Classics in Total Synthesis-I
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Lecture - 11
Prostaglandin (Johnson and Stork)

So, good morning and welcome back to the NPTEL lecture series on Classics in Total Synthesis part I. So, in the last lecture we talked about total synthesis of Prostaglandins by Professor Corey and today we will talk about two more total synthesis of prostaglandins one by Professor Gilbert Stork the other by Professor Carl Johnson.

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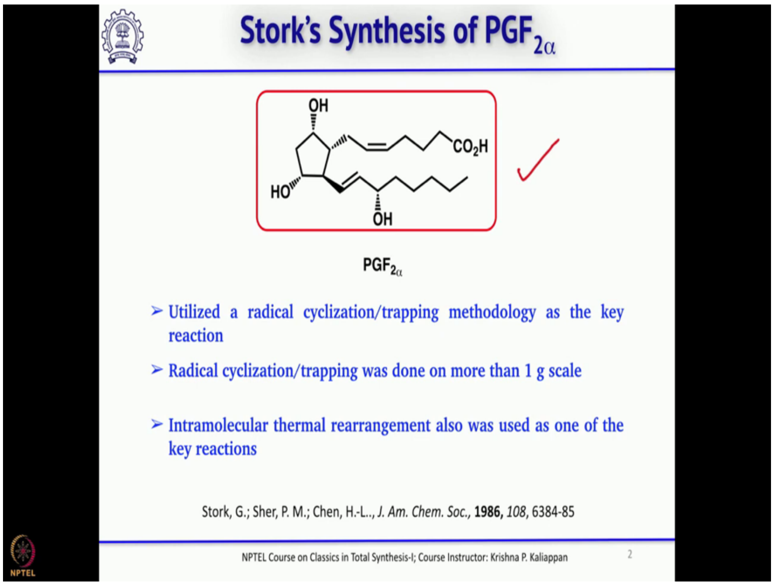

Stork's Synthesis of PGF$_{2\alpha}$

PGF$_{2\alpha}$

- Utilized a radical cyclization/trapping methodology as the key reaction
- Radical cyclization/trapping was done on more than 1 g scale
- Intramolecular thermal rearrangement also was used as one of the key reactions

Stork, G.; Sher, P. M.; Chen, H.-L., *J. Am. Chem. Soc.*, **1986**, *108*, 6384-85

So, first let us start with stork synthesis of PGF 2 alpha. As we know this is the structure of PGF 2 alpha. The key reactions which Professor Stork has used in the synthesis of prostaglandin PGF 2 alpha is a radical cyclization to form the a five membered ring and followed by trapping that radical that 5 exo radical 5 exo radical cyclization followed by formation of another radical which is trapped by an acceptor.

So, this is the key reaction in the synthesis of PGF by Stork and also he could do this reaction on a 1 gram scale and the next one is intramolecular thermal rearrangement which later called as Brook's rearrangement also was used as the key reaction ok.

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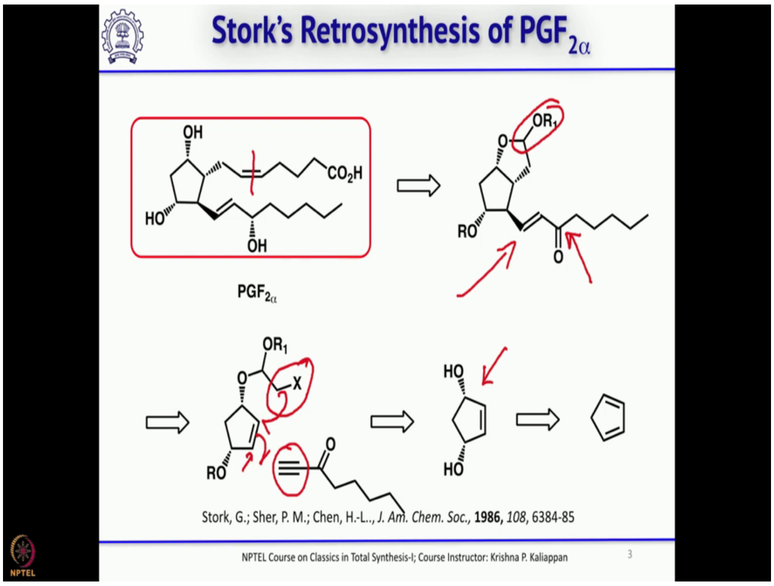

Stork's Retrosynthesis of PGF$_{2\alpha}$

Stork, G.; Sher, P. M.; Chen, H.-L., *J. Am. Chem. Soc.*, **1986**, *108*, 6384-85

How he has done the retrosynthesis? His idea was if you break this double bond if you break this double bond on the left hand side you will get aldehyde and in the right hand side you will get the corresponding triphenylphosphonium bromide. So, that you can do a Wittig reaction to get the cis double bond ok. Now once we have this aldehyde; aldehyde and alcohol if you combine the alcohol will attack the aldehyde to form a lactol.

And the lactol if you can protect. So, that is the precursor for PGF 2 alpha at the same time you can also keep this as carbonyl and later one can reduce it to get the corresponding allylic alcohol as required in the natural product. Now, the next step is the real key reaction as I said the radical cyclization followed by trapping of the resultant radical. So, what he did was? He prepared this halo compound ok now this can undergo a 5 exo radical cyclization on to this double bond that will generate a radical at this carbonyl ok.

Now if you add an acceptor like this ok. So, that can add to this triple bond. So, that will straight away give you this alpha beta unsaturated ketone ok that was the original plan, but let us see how he has achieved this particular transformation and this can be you know this five membered ring can be obtained from this diol and this can be obtained from cyclopentadiene ok. If you look at the earlier synthesis of PGF 2 alpha by EJ Corey there also the starting material was cyclopentadiene ok.

