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 - 07
Aza-Enolate alkylation
Lecture - 34
Ender's RAMP/SAMP based systems - II

So, welcome everyone. In continuation with our earlier module today we are going to talk about this lecture 34. And this lecture 34 the main concern was or main topic will be Ender's RAMP/SAMP based systems and we will trying to disclose more case studies based on this RAMP/SAMP.

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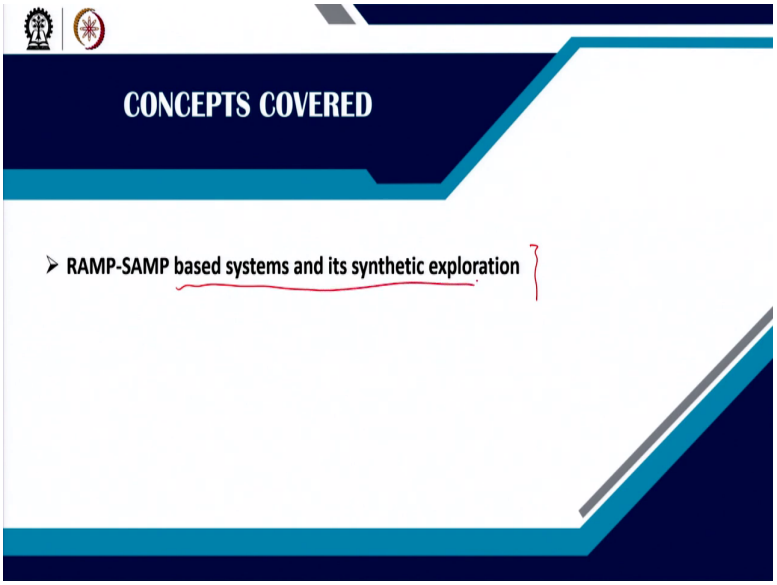

Main content which we are going to cover as I said RAMP/ SAMP based systems and its synthetic exploration ok.

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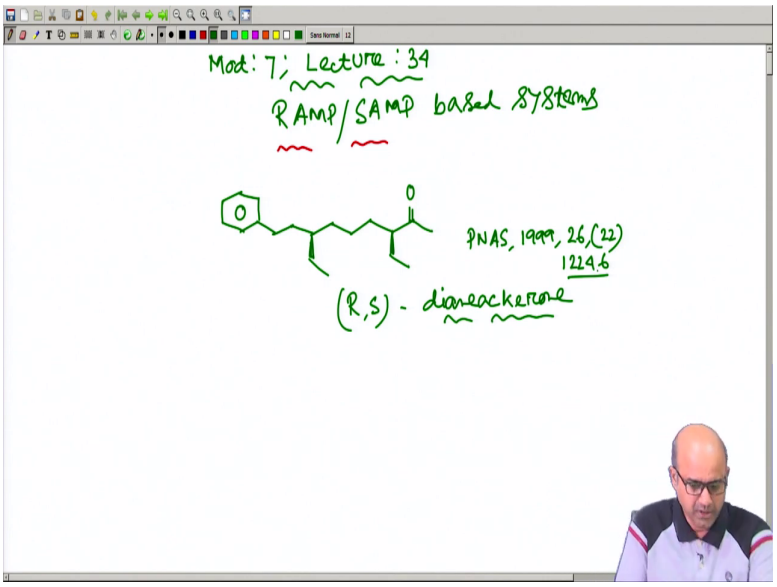

So, welcome back students. As we talked about we are mainly going to talk about this RAMP/SAMP based systems and its synthetic exploration and the very beginning part of today's lecture, we will talk about a total synthesis of a target molecule which seems to be a good target molecule which contains two stereocenters and two of the stereocenters has been fixed with the help of this RAMP SAMP based alkylation.

Now, this is the compound structure, this compound name is this R,S dianeackerone. Anyway, this compound was actually isolated from the Lacrimal gland of a rare species of crocodile and this probably does not signify anything, but the structure seems to be interesting as a pretty small structure and synthesis of this molecule was reported in a PNAS paper Proceedings of National Academy of Science in USA this was reported in 1999 and this was the volume and page number.

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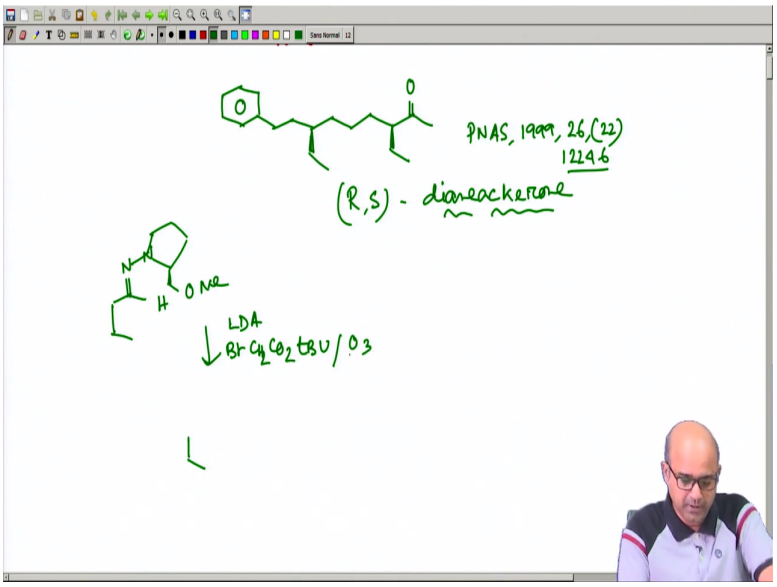

