Easy Access to 9-Epimers of Cinchona Alkaloids: One-Pot Inversion by Mitsunobu Esterification–Saponification

Łukasz Sidorowicz, Jacek Skarżewski*

Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, 50-370 Wrocław, Poland
Fax +48(71)3284064; E-mail: jacek.skarzewski@pwr,wroc.pl

Received 22 November 2010; revised 10 January 2011

Abstract: Cinchona alkaloids were efficiently converted into their 9-*epi* diastereomers. The applied one-pot procedure was based on the Mitsunobu esterification with 4-nitrobenzoic acid followed by in situ saponification of the ester. This method requires only one column chromatography, easily separating the *epi*-isomer from the native alkaloid and the Mitsunobu byproducts. The procedure gives higher yields and is operationally simpler than the previously used stereoselective hydrolysis of the corresponding sulfonic acid esters.

Key words: cinchona alkaloids, Mitsunobu reaction, inversion, alcohols, chiral pool

Easily available cinchona alkaloids, namely quinine (QN), quinidine (QD), cinchonine (CN), and cinchonidine (CD), (Figure 1) enjoy much interest as privileged catalysts, effective in numerous mechanistically different, enantioselective transformations.[1] Their additional advantage comes from the fact that they constitute near enantiomers. Often, the formation of the opposite stereoisomer of the product can be achieved using such pseudoenantiomeric catalysts.

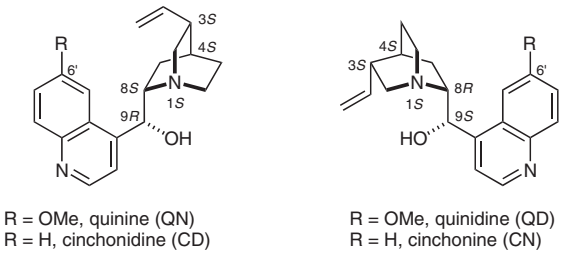
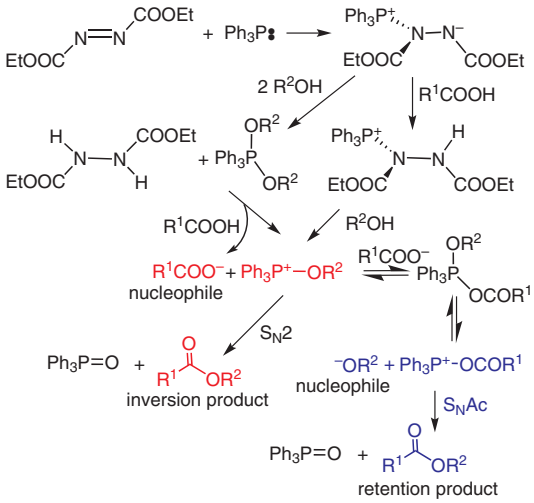


Figure 1

Their stereodifferentiating properties are mainly determined by configurations at the C8/C9 stereogenic centers.[1] Thus for the native, 8,9-*unlike* isomers, e.g. (8*S*,9*R*)-QN, the *anti-closed* conformation dominates, locating both the quinuclidine nitrogen atom and 9-hydroxy group far away from each other. In contrast, 9-*epi*-alkaloids (8,9-*like* isomers) form preferential conformations with both functionalities located closely, forming an intramolecular hydrogen bond that is absent in the native alkaloids.[2] Essentially, the unnatural alkaloids of 9-*epi*-configuration are available by the tartaric acid catalyzed hydrolysis of tosylates or mesylates of the native epimers.[3] However, in spite of recent improvements[3b] in the original Suszko method,[3a] the whole procedure is rather tedious, requiring two separate chromatographic purifications.

