Natural Products Synthesis

The Quest for Quinine: Those Who Won the Battles and Those Who Won the War

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For a long time, the synthesis of quinine constituted an elusive target. In 2004, which marked the 60th anniversary of the publication of the approach used by Woodward and Doering to synthesize quinine, two new stereocontrolled total syntheses of the natural product were accomplished. Together with the well-publicized first stereocontrolled total synthesis of quinine by Stork in 2001, these publications evidence the revival of interest of organic chemists in the synthesis of this compound, once considered a miracle drug. The recently disclosed syntheses of quinine also testify in a remarkable manner the huge progress made by organic synthesis during the last three decades since the first series of partially controlled syntheses of quinine by the group of Uskokovic. Following an account of the historical importance of quinine as an antimalarial drug and a brief description of the experiments which contributed to its isolation and structural elucidation, the first reconstructions of quinine and the total syntheses of the natural product are discussed.

From the Contents

1. Introduction

The year 2004 marks the 60th anniversary of the first communication by Woodward and Doering of their formal total synthesis of quinine,[1a] the most celebrated cinchona alkaloid that was claimed as "*the drug to have relieved more human suffering than any other in history*".[2] In its time, this epoch-making publication seemed to have ended the almost 100-year era of man trying to master this single natural product, which for centuries constituted the only effective remedy to malaria. The authors were therefore acclaimed as heroes.

Malaria is a life-threatening disease producing a debilitating condition which is caused by several species of the parasite *Plasmodium*. These parasites enter red blood cells, feed upon the protein therein, and destroys them. *Plasmodium* is transferred from an infected person to a healthy individual by the females of several species of *Anopheles* mosquitoes, which use human blood as a means to provide nourishment for their developing eggs.[3]

The parasite lodges in the mosquito's salivary gland and moves into the blood stream of the victim when it is bitten. The most conspicuous symptom of malaria is an intermittent fever that is associated with discrete stages of the life cycle of *Plasmodium*. Patients normally recover but they are weakened by the experience, being left listless and anemic. Repeated attacks can be observed many months or years after the initial infection because a form of the parasite becomes lodged in the person's liver. One form of malaria, caused by *P. falciparum*, can be quickly fatal, even to otherwise healthy individuals, because it can produce blood clots in the brain.

Malaria has affected mankind since the beginnings of recorded history and probably before.[4] Although malaria was associated with marshy areas since Hippocrates' time and was described by Thomas Sydenham around 1680,[5] its cause was unknown until 1880 when the French physician Alphonse Laveran discovered the parasite in patients' blood. Laveran, as well as the Italian physiologist Camilo Golgi, the British bacteriologist Sir Ronald Ross (who by the turn of the century discovered the role of the mosquito vector in the transmission of the disease), and the Swiss chemist Paul Hermann Müller (the inventor of DDT), were each honored with the Nobel Prize for their important contributions to the increased knowledge and better control of malaria.[6]

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Malaria has been designated as "*the most significant disease for world civilization over the past three millennia*";[7] the disease is still rampant in many countries, particularly those in Africa south of the Sahara. Even today, despite over 100 years of continuous research and a plethora of antimalarial drugs,[8] malaria remains a major disease, which affects approximately 40 percent of the world's population.[9] The World Health Organization (WHO) reported that there are between 300 and 500 million new cases worldwide each year and the disease claims between 1.5 and 2.7 million lives annually, mostly children.[10]

From a chemical perspective, what also marks Woodward's synthesis out as an important landmark is that it can be considered as the dawn of what was called "the Woodwardian era" of organic chemistry and the first of an impressive series of outstanding and increasingly daring accomplishments in the total synthesis of natural products. The 1944 publication by Woodward and Doering was the beginning of a series of events which would add excitement to the discipline of organic synthesis and give strong impulse to its subdiscipline of natural products synthesis. It was also the origin of the longstanding misunderstanding that Woodward and Doering were the first in achieving the total synthesis of quinine, a polemical controversy that persists even now.[11,12]

2. Quina: Bark from the New World That Cures Malaria

Malaria was brought to the New World by Europeans.[13] Ironically, the New World almost immediately exported the most efficient treatment to Europe for this disease, a supply that was set to continue for approximately 300 years afterwards.

The cinchona alkaloids are found in the bark of cinchona and Remijia species, which are evergreen trees originally part of the high forest (1500–2700 m) of the eastern slopes of the Andes mountains from Venezuela to Bolivia. Natives called the cinchona tree "quina-quina" ("bark of barks" in the native indian tongue) and seemed to have been aware of its antipyretic properties (it was also known as "ganna perides" or "fever stick"); they used the bark to treat fevers a long time before the arrival of the Spanish. Jesuits, particularly Father Antonio de la Calancha in Perú and Cardinal Juan de Lugo in Europe, are credited with the introduction of cinchona bark into medical use in Europe around 1640, after the perhaps serendipitous discovery[14] of its antimalarial properties in Peru (hence it was also known as Jesuit's bark, Cardinal's powder, Popish powder, etc.).[15] This fortuitous discovery seems to have taken place while the Count of Chinchon was Viceroy of this part of the Spanish colonies; according to a widespread legend, his wife, the Countess of Chinchon, was miraculously cured from malaria after being treated with a remedy made from cinchona bark specially brought to Lima from Loxa (now Loja, Ecuador).[16]

The Jesuits must also be credited with the spread of this remedy in Europe since Rome was the malaria capital of the world in the middle 17th century. A decisive contribution was also made by Robert Talbor, an English apothecary who cured many noblemen and several members of European royal families (including King Charles II of England and the son of King Louis XIV of France) from malaria. While Europe was involved in a controversy regarding the use of the new medicine, Talbor used a curative secret formula—which was shown after his death to be based on cinchona bark. The bark was officially introduced into the London Pharmacopoeia in 1677, and by 1681 it was universally accepted as an antimalarial substance.[17] The valuable properties of the medicine raised demand for the bark, which culminated in the installation of a Spanish-owned commercial monopoly and the beginning of the slow extinction of the natural cinchona forests because of overharvesting.[18] Such was the demand for the drug that there was always a shortage of cinchona bark in Europe, which for more than 200 years was imported from South America at great expense.[19]

Mankind seems to have learned a lesson from cinchona depredation: in recent times, it was realized that world demand for the powerful antitumor compound paclitaxel could result in extinction of its natural source, the Pacific yew tree. Pharmaceutical companies redirected their research towards the synthesis of semisynthetic derivatives and analogues; 150–200 years ago such environmental concerns did not exist.[20]

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Edmundo A. Rúveda graduated in pharmacy (1956) and biochemistry (1960) from the National University of Rosario (Argentina) and completed his PhD in 1963 with Prof. Venancio Deloufeu. He moved to England for post-doctoral studies with Prof. Alan Battersby (1964–1965) before returning to Argentina as Associate Professor and then Full Professor (1974) at the University of Buenos Aires. In 1975, after a short period in the pharmaceutical industry, he became Associate Director of the Institute of Chemistry at the University of Campinas (Brazil). In 1980 he returned as the Director of the Institute of Synthetic Organic Chemistry to the National University of Rosario, from which he has recently retired.

3. The Search for the Active Component in the Cinchona Bark

Written records of the use of plants as medicinal agents date back thousands of years. The oldest records come from Mesopotamia and date from about 2600 BC. These records indicate that instead of only one- or two-plant-based medicines finding their way into popular use, there were in fact many in use (up to 1000 in Mesopotamia).[21]

During the middle of the 18th century chemists began to take renewed interest in herbal remedies, including the cinchona bark. They became convinced that the dried and powdered herb contained an "active principle"—a definite chemical compound that was responsible for the plant's curative properties—a pure extract of which would provide an even better cure. A direct consequence of this reasoning was that in the early 1800s the active principles from plants began to be isolated. It was at this point that the effectiveness of medicinal natural products commenced to be attributed to science and not to magic or witchcraft.

During this age of discovery, reputed scientists of several European laboratories started to study cinchona bark. The concentration of the active principle of the bark differed according to its natural source and it seems that some degradation always occurred during the trip overseas to Europe, a feature that also encouraged adulteration. Therefore, their aim was to gain a better knowledge about its constituents, in particular its active principle, and detect the more frequent adulterations of this valuable product imported from overseas.[22]

In 1746 the Count Claude Toussaint Marot de la Garaye obtained a crystalline substance in France from the bark which he termed "sel essentiel de quinquina". A few years later, the two French chemists Buquet and Cornette introduced a new "sel essentiel de quinquina"; however, both proved to be the inactive calcium salt of quininic acid. In another failure, the Swedish physician Westerling announced in 1782 the discovery of the active principle, which he called "vis coriaria" and later shown to be "cinchotannic acid".[22b]

Antoine François Fourcroy systematically analyzed the bark by extracting it with water, alcohol, acids, and alkaline solutions. In 1790 he was finally able to obtain a dark red, resinous, odorless, and tasteless mass, which he called "chinchona red". Fourcroy claimed this to be the essential pharmacologic constituent of the bark; however, in contradiction to his affirmations, it was demonstrated that "chinchona red" was unable to cure malaria. Fourcroy also observed that the water placed in contact with the bark gave litmus a blue color—then a known property of alkalis—and that a green precipitate was produced when the infusion of the bark was treated with lime water. This French scientist was very close to entering the history books as the first to isolate quinine, but, surprisingly, he decided to abandon his research on the bark. Perhaps as a premonition, he commented that "*doubtlessly, this research work will lead some day to the discovery of a febrifuge for the periodic fever that, once identified, will be extracted from different plants*".[22b,38]

At the beginning of the 19th century the problem of the nature of the active principle of the Peruvian bark, as it was then called, still remained unsolved. In 1811 the Portuguese navy surgeon Bernardo Antonio Gomes extracted the bark of the gray variety with alcohol, added water and a small amount of potassium hydroxide, and observed the separation of a few crystals. Gomes called this substance cinchonine, which had been previously isolated by Duncan in Edinburgh from certain varieties of quina trees. Interestingly, it seems that the botanist Aylmer B. Lambert was also able to prepare the same compound; however, neither of them suspected the alkaline (alkaloidal) nature of the substance.

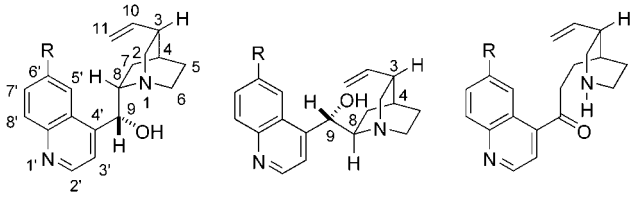
In 1817 the German Chemist Friedrich Wilhelm Sertürner[23] reported that morphine forms salts in the presence of acids, an observation that led him to the isolation of this important alkaloid. Driven by Sertürner's findings, Joseph Louis Gay-Lussac commissioned his colleague Pierre Jean Robiquet of the Ecole de Pharmacie of Paris with the task of searching for useful applications of the reported strategy. Robiquet's co-worker Pierre Joseph Pelletier was selected to conduct this study in collaboration with Joseph Bienaimé Caventou, a young student of pharmacology, and quickly led to the isolation of emetine (1817), strychnine (1818), brucine (1819), and veratrine (1919),[24] as well as other substances which the German chemist Wilhelm Meissner in 1819 termed alkaloids.[25]

In 1820 Pelletier and Caventou, experts in the isolation of alkaloids, began to work with the yellow bark of cinchona, known to be more effective against malaria than the gray bark employed by Gomes.[26] The alcoholic extract did not produce a precipitate when diluted with water and basified with potassium hydroxide; instead, a pale yellow gummy mass formed. The compound, which was extraordinarily bitter in taste, was soluble in water, alcohol, and diethyl ether. The latter feature was a key difference between its behavior and that of Gomes' material. Pelletier and Caventou cleverly demonstrated that the cinchonine isolated by Gomes was a mixture of two alkaloids which they named as quinine and cinchonine, thus successfully crowning a 70 year search.[27] Their original samples are now exhibited in London's Science Museum. The isolation of quinine allowed the quantitative evaluation of the quality of quina bark, the administration of a pure compound as a specific treatment for malaria, and the development of more accurate dose regimes.

Being pharmacists, neither of the Frenchmen risked demonstrating the curing ability of the newly isolated natural product; perhaps prophetically, they just mentioned that "*some skilful physician … joining prudence to sagacity … will conduct the appropriate clinical trials*".[27] These physicians quickly appeared and demonstrated that quinine was notably effective against the malarial fever, while cinchonine was inactive. The distinguished physiologist Francois Magendie gained broad experience in administering quinine to his patients and, by 1821, provided instructions for its use in the *Formulaire pour la préparation et L'emploi de plusieurs nouveaux médicaments.* In 1834 the surgeon of the French army, François Clément Maillot, who had previously used cinchona bark in Corsica, made successful trials of quinine with the troops in Argel and Ajaccio. Pure quinine rather than the powdered bark soon became the drug of choice for treating malaria.[5,28]

Pelletier and Caventou did not patent their invention, but instead were generously rewarded by their country with high positions and honors. The Academy of Sciences of Paris awarded the scientists the Montyon Prize, and Pelletier became the associate director of the Ecole de Pharmacie in 1832 as well as being appointed member of the French Académie des Sciences in 1840. Pelletier and Caventou established a factory in Paris for the extraction of quinine, an activity that is often mentioned as the beginning of the modern pharmaceutical industry.

The isolation of quinine paved the way for a series of new and interesting discoveries. In 1821 Robiquet isolated caffeine



cinchonidine, R= H
quinine, R= OMe

cinchonine, R= H
quinidine, R= OMe

cinchotoxine, R= H
quinotoxine, R= OMe

following the hypothesis that quinine should be present in the coffee tree, since this belongs to the the same family (the Rubiaceae) as the cinchona trees. Other alkaloids were later isolated from cinchona species: quinidine was isolated in 1833 by Delondre and Henry,[29] while in 1844 Winckler isolated what Pasteur termed in 1851 cinchonidine.[30] An additional 25 alkaloids related to quinine had been isolated by 1884 and an additional 6 were added between 1884 and 1941.[31]

Pasteur, the versatile French scientist, produced several "toxines" (cinchotoxine, quinotoxine—initially known as quinicine) by reaction of the natural bases with weak or diluted acids.[26e] His observations would prove to be of key importance 50 years later during the development of the first series of serious attempts to synthesize quinine; their importance can still be noticed today through the development of new approaches to the C8–N connection (see below). He also demonstrated the usefulness of quinotoxine as a resolving agent for racemic mixtures of acids.[26d,e]

4. The First Synthetic Approach to Quinine: Birth of a New Industry

By the 1800s the French, British, and Dutch all had colonies in malaria-infested areas. After the isolation of quinine by Pelletier and Caventou and the subsequent successful medical experiments demonstrating that this alkaloid was indeed the active antimalarial principle contained in the quina bark, demand for it started to rise. In the middle of the 19th century, both the alkaloid as well as the bark were always in short supply, since they were the only effective known treatment against malaria. It was regarded so critical strategically that it could determine the size and prosperity of an empire.[32] Two alternatives were considered possible to secure a continuous and abundant supply of quinine: the establishment of new plantations in areas other than South America and/or the chemical synthesis of quinine through the use of the then new science of organic chemistry.

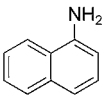
Examples of the first alternative (the story of which can be likened to that of rubber, wherein Sir Henry Wickham transferred seeds to Ceylon in the 1890s) include the several expeditions of Justus Hasskarl, Richard Spruce, Robert Cross, and Clemens Markham, as well as others representing European powers, in the search for plants, seedlings, and seeds of cinchona.[33] Most of the attempts at cultivating the cinchona tree as a source of quinine sound today either hilarious or tragic. They all met with failure because of a range of diverse factors that reveal the deep lack of precise botanical knowledge about cinchona and its biology. The French had little or no success, but the English partially succeeded in establishing cinchona plantations in Ceylon (modern day Sri Lanka) and India, which provided for their colonial army.[34] In a strange twist of fate, this strategy actually culminated in the establishment of productive Dutch plantations of cinchona in Java (Dutch East Indies, now Indonesia).[35] These Dutch plantations were made possible thanks to a small amount of seeds cheaply sold to the Dutch by a British trader, Charles Ledger,[36] in Peru and they constituted the basis of the Dutch control of the cinchona trade up to world war II. In these plantations the bark was removed in a controlled way and a continuous supply of quinine was obtained, much of which was supplied to those involved in colonial expansion.

The second strategy proved to be a much more demanding task. The indefatigable pursuit of synthetic quinine eventually resulted in it playing an important historical role in organic chemistry, both as a demanding target for structure elucidation and chemical synthesis. August Wilhelm von Hofmann, the German Director appointed to the recently founded Royal College of Chemistry, was the first to talk about the challenge of its synthesis. In a 1849 public address to the Royal College of Chemistry, Hofmann stated his intention of synthesizing the lucrative quinine as a way to demonstrate the ability of organic chemistry to solve social needs. In his words "*… it is obvious that naphthalidine [now α-naphthylamine], differing only by the elements of two equivalents of water might pass [into quinine] simply by an assumption of water. We cannot of course, expect to induce the water to enter merely by placing it in contact, but a happy experiment may attain this end by the discovery of an appropriate metamorphic process …*".[37]

The race for synthetic quinine was heating up by the middle of the 19th century. French scientists kept close track of developments across the English Channel, and in 1850 the French Society of Pharmacy made a call to the chemists in the following way: "*… during a long time, there has been an important problem to find a substitute for quinine with its same therapeutic effects … Therefore, we make a call … offering the amount of 4000 francs to the … discoverer of the way to prepare synthetic quinine*".[38] Participants were notified of the January 1, 1851 deadline and the requirement of submitting at least half a pound of the synthetic substance. Needless to say, nobody claimed the prize.

