Efficient Total Synthesis of Enantiopure (−)-Porantheridine

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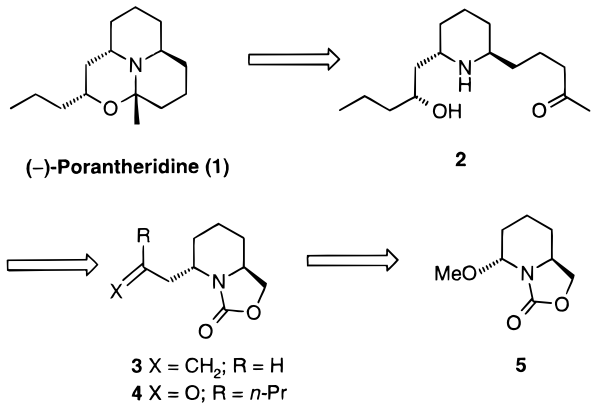
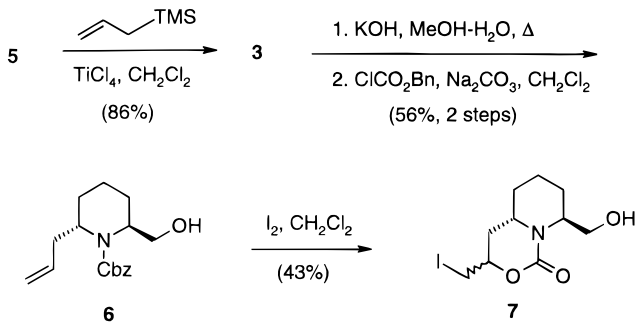
The tricyclic alkaloid (−)-porantheridine (**1**) was first isolated by J. A. Lamberton and co-workers in 1972 from the Australian bush *Poranthera corymbosa*.[1] Its absolute configuration was determined by X-ray analysis[1] and ascertained by the asymmetric synthesis completed by D. Comins and H. Huong in 1993.[2] We disclose herein a new approach to this alkaloid. Based on the retrosynthetic analysis shown in Scheme 1, compound **1** was viewed as resulting from an intramolecular cyclization of piperidine hydroxyketone **2** via a transient bicyclic iminium ion, as previously described.[2,3] The stereoselective elaboration of the 2-hydroxypent-1-yl lateral chain of compound **2** was expected to proceed with some level of 1,3-asymmetric induction, through chemical manipulation of the double bond of the allylic group of intermediate **3**, via either a diastereoselective epoxidation or an intramolecular halocyclocarbamation. Alternatively, diastereoselective reduction of ketone **4** was considered as a backup route to access intermediate **2**. In this strategy, the stereochemical issues were totally solved provided that **3** or **4** could be obtained in an enantiopure form. To fulfill this requirement, we envisioned that our recently introduced stereoselective preparation of trans 2,6-disubstituted piperidines[4] was particularly well suited. This approach indeed features a totally stereoselective nucleophilic substitution of the methoxy group of bicyclic amino ether **5**, via the corresponding *N*-acyl iminium ion.[4]

Substrate **5**, which was obtained from L-lysine through an electromethoxylation key step, smoothly reacted with allyltrimethylsilane in the presence of $TiCl_4$, to afford the corresponding derivative **3** in multigram scale.[4] Unfortunately, treatment of **3** with *m*-CPBA yielded a 1:1 diastereomeric mixture of the corresponding epoxides. On the other hand, to overcome this lack of facial selectivity and based on previous reports on the high level of 1,3-asymmetric induction in intramolecular iodocyclocarbamation,[5] we attempted such a reaction on intermediate **6**, derived from compound **3** in two steps (Scheme 2). However, in our case, treatment of **6** with iodine gave a disappointing 1:1 diastereomeric mixture of iodooxazinones **7** in modest yield.

