**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 - 02**
**Enolate alkylation of several carbonyl species**
**Lecture - 09**
**Seebach's SRS principle and related systems - II**

So, welcome back students and in continuation with our discussion, today we will be talking about this Module 2 and particularly in the Module 2 the main concept is Enolate Alkylation and the Lecture 9 which will be talking about Seebach's SRS principle and related system.

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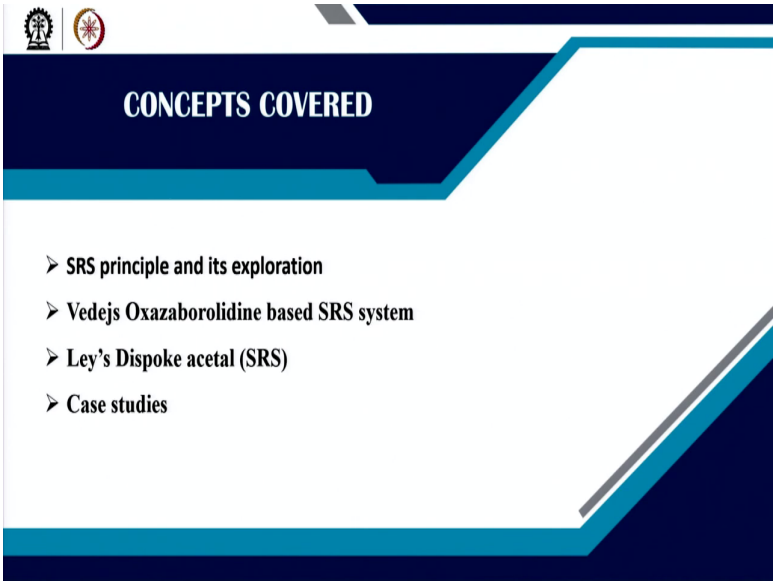


So, today in this module we will be mainly trying to cover SRS principle which already we have discussed. We will be trying to talk about some new SRS systems like Vedejs Oxazaborolidine Systems and Ley's Dispoke acetal system and few case studies related to different SRS system and its exploration.

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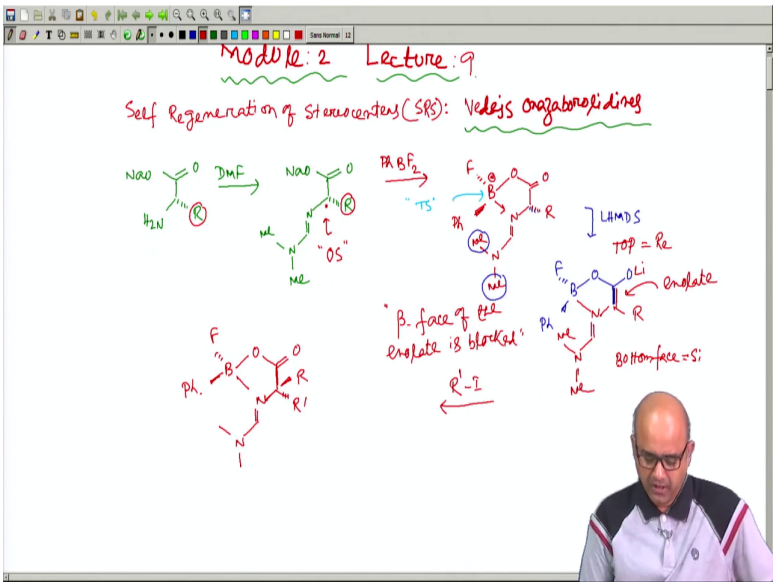


So, in continuation with the self-regeneration of stereo centers which we have discussed in the last lecture I mean Lecture 8 in Module 2, today we will be continuing the similar kind of discussion. And today we will be talking about a specific SRS system which is termed as Vedejs Oxazaborolidine which was reported by Edwin Vedejs.

Now, this system was kind of a bit of different than the traditional SRS system. So, I am just trying to give you a brief outline of that system and in that system in the initial step if amino acid was chosen as the main precursor I am just trying to write a general form of amino acid which is basically amino acid sodium salt.

Now, this amino acid sodium salt was initially reacted with dimethyl formamide and what is happening they basically condense with the amine part and this original stereo center of this amino acid was remain intact because that was not touched. And dimethyl formamide you all of you know that dimethyl formamide is having an aldehyde functionality which is basically a HCO. So, DMF was the condensing agent and this is the original stereo center in this molecule ok.

