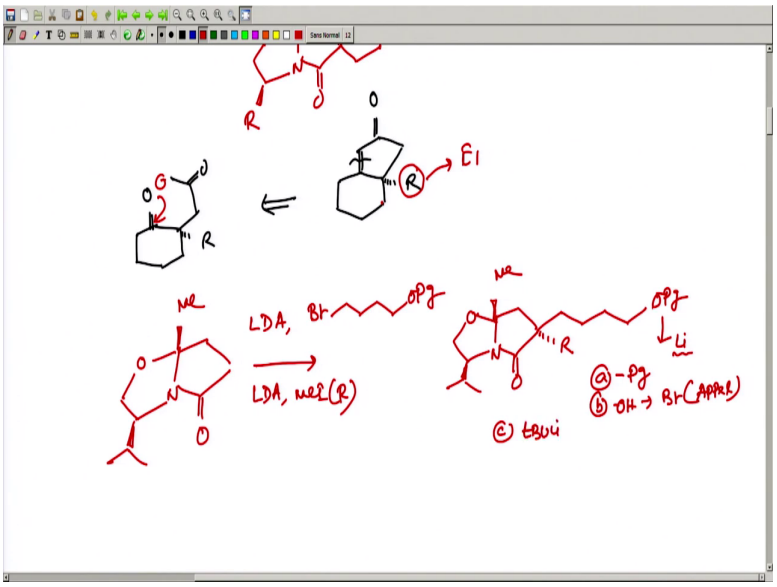

Now, this molecule also a bicyclic molecule and the structural features if you check for this molecule, it is 6 members with a 5-member ring. You have an angular R group and you have a double bond here, you have a ketone here. So, this is also again a kind of a if you try to write that 1, 2, 3, 4 is a 4, 4 di substituted cyclo pentenone part.

Definitely, we need to check that how this cyclohexane ring can be created. This could be your main drawback or main not drawback, main target. Definitely, a retro…….. suitable retro can you can devise. Now, retro will be you can just disconnect this bond at the very beginning, you put the R, you put CH2. So, then CO and methyl. So, this will be your intramolecular aldol part ok.

Now, how we can make such compounds? So, let me first then go back in a stepwise manner. So, the lactam part what we will going to take? We will be going to take the because the core structure is a cyclopentenone part. So, a gamma lactam based thing will be trying to use it; this, this, this ok.

Now, let have a closer look on this part. This will be definitely a R coming from one round of electrophile E1. The second will be coming from this CH 2 appendage and also makes you this CH 2 has a one handle which can later on act to the lactam part as an internal nucleophile. So, the nucleophile part we are not going to act from outside anyway. So, let try to figure it out.

So, LDA first you take the part. So, it is a 4 carbon. So, you can eventually try to use something like this Br 1, 2, 3, 4 opg ok, O-protecting group. This is your first electrophile and second electrophile is LDA methyl iodide. So, everything will be kind of similar, you just do the reaction. So, your methyl or R if this is R, I can just write instead of R. So, we have your R at the end and this will be CH2 CH2 CH2 CH2, 4 carbon, 1 2 3 4 Opg. Rest of the molecule will be remaining similar, that is a methyl.

Now, what I am saying that this Opg, if you can convert this Opg to a lithium means a nucleophile. Now, how you can do it? You just remove the Opg, that will give you alcohol, convert the alcohol means I just writing OH to a Br by Appel reaction that you can easily do it, Appel reaction. And, then see this bromo you can exchange with third butyl lithium to give you a lithium.

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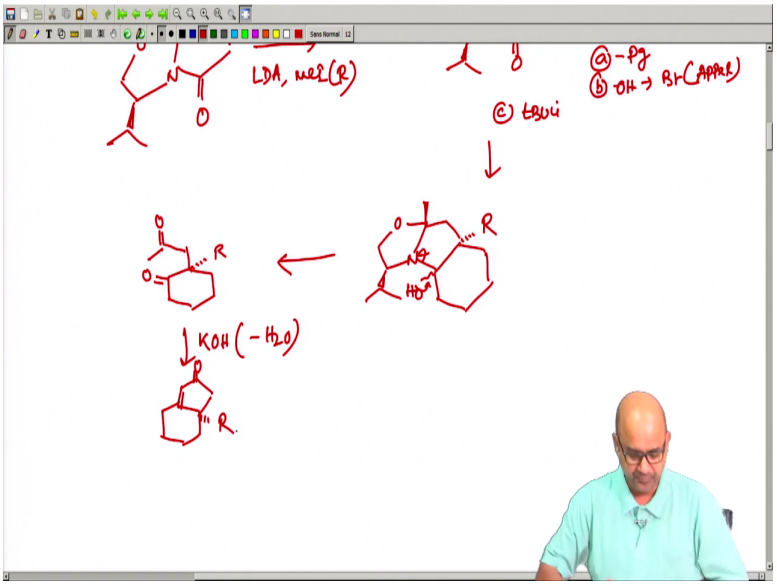