Scheme 1



Scheme 2



These poor results prompted us to examine the elaboration of the (2*R*)-hydroxypent-1-yl group via a two-step sequence. The first step required the installation of the 2-oxopent-1-yl chain from **5**, by direct nucleophilic displacement of the methoxy group using 2-(trimethylsilyloxy)pent-1-ene[6] as the nucleophile. As previously reported for other silyl enol ethers,[4] this reaction was expected to proceed with high diastereoselectivity to deliver trans 2,6-disubstituted piperidine **4**. In the second step, the carbonyl function in **4** was expected to be reduced diastereoselectively. However, this first approach was rapidly abandoned insofar as the 92:8 mixture of the regioisomeric silyl enol ethers generated from pentan-2-one[7] afforded, in turn, upon reaction with **5**, a mixture of regioisomers, which could not be separated. We then decided to prepare ketone **4** according to a two-step procedure (Scheme 3). Treatment of substrate **5** with silyl enol ethers **8**, readily available from ethyl butyryl acetate,[8] in the presence of TMSOTf, afforded piperidine derivatives **9** in 90% yield. As anticipated, this reaction occurred with total stereochemical control of the center α to the nitrogen atom, to deliver exclusively the trans 2,6-disubstituted piperidine moiety, and with no control at the α position of the β-ketoester substituent. Subsequent decarbethoxylation of this epimeric mixture afforded the desired bicyclic ketone **4** in 91% yield. Various reductive conditions[9] were then screened from **4** in order

(1) Denne, W. A.; Johns, S. R.; Lamberton, J. A.; Mathieson, A. McL.; Suares, H. *Tetrahedron Lett.* **1972**, *18*, 1767−1770.
(2) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851−8852.
(3) Gössinger, E. *Tetrahedon Lett.* **1980**, *21*, 2229−2232.
(4) David, M.; Dhimane, H.; Vanucci-Bacqué, C.; Lhommet, G. *Synlett* **1998**, 206−208.
(5) Wang, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465−6466.
(6) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300−304.
(7) Xie, L.; Saunders: W. H. *J. Am. Chem. Soc.* **1991**, *113*, 3123−3130.
(8) (a) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830−846. (b) Kusnezowa, I. K.; Michael, G.; Rühlmann, K. *J. Prakt. Chem.* **1976**, *318*, 413−419.

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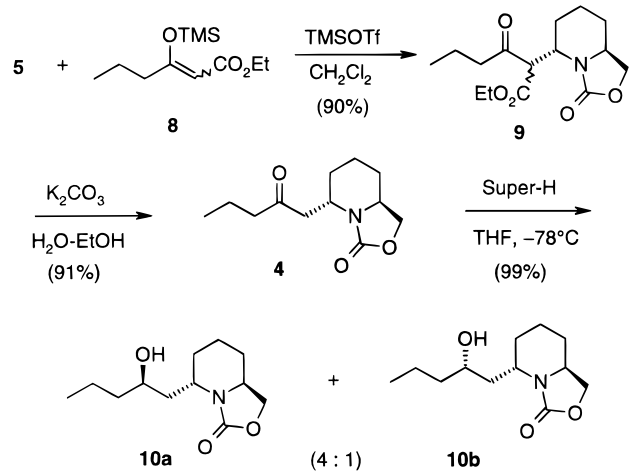
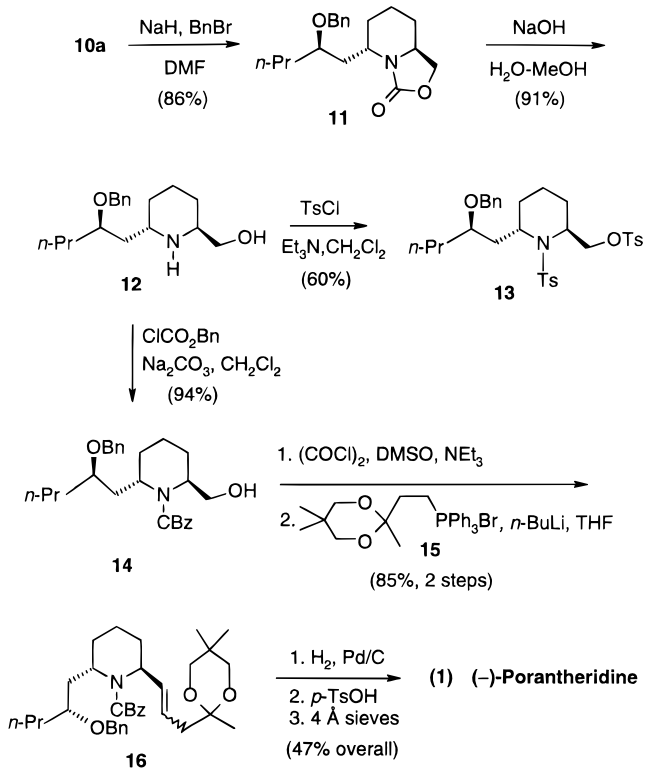
Scheme 3



to obtain selectively alcohol **10a** with an (*R*) configuration at the resulting new chiral center. The best results were obtained with trialkylborohydride, i.e., potassium tri-*sec*-butylborohydride (K-Selectride) or lithium triethylborohydride (Super-H) which gave a 4:1 mixture of alcohols **10a** and **10b**, in quantitative yield. Fortunately, the two epimers were easily separated by column chromatography. Their stereochemistries were established based on the X-ray analysis of the minor isomer **10b**, which was isolated as a crystalline solid. Noteworthy was the obtention of a reverse diastereoselectivity[10] upon treatment of ketone **4** with DIBAL-H.