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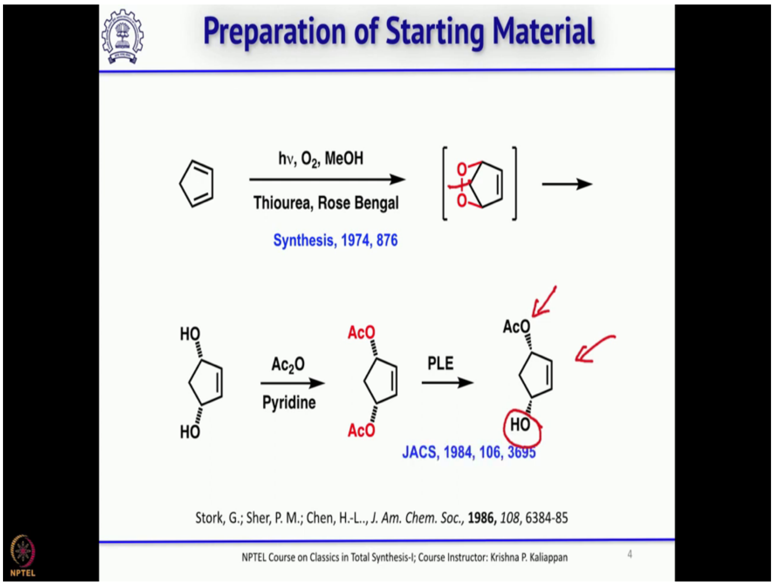

Preparation of Starting Material

hν, O_2, MeOH

Thiourea, Rose Bengal

Synthesis, 1974, 876

Ac_2O

Pyridine

PLE

JACS, 1984, 106, 3695

Stork, G.; Sher, P. M.; Chen, H.-L., *J. Am. Chem. Soc.*, **1986**, *108*, 6384-85

Now, let us see how he got this diol from cyclopentadiene. So, take cyclopentadiene and this is a known transformation and do a [4+2] cycloaddition with oxygen ok. So, why photochemical conditions required is normally oxygen is in triplet state is not it. So, it has to come to ground state. So, that is why photochemistry is used and since you use thiourea after this the O-O bond also gets cleaved under the same condition to get this corresponding diol ok.

But this is you know mesocompound one can easily resolve and for that you first protect this diol as diacetate. This diacetate enzymatically can be selectively hydrolyzed one of the acetates can be selectively hydrolyzed to get enantiomerically enriched one alcohol other one acetate. So, this was done successfully with pig liver esterase to get this corresponding you can see one of the hydroxyl group one of the acetate is hydrolysed to hydroxyl group the other one is acetate.

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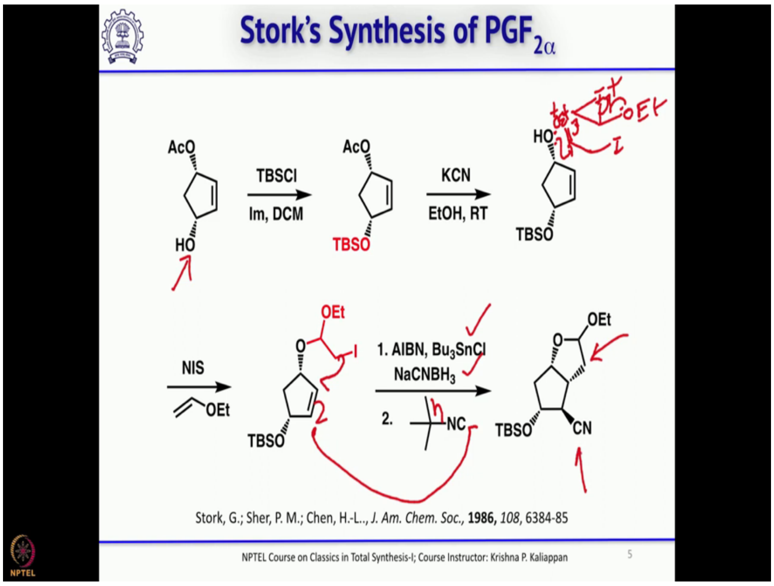

Stork's Synthesis of PGF$_{2\alpha}$

Stork, G.; Sher, P. M.; Chen, H.-L., *J. Am. Chem. Soc.*, **1986**, *108*, 6384-85

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Now, this is here this is an optically active compound ok. So, he took this compound then treated with TBS chloride. So, that you can protect this free hydroxyl group followed by hydrolysis of the acetate with catalytic amount of potassium cyanide and ethanol at room temperature now you get the corresponding allylic alcohol.

Next step is treatment of this allylic alcohol with ethyl vinyl ether in the presence of N iodosuccinimide. See what happens? When you treat with ethyl vinyl ether and N iodosuccinimide you get this compound ok. So, you can say iodonium ion ok. Now this will open this. So, what you get is corresponding OEt plus now the lone pair on the oxygen will attack and neutralize the positive charge.

So, that will give you this compound. So, ok that is the precursor required for the key radical cyclization that is 5 exo radical cyclization followed by trapping the resultant radical. So, what happens? You do this reaction with catalytic amount of azabisisobutyronitrile and tributyltin chloride and stoichiometric amount of sodium cyanoborohydride.

So, it forms as I said the radical attacks here and it forms a radical at this carbon. Now you do the trapping with tertiary butyl iso cyanide; that means, this radical which is formed here attacks the carbon and this CN bond breaks. So, what you get is the corresponding cyanide ok. So, now you can see you have made a five membered ring and also you have introduced a cyano group ok.

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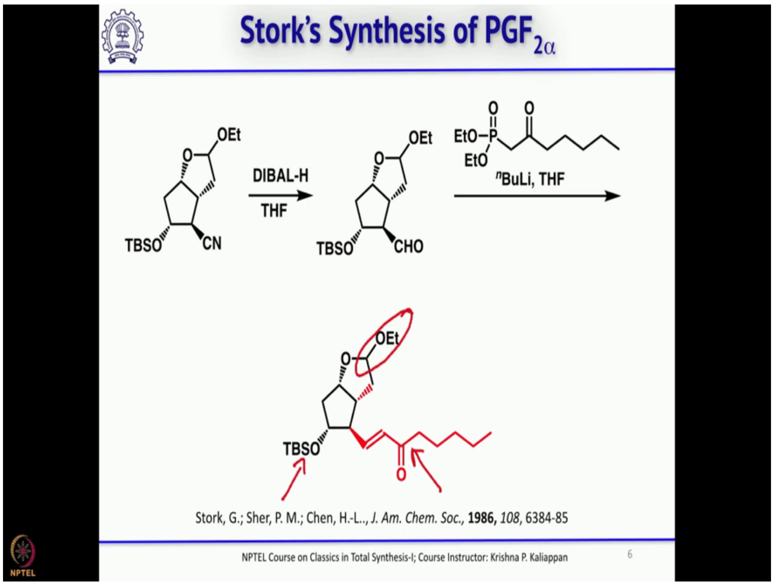

Stork's Synthesis of PGF$_{2\alpha}$

Stork, G.; Sher, P. M.; Chen, H.-L., *J. Am. Chem. Soc.*, **1986**, *108*, 6384-85

Once we have the cyanide then as you know you can reduce it with the DIBAL to get the aldehyde at low temperature you know -78 you can reduce the cyanide to aldehyde. Then carry out Wadsworth Emmons modification of Wittig reaction to get the trans double bond or E-double bond.

