A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 18
Specific Transformation

So welcome back students.

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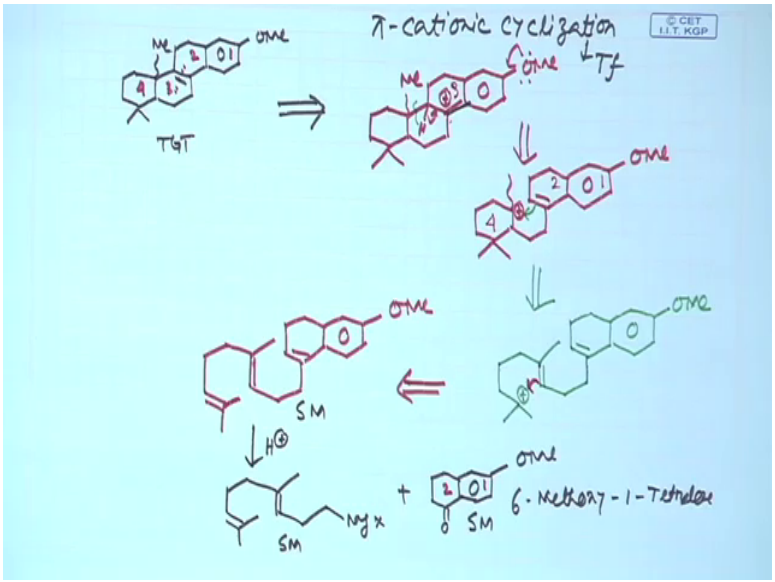

So, this week of this lecture, we will be talking about a very novel transformation it is named as pi cationic cyclization it is not a named reaction where is it very useful transformation you can call it as a transformation very important transformation and if you see we are giving a target molecule it is definitely a complex structure and it is a complex carbocyclic skeleton there are 4 rings are involved, here and as I said this pi cationic cyclization as a unique transformation we will try to explore how a different strategically useful retrosynthetic disconnection will help you to come to this final target or initially draw a retrosynthetic arrow and show you what are the possible bonds will be basically disconnecting it.

First let us draw the core structure keeping it mind these things will be here and the right-hand side you have a o methoxy here we didn't put the double bond here where is this double bond will be generated from a one to elimination of a carbocationic species something like this now this carbocation will be normally formed if you have a para methoxy means para methoxy benzyl cation. So, this carbocation is normally stabilized by this ome group. So, this

could be a one of the. So, first retro were basically making this double bond this hydrogen will then try to eliminate to give this molecule.

And as I said the driving force is the para methoxy benzyl cation it is normally stabilized by this para methoxy group electron releasing factor. So, this was the next retro. The next retro is crucial you check it carefully. Next retro will be trying to figure it out making the central ring is it there are 4 rings and now we will try to put a carbonyl amine on this carbon. So, we have basically disconnecting this particular bond, now what is the driving force the driving force is a tertiary carbocation.

Now, how this tertiary carbocation will lead you this intermediate ended to this target means this pi bond will undergo cyclization because pi bond is electron rich and once this pi bond pushes it is electrons to quench this carbocation you get this carbocation. So, it is likely that is why it is name is pi cationic cyclization the carbocations will be generated based on it is stability and in close proximity you have a pi electron. So, pi electron will try to stabilize or try to pushes it is electron to quench the carbocation. So, this is the all the intermediate, next intermediate which will be now drawing see it very carefully, this stepwise demonstration of how a complete structure can be thought of and now you say we will try to put a carbocation here I will put a carbocation here. So, this is again a 3-degree carbocation, now try to put the arrow this carbocation is in close proximity with this this pi. So, it causes it will give a carbocation here which is basically here now this pi electron will undergo electron shuffling to this carbocation it get a para methoxy benzyl things, stepwise carbocation will be generated and will undergo cyclization.

So, this will be now we will try to figure it out the what will be the suitable starting material put 2 methyls here and then you try to formulate the or try to figure it out the remaining ring. So, eventually all the 3 rings we basically disconnected. And this cyclization is pretty important. So, eventually if you have this compound where 3 different pi bonds are there now these 3 different pi bonds are basically positionally situated in such a way it is in close proximity to this carbocation.

