A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 16
Multiple Tf based strategies

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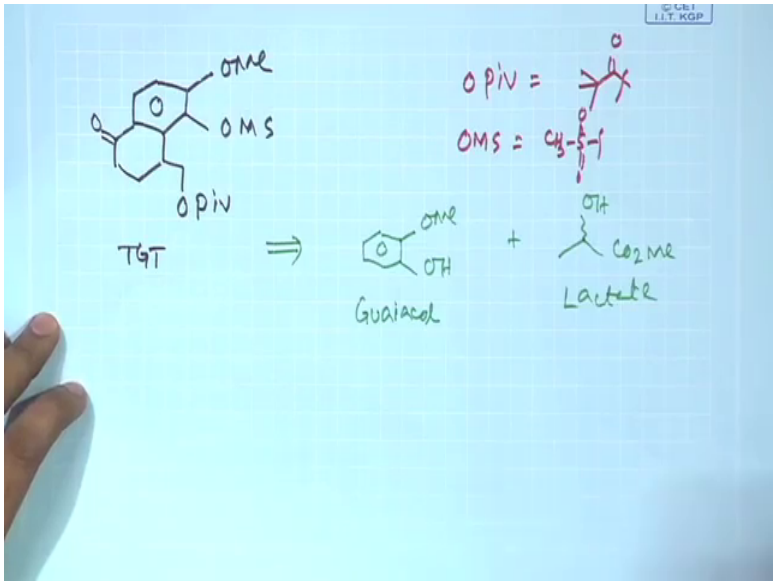

So, welcome back. So, in the last lecture where basically discussing a problem which you did not solve we just start it. We said a given your target molecule and the starting material was given guaiacol and a methyl lactate or this target molecule have some protecting group as in mesylate as well as pivoloyl. So, we will try to keep it as it is.

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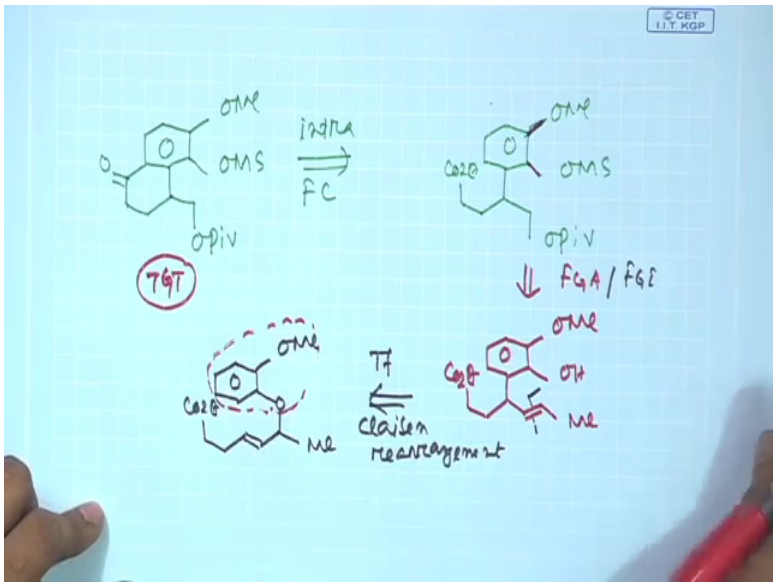

Now, we just discussed that a intramolecular friedel crafts reaction of this intermediate might be a good option and you explain that as ohmic oxy is orthvend para orienting. So, this is might be a viable option in it just hydrolyze this as step to make it the friedel crafts ring closer fine. So, next we need to do the remaining other part. And in this case we will try to keep it as a free alcohol, so this alcohol will be basically protected as a its mesylate it its simple functional group addition. Then this part will try to introduce some group which will be we explaining later on.

Now, this retro see it very carefully, this retro was very interesting. Now, it said that this pivoloyl group is basically nothing is a CH 2 OH means if you have a CH 2 OH you can protect as pivoloyl ester. So, now, if we have such intermediate, now you may has an a how you can think about so the intermediate.