Now, the choice of R you can choose depending on different naturally occurring amino acid. So, this is the original stereo center present in the molecule. Now, this compound was next subjected to treatment with a Lewis acid and this is the main key step in the overall SRS strategies.

We last time we said that in SRS after the initial covalent bond formation you are creating a temporary stereo center. In the original Seebach's work usually we have seen that the temporary stereo center is lying through around a stereo genic carbon, but in this case after treatment with the $PhBF_2$ it has been found that this boron helps for the coordination.

And initial this amino acid which was condensed with the dimethyl formamide it is now forms a kind of a cyclic chelate type of thing with the $PhBF_2$ and the temporary stereo center is actually now coordinating with basically this boron becomes a negative charge and now see the newly created stereo center at boron is the temporary stereo center which is been created.

The point to be noted that the phenyl ring is above because it has to be avoided the steric class between this two methyl mainly one of the methyl. So, if this phenyl goes above it can avoid that, in addition also it is having a remote methyl group which is alpha. So, this phenyl ring adopts beta orientation or beta orientation around the boron.

So, now for the next part was almost similar like the other enolate alkylation you treat with a base and the base which was preferred a lithium hexamethyl disilazide ok and then what you get, you basically you get an enolate around this thing. So, initial part your boron remains same which is the temporary stereo center ok, this you are going to have a enolate here.

So, this will be I will write try to write in a different color the double bond here OLi the metal and then you have this nitrogen and you have this thing, here is the R and your original dimethyl formamide is lying here ok. So, this seems to be the structure of the enolate.

Now, you can easily see the enolate structure the way it has been represented it, it means that the this enolate which is having the pi double bond and this sp2 hybridization the beta face of the enolate seems to be blocked beta face is blocked beta face of the enolate is blocked because it is occupied by a bulky phenyl group.

So, now, it is quite understandable that if you can now try to do a little bit of CIP nomenclature for this enolate face, the top face you see this is the top face seems to be the Re-face. So, top face is Re and the bottom face seems to be the Si face or Si face, you can basically do a typical analysis just put 1 2 3. So, CIP 2 so, this is this gives the clockwise rotation. So, the top face has to be Si now as electrophiles.

So, now, you can treat electrophile depending on your choice and let us say you treat with an electrophile which seems to be R1 I, I means iodo compound. So, now you can eventually get that enolate alkylation which seems to be now take place and this enolate alkylation now will take place from the opposite face of the phenyl.

That means, that the C R prime bond will be below or alpha and the R will be above, then you have remaining part all will be there, you can eventually write this ketone, this oxygen, the boron part is there and you have this phenyl and you have this fluorine and phenyl ok..

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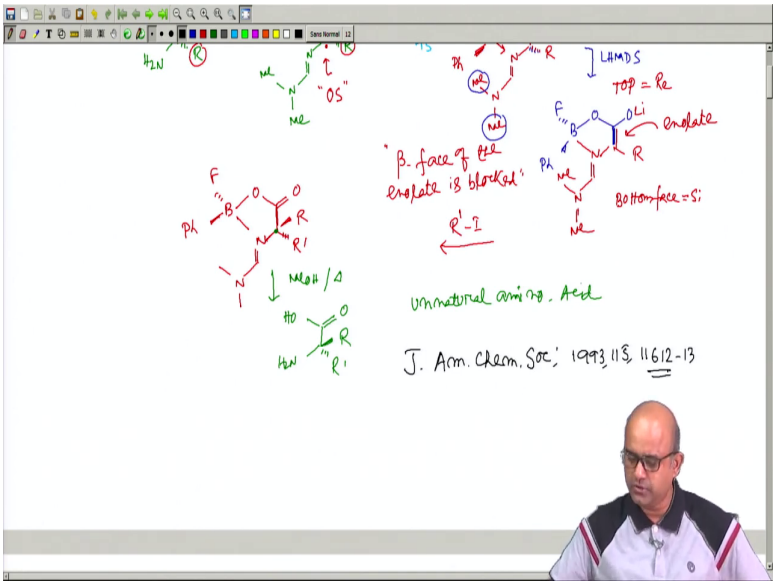


So, now, next is your so, the amino acid at this part is alkylated fine and now you just do an acidic hydrolysis. So, that was usually done by methanol and refluxing condition. And what it will give you? It basically will give you the corresponding alkylated amino acid. So, this alkylated amino acid will now have this part is H2N and this will be your R1 which is coming from the electrophile and this will be the original R.

