Classics in Total Synthesis-I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 52
Phorbol (Wender)

So, good morning and welcome back to classics in Total Synthesis lecture series and we have been discussing many total synthesis of complex natural products and we will continue our discussion on one more total synthesis of a complex natural product called Phorbol.

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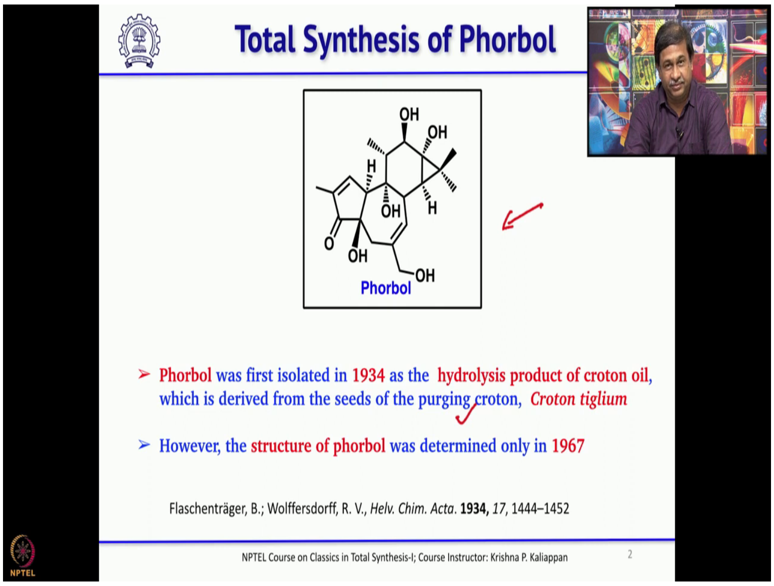

Total Synthesis of Phorbol

- ➢ Phorbol was first isolated in 1934 as the hydrolysis product of croton oil, which is derived from the seeds of the purging croton, *Croton tiglium*
- ➢ However, the structure of phorbol was determined only in 1967

Flaschenträger, B.; Wolffersdorff, R. V., *Helv. Chim. Acta.* **1934,** *17,* 1444–1452

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As you can see from here the structure is quite complex and this was isolated in 1934 from the seeds of *purging cotton*. And it took about another 43 years to determine the correct structure of phorbol, this is which is understandable considering the complex structure, it took much more time to propose the correct structure of phorbol.

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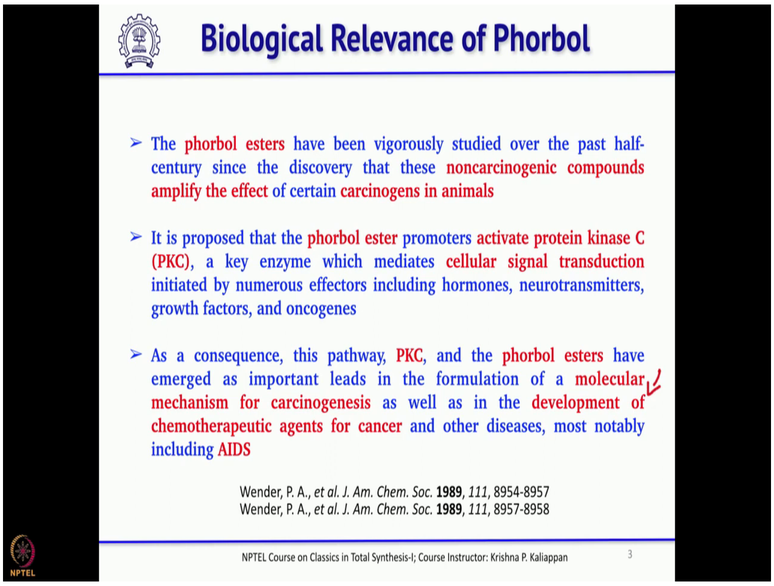

Biological Relevance of Phorbol

- The phorbol esters have been vigorously studied over the past half-century since the discovery that these noncarcinogenic compounds amplify the effect of certain carcinogens in animals
- It is proposed that the phorbol ester promoters activate protein kinase C (PKC), a key enzyme which mediates cellular signal transduction initiated by numerous effectors including hormones, neurotransmitters, growth factors, and oncogenes
- As a consequence, this pathway, PKC, and the phorbol esters have emerged as important leads in the formulation of a molecular mechanism for carcinogenesis as well as in the development of chemotherapeutic agents for cancer and other diseases, most notably including AIDS

Wender, P. A., *et al. J. Am. Chem. Soc.* **1989**, *111*, 8954-8957
Wender, P. A., *et al. J. Am. Chem. Soc.* **1989**, *111*, 8957-8958

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And it took another 22 years for the first total synthesis of phorbol reported by Paul Wender basically it has excellent biological activity profile. And particularly it helped in the development of many chemotherapeutic agents for Cancer and other diseases like aids ok. So, I will not go into the biological profile of this phorbol esters.

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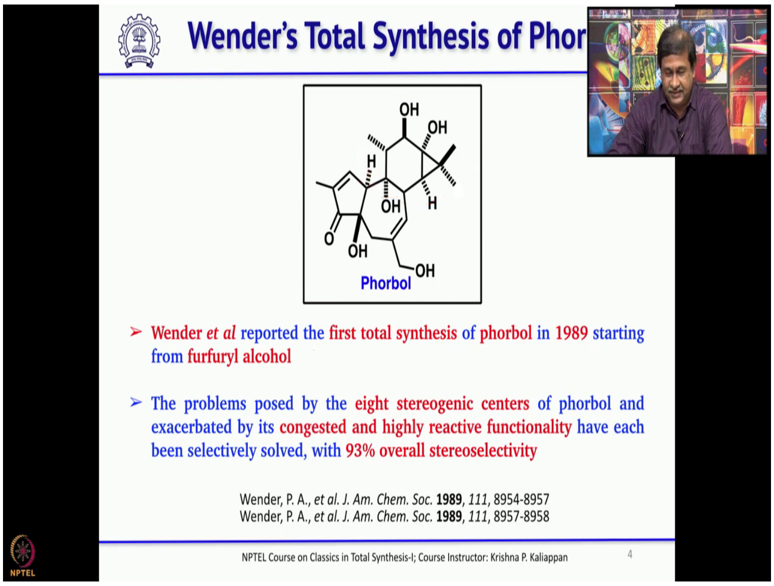