So, this is what you get. So, what is left? Now you have to reduce this to alcohol hydrolyse this lactol ethyl ether to lactol and do the Wittig reaction and followed by removal of this TBS group will give PGF 2 alpha.

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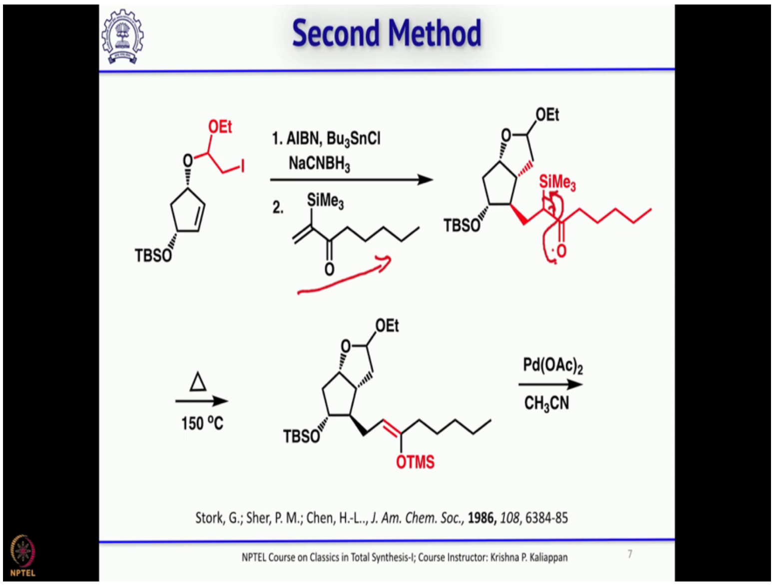

Second Method

Stork, G.; Sher, P. M.; Chen, H.-L., *J. Am. Chem. Soc.*, **1986**, *108*, 6384-85

So, he also attempted this same thing by a second method where the acceptor is different ok. So, what he did? He took the radical precursor and did the same condition except that acceptor was this alpha beta unsaturated ketone earlier what he did? He wanted to check how it works. So, he tried with tertbutyl iso cyanide. So, he could introduce the cyanide and then reduction of cyanide you got aldehyde once you have aldehyde of course, you can homologate further.

So, he wanted to directly trap that radical with this alpha beta unsaturated ketone. Did he do? Yes, he could successfully do after that when you heat it what will happen? Oxygen has got better affinity towards silicon than carbon ok. So, when you heat it this oxygen attacks the silicon and followed by breaking of CSi bond gives you the corresponding enol ether. So, this is also called Brook's rearrangement.

So, the migration of silicon from carbon to oxygen is called Brook's rearrangement. So, now, when you have enol TMS it is very easy to introduce a double bond by treating with palladium acetate is not it. So, very famous oxidation reaction.

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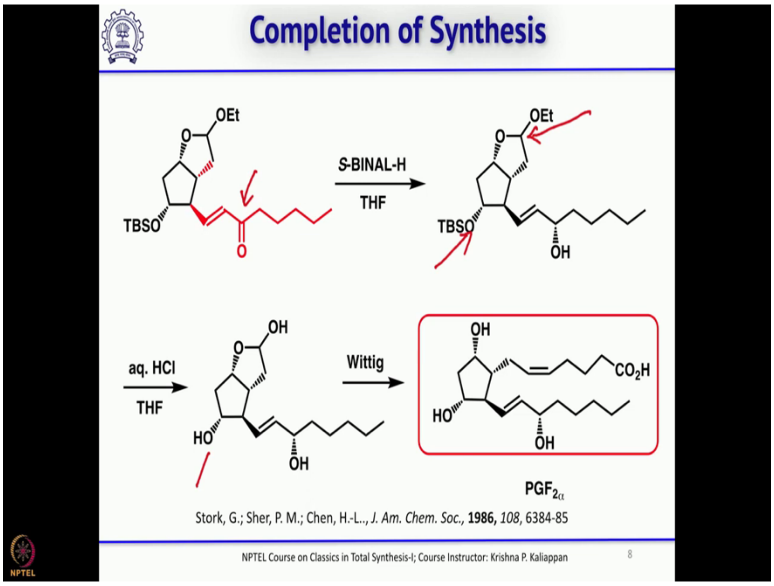

Completion of Synthesis

S-BINAL-H

THF

aq. HCl

THF

Wittig

PGF$_{2\alpha}$

Stork, G.; Sher, P. M.; Chen, H.-L., *J. Am. Chem. Soc.*, **1986**, *108*, 6384-85

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So, that gives the corresponding alpha beta unsaturated ketone. So, now, you can see both ways you could get this corresponding enone once we have this enone reduce with S-BINAL ok. So, that will reduce the carbonyl group and you will get one isomer as a major product you got the alcohol then treat with aqueous HCl.

So, aqueous HCl will hydrolyze the lactol ether to corresponding lactol and at the same time your TBS group also will be cleaved you get the corresponding hydroxyl group now you do the Wittig with the five carbon unit having a carboxylic acid at the terminal. So, you get PGF 2 alpha directly. So, overall if you look at the synthesis.

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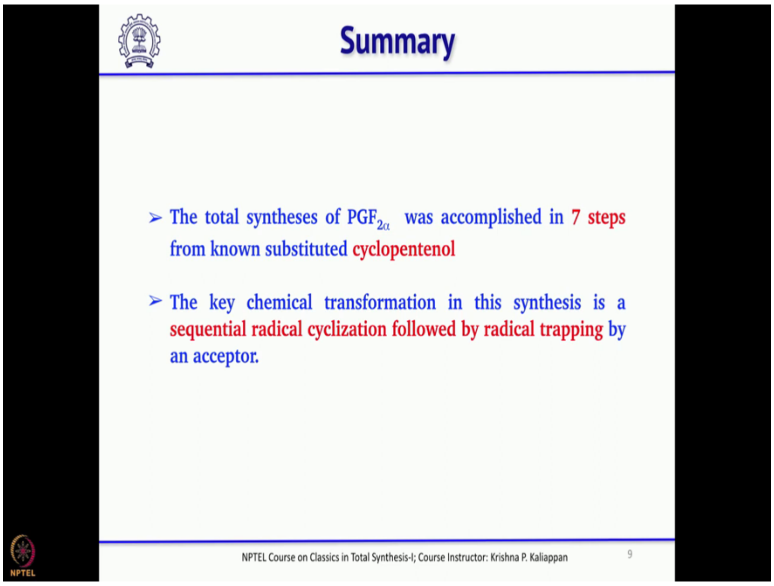

Summary

- The total syntheses of $PGF_{2\alpha}$ was accomplished in 7 steps from known substituted cyclopentenol
- The key chemical transformation in this synthesis is a sequential radical cyclization followed by radical trapping by an acceptor.

