Classics in Total Synthesis - I
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Lecture - 10
Prostaglandin (Corey)

So, Good morning and welcome back to this NPTEL lecture series on Classics in Total Synthesis part one. In the last few lectures, we have been discussing about total synthesis of natural products having four membered ring. So, now, in the next few lectures we will focus on natural products having five membered rings.

So, when you talk about five membered rings there are two classes of natural products which should come to your mind immediately one is prostaglandins, the other one is triquinane based natural products.

So, first let us start with prostaglandins, prostaglandins they were well known and during 1960's and then 70's got lot of attraction from synthetic chemists to develop new methodology for the synthesis of all the prostaglandins.

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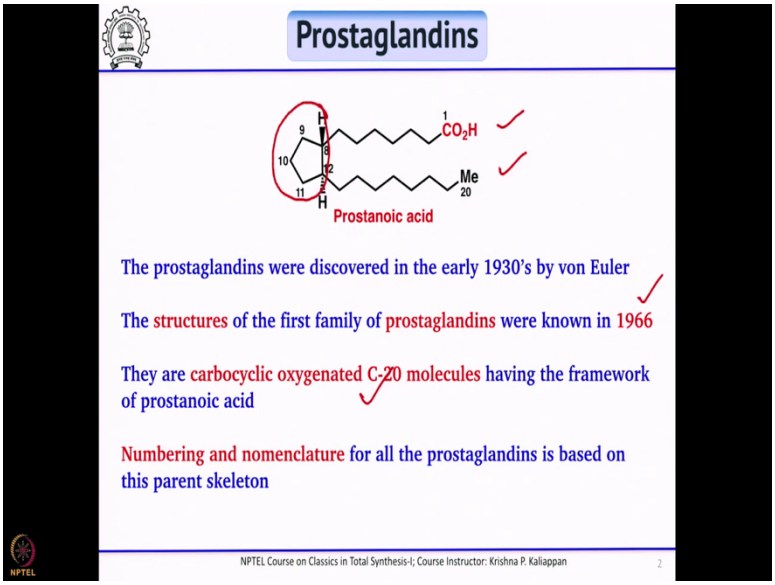

The prostaglandins as you can see has a cyclopentane has a cyclopentane with two side chains, ok two side chains. So, this is the core structure of prostaglandin which we can call it as prostanoic acid, ok that is the core structure.

So, most of these prostaglandins were discovered and reported in early 30s by Von Euler and of course, it was not easy to elucidate the structure of all these prostaglandins, it took about more than 35 years to illustrate the correct structure of prostaglandin, ok.

And once the correct structure of prostaglandins were identified then lot of action take took place from synthetic chemist to synthesize this compound. And I will at least talk about two total synthesis of prostaglandins one by E J Corey Nobel Laureate and the other by Gilbert Stork, ok.

So, if you look at this closely. So, they are all carbocyclic oxygenated C-20 molecules, ok. And in addition, they have two side chains, ok. So, one having carboxylic acid at the terminal the other one is having methyl group, ok. And how do you classify prostaglandins and how do you name it, ok it depends on the number of different functional groups present in the molecule.

The basic structure is same cyclopentane with two side chains, ok. When you want to classify it was based on two things one the functionalities present in the five membered ring, ok.

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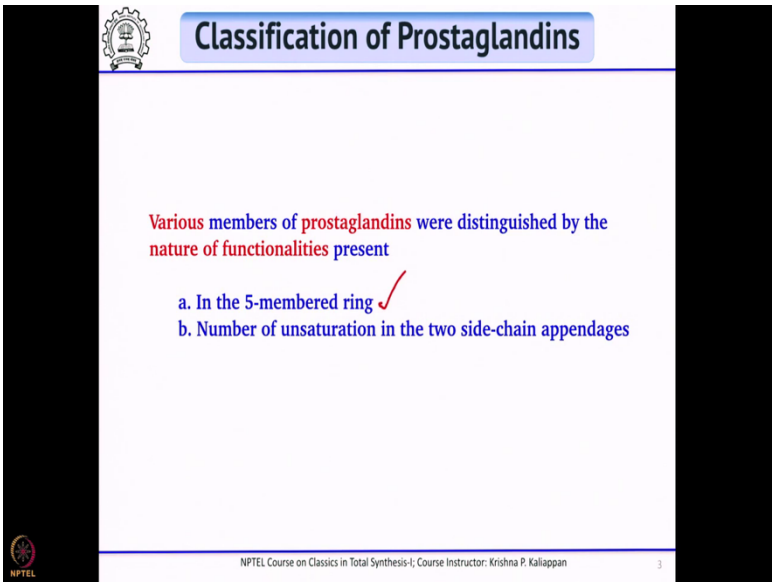

What are the functional groups present and how they are present? Ok. What is their relationship and then second one depends on the number of unsaturation number of unsaturation present in the two side chains, ok. Let us directly go into the Nomenclature.