Wender's Total Synthesis of Phor

Phorbol

- Wender *et al* reported the first total synthesis of phorbol in 1989 starting from furfuryl alcohol
- The problems posed by the eight stereogenic centers of phorbol and exacerbated by its congested and highly reactive functionality have each been selectively solved, with 93% overall stereoselectivity

Wender, P. A., *et al. J. Am. Chem. Soc.* **1989**, *111*, 8954-8957
Wender, P. A., *et al. J. Am. Chem. Soc.* **1989**, *111*, 8957-8958

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Rather I will talk more about Wender's total synthesis retro synthesis and how he constructed this interesting tetra cyclic compound with so, many chiral centers you can see here it is highly congested natural product having many chiral centers. And as I mentioned it took 22 years after the correct structure was proposed for phorbol to come up with the first total synthesis and is Wender's first total synthesis of phorbol was started from commercially available simple starting material called fufuryl alcohol ok.

There are eight stereogenic centers in the molecule and in that six are contiguous you can see the whole ring here all have stereo centers. So, highly contiguous stereo centers and he used a very interesting reaction called oxido pyrylium arene cycloaddition reaction ok. Its sort of [5+2] cycloaddition reaction oxido pyrylium alkene cycloaddition reaction I will come to that when I talk about retro synthesis as well as synthesis.

And this synthesis is a very very interesting synthesis and this retro synthesis if you look at he thought phorbol can be made from this tetra cyclic compound by few functional group transformation.

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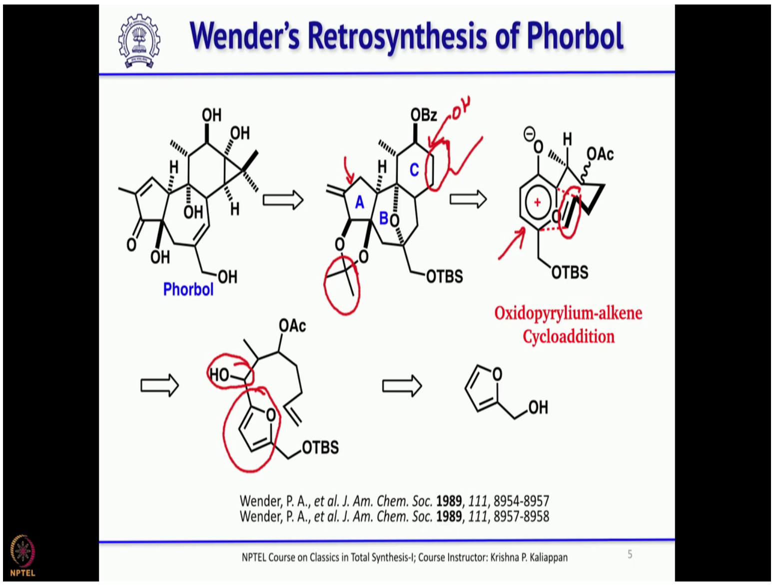

Wender's Retrosynthesis of Phorbol

Oxidopyrylium-alkene Cycloaddition

Wender, P. A., *et al. J. Am. Chem. Soc.* **1989**, *111*, 8954-8957
Wender, P. A., *et al. J. Am. Chem. Soc.* **1989**, *111*, 8957-8958

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First you know from here to phorbol what he has to do is to migrate the double bond from exocyclic to internal, then he needs to remove the protecting group and oxidize the secondary alcohol in the presence of tertiary alcohol. And here he has to introduce the dimethyl cyclopropane as well as introduce the hydroxyl group.

So, this functional group transformation though it is written in one step it requires about 10 steps or more to convert into phorbol ok and here he comes the key oxidopyrylium alkene cycloaddition reaction. So, this is the alkene ok this is the alkene and this is the oxidopyrylium ok this oxidopyrylium can be made easily from this type of furan with an alcohol here ok.

So, this can be easily made in one step and when it is made and if you have a double bond at appropriate place, it can undergo an intramolecular [5+2] cycloaddition reaction. We will look into this when we talk about total synthesis and how he got this tricyclic compound ok and this can be made from furfuryl alcohol in few steps ok using standard functional group transformation ok. So, let us see how he completed the total synthesis of phorbol starting from furfuryl alcohol ok.

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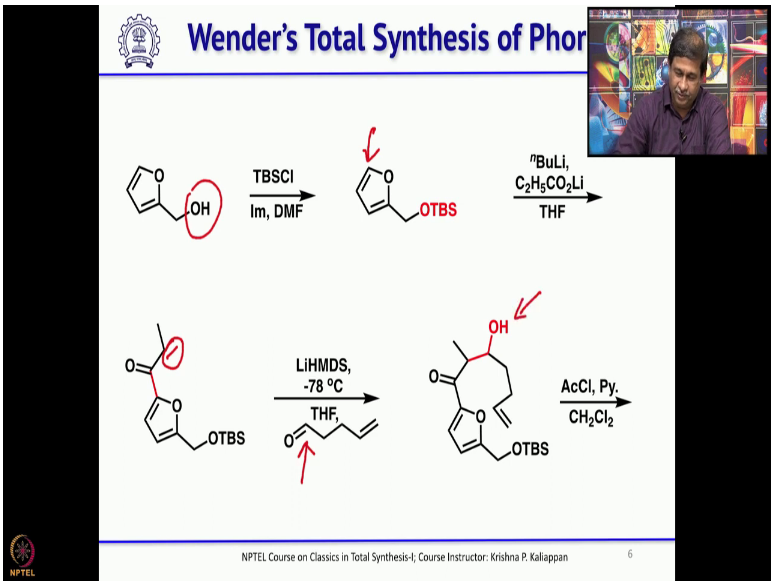

Wender's Total Synthesis of Phor

TBSCl
Im, DMF

^{n}BuLi,
$C_2H_5CO_2Li$
THF

LiHMDS,
-78 °C
THF,

AcCl, Py.
CH_2Cl_2

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The first he took furfuryl alcohol and protected the primary alcohol as TBS ether, now he deprotonate or lithiated at the other side and quenched with lithium propionate to introduce the propynyl group ok then he carried out an intermolecular aldol reaction first you generate the enolate with LiHMDS with this pentanal ok the pentanal you generate the aldol ok. So, this is an aldol ok.