Chemical synthesis was in its infancy at this time. The main reservoir of chemicals was obtained from coal and the petrochemical industry, both being important sources of starting materials for various scientific problems. Carbonization of coal to provide gas for lighting and heating (mainly hydrogen and carbon monoxide) also gave a brown tar rich in aromatic compounds such as benzene, pyridine, phenol, aniline, and thiophene. Scientific research in this field was often a matter of trial and error based on intuition. Furthermore, there were no appropriate concepts for structure—these ideas came a decade later with the invention of structural theory by Butlerov, Couper, Kekulé, and van't Hoff. Indeed, the tetravalency of carbon atoms was proposed in 1858 and Kekule's theory on the structure of the benzene nucleus was formulated in 1865.[39]

The theory of types was proposed in 1838 by Dumas as a method to explain the combining power of carbon and became the predominant way of thinking among the most prominent chemists.[40] Type formulas intended to indicate the chemical similarity of compounds, but they were by no means structural formulas. However, this theory had strong supporters and contributors such as Alexander Williamson[41] and August Wilhelm von Hofmann. Following previous work of Wurtz, Hofmann prepared primary, secondary, and tertiary amines in 1851 as well as quaternary ammonium salts and classified them as belonging to the new ammonia type after recognizing that these compounds were related to ammonia. The theory of types successfully predicted the existence of acid anhydrides, which had been discovered in 1852 by Charles Gerhardt—the chief exponent of the new type theory.[42] Therefore, nobody was surprised to hear Hofmann's proposal of synthesizing quinine by hydration of naphthylamine [Eq. (1)], an abundant by-product from the British coal and gas industry.

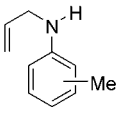


naphthalidine
(α-naphthylamine)

$$2\ C_{10}H_9N + 2\ H_2O \longrightarrow C_{20}H_{22}N_2O_2 \qquad (1)$$

The molecular formula postulated by Hofmann for quinine ($C_{20}H_{22}N_2O_2$) had two hydrogen atoms less than the correct formula ($C_{20}H_{24}N_2O_2$), which was established in Göttingen in 1854 by Adolf Strecker.[43] The establishment of the correct molecular formula for the natural product stimulated the beginning of the experimental phase of Hofmann's project, which was still guided by the simple atom-counting strategy. It is worth noting that urgent utilitarian objectives drove Hofmann's interest in this specific project: quinine was then a miracle drug and the economic support of the Royal College had started to decline because of the impatience on the part of its rich sponsors. They began to worry about the lack of results from their investments and strongly debated the true virtues of applied organic chemistry and its ability to produce something useful. This adverse climate was perceived by Hofmann as constituting a risk to the novel style and dynamics he had begun to impart to the College. On the other hand, organic synthesis was embryonic at that time, and Hofmann's proposal was daring.

During the Easter vacation of 1856, with the correct molecular formula of quinine in his hands and following his mentor's ideas, William H. Perkin decided to "reproduce" quinine. The 18-year-old disciple of Hofmann confidently began the quest by carrying out simple experiments, such as attempting a potassium dichromate mediated oxidative dimerization of "*N*-allyltoluidine" [Eq. (2)], in his home-

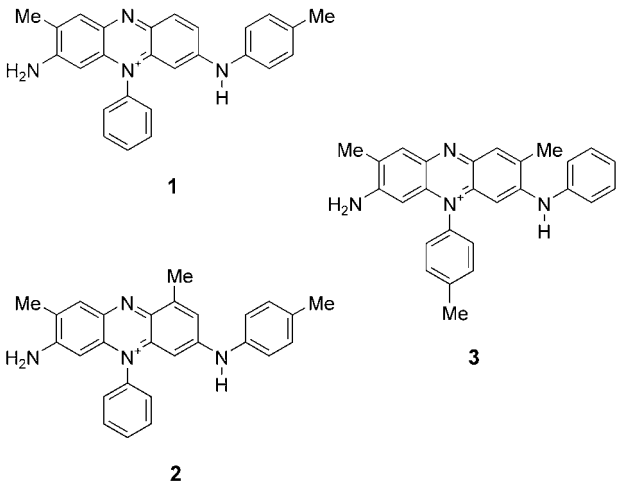


N-allyltoluidine

$$2\ C_{10}H_{13}N + 3\ [O] \longrightarrow C_{20}H_{24}N_2O_2 + H_2O \qquad (2)$$

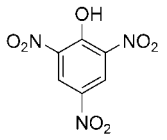
made laboratory in Shadwell, East London.[44] Since *N*-allyltoluidine is structurally nothing like half a quinine molecule, this attempt was utterly futile and he did not succeed. Undeterred, however, like a true Prince of Serendip—a prepared mind in search of unanticipated wonders—he must have observed something in the noxious, black coal tar derivative formed, which spurred him into next trying to similarly oxidize "aniline". Assuming that the primitive and useless atom-counting rule employed by young Perkin still governed his experiments, it is certain that his main objective was no longer the originally sought cinchona alkaloid.[45] Although Perkin did not produce quinine, he discovered to his amazement that after a series of clever manipulations his experiment produced a new dye and that this new dye was resistant to fade or run when subjected to washing or when exposed to sunlight. The compound was termed aniline purple and later called mauve by French designers, before becoming known as mauveine. The exact structure of the products resulting from the chemical transformations made by Perkin was studied more than one century later by employing modern high-field NMR techniques; these showed that mauveine has two major constituents: components A (**1**) and B (**2**), which differ from the previously postulated structure **3**.[46]

Colored substances were highly valued and much sought after as raw materials. Therefore, against Hofmann's recommendation, and in spite of a lukewarm response from local dyers, with the financial aid of his father (a builder) whom he managed to persuade to join the venture, Perkin developed the processes for the mass-production and use of his new dye. In 1857 he opened his factory at Greenford Green, not far from London, for commercialization of his discovery. Thus, young Perkin began work in the world's first large-scale organic chemical factory.[47] When Queen Victoria and Empress Eugenie publicly flaunted mauve dresses, his new dye became so popular that the period became known as the Mauve Decade. Moreover, the British post issued a penny stamp which became known as "penny mauve" or "penny lilac" and remained in use until 1901.

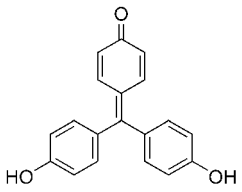


Before Perkin's discovery, all commercial dyes had been obtained from nature by crushing and squeezing insoluble dyes from vegetables, insects, and invertebrates, while employing poorly understood chemical methods for their manipulation. Natural colors were expensive and lacked the brightness we are accustomed to today. With the exception of indigo, they slowly faded on exposure to light or after successive washings. Perkin's aniline purple imparted a bright magenta appearance to diverse yarns which did not fade with time and exposure to other stress factors.[48]

Although picric acid had been produced in Lyon since 1849 and Runge had prepared aurin in 1834,[49] Perkin's



picric acid



aurin

discovery is considered to be a unique event that gave birth to the industry of the aniline dyes,[50] and Perkin's mauveine was one of the first industrial fine-chemicals. This dye was also the source of his personal fortune and an important stimulus for research towards a better understanding of the structure of molecules and their properties.[37] Perkin's industrial preparation of mauveine also signals the beginning of industrial organic synthesis. Many of the modern chemical and pharmaceutical giants such as BASF, Hoechst (now Aventis), Ciba–Geigy (now Novartis), and ICI (parts of which are now Astra–Zeneca and Syngenta) began as aniline dye companies. They later diversified to other products such as fragrances, agrochemicals, and pharmaceuticals. Dyes were employed in the 1880s to visualize pathogenic microorganisms and, by the end of the 19th century, synthetic dyes were being used and had fully replaced natural dyes.[47b,51] Dye research also led to the introduction of sulfonamides in 1936, but ironically, not one of these companies had synthesized quinine in their more than century lifetimes.

The history of chemical synthesis is replete with stories of both luck and perseverance. Similar to Friedrich Wöhler's accidental synthesis of urea[52] and Roy J. Plunkett's discovery of teflon,[14] Perkin's experiment was designed to produce a quite different product. Like his colleagues, Perkin's genius was not to throw away the reaction product but, prompted by unusual observations, to examine its properties. This he did by dissolving the dark and seemingly useless product in alcohol and then dipping pieces of silk into the resultant purple solution.

The key factors determining Perkin's success from his initial failure were the arrival of Hofmann in England, with the aim of creating a school of chemists, as well as Hofmann's contagious enthusiasm for research and his interest in high-impact research subjects, such as the study of organic bases found in coal tar. Also, Perkin's previous experience with dyes was important, as well as his motivation and personal characteristics as a passionate young scientist, with an interest in experimental research, and who relished taking the initiative. No less important was the fact that Perkin was a curiosity-driven person, who was gifted with powerful observational skills.

Paradoxically, the lack of a structural theory made a great contribution by allowing the design and execution of what nowadays could be considered a senseless and futile project condemned to failure before the start. Finally, the purity of the starting "aniline" also played a key role in Perkin's favor. Since the starting benzene was a coal tar derivative it was contaminated with toluene, which upon nitration and subsequent reduction gave a complex mixture of aniline and toluidines. As recognized even by early chemists involved with mauveine, the presence of *o*- and *p*-toluidine were vital for the formation of the most effective dye.

5. The Structure of Quinine

The three most important techniques currently for the elucidation of the structure of natural products are mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy, and X-ray crystallography. The structures of most natural products can be determined with relative ease with the first two techniques, and although X-ray crystallography is a more powerful tool, it requires that the compound in question be capable of producing good-quality crystals.

Quinine is of not too structurally complex and, despite the fact that these techniques are not infallible, today's organic chemists could hardly spend more than a few days determining the structure of the natural product accurately. Modern chemists, however, can hardly imagine how difficult this task was before the advent of these powerful analytical methods. During the late 19th and early 20th century analytical methods were scarce and "wet" chemical analysis was used routinely. Much of the organic chemistry of that time involved the exploration of chemical structures, and destructive approaches such as derivatization, degradation (a method that literally analyzed—breaking down a compound under a

known set of conditions, such as boiling the compounds in question with concentrated acids or caustic alkalis), and combustion were used to garner structural evidence.[53]

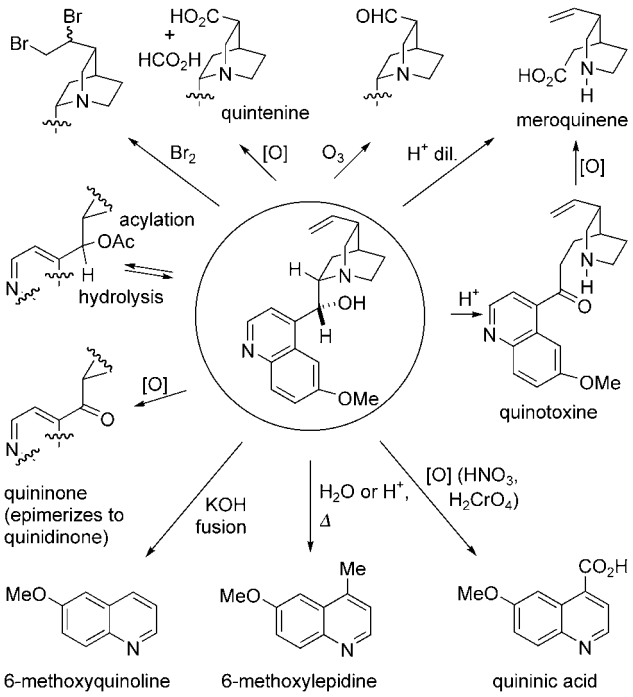
After Perkin's naive experiment and useful failure, there were no other serious attempts to synthesize quinine for the next 50 years. However, before the turn of the century, and with the new concepts of structural theory, organic chemists realized that the structure of quinine was more complex than previously thought and that complete structural elucidation ought to be the first stage in a stepwise rational approach towards the total synthesis of this alkaloid.

The structural elucidation of quinine, now a classic in organic chemistry,[54] was a formidable task and an extraordinary challenge at the time. Interestingly, however, it started with small advances such as Pasteur's demonstrations in 1853 that quinine was levorotatory and could be converted into the corresponding toxine by dilute acid,[55] before Strecker established the empirical formula of the natural product as $C_{20}H_{24}N_2O_2$ in 1854.[43] The whole effort directed towards the structural elucidation of quinine lasted more than 50 years, including a 20 year period of very intense activity in the laboratories of many prominent European chemists. This complex investigation, which also involved the related alkaloids cinchonine, cinchonidine, and quinidine, is one of the most illustrative examples of the joint use of functional group reactions, chemical degradation, and chemical intuition. The benefits of this research widely surpassed its original purpose, since the body of results which culminated in the structural determination of quinine and related alkaloids contributed much to our present chemical knowledge on pyridine and quinoline derivatives.[56]

The simplicity of the experiments is amazing; for example, initial ones carried out by Strecker himself,[43] and also by Skraup, demonstrated the tertiary nature of both nitrogen atoms.[57] Conventional acetylation followed by mild basic hydrolysis of the resultant monoacetyl derivative to regenerate quinine suggested the presence of a hydroxy group, a deduction which was confirmed by its conversion into the corresponding chloride with PCl_5.[58]

The presence of the vinyl group was deduced from experiments undertaken by Skraup, Königs, Hesse, and others, who observed that the alkaloid was easily attacked by permanganate, gave other characteristic reactions of alkenes, such as adding halogens and hydracids,[59] was ozonolyzed to the corresponding aldehyde,[60] and oxidatively degraded to a carboxylic acid known as quintenine with the release of formic acid (Scheme 1).[61] Cinchonine gave the same reactions, an observation which proved important for the joint structural elucidation of the four important cinchona alkaloids: quinine, quinidine, cinchonine, and cinchonidine.

Clues on the nature of the aromatic moiety of quinine were gained by degradative fusion with potassium hydroxide, which furnished 6-methoxyquinoline.[62] Meanwhile, experiments from the laboratories of Königs, Baeyer, and others leading to quinoline, lepidine[63] and 6-methoxylepidine (from cinchonine and quinine), cinchoninic acid (from cinchonine and cinchonidine),[64] and quininic acid (from quinine and quinidine)[65] provided insights on the attachment point of the non-aromatic portion of the molecule.



Scheme 1. Some of the reactions that provided clues to the structure of quinine.

Degradation experiments dilute acid conducted by Königs in 1894 allowed the isolation of a monocyclic structure to which the name meroquinene (μερος = part in Greek) was given.[66] This proved to be a key piece of knowledge for the establishment of the structure of the non-aromatic (quinuclidine) portion of quinine and it became an important fragment in future synthetic efforts. Since degradation of quinine, quinidine, cinchonine, and cinchonidine produced the same meroquinene[66,67] and oxidation of this product gave D-β-cincholoiponic acid,[68] the conclusion was drawn that the relative configuration at C3 and C4 was the same in the four alkaloids. Partial epimerization to α-cincholoiponic acid, however, clouded an otherwise clear stereochemical proof (Scheme 2).[69]

Another critical step in the determination of the chemical structure of quinine was the acquisition of quinotoxine,[55,70] a product already obtained by Pasteur in 1853 after exposure of quinine to a slightly acidic medium.[26e] This reaction and other characteristic chemical transformations, in which assistance of the quinoline moiety was fundamental, would prove to be of compelling importance during the early design of synthetic routes towards the natural product.

A series of papers published by G. Rohde and W. von Miller between 1894 and 1900[71] on the chemistry of quinotoxine suggested that the non-aromatic part of quinine could have a tertiary nitrogen atom as the bridgehead of a bicyclic structure. This proposal was rapidly accepted by Königs because it explained many previous observations from his research.[72] Before his death in 1906, Königs consolidated the structural knowledge on quinine.[67] In 1907 the German chemist Paul Rabe, who worked for almost 40 years on structural and synthetic aspects of quinine, demonstrated that

Extract from the tribute to Paul Rabe by Henry Albers and Wilhelm Hochstätter in *Chemischen Berichten* **1996**, *99*, XCI–CXI:

Paul Rabe was born in the town of Hoym, on August 24, 1869, son of the pharmacist Ludwig Rabe and his wife Antonie (née Faaß). When Rabe was 11, he entered the Gymnasium at the nearby city of Quedlinburg. He lived these years happily and without deprivations or worries under the intelligent guidance of his "Pensionmutter", the wife of preacher Hohmann, who instilled him her faith in God. Home and school influences, as well as education based on the high values of the classics, inclined Rabe towards science. School friendships were not a random encounter for him; he cultivated them until his death.

In 1890, after passing the Bachelor test, he decided to study chemistry. There can be little doubt, and this was later confirmed by subsequent conversations with colleagues, that his fathers pharmacy had left a lasting impression, which tipped the scales in his choice of career. Here Rabe met some of the most important chemists of his time. First, he spent two semesters at the Institute of his future teacher, Ludwig Knorr, who had just taken over the Professorship at Jena; then, he spent two semesters in Berlin, where the Director was A. W. von - Hofmann, and finally, in 1892, he went back to the University of Jena. Here, in July 1894, he started his Doctorate under the supervision of Knorr on the topic of antipyrin. In February of the following year he was promoted to Dr. Phil. Up until 1897 he was employed as an Assistant in Knorr's laboratory, but then started his career as an independent scientist, working on the isomers of benzylidene bis(acetoacetate), which led him to his "Habilitation" in May 1900. The next steps of his scientific career included his promotion to Assistant Professor in 1904, to Chief of the Division of Organic Chemistry in 1911, and finally on October 1, 1912, he was transferred from the main University to the Deutsche Technische Hochschule of Prague as Ordinary Professor, with duties concentrating on the experimental chemistry of organic materials.

