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# Stereocontrolled synthesis of quinine and quinidine

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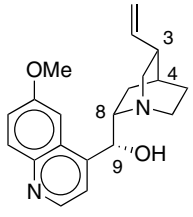
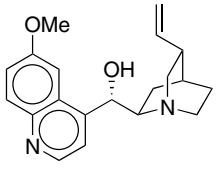
**Abstract**—Disubstituted cyclopentene was prepared from cyclopentene monoacetate and transferred into disubstituted piperidine via oxidative cleavage of the olefin moiety followed by piperidine ring formation. The piperidine was then condensed at the side chain with a quinoline part to afford the olefin precursor of quinine. Finally, the olefin was converted into quinine through the corresponding epoxide. Quinidine was synthesized in a similar way.


Quinine and quinidine have been used as effective therapeutic agents against malaria for over three centuries, and, recently, other medicinal applications have been reported for these alkaloids.[1] On the other hand, the unique structure of these alkaloids has attracted much attention as chiral catalysts in asymmetric reactions.[2] Usually structural modifications, when required, have been performed at the hydroxyl and/or amino group sites, providing moderate to high efficiencies in various reactions. In cases where efficiency is not high, modification of the structural backbone would be an alternative way of attaining higher efficiency. To execute research work along this line, it is indispensable to establish a flexible approach to these alkaloids.

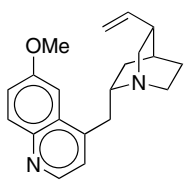



quinine (**1**)

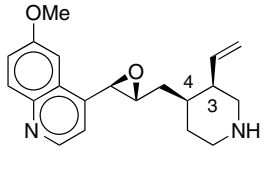



quinidine (**2**)

The results of the previous investigation over 50 years into the synthesis of these alkaloids are suggestive of achieving successful total synthesis. These works are briefly described in the first and stereoselective total synthesis of quinine (**1**) published by Stork et al. in 2001,[3] who prepared the 9-deoxy-quinine **3** in a stereoselective way through a 2,4,5-trisubstituted piperidine (Fig. 1). Previously, Uskokovic and co-workers[4] and Gates et al.[5] independently synthesized the deoxy-quinine **3** and converted it into **1** by hydroxylation using $O_2$ and *t*-BuOK with ~5:1 stereoselectivity. This step was modified by Stork ($O_2$, NaH, DMSO) to afford **1** more selectively (14:1). However, the synthesis seems hardly applicable to quinidine synthesis because the method developed is specialized for production of the key trisubstituted piperidine. Quite recently, Jacobsen and co-workers reported synthesis of **1** and **2**.[6] In his synthesis, the 3,4-disubstituted piperidine, synthesized with a 3:1 ratio regarding the *cis*/*trans* substitutions at C(3) and C(4), was transformed, after condensation with the quinoline part, into epoxide **4** (for **1**) and the diastereomeric epoxide (for **2**), respectively, through the Sharpless AD reaction, and each epoxide was converted




**3**




**4**

**Figure 1.** The previous intermediates for synthesis of quinine (**1**).

*Keywords*: Quinine; Quinidine; Piperidine; Cyclopentene-1,3-diol monoacetate; Epoxide ring opening.