Now, once you do the exchange, what you will find that. So, this is N, let me first finish this structure, this part, this group your methyl is there. Then, this, these things and then here you are having this is your R or methyl and here you are having a OH. Now, this OH will now try to give you the ketone part and you will get this auxiliary to be removed.

Now, see what you will ended up, you get a ketone here after this cleavage and then here you get a R, you get a CH2, you get a CO methyl; the initial compound which we have drawn. Now, rest what is very simple, you just do a KOH. So, intramolecular aldol dehydration and

that will actually lead to your desired compound which is this compound. So, such synthetic variation in an enantiomeric fashion you can actually create ok.

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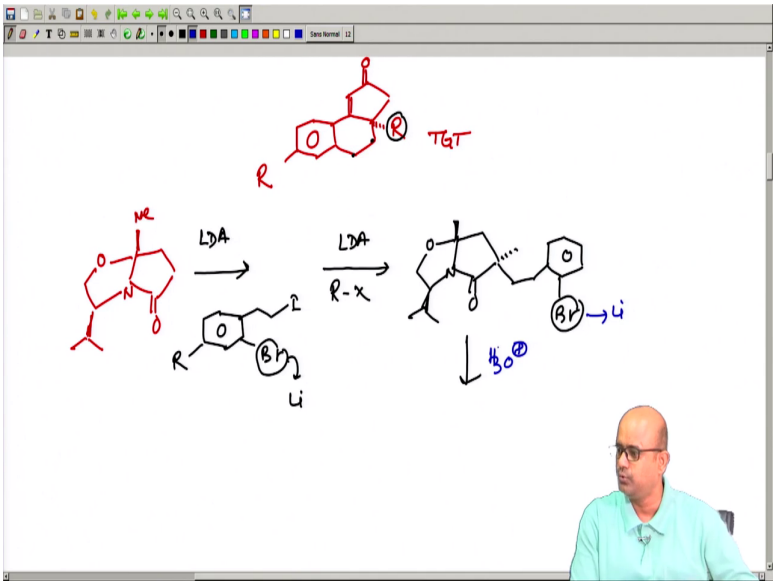

Now, next I just try to give you a little bit of complicated molecule which is a benz hydrindane. And, if you check its structure, its more or less similar of the earlier structure which just now we have drawn. But, in addition it contains an extra aromatic ring at the left hand side cyclohexane ring.

So, you can actually design a similar kind of pathway, if you now have to do it. So, if this could be your target molecule, let me first draw the bicyclic lactam which we are going to take. Everything remains almost similar, the basic structure or core structure will be more or less same. So, this is your bicyclic lactam.

As earlier here also you can think about by using this R as an electrophile and this as an electrophile. Now, here this compound already contains an already contains a CH2 CH2 ok. And, this could be this bond could be potentially a source of the another nucleophile or the lithium. So, let do the reaction in a stepwise fashion.

So, first LDA and try to write the electrophile like R. You take a BrCH2 CH2I. Now, this CH2 CH2 is these two and this Br can be later on converted to lithium which can attack fine. You do not isolate the compound, you do a second round of alkylation with LDA and if this is R depending on your choice you take a R x.

Now, what we will get? You get this CO, you get this and then your R will be below and here you get CH2, CH2 this and then you this as a Br. This is nitrogen, this is your angular methyl oxygen and this isopropyl group. Now, as I said this Br you exchange with a lithium. So, this can be converted to a lithium. Now, this lithium will now react with the lactam part and then if you do a hydrolysis in situ, in situ hydrolysis what you are going to get?