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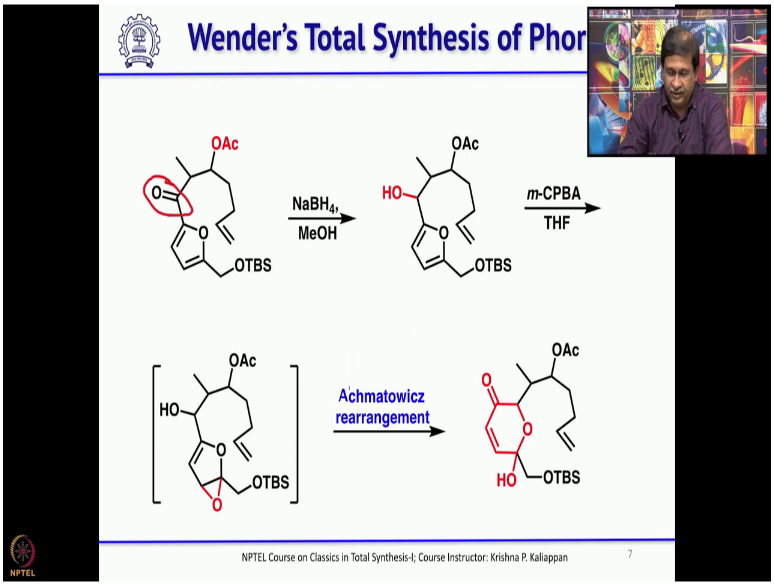

Wender's Total Synthesis of Phor

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Now, you protect the hydroxyl group ok you protect the hydroxyl group as acetate then carry out the key reaction that is first you reduce this ketone as I said you need alcohol there for carrying out the key oxido pyrylium alkene cycloaddition reaction. Once you have this alcohol treat with *m*CPBA the *m*CPBA first it forms epoxide here then it undergoes Achmatowicz rearrangement ok.

So, this I had already discussed and it when I talked about I think eleuthrobin I discussed about Achmatowicz rearrangement. So, that gives γ hydroxy pyrrolo then the next key step is the oxidopyrylium alkene cycloaddition.

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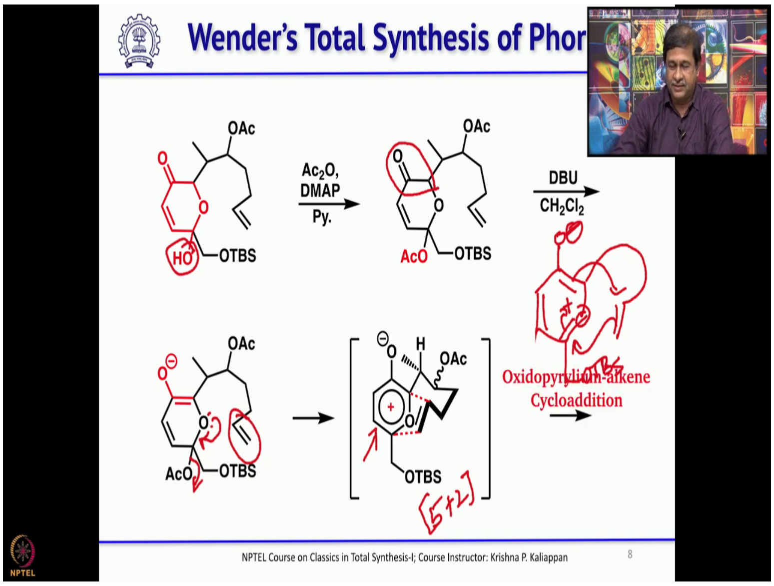

Wender's Total Synthesis of Phor

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So, this on treatment with acidic enolate ok. You protect this lactol as acetate then treat with DBU. So, the DBU it can form the enolate at the same time this lone pair ok this lone pair can push this acetate out ok. So, if you see this that forms this oxidopyrylium. So, this is a stable species ok this is a stable species and this double bond can undergo a [5+2] cycloaddition reaction an intramolecular [5+2] cycloaddition reaction.

So, I will leave it for some time so, that you can visualize ok first it forms this ok this is what happens now it can undergo cyclo addition like this ok.

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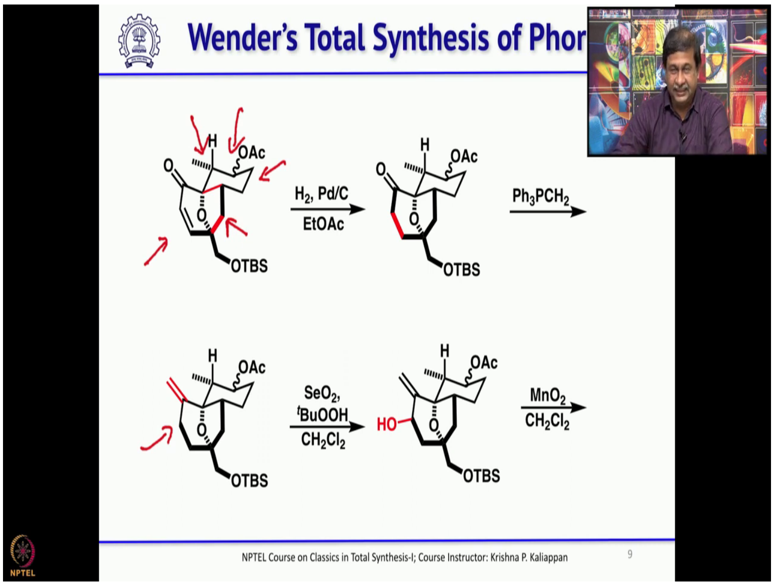

Wender's Total Synthesis of Phor

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So, when that happens you get this product ok it is a tricyclic compound then you get this 6 membered ring here, a 5 membered ring here and another 6 membered ring here. While doing that what you can notice is this methyl group occupies the more stable equatorial position and the acetate also the major isomer has acetate in the equatorial position ok. So, the major isomer upon hydrogenation you can remove the double bond then it is a simple we take to get the exocyclic double bond here.

