Classics in Total Synthesis-I
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Lecture - 23
Mevinolin

So, good morning everyone and welcome back to this NPTEL lecture series on Classics in Total Synthesis Part 1. So, we have been discussing about total synthesis of natural products having 6 - membered sub units, in the last lecture we talked about total synthesis of carpanone where in oxidative phenolic coupling and intramolecular Diels - Alder reaction as the key reaction to you know construct three rings in one pot.

And today we will move to another very interesting natural product called Mevinolin and why synthesis of mevinolin is important, why this natural product is important?

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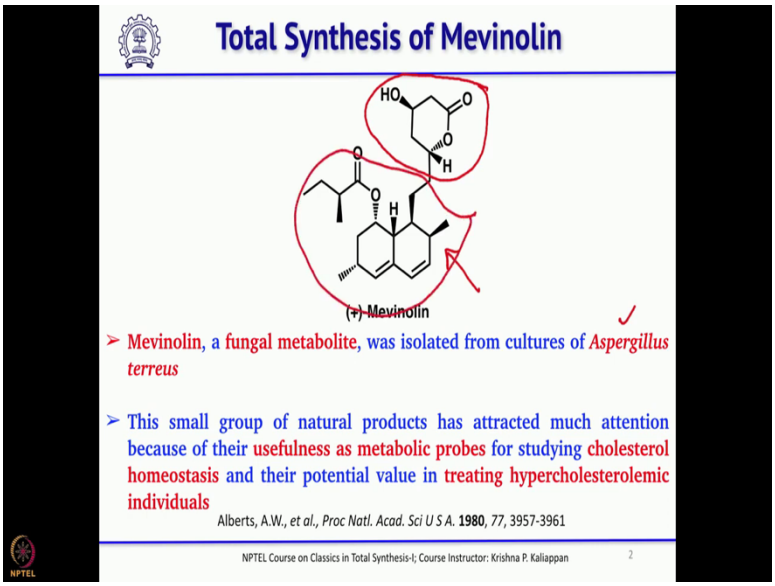

If you look at this natural product mevinolin, it is a fungal metabolite and it was isolated from the cultures of Aspergillus terreus. This is the starting point for the development of many cholesterol lowering drugs like atorvastatin, rosuvastatin and many such drugs were made are inspired by this particular natural product. And the key pharmacophore of mevinolin is this hydroxy 6 - membered lactone they use this key pharmacophore and changed only this whole unit ok.

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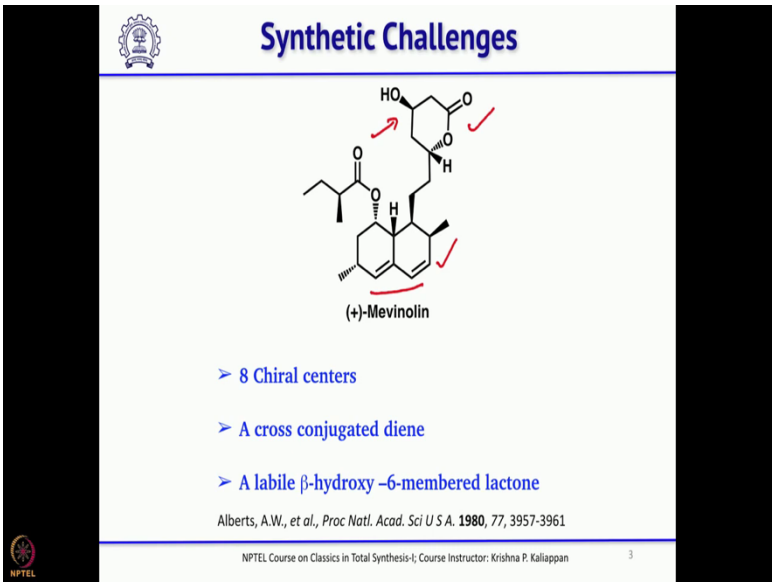

Now, let us see the total synthesis of mevinolin reported by Derick Clive from University of Alberta Edmonton and when you look at this molecule you can see it is a bicyclic compound and also having a 6-membered hydroxy lactone.

Overall, it has 8 chiral centers and also a conjugated diene ok and this hydroxy 6 - membered lactone if you have a close look at it this is nothing but an aldol is not it? So, nothing but an aldol so, there is a possibility of dehydration it is a labile beta hydroxy lactone and these are some of the challenges one would face when you have to plan for total synthesis of such molecule.

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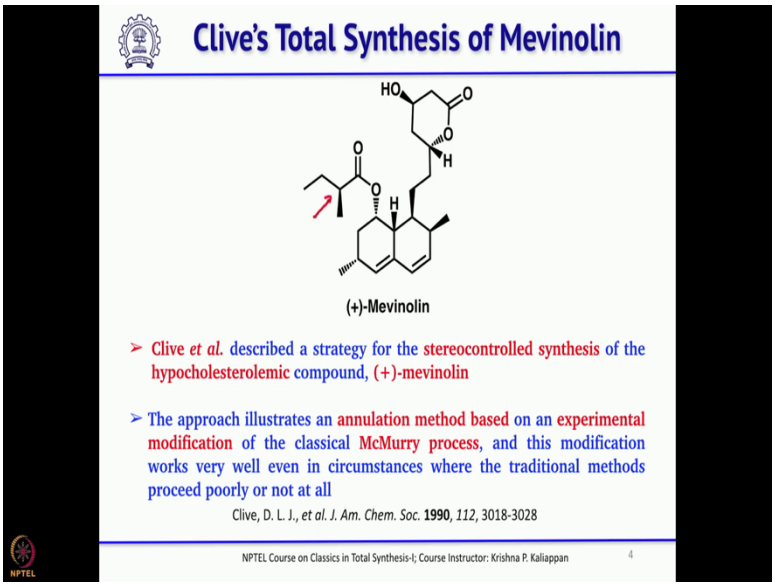

So, the synthesis which I am going to talk about today was reported by as I mentioned Derick Clive from Edmonton though this synthesis is little longer, but one would learn lot of new reactions in this total synthesis and his total synthesis involved few key reactions. One the use of Evans chiral auxiliary for making a 6- membered ring and in it also involved use of Evans chiral auxiliary to get introduce this chiral center and this chiral center.

So, he used Evans chiral auxiliary exclusively to introduce few chiral centers and he used the McMurry reaction. We saw McMurry coupling recently. So, he used McMurry coupling to introduce this particular double bond ok.

