A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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

Lecture – 35
Fg/Tf/SM based Strategies (Contd.)

So welcome back students. We are basically discussing a combination of all the strategies, which basically involves transformation based strategies, starting material based strategies and functional group based strategies. And couple of last lectures, we talked about how those strategies can be efficiently coupled, efficiently combined to access small molecular target, molecules through a proper Retrosynthesis disconnection.

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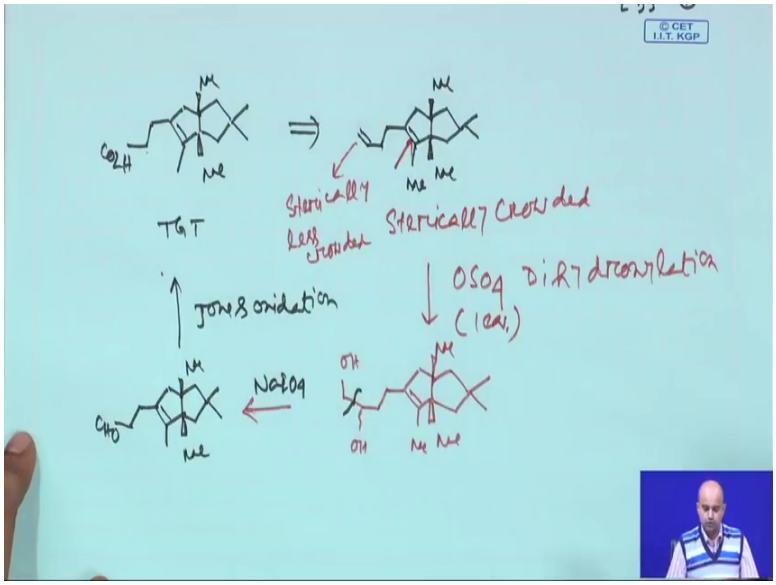

The same line will now give you a simple target molecule, which will now analyze, how this molecule will be accessed. So, this molecule is having a bicyclic structure and if you see its functional group pattern, this is molecule only having a carboxylic acid group, in the left hand side; the target molecule. The starting material I will be giving to you, to have a more direct approach.

Actually, the starting material is always given to you. You can directly think and it will be more direct approach, the starting material is not given to you N number of path. Pathways are possible and then you have to analyze all the pathways and that often takes

a longer time. So, for people like you were beginner in this field always, I will try to provide the starting material.

The starting material which is given to you is basically kind of a homoallyl appendages given. Now, if you try to coordinate through a skeletal disconnection, you will basically find that these homoallyl things, if you do a oxidative cleavage, you basically needs 1, 2, 3 is, CH 2, CH 2, CHO. So, if we do ozonolysis kind of thing, you basically can get the aldehyde, then you can do the oxidation.

But in reality in the molecule also you are having a double bond in the ring. So, in those cases you need to find a suitable method, which will basically control that this double bond will be only affected, without this double bond. Maybe you see this double bond is definitely electrical electronically reach, because it is tetra substituted, but on the contrary; this double bond is highly sterically crowded, this double bond is sterically very much congested or sterically crowded on the contrary. This double bond is sterically free or sterically less crowded.

So, based on the information we will now say that, if we have to touch particular one of this double bond, it is always better to do some reaction which can be controlled by sterically. And you see that this osmium tetroxide mediated dihydroxylation is always, you can control the regiochemistry.

If you use a one equivalent up of hetroxide the initial pathway goes through a cyclic osmium tetroxide formation and the cyclic osmium tetroxide formation will prefer to formed in a sterically less crowded environment. The point is, you have to use the one equivalent. So, then if you use this thing, the terminal double bond will be only affected and you will basically get this terminal double bond, which will be affected to give you the corresponding DIOL fine.

Now, we are almost there now, say that will be doing a Johnson Limoges Cleavage which you have already explained many times, that will basically give you the corresponding aldehyde, which structure will now draw the structure of this aldehyde, which is generated after this Johnson Limoges Cleavage CH 2 CH 2 CHO. Now, related to we just need to do a John's oxidation just oxidize, the aldehyde to it is corresponding acid, the target has been achieved.