Installation of the required 4-oxopent-1-yl moiety (see **2**) was envisioned by chain elongation of the hydroxymethyl group resulting from the opening of the oxazolidinone moiety of **10a**, following the benzylation of the free hydroxy group (Scheme 4). The required benzyl ether **11** was prepared in 86% yield from alcohol **10a** and then refluxed in a methanolic aqueous NaOH solution to deliver the corresponding amino alcohol **12** in 91% yield. At that point, we decided to introduce the 4-oxopent-1-yl appendage via a nucleophilic substitution of the corresponding tosylate by an appropriate organocuprate reagent. Bis-sulfonylation of amino alcohol **12** in the presence of tosyl chloride and Et_3N afforded in 60% yield derivative **13**, where the nitrogen atom has been protected[11] and the alcohol has been activated for nucleophilic substitution. Compound **13** was subsequently treated with a large excess of the cuprate species generated from the Grignard reagent of 4-bromo-2-butanone neopentyl glycol ketal and cuprous bromide.[12] Unfortunately, only the starting material was recovered along

Scheme 4



with the corresponding bromide. We then envisioned the formation of the desired carbon−carbon bond through a Wittig reaction. To this end, we first protected the amino function of compound **12** as a benzyl carbamate in 94% yield. Alcohol **14** was then oxidized under Swern conditions, and the resulting crude aldehyde thus obtained was subsequently involved in a Wittig reaction with the ylide, generated in situ from triphenylphosphonium bromide **15**.[13] The resulting olefin **16**[14] was isolated in 85% overall yield starting from alcohol **14**. Hydrogenation of the carbon−carbon double bond and reductive cleavage of both benzyloxy groups of compound **16** proceeded under an atmospheric pressure of hydrogen in the presence of Pd/C. The resulting ketal was then reacted under acid conditions to afford, via a tandem ketal cleavage/cyclization, the expected (−)-porantheridine **(1)**, as the free base in 47% overall yield, after neutralization with Na_2CO_3. An analytical sample of this material displayed ^{13}C and ^1H NMR spectra identical to those of synthetic racemic porantheridine.[3] The optical rotation was determined to be $[\alpha]^{19}_D = -25°$ (*c* 0.50, $CHCl_3$), in good agreement with those obtained previously for natural[1] and synthetic[2] (−)-porantheridine, namely $[\alpha]_D = -26°$ (*c* 0.57, $CHCl_3$) and $[\alpha]^{23}_D = -26.1°$ (*c* 0.38, $CHCl_3$), respectively.

In summary, the total synthesis of the naturally occurring alkaloid (−)-porantheridine has been achieved in nine steps and 20% overall yield from bicyclic amino ether **5**, readily available from L-lysine. This synthesis nicely documents the scope of our recently reported strategy for the stereocontrolled elaboration of trans 2,6-disubstituted piperidine substructures.

(9) As broadly estimated by ^{13}C NMR, the use of $NaBH_4$, H_2/Raney-Ni, and bis(2-methoxyethoxy)aluminium hydride (Red-Al) gave respectively a 1:1, 2:3, and 1:3 epimeric mixture of **10a** and **10b**. Reactions with H_2/Pd−C and LiAlH(*t*-BuO)$_3$ were ineffective.

(10) Similar behavior was observed by G. Solladié and co-workers for the reduction of *β*-ketosulfoxides: (a) Solladié, G.; Greck, C.; Demailly, G.; Solladié-Cavallo, A. *Tetrahedron Lett.* **1982**, *23*, 5047−5050. Unlike these authors, the use of additives such as $ZnCl_2$, $CeCl_3$, and $MgBr_2$ did not affect the observed ratios in the case of the reduction of ketone **4**: (b) Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435−438.

(11) Protection of the nitrogen atom as carbamate was not conceivable here, since we previously noticed that tosylation of compound **6** quantitatively led to the obtention of the bicyclic oxazolidinone **3** through intramolecular nucleophilic displacement of the tosylate group by the carbamate moiety.

(12) Paquette, L. A.; Kang, H. *J. Am. Chem. Soc.* **1991**, *113*, 2610−2621.

