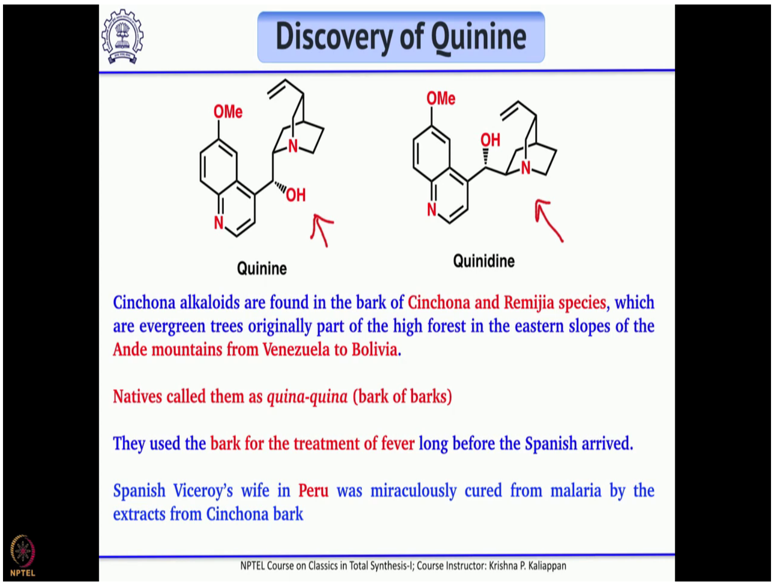
Classics in Total Synthesis-I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 32
Quinine

So, good morning everyone, and welcome back to the NPTEL lecture series on Classics in Total Synthesis part I. The last few lectures we have been talking about total synthesis of various alkaloids and today we will continue our discussion on the total synthesis of one more alkaloid called Quinine.

(Refer Slide Time: 00:43)



Discovery of Quinine

Quinine

Quinidine

Cinchona alkaloids are found in the bark of Cinchona and Remijia species, which are evergreen trees originally part of the high forest in the eastern slopes of the Ande mountains from Venezuela to Bolivia.

Natives called them as *quina-quina* (bark of barks)

They used the bark for the treatment of fever long before the Spanish arrived.

Spanish Viceroy's wife in Peru was miraculously cured from malaria by the extracts from Cinchona bark

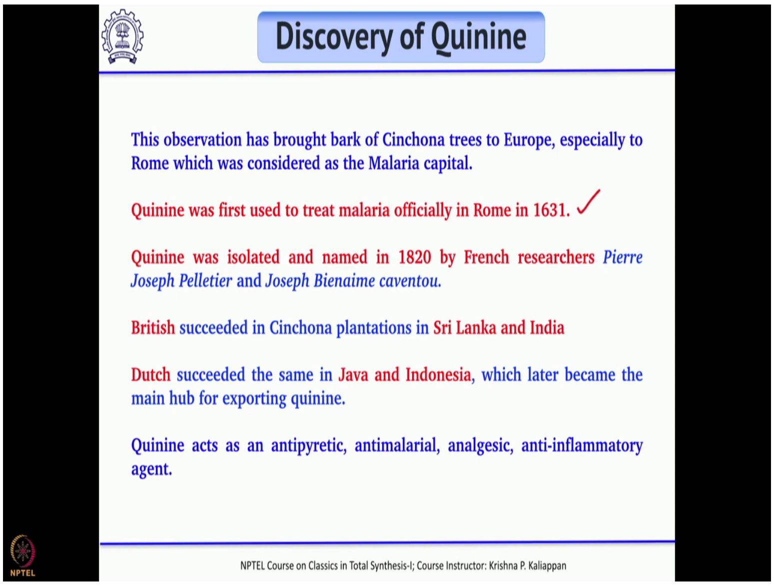
NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

And the quinine has a very interesting history, the structure of quinine is this one and you can see here there is another epimer which is called quinidine and these two alkaloids were found in the bark of Cinchona and Remijia species. So, these were originally part of the high forest in anti mountains from Venezuela to Bolivia in South America ok these two alkaloids are found in the bark of Cinchona and Remijia species.

And the South American natives they used to call this tree Cinchona tree as quina-quina bark of barks and as is the case with many natural products South American natives they have been using this bark for the treatment of high fever. And also much before the Spanish people arrived in South America as you know most of the South America was taken over by Spanish people in 16th and 17th and 18th century.

Interestingly, that discovery of quinine got major focus when one of the Spanish Viceroy's wife in Peru was diagnosed with malaria and she was cured by giving extracts of this Cinchona tree bark ok. So, this was a major impact of South America in the treatment of malaria in Europe.

(Refer Slide Time: 02:20)



Discovery of Quinine

This observation has brought bark of Cinchona trees to Europe, especially to Rome which was considered as the Malaria capital.

Quinine was first used to treat malaria officially in Rome in 1631. ✓

Quinine was isolated and named in 1820 by French researchers *Pierre Joseph Pelletier* and *Joseph Bienaime caventou.*

British succeeded in Cinchona plantations in Sri Lanka and India

Dutch succeeded the same in Java and Indonesia, which later became the main hub for exporting quinine.

Quinine acts as an antipyretic, antimalarial, analgesic, anti-inflammatory agent.

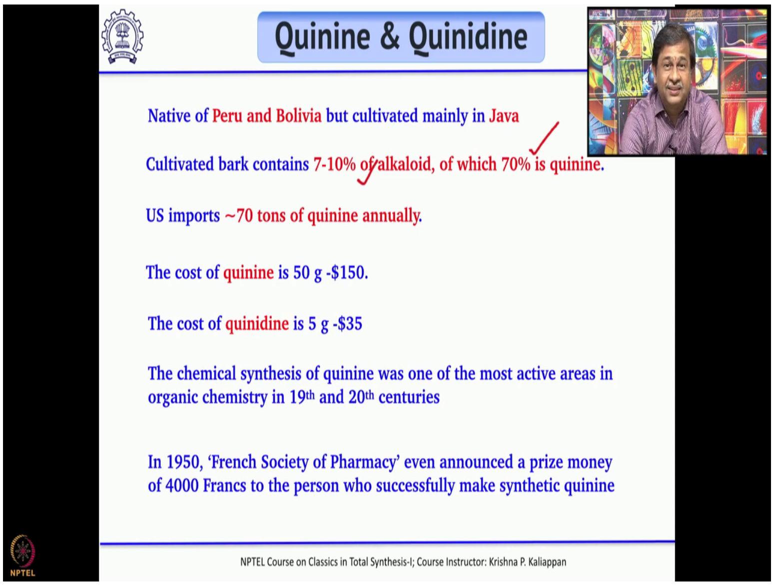
NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

Once this news came to Europe what happened? Automatically, the plantation of synchronous trees started in whole Europe particularly in Italy where the Rome was considered as the capital of malaria ok so, many people were suffering from malaria. And this was a big boom that the bark of Cinchona tree could be used for the treatment of malaria.

So, afterwards as you know people started using this extracts from the bark of Cinchona tree for treatment of malaria not only in Rome, but also in other parts of Europe. However, it took 200 years to isolate the pure form of quinine it took 200 years as I said. Only in 1820 two French researchers Pierre Pelletier and Joseph Caventou, so they isolated the pure form of quinine and afterwards British people they wanted to plant this in their colonies. So, they succeeded in planting this in India and Sri Lanka and then Dutch people also succeeded the same by planting in Java and Indonesia.

Incidentally, Java became the major hub for exporting quinine even today and quinine exhibits antipyretic, antimalarial, analgesic and anti inflammatory activities.

