The First Stereoselective Total Synthesis of Quinine

Gilbert Stork,* Deqiang Niu, A. Fujimoto,[†] Emil R. Koft,[‡] James M. Balkovec,[§] James R. Tata,[§] and Gregory R. Dake[⊥]

Contribution from the Department of Chemistry, Columbia University, New York, New York 10027

Received December 22, 2000

Abstract: The first entirely stereoselective total synthesis of (−)-quinine is reported.

Introduction

Quinine (**1**)[1] has occupied a central place among the many plant alkaloids which are used in medicine. For over three centuries, and until relatively recently, it was the only remedy available to deal with malaria,[2] a disease from which millions have died.[3–5] Rational attempts to synthesize quinine started early in the first half of the twentieth century[6,7] and eventually resulted in total syntheses in which 3 of the 4 asymmetric centers in the molecule were established stereoselectively.[8,9] An entirely stereoselective synthesis of quinine has, however, not yet been achieved. This paper reports our successful efforts to meet this challenge.

We first put our work in context with a brief survey of some of the previous synthetic efforts toward quinine. They go back almost a century and a half. One of the early ones has become part of the history and legend of chemistry: the well-known story of William Henry Perkin who, in 1856, when the
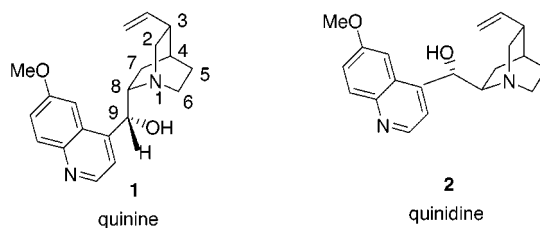

Figure 1.

empirical formula of quinine, $C_{20}H_{24}N_2O_2$, had only recently been settled, tried to produce the alkaloid by the oxidation of what was supposedly an *N*-allyl toluidine ($C_{10}H_{13}N$) according to the equation $2(C_{10}H_{13}N) + 3O = C_{20}H_{24}N_2O_2 + H_2O$.[10] Although the arithmetic was suggestive, it is hardly surprising that Perkin did not obtain quinine.

The correct connectivity between the atoms of the quinine molecule was eventually unraveled, largely as the result of the extensive work of the German chemist Paul Rabe,[11] who then began to consider the possibility of a synthesis of the alkaloid. This was quite a challenge since the presence of 4 asymmetric carbons in the quinine molecule means that the correct atom connectivity corresponds to 16 possible isomeric structures for the alkaloid. Even without the knowledge of the correct stereochemistry, Rabe chose to attempt to reconstruct quinine from a 3,4-disubstituted piperidine, originally named quinicine, and later known as quinotoxine (**3**),[1a] which had earlier been obtained by Pasteur[12] by acid-catalyzed isomerization of quinine (Scheme 1). And, indeed, Rabe claimed, in a very terse 1918 com-

[†] Novartis, Summit, NJ.
[‡] Deceased February 17, 1989.
[§] Merck & Co, Rahway, NJ.
[⊥] University of British Columbia.