For our ongoing project on the synthesis of various chalcogen derivatives of cinchona alkaloids[4] we often needed gram amounts of the 9-*epi*-alkaloids. In order to simplify their preparation we decided to examine a classical method for the inversion of chiral secondary alcohols, i.e. the Mitsunobu esterification and subsequent ester hydrolysis.[5] In spite of the high reputation of this well-established approach, there were also numerous reports on the esterification/hydrolysis sequence resulting in the retention of configuration. It especially happened for sterically hindered secondary alcohols, where the oxophosphonium activation of carboxylic acid prevails over that of the alcohol and the alcohol acts as a nucleophile (Scheme 1).[6]



Scheme 1 The simplified mechanism of the Mitsunobu esterification, for details, see ref. 6

The database screening revealed that the application of the Mitsunobu method to the inversion of cinchona alkaloids has not been reported as yet. On the other hand, the Mitsunobu reaction has already been used with these alkaloids for the preparation of azides/primary amines (HN_3 pK_a 4.72, Ph_3P, DIAD, followed by in situ reduction with Ph_3P; 45–65% yield)[7] and thioacetates (AcSH pK_a 3.33, Ph_3P, DEAD; 44–59% yield).[4c] Both reactions worked well, giving selectively the S_N2-type products in fair to

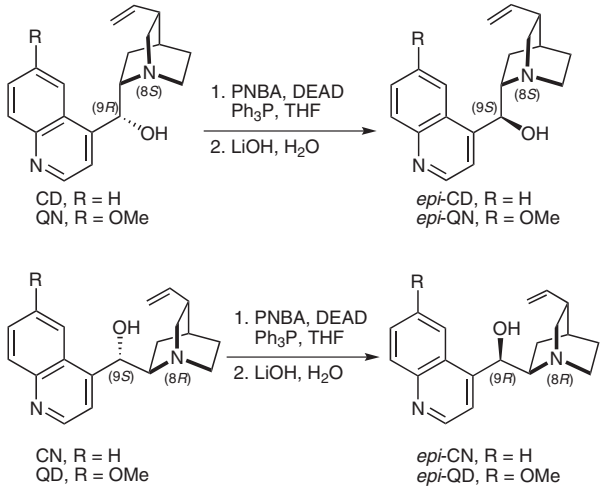
SYNTHESIS 2011, No. 5, pp 0708–0710
Advanced online publication: 31.01.2011
DOI: 10.1055/s-0030-1259483; Art ID: T22410SS

Table 1 Inversion of Cinchona Alkaloids by Mesyl Ester Hydrolysis and Mitsunobu Esterification/Saponification[a]

Alkaloid (R_f)[b]	*epi*-Alkaloid (R_f)[b]	*epi*-Alkaloid, this work		*epi*-Alkaloid, two steps	
		Yield (%)	$[\alpha]_D^{20}$ (EtOH)	Total yield (%)	$[\alpha]_D^{20}$ (EtOH)
QN (0.204)	*epi*-QN (0.575)	85	+39.2 (*c* 0.90)	74,[4c] 71[3b]	+39.5 (*c* 0.96)[4c]
QD (0.186)	*epi*-QD (0.584)	79	+96.5 (*c* 0.60)	68,[4c] 68[3b]	+96.9 (*c* 1.12)[4c]
CN (0.168)	*epi*-CN (0.602)	45	+113.8 (*c* 0.53)	48[8b]	+114.5 (*c* 1.07)[9]
CD (0.159)	*epi*-CD (0.611)	62	+55.1 (*c* 0.54)	66,[4c] 38[8a,b]	+55.6 (*c* 0.80)[4c]

[a] Reaction conditions: PNBA (1.1 equiv), DEAD (1.2 equiv), Ph_3P (1.3 equiv), then LiOH (5 equiv). For the details, see the experimental section.
[b] Eluent: $CHCl_3$–MeOH–Et_3N, 40:1:4.

good yields regardless whether the substrate was used in either native or *epi* configuration. However, it should be noted that the nucleophiles that have been used were much stronger than the carboxylate (carboxylic acid anion) needed for esterification.



