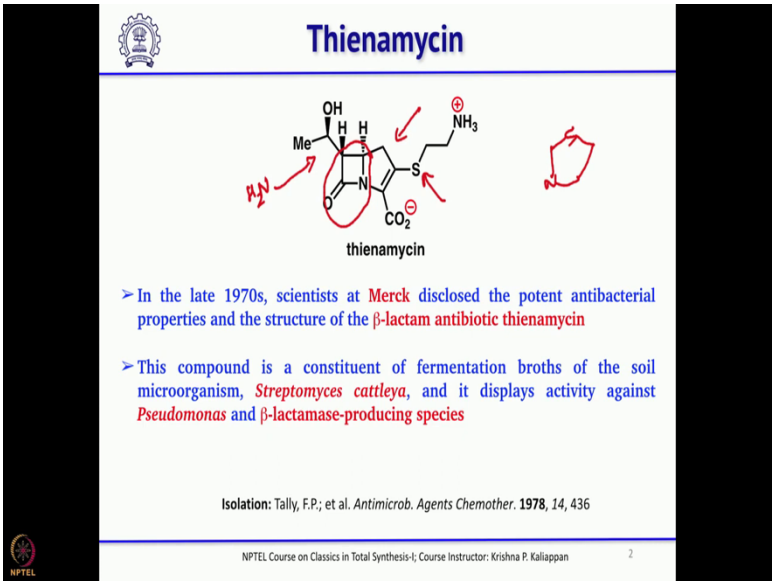
Classics in Total Synthesis - I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 09
Thienamycin (Merck)

Yeah, good morning and welcome back to the NPTEL lecture series on Classics in Total Synthesis, part I. So, in the last lecture we talked about the various methods for the preparation of beta-lactams and also the first total synthesis of penicillins. So, we continue our discussion on the total synthesis of four membered lactams and this time we will talk about total synthesis of another closely related natural product called thienamycin.

(Refer Slide Time: 00:51)



And if you look at thienamycin and it has a lot of similarities with penicillin both have this four-member lactam ok. And in the five membered ring there is a change you can see that, earlier in the five membered ring you will you would have noticed this is the five membered ring ok. Now, that S has come here, the S has come outside the five membered ring and also in the side chain earlier in penicillin you used to have NH_2 and that NH_2 is acylated ok.

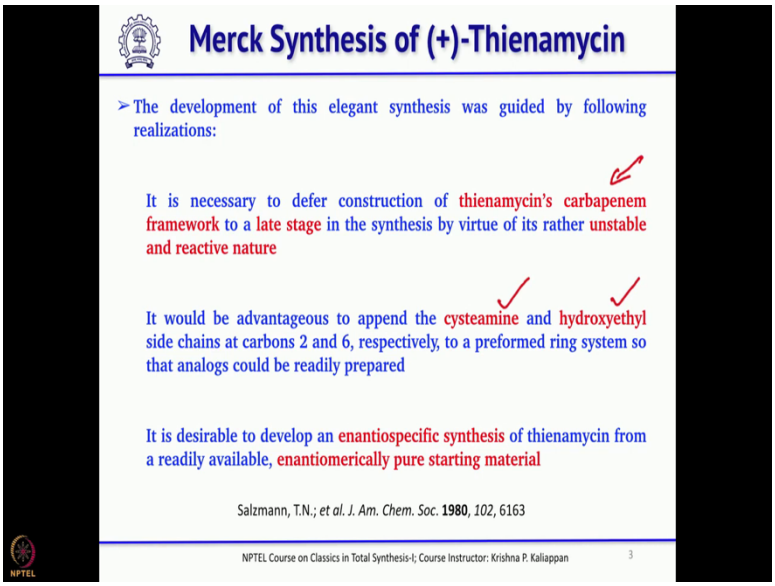
But here you what you have is CH_3CHOH; so, these are the major changes one can easily notice when you look at the thienamycin core structure with and compare it with

penicillin. So, as I mentioned while discussing about penicillin, penicillin actually created reel real you know major effect on the applications of penicillin-type natural products for the treatment of bacterial infection ok.

And after some time, the bacteria started developing resistance to the penicillins that is why the second level of antibiotics were really required to tackle all types of bacterial infection; so, that is how in when in 1970's a Merck group. So, they disclosed the structure of thienamycin which showed significant antibacterial activities, and also it was isolated from the fermentation broths of the soil microorganism called *streptomyces cattleya* ok.

And it showed very good activity against pseudomonas and beta lactamase producing species. So, this was second major break through in the antibiotic history.

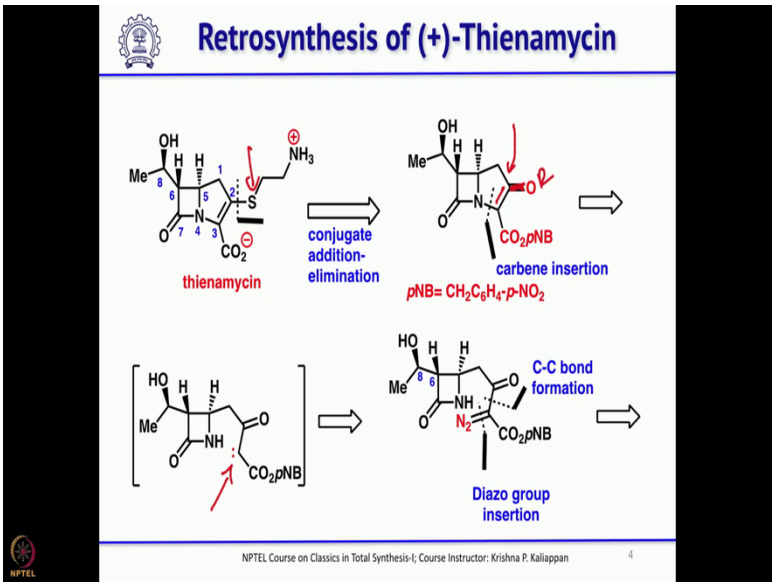
(Refer Slide Time: 02:56)



