A Study Guide in Organic Retrosynthesis: Problem Solving Approach.

Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture – 59
Synthon Concept Revisited

Welcome back students, so today I will be trying to give you something different which probably we have talked it, but not in detail we are trying to discuss synthetic equivalents.

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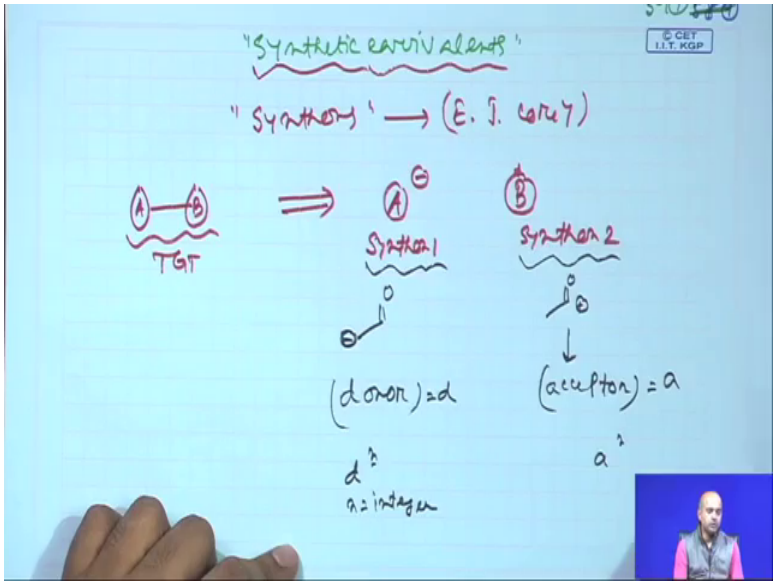

So, synthetic equivalents as I discussed earlier sometimes also referred as synthons. Now synthon the term first invented by Professor E. J. Corey who is also the principle fellow who first coined this term retrosynthesis.

Now, now Professor Corey's definition for this synthons says that, if you having a particular 2 different unit, as your target molecule you can simply do a disconnection based on a A minus and B plus just by simply polarite polarite addition and you may can make a new bond. Now this A minus can be called as a synthon 1 and B plus can be called as a synthon 2. Now this synthon concept probably is very well known established earlier, but the terminology synthon nowadays are no longer used its kind of a backdated.

Now, synthon probably the, you can simply say that your carbon ion is a synthon, your acyl cation in the fedex cup reaction is a synthon. So, this reactions we already known earlier, but from this view point you probably have been discussed. Now you will find that if you having a negative charge on your synthon, this synthons are normally termed as a donor, donor synthon or d.

And if you have a positive charge means that, which can act as acceptor, which can accept electron it will be termed as a acceptor. So, donor is basically stands for d and acceptor stands for a. Now depending on the number of carbon, this donor part is having it is abbreviated as d n and this is also a n. So, n could be a integer n could be a integer.

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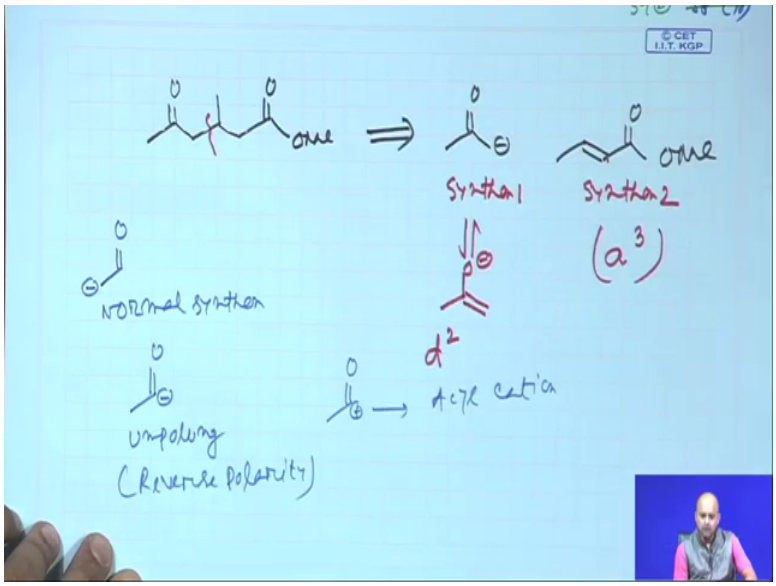

So, d n and a n is usually the terminological definition probably the of a very classic example from synthetic equivalent disconnection or synthetic or synthon concept in terms of retrosynthetic analysis will be visible from this particular example, where you say that if you having a this particular anion and this particular acceptor. Now, I am saying this one is a synthon 1, so you basically do a disconnection there and this is your synthon 2. Now this one is very stable this is basically a enolate anion and this is your michel acceptor. So, this is normally this is termed as a d synthon.