So, we are just going to discuss how such molecular synthesized with the help of this RAMP/SAMP based alkylation. So, before we go we just, but eventually due to lack of time probably retro synthetic analysis we cannot do. So, we will just try to do a normal forward synthesis. So, first you take a propionaldehyde as one of the one of the precursor and this RAMP and SAMP based one compound you choose the SAMP 1 and the electrophile was which you take this electrophile.

So, in the initial case LDA was there and the electrophile was a this Br CH2 CO2 tertiary butyl this kind of electrophile was chosen. So, this electrophile chosen means, if you now try to write this compound you will eventually find that sorry this is one carbon extra. So, you will be having this and then you try to do an ozonolytic cleavage. So, if you try to do, but ozonolytic cleavage initially was not done.

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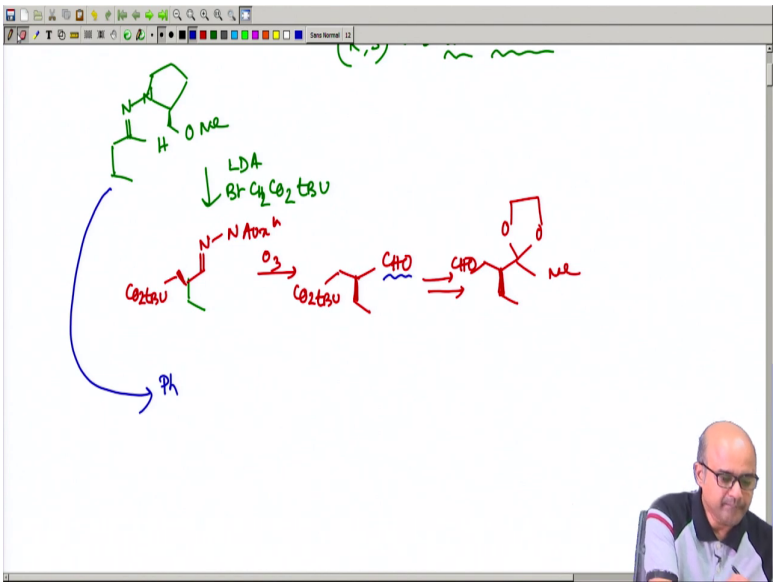

So, you just try to first do the N just write N auxiliary the same RAMP SAMP and definitely the working model it will be beta because the CH2OMe is beta. So, it will be CO2 tert butyl ok. Then if you immediately try to do the ozonolysis part what it will give you can just try to write just rearrange it this will be the aldehyde and this will be your CH2 CO2 tertiary butyl ok. Now this compound was like this you can eventually do an aldehyde. Aldehyde means, you can just I just do not write everything what I am trying to say…. you can from this compound you actually prepare another intermediate which is this.

Now, how you will do it I will explain just by the verbal mode of communication thing. So, it will be. So, what you do? You have a CHO here you have an ester CHO is much more reactive you do a methyl Grignard on this compound you do a methyl Grignard you do an oxidation and you protect this carbonyl compound. This CO2 tertiary butyl group you just reduce to CHO this is one of the intermediate.

Now, this intermediate if you can see this is actually coming from this part this ethyl is hanging this is the COMe and then CH2CHOCH2CHO. For other part you have to actually access from a different kind of compound. So, actually, I am just trying to write the same thing the same starting material which we have used earlier you take it ok.

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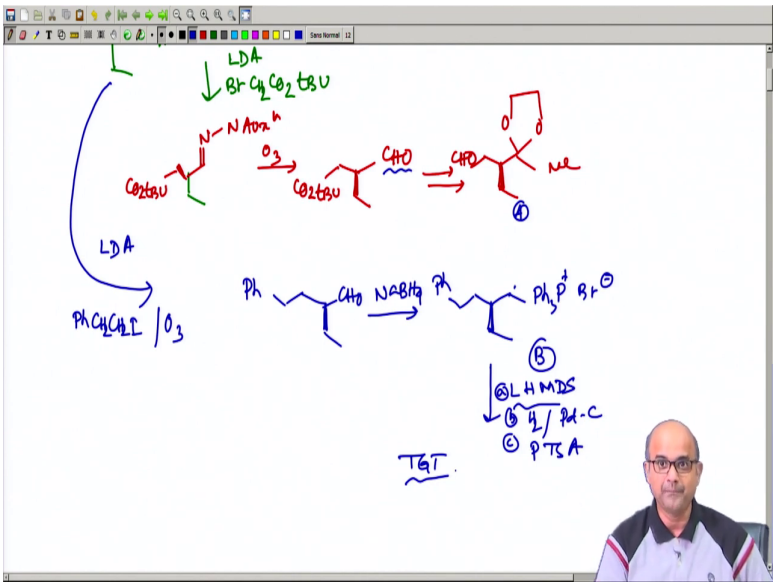