So, you can see you can basically create it unnatural amino acid of different constitution by using this kind of Vedejs oxazaborolidine SRS based stereo genic center regeneration. Now, this work was published in a very well reputed journal which is named as Journal of American Chemical Society and this was published in the year 1993 and this work gained significant application after that. So, this is the page number. So, now, by applying such strategy you can eventually try to use other SRS system also.

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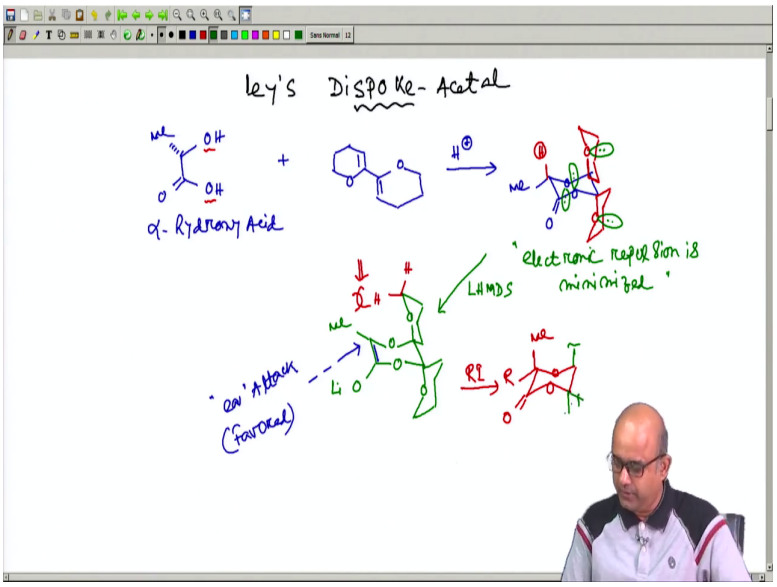


And next we will try to use another such SRS system which is now well known as Ley's Dispoke Acetal. Now, this name was pretty important dispoke. It is the spoke is eventually kind of a spoke of a wheel the cycle wheel you have seen bicycle there is a spoke ok, which basically holds the circular part. And the dispoke acetal a similar kind of precursor, but which is more or less the original hydroxy acid which was used by the Seebach was used.

Then the dispoke acetal the concept was bit different. What happened initially a simple alpha hydroxy acid mainly lactic acid was used as the precursor and this acid was eventually condensed with a Bis THF. Now this bis - THF was commercially available and this bis - THF was usually used as the condensating agent. Now all of us know that this tetrahydro this dihydropyran are used as the protecting group for hydroxy group.

Now, this bis dihydro pyran if you condense with this corresponding alpha hydroxy acid let me first draw the structure then it will be quite clear to you and then I can also understand I can also tell you that what is happening exactly. So, first I write a 6 membered ring and that I put the methyl group as an equatorial as it is below the plane in the original compound. Then you have this carbonyl which is coming from the alpha hydroxy acid, there are two oxygen; the hydroxy acid the C O O.

So, this O and this O seems to be acting as a two nucleophilic OH which basically reacts with two moles of dihydropyran. Now, fine and then on this part and on this part the dihydropyran ring is basically forms, I will try to write the chair form of both the compounds. And the

drawing will be you have to make little bit of practice for this drawing the chair form looks like a kind of a chair form.

So, you can see that this OH and this OH usually they attack at this position because that gives you a stable oxonium. So, basically you have a spiro cycle thing ok. Now, symmetrical thing so 1 OH comes here 1 OH comes here and you get this particular compound. Now, in this case the carbonyl is here. So, definitely your enolate will be mainly generating by abstracting this hydrogen.

But now if you observe the parent compound you can see that this parent compound there are couple of oxygen which seems to have the non-bonding electron or the lone pair electron. Now, this lone pair of the electron seems to be quite interesting I just try to draw a conformation where all this known lone pair electron on the oxygen they seem to be kind of far apart so that this will be having minimum of electronic repulsion from the non-bonding orbitals.

Now we found that this lone pair lobe is this way and this is the opposite way, even this seems to be this way because if it comes in here, it gets a electronic repulsion from this oxygen lone pair and this the bottom one seems to be like in this way because if it happens to be this way it has to be strong interaction ok.

So, this is the kind of a most stable conformation where electronic repulsion is minimized. This was the main part electronic repulsion is minimized and this was one of the main criteria because you do not have a steric factor to count over here, definitely steric factor is coming, but initial drawing seems to be quite important.