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So, the synthesis was done in only 7 steps ok done only in 7 steps starting from the cyclo the acetoxy or TBS protected cyclopentenol which is a known compound from cyclopentadiene which is a known compound from cyclopentadiene and this was achieved in 7 steps then the next key step was the 5 exo radical cyclization followed by trapping of the radical with acceptors ok.

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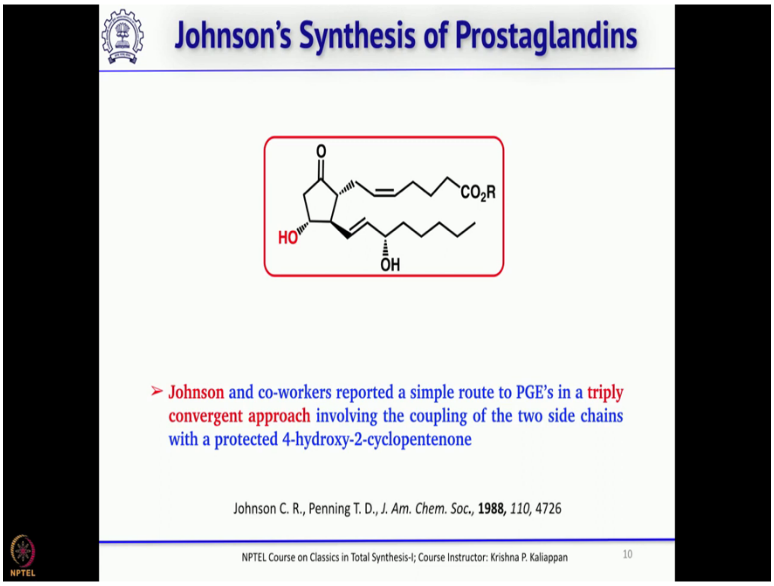

Johnson's Synthesis of Prostaglandins

- **Johnson** and co-workers reported a simple route to PGE's in a **triply convergent approach** involving the coupling of the two side chains with a protected 4-hydroxy-2-cyclopentenone

Johnson C. R., Penning T. D., *J. Am. Chem. Soc.*, **1988**, *110*, 4726

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Now, we will move to the third total synthesis of prostaglandins by Carl Johnson's group. So, here the key reaction was 1,4- addition to cyclopentenone followed by quenching the enolate with an electrophile. So, the two side chains are introduced in one step via 1,4- addition followed by trapping of the enolate ok. Basically what they have done is a substituted cyclopentenone was taken and then these two side chains were attached ok.

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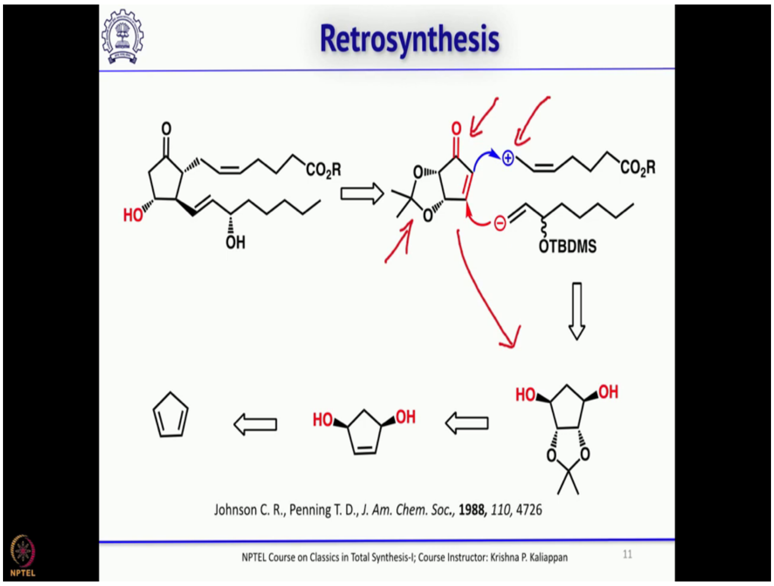

Retrosynthesis

Johnson C. R., Penning T. D., *J. Am. Chem. Soc.*, **1988**, *110*, 4726

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Let us see how they have thought about from retro synthetic point of view. So, they thought this can be obtained from this cyclopentenone having these two hydroxyl groups which are protected. The idea is this vinyl lithium species or vinyl copper vinyl lithium species followed by converting into copper add to this cyclopentenone in a 1,4- fashion and quench with this electrophile

And this can be obtained from this I will come to that how it is done and again the starting material looks almost same as what Gilbert Stork has used ok and that can be obtained from cyclopentadiene. So, overall if you look at the three synthesis which we discussed for the total synthesis of prostaglandins all the synthesis started with a five membered that is cyclopentadiene commercially available cyclopentadiene of course, cyclopentadiene is not commercially available as such it is available as cyclopentadiene dimer you have to crack it that is you have to make sure that it undergoes a retro four plus two cycloaddition to get cyclopentadiene.

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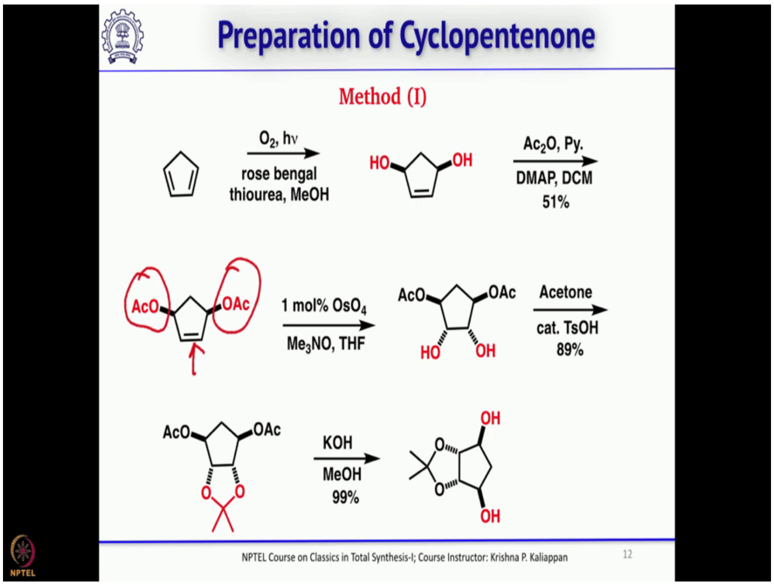

Preparation of Cyclopentenone

Method (I)

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So, how he did? So, there are two ways he prepared the chiral starting material the first method is almost similar to what Gilbert Stork has done, a four plus two cyclo addition of cyclopentadiene with oxygen followed by reduction of OO bond with thiourea you get the diol.