So, what we basically did? We did a regiochemical based oxidation or regioselective oxidation at this terminal olefin. We take the help of stearic condition or sterically crowd environment of this particular olefin. So, use a stoichiometric oxidant one equivalent only and then you can put a double bond which you can selectively dihydroxylate and then it chop it or cleave it, to get the aldehyde, then this earlier, it was oxidized to get the corresponding carboxylic acid. It was very trivial approach.

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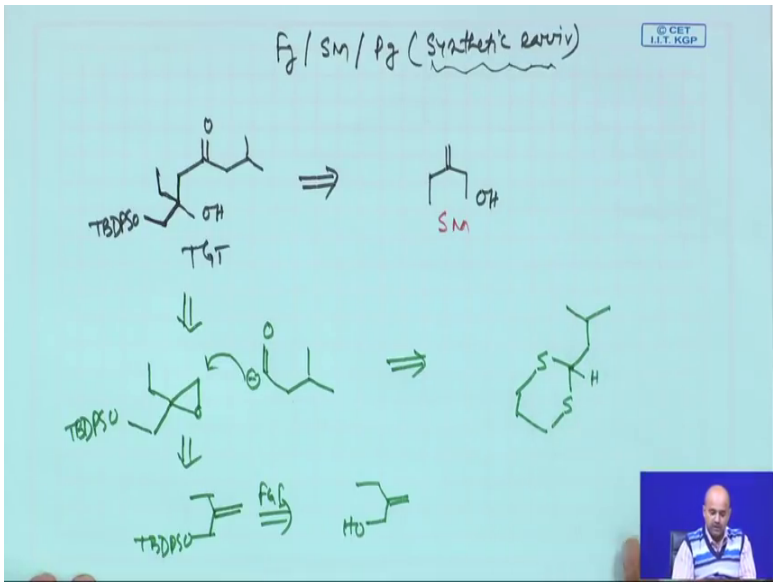

In the next particular problem which we will be try to assemble something else together. We will say that, this is a functional group, starting material as well as protecting group, it is also used a synthetic equivalent. So, all these strategies have been combined; now, the target molecule, which I am drawing now, the structure is, it is having a quaternary carbon is having a O TBDPS here, and this is having a ethyl group.

Structure looks little bit complicated, but that is why you have given the starting material, view the starting material which I am giving to you is, this compound and we said you have to use this synthetic equivalent. So, this part you have to basically device that, what synthetic equivalent or what particular synthetic equivalent. We will be using, we access this.

Now, try to correlate this starting material with this target. Now you can find it that only this oxygen will be probably coming from this, if you protect this, free hydroxy has, it is TBDPS charge. So, this spot TBDPS, this part and then you are having this ethyl group.

So, this part is this and this part is the ethyl and now this particular double bond might be this one, where you do something else.

So, now we will cut the molecule in a retrosynthetically pathway and you see how do cut the molecule, we say ethyl is there and then we say if you have a epoxide, something like this and then we say would be using a synthetic equivalents of this umpolung, with this umpolung, which will attack the sterically less crowded epoxide and this way to give you this target molecule.

So, now your job is how you can access the umpolung and how you can make this epoxide from the starting material. This part will be now doing it first, this looks absolutely similar, that if you have this compound with this TBDPS O, you can easily do a MC base epoxidation, which is nothing, you just need to do a FGI, through this standard protection of this primary alcohol.

Now, this umpolung you can basically create by standard technique and the best way you can create this umpolung, just take the corresponding 1 3 diehtane, which we normally often explore of the corresponding umpolung chemistry. So, what is the hydrogen, which will be abstracted and will generate umpolung.