So, now you put your base and base seems to be a similar kind of base like LHMDS and eventually now we can draw the enolate structure the enolate will be kind of oxygen and you have this O these things it will be flat enolate definitely and from a chair it could be kind of a I just do not draw a half chair, but try to put it in this way.

And then remaining two oxygen the spiro cycle thing you can fix it by drawing in this way, eventually this drawing probably you need to do couple of practice otherwise this drawing may not come very easy to all of you. So, oxygen lithium and then your methyl will be here because from sp3, now we create sp2. So, this is the sp2 enolate ok.

Now, eventually you can find that the what will be the electrophile trajectory. Normally in this case it has been found that the electrophile trajectory will be from this way because that gives you a less steric bias. So, is equatorial attack in the cyclohexane system which you have already earlier discussed in the substrate directed alkylation.

So, this equatorial attack is preferred or favoured and eventually the axial attack if it tries to be happen axial attack from the top angle this might be inhibited by this kind of axial methyl, which is originated from the tilting of the top tetrahydro pyran ring. So, axial attack from top face seems to be blocked or disfavoured.

And now if this electrophile approaches from the equatorial way, what basically you will get? The electrophile is you can write R I or R X and now you can simply write the original alpha hydroxy acid with the tetrahydropyran unit. So, this R will be now equatorial and the methyl will be axial and the other part I did not draw, but still you can draw it ok, you can draw it.

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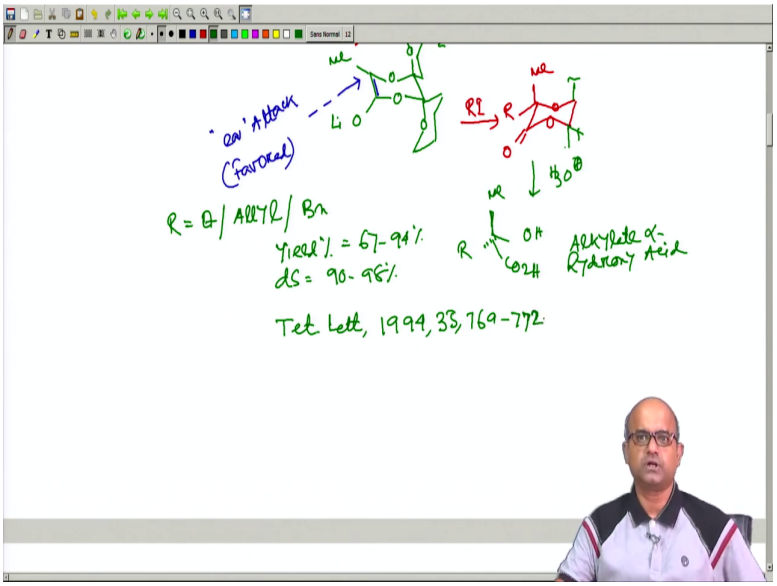


So, now what was next done? The next was basically simple hydrolysis simple hydrolysis, the moment you do the hydrolysis you can now see that from the chair form I will now try to put it this R will be below as the way it has been done. The methyl is above and I will put OH on my plane and CO2 H on my plane. So, this will be the final compound, where the you can now write that this compound is nothing, but an alkylated alpha hydroxy acid. So, the parent hydroxy acid which does not have a hydrogen over there is now alkylated.

Now a nature of R seems to be quite important has been found that R could be ethyl is very much well acting as a electrophile, allyl, benzyl both works pretty fine and the usual yield of this reaction is pretty good, yield percentage seems to be 67 to 94 percentage and diastereo selection means the asymmetric induction also seems to be pretty good, 90 to 98 percent based on different examples.

So, this particular work of Ley has been appeared in again an important journal its name is stated on the lecture which is published in 1994 is the year and volume is 35 and this is the page number. So, based on this sorry this is yeah. So, based on such dispoke acetal we will next just I will try to give you a problem, so that you can solve it.