(1) (a) Turner, R. B.; Woodward, R. B. The Chemistry of the Cinchona Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1953; Vol. 3, Chapter 16. (b) Uskoković, M. R.; Grethe, G. The Cinchona Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, p 181. (c) Grethe, G.; Uskoković, M. R. In *The Chemistry of Heterocyclic Compounds*; Sexton, J. E., Ed.; Wiley-Interscience: New York, 1983; Vol. 23, Part 4, p 279.
(2) (a) McGrew, R. E. The most significant disease for world civilization over the past three centuries. In *Encyclopedia of Medical History*; McGraw-Hill: New York, 1985; p 166.(b) Casteel, D. A. Quinine may be claimed ⋯ as the drug to have relieved more human suffering than any other in history. In *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Wolff, M. E., Ed.; John Wiley: New York, 1997; Vol. 5, Chapter 59, p 16.
(3) *Over 1 million deaths in 1999*; World Health Organization (WHO) Report 2000, World Health in Statistics, Annex Table 3.
(4) For a very recent discussion of the status of the malaria problem, see: *Science* **2000**, *290*, 428ff.
(5) The use of quinine has markedly decreased in recent years, but the U.S. still imported over 68 tons of quinine and its salts in 1999. Cf. U.S. Department of Commerce, *U.S. imports of organic chemicals for consumption*; Chapter 29, subheading 293921.
(6) Rabe, P.; Kindler, K. *Chem. Ber.* **1918**, *51*, 466. This extremely abbreviated announcement states that the conditions used 7 years previously for the related conversion of cinchotoxine to cinchoninone (Rabe, P. *Ber.* **1911**, *44*, 2088) were those used for the quinotoxine to "quininone" (now known to be quinidinone) transformation. On the other hand, the procedure for the aluminum powder reduction, stated to reduce "quininone" to quinine in 12% yield in the 1918 paper, was only revealed 14 years later (Rabe, P. *Annalen* **1932**, *492*, 242), using as example the reduction of hydrocinchoninone to hydrocinchonine (which is, incidentally, known to have the quinidine stereochemistry at C-8, C-9) because as Rabe understates it, the method used in his 1918 paper "ist noch nicht eingehend beschrieben worden".
(7) (a) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 849. (b) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860.

(8) (a) Uskoković, M.; Gutzwiller, J.; Henderson, T. *J. Am. Chem. Soc.* **1970**, *92*, 203. (b) Gutzwiller, J.; Uskoković, M. *J. Am. Chem. Soc.* **1970**, *92*, 204. (c) Uskoković, M.; Reese, C.; Lee, H. L.; Grethe, J.; Gutzwiller, J. *J. Am. Chem. Soc.* **1971**, *93*, 5902. (d) Grethe, G.; Lee, H. S.; Mitt, T.; Uskoković, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 5904. (e) Grethe, G.; Lee, H. S.; Mitt, T.; Uskoković, M. R. *Helv. Chim. Acta* **1973**, *56*, 1485. (f) Gutzwiller, J.; Uskoković, M. R. *Helv. Chim. Acta* **1973**, *56*, 1494. (g) Uskoković, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, J.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571. (h) Gutzwiller, J.; Uskoković, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576. (i) Grethe, G.; Lee, H. S.; Mitt, T.; Uskoković, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 581. (j) Grethe, G.; Lee, H. S.; Mitt, T.; Uskoković, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 589.
(9) (a) Gates, M.; Sugavanam, B.; Schreiber, W. L. *J. Am. Chem. Soc.* **1970**, *92*, 205. (b) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1974**, *96*, 8095. See also: (c) Speckamp, W. N.; Dijkink, J. *Heterocycles* **1974**, *2*, 291. (d) Brown, R. T.; Curless, D. *Tetrahedron Lett.* **1986**, *27*, 6005. (e) Wilson, S. R.; DiGrandi, M. J. *J. Org. Chem.* **1991**, *56*, 4766.
(10) Cf. the account presented much later, in his Hofmann Memorial Lecture, by Perkin: Perkin, W. H. *J. Chem. Soc.* **1896**, *69*, 596.
(11) Rabe, P.; Ackerman, E.; Schneider, W. *Ber.* **1907**, *40*, 3655, and numerous previous and later papers; cf. ref 1a.
(12) (a) Pasteur, L. *Compt. rend.* **1853**, *37*, 110. (b) Pasteur, L. *Ann.* **1853**, *88*, 209. For the structure, see: Rabe, P. *Ann.* **1909**, *365*, 366.