And the diol was protected as the diacetate and from here he changed its root. So, what he did? He did a dihydroxylation. So, when the dihydroxylation happened as you know the dihydroxylation both hydroxyl group will come opposite to these two acetates these two acetates are beta. So, the hydroxyl will come from alpha and the resultant diol was protected as acetonide by treating with acetone with a catalytic amount of para toluene sulfonic acid.

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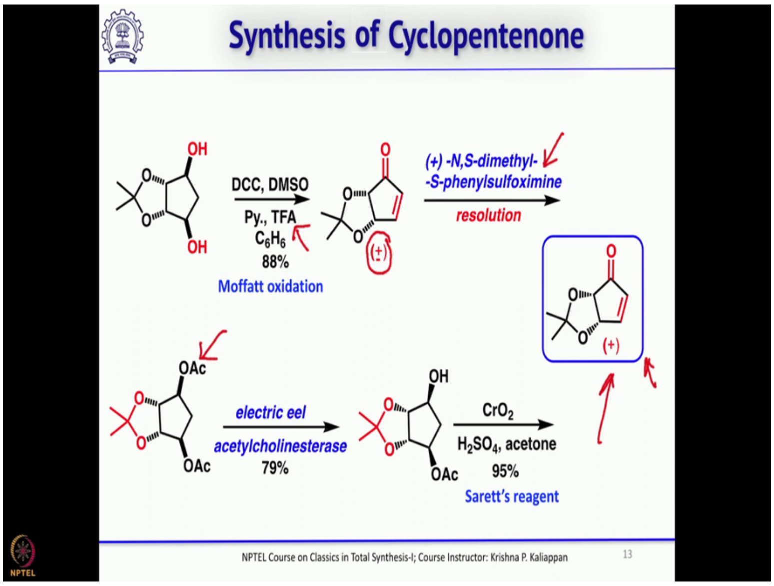

Synthesis of Cyclopentenone

DCC, DMSO

Py., TFA

C_6H_6

88%

Moffatt oxidation

(+)-N,S-dimethyl-

-S-phenylsulfoximine

resolution

electric eel

acetylcholinesterase

79%

CrO_2

H_2SO_4, acetone

95%

Sarett's reagent

Now, you hydrolyse. So, both acetate you get a diol this diol upon oxidation ok one of the hydroxyl gets oxidized and once it is oxidized to get the ketone the other hydroxyl group is nothing but its an aldol beta hydroxyl ketone. So, it undergoes elimination under the in the presence of trifluoroacetic acid. So, directly you get the cyclopentenone, but this is racemic in nature ok.

This racemic cyclopentenone can be resolved with this sulfoximine to get the only the required one you also can get the other one equal amount, but what you want is this one with that you can proceed further for the enantioselective total synthesis of prostaglandin and one can also use the diacetate for preparing the same.

So, you can use an enzyme to selectively hydrolyze this acetate and oxidize. So, alcohol will get oxidized to get the ketone and automatically and in the presence of sulfuric acid it will undergo elimination to get this compound.

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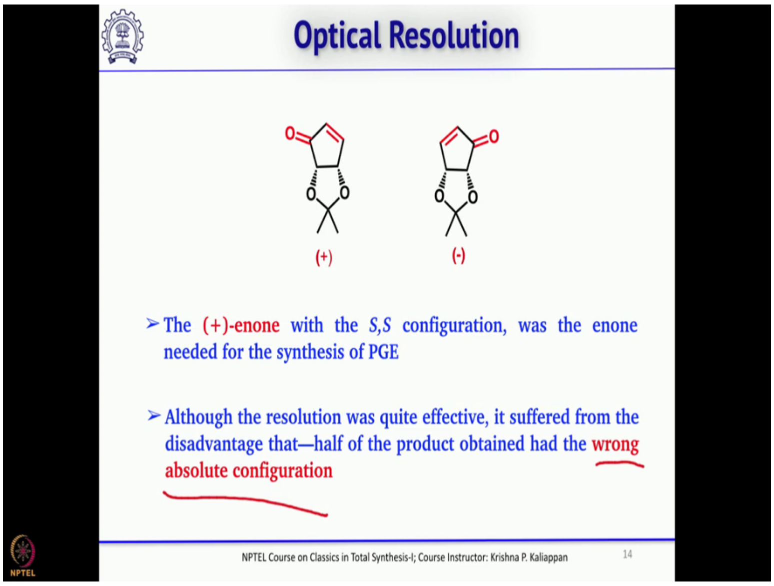

Optical Resolution

- The (+)-enone with the *S,S* configuration, was the enone needed for the synthesis of PGE
- Although the resolution was quite effective, it suffered from the disadvantage that—half of the product obtained had the wrong absolute configuration

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So, there are two ways one can make this cyclopentenone and this is the way you know normally optical resolution is done and only problem is the 50 percent with the other configuration you cannot use it further because that will not give the naturally occurring prostaglandin ok.

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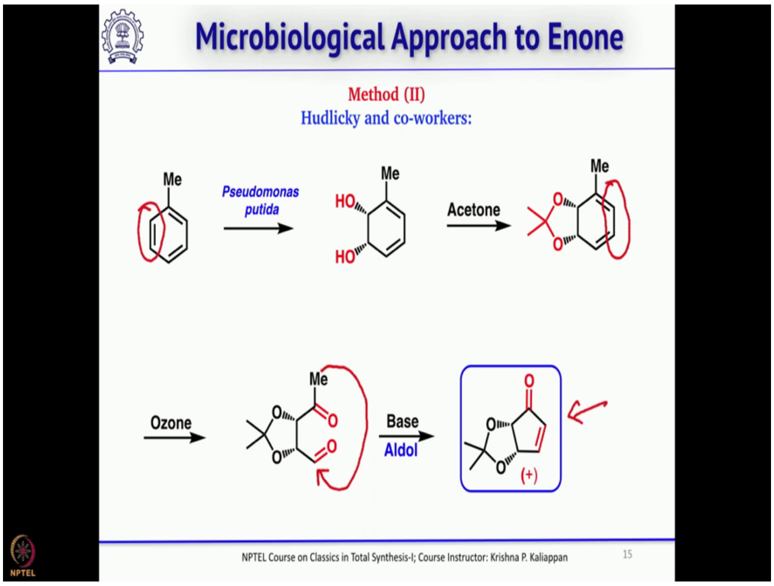

Microbiological Approach to Enone

Method (II)
Hudlicky and co-workers:

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So, you go with what you require the second method. So, that is why you know the second method was used in the second method which was developed by Hudlicky. So, that involved dihydroxylation of an aromatic compound. So, this microbiological process started with toluene commercially available toluene you can do this pseudomonas putida enzyme to do the dihydroxylation.