(13) (a) Sakata, Y.; Hirano, Y.; Tatemitsu, H.; Misumi, S.; Ochiai, H.; Shibata, H. *Tetrahedron* **1989**, *45*, 4717−4727. (b) Krohn, K.; Bernhard, S. *J. Prakt. Chem.* **1998**, *340*, 26−33.

(14) According to ^{13}C NMR, this Wittig reaction seemed to afford **16** as a single stereoisomer whose stereochemistry (*E* or *Z*) could not be assigned.

Experimental Section[15]

(2*S*,6*S*)-6-Allyl-*N*-(carbobenzyloxy)-2-(hydroxymethyl)-piperidine (6). A mixture of allyl oxazinone **3**[4] (1.62 g, 8.95 mmol) and KOH (17.5 g, 312 mmol) in water (45 mL) and methanol (75 mL) was heated at 120 °C (bath temperature) for 63 h. After cooling to room temperature, brine (38 mL) and CH_2Cl_2 (125 mL) were added. The reaction mixture was stirred and then decanted, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The obtained crude amino alcohol was dissolved in CH_2Cl_2 (55 mL), and Na_2CO_3 (2.1 g, 19.8 mmol) was added. After cooling to 0 °C, benzyl chloroformate (1.40 mL, 9.81 mmol) was added dropwise. The reaction mixture was stirred for 16 h and then filtered and concentrated in vacuo. Column chromatography of the residue (3:7 EtOAc/cyclohexane) yielded alcohol **6** (1.45 g, 56%) as a yellow oil: $[\alpha]^{23}_D = -32°$ (*c* 0.99, MeOH); ^{1}H NMR δ 7.40−7.15 (m, 5H), 5.75−5.50 (m, 1H), 5.15−4.85 (m, 4H), 4.30−4.12 (m, 1H), 3.95 (br s, 1H), 3.85−3.60 (m, 2H), 3.60−3.40 (m, 1H), 2.50−2.35 (m, 1H), 2.25−2.05 (m, 1H), 1.80−1.40 (m, 6H); ^{13}C NMR δ 156.2, 136.5, 134.9, 128.5, 128.0, 127.8, 117.1, 67.0, 65.0, 55.1, 52.6, 36.2, 25.7 (2C), 16.9; IR (neat) 3450, 1690 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.00; N, 4.84. Found: C, 70.43; H, 8.08; N, 4.85.

(5*S*,8*S*)-8-(Hydroxymethyl)-3-(iodomethyl)hexahydropyrido[1,2-*c*][1,3]oxazin-1-one (7). To a solution of piperidine **6** (146 mg, 0.51 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added iodine (519 mg, 2.05 mmol). The reaction mixture was stirred for 18 h at this temperature. After stirring at room temperature for 4 h more, a saturated aqueous solution of sodium thiosulfate (3 mL) was added. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Two successive column chromatography fractionations (3:7 EtOAc/cyclohexane then 1:9 EtOAc/cyclohexane) allowed the separation of the two diastereomers **7a** (35 mg, 21%) and **7b** (36 mg, 22%) as colorless liquids. For **7a** (less polar): ^{1}H NMR δ 4.60−4.45 (m,1H), 4.35−4.17 (m, 1H), 3.78 (t, J = 11.35 Hz, 1H), 3.61 (dd, J = 11.35, 4.40 Hz, 1H), 3.55−3.40 (m, 1H), 3.35 (dd, J = 10.40, 5.08 Hz, 1H), 3.25 (dd, J = 10.40, 8.13 Hz, 1H), 2.67 (br s, 1H), 2.17 (dt, J = 14.23, 6.88 Hz, 1H), 1.92 (ddd, J = 14.23, 6.23, 4.58 Hz, 1H), 1.70−1.15 (m, 6H); ^{13}C NMR δ 154.7, 73.1, 61.5, 53.4, 46.8, 32.8, 29.8, 24.9, 19.6, 4.6; IR (neat) 3340, 1680 cm^{-1}; For **7b** (more polar): ^{1}H NMR δ 4.70−4.50 (m, 1H), 4.30−4.10 (m, 1H), 3.74 (t, J = 11.30 Hz, 1H), 3.59 (dd, J = 11.30, 6.08 Hz, 1H), 3.55−3.35 (m, 1H), 3.30 (dd, J = 10.44, 4.43 Hz, 1H), 3.16 (dd, J = 10.44, 7.10 Hz, 1H), 2.50 (br s, 1H), 2.29 (ddd, J = 13.58, 4.70, 1.78 Hz, 1H), 1.75 (t, J = 13.58, 1H), 1.65−0.60 (m, 6H); ^{13}C NMR δ 154.2, 73.9, 61.5, 52.5, 49.6, 35.7, 33.0, 24.8, 18.8, 6.1; IR (neat) 3350, 1680 cm^{-1}.

