Classics in Total Synthesis-I
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Lecture - 57
Vineomycinone B2

So, good morning. And, welcome back to NPTEL lecture series on Classics in Total Synthesis. So, today, we will talk about a natural product which is highly substituted anthraquinone as core structure. So, that natural product is called Vineomycinone B_2 Methyl Ester.

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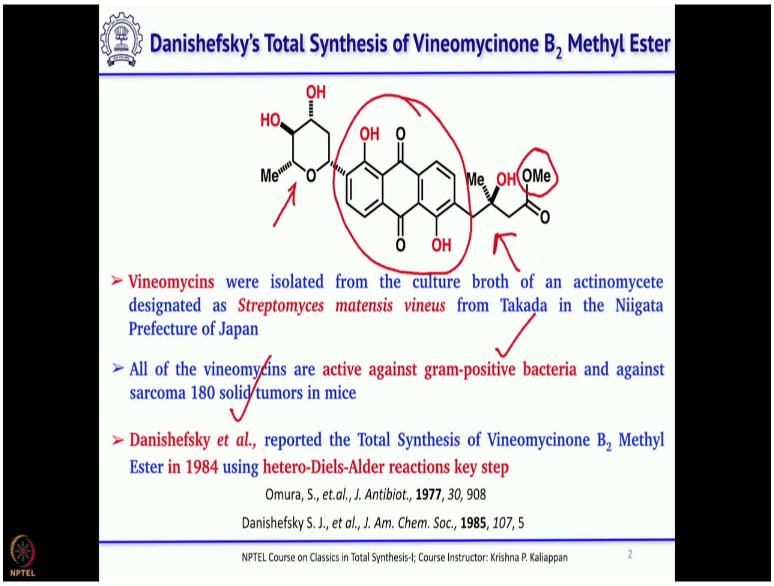

Danishefsky's Total Synthesis of Vineomycinone B_2 Methyl Ester

- Vineomycins were isolated from the culture broth of an actinomycete designated as *Streptomyces matensis vineus* from Takada in the Niigata Prefecture of Japan
- All of the vineomycins are active against gram-positive bacteria and against sarcoma 180 solid tumors in mice
- Danishefsky *et al.,* reported the Total Synthesis of Vineomycinone B_2 Methyl Ester in 1984 using hetero-Diels-Alder reactions key step

Omura, S., *et.al., J. Antibiot.,* **1977**, *30,* 908

Danishefsky S. J., *et al., J. Am. Chem. Soc.,* **1985**, *107*, 5

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Actually, this vineomycins have this common this dihydroxyanthraquinone as the core structure. There are quite a few vineomycins. But, today, what we are going to do is we are going to talk about a couple of total synthesis of this vineomycinone methyl esters. We can see this is there is a methyl ester. So, that is why it is called vineomycinone methyl ester.

So, all the vineomycins show exceptional activity against gram-positive bacteria and also against some tumours in mice. The two synthesis which we are going to talk about, today are from Danishefsky group and Tius group. Danishefsky synthesis used a very interesting hetero-Diels-Alder reaction to construct this dihydropyran ring and they also used a Claisen rearrangement to introduce the side chain on the right-hand side.

In addition, they also used a Diels-Alder reaction to construct the anthraquinone moiety. Let us see, how Danishefsky's group use these key reactions to complete the total synthesis of vineomycinone B_2 methyl ester.

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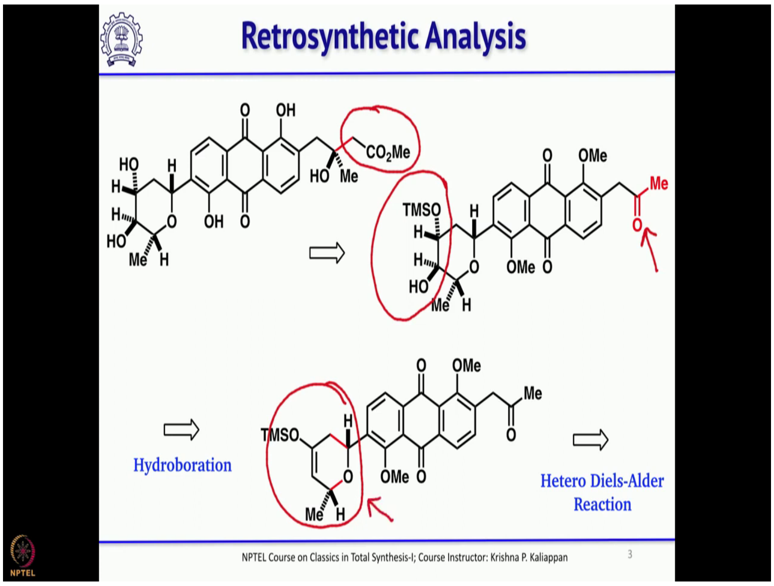

Retrosynthetic Analysis

Hydroboration

Hetero Diels-Alder Reaction

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First let us look at the retrosynthesis. So, they made this vineomycinone methyl ester from this methyl ketone using a Reformatsky type reaction. So, you one can easily see this CH 2 CO 2 Me group can be added to this methyl ketone via Reformatsky reaction. And, this, methyl ketone, if you look at carefully on the left-hand side that is this dihydropyran, ok.

So, this was converted into the di hydroxyl group here using hydroboration, ok. Hydroboration oxidation already there is a enol TMS, one more hydroxyl group was introduced using hydroboration oxidation.

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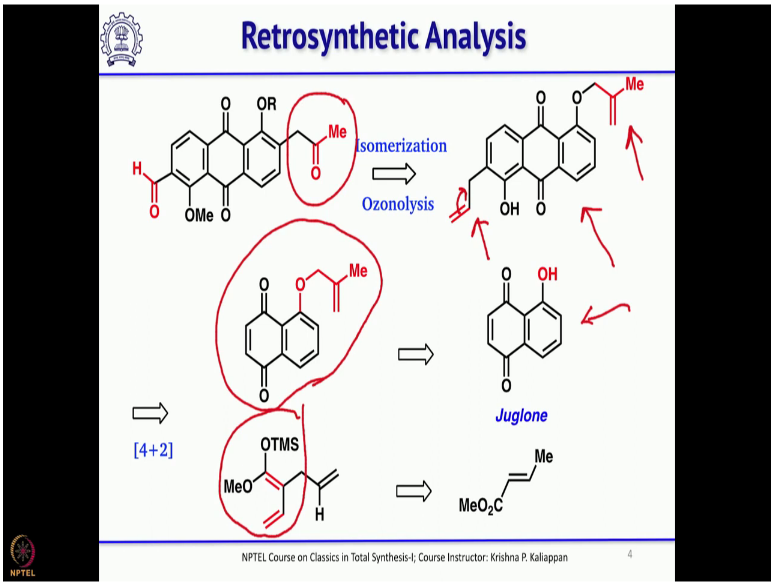

Retrosynthetic Analysis

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And as I mentioned, this particular dihydropyran unit was made through hetero Diels-Alder reaction, ok. You start with that aldehyde and then you do a Diels-Alder reaction with Danishefsky’s diene you get corresponding dihydropyran, ok. And this aldehyde can be obtained from this allyl group by isomerization of this double bond, ok. Once you isomerise the double bond it goes to the internal alkene which upon ozonolysis will give corresponding aldehyde.