So, one of the double bonds of benzene can be selectively dihydroxylated. Now we protect this hydroxyl the two hydroxyl which are cis with acetone. So, you get the corresponding acetonide then if you cleave these two double bonds under ozonolysis condition you get the corresponding keto aldehyde ok keto aldehyde. Now this ketone it can generate anion and attack this aldehyde in an intramolecular aldol reaction followed by elimination of water you get the same compound which we had discussed earlier starting from cyclopentadiene.

So, the second method differs from the other three synthesis where you know cyclopentadiene was used as a key starting material here the starting material used is toluene and again they use enzyme to introduce the two hydroxyl groups stereo selectively and followed by intramolecular aldol reaction to get the same starting material. So, once we have this substituted cyclopentenone, the next key step is the addition of the vinyl copper followed by quenching with the next side chain.

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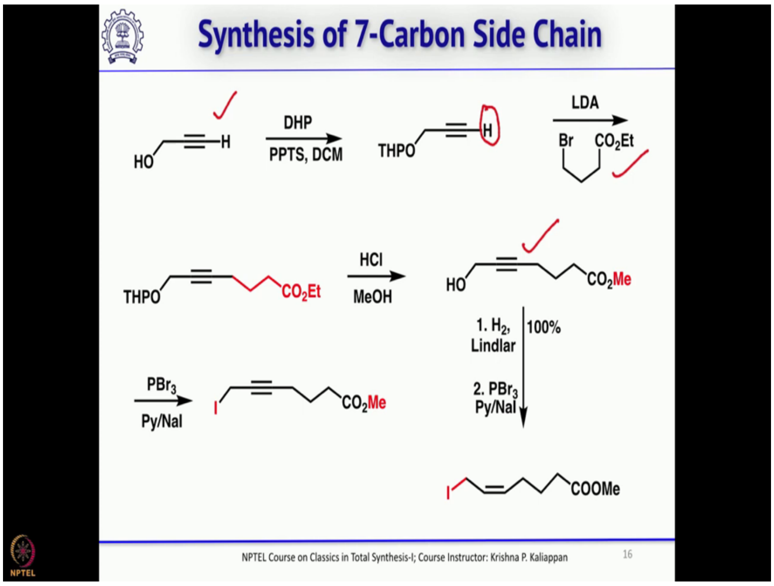

Synthesis of 7-Carbon Side Chain

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So, how did they do? Before that the side chain has to be prepared both the side chain one is 8 carbon other one is 7 carbon the 7 carbon side chain was prepared from propargyl alcohol protect the alcohol as THP ether and followed by removing this proton with LDA and quench with this bromo ester. Then the THP ether could be cleaved with

HCl methanol to release the primary alcohol and that can be converted into iodide by treating with PBr_3.

Then if you use Lindlar catalyst, this propargyl alcohol the substituted propargyl alcohol will be reduced to the alkene which is cis then you convert the alcohol into corresponding iodide ok.

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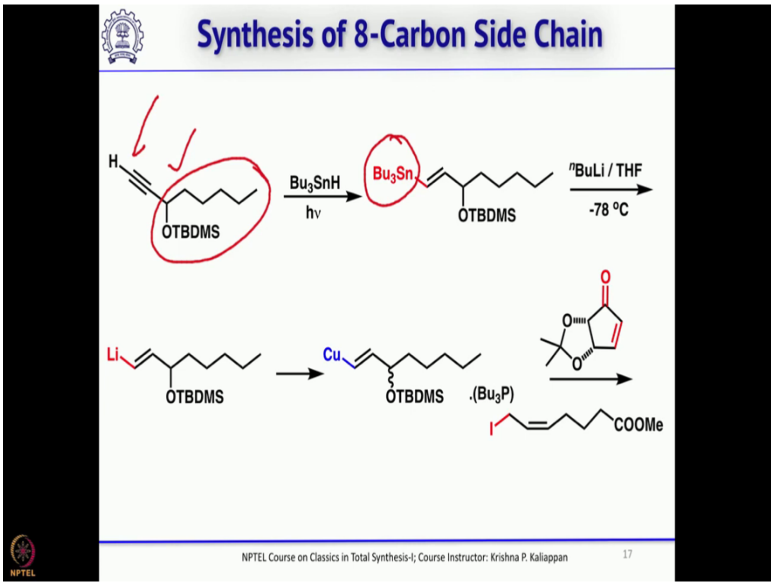

Synthesis of 8-Carbon Side Chain

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Same thing you can do with this also no problem the synthesis of the 8 carbon side chain started with this protected alcohol of course, this can be made in two steps from the corresponding aldehyde and add this lithium ethylene diamine you get the alcohol that alcohol you protect it as TBDMS ether you get the starting material. Now if you treat with tributyltin hydride under photochemical condition.

The tributyltin hydride is known to add to this triple bond to get trans double bond with a tributyltin group at the terminal carbon now if you treat with butyl lithium. So, this can be exchanged with lithium ok. So, you get lithium and this upon treatment with copper. So, the lithium-copper exchange will take place so, that it can undergo a 1,4- addition to the cyclopentenone.

So, that is what happens you take this and then treat with the substituted cyclopentenone followed by quenching with the cis allyl iodide ok which already discussed in the previous slide.

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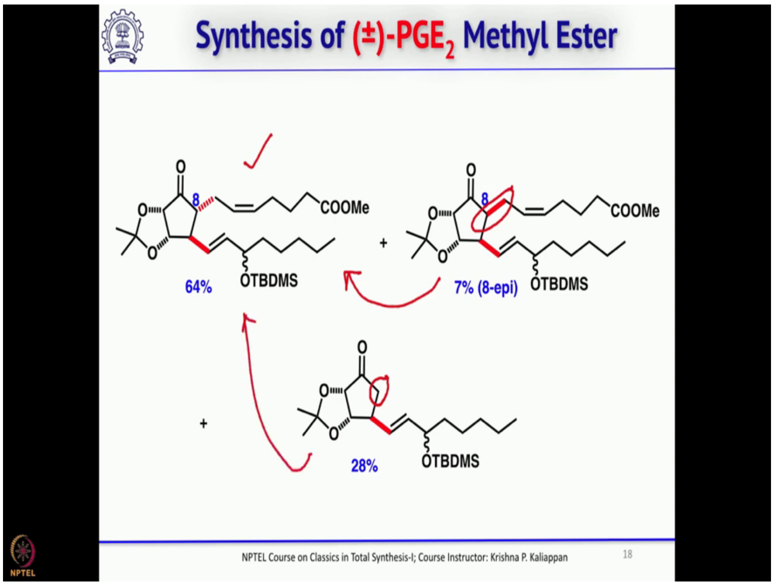

Synthesis of (±)-PGE$_2$ Methyl Ester

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So, this gives a mixture of three compounds one the required the trans disubstituted cyclopentanone in 64 percent yield, then the other two, one is the epimer at this carbon the third one is only 1,4- addition product the alkylation did not take place ok. Only one 1,4- alkylation did not take place. So, what we can do? You can convert this into required one by epimerisation and this you can convert into the required compound by alkylation.

