A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 42
Fg based Strategies (Contd.)

So, well come back student last lecture we have basically talked about few mechanism based strategies and we said that there are very unique transformation or unique transformations are known in the literature, where the mechanism is very key. If you know the mechanism of these transformations, you will able to formulate what kind of function group inter-conversion you will be able to do with those transformation.

So, we will try to simplify those strategies with some case studies; now initially the problem which will be now analyzing it is a very straight forward problem. We say a target molecule was giving to you whose structure is this structure; it is a bridged bicycle compound a cyclohexane is a core structure you have a two two ring bridge C H 2; C H 2 and this end you are having C O 2 m e.

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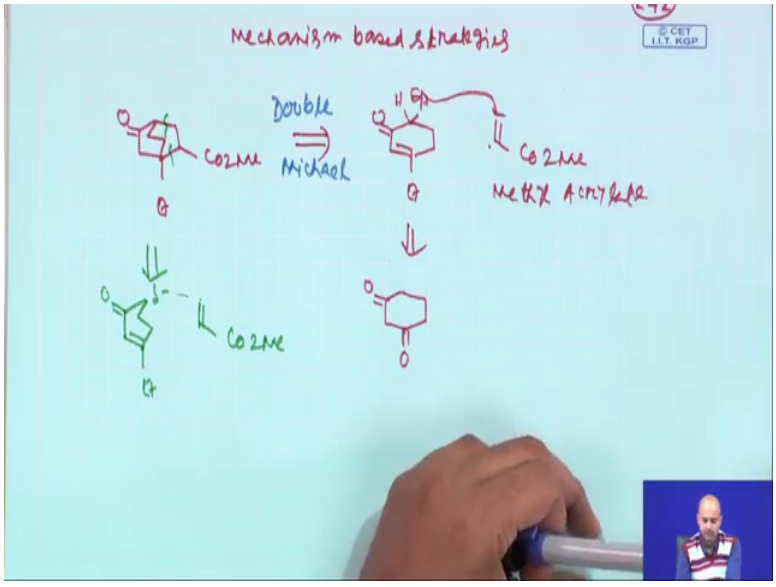

So, basically it two bi-cyclic or fused you have a quaternary carbon where a ethyl group is there. The starting material I say I am giving you the starting material which is; this kind of starting material and this starting material.

Now, the way I have drawn the starting material, it basically gives you that probably if you can simply do a double Michael edition simply do a double Michael addition; now this double Michael addition why I am why I saying it if you see the structure, the left hand side compound is a Michael acceptor.

The right hand sound wave is also Michael acceptor, but in addition the left hand set compound can have a acidic hydrogen acidic hydrogen here. So, this hydrogens are acidic; so, which can be easily picked up to generate a nucleophile. So, if you pick this hydrogen to generate a nucleophile it let attacks here.

Now once you attack here, this negative charge now comes here ok. Now this negative charge now acting as a nucleophile and attacks in a Michael fashion to this carbon. So, basically double Michael takes place your synthesis is quite attractive and it is quite feasible.

Now, this compound is commercial available even you can make this compound starting from this 1 3 cyclohexadione probably this chemistry we talked about ah many times in our class by aryllic disposition, aryllic transposition this compound ethyl sorry methyl acrylate is commercially available.

Now, the point is the molecule is definitely not a complexed molecule; is a medium sized molecule is a bridged molecule, but if you do the retro in this way that what I am doing we do the retro let us say we first cut this things this way. So, we write double bond O this and this part we write in this way. The core cyclo hexane we write it this way we say we will disconnect here as well as here. So, now we will put now this Michael acceptor.

So, here you are having a delta minus which can be easily generated and this part if you put a double bond this is basically a electrophilic carbon now. So, initially ones first Michael starts, then this minus will come here. The anion is basically transfer or relate from this carbon to this carbon. Now this carbon it is now gets this Michael acceptor in slow proximity and it undergone another round of Michael to complete the synthesis.