So, this compound if you just if this is the starting material or starting precursor we just subject to a H plus like standard way you do a markovnikovs reaction. So, this things will generate this stable carbocation which is the 3-degree carbocation, but these 3-degree carbocation will get this pi it will try to quench it here will give you a carbocation here which

is this, and then you basically get another pi electron another pi cloud here and that gives you this para methoxy benzyl thing. So, eventually their whole process basically you now need something like this.

And now if you try to do a retro that which will be the starting material or where for you access this starting material you will find that this starting material can be this is CH 2 CH 2 CH 2 CH 2 you put a Mgx kind of thing and then. So, if you have this particular carbonyl compound which is basically 1 2 3 4 5 6, 6 methoxy, 6 methoxy 1 tetralone 6 methoxy one tetralone now this 6 methoxy one tetralone will trying to do a grignard reaction CH 2 CH 2 mgx and basically give you oh and this CH 2 CH 2 they now do a simple one to an elimination of this alcohol and this hydrogen that will give you this starting material.

So, simple starting materials like this ketone and this grignard now this ketone has this 2 ring now I named this ring 1 2 is basically 1 and this 2 a ring 3 and ring 4 will be formed during our pi cationic cyclization. So, first take this starting material react with this grignard and do the elimination you will basically coming to this part now you have a 3 pi electronic things 3 pi bonds now you subject to this to a mineral acid initially you get this 3-degree carbocation. This 3-degree carbocation is normally stabilized very stabilized tertiary carbocation as all of us know then this 3-degree carbocation you get this particular pi (Refer Time: 09:58) on saturation you will try to react in this way to give you the ring 4.

The ring 4 is this one and you have a the newly generated carbonium ion which is again a 3 degree this one. So, ring 4 was already formed this is ring 2 this is ring 1 and then this carbocation will try to react with this this pi to make you ring 3 ring 3 and finally, you will find that this is gives you a para methoxy benzyl carbocation which is also very much stabilized. So, if you check this entire pathway we will find that this is a very useful transformation and as I said this reaction is named as pi cationic cyclization.

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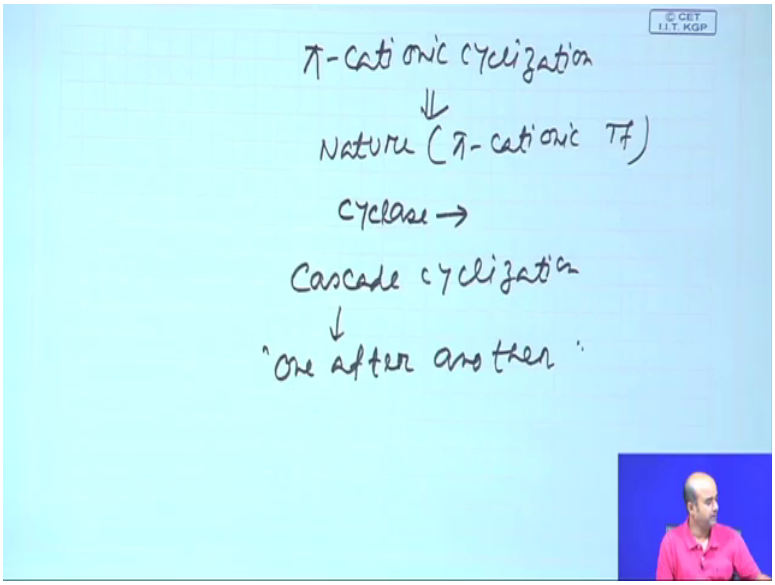

The cyclization takes part in one-part operation. No need to isolate any intermediate you just subject the initial starting material which was just drawn to you in the earlier slide.

This one you subject to mineral acid and then you keep on doing this reaction. This is very important reaction pi cationic cyclization and that was normally used by our mother nature. Our mother nature uses these pi cationic cyclization as a unique transformation to synthesize many of these natural products; particularly this natural products or this kind of structure was available in the nature you basically steroid framework by this kind of compounds are natural products and you will find that in mother nature it often uses this kind of simple pi cationic cyclization nature does not use the very sophisticated reagents like as I said (Refer Time: 12:12) and other oxidizing agent nature always uses very simple chemistry. Nature has his normally enzymes and this kind of enzymes are basically known as cyclase enzyme. Cyclase these enzymes react as I shown it is a sometimes you can call this reaction as cascade cyclization. Cascade the terminology basically means that one after another one after another.

