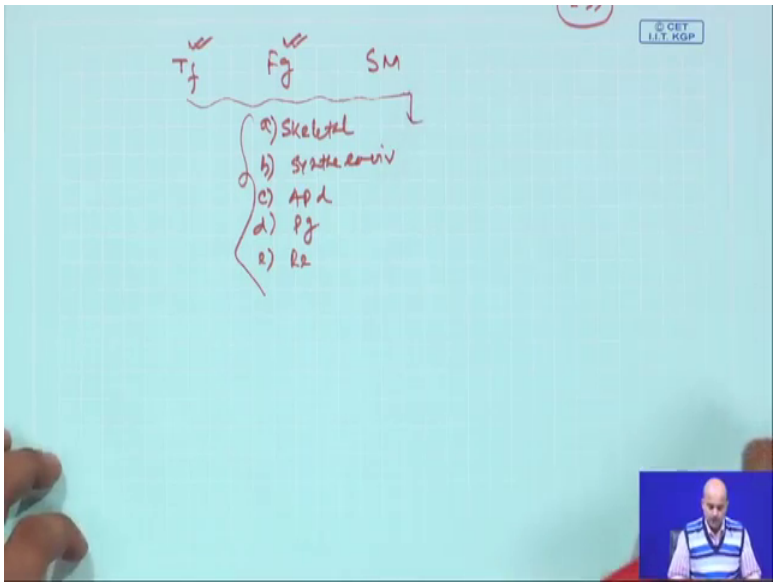
A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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

Lecture – 33
Starting Material (SM) based Strategy

So welcome back students; so, now we will be discussing another important strategies at the very beginning we said that.

(Refer Slide Time: 00:27)



We are mainly focusing on three strategies in a parallel fashion, we say transformation based strategies, functional group based strategies, and starting material based strategies are basically closely related and you cannot distinguish between them. Transformation we have covered and we said that there are key transformation, which will give you a idea that which transformation you need to use it to access a desired target.

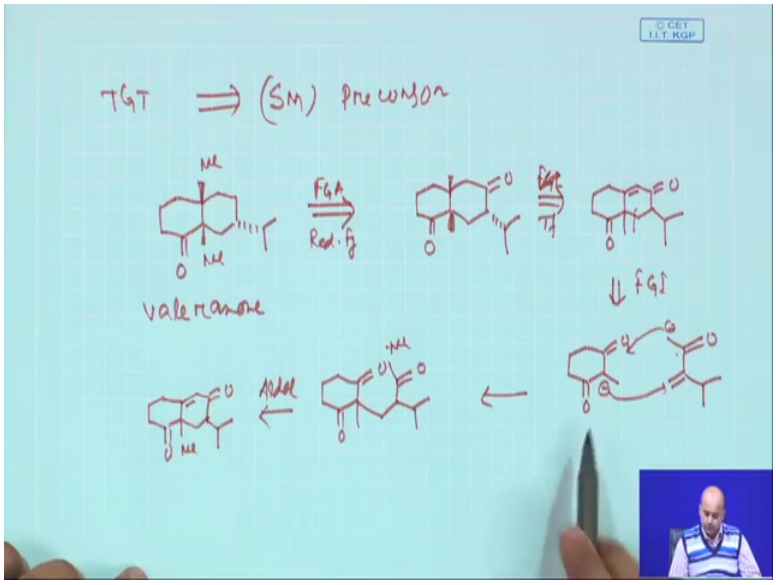
Functional group, we have already discussed in detail and particularly this functional group, we have talked about skeletal disconnection, we have talked about synthetic equivalence, we talked about appendage disconnection, we talked about protecting group based disconnection, and then we talked about redundant functionality.

So things have been covered, now starting material based is basically related to these strategies, but as I earlier also we talked about some cases we have given you a well-

defined starting material in a job is quite easy. So, in the starting material based strategies mainly we will try to figure it out, the starting material is given to you, and a target was also given to you, when you try to formulate if there are multiple routes can be designed or can be test back.

So, that a single starting material which is given to you can lead the way multiple pathway, and you can you have to individually analyze which pathway is much more viable to you based on the step. As well as the cost of the reagents and other things you have to take care.