Now, actually this intermediate at the very beginning it is not visible to you. We will try to go back further down the line then I will find that this intermediate one of the intermediate which will be prepared and then you do a oxidative cleavage here just original analysis kind of thing that will give the aldehyde that you can reduces sodium borohydrate. And then you get the free alcohol which you can predict as the o pivoloyl as though the phenolic group was protectize is mesylate. So, this is the functional group addition or you can say functional group inter conversion fine. So, the trying to give it.

The next transformation was absolutely fantastic next explu transformation was pretty and then you see the powerful way how complex structures are basically assembled. Now, this transformation a phenolic ether basically allyl phenolic all of us know that this kind of phenolic allyl ether will undergo a 3-3 claisen rearrangement. Now, how will explain when we talk about the for our pathway. So, this is a transformation which would know as a claisen rearrangement or 3-3 sigmatropic rearrangement that is why I am telling now if we go back you see that this mighty is basically coming from the guaiacol is part is a guaiacol o meoh. And this part is methyl oh might be the coming from the lactate part lactate part, we will do further retro by keeping this as your backup slide.

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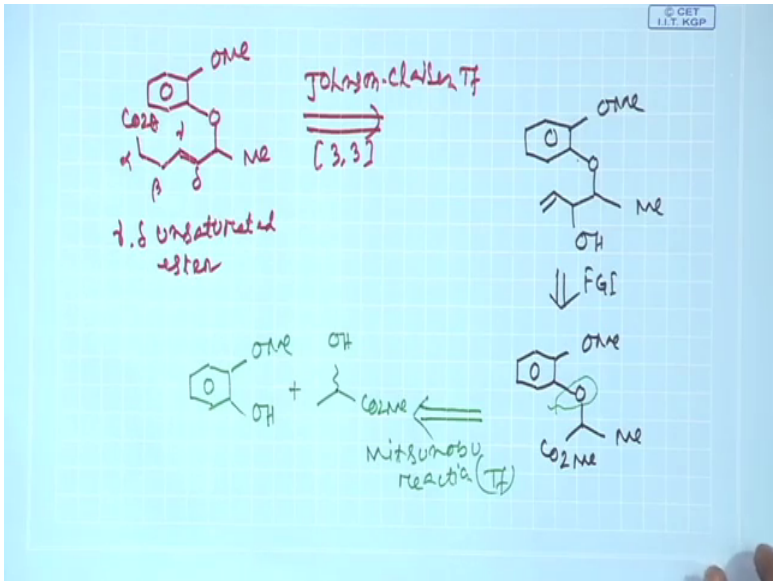

And then you draw the same intermediate which we earlier shown you as a claisen thing. So, this is the intermediate we need to prepare. Now, this intermediate if you have a close look alpha beta gamma delta. So, it is a gamma delta unsaturated ester and numerous time we told that if you have this kind of compound you can straight wise go to which transformation Johnson orthoester Claisen rearrangement Johnson-Claisen. So, it is a 3-3 sigmatropic based rearrangement is a very useful transformation Johnson-Claisen transformation. So, now, which particular allelic alcohol will undergo Johnson-Claisen rearrangement to give you this product, we will now try to formulate it, we know suitably substituted allelic alcohol will give it this product these you already know fine.

So, now we are basically simplifying the target molecule and coming very close to the starting material which have been provided to you. So, now you (Refer Time: 05:36) functional go inter conversion, and now come back to a intermediate to structure is basically this. Now, what we say we say will we did some FGI or functional go inter conversion on this ester part. This ester can be reduced to corresponding aldehyde, this aldehyde will this undergo vinyl magnesium bromide addition to give you the allelic alcohol, this is the intermediate for Johnson-Claisen transformation.

