Classics in Total Synthesis - I
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Lecture - 06
Cubane

Yeah good morning and welcome back to this course on Classics in Total Synthesis part I. In the last week we talked about you know brief introduction to organic synthesis, total synthesis, semi-synthesis and also we discussed a few natural products having 3 membered ring as one of the core structure.

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So, now we will move to 4-membered ring. So, when we talk about 4-membered ring there are quite a few natural products having 4-membered ring and of course, when you talk about non-natural product in the first and then foremost non-natural product that should come to your mind is Cubane.

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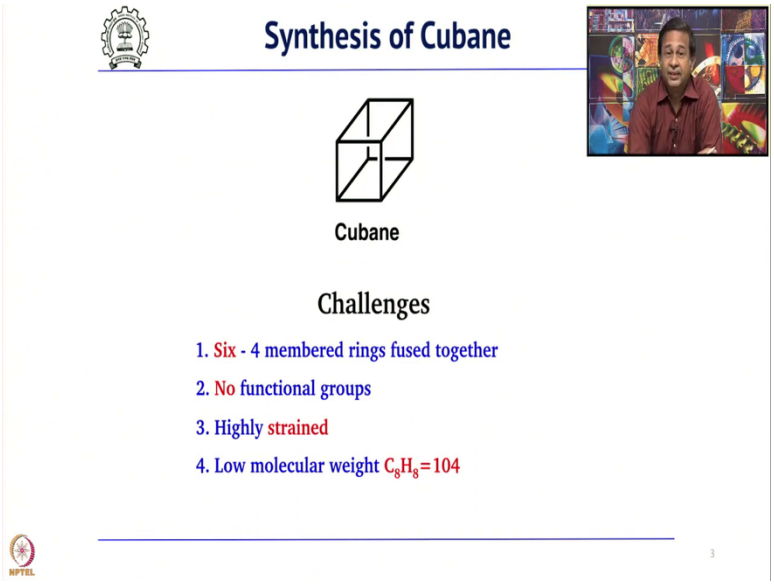

So, cubane is a very interesting compound and how many 4-membered rings are there in cubane? Look closely you can see there are six 4-membered rings fused together and when you talk about one 4-membered ring itself is quite difficult because of its ring strain and here you have six 4-membered rings and they are fused together; that means, the real challenge to synthetic chemist to make this cubane is very very high.

You know when you talk about total synthesis the molecule need not be very complex even small molecules can give its own trouble. So, one such case is cubane. It gives different types of challenges compared to other big molecules. The first and foremost challenges as I said there are six 4-membered rings which are fused together.

And second challenge which is not a real challenge, but from retrosynthetic point of view this is an important challenge. Cubane does not have any functional group. See always when you talk about retrosynthesis you look at a functional group you look at a strategic bond then only go for retrosynthesis. When the target molecule does not have a functional group then it is a problem is not it. So, you need to introduce a functional group and so on.

And obviously, it is very very strained ok. You have six 4-membered rings fused together and how much strain it will have you know ok. So, highly strained compound and molecular weight is 104, as you all know low molecular weight compounds are always difficult to synthesize ok.

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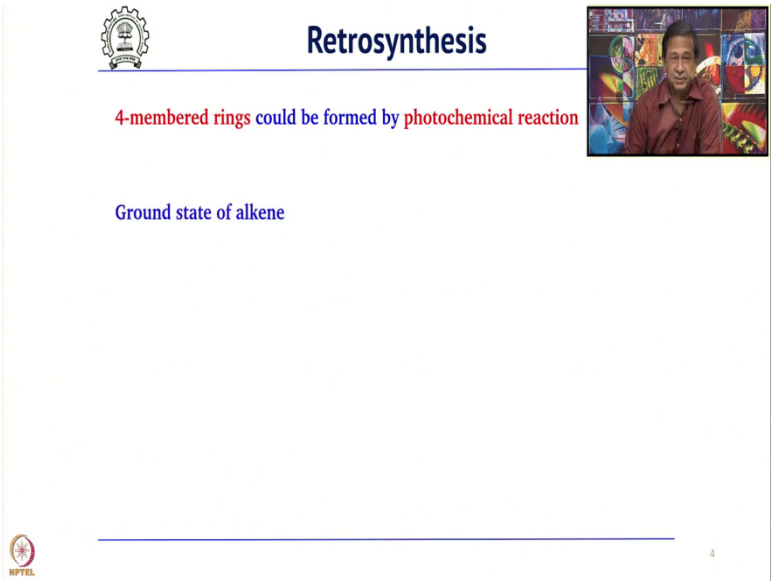

So, these are the four major challenges when we talk about cubane total synthesis and how this 4-membered rings can be synthesized ok. So, when you again talk about 4-membered ring and the first reaction which should come to your mind immediately is a photochemical reaction is not it, 2 plus 2 cycloaddition reaction.