(Refer Slide Time: 03:51)



Quinine & Quinidine

Native of Peru and Bolivia but cultivated mainly in Java

Cultivated bark contains 7-10% of alkaloid, of which 70% is quinine.

US imports ~70 tons of quinine annually.

The cost of quinine is 50 g -$150.

The cost of quinidine is 5 g -$35

The chemical synthesis of quinine was one of the most active areas in organic chemistry in 19th and 20th centuries

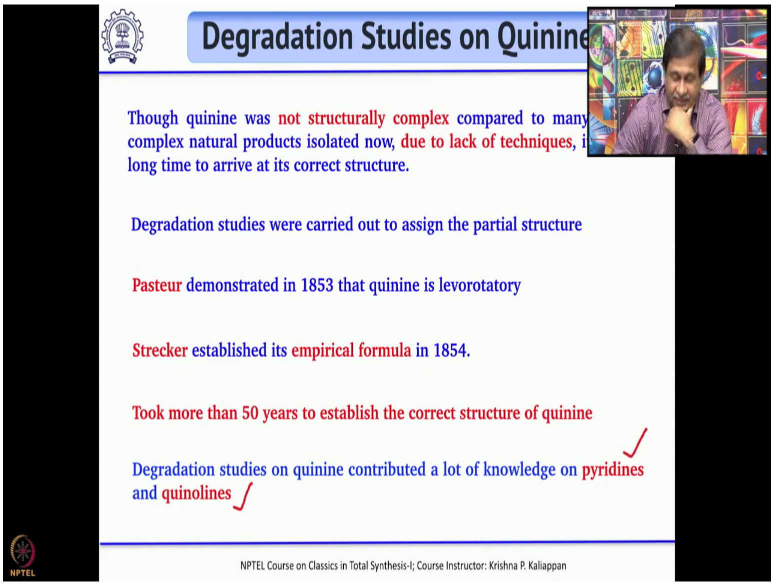
In 1950, 'French Society of Pharmacy' even announced a prize money of 4000 Francs to the person who successfully make synthetic quinine

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

And as I mentioned this is the major exporter of the cultivator bark is from Java and the cultivated bark of Cinchona tree has 7 to 10% of this alkaloids ok. Out of which 70% is quinine; that means, it has about 5% quinine if you take the bark and then cultivate it from that you can isolate 5% pure quinine which was exported in fact, US imports about 70 tons of quinine every year that is a major import.

The cost of quinine and quinidine differs little bit one gram of quinine cost about 3 US dollars whereas, one gram of quinidine cost about 7 US dollars. However, people were always interested in the chemical synthesis of quinine. In fact, if you look at 19th century and 20th century. So, one natural product which got maximum attention next to strychnine is quinine. In 1950 French Society of Pharmacy, they announced a cash price of 4000 Francs for the group which completes the chemical synthesis of quinine.

(Refer Slide Time: 05:18)



Degradation Studies on Quinine

Though quinine was not structurally complex compared to many complex natural products isolated now, due to lack of techniques, i long time to arrive at its correct structure.

Degradation studies were carried out to assign the partial structure

Pasteur demonstrated in 1853 that quinine is levorotatory

Strecker established its empirical formula in 1854.

Took more than 50 years to establish the correct structure of quinine

Degradation studies on quinine contributed a lot of knowledge on pyridines ✓ and quinolines ✓

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

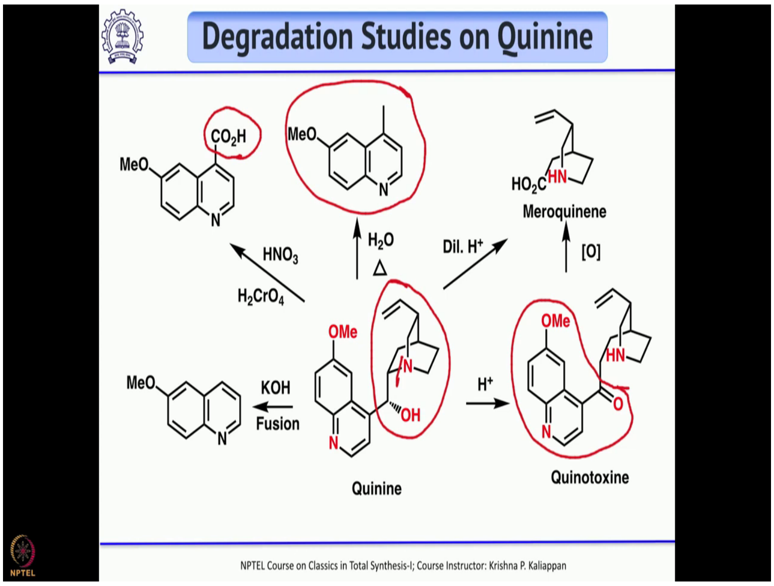
However, it took much more time to come up with the synthesis of quinine. In fact, I would say it took about hundred more years to come up with the synthesis of quinine. If you look at the structure of quinine, now you may feel that it is not structurally as complex as some of the natural products being isolated in recent years. However, one should also remember that when quinine was isolated there was no NMR no IR no mass spectrum.

So, without all these techniques one has to prove the structure of quinine then go for the total synthesis; obviously, it is a it must have been very very tough job to assign the correct structure of quinine first. So, those days whenever a natural product is isolated and if they find that natural product is showing exceptional activity then they use lot of degradation studies to assign partial structures first.

So, once they assign partial structures, then they try to link connect it to come up with the correct structure and always synthesis is considered as the final proof for confirming the structure of isolated natural products So, in 1853 Pasteur actually reported that quinine is levorotatory ok a year later Strecker establishes correct empirical formula then it took about 50 years ok. In 1907 Paul Rabe proposed the correct structure of quinine ok.

During this period though the synthesis of quinine was not accomplished lot of efforts were focused on synthesis of pyridine and quinolines. So, much literature has gone into synthesis of pyridines and quinolines.

(Refer Slide Time: 07:28)



Degradation Studies on Quinine

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

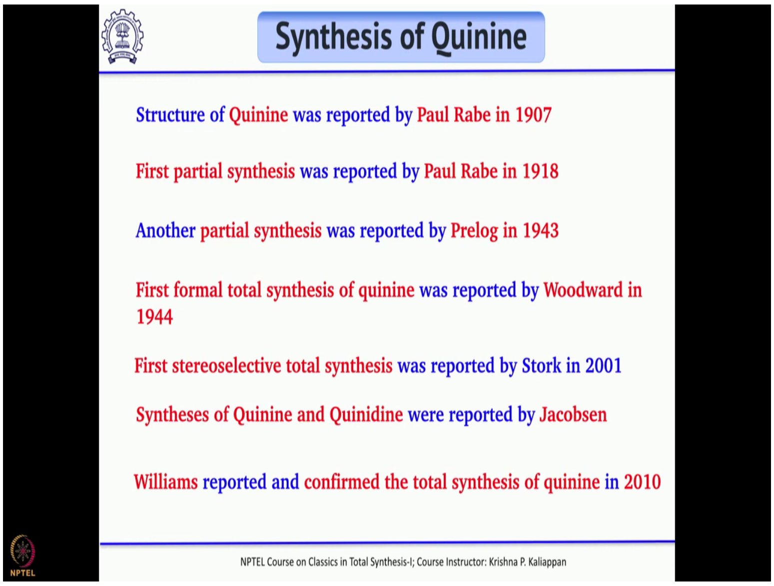
So, there are lot of degradation studies known on quinine, but in this particular slide I will talk about four or five reactions where quinine gave some important clue to assign the structure. When quinine was treated with acid ok strong acid it rearranged I should say it open this bond was cleaved to give a very interesting compound called quinotoxine ok.