In later years, Rabe recounted with fondness the days he spent in Prague, where under the monarchy of the Habsburgs he learned the rules of etiquette of the noblemen of the Viennese castles who wore two-cornered hats and ornamental swords as ensignia of rank, and where his future wife, Else Hess, was born. However, he siezed the opportunity to return to a prosperous German institute, when in October 1914 the senate of the free and Hanseatic city of Hamburg invited him to be the Director of the State Laboratory of Chemistry a few months before the outbreak of the First World War. Their four children were born in Hamburg, and the parents completely devoted themselves to their upbringing. They were not, however, spared the cruel hand of fate: they suffered the tragic loss of their eldest daughter and the untimely death of their only son during the Second World War. Therefore, Paul Rabe and his wife found refuge in their faith in God, and gave all their love to both of their remaining daughters, their son in law, and their grandchildren. The Rabe's beautiful house in Parkalle became the home for a troop of students, who came to participate in the warmth and wisdom of these adored people. The "Rabenvater" and "Rabenmutter", as they were jokingly known, in truth formed the hub of the working group since 1919, after the foundation of Hamburg University. The students flocked around their adored teacher and his wife, who brought warmth to any occasion. She guided special occasions with a steady hand and understood intuitively how to educate effectively. Every one who crossed the path of this extraordinary woman felt inspired. Else Rabe, who died on December 28, 1962, also thought along those lines.

Rabe was a classic scientist in the sense of William Ostwald. Science represented for him the pure quest for knowledge, far from any utilitarian deviations. His devotion to science was high and he always pursued the search of knowledge through experimental results and high-level research, never speculating about monetary profits. This attitude greatly influenced his publication standards, and placed severe limits to what he considered of novelty and publishable. If he did not feel confident enough with a result, then he would wait to secure the data, because he felt the danger of someone else publishing the results before him was less than having to publish a correction or have a correction pointed out to him.—In his function as teacher he placed a great emphasis on experimental chemistry—which included inorganic and organic chemistry—for which he prepared with extreme care.

Paul Rabe felt a strong connection with this large city, and thanks to his efforts, after the establishment of the University of Hamburg in 1919, the State Laboratory of Chemistry became an Institute of the University in 1921; besides his chair in organic and inorganic Chemistry, Rabe also directed the State Research Office. The newly established School of Mathematics and Natural Sciences appointed him as its first Dean, and he found many good friends among his colleagues. His coworkers, K. Kindler, H. Schmalfuß, E. Jantzen, H. Albers diversified from Rabe's original research subjects and extended the "Privatlabor" work through their own research and teaching at the Institute and in universities abroad. They and numerous other students could count on the care and ever watchful participation of their teacher.

Rabe's high-point as a scientist was reached on February 24, 1931, when one of his immediate collaborators brought to him one gram of fully synthetic hydroquinine. The ensuing party, which celebrated this extraordinary accomplishment, was unforgettable for all of the participants.

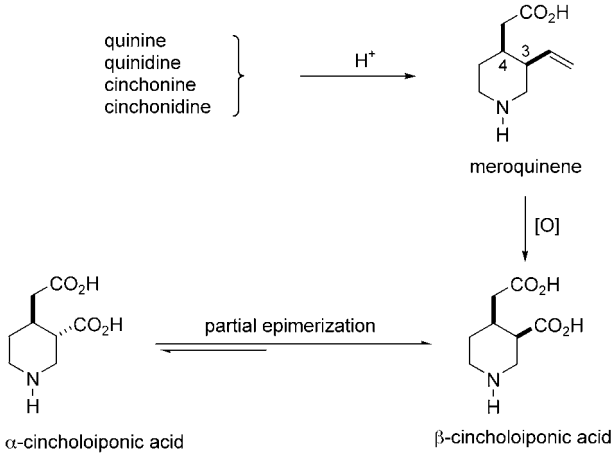
As far as it is known, Rabe did not participate in politics; he was moderately against National Socialism and in the winter semester of 1934/35 he even removed a notice from the notice board notifying of a boycott against Jewish students at his Institute. This behavior led to his premature retirement from his workplace; the authorities of the University of Hamburg, who had extended his appointment as Director of the Institute until 1939, decided his retirement should be effective from March 31, 1935, by enforcing the January 1935 enactment establishing the retirement age of university professors as 65.

Undeterred by this insulting procedure he continued his research work, now with very limited resources and, as in the old times when he was younger, with himself working at the bench. The outbreak of the war in 1939 challenged him with preserving his life and his family wellbeing; his house, severely damaged by the continuous bombings, was always full of people even worse affected. He bore everything with the calm composure of a philosopher.—

During the period 1942–1944 he returned to supervising young coworkers, when he was invited by his former students to the Institute of Organic Chemistry of the Technical University of Danzig as an old "chief" with laboratory experience and wisdom in life. Again, the "Rabenvater", as he was soon also jokingly known here, bestowed love and kindness on his extended family, which also included new Danziger colleagues.—

During the hard years after the end of the war, his friends and students tried to ameliorate the hunger and cold of the Rabes; some of them visited, bringing potatoes and cabbages in their rucksacks, instead of

flowers. In 1946, he became afflicted by an eye illness, which interrupted his desk work. An operation two years later partially restored his sight; deeply happy again he enjoyed walking and appreciating the beauty of nature, and content that he could once again share in the chemical literature. When Rabe was 80, in recognition of his long-standing work on cinchona alkaloids, the School of Medicine of the University of Hamburg awarded him the title of Doctor in Medicine, *honoris causa*. The German Society of Pharmacy also appointed him as an honorary member. At his 83th birthday, still active and spiritual, he rejoiced with family, friends, and students. However, his health rapidly deteriorated; a few days later, his strength suddenly left him, and with serene clarity he died on August 28, 1952. His last words were "nun est es aus" (it is over now).

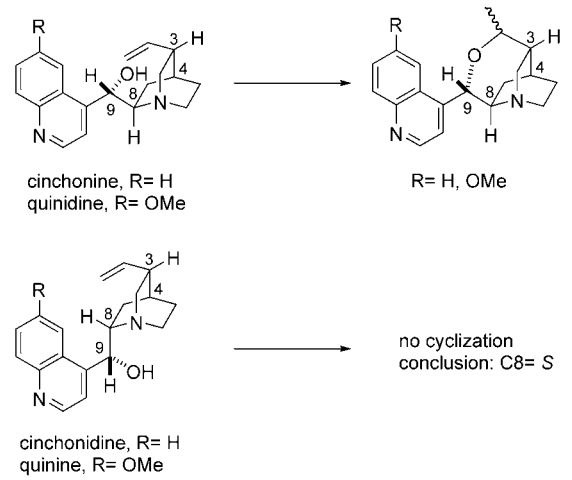


Scheme 2. The cinchona alkaloids and their configuration at C3 and C4.

the alcohol function in the alkaloids was secondary, and established its exact location by oxidation of cinchonine to cinchoninone.[73] Finally, by an irony of destiny, a short time after Perkin's death Rabe was able to suggest the correct connectivity of quinine in 1908.[73,74] As a result of the evaluation of a set of results from simultaneous studies carried out on the other alkaloids, this work allowed chemical structures to be proposed for them. Some stereochemical issues, however, would have to wait another three and a half decades to be definitively and unambiguously clarified.

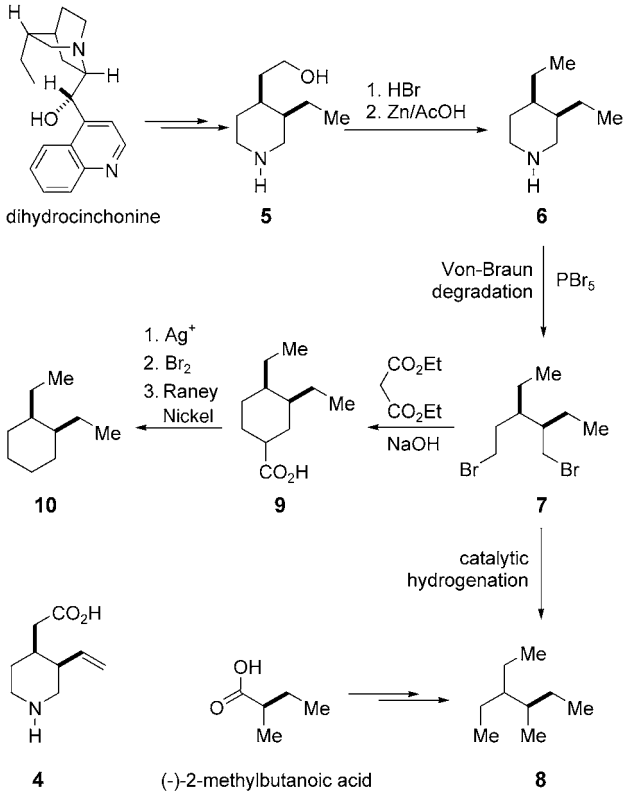
With the clues discovered in the 1920s that the C3 and C4 configuration was the same for the the four alkaloids, the C8 configuration was solved by evaluating the ability of quinine and its congeners to cyclize to oxepanes (Scheme 3).[75] The inability of quinine and cinchonidine to cyclize, whereas quinidine and cinchonine did, suggested that the C8 configuration of the former compound was what we now call *S*.[76] The C9 configuration of the cinchona alkaloids was rationalized in 1932.[77]

In 1944 Vladimir Prelog, who would go on to develop a long-standing experimental interest in stereochemistry, succeeded in unambiguously establishing both the *cis* relationship at the C3 and C4 centers and the absolute configuration of meroquinene (**4**), and hence of the quinuclidine moiety of



Scheme 3. Probing the C8 configuration of the quinine alkaloids.

the cinchona alkaloids, through clever chemical manipulations of a meroquinene derivative to simple hydrocarbons (Scheme 4).[78] Cinchonine was reduced to dihydrocinchonine and, in turn, this was degraded[79] to alcohol **5**; the alcohol was then transformed into 3,4-diethylpiperidine (**6**), which furnished dibromide **7** after a von Braun degradation with PBr_5. Catalytic hydrogenation of **7** gave (−)-3-ethyl-4-methylhexane (**8**), from which the absolute configuration of meroquinene was deduced by comparison with (−)-**8** (which was prepared from (−)-ethylmethylacetic acid of known absolute



Scheme 4. Prelog's unequivocal determination of absolute and relative configuration at C3 and C4.

configuration, secured by correlation with glyceraldehyde.[78b] On the other hand, malonic ester synthesis from **7** to furnish homochiral acid **9**, followed by decarboxylation, provided an optically inactive 1,2-diethylcyclohexane (**10**), thus providing conclusive proof of the relative *cis* arrangement of the C3 and C4 centers.[78a]

6. Rabe Provides the First Steps and the Synthesis of Quinine Seems To Become Simpler

At the beginning of the 20th century structural determination was in its infancy and final proof of the structure of simple degradation products was thought to require unambiguous synthesis of the compound with the suspected structure. In a few cases this could be done by synthesis of the natural product itself (for example, camphor),[80] followed by comparison with an authentic sample of the natural product.[81] Thus, synthesis, with complementary analysis, was often a matter of utilitarian necessity rather than the creative, elegant art form revealed by the work of many of the great synthetic chemists who characterize the second half of that century.

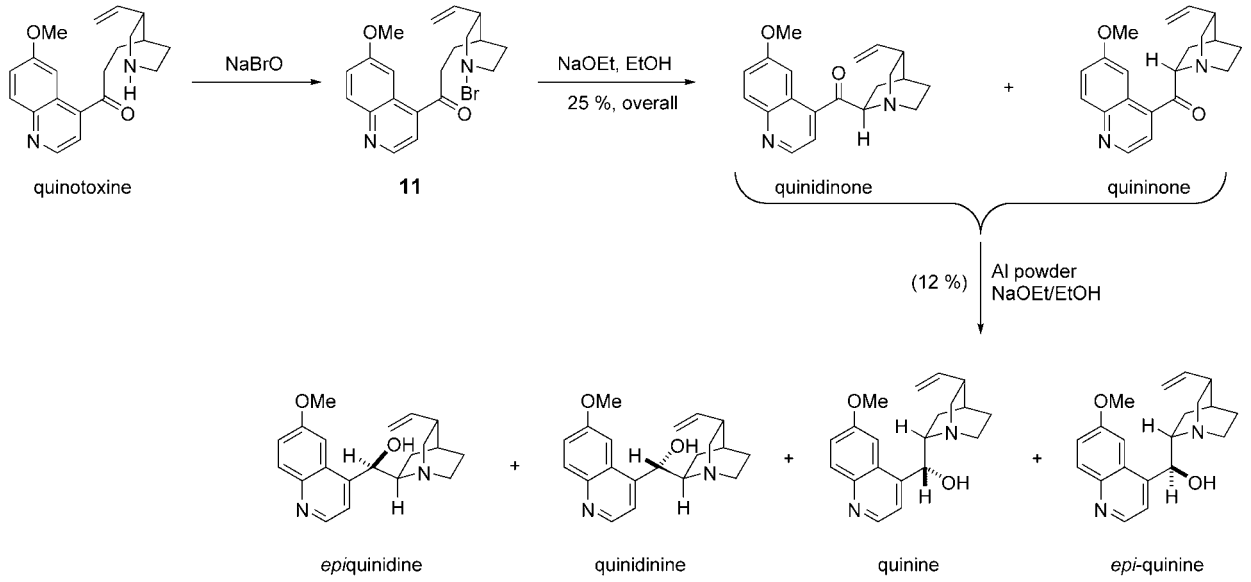
Just as countless shoeboxes filled with rattling gears and levers may testify to the fact that dismantling a clock is never as daunting as putting it back together, the reassembling (total synthesis) of quinine, even with the aid of more powerful tools than those at Perkin's disposal, would require decades of tenacious efforts.

At the beginning of the 20th century a number of research groups were making progress towards the synthesis, or at least the reconstruction, of quinine, and the research group of Rabe was publishing perhaps the most important results in this area. In 1908 Rabe reduced cinchonidinone to cinchonine, thus achieving a new and important breakthrough,[74a] while in 1909 he described the cleavage of cinchona ketones by the action of sodium ethoxide and alkyl nitrites which led to quinoline-4-carboxylic acid and meroquinene derivatives.[67b] In 1911 he succeeded in converting cinchotoxine into cinchonidinone by treatment of the former with hypobromous acid, followed by cyclodehydrobromination of the resultant *N*-bromo derivative with sodium ethoxide.[82] The same sequence yielded dihydrocinchonine when applied to dihydrocinchotoxine.[82b] In addition, in 1913, Rabe demonstrated the smooth condensation of aliphatic esters with ethyl cinchoninate to give β-ketoesters, from which quinoline-4-ketones were readily available by hydrolysis and decarboxylation.[83]

Without complete knowledge of the stereochemistry of quinine, Rabe chose to attempt its reconstruction from quinotoxine, a 3,4-disubstituted piperidine.[55] In 1918, in a very laconic publication entitled "*Uber die Partialle Synthese des Chinins*",[84] Rabe and Kindler outlined a synthetic sequence for the reconstruction of quinine and quinidine from quinotoxine (Scheme 5). This sequence was analogous to one previously employed, and involved the construction of the C8–N bond (C8–N approach) through the intermediacy of *N*-bromo compound **11**.[82] Reduction of the resultant quininone with aluminum powder in ethanol containing sodium ethoxide afforded a mixture of quinine (12%) and quinidine (6%).[85] This transformation was the first major step towards the synthesis of quinine since the famous failure of Perkin 50 years before.

Rabe's efforts in this field reached a high point in 1931 with the publication of the total synthesis of dihydroquinine,[86] then a major and highly acclaimed achievement, which employed the same strategy used in the 1918 report for the final steps. Taken together, these results suggested that the total synthesis of quinine could be accomplished from quinotoxine by using Rabe's protocol.

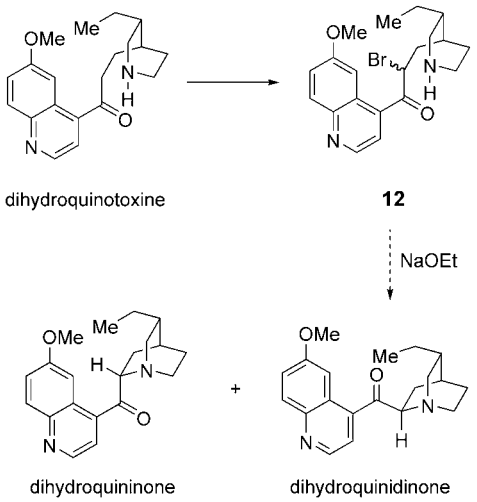
Unfortunately, however, perhaps because of wartime pressures, Rabe's procedure from his 1918 report was not cautiously reviewed and his claims were not fully substantiated. The key procedure for the reduction of quininone to quinine with aluminum powder was detailed 14 years later,[85] by the reduction of dihydrocinchoninone to dihydrocincho-



Scheme 5. Apparent course of synthesis of quinine developed by Rabe and Kindler in 1918.

