**A Study Guide in Organic Retrosynthesis: Problem Solving Approach**

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**Lecture – 40**
**Fg/SM/Tf based Combined Strategies (Contd.)**

So, welcome back student. We will basically discussing that several kind of mechanism based transformation will help you to access medium sized target molecules. And you said that if you are quite familiar of some important mechanism or mechanistical aspects of several transformations that will help you to design the retro synthetic pathway very efficiently.

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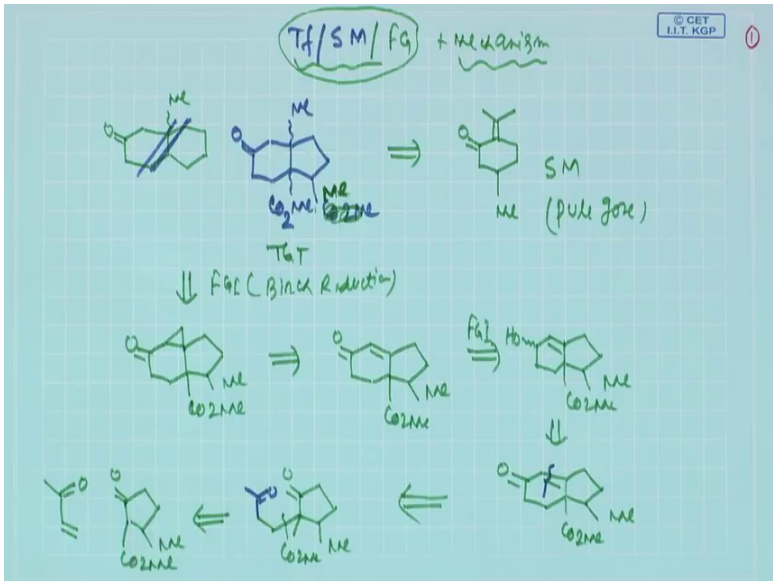


So, next target which we are trying to do it right now is a very interesting one. And this is basically combination of transformation as well as starting material, as well as functional group also will be trying to combine the three strategies together. In addition, the mechanism which is very important and plays the important role and designing the effective path way, we will be trying to focus in this particular problem. And initially, let us give you the target structure. The target structure is the structure is wrong, so we will draw it again.

The six member and five member based target where having a angular methyl the ring junction having a cyclohexanone and here you are having a CO 2 Me group. Now you

say this is the target molecule. The starting material was also given to you for your better understanding. This starting material is named as pule gone is easily available raw starting material or raw fix stock it. Basically at cetane carbon containing molecule is a tarpinode.

Now, if you see that target and the starting material initially, you will be little bit difficult scenario, because this target in the starting material you see that this functional group extra functional group like methyl has to be introduced here, one methyl extra then CO 2 Me and you have to form the ring. So, then you may think that though it is a probably a different ball game together. Now, do not get nervous, we will try to analyze through it is individual retro synthetic pathway. And now we will try to the retro based on the target structure available and how this target will we can try to access it, and we will try to correlate with this starting material which was given to you. So, initially we set if you can have this we are having any again some problem the starting methoxy will be here and these will be the methyl one.

So, target structure was basically a bit sorry for drawing the wrong structure. So, this is the target structure. So, now, I say if you have this molecule and you initially as I said this angular methyl of these things will be trying to introduce through a cyclopropane cleavage. The mechanism which we just explained in the earlier slide by a simple FGI through a birch reduction or sodium liquid ammonia reduction. And I said this cyclopropane can easily be constructed through a Simmons-Smith kind of cyclopropanation.

So now, try to get this things and this methyl. Now, we are saying that ok. This Simmons-Smith is fine, but you need to access this alpha, beta unsaturated ketone and I say you will be doing it from alpha beta unsaturated alcohol. The remaining part of the other structure is all similar. Now, say alpha beta unsaturated ketone, we can simply do a disconnection based on a known reaction which is our Luche kind of reduction and then this Luche kind of reduction will basically the same intermediate. Now, if you correlate that this methyl is here this CO 2 Me is here.

And now we are saying that this particular ring will be making through a Robinson annulation which was earlier discussed to you. CH 2-CH 2 because, we will be just now making this particular bond through a Michael aldol reaction, so you need CH 2 CH 2,

CH 2 CH 2, you need a CO here, and this methyl. You said this a standard Robinson annulation. Now, do the next round of retro and we are saying that we will be disconnecting here to basically give you a methyl vinyl ketone just by a methyl vinyl ketone. So, methyl vinyl ketone is commercially available, and you need to make these particular starting material which was here through this compound.