Then the same compound when it was oxidized when it was oxidized, it gave meroquinene ok. Meroquinene if you look at this does not have the quinoline part ok. The same meroquinene was observed when quinine was treated with dilute HCl for a long time ok continuous exposure of quinine dilute acid for long time converted quinine into meroquinene.

When quinine was treated with fused potassium hydroxide, they could get methoxy quinoline ok; that means, this whole portion disappeared ok. And when it was treated with nitric acid and chromic acid, they could get this quinoline with a carboxylic acid here ok then they took quinine reflexed with water ok. So, they could get this methyl methoxy methyl quinoline ok.

So, these are the important degradation studies which actually gave an idea about what could be the correct structure of quinine. However, you know as you know you have to make this compound then only you can propose the correct structure.

(Refer Slide Time: 09:26)



Synthesis of Quinine

Structure of Quinine was reported by Paul Rabe in 1907

First partial synthesis was reported by Paul Rabe in 1918

Another partial synthesis was reported by Prelog in 1943

First formal total synthesis of quinine was reported by Woodward in 1944

First stereoselective total synthesis was reported by Stork in 2001

Syntheses of Quinine and Quinidine were reported by Jacobsen

Williams reported and confirmed the total synthesis of quinine in 2010

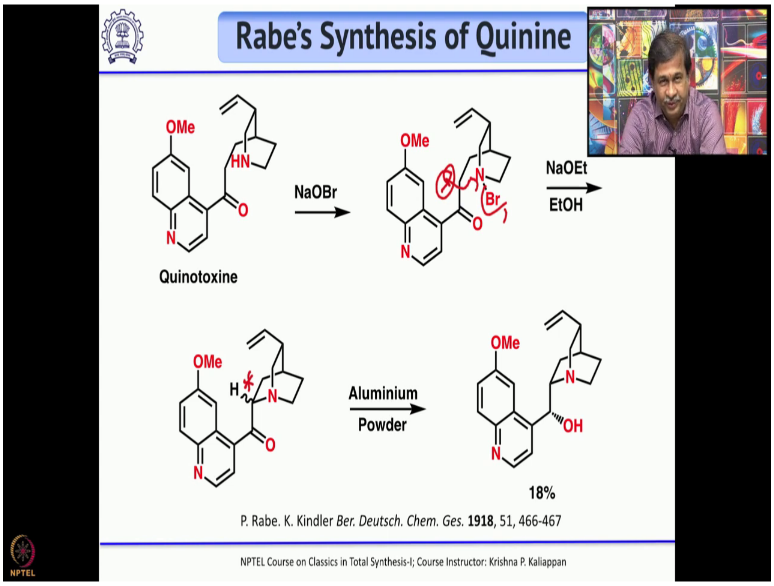
NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

So, Paul Rabe was the one who proposed the correct structure of quinine in 1907 and 11 years later he reported partial synthesis of quinine from quinotoxine. We will come to that little later and 25 years later another partial synthesis was reported by Vladimir Prelog, but in 1944 was the year where Woodward reported the first formal total synthesis of quinine. This was a big news among all synthetic chemist as well as for the world.

So, the synthesis of quinine was considered as a major breakthrough in chemical synthesis and it took almost 70 years for the first enantioselective total synthesis of quinine which was reported by Gilbert Stork in 2001. And another 10 years it took for Jacobsen to complete the total synthesis of quinine and quinidine using asymmetric catalytic reaction.

However, there was some controversy about the total synthesis of quinine reported by Woodward. So, there were few papers questioning the authenticity of the total synthesis of quinine reported by Woodward. So, Robert Williams from Colorado University and his team they completely you know they just followed the same route reported by Paul Rabe and completed the total synthesis of quinine thus confirmed that Woodward indeed completed the formal total synthesis of quinine. So, I will come to that when I talk about total synthesis of quinine and by Woodward.

(Refer Slide Time: 11:18)



Rabe's Synthesis of Quinine

P. Rabe. K. Kindler *Ber. Deutsch. Chem. Ges.* **1918**, 51, 466-467

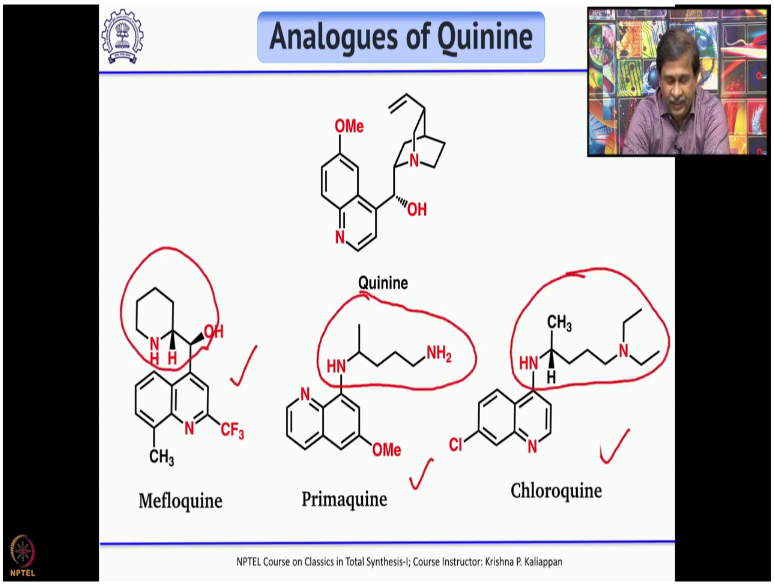
NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

So, the first partial synthesis of quinine as I said was reported by Paul Rabe and Kindler and how they reported was the degraded product quinotoxine, they took and then treated with sodium hypo bromide ok. So, that gave that N bromo compound ok this N bromo compound on treatment with sodium ethoxide ethanol. So, they could get this ketone ok it is a you know just you generate anion and then attack here goes and here they got a mixture of two compounds ok based on you know you can see that the this particular serious center they had two isomers.

This upon treatment with aluminium powder ok, this upon treatment with aluminium powder they could get about 18% of quinine which was recrystallized and then they could see you know complete you know the all the data are matching with their natural quinine. So, that is I how in 1918, this one can call it as relay approach.

That means, you know you start with a compound which was originally from the same natural product degraded compound then convert the same into the natural product which we already discussed when we talked about totals in sub strychnine by Woodward ok.

(Refer Slide Time: 12:51)



Analogues of Quinine

Quinine

Mefloquine

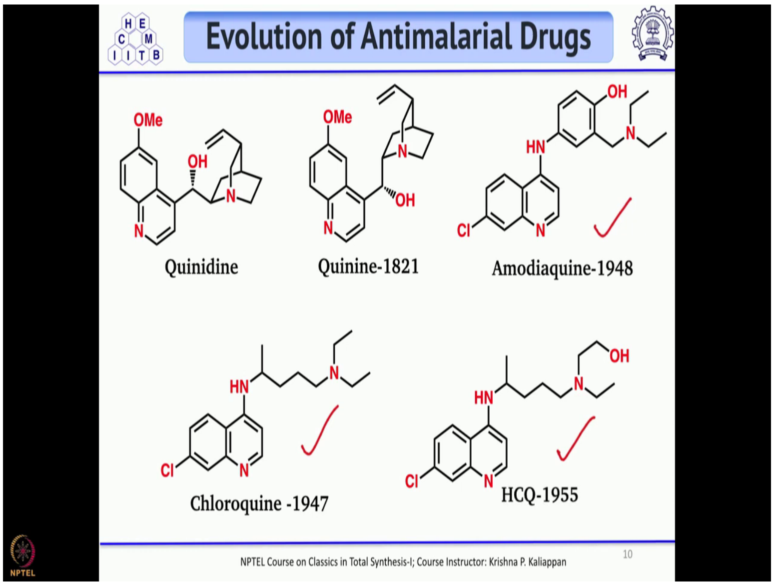
Primaquine

Chloroquine

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

And this quinine not only quinine is used as anti malarial drug, afterwards there are many drugs which were which came to the market based on the quinine structure. So, lot of structural activity studies led to the synthesis of mefloquine, primaquine, chloroquine. Now, all these drugs you can see quinoline part is same ok only this region is different ok.