So, you can call it d 2, so it is 2 carbon or you can need to and this is basically your acceptor system, just write acceptor the number of carbon if you can count this 1 2 3 probably this 3 is basically involved remaining part you can just exclusive it could be a

3. So, this way you can basically do the a retro based on donor synthon as well as acceptor synthon. And we have earlier explained that if you having a electron withdrawing group this one this kind of synthons are normal synthons because this negative charge can easily be stabilized. So, this is called normal synthon where the polarity remains same.

So, now if you having a synthon something like this, where the negative charge decides on carbon, carbon. Now normally carbon do not prefer this kind of charge it always prefers a this charge because oxygen is more (Refer Time: 04:58). So, this kind of synthons probably you all of you know is referred as umpolung synthon, or reverse polarity were the polarity has been reverse. And this is your acyl cation which probably you have earlier came across in the (Refer Time: 05:23) reaction.

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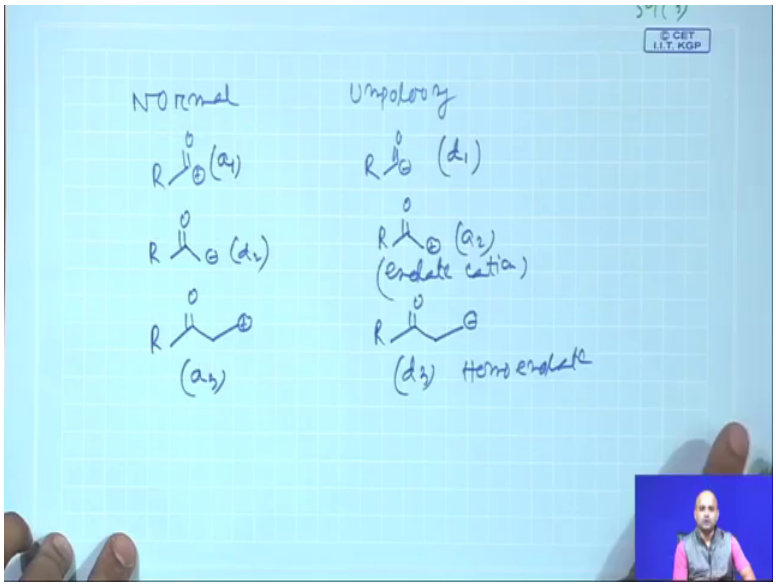

So, in these way you can basically categorize several synthons normal and umpolung synthon. Now, as you said synthons are usually not commercially available you know to prepare them in the lab. So, I am saying acyl cation is a normal synthon, but if you having a acyl anion which is umpolung. Now acyl cation is referred as a 1 and umpolung acyl anion is referred as a d 1.

Now next your enolate, enolate is absolutely known is a normal because a charge can be stabilized, but if you have a synthon like this which we called enolate cation. Now enolate cation is absolutely not stable species. So, is a umpolung there are very few

examples we are not going to talk about this enolate, enolate cation. Now you just change on the simple polarity, you will you can basically create different kind of synthetic equivalents. So, this is your a 3 and this is a homoenolate cation, so normally, normally carbon prefers plus minus plus. So, basically charge reverse is in this way plus then minus enolate then plus then minus.

So, in this case it will be a d 3 it is called homo enolate. So, this is just basically terminological disconnection where not going to talk in detail how these species are generated because this is beyond of our scope, now what I am trying to do, I will try to do some retro based on some target molecule then I will find how several synthetic equivalents are basically helpful and how this synthetic equivalents or synthons can be easily generated.