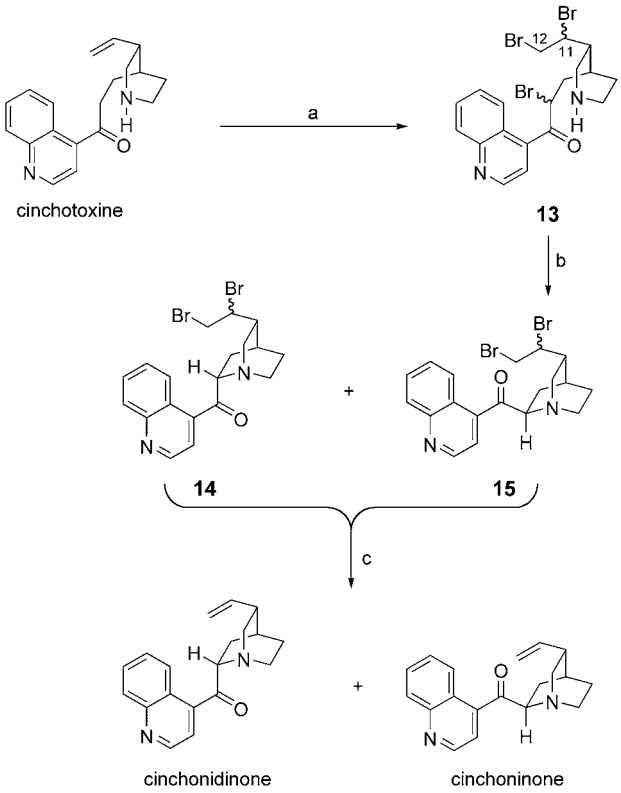
nine, which is known to have the same configuration at C8 and C9 as quinidine. Furthermore, Rabe commented in 1918 that his method "ist noch nicht eingehend beschrieben worden" (is not described yet in detail).[84] This would prove to be of paramount importance in one of the most important chapters of the history of the synthesis of quinine, which was written during the second World War. In the words of Professor Gilbert Stork *"[Paul Rabe] simply did not sufficiently document what he reported having done that one could be sure to do the relevant chemical transformations exactly the way he did them"*.[87] Moreover, Rabe's protocol proceeded without addressing the stereochemical problem, which means that a "total synthesis" along his synthetic scheme would always produce a mixture of isomers that required painstaking separation.

Interestingly, some years before Rabe's reconstruction of quinine, the research group of Kaufmann brominated dihydroquinotoxine with bromine in 48% hydrobromic acid to obtain mainly dihydroquinidinone after treatment of the α-bromoketone **12** with an alkaline alkoxide (Scheme 6). The same operation was carried out on dihydrocinchotoxine and provided dihydrocinchonidinone.[88] Their approach was proved correct three decades later, but during his time this procedure was regarded, unfortunately, as useful only for compounds devoid of a reactive vinyl group.



Scheme 6. The approach used by Kaufmann et al. for the synthesis of dihydroquininone and dihydroquinidinone.

Despite the poor resources available, the research groups of Kaufmann as well as Rabe were certainly very close to reconstructing quinine. In 1946 Woodward et al. transformed 11,12-dibromoquininone into quininone[89] by debromination with sodium iodide, and in a 1948 publication[90] Ludwiczakówna demonstrated that tribromides **13** resulting from the bromination of cinchotoxine with bromine in 48% hydrobromic acid could be cyclized with sodium ethoxide in ethanol to give good yields of a mixture of 11,12-dibromo ketones **14** and **15** (Scheme 7). These compounds could be debrominated with sodium iodide to yield cinchonidinone and cinchoninone. Furthermore, quininone and quinidinone were obtained when



Scheme 7. "Extended" Kaufmann approach to cinchoninone and cinchonidinone. Reagents and conditions: a) 48% HBr, Br_2, 70°C (97%); b) 1. NaEtO, EtOH; 2. HCl (81%); c) NaI, EtOH, reflux, 50 h (90%).

quinotoxine was submitted to the same procedure, and these steps became a complementary alternative to Rabe's approach. Interestingly, participation of α-haloketones such as those synthesized as intermediates by Kaufmann et al. in the Rabe-type cyclization of quinotoxine to quininone and quinidinone was decisively demonstrated by Gutzwiller and Uskokovic in 1973.[91] The feasibility of the protocol by Kaufmann et al., however, has never been tested in a total synthesis of quinine.

7. The Much Awaited Total Synthesis of Quinine

Chemistry blossomed between the two World Wars, and occurred at an ever-accelerating pace of discovery. Work done in chemical physics and physical chemistry did much to transform notions of how molecules are held together, how bonds are formed and broken, and how reactions occur. This more mathematically rigorous treatment of bonding and reactivity, particularly in the wake of quantum mechanics, gave novel theoretical grounding to structure theory and to the search for definitive structures of natural products. This search had begun in the 19th century and had continued unabated and largely unchanged by the reconceptualizations of chemical bonding during the 1920s and 1930s.

Organic synthesis made interesting progress; however, the lack of appropriate theoretical interpretation of reactions somehow slowed further advances. The gap between theoret-

ical chemistry and organic chemistry is clearly illustrated in a textbook of the period: "*No doubt the ultimate goal toward which organic chemistry is striving is that state in which fundamental laws and theories will have been developed to such an extent that it will be possible, in advance of experimental trial, to deduce a satisfactory method for the synthesis of any compound and to predict all its properties. Owing to the complex structure of most organic molecules, however, it seems probable that such a Utopian state is impossible of achievement and that organic chemists must content themselves with the more modest aim of augmenting what Gilbert Lewis gallantly calls their "uncanny instinct" by such exact science as they may find applicable*".[92]

At the age of 20, and after a meteoric 4-year stay at MIT—where he earned his BSc in 1936 and a PhD the next year—the child prodigy Robert Burns Woodward started working in 1937 as a post-doctoral fellow and later as a member of the Society of Fellows in the Department of Chemistry at Harvard University. He remained there for the next 42 years to become one of the preeminent organic chemists of the 20th century. Woodward made great contributions to the strategy of synthesis, to the deduction of difficult structures, to the invention of new chemical methods, and also to theoretical aspects.

During his successful scientific career he received numerous awards as well as the 1965 Nobel Prize for Chemistry for "*his outstanding achievements in the art of organic chemistry*". More than 400 graduate and postdoctoral students trained in his laboratories.

Many interesting natural products had been conquered by synthesis before 1940, such as tropinone (Willstätter: 1901; greatly improved by Robinson in 1917), camphor (Komppa: 1903; Perkin: 1904), α-terpineol (Perkin: 1904), haemin (Fischer: 1929), equilenin (Bachmann: 1939) and pyridoxine (Folkers: 1939).[11a,93] However, Woodward's explosive entry into the arena of natural product synthesis changed the history of this field, which would never be the same again.

The accomplishments of Woodward in his time were amazing; their spectacular nature not only stems from the relevance of the chosen synthetic targets, but also from the originality in his way of attacking the synthetic problems, the elegant solutions he provided to complex challenges, and the simplicity of the methods involved in applying those solutions. The catalogue of Woodward's achievements in the total synthesis of natural products include quinine [(±)-homomeroquinene (**17**) or (+)-quinotoxine, 1944], patulin (1950),[94] cholesterol and cortisone (1952),[95] lanosterol (1954),[96] lysergic acid and strychnine (1954),[97] reserpine (1958),[98] ellipticine (1959),[99] chlorophyll *a* (1960),[100] tetracycline (1962),[101] colchicine (1965),[102] cephalosporin C (1966),[103] prostaglandin F_{2a} (1973),[104] and his paramount achievement: the synthesis of vitamin B_{12} (1973, with A. Eschenmoser).[105] The total synthesis of erythromycin A was published in 1981,[106] after his death.

Woodward's genius contributed to the deduction of the structures of penicillin (1945),[107] patulin (1949),[108] strychnine (1947),[109] oxytetracycline (1952),[110] carbomycin (magnamycin, 1953),[111] cevine (1954),[112] gliotoxin (1958),[113] calycanthine (1960),[114] oleandomycin (1960),[115] streptonigrin (1963),[116] and tetrodotoxin (1964),[117] as well as others.[118] He unveiled the family of macrolide antibiotics, for which he also proposed a mode of formation in nature[119]—as he had done with the first proposal of the cyclization of squalene in cholesterol biosynthesis.[120]

The scientific world first knew Woodward through a series of publications (1940–1942) highlighting the correlation of ultraviolet spectra with molecular structure.[121] Those publications show his reduction of the ultraviolet spectra of many organic compounds to a few numerical relationships and demonstrate his remarkable powers of analysis and passion for scientific order. They also show how he readily adopted any seemingly relevant new technique that might improve his grasp of the chemistry of natural products. These correlations, his first chemical achievement, became known as the "Woodward rules" or sometimes as the "Woodward–Fieser rules" in acknowledgment of Louis and Mary Fieser's reformulation of them. Thus, at 24 years of age Woodward was able to accurately point out the mistaken findings of others by means of a general rule relating structural features to UV spectra. In the words of Lord Todd: "*He was one of those very rare people who possessed that elusive quality of genius … it seemed to me to herald a breakthrough in the use of spectroscopy in the study of molecular structure*".[122]

The Woodward rules, which foreshadowed Woodward's later work with Roald Hoffmann (leading to the Woodward–Hoffmann rules),[123] were a result of his early recognition that physical methods had far greater power than chemical reactions to reveal structural features. These rules were only the beginning of his championing the development of spectroscopic techniques, which have empowered chemists and greatly eased the problem of structure determination.[124]

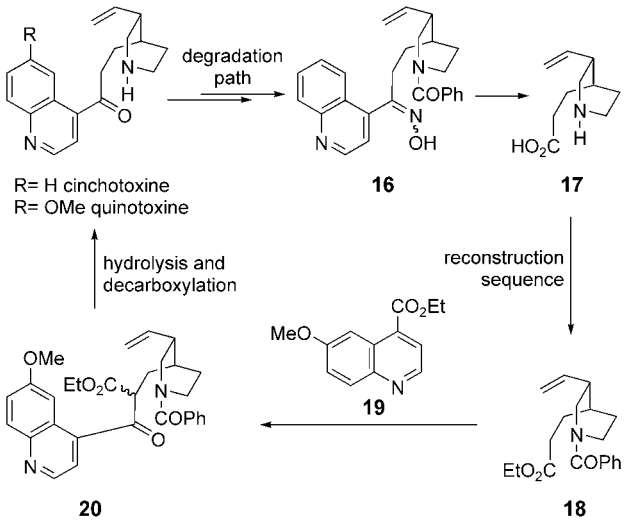
At the beginning of the 1940s, and with a towering career in front of him,[125a] Woodward was the right person to complete Perkin's work, and WWII played its role in accelerating the process. During WWII quinine supplies, which were considered critical for the allied forces, suddenly became scarce, thus causing thousands of soldiers to die after becoming infected with malaria during the campaigns in Africa and the Pacific. The cinchona plantations established in Java by the Dutch were the major sources of the European reserves of quinine, which were stored in Amsterdam. However, the German capture of Holland in 1940 and the Japanese military invasion of Java in 1942 abruptly cut these vital supplies.

In an expedition to Colombia, Ecuador, Peru, and Bolivia between 1943 and 1944, the botanist Raymond Fosberg and his co-workers collected and secured 12.5 million pounds of cinchona bark for the allied forces. In a desperate effort, cinchona seeds were also brought from the Philippines, germinated in Maryland (USA), and planted in Costa Rica.[126] The sudden cut in supply of quinine caused justified alarm and triggered the initiation of research programs directed towards the development of new antimalarial drugs.[127]

Edwin Land, a Harvard graduate and the founder in 1937 of the Polaroid Company, used quinine iodosulfate (herapathite) for the manufacture of light polarizers and became one of the first businessmen involved in the desperate search for

quinine or a substitute that would keep his company in business.[128] Woodward was a consultant to Land's company from 1940 and, in 1942, when Land required a quinine substitute, Woodward quickly solved his problem. This association was fruitful, since Land also agreed to financially assist Woodward's own synthetic project on quinine, which had been conceived a few years before while he was still a student.

At this time, others were working in closely related areas. Vladimir Prelog published his first paper in 1921, at the age of only 15, and began his first independent research around 1930 on quinine. His synthesis of quinuclidine in 1937 was a highlight, eventually leading to his interest in stereochemistry, the field in which Prelog became renowned and for which he was awarded the Nobel Prize for Chemistry in 1975.[129] In 1943 Prelog made a notable step forward when he degraded cinchotoxine to optically active homomeroquinene (**17**) and reconstructed quinotoxine with the aid of the degradation product (Scheme 8).[130] The first part of his procedure was



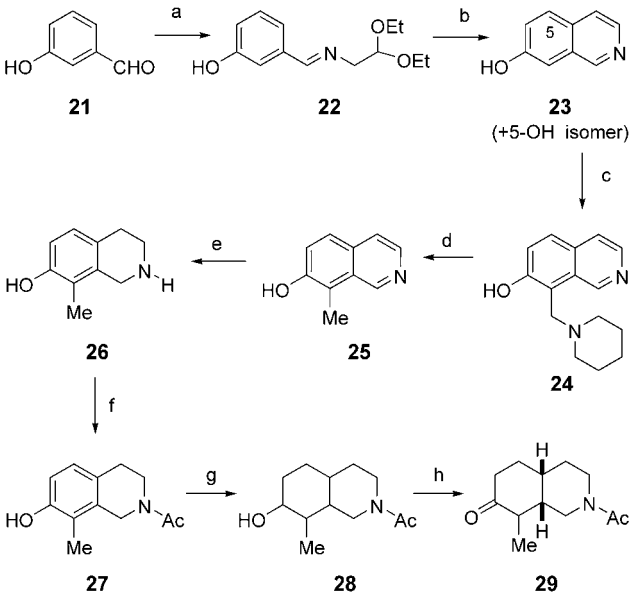
Scheme 8. The degradation and reconstruction of quinotoxine by Prošstenik and Prelog.

smoothly carried out through a Beckmann degradation through the intermediacy of oxime **16**, while reconstruction entailed transformation of homomeroquinene into protected derivative **18** followed by its Rabe condensation with ethyl quininate (**19**) to furnish β-ketoester **20**, which was conveniently converted into quinotoxine by hydrolysis and decarboxylation. Since Rabe has claimed success in converting quinotoxine into quinine, this step forward simplified the problem of a formal total synthesis of quinine to that of the total synthesis of enantiomerically pure homomeroquinene (**17**); it also strengthened Rabe's hypothesis that a route to quinine through quinotoxine was feasible.

The main challenge offered by the synthesis of the required homomeroquinene derivative was the correct introduction of the differentially substituted side chains, which ought to have a *cis* configuration. Although the syntheses were planned in advance, before the birth of of what we now call "retrosynthetic analysis", there was no rational and systematic approach to the design of synthetic strategies, and in the 1940s conformational analysis did not exist. The old masters in chemistry treated each synthetic target individually and obscurely related the final product to an appropriate starting material; therefore, success or failure was greatly influenced by their initial guesses.

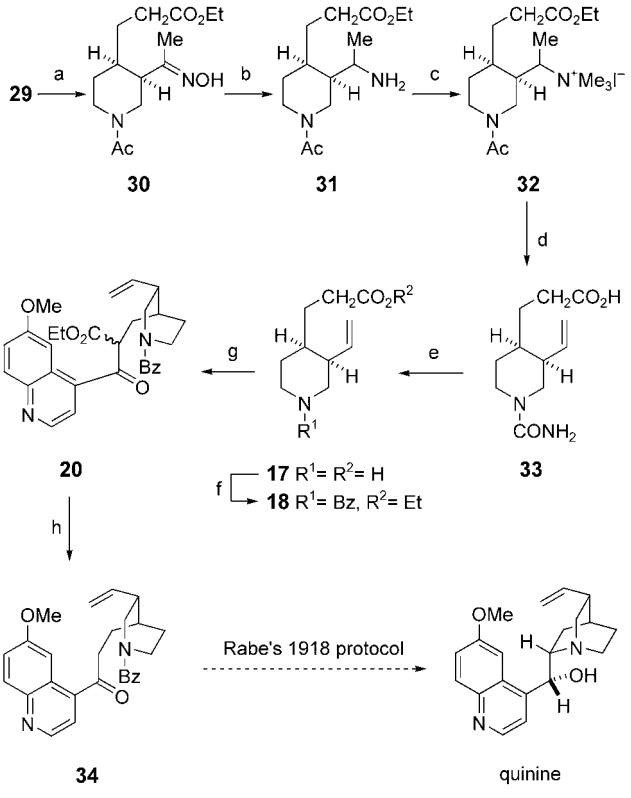
Woodward's thinking was guided by his deep knowledge of chemistry and chemical literature as well as by a great deal of chemical intuition. The genius of his contribution to the homomeroquinene/quinine synthesis challenge was in his unusual and novel treatment of that problem and consisted of installing an extra ring to secure the appropriate configuration of adjacent centers.[125] In a timely fashion, this ring was opened to reveal new and distinct functionalities. Like an artist's personal signature, Woodward recurrently used this feature with increasing mastery in the subsequent and more demanding syntheses of reserpine, vitamin B_{12}, and erythromycin A.[98,104,105]

Woodward ingeniously visualized that the basic homomeroquinene skeleton could be accessed from an isoquinoline (Scheme 9). Synthetic routes and protocols for the preparation of such compounds were available from the beginning of the century,[131] but truly innovative research cannot be planned to the last detail. Therefore, in practice these basic ideas necessitated slightly more effort than initially thought to yield the expected product and demanded a considerable number of synthetic steps, which were carefully carried out by the enthusiastic scientist and outstanding experimentalist William von Eggers Doering.



Scheme 9. The approach to quinine by Woodward and Doering: Preparation of the homomeroquinene derivative. Reagents and conditions: a) $H_2NCH(OEt)_2$ (94%); b) 1. 80% H_2SO_4; 2. NaOH, crystallization then H^+ (64%); c) piperidine, HCHO, EtOH (61%); d) NaOMe, MeOH, 220°C, 16 h (65%); e) H_2, Pt, AcOH; f) Ac_2O (95%); g) H_2, Raney nickel, EtOH, 150°C, 205 bar, 16 h [1:1 *cis*(crystalline)/*trans*(oil)]; h) $H_2Cr_2O_7$, AcOH; Et_2O/H_2O, diastereomer separation (28%).

