A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 29
Fg based Strategies (Contd.)

So welcome back students we are basically discussing functional group-based strategies and today we will be talking about guideline 5.

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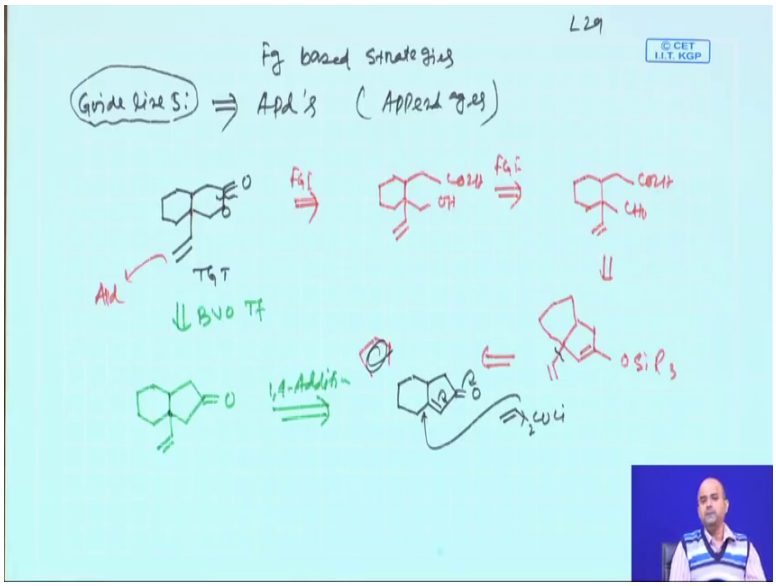

So, last week we talked about the protection group-based strategies, and you have said that several protection groups and protecting or protecting groups can be used in a synthetic operation, to a efficiently or a effectively tuned the chemical reactivity of several functional groups, the guideline 5 if you remember the functional group-based strategies, here we will be mainly talking about how you can introduce several appendages.

Now, appendages as I earlier discussed appendages are basically hanging functional group through a acyclic chain or a cyclic chain. So, particularly here we will be more focused on how to introduced different kind of appendages by using key chemical transformations, and which is basically purely based on functional group-based strategies. Now as obvious we will be talking about some target molecule, and the target molecule which I am now drawing at the beginning is having a bicyclic lactone structure.

Now, if you see the target, if it is the bicyclic lactone structure, and having a vinyl appendage we called is vinyl appendage which is hanging from this ring fusion ring fusion. So, this is the appendage we are talking about. So, how to introduce this kind of appendages, normally the there is absolutely no flexible rule depending on the FGI depending on the transformation you can introduce this appendage by any means any methods.

Now, as there are other functional group also need to be constructed. So, we will first try to formulate in this way, we say the if the appendage we would not be doing the disconnection at the beginning we, first doing the disconnection at this lactone the lactone basically was initially thought to be disconnected by this bond, through a FGI. So, you all know that hydroxyl acid can be easily be heated up, and that undergoes a simple condensation reaction with the help of water elimination to give you this lactone.

now this part this these things can be easily undergoing or retro synthetically disconnected through a common FGI, that aldehyde can be converted to the corresponding alcohol, and which then will condensed. Now this one now will be trying to give you a and then we need to is a ch2 these things we need to fuse this cyclic ring here the drawing was little bit fine. So, you just need the vinyl appendages here.

So now if you see this is the cyclohexane and it is vinyl appendages here, if you could do some kind of oxidative cleavage here that might give you this particular things, but you have a difficulties you also have a vinylic appendages here, but that can be easily be controlled by one equivalent of ozonolysis ozone, basically always touch the more substituted or more electronically rich double bonds. So, in that context this double bond in the ring which is more substituted is more electronically rich. So now, the appendage is disconnected, the appendage disconnection now was done by a, for say I will just try to put a ring in the this way, and then you see this appendage disconnection was now can be efficiently done by a vinyl copper lithium or a gilment reagent.

So, what happened, this is basically nothing a vinyl anion it basically comes here goes there and o minus. So, this in all you basically trap it, and then you have vinyl one double bond you have a in between is a vinyl ester, vinyl ester is a absolutely labile and the electronically rich also. So, you can do it selective ozonolysis here to come here. So, this part is basically the appendage insertion, now also there are other ways which also

you can be potentially use, now this molecule if you do a disconnection something like this.