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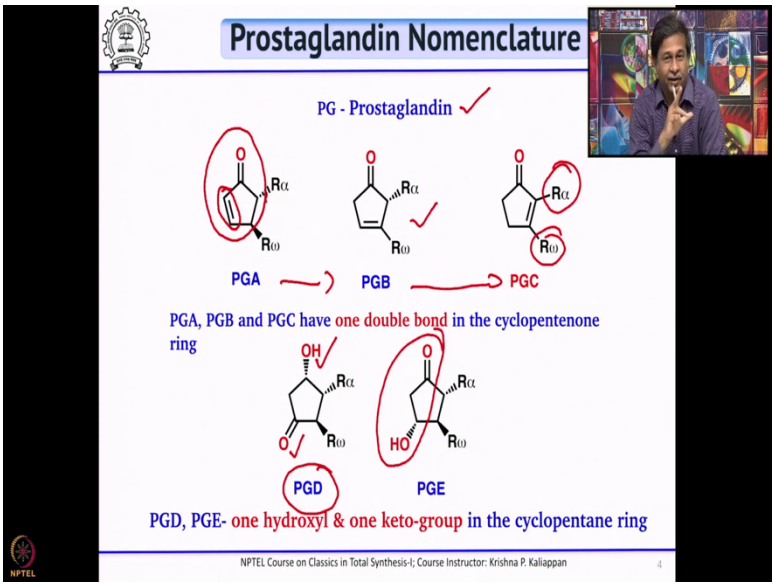

So, normally when you talk about prostaglandins they write PG, PG is the first two letters. So, the PG represents Prostaglandin PG means it is Prostaglandin. Then you see PGA, PGB, PGC, PGE, PGF what are these additional letter ABCDE? Ok.

PGA, PGB, PGC all of them have cyclopentenone, ok you can see this five membered ring is in the form of cyclopentenone. Well, but the double bond position changes from A to B to C when you go from A to B to C you can see the position of the double bond also migrates.

One is alpha beta unsaturated ketone then beta gamma unsaturated ketone, the other one is also alpha beta unsaturated ketone, but there are no chiral centers these two are no chiral centers, it's a tetrasubstituted compound, ok.

So, first one is alpha beta unsaturated ketone, but it is disubstituted double bond is disubstituted. Whereas, the second one it is trisubstituted and third one it is tetra-substituted. So, they are called PGA, PGB, PGC, ok all of them as you can see have one double bond, but the position of the double bond gives their name.

Then what is D and E here the double bond the double bond is replaced you do not have double bond instead you have a hydroxyl group, ok. And the hydroxyl group also it is beta hydroxy beta hydroxy means it's like aldol, ok beta hydroxyketone.

So, if the ketone is here and the hydroxyl is there then it is PGD, and if it is opposite then this is called PGE, ok PGA, PGB, PGC have cyclopentenone. PGD and PGE have one hydroxyl and one ketone we can call it as hydroxy beta hydroxy ketone or aldol in the cyclopentane ring still the two side chain are intact, ok.

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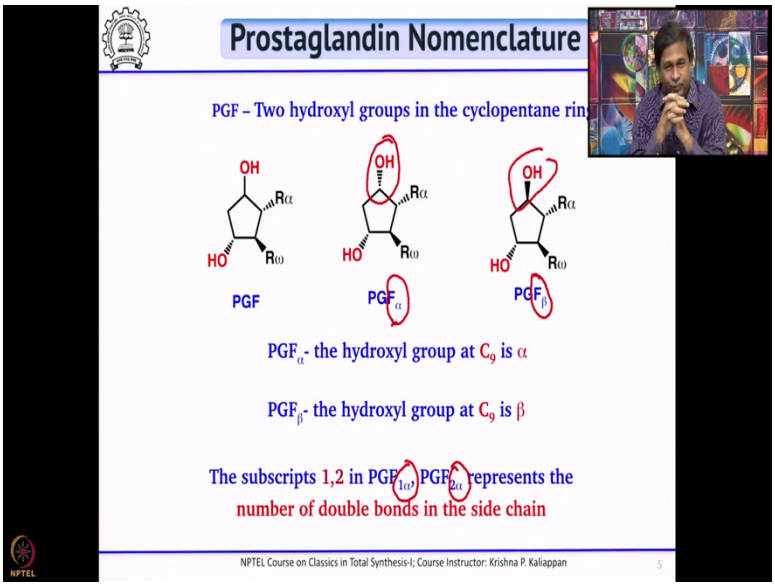

Now, we will come to the last category that is PGF. What is PGF? Here the ketone which was present in PGD and PGE they are reduced or in other words you have two hydroxyl groups in the cyclopentane ring they are called PGF.