After getting the exocyclic double bond when you treat with selenium dioxide you can introduce an oxygen functionality ok selenium dioxide is known to undergo allylic oxidation you get the corresponding allylic alcohol. Now when you treat with manganese dioxide, manganese dioxide are known to facilitate allylic oxidation to give α- β unsaturated ketone.

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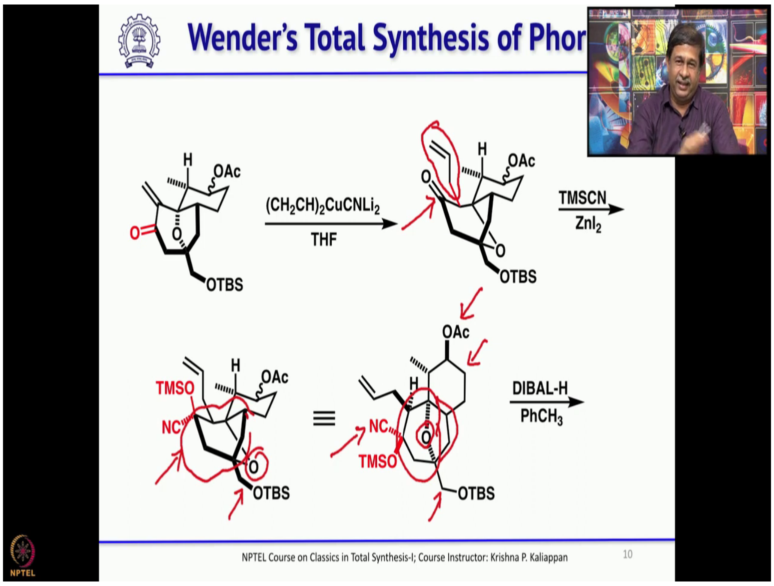

Wender's Total Synthesis of Phor

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Then you carry out a one four addition with vinyl copper ok or you can introduce an allyl group here already a double bond you add a vinyl. So, it becomes allyl group next to the carbonyl group ok. Then the ketone you can add TMS cyanide basically you are adding a cyanide to the ketone since you are using TMS cyanide, the cyano hydride is in situ protected as TMS ether ok. So, that is how you get the corresponding TMS protected cyano hydride.

So, this can be rewritten or redrawn like this again I will leave this for few seconds you just see how this was redrawn ok you can see this CH_2-OTBS here and this is the 7 membered ring ok you can see the 7 membered ring ok then this oxygen bridge is α this oxygen bridge is α ok. Then of course, you have the cyclohexyl group with methyl α and hydroxyl β but both are equatorial ok is that clear then you treat with DIBAL. What will DIBAL do?

DIBAL will do two things; one it will reduce the cyanide to aldehyde, two it will also reductively remove the acetate group is not it ester will be cleaved. So, you get corresponding hydroxyl group and then cyanide will be reduced to corresponding aldehyde ok.

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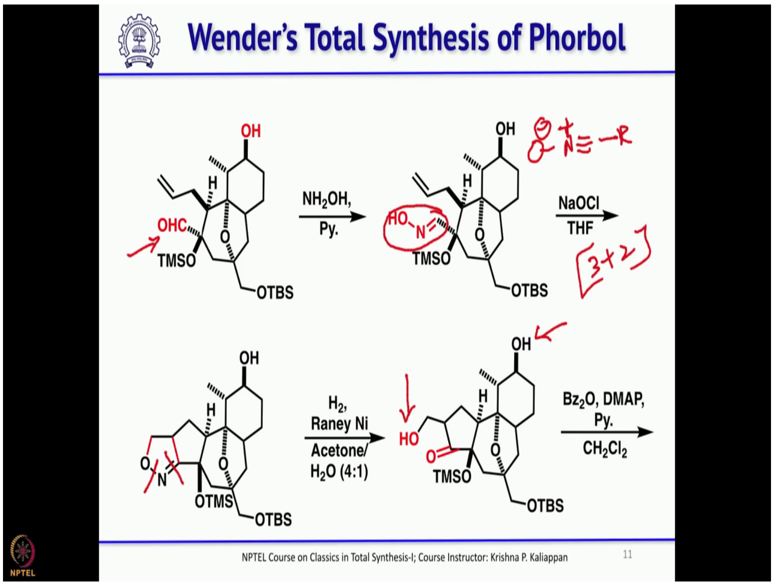

Wender's Total Synthesis of Phorbol

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In one step you do two things ester is hydrolyzed reductively hydrolyzed and cyanide is reduced to get the corresponding aldehyde. Now, you treat with hydroxyl amine to form the oxime. Aldehydes are known to undergo oxime formation upon treatment with hydroxyl amine then when you treat with hypo solution when you treat with hypo solution this oxime ok this oxime will form a nitrile oxide ok this oxime will form nitrile oxide.

Once the nitrile oxide is formed it will undergo an intramolecular dipolar cycloaddition reaction intramolecular one three dipolar cycloaddition or you can call it as intra molecular [3+2] cycloaddition reaction to give the corresponding 5 membered ring ok. When you get this you have to cleave this NO bond as well as hydrolyze the C=N.

Both can be done in one step under hydrogen analysis condition hydrogen analysis condition NO bond can be cleaved and under the same condition if you use water and acetone the imine the double bond NH which is formed that can be cleaved to get the corresponding ketone ok.