(5*S*,8a*S*)-Ethyl 3-Oxo-2-(3-oxohexahydrooxazolo[3,4-*a*]-pyridin-5-yl)hexanoate (9). To a cooled solution of compound **5** (1.80 g, 10.53 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added successively ethyl 3-(trimethylsilyloxy)-2-hexenoate[8] **8** (12.3 g, 53.48 mmol) and slowly trimethylsilyl triflate (4 mL, 20.70 mmol). The reaction mixture was allowed to warm to room temperature and then quenched with saturated aqueous solution of sodium bicarbonate. The organic layer was washed with water, and the combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (1:1 EtOAc/cyclohexane) allowed the separation of the two diastereoisomers **9a** (1.35 g) and **9b** (1.45 g) as yellow solids (90% overall yield). For **9a** (less polar): mp 74.5−75.5 °C; $[\alpha]^{23}_D = +56.5°$ (*c* 1.01, MeOH); ^{1}H NMR δ 4.79 (dd, J = 11.68, 4.30 Hz, 1H), 4.35−4.15 (m, 3H), 3.89 (dd, J = 8.60, 3.90 Hz, 1H), 3.82−3.65 (m, 2H), 2.69 (dt, J = 18.33, 7.10 Hz, 1H), 2.43 (dt, J = 18.33, 7.10 Hz, 1H), 1.85−1.37 (series of m, 8H), 1.28 (t, J = 7.13 Hz, 3H), 0.86 (t, J = 7.45 Hz, 3H); ^{13}C NMR δ 203.3, 167.7, 156.8, 68.1, 61.8, 60.3, 50.5, 49.0, 40.6, 30.0, 26.2, 17.9, 16.5, 14.0, 13.3; For **9b** (more polar): mp 74.5−75.5 °C; $[\alpha]^{24}_D = +78.4°$ (*c* 0.98, MeOH); ^{1}H NMR δ 4.72 (dd, J = 11.40, 4.93 Hz, 1H), 4.30 (t, J = 7.50 Hz, 1H), 4.15 (q, J = 7.10 Hz, 2H), 3.95−3.75 (m, 3H), 2.47 (br t, J = 7.18 Hz, 2H), 1.95−1.27 (m, 8H), 1.20 (t, J = 7.10 Hz, 3H), 0.87 (br t, J = 7.35 Hz, 3H); ^{13}C NMR δ 202.0, 167.3, 156.5, 68.0, 62.0, 59.3, 50.9, 48.8, 44.2, 30.2, 26.2, 18.0, 16.9, 13.9, 13.5; IR ($HCBr_3$) 1735, 1705 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.79; N, 4.71. Found: C, 60.72; H, 7.83; N, 4.78.

(5*S*,8a*S*)-5-(2-Oxo-pent-1-yl)hexahydrooxazolo-[3,4-*a*]pyridin-3-one (4). A mixture of compounds **9** (2.80 g, 9.43 mmol) and potassium carbonate (8.40 g, 60.87 mmol) in a 2:1 mixture of water and ethyl alcohol (40.5 mL) was stirred at 90 °C for 12 h. NaCl (1 g, 17 mmol) was then added, and the aqueous phase was extracted with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was subjected to purification by column chromatography (6:4 EtOAc/cyclohexane), yielding compound **4** (1.92 g, 91%) as a yellow oil: $[\alpha]^{24}_D = -10.8°$ (*c* 1.11, MeOH); ^{1}H NMR δ 4.55−4.45 (m, 1H), 4.37 (t, J = 8.10 Hz, 1H), 3.87 (dd, J = 8.10, 6.05 Hz, 1H), 3.75−3.60 (m, 1H), 2.64 ($^1/_2$ AB q, J = 7.8 Hz, 1H), 2.63 ($^1/_2$ AB q, J = 7.8 Hz, 1H), 2.55−2.30 (m, 2H), 1.85−1.25 (m, 8H), 0.87 (t, J = 7.40 Hz, 3H); ^{13}C NMR δ 208.2, 156.6, 68.3, 50.7, 45.9, 44.4, 43.1, 30.2, 27.2, 17.9, 17.0, 13.6; IR (neat) 1735, 1705 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.98; H, 8.52; N, 6.18.

