A Study Guide in Organic Retrosynthesis: Problem Solving Approach
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Lecture – 09
Tf/SM/Fg based strategy and its exploration for some simple target molecules

So, welcome back we are basically continuing the transformation based strategies, starting material based strategies and functional group based strategies in a combination way.

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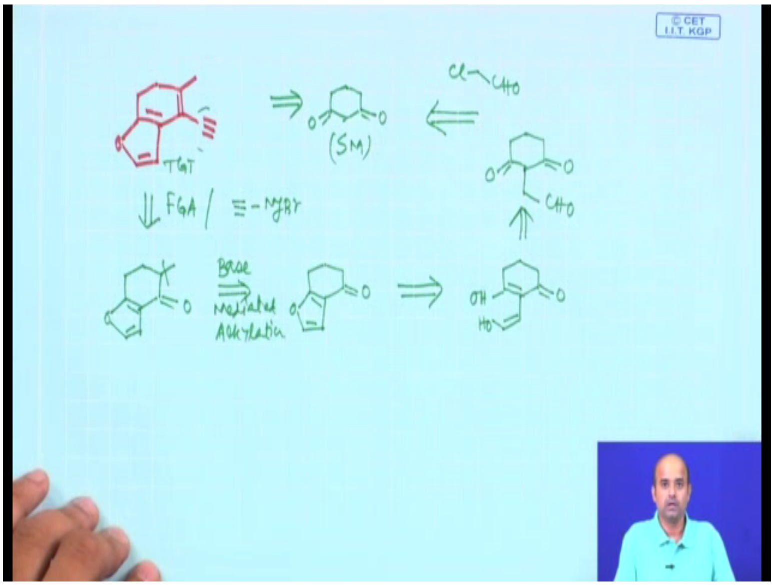

So, next will be trying to continue on the same topic and will give you target molecule which is little bit different than the earlier. The target molecule here having a structure is a bit complicated structure and we have not talked about any of the heterocycle molecule yet and this target is a heterocyclic based structure. You see the structure, it is having a furan ring fused with a cyclohexane kind of compound and there are a alkyne appendage means a acetylenic functional group was there at one end. The starting material I will try to give it so to make your job little bit easier, the starting material which was giving to you is a 1, 3 cyclohexane dione.

Eventually, this whole transformation is a unique transformation and if you try to figure it out the entire target first, let us analyze the target, then you try to go back that how it can be done. So, first we will be doing a functional group addition keeping the furan part remain similar and you see this compounds can be done in a functional group addition way, where basically you will be using a acetronic magnesium species, which is acting as a nucleophile. This nucleophile attached to this carbonyl you get a OH and this alkyne, then you do a simple want to elimination here to get the target molecule.

So, this intermediate how you can prepare? This intermediate again can be prepared if you are disconnecting this methyl group will be introduced at this stage, the remaining part is similar. So, you basically doing a base mediated alkylation with a methyl iodide as a electrophile, this a starting material, one of the starting material.

Now, we will try to construct the furan ring. Now, furan ring was thought to be making in this way, if you have a compound like this and this vinylic alcohol, this will undergo dehydration reaction to make this compound. Now, our initial starting material which was given is a cyclohexane 1, 3 dione, now see the cyclohexane 1, 3 dione was almost came in the design.

So, next if you are trying to do another round of retro that will give you some compound like this, this is basically very simple; simple formation. Now, this compound are is similar to this, if you analyze that this compound is very prone to analyzation, this acidic hydrogen is 1, 3 di ketone. So, it will be instantly analyze to this vinylic alcohol, this aldehyde also having acidic hydrogen that can also analyse to give you this vinylic alcohol. Now, both of this two vinylic alcohols will undergo dehydration reaction to give you furan. So, this thing is important and now this intermediate can be correlated back to this original starting material which was given to you, only thing is you need to introduce a hanging CH2, CHO group.

Now, this hanging CH2 CHO group can be introduced by a chloroacetaldehyde as a electrophile.

