A Study Guide in Organic Retrosynthesis: Problem Solving Approach

Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture - 38
Fg based Strategies in Combination with SM and Tf

So, welcome back students we are basically discussing a combination of starting material, functional group and transformation based strategies for small molecule or target molecules. And in the last lecture, we talked about a mechanism based approaches like we discussed Payne rearrangement as well as Baeyer Villiger based oxidation and its application.

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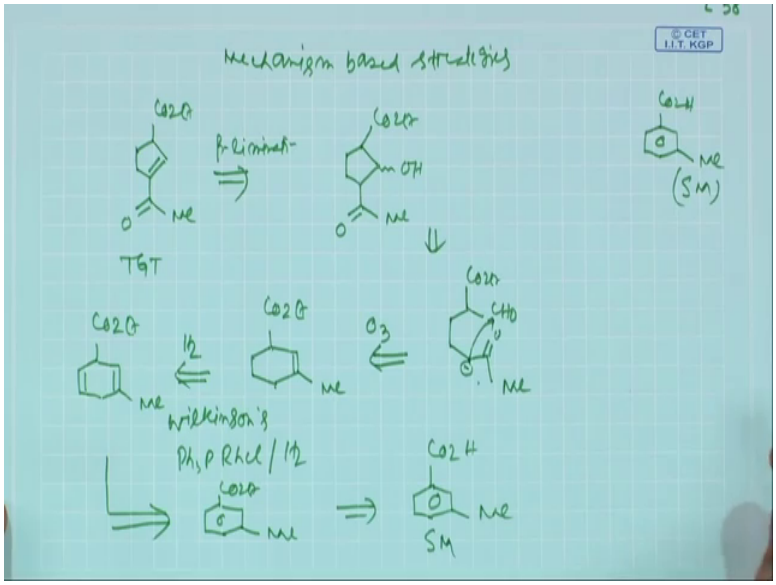

Now, today we will be trying to give you similar kind of mechanism based strategies, which are basically if you are quite sure about the mechanism of a key transformation that will help you to design some retro path way. The problem which was given now is a small molecule is a cyclopentanone structure and the target molecule is basically this one, is a alpha beta unsaturated carbonic compound which is having a cyclopentanone core structure.

Now, starting material initially I am giving it to you for your thinking independently the starting material which was given this a toluic acid, meta toluic acid starting material. And as you say; as you can see basically the target molecule is not aromatic, but the

starting material is aromatic. So, basically you need to think about a de aromatization reaction and you all know that dearomatization which is widely explored named as Birch reduction. We have explained Birch reduction in terms of its mechanism and how different kind of substituted aromatic group with electron releasing and with electro withdrawing that will give you two different regioisomeric product in the Birch reduction.

Now, here if you do the retro as it is a alpha beta unsaturated compound probably the best track retro will be the simple iodole dehydration, which we discussed many times. We say if you have a compound something like this, which will undergo a simple 1, 2 beta elimination, a beta elimination of a water molecule which is basically nothing a iodole dehydration. Now, you try to draw the parent diketone compound which will undergoing these iodole reaction you say if you having a compound about CH 2, CH 2, CH 2 three CH 2 will be there CH 2, CH 2, CH 2 then methyl. And then we say that this particular compound we will be trying to have a; this anion which will be reacting here ok.

Now, we will coming to this things little bit later on; we will find that there are other anions like this anion which is very extremely acidic because it blinks to its CO 2 and CHO, but in reality it would not form will come to it little bit later on now see how this entire diketone was visualized.

Now, this diketone if you now see this diketone can easily be made through a ozonolysis kind of ozonolysis or oxidative cleavage from this cyclo hexane derivative. So, you need 1, 2, 3, 4, 5, 6 this dicarbonate compound so, if CO 2 CHO CH 2 CH 2 CH 2 so, this three methylene will be here. So, is a oxidative cleavage ozonolysis now see we are almost close for this birch reduction partner now if this compound also can be synthesized from this compound.

Now, what you need to do we basically need to do a regioselective hydrozination at this double bond of this compound to access this, basically need a regioselective hydrozination and last class we have discussed that if you have a homogenous catalyst like Wilkinson's catalyst which is basically a triphenyl and phosphine, rhodium chloride and you do a hydrozination based on this catalyst and this is a very bulky catalyst this

will always try to ensure the sterically less hindered olefin is reduced faster and you can control the reduction.