Now, what is this is basically a Baeyer villiger transformation, a Baeyer villiger reaction in in principle it can basically give you 2 lactone product, if this bond migrates it gives you this, if this bond migrates it will give you this other lactone, but if this bond migrates because this is a more substituted. So, Baeyer villiger oxidation also is a good way to introduce these things, now this is basically you can now think about also using this one.

So, there is a start this starting material you do a vinyl copper lithium, vinyl copper lithium comes here and then gives you this compound simple 1 4 addition simple 1 4 addition. So, appendages are normally introduced at early stage or late stage depending on your functional group requirements, and you can you can basically think about introducing appendages at any point of time based on the appendage structure.

So, next couple of problems which will now discuss.

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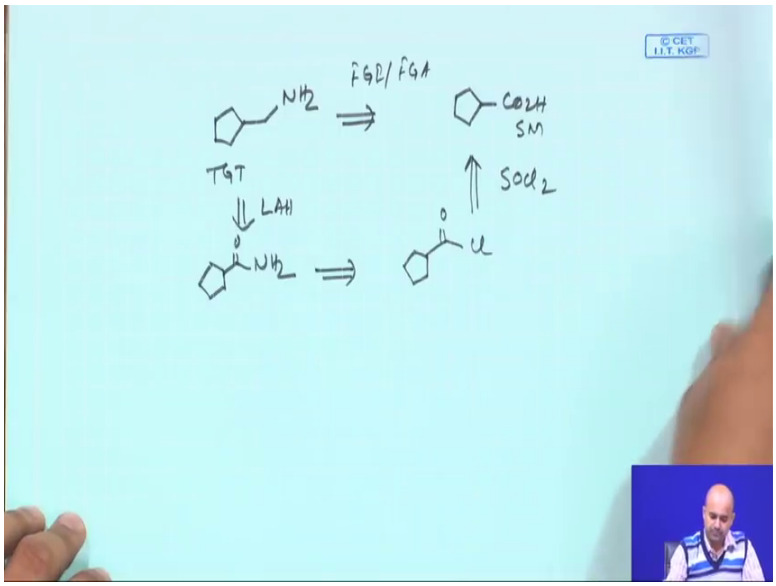

we will be having similar appendages disconnection, where the appendages also contains a functional group. If this particular molecule we say is a target molecule is the cyclopentyl methylamine, and the starting material which was giving to you cyclopentane carboxylic acid, it is basically purely FGI the starting material already having a appendage or this functional group here. So, this is in true sense you can simply

call it a FGI or functional group addition, now let us see what are the reactions you know which will basically give you to access this kind of compound, this is the amine. So, amine and principle can be synthesized, if you have a corresponding amide isn't it.

So, amide you selectively reduced by a reducing agent, like lithium aluminium hydride you get the is very, very conventional straightforward pathway, the amide can easily be prepared from corresponding acid chloride, an acid chloride can easily prepared from the corresponding acid by using simple thionyl chloride. So, this is a straightforward FGI manipulation, you just do couple of FGI isn't this is nothing else, there is no name reaction involved no transformation involved it is very simple FGI very simple FGI, you introduce the particular appendages starting from this functional group I think of this functional group.

now the similar way we will be talking about how different.

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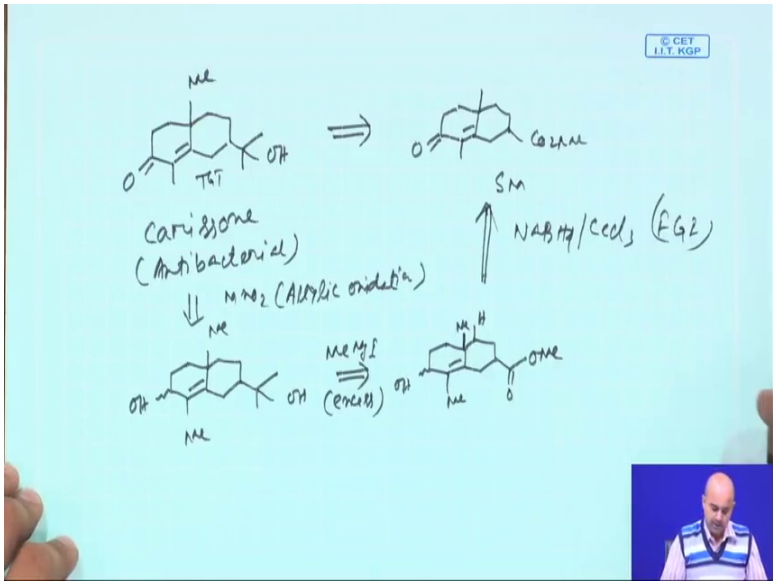