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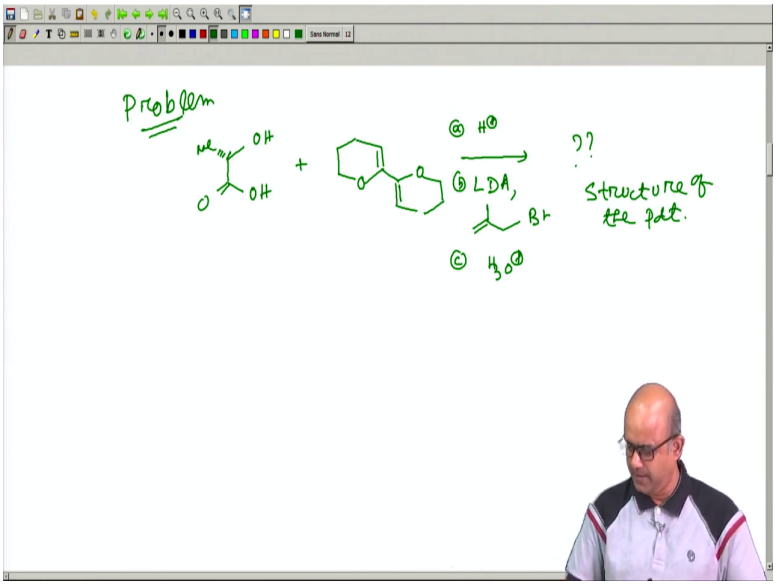


So, you can just try to give it as a try in your off time. So, you basically let me try to write a pretty general structure this lactic acid and you have this, you have this alpha hydroxy acid which is the lactic acid and you react with this bis dihydro pyran which just now we explained and once you try to condense these things you will basically get a compound fine.

So, initial step is you need H plus fine; next b is you need a base so, take LDA and I just try to write a compound which is an electrophile ok and then c is water hydrolysis. So, you need to predict what product is forming ok, structure of the compound. So, please just follow the model or follow the concept which was just now discussed to you in the earlier slide and I am sure you will be able to do it.

On the basis of similar kind of structure there is also another way which is a bit similar, but conceptually was almost same like this Ley's dispoke acetal, but this was based on a different kind of system which probably will now just give you a little bit explanation. So, one of this compound was used as a typical precursor of 1 ,2 glycol ok.

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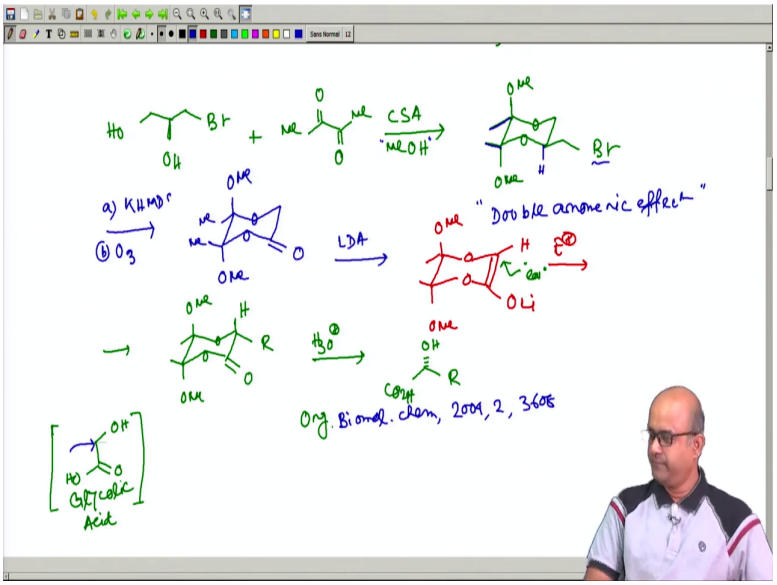


Now, this 1, 2 glycol was reacted with a 1 ,2 dicarbonyl compound this one to dicarbonyl compound and as all of us know that this glycol and 1, 2 dicarbonyl will initially form a acetyl type of compound we treat this reaction in presence of acid catalyst camphor sulfonic acid and methanol and we draw the compound structure in the three dimensional form by assuming a 6 member ring forms.

Basically so, this methyl let me draw the structure and then we will explain what is exactly happening ok. See, the parent compounds you have CH to Br this CH to Br ok OH OH OH OH. So, one edge is above the OH and this is the primary OH, now this is the ketone part Me M e CO CO, initially you get the OH which is later on converted to the corresponding methyl ether.

Now, in this case it was a double anomeric effect. I am sure all of us have quite familiar with the anomeric effect. Now, this double anomeric effect actually forces this methoxy group in the axial position which probably you can explain in terms of simple anomeric effect. So, this was the ground state conformation which seems to be pretty interesting.

