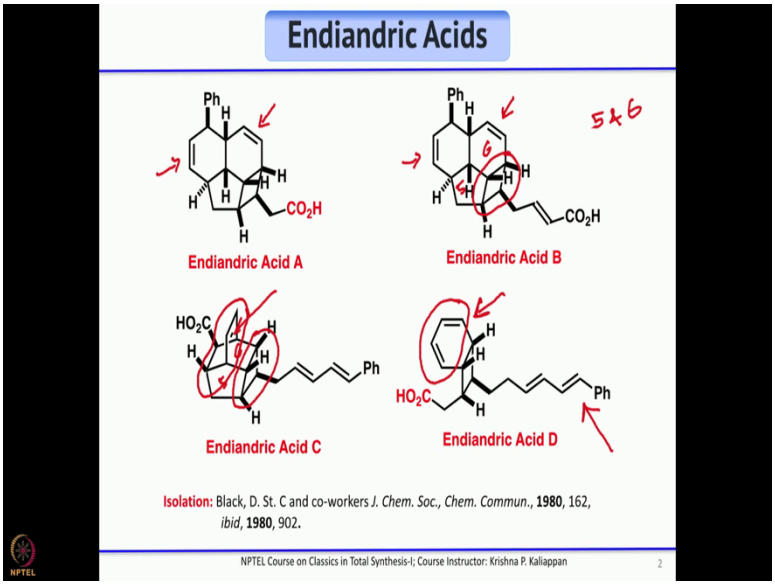
Classics in Total Synthesis - I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 07
Endiandric Acids

Good morning and welcome back to the NPTEL lectures on Classics in Total Synthesis part 1 and we have been discussing about total synthesis of natural products. And then last class we talked about total synthesis of a four membered ring which is not a natural product, but very important compound called cubane. So, today we will continue along this and then we will discuss about natural product synthesis particularly dealing with four membered ring.

(Refer Slide Time: 00:51)



And today's natural products are called Endiandric Acid and you can see here when you look at these two natural products B and C here there is nothing common, but when you have a closer look at you will find that these two have a four membered ring, is not it? And this four membered ring in the case of endiandric acid B and A you can see B and A this four membered ring is attached to a 5 and 6 membered ring, is not it?

This is 5 membered ring and this is 6 membered ring ok and same thing you can see in endiandric acid C also it is attached to a 5 and 6 membered ring. But these 5 and 6 membered ring are attached to another 6 membered ring in a different fashion ok and

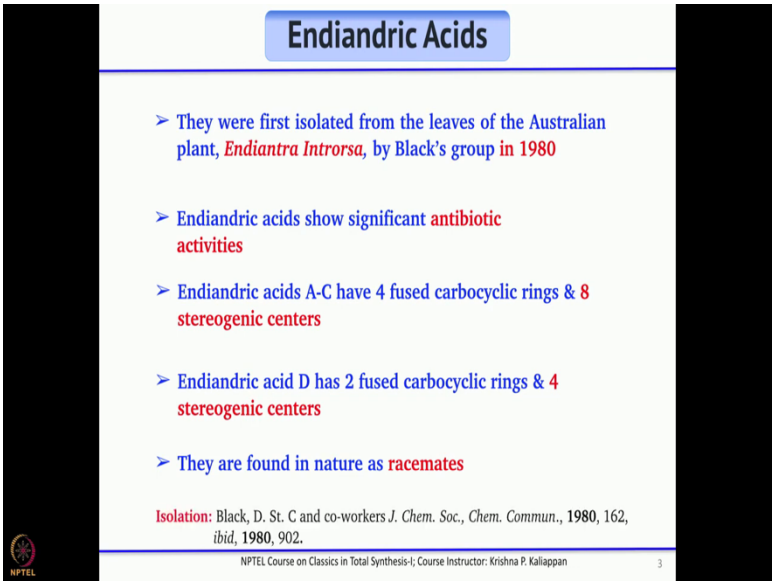
endiandric acid has a diene, which you can call it as cyclohexadiene and also a side chain which is another diene.

So these interesting natural products which were isolated as racemates was reported in 1980 ok by Black and if you closely look at these four natural products ok particularly let us start with the endiandric acid A and B. A and B have two cyclohexene moieties can you see two cyclohexene moieties. See whenever you see a 6 membered ring with a double bond that is cyclohexene substituted cyclohexene immediately one reaction which will come to your mind is Diels Alder reaction is not it one reaction which will come to your mind is a Diels Alder reaction.

And in endiandric acid you can see another 6 membered ring. This is a 6 membered ring with a cyclohexene ok with a double bond 6 memebered ring with a double bond a cyclohexene ring so; that means, all this endiandric acid, endiandric acid A, endiandric acid B, endiandric acid C could in principle be thought of being made from corresponding dienes and dienophiles through a Diels Alder reaction.

To support that if you look at endiandric acid D already you can see a diene ok, you can see a diene. So, in this diene you got two double bonds and if you are using this as dienophile one of the double bonds can act as a dienophile or if you are using this as diene this can act as a diene and the other one can will act as a dienophile ok.