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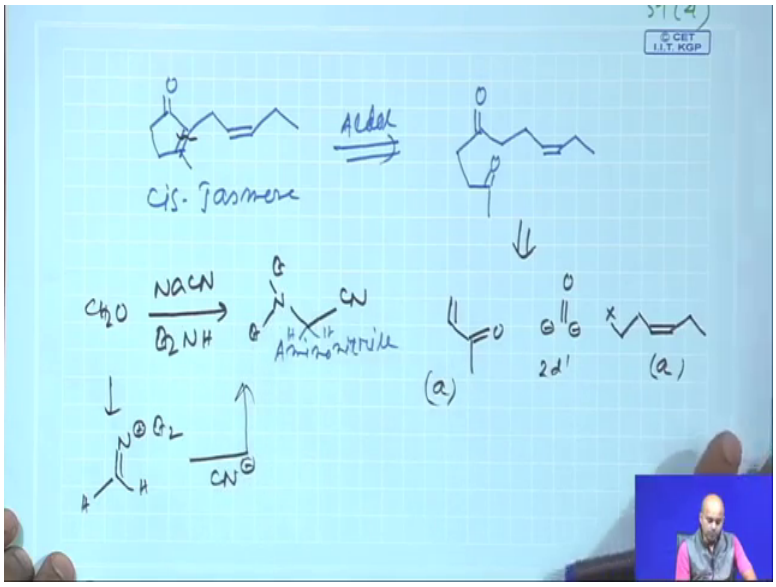

I am giving you a target molecule cis jasmine cis jasmone I will be doing a very standard retro because we do not have much time. So, if you do a standard retro through aldol transformation you will find that you basically needing a this compound this ok.

So, just basically need a aldol retro to make this molecule cis jasmone was used in the perfume industry, next what I am saying that if you can have a a synthon something like this synthon. So, what I am saying that now if you, if you visualize that this particular central carbon act as a d 1 umpolung, d 1 umpolung. So, is basically 2 d 1 umpolung and then you react with a alkyl alloy at this end you get this 1 and here you do a mickel type

of reaction with methyl vinyl ketone. So, this is your acceptor synthon, acceptor synthon this is your donor this is also acceptor synthon. So, 1 synthon having 2 donor side, so which can react with the 1 acceptor in the left hand, 1 acceptor with the right hand

Now, this kind of 2 d 1 synthon is already known as a formaldehyde 1 3 diethiane now here we will try to disclose some other synthon. If you have formaldehyde you react with sodium cyanide and react with E T 2 N H you basically get a compound named as amino nitrile N E T, N E T how you get you basically react first, formaldehyde with diethyl amine you basically get this amine then your cyanide attacks in the ammonium carbon. So, nucleophilic fashions you get this compound.

Now, this amino nitrile this amino nitrile is also acting as a d 1 synthon how the hydrogens attached to it or extremely acidic because you have a cyano you have electron withdrawn nitrogen continuing group. So, now, we will now try to visualize how this amino nitrile.

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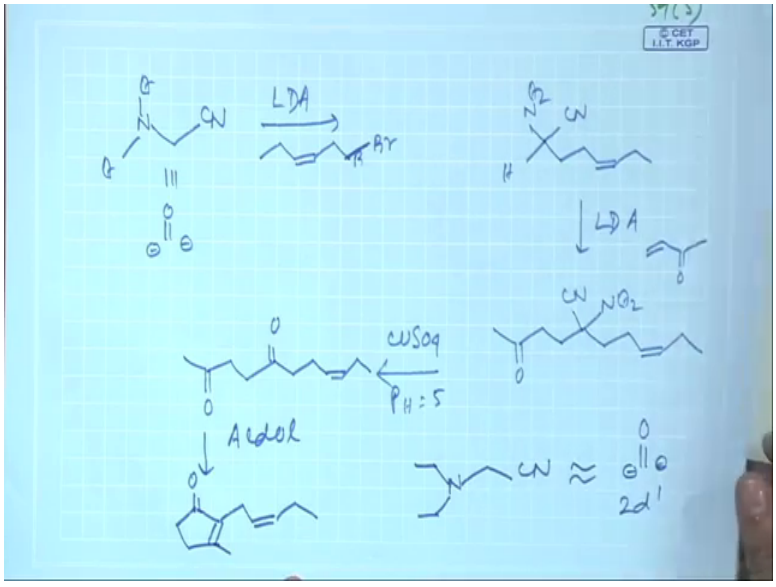

So, N E T E T C H 2 C N first I am reacting with L D A, I am saying that this compound is acting as your 2 D 1 synthon. So, L D A and the first acceptor synthon I am putting a bromo here, sorry 1 carbon extra, 1 carbon extra bromo then you see that NET 2 remains similar, C N similar 1 hydrogen is abstracted and you basically get this compound, fine next another round of base abstracted this hydrogen and then you react with another acceptor which is the methyl vinyl ketone.

So, you will basically get next you need to generate the carbonyl compound by simply doing a hydrolysis with copper sulphate, in a acidic medium. Now this hydrolysis was pretty obvious initially actually this copper sulphate and acidic P H first attack this amine to give you the O H here and then basically this is basically converted to a cyano hydrine, which then which then undergoing H in elimination to give you the parent carbonyl compound, we will get this compound.