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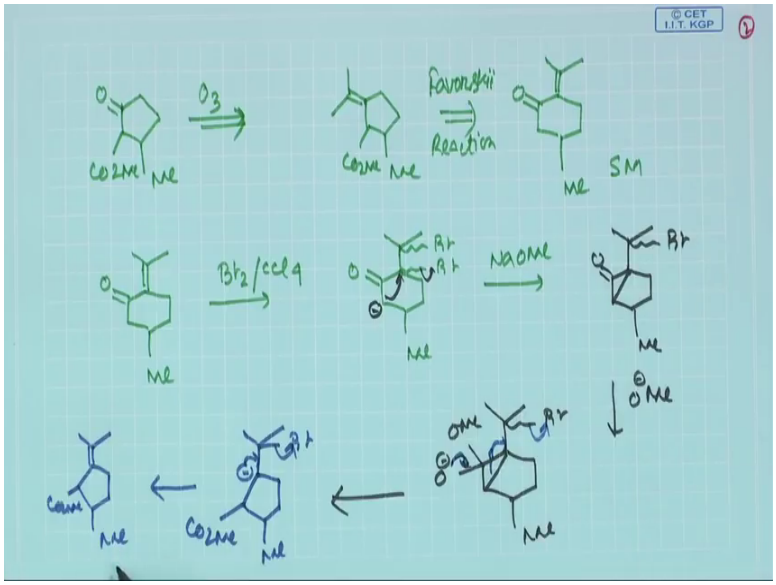


Now, I say the cyclopentanone which is be one of the intermediate, how you can construct it we say this cyclopentanone compound you might be thinking of making through this compound. Now, I am by ozonolysis reaction and then we are now closing it here, to this starting material which is pule gone. Now, this transformation can you getting some hint this transformation basically, you can used a Favorski type of reaction a Favorski reaction has I said is a ring construction reaction, but also you took think about this how this Favorski reaction will be doing it here. So, first take this starting material. Initially, you will be using bromine in carbon tetrachloride. Now, this bromine in tetrachloride will basically, brominate the double bond the isolated double bond to give you corresponding dibromide spaces, if Favorski always you said or you need a alpha bromo ketone.

Now, who react with sodium ethoxide or sodium methoxide here as it is the ester is methoxide ester so use a sodium methoxide. Now, once use a sodium methoxide initially this carbon ion will be generated and this will react with this bromo to give you the

cyclopropane intermediate in the Favorski reaction and having this Br here this the methyl. Now, see your OMe is already there, which act as a nucleophile and then you basically getting O minus OMe and then this Br is there.

This cyclopropane will now be cleaving cyclopropane will now cleave. This cyclopropane basically can cleave in different way once cyclopropane is cleaving it basically either can cleave in this bond or in this bond. But if it cleaves in this bond, you get a negative charge here and these negative charge is now getting a bromine in it is adjacent position that basically, so bromine is a good living group all of you know. So, what will trying to do you basically now cleave this is a modified Favorski reaction whenever you having a living group the ring cleavage is basically now taking place.

So, we will try to put the cyclopentane in this way these, this, a methyl is here and after this cleaving it basically gives you, so, methyl and CO 2 Me now, coming to adjacent and then a basically after this particular bond cleavage you have this negative here. So, this negative now triggers the elimination of this bromide and once this bromide elimination takes place will now get the compound which you are looking for Me CO 2 Me remains their and then you will basically getting this compound. So, it is the reaction basically goes in one sort this cleavage, this bond directly transfers here and bromine is liberated.

So, this nice demonstration of Favorski reaction where initial starting material having this pule gone with a isolated double bond. And these isolated double bond first you are brominating to make a dibromo spaces now once, this dibromonision takes place will then start with the Favorski reaction. So, Favorski reaction now give you a initial cyclopropane own intermediate with this bromine remains here now this O methoxy attacks the cyclopropanone and you get this compound. Now, as I said this cyclopropane cleavage will now be taking part on that sight, because a bromine is there, so it can now, quench these negative charge which has been generated. Negative charge will be now forming a pi double bond. So, now, this is the intermediate same.