And, you also see when you read literature you will see PGF alpha PGF beta, what does it mean? That means, the ketone which you reduced, ok here if it is alpha the stereochemistry is alpha then you write PGF alpha. If it is beta then you write PGF beta, ok. So, that is how the names are given for prostaglandins then you also see PGF1alpha PGF2alpha what does it 1 and 2 mean.

So, that means, the side chain you have two side chains it depends on the number of double bonds present in the side chain, ok. If they write 2 alpha that means, the side chains have two double bonds; if they write 1 alpha that means, it has only one side chain, ok. So, this is about the nomenclature of prostaglandin.

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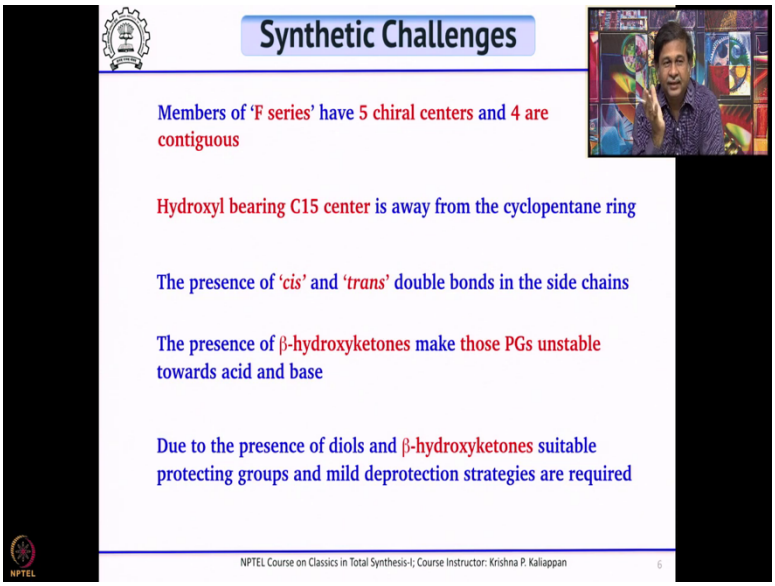

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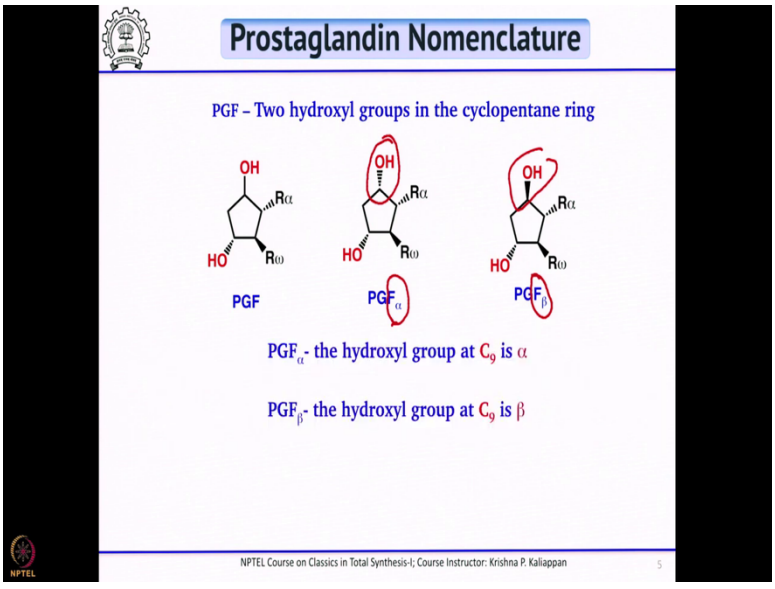

So, now let us see what are the challenges these molecules provided for synthetic chemist to make this compound. And if you look at the PGF series the PGF series have 5 chiral centers, ok. PGF have 5 chiral centers, 4 in the ring 4 in the ring and 1 in the side chain.

I will come to that later, but 4 in the ring 1 in the chiral center and the 4 in the ring they are contiguous, 4 contiguous chiral centers are present in prostaglandin. Then the

hydroxyl group which is present in the side chain it is little far away from the 4 chiral centers present in cyclopentane.

So; that means, sometimes it will be difficult to use the 4 chiral centers present in the cyclopentane to direct the hydroxyl group or introduction of hydroxyl group at C15. Then, when you look at the side chain one side chain has cis double bond the other side chain has trans double bond, ok.

One side chain has cis double bond other side chain has trans double bond. And the prostaglandins D and E have beta hydroxyketone that is aldol, ok. Once you have this aldol as you know they are slightly unstable when you treat that with acid or base, ok. So, one should be extremely careful when you reach that stage you should not use acid or base, ok.

