A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 51
Topological Strategies

Welcome back students. So, we are basically discussing topological based strategies or topology guided strategies and we have the discussed few case studies that how topological indistinct molecules are mainly a target molecule when you have multiple cyclic rings is there in the structure and sometimes cycling rings are very complex.

You have a like linearly few cyclic rings, angularly few cyclic rings. And we have basically instructed that try to follow few normal guidelines whenever you are dealing with the topological destruct molecules.

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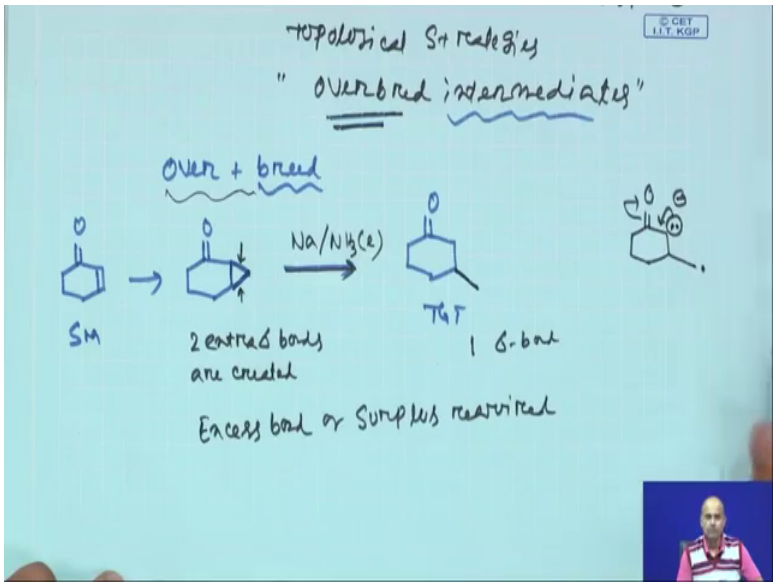

So, in this particular context will be today discussing a particular focused topics which is named as overbred intermediates. Now, overbred bear intermediates, this particular strategy or this particular concept was used for long time in the field of our synthesis, but particularly this terminology overbred was given very recently. Now, this basically means that over breed, breed basically you are creating excess thing which is not required.

Now, probably this whole concept will be quite clear if I give you a transformation something like this. I am saying that, I need to make this molecule starting from this molecule and I said you a pre requisite, do not use the Gilman reagent ok. So, now in those cases, if you are trying to use the Gilman region which is a straightforward case is restricted.

So, what people are suggesting you first create a cyclopropane ring to this double bond. So, you are basically adding extra carbon, but you are creating two new bonds. You are creating two new bonds; this one as well as the one. So, means that two extra sigma bonds, you are creating. Two extra sigma bonds are created. Now, is in the target molecule, you do not need that. You basically need one sigma bond. So, means that throughout the synthetic pathway or this final stage, you need to clip one extra bond.

Now, you may ask that if we require only one sigma bond, why you are creating sigma bond? Now this is basically the concept of overbred, you are creating extra bond or excess bonds or surplus bond. So, excess bond or surplus bond which is not required for your target molecule by initial looking, initial looking. Now we say that we will be doing a reductive cleavage through a sodium and liquid ammonia.

Now, this reaction we have already explained; this reaction basically goes through a single electron transfer pathway. You basically have a radical or this radical here which is the radical is basically quenched out, give you a negative charge and this negative charge is exceptionally stable which can be easily analyzed and then you basically. So, mainly this extra bond which is not required, we are basically cleaning it but initial visualization that you have to create extra bond.

So, this particular overbred strategy sometimes was very useful, sometimes very useful. Now, if I say that this overbred concept I am discussing at this moment to you, but some reactions involving the over intermediate was already discussed to you in this particular forum; will you agree or not?