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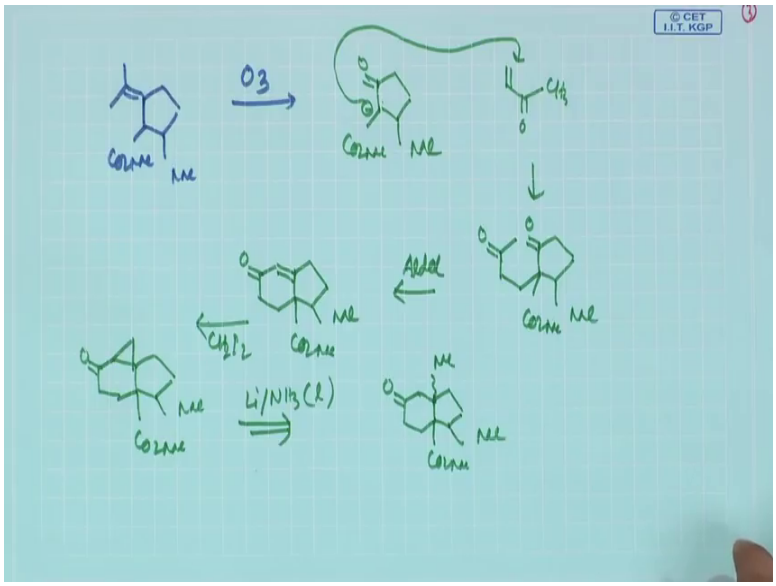


So, now what you do simply take this intermediate has we have drawn in the earlier slide CO 2 Me is here you put this. Now, do a simple ozonolysis. The simple ozonolysis will basically give you the cleavage of this double bond, and you will be generating the beta keto ester. A beta keto esters are very good substrate for Michael addition. So now, you are having methyl vinyl ketone. So, this carbon ion can be easily generated and reacts here. Now basically, what will get you get these methyl CO 2 Me CH 2 CH 2 write this double bond of ketone and this way. Now, this CO 2 Me is basically your angular CO 2 Me which is created up to the ring fusion, your carbonyl group remains here.

So now, you do the aldol. So, Michael aldol combination is your Robinson annulation. So, it will basically here, your CO 2 Me is angular, your methyl is angular. Now, no need to do the Luche reduction as was given in the original slide. Actually, the original problem the stereochemistry was given so as, stereochemistry was omitted you can simply now do the Simmons-Smith reaction here. The Simmons-Smith reaction will now give a cyclopropane. The cyclopropane will be generated here, and then everything is pretty much set now what you do, you just do a birch type of reduction lithium liquid ammonia or sodium liquid ammonia liquid. And then you ensure that this single electron is basically cleaves this bond which I explained earlier to yield you the compound which is now, the desired molecule you are looking for the methyl comes here, this CO 2 Me is there and this methyl is here.

So, eventually if you are not quite familiar of this Favorski reaction mechanism it will be bit difficult to visualize the main thing that is why I said if you come to this intermediate by conventional retro. Now, you have to link with how this intermediate can be correlated with this starting material through a Favorski reaction. A normal Favorski reaction is fine always you can start taking a alpha bromo ketone and subjected to base. But here, the starting material having a extra olefinic unsaturation that is what the bromine dibromination we do it here, this thing and this things. Then once you generate the carbon ion that will be giving the cyclopropanone thing. Now, one bromine is still there. Now, this bromine helps you to cleave the cyclopropanone towards its direction the regiochemistry is now basically fixed, because this bromine can undergo elimination with this newly generated negative charge.

And then the ring fragmentation of the cyclopropane basically goes through in this way and then you can come to here. Now once you come here, the relative part of the remaining part of the synthesis also absolutely simple and then you can simply quench. The quench the reaction mixture, you can get this product. Do a ozonolysis come here do a michael addition with a methyl vinyl ketone followed by aldol that gives you the alpha beta unsaturated thing. Your CO 2 Me methyl is in their respective position. And do a Simmons-Smith reaction with di iodo methyn cyclopropane, then you just cleave it with lithium liquid ammonia to complete the synthesis. So, this particular synthesis is very useful where we have discussed several transformation.