appendages or different functional groups need to be introduced at different reacting site of a given molecule, this particular problem which is based on a similar kind of approaches, it is basically a this compound is a natural product, it is name is carissone, it is a anti is having antibacterial property this compound is having antibacterial property.

Now, if you see the structure is a bicyclic compound and one in having alpha beta unsaturated ketone, one is having a tertiary alcohol, the starting material I say starting

material was given to you I have given a starting material, the starting material was also given to you fine. So now, you see that how you can correlate this starting material to this, there actually only differences with this starting material and this target is basically the starting material is having c o to m e, and the target is having a tertiary alcohol, basically this appendage this functional group you need to find tune it you need to find tune it, now if you do the retro of this particular target, it is mean is that some probably if you can protect these or something else you like you do a other way.

I say I will be not doing the protection, I will be doing this way. Now if you have this intermediate which is basically allelic secondary alcohol and a tertiary alcohol, you can do a selective oxidation by a allelic oxidizing agent like manganese dioxide, which is known for allelic oxidation, isn't it? Now coming to here this compound, basically is pretty much close which you now can think about a retro by putting other groups in a similar, sorry this is the ring junction this will be hydrogen this will be the methyl you put a ester.

Now, I said esters if you use excess methyl magnesium iodide, which is already talked to you, you basically get a tertiary alcohol that is fine. So now, use coordinate the starting material. So, how this starting material can be converted to this allelic alcohol, you can simple do by luche reduction sodium borohydride cerium chloride. So, all are basically very standard FGI very standard FGI. So, first take this starting material do a luche, it will come here then, this luche you do a excess methyl magnesium iodide excess, and you get the tertiary alcohol then this is the tertiary alcohol, is the allelic secondary alcohol you do a simple allelic oxidation.

So, we are basically we are not using any production, because allelic alcohols and tertiary alcohol tertiary alcohol there is no hydrogen there is no obstructable hydrogen. So, if in principle this would not undergo any kind of oxidation, that is the very standard straightforward problem a next one will be little bit complicated, but let us first do this structural analysis.

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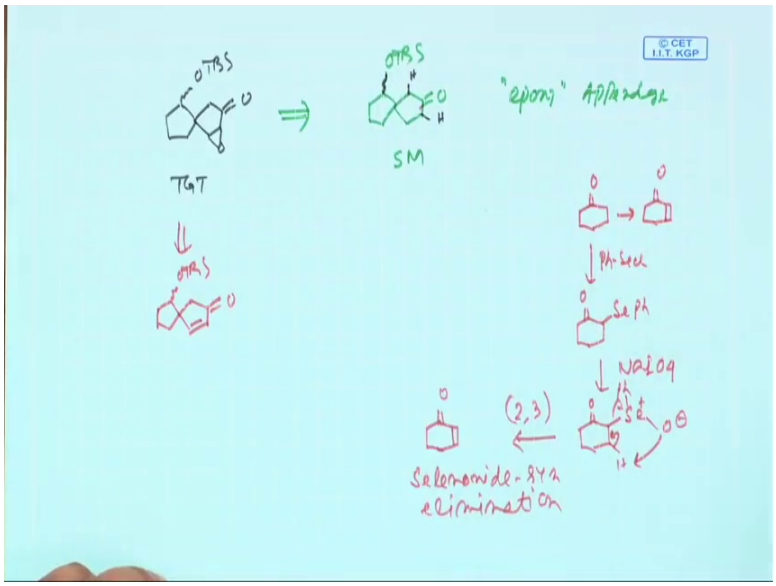

It is given as spirocycle compound, a spirocycle epoxide and this end having a t b s this was the target molecule was given to you, and the starting material which was also given to you is having similar structure.