So, one port reaction and eventually the chemical logic is very much clear chemical logics says that the stable carbocation will be generated.

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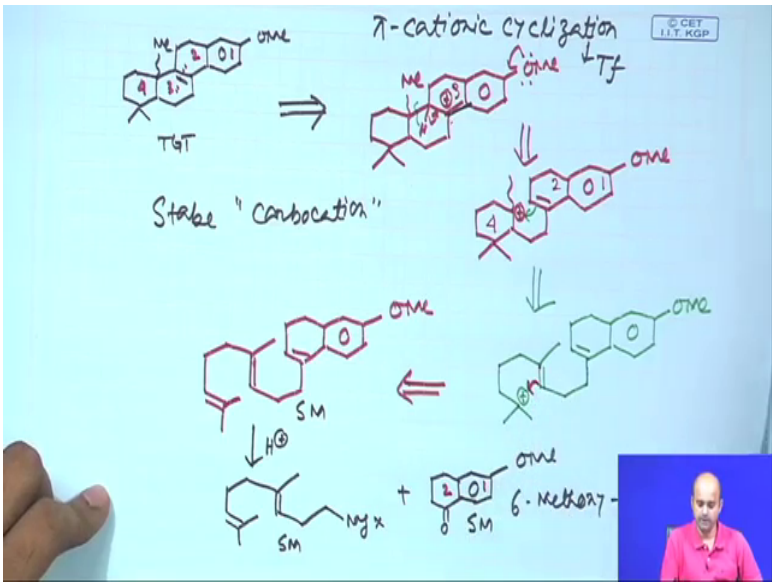

And the stable carbocation will try to react with this pi cloud and then at the end we will be basically getting the final product. So, the entire situation is as I explained in the thing. Next, we will try to visualize something else before that I give you a simple molecule.

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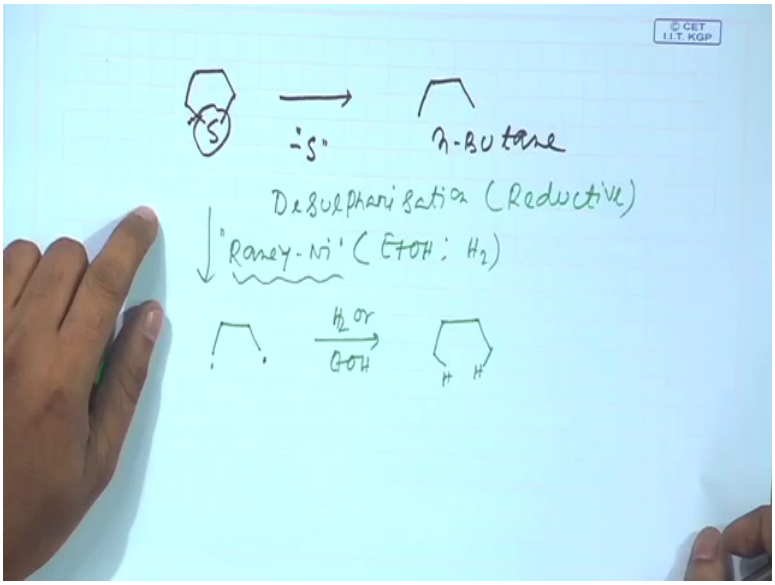

This molecule is tetrahydro thiophene. Now I said is it possible to synthesize this molecule from this tetrahydro thiophene now what is this? This molecule is basically butane 10 butane.

You may say that that if you can remove the sulfur this is done. When you remove the sulfur, I need to basically get rid of this sulfur fault. Essentially the reaction is basically a

desulphurization reaction desulphurization reaction, and in reality, this reaction was very efficient it was done by Raney nickel is a active species which have been commercially available Raney nickel is a nano particle form of nickel, and you using the reaction in a ethanolic solvent sometime you can use the hydrogen as a gas. Basically, you now raney nickel is strongly thiophile thiophile means it has a strong interaction or strong attraction to our sulfur.