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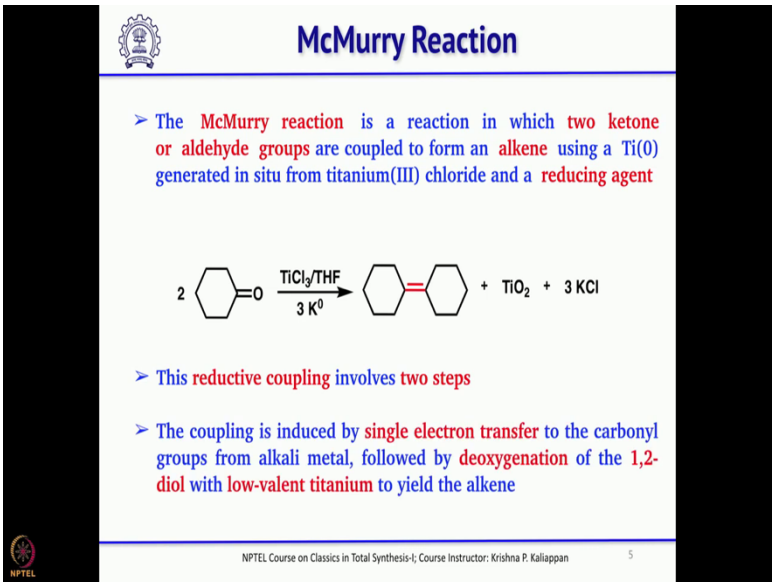

So, the McMurry coupling is nothing but if you have a ketone and if you treat with titanium 0 so, then it gives the dimeric product where you get a double bond. Basically, it involves two steps first it goes through the corresponding diol.

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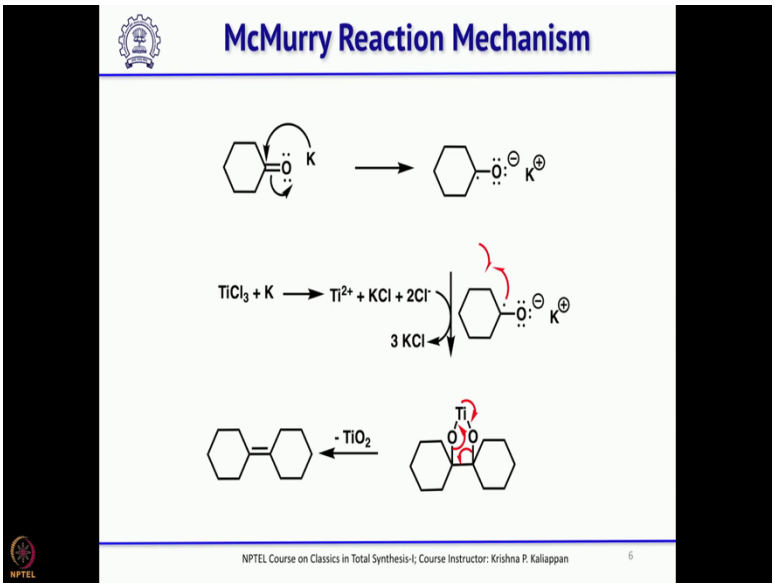

So, it is almost like pinacol coupling you have a ketone and then treat with titanium 0. And you get the diol and the diol is still connected to the titanium and it undergoes elimination of titanium dioxide to give the double bond ok. This is a well-known

reaction; one can sometimes stop at diol sometimes it will go all the way to the corresponding alkene.

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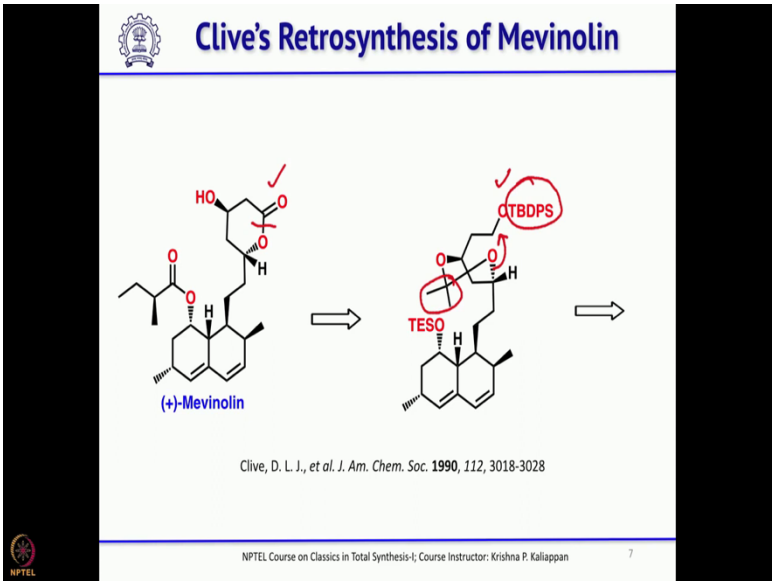

So, from his retro synthetic point of view the first disconnection was this C double bond O, his idea is this precursor if you remove the protecting group here as well as this acetonide. The primary alcohol can be selectively oxidized ok the primary alcohol can be selectively oxidized to aldehyde, once that aldehyde is formed this alcohol can intra molecularly attack that aldehyde to form lactol which can be further oxidized to give the corresponding lactone. So, he thought this should be the precursor for making mevinolin.

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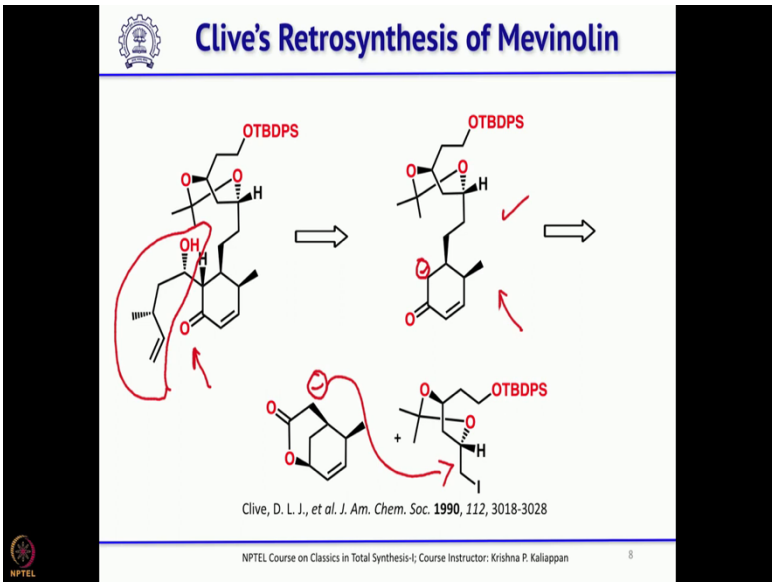

Now, this can be obtained from this intermediate ok. So, what he is planning is to use this aldehyde ok this aldehyde if you generate anion and quench with this aldehyde you can introduce this side chain ok. So, the aldol reaction and this can be obtained from this lactone. So, now, one can generate a carbanion and make enolate and then quench with this iodide that should give this particular intermediate ok.