And then with this starting material you actually do the alkylation with LDA followed by if you now check it will be Ph beta phenethyl iodide Ph CH2CH2I. Now, see there is Ph CH2 CH2. So, with this compound you just try to do it and then do an ozonolysis. So, now, what we will get? You get Ph, you get CH2 CH2 you write sorry just one minute give me little bit of yeah I just try to write the proper carbon chain you have. So, with this you have a CH2 CH2 Ph and then this ethyl is hanging here you have a CHO fine.

Now, this compound you first reduce sodium borohydride followed by an Appel reaction triphenylphosphine refluxing, you actually get the corresponding PPh3 plus Br minus and then your CH2 CH2 Ph. So, this is one basic salt this is the aldehyde. So, compound A and compound B you just condense with LHMDS or butyl lithium any suitable bases the moment you do you actually you now check the compound structure.

So, this CHO this CHO you will basically get a double bond here see this double bond here now this double bond you can simply hydrogenate. So, you first do the Wittig reaction followed by hydrogen then palladium charcoal and then this ketal group removal with a PTSA. So, that is give you target molecule now why this is synthesis is important? Because this target molecule you can actually create two stereocenter which are in the both the cases you actually create a asymmetric enolate alkylation through RAMP and SAMP method.

And this synthesis was pretty interesting. You know similarly let me give you some a homework kind of thing probably you can try to do both the synthesis by using this way.

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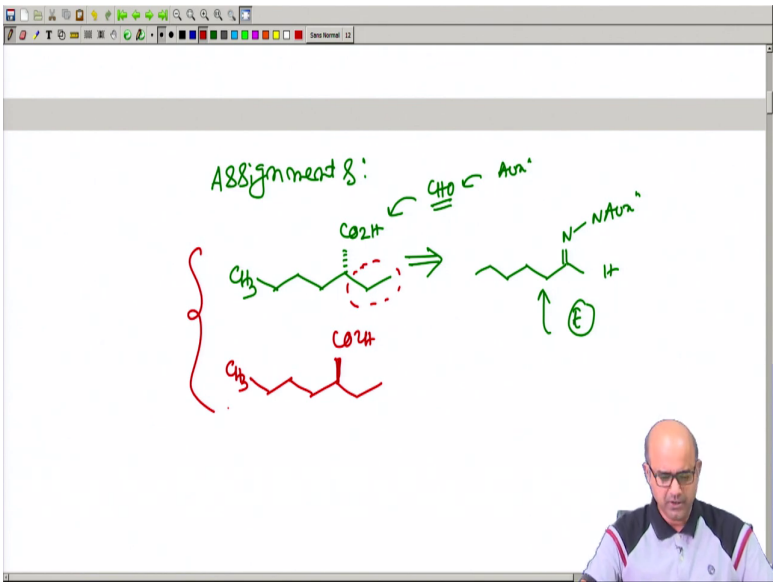

So, I will just try to give you few assignments. So, you please do it in your extra time or whenever you have a time. So, let me write this is CH3 there will be 4 carbon and then this will be a CO2H and this will be methyl ok. Now the idea was you have to try to do a simple RAMP SAMP based alkylation. Now if I give you a hint that probably could serve as a purpose now this CHO this CO2 H can be coming from C O H C H O. So, this you take it as a hint.

Now, this CHO will be coming from the auxiliary cleavage ok. So, what now you can try to do it? Let us say you try to take a this kind of simple auxiliary n your what auxiliary you take that you choose ok. So, this auxiliary then you add your electrophile. Now the electrophile will be probably you can used as a this particular compound ethyl.

So, you can add it and then you will find that this thing you can simply oxidize with the ethyl and the CHO will be oxidized to corresponding carboxylic acid. So, we have to usually design the synthetic pathway for similarly you try to do the other enantiomer means try to use the other enantiomer you can actually do it. So, both the compounds you can make it, you can use same auxiliary or different auxiliaries.

So, that is your choice if you want to take the same auxiliary, then you have to apply the synthon concept which we have discussed in the last class if you want to use different auxiliaries then you take RAMP and SAMP and just follow the similar sequence of reaction.

Now let me try to do another or some other synthetic procedures which is also one of the nice example for some exercise of such exploration of such compounds.