And because you have a beta hydroxyketone and diol and triols. So, the synthetic strategy should have proper protecting groups and also you should also have orthogonal protecting groups. Here two different protecting groups should be introduced and cleaved at different times, ok. So, these are the synthetic challenges one could expect while talking about total synthesis of prostaglandins.

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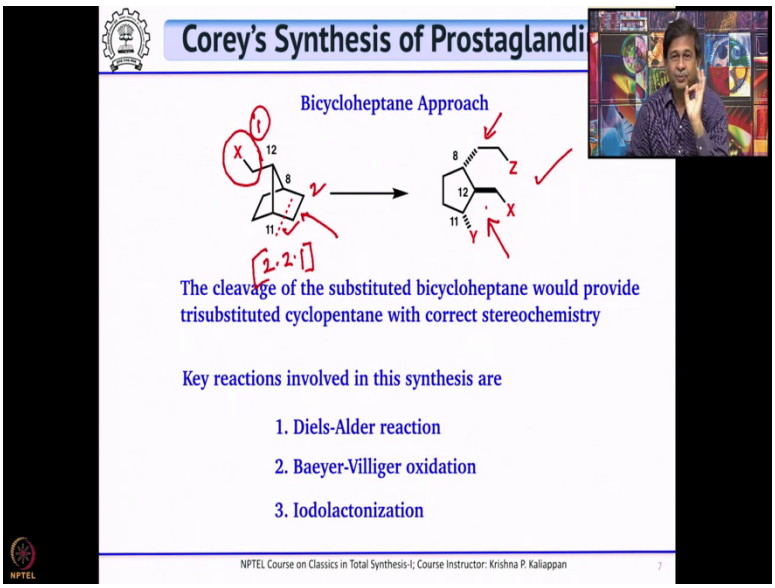

So, as I said there are quite a few total synthesis, but the first total synthesis was reported from Professor Corey's laboratory. Even today that synthesis is considered and one of

the best synthesis of prostaglandins. Their retrosynthesis is based on few key reactions. First of all, his basic idea is he called it as Bicycloheptane Approach; that means, he starts from this bicyclo[2.2.1] system, bicyclo[2.2.1] system having a CH_2X here, ok.

Now, what he does what he wants to do is to cleave this bond, ok when you cleave this bond that should get converted into a nicely cyclopentadiene cyclopentane and these two side chain, ok. You can see 1 and 2, two side chains can be easily introduced, ok. So, this becomes 1 side chain and this becomes side chain 2.

So, what is important is you have to cleave this bond, ok the cleaving that bond is very very important. And how you cleave accordingly you can fix the stereo centers of these 3 contiguous cuts that was his plan, ok. The whole thing involved 3 key reactions 1) Diels Alder reaction 2) Baeyer Villiger oxidation and third one Iodolactonization, these are the 3 key reactions which he used to synthesize prostaglandins, ok.

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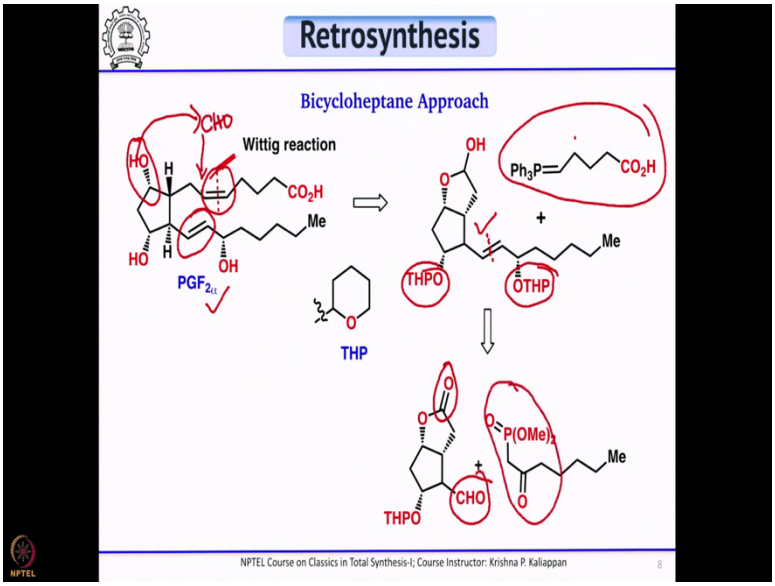

Let us see his Retrosynthesis. So, when you look at this molecule here for example, we start with PGF2alpha, ok. So, 2 alpha; that means, 2 double bonds are there is not it and alpha this hydroxyl is alpha, ok PGF. His first retrosynthesis is to disconnect the cis double bond, ok.

If you disconnect the cis double bond then what you should get is. So, this is the Wittig reagent the other portion this should be aldehyde is not it this should be aldehyde that aldehyde the hydroxyl group immediately will cyclize to form lactol, ok.