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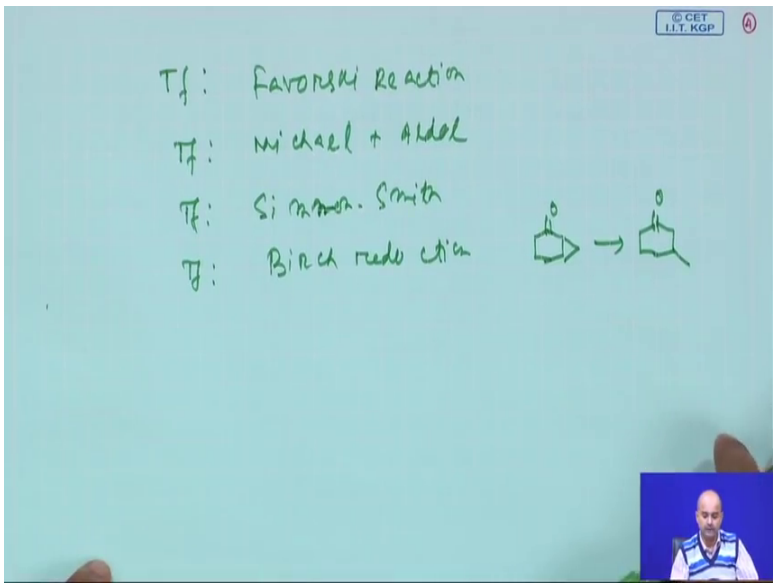

We talked about a Favorski transformation. Now, this Favorski reaction or Favorski rearrangement will definitely crucial for this particular pathway, as the initial bromo compound was not given. You have to generate the bromo compound by a di bromination. So, one bromine undergoes initial Favorski reaction to give you the cyclopropanone then the remaining bromine was essential for your another pie bond creation which will be then ozonolized to give you the ketone. You also use a Robinson annulation which is nothing but a Michael aldol combination.

You do a Simmons-Smith type of Simmons-Smith or Simmons-Smith reaction to give you the cyclopropane. And then finally, you do a birch type of reduction birch reduction to cleave the cyclopropane to complete the synthesis were you will be creating the methyl on the beta position that we explained that how it can be done. So, in these way a combination of a useful transformation and a very helpful and give you the desired target.

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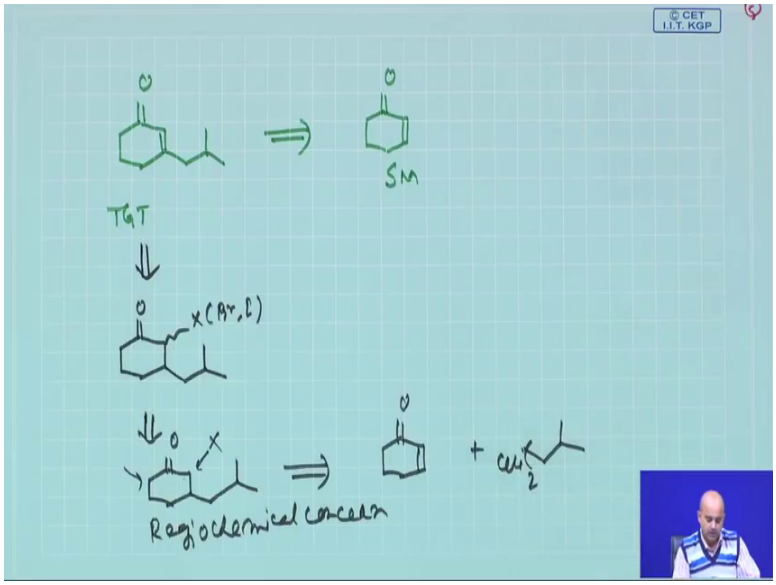


The next one, what I am going to say, it is a simple one, but will be the target is this molecule. And I say, you have to use this starting material simple cyclohexanone. Actually, in reality you can do a very straightforward retro, we say that ok. I will be having this compound, so if somehow you can have a X here, which you can an X means Br or iodo or something else you can do a elimination here, that is definitely possible. So initially, you need if you having a this compound, where you can introduce the bromine.

The point is the regiochemical issue will be big issue, because your beta position will be already blocked by a bulky isobutyl group. Now, introduction of a electrophilic bromine iodo or a bulky group like celeno ph may occur from this place not from this place.