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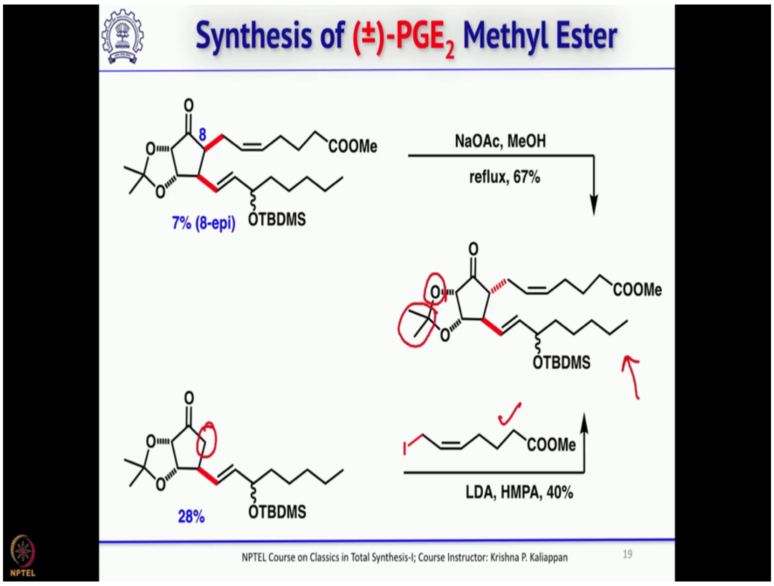

Synthesis of (±)-PGE$_2$ Methyl Ester

NaOAc, MeOH

reflux, 67%

LDA, HMPA, 40%

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So, both were done. So, epimerisation was done with sodium acetate methanol to get the required cyclopentanone, then the other one that is the mono alkylated that is only 1,4-addition product happened not the subsequent alkylation, you can treat with LDA and quench with the corresponding iodide you can convert into the required product. So, now, if you look at this intermediate, it has both C7, C8 side chain and what is not required is this oxygen and this three carbon unit ok.

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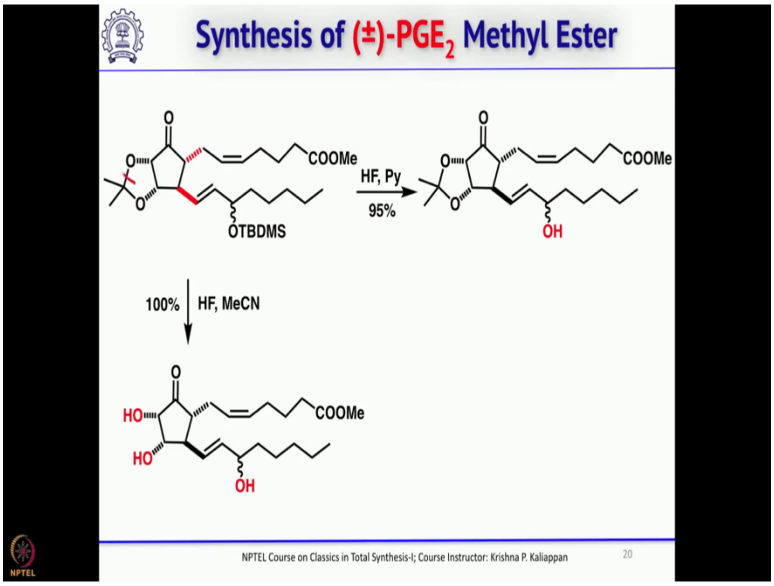

Synthesis of (±)-PGE$_2$ Methyl Ester

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So, that was easily done before that the hydroxyl group was released by removing the TBDMS group by treating with HF pyridine and one can also use HF in acetonitrile so, that not only TBDMS group will be removed, but one can also remove the acetonide ok.

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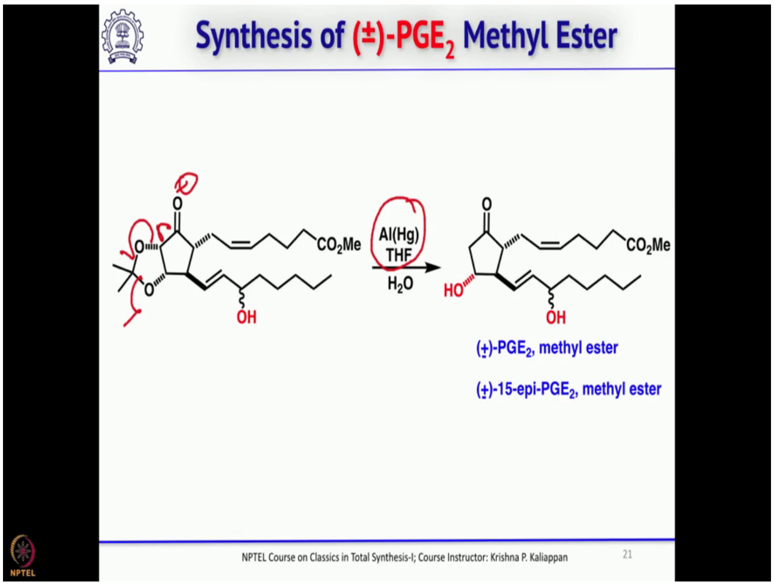

Synthesis of (±)-PGE$_2$ Methyl Ester

(±)-PGE$_2$, methyl ester

(±)-15-epi-PGE$_2$, methyl ester

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So, both were done under the same condition, but you do not want the extra oxygen is not it? That extra oxygen was removed by using aluminium amalgam. So, basically it gives a radical anion and this opens up and you get the acetone and the corresponding beta hydroxy compound ok. This is for racemic one.