So, there are two key reactions; one is aldol, another one is alkylation ok. Alkylation followed by aldol one get this precursor and here as I said the McMurry coupling will give the corresponding bicyclic compound.

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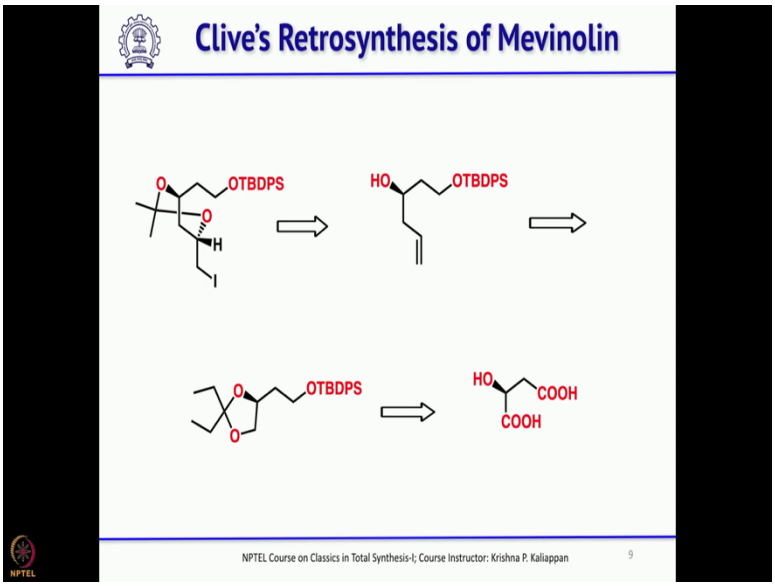

And, how these two fragments can be made? The fragment iodide can be made from this homoallylic alcohol ok and this can be made from maleic acid. I will come to that how this is made from maleic acid.

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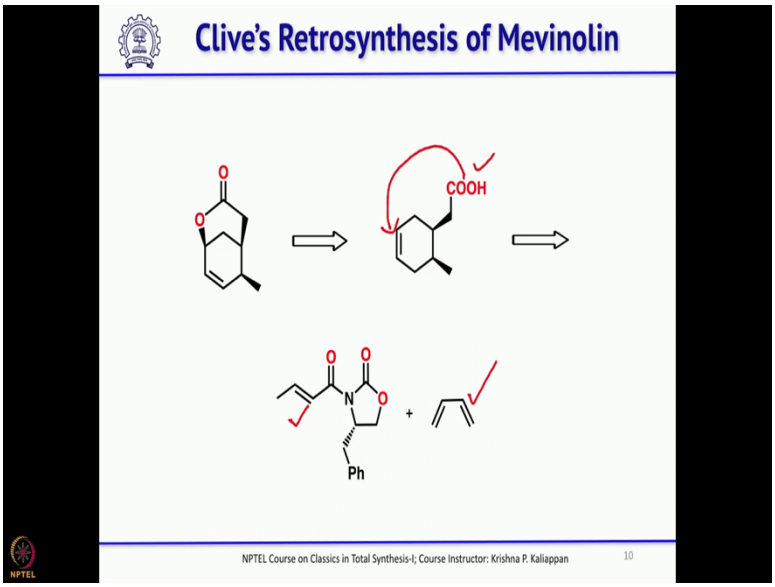

This lactone whenever you see a lactone and a double bond in one of the rings. Then one can think of using iodolactonization. So, if you have this double bond and carboxylic acid and this can undergo iodolactonization followed by elimination of HI one should get the double bond and this in principle can be obtained by inter molecular Diels - Alder

reaction between butadiene and the dienophile, which is attached to Evans chiral auxiliary ok.

So, that way the first step itself is the asymmetric Diels - Alder reaction ok using Evans chiral auxiliary.

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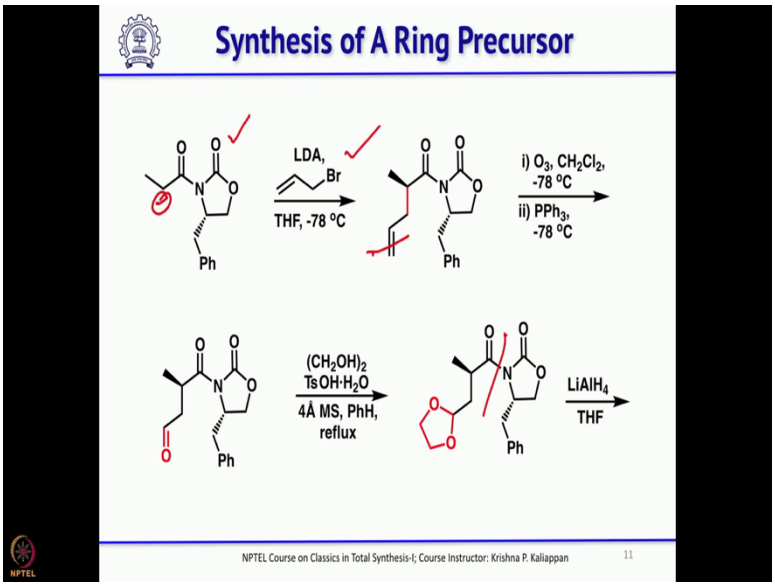

Now, let us see how he made each precursor and he combine A B and B C and so on first he started with this known compound which is made easily from you know Evans chiral auxiliary by attaching propionic anhydride. So, then you alkylate by treating with LDA you generate anion and quench with allyl bromide you get this intermediate.

And this upon ozonolysis ok, you get the corresponding aldehyde and that aldehyde you protect it as acetal using ethylene glycol and para toluene sulfonic acid.