So, this path way has a serious regiochemical concern. The regiochemical issues may not be solved, if we use this pathway. Now, this compound as I said, you can easily constructed by a simple Gilmen type addition, if you having a this kind of copper lithium. But as I said, this position is blocked by a bulky isobutyl group, your introduction of this electrophilic bromo or iodo will alpha to the carbonyl may occur in this position not here, and then you get a this product this is another target molecule.

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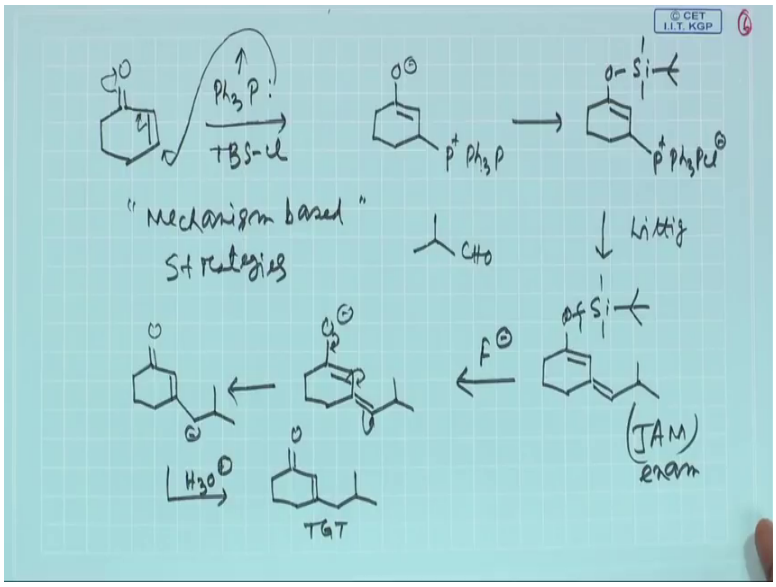


So, here is there a other way we say let us try to draw the starting material and formulate if there is a other way. Sometimes you can think about a very unusual nucleophile which normally we do not use in a nucleophile substitution reaction, with a triphenyl phosphine might be a suitable nucleophile, the phosphorous might be a nucleophile. Now, why tri phenyl phosphine was used that is a tricky question. We all know triphenyl phosphine kind of compound are a good source to generate the corresponding phosphonium species which helps in the Wittig reaction. So, here what we will trying to do we say that will be using this triphenyl phosphine as a nucleophile and use a TBS chloride.

Now, TBS chloride all why it was used first this undergoes a Michael type addition. Now, this tri phenyl phosphine becomes P plus and this basically comes here you are

having this O minus. So, initial generate a enolate comes to this position. Now, this O minus you are having TBS chloride, this is a ready for enolether formation you have this O Si methyl methyl tertiary butyl. And the chlorine here, can now utilize the tri phenyl phosphonium salt. So, what is this compound is basically a Wittig salt, the Wittig salt the is a alile Wittig salt. This is absolutely now, we are saying that will try to now introduce these compound as a Wittig salt and we will try to react with some of the aldehyde.

Now, what functional group you require on this point you need a isobutyl group. So, we will be using a this particular aldehyde isobutyl dehyde here for this Wittig transformation. As I say this is not a very unusual a this is not a usual transformation it is kind of a unusual thing, but still it gives you very nice approach. So now, we are basically making this compound. So, try to correlate with this target, target was basically this. So, this enol cinyl ethyl now needs to be hydrolyzed, because in the final target the silicon that is not there. So, what you do, you basically cleave it with provide source now provide source cleave this silicon florin bond basically, give you the enol back. Now, this enol is here and this enol will try to utilize its charge through this kind of regiments.

And this is now, very close to the target structure which we have drawn. Now, this minus this will be now accepting the proton from the acidic source if you use some water and will basically give you the. This particular problem once came in the JAM exam and this basically demonstrates the very nice OA, you can introduce different alkylic groups in a beta position to a alpha beta unsaturated ketone without using the standard Gillmen or other reaction.

So, what basically, we did we use tri phenyl phosphine as a nucleophile to generate the phosphonium species, this phosphonium species acting as a Wittig salt. The enol phosphonium ion, which is now trapped with this TBS chloride to give you the enol ether. So, this phosphonium salt will undergoes Wittig reactions with the aldehyde. This aldehyde was basically chosen based on the target molecule structure, depending on the structure the target which was this aldehyde. So, it will be something like this compound.