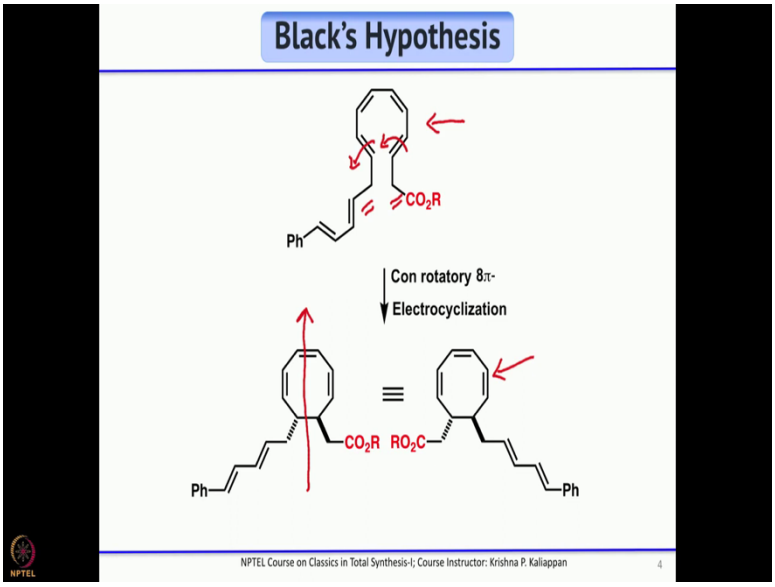
(Refer Slide Time: 03:43)



So, from the biological activity point of view, they show very good antibiotic activities and from structure point of view as you know they have 4 fused rings and overall 8 stereogenic centers though this molecules were isolated as racemates. Nevertheless it is very important to fix the stereochemistry.

Those days whenever group isolate natural products they also try to propose a synthetic pathway. A synthetic pathway in the sense how these natural products would have been made by nature so, that we call it as biosynthesis.

(Refer Slide Time: 04:24)

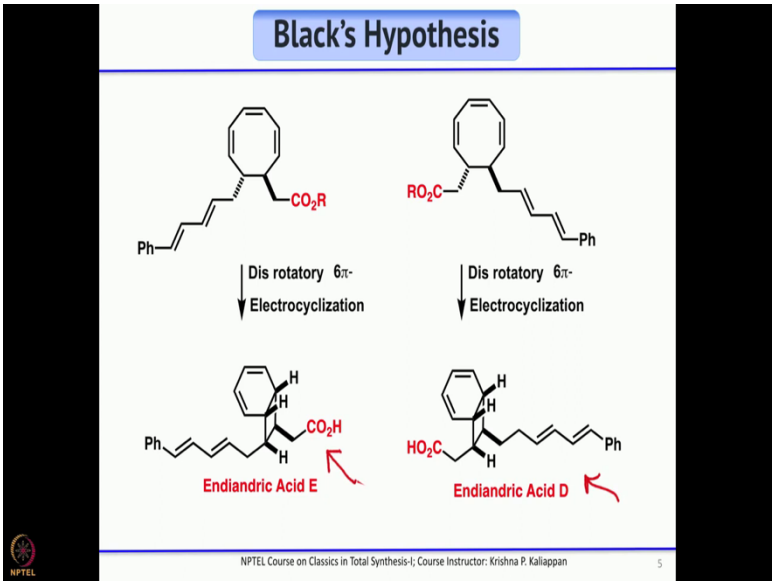


So, Black's group they proposed a hypothesis which is biogenesis what they proposed was if the nature has started with this tetraene having two side chains in the two side chains in the terminal carbon ok. Now, this tetraene you can say octa tetraene upon heating ok under thermal condition as you know when you see a conjugated tetraene, which reaction will come to your mind when you see a conjugate conjugated tetraene which reaction will come to your mind? A thermal electrocyclization reaction ok.

Since it is a 8 pi electron then under thermal condition con rotatory cyclization is allowed ok so, that should give you this cyclo octa triene ok. So, this is formed if you can see the con rotatory cyclization con rotatory as you know it is same side. Now, if you rotate this compound along this axis by 180 degree, if you rotate this compound along this axis by 180 degree you should get this compound, is not it?

So, what Black proposed was after this con rotatory 8 pi electro cyclization, still if you look at these two compounds you can see a conjugated triene a conjugated triene. So, the conjugated trine under the same thermal conditions. It can further undergo an electro cyclization reaction, but it is 6 pi electrons. So, the allowed is dis rotatory electro cyclization.

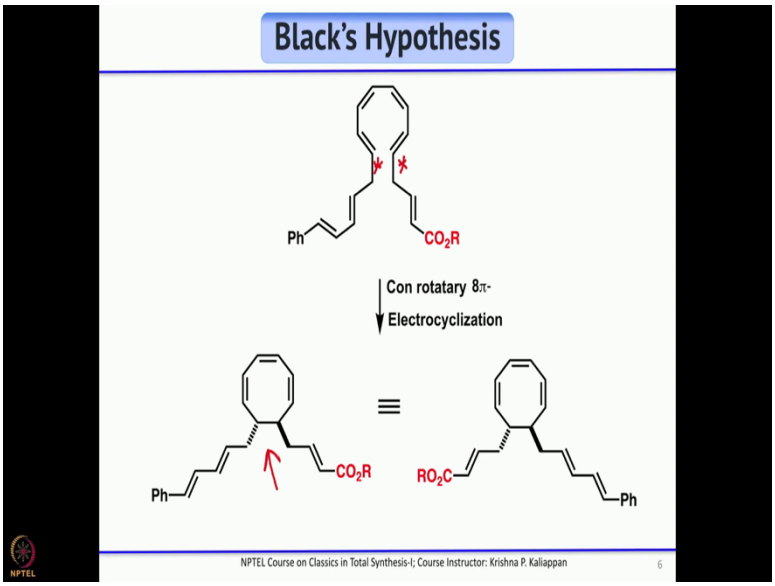
(Refer Slide Time: 06:13)



So, that should give you this compound though this was not isolated he proposed that it is endiandric acid E and that should be the precursor for one of the endiandric acid. And the other one ok if he does the same thing that is dis rotatory 6 pi electro cyclization, then one should get another natural product though it was not isolated he named it as endiandric acid D.