(5*S*,8a*S*)-5[(2*R*)-(2-Hydroxypentyl)]hexahydrooxazolo-[3,4-*a*]pyridin-3-one (10a) and (5*S*,8a*S*)-5[(2*S*)-(2-Hydroxypentyl)]-hexahydrooxazolo[3,4-*a*]pyridin-3-one (10b). To a cooled solution of ketone **4** (2.63 g, 11.69 mmol) in THF (40 mL) at −78 °C was added dropwise a 1 M solution of lithium triethylborohydride (Super-H) in THF (14.6 mL, 14.6 mmol). The reaction mixture was stirred for 12 h at −78 °C and then quenched at this temperature with a saturated aqueous solution of sodium bicarbonate (20 mL). The reaction mixture was then stirred at 0 °C (ice bath) for 30 min, and 35% aqueous hydrogen peroxide solution (10 mL) was added. After stirring for 30 min more, the reaction mixture was concentrated in vacuo. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (7:3 EtOAc/cyclohexane) allowed the separation of the two diastereoisomers **10a** (2.14 g, 81%) as a colorless oil and **10b** (483 mg, 18%) as a white solid. For **10a**: $[\alpha]^{22}_D = -5.7°$ (*c* 1.12, MeOH); ^{1}H NMR δ 4.38−4.29 (m, 1H), 4.05 (m, 1H), 3.85−3.75 (m, 2H), 3.65−3.52 (m, 1H), 2.90 (br s, 1H), 1.85−1.10 (series of m, 12H), 0.85 (t, J = 7.05 Hz, 3H); ^{13}C NMR δ 157.2, 69.2, 66.5, 50.6, 47.5, 39.7, 37.4, 30.6, 27.9, 18.6, 17.9, 13.9. For **10b**: mp 45.5−46.5 °C; $[\alpha]^{24}_D = +13.5°$ (*c* 1.08, MeOH); ^{1}H NMR δ 4.50 (t, J = 8.1 Hz, 1H), 4.32−4.10 (m, 1H), 3.97−3.55 (m, 3H), 3.55−3.30 (m, 1H), 2.00−1.05 (series of m, 12H), 0.90 (t, J = 6.53 Hz, 3H); ^{13}C NMR δ 158.4, 69.4, 67.0, 50.5, 45.9, 39.1, 38.8, 30.6, 28.2, 19.2, 18.2, 14.1; IR ($HCBr_3$) 3430, 1720 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.41; H, 9.32; N, 6.08.

(5*S*,8a*S*)-5-[(2*R*)-2-(Benzyloxy)pentyl]hexahydrooxazolo-[3,4-*a*]pyridin-3-one (11). To a mixture of NaH (0.84 g, 35 mmol) and tetrabutylammonium iodide (35 mg, 0.095 mmol) in anhydrous DMF (31 mL) was added a solution of alcohol **10a** (1.95 g, 8.59 mmol) in DMF (30 mL) at room temperature. The mixture was stirred for 1 h, and then benzyl bromide (1.13 mL, 9.50 mmol) was added. The reaction mixture was stirred for 16 h and then treated with 3 M HCl aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with aqueous 3 M HCl solution, dried over Na_2SO_4, and concentrated in vacuo. Column chromatography (1:1 EtOAc/cyclohexane) afforded the expected compound **11** (2.35 g, 86%) as a yellow oil: $[\alpha]^{22}_D = -13.7°$ (*c* 1.18, MeOH); ^{1}H NMR δ 7.31−7.19 (m, 5H), 4.48 (d, J = 11.38 Hz, 1H), 4.32 (d, J = 11.38, 1H), 4.02−3.91 (m, 2H), 3.75−3.45 (m, 2H), 3.35 (quint, J = 5.5 Hz, 1H), 2.00−1.80 (m, 2H), 1.60−1.15 (m, 10 H), 0.87 (t, J = 7.25 Hz, 3H); ^{13}C NMR δ 156.8, 138.5, 128.0, 127.5, 126.9, 76.4, 70.3, 68.0, 50.1, 47.2, 35.4, 34.2; 30.4, 27.7, 17.8 (2C), 14.0; IR (neat) 1750 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.79; H, 8.56; N, 4.37.