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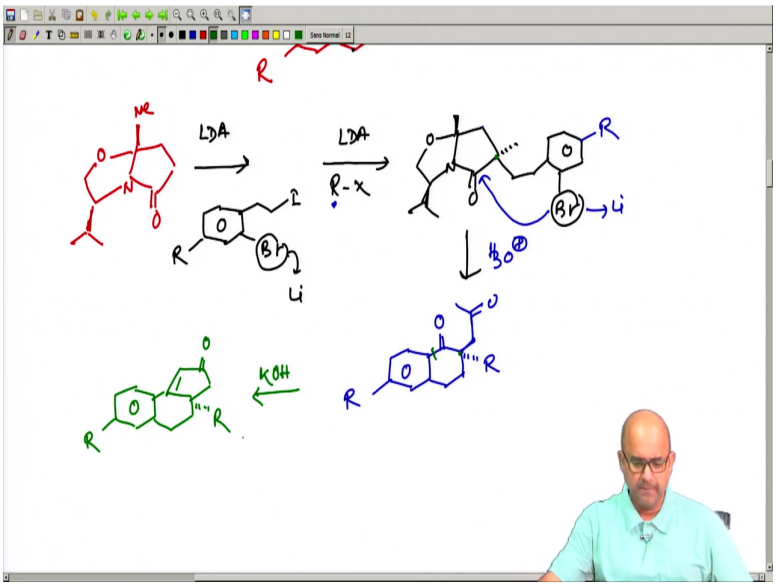

You are basically going to get. Now, this compound also has a R group which is meta I usually, if you take R group. So, now, you can see you get this which is your R here ok, then this CH2 CH2 will remain, this part is there and you get a ketone at this point ok. Now, here is your R which is the second electrophile, this R ok and then you have this CH2, this CH2, CO methyl. I hope this is quite clear to you.

What I am saying that this lithium will then attack here. Now, you can eventually count the number of ring structure which is going to form as a 1, 2, 3, 4, 5, 6, see this is the 6 member ring. This is the carbon bromine bond which is going to be created and this is this bond is this bond ok.

So, next is very simple, you just do an aldol dehydration by KOH treatment. And, what you are going to get? You will be eventually get sorry this aldol dehydration will now take place and you will be going to get the ring, just double bond was there, the ketone and you have this R. So, benz-hydrindane or hydrindone you can actually create. By similar way other

compounds also you can be created. Let me try to give you some of the assignments based on the intramolecular nucleophilic trapping.

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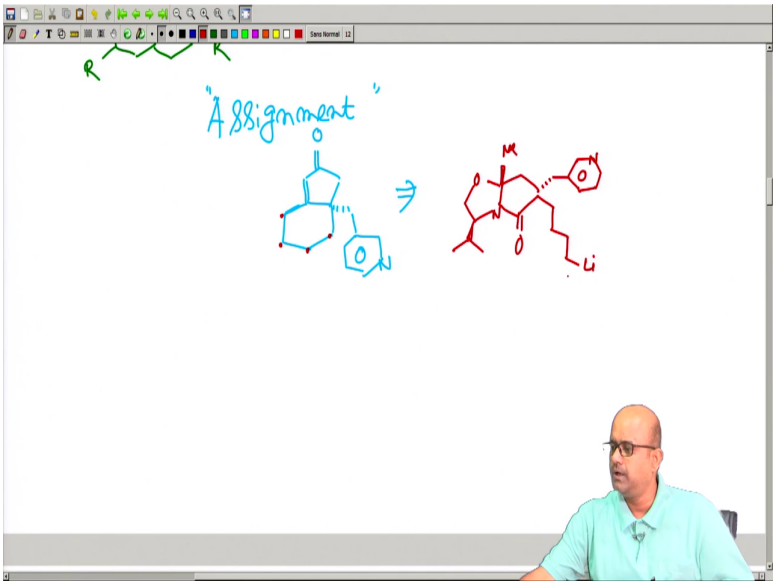

Now, we have seen the last two problems. The nucleophile seems to be an integral part of the lactam means that you have to have some functional group which you can easily convert to corresponding nucleophile which then react to the lactam carbonyl and do it. Now, let me give you a simple assignment which probably I am sure all of you can do it which is the double bond. Let me do a structural modification little bit because, this will.