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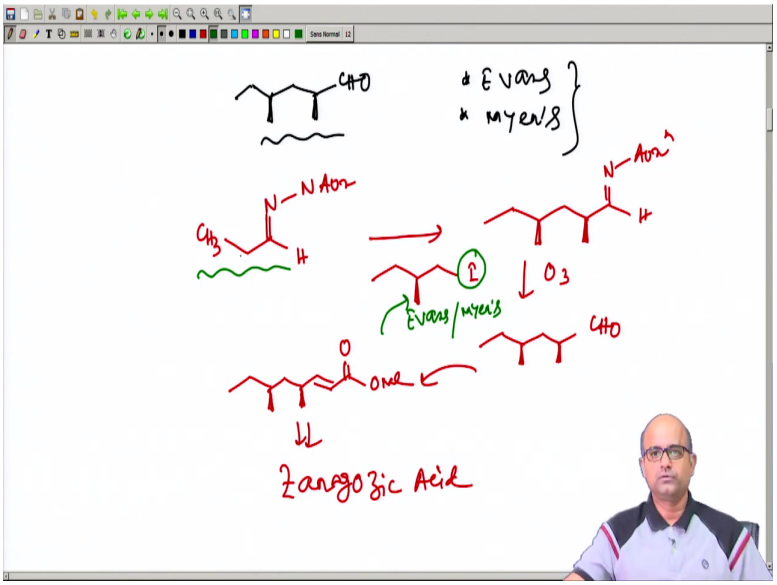

One such example which we are now going to discuss its actually a synthesis of some syn 13 dimethyl kind of compound which probably earlier we have seen that this kind of compounds you can definitely make through Evans or Myer's pseudoephedrine based auxiliary or other auxiliary.

But in such cases also here this RAMP/SAMP based method also you can do it. Now how you can do it? So, let me try to take the corresponding auxiliary N Aux with a this thing and definitely now you can create or you can use the electrophile which already having this pre existing stereocenter this I ok and then now you can easily find that this is already there. So, this could be another round of thing and then your auxiliary will be here N Aux.

Now, based on the stereochemistry you can choose it and then you can simply do an ozonolytic cleavage and then you can actually get the corresponding target molecule. Now this target actually was used as the precursor for zaragozic acid synthesis. So, this was first done a Wittig kind of olefination with these things and then which was synthetically manipulated to a total synthesis of a natural product whose name is zaragozic acid……and it is a complex natural product.

But what I am trying to say that such electrophile you can actually again create by different way. So, you can create this stereocenter through Evans or even your RAMP/SAMP or any other methods like Myer's and then you can use this electrophile as a this particularly hydrazone derived from the aldehyde and then you can use this as a CH2 I to create new stereocenter. So, such things can easily be done now few more extra point we will be trying to do it.

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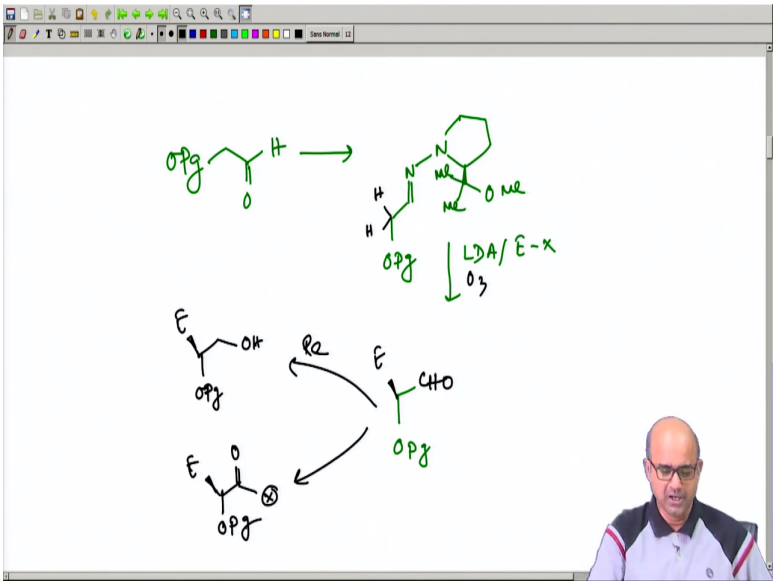

Let us say you have an O protected aldehyde at one end simple ethylene glycol derivative which you protect one end and then oxidize this end. Now, this compound you can actually try to use this compound as a precursor for this chiral hydrogen thing so, means that this aldehyde already having a pre existing stereocenter ok. Now here they have used a higher analog of RAMP or SAMP you remember earlier we talked about this higher analog this CH2 is replaced by 2 dimethyl ok.

So, this compound was initially prepared and then you treat with LDA followed by an electrophile of your choice. So, now, what will be happening? This is above. So, you will get CH2 OPg this hydrogens will be actually abstracted as these are the acidic hydrogen H and H any….. hydrogen. Now here you will get your carbon electrophile bond and then you treat with ozone you basically get a CHO.