So, if you look at this that is how the five membered ring the next five membered ring was made. Then what is required? You have to protect the hydroxyl groups as benzoate. So, both primary as well as the secondary hydroxyl groups were protected as benzoates.

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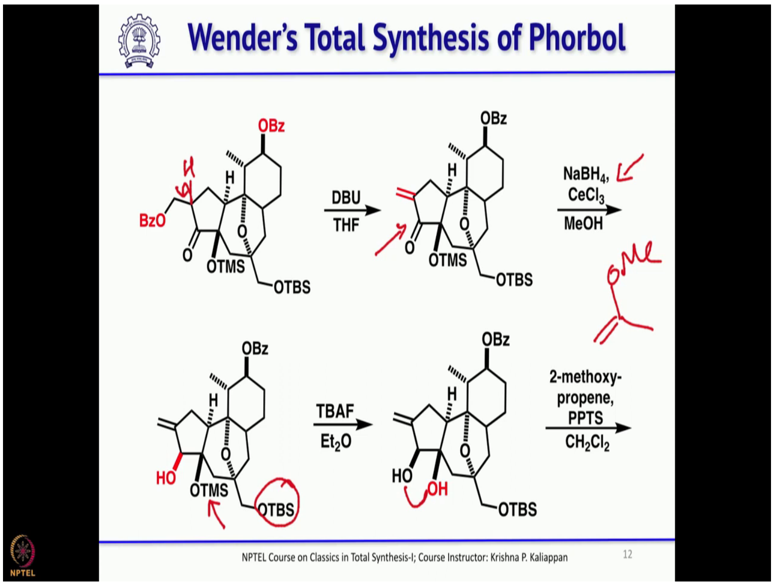

Wender's Total Synthesis of Phorbol

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Then, if you treat with DBU ok if you treat with DBU then this can undergo elimination ok this can undergo elimination to give exocyclic double bond the exocyclic double bond particularly when it is in conjugation with ketone they are little unstable. So, once this enone was formed immediately it was reduced under luche condition. So, luche condition is nothing but you treat with sodium borohydride in the presence of cerium chloride ok so, that facilitates the one two reduction.

So, you got the allylic alcohol, once you have the allylic alcohol, then you can selectively remove the OTMS in the presence of OTBS ok with TBAF. If you take one equivalent of TBAF, OTMS will be removed faster than OTBS ok. So, that was done. Then this is one two diol is not it the one two diol can be protected as acetonide. So, there are many ways one can protect one two diol.

So, what Wender used was treat with 2 methoxy propene. So, 2 methoxy propene is this compound. So, treat with 2 methoxy propene in the presence of PPTS you protect the one two diol as acetonide ok.

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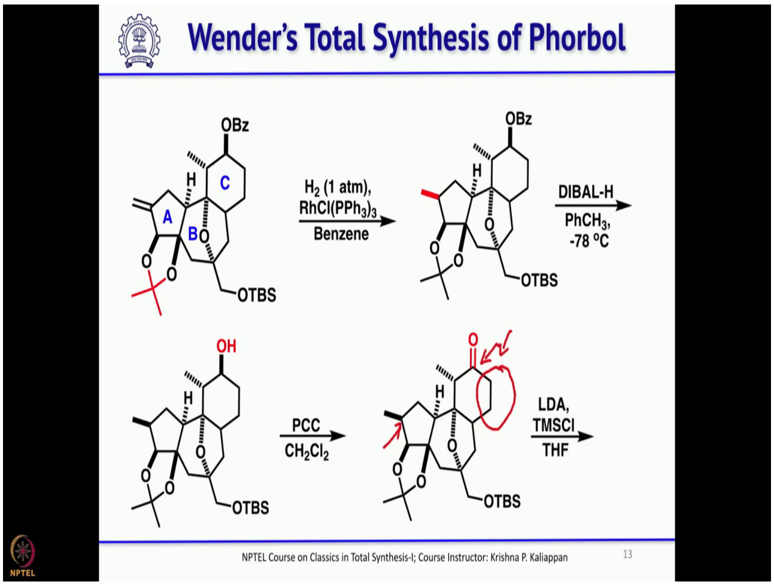

Wender's Total Synthesis of Phorbol

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Now, from there what you have to do is you have to reduce the double bond to get the β methyl and also the benzoate should be hydrolyzed and oxidized to ketone. So, this was done in three steps first reduce with Wilkinson catalyst so, that you get high selectivity you get the β methyl, then benzoic was removed by reductive removal DIBAL removed the benzoate to get the alcohol, then the alcohol was oxidized with PCC ok.

So, now you have got the ketone what is to be done is you know you have to introduce the dimethyl cyclopropane as well as the hydroxyl group. So, two things have to be done. So, what you need? First you have to introduce the enone the double bond should be introduced you treat with LDA and TMS chloride.

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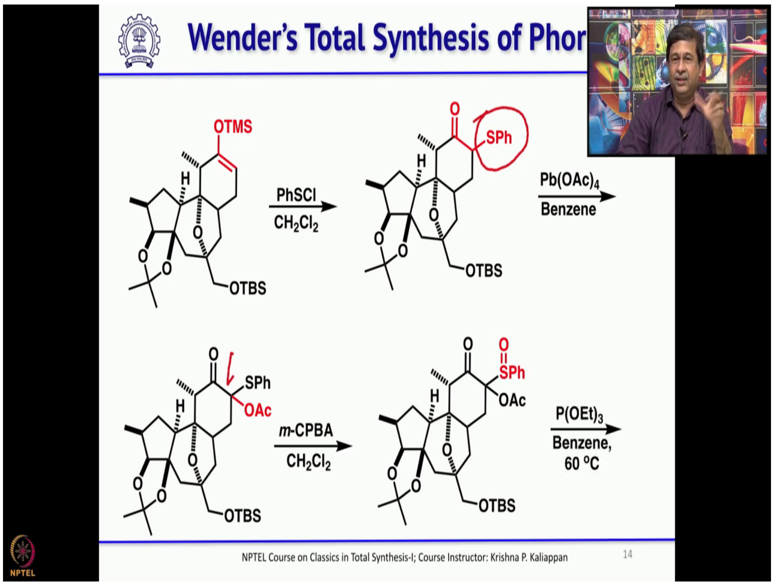

Wender's Total Synthesis of Phor

PhSCl, CH_2Cl_2

$Pb(OAc)_4$, Benzene

m-CPBA, CH_2Cl_2

$P(OEt)_3$, Benzene, 60 °C

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So, it forms the corresponding enol TMS ether ok it forms a corresponding in enol TMS ether. This on treatment with phenyl sulfonyl chloride you can introduce -SPh basically as I said what you needed to do is you need to introduce the double bond next to the ketone. So, there are many methods. So, he used this method once you have the -SPh the sulfide phenyl sulfide should be oxidized ok. So, what he did, he treated tetra acetate to introduce the acetate α to the sulfur ok.