And, if you look at this compound you can see here this also upon Claisen rearrangement followed by ozonolysis you can get this methyl ketone, ok. So, 3, 4 steps involved in this reaction in this particular transformation. And, this can be obtained again. So, this is the diene, ok this is the diene and this substituted naphthoquinone is the dienophile they can undergo an inter molecular Diels-Alder reaction and followed by aromatization to give is substituted anthraquinone, ok.

And, that can be obtained from commercially available natural product called juglone, ok.

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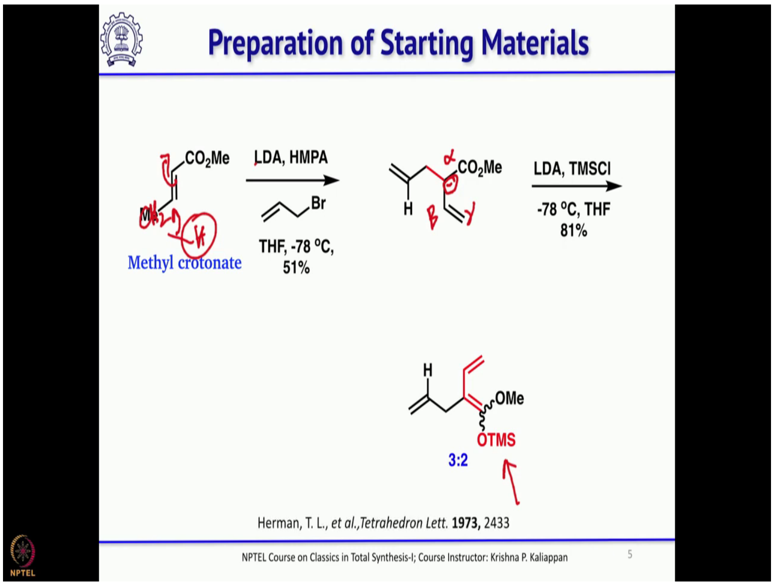

Preparation of Starting Materials

Herman, T. L., *et al.*, *Tetrahedron Lett.* **1973,** 2433

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Now, let us see how the forward synthesis took place. So, he started with again commercially available methyl crotonate. Now, if you treat with LDA if you treat with LDA, what will happen? This, CH_2, this will be picked up LDA will pick up this proton and it can generate anion here and that place one can quench with allyl bromide, ok. So, it picks up the γ proton and then quenching with allyl bromide at α position. So, that will give this α, β, γ.

So, β–γ unsaturated ester. This ester, as you can see this proton is still acidic is not it? So, you can generate anion and quench with TMS chloride. So, that will give you the corresponding starting diene which is required for Diels-Alder reaction with juglone, ok.

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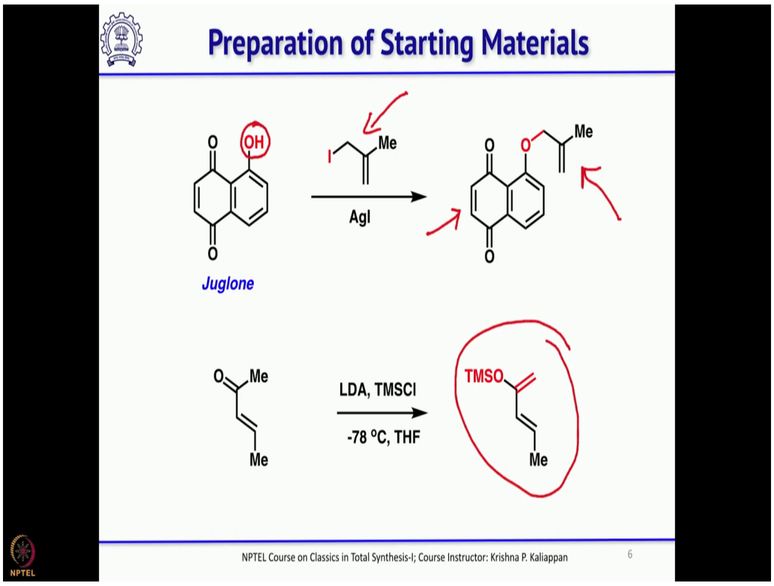

Preparation of Starting Materials

Juglone

AgI

LDA, TMSCl

-78 °C, THF

So, once this is made, then the juglone which is required for Diels-Alder was deprotonated that phenolic hydroxyl group was deprotonated and quenched with this allyl iodide to get the precursor not only for the Diels-Alder reaction. Because, as you can see this is the quinine moiety which can undergo Diels-Alder reaction and here this allyl ether which can undergo the intramolecular Claisen rearrangement.

The other starting material that is Danishefsky's diene was prepared from this enone using LDA and TMS chloride.