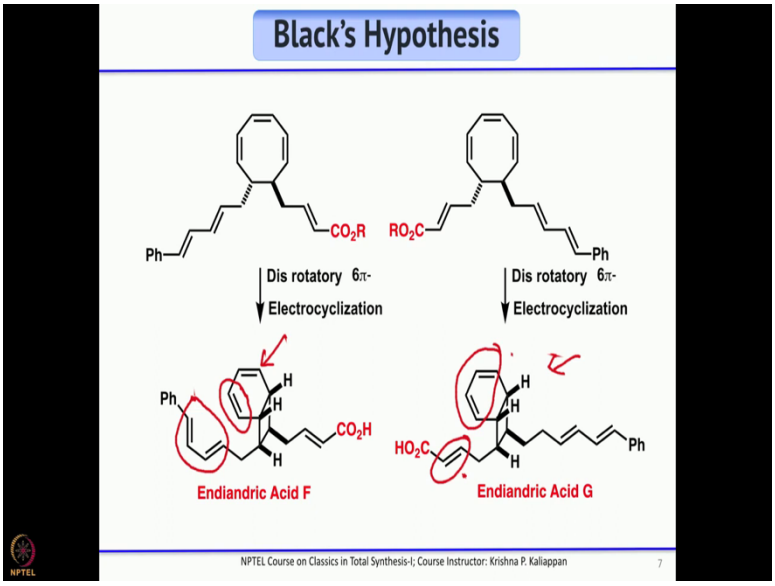
And that should form the precursor for making some other endiandric acid. So, the key thing was starting with a tetraene which undergoes successive 8 pi and 6 pi electro cyclization, that leads to the fused 6 and four membered ring ok that was his proposal.

(Refer Slide Time: 07:16)



And if you start with a different substituent here if you start with a different substituents at the terminal carbon, then again this will undergo another 8 pi con rotatory electro cyclization to give this cyclo octa triene. And again as I said you rotate it by 180 degree and then you will get this compound both as expected one can easily propose that this can undergo a 6 pi dis rotatory cyclization to give endiandric acid F ok. And same way the other one can give endiandric acid G.

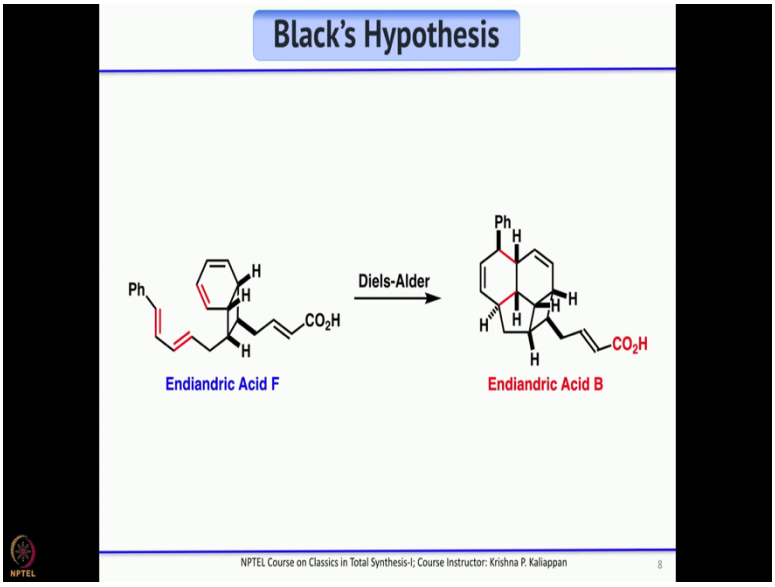
(Refer Slide Time: 07:51)



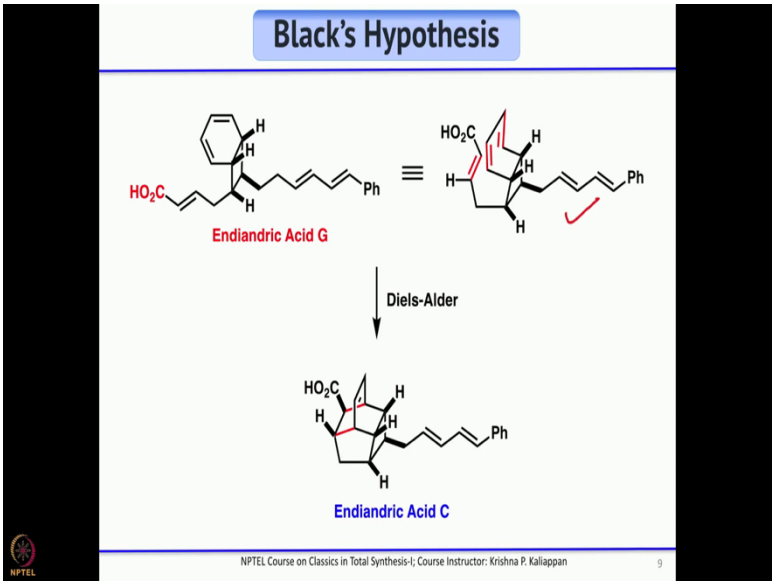
Now, if you look at endiandric acid F, it has a diene as side chain it has a diene as side chain and in this cyclo hexa diene, this double bond perhaps can act as a dienophile if that happens it can undergo an intramolecular Diels Alder reaction to give another endiandric acid whereas, in the case of endiandric acid G what you see is this will act as diene and the side chain alpha beta unsaturated carboxylic acid will act as a dienophile.

So, what will happen? This will act as a diene and this will act as a dienophile and both will undergo an intramolecular Diels Alder reactions to give another endiandric acid ok.