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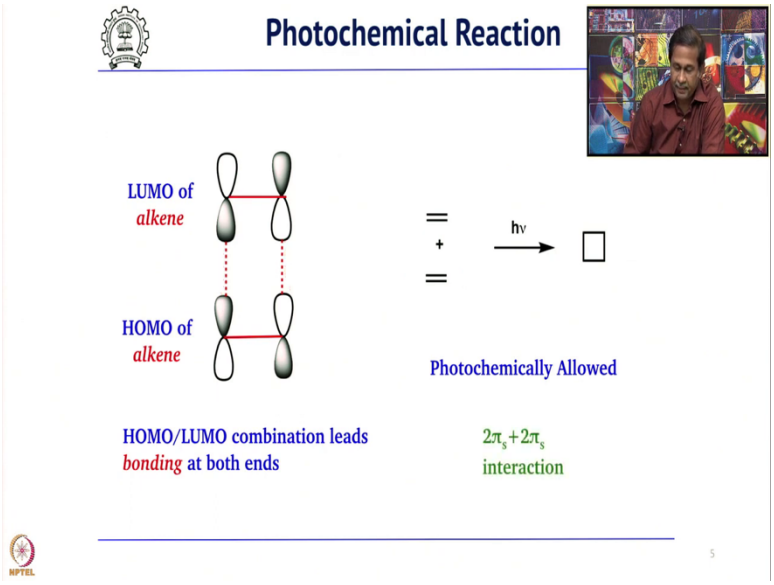

Photochemical reactions are widely applied for making 4-membered ring. So, now, as you can see this is the HOMO of alkene and then LUMO of other alkene, then you can

see nice overlap to form a 4-membered ring ok. So, there are several examples ok. So, this is the simplest example two ethylene molecule giving simple cyclobutane ok.

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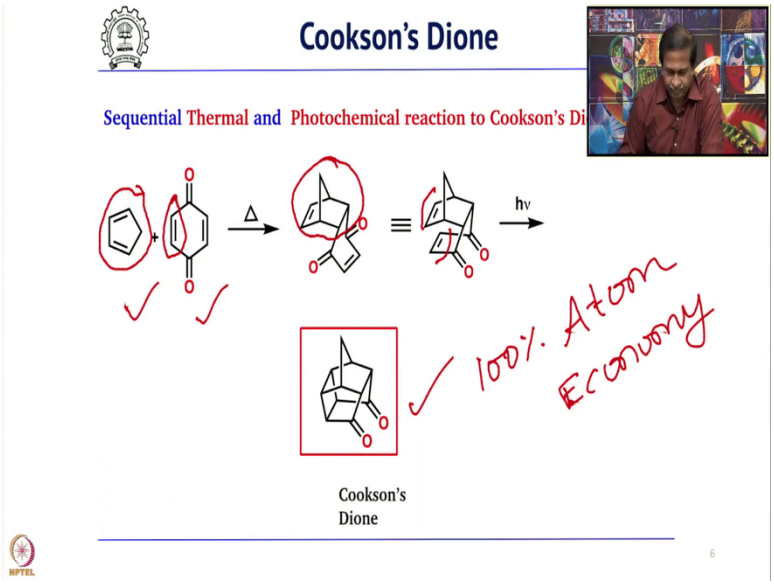

There are many complex reactions carried out using this 2 plus 2 cycloaddition before we actually go into the total synthesis of cubane I just thought you know show you one very interesting example which was reported much earlier is the preparation or synthesis of Cookson Dione. So, this Cookson Dione involves a sequential thermal and photochemical reaction ok.

It is done in two steps ok, it is done in two steps starting from cyclopentadiene and benzoquinone. You can see this is a diene ok and this is the dienophile this double bond is the dienophile and this undergoes a 4 plus 2 cycloaddition reaction to give this bicyclic adduct in principle its tricyclic adduct, but we consider this.

Now, this can be redrawn like this ok. Now when you redraw this molecule then you can see this double bond and this double bond they are very close to each other ok these these two double bonds are very close to each other, then on shining light this undergoes a 2 plus 2 intramolecular cycloaddition to give this very interesting strained dione ok.

This is called Cookson Dione because it was prepared by Cookson first time and in two steps. Remember cyclopentadiene, benzoquinone and you get 100 percent atom economy reaction ok. Whatever you started with in the starting material and you can see all that

here ok 100 percent atom economy ok, you do not lose anything. So, this is the beauty of all these cycloaddition reactions when you do cycloaddition reactions you will get 100 percent atom economy ok.

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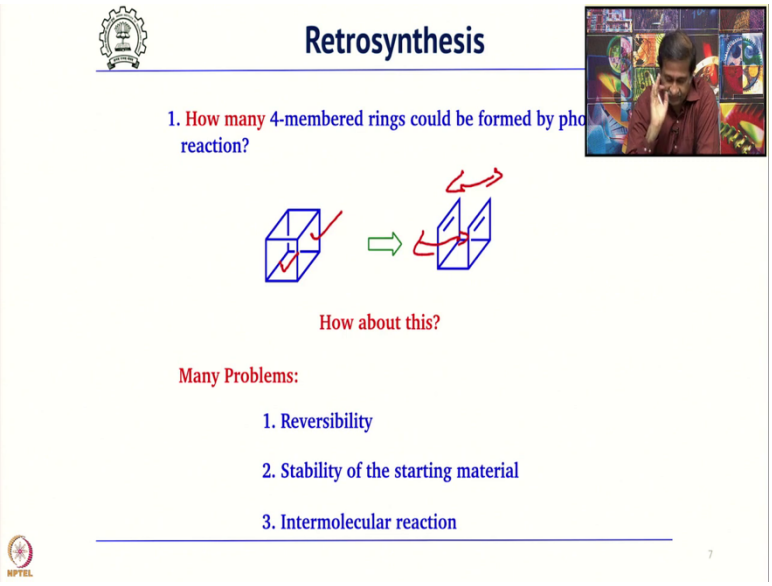

So, then if you want to do cyclobutane synthesis you start with first cubane and look at how many 4-membered rings are there as which we have already seen. There are six 4-membered rings are there. Now we know 4-membered rings can be made by photochemical reaction. The next question is how many 4-membered rings you want to make using photochemical reaction? How many 4-membered rings you want to make by photochemical reaction?