Scheme 1

Scheme 2
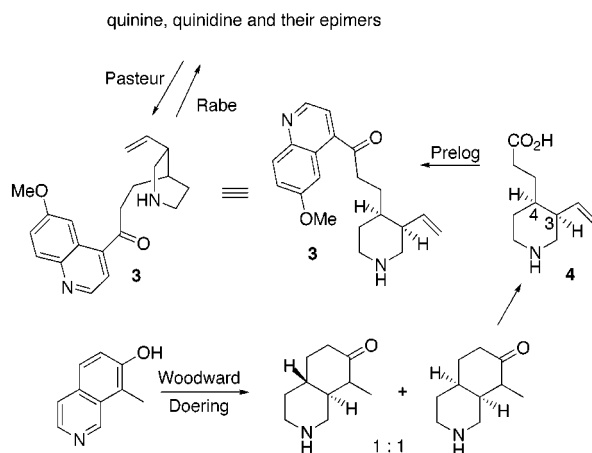
munication,[6] that he had succeeded in accomplishing that partial synthesis.

Twenty-five years later, Prelog and Proštenik[13] showed that the 3-vinyl-4-piperidinepropionic acid, known as homomeroquinene (**4**), which they had obtained as the proper enantiomer by degradation of quinotoxine, could be reconverted into the latter, thereby completing a route from homomeroquinene back to quinine, assuming the validity of Rabe's claim. A *formal* total synthesis of quinine was completed when Woodward and Doering announced in 1944[7] that they had succeeded in synthesizing homomeroquinene itself. As a synthetic route to quinine, it suffered from the lack of stereocontrol in the ingenious Woodward−Doering sequence to homomeroquinene, and from the low yields and the difficult separations of the 4 isomers anticipated from the Rabe scheme for the conversion of quinotoxine to quinine because that half of the construction did not involve any stereocontrol.[14]

The Stereochemical Problem

Stereocontrol was not a concern of synthetic organic chemists before 1940 or so, largely because the mechanistic and conformational underpinnings of modern organic chemistry were not yet part of synthesis design. In fact, the configuration of the C-8 and C-9 asymmetric centers of quinine was not yet known in 1918, when Rabe announced the reconstruction of

---

(13) Proštenik, M.; Prelog, V. *Helv. Chim. Acta* **1943**, *26*, 1965.

(14) Woodward and Doering did not claim to have confirmed Rabe's 1918 report, in a few lines, that he had succeeded in converting quinotoxine to quinine (although the basis of their characterization of Rabe's claim as "established" is unclear), nor is there any evidence that they produced any quinine in their own laboratories. But this was wartime, and the U.S. had been cut off from the Dutch East Indies, its major source of cinchona bark. The resulting anxiety may explain press accounts, notable for enthusiasm rather than for sober analysis, which created the quasiuniversal impression that the construction of homomeroquinene in 1944 meant that quinine had been synthesized: cf. inter alia: (a) Laurence, W. M. *The New York Times*, **1944**, *May 4*, 1: "The duplication of the highly complicated chemical architecture of the quinine molecule, hailed by leading scientists at Harvard and other institutions as one of the greatest scientific achievements in a century". (b) Manchester, H. *Sci. News Lett.* **1944**, *June 10*, 378ff: "Starting with five pounds of chemical they obtained the equivalent [?] of 40 milligrams of quinine". Remarkably, the confusion produced by these and hundreds of other contemporary reports has persisted to this day: inter alia: (c) *The Columbia Encyclopedia*, 6th ed.; Columbia University Press: New York, 2000; p 2344: "Chemical synthesis [of quinine] was achieved in 1944 by Woodward, R. B; Doering, W. E. ...". (d) *The Encyclopaedia Britannica*, 15th ed.; Chicago, 1997; Vol. 9, p 862: "[quinine's] total laboratory synthesis in 1944 is one of the classical achievements of synthetic organic chemistry". (e) *The Grolier Library of Scientific Biography*; Grolier Educational: Danbury, 1997; Vol. 10, p 167: "In 1944 Woodward, with William von Eggers Doering, synthesized quinine from the basic elements. This was a historic moment ...".
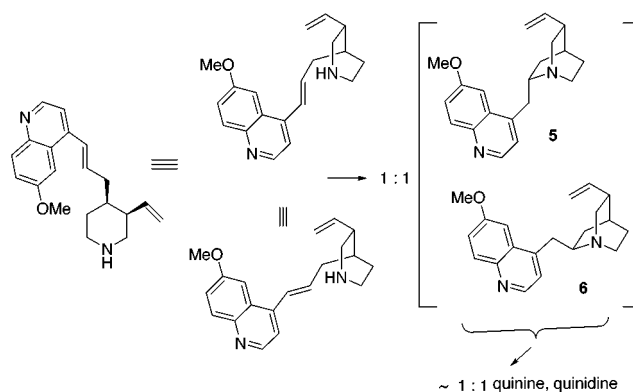
quinine from quinotoxine. By 1944, the cis relationship of the vinyl and propionic acid substituents at positions 3 and 4 of the piperidine ring of homomeroquinene had been established,[15] but the Woodward−Doering half of the synthesis was not stereoselective, and produced the precursors of their homomeroquinene target as a mixture of cis and trans stereoisomers, in roughly equal amounts.[16]