(Refer Slide Time: 02:18)



So, once your target is fixed and the starting material was given to you, starting precursor. Precursor or the starting material, now this was basically the very old approaches oldest approach and we will; as earlier we will basically discussing the problems with a particular given target. Now in this particular given target, we will be just trying to analyze what are the possible retro for this given target molecule, this molecule is a natural product this molecules name is valeranone, valeranone is a C 15 framework molecule this is squid terpenoid, you count its carbon it cannot count it will come as a C 15. So, valeranone is a natural product, and now initially we are not discussing what starting material to start.

We say that lets first do a conventional retrosynthetic pathway, and if you can come to a more than one pathway then we will analyze, which pathway is better and then we

follow the forward things. So, eventually initially the pathway which we say will be trying to have this groups are all there the stereochemistry was kept, but in the retro pathway we would not discuss about the stereochemistry. We say initially if you can introduced this kind of ketone adjacent to this isopropyl group probably a FGA is required now this is basically redundant functionality ok.

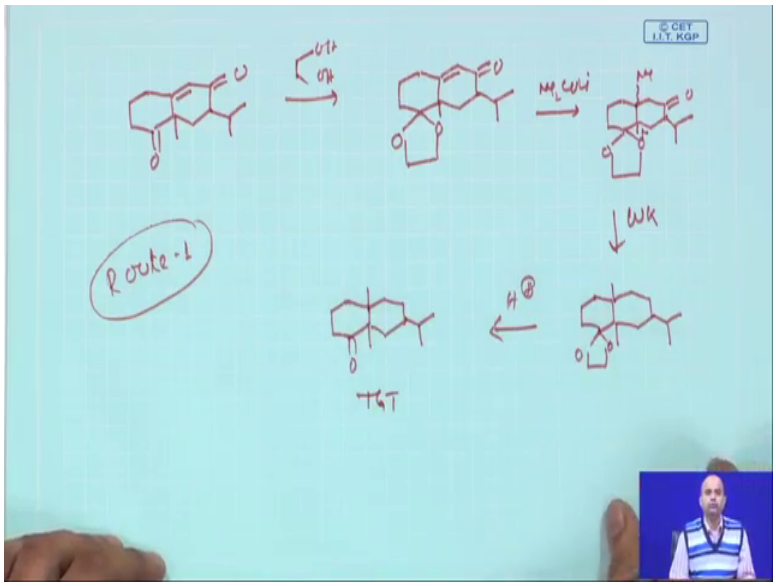
So, FGA based on redundant functionality we initially have devised, then we say if this can be done we will now do our next round of retro based on this kind of transformation. Now where it saying that we will be doing a functional group of group inter conversion all it is not a function of inter, this is basically a transformation is a 1 4 michael addition to a methyl nucleophile to this alpha beta unsaturated ketone system. Now we will try to simplify it, and now we are saying if you have this intermediate and a compound like this.

Now, this retro is pretty interesting and this retro basically will give you a favor of our earlier very well known retro or well known name reaction called Robinson annulation. Now this Robinson annulation what do you say initial step is michael. So, this is michael acceptor this is the nucleophile. So, first it will be coming here, now this things will now generate a negative charge here. So, initial this michael sorry this initial michael will takes place. So, this carbon carbon bond will be basically forming here.

Now, you are having another come here. So, in reaction medium if you have a base this can undergo aldol michael reaction. So, try to formulate the mechanism which will allow this particular transformation so, initially you get these things methyl. So, now, this methyl will you we have to extract a proton from this acidic methyl hydrogen and that will undergo a aldol reaction. So, basically have this aldol, then and which will then lead to the lead to the product the michael aldol adduct and the structure is like this your methyl is remain here fine.

So, this route looks quite viable. So, you are basically here, now that your next forward pathway is how you can selectively do some reaction here. Now initially you have a saturated carbon, you have a unsaturated carbon saturated carbon, as it is a highly reactive you can protect this saturated carbon do some protection here, do some protection here saturated carbon. So, I take this saturated carbon or this particular intermediate.

