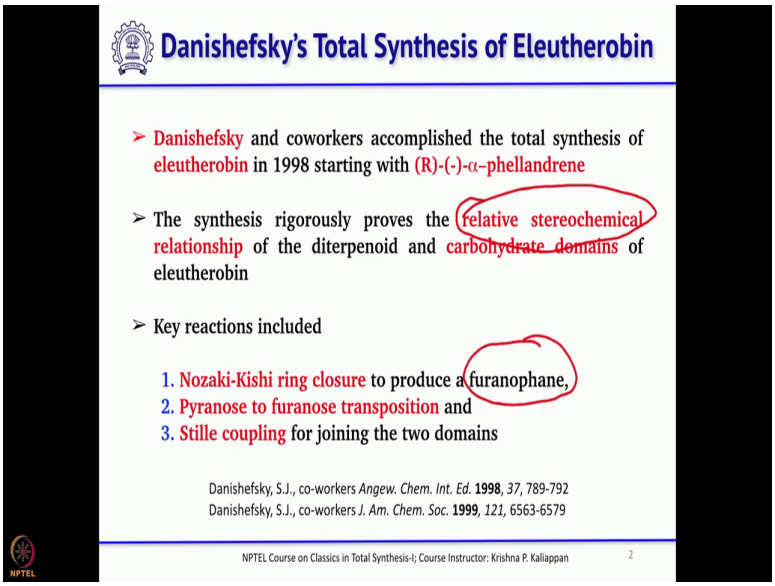
Classics in Total Synthesis-I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 51
Eleutherobin (Danishefsky)

Hi, good morning and welcome back to the course on Classics in Total Synthesis Part - I. And we have been discussing total synthesis of various natural products in the last lecture. We talked about the total synthesis of a marine natural product called Eleutherobin and where we talked about the total synthesis reported by K. C. Nicolaou.

(Refer Slide Time: 00:44)

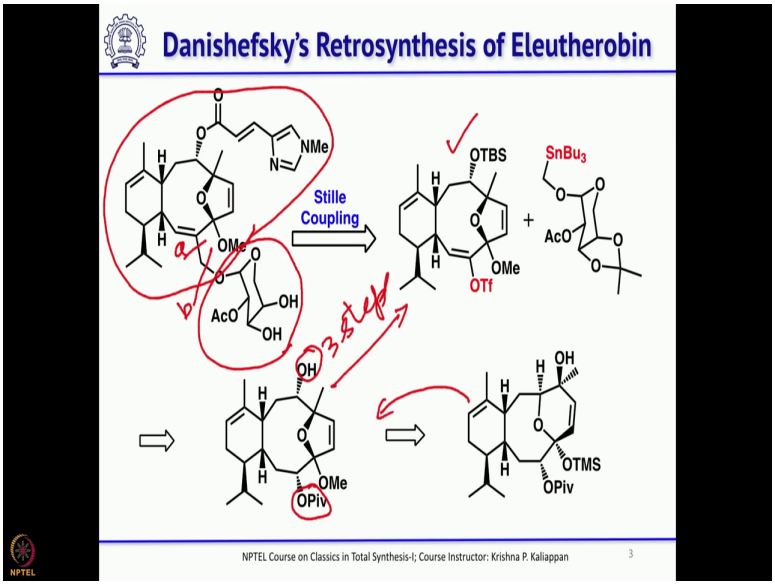


So, today we will talk about another total synthesis, but this time reported by Danishefsky. And in the case of Nicolaou's total synthesis he started with the carbon their monoterpene and here Danishefsky started with another monoterpene called α phellandrene. And his work required you know lot of stereo chemical studies, particularly with respect to carbohydrates. So, that he could prove the correct isomer of the final natural product that is eleutherobin.

And his total synthesis involved three important key reactions - 1 is the Nozaki-Kishi Hiyama ring closure reaction to form the five membered ring, and the 2nd key reaction which is also very interesting rearrangement that is pyranose to furanose and furan to

pyranose ok. So, these two key reactions he had used to first convert the furan ring into pyranose, and then later the pyranose ring was converted into five membered furanose ring. The 3rd key reaction was the Stille coupling between the carbocycle and the carbohydrate moiety to form the core structure of eleutherobin.

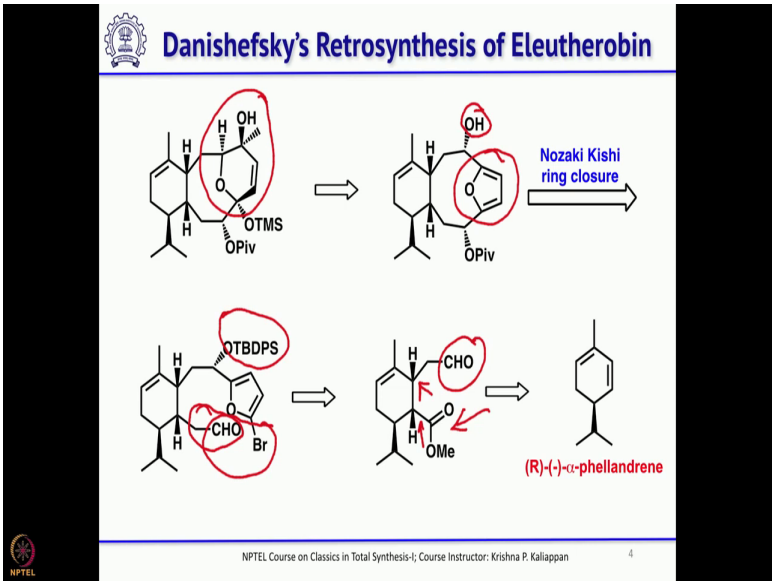
(Refer Slide Time: 02:08)



So, from retrosynthetic point of view as you can see here it is very clear; you have a complete carbocycle and a sugar units ok. So, the easiest way to disconnect is, just you can disconnect either here or here. So, if you are using stille coupling, then the disconnection of bond a is better than disconnection at bond b. So, the Stille coupling disconnection gives Danishefsky, these two fragments. And at the left hand side you have the vinyl triflate and the right hand side you have the tri butyl tin derivative, which is required for the Stille coupling.