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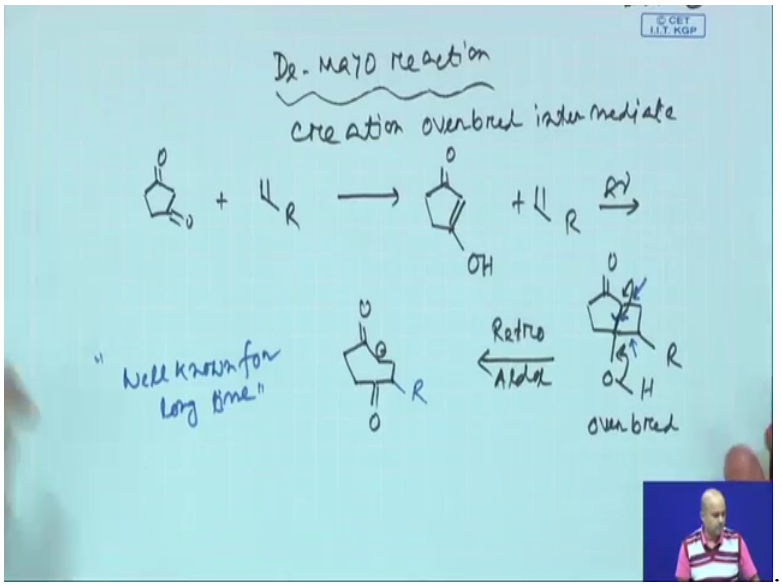

I am saying that this particular reaction De Mayo reaction; this principally basically nothing but a creation of a overbred intermediate.

Now, if you remember the De Mayo reaction which you have discussed very frequently or very often during our whole course of discussion, creation of overhead intermediate through De Mayo reaction. Now, De Mayo reaction, what is that? We said that De Mayo reaction is basically reaction of a 1, 3 diketone plus a olefin.

Now, initially we says that 1, 3 diketone basically will analyze to give you this compound and then the olefin reacts under photochemical fashion to give you a 2 plus 2 photocycloaddact. Now this photocycloaddact, eventually is nothing but a overweight intermediate because this ring is now strained. Now, as I said, now this overbred intermediate will tend to open it up through a Retro Aldol pathway. A Retro Aldol pathway, basically it will open up in this way.

It will only open up in this way because that will give you the stable carbonium ion, sorry carbon anion minus here and then double bond O. So, now, the newly created ring is 7 membered ring. So, this is your overbred. So, basically these two extra sigma bond, these two extra sigma bond you have created. Fine. This sigma bond is earlier there, now what you are doing.

In this case, you created two sigma bond and then you are cleaving the earlier sigma bond which was present in the molecule and this was the main concept of overbred intermediate which was basically well known for long time. I am saying that well known for long time, well known for long time or you have been practicing it for long time but this terminology was very recently given, very recently given.

So, whatever intermediate was basically in principle.

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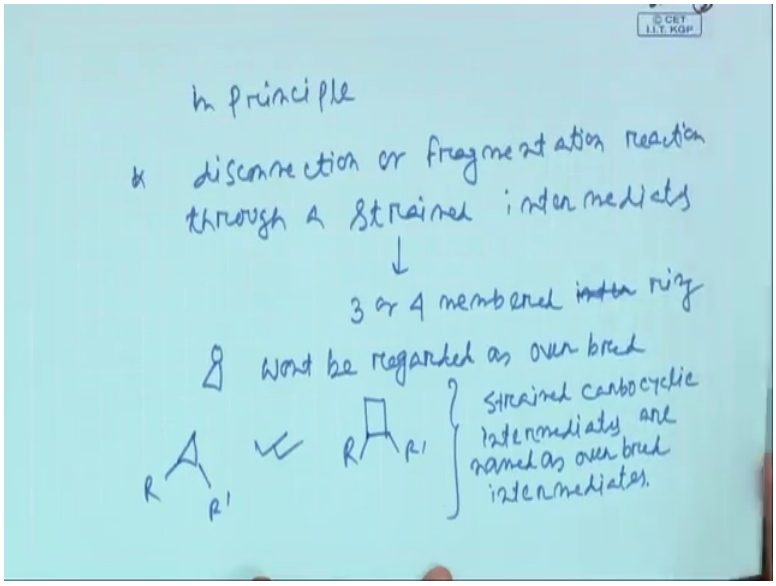

In principle, what exactly it is; is basically a disconnection or fragmentation, is basically a fragmentation kind of reaction; fragmentation reaction through a, through a strained intermediate, strained intermediate. In usual cases, the overbred intermediates are normally 3 member or 4 member intermediate, 3 or 4 member intermediates are usually regarded as strain intermediate; 3 member and 4 membered intermediates or 4 membered rings.