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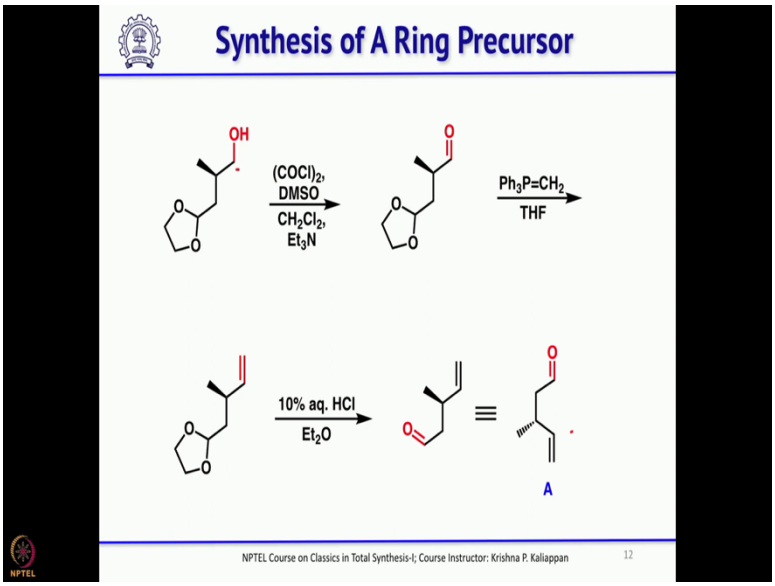

Now, you can remove the chiral auxiliary once this is done you remove the chiral auxiliary to get the corresponding alcohol. Now, from this alcohol to this aldehyde so, you could do in few steps first Swern oxidation, you get the ketone then do the Wittig, you get the corresponding double bond then remove the acetal you get the corresponding aldehyde.

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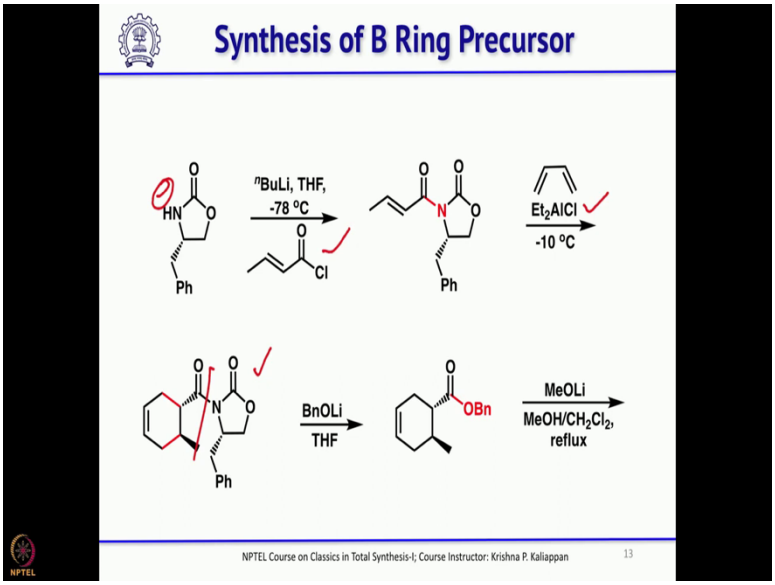

So, that is the fragment A. So, you have the fragment A now we will see how the fragment B was synthesized. Again, he started from Evans chiral auxiliary and here you

generate anion by treating with butyl lithium and quench with crotyl chloride. So, now, you have successfully attached the dienophile to Evans chiral auxiliary.

The next key step is the inter molecular Diels - Alder reaction with butadiene. So, that was done using diethyl aluminum chloride as the Lewis acid at minus 10 degrees you get this trans isomer, one isomer ok. So, next step you have to cleave this. So, that is normally done with lithium benzoate. So, now, you have the ester that ester can be exchanged with you know OMe by treating with LiOMe. So, you get corresponding methyl ester.

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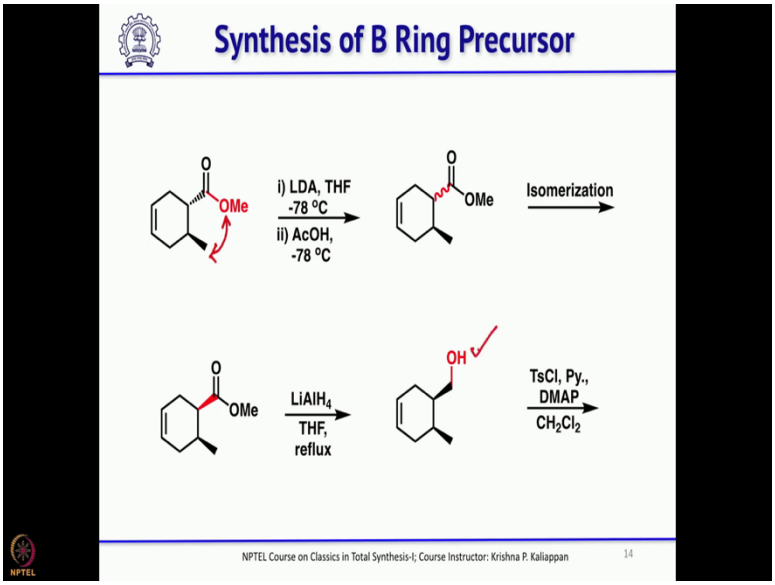

So, this methyl ester if you look at this structure these two substituents are trans, but in mevinolin you need methyl and ester they are cis to each other not only that. The ester should be having one more extra carbon atom here this is direct ester what you need is CH_2COOH and also switch to each other methyl and the CH_2CO_2Me should be cis to each other.

So, the first step is you know you have to isomerize. So, the isomerization is done using base strong base then you treat with lithium aluminium hydride ok. So, ester is hydrolyzed to corresponding alcohol and the tosylation you convert this primary alcohol into a good leaving group.

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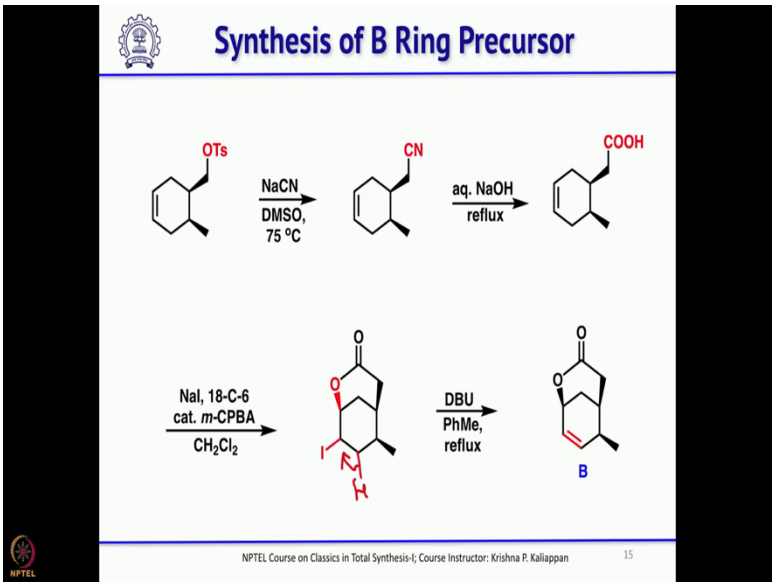

And treat with sodium cyanide in DMSO an SN_2 reaction this way you homologate ok. The cyanide upon hydrolysis you give the carboxylic acid and that is set for now the key iodolactonization. So, treatment with sodium iodide and catalytic amount of m- CPBA so you get the corresponding iodolactone, this iodolactone now upon treatment with DBU it undergoes elimination to give the fragment B. So, we have synthesized fragment A and we also have synthesized fragment B.