So, for example, you do a simple retrosynthesis and then see whether you can make three 4-membered rings ok, three 4-membered ring. Basically you are making only one 4-membered ring, but while making automatically you while making one 4-membered ring you are making two more 4-membered rings. See here the 4-membered ring will be formed between these carbon atoms, but while doing that you get this ring as well as this ring.

So, overall you are making three 4-membered rings, but by carrying out only one 2 plus 2 cycloaddition reaction ok. So, logically this sounds good ok. So, the cyclobutane see this cubane can be disconnected and this could be the precursor for making cubane, but in reality as you know in synthesis one can write retrosynthesis based on the knowledge

of wide range of organic reactions, but when you go to lab many of them would not work. Here you do not have to even to go to lab.

You can say straight away this scheme is not good why? One this reaction is reversible ok because of you know strain this will be reversible and it can come back. Second the stability of the starting material starting material may not be very stable and third and foremost is this can undergo instead of intramolecular 2 plus 2 cycloaddition. Why it should undergo only intramolecular 2 plus 2 cycloaddition?

It can undergo intermolecular 2 plus 2 cycloaddition, one molecule can undergo 2 plus 2 with another molecule and that can undergo 2 plus 2 with another molecule. If that happens as you know finally, you will end up in getting a polymer ok. So, though this idea is very good to construct three 4-membered rings in one step by doing only one 2 plus 2 cycloaddition reaction there are problems ok. Though it is logical, but in practical this is not a good scheme.

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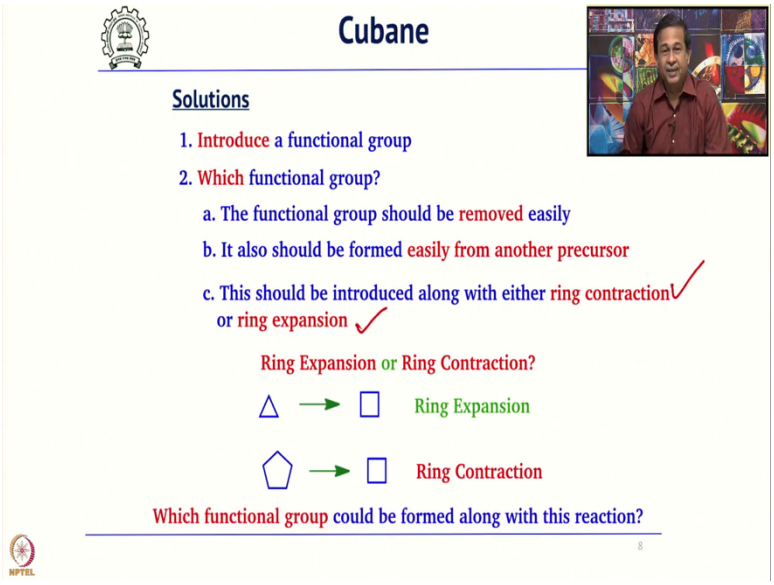

So, how to avoid this? What are the various solution possible? First of all as I mentioned when you look at cubane, cubane does not have any functional group ok. So, you need either a functional group or a strategic bond because that only will act as a tool ok handle for further retrosynthesis.

So, whenever you do not see a functional group or whenever you do not see a strategic bond in your target molecule please remember first thing you should do is introduce a functional group ok. Once you introduce a functional group that functional group will be your handle ok using that functional group you can further disconnect. So, that should be your first priority.

Yes we have to introduce a functional group then which functional group? Ok there are so many functional groups ok. So, here again you have to break your head which functional group you have to introduce? Well you can introduce a functional group, but at the same time you should also know in the end when you go forward that functional group should also be removed easily.

It should be easily introduced and easily removed ok. These are two things we should know when you talk about choosing a functional group ok. Yes it should be easily made that is very important from simple reaction and from another easy precursor. So, one way to think about is when you introduce a functional group can you think of another reaction; that means, you are going to make a 4-membered ring ok, you are going to make a 4 membered ring.

So, can you make this 4-membered ring either via ring contraction or ring expansion ok, either via ring contraction or ring expansion and during the process you should also introduce a functional group its clear. You are thinking about ring contraction or ring expansion when you do this reaction you also introduce a functional group ok its two in one.

So, then next question is whether you want to do ring expansion or ring contraction? Which one is better? Ring expansion means you should start with a 3-membered ring and then go to 4-membered ring and for ring contraction you should start with a 5-membered ring and end up in 4-membered ring.

So, these are two options and which one we will choose and as I said not only you should ring expand or ring contract, but also introduce a functional group in this same reaction ok. So, let us see what are the reactions possible ok, what one can try?