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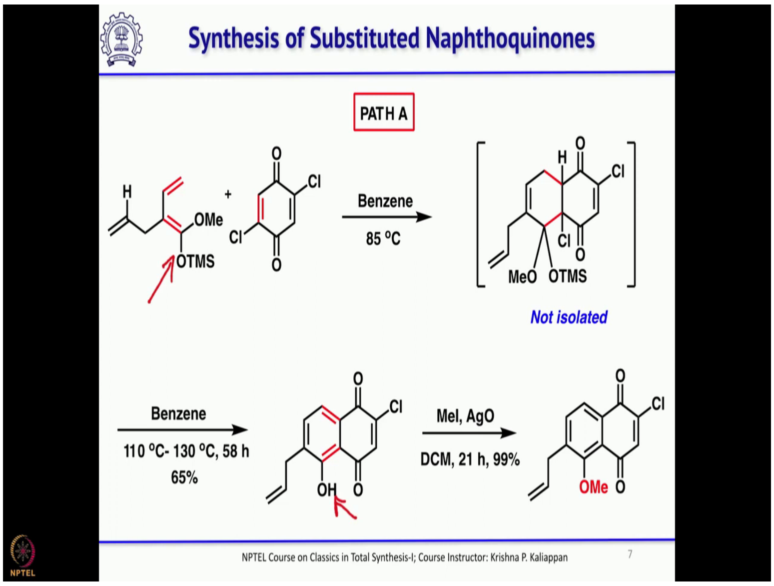

Synthesis of Substituted Naphthoquinones

PATH A

Benzene

85 °C

Not isolated

Benzene

110 °C- 130 °C, 58 h

65%

MeI, AgO

DCM, 21 h, 99%

Now, let us see how the Diels-Alder reaction worked. So, first we started with this diene which was prepared from methyl crotonate and Diels-Alder reaction with 2, 5-dichloro benzoquinone 2, 5-dichloro benzoquinone. Gave this intermediate, of course, this is unstable. So, it was not isolated it underwent elimination of HCl also methanol to give this hydroxy naphthoquinone, ok.

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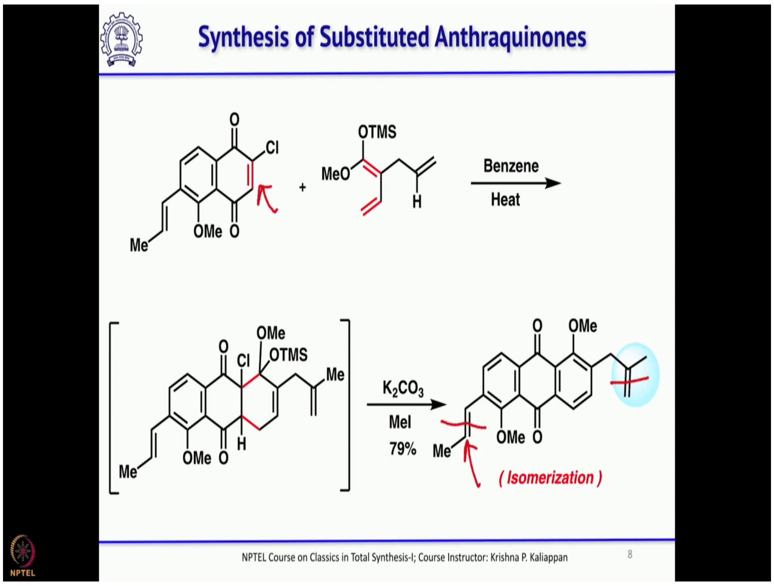

Synthesis of Substituted Anthraquinones

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Then the free hydroxyl was methylated, ok the free hydroxyl was methylated followed by isomerization of the double bond. That allele group was isomerized using Wilkinson catalyst. Then, the next Diels-Alder reaction was done on this chloro-naphthoquinone, ok. So, that gave this intermediate which was subsequently aromatized to give this compound, ok.

Now, you can see here, you have the double bond which can be ozonized to get aldehyde and here also you can get this ketone, ok. So, this is one way they prepared the key anthraquinone.

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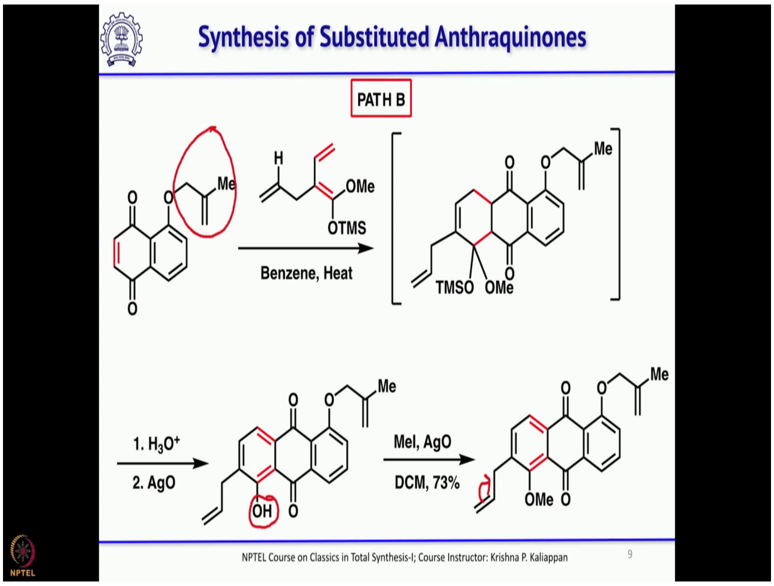

Synthesis of Substituted Anthraquinones

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They also used another method to prepare the same intermediate where they started from juglone, which I already mentioned. And, they allylated with this allyl bromide substituted allyl bromide. Then, Diels-Alder reaction with this diene followed by aromatization he could get this compound. Now, you methylate this phenolic hydroxyl group and what you need is to isomerize the double bond to internal alkene.

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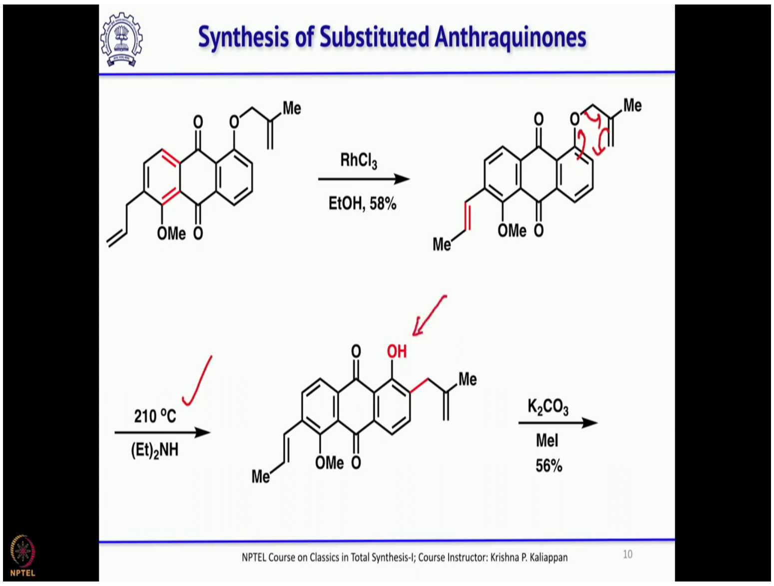

Synthesis of Substituted Anthraquinones

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So, that was done again with rhodium chloride. You can isolate the double bond. So, you can isomerize the double bond and then when you heat it at 200 degrees, then the Claisen rearrangement takes place. So, that migrates the allyl group to *ortho* position.