So, this CHO is what? Now this is actually hydroxyl aldehyde alpha hydroxyl aldehyde you can synthetically manipulate such aldehydes in a different way you can just do a reduction

and then if you do a reduction you get Opg you get a CH2OH you get AEE. So, basically you get a 1-2 ethylene glycol derivative which is stereocenter you can synthetically manipulate to other things you can change the oxidation state of this aldehyde to you can derive several carbonyl compounds. So, based on your choice ok you can reduce to alcohol by the first way you can oxidize to carboxylic acid then you can convert to amide or something.

So, this is basically kind of a lactic acid derivative or high order lactate ok. So, these things are pretty well you can plan……. judiciously you can choose even other synthetic potentials if you have a thio group here.

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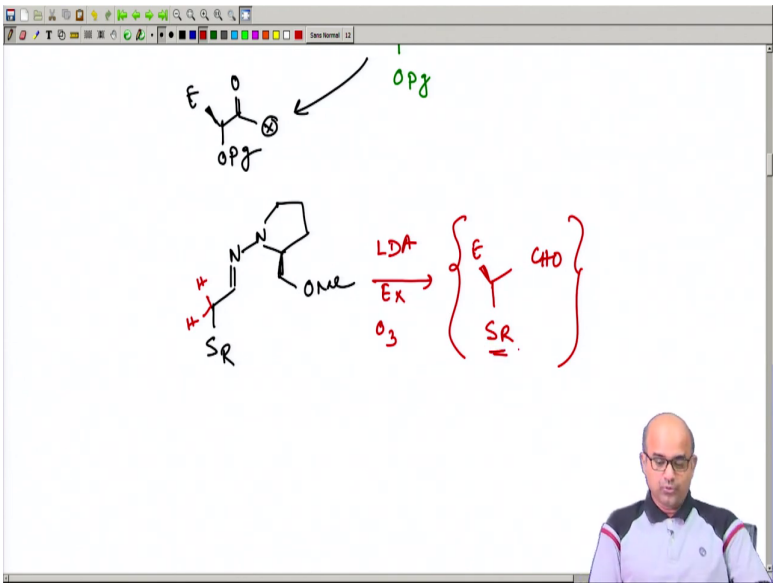

This thio aldehyde also similarly synthetically can be used same like the oxygen containing protecting group and these are also served as a good precursor for such alkylation. Now, here also similar thing happens, you have these two enolisable hydrogen which eventually can be picked up the electro electrophile is your choice and then you treat with ozone.

So, you can eventually get a sulfur containing alkylated thing this and CHO. So, now, see a variety of intermediates with different functional groups can be created. So, you can have a sulfur containing thing and obviously, as I talked about oxygen and sulfur nitrogen also can potentially be used and usually nitrogen kind of compound also very effectively be used.

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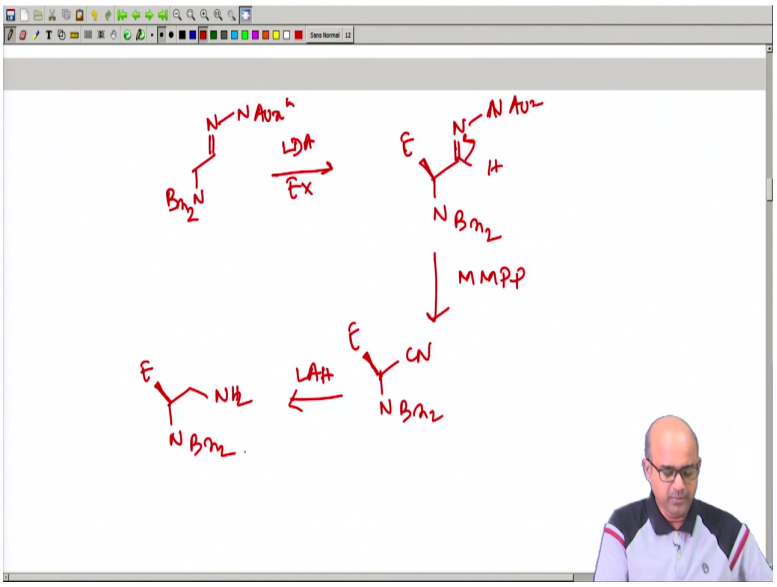

And in such cases the idea was more or less similar, you take the auxiliary means the RAMP or SAMP and then you have a LDA which are electrophile of your choice, then here you can definitely cleave the oxidative cleave, but normally people try to do in a different way what they do? This is fine you have a carbon electrophile bond and this double bond N with N auxiliary.

Now, this hydrogen if you can remove with an oxidizing agent normally MMPP Mono Magnesium per-Phthalate is basically gives you a cyanide derivative ok. Now this cyanide means you get NBn2 this center has been fixed you get CN you can eventually reduce this cyanide to corresponding amine. So, there are more synthetic avenues are opened up and you get CH2 NH2 and you get NBn2.