So, which is our desired compound you do the aldol and you can end up with the target molecule cis jasmone. So, what we now formulate in this entire synthesis if you having a diethyl amino nitrile which can be visualized as a 2 2 d 1 species is a very unique reaction to to convert the synthesis. Now, same compound is this particular jasmine.

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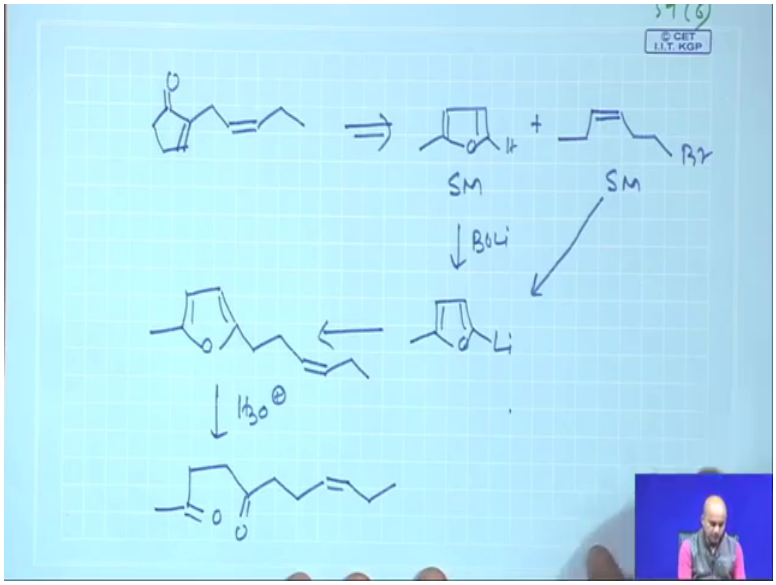

The cis jasmone, now I am saying that this compound you can also make through a or you can easily synthesize through a another class of starting material. And here what I am saying that you can make this compound through this starting material as well as this starting material. Now if you now try to analyse this retro in earlier sense will have this starting material now this starting material, if you react with butyl lithium the feuron basically this acidic hydrogen was first removed and give a lithiarade species.

Now this (Refer Time: 13:46) species this one basically react, to give you a C H 2, C H 2, C H 2 double bond this things. Now feuron compounds can easily be opened up to a 1 fold dicarbonyl compound, just by acquas hydrolysis and then you will find that you

basically get this 1 4 dicarbonyl compound. Now this this dicarbonyl compound now you are basically, basically visualizing the entire, entire concept in term of synthetic equivalents in this way in this way, so a saying that a properly substituted feuron which is.

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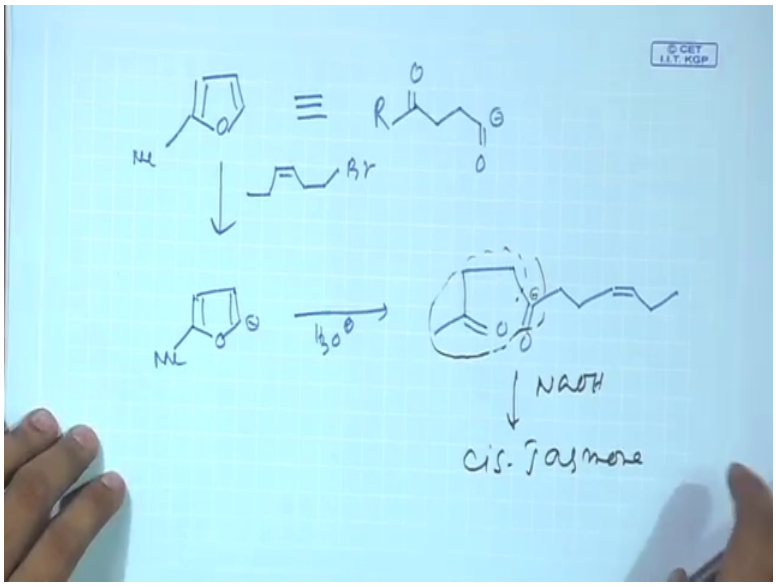

Basically these methyl can act as a R C double bond O C H 2 C H 2 C double bond O minus. Now this is also umpolung, but it is a umpolung the number of carbon has been basically intriched now what we say we said that it this feuron we are reacting with this electrophile whose electrophile structure we have already given, the feuron initially was reacted with a butyl lithium and you get this minus and this methyl, now this minus is actually visualized as this M E C O, M E C O, C H 2, C H 2 C O minus C O minus.