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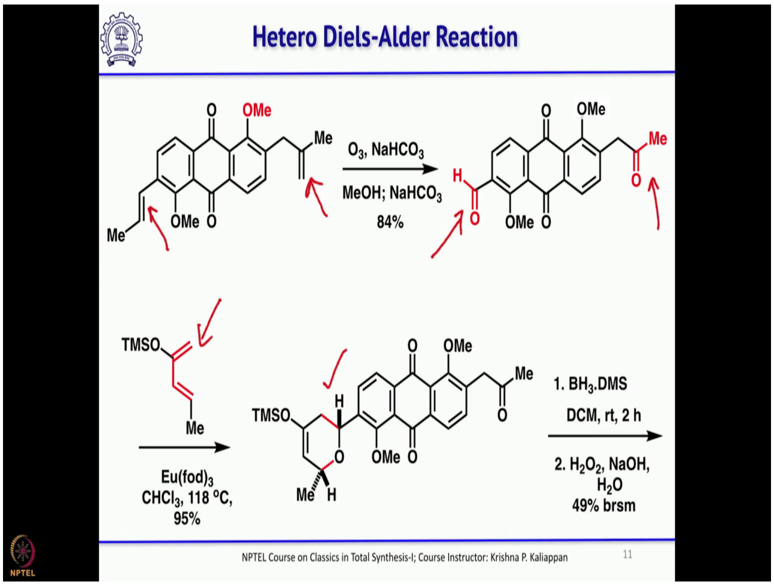
Hetero Diels-Alder Reaction

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Then, you can methyl this phenolic hydroxyl group as well and followed by ozonolysis you get this side ketone this upon ozonolysis will get ketone and this side you will get aldehyde, ok. This is a highly substituted anthraquinone moity which is the core unit of vineomycinone B_2. So, what needs to be done is one has to do a hetero-Diels-Alder reaction on the aldehyde on the left-hand side and then one has to add the $-CH_2-CO_2Me$ through Reformatsky type reaction, ok.

So, he carried out the hetero-Diels-Alder reaction with this diene, followed by you know isolation when he did the Diels-Alder reaction with this diene you could get this dihydrofuran which upon hydroboration, ok.

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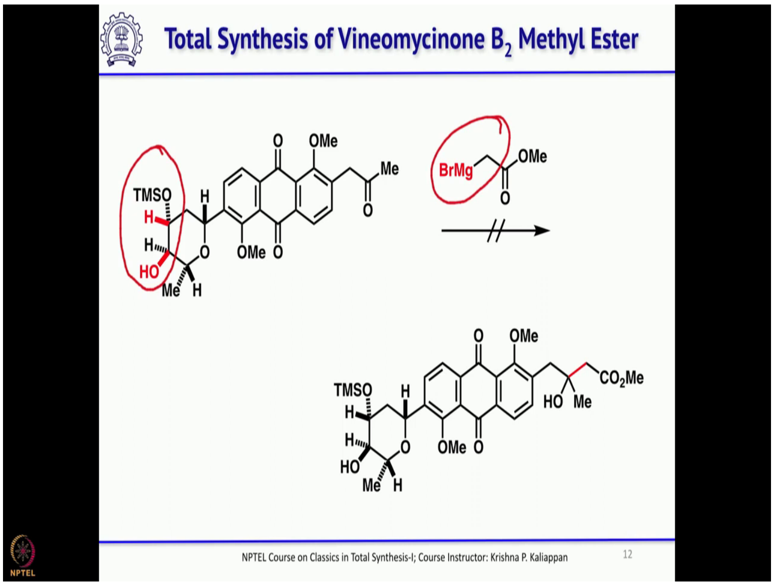

Total Synthesis of Vineomycinone B$_2$ Methyl Ester

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Which upon hydroboration followed by oxidation with hydrogen peroxide and sodium hydroxide you can see the required diol was obtained, ok So, now the diol is there. Next is to carry out the corresponding Grignard reagent. So, the Grignard reagent did not work. Actually, original plan was to carry out Reformatsky reaction. So, here he tried this the α-bromo methyl acetate and form the Grignard and this reaction did not go.

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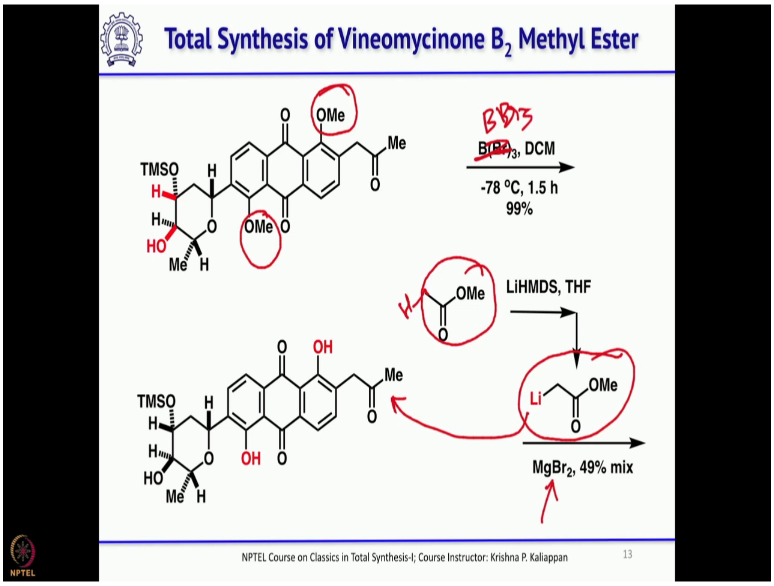

Total Synthesis of Vineomycinone B$_2$ Methyl Ester

BBr3

BBr$_3$, DCM

-78 °C, 1.5 h

99%

LiHMDS, THF

MgBr$_2$, 49% mix

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So instead, so, what he did? So, they removed both methoxy group, ok they removed both methoxy group with BBr$_3$; with BBr$_3$ both methoxy were removed then, from methyl acetate this proton was deprotonated using lithium hexamethyldisilazide, that litho derivative was added to the ketone, ok. And, of course, to facilitate that magnesium bromide diethyl ether also was added.