(Refer Slide Time: 13:27)



Evolution of Antimalarial Drugs

Quinidine

Quinine-1821

Amodiaquine-1948

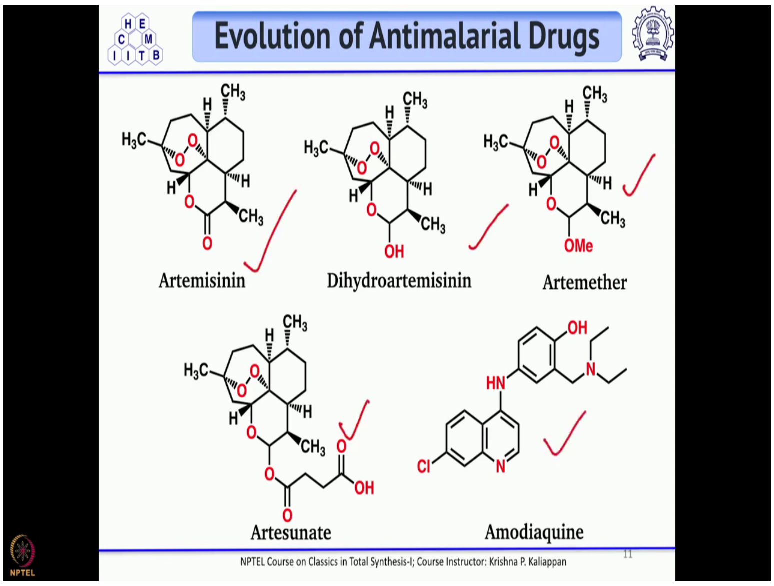
Chloroquine -1947

HCQ-1955

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

Then this is quinidine and this is amodiaquine this is chloroquine and this is called HCQ. So, HCQ as you know it was given for the treatment of Covid recently.

(Refer Slide Time: 13:44)

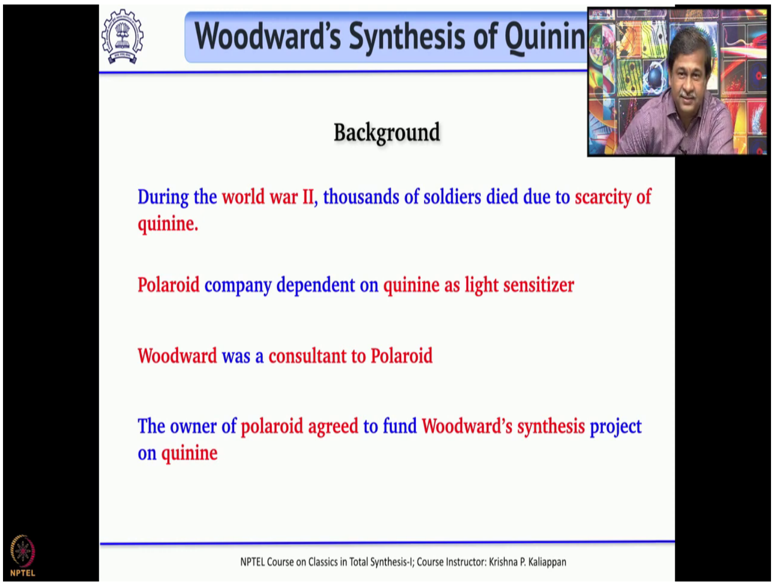


Evolution of Antimalarial Drugs

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

And off late a completely new set of drugs are being used for the treatment of malaria based on this peroxide natural product called artemisinin. So, artemisinin, dihydroartemisinin, artemether, artesunate that is artemisinin if you treat with succinic anhydride you get this artesunate then this can be given along with amodiaquine for the treatment of malaria ok.

(Refer Slide Time: 14:15)



Woodward's Synthesis of Quinin

Background

During the world war II, thousands of soldiers died due to scarcity of quinine.

Polaroid company dependent on quinine as light sensitizer

Woodward was a consultant to Polaroid

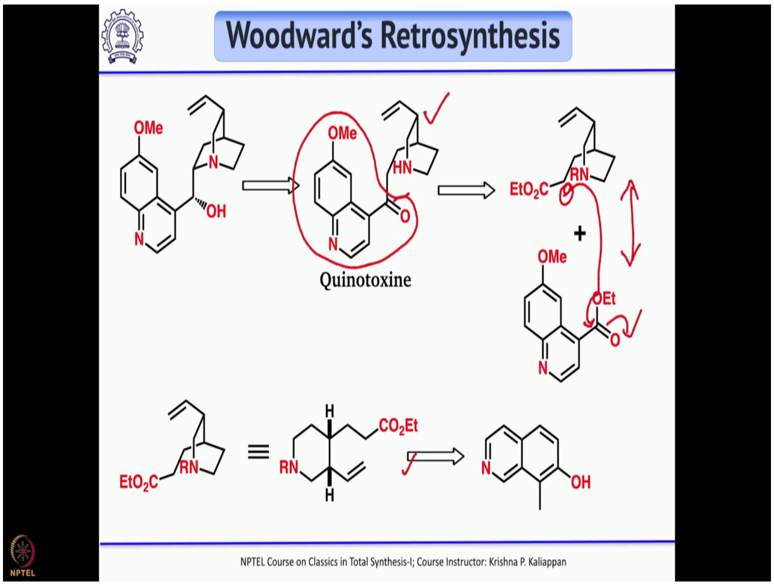
The owner of polaroid agreed to fund Woodward's synthesis project on quinine

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

Now, let us see how Woodward reported the synthesis of quinine. So, as I said in 19th century as well as early 20th century, so people spend lot of time on the chemical synthesis of quinine. And during the Second World War so, many soldiers died because of their non availability of quinine ok and that time the Polaroid company very well-known and very famous company.

So, they were using quinine for a different reason. So, they were using quinine as a light sensitizer ok that is photo company ok as a light sensitizer and Woodward has been consultant to this Polaroid company. So, the Polaroid company asked him whether he can develop a good method for the synthesis of quinine. So, that is how the Polaroid company funded the project on the synthesis of quinine ok.

(Refer Slide Time: 15:14)



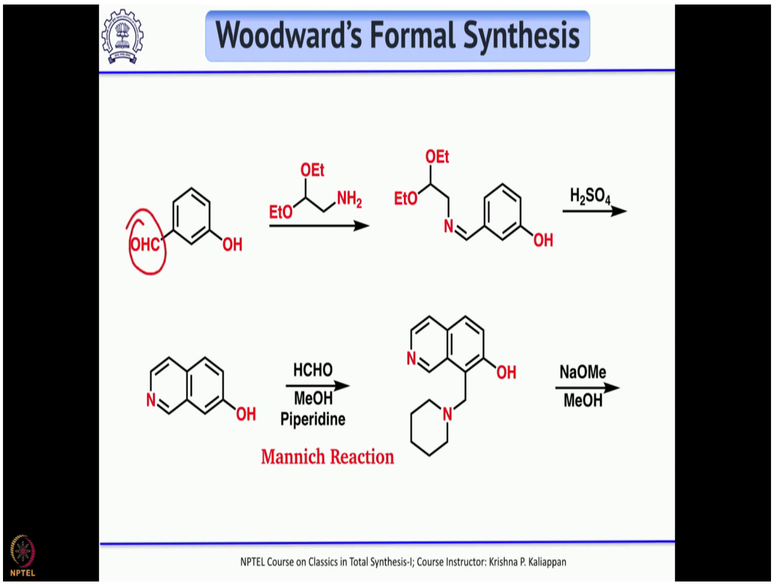
Woodward's Retrosynthesis

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

So, according to Woodward quinine can be made from the quinotoxine because the quinotoxine has been already converted into quinine by Paul Rabe and Kindler. So, he thought if he makes this then that should constitute what we call it as a formal synthesis of quinine and this quinotoxine can be obtained from this as well as the corresponding ester ok *via* a Claisen reaction ok.