Now, this particular starting material will be easily coming from this toluene ester which you can easily prepare on this toluic acid as a starting material. So, we have basically disconnected the molecule through a couple of a interesting transformation and also if you are quite sure about the birch reduction mechanism then you can predict this pathway.

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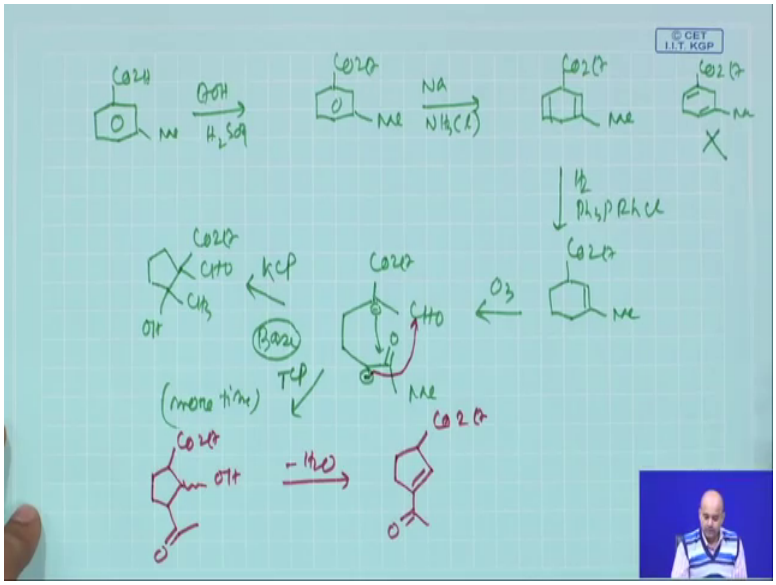

Now, the forward pathway we will go to the forward pathway now this toluic acid first you do a esterification reaction EtOH concentrated sulphuric acid, you esterified the molecule to give the corresponding ethyl toluate.

Then do the birch reduction with sodium liquid ammonia that and now here I say this is a mechanism based strategy to keep in the mind that you always get this regioisomer, you never get this regioisomer in the birch reduction if you having a electro withdrawing group here. So, that is the most important thing here now I will say you do a hydrozinisation with a Wilkinson's catalyst that will give you the hydrozination at sterically less hindered olefin sight and you are here.

Now, do the ozonolysis which was earlier device for this retro then you will find that you basically get CO 2 CHO and then CH 2 CH 2 CH 2 your this things and this things. Now,

I say there will be possibilities you could treat this compound with base this hydrogen seems to be mostly acidic and if this hydrogen reacts it will also get a compound what will find the CO 2 Et and CHO reacts and you basically get you can get this kind of Aldol also. This kind of Aldol its in principle it is possible because this hydrogen is much more kinetically acidity.

So, in kinetically controlled condition you might get this Aldol, but I say our product is something different you have to have a alpha beta unsaturated aldehyde. So, probably if this Aldol under goes elimination you can have elimination here or elimination here, but you never get the elimination here because there is no beta hydrogen.

So, alpha beta unsaturated aldehyde from this Aldol you can never make now think about other condition which is thermodynamically controlled because now this enolate is thermodynamically more stable because having a extra methyl group here extra alkyl group here. So, means that you allow the compound to react with base for more time for more time so, more time basically will give you the thermodynamically controlled enolate and then this hydrogen will be abstracted and will react to this aldehyde react with this aldehyde and then we can get this particular Aldol which is required for us.

So, now, see you can easily do the beta elimination and you can now get the desired compound as we earlier discussed. Now, what does the eventually the take home messages the take home message is basically we are saying that if you having a clear cut idea about the mechanism of birch reduction then you can predict which regioisomer is forming and then mechanism of Aldol reaction mechanism of Aldol dehydration.

