A Study Guide in Organic Retrosynthesis: Problem Solving Approach.

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Lecture – 58
Stereochemical Strategies (Contd.)

Welcome back students we are basically discussing stereo chemical strategies.

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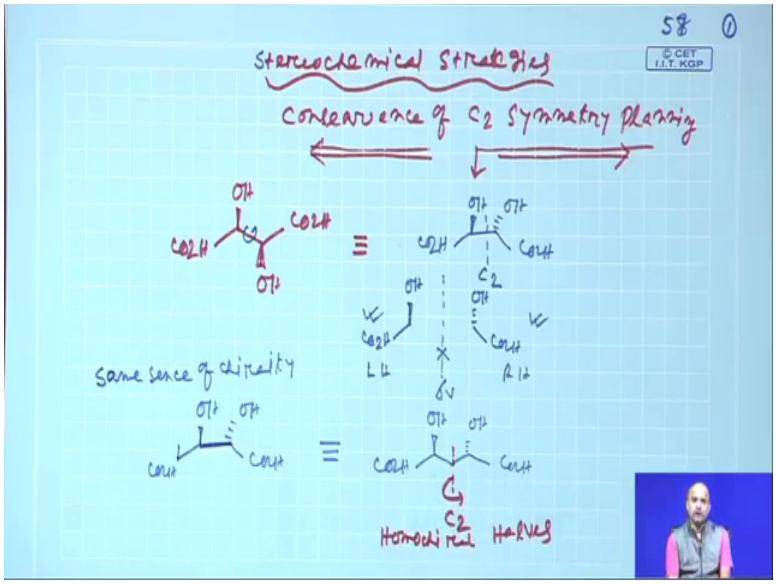

And today we will try to give you the final note on stereo chemical strategies, and we will basically discussing today a concept which we already explained you many times the title of today's talk will be consequence of C 2 symmetry in synthetic planning.

Now, when you talk about symmetry based strategies, we have mainly focused on sigma V continuing molecule and we said that perfectly symmetry molecule which does possess a sigma V, we can have a proper guideline for synthesizing those molecules and strict maintenance of symmetry was always necessary. At that point we also said that another symmetry elements C 2 symmetry element plays a very unique role in synthetic design. And throughout some of for experience or problem when you said that if you have C 2 symmetry in your molecule, if it is constitutionally symmetrical the left half and right half becomes homotopic that is having extra advantage.

Now, before we try to go into detail, I will just again draw a very simple C 2 symmetric molecule, which is basically a chiral molecule is a chiral pool is a tartaric acid. Now tartaric acid the way it has been written you can just allow the rotation around this carbon and then you can write this chiral tartaric acid in this way. Now this is a very unique example of constitutionally symmetrical molecule were left half and right half is similar because their sense of chirality is similar, and this molecule basically possess a C 2 symmetric. Now if you try to just think in a different way, I will say that tartaric acid will write in this way the hydrogen they have omitted and then I am saying that the right hand side I will be write in this way.

Now, the particular central bond we did not draw it. Now you see this 2 molecule they do not have a plane of symmetry, and now it is quite clear if they have plane of symmetry why I always said that if you have a sigma V this left half and right half is enantio topic. Now see this tartaric acid the left half and right half having same sense of chirality, because this O H is here above and this O H is below, but you are viewing it from the opposite side. So, they exactly have a same sense of chirality.

So, for C 2 symmetry the point is same sense of chirality is very important. So, in terms of C 2 symmetry you can always say that if you having a molecule, let us take the take the tartaric acid example, I am saying that tartaric acid is this and I am saying that the left half and right half having exact same sense of chirality and this bond are basically making in this way. Similarly, you can also device molecule like this where you can find that you put some extra methylene this also has a perfect C 2 symmetry.

So, means that you have a methylene spacer, so this methylene spacer joints the 2 homo chiral halves this halves homo chiral means they have a same sense of chirality, homo chiral halves means 2 half, which is having same sense of chirality have been fused through a achiral methylene breach.