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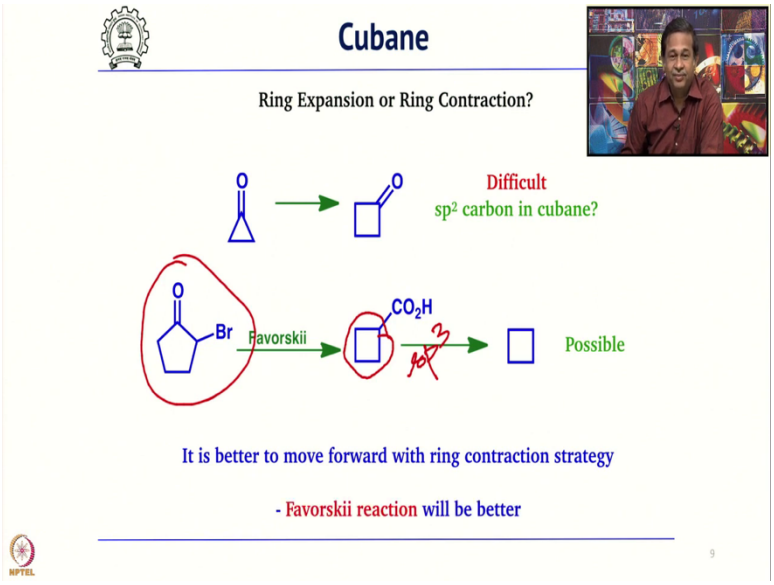

For example, if you are talking about ring expansion take cyclopropanone ok take cyclopropanone. If you treat with diazomethane ok it can undergo a ring expansion reaction to form cyclobutanone. But, the problem is in the end product; in the end product where you see cubane cubane all carbon atoms are sp3 all carbon atoms are sp3 ok. Here you have one sp2 carbon atom.

So, then again you have to you know remove this ketone. So, its little bit tedious. However, when you think about converting a 5-membered ring into 4-membered ring ok 5-membered ring into 4-membered ring that is a ring contraction. One reaction should come to your mind is Favorskii rearrangement ok; alpha haloketones and treatment with base can undergo Favorskii rearrangement the ring contraction.

So, if you take a 5-membered ring with a halogen at alpha position with respect to the ketone. Now the Favorskii rearrangement can give a cyclobutane. Here all the carbons are sp3; all the carbons are sp3. Now, if you remove the carboxylic acid if you decarboxylate you will get cyclobutane.

So, it is very obvious between these two that is from ring contraction and ring expansion method, from cyclopropanone to cyclobutanone and cyclopentanone to cyclobutane the second method that is ring contraction by Favorski rearrangement is much much better in terms of getting cyclobutane with all sp3 carbon atom ok. So, that is what we choose. So, it is better to go with ring contraction strategy for the synthesis of cubane ok.

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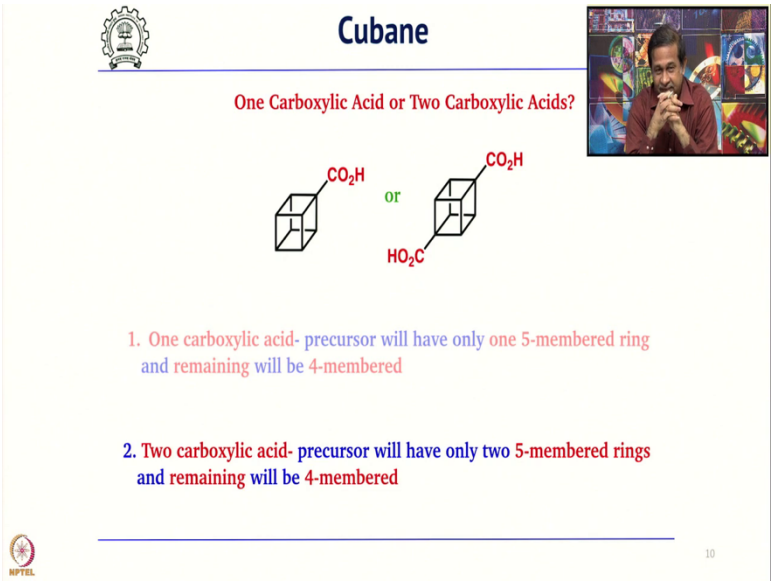

Now, next question; so you know you identified to use Favorskii rearrangement as the key reaction to make cyclobutane. So, that it will form cyclobutane with one carboxylic acid. So, can we use only one carboxylic acid? Can we think of two carboxylic acid? So, suppose if you make the precursor as this. So, then you can also think about cubane having two carboxylic acid ok. So, then you have to do two Favorskii rearrangement in the same pot ok, two Favorskii rearrangement in the same pot.

So, which one will simplified? If you take one carboxylic acid if you take one carboxylic acid then the precursor will have one 5-membered ring ok precursor will have one 5-membered. In fact, ideally speaking there will be two 5-membered ring ok. Whereas, if you take two carboxylic acid you will have more 5-membered rings ok, you will have more 5-membered rings; that means, by doing this if you convert more 4-membered rings into 5-membered rings then your job is becoming much simpler is not it?

It is better to construct 4-membered ring in the end rather than in the beginning. So, obviously between these two choices one should prefer to have two carboxylic acid or in other words introduce two carboxylic acids to cubane then start the retrosynthesis ok.