So, now, for the synthesis of the carbocyclic derivative that is a tricyclic compound, the triflate can be obtained from this protected alcohol by removal of the pyrolite group, oxidation to ketone and followed by enol triflate formation. One can easily convert this into the required triflate in three steps, after protection of this hydroxyl group. Now, this five membered ring as I said, this is one of the key reactions, where the pyranose form ok; where the pyranose form was converted into furanose form using acidic condition ok.

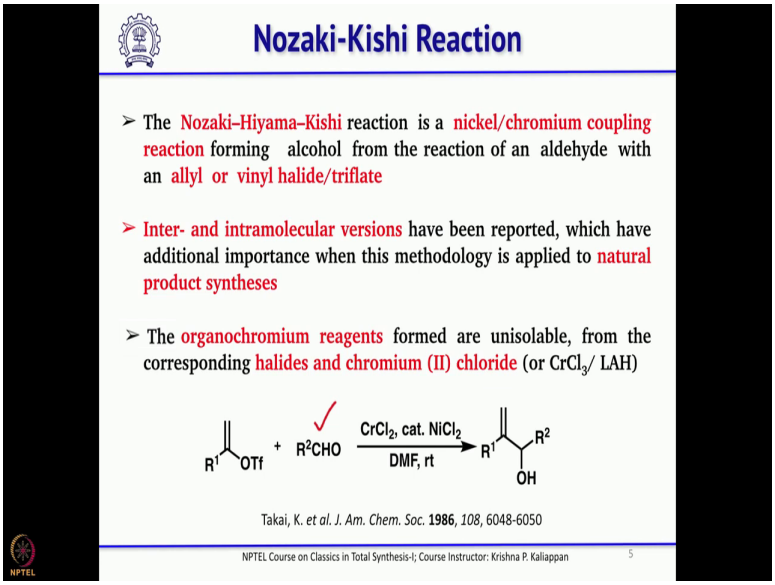
(Refer Slide Time: 03:35)



This pyranose form again was obtained from furan ok. So, here using this hydroxyl group an epoxidation of one of the double bonds of furan followed by the rearrangement, one can easily get this six membered pyranose ring ok. That was the second key reaction and the third key reaction is the intramolecular Nozaki Kishi ring closure reaction between this the bromo-furan and this aldehyde to form the ten membered ring.

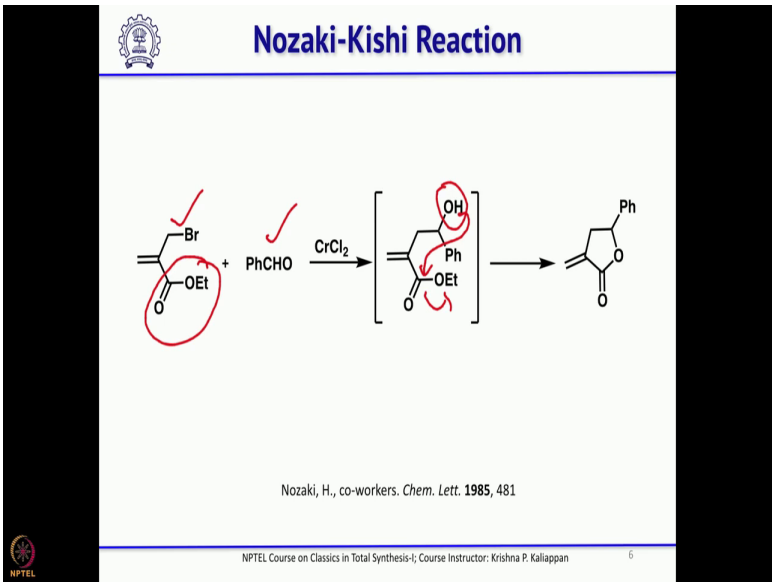
So, now, if you look at this it is very easy, if you have this aldehyde and you can use the lithio bromo-furan addition to this aldehyde to generate this chiral center with OH. And for the southern hemisphere, you need -CH_2CHO that can be obtained from this ester by reduction and homologation ok. So, now, these two substituents, these two substituents on this six membered ring, can be easily introduced from phellandrene. Here commercially available monoterpene using photochemical reaction as the key reaction ok.

(Refer Slide Time: 05:07)



So, as I said there are two key reactions, which he has used. At least I will talk about one key reaction that is Nozaki-Kishi reaction. Nozaki-Kishi reaction is nothing but, if we have a vinyl triflate or vinyl halide and this on treatment with aldehydes in the presence of chromos chloride, you will get an allylic alcohol. This reaction can be done intermolecularly as well as intramolecularly. Basically, if you want an allylic alcohol, so this is one of the very important transformations.

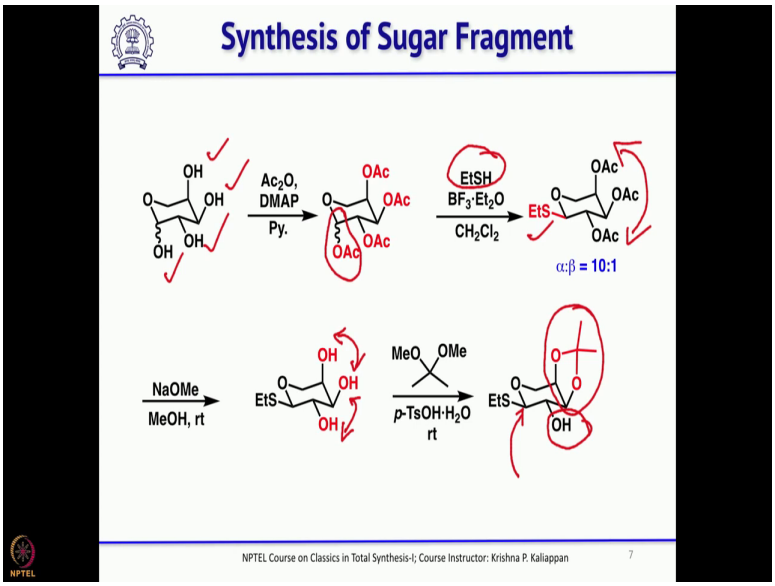
(Refer Slide Time: 05:41)



