Asymmetric Synthesis of (–)-Porantheridine

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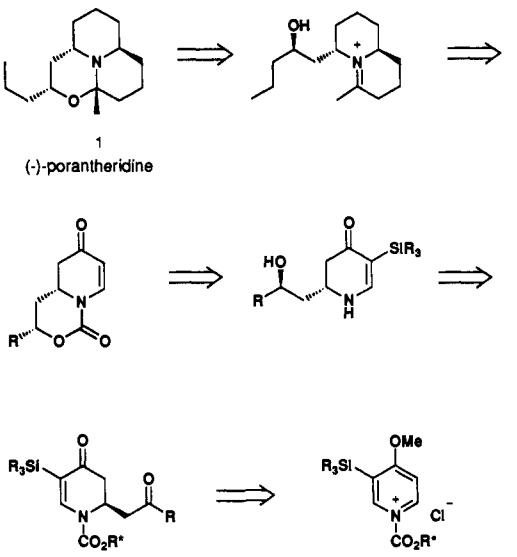
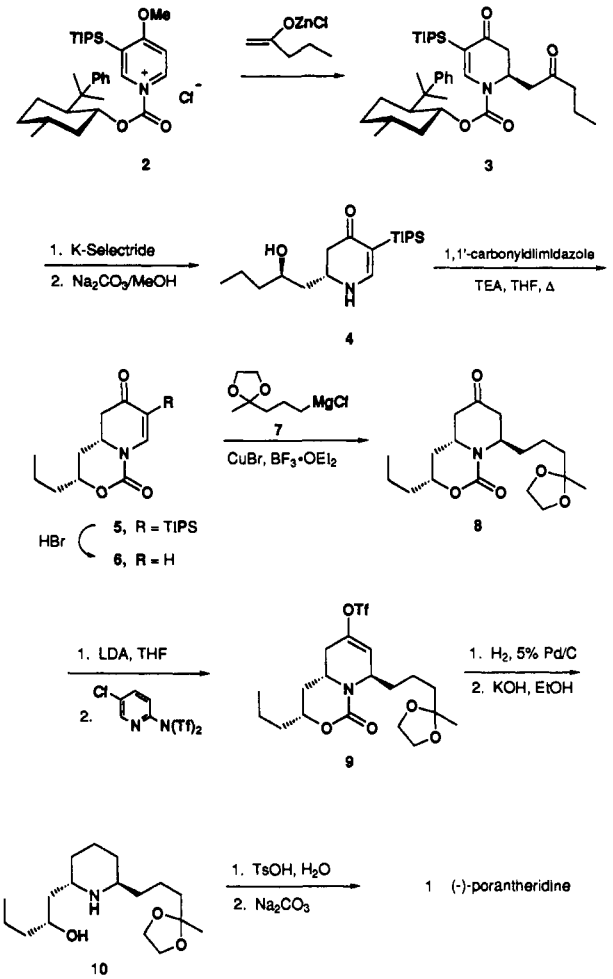
Porantheridine, a novel alkaloid of *Poranthera corymbosa* isolated by Denne and co-workers, has been shown by X-ray crystallography to possess structure **1**.[1] We report herein the first enantioselective synthesis[2] of this interesting tricyclic alkaloid utilizing a modification of our recently developed asymmetric synthesis of 1-acyl-2,3-dihydropyridones.[3] The synthetic plan followed the retrosynthetic analysis shown in Scheme I.

We envisioned the first intermediate arising from the addition of a metallo enolate to a chiral 1-acylpyridinium salt. Although Grignard reagents[3] and (triphenylsilyl)magnesium bromide[4] have been added to certain chiral 1-acylpyridinium salts with high diastereoselectivity, the analogous asymmetric reaction using metallo enolates had not been investigated.[5] The pyridinium salt **2** was prepared *in situ* from 4-methoxy-3-(triisopropylsilyl)-pyridine[3a] and the chloroformate of (–)-8-phenylmenthol.[6] Addition of the zinc enolate of 2-pentanone (3 equiv; LDA, $ZnCl_2$/Et_2O, THF, –78 °C) gave after acidic workup and purification the dihydropyridone **3**, mp 83–84 °C, in 89% yield (Scheme II). Analysis of the crude product showed that the reaction proceeded with a diastereoselectivity of 92%. The absolute stereochemistry of the newly formed stereogenic center at C-2 of **3** was assigned the *R* configuration by comparison of its ^1H NMR spectrum with spectra of similar compounds of known configuration.[3] The direction of asymmetric induction is the same as that observed in the reaction of **2** with Grignard reagents.[3] We believe that the mechanism responsible for the stereocontrol is similar to that proposed for the Grignard reaction of **2**, being one of steric approach control.[3a] Stereoselective reduction (>96% de) of **3** with K-Selectride (1.25 equiv, THF, –78 °C), followed by treatment of the crude product with Na_2CO_3/MeOH (reflux, 6 h), gave an 89% yield of hydroxydihydropyridone **4** [mp 136–137 °C; $[\alpha]^{23}_D$ +216° (*c* 1.5, $CHCl_3$)] and recovered (–)-8-phenylmenthol (89%) after chromatography (silica gel, 20% EtOAc/hexanes). Both the C-2 carbon and the carbinol carbon of **4** possessed the *R* configuration as determined by NMR and single-crystal X-ray analysis. The bicyclic carbamate **5** was prepared from **4** in 91% yield using 1,1′-carbonyldiimidazole (THF, TEA, reflux). The triisopropylsilyl (TIPS) group was removed with 30% HBr/HOAc in CH_2Cl_2 (room temperature, 24 h) to provide **6**, mp 103–104 °C, in 92% yield. Copper-mediated 1,4-addition of Grignard reagent **7**[7] (CuBr, BF_3·OEt_2, THF, –78 °C) to **6** gave *trans*-piperidone **8** as an oil in 81% yield. The trans product was anticipated on the basis of stereoelectronically preferred axial

Scheme I



Scheme II



(1) Denne, W. A.; Johns, S. R.; Lamberton, J. A.; Mathieson, A. M.; Suares, H. *Tetrahedron Lett.* **1972**, 1767.