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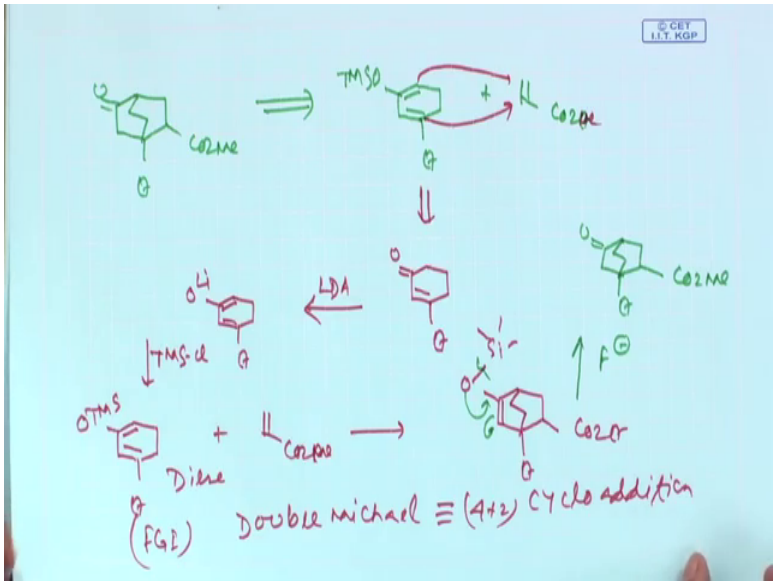

There is also another way through which you can visualize the entire synthesis. I will try to analysis whether this molecule can be disconnected in another way. The answer is yes definitely you can do it; now see how we can do it.

Next I am saying probably if you have this kind of structure or this kind of dine as a deal seller 4 pi system, you can easily do a 4 plus 2 cyclo addition by simply doing this doing this that is a absolutely doable. And now this compound can easily be constructed if you have this ethyl.

So, what you do? You basically first picks up this acidic hydrogen by a base LDA you initially get the enol or oli. This one now you react with TMS chloride trimethylsilyl chloride, you get the enol silyl ether OTMS and this is basically your acting as a diene; to now you react with the ethyl acrylate in 4 plus 2 fashion.

So, eventually what we will get? The bridge structure will write in this fashion, you get this C O 2 et, you get this ethyl, you get a double bond with this O S i m a 3. Now you say if you react with a fluoride source you basically give the oxygen silicon cleavage and then it come backs, it basically protonates to give you the enol which is then tautomerizes to give you the target molecule which was this structure this will be C O 2 m e. So, it will be C O 2 m e, but C O 2 it is a similar basically C O 2 m e.

So, now I say that by this mechanism it is evident that a double Michael, a double Michael is equivalent to a 4 plus 2 cycle addition is not it. So, in terms of FGI in terms of FGI a double Michael is nothing a 4 plus 2 cycle addition.

So, I have shown this by a example which gives you a very nice demonstration how a bridged compound can be construct from a same starting material. The starting materials in both the cases are similar; we use this 1, 2, 3; 3 ethyl cyclo hexinone for both the cases and methyl acrylate as a dienophile.

So, we will keep on continuing our discussion with similarly kind of mechanism based strategies.

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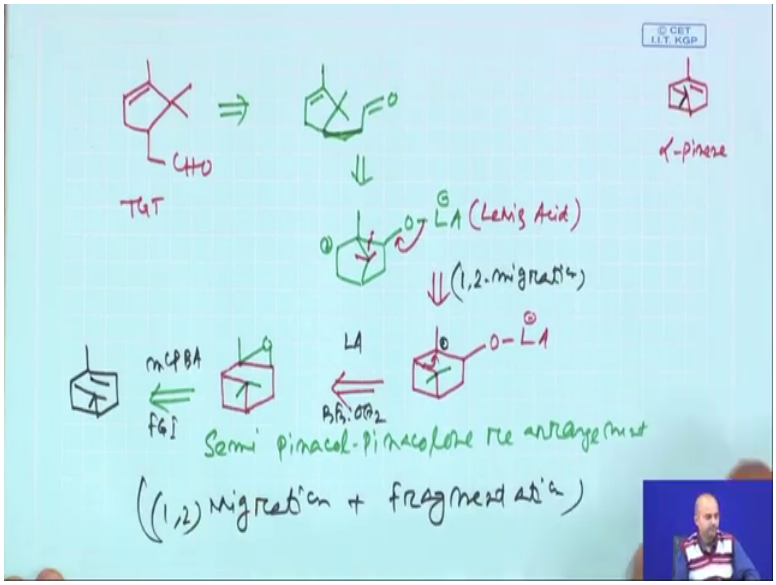

Now I will trying to do; I will give you a target molecule which structure is a 5 member based aldehyde; aldehyde target. The starting material I am keeping at the extreme right hand side, the starting material also given to you. The starting material is basically named as alpha pinene there are two methyls here in between is named is alpha pinene alpha pinene. You have a 6 number ring now the bridge structure you have two methyls here in between this a there is a one methyl, there is a one methyl.