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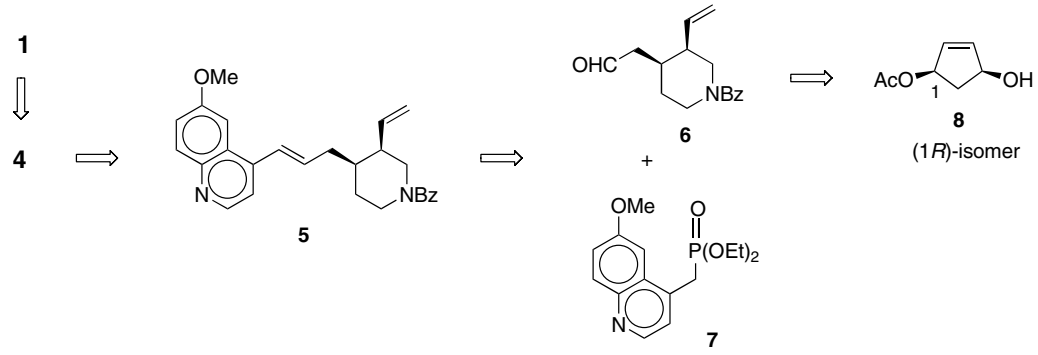
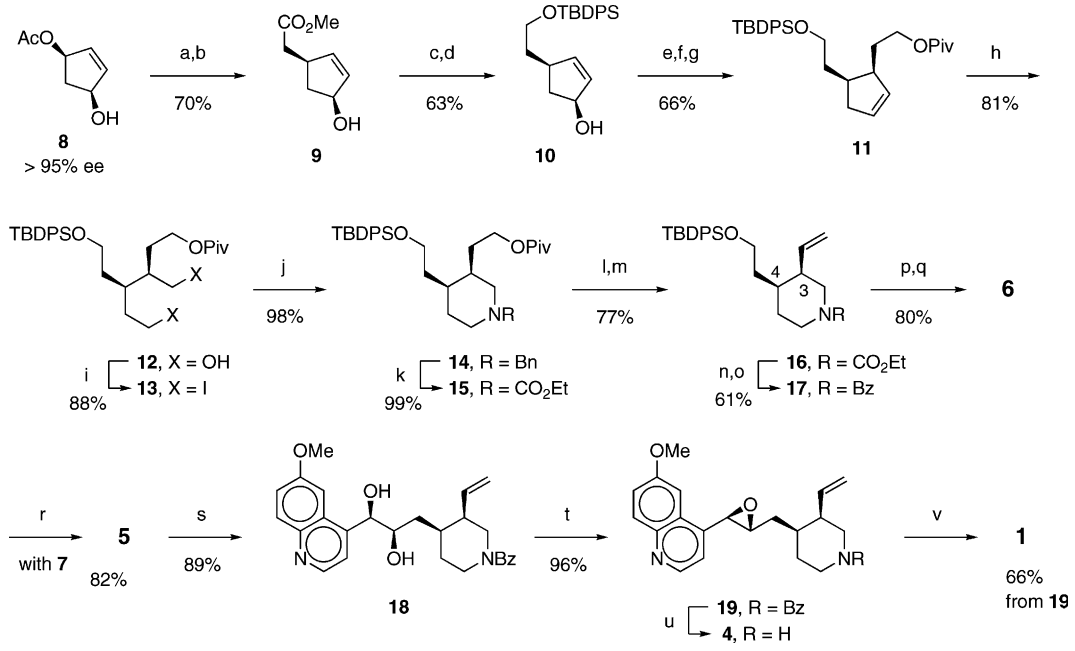
into the target alkaloid. These epoxides were originally synthesized and cyclized to these alkaloids by Uskokovic and co-workers,[4] though at that time the synthesis of the epoxide was nonstereoselective.[7] Herein, we report stereoselective synthesis of a 3,4-disubstituted piperidine and its conversion into **1** and **2**.

We have chosen epoxide **4** as the key intermediate of **1**, and envisioned a synthesis of **4** as illustrated in Scheme 1 from olefin **5**[8] by using steps consisting of the Sharpless et al. asymmetric dihydroxylation[9] and subsequent epoxide ring formation.[10] On the other hand, we selected piperidine aldehyde **6** and quinoline phosphonate **7** as the parts of olefin **5**. While a number of synthetic methods of the 3,4-disubstituted piperidines of this type (the acid is known as meroquinene) have been reported,[11,12] we investigated an alternative route starting with acetate **8**[13] because a variety of carbon nucleophiles as substituents on the piperidine ring can be installed on the cyclopentene ring by using reactions developed by us[14,15] and others.[16] The strategy based on these reactions is a synthetic advantage to execute the study mentioned above. On the other hand, the previous syntheses of the substituted piperidines seem to lack such flexibility.