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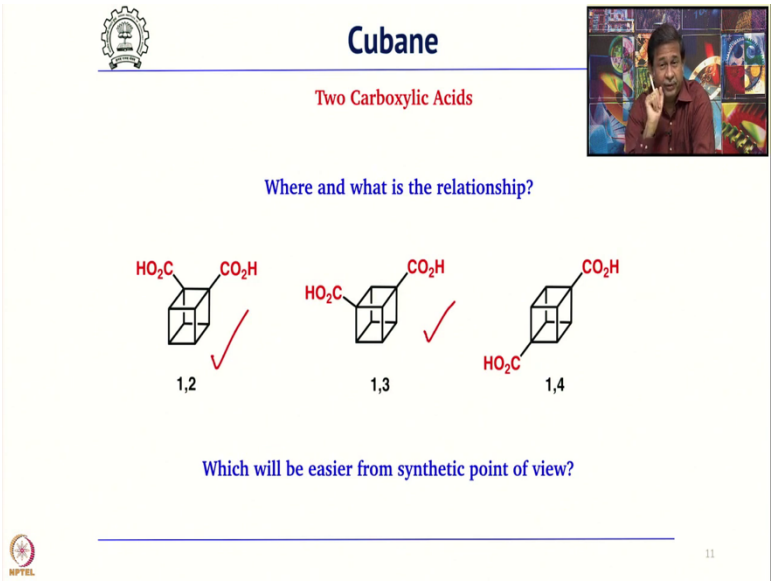

So, when again when you want to introduce two carboxylic acid where will you introduce? Like aromatic system you can have 1, 2 position 1, 3 position and 1, 4 position is not it. So, this is 1, 2 dicarboxylic acid then you have 1, 3 and also you have 1, 4 ok. So, all are possible because theoretically all are possible, but in from the experimental point of view from the synthetic point of view which one will be easier?

Which one if you take and then move forward that will give you simpler starting material ok? So, that is what the major point about retrosynthesis is not it. Between these three which one will be the best precursor ok?

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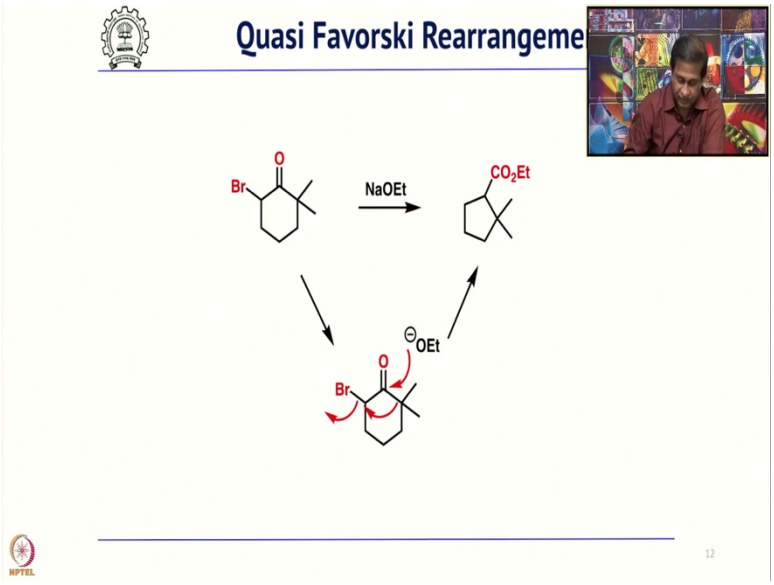

So, when you look at this we know what is Favorskii rearrangement, we also should know what is quasi Favorski rearrangement. See quasi Favorskii rearrangement is the one where carbanion is not formed or enolate is not formed. Here if you take this alpha haloketone what happens? When you treat with sodium ethoxide ok the sodium ethoxide which attacks the carbonyl ok, then this bond migrates and then your bromide goes and that will give you directly this 5-membered ring.

So, in cubane we will talk about quasi Favorskii rearrangement and not Favorskii rearrangement, Favorski rearrangement is a broad one. Quasi Favorskii rearrangement is subset of Favorskii rearrangement ok.

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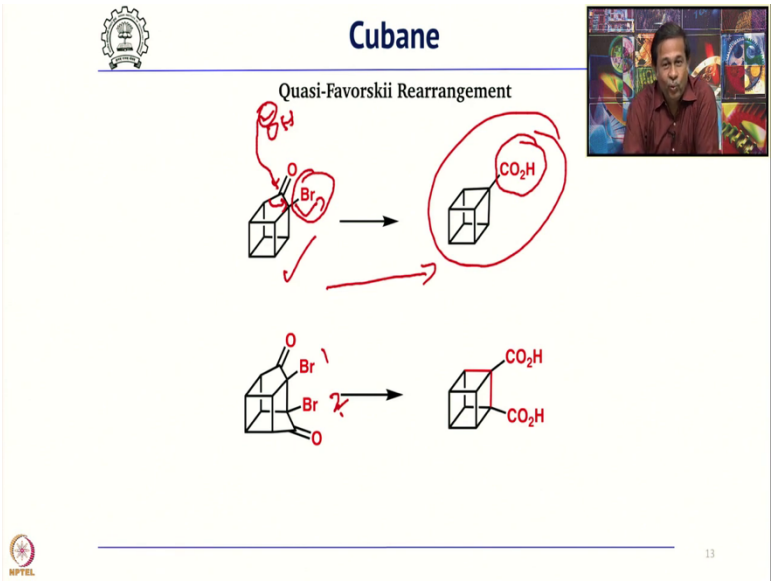

So, this you should know and if you are using one carboxylic acid this should be the precursor ok. Now, you can see OEt or OH ok OH will attack here and this bond will come and it will remove the bromine and that will give you the carboxylic acid one carboxylic acid and ideally if you look at carefully from left to right ok. Left to right when you see where the bromine was earlier? Where the bromine was earlier the same place carboxylic acid comes ok.