And one can also get homo allylic alcohol using similar conditions. Here instead of vinyl bromide what you need is an allyl bromide. So, allyl bromide on treatment with aldehyde in the presence of chromos chloride, it gives homo allylic alcohol. And if we have an

ester at appropriate place, then the homo allylic alcohol which is formed can also intramolecularly attack the carbonyl group of the ester forming a lactone ok. So, this Nozaki-Kishi reaction has been widely used for making allylic and homo allylic alcohols and also many macro cycles.

(Refer Slide Time: 06:24)



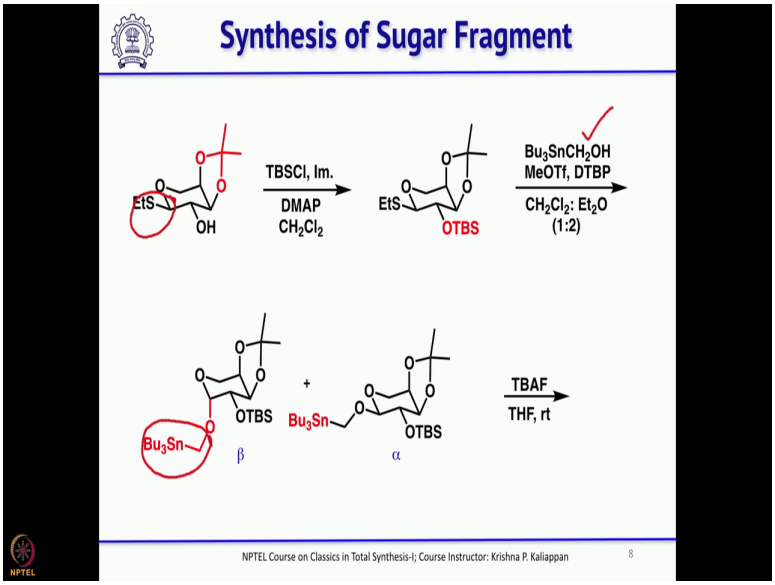
So, now let us see how Danishefsky's group synthesized eleutherobin. And as I said the synthesis of eleutherobin requires synthesis of 2 different fragments. One the carbocyclic A, B, C in fragment, the other one is sugar fragment. So, now, let us start with the synthesis of sugar fragment for which he started with the commercially available D-arabinose and the first step was the per acetylation that is all the hydroxyl groups including the lactal hydroxyl group were acetylated with acetic anhydride and DMAP.

Then this particular anomeric acetoxy group ok; can be easily displaced with ethanethiol under lewis acidic condition and here you can see the α I number is the major isomer ok. So, once you have that then the three acetates ok; three secondary acetates can be easily hydrolyzed by treatment with sodium ethoxide methanol. Now, if you look at this triol, these two hydroxyl groups are *cis* to each other.

And these two are *trans* to each other. So, one can easily protect the *syn* diol to get the corresponding acetonide under standard conditions. Now, what needs to be done is you have to introduce a CH_2O $SnBu_3$ and also protect this hydroxyl group. So, these are the

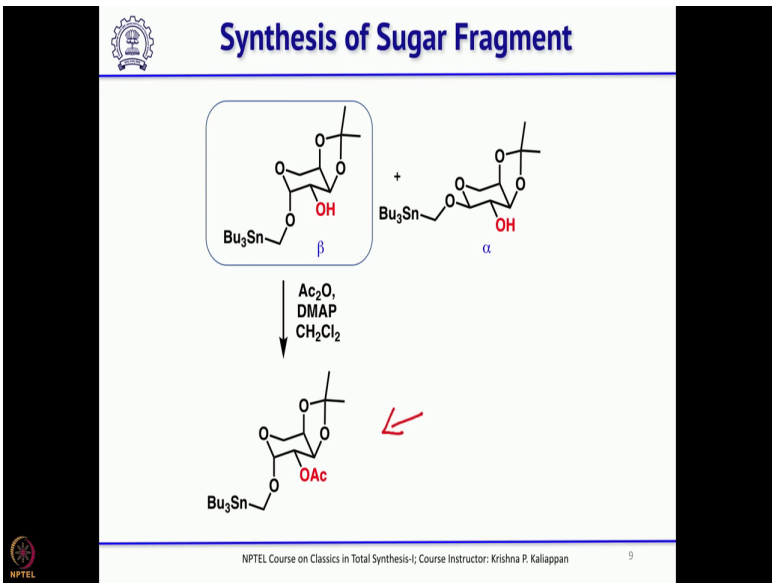
two things left for the synthesis of sugar fragment with tributyl tin group, which is required for Stille coupling.