Now, C 2 symmetry plays a very important role in synthetic design a particular will be explaining with the help of help of tartaric acid example first and at the nature a many of the natural products are C 2 symmetric mainly due to the fact that sometimes 2 homo chiral or same sense of chiral molecules basically dimerized.

So, if they dimerized one is say r configuration one is says configuration sorry r configuration both the having same configuration dimerize through a achiral spacer and

gives a C 2 symmetry molecule. Means that if you have a only r isomer if you can join through a achiral spacer, you can access those target molecule. So, you basically need a same sense of chirality to access C 2 symmetric molecule that was very important.

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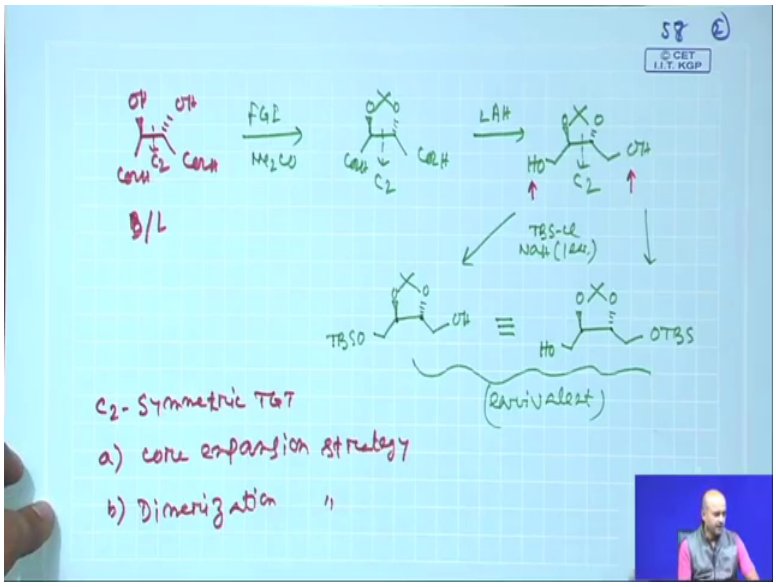

Now, coming to the tartaric acid case, I say you are having this tartaric acid this either D sorry D or L and is having a perfectly C 2 symmetric. We will try to do some synthetic reaction initially I say ok. Now the consequence of C 2 symmetries as it is constitutionally symmetrical the left half and right half they are homotopic means that this O H and this O H are homotopic, this C O 2 H this C O 2 H are homotopic, homotopic means they are basically exactly equivalent.

So, now I say I will reflux this compound with acetone, so means that this things will be now will giving you this compound acetonide protected. Now I am saying that access lithium aluminium hydride I will now put it here. So, both these carboxylic acid will be now converted to O H, now C 2 remains here, C 2 remains C 2 remains the symmetry element remains.

Now, by doing these now I am saying that this C H 2 O H and this C H 2 O H are homotopic. So, what does it mean means that, now I am giving you a simple 1 equivalent of TBS chloride, sodium hydride, 1 equivalent basically the McDougal's protocol, McDougal's protocol which you have earlier explained. So, you explain that 1 C H 2 O H will be protected its fine, so now; we are trying to do the protection.

So, first time I will put the protection on the left hand side it gives you this compound, and then now on the other side I will do the protection here. Now this compounds are basically same, this compounds are same because if you take any of this compound just rotate 180 degree, and then in plain rotation they will give you the same compound that is the beauty that is the beauty of C 2 symmetry, because they are fuse to it same homo chiral halves they are basically equivalent. Now sometimes if this is equivalent you cannot do by simple symmetry analysis what they advice you assign the R S configuration of this 2 centre, these 2 centre you will find that R S for these and R S for these will be same this compounds are basically same.

Now, in C 2 symmetry we or if you have a C 2 symmetric target molecule I am saying that now if you have a C 2 symmetric target molecule, C 2 symmetric target basically we follow 2 different strategies the 1 the strategy first one is named as core expansion strategy, core expansion strategy. And second one is name as dimerization strategy now both the strategies are basically similar in sense in case of core expansion I will be just explaining what is core expansion strategies.