The mechanism was not very much well established, but it will propose that probably a diradical pathway might occur which is further quenched by hydrogen all the ethanol which was used as a solvent to give you the butane hydrogen hydrogen. So, this particular reaction it is called Reductive desulphurization, Reductive desulphurization the very unique transformation and next we will be using this transformation for a given target. This information will be useful for you that will be using a Reductive desulphurization for our next target.

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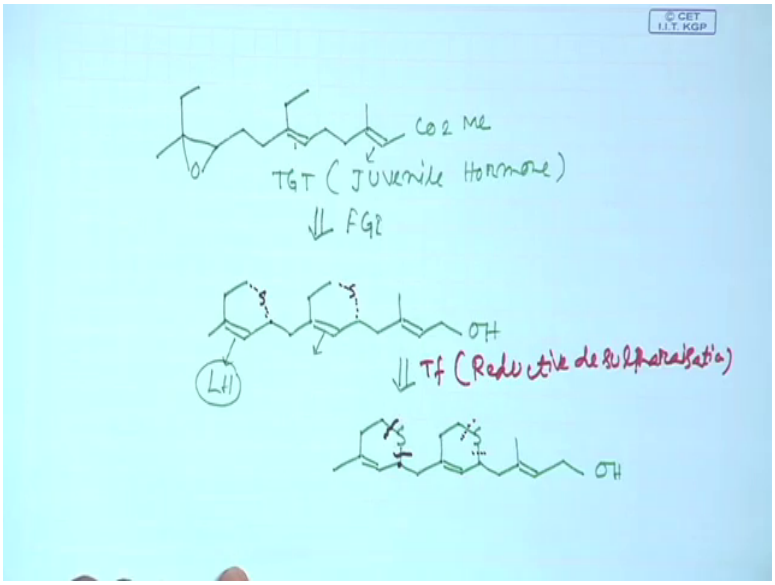

Now, let us draw the target molecule. Target is little bit complex, but nevertheless you try to get the target very efficiently. This is a natural product this is a natural product and this natural product was basically named as Juvenile hormone naturally. Juvenile hormone is a material product which was existing in many of the insects one they are in Juvenile stage means they have just born and this particular compound act as their going they this compound helps to go them as is named as Juvenile hormone.

Now, you see this target molecule will be using the transformation which we just now explore is called reductive desulphurization before that we will just cut the molecule in a very simplified fashion this molecule if you see the structure it is having an epoxide at one end and one end having a alpha beta unsaturated ester in between the molecule having a one pi electron here and there is a methyl is a methyl. So, this is the structure. So now, do a standard retro you have any ethyl here another ethyl group is there. So, we will try to do the retro. And we say this molecule can be accessed from this kind of compound.

Now, how if you know analyze the molecule final end is one allylic alcohol. So, allylic alcohol can be oxidized the corresponding acid and then acid can be transferred to corresponding ester by a simple FGI. Now if you have this compound or this compound there are 3 double bonds 1 2 3, probably these 2 the central one, this one and this one is more electron rich because these highly substituted and the left hand double bond left hand double bond is statically less congested.

So, probably after this allylic alcohol if you do a oxidation and esterification now this double bond becomes electron deficient this is electron rich this is electron rich and select the epoxidation can be done here, we will discuss this one later on before that now explain the our key strategy which is very much important. We will try to now use the reductive desulphurization chemistry which we just now explained in the earlier slide we called here we will be using a transformation based on Reductive desulphurization.

Now how you see this things ethyl if you now try to cut this bond and this bond by replicating the sulfur you basically get CH 2 CH 2 dot radical that will be quenched by this ethanol or hydrogen to give you ethyl here. And this what you will get a simple these things. So, this is basically your sulfur part we just try to put here this will be another ethyl and you are putting a another sulfur here. So, this 2 steps are basically this reductive things are absolutely important and until and unless you know this transformation is very difficult to analyze fine. So, we are here and then we will be cut down the molecule to a further simplifying structure.