So, once you do this reaction and after hydrolysis you basically get the product which is require for your jasmone synthesis. Now see the feuron part is basically giving you M E C O, C H 2, C H 2, C O minus this minus and then you are approaching the electrophile. Now this one by similar way if you do a aldol reaction it will give you cis jasmone, cis jasmone structure was already discussed you in the earlier slide in similar way you can basically basically carry out many synthetic experiences.

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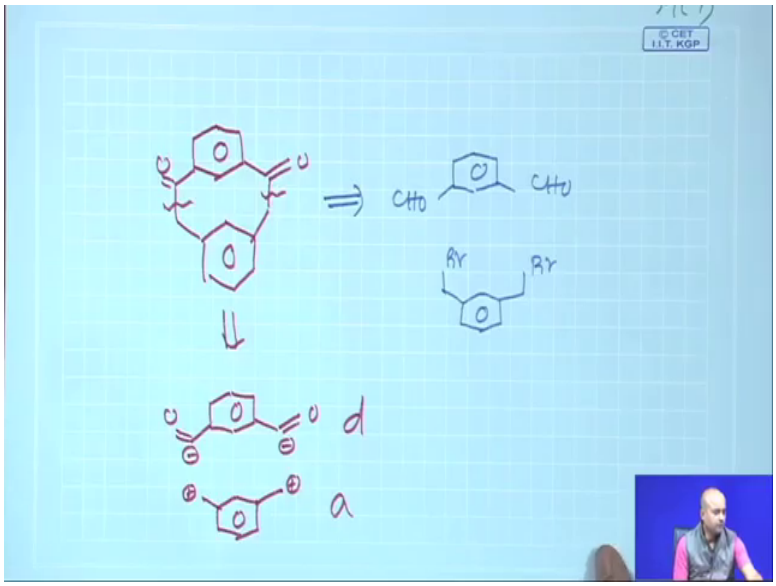

So, synthetic exercises let is try to figure it out very simple synthetic equivalents, so how you can make this compound, now, if you see this compound can be easily made if you having a this particular dialdehyde and this as a electrophile. So, what you need to do you basically cut here cut here and visualize as a C O minus C O minus, now this C O minus basically will be now reacting with this.

So, this is basically donor synthon this donor synthon will be now reacting with a this acceptor and this acceptor, which you have explained chorest terminology donor synthon donor acceptor. So, in similar way you can basically basically do the couple of exercises a similar kind of exercises now I am be doing.

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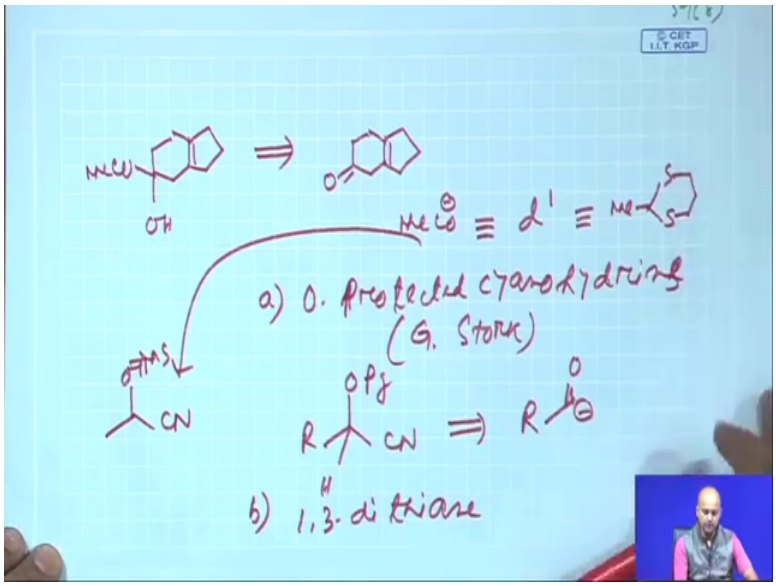

I am saying you are given a target molecule whose structure is this the starting material is which was given to you is this ok. So, what you basically need you just need a M E C O minus as a donor species.

Now, this donor is a basically umpolung I remember earlier we have also discussed this kind of umpolung you can also synthesize through O protected cyanohydrin the chemistry which was a first discovered by professor gilbert stork, O protected cyanohydrin go back to your earlier lecture O protected cyanohydrins professor gilbert stork was the instrumental for this reaction, where I said that if you having a O protected cyanohydrin you can easily abstract this hydrogen and that can basically give you a very nice umpolung species.