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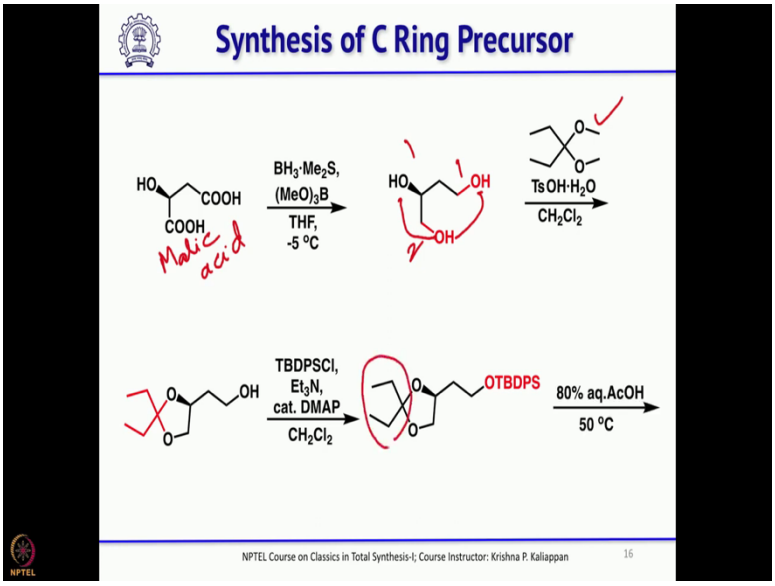

Then what you should do, you have to prepare this fragment C then you have to combine fragment B and C followed by combining with ABC. So, for the fragment C he started with commercially available maleic acid. So, this is maleic acid ok. So, he took this maleic acid and reduced with borane. So, borane is known to reduce carboxylic acid to corresponding primary alcohol.

So, now, upon complete reduction both the carboxylic acids are reduced to primary alcohol. So, you see two primary alcohols and one secondary alcohol ok. So, one can easily protect these two primary alcohols or one can easily protect one primary alcohol and this one secondary alcohol.

If you treat with ketones or protected ketone then one primary alcohol and the secondary alcohol will be protected and it should be 5 membered ring ok. That is faster the formation of 5 membered ring is faster at the same time if you treat with benzaldehyde then the formation of 6-membered acetal is faster so, that you will get.

So, you can choose whichever you want accordingly you can use either ketone or you can you use benzaldehyde ok. Since, he needs the 5 membered ketal he exchanged with this 5 membered ketal to get the 5 membered ketal then the primary alcohol was protected as TBDPS ether ok.

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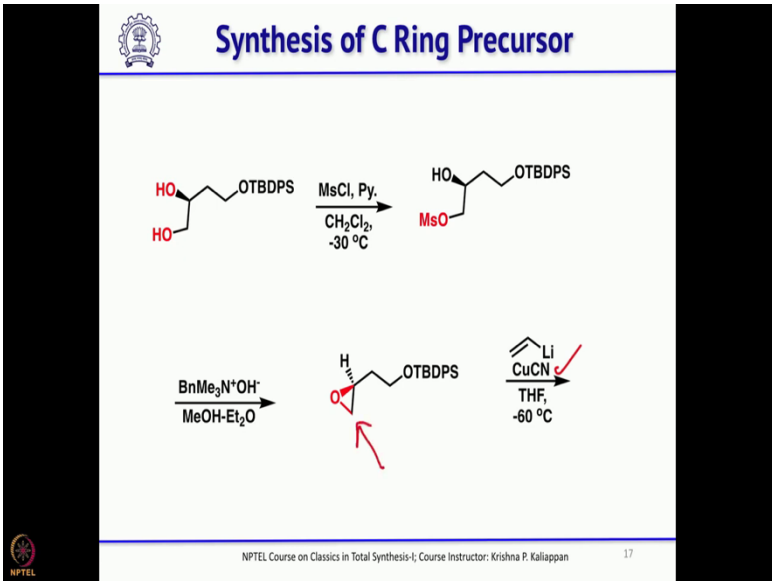

Then you remove the ketal using 80 percent acetic acid, you get back your diol and the primary alcohol can be selectively mesylated in the presence of secondary alcohol. So, you do that and then treatment with base, here benzyl trimethyl ammonium hydroxide. So, it forms the corresponding epoxide ok. Then open this with vinyl lithium ok open this with vinyl lithium and with copper cyanide. So, it is opening up the epoxide from this side. So, you will get the corresponding vinyl group.

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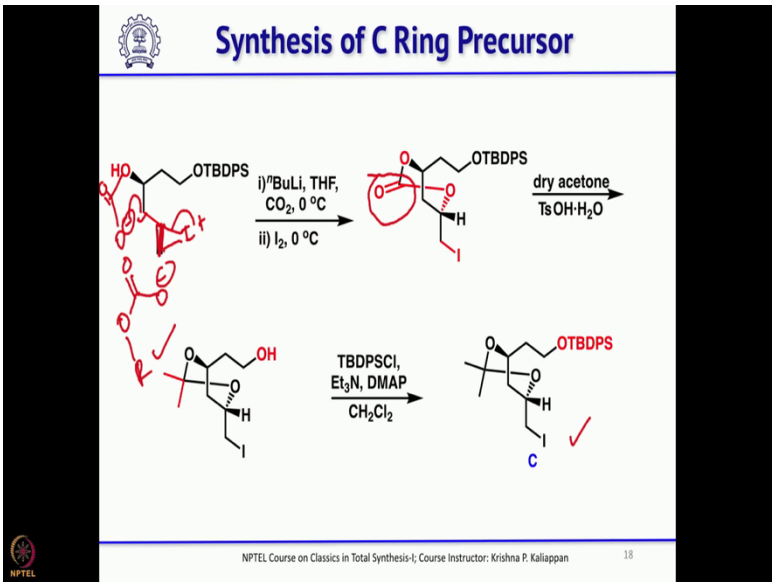

So, now what you got is homo allylic alcohol ok, from homo allylic alcohol to this iodide stereo selectively it was done again using another key reaction. So, we already discussed iodolactonization ok, this is analogous to iodolactonization where instead of COOH what they have used this OCOO minus O O; OC double bond OO minus. They have used this and opened the iodonium ion, how they have done it they took this homoallylic alcohol and treated with butyl lithium ok.