Now, you cleave the enol cinyle ether with this you get the enolate, a simple anion relay it comes here and this quenched of with this aquas acidic condition, and you get your target molecule. The point is this is a very nice demonstration of mechanism based strategy. This mechanism is very simple and then it will basically also giving you the

idea that how key transformation or a now this case you are basically generating a Wittig elite or Wittig salt in the reaction mixture by using a tri phenyl phosphine as a nucleophile that basically sets of the entire thing.

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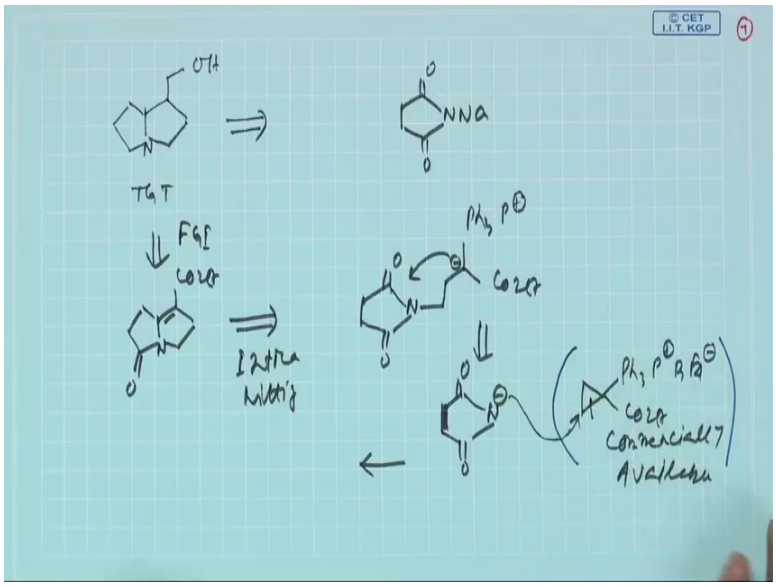


We will be trying to solve another problem, which I believe is little bit complex, but the target molecule was this target. The starting material which was given I have just given you a succinimide sodium succinimide. Now, time we do not have too much time you just try to do the retro in a conventional way. And you say that this compound you can access from this way by simple doing a hydrozination here, this CO 2 it can be reduced to lh as well as this amide, will be also reduced to give this amine, cyclic amine.

Now, the retro, which I am drawing here basically based on this succinimide structure. I say this thing will now CH 2 CH 2 will give you a this kind of phosphonium thing as a minus you can basically do a intra molecular Wittig. Now, trying to visualize this thing the succinimide N minus and this particular Wittig elite has been chosen. This is a very unique Wittig elite based on cyclopropane thing. The cyclopropane as I said they are very unstable a this minus is symmetrical thing. This minus will basically try to attack one of this cyclopropane methyl group. And then basically, cleaves this particular thing you put a minus here, because this minus is stabilized by this CO 2 (Refer Time: 31:03) group.

So, if you do a standard nucleophilic addition on a cyclopropane based Wittig this is actually commercially available. So, what you do you basically get this compound. After this opening you get this compound. And this compound undergo intermolecular Wittig now I say intra Wittig. Now, once the intra Wittig is done, you get this amite from this part, and you get a alpha beta unsaturated ester. Now, you simply doing a lh mediated reduction. So, this lh reduction will first give you this amide two amine and then CO 2 group will be also reduced to CH 2 O H, the double bond may remain here you can just reduce the double bond with palladium charcoal and hydrogen. So, this is basically simple FGI.

So, this transformation until now let us you know the particular this kind of Wittig salts are commercially available. Probably it is difficult to design, but once you know that this kind of Wittig salt is exist, you can just think about the mechanism how this Wittig salt or this nucleophile can cleave this Wittig cyclopropane Wittig and you give you a 2 carbon extension by this CH 2 CH 2. And this negative charge comes here because it is stabilized by the CO 2 et.

So, by this way by combining different mechanistical aspects of key transformation, you can basically design very efficient path way of certain molecule entities and target molecules which we have explained. For this example, and it is simple starting material like succinimide sodium salt can be said as very good starting material to generate this kind of bi-cycling nitrogen containing compound and this compound is very much available in many of the natural products many of the natural occurring alkalines.

So, we will continue our lecture in the next lecture, till then have a good time. And just go through the assignments and try to solve the assignments, and I will be seeing you again in the next lecture.