So, you can see you can generate anion and attack here and you will get a β keto ester and then β keta ester decarboxylation will give quinotoxine. So, now, he has to make these two starting materials are key intermediates. So, the first one you can draw like this ok can be made from this hydroxy pyridine ok and this for the hydroxy pyridine we started from the meta hydroxy benzaldehyde.

(Refer Slide Time: 16:17)

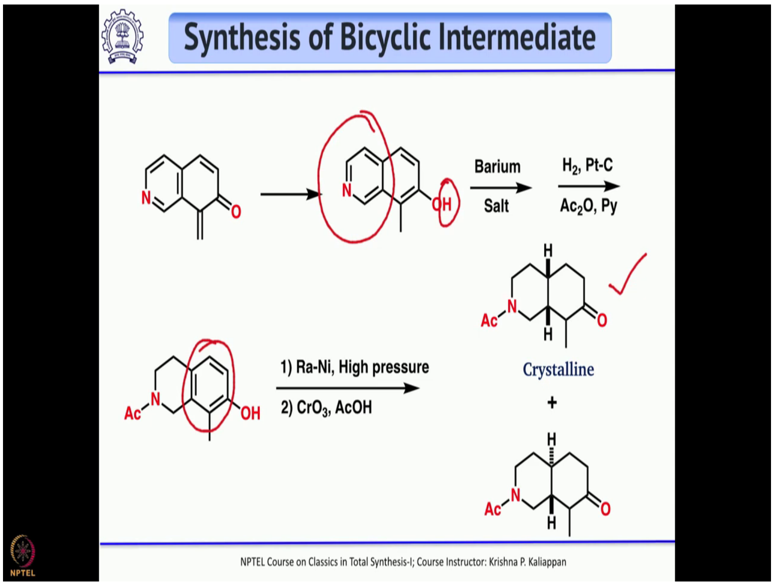


Woodward's Formal Synthesis

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

So, you take meta hydroxy benzaldehyde and treat with this amine ok. So, this first undergoes the imine formation on the aldehyde ok then it undergoes an intramolecular cyclization on treatment with acid to give hydroxy isoquinoline, then you do a Mannich reaction. So, introduce the -CH2 piperidine group at α to the hydroxyl group.

(Refer Slide Time: 16:54)



Synthesis of Bicyclic Intermediate

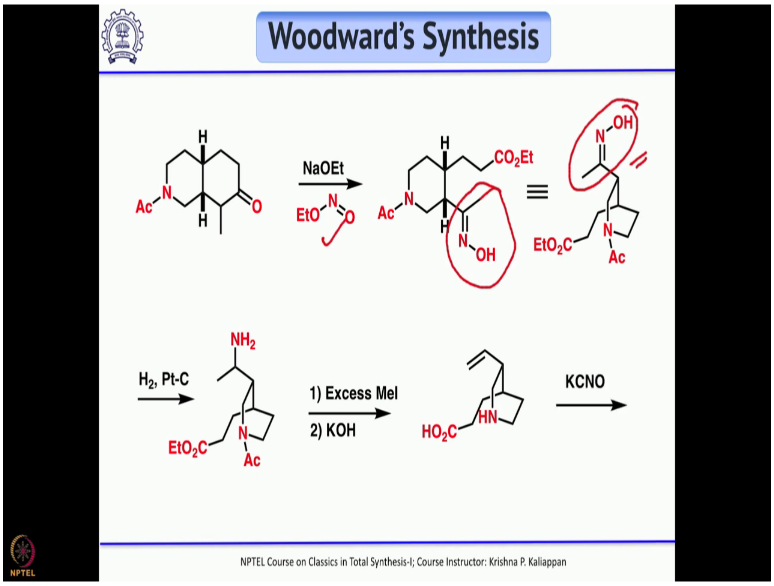
NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

Then you treat with sodium methoxide and methanol you get this and that was converted into the corresponding methyl hydroxy isoquinoline ok. This one treatment with barium salt ok. So, basically you the protonate the acidic phenolic proton then you do the hydrogenation ok when you do the hydrogenation, the hydrogenation takes place at the pyridine aromatic amine ok.

Then you do the next step that is high pressure hydrogenation of the phenolic aromatic ring followed by oxidation of the hydroxyl group to corresponding ketone using chromium trioxide and acetic acid. So, he got a mixture of these two where this is the major product because since you are using high pressure hydrogenation and when you use hydrogenation *cis* product should be the major product. So, that was a major product.

So, once you had the major product and that also was crystalline. So, once it is crystalline it is easy to isolate and proceed further.

(Refer Slide Time: 18:03)



Woodward's Synthesis

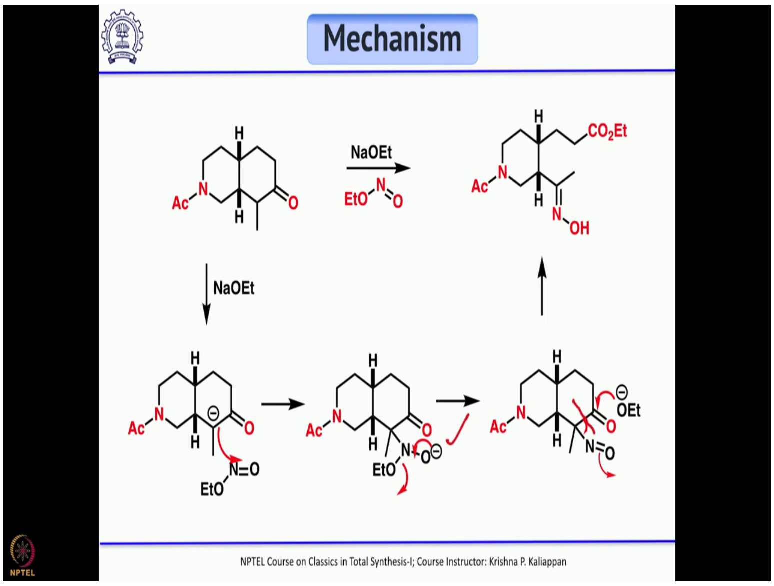
NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

So, he took the crystalline compound ok and treated with sodium ethoxide and this particular reagent. So, this reagent is known to introduce -NO group ok known to introduce nitroso group next to the ketone. So, when he did that what he got was this compound I will come to the mechanism of this a little later. Basically, the idea is to convert this into a double bond ok you need a double bond vinyl group, is not it? Basically that idea is to get or convert this oxime into double bond. So, you can see that you know see this whole thing should be a vinyl group ok.

Then you reduce oxime to -NH_2 ok you can do with LAH or you can also do it with hydrogenation condition. Now if you treat with excess methyl iodide what will happen?