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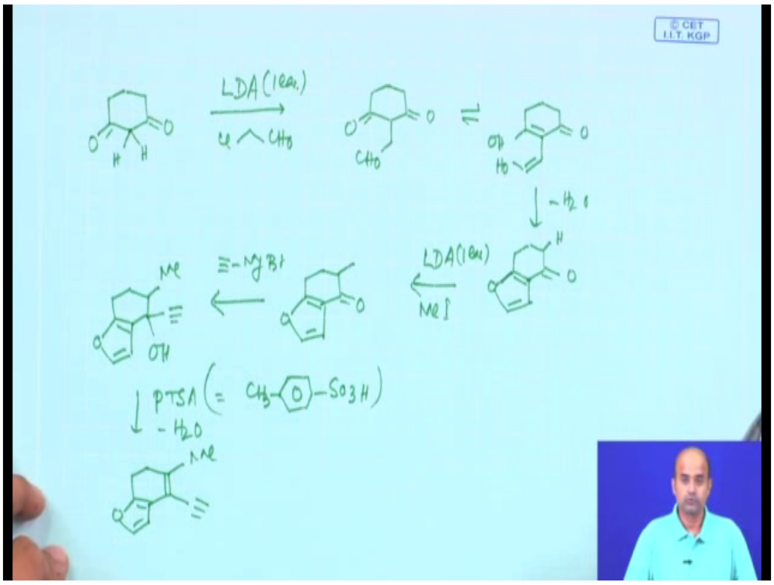

So, go back to the synthesis in a forward path way, so initial we will start with the starting material which was given to you a cyclohexene 1, 3 dione, you do a base mediated alkylation LDA, this is the most abstractable acidic hydrogen, one equivalent of LDA and then you react with chloroacetaldehyde. So, you will get the corresponding alkylated product and then you allow this compound to analyze. So, it basically forms this analysation as well as this aldehyde also will be analyzing to give you this and then sample dehydration reaction will basically give you the furan core, this furan part and this molecule.

So, next was very simple as was as discussed in the earlier part, you do a again a one round of LDA and methyl iodide. Now, this will be the hydrogen which will be abstracted one equivalent of LDA, one equivalent of methyl iodide, we will basically get this compound of furan part remain intact. So, we are almost close to the target molecule, next we said that you need a alkyne grignard reaction, alkyne grignards or can be easily generable easily generated and you do a nucleophilic addition on this carbolic compound will basically get this alcohol.

Next, we said you just do a dehydration reaction by using this compound with PTSA, what is PTSA? PTSA is para toluene sulfonic acid which is a dehydrating agent and then we basically undergo 1, 2 elimination and which will did you the target molecule which is. So, the inter path way of this complex molecule which was looking a bit complex at the beginning, we are trying to do a very methodical or strategical approach that how stepwise retro synthetic disconnection which will help you to go reverse direction to come to the starting material which was given.

So, this is the power of retro synthetic disconnection, you do the initial reverse pathway, which was just shown you here, do a reverse pathway then we know trying to the forward path way, you start with the starting material and do the forward sequences as described in the reverse arrow. Only, thing is you have to remember that each and every step you need to put down the proper reagent and proper reaction condition.

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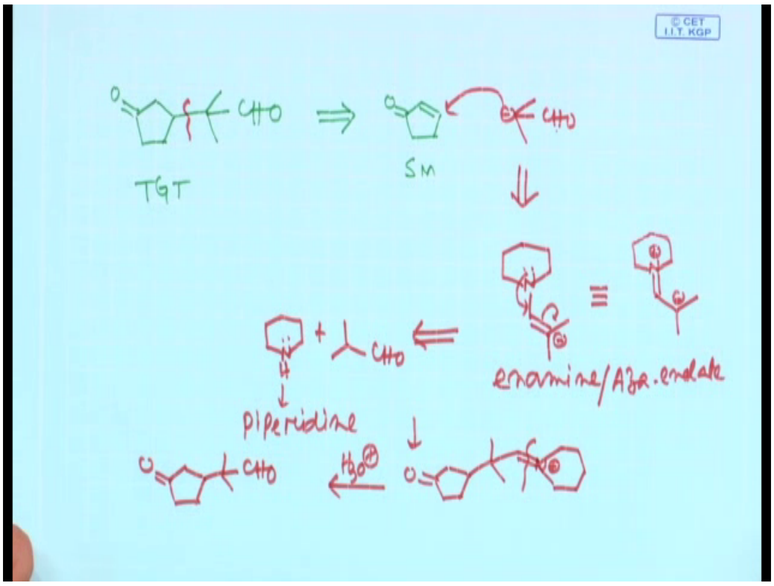

The next one will be a similar kind of thing but we will be talking about a potential useful transformation which is named as aza enolate alkylation. The target molecule was this and to make your thinking simple we will give you the starting material also, I said this compound needs to be prepared from a cyclopentenone.