Now, take this compound and you actually try to do some reaction. Now, what was done initially? Initially you treat this compound with a base potassium hexamethyldisilazide and then treat with ozone. So, initially what is happening? This potassium methyldisilazide there is a hydrogen ok, it undergoes simple 1,2 elimination creates a double bond and then that is the extract double bond is undergoing a oxidative cleavage with the this ozone.

Remaining part all of this compound remains same, now such systems is now can be also regarded as a extended form of Ley's dispoke acetal. Now, you see in the earlier case we have a cyclic THP, but here we do not have a cyclic THP. But still now what you can do? You can now treat a base like LDA ok.

So, what we will be getting? You will be definitely getting an enolate. Now, this enolate structure we can try to write as a planar structure O lithium and this is basically the hydrogen, most of the other part was there OMe, this OMe is axial due to the due to the typical anomeric effect.

Now fine, here also similar thing basically happening the equatorial approach the equatorial approach of electrophiles. So, now, you treat the electrophiles. So, for electrophile you can see that the equatorial approach is preferred ok, equatorial approach. So, obviously, as a cyclohexanone system so, equatorial approach seems to be much more preferred.

And then what that will lead to you? You can eventually try to write the compound that carbonyl has been regenerated, your R is now here, R is now here means this and you get this remaining part are all as it is and your methyl, methyl. Now, you can simply do a hydrolysis to generate a hydroxylated or alkylated alpha hydroxy acid.

Now, see what basically we did. We actually take a diol and we just try to use this 1, 2 di ketone compounds dicarbonyl compounds for generation of this particular cyclic structure and where actually this self-regeneration of stereo center was kind of applicable and you can start we can start from a non hydroxy acids to generate a hydroxy acid.

The main precursor of this carbonyl compound is basically this carbonyl compound. So, this is what? This is actually an equivalent of a glycolic acid. Glycolic acid structure is what? Glycolic acid structure is COOH CH2 OH. So, see this is the precursor of this enolate generation. So, this glycolic acid is the main factor here. So, glycolic acid could be the. So,

here what you did? You basically did an enolate generation of glycolic acid and then with this concept we put a substitution at this position.

This was reported in a well known journal again which is named as Organic Biomolecular Chemistry, it was published in year 2004, the volume is 2 and the page number is 30 3608. So, with such systems which have been widely explored for this SRS concept, now what I am trying to do?

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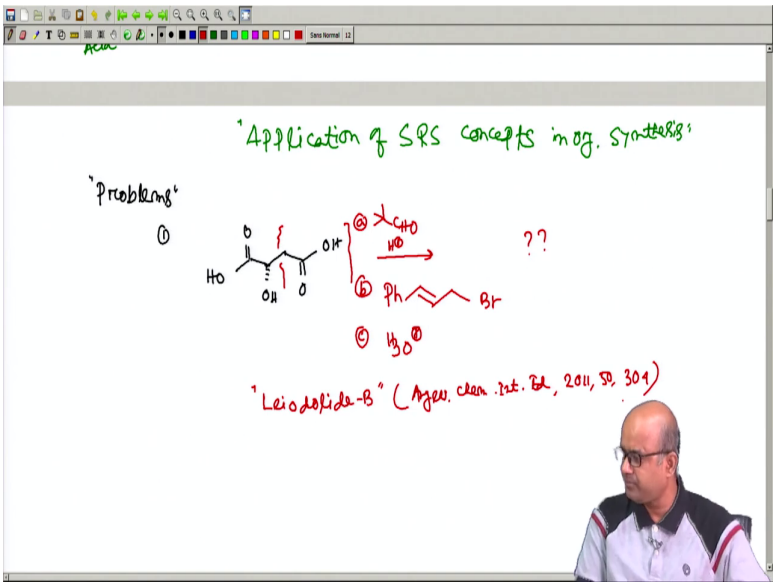


We will just try to explain a little bit of application of SRS concept. Application of SRS concept in organic synthesis means how we can apply such strategically important reaction in the field of organic synthesis and how different valuable intermediates or some biologically active natural product have been synthesized with the help of this strategy. So, in this case we will be basically trying to give you some of the problems which you might solve it. The concept was already talked about.

Let us say the first one we give it to you it is similar like which already we talked about, but in this case we take a different hydroxy acid which is malic acid which is not a lactic acid. Now in malic acid the basic thing is the difference is this part this particular part instead of the methyl we have a CH2 CO2 H. So, this compound we take, we react with tert butyl aldehyde or pivalaldehyde fine number in presence of H plus ok.