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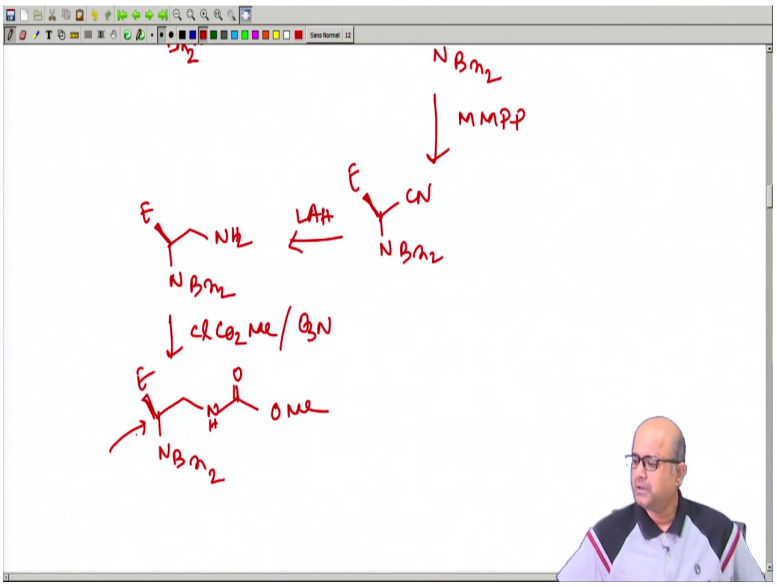

So, basically you get a diamine derivative. And then this was also later on synthetically further manipulated to treating with this chloroformate with triethyl amine you actually get a amino acid kind of derivative. This is E this E choice you can do it CH2 N H C double bond O …..OMe. So, such amino acid derivative or its not amino acid it is basically kind of a carbamate derivative and you can get such compounds in the asymmetric fashion.

So, RAMP/SAMP based methods will be quite useful we will rapidly try to talk about some cyclic systems which seems to be quite interesting.

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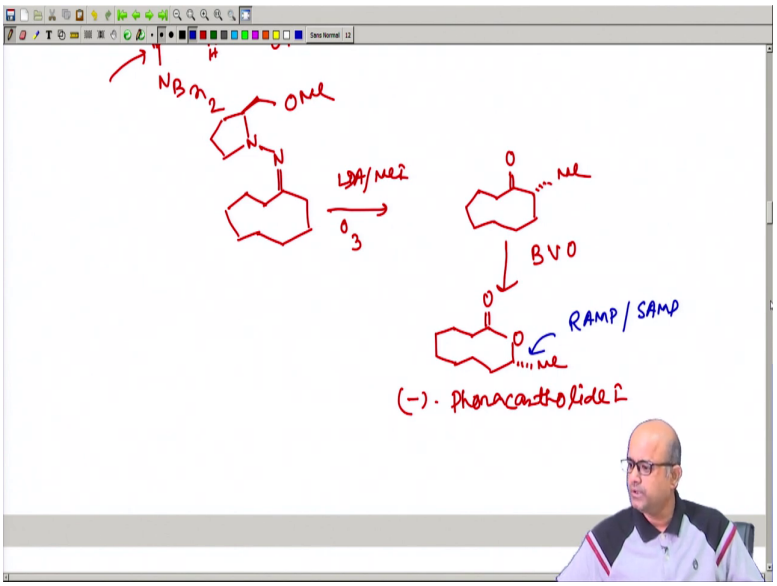

Now, some cyclic systems usually we will be trying to talk about. Now for cyclic system as I am saying for cyclic system definitely you have a regiochemical issues, but more or less you can have a symmetrical cyclic system. So, that will take care of the things you can write this nine membered ring in a bigger way these are basically symmetrical for sake of drawing I have just drawn in this way ok. So, you can have LDA, you can have methyl iodide and followed by you can have an ozonolysis.

So, you can eventually try to write this thing that after this alkylation you can get this compound ok. Now once you get this compound this potentially in the last case we talked about a Baeyer Villiger oxidation you can do a Baeyer Villiger oxidation and this is more substituted compound. So, definitely now you can have a Baeyer Villiger oxidation towards more substituted thing and you can oxygen will migrate towards this carbon.

So, then you will usually get this compound and this compound is a natural product and the stereochemical retention is the main factor for the Baeyer Villiger oxidation. So, this compound is a natural product and its name is phoracantholide. So, phoracantholide I is a ten member lactone with a stereocenter and this can be nicely created with this stereocenter actually was fixed by this RAMP/SAMP based alkylation method.

This is the main synthetic pathway. We are not going to talk about few things more now let me talk about some other things which one of the structures probably we have remained let me explain another synthesis.