The first successful efforts toward a stereoselective quinine synthesis were reported 55 years ago.[17] The synthesis of the ethyl ester of (±)-*cis*-3-ethyl-4-piperidineacetic acid (dihydromeroquinene, also known as cincholoipon) illustrated a possible path to the creation of the substituted piperidine stereochemistry required for a "Rabe route" to the quinine alkaloids, but although the synthesis deserves some notice as one of the earliest successful examples of stereorational planning related to natural product synthesis, there was still no solution to the problem of stereocontrol of the crucial asymmetric centers at C-8 and C-9.

A quarter of a century passed before further progress toward a stereoselective total synthesis of quinine was achieved by Uskoković, Gutzwiller, and their collaborators at Hoffmann-La Roche.[8] That impressive achievement was illustrated by a number of syntheses of quinine in which the quinuclidine ring was created by forming the bond between N-1 and C-8. That strategy, which may be called the Rabe connection, was endorsed by the workers who followed Rabe, starting with Woodward and Doering,[7−9] presumably because of the attractive structural simplification it seemed to offer.

The problem with that approach, however, turned out to be the difficulty of achieving stereospecificity, or at least high stereoselectivity, involving the C8 and C9 centers, with the result that even the largely stereocontrolled Hoffmann-La Roche synthesis produced quinine together with an equal amount of quinidine (**2**), that isomer which is epimeric with quinine at both of these centers.

A very important observation was made, however, by the Hoffmann-La Roche chemists who discovered[8h] that the 1:1 mixture of deoxyquinine (**5**) and its C-8 epimer, deoxyquinidine (**6**), which results from one of their syntheses (cf Scheme 2), could be oxidized to a mixture consisting largely of only two of the four possible secondary alcohols, one of them quinine and the other quinidine. They verified the implication of that

---

(15) Prelog, V.; Zalan, E. *Helv. Chim. Acta* **1944**, *27*, 535.

(16) The ingenious, carefully documented,[7b] separation of the mixture of the *cis*- and *trans*-hydroisoquinolone precursors of homomeroquinene is a tribute to the experimental acumen that is also displayed in the further details of the experimental work on the synthesis of homomeroquinene.