So, basically point is if you now try to correlate the starting material of the target molecule, you need to introduce a epoxy appendage. So, you need to basically introduce the epoxy appendage, at this part of this carbon compound, this epoxy appendage to bring the epoxy appendage basically, you need to create a double bond a pi bond. So now, let us do the retro. So, if you now try to do the retro this part will be your OTBS your so, basically if you have this compound you can easily create the epoxide.

Actually, starting from this compound to create this compound seems to be little bit problematic, now if you remember earlier we said that cyclohexenone can be converted to cyclohexen1 by selectively introducing a phenyl selenium chloride. So, it basically gives you a S e P h, and then this S e P h was subjected to oxidative rearrangement, which basically sodium perorate, it reacts in this way selenium plus o minus and ph, now this o minus abstract this hydrogen, and is undergoing a 2 3 sigma tropic rearrangement, 2 3 sigmatropic rearrangement to give you a cyclohexenone which was already known it is called selenoxide elimination, selenoxide syn elimination, and this is one of the very well-known method to introduce a particular alpha beta unsaturated double bond adjacent, to the carbonyl group in addition you can do by other ways also.

Now, here if you see you need to do similar kind of chemistry, but here you are having basically, 2 hydrogen or 2 alpha positions, where in principle the selenium can attack now out of this 2 hydrogen, you will find that this one is a relatively difficult because, it is close to the OTBS thing. So now, we will do the forward synthesis by analyzing the a steric bulk of this OTVS group.

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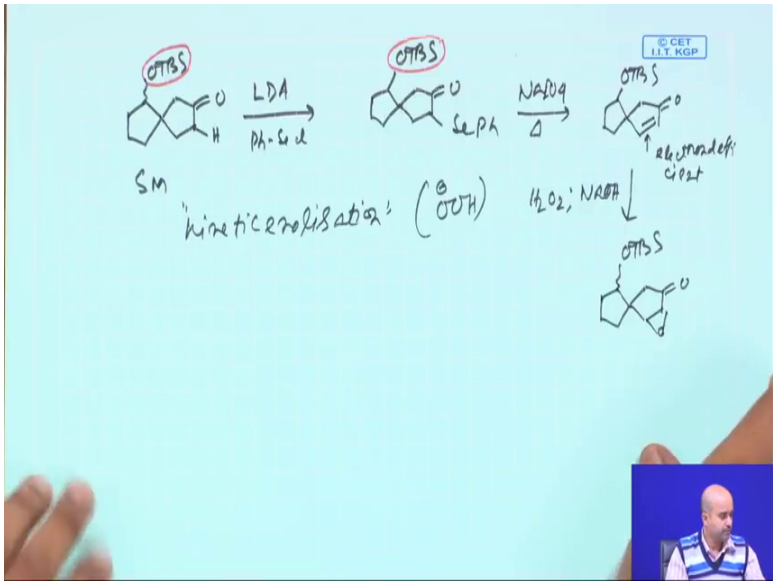

which was present in the starting material starting material is this.

now I say I will be using a LDA. So, LDA basically will try to pick up this hydrogen which is kinetically is irrelevant, and then you use P h S e C l. So, basically you will get this S e P h. So, steric bulk of particularly this group steric bulk of this group basically dictates, that whether this hydrogen will be obstructed or this will be obstructed and this is in close proximity this hydrogen one be obstructed by the base, and now as it is already obstructed you just do the selenoxide syn elimination, sodium power iodide and little bit heat a basically end up with OTBS and this.

Now, see you have already created a alpha beta unsaturated carbonyl thing, and your target you now need to introduce a epoxy appendages, now you just say you cannot use m c p b a because this double bond is already electron deficient, this double bond is now electron deficient and m c p b a is also a electron deficient oxidizing agent, now so, here you need to use a different reagent conditions which you already used earlier, is the

hydrogen peroxide and sodium hydroxide that basically gives you a hydro peroxide anion.

And then if you react this hydro peroxide and hydrogen peroxide combination, basically end up with this epoxide. To this epoxide appendage introduction was efficiently done by a series of reaction not series of reaction the initial thing is a kinetic enolysation, a kinetic enolysation kinetic enolysation because the steric bulk of this OTBS group will make it possible the sterically less crowded or lessed less congested hydrogen will be obstructed by the base (Refer Time: 20:20) phenyl selenium chloride then look at s e p h selenoxide syn elimination, they now do a electron deficient the development becoming electron deficient.