This is a famous rearrangement ok try to find out what is this rearrangement ok. Now you oxidize the sulfide oxidize the sulfide with *m*CBBA ok S becomes sulfoxide.

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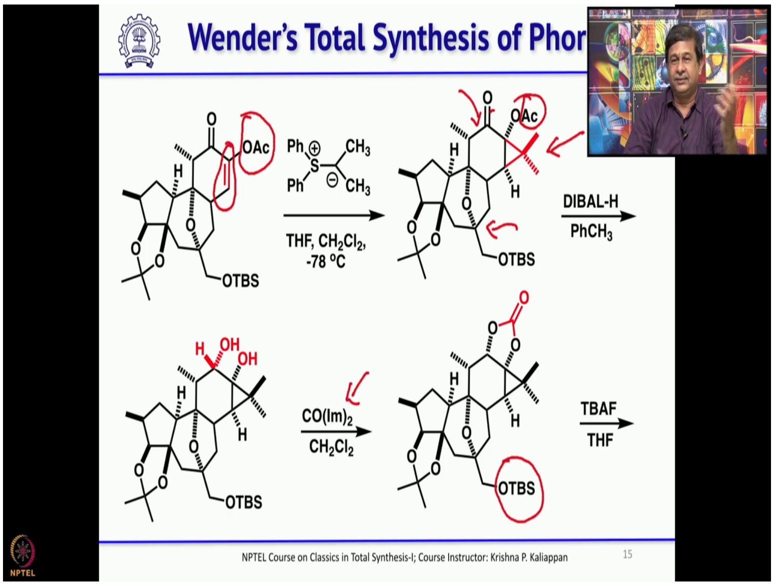

Wender's Total Synthesis of Phor

$Ph_2\overset{\oplus}{S}-\overset{\ominus}{C}(CH_3)_2$

THF, CH_2Cl_2, -78 °C

DIBAL-H, $PhCH_3$

$CO(Im)_2$, CH_2Cl_2

TBAF, THF

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The phenyl sulfoxide if you heat it, it will undergo elimination sin elimination to introduce the double bond. So, what you have done if you look at this from the ketone not only introduce the double bond, you also introduce an acetate ok. You need a hydroxyl group at that position and the double bond is required for introducing the dimethyl cyclopropane. So, both are done using the enol TMS chemistry to introduce a double bond as well as the acetate.

Once this is done then you do the sulfur elite reaction the sulfur elite reaction to introduce the dimethyl cyclopropane ok. So, that is like one four addition and then when it comes back it will expel di phenyl sulfide ok. So, successfully the dimethyl cyclopropane was introduced and it also has the acetate now what you need to do? You have to reduce the ketone and also open this oxygen bridge ok you do not need the oxygen bridge.

So, you have to open the oxygen bridge. So, first the ketone was reduced to get the alcohol and when you know when you use di bal not only the ketone will be reduced, but also the acetate will be reductively removed ok. So, you get a sin diol and that was protected as cyclic carbonate once you have sin diol whether you can protect as acetone or you can protect as carbonate ok.

The cyclic carbonate protection was done by treating with carbonyl di-imidazole carbonyl di imidazole is a very good reagent for converting one wo diol into cyclic carbonate then you remove the TBS group ok.

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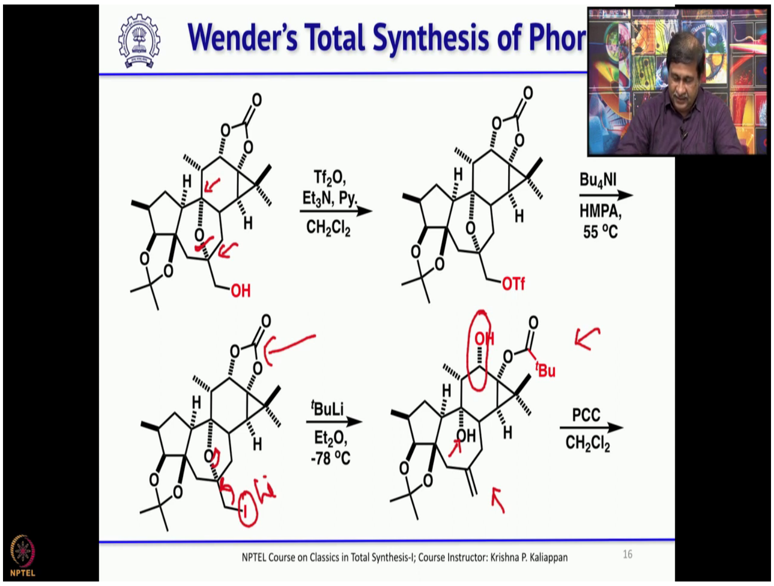

Wender's Total Synthesis of Phor

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Since there is no other silyl protecting group, it is very easy to remove the TBS group with TBAF to get the primary alcohol. Next the major step as I said is to cleave this oxygen bridge because you need a hydroxyl group here ok and also you need a double bond here. So, the hydroxyl group was first converted into triplet then using Fingers stain reaction the triplet was converted into iodide.

So, for opening this oxygen bridge he treated with tertiary butyl lithium. So, the tertiary butyl lithium what will happen? This will exchange with tertiary butyl lithium to form the corresponding litho derivative, then that can open up this bridge to give the exocyclic double bond and the hydroxyl group ok. So, that was the idea, but at the same time what happened?

