


Classics in Total Synthesis - I
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Lecture - 08
Penicillin (Sheehan)

Good morning everyone and welcome back to this NPTEL lecture series on Classics in Total Synthesis Part I. So, we have been discussing about three-membered ring containing natural products and their total synthesis and recently, we started discussing about four-membered ring and non-natural products. We just completed the discussion on the synthesis of cubane. So, now, we will move to some interesting and naturally occurring compounds and how they have been synthesized.

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Penicillins

CC1(C)SC(=O)N2C(=O)N(Cc3ccccc3)C(=O)N12C(=O)O


Penicillin V

> In the late 1920s Sir Alexander Fleming discovered a substance capable of destroying pathogenic bacteria. This substance is produced in nature by the mold *Penicillium notatum* and it was named Penicillin

> Chain, Florey and co-workers reported that penicillin displays remarkable *in vivo* activity against a variety of pathogens

Isolation: Fleming, A. *Brit. J. Exp. Path.* **1929**, 10, 226

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So, when you talk about four-membered ring immediately, one natural product which should come to all your mind is penicillin. So, penicillin as you know it has a great history and it was discovered by Sir Alexander Fleming in 1920 and that was considered as one of the greatest discoveries because during the world war, many people died and with the isolation of penicillin, later you know they could change the treatment for people who are infected seriously during the war.

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Penicillins

> Chemotherapeutic potential of penicillin motivated the institution to initiate a massive, cooperative British-American program during the Second World War which had as its principle objectives

1. The elucidation of the molecular structure of penicillin ✓
2. The development of a practical path for its chemical synthesis ✓
3. Large-scale production of penicillin by fermentation methods ✓

> The goal of achieving a practical synthesis of penicillin could not be reached before the end of the war

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And this penicillin, if you look at the history of penicillin, after seeing the potential of penicillin, USA and UK, they come up with a real you know high level of target and what they wanted to do was first of all, so they know when they isolated penicillin, they know it is it is an excellent antibiotic. But they did not know the structure.

So, the first objective was to elucidate the structure and what is the correct structure of penicillin ok. Once you isolate, once you elucidate the structure, then the next step is whether we can we should be able to synthesize this chemically ok; chemical synthesis in the laboratory is the second objective.

Once it is done at the laboratory level, then it should be possible to scale up and at the same time, they were also looking at the third option that is whether penicillins can be synthesized or can be made on a large scale through fermentation ok. So, these were the three major objectives during the Second World War, how to produce more penicillins because this was very much required as you know many people died in the Second World War not due to the opposition; but due to the infection.

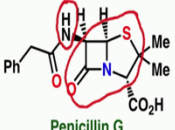
So, that was a serious problem and they wanted to address this as early as possible. But however, as you know this is not an easy task. It took more time and the synthesis of penicillin somehow could not be achieved during the Second World War. It took almost 10 years later to achieve the first total synthesis.

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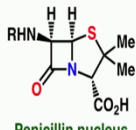

Penicillins

✓

> Professor Dorothy Crowfoot-Hodgkin of Oxford University elucidated the structure of penicillin G by X-ray crystallography



Penicillin G



Penicillin nucleus


> Penicillins are a family of closely related substances which differ only with respect to the acyl grouping attached to the nitrogen atom that is α to the lactam carbonyl

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And from the structure point of view, the correct structure was elucidated with the help of X-ray and that was done by Nobel laureate Professor Dorothy and if you have a close look at this penicillins, you can see one core structure is a beta-lactam ok; the four-membered beta-lactam and that is fused with say a five-membered ring ok that is fused with a five-membered ring.

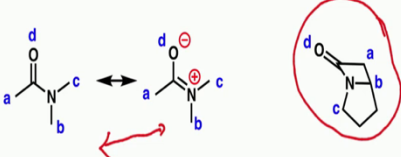
So, this is the core structure for all penicillins ok and what you also see is this amino group adjacent to the carbonyl group; amino group adjacent to the carbonyl group and which is acylated ok which is acylated with various acyl group ok.

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**Penicillins**

> The most striking and challenging structural feature of penicillin is its **four-membered β -lactam ring**; this strained substructure is the locus of penicillin's **unstable and reactive nature** and is responsible for its **potent antibacterial activities**

> Woodward reasoned that the **β -lactam ring** of the penicillins does not exhibit stability of a typical amide because it is **fused to a five-membered ring**

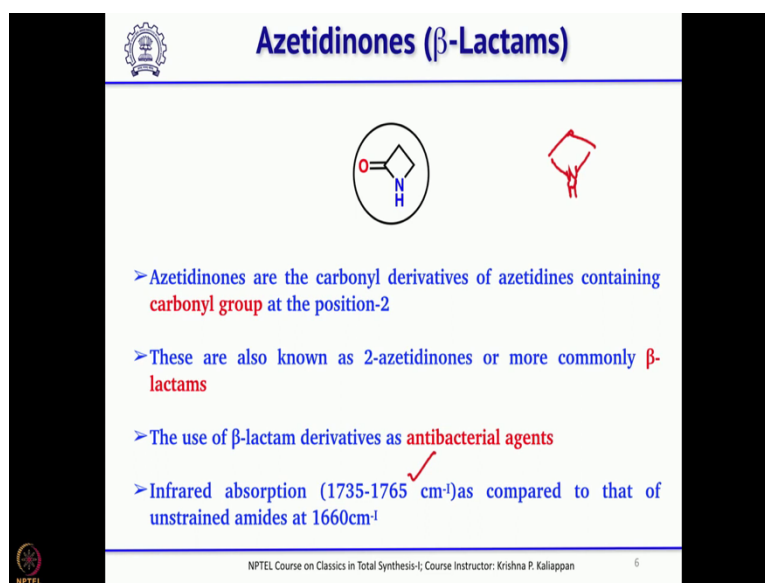


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And when you look at this four-membered lactam ok, this four-membered lactam, it is quite unstable compared to normal amides or normal lactams. As you know cyclic amides are called lactams and compared to five-membered, six-membered lactams; the four-membered lactam is quite unstable and of course, when it is unstable it can also react faster. So, what Woodward told was it is not like a normal amide ok.