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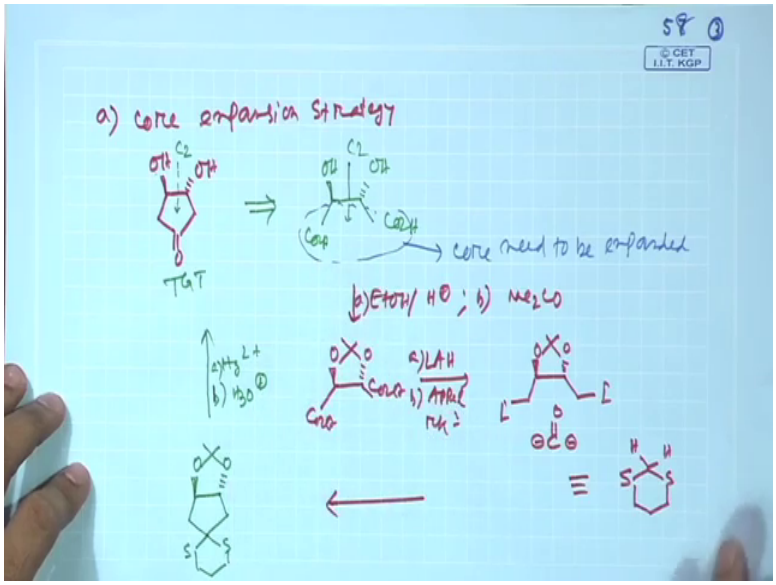

So we are basically discussing, if you having a C 2 symmetric target molecule core expansion strategy we say there is a strategy which named as core expansion strategies. Now, what we will do I will give you a target molecule I am saying I am giving you a

target molecule the target molecule structure is 1 2 3 3 4 dihydroxy cyclopentanone, now see the stereochemistry this molecule having a nice C 2 symmetry ok.

So, now, I am saying that your starting your starting material has to be tartaric acid ok, has to be tartaric acid now actually this problem in reality we have analysed earlier when we talked about the synthetic equivalents, but still it is a very unique strategies now I am saying that this starting material also have a C 2 symmetry. Now see this O H and this O H belongs to this O H and this O H only thing is you need to expand this O A. So, basically this core has to be needs to be expanded this core, so this is the core I am saying this particular core needs to be expanded.

So, core need to be expanded that is why it is called core expansion strategy, then reality how it was done if you having a tartaric acid as I said first you convert the carboxylic acid to diester by a ethanol H plus treatment number a, number b just protect with this acetonide. Then what we will get we will basically get this acetonide protected C O 2 E T, C O 2 E T, you do a lithium aluminium hydride reduction, and then do a apple reaction apple reaction now this reactions basically we have already studied.

So, we are not discussing in it detail, so what we will basically get you get this C H 2 I C H 2 I, now in core expansion strategies the left half and right half are reacted in a same way I mean you basically expand through both way and then I am saying that you try to react with a D 1 umpolung 2 D 1 umpolung.

Now, 2 D 1 umpolung you can basically easily generated from a formaldehyde diethiane. So, then this basically after this alkylation your synthesis will be almost completed. So, only thing is you need to remove the diethiane group by H g 2 plus first and then you remove this acetonide protection by a acidic treatment you get your target molecule. So, this is in principle the core expansion strategies and C 2 symmetry remains intact, C 2 symmetry remains intact, we will next show that how I will next, next analyse how this dimerization strategy is in.