Now, how this ether will be accesses, the starting material now you can see this is basically guaiocol part and this is a lactated part. You just need the guaiocol phenolic oh and the lactate hydroxy group undergoing a etherification reaction. And this reaction again a very unique transformation is named as mitsunobu reaction, it is a very unique transformation. And the a mechanism of mitsunobu reaction will be not discussing here, but if you try to have a feeling why mitsunobu reaction is very important, you to try to analyze I am saying that this phenolic hydroxy group and this lactate hydroxy group needs to undergoing a etherification reaction.

Now, eventually if you are trying to do a simple SN 2 reaction here with this as an necrophile is very difficult because we always know that hydroxyl groups are not very good leaving group, you need to make hydroxy to a better leaving group by making either tosylate or mesylate. Now, in this particular instances mitsunobu reaction play a very important role.

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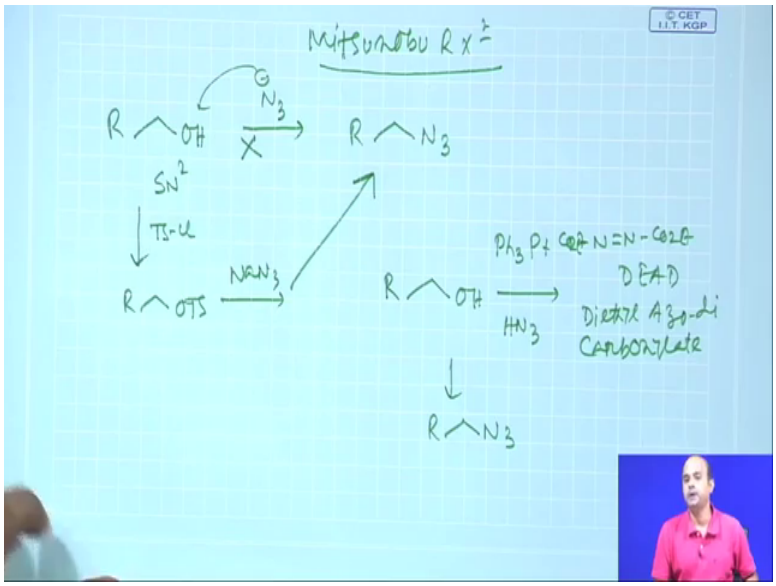

Mitsunobu reaction, we will explain what is mitsunobu reaction little bit we do not talk about mechanism; we will explain the mechanism later on. Now, I will give you a simple problem. I am giving you primary alcohol and I say you convert this primary alcohol to agyte one-step. Now, one-step is big difficult because I said hydroxy groups or primary hydroxy groups are not good leaving group. So, if you try to figure it out in agyte necrophile to attack here in a SN 1 or SN 2 fashion, you are definitely going to be fail because alcohols are not doing good leaving group. The classical solution is you convert this alcohol to tosylate by making it OTS, and then you react with a necrophile to come to this product. So, 2 SN 2 takes place together so tosylate it is a better leaving group.

Now, the mitsunobu reaction can handle the situation quite well. Mitsunobu reaction we are using a set of reagent one is tri phenyl phosphine plus we using a reagent whose name is NN diethyl as you die carboxylate, whose abbreviated as DEAD is diethyl azo di carboxylate which was abbreviated as DEAD. Now, mitsunobu reaction and then you can put your necrophile you can even put hydraulic acid HN 3 and you will get N 3.

Now, mitsunobu reaction take care of a very important aspects it tries to make alcohol as a better leaving group with the help of triphenylphosphine. The alcohol will react with triphenylphosphine sequence sequential manner and then find is alcohol is activated to a oxygen phosphorous bond, phosphorous oxygen bonds are very strong. And the byproduct similar like Wittig reaction if you remember we have a carbonyl compound

you react with the vitaglide the final byproduct is triphenylphosphine oxide. So, the oxygen which is coming from the carbonyl compound that makes the P double bond to triphenylphosphine oxide, the another very important aspect. So, mitsunobu reaction as I said straight way solution to make a alcohol as a better leaving group.