This is for simplicity you should remember. Where the carboxylic bromine is there the same place carboxylic acid comes ok. Now, look at this compound, there are two bromines and their relationship is 1,2 is not it? There are two bromines their relationship is 1, 2. So, that means, at the end of this quasi Favorskii rearrangement you should get the corresponding 1, 2 dicarboxylic acid.

We are just extending what we have discussed here ok, wherever bromine is there carboxylic acid will come. So, if the bromines are 1, 2 related and in the end you also will get 1, 2 dicarboxylic acid.

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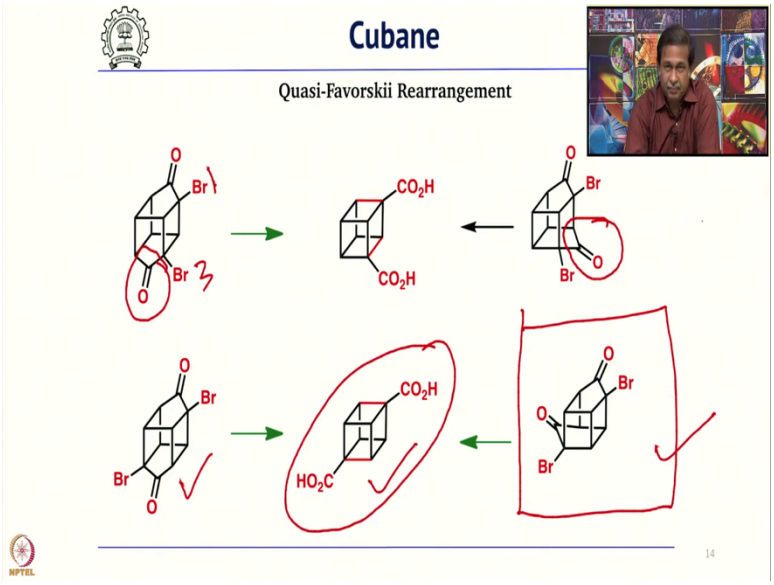

So, now look at this example this is 1, 3 ok, then that will give you 1, 3 dicarboxylic acid. There is another possibility you know this 5-membered ring this 5-membered ring is here. In this example 5-membered ring is on the right hand side, but both will give 1, 3 dicarboxylic acid, because look at the relationship between the two bromines they are 1, 3 related ok.

Now for 1, 4 so this is one possibility that will give 1, 4 dicarboxylic acid and this is another possibility where the cyclopentanone is on the left hand side. So, both will give you 1, 4 dicarboxylic acid. So, now among these three options which one we will choose among these three option which one we will choose and then see how that will give a proper retrosynthetic pathway to simpler starting material. So, what we can do is let us take this precursor ok.

So, this is a compound which upon decarboxylation will give you cubane and this in principle can be made from this using quasi Favorskii rearrangement. So, now let us take this as the target molecule ok then go further ok.

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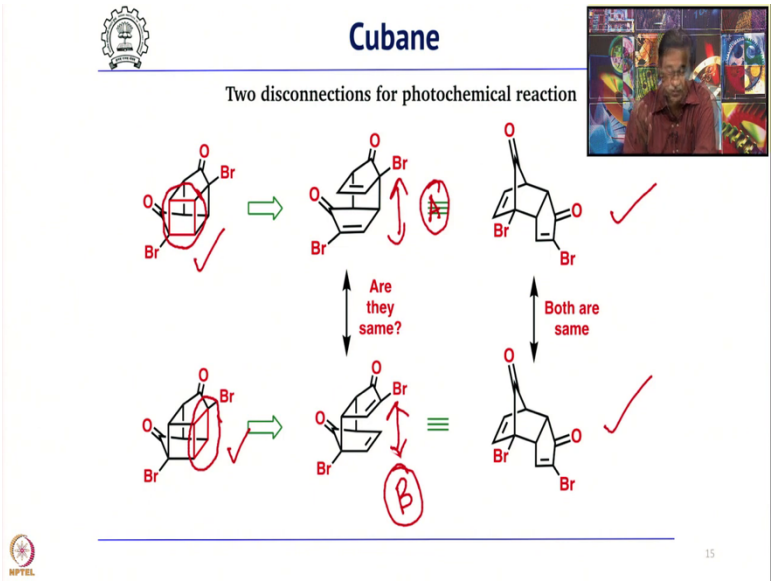

So, this is what we have taken and how many 4-membered rings are there now in this how many 4-membered rings? Two 4-membered rings. In cubane we have six by doing two quasi Favorskii rearrangement in one step in retrosynthesis. We removed four 4-membered rings we have only two 4-membered ring because that is a significant reduction in the complexity as well as removing the strain ok.

So, the quasi Favorskii rearrangement retrosynthesis has helped. Now what we should do? We should do a photochemical disconnection. So, you should form you should look for 4-membered ring and try to do a retrosynthesis. So, first let us take the front four 4-membered ring ok. If you make this front 4-membered ring using 2 plus 2 cycloaddition, will you consider this as the precursor?