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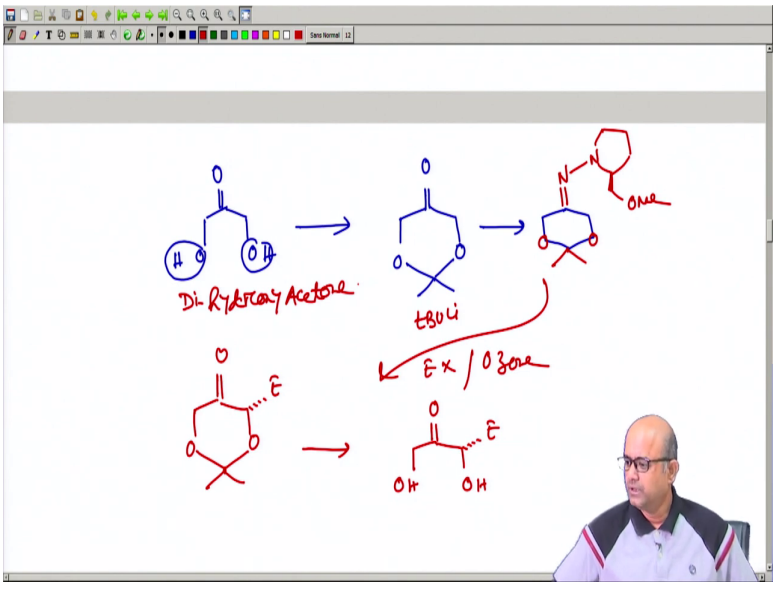

In the cyclic part we already talked about. Now this compound is pretty important this compound is name is dihydroxyacetone……. this dihydroxyacetone is a good synthetic intermediate if this hydroxy group are protected. So, this hydroxy group are usually protected as its acetonide derivative and then you can actually use it. Now this looks like a cyclohexanone kind of compound again and then you just take this compound and do way a derivatized with your RAMP or SAMP symmetric compound definitely this cyclic alkanone is a symmetrical alkanone.

And then you take this compound what you do? You treat with a base Tert butyl lithium I mean it is a normal base and then electrophile the electrophile you choose and then your ozone. The electrophile if you now see the ozone will be there you have this, you have this and you can treat it there.

Now this acetonide group actually can be cleaved. So, once you cleave this acetonide you will find that further functionalization can be possible and actually this carbonyl group you can further reduce you can get a tri hydroxy compound you can deoxygenate it you can deoxygenate it.

So, this kind of the dihydroxyacetone derivative was actually used for few purposes and such dihydroxyacetone derivative serve as a good precursor for some synthetic exercises. Now in continuation to this synthesis if the just followed the same way if the electrophile E if you use a electrophile which seems to be a having this kind of structure I CH2 CH2 this let us say O…… let us say O this.

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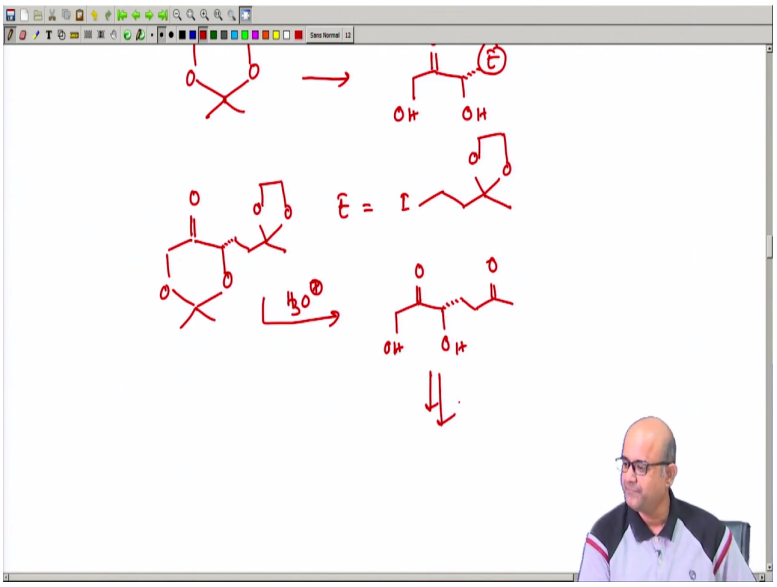

Now, if you have this electrophile. So, now, try to write the structure of the compound after the RAMP SAMP alkylation. So, you will get this ok CH2 CH2 this O this O this. Now you just treat this compound with $H3O^+$ on treating with H3O plus actually what we are getting you get a CH2OH you get a CH OH and this here you get a this this this CO.

Now, actually such compounds probably gives you a more synthetic flexibility and actually such compounds we have earlier used.

