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Improved synthesis of quinine alkaloids with the Teoc protective group

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Abstract—TeocCl (Teoc: $C(=O)O(CH_2)_2TMS$) generated in situ was conveniently used for trans-protection of the *N*-Bn piperidine intermediate to *N*-Teoc piperidine. Later, deprotection of the Teoc group and the subsequent quinuclidine ring formation was achieved with CsF in a domino fashion to afford the quinine alkaloids.

Recently, we have established a synthesis of the quinine alkaloids (**1** and **2** in Fig. 1).[1] The synthesis features (1) stereo- and regioselective installation of the two substituents on the cyclopentene ring of readily available **3** followed by transformation of the cyclopentene into piperidine **4**; (2) assembly of the full carbon structure from the piperidine aldehyde derived from **4** and the quinoline phosphonate; and (3) construction of the quinuclidine ring through an intramolecular epoxide ring opening by the piperidine nitrogen (Scheme 1). The high stereoselectivity thus achieved for the first time allows a secure access to analogues as well, and is advantageous over the recent syntheses of these alkaloids.[2] However, two trans-protections of the nitrogen in the piperidine ring, that is, *N*-Bn to *N*-CO_2Et and *N*-CO_2Et to *N*-COPh at the later stage, make the sequence somewhat lengthy.

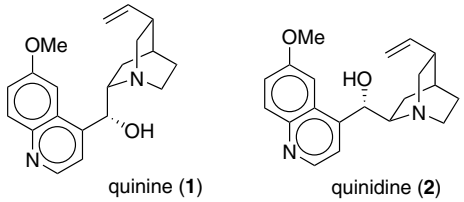
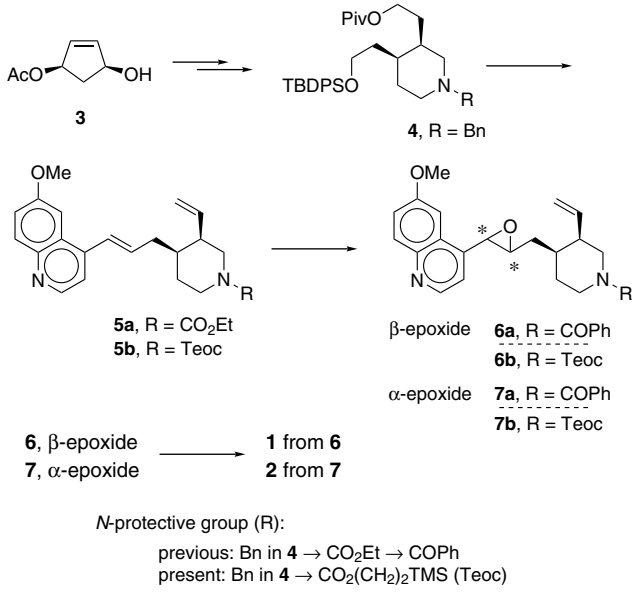


Figure 1. The structures of quinine and quinidine.



Scheme 1. Protective groups of the piperidine nitrogen used previously (Bn, CO_2Et, COPh) and presently (Bn, Teoc) in the synthesis of quinine and quinidine.

To achieve the synthesis in a shorter way, we chose the Teoc group ($CO_2(CH_2)_2TMS$) as a new protective group from those formulated as CO_2R[3] based on the fact that the *N*-Teoc group had been removed under mild conditions.[4–6] However, isolation of Teoc-Cl (**8**) is operationally intricate due to its thermal instability.[7,8] Moreover, the separation of the amine residue(s)[9] derived from

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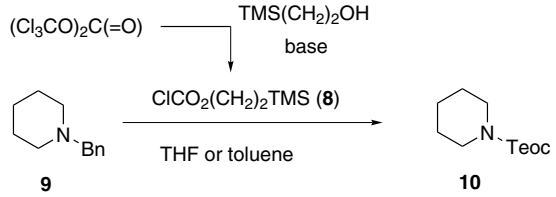
Bu_4NF used for deprotection of the *N*-Teoc group remained unsolved. Herein, we present a convenient procedure for trans-protection of *N*-Bn to *N*-Teoc and clean deprotection of the *N*-Teoc group under new conditions. By using these findings, synthesis of the quinine alkaloids was substantially revised.