Now epoxide, would not be regarded as a over bred intermediate. Epoxide is normally quite stable and epoxide basically can easily be opened up by nucleophiles. So, epoxide would not be regarded as a would not be regarded as a overbred, regarded as overbred but if you have a cyclopropane ; like this kind of cyclopropane.

If you have cyclobutane, cyclobutane they will be regarded as a overbred intermediate and in addition if you have some extra loops which will basically facilitates the ring

opening, these are also very useful, useful guidelines. So, usually we always say that a strained carbocyclic intermediate, strained carbocyclic means the ring contains all the carbon; strained carbocyclic intermediates intermediates are named as overbred intermediates; named as overbred intermediates.

So, this particular disconnections are basically little bit out of the track means you are creating extra bonds and then in reality you may not require all those extra bonds. Probably, we will give a schematic view.

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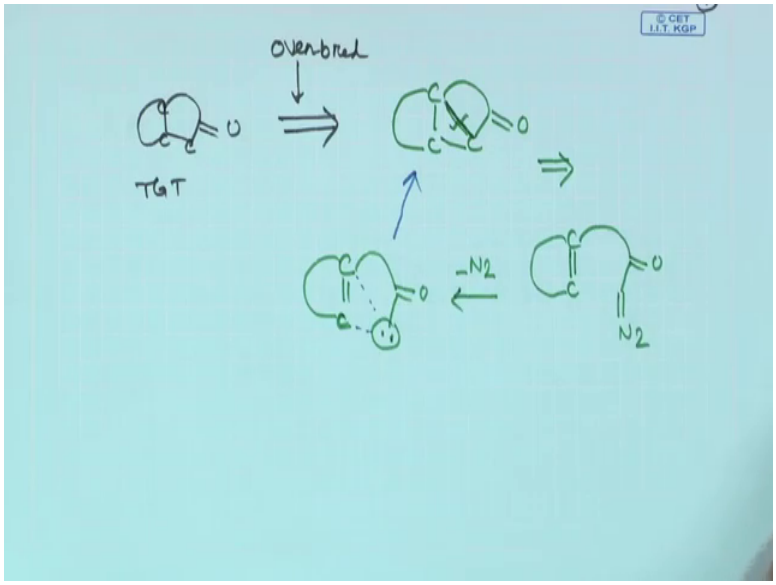

We say this is a and then I am saying that, let us say you are having this particular compound is a carbon, carbon, carbon, the ring structure ok.

Now, I am saying that this is your target molecule. So, in normal, normal scenario you can have other standard FGIs but if you are trying to use a overbred concept, a overbred concept, what I recommend or what I suggest that probably you do a disconnection first this and then you put carbon, then you put C, double bond O to first make this bond.

So, this is your initial bond or initial strain intermediate. Now, this introverted is a 3 member intermediate. So, this bond is not required in the target but if you now clip this bond, you will get this target. Now, 3 member ring was often not easy to make, but there are certain reactions which will allow you to make the 3 membered ring. One of such reaction probably all of you know is the carbine addition to a double bond.

So, if you have some compound like this, a Diazo carbine; remember in last class we talked about Regitz Diazo transfer. So, this is similar kind of reaction. So in reality, what this reaction will be given to you. It basically give you a acyl carbene by elimination of a nitrogen. So, you basically get the acyl carbene. Now these acyl carbene will undergo 2 plus 1 cyclo addition.

So, this and this to give you this product and then this intermediate is now reductively cleaved, reductively cleaved to give you this target. So, this is say demonstration how this overall intermediate can be used as a similarly you can have a another target.

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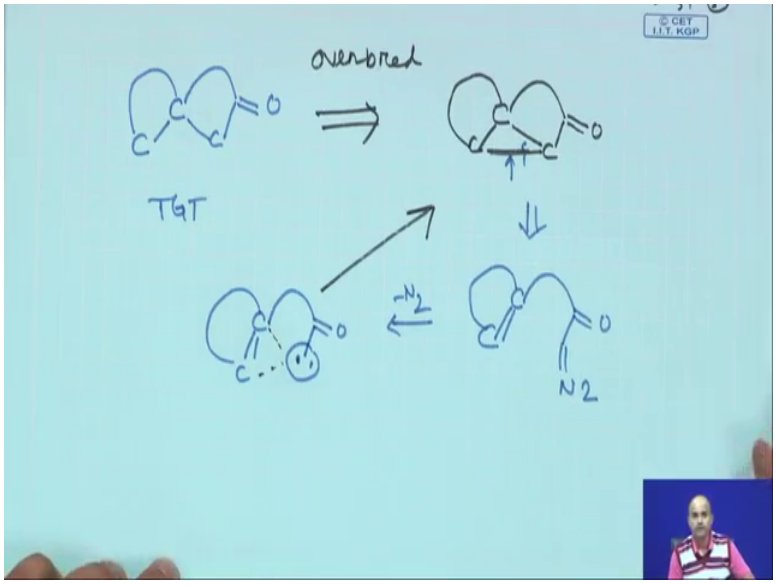