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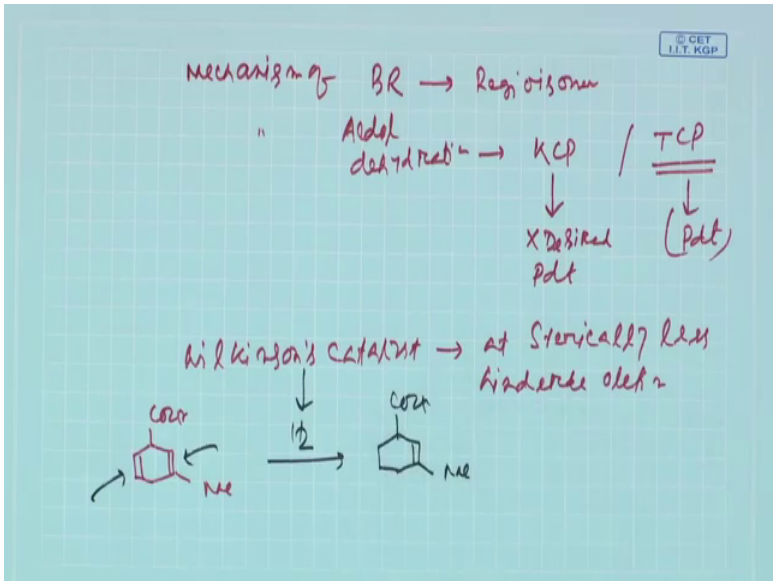

So, we said Aldol dehydration there are two possibilities kinetically controlled product and thermodynamically controlled product, but if you try to allow the kinetically controlled product you would not get the desired product in this case.

Now, if you allow the thermodynamically controlled product means that you allow the starting material to generate the thermodynamically most stable enole you get the desired product. So, if you have a clear cut concept about the mechanism of the Aldol dehydration then you will be able to do this transformation and then finally, we talking about a Wilkinson's catalyst which is sterically bulky catalyst and fix or will undergo hydrozination at sterically less hindered olefin will be hydrozinated.

Let us say for this particular case you are having CO 2 t here methyl here so, there are two hardination sight this or this is sterically less hindered. So, this will be hydrozinated with this catalyst and basically you will get CO 2 et and this double bond. Now, this double bond will be doing the oxidative cleavage, basically a combination of a reaction which will help you to design the entire pathway in very efficient manner.

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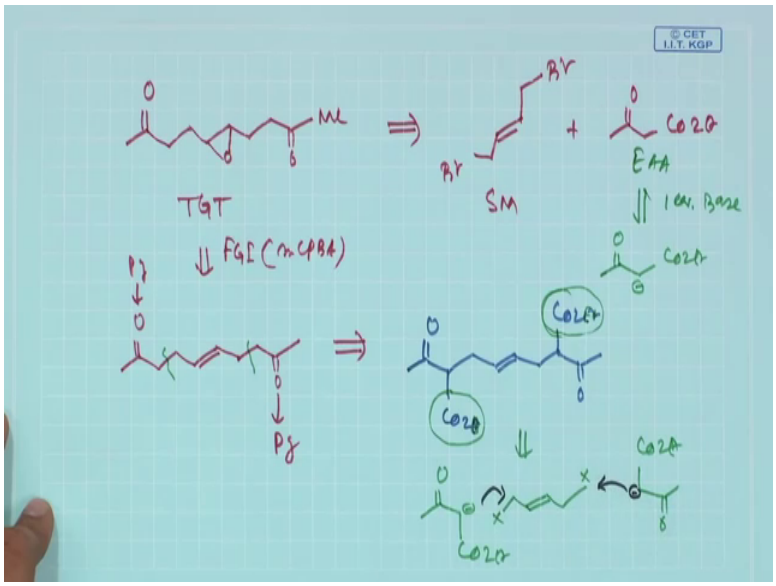

The next problem which will be now discussing its interesting one, but here the mechanism we have already discussed same like birch reduction. So, you would not focus about the mechanism much we will say that how this reaction was visualized the target molecule is this and I say this target molecule can be accessed to this starting material with this CH 3 CO CH 2 CO 2 et right.

Naturally this seems to be simple if you see this target you can basically visualize the target might be achieved from something like this compound and if you have this olefin and ketone, you can do a FGI through mCPBA based and as I say mCPBA will also have the possibility to undergo or to make this Baeyer Villiger reaction possible.

So, probably this ketone you need to protect it so, this ketone needs to be protected Pg, let us first formulate the disconnection then we will come to the forward synthesis. Now, here the starting material is given ethyl acid to acetate is a very simple starting material and ethyl acid acetate we all know if you treat 1 equivalent of base. It basically gives you this carbon ion because this highly kinetic acidic this hydrogen is extremely acidic.

So, 1 equivalent of base will give you this now will now formulate that this part and this part is your starting material the double bond CH 2 x CH 2 x. So, now what we are visualizing we say we put this CO 2 et here and then we do the this connection. So, this now looks absolutely perfect what you need to do you basically need to remove this

dicarboxylate ester by simple acid hydrolysis are basic hydrolysis and decarboxylation this are basically betaketo ester so, after hydrolysis this will give you betaketo acid .