Or in other words if you have this lactol then one can do a Wittig reaction to get this compound, but before that you have to protect the hydroxyl group, here the hydroxyl group is protected as THP ether that is tetrahydropyranyl ether, ok.

Now, the lactol can be obtained the lactol can be obtained by DIBAL reduction of this lactone, and if you have this aldehyde this double bond can be obtained from this aldehyde by Wadsworth Emmons modification, ok. So, this is very easy and that also will give you trans double bond. A simple Wittig will give cis double bond and this Wadsworth Emmons modification will give you the trans double bond, ok.

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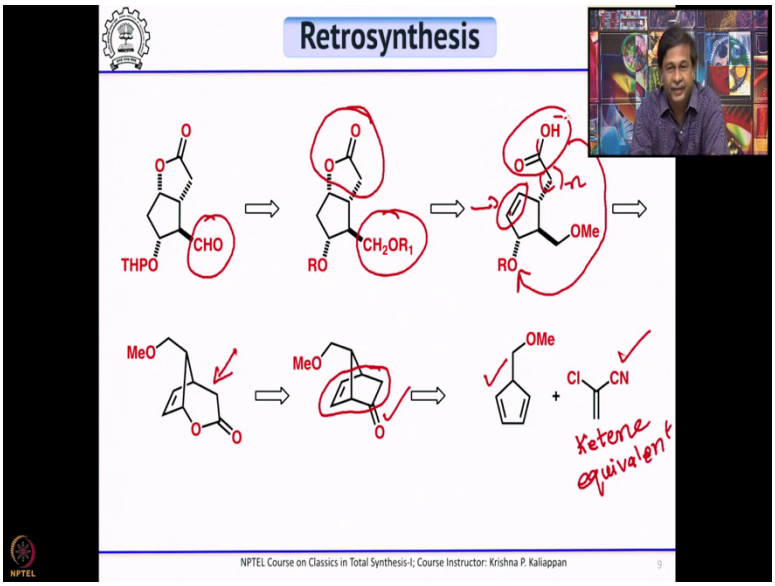

The next step is how to get this bicyclic aldehyde, ok. So, the aldehyde of course, can be used as protected form of the primary alcohol then this lactone five membered lactone. So, whenever you want to synthesize a five membered lactone again one reaction which should come to your mind is iodolactonization.

Iodolactonization; that means, if you have a double bond and if you have a carboxylic acid if you treat with iodine or potassium iodide in the presence of sodium bicarbonate,

first iodonium ion will form here followed by attack of this carboxylate it will open up the iodonium ion to give iodo lactone.

That iodine can be easily removed with tributyltin hydride, ok. So, what you need is this double bond and then carboxylic acid, depending on the ring size you can have this either CH_2 or $(CH_2)n$, ok. Normally five membered and six membered work very well.

This, how will you get it, ok if you look at here the advantage is very creative this carboxylic acid and this hydroxyl group, this carboxylic acid and hydroxyl group if you connect it, if you connect it then that will give you this seven membered lactone, ok. What you have done this CH_2COH you are connecting with this one, ok.

Now, how will you get this lactone? What are the reactions we know to get lactone? One of the simplest and straight forward reaction to get lactone is to get from carboxylic acid and alcohol. But that is what you want here ok, but this lactone one can get it from Baeyer Villiger oxidation.

If you do a Baeyer Villiger oxidation of this ketone that will give you the six membered lactone, ok. And this as soon as you look at this molecule you can see a cyclohexene, ok you can see a cyclohexene. So, cyclohexene again next very important reaction which should come to our mind is Diels Alder reaction, that in principle should give you the diene and the ketene equivalent.

As you know ketene cannot be used in Diels Alder reaction as dienophile because ketene undergoes dimerization, they are unstable. So, normally people use ketene equivalents either nitro ethylene or alpha chloro acrylonitrile. So, this is called ketene equivalent, ok. One can use ketene equivalent to get the corresponding ketone, ok.