(Refer Slide Time: 08:11)



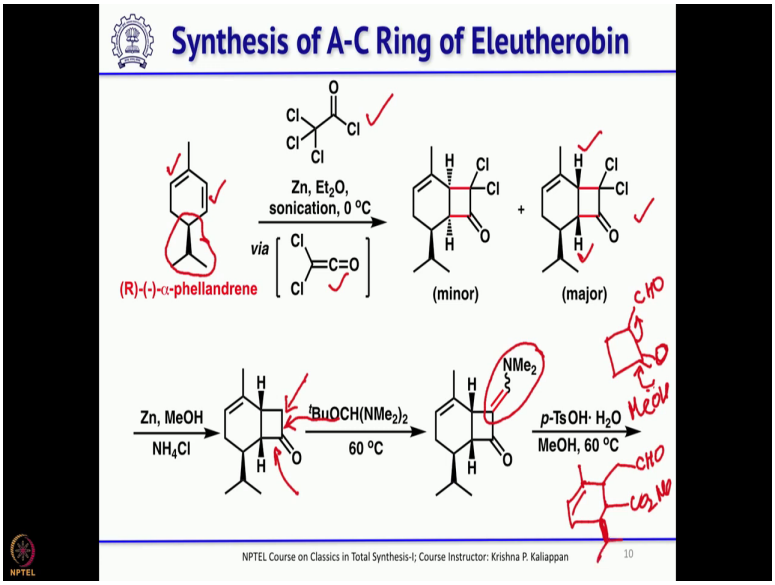
So, you take this free hydroxyl group. Now, protect the hydroxyl group as TBS ether, protect the hydroxyl group as TBS ether. Then treat this anomeric thioether with tributyl tin methanol, tributyl tin methanol in the presence of methyl triflate. So, that gives you the required, you can see CH_2 $SnBu_3$. So, here β isomer is the isomer, which is required for the Stille coupling.

(Refer Slide Time: 08:52)



So, now, removal of that TBS group by fluoride reagents like TBAF will give the hydroxyl and simple acetylation gives you the fragment required for the stille coupling ok. So, now, a synthesize the sugar fragment successfully in few steps starting from D-arabinose. Now, let us look at the synthesis of A B C ring of eleutherobin starting from a chiral monoterpene called phellandrene.

(Refer Slide Time: 09:20)



So, the phellandrene; so, this is the structure of phellandrene. Now, if you look at this structure of phellandrene, there are two double bonds. One is a tri substituted double bond, other one is a disubstituted double bond. And as I mentioned, when I talked about the retrosynthesis, it involves a photochemical reaction. So, it has two double bonds and selectively one of them has to undergo [2+2] cycloaddition reaction.

So, as I said one is tri substituted, other one is disubstituted and between these two for steric reasons, one can selectively carry out photochemical [2+2] cycloaddition reaction with the disubstituted alkene. The other alkene was the dichloroketene. The dichloroketene can be easily obtained by treatment of zinc with trichloroacetylchloride or one can also get it from dichloroacetylchloride with mild bases like triethylamine. So, now, once you do this reaction, what you get is a mixture of two isomers.

And once the dichloroketene is formed, because of the presence of the bulky isopropyl group in β position, this dichloroketene will come only from the α side ok. So, that is how these two hydrogens you can see when it approaches from the α side, these two

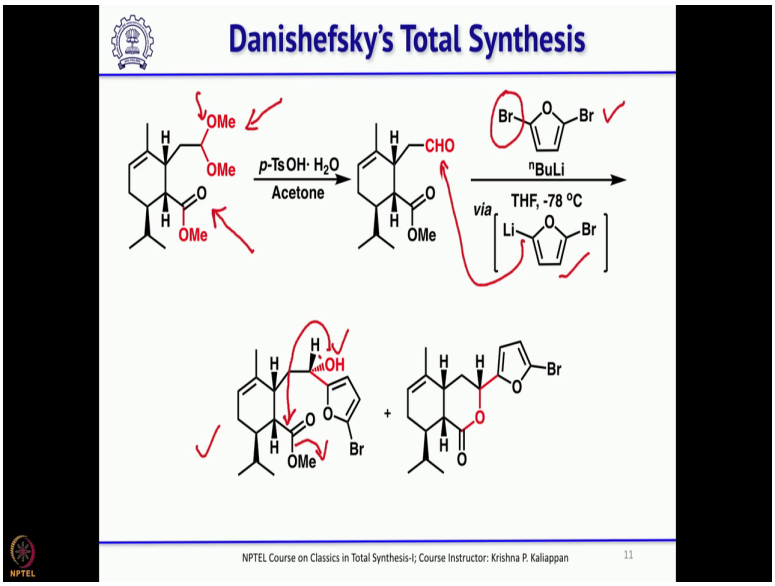
hydrogens will be β. So, this is the major product. Once you have this the two chlorines can be easily exchanged with hydrogen by treatment with zinc methanol.

So, zinc methanol removes the two chlorines. Now, we have to open the cyclobutanone ring ok. So, one way is to introduce a functional group here ok. You can introduce a functional group and open this cyclobutanone, and if you use Baeyer-Villiger oxidation. So, then it will open up here, which is not required we need to open the cyclobutanone at this place.

So, for that it is easy to introduce an aldehyde equivalent ok. If you look at this, so this is an aldehyde equivalent, if you hydrolyze this enamine ok. This is an enamine basically it is a enamine derived from dimethyl formaldehyde, protected dimethyl formaldehyde ok. So, now, this enamine upon hydrolysis with para toluene sulfonic acid, so what will happen? So, you will get first you will get an aldehyde like this ok.

Then under acidic condition under acidic condition that is with methanol, what will happen? The methanol will attack here and open up. So, that will give you the corresponding ester that is you will have this aldehyde and ester ok. You will have this corresponding aldehyde an ester ok.