Scheme 2

We decided to examine the standard esterification of the native alkaloids with 4-nitrobenzoic acid (PNBA pK_a 3.44). The first experiment performed with quinine (QN) [PNBA (1.1 equiv), DEAD (1.2 equiv), Ph_3P (1.3 equiv), 0 °C] gave the crude product containing 72% of the *epi*-ester, 3% of the ester of native configuration, and 9-*epi*-quinine (10%), along with native quinine (9%). The sample composition was evaluated by integration of the low-field ^{1}H NMR resonances originating from the respective 2′-quinoline hydrogen atoms. The inverted quinine ester was isolated, fully characterized, and compared with the separately synthesized 4-nitrobenzoic acid ester of native quinine. Both compounds were prone to hydrolysis which explains the presence of *epi*-quinine and quinine in the crude product. Taking into account the steric hindrance around the 9-hydroxy group we considered this outcome as quite satisfactory. In turn, all four alkaloids were esterified in the same manner and subsequently the obtained mixtures were treated in situ with aqueous 1 M lithium hydroxide solution. The reaction products were easily purified by column chromatography resulting in samples of analytical purity (Scheme 2). It is noteworthy that the native and *epi* alkaloids markedly differ in their R_f values (Table 1), thus they are easily separated by chromatography on silica gel. Our present results are compared (Table 1) with the highest reported yields of the literature procedures (the preparation and inversions of mesylates in two separate steps, both requiring chromatography). While quinine and quinidine were inverted in high yield, improved against the previous method, both cinchonine and cinchonidine gave yields similar to the former two-step method. Nevertheless, it is noteworthy that the present one-pot inversion procedure requires only one column chromatography, easily separating the *epi*-isomer from the native one and the Mitsunobu byproducts.

In order to further examine the applied reaction conditions we tested the influence of solvents, acids, and amounts of the reagents. Thus, attempting to improve the yield of cinchonine inversion, instead of tetrahydrofuran we used pyridine, toluene, or *N*,*N*-dimethylformamide getting 40, 22, and 15% of *epi*-cinchonine, respectively. For all four alkaloids the experiments using 3,5-dinitrobenzoic acid or chloroacetic acid with diethyl azodicarboxylate (1.2 equiv) and triphenylphosphine (1.3 equiv) in tetrahydrofuran at 0 °C for 72 hours did not improve our previous results. Improved yields were also not observed with doubled amount of PNBA/DEAD/Ph_3P in tetrahydrofuran at 0 °C for 24 hours.

In summary, the developed one-pot procedure for the Mitsunobu PNBA esterification followed by ester saponification can be recommended as an operationally simple and quick procedure for the inversion of configuration at the 9-stereogenic centers of cinchona alkaloids.

All solvents were purified and dried by standard methods. The starting cinchona alkaloids were commercially available and were used after drying by azeotropic distillation with toluene. Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker CPX (^{1}H, 300 MHz) spectrometer using TMS as internal standard. Optical rotations at 578 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. HRMS were recorded on a Waters LCT Premier XE (TOF/ESI) apparatus. Silica gel (60–120 mesh) was used for chromatographic separation. Separations of

products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck. TLC was performed using silica gel 60 precoated plates (Merck).

9-*epi*-Quinine 4-Nitrobenzoic Acid Ester

A stirred suspension of quinine (1.0 mmol, 324.4 mg), Ph_3P (1.3 mmol, 262.3 mg), and PNBA (1.1 mmol, 183.8 mg) in anhyd THF (10 mL) was placed in an ice-water bath for 10 min. Then DEAD (1.1 mmol, 171 μL) was added dropwise via syringe. After the addition of DEAD, the homogenic mixture was stirred at 0 °C for 20 min, then at r.t. overnight. The solvent was removed in vacuo and the crude product was isolated by column chromatography (EtOAc) giving after vacuum drying an oil (353 mg, 74%); R_f = 0.118 (EtOAc).