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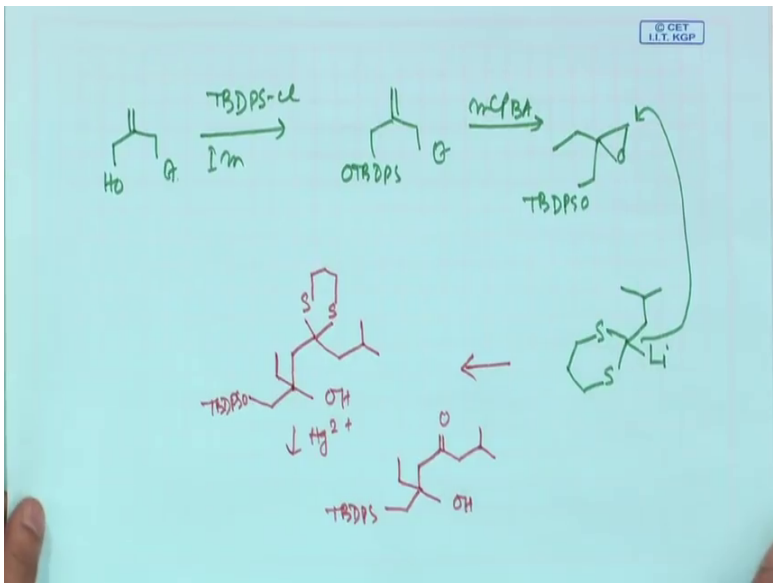

Now, coming to the forward synthesis. So, you start with the compound which was given to you. So, first protected, which is TBDPS chloride TBDPS. We already explained is a

protecting group imidazole, only one equivalent protection is required, because there is only one hydroxy group. So, it will be O TB DPS, you use MCPBA as epoxidizing agent. So, basically now you will find, you will get this epoxide, we will try to write it in this way.

Now, here we will be using this umpolung, which is basically having this 1 3 diethane moiety. We basically picked up the hydrogen by a base and put a lithium, means a negative charge. So, this negative charge now, attack this epoxide from a strically less ended site and then you will find how this.

So, epoxide will be now opened up and you basically get this TBDPS, will be there. You have this OH, which has been generated, you have this ethyl. So, all this quaternary centered, quaternary carbon is now generated and then you are having this CH 2 and your umpolung is here and remaining your isobutyl is here.

So, now we just need to do a demusting this protecting group by AG 2 plus and then you see, you basically can access your product very efficiently. So, your TBDPSO and your ethyl group. So, by simple functional group manipulation, you can effectively combined as the functional group based strategies, as well as starting material was given to you and we used the protecting group as well as synthetic equivalents in the form of 1 3 diethane, to compete the synthesis, the very nice demonstration or a combination of couple of different strategies all together. The similar line we will be talking about, another problem whose structure is this.

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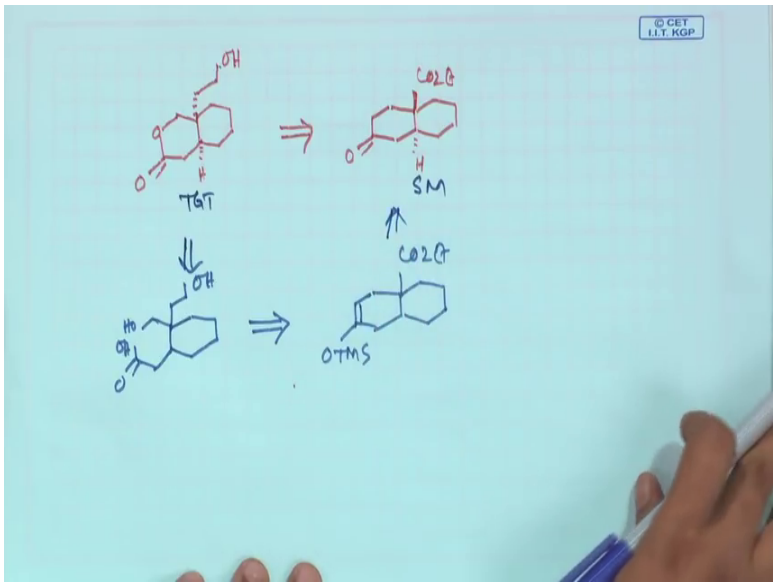

We said you were having a particular compound of this structure, the starting material was also given to you, the starting material which was given to you is having this bi cyclic ketone to this CO 2 eT here, the stereochemistry was not issue, but eventually that can be nicely taken care, we did not have anything.

Now, if you see this target and this starting material only, difference is probably you can make it out the starting material, in this ring there is no oxygen, the target you are having, you are oxygen here, now you figure it out, if somehow this CO 2 eT can be converted to CH 2 OH and that can be put in the ring and then this CH 2 and this CH 2 can come here, that will give you the CH 2 OH.