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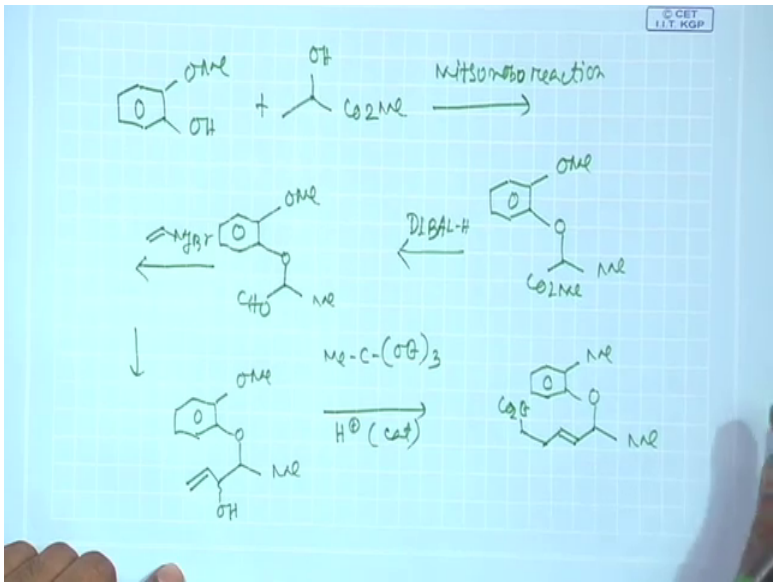

So, now we will go back to the original problem, which was given to you. So, first you are having guaiocol and your lactate. We did not discover stereochemistry, so that is why we put a simple bond, we did not put a alpha or beta bond. So, now, here we do a mitsunobu reaction. We will explain the mechanism little bit later when we talk about functional group based strategies. The mitsunobu is very useful and you will be basically getting the corresponding ether like this. This is one of the intermediate, which you earlier explained.

Now, what you do, you need to introduce allelic alcohol functionality here. So, selectively you can reduce this alcohol in ester in one step, but it with dibal diisobutylaluminum hydride which you already explained is a basically a mild reducing agent. So, we will be having this aldehyde as your main product fine, and then you react this aldehyde with a vinyl magnesium bromide. So, the product will basically allelic alcohol which is the intermediate which is required for your Johnson-Claisen rearrangement, this is the thing.

So, now, you subject this compound to Johnson-Claisen means you need trimethylorthoacetate in presence of a acid catalyst I say acid catalyst. So, you will be basically getting this thing and then you will get the gamma delta unsaturated registers follow the standard mechanism of Johnson orthoester Claisen rearrangement which have been discussed you numerous time. So, now, is alpha beta gamma delta. So, this is the alpha beta gamma delta unsaturated ester which is one of the intermediate. So, now, we will be trying to do something else.

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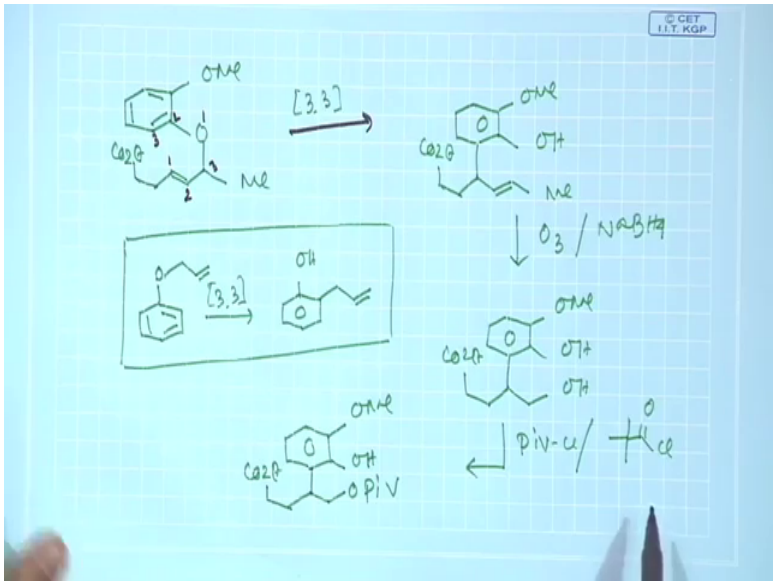