Now, if you do a disconnection just by using a very standard disconnection, you will see that let us put a break here and then if you have access of something like this kind of anion, which will attack in a michael fashion, but in reality this anion probably you would not get it, I mean you can basically think about this kind of an anion, but how to access this kind of anion, then your a unique transformation which is named as enamine alkylation will come into picture. We are just drawing some species which is basically a enamine. Now, enamines are what? E amine, this part is e this part is amine, it is called enamine. You can also name them as aza enolate, you know enolate; enolates are basically nothing oxygen containing the double bond containing compound, this is enoles, but aza oxygen is replaced by a nitrogen.

Now, this enamine aza enolate you can simply prepared by taking a secondary amine with a suitable aldehyde like isobutyraldehyde. Now, how this reaction goes this nucleophilic amine attacks to the aldehyde carbonyl and then simple water elimination takes place to give you this enamine or aza enolate. Now, enamines are very strategically useful intermediate. Now, how this enamine will then react to this electrophilic Michael accepted means somewhere you have to generate this enamine as a nucleophile. Now, this lone pair we are basically forward this lone pair will try to do a electron relay and put this negative charge here. So, in principle it will basically you can visualise the entire enamine as a.

Now, this nitrogen will be plus and then it will be iminium things. So, negative charge now resides here. So, this is basically equivalent of these things. So, emi, emi the CHO this carbon is basically after you remove this emine part which will be giving this CHO. So, initially you react this compound which is named as piperidine, the secondary amine cyclic amine with this isobutyraldehyde, you get this enamine first, then under this reaction condition enamine you need to isolate it, you react this enamine with this starting material. Now, the lone pair of this enamine will make this things this negative charge comes here, now this one will know attack in a 1, 4 fashion.

Now, why it would not attack in the 1, 2 fashion, problem the study crowding, this nucleophile is a pretty bad nucleophile having it is 2 methyl groups are here. So, it will attack this fashion, then you will basically get this methyl is there and then you can put this entire this, your nitrogen plus, is now becoming a emine. Now, you simple emine you can basically hydrolyse it to simple hydrolysis by aqueous workup.

So, this part will be knocked down and then you can come back to your aldehyde which was the original target. So, this transformation is basically based on a enamine or aza enolate alkylation and we potentially took a compound cyclopentenone and where you are making a new carbon-carbon bond through enamine alkylation and this is a very powerful method to make a new carbon-carbon bond, probably you can find in many text book how this enamines are functionally manipulated or synthetically manipulated to give you very useful intermediates.

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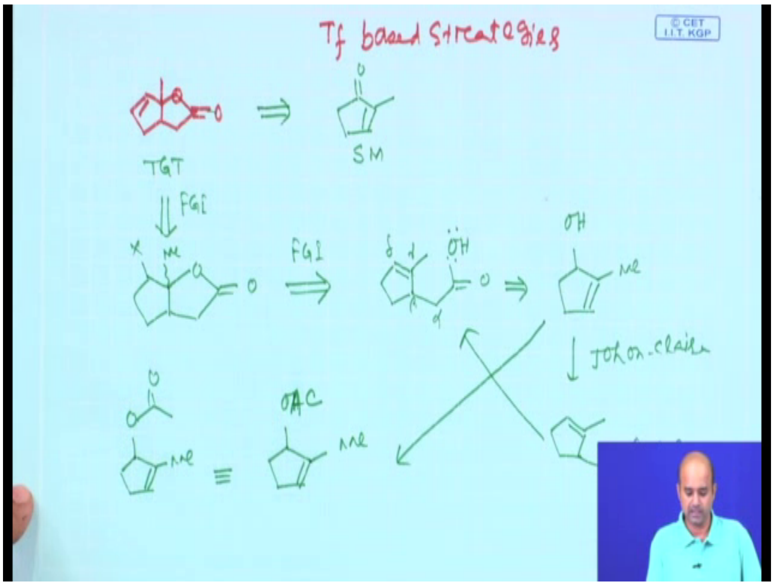

So, as you said we are trying to give you a compliancy for idea about the different transformation based strategies. So, next we will be talking about some useful strategies which is also very important we first draw the target molecule which is, which need to be synthesized. The target molecule having a structure something like this and let us say I will give you the starting material also, the starting material was a simplified starting material is cyclo pentenone.