(2*S*,6*S*)-2-(Hydroxymethyl)-6-[(2*R*)-2-(benzyloxy)pentyl]-piperidine (12). A solution of compound **11** (2.4 g, 7.57 mmol) and NaOH (15 g, 375 mmol) in a mixture of water (36 mL) and MeOH (66 mL) was heated at reflux temperature for 64 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. Concentration in vacuo gave a crude product which was

(15) For general experimental information, please see Dhimane, H.; Vanucci-Bacqué, C.; Hamon, L.; Lhommet, G. *Eur. J. Org. Chem.* **1998**, 1955−1963.

purified by column chromatography (88.5:10:1.5 CH_2Cl_2/MeOH/NH_4OH (28%)) yielding amino alcohol **12** (2 g, 91%) as a yellow oil: $[\alpha]^{22}_D = -20.9°$ (*c* 1.03, MeOH); ^{1}H NMR δ 7.55−7.30 (m, 5H), 4.70 (d, J = 11.55 Hz, 1H), 4.57 (d, J = 11.55 Hz, 1H), 3.75−3.45 (m, 3H), 3.20−3.00 (m, 2H), 2.33 (br s, 2H), 2.00−1.25 (m, 12H), 1.06 (t, J = 7.08 Hz, 3H); ^{13}C NMR δ 138.8, 128.4, 127.9, 127.6, 77.1, 70.7, 63.4, 52.0, 48.0, 39.0, 36.1, 31.6, 27.3, 20.0, 18.3, 14.4; IR (neat) 3400 cm^{-1}.

(2*S*,6*S*)-Toluene-4-sulfonic Acid 6-(2-(benzyloxy)pentyl)-1-(toluene-4-sulfonyl)piperidin-2-yl Methyl Ester (13). To an ice-cooled mixture of amino alcohol **12** (458 mg, 1.57 mmol) and tosyl chloride (1.20 g, 6.32 mmol) in CH_2Cl_2 (3 mL) was added dropwise Et_3N (3 mL, 21.5 mmol). The reaction mixture was then stirred at room temperature for 5 h. Water (10 mL) was added, and stirring was continued for 1 h. The separated organic layer was washed with 3 M aqueous HCl solution. The combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo, and column chromatographed (1:4 EtOAc/cyclohexane) to afford compound **13** (567 mg, 60%) as an oil: $[\alpha]^{25}_D = -17.8°$ (*c* 1.03, MeOH); ^{1}H NMR δ 7.57 (d, J = 8.33 Hz, 2H), 7.47 (d, J = 8.33 Hz, 2H), 7.20−6.90 (m, 9H), 4.35−3.90 (m, 4H), 3.80−3.55 (m, 2H), 3.10−2.95 (m, 1H), 2.26 (s, 3H), 2.20 (s, 3H), 1.70−0.90 (series of m, 12 H), 0.68 (t, J = 7.08 Hz, 3H); ^{13}C NMR δ 145.0, 143.1, 139.3, 138.7, 132.8, 130.0, 129.6, 128.4, 128.0, 127.9, 127.6, 127.2, 75.4, 70.4, 54.4, 52.8, 36.1, 35.9, 27.0, 26.4, 21.7, 21.5, 19.0, 18.4, 14.2; IR (neat) 3050, 815 cm^{-1}.

(2*S*,6*S*)-*N*-(Benzyloxycarbonyl)-2-(hydroxymethyl)-6-[(2*R*)-2-(benzyloxy)pentyl]piperidine (14). To a mixture of compound **12** (0.8 g, 2.75 mmol) and sodium carbonate (290 mg, 20.74 mmol) in CH_2Cl_2 (15 mL) was added dropwise benzyl chloroformate (390 μL, 2.73 mmol). The reaction mixture was stirred for 19 h and then filtered and concentrated in vacuo. Column chromatography (1:1 EtOAc/cyclohexane) afforded the expected compound **14** (1.1 g, 94%) as a colorless oil: $[\alpha]^{20}_D = -11.9°$ (*c* 0.97, MeOH); ^{1}H NMR δ 7.40−7.05 (m, 10H), 5.10 (s, 2H), 4.50−4.25 (m, 3H), 4.00 (br s, 1H), 3.80−3.55 (m, 2H), 3.50−3.15 (m, 2H), 2.00−1.10 (series of m, 12H), 0.79 (t, J = 7.08 Hz, 3H); ^{13}C NMR δ 156.2, 138.8, 136.6, 128.6, 128.4, 128.1, 128.0, 127.9, 127.6, 76.0, 70.6, 67.3, 65.0, 55.7, 50.6, 35.9, 35.3, 27.2, 26.9, 18.4, 18.3, 14.3; IR (neat) 3450, 1685 cm^{-1}. Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.38; H, 8.29; N, 3.29. Found: C, 73.39; H, 8.38; N, 3.25.