(Refer Slide Time: 12:22)



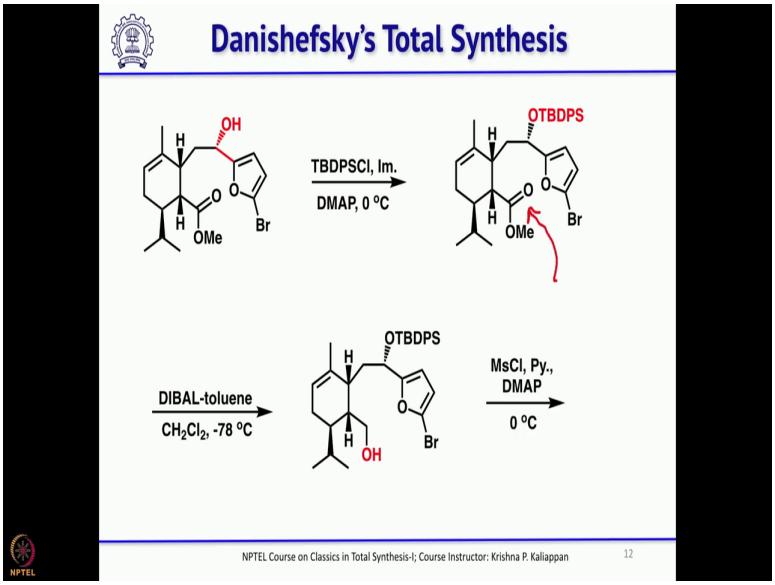
This is the product you get. Is it clear? So, now what you need to do? One you have to add the furan ring to this aldehyde. Now, it is protected aldehyde. Other one you have to

homologate this ester, is not it? What you need is a -CH_2 CHO. Already you have -CH_2 CHO here, but here you have only -CO_2 Me. So, that should be homologous ok. So, first you remove this acetal ok. p-toluene sulfonic acid and water, you remove the acetal you get the aldehyde.

Now, once you have the aldehyde take this 2, 5 di bromofuran this on treatment with butyl lithium. So, one of the bromines will be exchanged with lithium to get the corresponding lithio species. This furan lithium that is bromo furan lithium will add to this aldehyde. So, you have aldehyde and ester and as you know aldehyde is more reactive than ester.

So, once it adds to the aldehyde. So, what you get is a mixture of this alcohol, which is as a result of direct addition of this lithio species to the aldehyde and the second product is nothing but, this alcohol attacking the ester carbonyl and forming the six membered lactol ok. See these are the two products and the major product is this alcohol ok. So, now, you have the alcohol.

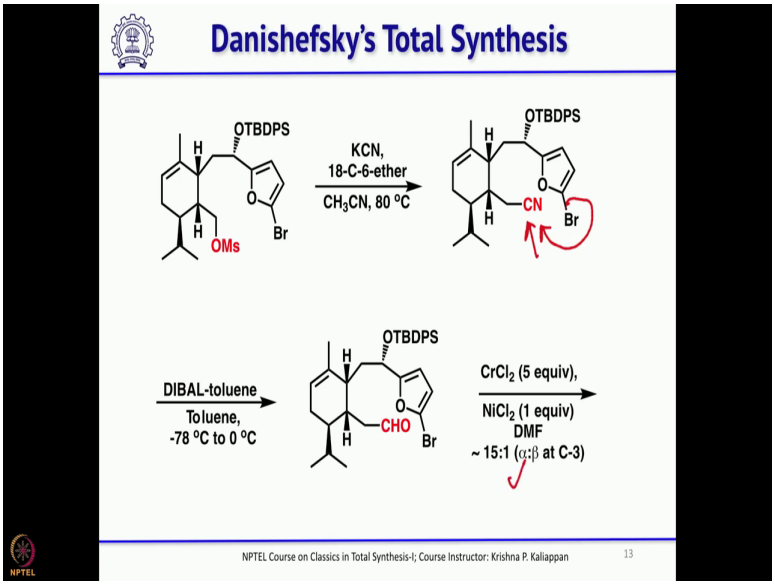
(Refer Slide Time: 13:59)



Next step is to protect the alcohol. So, the alcohol could be protected as TBDPS ether and the standard condition. Then, now you need to homologate this ester ok. How do you do? Ok, you have to first reduce then that -CH_2 OH should be homologate. So, the reduction is normally done with DIBAL, if you use excess DIBAL you will get the corresponding alcohol. So, here they use excess DIBAL. So, that you get the primary

alcohol. Now, the primary alcohol can be homologated through mesylation. So, first you mesylate the primary alcohol,

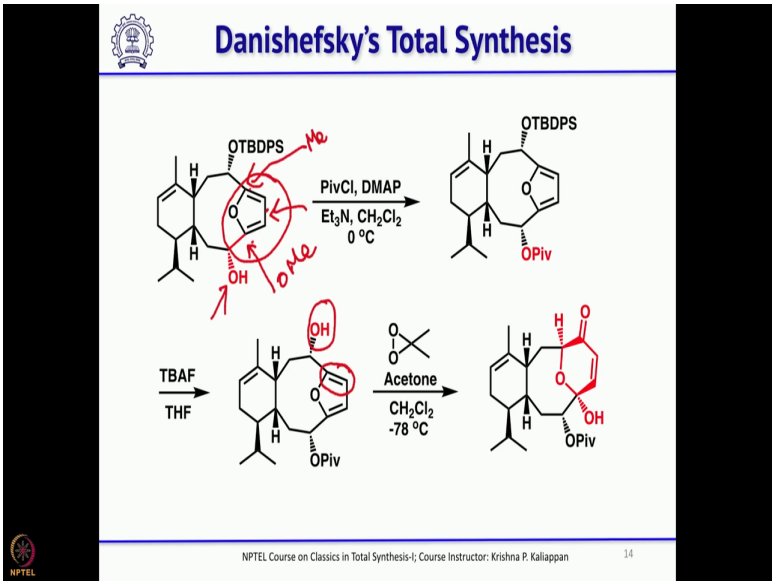
(Refer Slide Time: 14:38)



To get the mesylated compound. This upon treatment with potassium cyanide ok. When you this is a good leaving group mesylate. So, now, if you treat with potassium cyanide in the presence of [18 crown 6] ether, you get the corresponding cyanide -CH_2 CN ok. So, what we need now this cyanide should be reduced to aldehyde, then the intramolecular cyclization should takes place ok.

So, DIBAL reduction of cyanide will give you aldehyde. So, that was a very clean reaction, then the second key reaction ok. So, the second key reaction in the total sense of Danishefsky is the Nozaki-Kishi reaction. So, this upon intramolecular Nozaki-Kishi reaction gave the corresponding 10 membered ring, wherein the α isomer. α isomer was the major product.