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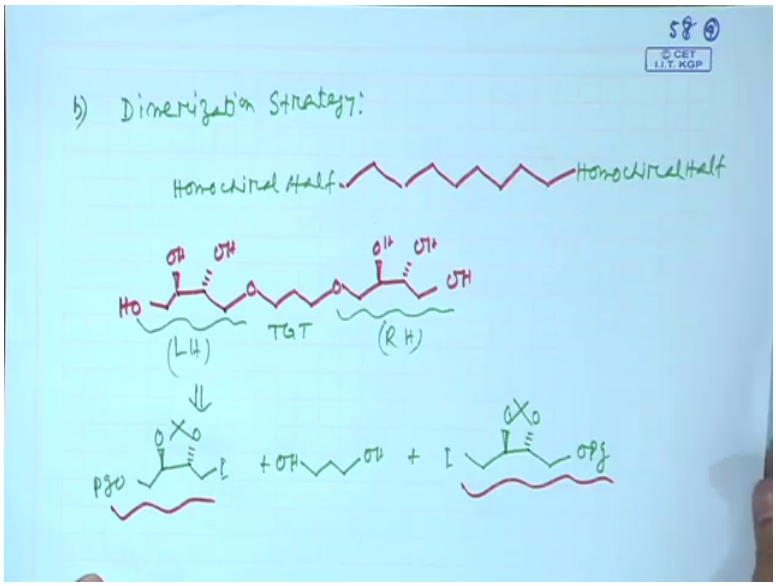

This dimerization strategy was basically a similar like core expansion strategy, but as I say dimerization means that may be your target molecule is such that you need to dimerize the 2 homo chiral halves. So, your compound will be something like this you have a 1 homo chiral halves half and you have a another homo chiral half homo chiral half means they have a same sense of chirality, if they are enantiomeric to nature they will be hetro chiral.

Now here I am saying this homo chiral half and 2 homo chiral halves you basically dimerize through some achiral spacer achiral spacer. So, now, next I am giving you target molecule then see how you can analyse it I am saying you target molecule is ok.

I am saying that this is a target molecule, now if you analyse very closely it is basically a C 4 tartaric acid building block on the left hand side, its left hand side having a 1 chirality and this right hand side have the exactly the same chirality. So, that is why both the halves are homo chiral and then you are dimerizing it through a achiral spacer.

So, eventually this things you can easily prepare if you just try to have a compound like this. So, basically trying to simplify the structure in terms of C 2 symmetry, and now I am saying that if you have this compound this compound and this achiral spacer you can simply do a S N 2 tide of type of ether formation to this to complete the target molecule. Now, this left half and this right half are basically same is a same compound or homo

chiral halves, now eventually this compound you can easily make as discussed earlier, so how you can make this compound.

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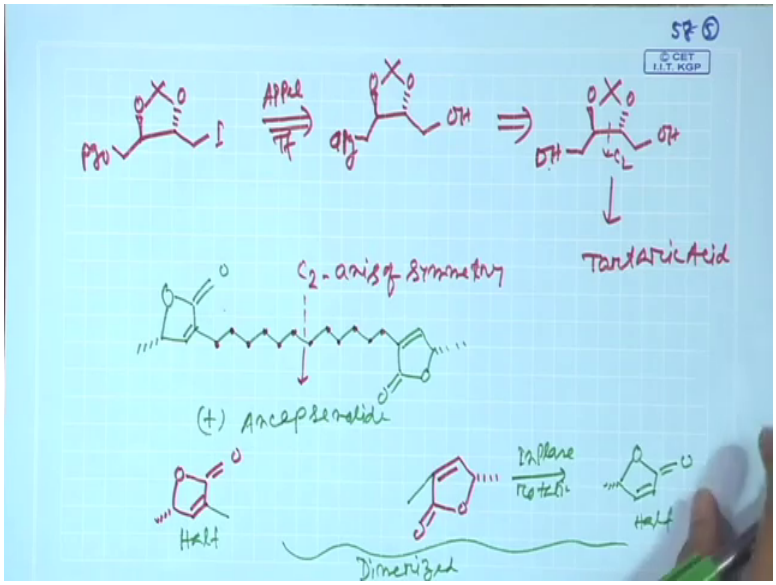

This compound you can easily make if you having this free alcohol by simple apple reaction O P G by apple transformation apple is very known to you, and this 1 definitely you can easily prepare from the C 2 symmetric diol just by mono protection O H. So, this you can prepare from tartaric acid now this part your C 2 symmetry there.