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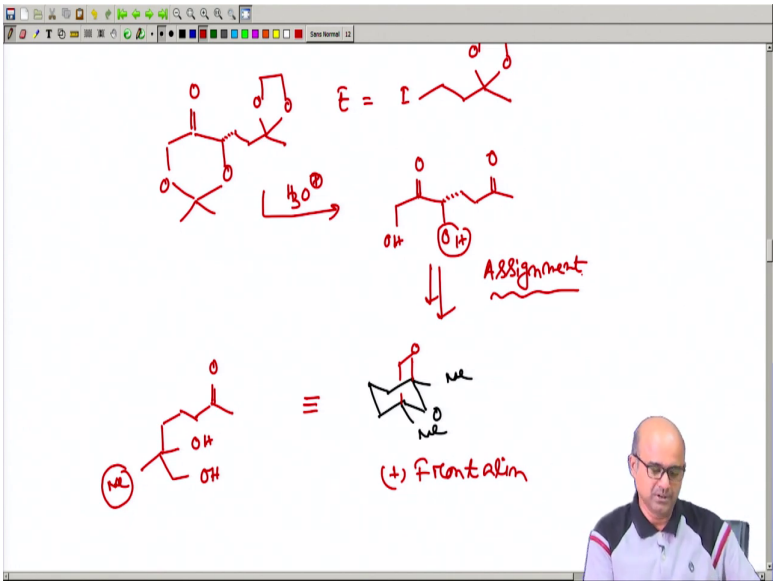

If you remember in the lecture note we have synthesized a compound name Frontalin which is a pheromone. Now this intermediate also can be used in the synthesis of Frontalin this is the oxygen part here and this is a methyl equatorial methyl, this is another methyl and we will now try to do the structure correlation how this compound can be met with this.

Now, if you see this is looks like you have a methyl then there are so, this oxygen if you try to deoxygenate. So, now, take this as a home assignment…… how this structure to this compound this is basically a Frontalin and this synthesis also was reported. So, you have to do little bit of a synthetic group manipulation that how you can convert this RAMP /SAMP based alkylated product to obtain this Frontalin.

So, normally this Frontalin structure if you think it is a usually a cyclic acetal. So, it means that if you just let me try write it if you have a ketone, if you have a typical methyl and then we just try to give a CH2 CH2 CH2. So, write 3 carbon CH2 CH2 CH2 1, 2, 3 1, 2, 3 and with this carbon you have a now a methyl you have a OH and you have a CH2OH.

So, this you need to be little bit of manipulatation. Now it looks like that from this structure how you can do it? If you have a Me CO CH2 CH2. So, Me CO CH2 CH2……. 2 CH2 then you have this COH So, means you have to deoxygenate this ok and then at this carbon you have a some addition should be done on this methyl because where from this methyl is coming.

So, this you need to be take care of this and if you try to do probably this synthesis as a home assignment that will be a nice take home assignment. But usually if you check the synthesis of these things the crucial part was the RAMP/ SAMP based alkylation. And in the next lecture we will be mainly talking about this dihydroxyacetone based compound and how these compounds can be synthetically manipulated for several dideoxy sugars by using this RAMP and SAMP based alkylation methods.

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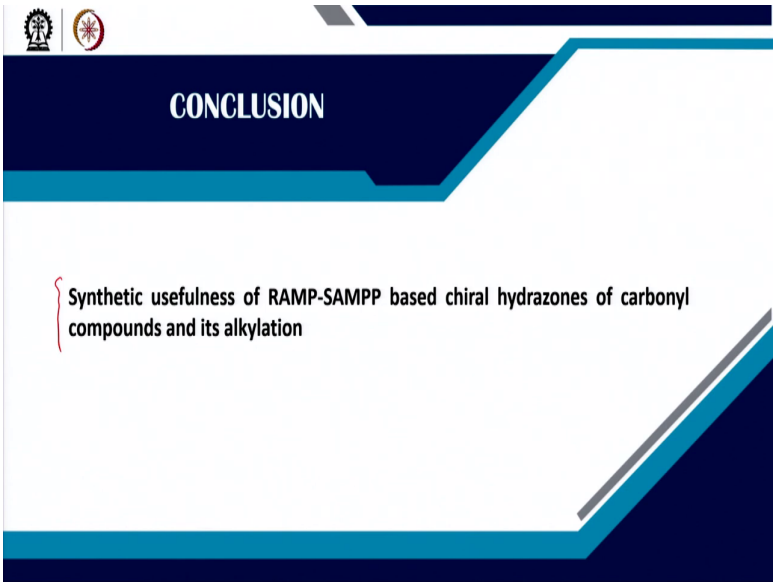

So, as a concluding remark after today's lecture you have seen that synthetic usefulness of RAMP/SAMP based chiral hydrazones was really very useful and you can use such synthetic strategies for creating a new carbon carbon containing stereogenic center through an enolate alkylation strategies. And then later on such compounds can synthetically be manipulated to various or numerous value added products such as natural products or chiral intermediates, we will deal or we will discuss some more things in the subsequent classes.

Thank you.