So, now let us do the retro, we are now saying that if you having this kind of hydroxy acid, which can give you this lactonization thing, also this OH eventually this. There are two different OH and you need to make sure, that only this OH reacts with this lactone or otherwise, you can basically protect one of this OH. Now, here how you can formulate that, this compound will try to generate this. Now, we say that we formulate an intermediate, if you are this intermediate you basically do an ozonolysis right. So, ozonolysis what we give you CH 2 C double bond OTMS or a carboxylic acid and this part is CH 2 CHO, which you can reduced to give you the corresponding alcohol, as it is here.

Now, this CO 2 eT somehow if you can convert it to CH 2 OH, this may do the ring closing. So, it was basically formulated in this way. Now, let us see how this forward pathway can be figured it out, this is the starting material, which was given to you, basically a bicyclic ketone.

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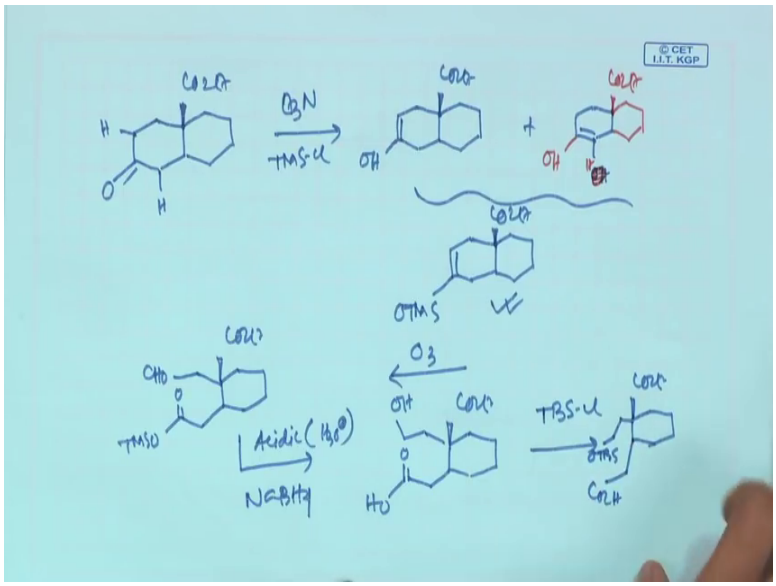

So, initially what we do? Basically, create a triethylamine to generate the enolate. Now, the enol; there are one acidic hydrogen, this is one acidic hydrogen. So, in principle two; enolethers will be basically formed either this enol, where you have this CO 2 eT or you may have this enol formation sorry. It is basically double bond here, as a hydrogen you have this enol.

Now, this enolether we have set, will be trapping it with TMS chloride, then principal, you should get two of the enolether, one will be minor. Now, it is our synthetic pathway. Now, you do not know which one will be major, which need this one. So, just keep it this enol, but remember this enol also is the probable reaction product. Now, this enol if you now do the ozonolysis so, what you will get? C double bond O TMSO, may you have this CO 2 eT here, and then you this CH 2 CH 2 CH O CHO.

Now, I am saying, I am now doing acidic work up to get rid of this TMS, ether acidic work up just by treating with H plus in addition will be also using a sodium borohydride to reduce this aldehyde. So, what I now will get. So, basically get this hydroxy acid kind

of thing. Now, this acid and this alcohol can undergo ring closing, but that will now give you the seven member ring lactone, which is not desired by us.

So, now what you can do? You can simply protect this hydroxy group, first you can protect the hydroxy group, first that also you can do, otherwise let us protect this hydroxy group by say TBS chloride, just trying to give you a CO 2 eT is here, CH 2 CH 2 OTBS and this is your CH 2 CO 2 H. Now, you need to do a ring formation reactions lactone, to make this lactone.