So, ketone then this and you have a double bond, this ketone and this part we are having a group which is this. Now, this seems to be quite simple because we have already talked about such molecule. So, what basically you need? You actually need this kind of lactam, if you can take this kind of lactam your purpose will be solved.

So, let me take the 5-member lactam, nitrogen, C double bond O. This part is oxygen, this and then you check that you basically need this 2 electrophile. Now, one of the electrophile is your pyridine part, the 3 pyridine benzyl bromide kind of thing and the other part is your all this CH2, the 4 CH2 which you need to have. So, means CH2 CH2 CH2 CH2 Li. So, now, you can close the ring anyway.

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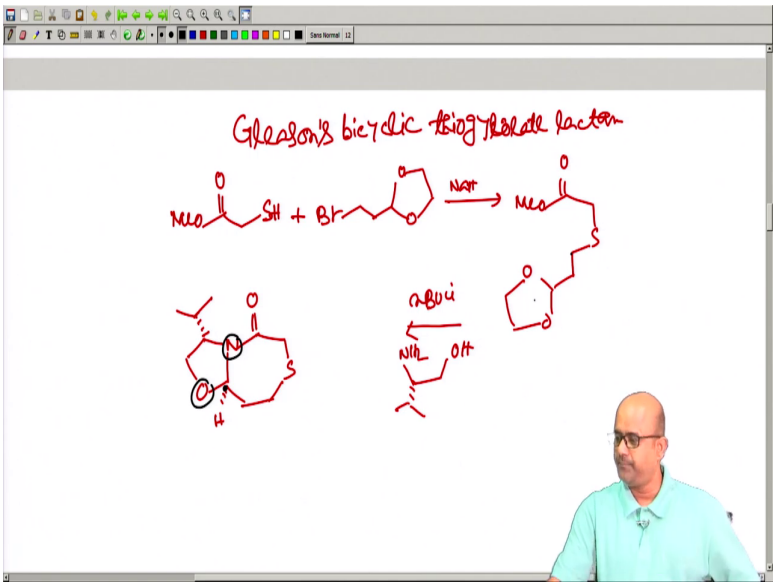

So, we will try to cover another bicyclic lactam which we called Gleason's bicyclic thioglycolate lactam. So, this was definitely a latest addition in the field of asymmetric synthesis and this was moreover kind of simple gycolate lactam. If you are let me try to give you how this compound was prepared. This compound was also a bicyclic lactam.

Initially, this thioester was treated with this bromo compound which was protected something like this. And, then a simple SN2 reaction was there and you will get this MeO-C double bond O CH2 S. So, as thio is an integral part and you get the aldehyde as protected ok. And, this compound is now treated with n butyl lithium and your valinol, valinol means the S valinol S or R depending on your choice. So, this kind of valinol which you have often used in the case of Evans (Refer Time: 24:58). And, actually now the moment you do this reaction, I will explain how it is happening.

But, just try to give you actually get a 5 and 7-member lactam ok. Now, this lactam if you check the structure where from is coming? This COMe you will having the amine part. So, CON CH2 CH2 OH. So, this amine, this NH and this OH reacts with this CHO, this CHO means S CH2 CH2 CHO. So, this is usually the way it has been done.

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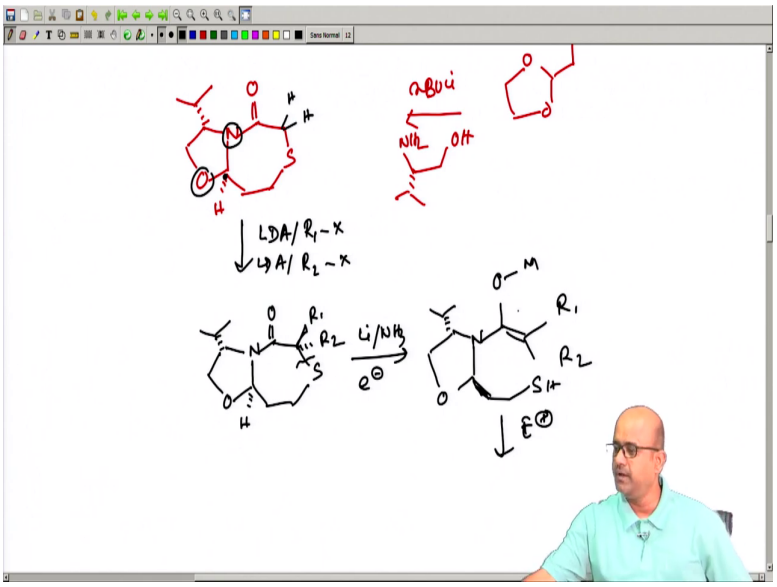