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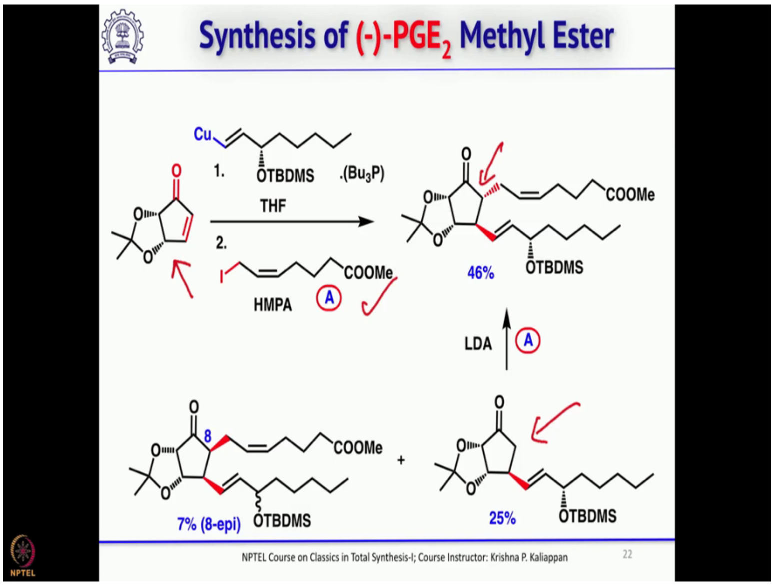

Synthesis of (-)-PGE$_2$ Methyl Ester

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How about the chiral one. Say chiral one already we know how to make this follow the same process that is do 1,4- addition quench with the corresponding allyl iodide you get 46 percent yield of the required product of course, the other products are mono alkylated product that is the only 1,4- addition took place the subsequent alkylation did not take place then you got the epimer at this position ok.

So, no problem as I already discussed the 8 epimer can be further you know treated with base to get the required one and of course, this 25 percent of the product where only 1,4-addition took place can be converted into this by additional treatment with LDA and quenching with the corresponding allyl iodide ok.

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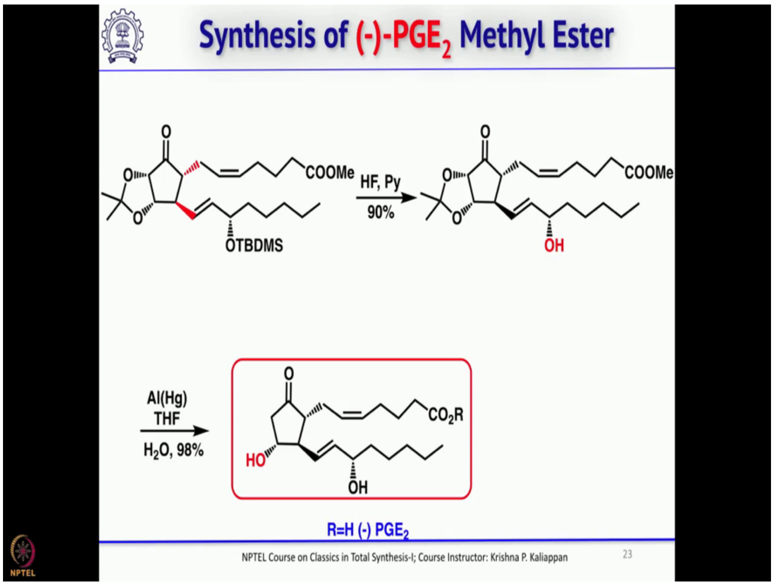

Synthesis of (-)-PGE_2 Methyl Ester

HF, Py
90%

Al(Hg)
THF
H_2O, 98%

R=H (-) PGE_2

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From here to PGE_2 methyl ester we already discussed on the racemic one. So, HF pyridine remove the TBDMS group and aluminium amalgam removes the acetonide group. So, that is how Carl Johnson could complete the total synthesis of PGE_2 in an optically active form.

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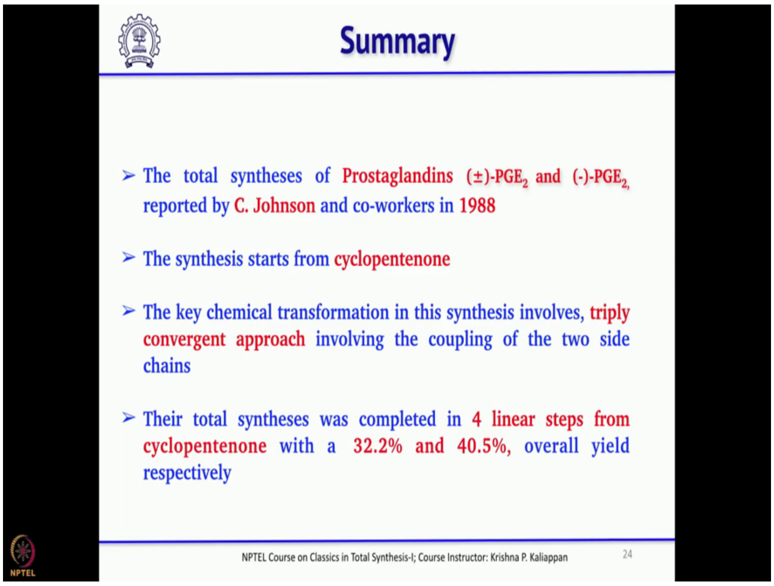

Summary

- The total syntheses of Prostaglandins (±)-PGE_2 and (-)-PGE_2, reported by C. Johnson and co-workers in 1988
- The synthesis starts from cyclopentenone
- The key chemical transformation in this synthesis involves, triply convergent approach involving the coupling of the two side chains
- Their total syntheses was completed in 4 linear steps from cyclopentenone with a 32.2% and 40.5%, overall yield respectively

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So, to summarize prostaglandin PGE_2 both racemic and optically active minus isomer was reported by Carl Johnson and co-workers in 1988. In one synthesis they started with cyclopentadiene as the starting material and in the other synthesis they followed Hudlicky’s protocol.

Wherein they started with toluene and then do enzymatic di hydroxylation to introduce the two chiral centers and these two chiral centers were responsible for the introduction of the two more chiral centers where you have to introduce the C8 side chain and C7 side chain. Overall if you look at this whole transformation it's a triply convergent approach; that means, you have cyclopentenone and you add the C8 side chain and followed by quench with C7 side chain.

So, triple convergent approach and overall this synthesis was achieved in four longest linear steps with a yield of 32-point percent and 40.5 percent respectively for racemic and asymmetric synthesis ok.

So, thank you, I will stop here today.