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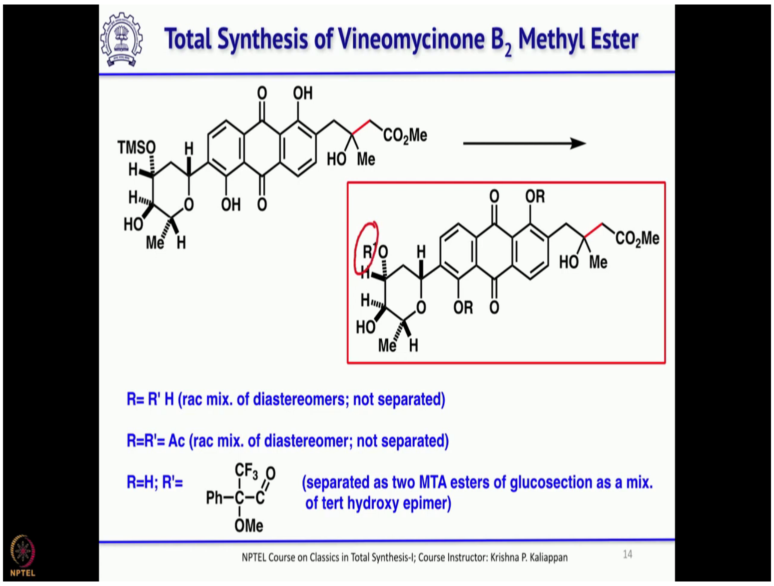

Total Synthesis of Vineomycinone B_2 Methyl Ester

R= R' H (rac mix. of diastereomers; not separated)

R=R'= Ac (rac mix. of diastereomer; not separated)

R=H; R'= $Ph-C(CF_3)(OMe)-C(=O)$ (separated as two MTA esters of glucosection as a mix. of tert hydroxy epimer)

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So, now this reaction worked very well. And, that was converted into corresponding vineomycinone B_2 methyl ester after removing the TMS, ok.

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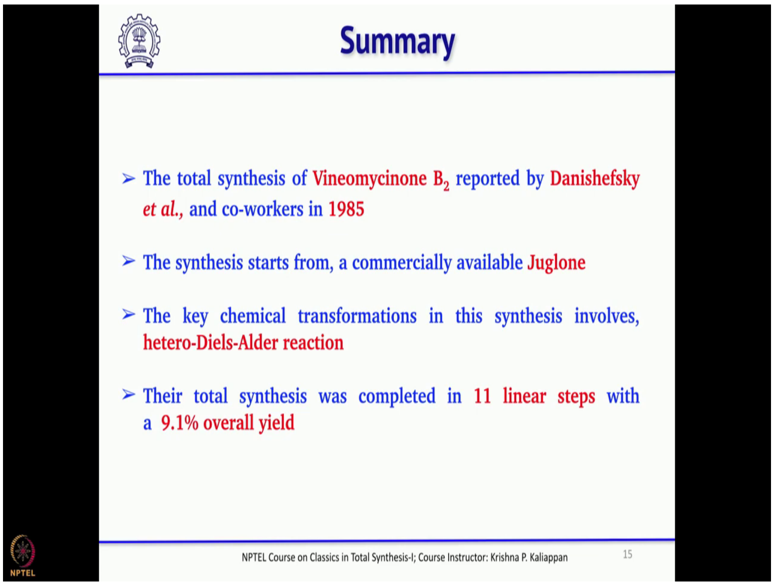

Summary

- The total synthesis of Vineomycinone B_2 reported by Danishefsky *et al.*, and co-workers in 1985
- The synthesis starts from, a commercially available Juglone
- The key chemical transformations in this synthesis involves, hetero-Diels-Alder reaction
- Their total synthesis was completed in 11 linear steps with a 9.1% overall yield

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So, that is how this total synthesis was accomplished and it started from commercially available natural product called juglone and it involved hetero-Diels-Alder reaction, normal Diels-Alder reaction, Claisen rearrangement as key reactions to synthesise this compound. Overall, he took about 11 longest linear steps with a yield of 9%, ok. So, 9% overall yield is a very good strategy.

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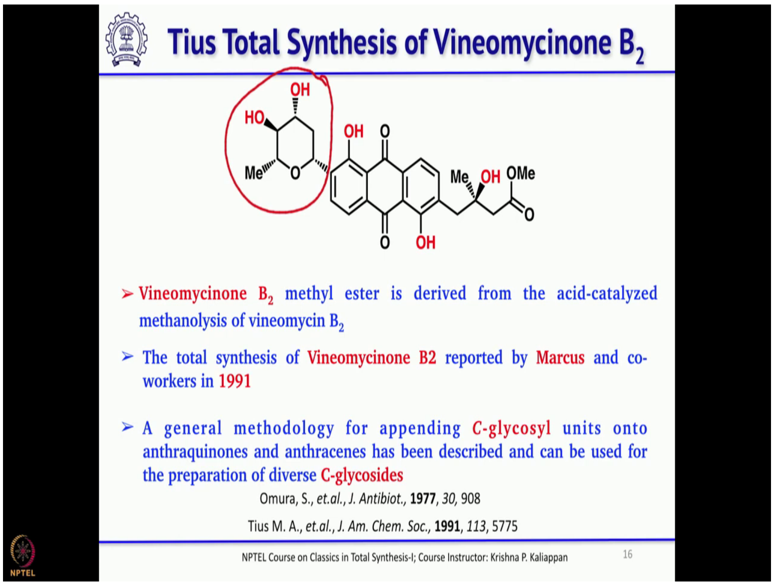

Tius Total Synthesis of Vineomycinone B_2

- Vineomycinone B_2 methyl ester is derived from the acid-catalyzed methanolysis of vineomycin B_2
- The total synthesis of Vineomycinone B2 reported by Marcus and co-workers in 1991
- A general methodology for appending *C*-glycosyl units onto anthraquinones and anthracenes has been described and can be used for the preparation of diverse C-glycosides

Omura, S., *et.al., J. Antibiot.*, **1977**, *30*, 908

Tius M. A., *et.al., J. Am. Chem. Soc.*, **1991**, *113*, 5775

And, now, let us see the second total synthesis which is chiral one and this was reported by Marcus Tius. So, he the left-hand side glycol pot he started from D-gulcol, ok. So, d-glucol was you know key starting material to introduce the chiral center, ok.