During the synthesis, 3-hydroxybenzaldehyde (**21**, accessible in two steps from 3-nitrobenzaldehyde) was transformed into isoquinolin-7-ol (**23**) via Schiff base **22** by employing the Pomerantz–Fritsch isoquinoline synthesis.[131] This starting isoquinoline was converted into its 8-methyl derivative **25** through the intermediacy of piperidine **24**.[132] In turn, **25** was partially catalytically hydrogenated to the tetrahydroisoquinoline **26**, which was isolated as its *N*-acetyl derivative **27**, while a second catalytic hydrogenation furnished **28** as a complex diastereomeric mixture.[133] This mixture was simplified by oxidation to the related ketones, with concomitant epimerization of the tertiary carbon center next to the carbonyl group. Separation of the diastereomers was aided by the lucky formation of the hydrate of compound **29** with a *cis* ring junction: ring opening of the latter through preferential nitrosation of the tertiary carbon atom next to the carbonyl group furnished the oxime **30** (Scheme 10). Conservation of the crucial *cis* geometry of the substituents on the piperidine ring in **30** marked the success of the strategy for building both adjacent side chains. Reduction of **30** provided amine **31**. Exhaustive methylation of **31** afforded **32** and then a Hofmann elimination was employed to install the vinyl moiety and generate the intermediate product protected as a uramido derivative (**33**) to facilitate its isolation. The uramido derivative **33** was finally subjected to an acid hydrolysis to regenerate homomeroquinene (**17**).[134] Since Prelog had earlier prepared quinotoxine from homomeroquinene, and assuming the validity of Rabe's protocol to access quinine from quinotoxine, Woodward's synthesis of homomeroquinene meant that all the stepping stones for a formal total synthesis of quinine appeared to have now been bridged. However, his synthetic homomeroquinene (**17**) was racemic, thus prompting Woodward to go one step further and include a resolution in his synthesis. This was achieved by conveniently protecting **17** as its known *N*-benzoyl ethyl ester **18**, thus setting the stage for a Rabe condensation, which he carried out following the method developed by Prelog by using the readily available ethyl quininate **19**.[135]



Scheme 10. The approach used by Woodward and Doering to synthesize quinine: Completion of the synthesis. Reagents and conditions: a) EtO-N=O, NaOEt, EtOH (68%); b) H_2, Pt, AcOH, 1–3 bar; c) MeI, K_2CO_3 (91% overall); d) 1. 60% KOH, 180°C, 1 h; 2. KCNO (40%); e) 1. dilute HCl, EtOH, reflux (100%); f) PhCOCl, K_2CO_3 (96%); g) ethyl quininate (**19**), NaOEt, 80°C; h) 1. 6 N HCl, reflux (50%); 2. resolution with D-dibenzoyl tartrate (11%). Bz = benzoyl.

Subsequent hydrolysis and decarboxylation of the resultant β-ketoester **20** gave DL-quinotoxine derivative **34**, which was hydrolyzed to DL-quinotoxine and the latter carefully resolved with D-dibenzoyl tartaric acid.[136] Finally, after little over a year of feverish work, on April 11, 1944 Woodward and Doering obtained a precious 30 mg of synthetic D-quinotoxine which—with Rabe's procedure being repeatable—could be considered the first entry into synthetic quinine. Woodward had crossed the finish line that he had first spotted so many years previously and this accomplishment somehow turned him into a veritable demigod in his field.

In the middle of WWII, and with natural quinine supplies cut by enemy forces, news on this breakthrough rapidly found its way from the University laboratory to the national press. Thus, The New York Times enthusiastically hailed the achievement in its May 4 edition with the heavyweight title "*Synthetic Quinine Produced, Ending Century Search*". In the article that followed below, it remarked the accomplishment of "*the duplication of the highly complicated chemical architecture of the quinine molecule*" that had been achieved, a feat that was considered "*as one of the greatest scientific achievements in a century*".[137] The Science News Letter[138] also echoed this praise by highlighting that this accomplishment, highly useful to the war effort, was done "*… without the help of a tree*"; the same journal commented that "*starting with five pounds of chemicals they obtained the equivalent of 40 mg of quinine*". A cartoon in the May 28 issue of the Oregon Journal commented on the good news, which also appeared in the June 5 issue of the well-known magazine Life, wherein it was covered under the title of "*Quinine: Two Young Chemists End a Century's Search by Making Drug Synthetically from Coal Tar*".[139]

In contrast to Perkin's attempt ending in mauveine, which met with commercial success, Woodward's synthesis of quinine was not amenable to large-scale commercial production. In spite of the hype and wishful thinking surrounding the synthesis, which gave Woodward immense popularity, commercial production of quinine by the newly devised strategy would have cost approximately 200 times more than its natural equivalent if, indeed, it was feasible. Moreover, it would have taken years of research to optimize the process and reduce the prices down to reasonable levels, and by that time alternative synthetic drugs could have been made available for treatment.

Quinine has five stereogenic centers, two of which (the quinuclidine nitrogen atom and C4) constitute a single

asymmetric unit because of their bridgehead location. The Woodward–Doering synthetic scheme successfully built two of them selectively by laborious diastereomer separations and chemical resolution. Despite the complexity of the synthetic route, it was carried out with conventional reactions and reagents that were available to any chemist of that time, protecting groups were hardly used, and one third of the reactions were run at room temperature. The synthesis suffered from low yields and lacked stereocontrol at every center, particularly because of the anticipated need to separate the four diastereomers resulting from the use of Rabe's 1918 protocol in which quinotoxine was transformed into quinine. However, the synthesis was completed in a few months,[140] was Woodward's first total synthesis, captured admiration and public imagination, and represented in its time an important and unmatched accomplishment, which remained as a scientific milestone. Indirectly, the Woodward–Doering synthesis of quinine signaled the way organic synthesis would head in the next few decades. It is not too far from the truth to state that many modern synthetic medicines owe their being to the impulse given to the field by complex challenges such as that of quinine.

Woodward tackled increasingly daring synthetic targets throughout his career and demonstrated that an understanding of chemical reaction mechanisms made it possible to plan and successfully execute extended sequences of reactions to build up complex compounds in the laboratory. Stereocontrol was of little concern in the days when the synthesis of quinine was carried out, mainly because chemists lacked many of the currently available synthetic tools, including the physical and chemical concepts that form the basis of stereochemical control. Moreover, stereochemistry was then not deeply considered in synthetic designs and some chemists even expressed a lack of interest in the challenge.

The couple of publications reporting the experimental details on the synthesis of D-quinotoxine, which appeared in 1944 and 1945 under the same title ("*The Total Synthesis of Quinine*"),[1] meticulously informed the reader about the series of synthetic manipulations leading to D-quinotoxine, in what could be termed a formal total synthesis of quinine. However, experimental evidence on the synthesis of the natural product from synthetic D-quinotoxine was not provided, merely relying on Rabe's 1918 paper and procedure, which for some reason they qualified as "established".[141] Nevertheless, and perhaps because of anxiety caused by wartime needs, the series of chemical transformations reported in the 1944 and 1945 publications by Woodward and Doering started the legend that quinine had finally been completely synthesized.

Unfortunately, Rabe's method would prove to be unreliable, thus necessitating the need for additional time and efforts before the claim could be made for the achievement of the first total synthesis of quinine. It is noteworthy, however, that as part of his effort to convert quinine into valuable quinidine, Woodward shortly afterwards disclosed a very efficient method for accessing quininone from quinine by reaction of the former with potassium *tert*-butoxide and benzophenone, and the reduction of the ketone with sodium isopropoxide to afford a mixture of quinine (ca. 30%) and quinidine (ca. 60%).[89] Thus, cyclization of quinotoxine to quininone remained the weakest link in the chain of reactions from isoquinolin-7-ol to quinine in the Woodward–Rabe approach.

8. Mastering the C8–N Strategy: The First Total Synthesis of Quinine and Variation on the Theme

Cinchona alkaloids, mainly quinine and quinidine, are of high industrial importance. Approximately 300–500 tons per annum are produced commercially by extraction of the bark from various cinchona species that are now widely cultivated. About 40% of the quinine goes into the production of pharmaceuticals, while the remaining 60% is used by the food industry as the bitter principle of soft drinks, such as bitter lemon and tonic water. Quinine is employed for the treatment of chloroquine-resistant malaria, while quinidine is still prescribed in human therapeutics as an antiarrhythmic to regulate heartbeat.

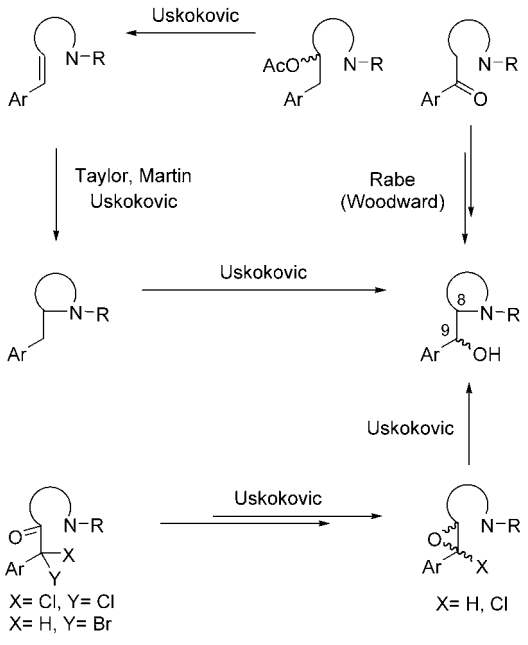
Derivatives of the cinchona alkaloids also serve as highly versatile chiral auxiliaries in asymmetric synthesis, and are perhaps the most remarkable example of a specific class of chiral catalysts. The key structural feature responsible for their synthetic utility is the presence of the tertiary quinuclidine nitrogen atom, which renders them effective ligands for a variety of metal-catalyzed processes. In addition, the nucleophilic quinuclidine nitrogen atom can also be used directly as a reactive center for enantioselective catalysis. The cinchona alkaloids have proven to be useful in an astonishing variety of important enantioselective transformations, including the Sharpless asymmetric dihydroxylation reactions, enantioselective Diels–Alder reactions, hydrocyanations, [2+2] cycloadditions, Michael additions, SmI_2-mediated reductions, dehydrohalogenations, and hydrogenations.[142] In addition, examples of quinine as a chiral resolving agent are numerous[143] and new examples are still being reported at a steady rate. The recent use of quinine and quinidine for the chromatographic and electrophoretic separation of enantiomers[144] suggests that interesting applications of cinchona alkaloids will keep on growing. Industrial preparation of active pharmaceutical ingredients such as the antidepressant oxitriptan, the widely used anti-inflammatory and analgesic naproxen, and the calcium antagonist diltiazem have been described in which cinchona alkaloids were employed as resolving agents.[145]

The regular use of analytical instruments introduced after WWII produced a second revolution in organic chemistry which paralleled that first revolution made by structural theory almost one century before. This enabled limits to be set on what claims chemists could make about chemical structures and stabilized their concepts of both chemical structures and reaction mechanisms. In addition, the popularization of preparative thin-layer chromatography and column chromatography greatly eased separations, while gas chromatographic techniques facilitated analysis of minute amounts of samples and made estimations of purity easier.

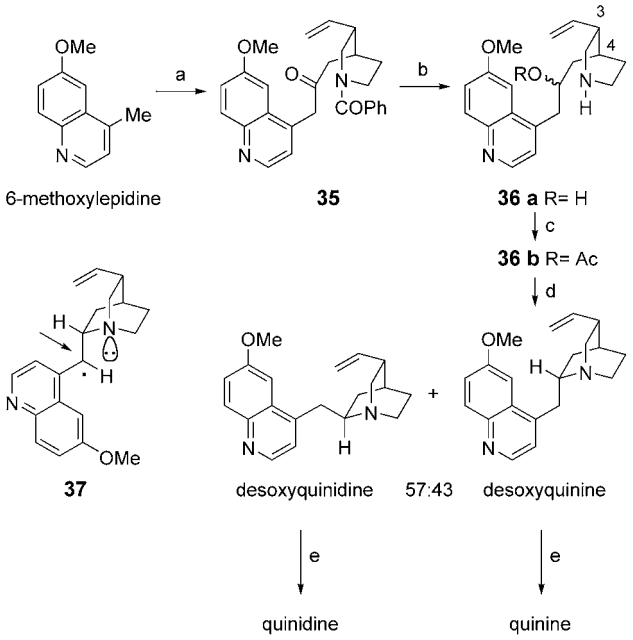
In the beginning of the 1960s, almost two decades after Woodward's acclaimed achievement, a group of Hoffman–La Roche (Nutley, New Jersey) researchers became interested in the synthesis of cinchona alkaloids. An extensive series of experiments was carried out under the leadership of Milan R. Uskokovic in which literature procedures were repeated and new protocols devised for accessing the pharmaceutically important cinchona alkaloids. The team developed new syntheses of homomeroquinene, which it used for the preparation of quinotoxine by either employing Rabe's condensation with ethyl quininate (Schemes 8 and 10) or by reaction with 6-methoxy-4-quinolyllithium (**52**).[146] In turn, this accomplishment allowed Uskokovic's group to demonstrate that the nitrogen atom of quinotoxine could be chlorinated with sodium hypochlorite and that α-chloro derivatives, analogous to the bromoketone **12** previously prepared by Kaufmann (Scheme 6), could become intermediates in the Rabe-type conversion of quinotoxine into quininone and quinidinone. The yield for this conversion was more than 70% when a strong acid was employed instead of the base treatment reported by Rabe and when the ketones were transformed into either a 1:1 mixture of quinine and quinidine or selectively into quinidine by reduction with diisobutylaluminum hydride (DIBAL-H).[91,147] This research made it evident that Rabe's original procedure was unsuitable for producing quinine, unless it was substantially modified.

Researchers at Hoffmann–La Roche came closer to a stereoselective total synthesis of quinine in the 1970s after concentrated efforts on mastering the C8–N approach for the formation of the quinuclidine ring. In 1970 they disclosed a total synthesis of quinine, which was the first of a series of total syntheses of this natural product based on such an approach to be published during that decade (Scheme 11). The weak point of this approach was its characteristic poor stereocontrol, which led to the generation of stereoisomers at C8. Furthermore, some modified protocols incurred the formation of undesired stereoisomers during the installation of the functional group at C9, thus limiting the attractiveness and usefulness of the method. This study, however, resulted in the development of considerably more efficient strategies that allowed a better control of the configuration at two of the stereogenic carbon atoms in the quinuclidine portion of the molecule.

The initial strategies used by Uskokovic and co-workers (Scheme 12) were similar to that of Woodward and Rabe in the sense that they used the C8–N approach and the pivotal intermediate was a meroquinene derivative. However, better steric control at key stages and the use of more efficient transformations improved the overall yield compared to that obtained by Woodward's route.



Scheme 11. Synthetic variations of the C8–N approach used during the 1970s.



Scheme 12. Synthesis of quinine by Uskokovic and co-workers in 1970. Reagents and conditions: a) 1. LDA, −78 °C; 2. *N*-benzoylmeroquinene methyl ester (**41b**; 78%); b) DIBAL-H (85%); c) $BF_3{\cdot}Et_2O$, AcOH (96%); d) NaAcO, AcOH/benzene (via **44b**; 79%); e) KO*t*Bu, $^1O_2$, *t*BuOH, DMSO (40%). LDA = lithium diisopropylamide.

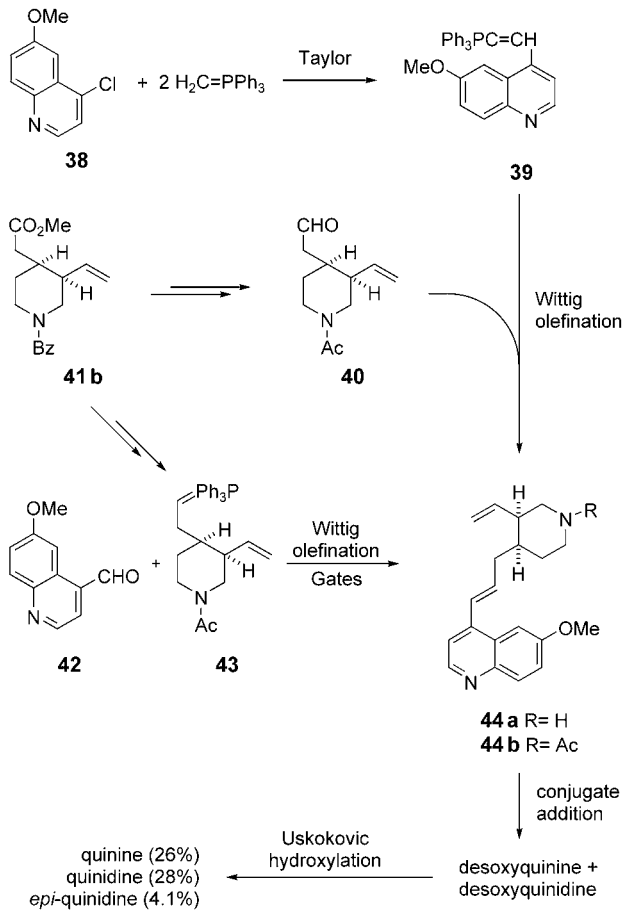
During the synthesis, the lithium anion of 6-methoxylepidine[148] was condensed with racemic *N*-benzoylmeroquinene methyl ester (**41b**) and the resultant ketone **35** was reduced to alcohols **36a** with DIBAL-H, which also removed the *N*-benzoyl protecting group. The racemic mixture of diastereomeric alcohols **36a** was resolved with D-dibenzoyltartaric acid and the required 3*R*,4*S* enantiomer was transformed into the related acetates **36b** by a $BF_3{\cdot}Et_2O$ catalyzed acetylation. Finally, construction of the quinuclidine ring proceeded by conjugate addition of the piperidine nitrogen atom to vinylquinoline intermediate **44b** (see Scheme 13),[149] which was formed in situ by elimination of the acetate to yield a mixture of the previously known desoxyquinine and desoxyquinidine in a ratio of 57:43 (Scheme 12).[150] The

most interesting step of the synthesis was the last one, which was based on an important observation previously made within Uskokovic's group: In an extraordinary example of 1,2-asymmetric induction not involving a carbonyl group, the necessary functional group was cleanly introduced at C9 with the correct configuration (and a stereoselectivity of approximately 5:1) by an autooxidation with oxygen catalyzed by potassium *tert*-butoxide. Almost equal amounts of quinine and quinidine were produced, when it was used directly on the mixture of C8 isomers. Dimethyl sulfoxide was employed to reduce in situ the intermediate hydroperoxides formed.[151] From an industrial viewpoint, the synthesis was considered satisfactory when the comparatively higher commercial value of quinidine with respect to quinine was taken into account. The autooxidation was an efficient transformation and its fortuitous stereochemical result constituted a remarkable step forward. The reaction outcome (selective access to *erythro* amino alcohols) was attributed to the "*preferred backside attack of the oxygen radical anion on the intermediate radical … in order to avoid the repulsive force of the quinuclidino nitrogen free electron pair*" (see **37** in Scheme 12).[152] This strategy would be employed as the final step of a much improved and more controlled synthesis 30 years later. Before Uskokovic's synthesis of quinine,[153] there was no truly dependable published protocol for completing the last crucial steps of the synthesis of the natural product.