And then now you again try to figure it out, so we said the next transformation which you have device in the retro pathway is basically a 3, 3-claisen kind of rearrangement of allyl phenolic ester. So, what would I try to do we put the aromatic range as it is. Now, you see you see 1, 2, 3, 1, 2, 3. So, 3, 3-sigma tropic rearrangement or Claisen rearrangement will be taking place and then once this 3, 3-sigma tropic rearrangement will take place will basically get the this phenols here and then this part will be your. So, just using a reaction of something like this probably you have all studied this reaction 1, 2, 3, 1, 2, 3 this reaction probably all of you studied, the reaction of O allyl ether will basically gives you by standard claisen rearrangement, the 3, 3-rearrangement fine. This is the key reaction which we have used.

So, now you are here. There are almost very close very close. Now, what is now required it do a oxidative cleavage just by original analysis, then you reduce this aldehyde the

generator aldehyde by sodium borohydride. And then you do the free alcohol which was generated here, you can write it down we write it down the free alcohol free alcohol which you can now put it with this compound which name is pivoloyl chloride which wrapped it is basically nothing tertiary butyl COCl it is a acid chloride. And then it is basically give you the corresponding pivoloyl ester, it will give you the o pivoloyl, this part is remained similar, absolutely no issue. Your free phenolic OH is there and if you remember this three phenolic OH needs to be converted to the corresponding methyl.

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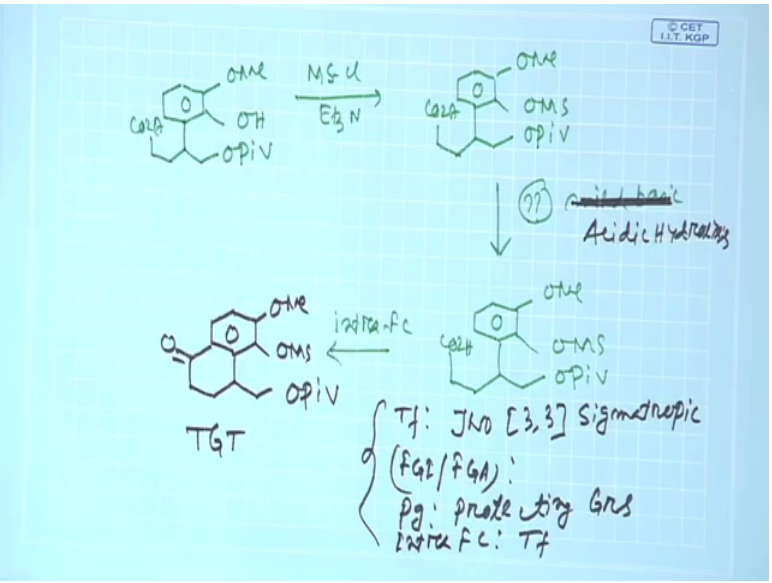

We will take the structure as it is and then we will try to finish it up the remaining part of the synthesis. And let us see how it was done. The intermediate which was drawn in the earlier piece of paper is having something like these structures. And then as I said you need to do a mesylate production of this free phenolic OH. We treat with mesylate chloride trithylamine you get the corresponding mesylate derivative o mesylate led this part it is remain similar.

Eventually now you need to do intermolecular friedel crafts reaction. So, this basically you can hydrolyze these things this ethyl ester, and get the corresponding acid to undergo a intermolecular friedel crafts reaction, where but on the contrary this O pivaloyl group might also undergo hydrolysis that is a trick. So, probably for this these chemo selective things we are trying to trying to avoid you can just put a very mild hydrolysis condition which will only clip this one. And then once you here you will get this thing CO 2 H, but

in the sequences if some of the pivaloyl group is lost or hydrolyzed that also can be possible, but eventually you can again come back to the original pivaloyl by just would being a functional group manipulation.