(Refer Slide Time: 07:38)

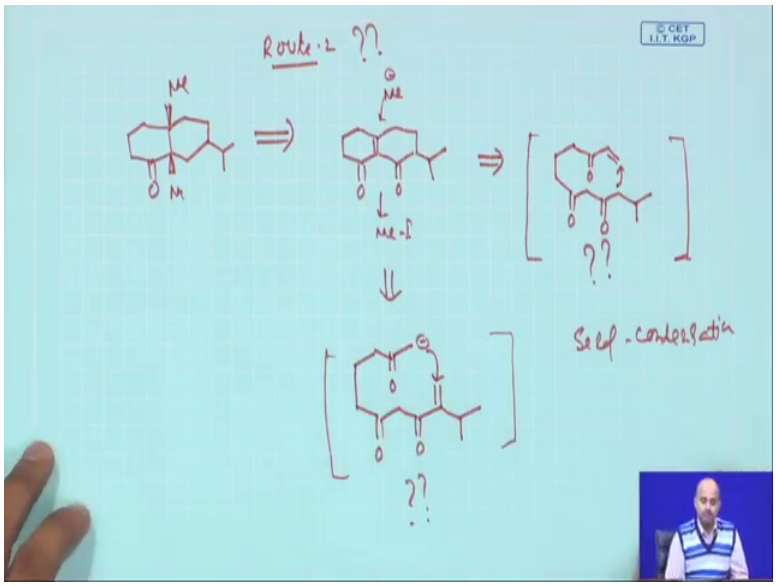


And then I say saturated carbon unsaturated carbon so, do the protection here with ethylene the alcohol, the all the remaining part will remain similar methyl is here.

Now, you do a methyl copper lithium the gilman to introduce the this methyl. So, just we are also talking about the forward pathway, which will help you how you can see the entire synthetic pathway methyl, methyl your isopole is here. Now basically what you need you just do a Wolff Kishner type of reduction so, Wolff Kishner type of reduction will then deoxy annotate this, ketone this methyl, methyl and you have this now you just removed the particular protecting group here, to get the target molecule. So, this is your valeranone target molecule.

So, the route one which is basically very nicely demonstrated, and we have absolutely no issue with this route.

(Refer Slide Time: 09:13)



The similar way you can have a come to another route, which will show that how a different target molecule or a sorry if same target molecule, you can design different starting material based approaches, and how a single target can be disconnected through a different starting material. Now I will be take talking about route 2, now route 2, I say there might be another route though this route is little bit unconventional, but straight this is also possible. And I say if I have this kind of bicyclic compound, we will be doing a michael addition here, to introduce the methyl group in a methyl minus ok.

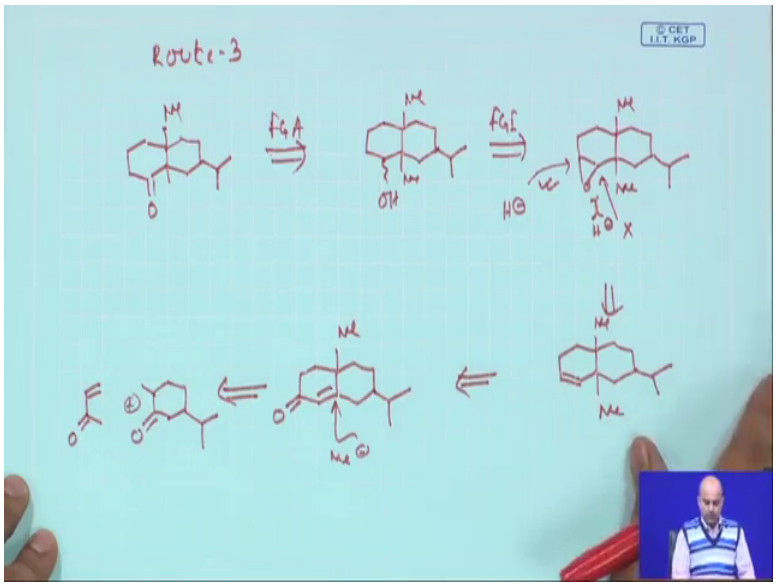
And then this will be generate a annulate here, that will be trapped with a methyl electrophile methyl iodide. So, looks logically possible while then how you can make this compound. Now for these compound you are making was little bit looks like some this way, I said we will be trying to give you a retro something like this. Now what this retro basically says this retro says, if you can have a initial carbon ion generation here, that can give you this carbon carbon bond through a michael addition, and once this michael was done you can close this thing through a aldol pathway.

But actually this substrate itself was very tricky, because there are many carbonyl groups are there, and you will be basically having numerous acidic hydrogen, which will be picked up by the base and eventually self aldol condensation will be a big problem. So, this substrate will put a big question mark big question mark. So, eventually in the similar pathway you can also think about another substrate which is also. Now let us will

formulate its say this one also a relatively, similar kind of pathway which also might be possible, how this negative will generate to give through this michel pathway, and then you have this aldol pathway.