In 1974 Taylor and Martin disclosed their approach to quinine from 4-chloro-6-methoxyquinoline (**38**), via olefin **39**, which acted as a nonisolable transient intermediate (Scheme 13).[154] Their procedure became a method for the direct introduction of alkyl and alkenyl groups into heterocyclic nuclei and involved the nucleophilic displacement of a suitable leaving group on the heterocycle by a Wittig reagent, followed by the transformation of the resultant heterocyclic ylide into alkyl- or alkenyl-substituted heterocycles by hydrolysis or reaction with aldehydes, respectively.[154]

The synthetic sequence towards quinine, which can be considered a new route to olefin **44b**, has the same drawbacks with the formation of diastereomers as the protocol developed by Uskokovic and co-workers. The sequence consisted of the preparation of ylide **39** and its olefination with *N*-acetylpiperidineacetaldehyde derivative **40**, which was easily prepared from the known *N*-benzoylmeroquinene methyl ester **41b**. Hydrolysis of the *N*-acetyl protecting group (**44b** → **44a**) occurred with concomitant spontaneous intramolecular Michael addition of the piperidine nitrogen atom to the double bond generated in the Wittig reaction to produce the expected mixture of desoxyquinine and desoxyquinidine. Interestingly, this mixture could be induced to revert to the starting olefin by refluxing it with acetic anhydride. The diastereomers of this hard-to-separate mixture were, nevertheless, individually oxidized by using the procedure developed by Uskokovic and co-workers and the resultant alkaloids isolated as the corresponding tartrates.

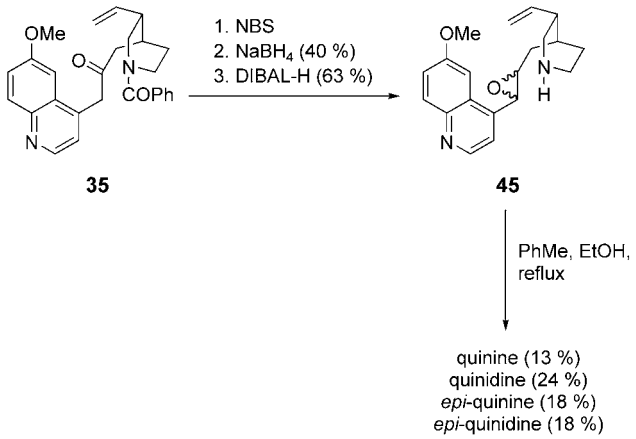
A previous sequence published in 1970 by Gates et al.[155] (which was disclosed simultaneously with that of Gutzwiller and Uskokovic[153]), also entailed the preparation of olefin **44b**; however, in this case phosphorane **43**, which is derived



Scheme 13. Syntheses of quinine by the research groups of Taylor and Gates.

from meroquinene alcohol,[156] and aromatic aldehyde **42** were employed in a Wittig reaction and the *cis*/*trans* mixture of olefins so obtained equilibrated with acetic acid to afford exclusively the more stable *trans* alkene (Scheme 13). Gates et al. did not devise a protocol for the required construction of the alicyclic moiety, and considered his route explicitly as a partial synthesis of quinine. The key meroquinene bromide employed was produced by functional group transformations of meroquinene derivatives obtained by degradation of quinidinone, or by employing Uskokovic's synthesis.[147b]

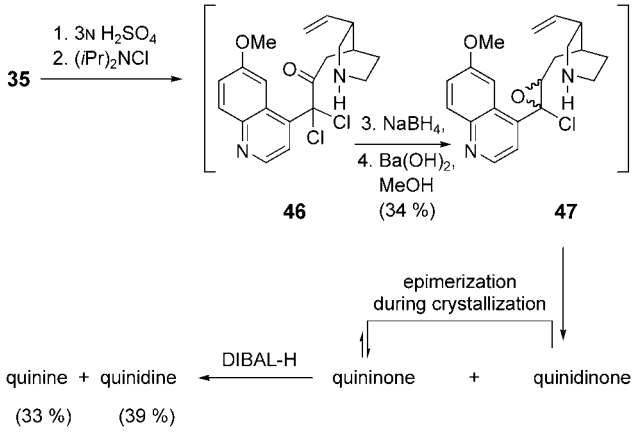
In a modification of his previous synthesis Uskokovic and co-workers also performed the key C8–N ring-closing reaction through the ring opening of an epoxide (Scheme 14), which allowed the simultaneous installation of the secondary alcohol at C9.[91] This alternative sequence, which would become relevant two decades later as a strategy for the fully controlled access to quinine, started with known ketone **35**, which was prepared in enantiomerically pure form by employing the semisynthetic, optically active meroquinene. Installation of the epoxide was carried out by benzylic bromination with *N*-bromosuccinimide (NBS), followed by reduction of the α-bromoketone to a mixture of bromohydrins as well as spontaneous cyclization. Unfortunately, the transformation took place in a disappointing 40% yield and all four possible epoxides were formed. DIBAL-H assisted



Scheme 14. Synthesis of quinine by the amino epoxide ring closing approach by Uskokovic and co-workers (1970).

reductive removal of the *N*-benzoyl protecting group to give **45** then set the stage for the nucleophilic ring opening and cyclization, which as expected produced mixtures of the four possible diastereomers at C8 and C9. Thus, this initial version of the amino epoxide ring opening approach proved inefficient and lacked the elegance of the auto-oxidation procedure for functionalization at C9.

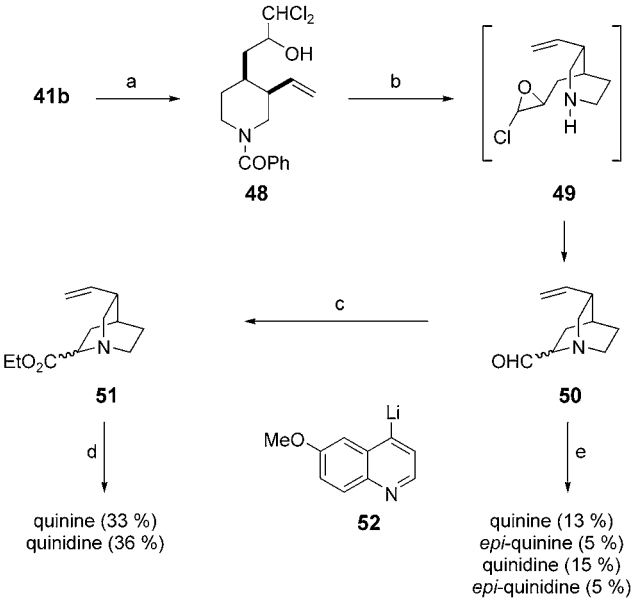
In a further modification of the basic strategy,[152] the formation of the crucial C8–N bond was achieved with concomitant installation of the carbonyl group at C9, through the cyclization of aminochloroepoxide **47** (Scheme 15).[157]



Scheme 15. Synthesis of cinchona alkaloids by the amino chloroepoxide ring-closing approach by Uskokovic and co-workers.

Reminiscent of the amino-epoxide approach, chloroepoxide **47** was prepared by benzylic chlorination of **35** followed by sodium borohydride reduction of the resultant ketone **46** with spontaneous formation of an oxirane. The *N*-benzoyl protecting group was then removed hydrolytically with barium hydroxide; under these conditions cyclization took place to furnish a spontaneously equilibrating mixture of quininone and quinidinone. Fractional crystallization provided crystals of the less-soluble quinidinone, while the quininone, which remained in the mother liquor, was epimerized to quinidinone and formed in a yield of 80% of the original mixture. Gutzwiller and Uskokovic later demonstrated that the highly diastereoselective DIBAL-H mediated reduction of the carbonyl group could be modified by altering the reaction conditions to provide either a roughly 1:1 mixture of quinine and quinidine or allow preferential access to quinidine.[152]

Despite mastering the "historical" C8–N approach for construction of the quinuclidine bicycle, and having limited success with the autooxidation strategy or the highly diastereoselective DIBAL-H mediated reduction of carbonyl compounds for functionalization at C9, by the end of the 1970s chemists were still unable to appropriately control the transformations leading to all the stereocenters, particularly the C8 center. The Uskokovic team had no better luck when in 1978 they disclosed two slightly different syntheses of quinine by using the novel C9–C4′ approach (Scheme 16).[158]



Scheme 16. Synthesis of quinine by the C9–C4′ coupling approach by Uskokovic and co-workers (1978). Reagents and conditions: a) 1. DIBAL-H; 2. PhCOCl; 3. Cl_2HCLi (59%); b) KOH, benzene; c) 1. $AgNO_2$; 2. $EtOH/H^+$; d) 1. **52**, Et_2O, −78°C (30–40%); 2. DIBAL-H (59%); e) **52**, Et_2O, −78°C.

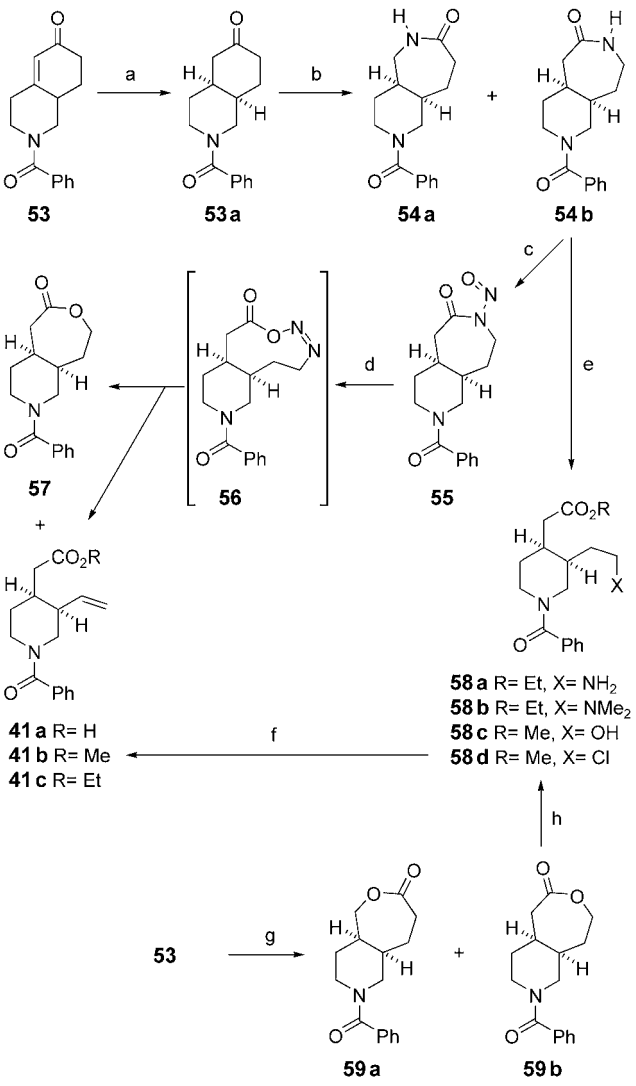
This new route was the first departure from the C8–N approach, which had reigned supreme for 70 years. Problems with low yields and control of the configuration at C8 in the key quinuclidine intermediates, however, remained as major drawbacks. Certain characteristics from previous syntheses emanating from this research group are clearly seen in the new strategy, such as the aminochloroepoxide cyclization employed for accessing the key quinuclidine intermediates **50** and **51**,[159] which were prepared and used as diastereomeric mixtures. This approach can, therefore, be considered as a crypto-C8–N approach. Aldehyde **50** was highly unstable and needed to be employed immediately after its preparation, while ester **51** was more stable and amenable for use.

All of the syntheses of quinine performed during the 1970s by the C8–N approach relied heavily on protected

meroquinene derivatives, which became interesting synthetic targets during the 1970s and afterwards.[160] Enantiomerically pure meroquinene derivatives, were employed in the syntheses of Gates, Taylor, and that of Uskokovic (employing opening of the aminoepoxide); however, they were semisynthetically obtained by degradation of quinidinone.[156]

Uskokovic et al. disclosed their first synthesis of *N*-benzoylmeroquinene (**41a**) by a sequence vaguely reminiscent of Woodward's (Scheme 17) for his preparation of homomeroquinene (**17**).[160i,j] The cumbersome approach started with the catalytic hydrogenation of *N*-benzoylhexahydroisoquinolone (**53**), which provided a *cis*/*trans* mixture of octahydro derivatives in which the required *cis* diastereomer **53a** was favored.[161] A Schmidt rearrangement of **53a** furnished a mixture of lactams **54a**,**b**, which were separated. Lactam **54b** was in turn transformed into a mixture of lactone **57** and meroquinene **41a**[162] via the nitrosoderivative **55** and the rearranged diazolactone **56**.[163] A less-effective sequence involving ethanolysis of **54b**, with reductive methylation of the resultant amino ester **58a** to the *N*,*N*-dimethylamino derivative **58b**, followed by pyrolysis of its *N*-oxide, was also disclosed as an approach to the related ester **41c**. An alternative approach to **41c** was also problematic: Baeyer–Villiger oxidation of **53a** to lactones **59a**,**b** and ring opening with concomitant esterification of the lactones, followed by substitution of the hydroxy group of the resultant **58c** by chloride (**58d**) and dehydrohalogenation provided another access to racemic **41b** (Scheme 17). Although the isoquinolone **53a** was successfully resolved, thus providing a potential route to optically active meroquinene, the number of hard-to-separate mixtures which characterized this protocol deterred it from being used as a source of the optically active **41b**.

A better and more practicable synthesis of **41a** was achieved from pyridine derivative **60**, which is easily available from β-collidine (Scheme 18). Hydrogenation of the heterocycle to *cis*-**61** (*rac*-cincholoipon methyl ester), originally synthesized stereospecifically by Stork et al. in 1946,[164] was followed by its resolution with (+)-tartaric acid and the ingenious application of a Hofmann–Löffler–Freytag remote halogenation[165] on the appropriate enantiomer **61a**. Protection of the nitrogen atom furnished **58d**. Dehydrochlorination to form **41a** completed this concise sequence. A Japanese team synthesized meroquinene, thus claiming a formal total synthesis of (±)-quinine.[160k,l]



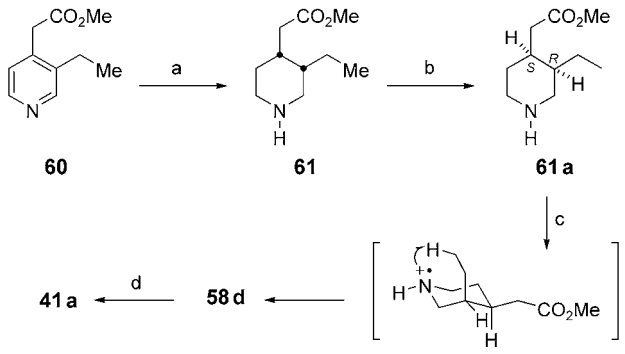
Scheme 17. Synthesis of *N*-benzoylmeroquinine (**41a**) by Uskokovic and co-workers. Reagents and conditions: a) H_2, Rh/Al_2O_3, HCl/EtOH; b) NaN_3, PPA, 60°C,16 h (100%, **54a**:**54b** = 1:2); c) N_2O_4 (100%); d) 125°C (**41a** = 48%; **57** = 30%); e) 1. 5% HCl, EtOH (65%); f) from **58a**: 1. HCHO, HCO_2H; 2. H_2O_2; 3. Δ (85%); from **58d**: 1. NaOH, MeOH (99%); 2. KO*t*Bu, DMSO, 70°C, 7 h (85%); g) mCPBA, $NaHCO_3$, RT, 24 h (94%); h) 1. MeOH, HCl (36%); 2. CCl_4, PPh_3, DMF, RT, 21 h (18%). PPA = polyphosphoric acid, *m*CPBA = *meta*-chloroperoxybenzoic acid.