So, now if you count the number of carbon everything remains same; you are having a 6 membered with 4 member bridged; in this compound only the 5 member thing. So, means that some kind of fragmentation was taking place, you have a 5 member here, you

have a 6 member and 4 member. So, basically now ring; new size of ring might be forming by some different kind of reaction.

Now, what I do? We write this particular cyclo pentene based compound in a different way. We say let us write this compound C H 2 oh sorry it is a one correct one less basically C H 2; C H O C H 2 C H O and then this compound is basically nothing this methyl you have a double bond. So, this compound was basically rearranged to write in this way because that will basically formulate how you can go back literally.

Now, I am saying that this compound can be constructed, if you having a something like this. Now what is this? This is basically a two methyls are here; methyl methyl now what I am saying now if this particular bond undergoing fragmentation; it undergoes fragmentation, this Lewis Acid comes here; it basically fragments to give you a this fragmentation. And then it gives a negative charge here and this negative charge basically now quenches this positive charge to yield this product.

So, this is a purely mechanism based things; now what is LA? LA basically stands for a Lewis Acid which you have used earlier. Now if this kind of rearrangement reminds you something that it let us a let us continue our another round of a retro.

Next retro is which was set this oxygen is coordinating with the Lewis Acid fine and then now what I am doing I am putting a; or rearrangement another carbanion ion in this way putting this methyl here. And now I am saying that this carbonium ion is having this structure.

Now, the point is if you have this carbon ion intermediate as it is a 6 member and 4 member probably it try to rearrange to this one two fashion. So, this bond migrates to give a 5 member system. Now this carbonium now is definitely is not that much stable. So, what happened this Lewis Acid now trying to fragment it the bridged bond; it will give you fragmentation here and though when this bonds fragments, the electronic part of this particular bond remains here. And that will basically quench the electronic deficient carbonium ion to give you the olefin.

It is a purely mechanism based strategy now you we will try to find it out how this structure was linked. Now I am saying that this is almost close to the starting material,

how you can formulate? You have two methyl group which I am writing in a green color and if you have a epoxide something like this.

Now epoxide opening to Lewis Acid; through Lewis Acid this is a very classical reaction we called semi pinacol pinacolone type of rearrangement or manual type of rearrangement. So, basically in principle is nothing it is a basically semi pinacol; pinacolone rearrangement or a manual time of type of rearrangement. Now this epoxide, you can easily construct it from this alpha pine in through a mcPBA based FGA.

So, now we write this starting material this two methyls are here. So, do the epoxidation with mcPBA by standard FGA or FGI and then here use a Lewis Acid. Normal Lewis Acid which was preferred is boron tri fluoride diethyl ether.

And initial coordination basically opens up the epoxide to a more stable 3 degree carbonium ion. Then this 3 degree carbonium ion basically will undergo 1, 2 migration; 1, 2 migration to give you the more stable ring structure; the 4 member rings seems to be pretty much unstable.

Then this ring structure will migrate in this way to give you a carbonium ion like this. Now carbonium ion will definitely now tries to undergo fragmentation, this fragmentation is important which probably; is not a common part of this semi pinacol pinacolone rearrangement or manual rearrangement.

In manual rearrangement we never had this fragmentation, we basically have the migration or rearrangement, but this is a migration or 1, 2 migration followed by fragmentation that was very unique reaction makes this reaction is a bit unique one. So, in these way basically you can simple formulate how this mechanism driven pathways is operative for a particular set of reaction.