The tertiary butyl lithium added to the cyclic carbonate also ok it added and he got this ester ok next step the hydroxyl group you need β. So, you have to invert that either one can do ether Mitsunobu reaction or you can oxidize and reduce it. So, Wender followed the second method that is you oxidize the secondary alcohol with PCC to get the ketone then you reduce with bulky reagent sodium tri acetoxy borohydride ok.

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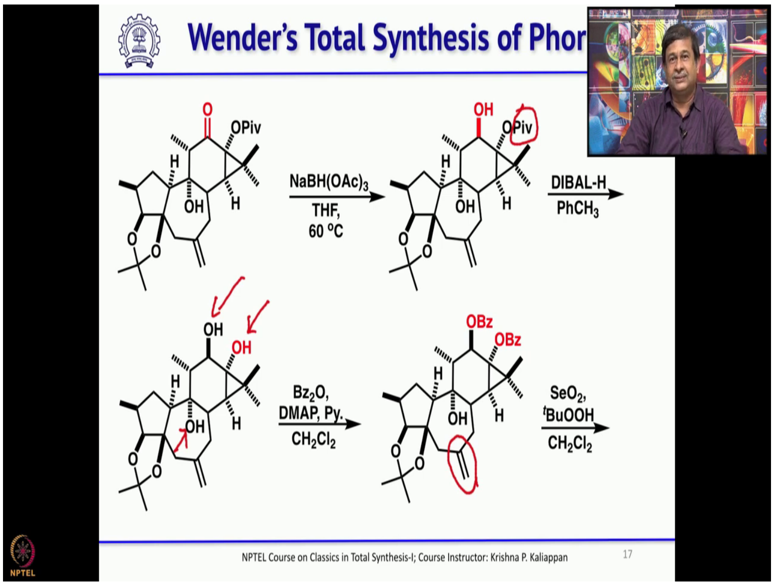

Wender's Total Synthesis of Phor

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So, you get the required β alcohol then reduce with di bal ok reduce with DIBAL again the pivaloyl group group was reductively grieved to get the corresponding the ok. Now both alcohols the secondary and tertiary were protected as benzoate ok were protected as benzoate and this hydroxyl group ok which is sterically little bit crowded was not protected, then this exocyclic double bond this exocyclic double bond first it has to go inside.

So, for that what he did was he did allylic oxidation with selenium dioxide, catalytic amount of selenium dioxide in the presence of more than stoichiometric amount of tertiary butyl hydro peroxide to get the allylic alcohol.

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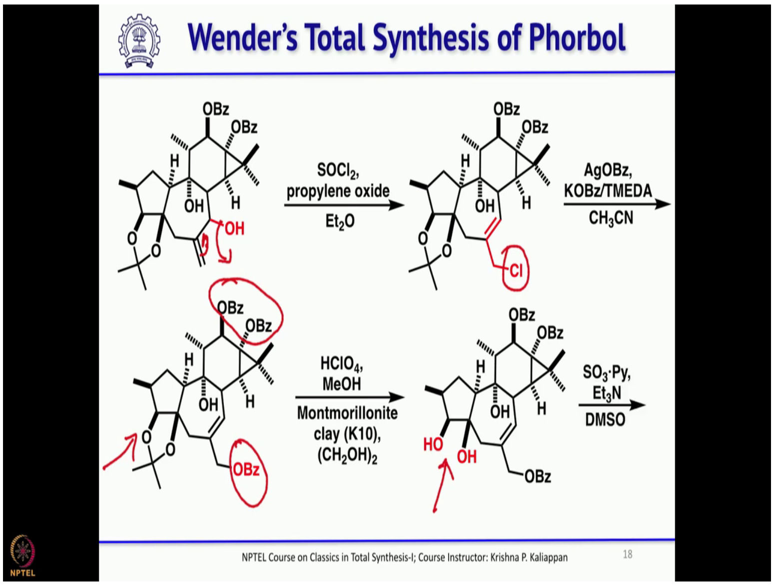

Wender's Total Synthesis of Phorbol

$SOCl_2$, propylene oxide, Et_2O

AgOBz, KOBz/TMEDA, CH_3CN

$HClO_4$, MeOH, Montmorillonite clay (K10), $(CH_2OH)_2$

$SO_3 \cdot Py$, Et_3N, DMSO

Now, the double bond migration oxidative transposition the double bond migration was done by treating with thionyl chloride thionyl chloride and propylene epoxide. So, the double bond migration took place as well as the hydroxyl group was converted into the chlorine ok it is SN_2 phi by h reaction then the chloride was treated with silver benzoate silver benzoate it is a typical SN_2 reaction and the chloride was replaced by O-benzoate.

And again now you have introduced the benzoate here already there are two benzoates. So, what we need to do is after protecting these three hydroxyl group, now we have to remove the acetonid here and oxidize the secondary alcohol keeping the tertiary alcohol. So, the acetonid was cleaved using perchloric acid to get the diol, once you have the diol as you can see here one is secondary alcohol other one is tertiary alcohol.

Secondary alcohol can be easily oxidized. So, what he has done is he has treated with SO_3 pyridine DMSO to get the ketone.