9. After 55 Years: A Modern, Stereocontrolled Synthesis of Quinine

Professor Gilbert Stork of Columbia University has been one of the most prominent leaders in the field of organic synthesis for over half a century. In the 1940s and 1950s he introduced the concept of stereoselective organic synthesis through the Stork–Eschenmoser hypothesis for polycyclic terpenoids and steroid synthesis, which enabled the stereorational total synthesis of cantharidin[164b] and, before that, of *rac*-cincholoipon.[164a,166] Among other outstanding accomplishments, Stork created a number of fundamental synthetic methods which enriched the synthetic chemist's arsenal, such as enamine and silyl enol ether carbon–carbon bond-forming methodologies and radical cyclizations.[166b]

Stork proudly confessed that it was the structure of quinine that he first saw in *Chemical Abstracts* while an undergraduate at the University of Florida which started his fascination with the challenges of organic synthesis.[166b] He began his quest for a stereochemically controlled total synthesis of quinine just two years after Woodward and Doering announced their success, and published his above-mentioned stereoselective synthesis of racemic ethyl cincholoiponate, a dihydromeroquinene derivative.[164]

His early efforts became entangled in a stereochemical thicket and a quarter of a century had to pass before he could

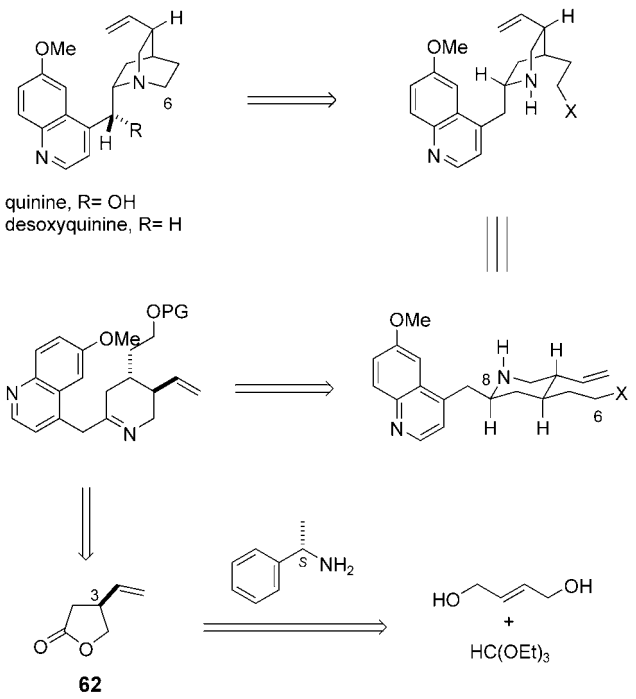


Scheme 18. Synthesis of meroquinine from **60**. Reagents and conditions: a) H_2, dilute HCl, PtO_2, 70 atm, 60 °C (88 %); b) resolution with L-tartaric acid (25 %); c) 1. NCS, Et_2O, 92 %; 2. F_3CCO_2H, *hν*, 200 W, 50 min (84 %); d) 1. NaOH, MeOH, RT (99 %); 2. KO*t*Bu, benzene/DMSO, 70 °C, 7 h (88 %). NCS = *N*-chlorosuccinimide.

make substantial further progress. He worked on and off on the problem, but in the eyes of many competitors he seemed to have abandoned this natural product as a synthetic target. Fortunately for science, however, Stork's ability to synthesize complex molecules was once more reiterated through his well-publicized report of a highly stereoselective total synthesis of quinine, which included the stereospecific installation of the C8 stereocenter.

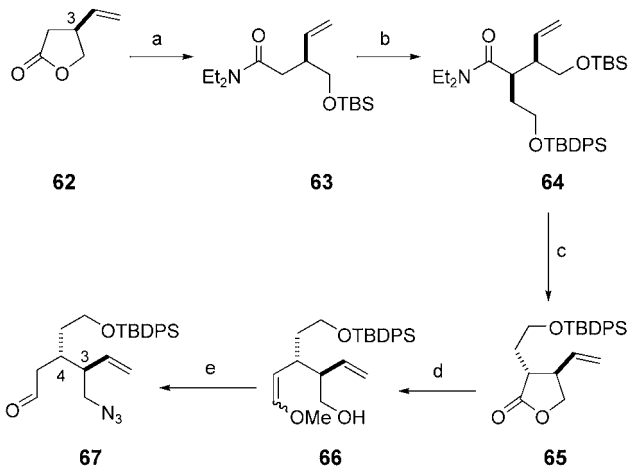
Before Stork's intervention, Rabe's route had long dominated the synthetic approaches to quinine because of the remarkable structural simplification involved in the C8–N coupling. To avoid the pitfalls of this strategy and achieve his goal, Stork had to take a novel and previously unexplored approach, which consisted of performing a C6–N connection (Scheme 19). His route also benefited from the advances made in terms of reagents, reactions, and conformational analysis during the preceding decades when the synthesis of quinine was an almost unattainable target. The key feature of his synthetic design was the observation that the C6–N strategy generated a trisubstituted piperidine—a compound that at first sight looks to have structural complexity similar to that of quinine. Thinking retrosynthetically, however, the synthetic problem has been simplified by considering that the related tetrahydropyridine would be a good precursor to this compound. This route looks feasible if stereospecific reduction of the tetrahydropyridine from its less-hindered face is accomplished. This compound is also an excellent choice as an intermediate, since its preparation requires placement of only two adjacent side chains with the appropriate configuration, thereby greatly reducing the burden of the synthetic problem.

The starting material for the synthesis of the non-aromatic quinine framework was Taniguchi's lactone (**62**), which is easily available from but-2-ene-1,4-diol and triethyl orthoformate.[167] Appropriate choice of the optically active α-phenethylamine enables selection of one of the intermediate diastereomeric amides and thus gives access to either one of both enantiomeric lactones. The precursor of the quinuclidine ring **67** containing nine carbon atoms was efficiently obtained through a series of carefully planned chemical manipulations.[168] In an unforeseen complication, the lactone had to be opened with a nucleophile to generate the related amide **63**



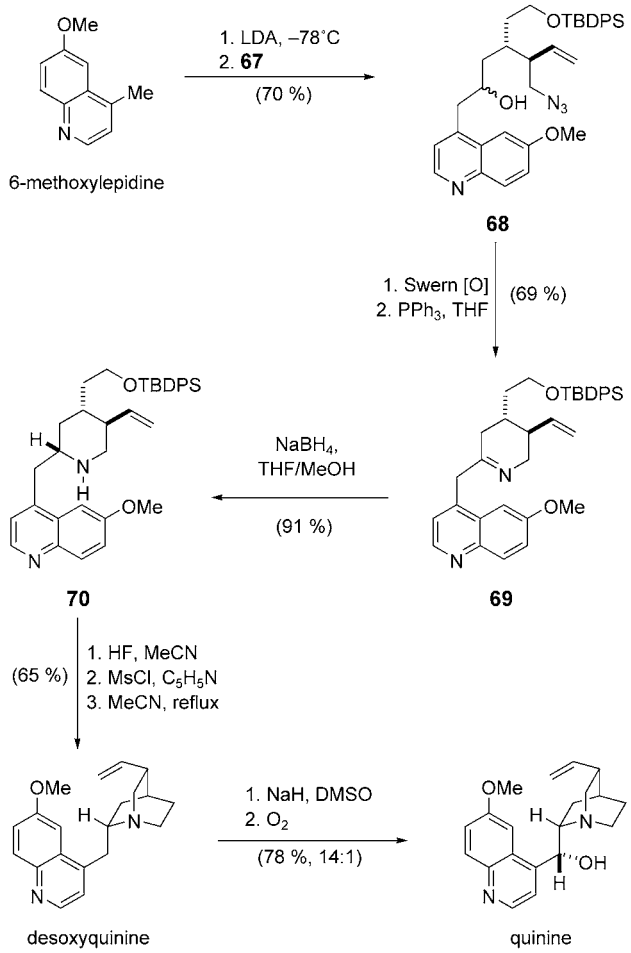
Scheme 19. Retrosynthetic approach to quinine by Stork et al. PG = protecting group.

for the proper introduction of the required C_2 side chain (**64**). Ring closure of **64** to give lactone **65** was followed by reduction to the corresponding lactols and subsequent Wittig homologation to give **66** (Scheme 20). This procedure left a primary alcohol suitable for the introduction of a nitrogen atom by means of a Mitsunobu-type azidation.[169] Reminiscent of the first synthesis of quinine by Uskokovic et al., Stork et al. coupled the 6-methoxylepidine anion with aldehyde **67**



Scheme 20. Synthesis of quinine by Stork et al. by chemical manipulation of Taniguchi's lactone. Reagents and conditions: a) 1. Et_2NAlMe_2; 2. TBSCl, imidazole (79 %); b) 1. LDA, −78 °C; 2. $ICH_2CH_2OTBDPS$ (79 %, 20:1); c) 1. PPTS, EtOH; 2. xylene (93 %), d) 1. DIBAL-H; 2. $Ph_3PCH(OMe)$ (93 %); e) 1. $(PhO)_2P(O)N_3$; PPh_3, DEAD; 2. 5 N HCl (74 %). DEAD = diethylazodicarboxylate, PPTS = pyridinium *p*-toluenesulfonate, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

and oxidized the resultant mixture of alcohols **68** to the corresponding ketone. A Staudinger reaction, which took place with concomitant cyclization, was implemented to produce tetrahydropyridine derivative **69** (Scheme 21).[170]



Scheme 21. Synthesis of quinine by Stork et al.: The final steps. Ms = methanesulfonyl.

The key enantiospecific reduction of the tetrahydropyridine with sodium borohydride was then performed. This procedure, which entails an axial addition of a hydride ion to an iminium intermediate, gave **70**,[171] with all three stereocenters of the quinuclidine ring with the correct configuration. This was probably a consequence of the formation of the conformationally favored chair form of **69** in which the side chains adopt equatorial dispositions. Subsequent transformation of the silyl ether into a suitable leaving group was then followed by intramolecular cyclization to furnish, specifically and exclusively, desoxyquinine, which was finally converted into quinine by the elegant autooxidation described by Uskokovic et al. The use of sodium hydride and dimethyl sulfoxide as the solvent conferred improved selectivity (14:1) to this transformation.

Interestingly, the groundbreaking synthesis Stork et al. uses less catalytic reactions than the sequence developed by Woodward et al., employs carbon–carbon bond forming reactions rather than chemical degradation for the synthesis of the alicyclic moiety, and resorts to the different stabilities of a pair of silyl ethers for the differentiation of two primary alcohols. The sequence is extremely simple in its design and amazingly efficient, such that it was likened to a ballet: "*An inexperienced observer of a great performance might leave with a view that there are no new steps. But one schooled in the field will see the exquisite choreography, the remarkable timing, the efficiency of execution, and the economy of movement—and leave inspired*".[172]

Paralleling Woodward's success, and despite of its lack of value as a commercial source of quinine, the synthesis received worldwide attention and important media coverage. Among the scientific community members, chemistry masters considered Stork's contribution as an "*absolute classic*",[87] and "*a work of tremendous historical value*". Another opinion was that "*the Stork paper is written with an insight and historical perspective (as well as correcting some myths) rarely seen in the primary chemical literature, and should be required reading for all students of organic chemistry*".[173]

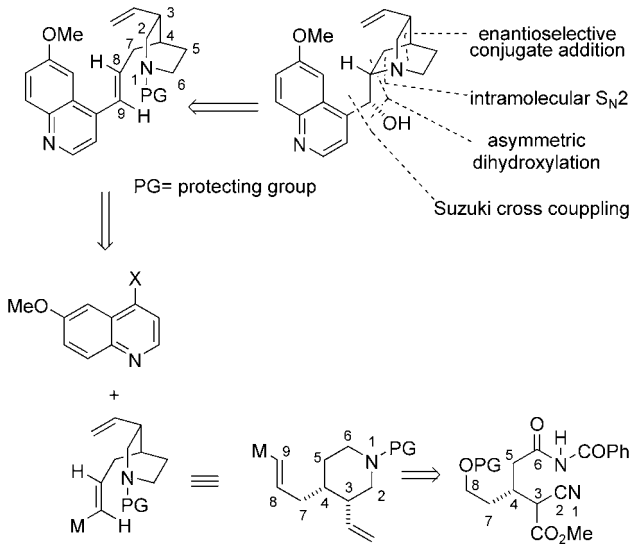
10. The Resurrection of the C8–N Strategy: A Catalytic Enantioselective Total Synthesis of Quinine

The C8–N strategies devised by Uskokovic and coworkers,[91,147a] Taylor and Martin,[154] and Gates et al.[155] in the 1960s and 1970s for the formation of quinuclidine relied on conjugate addition of an amine to a vinylquinoline or the related epoxide or chloroepoxide. The first of these transformations produced diastereomeric mixtures, because of the unselective addition of the amine to the olefin. The lack of stereocontrol at C8 in the protocols of Taylor and Martin as well as Gates et al. resulted because the epoxides could not be synthesized stereoselectively from vinyl arenes; this problem also caused the syntheses to lack stereocontrol at the C9 position.[174] The demands of such a strategy could not be fulfilled with the resources of the arsenal of chemical transformations available. The reagents required did not become available until one decade later.

One of the most intensively studied areas of current research is the selective synthesis of optically active compounds. Numerous chiral auxiliaries and catalysts have been developed which approach or sometimes even match the selectivity observed in enzymatic reactions. These catalysts not only accelerate chemical reactions, but can also exert remarkable kinetic control over product distribution. The novel term "chemzyme" was coined by Corey and Reichard[175] to collectively designate those chiral chemical catalysts exhibiting enzyme-like features and complete selectivity. Many useful chemzymes have been developed during the last decade.

Professor Eric N. Jacobsen from Harvard University, who has emerged as an outstanding chemist in the area of designing and discovering selective catalysts for use in organic synthesis, published, with his research group, a new breakthrough: a catalytic and highly stereocontrolled total synthesis of quinine and quinidine.[176] His strategy enabled the

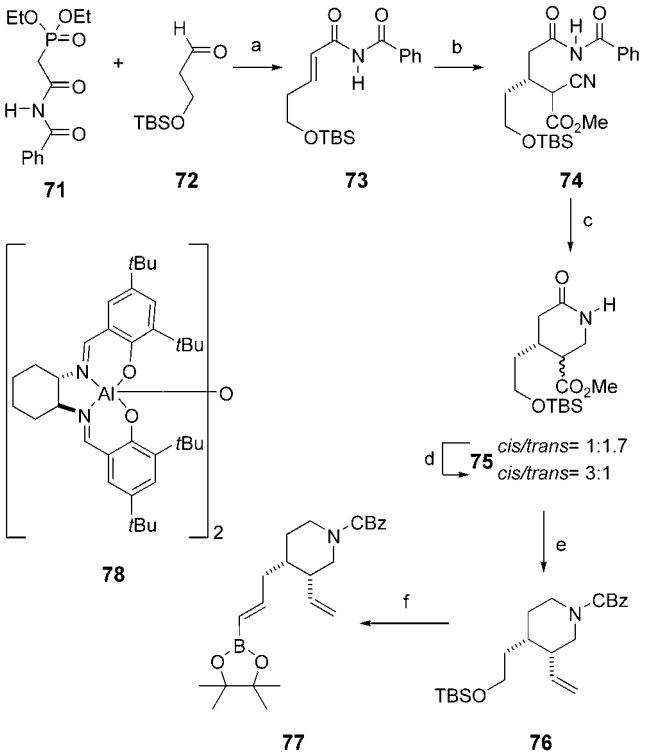
simultaneous control of the configuration at the C8 and C9 stereocenters in the final product and allowed either one of the two commercially important cinchona alkaloids to be selectively secured, simply by changing the nature of the chiral catalyst employed in this key step. The fundamental part of his strategy is a modern and stereocontrolled version of the aminoepoxide cyclization conceptually established by Gutzwiller and Uskokovic in the 1970s.[91] Interestingly, the catalysts used are cinchona alkaloid derivatives, as the crucial step is a modification of the well-known Sharpless asymmetric dihydroxylation (Scheme 22).



Scheme 22. Retrosynthetic analysis of quinine by Jacobsen and co-workers.

The overall strategy of Jacobsen and co-workers hinges upon four fundamental C–C, C–N, and C–O bond-forming reactions: a catalytic enantioselective conjugate addition to establish the C4 stereocenter, a convergent catalytic Suzuki cross-coupling reaction to join the quinoline ring to a chiral alicyclic unit, an asymmetric dihydroxylation for the construction of the C8 and C9 stereocenters, and an intramolecular amino epoxide S_N2-type cyclization for the stereospecific synthesis of the quinuclidine bicycle with the correct configuration at C8.