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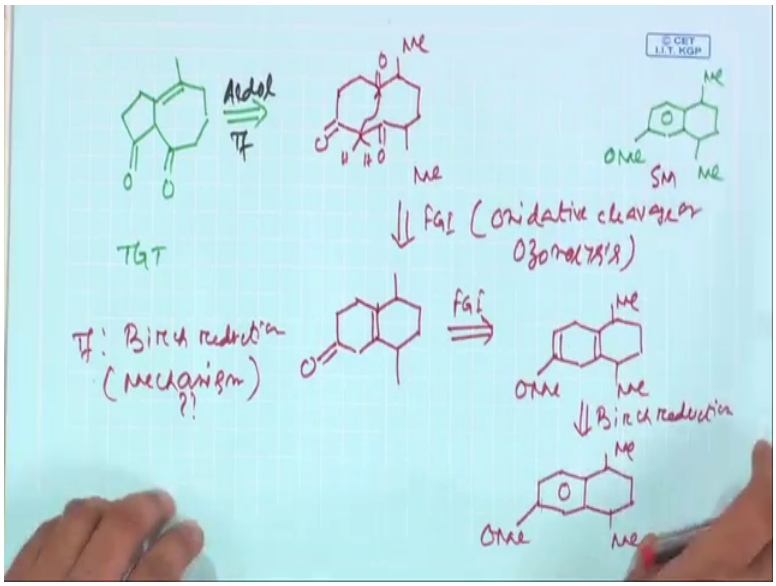

Next problem is a basically not a mechanism based strategies, but you can fit it eventually just if pure demonstration of functional group based transformation and other transformation. I put a 5 member ring and 7 member ring and this kind of way. So, the I say that this is your target.

The starting material which I am giving here at the extreme right hand side; I am saying the starting material which is given to you as basically having this starting material which is basically a tetrahedron naphthalene derivative. Now see the structure it is basically a ome methoxy O m e which is a starting material.

Now, we will initially let us do the retro probably at the very beginning, it is a we will initial talk about a simple aldol transformation; now how. We say if you have a di carbonyl compound something like this; now this diagram will come as pretty interesting it is basically a 1 3 di carbonyl compound. So, you might expect that this hydrogen is much more kinetically acidic.

So, immediately it will be picked up and then this will attack to this carbon. And now basically 1, 2, 3, 4, 5 and the right hand side ring will be 1, 2, 3, 4, 5, 6, 7. So, this aldol basically we are talking about ok; now this di ketone if you do the next retro or next FGI which is the FGI for di ketone is very interesting, you can basically do a oxidative cleavage or ozonolysis oxidative cleavage or ozonolysis.

Now, we are going to do it we will try to correlate with the starting material which was given to you. We say something like this if you are having as a intermediate which will immediately give it to this intermediate; its fine this part is fine. Now try to correlate with this staring material the starting material was given here.

Now, this is basically reminds you that if you have this kind of compound, which basically undergoing enol ether hydrolysis and can give you this kind of ketone. Now this ketone has a tremendous tendency to isomerize here because this is a the rearranged one is alpha beta unsaturated ketone. But eventually you no need to take longer time immediate you subject to the ozonolysis fine. Here now you will be doing a Birch reduction of the parent compound.

Now, Birch reduction the mechanism all of you are familiar and we have also explained earlier that if you have a electron releasing group, the radiochemistry was explained to you. So, the radiochemistry basically for electron releasing group you get this radio chemistry; this compound. So, Birch reduction is a very useful reduction.

So, now this entire transformation you can basically formulate what things you need to know? You need to know a birch reduction the transformation, but the point is the mechanism you have to emphasize that if you having a electron erasing group in one of the aromatic ring, oh what particular radio isomers they are going to get ? This part is very important.

So, once this part is done remaining thing is absolutely simple. You just do a FGI through enol ether hydrolysis, oxidative cleavage and complete the synthesis. So, it was very; obviously, and those kind of a synthesis can easily be done.