I am just giving you a schematic view and I say this compound is basically having this structure. It is kind of a spiro cycle structure ok, spiro cycle structure.

Now, I am saying that, if you have to apply a concept of overbred, you first do the disconnection just by joining this carbon with this carbon and how the intermediate now looks like this and this. So, basically you now make the new bond here, new sigma bond here through this cycle propane or carbo cyclic strain intermediate. So, this is your overbred.

Now, in forward pathway, you basically clip this cyclopropane ring to get your target molecule. Now the how this acyclic compound you can gate. You now do a this 2 plus 1 acyl diazo cyclo addition which is basically will give you this kind of intermediate. So,

you can generate acyl carbene here and then it will basically undergo the 2 plus 1 cyclo addition. So, you shine light double bond C and then double bond O, you get this acyl carbene which is now undergoing 2 plus 1 cyclo addition to give you this cyclopropane.

So in principle, this acyclic carbene chemistry and the survivor intermediate was known very long ago and probably the people are using it also but they are not giving this terminology. Recently they have given this particular terminology which seems to be very useful.

In order to do, we would not spend much time I just speak particular one example for a target molecule and then I will see how this overhead intermediate concept was nicely demonstrated or the intermediate target molecule which I am now going to discuss to you is a very interesting molecule and a structure is also very interesting.

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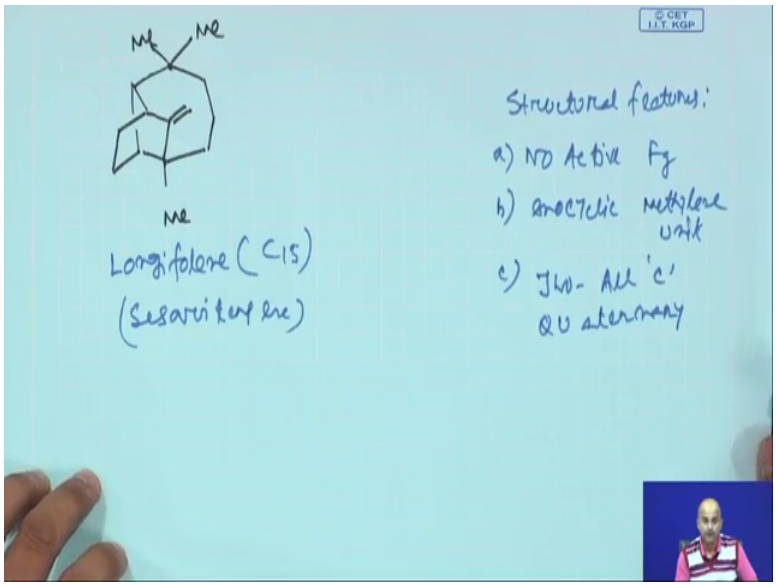

The structure is having very unique topological features and this molecule having this structure. This molecule name is Longifolene, Longifolene. You count the carbon is C 15. Carbon framework is a basically sesquiterpene is a natural product having some biological activity. Now, Longifolene and if you see it is structural features whenever you try to get a target molecule, you first analyze it is structural features.

Longifolene there are absolutely no active functional group, no active functional group, no active Fg ok. There is only one exocyclic methylene group, exocyclic methylene unit,

methylene unit ok. Then, it is having one and two, two all carbon quaternary carbon, all carbon quaternary means fully substituted with carbon containing center and then the topology is very interesting. You have a 6 member ring from the bridge, it gives you another 7 membered ring which is connected to this part.

So, there is a bridge cyclohexane and then from the bridge, it was there. Now actually this was the one of the on the classic molecule, this Longifolene which attracted the attention of synthetic organic chemist for a long time and there are there are a few nice synthesis reported in the literature for particularly this molecule which gives a nice demonstration of how strategically useful reactions can be applied to construct complex carboxylic structure.