So, if you look at normal amide, you can see this can exist like this; whereas, in the case of a four-membered lactam ok, it cannot exist like this. So, that is where the reactivity of beta-lactam comes into play.

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The slide features a title 'Azetidinones (β-Lactams)' at the top center. To the left of the title is a small logo. Below the title, there are two chemical structures: a 2-azetidinone ring (a four-membered ring with a nitrogen atom and a carbonyl group at the 2-position) and a red skeletal structure of a penicillin molecule. Below these structures is a list of bullet points:

- > Azetidinones are the carbonyl derivatives of azetidines containing **carbonyl group** at the position-2
- > These are also known as 2-azetidinones or more commonly **β-lactams**
- > The use of β-lactam derivatives as **antibacterial agents**
- > Infrared absorption (1735-1765 cm^{-1}) as compared to that of unstrained amides at 1660cm^{-1}


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And if you look at literature, how this beta-lactams were made ok. So, the beta-lactams the parent structure that is the four-membered compound with NH that is this compound is called azetidines ok. So, beta-lactam means azetidine with a carbonyl group at 2 position ok. A common name we always call it as beta-lactams, but you know IUPAC names are you know different.


Four membered the beta-lactams are called azetidinones ok from the IUPAC and as we have seen penicillins and there are many other substituted penicillins which are well known as antibacterial agents. From the spectroscopic point of view, when you take IR of all these beta-lactams, you will see a significant absorption at between 1735 to 1765.

Normally, when you look at simple amides or six-numbered lactam, you will see a strong absorption at 1660. So, you will see clear difference close to 100 ok. So, that tells the presence of beta-lactam. When you make beta-lactam, the best way to see is just to take IR and then, see you have got beta-lactam ok. Because you will see a clear absorption around 1750 that will confirm that you have made beta-lactam.

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Synthesis of β -Lactams



- > Cyclization reaction ✓
- > Cycloaddition reaction ✓
- > Ring expansion reaction ✓
- > Insertion Reaction ✓
- > From Azetidines ✓

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So, how these beta-lactams were made; before I talk about the total synthesis of penicillin ok, how these beta-lactams are generally prepared. So, there are five common reactions which you know have been successfully used to make these beta lactams. One, one can use cyclization ok; intramolecular cyclization to form this four-membered ring. Two, one can also think about using cycloaddition reaction ok. So, when you have four-membered ring, then immediately you can also think about using 2 plus 2 cycloaddition reaction.

Three, ring expansion; that means, you know you have a three-membered ring; from three-membered ring, you can expand to four-membered ring and four, this also quite frequently used in the synthesis of beta lactams is insertion reaction ok. So, either you can do carbon insertion or nitrogen insertion ok. The last one is from azetidines ok. So, these are the five common types of reactions which are routinely used and regularly used to make various beta-lactams.

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Synthesis of β -Lactams

Cyclization reactions

- > Intramolecular cyclization of β -amino acids in the presence of certain reagents including acyl chloride, phosphorus trichloride and thionyl chloride provides β -lactams
- > However, β -aminopropionic acids are not cyclized to β -lactams on heating, but undergo elimination reaction providing amines and acids

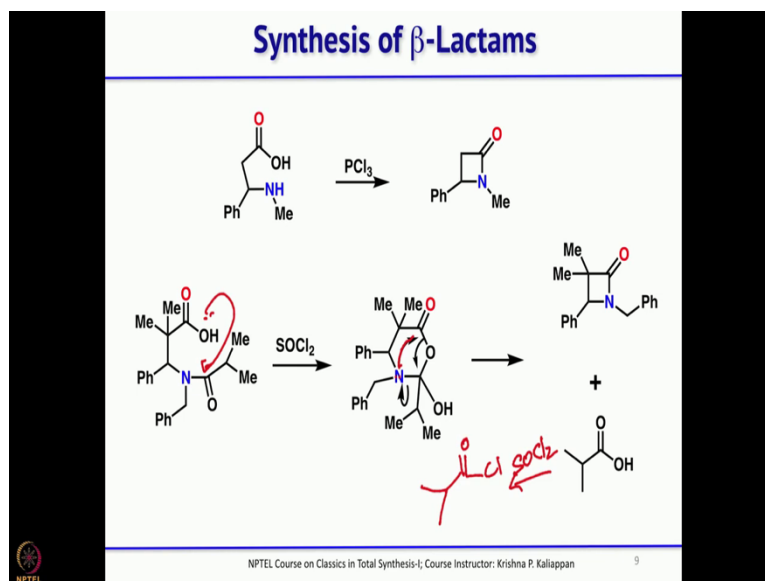
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First, let us start with cyclization reaction. Cyclization reaction normally if you have a beta amino acid ok, if you have a beta amino acid, then if you treat this beta amino acid with acyl chlorides, PCl_3 , SOCl_2 ; then it can form beta lactams. But isolation is very important because these are quite unstable, you should quickly isolate to get the corresponding beta-lactams.

However, when you have beta amino propionic acids ok, then if you heat it for a long time; if you heat it for a long time, there is a possibility of beta elimination. So, when beta elimination takes place, you will get a amine and the carboxylic acid. I will just show that example. So, here you know you see this is alpha, beta ok. So, beta amino acid. This on treatment with acyl chloride ok. So, basically, so acylation takes place at the carboxylic acid followed by the nucleophilic attack of the nitrogen, you get the corresponding beta-lactam.