$[\alpha]_D^{20}$ –79.9 (*c* 0.8, CH_2Cl_2).

IR: 2938, 1723, 1621, 1526, 1268, 1102, 718 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.81–0.86 (m, 1 H), 1.42–1.51 (m, 1 H), 1.52–1.61 (m, 2 H), 1.62–1.69 (m, 1 H), 2.25–2.32 (m, 1 H), 2.71–2.83 (m, 2 H), 3.21 (dd, *J* = 14.01, 10.2 Hz, 1 H), 3.29–3.41 (m, 1 H), 3.59 (q, *J* = 9.3 Hz, 1 H), 3.99 (s, 3 H), 4.95–5.05 (m, 2 H), 5.75–5.87 (m, 1 H), 6.72 (d, *J* = 10.2 Hz, 1 H), 7.38 (dd, *J* = 9.3, 2.7 Hz, 1 H), 7.50 (d, *J* = 4.5 Hz, 1 H), 7.64 (d, *J* = 2.7 Hz, 1 H), 8.02 (d, *J* = 9.3 Hz, 1 H), 8.14–8.24 (m, 4 H), 8.77 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.2, 158.3, 150.6, 147.6, 145.0, 141.6, 141.0, 135.5, 132.0, 131.0, 127.8, 123.5, 122.0, 120.5, 114.6, 101.6, 72.5, 59.3, 56.1, 55.7, 41.4, 39.6, 28.0, 27.3, 25.3.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{28}N_3O_5$: 474.2029; found: 474.2041.

Quinine 4-Nitrobenzoic Acid Ester

PNBA (167 mg, 1 mmol) and $SOCl_2$ (2.0 mL) placed in a 2-neck round-bottom flask were refluxed for 3 h and excess $SOCl_2$ was removed in vacuo. After drying for 2 h in vacuo CH_2Cl_2 (5.0 mL) was added. The round-bottom flask was secured with drying tube ($CaCl_2$), cooled in an ice bath, Et_3N (210 μL, 1.5 mmol), and then quinine (1.0 mmol, 342 mg) in CH_2Cl_2 (5.0 mL) were added dropwise. The mixture was stirred 15 min at 0 °C, then overnight at r.t. The resulting mixture was washed with H_2O (2 ×) and brine (1 ×), and dried (Na_2SO_4). The solvent was evaporated in vacuo and the product was isolated by column chromatography (silica gel, EtOAc) yielding the ester (298 mg, 63%); mp 151–153 °C ($CHCl_3$–hexane); R_f = 0.091 (EtOAc).

$[\alpha]_D^{20}$ +150.0 (*c* 0.5, CH_2Cl_2).

IR: 2941, 1727, 1621, 1527, 1268, 1100, 718 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.70 (m, 3 H), 1.85–2.05 (m, 2 H), 2.25–2.35 (m, 1 H), 2.60–2.75 (m, 2 H), 3.05–3.20 (m, 2 H), 3.55 (q, *J* = 2.1 Hz, 1 H), 3.98 (s, 3 H), 5.00–5.10 (m, 2 H), 5.80–5.92 (m, 1 H), 6.75 (d, *J* = 7.20 Hz, 1 H), 7.38 (dd *J* = 9.3, 2.7 Hz, 1 H), 7.42 (d, *J* = 4.5 Hz, 1 H), 7.50 (d, *J* = 2.7 Hz, 1 H), 8.02 (d, *J* = 9.3 Hz, 1 H), 8.20–8.33 (m, 4 H), 8.74 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 163.9, 158.1, 150.8, 147.5, 144.9, 143.0, 141.6, 135.1, 132.0, 130.8, 127.0, 123.8, 121.9, 118.8, 114.8, 101.4, 75.4, 59.4, 56.7, 55.7, 42.6, 39.6, 28.0, 27.6, 24.6.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{28}N_3O_5$: 474.2029; found: 474.2041.