So, in principle 1 3 diethiane, 1 3 diethiane definitely you can use 1 3 diethiane chemistry you can also use this O protected cyanohydrin chemistry as this type of so this is simple things. So, now, how you can basically generated if you can take this compound as your starting material the reaction is simple in addition also you can take this compound O T M S cyanide it basically O protected cyanide. So, both the chemistry you can easily do and try to remember in our biological system also this kind of umpolung chemistry was often very much in action.

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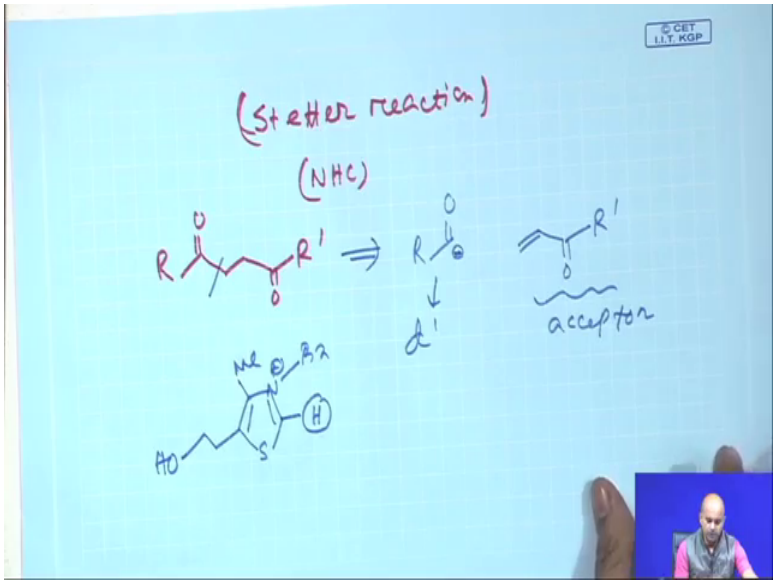

In our biological system this kind of intermediate was very much in action in particularly we have also discussed a stetter reaction earlier stetter reaction earlier, we say that stetter reaction is a synthetically very useful reaction, which which is basically catalyzed by N A 2 cycle carbon chemistry or N A cycle carbon and if you now try to do a simple disconnection of molecule like this 1 4 dicarbonyl compound you can easily do the disconnection followed by this you can say that this is a your donor this is your acceptor.

So, basically a mickel version of reaction, but where you use a umpolung nucleophile through a donor species and this is your acceptor synthon. And this is in principle named as stetter reaction where we use the N A 2 cycle carbon a standard N A 2 cycle carbon structure I am now drawing it here which is basically if you remember the mechanism of benzoin condensation a similar kind of mechanism and this is 1 heterocycle carbon, where this particular hydrogen is the key factor of for its main activity stetter reaction mechanism.

We are not going to discuss in detail we already have it we already did discussed the mechanism earlier. Now what I am trying to do I will analyse a similar kind of synthetic equivalents now here I will give a target molecule.

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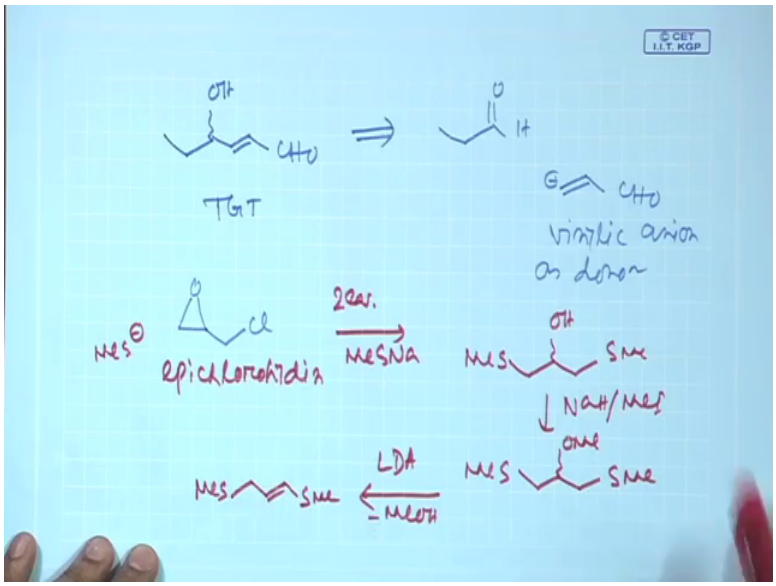

I am saying I am giving you target molecule is alpha beta unsaturated aldehyde, now the starting material which was given to you a simple propanaldehyde. So, in terms of synthetic equivalents if you have to do the disconnection what basically you need you need a this kind of vinylic anion as your donor species, vinylic anion as donor its definitely difficult to visualize, but this was first reported by professor Corey in this way if first take this compound, whose name is epichlorohydin epichlorohydin react with 2 equivalent of M E S N A methyn thiole its sodium salt.