So, now, we are almost close so, you can basically try to get these with a minus with double bond CH 2 x with double bond CH 2 x yes. So, we say this minus this minus will react in a normal alkylation mode and basically you can get this target, but in rule we have to make sure the proper care of the stereo chemistry has been taken care sorry not stereo chemistry it is basically proper care of this protecting group.

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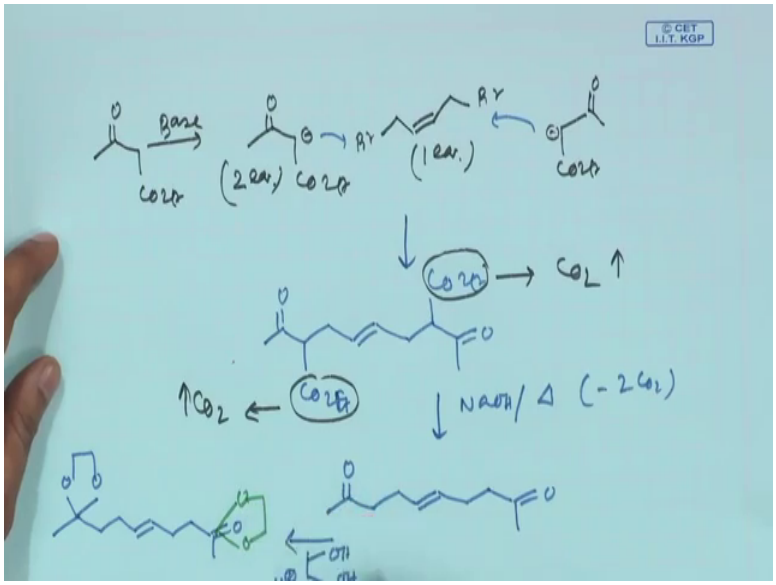

So, this protecting group you need to be very careful now start with this ethyl acito acitate I said you generate this anion by simple base. So, we are doing it now 2 equivalent if we use this compound as a 2 equivalent and we use this bromo. We are seeing that this compound 2 equivalent and this compound 1 equivalent because this compound is having 2 electrophilic sight.

This compound is having 1 here and the another will be this sight there is some control is essential and then you can basically have this alkylation to give you the compound which we are looking forward CH 2. Now, here I said you first do this decarboxylation here you just do the basic hydrolysis and heat it.

So, 2 equivalent of carbon dioxide will release and then will give you the product this so, here this things this things will be hydrolyzed will give you carbon dioxide gas. Now,

you are here you can in principle directly use mCPBA, but we will see there are ketones here that might undergo Baeyer Villiger oxidation. So, a protection group might help you so, how do you protect it you treat with ethylene glycol and simple h plus this compound will be now protected as it is double bond will remain similar CH 2 CH 2 yes.

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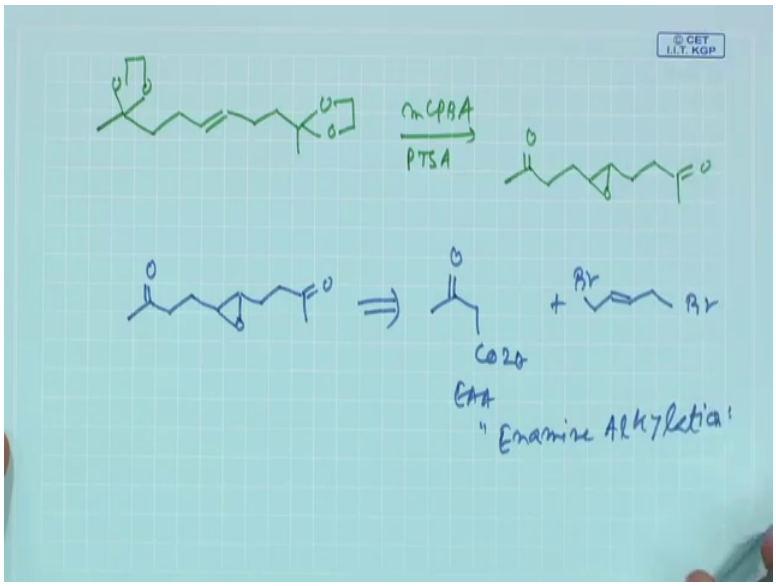

So, now take this compound as it is now take draw this compound again by keeping other structural element as same I said the other oxygen we did not protect here. So, if you can think it this also needs to be protected this also needs to be protected so, fine now you do the mCPBA best reaction.