(Refer Slide Time: 09:02)



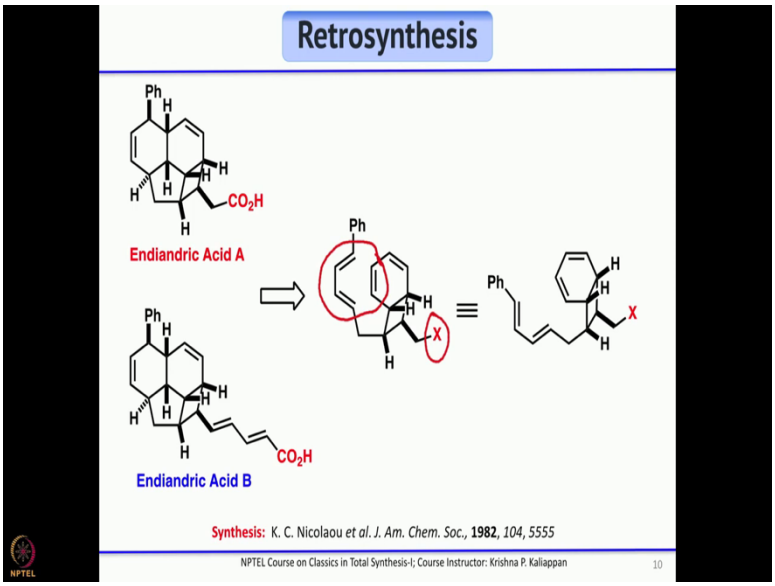
(Refer Slide Time: 09:14)



So, as I mentioned this is what he proposed. So, endiandric acid F should give endiandric acid B through this intramolecular Diels Alder reaction and endiandric acid G, which can be written this way ok, just I leave it for a few seconds for you to understand ok. Now this upon intra molecular Diels Alder reaction should give endiandric acid C ok.

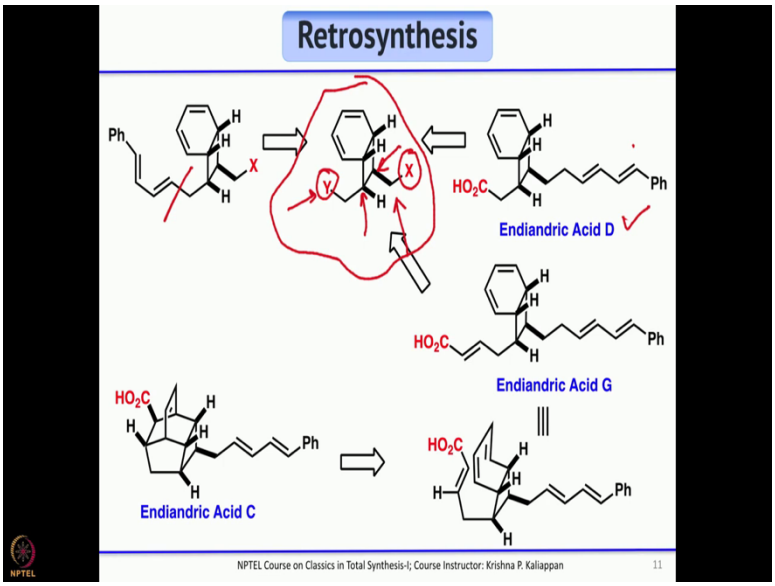
This is what Black proposed after isolating these natural products that from synthetic point of view all this can be made by combination of pericyclic reaction that is electro cyclization and Diels Alder reaction. So, taking this as a challenge Nicholau's group they proposed a beautiful retro synthesis and later executed a couple of years later they could complete the total synthesis of all this endiandric acid.

(Refer Slide Time: 10:07)



So, their idea is both endiandric acid A and B can be made from one common intermediate ok. You can see X can be homologated to get endiandric acid B otherwise you know you can easily convert this into endiandric acid A. The key reaction is only the intramolecular Diels Alder reaction the key reaction is only the intramolecular Diels Alder reaction. Now, this intermediate which can be written like this now, how you can make this intermediate ok.

(Refer Slide Time: 10:49)

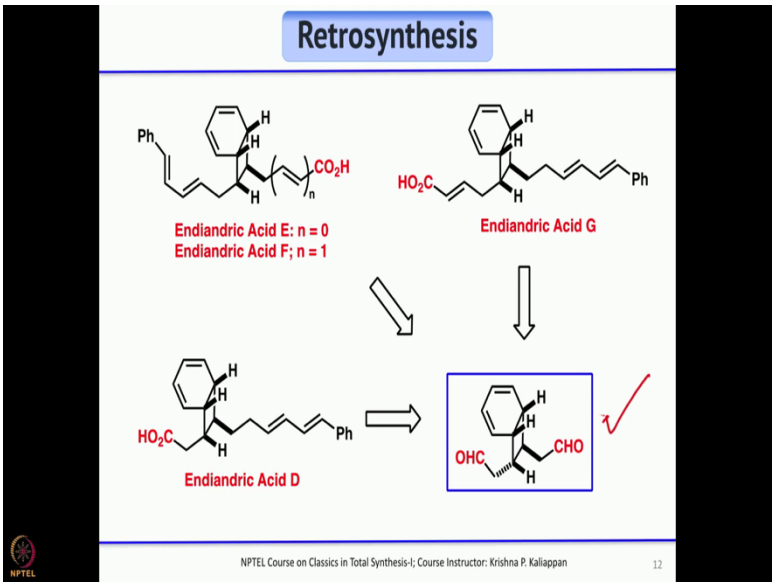


So, he thought if he break this bond if you break this bond, now you have two different substituents, which is attached to the cyclo butane ok one is CH_2Y the other one is CH_2X ok. This idea is the Y can be easily homologated then if you look at this carefully endiandric acid D also can be obtained from this particular intermediates ok. If you homologate X you will get D; if you homologate Y you will get this intermediates ok.

Next the endiandric acid G that also can be obtained from the same intermediate, it is just a matter of functional group manipulation ok. Some functional group manipulation and then transformation one can get all the endiandric acid from this particular intermediate ok.