So, initially epoxyte opening will takes place by M E S minus M E S minus as well as S N 2 with this C l. So, you will basically get M E S epoxyte opening will give you the alcohol and this S M E, then free hydroxyl was protected as a sodium hydride and methyl iodide.

Now, this reaction was give you this methoxy protected ether, then L D A was used as a reagent to facilitate 1 equivalent of methanol elimination from this O M E N H. Now this elimination basically gave you a alyl phenyl sulphide, alyl phenyl sulphide, now here if you react this alyl phenyl sulphide with 1 equivalent of base then you see how this reaction takes place.

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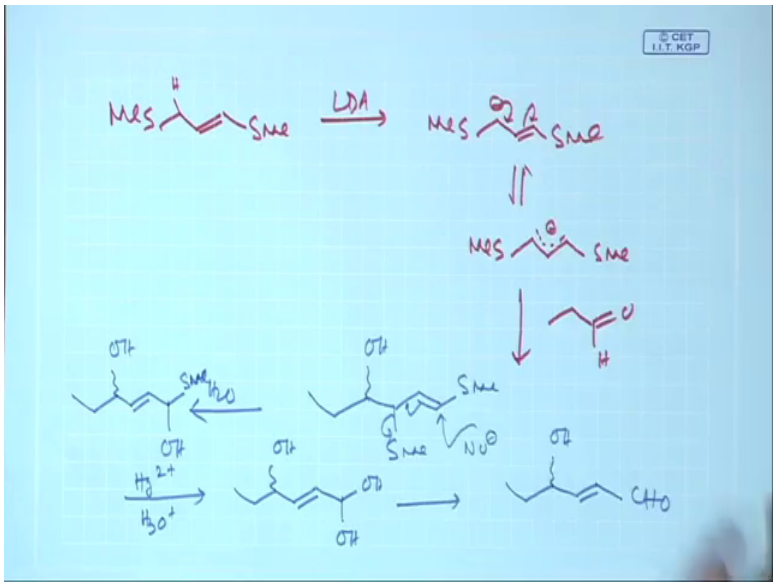

So, you have a alyl this and vinyl you react with a base initially this hydrogen will be abstracted and will basically getting this carbon ion. Now this carbon ion is stabilised to give you a canonical structure or symmetrical structure. So, this is very much stable carbonium ion symmetrical carbonium ion now this things was reacted with this your N proponal.

So, N propanal reacts and the initially what you get you get this O H you get this S M E, and S M E fine. Now eventually a water molecule was reacted here and is found at this nucleophile philic water initially coming attacking to this vinyl sulphide, to undergoing this kind of elimination and then after this elimination you basically get this S M E and O H, now this is what this is basically a thioacetal this a thiol is there and a O H is there.

So, now, you simply deprotect this thiol with H g 2 plus followed by aquas work up you will get O H O H and this compound is simple is a acetal which will instantly opened it up and will give you the required compound. So, in the whole process, so you can basically, basically formulate this initial compound which have been synthesized this alyl vinyl sulphide was the equivalent of this vinylic aldehyde, vinylic aldehyde.

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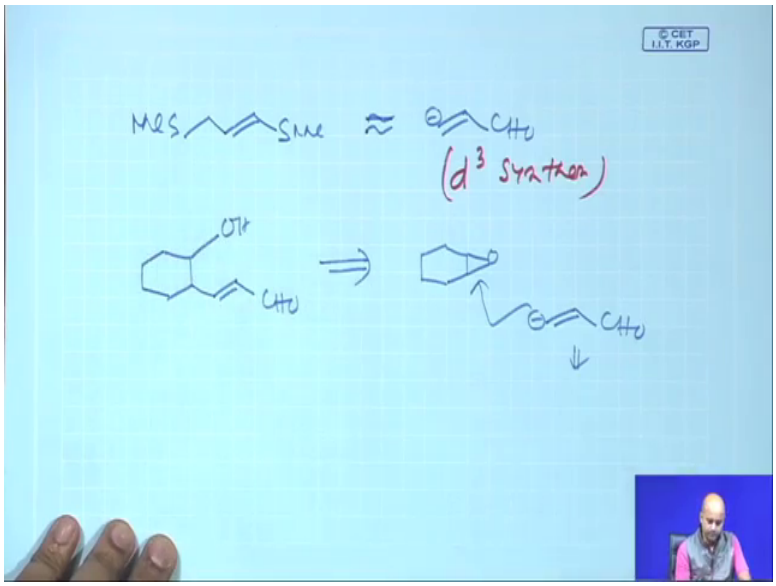

So, whole process was basically it was acting as a d 3 kind of synthon sorry d 3 kind of synthon definitely and this is a donor species, donor synthon reacting with a acceptor synthon in principle this particular synthon was used in many many synthetic synthetic problems probably I will give you the next problem, which is based on something like this what I am saying that how you can make this compound.