Now, for this molecule, if we again do the structure or I would not do the structure drawing it completely; I will rather do the Retro. So, I initially visualize that; if I have something like this 1, 2, 3.

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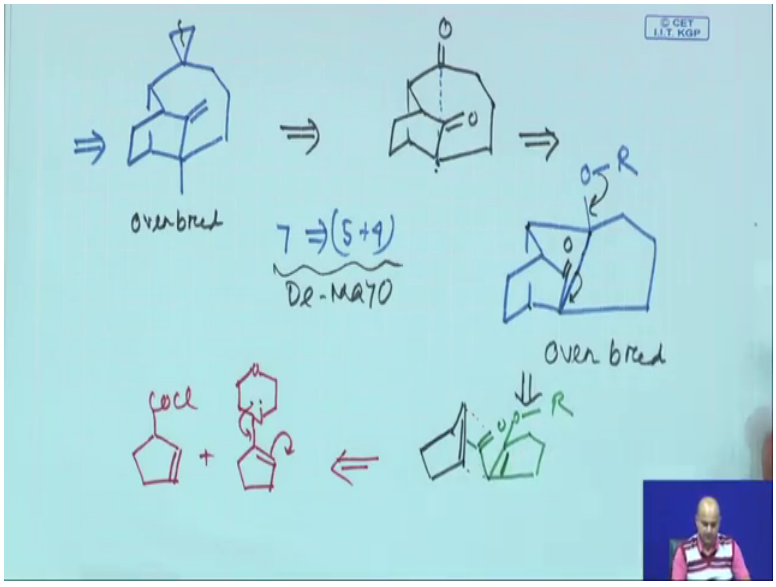

If I have something like this kind of intermediate, probably I can this is basically nothing overbred.

If I chop this cyclopropane, I will get the gem dimethyl. This was one of the speculation or one of the proposal. So, this is a real overbred which was initially proposed. Now, I will try to further do the retro and then I will, I say that now if you have this dicarbonyl

compound 1, 2, 3, this dicarbonyl compound; for this dicarbonyl gives you a access to this intermediate or this cyclopropene overbred fine.

Now, if you see this dicarbonyl structure you try to count it, 1, 2, 3, 4, 5, 6 and this is 1, 2, 3, 4, 5, 6. So, this dicarbonyl was the main features of this particular compound. Now the disconnection what I will next draw it, it probably before that what I try to do, I will just try to analyze in this way.

Now, you find that you have a bridge structure and if you have something else. The metal ring is basically 1, 2, 3, 4, 5, 6, 7. The guideline is 7 member ring, you can basically construct from 5 member and 4 member ring through a De Mayo type of reaction and also De Mayo is also cyclobutane containing over bred.

Now, you see if you can connect this 2 bonds together, your right hand side is 1, 2, 3, 4, 5 and left hand side is 1, 2, 3, 4. So, if you now do a retro and then now connect this things here, this is a particular bond and then now I am saying this O, R and the central thing you are having a carbonyl. So, this is what, this is basically a 5 member ring on the right hand side and a 4 member ring with this bridge 1, 2, 3, 4.

Now, what is it? If you make this overbred, this overbred, it undergoes Retro Aldol kind of reaction if your R is H this is strained. So, it will cleave in this way and this sigma bond will try to cleave and put a negative charge here. This is stabilized by this carbonyl. So, the right hand side 7 membered ring, we have disconnected through a another complex. Bridge thing; obviously, there a 4 member and a another 5 member. So, which basically followed the earlier guideline and the retro is basically based on a De Mayo reaction.

Now, this gives you a very crucial disconnection, how to now construct the 2 pi and 2 pi system through a intra molecular photo cyclo addition. So now, basically what you will be doing it; you just now use a cyclopentane thing with this, with this and then from here, I will use a different pen; from here because this is your bridge carbon, this is your bridge carbon.

From here you have this C, O ok, C, O, then you try to figure it out your another 2 pi system which will now give you the cyclo, another cyclo pentene thing is this, this double bond and here is your O and R. So, this retro was absolutely brilliant in terms of

strategically disconnection. Now, see what I basically are is basically proposing here, you have a 2 pi this point, you have a 2 pi at this point ok.