(2) A racemic synthesis of porantheridine has been reported, see: Gössinger, E. *Tetrahedron Lett.* **1980**, *21*, 2229; *Monatsh. Chem.* **1980**, *111*, 783.

(3) (a) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. (c) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672. (d) Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197. (e) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807. (f) Al-awar, R.; Joseph, S. P.; Comins, D. L. *Tetrahedron Lett.* **1992**, *33*, 7635.

(4) Comins, D. L.; Killpack, M. O. *J. Am. Chem. Soc.* **1992**, *114*, 10972.

(5) For the addition of metallo enolates to achiral 1-acylpyridinium salts, see: (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1984**, *25*, 3297. (b) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 2219. (c) Courtois, G.; Al-arnaout, A.; Migintac, L. *Tetrahedron Lett.* **1985**, *26*, 1027.

(6) (a) Optically pure (–)-8-phenylmenthol was purchased from Aldrich Chemical Co. or prepared according to a literature procedure: Ort, O. *Org. Synth.* **1987**, *65*, 203. (b) The chloroformate of (–)-*trans*-2-(α-cumyl)-cyclohexanol ((–)-TCC) can be used with equal effectiveness. Comins, D. L.; Salvador, J. M. *Tetrahedron Lett.* **1993**, *34*, 801. (c) For an excellent review on cyclohexyl-based chiral auxiliaries, see: Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

(7) The Grignard reagent was prepared in the usual manner in THF from the commercially available chloride (Aldrich Chemical Company, Inc.). Feugeas, C.; Normant, H. *Bull. Soc. Chim. Fr.* **1963**, 1441.

(8) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 6.

0002-7863/93/1515-8851$04.00/0

addition to the enone of **6**.[8] The crude product contained the trans and cis diastereomers in a ratio of 95:5.

At this stage, the synthetic plan called for reductive deoxygenation of the ketone carbonyl of **8**. This was accomplished by catalytic hydrogenation[9] of the intermediate vinyl triflate **9**, prepared using LDA and *N*-(5-chloro-2-pyridyl)triflimide.[10] The crude vinyl triflate[11] was reduced in the presence of Li_2CO_3 (H_2, 5% Pd/C, EtOAc, 1 atm) to provide the corresponding piperidine in 77% overall yield for the two steps. Subsequent hydrolysis (KOH, EtOH, reflux, 2 days) gave the amino alcohol **10** as a colorless oil [$[\alpha]^{23}_D$ −10.2° (*c* 0.53, $CHCl_3$)] in 85% yield. The final step of the synthesis was carried out by treating **10** with $TsOH \cdot H_2O$ in benzene (1 equiv, reflux, 3 h; 4-Å molecular sieves, reflux, 3 h). Workup with Na_2CO_3 and chromatographic purification gave (−)-porantheridine (**1**) as a colorless oil (66%), which had a specific rotation and NMR data completely in agreement with literature data;[12,13] $[\alpha]^{23}_D$ −26.1° (*c* 0.38, $CHCl_3$) [lit[1] $[\alpha]_D$ −26° (*c* 0.5, $CHCl_3$)].

The first asymmetric synthesis of porantheridine has been accomplished in eight steps and 23% overall yield from readily available 4-methoxy-3-(triisopropylsilyl)pyridine. The chiral auxiliary, (−)-8-phenylmenthol, was recovered in high yield early in the synthesis. The formation of each of the four stereogenic centers was carried out with a high degree of stereocontrol, greater than 90% diastereoselectivity for each reaction. The conciseness of this synthesis and the stereocontrol obtained demonstrate the potential of metallo enolate addition to chiral 1-acylpyridinium salts for the enantioselective preparation of various alkaloids. The scope of this reaction and its application toward the asymmetric synthesis of other natural products are under study in our laboratories.

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Supplementary Material Available: Listings of full spectroscopic and analytical characterization of **1**, **3–6**, and **8–10**, an ORTEP drawing of **4**, and tables of X-ray crystallographic data, including thermal and positional parameters, bond lengths, and bond angles for **4** (17 pages). Ordering information is given on any current masthead page.

(9) (a) Jigajinni, V. B.; Wightman, R. H. *Tetrahedron Lett.* **1982**, *23*, 117. (b) Subramanian, L. R.; Martínez, A. G.; Fernández, A. H.; Álvarez, R. M. *Synthesis* **1984**, 481. (c) See ref 3b.

(10) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(11) The crude vinyl triflate **9** contained approximately 10% of the regioisomeric olefin.

(12) The spectral properties of (−)-**1** were in agreement with reported data.[1,2] See supplementary material.

(13) All new compounds were spectroscopically characterized and furnished satisfactory elemental analyses (C, H, N, ±0.4%) or high-resolution mass spectra. Details are provided in the supplementary material.