So, as C 2 symmetry is there you can basically do the mono protection and no matter where you will protection group goes it will basically give you same compound. So, this halves and another same halves, so thus 2 homo chiral halves are basically dimerized through achiral spacer and that gives you a target.

Now, in nature you will find many C 2 symmetric compound do exist, I will try to give you some example just for your structural view point. So, the idea will be quite clear this is 1 of the C 2 symmetric compound there are few methylene bridges in between not bridges basically C H 2 C H 2 there are 12 methylene in between 1, 2, 3, 4, 5, 6, 7, 8.

So, this compound is basically a kind of a diamer where 2 homo chiral halves are joint. Now this compound is a natural product is a gamma lactone based natural product its name is ancepsenolide, if you see it structure ancepsenolides probably you can say that this methylene groups are the achiral spacer and in reality. So, I will just analyse the

structural view point and eventually this molecule does have a perfect C 2 axis of symmetry. So, now, if I try to say that, if you have this compound and if you have this compound what you basically need to do you basically connect here, and connect here.

Now, this compound and this compound are basically similar, because in plane rotation of this compound in plane I am now saying in plane rotation that is basically give you the same compound which was written in the right hand side. So, this 2 homo chiral halves this half this half and this half is basically dimerized dimerized through this achiral spacer that was pretty important and that is gives you the ancepsenolide.

So, the either in nature there are similar kind of compounds do exist and sometimes if you find this kind of C 2 symmetry compounds, or there in your structure you synthetic experience is or synthetic strategies will always tell you that you start with a same sense of chirality now we will try to do the ancepsenolides retro.

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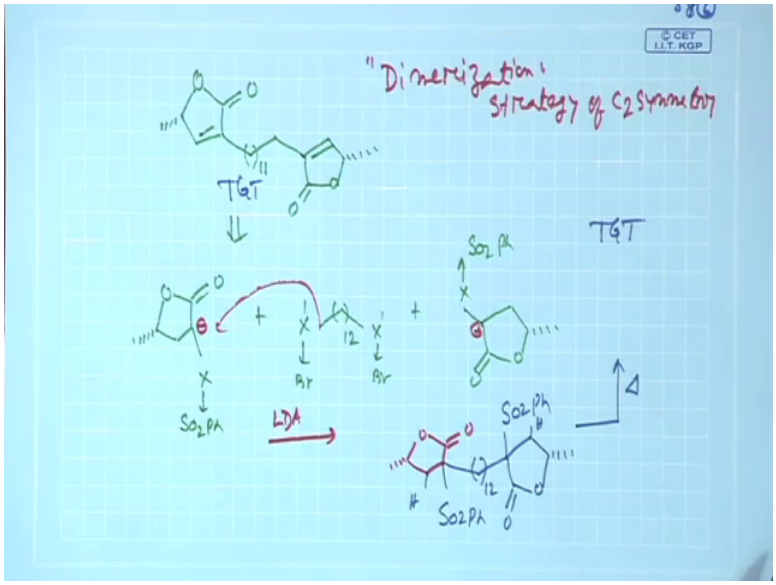

You first draw the retro you will probably would not discuss it in detail we will just try to give you a idea how this ancepsenolides can be done in reality through a dimerization strategy.

So, this basically falls to a dimerization strategies and here there will be C H 2 twelve actually. So, C H 2 you can just put C H 2 11, 1 C H 2 11, 1 C H 2 12.

So, this basically the achiral spacer now what I say I am saying that if you have some compounds something like this you need to put some reaction or some group where you can find that. So, I am saying x x C H 2 12 and then you are having this another homo chiral halves of the same lactone put is x x prime, x prime, now I am saying if you have this 2 compounds, this 2 compounds the same sense chirality is similar now x this x we are not putting in stereo centres because finally, if you see the double bond is has to be created here double bond has to be created.

Now, if I say that this x prime and x prime are good living group like bromo or bromo and this x is a electro withdrawing group like sulphone S O 2 P H S O 2 P H, then the strategy will be quite similar or quite simple. Now I am saying that if x is S O 2 P H you can easily generate a carbon ion here use adjacent to the carbonyl and adjacent to the S O 2 P H, same thing can happen here you can easily generate a carbon ion here now this 2 carbon ion basically having a same sense of chirality will now react with these 2 bromo in the left hand side as well as right hand side.