(Refer Slide Time: 15:38)

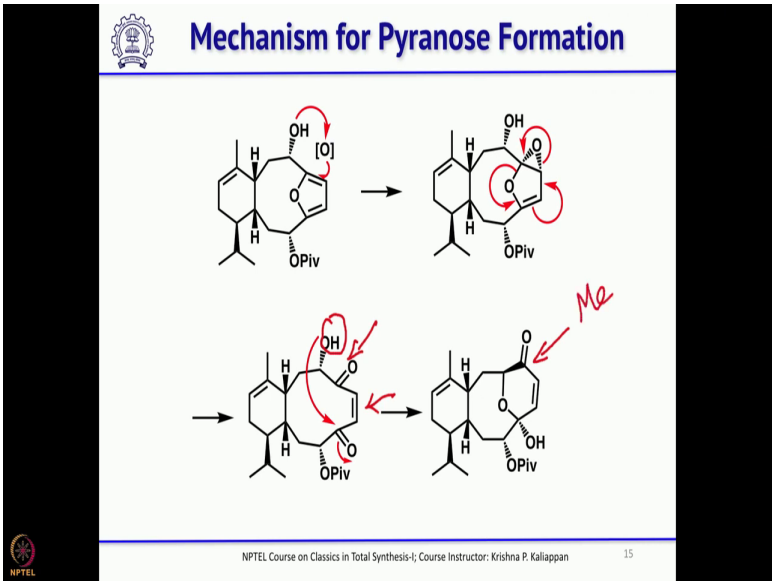


The hydroxyl group which is α is the preferred product, which you can see they got 15:1 ratio of a α and β, α ok. So, now, if you look at this particular structure you have the six membered ring in place. The b ring that is the ten member ring is in place. Now, what you need to do is you have to convert this furan, convert this furan. One you have to get a double bond here, you have to introduce a methoxy group here, and you have to introduce a methyl group. So, three things one has to do.

One introduction of methyl group, introduction of double bond, and introduction of methoxy group here. But, at the same time you should know this two double bonds should not be there in furan ok. So, what did they do? Before you do this, you need to protect the newly formed hydroxyl group ok. So, that was protected as pivalate ester by treating with pivaloyl chloride, then you can remove the TBDPS group ok. So, standard TBAF tetra butyl ammonium fluoride treatment will remove the TBDPS to give the corresponding alcohol.

So, once you have this alcohol, if you look at the relationship between this double bond and this hydroxyl allylic alcohol ok. That hydroxyl group will direct the incoming per-oxidizing agent. So, that you will get α epoxide. So, what happens, once you treat with dimethyl dioxolane DMD, you get the corresponding pyranose ring. So, not only epoxide is formed, it undergoes a rearrangement ok; so, well known rearrangement to form this hydroxy pyranose. How does it happen?

(Refer Slide Time: 17:39)

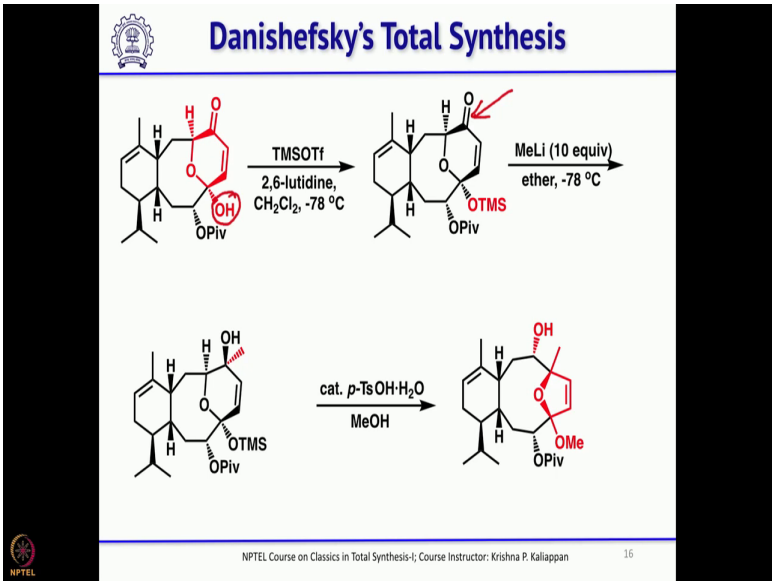


It is very simple, it is well known in the literature. So, first as I said it form the epoxide of the double bond, which is close to the hydroxyl group. It is like allylic alcohol called epoxidation. Once it is formed, then you can see the arrows the opening of this five membered ring gives rise to this enedione ok. It is basically nothing but, if we have 1, 4 di ketone on treatment with acid you will get furan ok. 1, 4 di ketone, if you treat with acid you will get furan. The same thing it is a reverse reaction, but since you are using oxidation you get extra double bond ok.

It is just the reversal of acid treatment 1, 4 di ketone to furan. Here what you are doing is you are using an oxidizing agent. So, that is why you introduce a double bond as well. Once this enedione is formed, then intramolecularly the hydroxyl group here will attack the ketone to form the six membered ring ok. So, what you have done now, you have oxidized the furan ring and while doing that it underwent a ring expansion reaction to form a hydroxy pyranose ok.

And this is also good in one sense, that if you look at the natural product. If you look at the natural product, you need to introduce a methyl group here you need to introduce a methyl group here.