And let us see how thienamycin was synthesized by Merck, initially they did enantioselective synthesis and later they also reported a bulk scale racemic synthesis of thienamycin. First let us look at the enantioselective synthesis of thienamycin and their idea was first they want to construct the carbapenem framework at a later stage the carbapenem framework the bicyclic framework ok that they wanted to construct at a later stage.

And then they wanted to you know append cysteamine and hydroxyethyl side chains at preformed ring system. Once the rings are formed then they can attach these two. And initially they wanted to do the enantiospecific synthesis ok start with the enantio enantiomerically pure starting material.

(Refer Slide Time: 03:58)



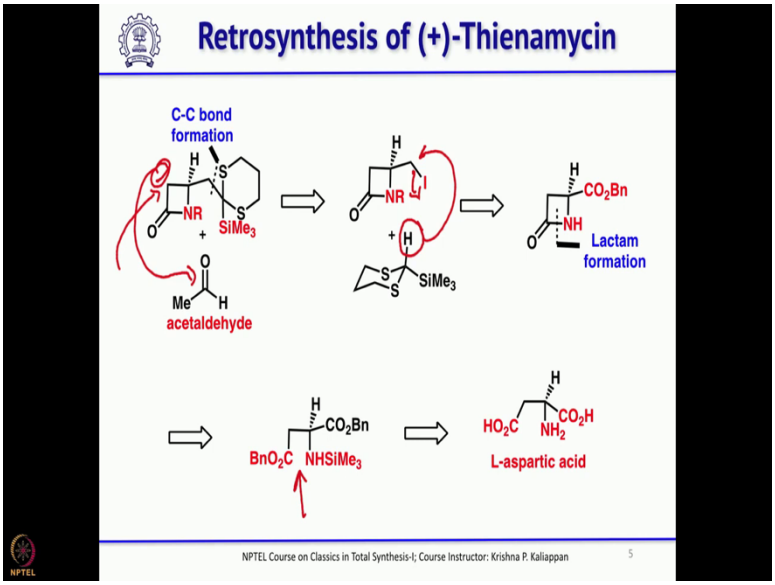
So, let us see how they propose the retrosynthesis for thienamycin and how they went ahead and completed the thienamycin thienamycin. So, the thienamycin; so, if you look at this structure the first retrosynthesis involved the cleavage of this bond, C-S bond. The idea is this can be introduced through an addition elimination reaction; say for example, if you have a beta keto ester ok if you have a beta keto ester. So, then one can make the corresponding enol ether, one can make corresponding enol ether or you can make the corresponding vinyl chloride.

So, then if you treat with this corresponding thiol it can undergo a one four addition the conjugate addition followed by elimination; so, that way it is easy to introduce this thiol group. Next that is a key reaction where he wanted to introduce the CN bond and make the five membered ring through the carbene insertion ok, CN bond formation through carbene insertion ok.

When you talk about carbene insertion; obviously, the precursor is the corresponding diazo compound. The diazo compound can be easily prepared from the beta keto ester,

beta keto ester if you have and then treat with base and then tosyl azide you can easily introduce the diazo compound ok, so that is a precursor for this.

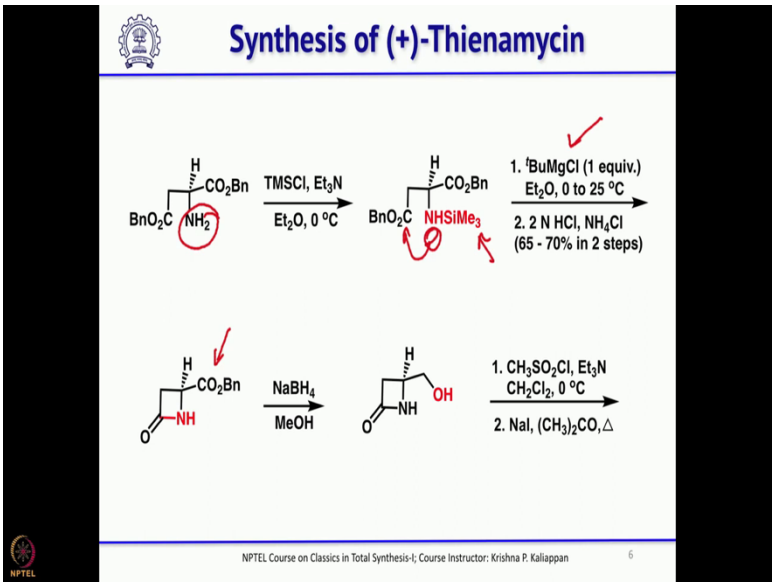
(Refer Slide Time: 05:28)



So, now this is a monocyclic compound and one can easily do it through, first you can see here this aldol reaction you generate anion and then do an aldol with acetaldehyde you will introduce the CH_3CHOH the side chain. And here this can be made by simple alkylation that is if you have TMS 1,3-dithiane and treat with butyl lithium you can generate anion and that can attack an SN_2 substitution you can introduce this.