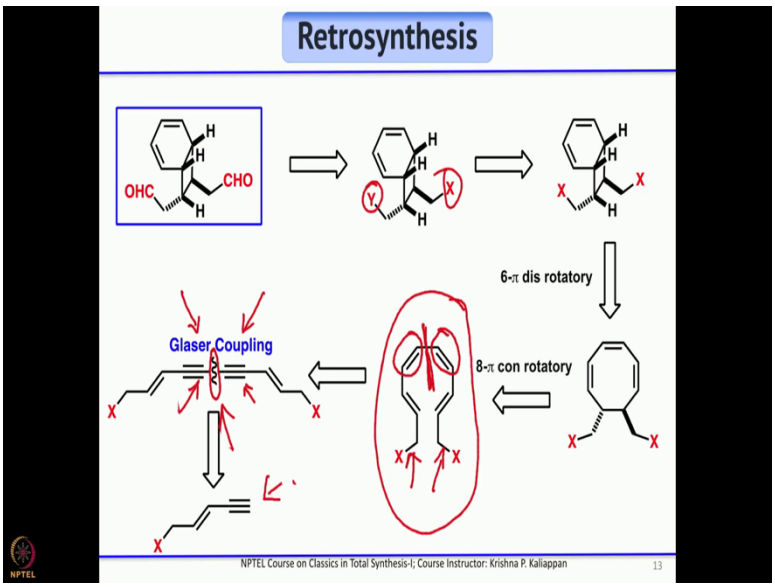
And if you look at endiandric acid G already I told you Black proposed that this upon heating will give endiandric acid C. So, overall to make all this endiandric acid what one needs is to prepare or synthesize this key intermediate. So, from one starting material it should be possible to make all the endiandric acid.

(Refer Slide Time: 12:28)



So, this is what Nicolaou proposed and this is endiandric acid E F G D and all this he wanted to make from this intermediate ok.

(Refer Slide Time: 12:42)



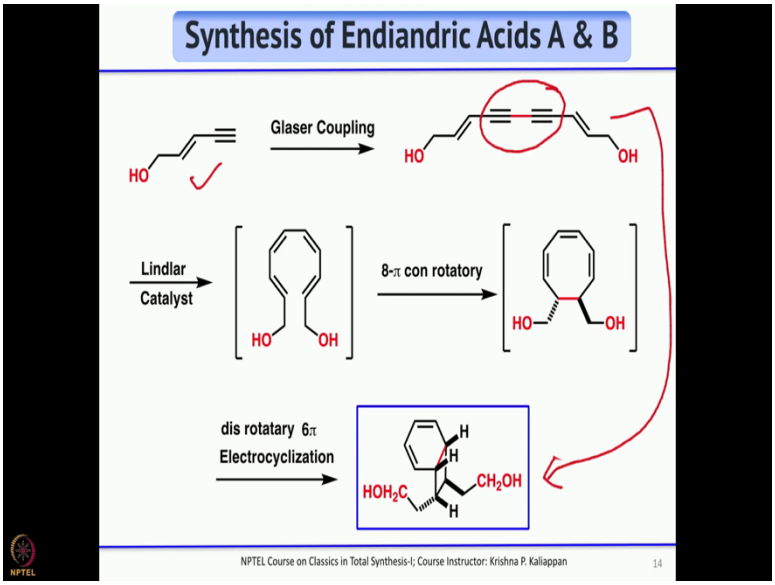
And this intermediate how one can make? As I said the CHO should be differentiated because it is important then only one side you can homologate. So, he made it as X and Y and this can be obtained from this cyclo octa triene and the cyclo octa triene can be made from the octa tetraene with two substituents at the terminal carbon ok. Now, if you

look at this carefully if you break this bond, if you break this bond and convert these two double bonds into triple bond.

If you break this bond and convert the adjacent two double bonds into triple bond, you will get this, but from synthetic point of view forward direction how will you do? If you do a Lindlar catalyst hydrogenation ok then, these two triple bonds these two triple bonds will be reduced to *cis* alkene.

These two triple bonds will be reduced *cis* alkene that will give you this tetraene ok and how will you get this symmetrical compound? It is very easy again you break this bond that is the bond between two triple bonds which is normally obtained by Glaser coupling ok. So, that will lead to this as the starting material ok.

(Refer Slide Time: 14:30)

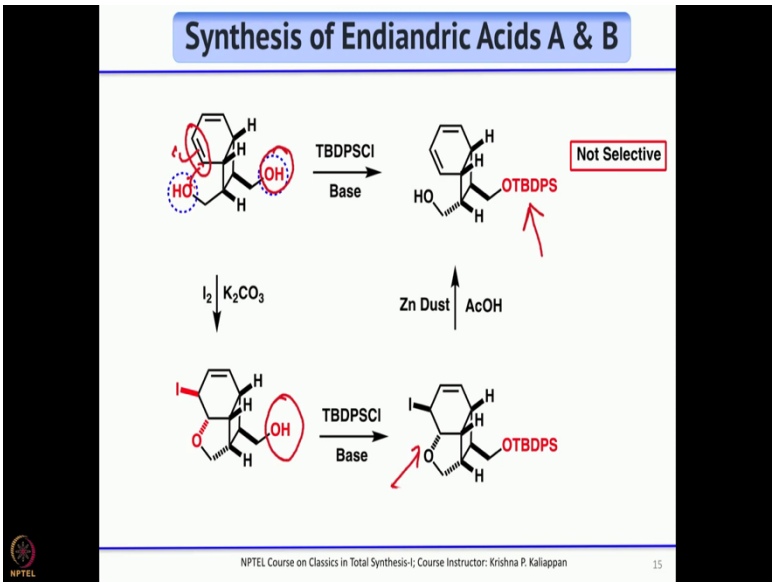


The starting material is now very simple. So, what he did was he started with this allylic alcohol having a triple bond at the end. Now Glaser coupling gave the diyne ok. Once you have this diyne then Lindlar catalyst treatment gives you the tetraene, but what happens, when you treat this diyne ok when you treat this diyne with Lindlar catalyst it does not stop there.