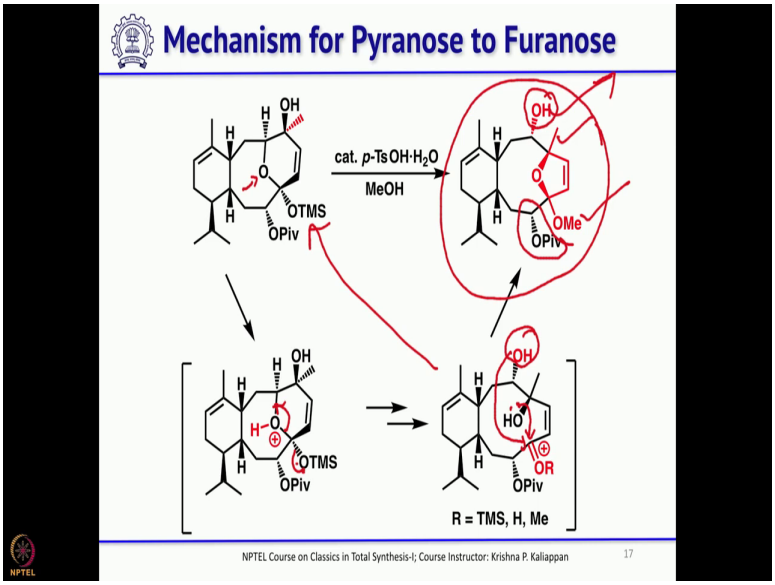
(Refer Slide Time: 19:29)



So now, this is this has become easy, because you have an enone ok. You have an enone, then it should be easy to introduce the methyl group here. So, how did they do? First you protect this lactone ok. So, protect it as TMS ether, then you add methylthium ok. So, methylthium addition to the enone comes from α side that methyl group comes from α side to get the β alcohol, then you treat with acid ok. Here when you treat with the acid, this pyranose ring rearranges back to the furanose ring.

Here the pyranose ring rearranges back to the furanose ring. So, how does it happen? It is a very interesting again a rearrangement, it is like shuttle triflate rearrangement. Once it was five membered ring that is furan, furan to pyranose now pyranose to furanose ok. It is like shuttle triflate rearrangement, how did this happen?

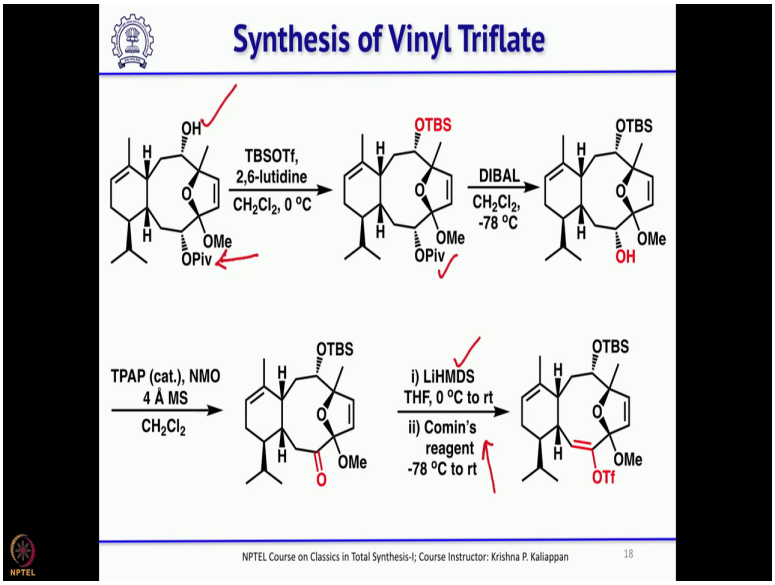
(Refer Slide Time: 20:23)



The moment you protonate, what happens? This oxygen gets protonated and then this lone pair on the OTMS opens this. So, what you get? This oxonium ion ok. Now, if this hydroxyl group attacks back, if this hydroxyl group attacks back you get the same pyranose ring. Whereas, if this tertiary alcohol attacks this carbonyl, then you will get furanose ring, is not it? So, that is what happens. Here the tertiary alcohol attacks the oxonium ion carbon to get the five membered ring.

So, now this is very easy to see all the functional groups required for the synthesis of eleutherobin is in place. You have a hydroxyl group here ok, then the OMe is there, methyl also and what you need to do is you have to convert this into enol triflate and also the northern hemisphere hydroxyl group you have to esterify ok. These are the two things he needs to do to complete the total synthesis of eleutherobin ok.

(Refer Slide Time: 21:48)

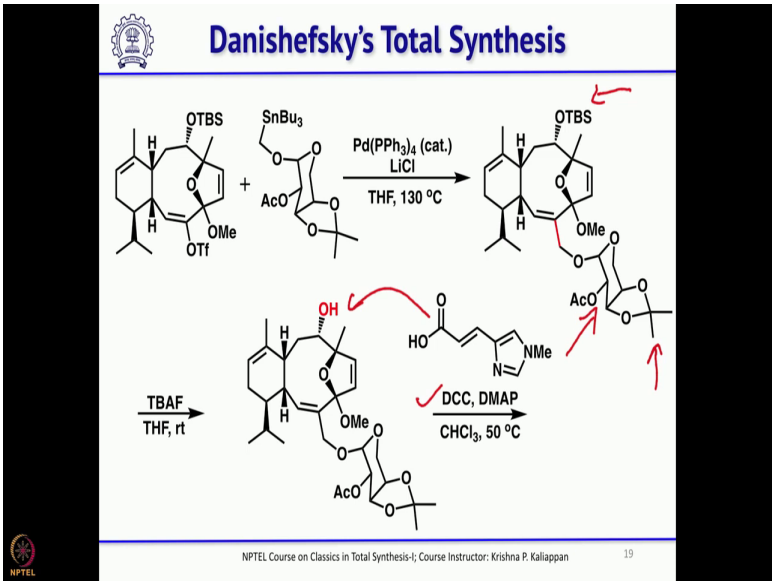


So, what did he do first he protected the hydroxyl group ok. He protected the hydroxyl group as TBS ether ok. So, that you can remove the pivaloyl group and make it as vinyl triflate and then couple with tributyl tin derivative of the sugar to attach the sugar fragment ok. So, you protected the hydroxyl group, then you reductively remove the pivalate tester.