And this can be obtained the four membered lactam can be obtained from the corresponding ester and simple lactamization between these two protected amino acids can lead to the lactam. And this is nothing but L-aspartic acid which is commercially available ok, this can be easily made from the commercially available L-aspartic acid.

(Refer Slide Time: 06:37)

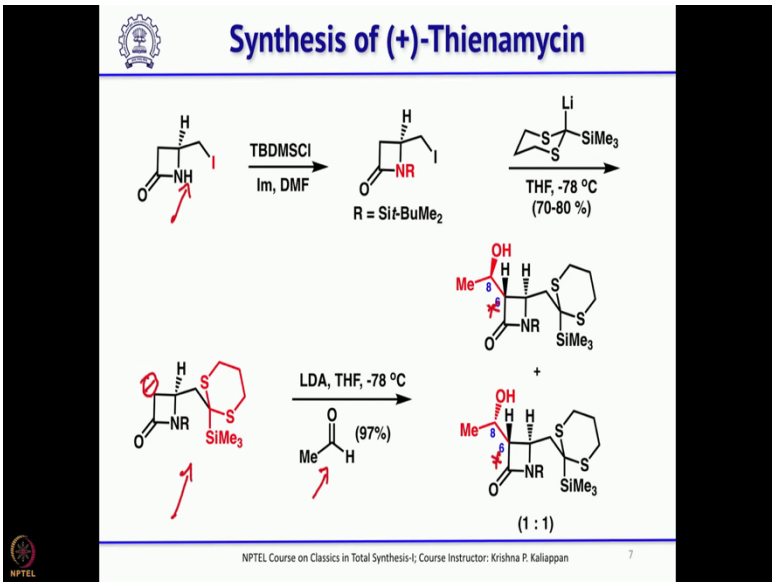


Now, let us see how they have accomplished the total synthesis of thienamycin. L-aspartic acid where the both carboxylic acids were protected as benzyl ether ok. Then the NH_2 was protected with the transient protecting group like TMS chloride. Why I am saying transient protecting group is you know there are different types of protecting groups. The transient means it is used for one or two steps ok, labile protecting group just use it for one or two steps and then cleave it; so, the TMS is one such transient protecting group.

Now, after that you treat with base; here, now base is a tertbutyl magnesium chloride. So, it generates anion and then attacks intra-molecularly the carbonyl group of the benzyl ester to form the four membered lactam ok. Then once it is done that the TMS group can be easily cleaved by treatment with 2 normal HCl. So, the four membered lactam is formed, then the ester group should be reduced selectively in the presence of four membered lactam ok.

So, that is selectively done by reducing with sodium borohydride ethanol to get the primary alcohol, the primary alcohol should be converted into the iodide ok. This was done in two steps first convert the primary hydroxyl group into mesylate and followed by Finkelstein reaction you treat this mesylate with sodium iodide in acetone you get the corresponding iodide.

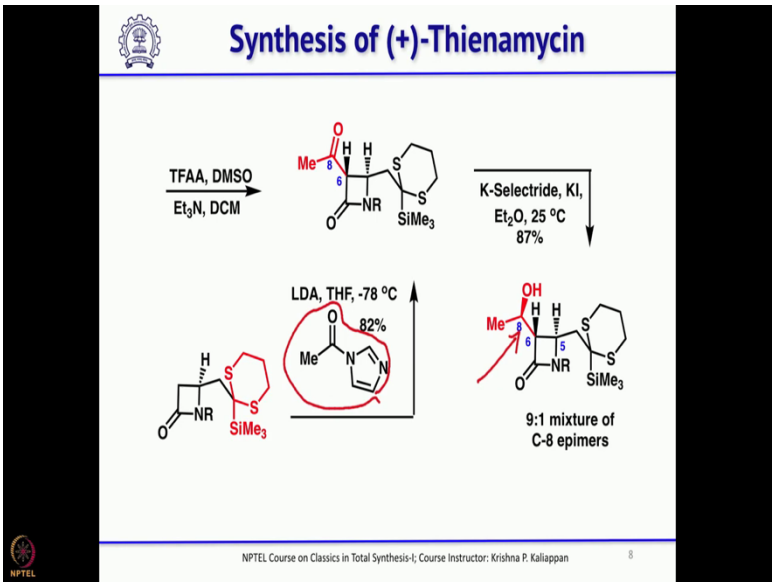
(Refer Slide Time: 08:05)



Now, this NH the amide NH was protected as TBDMS by treating with TBDMS chloride. Then you take this 2-lithio 2-trimethyl silyl 1,3-dithiane, you get the corresponding alkylated compound ok, it is a simple SN_2 reaction. Then you can generate anion with LDA quench with acetaldehyde, so get the aldol product.