What happens? It undergoes first the 8 pi con rotatory cyclization as predicted and proposed by Black and it does not stop there it goes further it undergoes 6 pi rotatory electro cyclization to give this intermediate and this is a product ok. Directly you can see

in one step he gets this key intermediate, which is required for synthesis of all endiandric acid. So, now, having got this bicyclic compound with 2 CH_2OH which are opposite to each other the next step should be to differentiate these two CH_2OH, is not it. So, if you can differentiate these two OHs then you can functionalize on the other side.

(Refer Slide Time: 15:54)



So, with that idea he was trying to protect he thought this CH_2OH will be more you know open ok, then it will be easily protected, but in reality when he was trying to protect the CH_2OH selectivity was poor both the hydroxyl groups could be protected by TBDPSCl. So, what he has to do, he has to follow an indirect method where one can protect one of the hydroxyl groups.

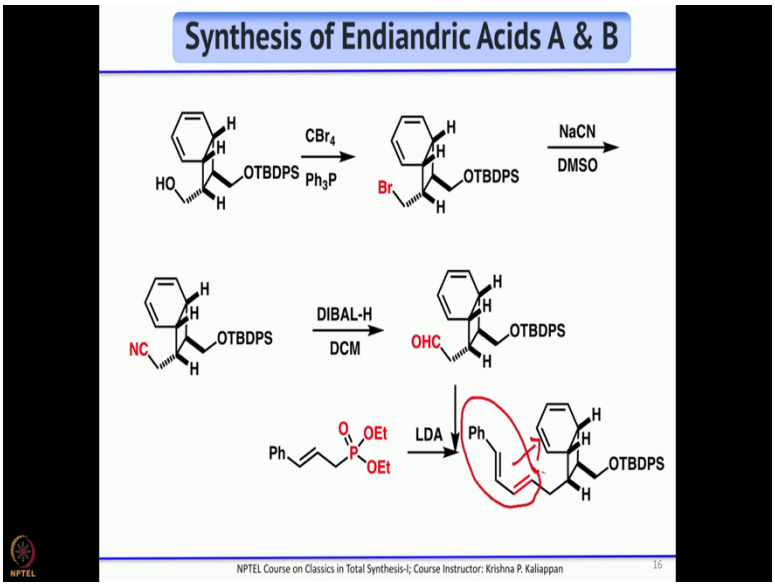
So, what he did was he carried out an Iodo etherification reaction, Iodo etherification reaction. So, when you have a double bond when you have a double bond and CH_2OH adjacent to that, then when you treat with iodine the double bond the iodine will add to the double bond it will form iodonium ion and in the presence of base this OH lone pair can attack and opens the iodonium ion.

So, this is a well-known reaction like Iodo lactonization it can form Iodo ether. The advantage is by using this you can protect the double bond as well as a hydroxyl group ok. It is a dual protection you are protecting the double bond as well as the hydroxyl group once you have done that now you can protect the other primary alcohol.

So, that was easy TBDPS chloride with base you can protect the primary alcohol as TBDPS ether once that is protected now you have to regenerate the double bond and the alcohol that is easily done with zinc dust and acetic acid ok, zinc dust and acetic acid will release the double bond as well as CH_2OH.

So, basically originally he was expecting this reaction to be very clean in one step you should be able to selectively protect one of the primary alcohols, but he could not so, it needed three steps Iodo etherification reaction followed by protection of the other primary alcohol then, releasing of the primary alcohol as well as double bond by treating with zinc dust and acetic acid ok. So, now, he has differentiated the 2 CH_2OH.

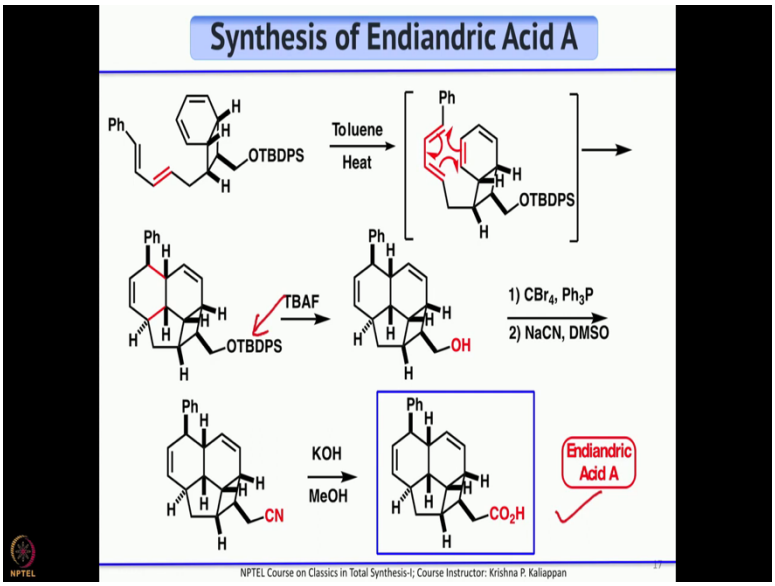
(Refer Slide Time: 18:17)



What is the next step? Now you have to homologate the other alcohol, first you convert that alcohol into a good leaving group. So, first is easy to make convert into bromide then, you need to homologate. So, simple SN_2 displacement reaction with sodium cyanide in the presence of more polar solvent DMSO you could get the cyanide.