Since the isolation of pure **8** is technically intricate, triphosgene[10] and $TMS(CH_2)_2OH$ was mixed in a 1:3 molar ratio in the presence of a base at room temperature for 1 h in THF, and **8** thus prepared was used for trans-protection of the model *N*-Bn piperidine **9** at room temperature overnight (Scheme 2 and Table 1). First, **8** generated with pyridine was used for the trans-protection (entry 1). However, the HCl salt of **9** was formed probably as a consequence of decomposition of the reagent **8** under the conditions applied. Next examined were *n*-BuLi, NaH, and K_2CO_3. The latter two bases afforded the desired product **10** and the HCl salt of **9** (entries 2 and 3). To quench HCl effectively, excess K_2CO_3 was used to improve the result substantially (entry 4). The K_2CO_3 version was repeated in toluene,



Scheme 2. Trans-protection of the *N*-benzyl piperidine by Teoc-Cl.

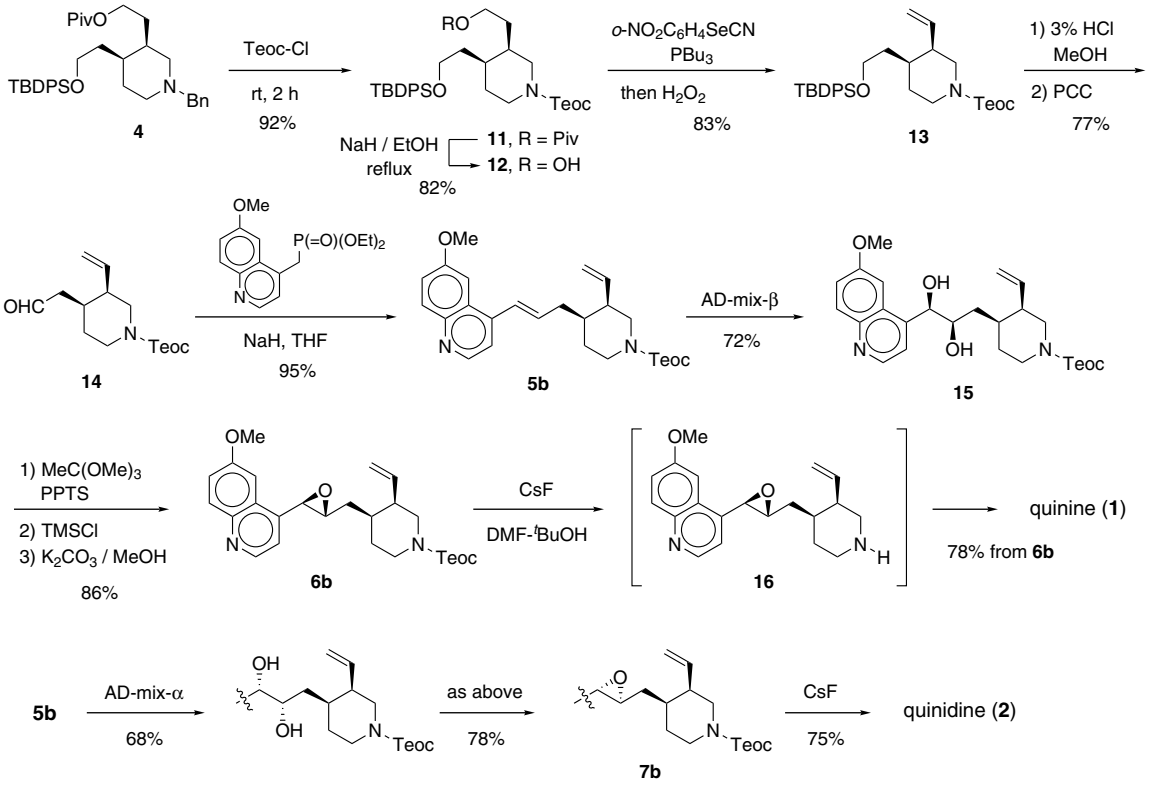
Table 1. Trans-protection of piperidine **9** into **10** with TeocCl (**8**) prepared in situ[a]