Now, again I am saying this starting material is very dicey, because you are having too many carbon compounds in the compound, and all this will be basically leading to self-condensation, and it is very difficult to handle these substrates are these two substrates are very difficult to handle, that is why this route 2 will put a big question mark though its logically valid. So, this target by using this starting material it might give you the desired target, but we are absolutely not sure what will be the reaction yield.

(Refer Slide Time: 12:56)



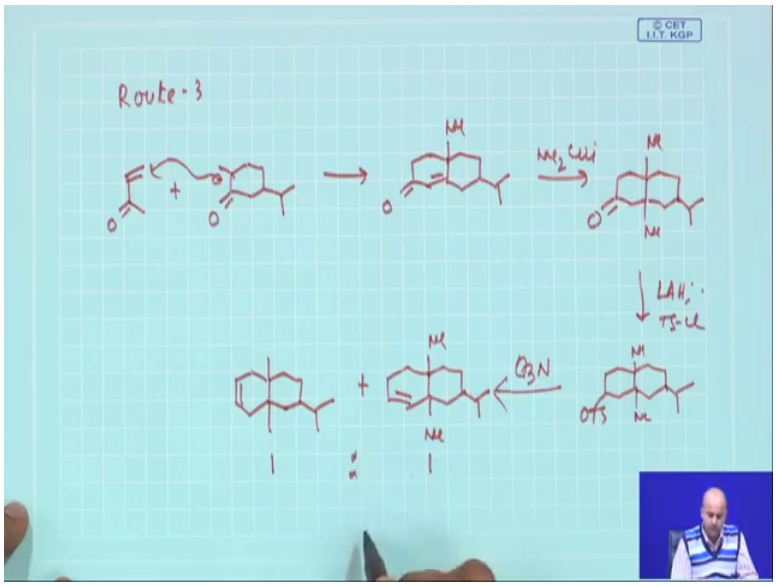
Which will be now drawing which will be now analyzing, you have a methyl for this ISO polythene.

The next route which I am now giving the first will be a functional group addition, and we say that the functional group addition, will basically put the way OH here; the remaining groups are remain same. This OH you can basically create from or access from this epoxide, assume that it is a FGI, when a hydride will come from sterically less in that side, there is hydride can come from here or hydride can come from there, but if hydrate come from this side, this is more facile because sterically less in that this side is blocked that is why this is not feasible.

So, this load route is quite feasible now how to access this epoxide, how to access this epoxide. So, for this epoxide definitely you need a double bond something like this, you need a double bond with this 2 methyl fine, and then I say if you have this double bond you can basically formulate a another reaction, which is our known Robinson annulation now see this route, this particular transformation how you can going to access, it we said that fast will put a methyl minus in 1 4 fashion. 1 4 fashion to give you this CO and Me we will discuss this pathway little bit later on.

Now, if you can analyze this is gives you a very standard Robinson annulation pathway. So, you will basically give you this compound, this compound, and your methyl vinyl ketone. So, now, you try to analyze the route 3, route 3 and we see how this route 3 also is possible.

(Refer Slide Time: 15:41)



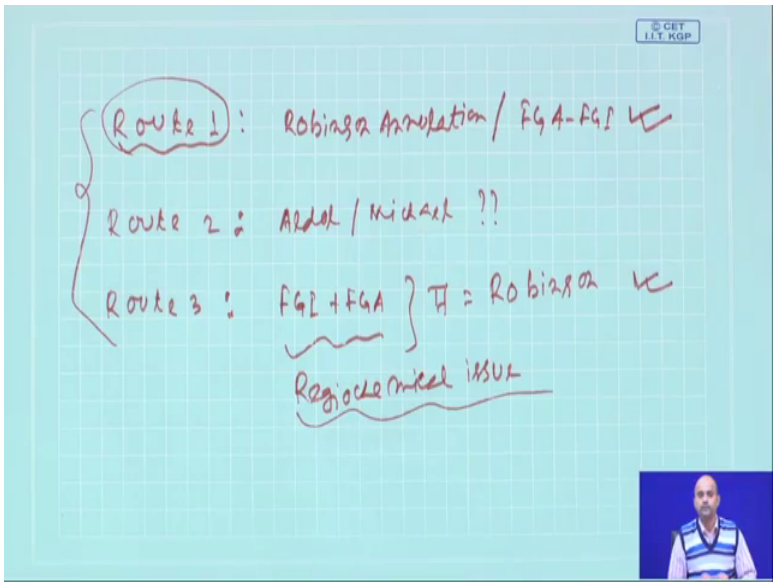
So, route 3 will say you are using a methyl vinyl ketone, and this cyclo hexanon based compound. So, initially your michael followed by aldol will basically give you, this bicyclic enone. Next you need to introduce this angular methyl. So, do a Me 2 Cu Li mediated 1 4 addition, and then see if you do a 1 4 addition basically come here.