And then so, you can basically get the cis oxolane. The cis oxolane already we have talked about. So, this kind of oxolane actually you will be you will be getting ok. Now this oxolane once you get you will find that the two substitution of this oxolane will be in particular diequatorial which is the most important part in your initial assumption.

So, take this oxolane and then you have to react with some electrophile. So, this electrophile here now I will be giving to you what to the electrophile. So, see. So, electrophile; what electrophile I am now giving to you? I am giving it to a cinnamyl bromide ok. So, you need to predict the product and then finally, you cleave the oxolane $H_3O_+$.

So, one of such problem you can solve it and this kind of reaction was usually used for very recent days also and actually one such application was for the synthesis of a molecule named as Leiodolide B. Leiodolide B which is one of the intermediate has been synthesized by using this kind of SRS concept which was appeared in Angewandte Chemie very prestigious journal in the field of organic chemistry and as well as chemistry.

So, and this is kind of a recent one which is a kind of 10 years ago this work has been published ok. Such thing gives you a pretty good understanding that such concept was still applied.

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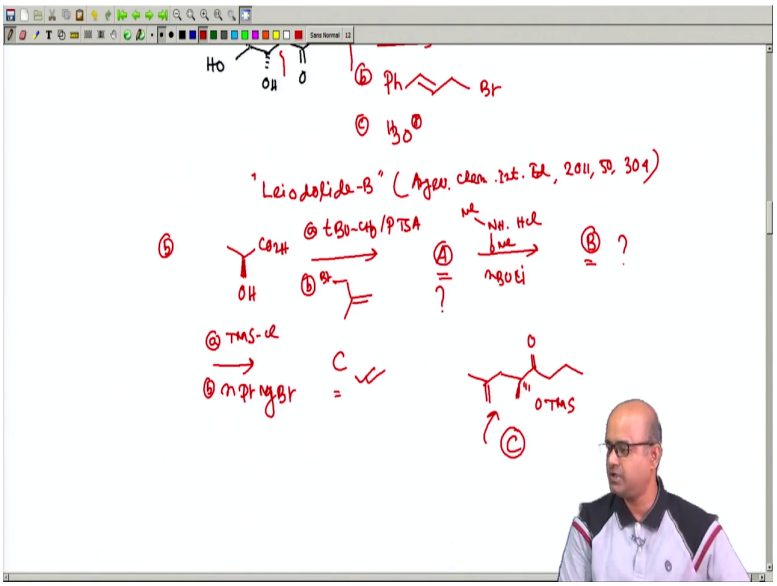


There will be another one which is seems to be pretty much straight forward. I will give you a compound like lactic acid which all of us know and this lactic acid will be now at the first

reaction we treating with tert butyl CHO as well as H plus as a source. So, para toluene sulfonic acid we will be using.

Number 2, we will be using a electrophile which is methallyl bromide ok; methallyl bromide ok. And now once we react this thing you get something called A ok. So, please write the structure A ok and then this A was treated with a different compound which is now all of us know it is basically called Weinreb amide. So, this amine salt Weinreb amine and in presence of little bit of base, so, you get n butyl lithium, you get another compound B.

Now, this Weinreb amine was basically used to cleave the dioxolane which earlier we used to cleave by acid, but here you can cleave by different other reagents Weinreb amide. And the moment you get the Weinreb amide, you treat this Weinreb amide with two different other reagents; one is the first TMS chloride followed by n propyl magnesium bromide n propyl magnesium bromide. So, please try to predict the structure of this all A, B and C.

So, these things will basically give you a quite good idea. So, the final structure I can just give it to you that what could be the final structure which might be helpful. So, final structure I will just write it down. You can eventually take a note of the thing. It will be OTMS, it will be C double bond O, it will be n propyl. So, this is the structure of the C ok, C structure is this. So, A structure you have to predict and B structure you have to predict.