So, this is basically the dimerization, we put the achiral spacer and left hand and right hand and trying to fuse it with 2 homo chiral halves. So, if you do this things next see what kind of compound see you just treat with a base now how this how this chiral halves we are accessing probably we are not discussing it here. So, I am writing S O 2 P H and then you will be basically having S O 2 P H. So, in between there are 12 methylene.

Now things are absolutely simple you basically need to do a elimination of this hydrogen elimination of this hydrogen. So, yesterday we talked about a selenoxide elimination, similarly sulfoxide elimination also quite possible. And now if you can simply heat this compound simply heat this compound your 1 2 sulfoxide seen elimination will takes place. So, elimination will takes place and that will basically give you the target molecule target molecule.

So, what exactly we do it is basically a dimerization strategy we have used the dimerization strategy is we have said that it is a you basically take 2 homo chiral halves, and dimerize through the achirals spacer there is a very nice demonstration of dimerization strategy if your target is having C 2 symmetry C 2 symmetry. So, that is

very important that is very important to memorize all those things, now, couple of molecules flow like an doitere which might have.

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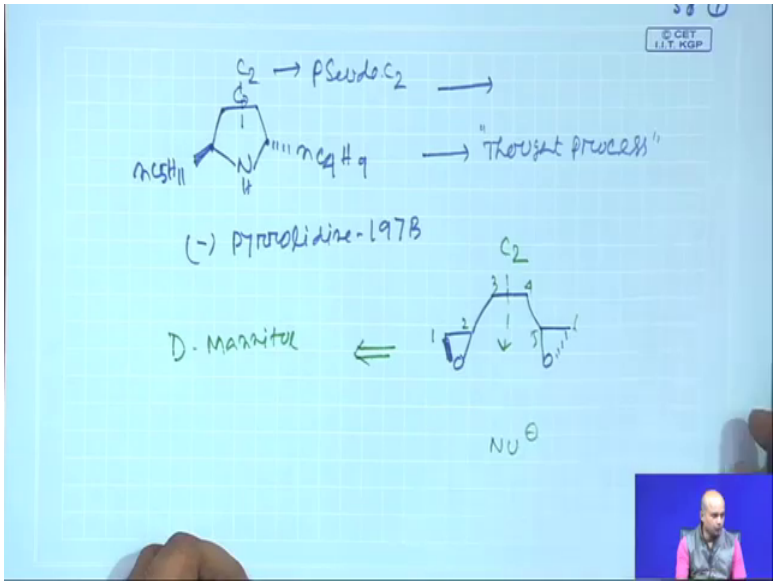

Now this particular example is very important, this n Spiro let in compound this compound it looks this compound is a natural product name is pyrrolidine 197 B. Now you see structure if both the groups are same then the molecule has been perfectly C 2 symmetric, but as both the groups are not perfectly same this molecule now belongs to a pseudo C 2.

Now pseudo C 2 are also similar like C 2, like we call pseudo symmetry similarly you have a pseudo C 2 symmetry element in this molecule, now for this kind of pseudo C 2 also you can exactly apply the similar kind of strategy, what you do for the C 2 symmetric strategy because C 2 symmetry the advantage is you can start with a homo chiral or same sense of chiral chiral precursor now here you need to create 2 particular stereo centre.

Now, probably I will give you as a thought process you go and you start thinking on your own that how this compound can be created, but let us try to give you a hint that how this compound you, you can create it now, if you see the structure this compound basically having 2 methylene in between 2 methylene in between. So, I will put this 2 methylene in between in between and then I will try to draw the base epoxyte.