Now, the retro which was next drawn is basically you have to generate a olefin, if you can see the earlier earlier piece of paper. So, now, you have to reduce these things to lithium aluminum hydride, and convert this alcohol to corresponding tosylate you know what intermediate, you will basically getting you basically get intermediate this. Now

this compound is a tosylate and you heat it, with triethylamine simple 1 2 elimination will takes place, and basically you will be expecting the formation of 2 regio isomeric product, this one as well as this one methyl methyl.

Now, both the product might be form in a equal amount, because you do not have a stability factor which can be counted that this product will be formed in excess. So, eventually this is the desired product, but you also have a regioisomer which may formed in one is to one ratio. Now once this product is formed you go back to our earlier things to take this product do the epoxidation LH opening, and access the product. So, now in a summary we will try to now analyze all the routes.

(Refer Slide Time: 18:06)

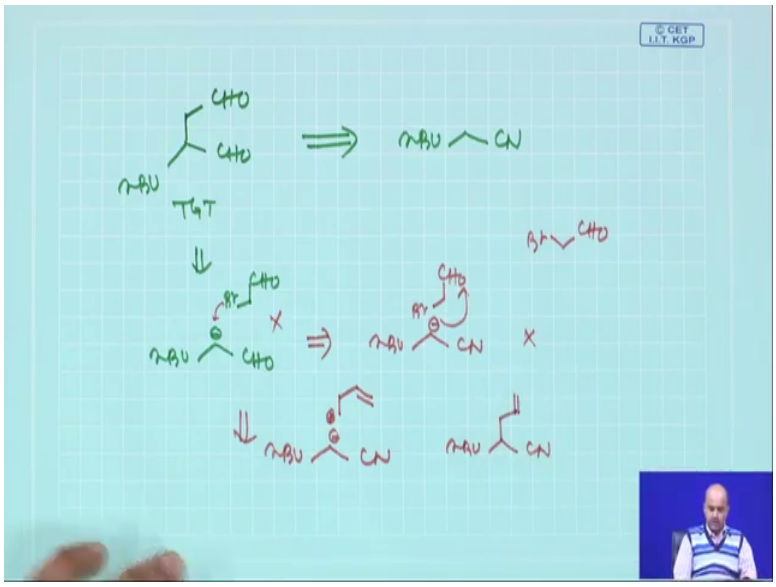


So route 1, route 2, and route 3. So, route 1 what are the transformation we are using basically is a Robinson annulation is the main transformation, and we also use couple of functional group addition or FGI, and it looks absolutely feasible. Route 2 which was basically again based on a aldol michael pathway, but this route is a little bit dicey at the starting material which contains a multiple carbonyl groups, route 3 also based on couple of FGI plus functional group addition, and the trans key transformation is again the Robinson annulation all right though it looks feasible.

But this route is having a regiochemical issue, regiochemical issue means which regio isomer is forming so, basically the the desired regioisomer may not form in good yield. So, you have a yield related issue. So, based on the whole a three different routes, I

would rather prefer the route 1 which does not have any ambiguity. So, this route looks absolutely perfect, because this route will allow you access of this desired target without any question.

(Refer Slide Time: 20:43)



You can control the all the effective pathway the reagents are pretty easy, the starting materials are pretty easy, and throughout the entire pathway you do not have any regiochemistry issue, which needs to be addressed and where the route 2 the starting material seems to be absolutely difficult to access. This is a poly carbonyl compound which can undergo cell condensation reaction, route 3 looks fine, but at the initial stage when you doing this elimination reaction that will give you two regio isomers.

So, that also big problem associated with that route. So, in the starting material based approach our main thing will be basically focused on, how a target you can access with the help of the starting material which was given to you, or definitely this approach is similar with the earlier approaches. So, we will be basically trying to solve many problems, as discussed earlier. The first one is very simple problem which is given to you, this is a dialdehyde the starting material which I have given to you is a nitrile compound.