Now, we go back to the retro pathway based on whatever transformation we can think of. Which is the target molecule is basically if 5 member lactone in one end and one end it is having a cyclopentene structure; the starting material is basically having a cyclopentenone with a methyl in it is. So, try to correlate this, but initial correlation will be difficult, now until and unless you know this transformation probably that will bit difficult, but eventually we will try to do it.

We initially says that we will be putting a x group here, now x is a supposed to be a good living group which undergoes elimination of h x to put this double bond here, so is a functional group interconversion. Now, try to figure it out the next part, next part we say, so we need to introduce the x, which will serve as a living group the methyl part remain here.

Now, we will be drawing a intermediate whose structure is something like this. Now, why we drew this retro, we have already talked about some reaction named as halolactonization; we say halolactonization is very usefully reaction where you can first make a bromonium or halonium ion then you have a internal nucleophile or intra molecular nucleophile which attacks the bromonium ion to give you this things.

Now, if you have this acid, this acid is what kind of acid? You would try to give the nomenclature is alpha, beta, gamma, delta, it is a alpha, beta is basically gamma, delta unsaturated acid. Now, this things you will doing iodolactonization reaction and then this OH of this carboxylic acid will put this ring closing to give you a lactone or now, we have to you already know that gamma delta unsaturated carbolic compounds can be prepared by Johnson orthoester claisen rearrangement.

So, the earlier information which we just told you earlier, that you can use it right now. So, we have to basically now try to figure it out, a simple allylic alcohols is not it, have to do a simple allylic alcohols. Now, these allylic alcohols if you do a Johnson orthoester rearrangement, you can basically Johnson orth johnson claisen rearrangement which I have already discussed you can create this CO 2 ET.

Now, which is nothing a alpha, beta, gamma, delta unsaturated carboxylic acid. You basically hydrolysed this acid to come back to the, for in jester to come back to acid do halolactonization, fine. Now, there are potentially other reactions which will also give you similar other transformations, this reaction is now we will be discussing. You take this corresponding allylic alcohol, react with I mean put it like a acetate. Now, acetate is basically what? Is basically O CO CH 3, so now, we will try to use a similar kind of 3, 3 sigmatropic rearrangement, which is named as Ireland claisen rearrangement, is a similar variation of Johnson orthoester rearrangement is named as ireland claisen rearrangement.

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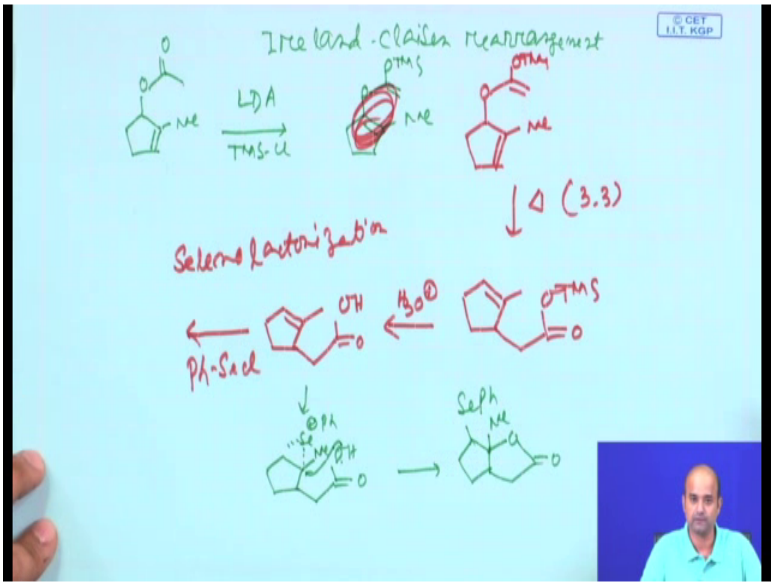

Now, what exactly this transformation is? The transformation basically is you have a this methyl O CO CH3, you treat with a base LDA and put a trimethylsilyl chloride. So, initially LDA will abstract this acidic proton to give you enolate and this enolate will be then trapped as it is enole silyl ether is this. Now you see is a 1, 2, 3; 1, 2; 1, 2, 3; 1, 2 oh sorry this double bond was have been replaced. So, you can have a structure which was initially this, yeah O S, this is a structure.