So, you go homologate it that CH_2 to CH_2 cyanide. Now the cyanide can be easily reduced with the DIBAL to get aldehyde then, that aldehyde upon through a Wadsworth Horner Emmons Wittig reaction you get the diene ok. So, that aldehyde now is converted into the diene as we discussed during the retro synthesis once the diene is formed then this can undergo Diels Alder reaction with one of the double bonds of the cyclo hexene ok.

(Refer Slide Time: 19:15)

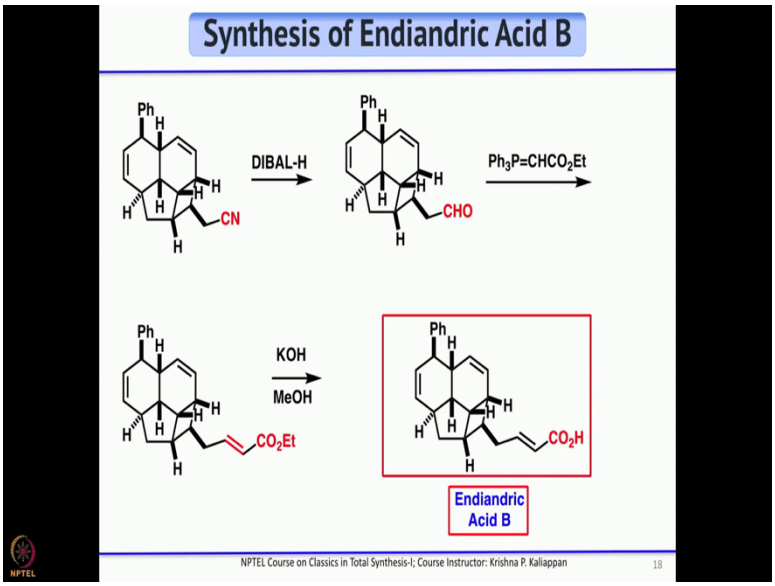


So, what you need to do is just heat it. So, take this compound treat with toluene and it undergoes intramolecular Diels Alder reaction IMDA type 1 to give tetracyclic compound ok this tetracyclic compound. Now what is required? You need to remove the protecting group right, whatever functional group you have to do you have to attach.

Removal is very easy you use TBAF any flourine source will remove the TBDPS group. Now you got the CH_2OH again like how you have done on the left hand side convert the hydroxyl group into a good leaving group, convert the hydroxyl group into a good leaving group that is bromide and then followed by displacement reaction with cyanide you get CH_2CN.

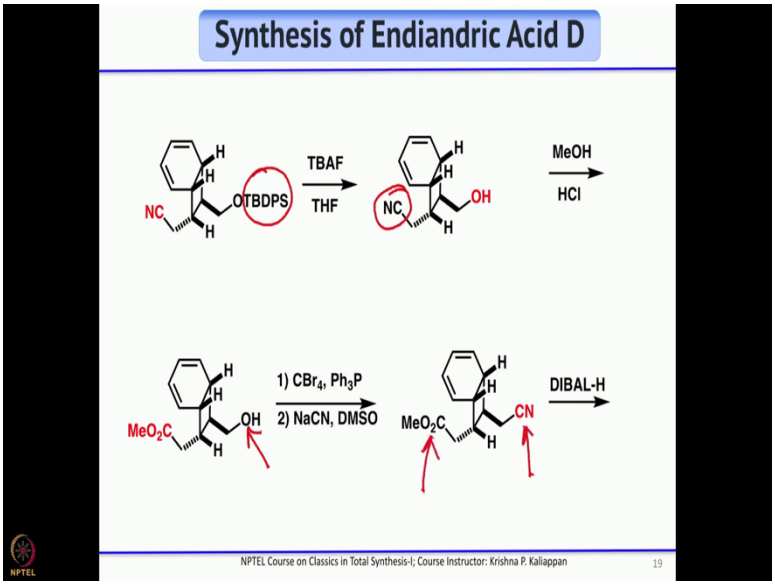
Now, you hydrolyze you get endiandric acid A ok. Simple hydrolysis of cyanide will give you carboxylic acid and that compound is nothing but endiandric acid A. So, from this common intermediate the first natural product which was isolated from that is endiandric acid has been successfully synthesized ok.

(Refer Slide Time: 20:32)



Then to go for endiandric acid B. So, the cyanide if you reduce with DIBAL you get the aldehyde then followed by your Wittig, stabilized Wittig you get the alpha beta unsaturated ester then again hydrolysis of the ester will give you a endiandric acid B ok. So, from the same intermediate. So, now, Nicolaou's group could synthesize two natural products one is endiandric acid A the other one is endiandric acid B.

(Refer Slide Time: 21:05)

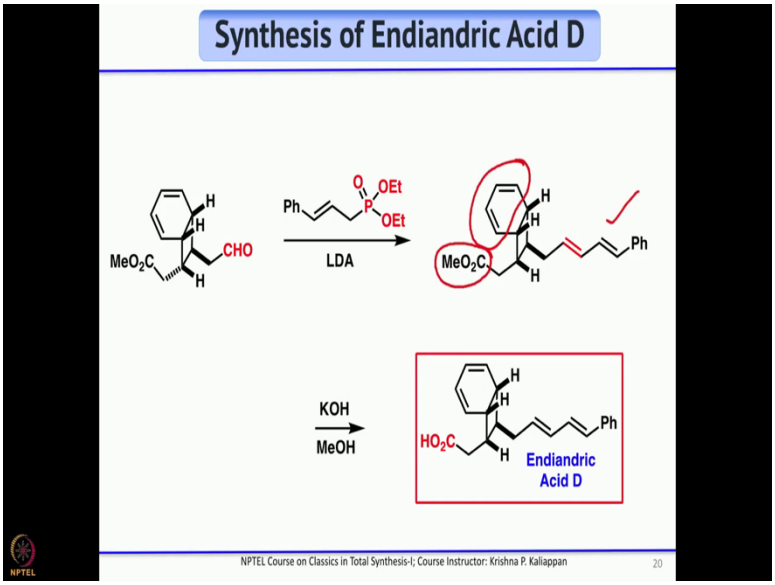


Then we have to go for endiandric acid D. So, the endiandric acid D is slightly different than endiandric acid A and B. So, what he did? The same cyanide which was a original

intermediate for synthesis of endiandric acid A and B. Now, you keep it as such the cyanide is not attacked, but remove the TBDPS group with TBAF you get the alcohol then, you hydrolyze the cyanide you hydrolyze the cyanide to ester with methanol HCl then you convert the CH_2OH into cyanide.