So, the with butyl lithium forms O minus then when you add carbon dioxide it forms this OCOO minus, then when you add iodine the iodine will form here the corresponding iodonium ion, is not it? And here you have OCOO minus this OCOO minus will open this and you will get the corresponding iodo cyclic carbonates ok, iodo cyclic carbonate.

And this iodo cyclic carbonate now, if you treat with dry acetone and para toluene sulfonic acid two things happen; one this carbonate, carbonate is hydrolyzed and you get back the diol ok your carbonate is hydrolyzed to get back your diol and the diol is

protected as acetonide at the diol is protected as acetonide, then you protect the free primary alcohol as TBDPS ether tertiary butyl diphenyl silyl ether.

So, what he has done what we have discussed so far is how to make the three fragments namely A B and C.

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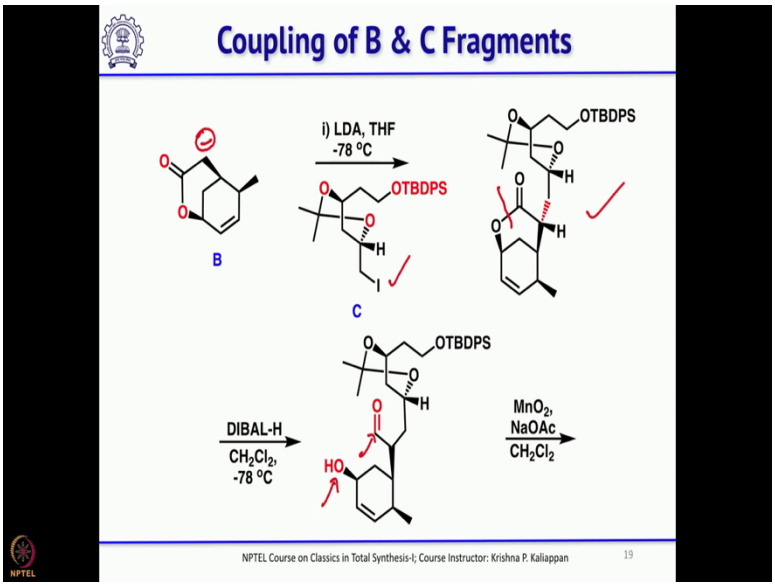

So, he has made successfully these three fragments, the next step is to combine B and C fragments. So, this fragment B if you treat with LDA one can generate anion. So, that can form the corresponding enolate and the enolate we can quench when you quench the enolate with this iodide so, you get this fragment ok.

Next step is treatment with DIBAL. So, DIBAL if you look at this you have a lactone and one equivalent of DIBAL at low temperature this lactone can be reduced to corresponding hydroxy aldehyde ok. You have a hydroxyl group and you have aldehyde ok. Basically, lactone to lactol, lactol is nothing but hydroxy aldehyde then this aldehyde upon further treatment with manganese dioxide.

So, the aldehyde remains same whereas, the allylic alcohol the allylic alcohol will be oxidized with manganese dioxide to form the corresponding alpha beta unsaturated ketone.

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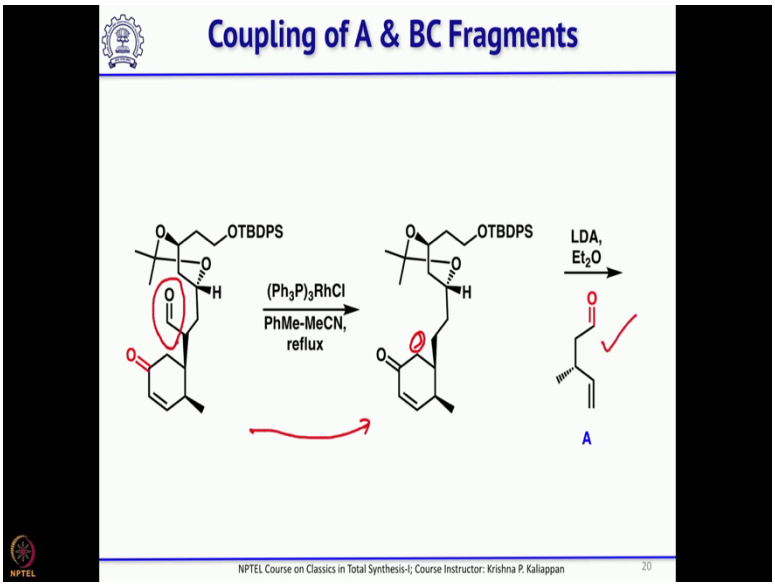

Now, from here to here which reagent one can use. So, what is happening here? If you look at carefully between the left hand side compound and the right hand side compound so what is missing? I will give 20 seconds, just check from the left side left hand side compound to right hand side compound what is missing, which functional group is missing and how that can be achieved in a single step through a well-known reaction ok.

If you look at carefully, you do not see this aldehyde is not it? You do not see this aldehyde in the product normally such decarbonylation of aldehydes are done using Wilkinson catalyst, Wilkinson catalyst is known to decarbonylate. So, that is what he has done. So, once you have this next step is again you generate anion make the enolate and quench with the fragment A.