Entry	Base	Equiv	Solvent	Yield of **10** (%)
1	C_5H_5N	3	THF	0[b]
2	NaH	3	THF	45[b]
3	K_2CO_3	3	THF	85[b]
4	K_2CO_3	10	THF	98
5	K_2CO_3	3	Toluene	90
6	K_2CO_3	10	Toluene	99

[a] The reaction was carried out for 12–14 h at rt with TeocCl (**8**, 3 equiv in theory), which was prepared in situ from triphosgene (1 equiv) and $TMS(CH_2)_2OH$ (3 equiv) with a base specified.
[b] The HCl salt of **9** was produced.

which produced slightly better results than those in THF (entries 5 and 6 vs entries 3 and 4).

The best conditions found above (entry 6)[11] were applied to the real 3,4-disubstituted-*N*-Bn-piperidine **4** to produce **11** in 92% yield, which was transformed into aldehyde **14** in good yield (Scheme 3). Wittig-type reaction of **14** with the anion derived from the quinoline phosphonate and NaH furnished olefin **5b** exclusively.[12] Dihydroxylation of olefin **5b** with AD-mix-β proceeded at room temperature to obtain diol **15** in 72% yield,[12] which was converted into trans epoxide **6b** in 86% yield. In a similar way, diastereomeric epoxide **7b** was synthesized from olefin **5b** through dihydroxylation with AD-mix-α.[12] During the transformation, the Teoc group was proven to be stable under acidic, basic, and oxidative conditions. Particularly, noteworthy is the compatibility with NaOEt in refluxing EtOH used for



Scheme 3. Improved synthesis of the quinine and quinidine.

conversion of **11** to **12** and with 3% HCl in MeOH at room temperature used for deprotection of the TBDPS ($SiPh_2Bu$-*t*) of **13**.

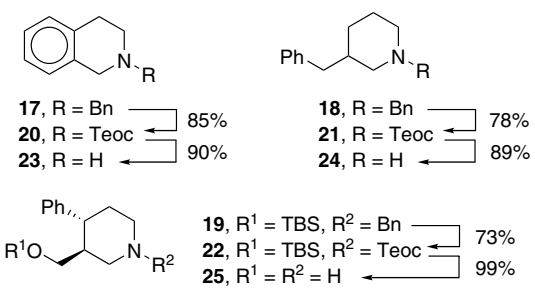
Deprotection of the Teoc group in **6b** was first carried out according to the literature procedure[7b] with Bu_4NF (3 equiv) in refluxing THF. The deprotection proceeded quite successfully as expected. However, piperidine **16** thus formed was contaminated with the chromatographically inseparable amine(s) probably attributed to amine(s) derived from Bu_4NF and/or an impurity involved in the commercial bottle.[9] The amine impurity was not separated even after its conversion to quinine (**1**).

Inorganic salts such as KF and CsF were next examined as a reagent for deprotection of the Teoc group using a model compound **10**. Reaction with KF (10 equiv) in refluxing MeCN and that in refluxing DMF proceeded marginally in both runs, and **10** was recovered unchanged. On the other hand, deprotection with CsF (5 equiv) in refluxing MeCN (bp 81 °C) was observed to a slight extent. Attempts to speed up the deprotection in other solvents such as EtCN (bp 97 °C), MeCN/DMF (9:1), and MeCN/DMI (9:1) under reflux were unsuccessful. In contrast, complete deprotection was realized with CsF (5 equiv) in DMF at 90 °C.