And if you heat it if you heat it, it undergoes a Retro Michael ok; it undergoes a Retro Michael to give the corresponding amine and alpha beta unsaturated carboxylic acid. So, this is the major drawback; when you do such cyclization reaction, you should never heat it ok, when you have beta amino acid.

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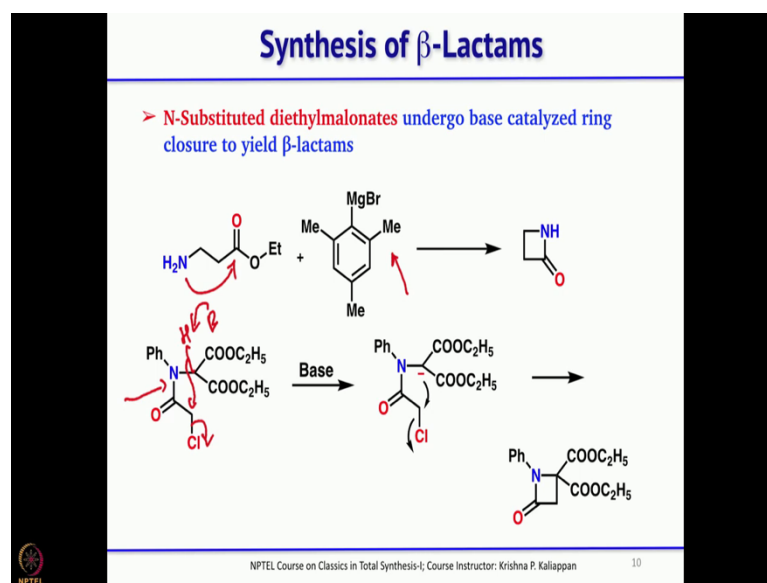


Then, same beta amino acid as I said acyl chloride, PCl_3 , SOCl_2 could be used for cyclization. So, PCl_3 will give the same beta-lactam and if you protect the nitrogen, if you protect the nitrogen and then, treat with thionyl chloride; so, what will happen? This carboxylic acid intramolecularly can attack the amine ok.

So, then, once it is here, then as you can see here this nitrogen lone pair can attack intramolecular to the carbonyl and it can rearrange to give four-membered lactone and the carboxylic acid, this isobutyric acid and this isobutyric acid still SOCl_2 is there, is not it? So, what will happen? It will go to the corresponding acid chloride isobutyric acid chloride ok.

So, you can use PCl_3 , you can use SOCl_2 , you can also use CH_3COCl to form this type of beta lactams, starting from beta amino acid; only thing is you should not heat it. When you heat it, you will get the amine and alpha beta unsaturated carboxylic acid.

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Now, if you look at this example ok, again cyclization takes place, but for NH_2 to cyclize NH_2 to cyclize you need a base and a hindered base the here, Grignard is used to remove this proton and that can cyclize to give a four-membered lactam ok.

So, the hindered Grignard Reagent is used as a nucleophile base to form this four-membered this one and in this example as you can see here this is the most acidic proton, is not it? So, if you treat with base ok, even triethylamine or sodium ethoxide. So, it can pick up the proton here and intra-molecular $\text{S}_{\text{N}}2$ -type cyclization should give the corresponding beta-lactam. So, this particular example is slightly different than the three examples which I discussed.

So, the earlier example amine, the primary amine; primary amine intramolecularly attacks the carbonyl group ok. Carbonyl group having a leaving group. Here already you can see the amide bond. So, amide bond is already formed. The earlier cases amide bond that is a lactam bond is formed during the key reaction.

Here in this case the $\text{S}_{\text{N}}2$ substitution takes place ok. Anion is generated and you have a good leaving group that is a chloride or bromide or iodide, the intra-molecular $\text{S}_{\text{N}}2$ like reaction takes place to give corresponding beta-lactam.

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Synthesis of β -Lactams

- > Cyclization of β,γ unsaturated Hydroxamates:
- > Bromine induced cyclization via the formation of bromonium ion intermediate
- > The presence of a phenyl group at the γ -position fails to provide β -lactams
- > The regioselectivity of opening of the bromonium ion intermediate is reversed due to the formation of stabilized benzylic carbonium ion

$R = \text{alkyl}, -\text{CHCOOR}, -\text{CH}=\text{CH}_2$

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Then, one can also use beta gamma unsaturated hydroxamates; beta gamma unsaturated hydroxamates, what is that? You can see. So, this is called hydroxamates ok, then you have alpha beta gamma. Beta gamma unsaturated hydroxamate.

Now, on the double bond, if you add iodine, if you add bromine. So, then, it can form the corresponding iodonium or bromonium ion; is not it? Once this is formed, then intramolecularly nitrogen can attack and open the corresponding iodonium or bromonium ion. So, that will give you the corresponding four-membered lactam that is a beta-lactam ok.

So, basically you are doing iodo lactamization or have bromo lactamization ok. So, that is how you make this beta-lactam and this also can be easily cleaved N-O bond can be cleaved under hydrogen analysis condition to get the free NH.

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Synthesis of β -Lactams

- > Cycloaddition reaction:
 - > Cycloaddition of olefins to Isocyanates:
- > The reaction of nucleophilic olefins with isocyanates provides β -lactams involving [2 + 2] cycloadditions
- > The reaction proceeds with the formation of dipolar intermediate involving electrophilic attack at the olefinic site by an isocyanate group

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Then one can also think about using cycloaddition reaction. So, 2 plus 2 cycloaddition reaction. So, when you want to use 2 plus 2 cycloaddition to form beta-lactam, so one portion should be alkene; the other portion should be isocyanates ok. So, isocyanates are easy to make ok.