So, you need the electron reach oxidizing agent, and that is basically undergoing is not a oxidizing agent nucleophilic types of attack fast, is OH minus attack in the one for Michael fashion, and then you have this particular epoxide appendage can be introduced, this is a very nice and interesting strategies, next poll m will be trying to figure it out on a similar kind of thing.

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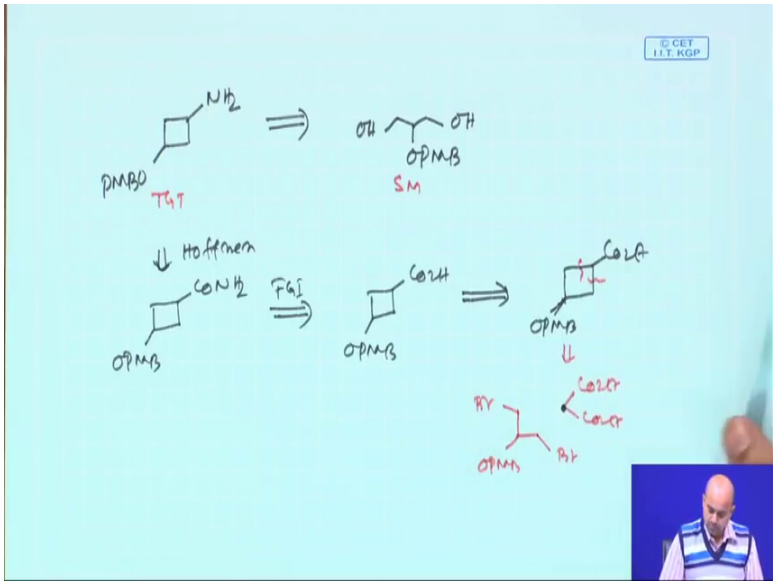

You say you are giving a cyclo butane based target, and the appendage where you need to introduce ANH 2 appendage, this particular functional group or appendage well the starting material also is given to you, I have given you the starting material, I said I am giving this starting material this one.

Let we try to analyze that how you can close it, see the number of carbons are almost similar this starting material is having 3 carbon 3 carbon framework 1,2,3 this 1,2,3,4. So, one carbon extra you need to introduced at some point, now do a very standard FGI, the initial FGI which will be thinking it is something like this, is a very name very well-known name reaction is the Hofmann type reaction Hofmann rearrangement amide to amine RCONH2 to RNH2, which is a standard reaction? which probably all of you are known in this 10 past to chemistry. So, Hofmann reaction is a very important reaction and now this Hofmann amide basically you can easily construct from the corresponding carboxylic acid, this is also now a very well-known FGI, now this FGI now try to correlate how the starting material can be will be created from a corresponding carboxylic ethyl ester OPMB, now what we will do we will basically cut here cut here, and then now we will do a disconnection which is the main disconnection, is a OPMB we put we said C h to B r, and C h to B r or any good living (Refer Time: 23:25) and then here we will be had having a diethyl malonate kind of thing, which will basically gives this this particular carbon.

Now, diethyl malonate as all of you know now then now let us go to the forward synthesis. So, forward synthesis start with

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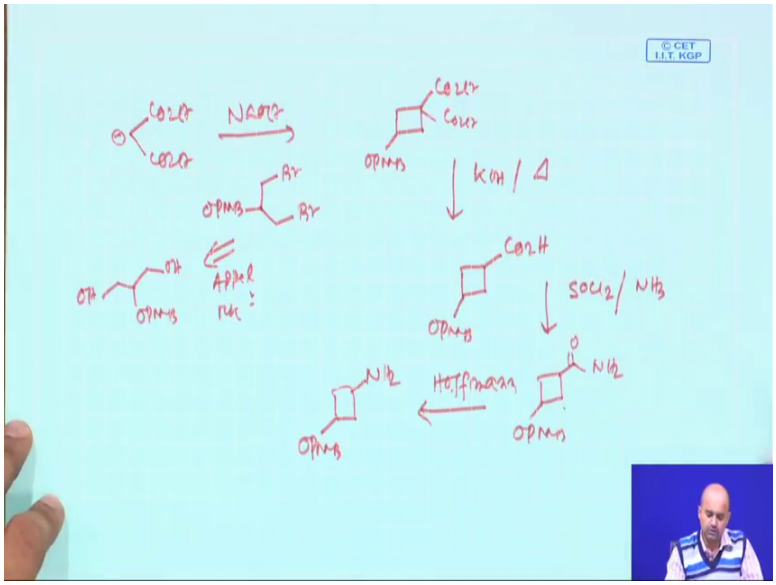