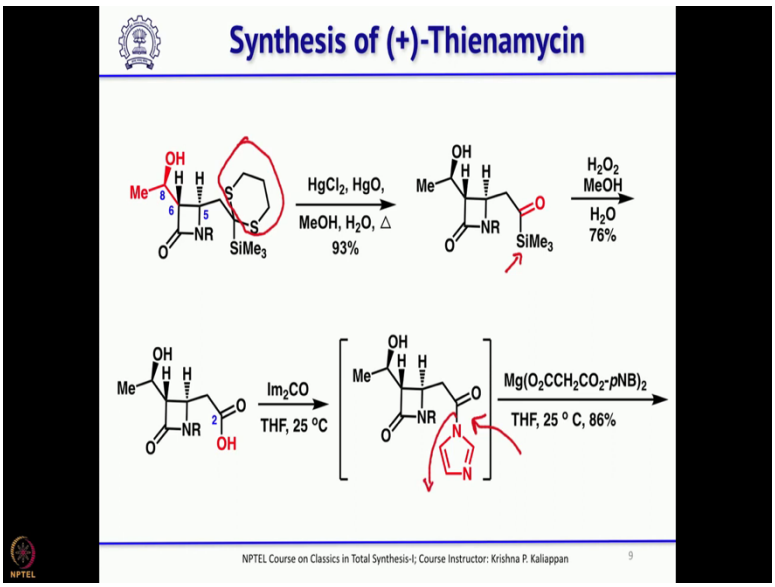
But you get a mixture 1:1 ok 1:1, and in this case, you see this stereo center is fixed ok; whereas, the hydroxy carbon the hydroxyl group attached to carbon, there he got mixture 1:1 ok. So, what he did he took this mixture and then oxidized ok, he took this mixture and oxidized.

(Refer Slide Time: 09:04)



And same thing the same ketone what he did he also got it in one step. Instead of doing aldol followed by oxidation, he took this lactam and then treated with the LDA and N-acetyl imidazole ok, you treat with LDA and treat with N-acetyl imidazole he got the same product ok. Now, when you reduce this ketone with K selectride, he got 9:1 ratio of the expected product and 1 is the unwanted product unwanted isomer ok.

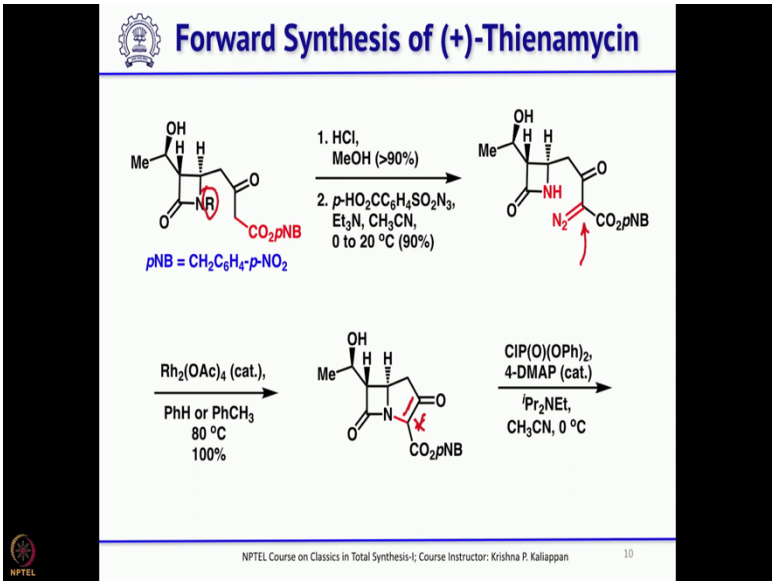
(Refer Slide Time: 09:47)



So, then you took the major one and then treated with mercury chloride and mercury oxide; so, that is to remove this ketal ok. The ketal group was removed to get the

corresponding ketone as you want acid the TMS group was treated with hydrogen peroxide to get the carboxylic acid ok. So, once you have the carboxylic acid convert into the corresponding imidazole ok, then you remove this or do a SN_2 reaction with para nitro benzyl CO_2CH_2 that CH minus attacks this carbonyl and this imidazole comes out; so, what you get is this compound.

(Refer Slide Time: 10:26)



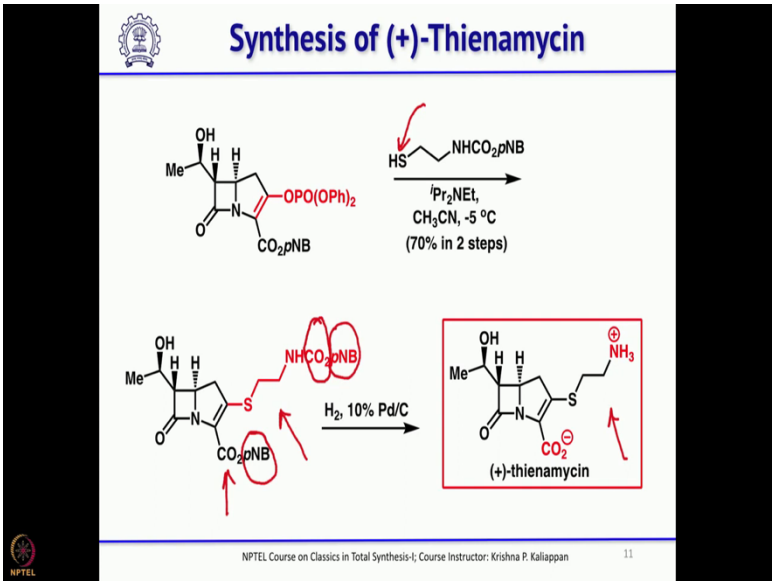
So, basically what they have done is to prepare the precursor for making or introducing the diazo compound. For the introduction of diazo compound, you need a beta keto ester ok; so, that is what they have done. And here R is still the TBDMS group; so, once you have this treat with HCl methanol and treat with para toluene sulfonyl azide triethylamine.

So, HCl methanol removes the TBDMS group then the tosyl azide as I said introduces the diazo group the tosyl azide introduces the diazo group. Now, you treat with dirhodium tetraacetate and it forms the carbene and NH insertion immediately takes place to get the five membered ring ok. This is a very very interesting method to make the five membered ring.