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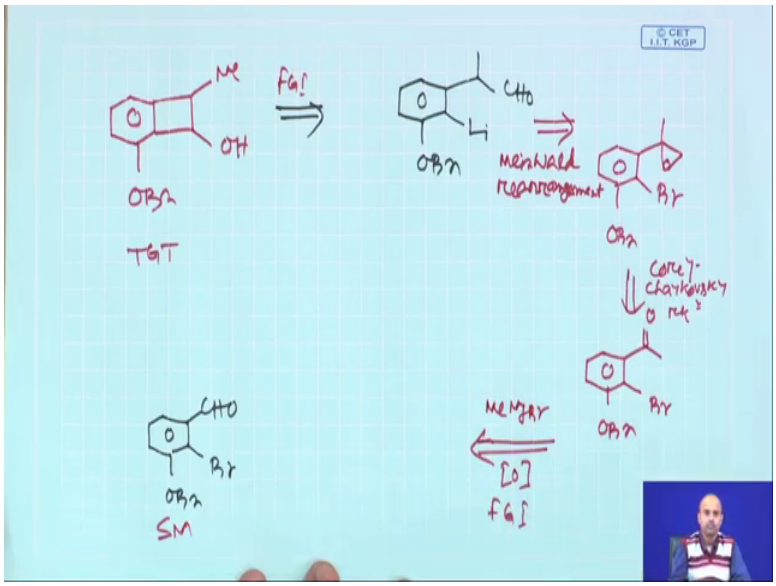

We will try to conclude the whole session just be giving you another example; this example is little bit different than the others. Because the compound here is a benzene ring fused with a cyclo butane thing other targeted molecule.

Now, here you as said this kind of transformation you can easily do with a help of multiple transformations or several key transformation coupled together. There might be many other pathways, but here Bn stands for basically benzyl, Bn stands for benzyl.

So, initially what target I am I am not giving you the starting material initially, I will otherwise I will let me give you the starting material also. I am drawing the starting material here; the starting material is something like OBn, B r and C H O; OBn, B r and C H O. So, this starting material I am giving to you.

Now, I am saying that the retro which will be now device here; I put something like this retro; I say the cyclo butanol can be synthesized through a intramolecular organolithium coupling with this lithium, with this aldehyde; so, it is a FGI fine. Now this aldehyde; now see how I am doing it; which is this lithium will be can be generated at a later stage with the exchange of butyllithium or or tert butyllithium to give you the lithium this spaces.

Now, here I say if you have this epoxide; this epoxide side you can basically do a manual type of rearrangement or the rearrangement which we have just discussed that BF 3 or

lewissremediated semi pinacol, pinacolone type of rearrangement will give you this compound; their mechanism probably now you are quite familiar. Initially you have to quadrant with the Lewis Acid and then now open up this particular epoxide.

So, initial suggest that you can basically opening up this thing, by putting a hydrogen or putting a carbonium ion here; then one of this hydrogen here migrates and you get this aldehyde through a manual rearrangement. Now find here now how you can access this particular aldehyde or this particular epoxide. Now you say that if you have this compound C O C H 3; you can easily do it.

Now the particular reaction, we already explained long ago is called Corey Chaykovsky reaction. So, Corey Chaykovsky reaction of this ketone will give this epoxide. Now this things is now quite similar to the starting material what basically you need to do now; you just do a methyl magnesium bromide and oxidation; it is FGI.

So, in formal pathway; we have to do the formal or the sorry the forward pathway.

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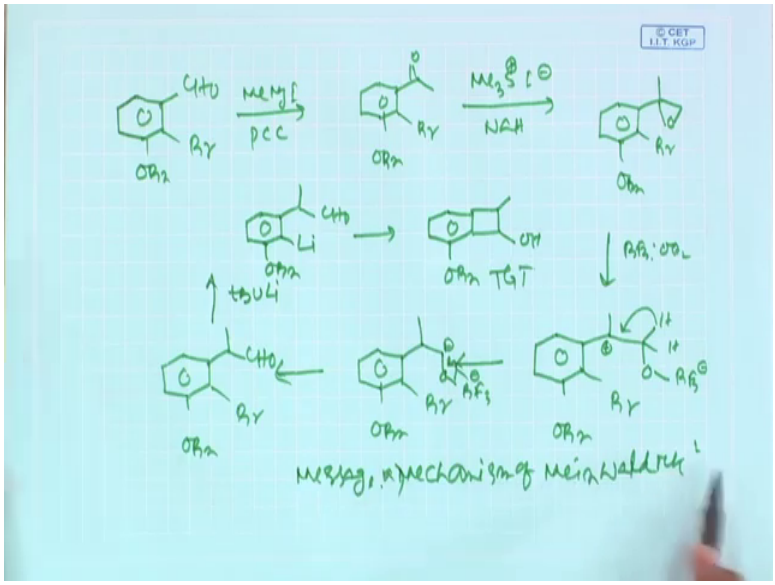