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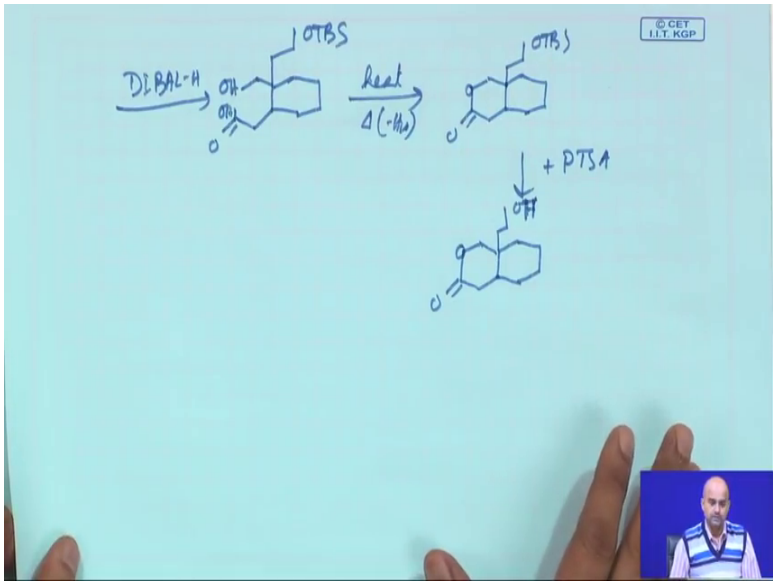

So, now, react with DIBAL. DIBAL basically reduces the corresponding ester 2 is alcohol and then this is basically your protected thing. Now, if you do not protect and proceed DIBAL here that also you can do, then it will give you CH 2 OH CH 2 CH 2 OH then if you can try to lactonise, it will basically have a two possibilities, it can give you six member lactone as well as seven number lactone. So, to try to avoid the possibility of the regiochemical issues, you did production. Now, this compound is subjected to heat, you can get rid of water molecule and basically this is now, you will get this TBS group. Now, can be removed by PTSA treatment Para toluene sulfonic acid, which will now the ladio, this OH and then your is a lactone.

So, the main take home message is you explained a couple of functional group interconversion and then you couple a strategy of a strategic use of a protecting group

and then simple function of the interconversion to correlate the target molecule, with the starting material and then you can basically finally, conclude your synthesis.

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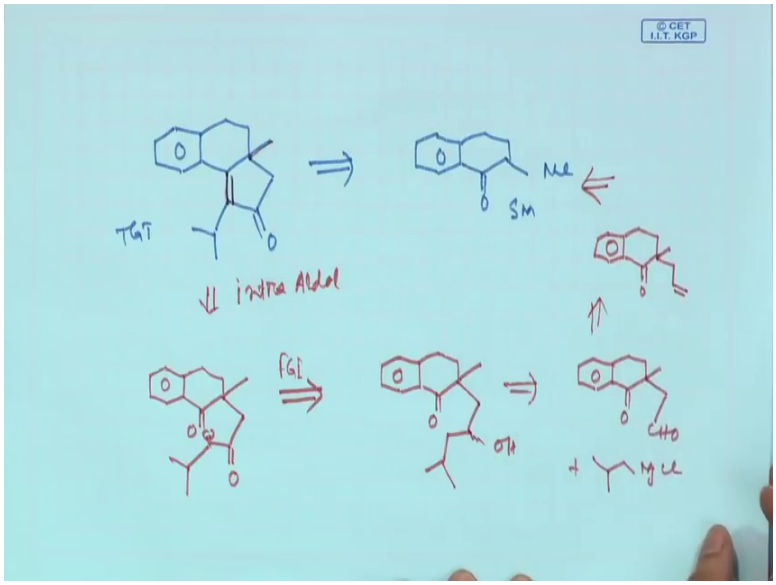

The similar kind of molecule we will discuss. Now, this molecule if you see, we have actually talked about this kind of molecules earlier, but still again we will be discussing the molecule is alpha beta unsaturated ketone, a starting material was given to you is basically two methyl alpha tetra lone. So, the target, this is the starting material. Now, see the target, this target is basically having alpha beta unsaturated ketone here, and this correlation is this, methyl is there.

So, probably you need to introduce something here; then you use this carbonyl group to close the ring. So, if you try to do this kind of disconnection, the first thing will come into your mind by using intramolecular aldol reaction, that is pretty obvious actually. So, if you have something like this structure, yes. So, do a you generate a carbon ion here to do aldol? So, basically I call it as a intramolecular aldol.