But the stereo center is it important? No, because if you look at the natural product thienamycin you have a double bond here is not it. So, that chiral center is not important; so, what you do take the beta keto ester and treat with phosphoryl ok, diphenyl phosphoryl chloride ok that forms the enol phosphate. If you have beta keto ester and

then treat with diphenyl phosphoryl chloride, it forms the corresponding beta keto; so, corresponding enol phosphate ok.

(Refer Slide Time: 12:08)

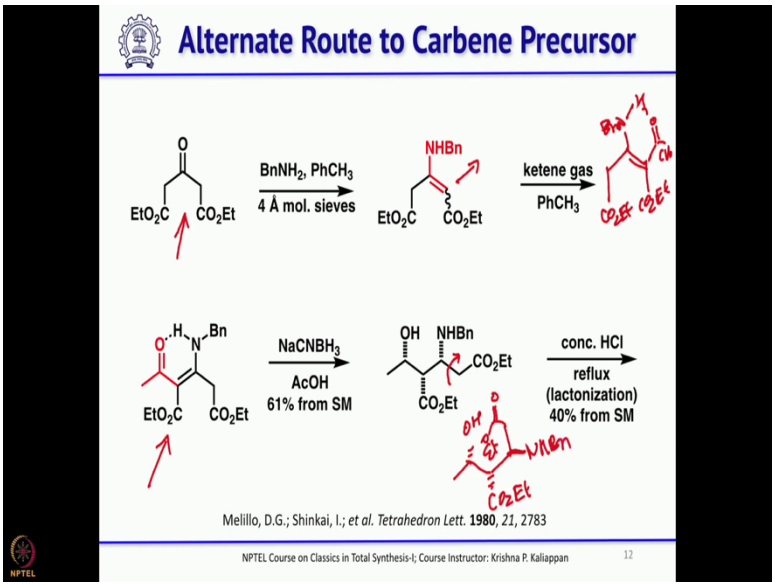


This enol phosphate again as I said it can undergo a one-four addition followed by elimination that addition elimination reaction with this thiol will give you the expected product ok. So, now, what is required in the total synthesis of thienamycin? You have to remove the para nitro benzyl group without touching the double bond ok. Hydrogenolysis gives the corresponding carboxylic acid and you can see there are two para nitro benzyl one here and one there.

So, this will lead to carboxylic acid and here this will also remove the carbon dioxide, because that is a protecting group NH_2 is protected as NHCOO*p*NB. So, when you remove the para nitro benzyl group, the carbon dioxide also will go and you will get NH_3; so, then that will be in the zwitterionic form. So, that is how they completed the enantiospecific total synthesis of thienamycin.

And then they wanted to develop a scalable method for the thienamycin and for that they first they developed a scalemic method that is a racemic method for the synthesis of thienamycin.

(Refer Slide Time: 13:31)

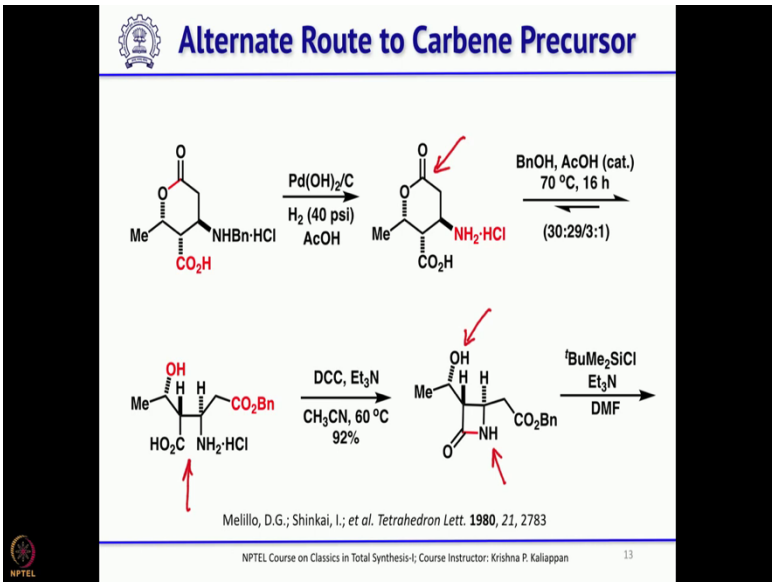


So, what did they do and how did they do. So, they started with this commercially available beta keto ester I can see. So, this one has a 2 esters is not it, this one treatment with benzyl amine ok; so, it can form enamine is not it. So, in the presence of molecular sieves it forms in enamine, that enamine when you treat with ketene when you treat with ketene it can undergo at this position ok. So, it can undergo at this position basically you introduce $SCOCH_3$ ok, N-acylation take place ok.

So, I have written the other way other side in case 180 degree you have to rotate. So, you will get this compound or I can write that structure; so, that you know you will not get confused because both are same. So, this is NBn, then $COCH_3$ you can see that. So, this I have rotated 180 degree ok. Now, when you reduce this ketone ok, when you reduce this ketone with sodium cyanoborohydride in the presence of acetic acid ok not only it is reduces the ketone.

But also the enamine portion ok that gives you can see 3 stereogenic centers ok that fixes of course, it is a racemic ok; so, you get the exactly opposite isomer also. Now, if you treat with concentrated HCl, if you treat with concentrated HCl; so, this bond rotates ok this bond rotates. So, what will you get is what you will get is this one and that will undergo intramolecular cyclization to give this lactam.