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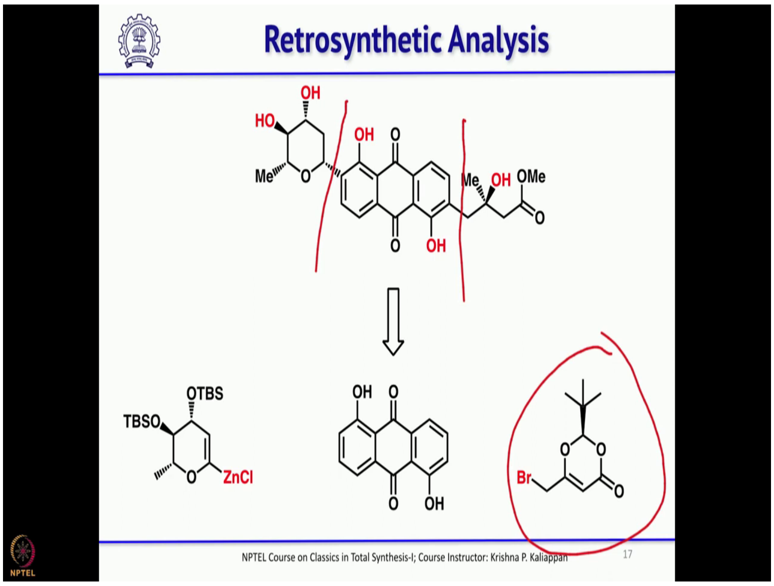

Retrosynthetic Analysis

And according to him, it and this vineomycinone can be easily disconnected into three fragments. So, this is one fragment and then middle the dihydroxy anthraquinone is the second fragment and the third fragment comes from this intermediate, ok. These are the three fragments you could easily disconnect, very logical.

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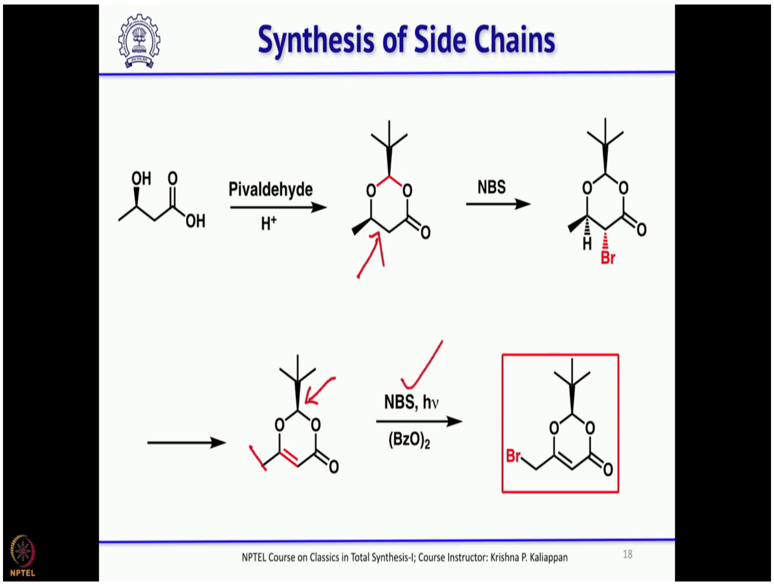

Synthesis of Side Chains

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Now, let us see how he made these three fragments and then combined all. He started with β hydroxy carboxylic acid; this upon treatment with pivaldehyde in the presence of acid, it gave this protected compound, ok. Now, he wanted to introduce a double bond here.

So, that was done first bromination, followed by elimination, he got the double bond and still you can see there is one stereocenter, then the allylic bromination was carried out with NBS under photochemical condition. So, one side chain is already prepared.

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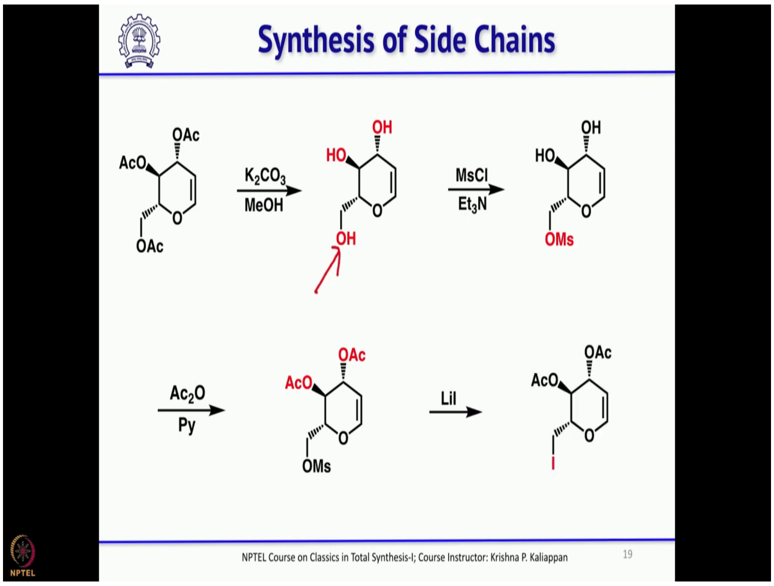

Synthesis of Side Chains

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The second side chain he started with D-glucol, ok the triacetate was hydrolyzed to get the triol, then the primary alcohol was mesylated, then both the secondary alcohols were acetylate, ok. The mesylate upon treatment with lithium iodide, the mesylate is converted into the corresponding iodide.

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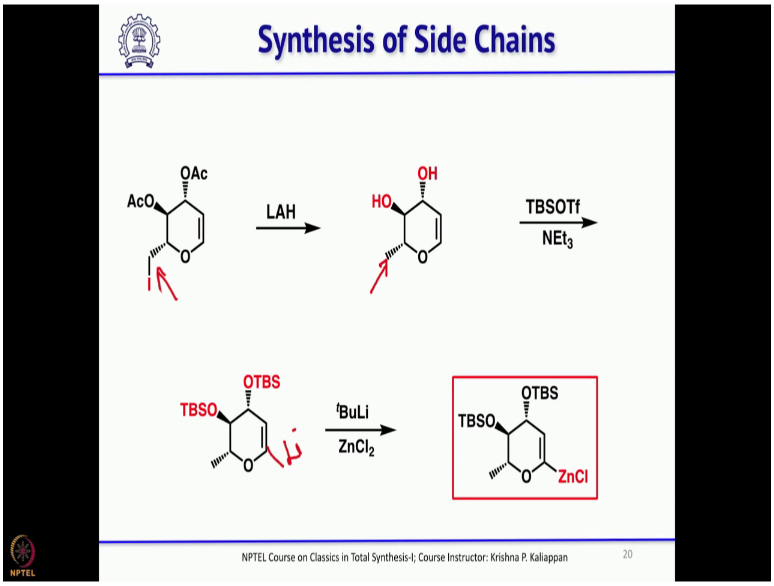

Synthesis of Side Chains

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Now, upon treatment with LAH, so this iodide will be displaced by hydride and ester also will be reductively removed. So, you basically what you have done is from the d-glucol the -CH_2OH is converted into -CH_3, ok. And, both the hydroxyl groups were protected as TBS ethers. Then treatment with butyl lithium, tertiary butyl lithium one can generate, anion here and that was exchanged with zinc for the Negishi type coupling, ok.