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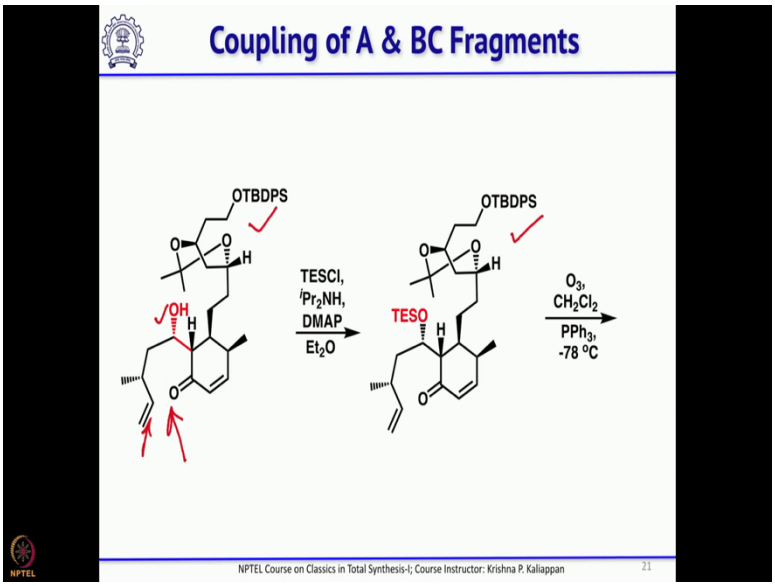

So, that will give you this alcohol ok. So, what you have to do? So, you have the precursor for the lactone and now you have to combine this ketone with this double bond original plan is you have keto and aldehyde and then do a McMurry coupling, but if you have to do you have to protect this hydroxyl group.

So, the hydroxyl was protected as TES ether that is triethylsilyl ether and then for the preparation or for the synthesis of the keto aldehyde, which is required for the key McMurry coupling the double bond was cleaved using ozonolysis to get the keto aldehyde.

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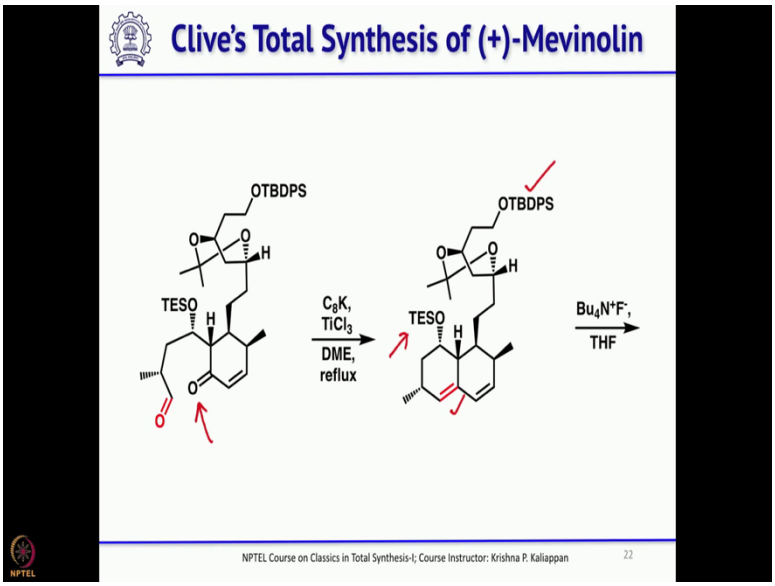

The keto aldehyde then upon treatment with titanium trichloride and potassium naphthalenide it generates titanium 0 and the titanum 0 facilitates the intramolecular McMurry coupling. So, that facilitates the intra-molecular McMurry coupling to form the bicyclic ring.

So, now, if you look at this compound, the trans diene is formed using the key McMurry coupling. Now, this particular intermediate has all the chiral centers, this particular intermediate has all the chiral centers required for the synthesis of plus mevinolin. So, what needs to be done is as I said this TBDPS group should be cleaved the TES also should be cleaved and the lactone should be formed, is not it?

That will complete the total synthesis of mevinolin.

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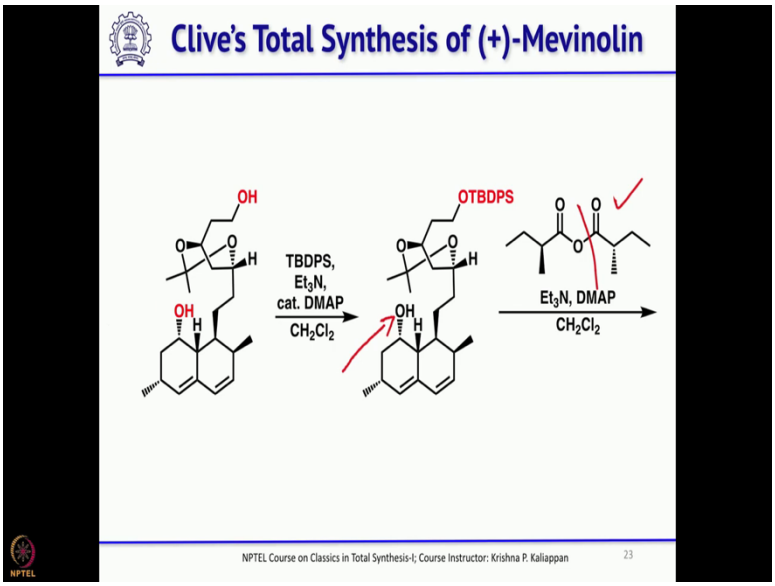

So, you treat with tetra butyl ammonium fluoride is known to remove silyl protecting group. So, you can remove both TBDPS and TES. So, you have the primary alcohol and the secondary alcohol and now you protect the primary alcohol again now you protect the primary alcohol again as TBDPS ether then you have to attach the side chain here the secondary alcohol you have to attach the side chain. So, that side chain was attached by using mixed anhydride mixed anhydride of this carboxylic acid.

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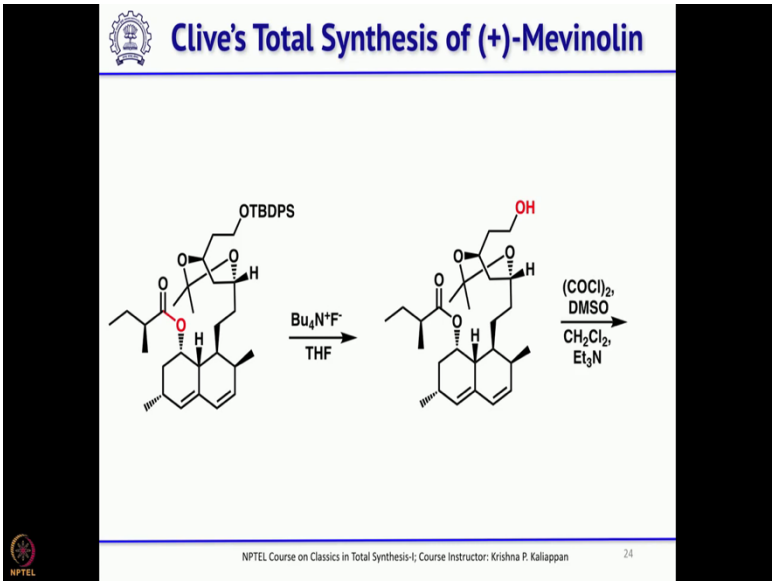

So, now that will give you the corresponding the last, but one precursor ok. So, now, what is left is only the formation of 6-membered lactone. So, it is quite easy again remove the TBDPS using tetra butyl ammonium fluoride you get the alcohol and then alcohol was oxidized under Swern condition to get corresponding aldehyde.