It will form the corresponding quaternary salt ok it will form the corresponding quaternary salt and this one treatment with potassium hydroxide will undergo Hofmann elimination to give the less substituted alkenes ok. So, once you have that then you treat with potassium cyanate and before that I will just give the mechanism of the introduction of the nitroso group.

(Refer Slide Time: 19:23)



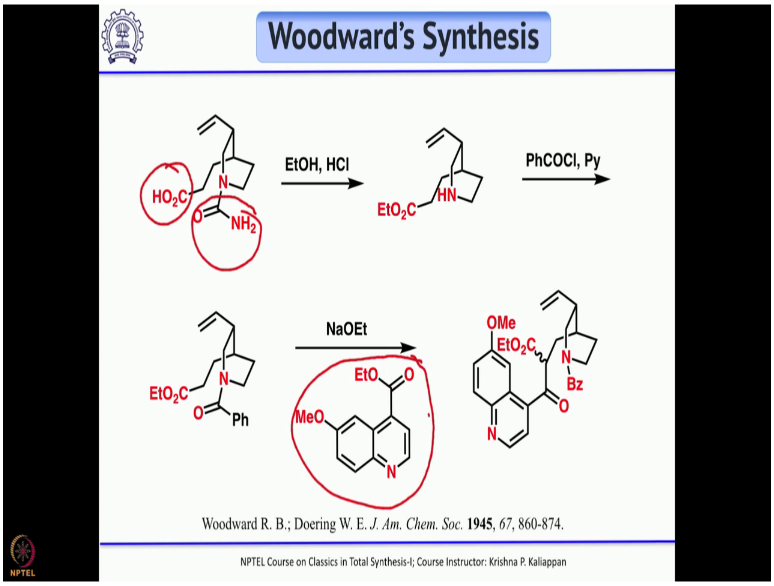
Mechanism

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

So, you have this and treat with sodium ethoxide and NaOEt, you get this compound is not it? So, the mechanism is first it generates enolate ok then upon treatment with nitroso compound the enolate that is the carbon ion attacks the nitrogen of no to give this particular intermediate. Now, what will happen? This O^- will come back and eliminate the OEt.

So, basically as I said it is a good reagent to introduce the no group ok; however, next when you use sodium methoxide because sodium methoxide is a base which you have to use to introduce the -NO group. Now the sodium ethoxide will attack the carbonyl group and this bond will break ok this bond will break and that will give you the corresponding oxide ok.

(Refer Slide Time: 20:33)



Woodward's Synthesis

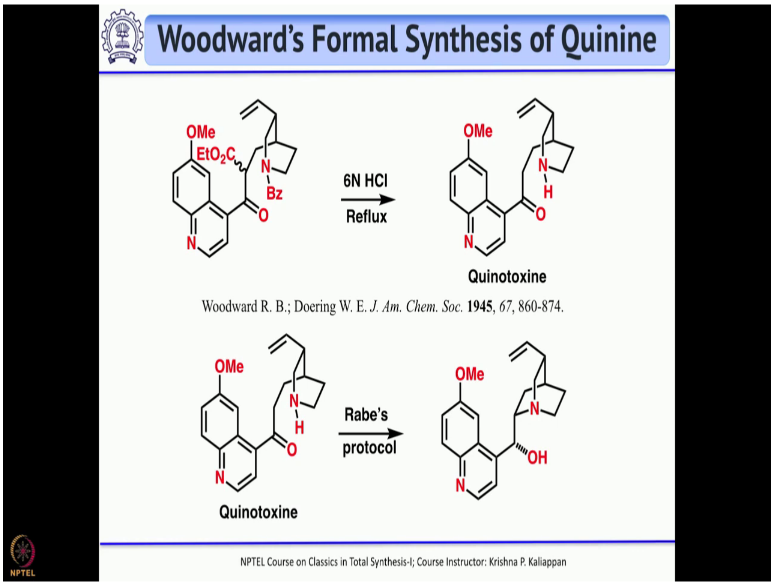
Woodward R. B.; Doering W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860-874.

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

So, then let us see and with this key intermediate in hand the next is you have to make this carboxylic acid as ester because for the Claisen reaction you need this ester then treat with ethanol and HCL. So, ethanol and HCL not only converted the carboxylic acid into ester, but also hydrolyze this urea derivative to corresponding NH. Now, on treatment with benzyl chloride ok it is like a Schotten Baumann reaction, you benzoylate this is secondary amine, then you have this ester ok this known compound ok then you do the Claisen reaction.

So, the Claisen reaction gives the β keto ester ok this β keto ester can be decarboxylated with (6 N) HCl.

(Refer Slide Time: 21:23)



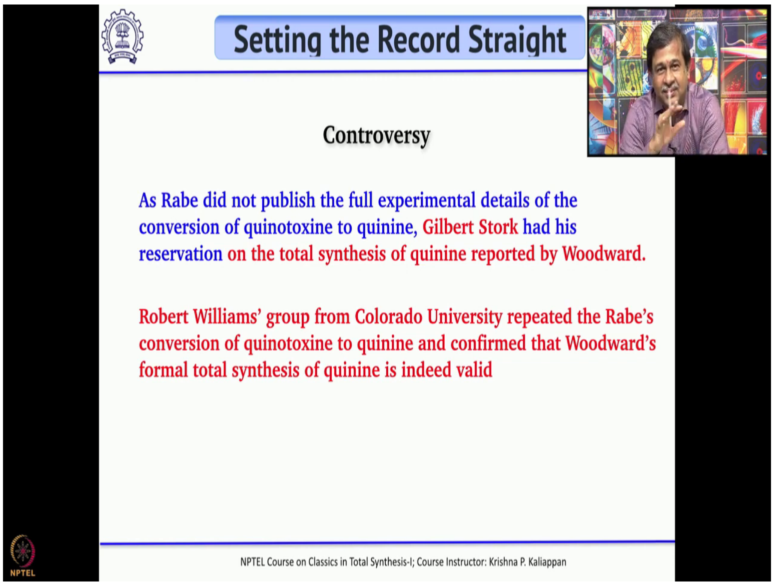
Woodward's Formal Synthesis of Quinine

Woodward R. B.; Doering W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860-874.

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

So, if you reflex it for some time you get quinotoxine ok. So, this is how Woodward completed the formal synthesis of quinine because he synthesized only quinotoxine and quinotoxine has been already converted into quinine by Rabe. So, this constitutes a formal total synthesis of quinine.

(Refer Slide Time: 21:54)



Setting the Record Straight

Controversy

As Rabe did not publish the full experimental details of the conversion of quinotoxine to quinine, Gilbert Stork had his reservation on the total synthesis of quinine reported by Woodward.

Robert Williams' group from Colorado University repeated the Rabe's conversion of quinotoxine to quinine and confirmed that Woodward's formal total synthesis of quinine is indeed valid

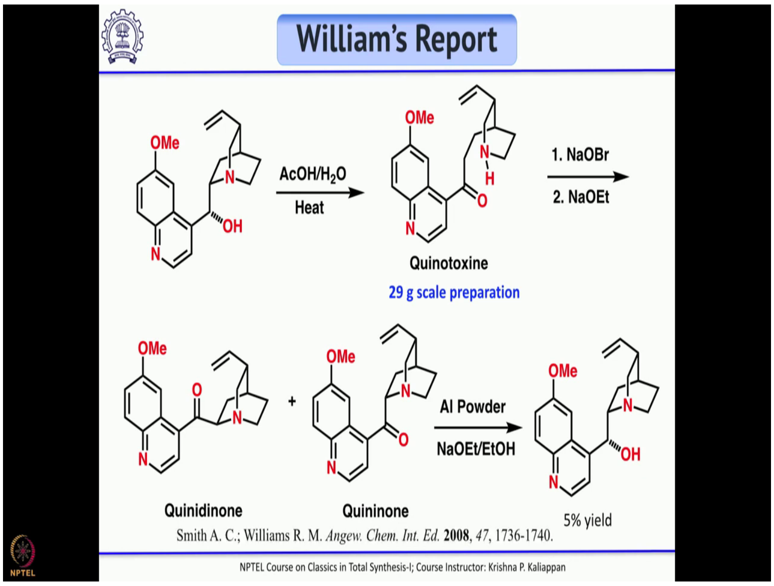
NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

However, there was some controversy see what happened? Paul Rabe when he reported the synthesis of quinine from quinotoxine, he did not publish the complete experimental details. Later he published several other papers related to the synthesis of many closely related synchronous alkaloid, but he never published the full experimental details of quinotoxine to quinine.