So, you have isocyanate and then, double bond and this can undergo a spontaneous 2 plus 2 cycloaddition to give the corresponding your beta-lactam. If you use chloro sulfonyl isocyanate ok, chloro sulfonyl isocyanate, you will get this beta-lactam and then, the chloro sulfonic group can be easily removed. If you take this and then treat with water just a water that is sufficient that will cleave the SO_2Cl .

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Synthesis of β -Lactams

- > Ring Expansion Reactions :
- > The ring expansion using nickel carbonyl occurs with the insertion of CO into the less substituted C-N bond
- > Cyclopropanes also undergo ring expansion reaction with the formation of β -lactams

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Ring expansion; so, ring expansion is a very interesting and important reaction because as such four-membered ring itself is strained and you are getting this four-membered ring from another strained compound that is three-membered ring. So, from that angle, one strain to another strain, it takes place ok.

Say for example, if you have the cyclo propane ok; cyclo propane having a hydroxyl group and amine attached to the same carbon, hydroxyl and amine attached to the same carbon ok. Now, if the N-H is converted into N-Cl then treatment with silver salts as you know when you take any N halide treat with silver salt, first thing is silver chloride you know will come out and then, you will have a positive charge on the nitrogen.

Then, the cyclopropane will open up and migrate to the positive charge on the nitrogen and now, the positive charge will be on the carbon having hydroxyl group. So, the loss of proton will give you the four-membered ring ok. So, this is another interesting way to make the four-membered beta-lactam ok.

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Synthesis of β -Lactams

- > **Carbene Insertion reaction:**
- > Rhodium (II) acetate catalyzed decomposition of **diazoacetamides** with bulky N-substituents also involves methylene insertion in the carbon-carbon bond providing β -lactams
- > β -Lactams are also obtained by the photolysis of **chromiumcarbene** complexes in the presence of imines involving methylene group insertion

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Then, as I said another interesting reaction to make beta-lactams is carbene insertion ok. If you can generate carbene; carbenes are generally you know made from diazo compound ok. So, if you have a diazo compound and then, treat with Rhodium, di rhodium tetra acetate ok. So, then, it can generate in situ carbene or carbenoids, since you are using rhodium metal, it is a rhodium carbenoid that can you know immediately undergo a carbene insertion at this carbon to give the corresponding beta-lactams ok.

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Total Synthesis of Penicillin V

> **Professor J. Sheehan** and his group at **MIT** reported the first rational total synthesis of **penicillin V** in 1957

Penicillin V

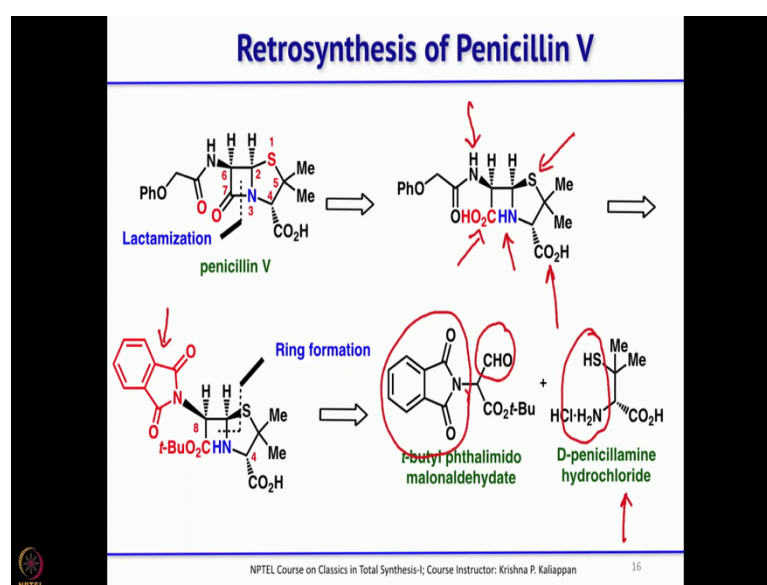
Sheehan, J.C.; Henery-Logan, K.R. *J. Am. Chem. Soc.* **1957**, *79*, 1262

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So, now, we discussed quite a few methods for making beta-lactams ok. Now, we will move to how penicillin was discovered ok; the penicillin the antibiotic well-known antibiotic great history behind this isolation of penicillin and the use of penicillin. But how the first total synthesis of penicillin was accomplished.

Professor Sheehan from MIT and his group, they spent several years you know you can see when it was is 1920 ok. So, they send they spent many years on the total synthesis of penicillin and finally, their sustained efforts led to the first total synthesis in 1957 ok.

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Let us see how he has synthesized and what is what was his retro-synthetic plan. The first bond to be disconnected obviously, was the lactam bond ok; you cleave the lactam bond and you get a carboxylic acid and amine ok. So, you have a carboxylic acid and an amine. So, basically what you are going to do is you are going to make C N bond ok.

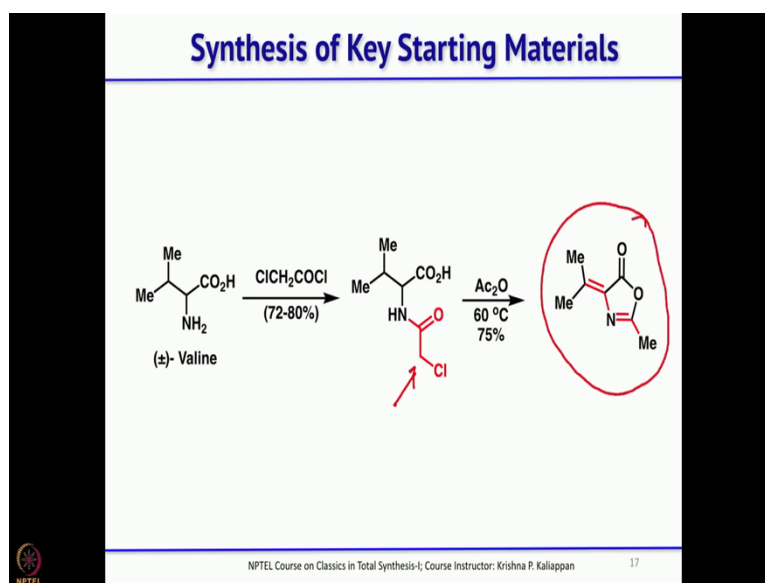
So, when you have a amine and carboxylic acid, you can use many coupling reagent ok. Then, if you look at the right hand side, so that is a protected aldehyde; is not it? That is a protected aldehyde ok. So, you need aldehyde and then, the aldehyde if you treat with this amino thiol ok, then it can protect and before that if you look at this amine, amine is already protected and to start with, you need a protected amine.