(2*S*,6*S*)-*N*-(Benzyloxycarbonyl)-2-[3-(2,5,5-trimethyl[1,3]-dioxan-2-yl)propen-1-yl]-6-[(2*R*)-2-(benzyloxy)pentyl]piperidine (16). To a cooled solution of oxalyl chloride (190 μL, 2.18 mmol) in CH_2Cl_2 (25 mL) at −78 °C was added dropwise DMSO (310 μL, 4.37 mmol). After stirring for 15 min, a solution of alcohol **14** (616 mg, 1.45 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C, and then triethylamine (930 μL, 6.68 mmol) was added. The reaction mixture was allowed to warm to room temperature. Et_2O (50 mL) was then added, and the organic layer was washed with water before drying over Na_2SO_4. Concentration in vacuo afforded crude intermediate aldehyde.

To a cooled solution of triphenylphosphonium bromide **15**[13] (1.81 g, 3.63 mmol) in THF (25 mL) at −40 °C was added a 1.35 M solution of *n*-BuLi in hexane (2.95 mL, 3.98 mmol). The mixture was stirred for 30 min at this temperature before the dropwise addition of a solution of the previously obtained aldehyde in THF (5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 2 h more. Water (30 mL) and NaCl (1 g, 17 mmol) were then added. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (1:4 EtOAc/cyclohexane) yielded compound **16** (692 mg, 85%) as an orange oil: $[\alpha]^{19}_D = +37.9°$ (*c* 1.05, MeOH); ^{1}H NMR δ 7.80−7.30 (m, 10H), 6.00−5.65 (m, 2H), 5.50−5.20 (m, 2H), 5.05−4.85 (m, 1H), 4.69 (AB q, J = 11.5 Hz, 2H), 4.45−4.25 (m, 1H), 3.80−3.50 (m, 5H), 2.85−2.65 (m, 2H), 2.40−1.35 (series of m including s at δ 1.55, 3H, total 15H), 1.30−0.85 (m, 9H); ^{13}C NMR δ 155.9, 139.1, 137.0, 133.0, 128.5, 128.4, 127.8, 127.7, 127.4, 125.2, 98.9, 76.4, 70.4, 70.2, 66.8, 50.1, 49.8, 38.2, 36.0, 35.0, 30.0, 28.0, 25.6, 22.7, 22.6, 21.2, 18.6, 16.0, 14.3; IR (neat) 3050, 1705 cm^{-1}. Anal. Calcd for $C_{35}H_{49}NO_5$: C, 74.57; H, 8.76; N, 2.48. Found: C, 74.58; H, 8.86; N, 2.42.

Porantheridine (1). Compound **16** (198 mg, 0.35 mmol) dissolved in MeOH (10 mL) was subjected to hydrogenation (1 atm) in the presence of 10% Pd/C (198 mg) at room temperature for 5 h. The mixture was then filtered over a Celite pad, which was rinsed with MeOH. The solvent was evaporated in vacuo yielding an intermediate amino alcohol (110 mg, 92%). A mixture of the latter and *p*-TsOH (65 mg, 0.34 mmol) in benzene (5 mL) was stirred at reflux temperature for 3 h, at which point 4 Å molecular sieves (3 g) were added. Stirring at reflux temperature was continued for 3 h. The reaction mixture was then filtered and the solid residue washed with Et_2O. The organic layer was stirred in the presence of Na_2CO_3 (2 g, 19 mmol) for 15 min before filtration and evaporation of the solvent in vacuo. Column chromatography (2:8 CH_2Cl_2/MeOH) of the residue yielded expected porantheridine **(1)** (39 mg, 47% from **16**) as a colorless oil: $[\alpha]^{19}_D = -25°$ (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 4.05−3.85 (m, 1H), 3.80−3.60 (m, 1H), 3.05−2.85 (m, 1H), 2.05−1.10 (series of m, 21H), 0.92 (t, J = 7 Hz, 3H); ^{13}C NMR δ 86.2, 69.1, 49.5, 48.4, 40.0, 39.2, 34.1, 34.0, 30.8, 27.3, 23.7, 19.7, 19.3, 18.0, 14.3.

Supporting Information Available: ^{1}H and ^{13}C NMR data for **1**, **7**, **12**, and **13** and X-ray structural analyses of alcohol **10b** containing ORTEP diagram, crystal data, tables of atomic coordinates, thermal parameters, bond lengths and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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