(17) Stork, G.; McElvain, S. M. *J. Am. Chem. Soc.* **1946**, *68*, 1053. The *cis*-stereochemistry claimed for that 3,4-disubstituted piperidine has been confirmed: Sundberg, R. J.; Holcomb, F. D. *J. Org. Chem.* **1969**, *34*, 3273.
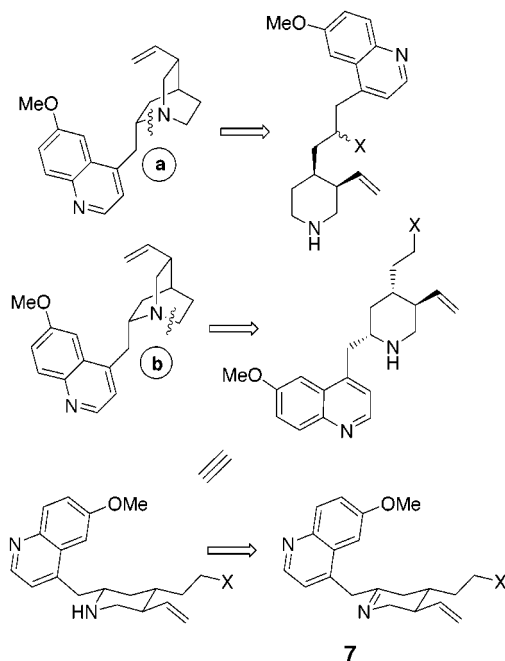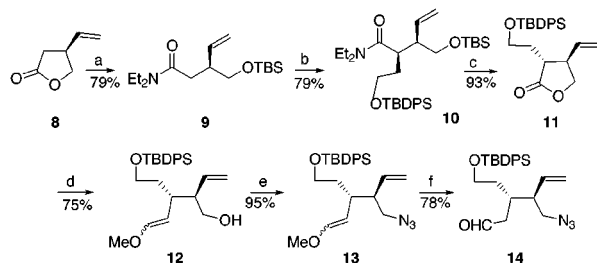
Figure 2.

Scheme 3[a]

[a] Conditions: (a) (1) Et₂NH/AlMe₃, (2) TBS−Cl/lmidazole/DMF. (b) LDA, −78 °C, ICH₂CH₂OTBDPS. (c) PPTS (0.3 equiv), EtOH, 12 h, then xylenes, reflux 8−10 h. (d) (1) DIBAL-H, −78 °C, (2) Ph₃P=CHOMe. (e) PH₃P/DEAD, (PhO)₂P(O)N₃. (f) 5 N HCl, THF/CH₂Cl₂.

result by showing that pure deoxyquinine (obtained from natural quinine by C-9 deoxygenation) regenerated quinine under their oxidation conditions. It followed that a stereoselective synthesis of quinine would finally be achieved *if a stereospecific synthesis of deoxyquinine could be effected*. Such a synthesis became our goal.

We first noted that the formation of the ∼1:1 mixture of deoxyquinine (**5**) and its C-8 epimer (**6**) mentioned above followed construction of the quinuclidine ring by intramolecular conjugate addition to a 4-alkenylquinoline. In the *absence* of the vinyl group on the incipient quinuclidine, the two adducts would be mirror images, as would the transition states to their formation. Practically the same situation obtains in the *presence* of the vinyl group because it can adopt a conformation in which it would have only a minor effect on the relative energies of the transition states to either **5** or **6**, thus resulting in equal amounts of these C-8 isomers. A totally different situation would, however, be expected if the C-8 asymmetry arose from closure to a piperidine, rather than to a quinuclidine. Such a scheme would require abandoning the time-honored Rabe connection (shown as **a** in Figure 2) in favor of the closure shown by **b**. Adoption of the latter construction would lead to the corollary that the vicinal substituents on the piperidine precursor would now have to be trans. This is not a serious problem, but it leads to the further corollary that the piperidine ring in such a scheme would now have to be trisubstituted because it would bear an additional, and stereodefined, substituent (cf. **7**). At first sight, the increase in complexity hardly seemed a step in the right direction.

We concluded, however, that the benefits would be substantial. A major problem with the *cis*-3,4-disubstituted piperidine intermediates of previous quinine syntheses is that their two possible chair conformations would be similar in energy. Such a situation would make control of stereochemistry difficult to achieve in further transformations. In contrast, trans vicinal substituents on a piperidine intermediate suitable for our purpose would ensure the specific chair conformation in which those substituents are equatorial (cf. **7**, Figure 2).