And now will be basically connecting this 2 pi and this 2 pi through a photo cyclo addition and then basically you will be trying to make this strain overbred. Now this particular compound was proposed to, synthesized through a stork enamine reaction which probably we have explained earlier. So, normally you use a morpholine based enamine.

Now, what is normally we know that, enamines this compound where you can easily react to a electrophilic species. Now the electrophilic species is here it acyl chloride, acyl chloride. So, basically now this enamine alkylation takes place and gives you this particular compound. So, now we will do the forward synthesis. So, synthesis starts from.

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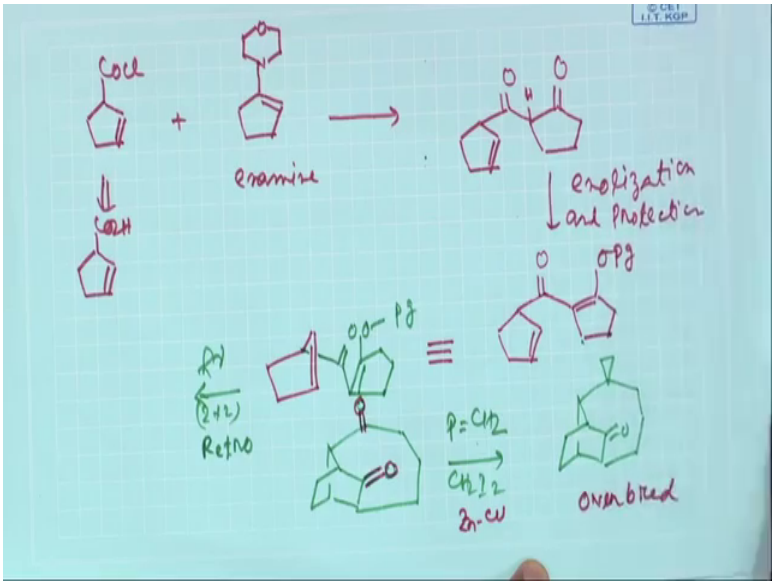

This acyl chloride which is basically, you can easily get from this carboxylic acid and you also react to it a cyclopentanone enamine ok, a circular pentagon enamine.

Now, as I said enamine alkylation will basically give you. So, enamine alkylation will basically give you a diketone, a diketone. So, this part is your cyclopentanone and this part is your enamine, the double bond which supplies a one of the 2 pi is here. Now see this compound is basically 1, 3 diketone, is a 1, 3 diketone; is not it. So, this 1, 3

diketone, you can now simply do a enolization and protect with a suitable protecting group and protection of this thing.

So, then what will get you basically get this compound, your O pg. Now this O pg is basically you can simply write it as we have written earlier. This is your one part, this is your this part, then you try to switch the bond from here you have your C, O, your C, O then your this entire part which basically gives this cyclopentane thing which is O pg. Is it now clear? The 3 CH 2 remains here 3 CH 2 remains here.

Now, you do a h nu 2 plus 2 photo cyclo addition. So, once you do this 2 plus 2 for the cyclo addition followed by the Retro Aldol cleavage. So, first basically you will be making this particular bond, this and this then retro cleavage will give you the intermediate which you already discussed the pathway that how you can do this, will basically now get the crucial things 1, 2, 3, 4, yes you get this particular diketone.

Now, for this diketone you have to, then basically use couple of other things. Here is the one ketone, here is this ketone. Now, out of this 2 ketone, this ketone is spherically more free. I mean aesthetically less congested. Now this ketone is spherically buried inside the ring. So, you do a one equivalent of Wittig followed by a Simmon Smith reaction that basically gives you the cyclopropane overbred right.

And then this cyclopropane over bred, cyclopropane overbred, you basically cleaved with hydrogen and platinum surface ok.