So, normally, they use phthalimide because phthalimide if you treat with hydrogen, so the phthalyl group can be cleaved and then, you will get back NH_2 . So, for protection of

NH₂ olden days, they used to use phthalic anhydride method ok and this can be easily cleaved as I said this aldehyde and this amino thiol ok.

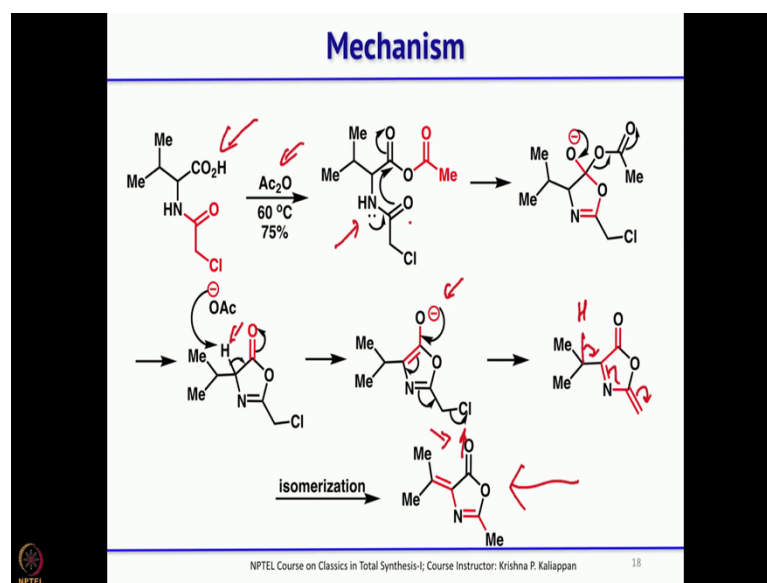
So, they can this aldehyde can be protected to give this right hand side portion and this upon hydrolysis with NH hydrazine will give you NH₂. So, the first target is to make this D-penicillamine hydrochloride in optically active form ok. That was the first task for Sheehan to accomplish.

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So, he started with racemic Valine and then, treated with chloroacetyl chloride. So, you have NH₂; the NH₂ is acetylated with chloroacetyl chloride. So, next step is a very interesting reaction. This upon treatment with acetic anhydride ok; this treatment with acetic anhydride, he got a very interesting compound ok.

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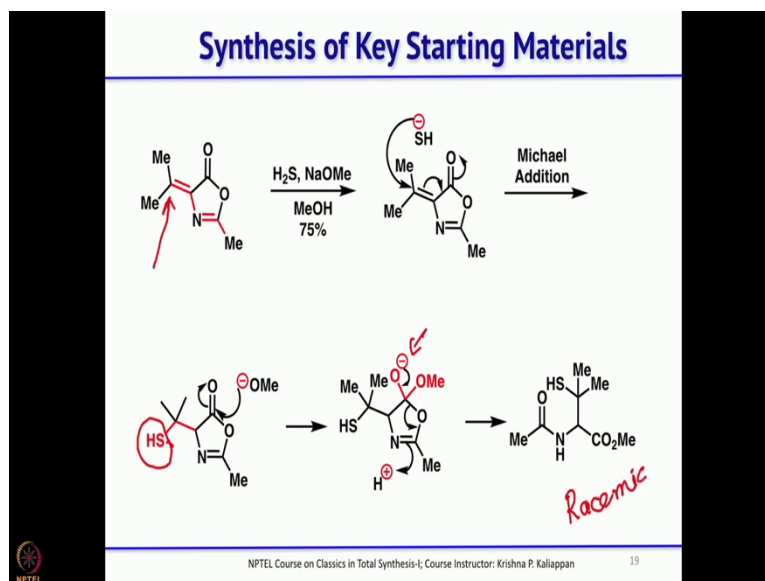


How did this happen, let us see. So, first the chloroacetyl chloride treatment with the acetic anhydride, this carboxylic acid is acetylated. The first step is the acetylation of carboxylic acid; that means, mixed anhydride of this carboxylic acid and acetic acid. So, that gives this intermediate. Now, the lone pair on the nitrogen moves to this carbonyl and this carbonyl oxygen intramolecularly attacks the anhydride and gives this five-membered ring ok.

You can see the five-membered ring, I leave it for a second for better understanding ok. So, now, the OAc minus, OAc minus which came out can pick up this hydrogen because this hydrogen is acidic, is not it? This hydrogen is acidic. So, OAc minus picks up this hydrogen and forms this di enolate and you can see if this molecule, there is a push-pull factor. You have a negative charge on the oxygen and you also have a leaving group here. So, this is a classical example for such elimination. So, you get this unstable compound ok.

This unstable compound immediately will isomerize ok. That will give you the product which I showed in the previous slide ok. So, Valine upon treatment with chloroacetyl chloride followed by acetylation in two steps, he got this interesting product. Good. So, how this can be it can be converted into penicillin? So, treat with hydrogen sulfide. So, hydrogen sulphide, sulfur you know they tend to add one-four.