As we will see presently, it was, indeed, the selection of the trisubstituted tetrahydropyridine **7** as our goal that led to the

control of the stereochemistry at C-8, and to our stereospecific construction of deoxyquinine.

Stereospecific Construction of Deoxyquinine

As starting material for the construction of the 2,4,5-trisubstituted piperidine **7**, we chose the known (*S*)-4-vinylbutyrolactone (**8**)[18,19] (Scheme 3). We selected a protected iodoethanol for the required introduction, trans to the vinyl group, of a substituent that would eventually become the 4-substituent of piperidine **17**. We had initially used a mesitoate ester for that protection, but base-catalyzed reactions at a later stage of our synthesis led to serious difficulties resulting from the unwanted deprotonation of the mesitoate methyls, and we eventually turned to the *tert*-butyldiphenylsilyl (TBDPS) protecting group.

Direct alkylation of 4-vinylbutyrolactone (**8**) with protected iodoethanol derivatives was not as satisfactory as the somewhat more involved, but efficient, process involving opening of the vinyl lactone with diethylamine, protection of the resulting primary hydroxyl as its TBS derivative **9**, and alkylation of the resulting diethylamide to give **10**. The desired (>20:1) *trans*-3,4-disubstituted butyrolactone **11** was then readily obtained by selective removal of the TBS group with *p*-toluenesulfonic acid in ethanol, at room temperature, followed by refluxing the resulting hydroxyamide in xylene. Elaboration of **11** toward our trisubstituted piperidine intermediate now required the addition of a carbon atom and replacement of the ring oxygen by a nitrogen. The first of these goals was achieved by reduction of **11** with diisobutylaluminum hydride to the corresponding lactol, followed by Wittig reaction with methoxymethylene triphenylphosphorane to give **12**. Reaction of the latter with diphenylphosphoryl azide[20] now converted the liberated primary hydroxyl to an azido group to form **13**, from which aqueous acid hydrolysis, in a two-phase system, at room temperature, led to the azido aldehyde **14**, in ∼60% overall yield from lactone **11**.

With the azidoaldehyde **14**, we had reached a suitable intermediate for the construction of the required piperidine. That construction (Scheme 4) started with the addition of the lithium salt of 6-methoxy-4-methylquinoline to the carbonyl group of **14** to produce the expected secondary alcohol **15** in ∼70% yield. Alcohol **15** was obtained as a mixture of two epimers, a fact of no consequence because the mixture was converted by Swern oxidation to the corresponding azidoketone, the intermediate

(18) Kondo, K.; Mori, E. *Chem. Lett.* **1974**, 741.
(19) Ishibashi, F.; Taniguchi, E. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4361.
(20) Lal, B.; Pramanik, B. M. I.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977.

Scheme 4

Scheme 5
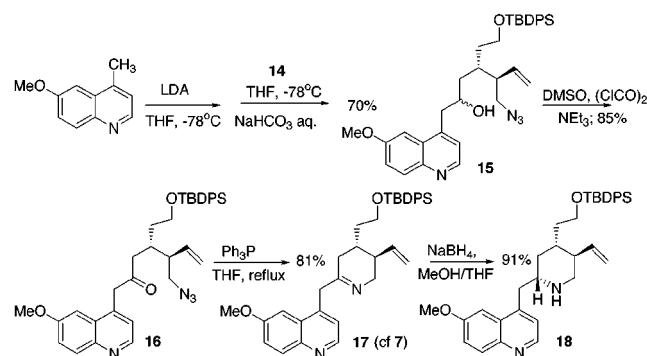
we planned to use for cyclization to a piperidine system via an intramolecular Staudinger reaction.[21,22] In the event, the azidoketone **16** was smoothly converted to the anticipated tetrahydropyridine **17** by refluxing with 1 equiv of triphenylphosphine in tetrahydrofuran.