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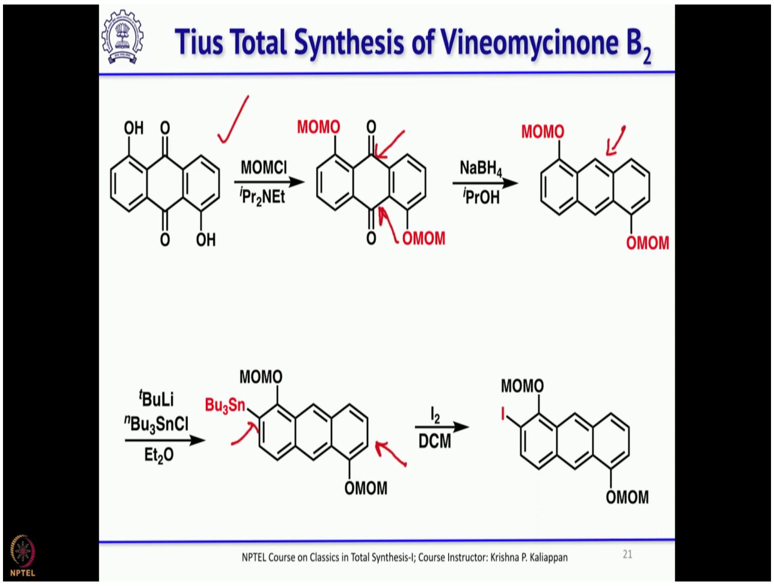

Tius Total Synthesis of Vineomycinone B_2

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Then, for the middle portion, this is a commercially available di hydroxy anthraquinone. Take this and protect both hydroxyl groups as MOM ether, ok. Then reduce this two ketones reduce these two ketones with sodium borohydride isopropanol completely to get the corresponding aromatic one, ok from anthraquinone that is dihydroxy anthraquinone, what we have done is dihydroxy protected anthracene, ok. So, then it is a symmetrical compound.

So, treatment with tert-butyl lithium, either it can generate here or here does not matter both are same, then exchange it with tributyl tin chloride, ok. So, then you exchange that with iodine, ok the tributyl tin can be easily exchanged with iodine by treatment with iodine.

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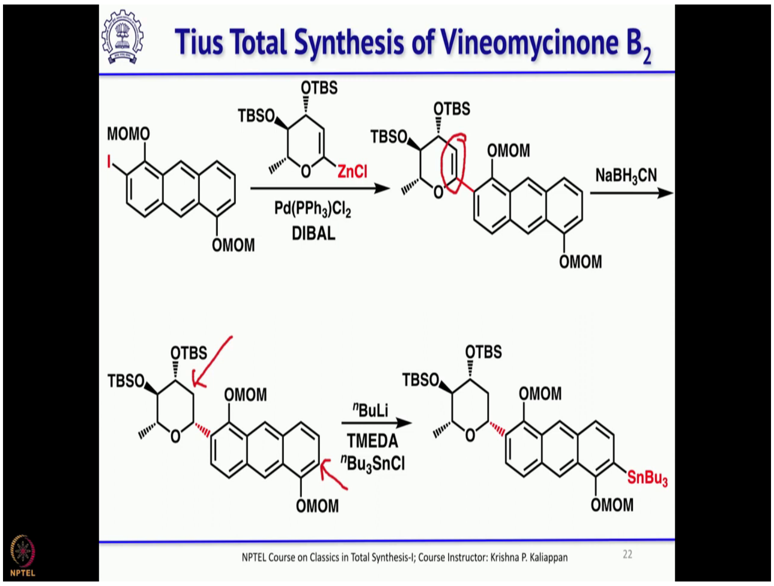

Tius Total Synthesis of Vineomycinone B$_2$

So, this side you have iodine and that side you have zinc. So, then do the key Negishi coupling to get or introduce the C-C bond, ok. Then, this sodium cyanoborohydride will reduce this enol ether, ok the sodium cyanoborohydride will reduce the enol ether stereo selectively to get exact tetrahedron pyran unit with all stereo centres fixed.

Now, what is left? As you know, you have to introduce a tin group here and then attach the CH$_2$ side chain, ok. So, first introduce the tin by treating with n-butyl lithium and then try quenching with tributyl tin chloride.

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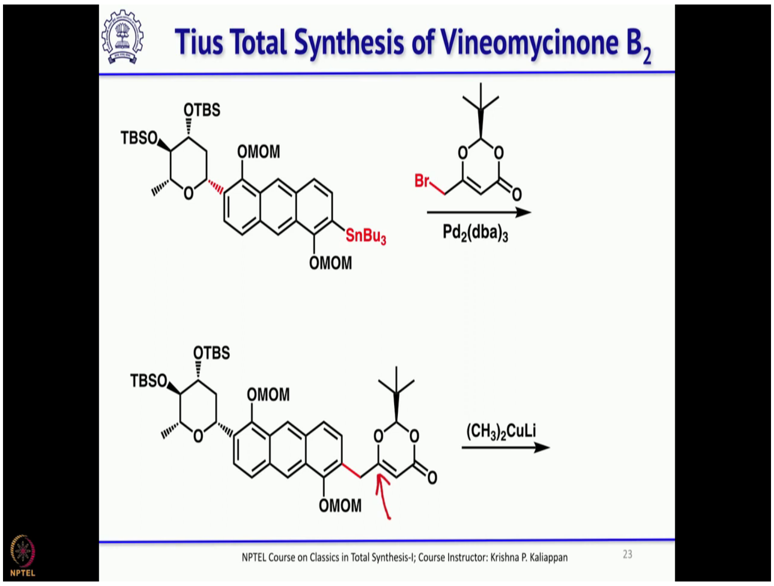

Tius Total Synthesis of Vineomycinone B$_2$

And this upon coupling again, this time it is like still a coupling. So, that gives the corresponding side right-hand side chain, ok. So, if you look at this what is missing is a methyl group at this carbon. But you have enone. So, one can easily introduce a methyl group using Gilman's reagent.