So, now, see you 1, 2, 3; 1, 2 3. So, you can now subject this compound with simple heat which will ensure the 3 3 sigmatropic rearrangement take place and you basically now get this TMS ester. The TMS ester is basically you can hydrolyse it by aqueous acidic workup, which will give you the carboxylic acid.

The carboxylic acid you can do the ring closing by halolactonization, we will try to do a another reaction which is named as selenolactonization; seleno lacto nization. What is that? We will subject to a compound name as phenyl selenium chloride is having similar properties of a iode or bromo, it will basically give you a first a seleno species and this seleno species will be a in similar way; the same way iode or bromo species attacks.

Now, this oxygen internally attack to this carbon, in a nucleophilic fashion and then basically you will be getting the seph here, next step is you have to get rid off the selenium things. For that reason, for that purpose it is a useful transformation we called selenoxide syn elimination, the transformation next will be using selenoxide elimination.

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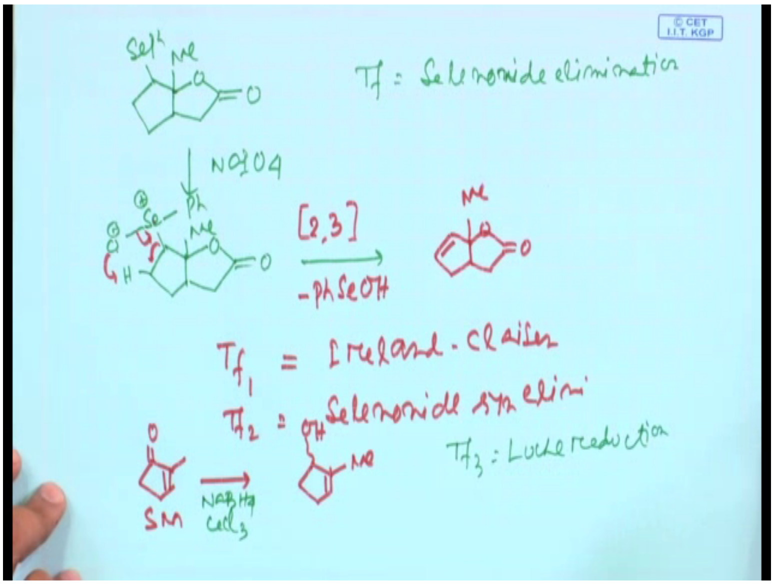

So, what it is exactly? You take this compound with a sodium periodate which is basically oxidise the selenium first to give you Se plus O minus and Ph.

Now, we need to have a 1, 2 elimination to get the target molecule. Now, selenoxide will get a hydrogen in it is close proximity, this hydrogen. Now, this selenoxide syn elimination is basically a 2, 3 sigmatropic rearrangement, basically 1, 2 is a 1, 2, 3. So, it basically fix up this hydrogen and then this things takes place.

So, now, only this is a close transition state to cyclic transition state and after this reaction takes place you basically get the O is there, this methyl is there and the final product which will be eliminated as phenyl selenol, selenic acid, phenylselenol actually. So, PhSeOH will be released and this was called selenoxide syn elimination, you can also do a iodolactonization, do the h i elimination, you can do a bromolactonization, but this is a another important reaction selenoxide syn elimination.

So, what are the transformation were used for this particular target Tf1 transformation 1, we use a Ireland claisen rearrangement, we use selenoxide syn elimination and the starting material was given to you a cyclo pentenone and from the initial starting material you need to do a 1, 2 reduction to convert it to a allylic alcohol. How you can do it? We have discussed it, then simply do by a luche reduction just by reacting with sodium borohydride and cerium chloride. So, the, which does not attack the alpha, beta unsaturated esters only attack the 1, 2; 1, 2 carbonyl; 1, 2 carbonyl reduction takes place, 1, 4 is unaffected is a chemoselective reduction.