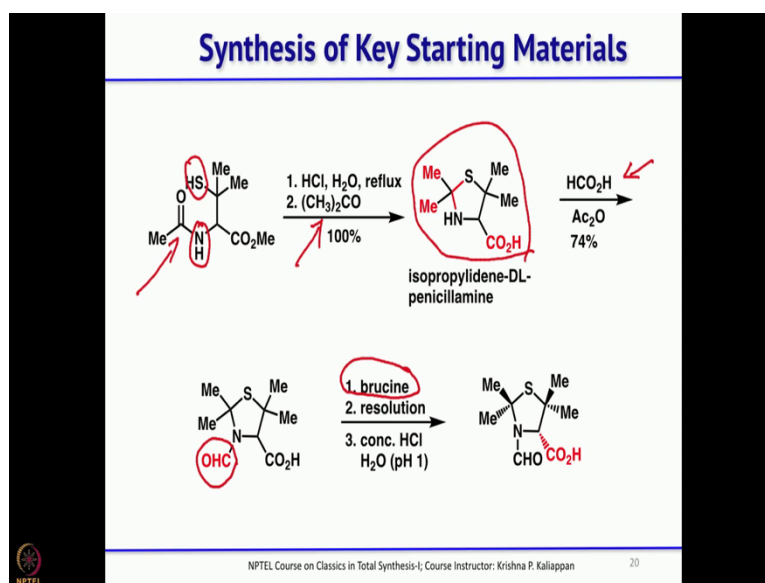
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So, hydrogen sulfide in the presence of sodium ethoxide; that means, you are adding SH minus ok. So, the SH minus can add in a one-four fashion at this carbon. So, that will lead to your five-membered ring and this exocyclic double bond is missing; but you introduce the SH as you know in penicillin you need that thiol and then, hydroxyl group that is a D-pencilliamine. So, now, if you treat with sodium ethoxide, if you treat with sodium ethoxide, this five-membered ring will open.

How it will open? This is a mechanism first methoxy adds to the carbonyl and then, O minus when it comes back you know it opens a five-membered ring and it gives this open chain compound ok. Is it chiral? Is it chiral? No, it is racemic because we started with racemic compound ok. So, you have this, then how you can resolve it ok; penicillin is an optical active compound, how you can resolve?

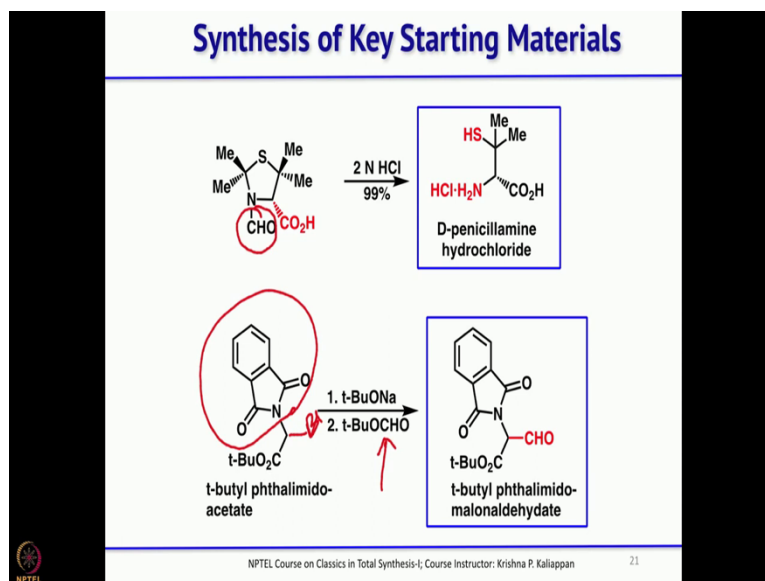
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So, first you protect this NH and this SH ok and for that, you have to remove the acetyl group. So, the acetyl group you remove with HCl. So, you get NH₂. That NH₂ on treatment with acetone, you protect the compound ok and as you can see here, this is racemic compound DL and they tried to resolve at this stage, but resolution was difficult. So, what they did they treated with formic acid and acetic anhydride. So, formic acid and acetic anhydride, they could introduce this aldehyde; the N was protected ok.

Now, this racemic mixture was resolved with a with an alkaloid called brucine ok. The racemic mixture was resolved with an alkaloid called brucine ok. After resolution, so then we just add acid to get back this chiral ok.

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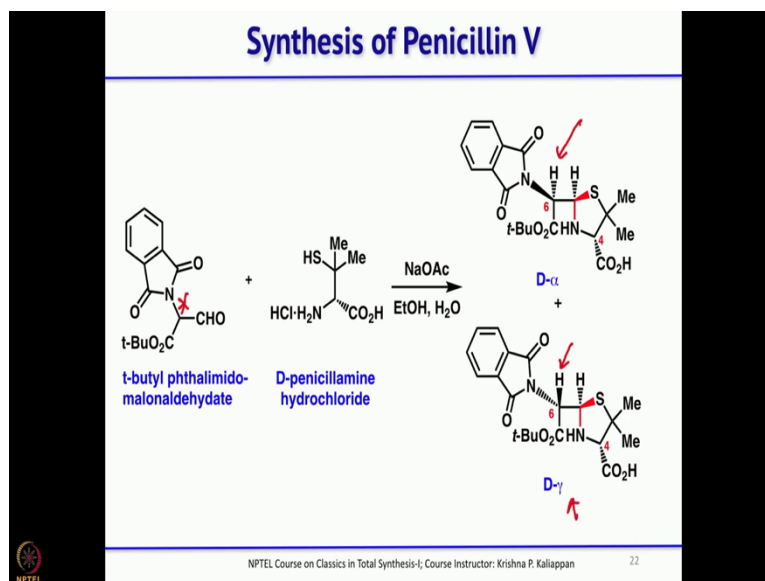


So, this is optically active now ok. This upon hydrolysis with HCl. So, what will happen this N-CHO; the CHO will go and then, you will get the NH₂. Since you are using HCl, it is formed as the corresponding hydrochloride salt; D penicillamine hydrochloride salt ok.