Now, this compound once you try to react with successive round of electrophile, you will see that this 2 hydrogen seems to be kind of abstracted. So, you can just LDA, R1X followed by LDA, R2X. The mode of asymmetric induction will be explaining little bit later on, but initially you will get this. So, just you will get a quaternary stereo centre. And, then this part is your valinole part, on principle the similar structure of the Meyer's bicyclic lactam.

And, then now this compound was cleaved with lithium liquid ammonia by a single electron donation. This carbon sulphur bond actually have been heterolytically be cleaved ok, this particular bond cleaved. And, the moment it has been cleaved, you actually get a dot, dot means a single electron, another single electron comes from here you get an anion. So, finally, what you get? You get a O, you have a metal and you get this R 1…… R 2.

So, you are cleaving this enolate this lactam you get CH2 CH2 SH and now you will find that this is the thing. Now, this is hydrogen is below. So, this will be above and next you can react with some electrophile, where this group controls the approach of the electrophile. Now, let me go to little bit of more structural features, how this origin of asymmetric induction you can explain.

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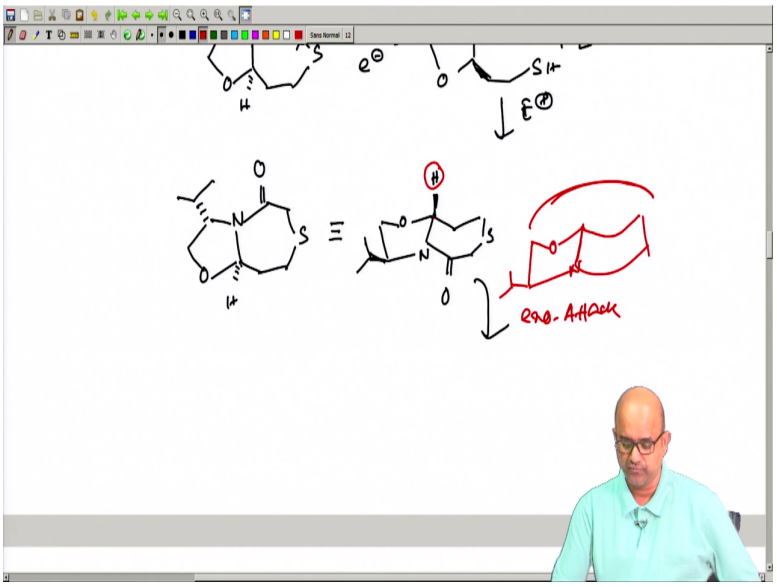

Now, for this part we will write the bicyclic lactam or thioglycolate based lactam. So, initially you have this, you have this valinole and then this O, this you have a hydrogen here, you have a two CH2. Now, this compound usually if you try to draw its three-dimensional structure, you can just write in this way. Same like a bicyclic lactam mode of analysis.

So, nitrogen is below like the earlier compound, the carbonyl will be here. There will be CH2, there will be S and it is a 7-member ring. So, this, this, this, this CH2 CH2 and this seems to be a kind of a combination of a chair as well as board. And, this part you have same like this oxygen, you have an envelope kind of 7-member ring, you have this and this isopropyl group occupies a pseudo equatorial position.

So, this is your kind of more or less the structure which you can see. Now, normally for this kind of structure earlier the Meyer's bicyclic lactam, though the isopropyl group plays an important role here. It has been shown that the structure of this ring actually gives you the enantio preferences. Now, you can see that these structures would like this is 1 ring, this is the pivotal bond.

The ring is more or less open in the top face, more or less open in the top face and bottom face seems to be squished. So, this could be the reason the top face seems to be more open, because the isopropyl group may not come into picture and here you have a hydrogen group. Remember, the Meyer's bicyclic lactam we said that if you have hydrogen, things might be undergoing a different perspective; exo-endo selectivity is not that good.