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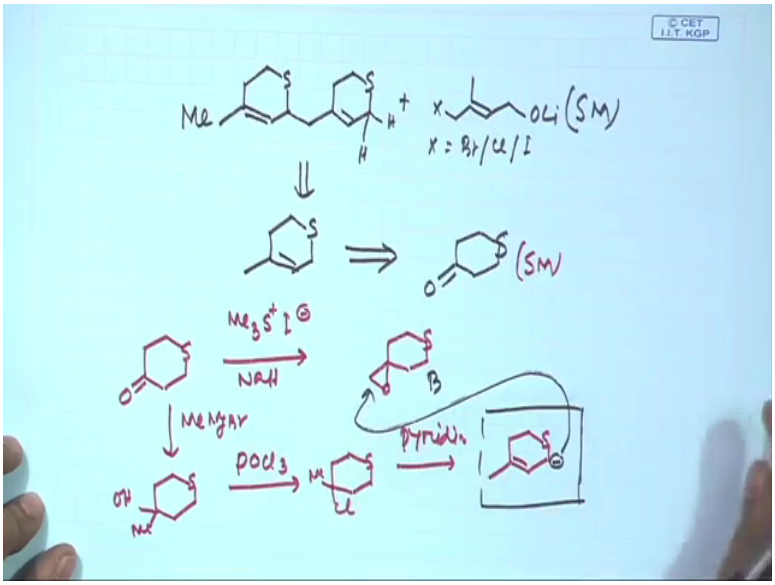

We will try to use the same chemical analogy. This is one of the intermediate we say and then we say that you take it structure the final structure or this structure were basically trying to give a retro here give a retro here and then we will basically say that we will try to introduce this part to a this x, x could be bromo or chloro or iodo.

Now, how this sulfides this cyclic sulfides there are hydrogens here you can easily abstract them by simple base, because they close to electro withdrawing sulfur as well as the allelic. So, this is an electrophilic center and you can really react with a allelic halide is a electophile this our initial reaction. And then this compound. So, this is basically one of the starting material at this this tetrahydro thiophene or dihydro thiophene you can easily prepare starting from a this compound we will explain how.

And this initial starting material was physically prepared from a compound like this. If cyclohexanone analog where the 4 position the CH 2 has been replaced by a sulfur group. So, this is the starting material which will be using as a commercially available keep starting material now we have to. Now formulate how you can do it. Take the starting material which was the thiophene based starting material we will do a series of reaction the very beginning we will be doing a corey chaykovfsky reaction which was already explained to you by a sulfonium iodide mediated epoxidation.

So, this compound basically will give you this epoxide with a starting material fine and then this studying compound you react to it Me MgBr methyl magnesium grignard. So, it basically

give you OH Me now this OH Me. So, basically convert this alcohol to corresponding choride by POCl 3 a standard chlorinating again that will give you the alcohol to chloride and methyl will be there and then you treat pyridine as the base will basically get this compound.

Now, this allelic sulphide is a very interesting percussion if you subject this allelic sulphide with base it will be generating this anion. Now this anion will try to react with this epoxide in a spherically less in their way. So, in next step you basically react this.

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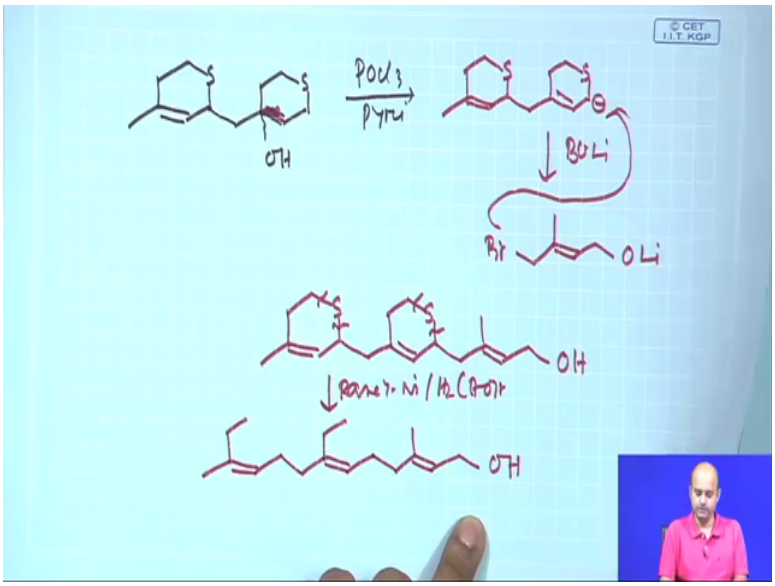

These things aren't it? And then you try to react with this epoxide this which basically reacting with this epoxide what you get this, and then you do the same thing you treat with POCl 3 and pyridine sorry this is does not that the double bond is basically the single bond single bond this double bond will be now generated yes.