The other one, so now, you have the D-penicillamine hydrochloride and you need the aldehyde from the other side. So, first you start with tertiary butyl phthalimido acetate ok. So, this is very easy you to prepare. You take phthalimide and then, treat with corresponding bromo compound ok.

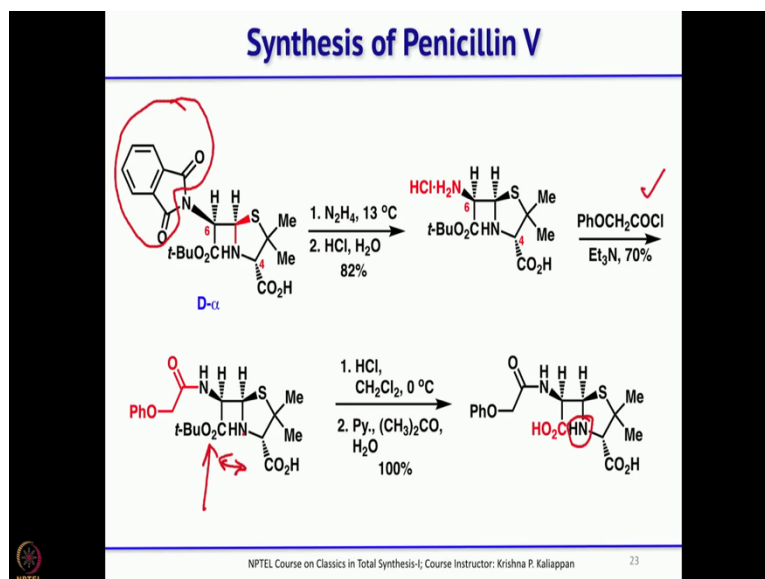
So, then simple nucleophilic substitution, you will get this compound. This on treatment with sodium tertiary butoxide and to introduce this CHO ok, introduce this CHO, you treat with tertiary butyl formate; tertiary butyl formate. So, you get the corresponding tertiary butyl phthalimido malonaldehyde ok.

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Now, you mix these two ok to protect the aldehyde. So, when you do that, you get a mixture. Why you get a mixture? If you look at this carbon that is racemic; is not it? So, you get a mixture at this carbon. So, you can call this as D-alpha and you can call this as D-gamma, but both could be separated.

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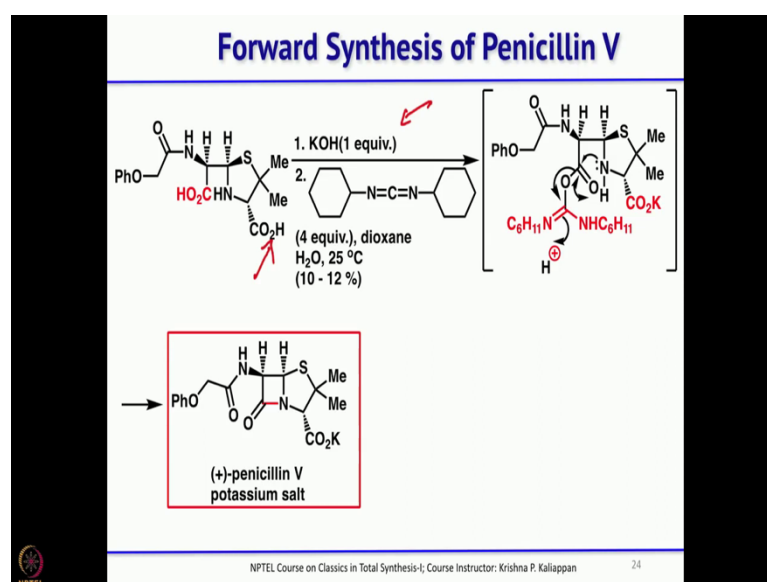


So, take that D-alpha and what you need? You need NH₂ and this phthalimide protecting group can be easily cleaved by treatment with by treating with hydrazine ok. So, you treat with hydrazine, the phthalimide protective group goes, you recover your NH₂.

Now, if you treat with HCl, you isolate the corresponding hydrochloride as salt ok. Then, you treat with base that is triethylamine and then, do the acetylation. So, this acetylation, you do with phenoxy acetyl chloride ok; phenoxy acetyl chloride. So, now, what you need to do? You have to hydrolyze this tertiary butyl ester, then do the coupling. You have NH carboxylic acid afterwards, then you have to couple.

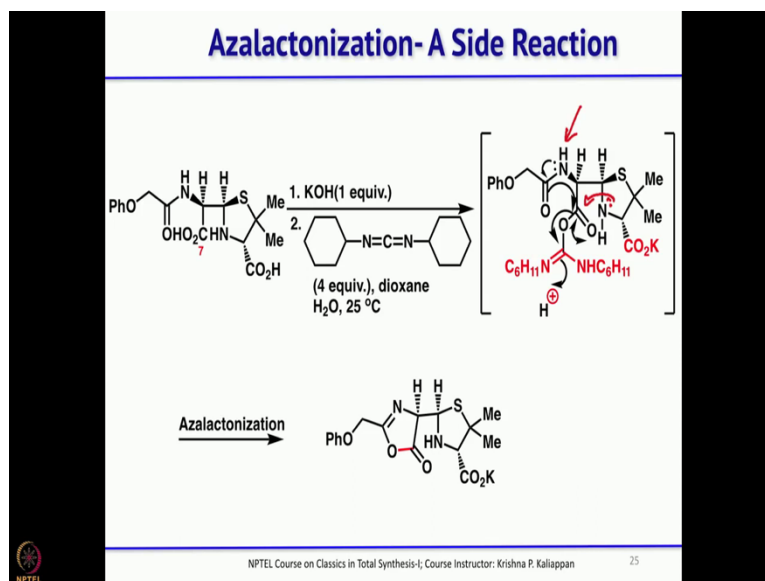
So, HCl will remove the tertiary butyl ester ok and then, you treat with pyridine that is just to you know when you when you treat with this NH also will be in the form of NH HCl.