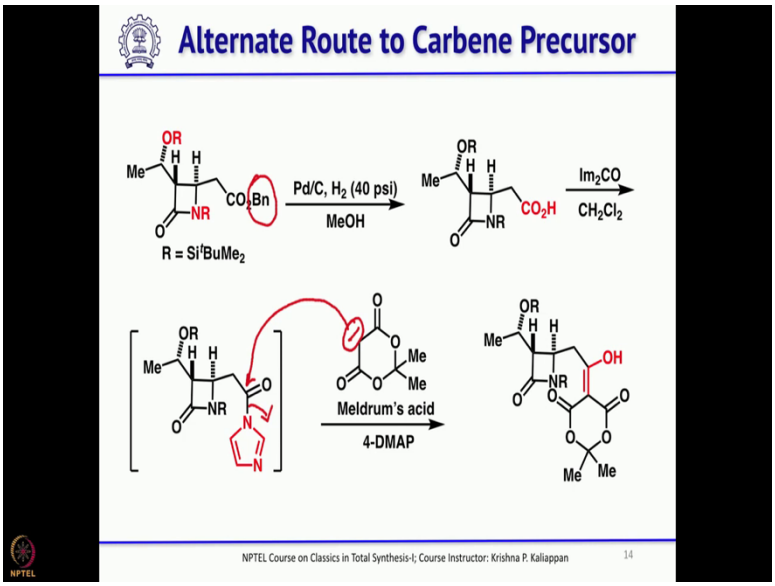
(Refer Slide Time: 15:47)



So, what you got is six membered lactam; of course, the ester also will be hydrolyzed to carboxylic acid ok. Next the benzyl group you do not want it has served this purpose; so, you cleave it under hydrogenolysis condition to get the corresponding amine. Then you open it up open the lactam with benzyl alcohol ok, when you open the benzyl alcohol this is what you get ok.

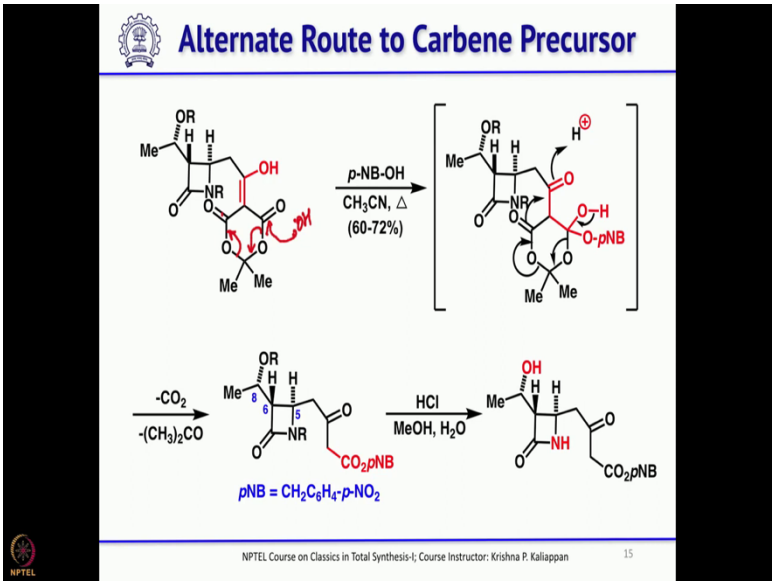
Now, what you need to do? You have to make the beta-lactam; so, that is normally done with DCC that is Di cyclohexyl carbodiimide you get the beta-lactam. Then protect both secondary hydroxyl group as well as the beta-lactam NH with TBS ok.

(Refer Slide Time: 16:40)



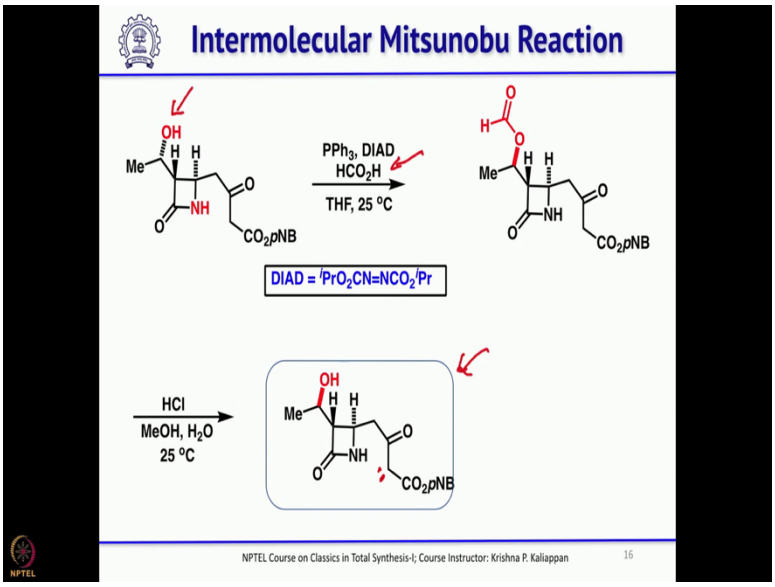
Then you remove the benzyl group of the ester under hydrogenolysis condition, then treat with CDI that is Carbonyl Di Imidazole ok, you get this compound. Then you treat with Meldrum's acid ok. So, the Meldrum's acid, what it does? It generates anion here and then attacks this carbonyl and this comes out ok. So, now it is like a triketone ok, keto here you have ketone and then you have 2 ester; so, because of stability the ketone will be in the form of enol ok.