So, this is the compound which was shown as a one of the intermediate here same compound the same compound. Now this compound again you can treat with base butyl lithium it will generate this carbon ion here and here you will reacting with this as I said called O lithium and this CH 2 Br as a electrophile. So, this will attack here and then what we get you basically get the simple electrophilic addition product, the electrophilic addition product air you can quench it with this.

So, almost close fine you do this Raney nickel treatment Rraney nickel hydrogen or ethanol. So, this sulfur cleavage will be there this sulfur cleavage will be there and then you basically

get a ethyl group here this part remains same if there will be a hydrogen same thing again. So, get this one which is our initial on the intermediate. So, almost closed we almost closed you take this starting material and you do a oxidation to get this corresponding carboxylic acid esterified with diiodomethane.

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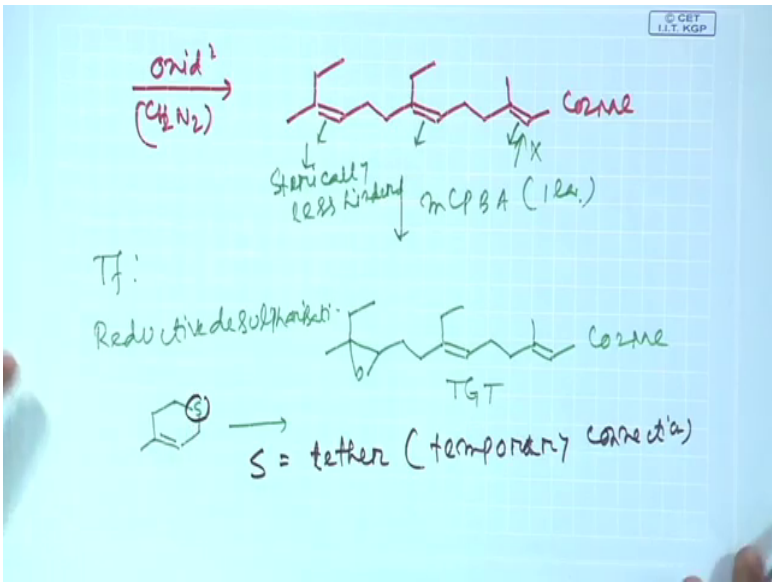

So, what we will get? You basically get double bond CO 2 me now there are 3 double bond this is electron deficient this is electron rich this is electron rich. So, we will treat with one equivalent drop mCPBA one equivalent mCPBA as we know this is electron deficient oxygen. So, it would not touch this double bond it would not touch it may touch this it may touch here, but definitely as I say this is sterically less convinced step sterically less convinced step less hindered.

So, you can expect that these things will be now epoxidized. So, this is your final product of the target molecule which we have earlier shown. So, this entire pathway basically gives you the juvenile hormone the juvenile hormone which was the main target molecule. So, this is the target which have been achieved the transformation which is used basically a reductive sulfurization as I said and remember this sulfur basically acting as a temporary connection. Productive desulfurization who used desulfurization and as I said the crucial reaction is basically a this sulfur which we are basically removing.

The sulfur acting as a temporary connection. So, sometimes this is known as tether what is tether? Tether is basically temporary connection temporary connection or temporary bonding.

And this temporary connection was not required in the final target. And this was very useful by using a sulfur tether reaction, but eventually the reaction main reaction is reductive desulphurization which will give you a very useful functional good assembly and you can see that this final the target molecule was nicely achieved by using a reductive desulfurization chemistry.

So, probably similar kind of things we will be explaining in a subsequent lectures. So, till today just go through the reductive desulfurization technology that how this reductive desulphurization method helps of this sulfur tether chemistry helped to get access of some of the intermediates which is very useful in synthetic organic chemistry, and we have shown that at this this particular sulfur-based tether is very usefulmethod to give you a efficient target. So, we will be see you in the next lecture till then goodbye.