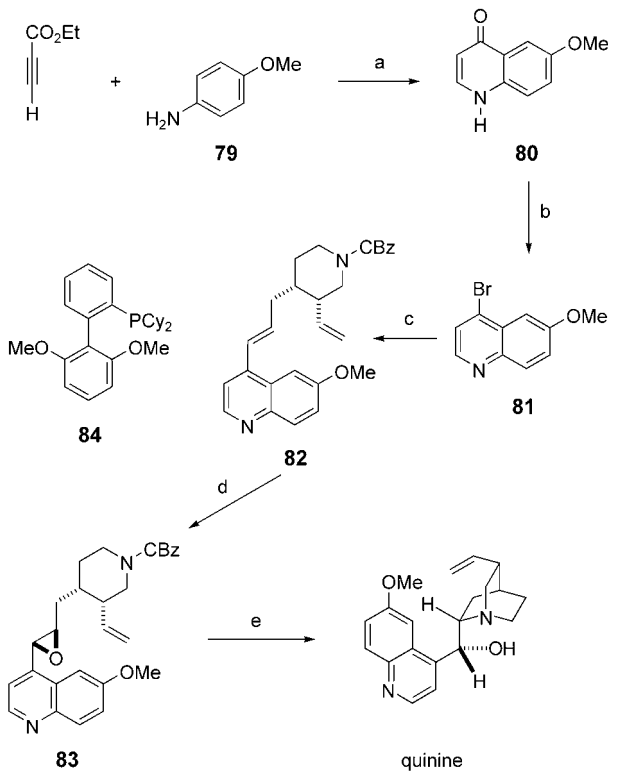
The alicyclic fragment required for the Suzuki cross-coupling reaction was readily accessed by following the sequence depicted in Scheme 23. Olefination of protected aldehyde **72** with imidophosphonate **71**[177] proceeded with high *trans* selectivity to give **73**.[178] Enantioselective conjugate addition of methyl cyanoacetate to **73** in the presence of (*S,S*)-(salen)–aluminum complex **78** (salen = *N,N*′-bis(salicylidene)ethylenediamine dianion)[179] gave **74**, and a hydrogenative lactamization with a Raney nickel catalyst afforded **75**. The inconvenient *cis/trans* diastereomeric mixture (1:1.7) of esters obtained was transformed into a more desirable 3:1 *cis/trans* mixture by a clever selective deprotonation/reprotonation sequence. After a transformation of the functional groups a Wittig olefination was performed,[180] which installed the required vinyl moiety of **76**. Removal of the silyl protecting



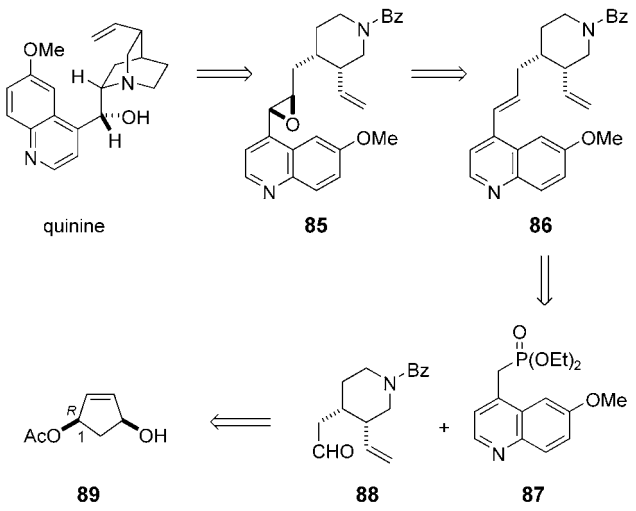
Scheme 23. Synthesis of quinine by Jacobsen and co-workers: Construction of the alicyclic fragment. Reagents and conditions: a) *n*BuLi, THF, −78 °C–0 °C (84%, $E/Z > 50:1$); b) $NCCH_2CO_2Me$, (*S,S*)-**78** (5 mol%), *t*BuOH, C_6H_{12}, RT (91%); c) Raney Ni, H_2, toluene/MeOH (3:1), 44 bar, 80 °C, 12 h (89%); d) 1. LDA, THF, −78 °C; 2. 5% H_2O/THF, −78 °C; e) 1. $LiAlH_4$, THF; 2. CBz_2O, Et_3N, CH_2Cl_2 (51%); 3. chromatographic separation of diastereomers; 4. TPAP, NMO, CH_2Cl_2; $Ph_3P^+MeBr^-$, KO*t*Bu, THF, 0 °C (73%); f) 1. TBAF, THF; 2. TPAP, NMO, CH_2Cl_2 (86%); 3. Cl_2CHB(pinacolate), $CrCl_2$, LiI, THF (79%, $E/Z > 20:1$). CBz_2O = dibenzyl dicarbonate, NMO = *N*-methylmorpholine-*N*-oxide, TBAF = tetrabutylammonium fluoride, TPAP = tetrapropylammonium perruthenate.

group, followed by oxidation of the resultant alcohol to the corresponding aldehyde and olefination with dihalomethylboron pinacolate under Takai conditions selectively furnished the necessary (*E*)-vinyl component **77**.[181] On the other hand, preparation of the appropriately substituted bromoquinoline **81**, previously employed for the synthesis of quinine,[44b] was straightforward, and achieved by condensation of *p*-anisidine (**79**) with methyl propiolate, followed by microwave-assisted bromination of the resultant **80** with concomitant aromatization.[182] The two fragments were joined through a Suzuki cross-coupling reaction in the presence of ligand **84** to give vinyl quinoline **82** (Scheme 24). This latter compound is reminiscent of **44b**, a common intermediate in earlier quinine and quinidine constructions (Scheme 13).

A Sharpless asymmetric dihydroxylation procedure using the AD-mix-β reagent mixture[183] allowed convenient access to the required epoxide functionality (**83**) through an intermediate halohydrin,[184] while microwave-assisted nucleophilic attack of the oxirane by the deprotected secondary amine[185] completed the correct installation of the quinuclidine core and the synthesis of quinine.[186]



Scheme 24. Synthesis of quinine by Jacobsen and co-workers. Reagents and conditions: a) 1. MeOH, RT, 12 h; 2. Dowtherm A, 250 °C, 30 min (63 %); b) Ph_3PBr_2, MeCN, microwaves, 170 °C,15 min (86 %); c) **77**, $Pd(OAc)_2$, **84** (2.5 mol %), K_3PO_4, H_2O, THF, 16 h, RT (89 %, $E/Z > 20:1$); d) 1. AD-mix-β, $MeSO_2NH_2$, *t*BuOH, H_2O, 0 °C (88 %, d.r. > 96:4); 2. $MeCH(OMe)_3$, PPTS (cat.), CH_2Cl_2; 3. MeCOBr, CH_2Cl_2; 4. K_2CO_3, MeOH (81 %); e) 1. Et_2AlCl, benzenethiol, 0 °C–RT; 2. microwaves, 200 °C, 20 min (68 %). Cy = cyclohexyl.



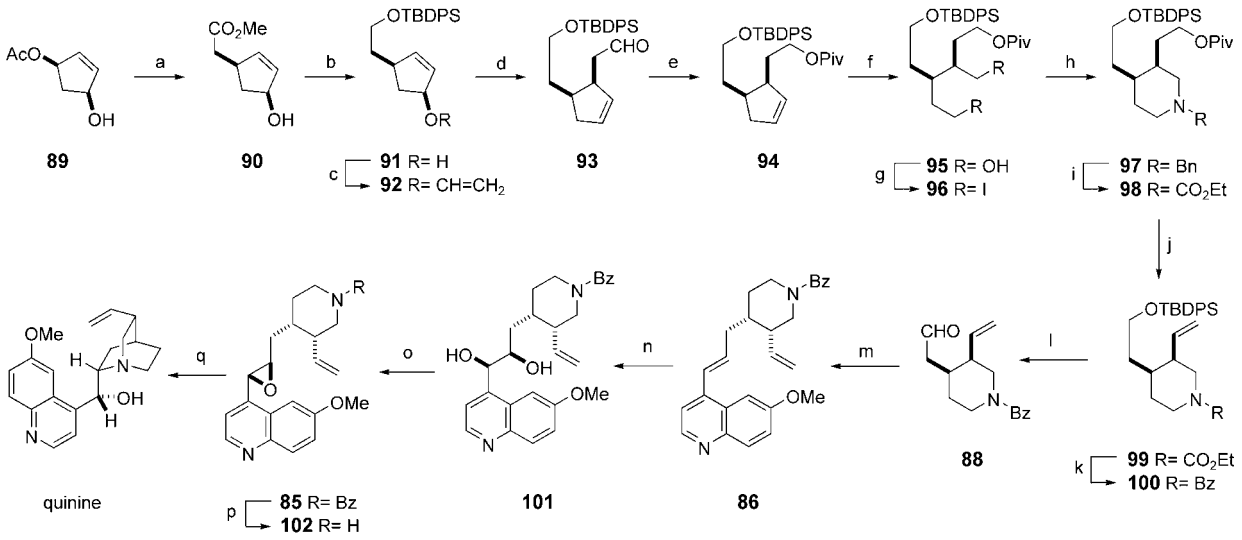
Scheme 25. Retrosynthetic analysis of quinine by Kobayashi and co-workers.

11. Another C8–N Strategy: The Latest Total Synthesis of Quinine

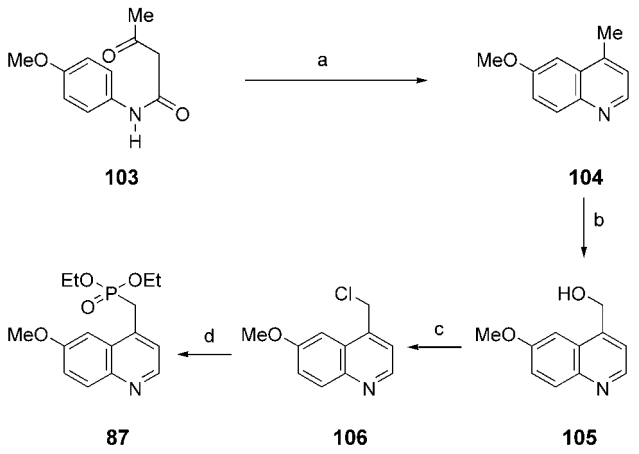
More recently, however, a Japanese research group headed by Kobayashi disclosed a total synthesis of quinine.[187] Their route follows a more classical synthetic approach and is strongly based on previous experience accumulated during the research of Uskokovic et al.,[91,147a] Taylor and Martin,[154] and Jacobsen and co-workers.[176] Its novelty, however, resides in its original and highly stereocontrolled synthesis of the meroquinene moiety. Their retrosynthetic analysis of the natural product (Scheme 25) shows that the epoxide **85**, analogous to **83** and reminiscent of **45**, is formed, which in turn is assumed to come from *E*-olefin **86**, similar to **82** and **44b**.[153b,154,155] Formation of the critical C–C double bond leading to **86** through the use of organophosphorous reagents is the key step for joining the known alicyclic fragment **88** to the aromatic moiety **87**. The synthesis of **88**[160] employs the readily available 1*R* enantiomer of monoacetate **89**,[188] which contains all of the five carbon atoms required to build the piperidine ring of **88**.

Reaction of allylic monoacetate **89**[189] with dimethyl malonate under palladium catalysis furnished ester **90** as a single enantiomer in almost quantitative yield (Scheme 26).[190] Reduction of the ester and selective protection of the resulting primary alcohol provided intermediate **91** in 63 % yield. Pivalate **94** was then synthesized by employing a sequence involving formation and Claisen rearrangement of the vinyl ether **92** derived from **91**, followed by reduction of aldehyde **93**, and conventional protection of the resulting alcohol with pivaloyl chloride. Ozonolysis of **94** with a reductive work up led to diol **95**, and subsequent formation of the corresponding diiodide **96** under Mitsunobu conditions set the stage for the construction of the piperidine ring of **97** by dialkylation of benzylamine. Replacement of the *N*-benzyl group of **97** with CO_2Et (**98**) afforded the characteristic vinyl group of the meroquinene aldehyde fragment. This was achieved by selective deprotection of the pivalic acid ester, followed by phenylselenenylation of the free primary alcohol with Grieco's reagent,[191] its subsequent oxidation to the corresponding selenoxide and final elimination to give good yields of **99**. A second replacement of the *N*-protecting group to give **100** was implemented by hydrolysis of the carbamate and benzoylation of the resulting free secondary amine. These successive changes in the nitrogen protecting group are necessary because selenoxide elimination apparently cannot be carried out on benzoyl derivatives. Finally, mild desilylation of **100** liberated the remaining primary alcohol, which was smoothly oxidized to the anticipated key intermediate **88**. The aromatic component **87** was prepared from keto amide **103** (Scheme 27).[192] Cyclization with sulfuric acid and subsequent dehydration with phosphorous oxychloride provided **104**. Functionalization of the methyl group with *m*CPBA afforded **105**,[193] and finally phosphorylation with the aid of thionyl chloride and intermediacy of the related chloride **106** afforded **87**.

The aldehyde **88** was coupled with the phosphonate **87** by using sodium hydride as the base and the product **86** submitted to Sharpless' asymmetric dihydroxylation with AD-mix-β to furnish **101**.[142a,183] Analogous to the protocol of Jacobsen and co-workers, diol **101** was converted into the



Scheme 26. Synthesis of quinine by Acharya and Kobayashi. Reagents and conditions: a) 1. $CH_2(CO_2Me)_2$, *t*BuOK, $[Pd(PPh_3)_4]$ (cat.); 2. KI, DMF, 125 °C (70%); b) 1. $LiAlH_4$; 2. TBDPSCl, imidazole (63%); c) $H_2C{=}CHOEt$, $Hg(OAc)_2$ (cat.); d) 190 °C; e) 1. $NaBH_4$; 2. *t*BuCOCl, Et_3N, CH_2Cl_2 (66%); f) 1. O_3, *n*PrOH, [78 °C; 2. $NaBH_4$ (81%); g) I_2, PPh_3, imidazole (88%); h) $BnNH_2$, dioxane (98%); i) $ClCO_2Et$, PhMe (99%); j) 1. NaOEt, EtOH; 2. *o*-NO_2-C_6H_4SeCN; PBu_3, THF; 3. 35% H_2O_2, THF (77%); k) 1. MeLi, 0 °C; 2. BzCl (61%); l) 1. TBAF; 2. PCC (80%); m) **87**, NaH, THF, RT (82%); n) AD-mix-β, 0 °C; o) $MeC(OMe)_3$, PPTS (cat.), CH_2Cl_2, TMSCl, K_2CO_3, MeOH (95%); p) DIBAL-H, PhMe; q) DMF, 160 °C (66% from **85**). PCC = pyridinium chloroformate, piv = pivaloyl, Bn = benzyl.



Scheme 27. Synthesis of key intermediate **87** by Kobayashi et al. Reagents and conditions: a) 1. H_2SO_4; 2. $POCl_3$; 3. Zn, AcOH (72%); b) *m*CPBA, CH_2Cl_2, RT; 2. Ac_2O, RT; 3. K_2CO_3, MeOH (43%); c) $SOCl_2$, CH_2Cl_2, reflux (71%); d) H-P(=O)$(OEt)_2$, *n*BuLi, THF (70%).

related epoxide **85**,[184] which was reductively deprotected with DIBAL-H to provide the last intermediate **102**. Unlike the procedure of Jacobsen and co-workers in which microwaves were used, the synthesis was completed by nucleophilic ring opening of the epoxide under purely thermal conditions and furnished quinine in a yield of 66% from oxirane **85**. Compound **45**, an epoxide similar to **85** and **83**, has been previously synthesized nonstereoselectively by Uskokovic et al. Both the Jacobsen and Kobayashi research groups solved the selectivity problem associated with the amino epoxide cyclization by making the "correct" oxirane.

12. Concluding Remarks

More than 85 years have passed since Rabe's claim to have reconstructed quinine and sixty years since Woodward and Doering shocked the world with their claim to have accomplished the first total synthesis of quinine. We are also approaching the 150th anniversary of Perkin's historic experiment. So, what does the resurgence of the interest in quinine manifested through the recent total syntheses by the research groups of Stork, Jacobsen, and Kobayashi mean?

In recent years the chemical community has witnessed the power of total synthesis through the syntheses of scarcely available and structurally complicated targets such as paclitaxel, palytoxin, and the ecteinascidins,[194] to name but a few of the successfully completed ventures. Why should the relatively simple quinine, now clinically overshadowed by synthetic antimalarial drugs, no longer a miracle drug, and more than abundantly available for its main use to be in the preparation of tonic water, be catching the attention of renowned chemists?

Organic chemistry has evolved into a well-established branch of science and has become such a sophisticated and demanding area that the synthesis of natural products is no longer just oriented towards proof of structure, but to the testing of new reagents, reactions, concepts, and strategies. Factors such as atom economy, stereocontrol, overall simplicity, and environmental impact have become the new principles orienting the development of this discipline.

Unlike any other endeavor, quinine has been a long-sought synthetic target, with an aura of elusiveness. Perhaps the most important reasons behind the recent syntheses of quinine are those confessed to by Stork himself: "*the value of a quinine synthesis has essentially nothing to do with quinine*

… it is like the solution to a long-standing proof of an ancient theorem in mathematics: it advances the field".

In this context, the distinguished achievement made by Jacobsen and co-workers is highly symbolic: it comes almost 60 years after the accomplishment of Woodward and Doering. Both syntheses of quinine were carried out by employing "state of the art" chemical knowledge, chemical thinking, and chemical reagents, and both resorted to the same, almost one century old C8–N approach. Although all of the chemicals and all the reactions were available to both scientists, they both developed unique strategies towards the natural product.

Every scientific achievement must be judged by the standards of its time. There is a clear evolution from the protocol of Woodward to those of Kobayashi and Jacobsen through those of Uskokovic, Gates, Taylor, and Stork and provides clear proof of lessons learned in synthetic methodology and strategy over the intervening years. They are also strong signals that the total synthesis of natural products, considered by many as the most demanding form of organic chemical research, which Woodward enriched and stimulated so profoundly in the past, did indeed become a major endeavor in organic chemistry.[195,196] Organic synthesis is still developing and has a bright, strong, and promising future. Thus, one thing is assured: although Kobayashi et al. have described the most recent and perhaps one of the most efficient total syntheses of quinine, it will not be the last.

Addendum

In addition to being the 60th anniversary of the first paper by Woordard and Doering on quinine, 2004 also marks the 25th year since Robert B. Woordward's untimely and unfortunate death. A short and useful account on Woodward's personal and professional life can be found in ref. [197].

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