So, we start from this compound OBn, B r, C H O; methyl magnesium iodide I say pcc oxidation will basically end up with this ketone. Corey Chaykovsky reaction; so, basically tri methyl sulfonium iodide and sodium hydride will basically get the corresponding epoxide corresponding epoxide, you get this.

Now, you put the BF 3 threat for your manual rearrangement. So, initial you open up the epoxide O BF 3 minus, you have this things there are two hydrogens, one hydrogen migrates here; if one hydrogen migrates you basically get a positive thing here and in this positive things.

Now quench this carbonium ion you basically get the OBn, B r methyl C H O. So, mechanism of manual rearrangement is very crucial; so, if you are not sure with the mechanism of manual rearrangement; now you exchange this bromide with this lithium with the sterically bulky lithium group like tertiary butyl lithium. And then you will find that you will generate a lithium species the phenyl ring and then your C H O is here, it will immediately undergo intramolecular nucleophilic reaction at the aldehyde. And then basically you get this cyclo butane derivate; benzo cycle butane derivative.

So, by this way your target molecule can be easily achieved. And now if you are trying to give you the key message or key information, the key message is your mechanism of manual rearrangement is very important.

Mechanism of manual reaction that basically gives the main foundation that how you can carry out the entire reaction. The similar kind of strategies we will basically talk about little bit later. But now we will try to summarize till today what we have discussed.

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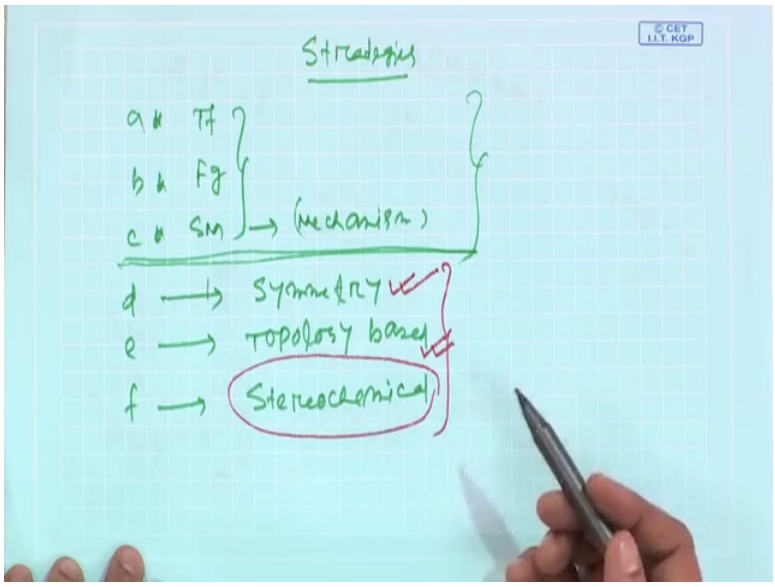

But the very beginning we say it the our strategies which be will be mainly focused on 6 different topics. Topic 1 is transformation base, topic 2 is functional group base, topic 3 is starting material based.

We basically club these three strategies together and in addition we talk about some mechanism based strategies which are also part of this entire 3 strategy. So, strategy a, strategy b, strategy c; now we have also formulated remaining 6 strategies which were not very much important, but also plays the integral role; we say strategy like symmetry based strategies for designing a retro pathway, then we said topology based strategies; topology based strategies and then stereo chemical based strategies stereo chemical strategies.

So, still today we have basically covered this 3 part because 3 part is the main highlight of a elementary courses, which I am offering. Now our remaining part of the lecture, we will be basically focusing on first we talked about symmetry based strategies, then we will try to talk topology based strategies and then we will talk about stereo chemical based strategies and then will have a concluding remark and we will try to sum it up.

So, please go through the entire transformation, functional group and starting material based strategies. We will see you in the next lecture, till then good bye.