We approached the next step with some apprehension because the success of what we intended as a stereospecific synthesis of deoxyquinine depended on the assumption that the specific half-chair conformation which places the vinyl group and the protected hydroxyethyl chain in equatorial orientations (cf. Figure 2) would result, via the anticipated[23] axial addition of hydride to an imminium intermediate, in placing the quinolylmethyl substituent in the equatorial orientation corresponding to the specific C-8 configuration required for the eventual deoxyquinine. This proved to be the case: spectral data, especially ^{13}C NMR, showed that the piperidine **18** (**7**, X = OTBDPS) was produced as a single compound, in 91% yield, by addition of sodium borohydride to a solution of **17** in a 1:1 mixture of tetrahydrofuran and methanol. That the resulting trisubstituted piperidine **18** was the expected correct epimer at C-8 followed from its further conversion to deoxyquinine.
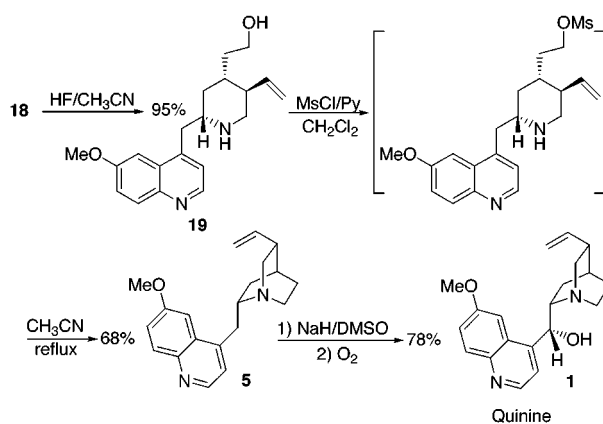
The conversion started (Scheme 5) with the quantitative removal of the silyl protecting group with aqueous hydrogen fluoride in acetonitrile to form **19**. We were now ready to close the quinuclidine ring, an operation that required changing the primary hydroxyl into a suitable departing group. On the face of it, that transformation might be expected to require temporary protection of the piperidine amino group, but our previous experience with a somewhat related situation suggested that mesylation–cyclization, directly on **19**, could well succeed.[24]

In fact, treatment of **19** with 1 equiv of mesyl chloride in methylene chloride, in the presence of pyridine, followed by refluxing of the crude product in acetonitrile, afforded, after liberation from the methanesulfonate salt, deoxyquinine (**5**) in ~70% yield after Flash chromatography.

Completion of the Quinine Synthesis

The formation of quinine by oxidation of deoxyquinine with oxygen in *tert*-butyl alcohol–DMSO, in the presence of potassium *tert*-butoxide, proceeded selectively, as had been found by the Hoffmann-La Roche group. In our hands, a somewhat higher stereoselectivity (quinine:epiquinine ~14:1) was obtained by effecting the oxidation in the presence of sodium hydride in anhydrous DMSO. The synthetic quinine, thus obtained in 78% yield, had high-resolution mass and ^{1}H and ^{13}C NMR spectra essentially identical with those of an authentic sample from Sigma. The melting point and specific rotation of the monotartrate of our synthetic quinine also agreed with the reported values: mp 211.0–212.0 °C (lit.[8f] mp 211.0–212.5 °C); $[\alpha]_D^{21.3}$ −154.7 (*c* 0.67, methanol) (lit.[8f] $[\alpha]^{25}_D$ −156.4 (*c* 0.97, methanol).

Supporting Information Available: Detailed experimental procedures and copies of the ^{1}H NMR and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA004325R

(21) Inter alia: Knouzi, N.; Vaultier, M.; Carrie, R. *Bull. Soc. Chim. Fr.* **1985**, 815.

(22) For a related sequence, cf.: Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977.

(23) (a) Valls, J.; Toromanoff, E. *Bull. Soc. Chim. Fr.* **1961**, 758. (b) Toromanoff, E. *Bull. Soc. Chim. Fr.* **1966**, 3357. (c) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; p 211.

(24) See also: Narasaka, K.; Yamazaki, S.; Ukaji, Y. *Chem. Lett.* **1985**, 1177.