So, mCPBA will give the epoxide here and then you treat with simple mild acid sulphonic acid to remove the ethyl functionality and that will now give you the target molecule which was desired which was now desired now, there are other ways to do this synthesis also. So, this target which was usually which is initially given like this particular target I am not going to explain that strategy, but I will give you a clue. This compound also can be synthesized by using this ethyl aceto acetate as well as this corresponding bromide by enamine alkylation enamine alkylation also you can use it.

But the process which we I just shown is very simple and is technically absolutely no issue you can control the chemoselectivity, by just protecting the carbonyl functionality in presence of the olefin, then you do the epoxidation on the olefin. Similar, kind of

problems are always there and basically you will find that next problem which will be now discussing is a very interesting problem.

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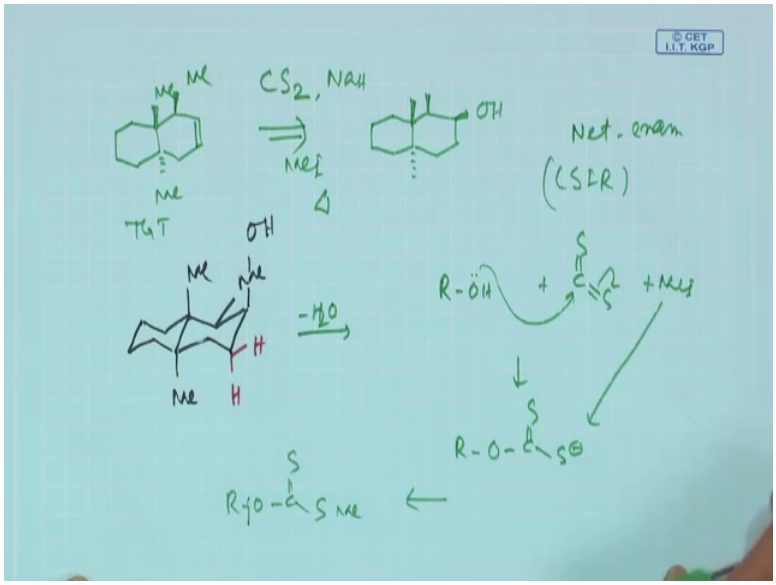

Here, you need to think about little bit about the stereo chemistry now this part is important as I said the compound which was given to you having a hydro carbon unit this is basically two six member rings are fused.

And you have a methyl transfusion this methyl is up and this methyl is down the target molecule which was this one, the starting material which was given here. Now, we will see the starting material how you can correlate with this target molecule there is hydroxyl group is there. Now, basically from hydroxyl group is you are creating a olefin center initially you can think that simple elimination might be possible definitely simple elimination is absolutely with no issues you can do it.

But now, what will try to do I will draw the stereo chemistry of the given molecule the cyclohexane chair form, here in the I am drawing the stereo chemistry of this starting material actually cyclohexane chair form, cyclohexane chair form. Now, this is methyl is up this methyl is down this is basically trans decline means this cyclohexane equatorial equatorial gives you a trans now this methyl and this methyl is seized this methyl is axial. So, this methyl as to be equatorial and this methyl and OH are now seize. So, this OH has to be also axial so, that the drawing is pretty important in a three dimensional form.

And then now you see then now you see that how a probably a elimination always takes part, if you just simply heat this compound through a water elimination that is always possible always possible, but this particular example was taken from a net exam which is a council of scientific and industrial research who basically gives the fellowship. It is called as a CSIR exam which gives you a nice fellowship if you want to do GRA for SRF after your MSC program like if you want to do PHD this is a one of the good exam you have to qualify.

Now, particular this case the reagents was given like they have given carbon disulphide, sodium hydrate and methyl iodide and heat is there. Now, this particular reagent is giving does this reagents sequences giving you some hint, if you remember Barton McCombie reaction we have similar kind of reagents we talked about. Now, what exactly is this R-OH plus C double bond S, C double bond S and methyl iodide now what is happening this comes here ok.

And then you basically get a xanthate ester C double bond S, S minus this S minus reacts with this methyl iodide to give you this methyl xanthate S Me and in Barton deoxidation reaction Barton McCombie, who is now signed light with the presence of a radical initiator d u 3 sn (Refer Time: 25:06) aibn to keep this heterolytic cleavage you basically get the hydro carbon. Now, this particular reaction is named as Chugaev elimination or Chugaev elimination.