diethyl malonate react with a base sodium ethoxide, generate the carbonyl one equivalent there are 2 acidic hydrogen. So, in principle both can be obstructed one by

one, and the electrophile which is there is B r, now this B r it can be easily synthesized on the starting material which is given to you by a double apple reaction, apple reaction we have already talked about the double apple reaction.

So now you do the successive round of coupling with these diethyl malonate to get this product C o 2 e t, now what you do you basically do the hydrolysis base hydrolysis and heat it. So, one it will be dicarboxylic acid and upon heating, mono decarboxylation takes place and will basically get this carboxylic acid cyclobutane carboxylic acid. So now, almost quite close. So, what you do you convert this carboxylic acid to corresponding acid chloride by treatment with thionyl chloride, and then ammonia treatment which will basically give you the corresponding amide corresponding amide, you will get and then you do the Hofmann rearrangement that will basically give you the corresponding amine.

The transformation was very simple, but the appendages which we introduced a amine appendages, and it was with the help of a particular diethyl malonate which basically gives you the one carbon. So, this is 3 carbons starting material we introduced a one carbon extra to close the cyclobutane ring and then finally, you complete the synthesis. So, this is the very simple way or straightforward way, you can continue this kind of a approaches we will be stopping our discussion by discussing a very simple molecule a simple target molecule.

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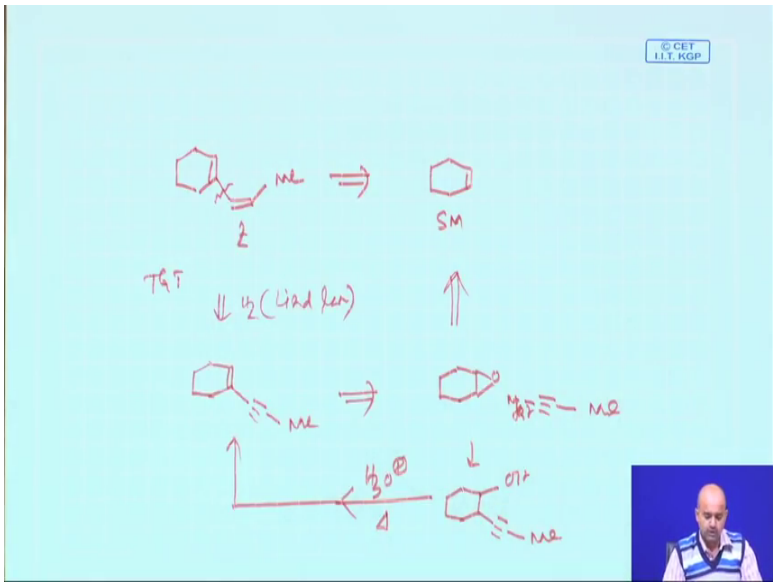

the target molecule is basically something like these, for the double bond geometries z, the target molecule I say and the starting material which was given cyclohexene a starting material was given to you.

Now, if you try to analyze this thing, we will say that this is a basically the appendage, this is the appendage which needs to be introduced. So now, let us disconnect if you are having a compound like this. So, you can basically do a hydrogenation with lind ler catalyst, this appendage now how you can introduce a alkyne appendage, alkyne appendage can be converted to a olefinic appendage by hydrogenation, now we see this particular alkyne appendage you can easily created, if you having a M g b r and this you can easily constructed from this cyclohexene.

So, what you do you first react with alkyne magnesium bromide ring will open up, you will get this OH, and this alkyne the product which will basically get a OH, and this ethyl next basically you need to want to elimination by simple acid treatment and heat, that will basically give you the in ein and then you do a selective alkyne reduction with the lind ler catalyst. So, this also basically gives you a very nice demonstration of this appendage insertion or appendage introduction or through a stepwise way. So, we will continue this appendage disconnection in next week also, and till then go to the assignments and try to study and have a good time, goodbye.