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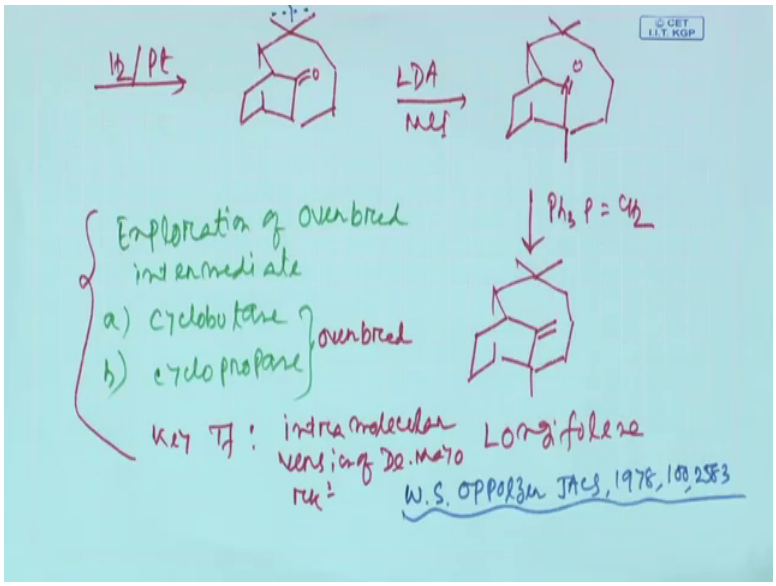

So, do they do a hydrogenation. Now, I will find that the cyclopropane will be symmetrically cleaved to give you the gem di methyle and here you are having this ketone.

But now, you are almost very close. You basically need to introduce the methyl group here. So, treat with LDA and methyl iodide, then what you will get to basically get the methyl insertion at this position, remaining part all are similar. Now, we are almost close to the synthesis. Next step is basically you need to do a another round of Wittig reaction to complete the synthesis. The di methyl is here here here and this is your Longifolene.

Now, this is absolutely delightful experience or delightful exercises for a exploration of overbred concept; exploration of overbred intermediate, overbred intermediate. Now the take home message is we will basically use two overbred. We use a cyclo butane containing overbred, cyclo butane containing overbred as well as we use a cyclopropane containing overbred. So, both the overbreds in principle were used here and the key reaction or key transformation which basically helps you. We already talked earlier a intramolecular version of De Mayo reaction.

A intramolecular version of De Mayo reaction, intramolecular version of De Mayo reaction. What is nothing basically, a 2 plus 2 reaction followed by a Retro Aldol cleavage. So, now the entire pathway you can basically formulate they are starting from very simple starting materials like this, acyl chloride and this cyclopentanone based

enamine. The reactant is simple straightforward fashion to give you this 1, 3 dicarbonyl compound.

Now, this di carbonyl compound anolyzation is very fast, basically picked up this hydrogen to form this enol. Now, this enol normally you can basically simply do a protection O pg then, your main 2 plus 2 cycloaddition which basically gives you the 4 member over bred. This over bred intermediate and the structure, we have basically drawn in the earlier, earlier part and we have shown you how this 4 member overbred has been really generated.

Now, once the 4 member overbred has been generated, you remove the pg to make this free OH, then this O OH undergoing a Retro Aldol reaction to release the strain of the cyclo butadiene system. So, once the cyclo butadiene strain has been released, you basically get the diketone compound.

Now, out of these two diketone as I said, you are having one ketone here, one ketone here. This ketone is basically buried inside the 7 membered ring; is spherically more congested. On the contrary, if you have this ketone, this ketone is free. You do a Wittig reaction here first to get the double bond, then you do a Simmon Smith CH 2, I 2 and zinc copper couple, then you will say that you get a another overbred, another overbred. You get a another overbred.

Now, this overbred is now again cleaved with hydrogen platinum to give you the gem di methyl. So, in reality the bond is basically this. You are cleaving this bond. So, surplus bond you are basically cleaving. If we get this compound fine your next part is just to introduce the endo methyl group here by LDA methyl iodide, you do it you and then you will do a Wittig reaction, one out of Wittig reaction to complete the synthesis.

Does it absolutely brilliant visual demonstration and this particular synthesis is reported by professor Oppolzer in 1979, sorry 1978. Professor Oppolzer was one of the brilliant organic synthetic chemist. So, just try to give him a tribute that this synthesis was reported as a old from Oppolzer.

And the entire synthetic scheme was a basically demonstrated in the entire, entire, entire slides. So, now, you can see that over intermediate it is a very powerful concept through

which you can create extra bond and depending on a requirement, you can remove those surplus bonds through a unique fragmentation reaction.

But definitely the fragments reaction has to be chemically driven approach or chemically logic divine approach. So, we will we will try to put this overbred concept as the end probably over but intermediate. We were not going to discuss it.

In the next class, we will be talking about next lecture we will be talking about stereo chemical strategies; the strategies which are now the final strategies.

So, till then have a good time. Bye.