(Refer Slide Time: 17:30)



Once you have this, then you treat with para nitro benzyl alcohol. So, the para nitro benzyl alcohol ok, it attacks here ok; then this acetone which is a stable group which will come out ok. And this is in the keto form then this carbonyl group attacks; so, what you get is this beta keto ester ok; basically, what you get is beta keto ester. So, once you have this, then you remove the TBDMS group ok, both O-protected, N-protected TBDMS group you remove.

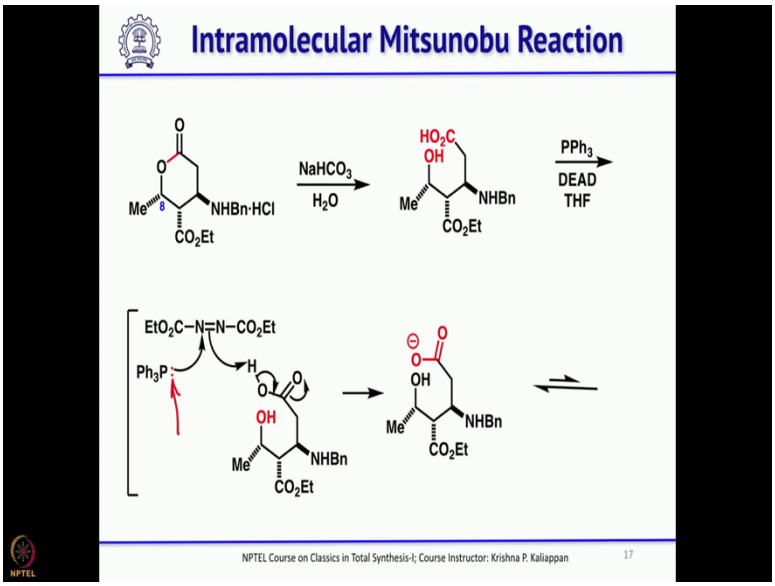
(Refer Slide Time: 18:14)



Then you take this hydroxyl group you can see this hydroxyl group which is alpha; but, in thienamycin it should be beta. So, how one can do? Either you can oxidize and then reduce it or one can also think about Mitsunobu reaction, because by this time the synthesis was started Mitsunobu reaction came into place. So, one can use Mitsunobu reaction which is nothing but it will invert the stereocenter.

So, the acid which you used was formic acid; so, you got OCHO. Then if you do hydrolysis, OCHO gets hydrolyzed and then you get OH. So, now, you can see this is the key intermediate is not it this is a key intermediate in the total synthesis of thienamycin reported by the same group, but that was enantiospecific this they wanted to do in large quantity. So, what is left is you have to generate the carbene here and then CN bond formation ok; then the enol ether and then addition of thiol will complete the total synthesis.

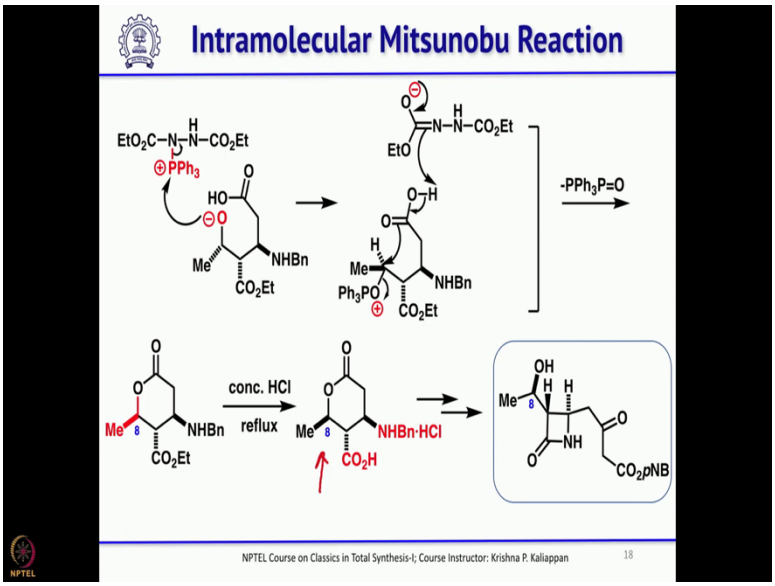
(Refer Slide Time: 19:25)



They also tried intramolecular Mitsunobu reaction ok. So, there intramolecular Mitsunobu reaction they tried with formic acid, they also tried intramolecular Mitsunobu reaction. When they started with this lactone what they did? They just hydrolyzed; they hydrolyzed this lactone to carboxylic acid hydroxy carboxylic acid then they treated with triphenylphosphine, DEAD ok.

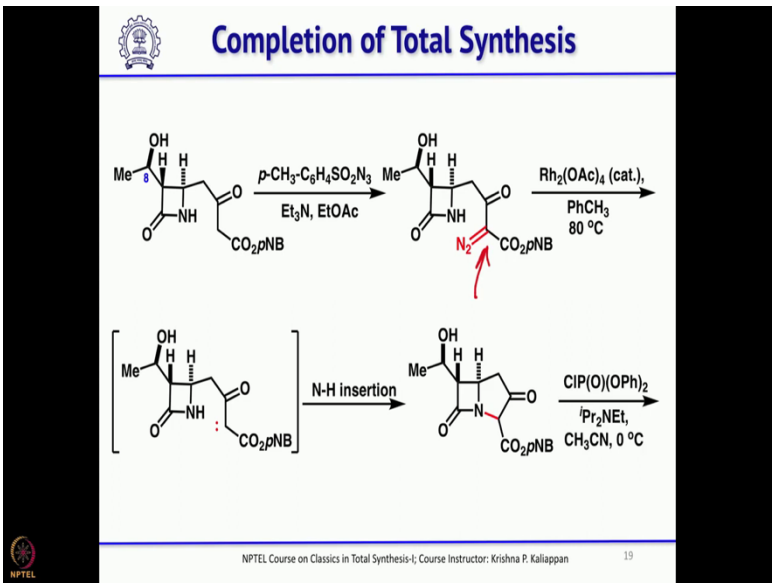
So, that is a mechanism as you know the carboxylic acid first triphenylphosphine attacks the diazo and then the diazo picks up the proton from carboxylic acid and then you form the CO_2 minus.