So, pivalate tester can be reductively removed ok, it is an ester, is not it. So, if you reduce the DIBAL, the pivalate ester gets cleaved and then you will get the hydroxyl group. Hydroxyl group was then oxidized with tetra n propyl ammonium perruthenate and NMO to get the ketone. So, once you have the ketone, the next step is to make the enol triflate. So, this was successfully done by making the enolate with LiHMDS.

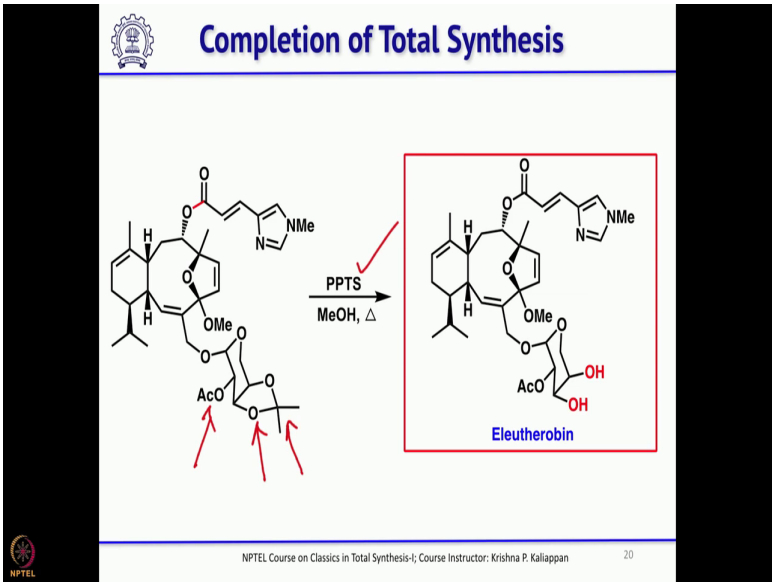
The triflate was introduced using well known Comin's reagent ok. So, now, the enol triflate is made. So, that means, the whole carbocyclic core structure of eleutherobin is ready and already we have discussed the synthesis of sugar fragment. So, what we need to do is we have to couple this triflate with the tin derivative using Stille coupling.

(Refer Slide Time: 23:11)



And Stille coupling work very well with tetrakis palladium to give the complete structure of the eleutherobin. So, what is left now is you have to remove the TBS attach the side chain, then remove the acetonide and acetyl group. So, these are the three things left for the total synthesis of eleutherobin. So, first easiest is to remove the TBS group ok. Treatment with TBAF you remove the TBS. Next, you have to attach this side chain ok. So, this α-β unsaturated acid is a is a known compound.

(Refer Slide Time: 24:00)

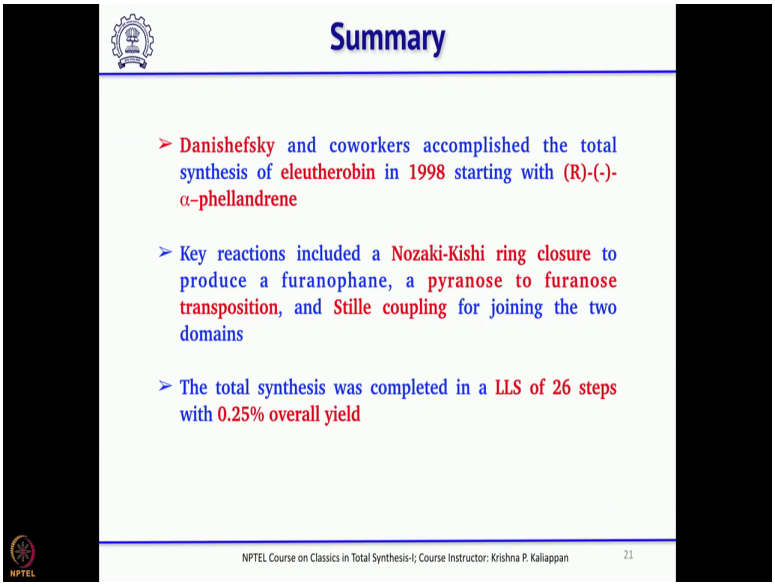


And now using DCC you can couple this carboxylic acid with alcohol to introduce the side chain on the northern hemisphere ok. Now, what is left? You have to remove the

acetate and you have to remove the acetonide ok. So, both are done in one step. Actually, if you look at the eleutherobin, this acetate is intact. Acetate is required in eleutherobin.

Only you need to remove this acetonide ok. You have to remove only the acetonide and that was done easily by treatment with PPTS, methanol you remove the acetonide and that gives eleutherobin. So, that is how we could complete the total synthesis of eleutherobin and if you look at the total synthesis of eleutherobin reported by danishefsky.

(Refer Slide Time: 24:49)



So, he started with two commercially available as well as naturally occurring compound for the carbocycle is started with the monoterpene called α phellandrene. And for the sugar fragment he started with D-arabinose a commercially available sugar ok. Then there are three key reactions, which he used one the Nozaki-Kishi reaction to form the ten membered ring.

And then second the ring expansion of furan ring to pyranose. And the third one is the pyranose to furanose that is six membered to furanose five membered ring was done under acidic condition. There is the fourth key reaction that is that Stille coupling between the carbocyclic triflate and then tri butylene tin derivative of sugar fragment ok. So, these are the four key reactions which Danishefsky used to synthesize eleutherobin.

Overall, this total synthesis was accomplished in 26 longest linear steps and with an yield of 0.25%. So, considering the molecule, considering the complexity of the natural product 0.25% overall yield is really a healthy one ok. So, this way if you look at the two total synthesis, which we have discussed on eleutherobin, Nicolou Nicholou's total synthesis and Danishefsky's total synthesis actually, involves some key reactions and also new chemistry were developed during these two total synthesis ok.

Thank you.