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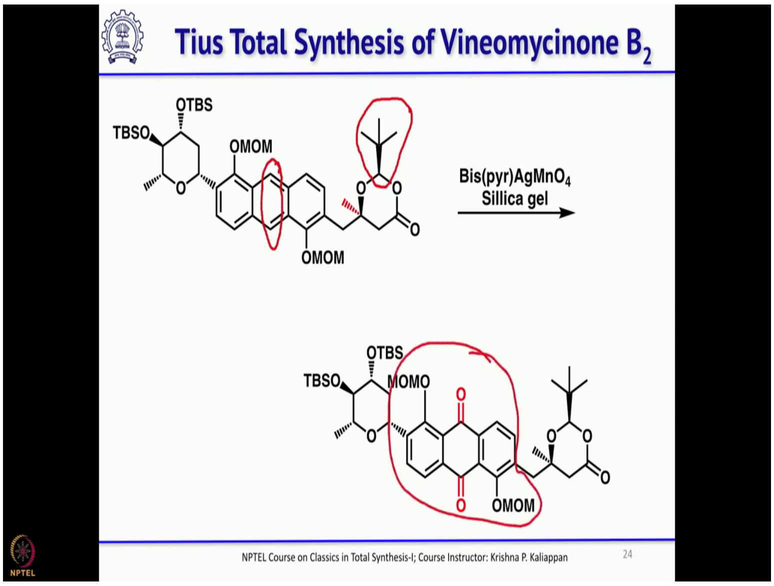

Tius Total Synthesis of Vineomycinone B_2

Bis(pyr)$AgMnO_4$
Sillica gel

So, that is what he did. That methyl 1, 4-addition took place highly stereo selectively because of the presence of the tertiary butyl group, ok. Then, what needs to be done? If you look at this middle ring of this anthracene and the natural product it is anthraquinone that mean this diene should be oxidized to diketone. So, that was done to get the corresponding di substituted anthraquinone, ok.

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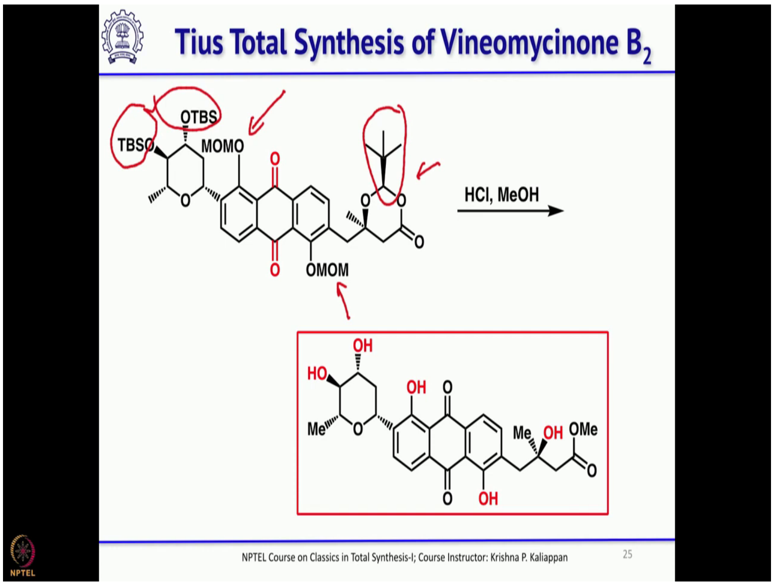

Tius Total Synthesis of Vineomycinone B_2

So, what is left? You have to remove this tertiary butyl group, you have to remove both MOM’s and you have to remove both TBS group. So, if you treat with HCl. So, this will remove and then you also will get methyl ester MOM group will go and also TBS group will go. So, it is a complete global deprotection followed by esterification. All were done in 1 step to complete the asymmetric total synthesis of vineomycinone B 2.

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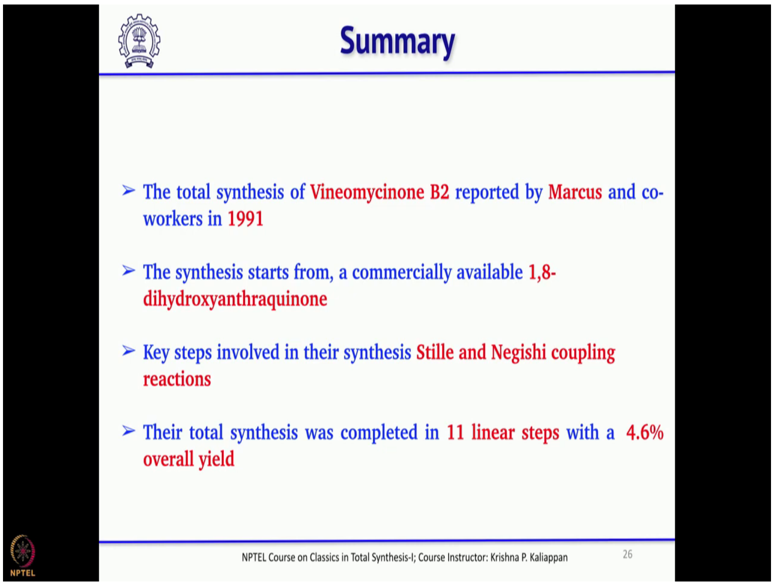

Summary

- The total synthesis of Vineomycinone B2 reported by Marcus and co-workers in 1991
- The synthesis starts from, a commercially available 1,8-dihydroxyanthraquinone
- Key steps involved in their synthesis Stille and Negishi coupling reactions
- Their total synthesis was completed in 11 linear steps with a 4.6% overall yield

So, in summary the Marcus Tuis and his co-workers completed the total synthesis of vineomycinone B_2 in the early 90s and they started with commercially available 1,8-

dihydroxyanthraquinone and also D-glucol on the left side and the other side they started with β hydroxy carboxylic acid which is also commercially available, ok.

There are two key reactions which they used, one Negishi coupling on the left-hand side and Stille coupling on the right-hand side. And, the last to introduce a chiral center on the right-hand side side chain they used Gilman reagent to introduce the quaternary center, ok.

So, they took about 11 steps and overall yield was 4.6 %. Considering the complexity of the molecule and also the first asymmetric total synthesis this is a significant achievement, ok. So, I will stop here and then we will continue our discussion with one more natural product and complete the syllabus of this particular course. So, we will discuss tomorrow about the total synthesis of another complex natural product called zaragozic acid, ok. Until then see you.

Thank you, bye.