Synthesis of the piperidine aldehyde **6** through key cyclopentene **11** and its conversion into quinine (**1**) are presented in Scheme 2. Monoacetate **8** (>95% ee) was converted into methyl ester **9**. High yield of 98% for step a was attained by using the conditions recently developed by us.[17] Reduction of the ester and selective protection of the primary hydroxyl group furnished **10** in 63% yield. Claisen rearrangement with vinyl ether and $Hg(OAc)_2$ as a catalyst at 190 °C afforded aldehyde, which upon reduction with $NaBH_4$ and subsequent




**Scheme 1.** Retrosynthesis of quinine (**1**).



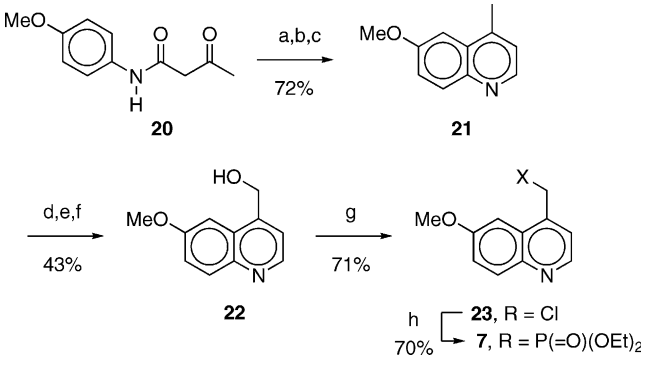

**Scheme 2.** Synthesis of quinine (**1**): (a) $CH_2(CO_2Me)_2$, *t*-BuOK, $Pd(PPh_3)_4$ (cat.); (b) KI, DMF, 125 °C; (c) $LiAlH_4$; (d) TBDPSCl, imidazole; (e) $CH_2$=CHOEt, $Hg(OAc)_2$ (cat.), 190 °C; (f) $NaBH_4$; (g) *t*-BuCOCl, $Et_3N$, $CH_2Cl_2$; (h) $O_3$, *n*-PrOH, −78 °C, then $NaBH_4$; (i) $I_2$, $PPh_3$, imidazole; (j) $BnNH_2$, dioxane; (k) $ClCO_2$ Et, toluene; (l) NaOEt, EtOH; (m) *o*-$(NO_2)C_6H_4SeCN$, $PBu_3$, THF then 35% $H_2O_2$, THF; (n) MeLi, 0 °C; (o) BzCl; (p) TBAF; (q) PCC; (r) **7**, NaH, THF, rt; (s) AD-mix-β, 0 °C to rt; (t) $MeC(OMe)_3$, PPTS (cat.), $CH_2Cl_2$, TMSCl, $K_2CO_3$, MeOH; (u) DIBAL-H, toluene; (v) DMF, 160 °C.

protection of the resulting hydroxyl group as the pivaloyl ester (Piv = *t*-BuCO) produced the key cyclopentene **11** in good overall yield.

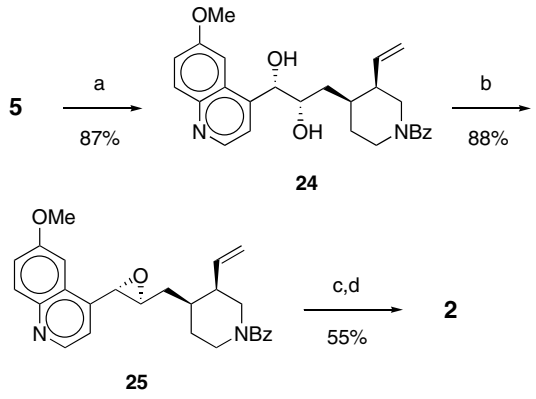
With the necessary substituents for piperidine aldehyde **6** being installed as masked forms, construction of the piperidine ring was then studied. Ozonolysis of cyclopentene **11** in *n*-PrOH[18] at −78 °C followed by reductive work-up with $NaBH_4$ afforded alcohol **12**, which was converted into iodide **13** in 72% yield from **11**. Nucleophilic amino cyclization of **13** with $BnNH_2$ in dioxane at 100 °C produced the *N*-benzyl piperidine **14** quantitatively. The N-protection was changed to the ethoxycarbonyl group with $ClCO_2Et$ to produce the piperidine carbamate **15** in good yield. Transformation of **15** with EtONa in refluxing EtOH furnished the alcohol, which was converted into olefin **16** by the Grieco et al. protocol.[19] The overall yield of **16** from **13** was 75%. The N-protective group ($CO_2Et$) of **16** was altered to the benzoyl group at this stage to produce the benzoyl amine **17** in 61% yield.[20,21] Finally, the TBDPS group was removed with TBAF, and the resulting alcohol was oxidized with PCC to the key aldehyde **6** in good yield.