So, Gilbert Stork who completed the first asymmetric synthesis of quinine he had his own reservation when this full experimental details were not known for the conversion of quinotoxine to quinine, then the total synthesis of quinine reported by Woodward may not be valid, is not it? So, he has made after all he has made only quinotoxine he has not made quinine he thought that since quinotoxine has been already converted into quinine by Paul Rabe he did not carry out the conversion of quinotoxine to quinine.

So, there are many papers and finally, Robert Williams and his student from Colorado University they took upon this project repeated the same reactions reported by Paul Rabe in his paper on the conversion of quinotoxine to quinine and they could indeed get quinine in 5% yield. So, that confirms the formal total synthesis of Woodward is valid.

(Refer Slide Time: 23:35)



William's Report

$AcOH/H_2O$

Heat

1. NaOBr

2. NaOEt

Quinotoxine

29 g scale preparation

Quinidinone

Quininone

Al Powder

NaOEt/EtOH

5% yield

Smith A. C.; Williams R. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1736-1740.

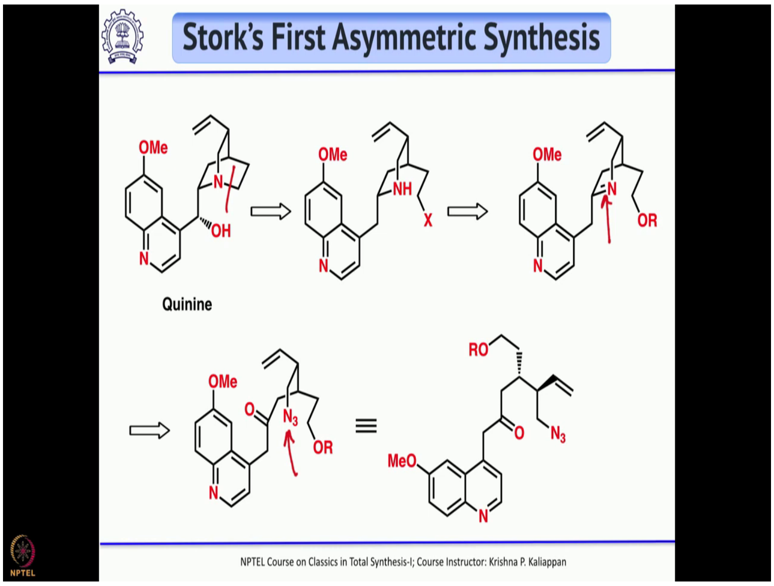
NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

So, what did William do? So, William first they made the quinotoxine from quinine. So, they made about 30 grams of this reasonably large scale from quinine, then they treated with sodium bromide followed by treatment with sodium ethoxide these are the same conditions reported by Paul Rabe and they got the mixture of these two ketones ok; these two ketones.

So, one is quinidinone other one is quininone. So, the reduction of quininone will give quinine the reduction of quinidinone will give quinidine according to Paul Rabe they used aluminium powder. So, aluminium powder and then sodium ethoxide ethanol they could isolate 5% yield of quinine. So, they felt that whatever aluminium powder Paul Rabe would have used may be different that is the reason why they were getting 18% yield and in 2010 Robert Williams they might have got the highest impurity aluminium powder sometimes impurity plays a role.

So, they suggested that impurities present in aluminium powder used by Paul Rabe might have played a role for getting higher yield of quinine from quininone. So, what is important was this actually confirmed that conversion of quinotoxine to quinine as reported by Paul Rabe could be repeated and so, the formal synthesis of quinine by Woodward is valid ok.

(Refer Slide Time: 25:24)

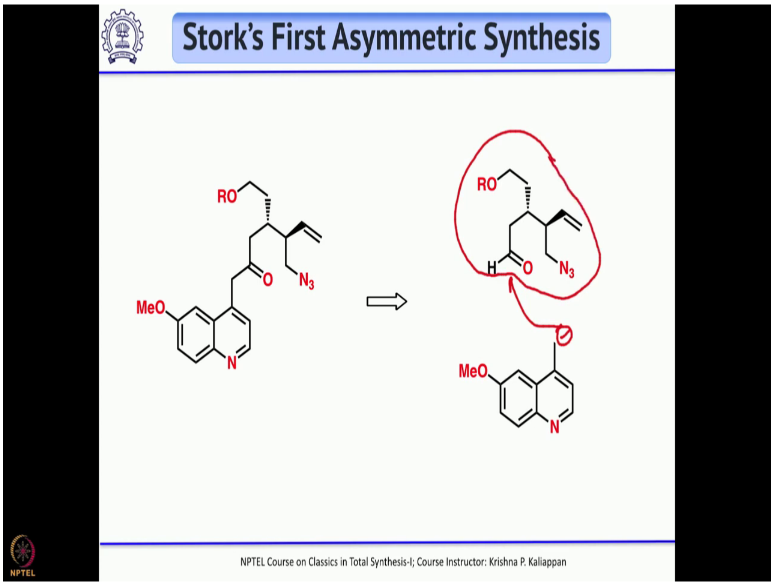


Stork's First Asymmetric Synthesis

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

So, now, I will quickly talk about Stork's first asymmetric total synthesis of quinine and until then there was no report on asymmetric synthesis though there were many racemic synthesis known and the first key step was the S_N2 substitution then this can be obtained by the reduction of the corresponding imine this imine can be obtained from the ketone and azide. So, if you do a starting reaction the $-N_3$ you can reduce to $-NH_2$ that will automatically form imine by reacting with the ketone.

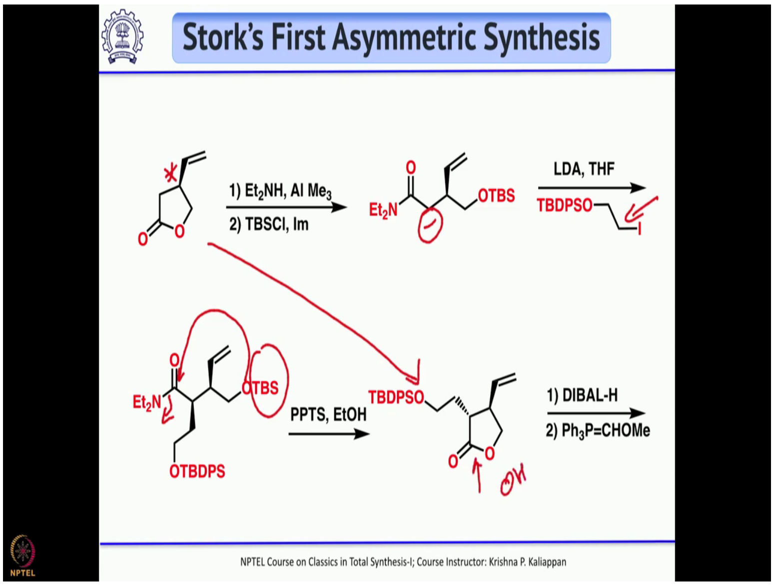
(Refer Slide Time: 26:05)


Stork's First Asymmetric Synthesis

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

And this can be redrawn like this and this can be obtained by in two steps by treating this compound with butyl lithium and adding to the aldehyde you will get an alcohol that alcohol upon oxidation will get the ketone. So, basically the major focus of this work should be on preparing this compound.