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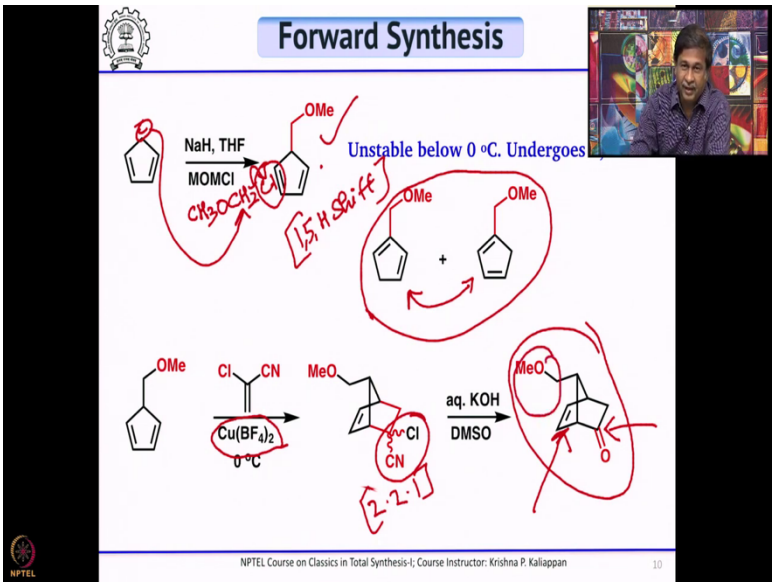

Now, let us see the synthesis. So, for the synthesis first he started from cyclopentadiene, ok. Cyclopentadiene and when you treat with sodium hydride you know it can generate anion, right the cyclopentadiene anion is aromatic is not it. So, you can easily generate a anion.

Now, quench with methoxy methyl chloride that is CH_3 methoxymethyl chloride is CH_3OCH_2Cl. So, this is the leaving group, ok. Then this will attack here and your chloride goes, once the chloride goes what we get is CH_2OMe, ok. This is what you need here there is one small problem the problem is.

So, this is this is cyclopentadiene, ok once we have cyclopentadiene it can undergo various 1, 5 hydrogen shift, ok. So, if you are doing this reaction above 0 degrees above 0 degrees it can undergo 1, 5 hydrogen shift to form these two dienes also, ok.

So, that means, not only while making this compound one should do the reaction below 0 degree and remove the solvent also below 0 degree, but also when you do the Diels Alder reaction you should do below 0 degrees.

So, those days as you know the Diels Alder reaction were done at high temperature, you know either in seal tube or refluxing in benzene or refluxing in toluene and so on. So, now, if you have to use this diene this particular diene without isomerizing to other two dienes via 1, 5 hydrogen shift.

The next step that is the Diels Alder reaction should be done at 0 degrees or less. So, what he did he took this compound and then treated with alpha chloro acrylonitrile in the presence of copper fluoroborate.

The copper fluoroborate helps to do this reaction at very low temperature you can do it sub zero and when you do that you get the corresponding bicyclo[2.2.1] adduct bicyclo [2.2.1] adduct. So, now, you got this chloro acrylonitrile adduct as you know this is a synthetic equivalent of ketene.

So, next step is the hydrolysis of the acrylonitrile adduct to get corresponding ketone, ok. So, as we have seen in the retrosynthesis, we could successfully make this bicyclo [2.2.1] ketone, ok. The next step is to carry out Baeyer Villiger oxidation.

So, when you use mCPBA, ok when you use mCPBA there are two possibilities. One, it can epoxidize the double bond two, it can undergo Baeyer Villiger oxidation. So, between these two Baeyer Villiger oxidation takes place, because if you look at this double bond the CH_2OMe is just above the double bond and that protects the double bond from attack by mCPBA, ok.

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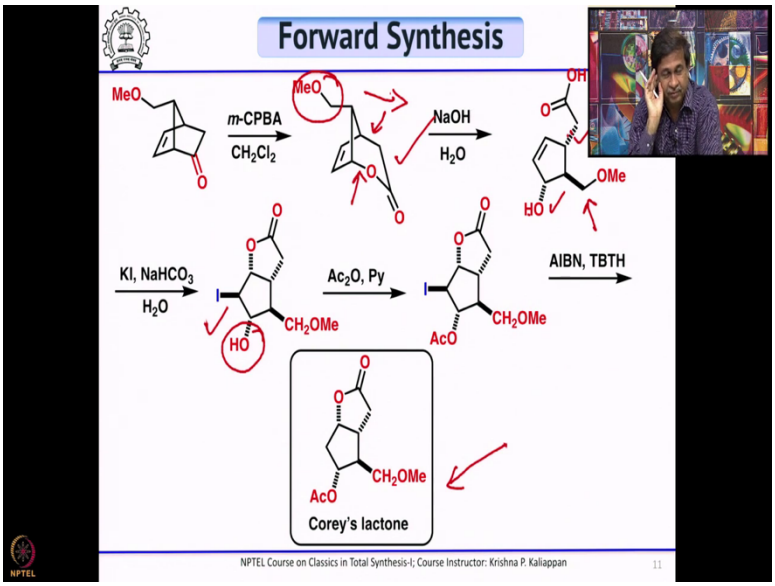

So, that is how when you do the Baeyer Villiger oxidation of this ketone with one equivalent of mCPBA, you get this bicyclic[3.2.1] lactone, ok. Then; obviously, next step is open this up to get the corresponding hydroxycarboxylic acid.