Inversion of Cinchona Alkaloids; General Procedure

To a stirred suspension of the alkaloid (1 mmol), Ph_3P (1.3 mmol) and PNBA (1.1 mmol) in THF (10 mL) placed in an ice-water bath was added DEAD (1.1 mmol) dropwise via syringe. The mixture was stirred at 0 °C for 20 min, at r.t. for 3 h, and then again cooled to 0 °C. 1 M LiOH in H_2O (5.0 mL) and MeOH (1.0 mL) were added and the mixture was stirred at r.t. overnight. Organic solvents were evaporated in vacuo and the residue was quenched with H_2O (5 mL) and CH_2Cl_2 (15 mL). The organic phase was separated, washed with brine, and dried (K_2CO_3). The solvent was removed in vacuo and the product was purified by column chromatography [silica gel, 1. $CHCl_3$–*t*-BuOMe, 3:1 (to remove Ph_3PO and most of the diethyl hydrazine-1,2-dicarboxylate), then 2. $CHCl_3$–MeOH–Et_3N, 40:1:4 (to isolate the corresponding *epi*-alkaloid)].

When the above procedure was scaled up to 1 g of the alkaloid (ca. 3 mmol), all the reagents but THF solvent (15 mL) were used in triplicate amounts.

Acknowledgment

We are grateful to the Polish Ministry of Science and Higher Education for financial support; Grant No. N204 161036. Ł.S. thanks for a fellowship co-financed by European Union within European Social Fund.

References

(1) (a) Kacprzak, K.; Gawroński, J. *Synthesis* **2001**, 961. (b) Hoffmann, H. M. R.; Frackenpohl, J. *Eur. J. Org. Chem.* **2004**, 4293. (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Connon, S. J. *Chem. Commun.* **2008**, 2499. (e) *Cinchona Alkaloids in Synthesis and Catalysis, Ligands, Immobilization and Organocatalysis*; Song, C. E., Ed.; Wiley-VCH: Weinheim, **2009**. (f) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229.

(2) Caner, H.; Biedermann, P. U.; Agranat, I. *Chirality* **2003**, *15*, 637; and refs cited therein.

(3) (a) Suszko, J.; Szeląg, F. *Bull. Int. Acad. Pol. Sci. Lett. Cl. Sci. Math. Nat., Ser. A* **1936**, 403; *Chem. Abstr.* **1937**, *31*, 1816. (b) Braje, W. M.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2085.

(4) (a) Zielińska-Błajet, M.; Kucharska, M.; Skarżewski, J. *Synthesis* **2006**, 1176. (b) Zielńska-Błajet, M.; Siedlecka, R.; Skarżewski, J. *Tetrahedron: Asymmetry* **2007**, *18*, 131. (c) Zielińska-Błajet, M.; Skarżewski, J. *Tetrahedron: Asymmetry* **2009**, *20*, 1992.

(5) (a) Mitsunobu, O.; Kimura, J.; Fujisawa, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 245. For general reviews on the Mitsunobu reaction, see: (b) Mitsunobu, O. *Synthesis* **1981**, 1. (c) Huges, D. L. *Org. React.* **1992**, *42*, 335. (d) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763. (e) But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340. (f) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551.

(6) (a) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967. (b) Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2005**, *70*, 3079. (c) Schenk, S.; Weston, J.; Anders, E. *J. Am. Chem. Soc.* **2005**, *127*, 12566.

(7) (a) Brunner, H.; Bügler, J. *Bull. Soc. Chim. Belg.* **1997**, *106*, 77. (b) For a recent example, see: Kacprzak, K.; Gierczyk, B. *Tetrahedron: Asymmetry* **2010**, *21*, 2740.

(8) (a) Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *J. Org. Chem.* **2003**, *68*, 4944. (b) Franz, M. H.; Röper, S.; Wartchow, R.; Hoffmann, H. M. R. *J. Org. Chem.* **2004**, *69*, 2983.

(9) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053.