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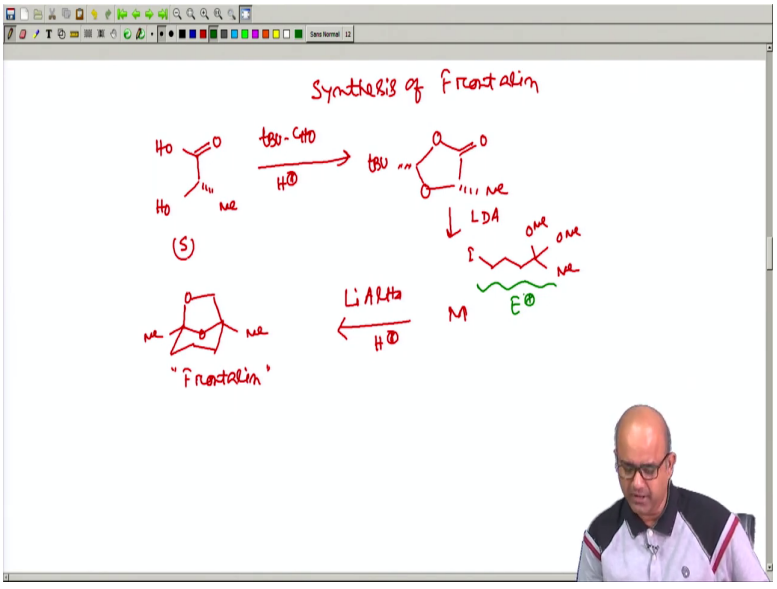

So, please try to do it and in other case we will be; I will just try to close with another thing which is synthesis of frontalin, which is one of the pretty nice application of this SRS strategy in this way. Now, synthesis of frontalin, which is a pheromone which was secreted by frontal gland of some mammalian species.

Now, lactic acid was used as a starting precursor which is S lactic acid and then this lactic acid was treated with as usual this pivalaldehyde tert butyl CHOH plus. So, you know what you get. So, you basically you will be getting this cis compound, let me write first. This cis compound you will get. So, methyl is cis here and this tert butyl is cis here. So, this kind of dioxolane you get.

Now, fine and next there is an electrophile was very judiciously chosen and first you treat with LDA and then the electrophile. I draw the structure of the electrophile; a iodo iodo iodo three carbon is there; 1 2 3 and then you will find that let us say di acetal of this compound ok. So, this is the iodo compound. So, you will be getting a compound let us say name a; M ok and this place you can easily try to do it ok.

And then finally, this a M if you treat with lithium aluminium hydride followed by H plus you get a compound whose structure I am just try to write whose name is frontalin. Frontalin is a natural product which have been isolated as I said from the frontal gland of some mammalian species. Now, see the structure of the frontalin was having this structure. So, you have to basically explain how this product is forming ok. So, you get frontalin as a main product.

This you can eventually you can explain it. So, first treat this one as the electrophile; so, this one as the electrophile. The stereochemistry tert butyl so, it will be opposite attack ok and then lithium aluminum hydride means the lactin will be cleaved ok. So, this is all for today. In the subsequent class we will be talking about a few more application of SRS derived different systems and its application.

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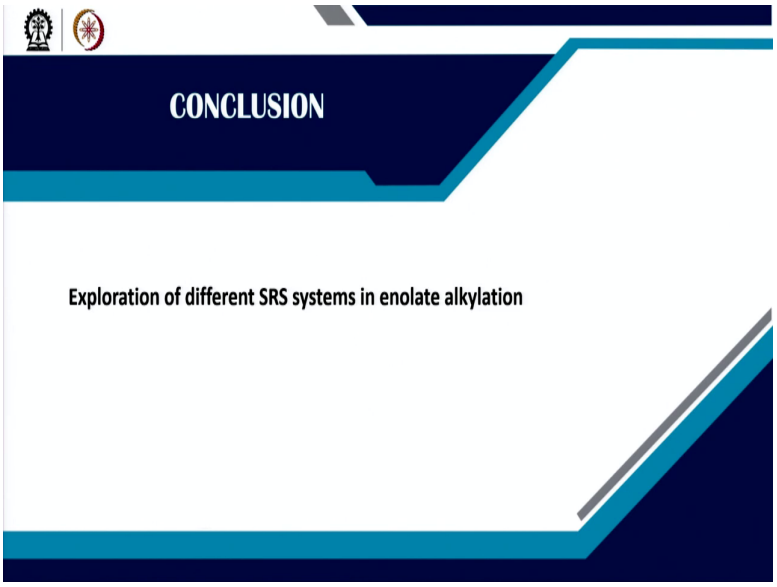


So, as a concluding remark you can see that SRS system plays a very important role in the field of asymmetric organic synthesis and actually this SRS system is so powerful that you can create new stereogenic center depending on your choice. And you can manipulate the functional group inter conversion in such a way that depending on your desired target you can control the outcome of the reaction.

So, thank you very much. We will see you in the next class.