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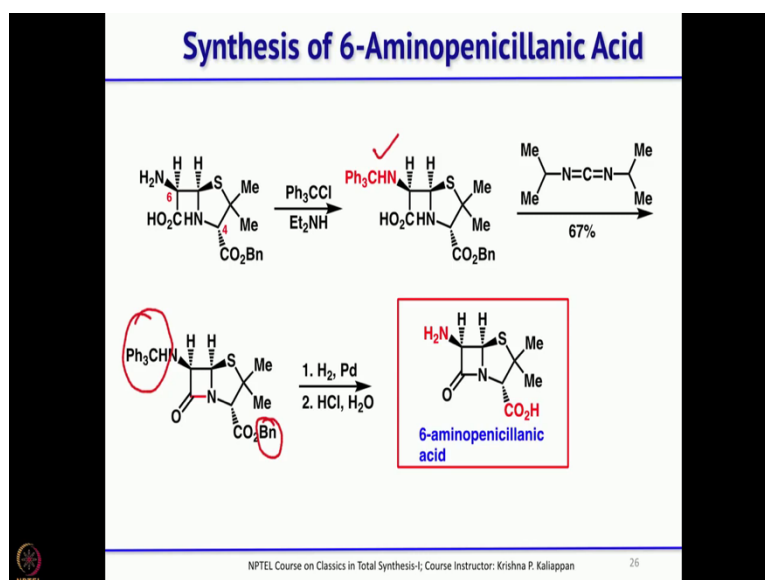
So, you have to treat with pyridine get back the free amine. Once you have the free amine, treat with DCC ok. So, the DCC is a good coupling reagent for making lactam, but before that, you have to treat with one equivalent of potassium hydroxide to deprotonate this carboxylic acid ok. So, that becomes CO₂ minus, then you add this DCC. Then, the DCC undergoes the intramolecular lactam formation ok. So, that is how you get the penicillin 5 potassium salt.

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There is one side reaction which takes place in this synthesis. So, when you have this, when you treat with DCC, what you get is this five-membered azalactone ok. Instead of this nitrogen attacking, what happens? The nitrogen lone pair on the acyl group ok that comes and then the carbonyl group attacks and it forms the five-membered azalactone. So, this also you get a decent amount as a side product.

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So, this 6-amino penicillanic acid that is without the acyl group. So, how one can make? Because if you look at the earlier synthesis, so we went with acyl group; finally, only we

did the coupling. Is not it? So, here what you do? The NH_2 , first you protect it as the trityl; NH trityl group, then you do the coupling ok, you can couple with either DCC or di isopropyl carbodiimide to get the beta-lactam.

Now, you need to remove the benzyl group and then trityl group. So, both can be done in one step that is upon hydrogenolysis followed by HCl treatment, one gets the 6-amino penicillanic acid.

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The slide is titled "Summary" in blue text at the top center. It contains four bullet points in red and blue text, each preceded by a red arrowhead. The first bullet point mentions Professor J. Sheehan and his group at MIT reporting the first rational total synthesis of penicillin V in 1957, with a red arrow pointing to the year. The second bullet point lists the starting materials: t-butyl phthalimido malonaldehyde and D-penicillamine hydrochloride. The third bullet point describes the key step as Michael addition and mild lactamization using DCC. The fourth bullet point states that the synthesis was completed in 8 steps with an overall yield of 0.69%. At the bottom left is the NPTEL logo, and at the bottom center is the course information: "NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kallappan" and the slide number "27".

Summary

- > Professor J. Sheehan and his group at MIT reported the first rational total synthesis of penicillin V in 1957
- > The synthesis commenced from t-butyl phthalimido malonaldehyde and D-penicillamine hydrochloride
- > The key step included Michael addition and mild lactamization method involving DCC
- > The total synthesis was achieved in 8 steps with an overall yield of 0.69%

NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kallappan 27

So, to summarize what Sheehan has done there was the first and very elegant total synthesis of penicillin and you can see way back in 1957. So, such a unstable reactive final compound penicillin 5 was made by Sheehan and his group in 1957 and the synthesis started with commercially available Valine ok and also from phthalimide, just you take phthalimide and then, you know treat with bromo ethyl acetate to get the other starting material.

So, it was very simple and straightforward starting materials which are commercially available and he had used this successfully to make the total synthesis of penicillin.

And the key reactions when you talk about the key reaction, the Michael addition of SH minus was one of the key reactions and the coupling reagent was used to couple the amine and carboxylic acid intra-molecularly to form the four-membered ring. Overall, the total synthesis was accomplished in eight steps with a overall yield of close to 0.7

percent. So, considering that, this is the first total synthesis, this was a significant achievement; of course, there are many total synthesis of penicillins later, but in the long run, the huge quantities of penicillins and its derivatives were made only through fermentation method.

After fermentation, once you get the penicillin, then one can do lot of synthetic modification to get other penicillin like natural products; but large quantities of penicillins are made only by fermentation. So, with this, I will complete total synthesis of penicillin and we will discuss about other natural products belonging to this in the next couple of classes. For example, thienamycin and lactacystin, these two we will discuss in the next couple of classes.

Thank you.