Now if you visualize is a target molecule or you then you do the simple retro if you have epoxyte as a electrophile you react with this vinylic anion it can open up and will give you this compound, now this you can easily prepare as mentioned earlier. So, this is this is very simple you can do it very straight forward way.

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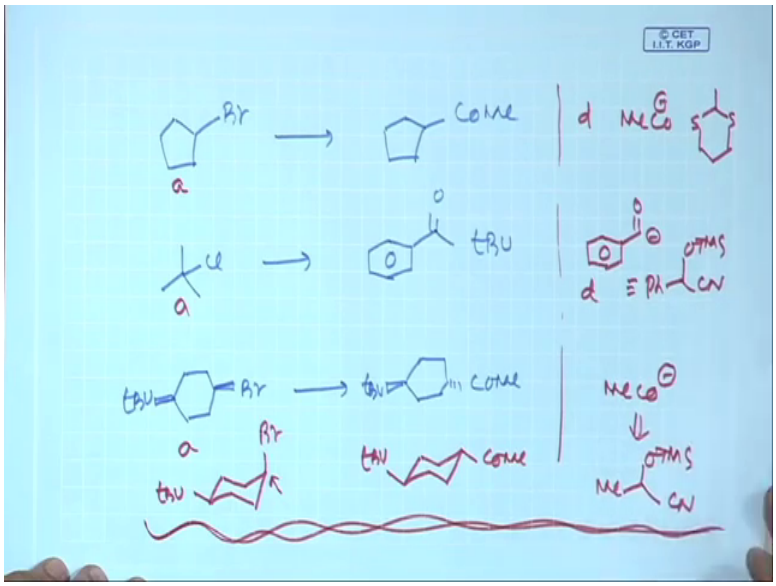

We will try to conclude by using couple of interesting problems I will just give it you and lest see how you can analyse or you can solve the first one is simple, the second one I am giving you a this 1. So, third one a tertiary butyl and the bromide which has been converted to corresponding t b u c o m e. Now if you analyse all the problem all the problems are basically based on synthetic equivalents.

So, you can simply think of that is in this case if you have a m e co minus you can do a umpolung type of alkylation in particular this case the electrophile is here. So, all this case this as this compounds are basically acceptor acceptor, acceptor. So, this is your donor in this case your donor should be something like this donor and in this case your donor will be again the same m e c o minus, m e c o minus. Now in third case you have to look about the stereochemistry the starting compound is tertiary butyl the cis compound ok.

Now, final product which was given is a trans that is obvious because as a doing S N 2 reaction of this m e c o minus it always attack from the back side attack S N 2. So, you get this c o m e now what is the source of this m e c o minus you can easily use this 1 3 diethiane chemistry, optic this acetaldehyde thiol protected or even you can use this as a stork O as O protected cyanohydrin this also you can use this one is very useful this one you can use the stork O protected cyanohydrin, by using this corresponding o t m s c n, and here tertiary butyl chloride which is sterically bulky and was used as a electrophile

the reaction basically goes well you have probably need to do a little bit refluxing or you need to put a thermal energy. So, all this particular transformation you can easily accomplish easily, easily accomplish with the help of your synthetic equivalents.

So, synthetic equivalents there are there are many things to be discussed, but definitely as we do not have a enough time we will try to provide you few assignments, which you can solve based on this information which you shared in the class and in the final lecture which will be which will be giving to you next we will try to provide you a complete story or try to basically summarize you.

So, what will I have to do I will pick up a natural product and the strategies which you have discussed till today starting from transformation substrate functional group as well as topology and stereochemistry? If it is possible normally stereochemistry we tried to avoid because stereo chemical strategies often need a very complex molecule and if you have a if you have a relatively complex molecule then explanation of this stereo chemical strategies will be much more beneficial.

So, eventually in the final lecture we will try to give you a gist over all gist by taking as a taking a medium size molecule as a target molecule and we will try to correlate till today what we have discussed we will try to basically summarize here, so have a good time till then good bye.