Now, try to correlate this with the given starting material. How can make it? I say this starting material will be now, can be easily prepared if you having this compound just by a FGI oxidation, then I said, this also can be easily prepared if you have this corresponding aldehyde and you use a Grignard Mucl. Now, this I say, you can now, come to very close of this starting material. I say if you having a compound like this you

can chop it through ozonolysis and then now, it can be simply by a electrophilic alkylation.

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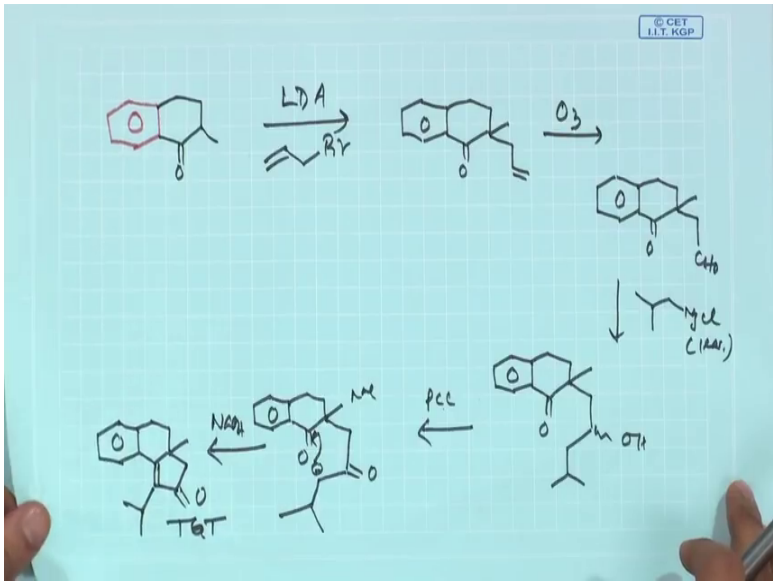

So, your synthesis will now start in a forward path way. We will start from this alpha tetra lone compound, which is discompound LDA 1 equivalent and allyl bromide. So, basically get all carbon quaternary to your center. Now, we say, we will cleave it through ozonolysis, the oxide diplivage. All carbon quaternary centered here, and then this terminal olefin will be now chopped, to give you this CH 2 CHO.

Now, we will be using isobutyl magnesium chloride, which will now give this, a ketone and aldehyde. So, a normally aldehydes are much more reactive. So, you can use one equivalent of this magnesium chloride and this ketone is also sterically very much congested. So, normally this will react here and it will give you these things. Now, you can do a PCC based oxidation to get this ketone, and now you subject it, subject this ketone with a base normally, sodium hydroxide make sure this carbon ion is generated, it attacks here.

So, 1, 2, 3, 4, 5; so, in the aldol fashion, it will be undergoing intramolecular aldol dehydration and the product which will be now getting is having a five member ring here, you have a double bond here, this isopropyl group and this carbonyl. So, it is a very straightforward disconnection, but stepwise you disconnecting it, the transformation.

What you are using is a LDA and allyl bromide at the very beginning. You know, do oxidative cleavage of this double bond, you use isobutyl magnesium chloride.

Now, you remember that here, we basically having a ketone as well as aldehyde. Now, here in principle, we should do a protection, but that will take care that will definitely increase the number of steps. So, what we did? We said that aldehydes are much more reactive than the ketone. So, you can control the activity of aldehyde by using stoichiometric one equivalent of Grignard and narration this ketone is spherically very much congested. We use this isobutyl magnesium chloride, one equivalent to get this secondary alcohol. This is a mediated oxidation that will give you the ketone.

Now, we have a dike tone, in out of this dike tone only this ketone is having alpha hydrogen here, as well as here. Now, this hydrogen, if it abstracted, there is no possibility, you can aldol reaction takes place. Only this hydrogen will be abstracted by this base and then it can undergoes intramolecular aldol reaction followed by water elimination, to give you this target molecule. So, simple starting material can be efficiently used and then you can get access of a complex tricyclic molecule. Now, initial target molecule is a complex tricyclic molecule.

So, we will keep continuing your discussion, based on this same strategically focused point and I will mainly talk about starting material functional group based strategies and transformation base strategies, in a combinative way. So, we will just try to analyze all the lecture slides very carefully. Go through the assignments, which you have given and till then have a good time; so, goodbye.