(Refer Slide Time: 20:07)



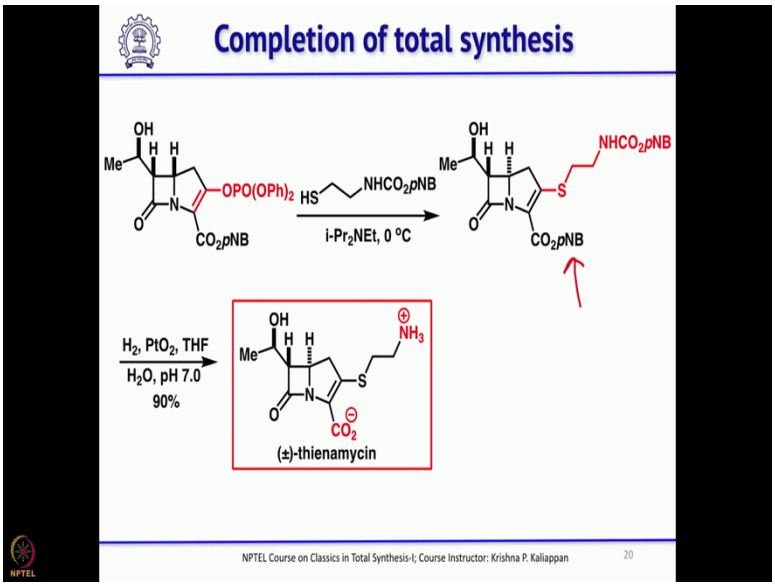
Now, this OH will attack the triphenylphosphine and you get this intermediate that is $OPPh_3$. And then the carboxylic acid will intra molecularly attack and in a SN_2 fashion you get this compound ok; this upon hydrolysis you get you have inverted the stereo center here ok. So, then you can follow the same process ok, one can follow the same process to get this intermediate. Once you have this intermediate, then diazotization, carbene insertion ok and then enol ether formation and then thiol addition will give thienamycin.

(Refer Slide Time: 20:47)



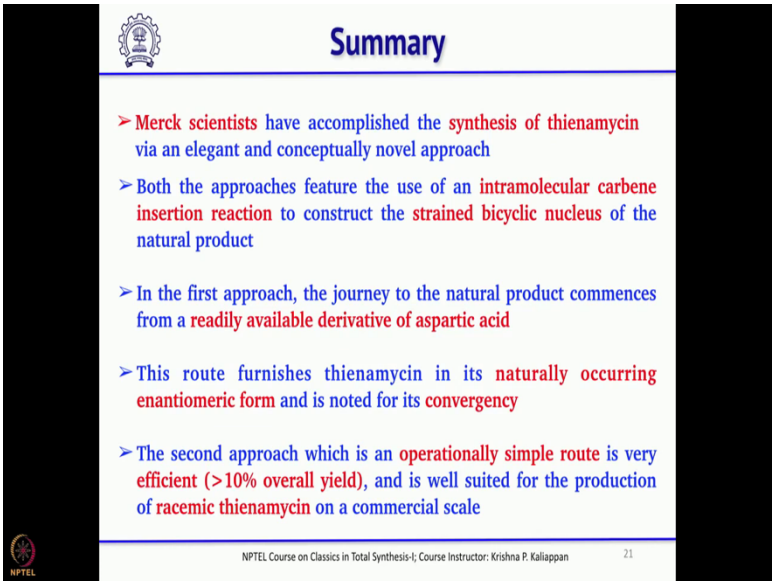
So, standard you have the alcohol, diazotization you introduce the nitrogen; then treat with dirhodium tetraacetate to generate the carbene and that undergoes intramolecular NH insertion. And then followed by treatment with diphenyl phosphoryl chloride in the presence of Hunig's base gives the enol phosphate.

(Refer Slide Time: 21:09)



And 1,4-addition followed by elimination and removal of this benzyl para nitro benzyl group gives thienamycin. So, this they have done in racemic method, but this can be done in large quantity compared to the earlier method.

(Refer Slide Time: 21:31)



To summarize, so what Merck's scientists have done is they have reported two total syntheses of thienamycin. The first one is an enantiospecific one, and the second one is racemic synthesis in both cases they have used intramolecular carbene insertion reaction as the key reaction to make the five membered ring. In the enantiospecific synthesis they started with commercially available aspartic acid as the chiral amino acid; so, that they ended up with optically active thienamycin.

In the second case that is a racemic one; so, they used intramolecular as well as intermolecular Mitsunobu reaction as one of the key reactions. And overall yield also was much better compared to the first one; nevertheless, the second method is a racemic one ok. So, thank you I will stop here and I will talk about one more total synthesis in this before we move to other natural products.

Thank you.