So, now you do a intra friedal craft. Here you can say you will do a mild basic hydrolysis or on the way you can basically do a acidic hydrolysis which is much more relevant. The acidic hydrolysis will basically pick up this one not the bulky this hydrolysis not the bulky this tertiary butyl group. So, you can the base solution is you can do a acidic hydrolysis. So, here do an intermolecular friedel crafts reaction and then your target structure can be achieved.

So, this is the target, we have given in the very beginning. So, see it, it is a very powerful transformation based approach. We have used couple of interesting transformation, what are those we used two sigma tropic rearrangement two 3, 3-sigma tropic rearrangement one is the simple allyl ether phenol and its corresponding claisen rearrangement, another is the Johnson-Claisen variant of the claisen rearrangement. Then we basically do couple of functional group inter conversion, functional group addition whatever way you can say. We use couple of protecting group based strategies protecting group, we use couple of protecting group based strategies. And then at the end, we use a intramolecular friedel craft reaction. We use intra friedal craft as one of the main transformation.

So, in the whole as I said transformation based strategies functional group base strategies starting material based strategies all are interlinked. Here I have given you a target are giving you a starting material. So, basically you can fit the inter strategies in any of the given strategies, you would like to fit in. So, that is I said transformation, functional group and starting material this strategically basically overlapped, you cannot discuss them separately. Now, all the examples which will be covering here, I having core theme, they basically always transformation, functional group and the a starting material based approaches.

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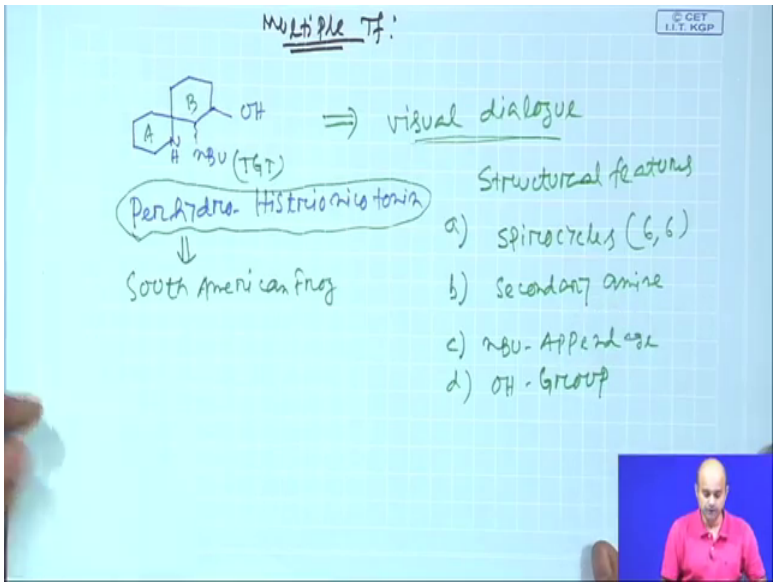

So, probably in the next problem, we will talk about something similar and this is will be again trying to focus it out multiple transformation based strategies. As I said multiple transformation based strategies where you can think about a little bit complex structures and the structure is definitely complex; and in the starting material was given you can correlate the starting material with a given structure then you can come back. Now, see this target will be next going to give it to you. The target molecule is a natural product.

For the sake of simplicity, I have not given you the stereochemistry because we have we have not discussed you this molecule is a natural product and its name is per hydro histrio nicotoxin. It is basically toxin molecule toxin molecule which have been isolated from a South American frog is isolated from in from the skin of South American frog. And based on the scientific name of the South American frog, the name histrio nicotoxin has been derived. I do not remember exactly the scientific name but this molecule is basically toxic.