Now this epoxyte basically is a 6 carbon epoxyte, if you remember this epoxyte we have synthesized in chiral pool strategies from D mannitol, D mannitol now as this epoxyte a C 2 symmetric you can basically functionally manipulate this epoxyte to basically by using some suitable nitrogen nucleophile possible now this compound is C 2 symmetric means that if you use 1 equivalent of nucleophile probably it can no matter if it attacks here or by attacks here it will give you the same compound. So, initial for pseudo C 2 molecule is always advisable you start with a perfect C 2 symmetry and then take the help of the homotopicity.

Now, here basically depending on this C 5 H 11 C 4 H 9 you can open the epoxyte. So, C 5 H 11 means only 1 C H 2 is there. So, now, you can think about opening with one carbon extra nucleophile, then you have this O H here same thing you do it here also you get O H O H and then this O H O H you basically need to convert to corresponding Amin. So, you can convert this O H to some mesylate then you can replace it with ammonia 2 that access of this target molecule. So, this, so not be a problem for you similarly I will try to write another molecule which is also a.

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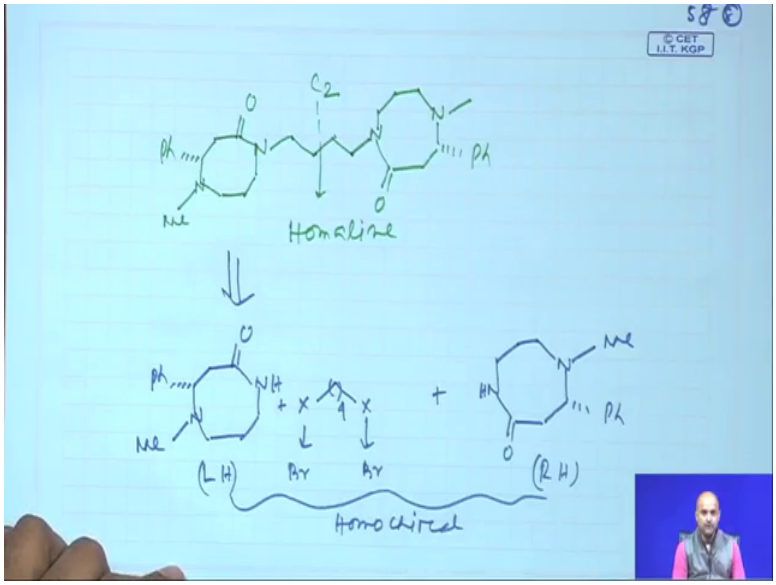

C 2 symmetric natural product and this is compound having a 8 member structure and this eight member structure is having this particular on the left hand side and then with this nitrogen you have this achiral spacer. So, 1 2 3 this 3 I think its four yeah this is a

this 4 carbon then you are having this. So, left hand this same compound now was this compound.

Now, if you this compound is a natural product is compound name is homaline, homaline this also again a C 2 symmetric compound, C 2 symmetric compound, the C 2 symmetric compound. Now if you see it you do this target analysis we will find that if you have this particular compound as your starting material and then you can basically couple with 1 2 3 4 you can just couple with x and x it is a 4 carbon x stands for bromide, bromide and then this right hand side you write the same compound in a day opposite way. Now this opposite way means these compounds are basically same sense of chirality. So, this strategical exploration through C 2 symmetry was very useful.

Now, this left half and this right half are basically homo chiral or they have a same sense of chirality, same sense of chirality. So, now, you can basically make it and do not worry if you if you cannot make this this compound if you can make this compound is fine, but your, your visualization should, should basically guide you if you have 2 same set of chirality you can just join them through achiral spacer to give you a perfectly C 2 symmetric molecule.

So, C 2 symmetry in that way is very useful and nature always prefers normally been in nature you will find more C 2 symmetric compound than sigma V continuing compound because nature always prefers homo chirality. In case, of sigma V if the molecule does belong a sigma V means that 2 hetro chiral halves has to be fused because you have a mirror plane of symmetry which bisects into 2 enantiomers.

So, that is a hetro chiral half, so in that way C 2 symmetric is very useful is very informative and see probably will stop the stereo chemical strategies here we will try to explore a few things because we have probably few lectures left and. So, have a have a good time till then good bye.