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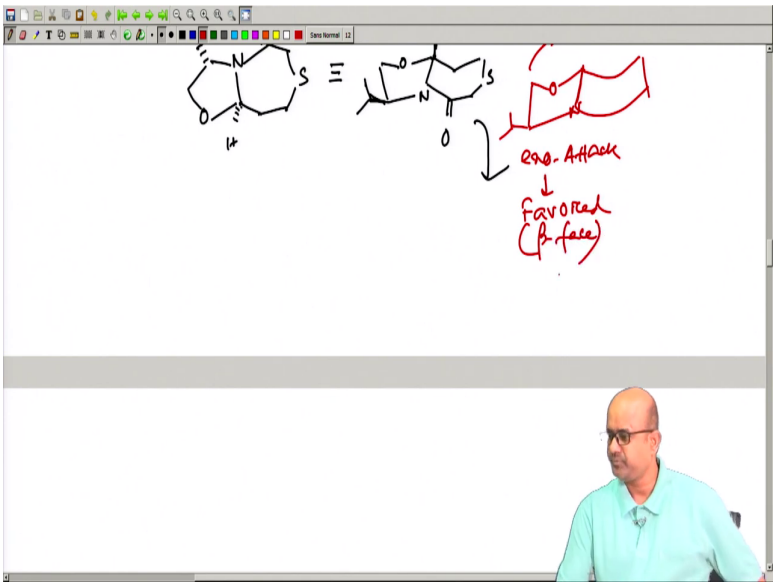

But, in this case the exo attack seems to be preferred only due to the fact that the ring is flat on the top side. You see the ring structure is such a ring is flat on the top side. So, exo attack is favoured, exo attack means attack from the beta face, beta face attack.

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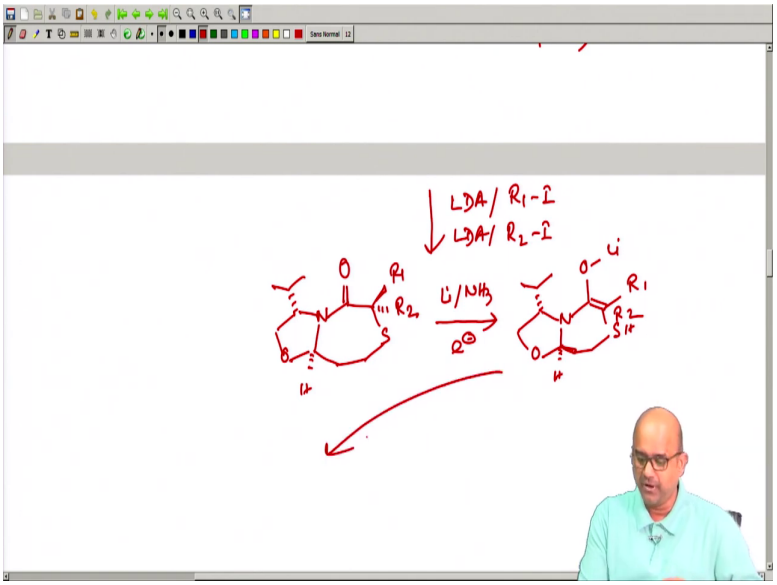

So, now if you can try to do a successive round of let say LDA, you treat with R1I, then LDA then R2I. So, means that second electrophile is R2. So, R2 is going to be attacked from the top face ok. So, you can just write the original structure of the compound N CO. Now,

remember here we put the ketone down, but the original structure ketone is up. So, you have to be bit careful about drawing the correct structure for all the compounds.

So, this is your carbon, you have a hydrogen here, CH2, CH2 S. And, this part is your valinol part, this group and this, this. So, now as I said the R2 will be will be definitely the. So, first is your R1, second is R2. Now, you get this compound its fine. And, then what you try to do? You actually put with a batch type of condition with single electron as a donor. And, the moment you put a single electron here, this thing everything remains similar your N and this is CH2 will be above SH.

Now, the OLi and you get a enolate, this R1 and R2. So, you have created a stereo centre, then you have destroyed it. Now, the next beauty was why you destroyed it?