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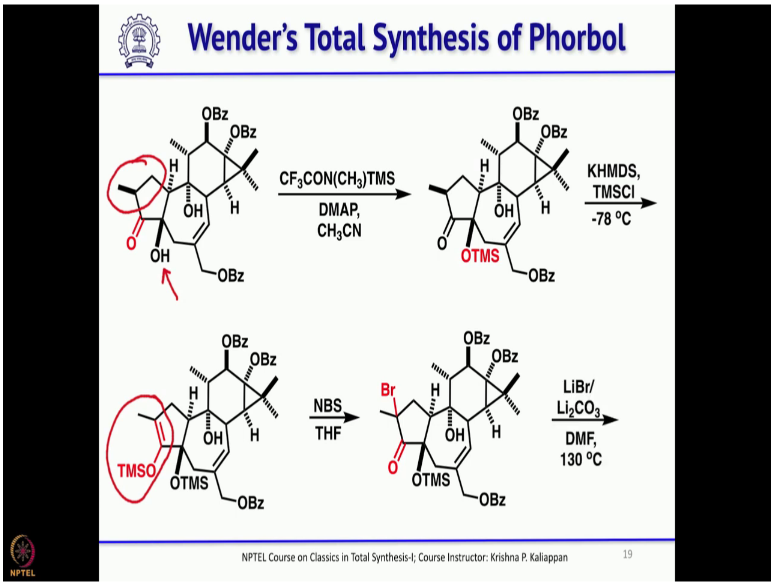

Wender's Total Synthesis of Phorbol

$CF_3CON(CH_3)TMS$, DMAP, CH_3CN

KHMDS, TMSCl, -78 °C

NBS, THF

LiBr/ Li_2CO_3, DMF, 130 °C

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Now the next step is to introduce the double bond here ok. So, for that he has to protect the tertiary alcohol so, that was protected as TMS ether then you generate the enolates ok. So, the enolate was generated and quenched with TMS chloride to get the corresponding enol TMS ether. Once you have the enol TMS ether you can brominate ok if you treat with NBS you get the α bromo ketone.

Once your α bromo ketone then elimination of HBr is possible and that was done with lithium bromide lithium carbonate under high temperature elimination takes place to introduce the double bond ok.

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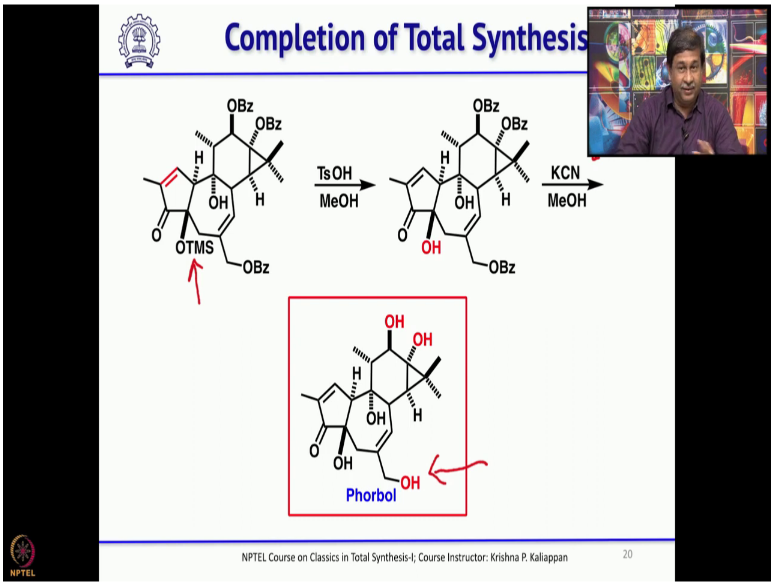

Completion of Total Synthesis

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So, now, if you look at the structure it has almost all the functional groups in correct place. So, what he needs to do? You have to remove the TMS group to the tertiary alcohol then the three benzoates three benzoates should be removed. So, that was done with potassium cyanide and methanol that underwent clean hydrolysis of benzoate to give the phorbol. The phorbol synthesis was one of the classical total synthesis accomplished in 80's.

Once you have this of course, the primary hydroxyl group can be easily treated with various carboxylic acid or functionalized carboxylic acid to form many esters. That is how the structural activity relationship studies on four ball esters were done for medicinal chemistry.

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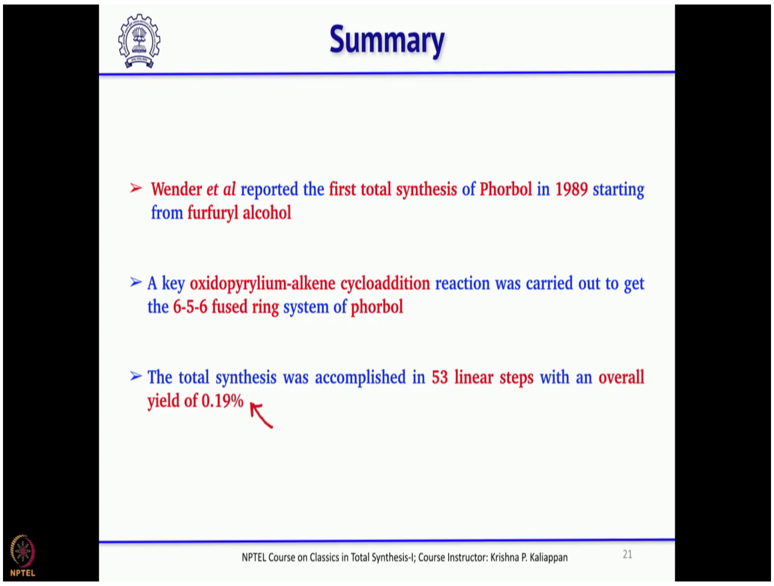

Summary

- Wender *et al* reported the first total synthesis of Phorbol in 1989 starting from furfuryl alcohol
- A key oxidopyrylium-alkene cycloaddition reaction was carried out to get the 6-5-6 fused ring system of phorbol
- The total synthesis was accomplished in 53 linear steps with an overall yield of 0.19%

So, if you look at the total synthesis of Wender. So, he has used a very important key reaction one achmatowicz rearrangement, two the oxide pyrylium alkene cycloaddition ok then he also used a very interesting opening of the oxygen bridge using tertiary butyl lithium.

The number of steps involved in the synthesis of phorbol is reasonably high, but considering the complexity one should understand that it is not easy to accomplish the total sentence of phorbol without taking too many steps. So, the total number of steps involved in the synthesis of phorbol was 53 with an overall yield of point close to 0.2% ok.

Nevertheless, this was the first total synthesis of phorbol and of course, there are other synthesis later and with this we complete the total synthesis of some complex natural products we will continue our discussion on synthesis of some more complex natural products in the next few lectures ok.

Thank you.