Keeping in mind the above conditions for deprotection of the *N*-Teoc group and the conditions for the subsequent quinuclidine ring formation by the intramolecular attack of the nitrogen to the epoxy carbon, reaction of **6b** with CsF was conducted in DMF/*t*-BuOH (9:1) at 110 °C for 12 h. The domino reaction proceeded cleanly, and quinine (**1**) was obtained in 78% yield from **6b** after chromatography on silica gel.

Similarly, diastereomeric epoxide **7b** furnished quinidine (**2**) in 75% yield upon exposure to CsF under the above reaction conditions (Scheme 3).

Finally, generality of the new protocols for the trans-protection with **8** synthesized in situ and for the CsF-promoted deprotection of the *N*-Teoc group was briefly studied. As is summarized in Scheme 4, trans-protection of *N*-Bn amines **17**–**19** in toluene at room temperature proceeded in high yields and deprotection of the *N*-Teoc amines **20**–**22** with CsF was cleanly accomplished in DMF at 90 °C for 1 h, thus allowing easy isolation of the corresponding amines **23**–**25** by chromatography.



Scheme 4.

In summary, the synthesis of quinine (**1**) and quinidine (**2**) was accomplished with the *N*-Teoc group in shorter steps and higher overall yield than those recorded in the original synthesis: with the Teoc group, nine steps from *N*-Bn piperidine **4**, 22.1% and 18.2% yields for **1** and **2**, respectively; with the original groups, 12 steps from **4**, 17.2% and 12.8% yields. Moreover, the last two reactions (deprotection and cyclization) proceeded in a domino fashion quite cleanly and efficiently with CsF.

Acknowledgements

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5. (a) Reagents/conditions used for deprotection of *N*-CO_2R groups ($CO_2CH_2CCl_3$ with Zn in AcOH,[5a] $CO_2CH(Cl)CH_3$ in MeOH,[5b–d] and $CO_2CH{=}CH_2$ with Br_2 or NBS[5e]) seemed incompatible with our strategy for synthesis of the quinine alkaloids due to hard conditions, instability of the protective group as such, and/or inconvenience of the reagent Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, 1325–1327; (b) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081–2082; (c) Gubert, S.; Braojos, C.; Sacristán, A.; Ortiz, J. A. *Synthesis* **1991**, 318–320; (d) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195–196; (e) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567–1570.
6. The Cbz group used in Jacobsen's synthesis is removed by using Et_2AlCl/thioanisole.[2b]

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8. In practice, temperatures below +40 °C are recommended[7a] for the preparation of **8** from phosgene and $TMS(CH_2)_2OH$ and isolation of **8** was carried out by distillation into a liquid nitrogen trap without heating.[7b]
9. Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F. *J. Org. Chem.* **1990**, *55*, 5324–5335.
10. While a solution of phosgene in toluene was used previously,[7a] solid triphosgene was studied to carry out the reaction in a safer way.
11. General procedure: To a solution of 2-trimethylsilylethanol (0.088 μL, 0.62 mmol) and potassium carbonate (283 mg, 2.05 mmol) in toluene (0.7 mL) at 0 °C was added triphosgene (61 mg, 0.21 mmol) in toluene (0.7 mL) dropwise. The mixture was stirred at room temperature for 1 h, and re-cooled to 0 °C. To this was added a solution of **9** (36 mg, 0.21 mmol) in toluene (0.7 mL) at −20 °C. The mixture was stirred at room temperature for 2 h. The reaction mixture was poured into saturated $NaHCO_3$, and the mixture was extracted with EtOAc twice. The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography of the residue (hexane/EtOAc = 10:1) afforded the desired product **10** (47 mg, 99%).
12. The stereoisomer and the starting compound were not detected by ^1H NMR spectroscopy and TLC analysis.