A two step standard protocol converting into CBr_4 converting into the corresponding bromide followed by SN_2 displacement you get the cyanide. Now, treat with DIBAL ok. So, when you treat with DIBAL there are two possibilities you know one the cyanide can be reduced to aldehyde at the same time ester also can be reduced.

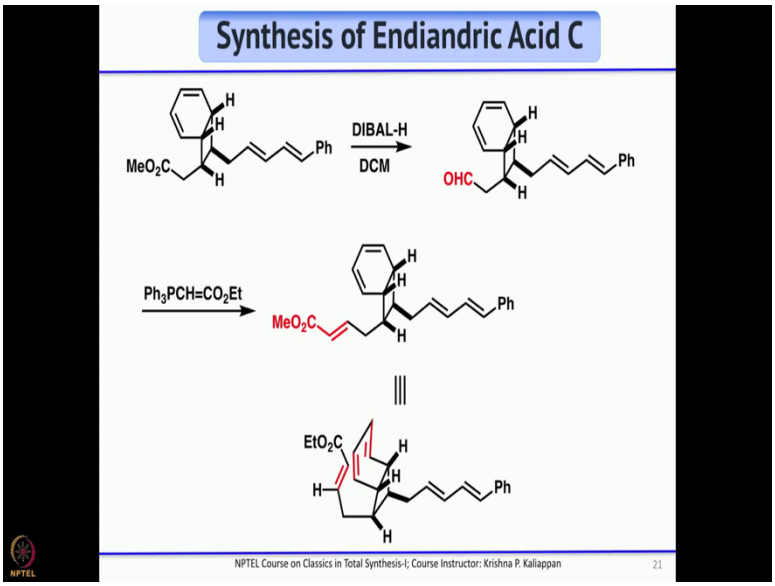
(Refer Slide Time: 22:12)



But between cyanide and ester cyanide is more reactive towards DIBAL. So, you get only the cyanide being reduced to get the aldehyde then again you do the Wittig. So, you get the corresponding diene. So, what you should do now hydrolyze the ester that will give you endiandric acid D, ok.

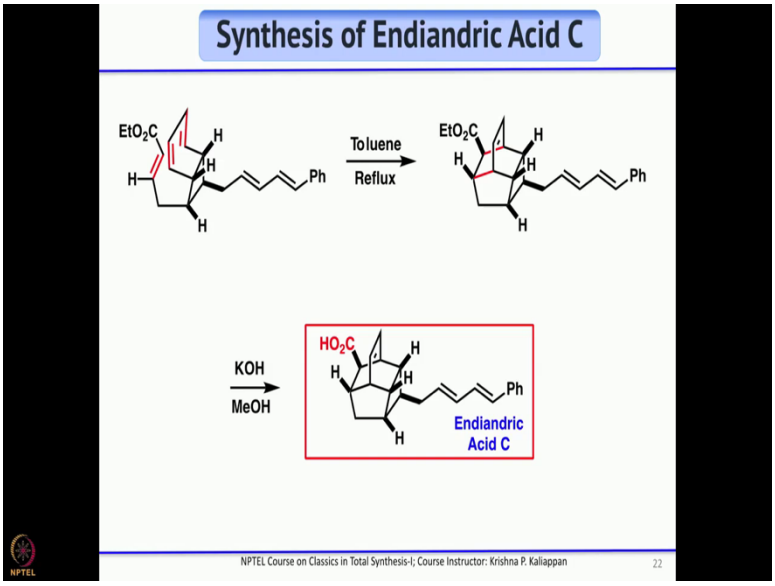
If you hydrolyze the ester you will get endiandric acid D.

(Refer Slide Time: 22:42)



And for endiandric acid C what you should do you have to reduce the ester with DIBAL to get aldehyde, then you do the stabilized Wittig reaction to get alpha, beta unsaturated ester. Now, if you do the intramolecular Diels Alder reaction ok this compound can be written like this.

(Refer Slide Time: 23:06)



Now, if you heat this ok. Now, if you heat this with toluene you will get the intramolecular Diels Alder reaction product alpha beta unsaturated ester. Now, the ester upon hydrolysis you will get corresponding natural product endiandric acid C.

So, if you look at the whole sequence what Nicolaou has cleverly used was Lindlar catalyst hydrogenation of triple bond, two triple bonds into cis double bond and during that period conrotatory you know 8 pi cyclization followed by disrotatory 6 pi cyclization takes place to give a bicyclic compound where, the cyclo butane is already there.

Then from this common intermediate from this common intermediate he could successfully convert the diol into the corresponding OTBDPS and the other one as a leaving group from that intermediate you could go all the way to complete the total synthesis of endiandric acid A, endiandric acid B, endiandric acid C.

So, this is one of the classical examples wherein, the proposed bio-genetic pathway has been successfully you know established and executed in synthetic laboratory by clever design of starting material ok. So, I will stop here regarding the synthesis of four membered natural products and then we will move to synthesis of five membered natural products from tomorrow ok.

Thank you.