(Refer Slide Time: 26:26)

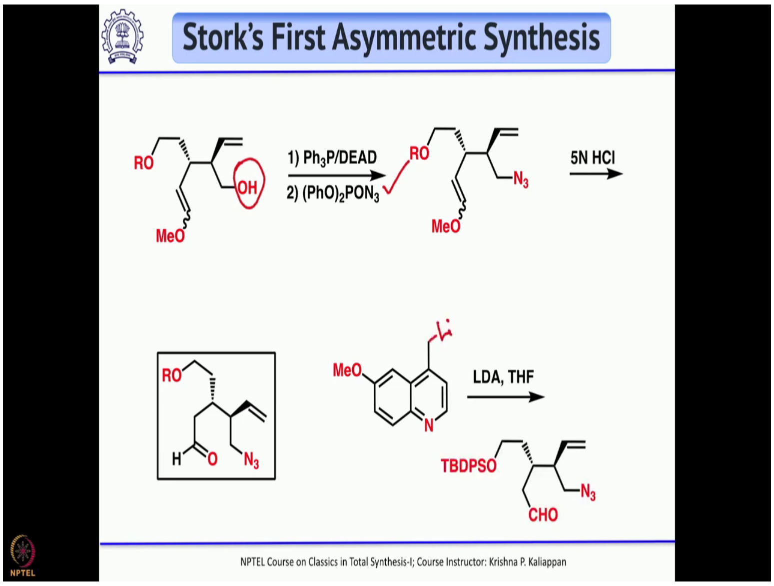

Stork's First Asymmetric Synthesis

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

So, he started with this known compound and with a established chiral center one chiral center is already there. So, and then he opened this five-member lactone with trimethyl aluminium and diethyl amine and protected the primary alcohol as TBSCI ok. Then you generate the enolate here ok. So, by treating with LDA you generate the enolate and quench with this iodide ok. The two carbon alkylation takes place this upon treatment with PPTS.

So, the TBS group can be selectively cleaved once it is cleaved then it cyclists to give the 5 member lactone. Basically if you see what you have done is you have attached a 2 carbon unit at α position of this lactone ok. Then it is an ester it is a cyclic ester lactone, if you reduce with DIBAL you will convert this lactone into lactol this upon enol ether vatic you will get corresponding enol ether.

(Refer Slide Time: 27:34)

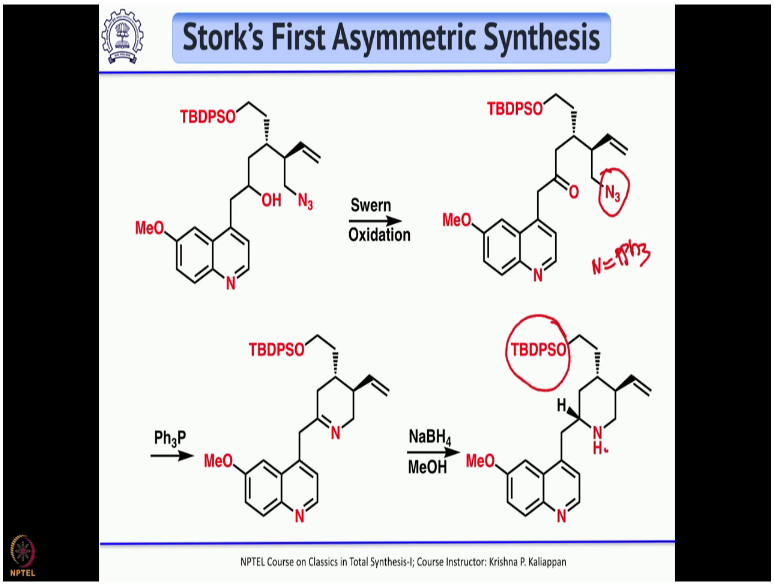


Stork's First Asymmetric Synthesis

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

This upon treatment with triphenyl phosphine dead and this diphenyl phosphoryl azide it basically Mitsunobu reaction converts this -OH into azide followed by hydrolysis of enol ether you get the aldehyde ok. Once you have this aldehyde, so this is a known compound treat with LDA. So, you generate the corresponding lithium derivative add to this aldehyde you get the corresponding alcohol.

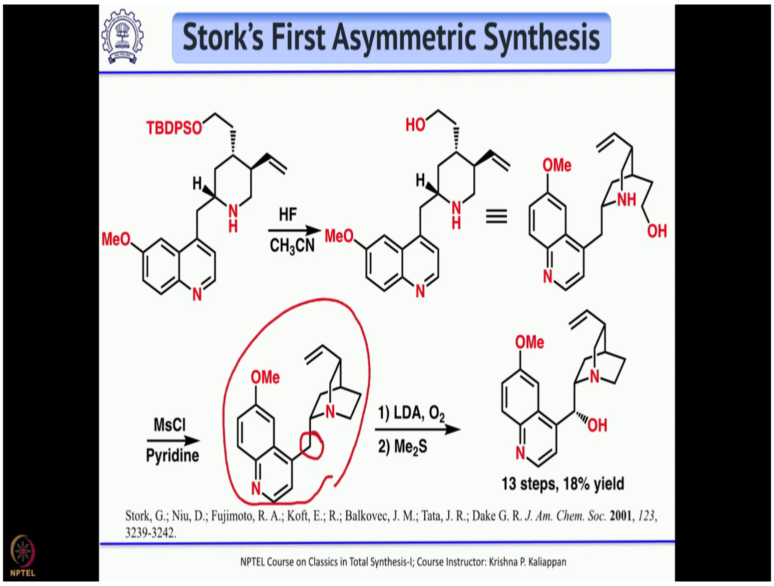
(Refer Slide Time: 28:05)


Stork's First Asymmetric Synthesis

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

So, now swern oxidation will give the ketone and treatment is triphenyl phosphine. So, triphenyl phosphine will form immuno phosphorene that immuno phosphorene intramolecularly undergo aza Wittig like reaction to get the corresponding 6 membered cyclic imine. Once you have this then reduction with sodium borohydride sodium borohydride will reduce the imine to give the corresponding substituted piperidine derivative ok. So, what you need to be done this TBDPS group should be removed converted into a leaving group so, that the cyclization can take place.

(Refer Slide Time: 28:50)


Stork's First Asymmetric Synthesis

13 steps, 18% yield

Stork, G.; Niu, D.; Fujimoto, R. A.; Koft, E.; R.; Balkovec, J. M.; Tata, J. R.; Dake G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.

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

So, the TBDPS was removed using HF in acetonitrile and followed by treatment with methyl chloride the S_N2 displacement take took place to give the core structure of quinine. So, what is left is introduction of the hydroxyl group. So, that was done by treating with LDA and in fact, it is known in the literature where they have used potassium tertiary butoxide followed by oxygen treatment and removal of extra hydrogen of the peroxide with dimethyl sulfide gives quinine.

Overall, if you look at this whole synthesis reported by star it involved 13 longest linear sequence with an overall yield of 18%. 18% overall yield for 13 step is really very good synthesis and also this the first asymmetric synthesis of such a complex natural product known in the literature.

Thank you.