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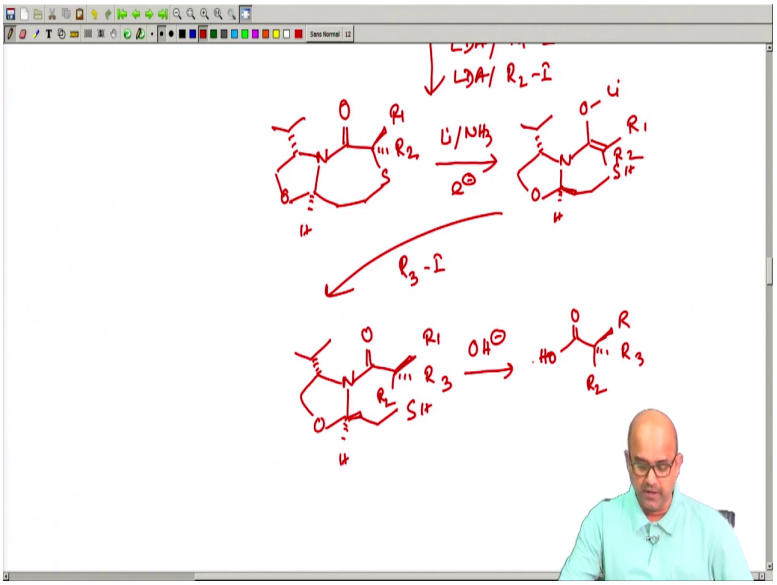

Because, you can further create a enolate and now you can add another electrophile, let say R3I. Now, what will be the course of this R3I? In this R3I, R3I will be opposite to this CH2 CH2SH, because this is beta ok. Now, you have to draw the structure CH2O, this nitrogen, this, this. So, CH2 CH2 SH, then your C double bond 2 and then see you see R1, you can write as a R1 above. R2 you can put in the plane and this R3 you can put in the below.

So, all carbon quaternary centre you can eventually create and this is the way you just then do it a hydrolytically cleavage OH minus or do a reductive cleavage. And, actually you can now create all carbon quaternary stereo centre. But, actually this Jason's sorry Gleason's

thioglycolate based lactam is not that popular yet like the Meyer's bicyclic lactam. But, as the literature report was there I have just shown to you.

And we in the next class, we are going to discuss few more problems based on this bicyclic lactam and how you can solve it. Also, you can discuss how the Meyer's oxygen based carboxylic acid enolate alkylation.

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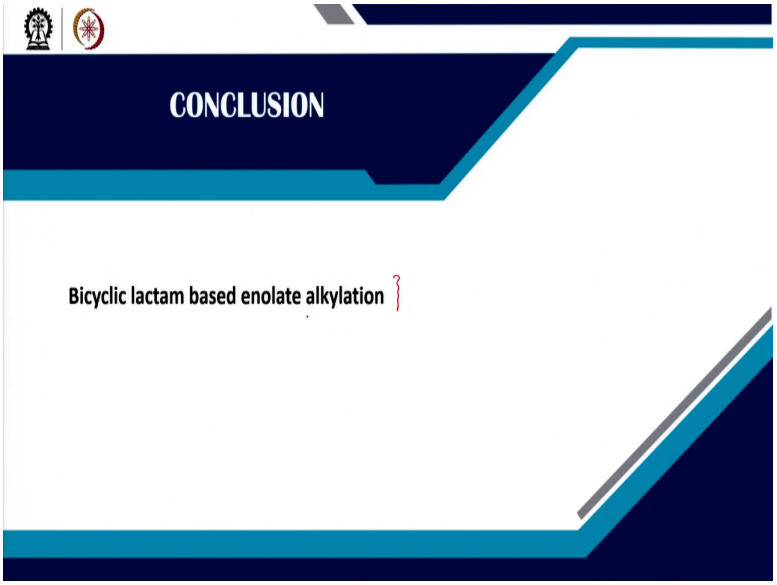

So, in the concluding remarks we can say that Meyer's bicycle lactam as well as related other lactam like Gleason's thioglycolate based bicyclic lactam plays a very important role. And, you can eventually see that a large number of enantiopure and chiral compounds can be synthesized by successful exploration of enolate alkylation on those lactams in asymmetric fashion. So, we will see you in the next lecture for some other topic

Thank you.