But nevertheless if you see the structure, the structure is pretty interesting. Now, as I said you start communicating visually a very beginning we said start doing a visual dialogue with the molecule. Now, what the structural features this molecule does have as I said structural features is very important. What are the structural features this molecule does have? This molecule basically having a spiro cycle framework, spiro cycles, spiro cycles and the rings are basically 6, 6, two 6, 6 rings are there. These molecules have a amine

functionality, secondary amine secondary amine functionality fine. And then you will see this molecule has some other groups its having a n butyl appendage and then it is a having a hydroxy group at the right hand side right hand side ring. There are two rings actually A ring, B ring.

Actually in two sense this molecule is not the natural product a natural product is something else. I have just put a smaller fragment of the natural product in the natural product, there are some other functional groups here. So, initially what I said this molecular is natural product, it is not true actually, then a real natural product is something else, but the natural product having is structural similarities exactly the same only thing is you would be having extra pentyl group here. So, I am just picked up the synthesis for this molecule to explain how the particular transformation based approach is very powerful and how the retro can be done in a sequential manner.

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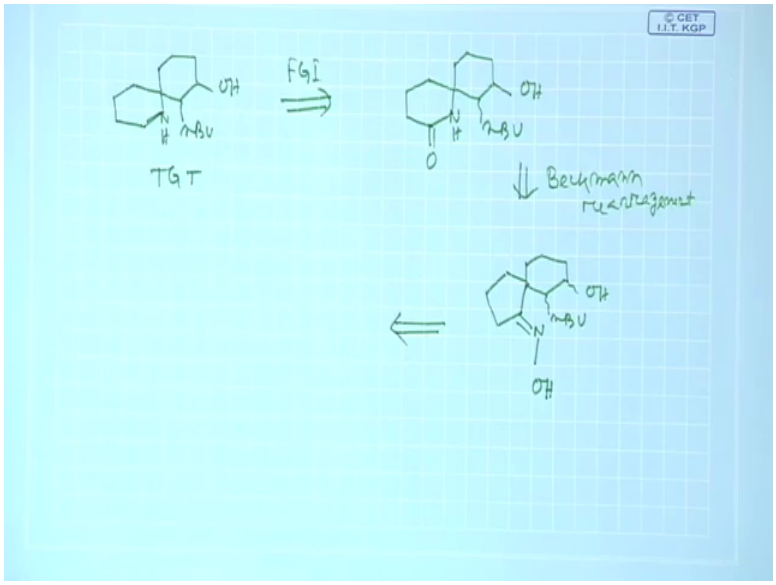

Now, this is the initial visual dialogue, you can start with the molecule and analyze the structural features or the structural features this molecule does have. So, then we will try to do the retro. We will try to do the retro. The retro as I said is n h is n butyl this is a OH, it is the target molecule the retro. Retro vise the very beginning will be using a very powerful transformation reductive transformation which will basically convert a amide to corresponding amine is the functional group based inter conversion. We all know amide can be converted to corresponding amine through a reductive way. To take a

amide to react with Lh lithium aluminum hydride basically get the amine is a very standard textbook chemistry, so the FGI.

Next is important because this reaction I am sure all of you know it this is the powerful transformation, which is required. And this powerful transformation if I write the structure you would simply jump into that said I know it now what is this, this transformation is basically based on a Beckmann rearrangement. Now, Beckmann rearrangement all of us know it and Beckmann rearrangement basically if it undergoes to a cyclic oxin, I will get a ring expanded amide. So, the basic transformation is a beckmann rearrangement based transformation.

Now, as the time is limited probably the remaining part of the synthesis we will discuss in the next class. So, first what I am going to say when you go back to the home, you analyze this target molecule, analyze this target molecule try to give a thinking and initial two retrosynthetic pathways we have discussed. And if time permits you analyze in your own. Then when I come back for the next lecture, then we will try to correlate whether pure pathway and my given pathway are similar or different that will basically give you that you are going on the right track.

See you in the next lecture, till then goodbye.