So, that is very easily done by alkaline sodium, sorry sodium hydroxide. So, now, you got the hydroxy carboxylic acid. The important feature of this reaction is these 2 C-C bond and CO bond they are cis to each other they are cis to each other. So, same thing you can maintain whereas, if you look at the CH_2OMe this is opposite to this CH_2.

So, that way you can see this is beta whereas, these two are alpha. So, the stereochemistry also is correctly fixed though it is racemic, but relatively if you see they are trans to each other, ok. So, now, you have a hydroxy carboxylic acid the next step is the iodolactonization.

So, the iodolactonization can be done by treating with potassium iodide and sodium bicarbonate sodium bicarbonate remove the hydrogen of carboxylic acid potassium iodide forms the iodonium ion and the intra molecularly the carboxylate attacks and you get the corresponding iodolactone.

So, as I said that iodine is not required because you need only the lactone and not the iodine. So, it can be easily removed by treating with tributyltin hydride and AIBN. So, before that one should protect the hydroxyl group as acetate. So, you protect the hydroxyl group as acetate then treat with tributyltin hydride you get the lactone that lactone is called Corey's lactone, ok.

This is one of the very important lactone in the total synthesis of prostaglandins, ok. Other many people made this lactone by a different method and some people use this lactone and then made prostaglandins, but this Corey's lactone is well recognized in the total synthesis of prostaglandins.

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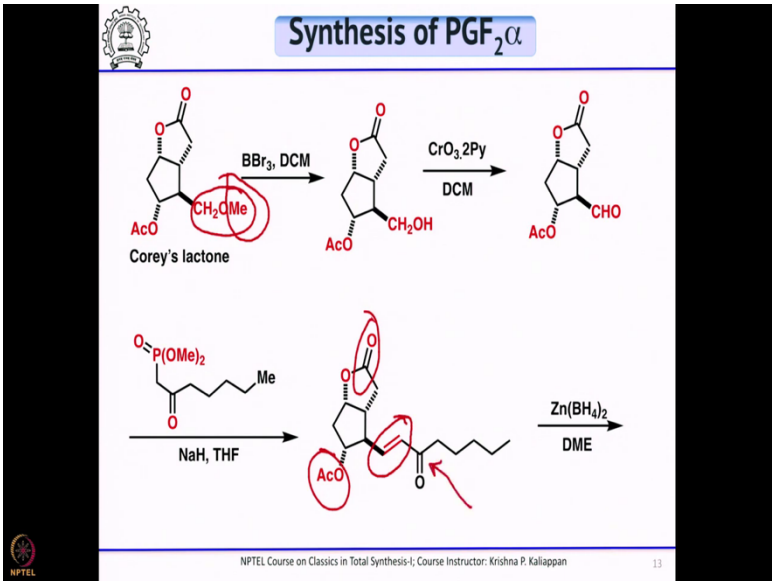

So, once we have this now the next step is to elongate one of the side chains, ok. Next step is to elongate one of the side chains. So, you have CH_2OMe, ok if you use BBr_3 BBr_3 is known to cleave OC bond, ok.

So, it will cleave the methoxy, ok you get the corresponding alcohol CH_2OMe because it is SN_2 displacement it is easy to cleave methyl. So, once you have the CH_2OH next step is to oxidize. So, you can oxidize the CH_2OH using chromium trioxide pyridine complex. So, you get the corresponding aldehyde.

Now, you can do the Wadsworth Emmons Wittig reaction to get the trans double bond, ok. Now the trans double bond is fixed, ok what is the next step you have to reduce the ketone, ok. You have to reduce the ketone in the presence of acetate and lactone.

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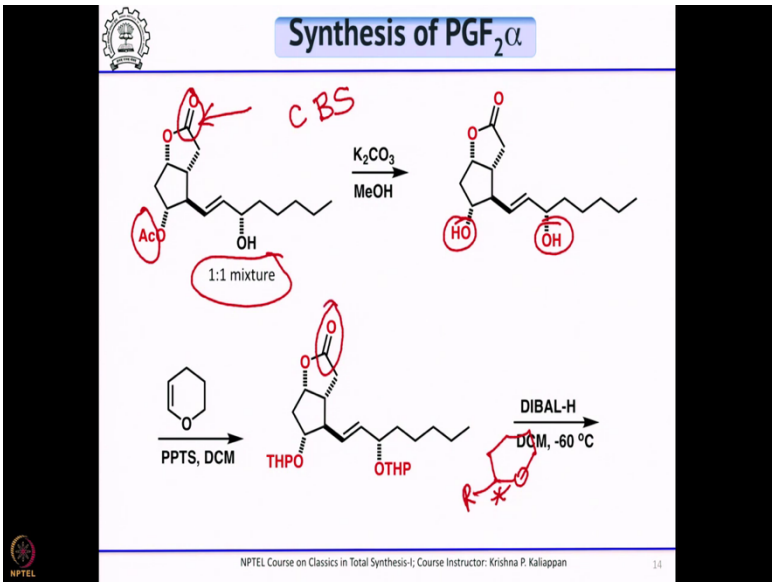

So, zinc borohydride successfully can reduce the ketone particularly the alpha beta unsaturated ketone. So, it initially he could reduce it to the corresponding allylic alcohol, but what he got was mixture. Later he developed you know other reagents for example, CBS reagent Corey Bakshi Shibata reagent to get exclusively only one isomer, ok.