So, transformation 1 is Ireland claisen, transformation 2 is selenoxide syn elimination, transformation 3 we used a luche reduction. So, basically the entire pathway you can formulate the combination of multiple transformations. We used a very simple 1, 2 reduction by luche pathway, then you use a Ireland claisen to come back to generate the gamma, delta unsaturated esters with this starting material and then we do a selenoxide syn elimination after the selenolactonization or the respective lactonization takes place.

The selenolactonization is basically as you said the 2, 3 sigmatropic rearrangement first you need to oxidize selenium to a proper oxidizing regent by sodium periodate, then you make sure the 2, 3 sigmatropic takes place is a thermal reaction this O minus abstracts hydrogen and the electrons shifting is this way, you get the particular target molecule which is desired for this transformation.

So, eventually the power of this multiple transformation based strategy is very useful and definitely I will request all of you to study as many transformation as you can through a standard textbook or through the see in (Refer Time: 28:07) whatever resources are available to you just go through it and then try to figure it out whether those reactions will be quite useful for you for a given set of transformations.

As I discussed in particular 2, 3 problems the first one we are talking about a furan derived compound in this week and then the second part we talked about this Ireland claisen rearrangement, which is basically nothing but a extensive version of a or extend version of a Johnson orthoester claisen rearrangement, 3, 3 sigmatropic rearrangement and that take over massage is, if you having a some delta, gamma, unsaturated esters something like this straight forward you can go back to the Johnson orthoester claisen rearrangement as your main transformation.

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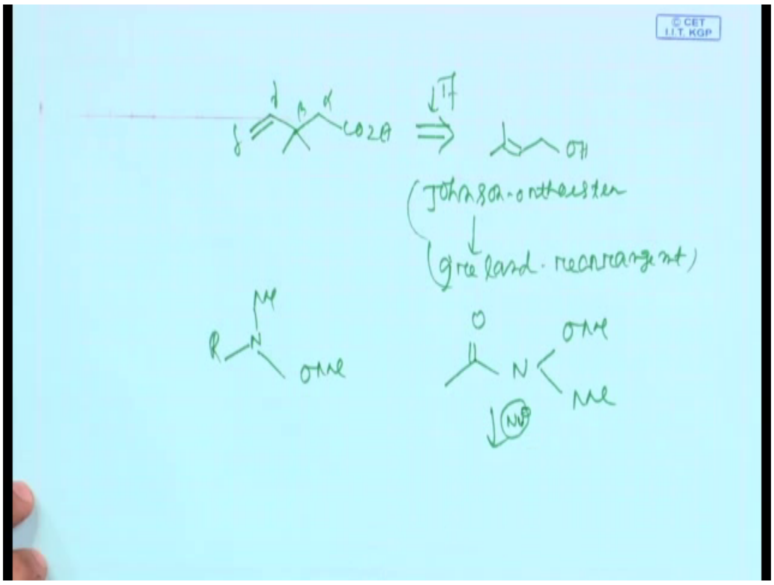

Transformation will be Johnson orthoester claisen rearrangement and then the Johnson orthoester claisen rearrangement will give you the gamma, delta, unsaturated ester, is similar like you also talked about Ireland claisen rearrangement, which is basically nothing a modified version of a claisen reaction and that will also give you a gamma, delta, unsaturated carbonyl compound and the rest of the things are basically functional inter conversion, you have to convert whatever functional group we have generated.

Like, for this one case we talked about weinrub ketone synthesis, after the Johnson orthoester tooks place you have this ester, you can convert the ester to corresponding amide because your target molecule has to have a ketone. So, esters are highly reactive then you try to reduce the activity of the ester, by converting the ester to corresponding amide and this amide which we used is a weinrub amide and weinrub amide having a ome group, is a having ome group, this ome group basically helps.

So, if you have a amide like this ome and this ome basically how it helps? It basically helps with chelation. So, the chelate is rock stable does not matter how much equivalent nucleophile you add, the chelate will remain stable, then you just quench it with the acid, you get the 1 equivalent addition of nucleophile.

So, in the next week we will be talking about this entire transformation functional group and we will keep on discussing several known transformation based strategies as well as if there are some unknown transformation, we will discuss the mechanism in detail, then you can try to figure it out, how this a pathways can be simplified and you all of you can get some benefits out of this.

So, we will see you in the next week, until then goodbye.