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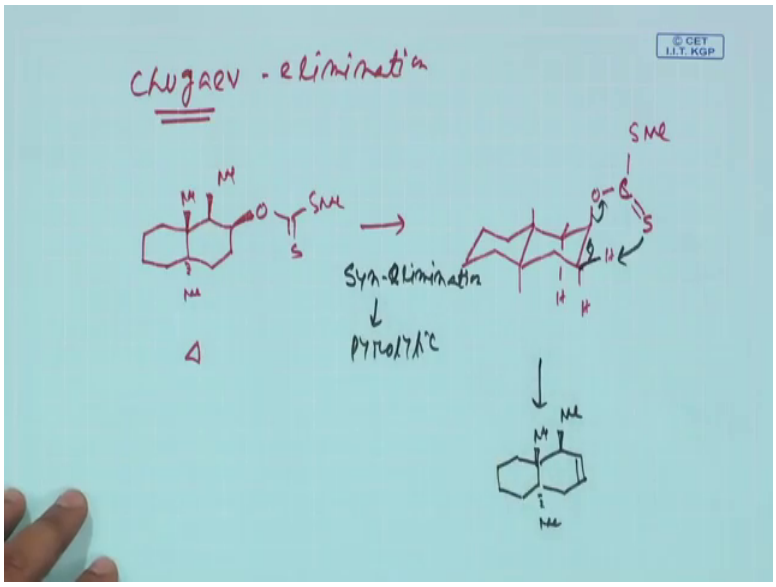

So, Russian scientist Chugaev who first take this xanthate ester he first so, initial if you take the starting material. The starting material which was given in the earlier slide we basically have this methyl, this methyl and then another methyl is here and basically you will be having this xanthat ester S SME. So, this is heat it under strong heating condition you will get the elimination product which was the target molecule.

Now, I will draw the three dimensional picture this is methyl, methyl this methyl is here, but having this hydrogen below this hydrogen's are definitely there and then you are having this O C sorry O C, O C double bond S and this SMe. The mechanism which was proposed by this fellow Chugaev he said that this elimination is basically a Syn elimination.

Normally you always talked about anti elimination that that hydrogen and the leaving group has to be the anti peripin arrangement, but this is the example where Syn elimination takes place. Now, if you closely analyze the mechanism basically goes to this way this sulphide this basically abstract this hydrogen and this comes here and this basically knocks down the entire thing. So, in these way this reaction takes place and this is basically has to be go through a Syn elimination it is sometime called as Syn pyrolytic elimination, syn pyrolytic means you are supplying enough heat.

So, now if you see if this reaction goes means that the geometry of this alcohol and the hydrogen has to be seized axial equatorial seize. There is no other hydrogen which is seize with this alcohol this hydrogen is trans this hydrogen is trans. So, now, the after the elimination basically the product will be formed which we have explained just now this methyl remains here this methyl remains here, this other methyl will be also things the OH will be just eliminated.

So, now if you are not quite sure about the stereo chemistry then also you can able to do it you just remember that this elimination normally goes through a Syn elimination. Now, if you see if I say that stud why you have to study the Chugaev elimination probably there are other ways you can do it, but if in the exam they give you the reagent sequences that this alcohol is subjected to or it subjected to or reacted with this set of reagent carbon disulphide, sodium hydride and methyl iodide and it is heated. If you know the particular mechanism of this reaction you can easily formulate how this Chugaey

elimination or Syn elimination takes place and finally, the olefin will basically generating.

So, those kind of mechanism based reaction is very important and that will give you a clear cut idea how different mechanisms are basically controlling the pathway of several reactions. So, if you study a particular reaction initially try to feel the mechanism try to get the inner chemical logic of the mechanism and that inner chemical logic of the mechanism will basically guide you that how a retro synthetic problem can visualized.

So, normally this kind of mechanism based approaches are basically closely associated with transformation based approach. Transformation means what basically a single based transformation where one functional group is converted to another functional group, but in between there are certain chemical steps which we are basically called mechanism that mechanism, if you are quite familiar if you are having sound knowledge of the mechanism then basically you can think that if this mechanism goes to this way this product might be obtained. So, like there are few example we talked about in the mechanism based approaches we will be talking about some more example till then good bye have a good time.