Lot of chemistry was developed using the prostaglandin total synthesis project then, the acetate to be removed why acetate should be removed? The next step should be to attach the second side chain is not it.

So, second side chain means you have to reduce lactone to lactol then do the Wittig, but the problem is if you reduce with the DIBAL if you reduce with the DIBAL not only the lactone will be reduced, but acetate also will be hydrolyzed ok not only the lactone will be reduced acetate also will be hydrolyzed. So, you have to hydrolyze the acetate to get the diol and reprotect that.

Now, you protect the hydroxyl group both hydroxyl groups as THP ether though THP ether is not a good protecting group, for the simple reason that the THP will give additional chiral center. See THP is nothing but, ok you can see it will create additional chiral center, ok. But if you are using for one or two steps its ok, but for a longer sequence do not use THP, ok. So, now, after protecting this as THP next is to reduce the lactone to lactol, ok.

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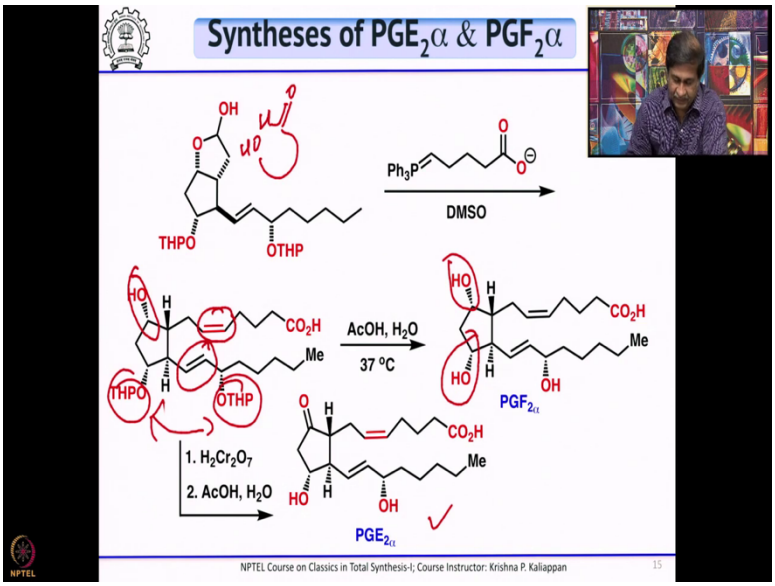

So, that was easy to get the lactol once you have the lactol, the lactol is nothing, but your aldehyde and OH is not it? Lactol is nothing, but aldehyde and the hydroxyl group. Then you can do the Wittig, ok. The simple standard Wittig when you do on this lactol you get the corresponding cis alkene. So, now, you see we have already introduced the trans double bond, now we have introduced successfully the cis double bond.

So, what is left in the synthesis of PGE 2 alpha and PGF 2 alpha, 2 means two double bonds are already there, ok. E 1 has ketone F both are hydroxyl group. If you remove the THP if you remove the THP, then you get directly PGF 2 alpha. So, that was done with it acetic acid water, you take this carbon treat with acetic acid water at about little bit higher ambient temperature you get PGF 2 alpha, ok.

Now, you want one of the hydroxyl group to be oxidized, one of the hydroxyl group to be oxidized to ketone. But it will be very difficult to oxidize one of them, ok. So, how do you do before you remove the THP not this one this one to be oxidized.

Before you remove the THP oxidize the hydroxyl to ketone, ok before you remove the THP oxidize the hydroxyl group to ketone then in the second step you remove both THP. So, that will give you PGE 2 alpha, ok. So, from the same intermediate that is Corey's lactone one can easily make PGE 2 alpha, PGF 2 alpha.

This is not a chiral one this is racemic one and for the chiral one what he has done is, here a chiral Diels Alder reaction a asymmetric Diels Alder reaction he has done. Followed by even the reduction of ketone to alcohol he has used CBS reduction to get only one isomer.

I will discuss that how he has done asymmetric version of prostaglandin in the next class, and I also will talk about Gilbert Stork's Total Synthesis of Prostaglandins using a very interesting radical cyclization as the key step, ok.

Thank you.