Now, you see there are two double bonds this can undergo 2 plus 2 cycloaddition and interestingly if you look at this when you do this two 4-membered rings are formed ok. So, one two two 4-membered rings are formed. Basically so far what we have discussed is in two steps you remove completely 4-membered ring, quasi Favorskii rearrangement you removed four 4-membered ring and using photochemical reaction you removed two 4-membered rings ok.

So, now if you look at this you can look at this compound you can see only 5-membered ring no 4-membered ring ok. Now same compound instead of making the front 4-membered ring suppose if you make the side 4-membered ring using 2 plus 2 ok then see

what is the precursor; Obviously, this is the precursor. Again there are no 4-membered rings in the precursor both are 5-membered ring.

Now, my question is just look at this assume that this is A and this is B my question to you is whether A and B are same; A and B are same are they same? I will give 30 seconds just to see whether these two are same and how many of you agree. Yes they are same ok. If you redraw this structure if you redraw this structure this is what you get and same way if you redraw this structure you get this compound.

Now, you see both are same; both are same. So, it does not matter whether you make the right hand side 4-membered ring or the front 4-membered ring using 2 plus 2 cycloaddition both are starting from the same compound ok. So, now what you have to do? You have to do a retrosynthesis of this compound as such you can see this is obviously, a Diels Alder product.

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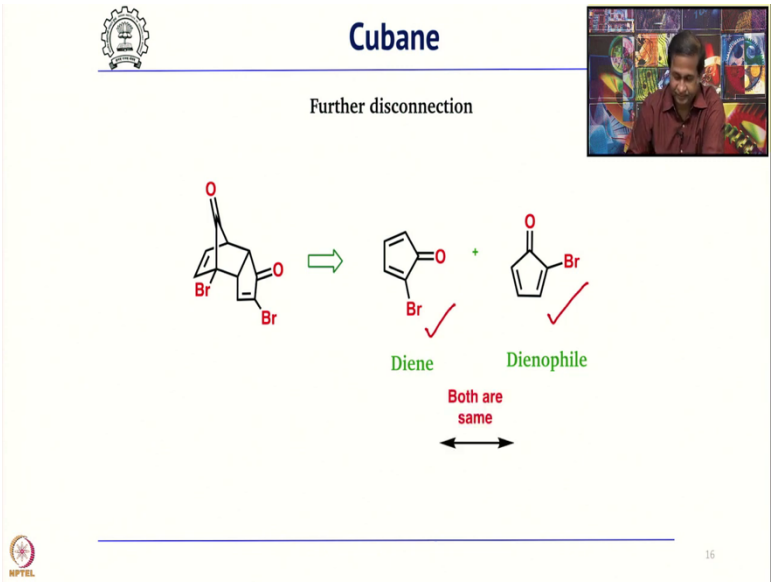

So, that means, what should be the precursor? The precursor is the same diene dienophile both are same. One will act as a diene and other one will act as a dienophile ok. As you know cyclopentadienone is not stable. So, as soon as it is formed it should undergo 4 plus 2 cycloaddition reaction.

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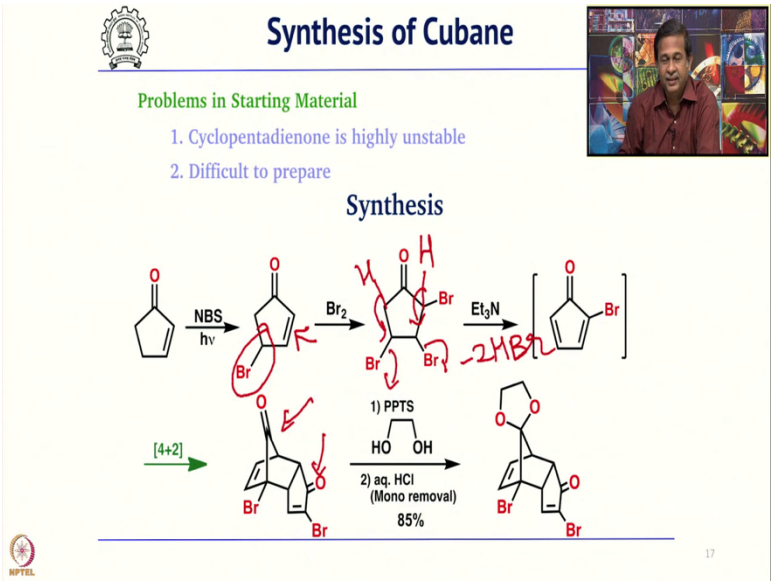

So, how we do? It is simple we start from cyclopentenone ok, you start with cyclopentenone and carry out allylic bromination ok allylic bromination with NBS under photochemical condition. Now, you add bromine. So, bromine will add to this double bond. So, you get a tribromo compound ok. So, in two steps we introduce three bromines. Now if you treat with triethylamine what will happen you know these two protons are acidic is not it. So, this can undergo elimination this can undergo elimination.

So, minus 2 HBr will give you your starting material that is 2 bromo cyclopentadienone and as I said that once you prepare it is unstable immediately it will undergo 4 plus 2 cycloaddition and you get the next step very easy very easy starting from commercially available cyclopentenone ok in three steps you get this bicyclic compound.