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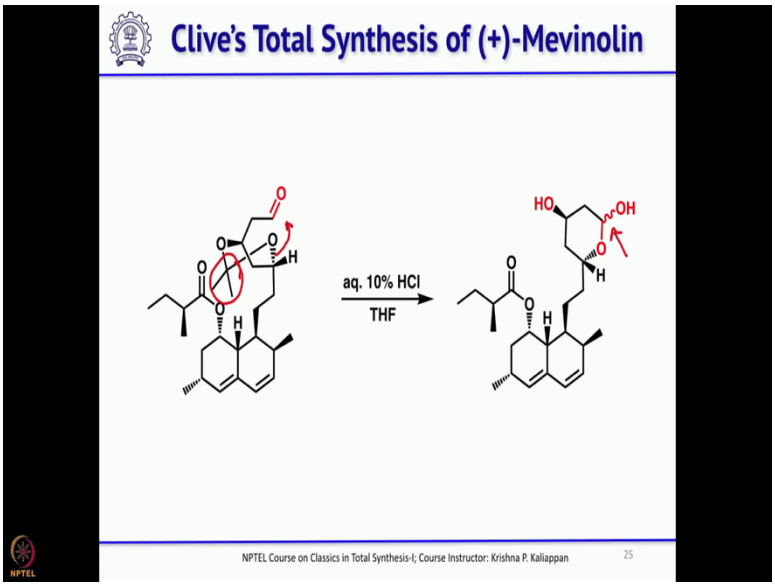

Then removal of this acetonide ok under acidic condition will give this alcohol will add to the aldehyde to form the corresponding lactol ok. So, now, if you look at this intermediate and compare with the structure of mevinolin what this missing is this lactol should be oxidized to corresponding lactone.

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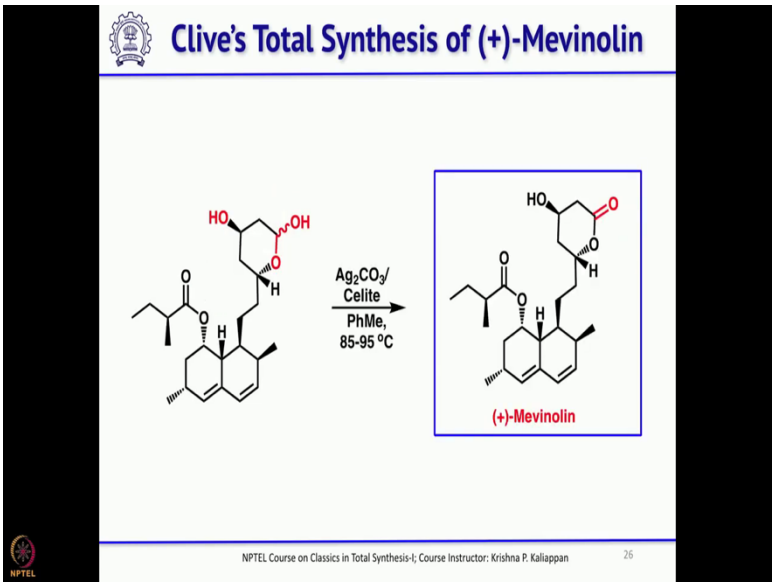

So, that was done using Fetizon's reagent. So, Fetizon's reagent is nothing, but silver carbonate on Celite so, which is a well-known reagent for selective oxidation of lactol to corresponding lactone without touching other hydroxyl group. So, the Fetizon's reagent gave the final natural product that is mevinolin. So, that is how Clive's group could successfully complete the total synthesis of mevinolin and if you look at this molecule as I mentioned. So, this is a key starting point for the synthesis of several cholesterol lowering drugs like atorvastatin, Lipitor and so on ok.

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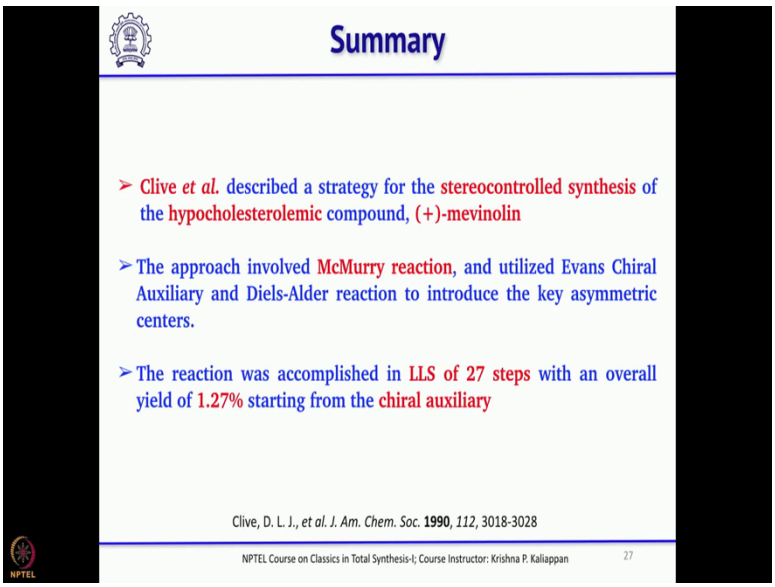

And to summarize Clive *et al* reported very highly stereocontrolled synthesis of a natural product namely mevinolin and the key reactions involved in this synthesis are McMurry coupling to form the cyclohexene and Evans Chiral Auxiliary was used for Diels - Alder reaction and alkylation. And also iodolactonization was used to get a lactone and a double bond and another interesting reaction which was used is iodo carbonate formation ok iodo cyclic carbonate formation. So, that was also very very interesting reaction to create one more chiral center.

The whole sequence to accomplish the total synthesis of mevinolin involved the longest linear sequence of 27 steps, which is understandable considering the complexity of this molecule and yield was about 1.27 percent starting from Evans chiral auxiliary.

Nevertheless, this was one of the clever synthesis and may not be very efficient, but it involve many key reactions to accomplish the total synthesis of mevinolin. So, I will stop here and then we will discuss more about natural products having 6- membered sub unit in the next lecture ok.

Thank you.