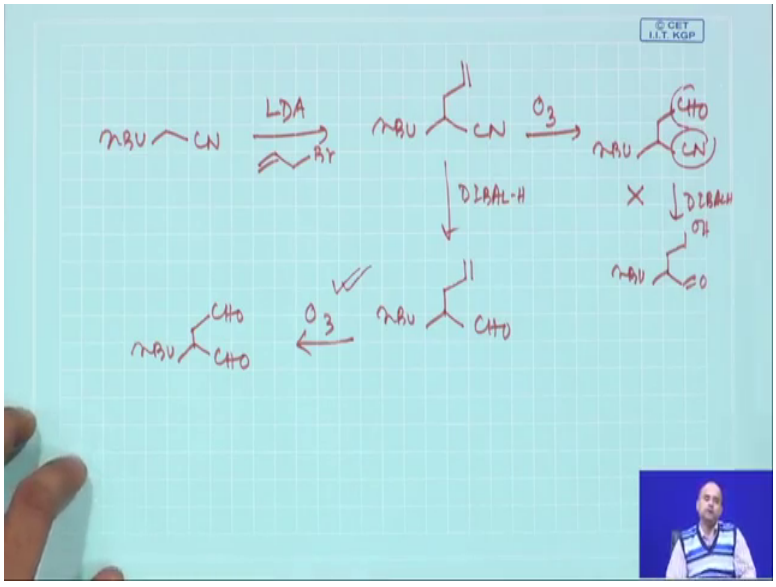
Now, all of us know that nitrile can be converted to CHO that is for sure, but then you need to introduce another you need to introduce another CH 2 CH 2 group here. So, let us say first do this thing here. So, I will put a minus here and I say if you having a CH 2

Br, if we having a bromo acetaldehyde that can act as a electrophile and that basically can attack here. Now it was a bit difficult, because you are going to do a base mediated reaction. So, carbon ion is there it can undergo aldol reaction, self aldol reaction many thing can takes place.

So, I will probably recommend this route is not feasible instead, you as the starting material was a nitrile you take this starting material, and then you find whether this CHO CH 2 Br can be act as the electrophile it looks it looks promising, but eventually when you generate this carbon ion here, probably this carbon ion can undergo self aldol reaction of this electrophilic aldehyde is aldehyde. So, this particular group how you can introduced Br CH 2 CHO, I say let us try it other way I say let us put these things, then if you can fuse a allyl group here, this allyl as a electrophile then it looks quite possible.

So, you intermediate if the intermediate is having this structure it was absolutely fine. You are need to just do a oxidative cleavage. So, now, then go to the forward path way.

(Refer Slide Time: 23:44)



To start with n butyl CH 2 CN treat with base LDA, and treat with alile bromide, and then this allyl bromide react here to give you this alkylated product. So, here you straight way do the ozonolysis straight way to the ozonolysis, and that will basically give you CHO. Now you have a difficult situation, because here now if you do a dibal reduction cyanine will be reduce that is fine.

But you also have this aldehyde, which will be also now reduced to the corresponding alcohol. So, ozonolysis you need to be very careful, that what where which place you can do with the ozonolysis. So, now here if you use the so this route is discarded. So, now, here if you do the dibal first, the dibal first is fine, then you do the ozonolysis, then you do the ozonolysis then basically you are in perfect shape ozonolysis does not cause any disturbance to the corresponding aldehyde and you can fit here.

So, as discussed earlier you might have a 2 or 3 different possible rules, but you need to pick the best route which looks perfect according to the chemical logic, and then also in the earlier page we have talked about that you can think about using the using the bromo acetaldehyde as a electrophile, which in principle you can do it, but bromo acetaldehyde is very difficult to synthesize. On the contrary if you use a allyl halide or allyl bromide, which is pretty easily available and allyl bromide; allyl, you can simply create this double bond to generate the CH 2 CHO. So, this is perfectly easily accessible and you can have a absolute control.

So, we will try to continue our discussion on the topic which we have just started starting material based or based strategies, and we will give you a target we will give you a starting material we will try to formulate whether there are many routes are possible or not, then each and every steps each and every routes, will analyze very closely, and they chose the best route which is suitable according to the chemical logic. So, have a good time see you in the next lecture.