So, now one can think of doing two quasi Favorskii rearrangement in one step, but they face lot of problem. So, they wanted to go sequential. So, what they did? They protected both ketones ok then selectively they removed one of them that is this side. So, they could keep the top carbonyl group being protected ok.

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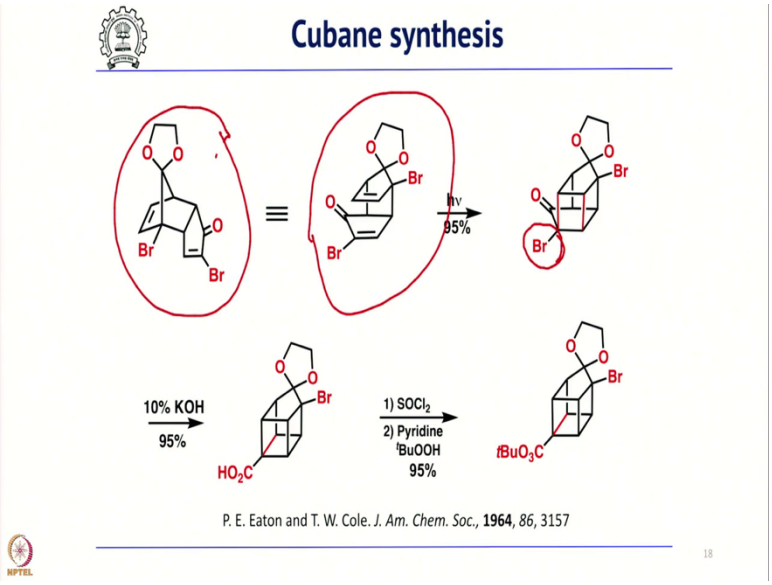

Then the next step is the 2 plus 2 cycloaddition reaction. So, the this can be written already we discussed is not it. This can be written like this ok. Then if you do 2 plus 2 cycloaddition reaction you get this compound. So, what we have done so far is we have introduced two cyclobutane ring two cyclobutane ring, then we have to introduce 4 cyclobutane rings.

So, what you can do? Carry out the quasi Favorskii rearrangement. So, at this position you will get carboxylic acid and the 5-membered ring also will become 4-membered ring. So, now what we have done? How many 4-membered rings we have done? Four 4-membered rings we have done. First we did using photochemical condition you did two and using quasi Favorskii rearrangement you did two more ok.

Next what you should do? Obviously, you have to remove the handle. The handle here is carboxylic acid, the carboxylic acid first you convert into acid chloride and then treat with tertiarybutyl hydroperoxide. So, you get the peroxy compound. Then heat it with the cumene. So, this was reported by Philip Eaton from University of Chicago, I will come to that little later.

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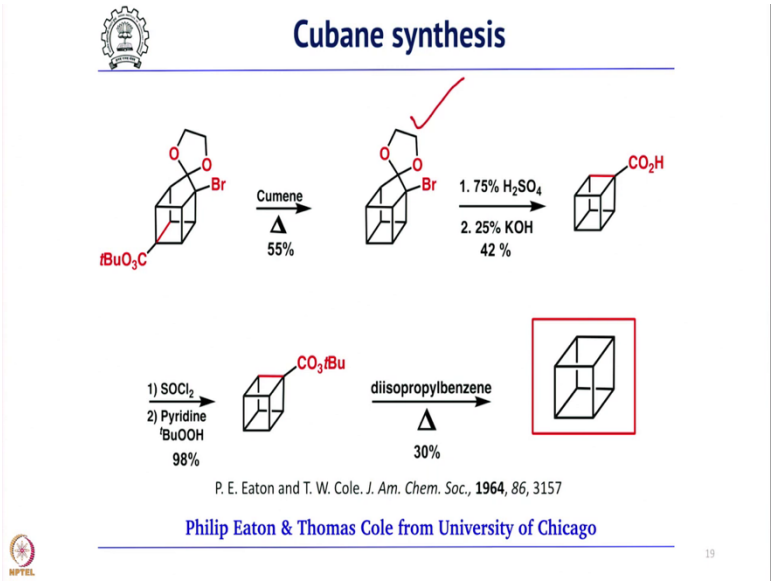

So, then this upon heating with cumene it undergoes decarboxylation and you get the corresponding cubane with ketal and bromine intact. Next you have to remove the ketal then do the quasi Favorskii rearrangement. So, why when you do this now you introduce all the six 4-membered rings. If you look at this synthesis carefully each step that is when you are introducing a cyclobutane ring each step you introduce two cyclobutanes, each step you introduce two cyclobutane.

So, once you have the carboxylic acid treat with thionyl chloride and then tertiary butyl hydroperoxide and followed by heating you get the cubane. So, this is one of the classical synthesis of a non-natural product called cubane and this was reported by Philip Eaton and Thomas Cole from University of Chicago in 1964 and afterwards several derivatives of this cubane was synthesized and used particularly army people were interested in several derivatives of this cubane ok.

So, with this I think to summarize what we have done is today we briefly started with 2 plus 2 cycloaddition reaction under photochemical condition, then we did a proper retrosynthesis for cubane. Then using quasi Favorskii rearrangement and 2 plus 2 cycloaddition we could successfully construct six 4-membered rings of cubane and then completed the total synthesis of cubane ok, see you.

Thank you.