Phosphonate **7** was synthesized from commercially available **20** (Scheme 3). At the outset, **20** was converted into quinoline **21** by the literature procedure.[22] The methyl group on the ring was then oxidatively transformed into the hydroxymethyl group according to the method of Unno et al. and Isobe.[23] Remaining conversion was accomplished under the conditions presented in Scheme 3, furnishing the key quinoline **7** in 50% yield from alcohol **22**.

Condensation of the key piperidine **6** with anion derived from the quinoline **7** and NaH produced olefin **5** in 82% yield (Scheme 2). Dihydroxylation of **5** with AD-mix-β proceeded as usual and the resulting diol **18** was converted into epoxide **19**[24] in 85% yield (two steps) by using the protocol developed by Sharpless and co-workers.[10] Finally, the *N*-benzoyl group was removed and the resulting **4** underwent cyclization with the nitrogen atom in hot DMF to furnish quinine (**1**) in 66% yield from **19**. Quinine thus synthesized was identical with that obtained from Sigma by $^1H$ NMR spectroscopy and TLC analysis.




**Scheme 3.** Synthesis of quinoline phosphonate **7**: (a) $H_2SO_4$; (b) $POCl_3$; (c) Zn, AcOH; (d) *m*-CPBA, $CH_2Cl_2$, rt; (e) $Ac_2O$, rt; (f) $K_2CO_3$, MeOH; (g) $SOCl_2$, $CH_2Cl_2$, reflux; (h) H–P(=O)$(OEt)_2$, *n*-BuLi, THF.




**Scheme 4.** Synthesis of quinidine (**2**): (a) AD-mix-α, 0 °C to rt; (b) $MeC(OMe)_3$, PPTS (cat.), $CH_2Cl_2$, TMSCl, $K_2CO_3$, MeOH; (c) DIBAL-H, toluene; (d) DMF, 160 °C.

In a similar manner, olefin **5** was converted into the corresponding diol **24** with AD-mix-α, and the same transformation as described above furnished quinidine (**2**) in good yield (Scheme 4).

## Acknowledgements

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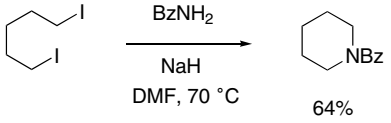
20. A model reaction of $I(CH_2)_5I$ with $BzNH_2$ and NaH successfully afforded the piperidine benzoyl amide in 64% yield. However, reaction of **13** with $BzNH_2$ under similar conditions was unsuccessful.

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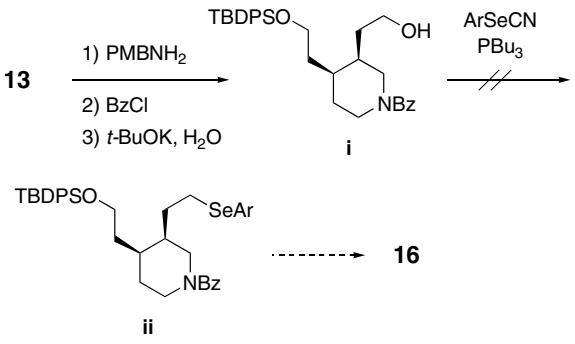
21. An attempted conversion of the *N*-benzoyl piperidine alcohol **i**, prepared from **13** by the sequence shown below, into selenide **ii** was unsuccessful in our hand.

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24. Characteristic $^1H$ NMR signals (300 MHz, $CDCl_3$) for epoxide **19** and its diastereomer synthesized through oxidation with AD-mix-α are $\delta$ 4.15 (d, $J = 1.8$ Hz) and 4.17 (d, $J = 1.8$ Hz), respectively, for proton at C(9).