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A Facile Asymmetric Route to (−)-Aphanorphine

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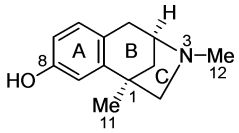
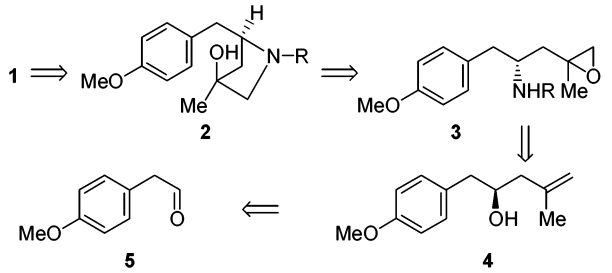
Abstract: 8*O*-Methylaphanorphine was synthesized from 4-methoxyphenylacetaldehyde in 36% overall yield and in nine steps, featuring the formation of ring B via a Friedel−Crafts alkylative cyclization with the concomitant stereospecific introduction of the benzylic quaternary carbon center. The current work constitutes an efficient enantioselective formal synthesis of 3-benzazepine marine alkaloid (−)-aphanorphine.

(−)-Aphanorphine (**1**) is a tricyclic 3-benzazepine alkaloid isolated by Shimizu and Clardy in 1988 from the freshwater blue-green alga *Aphanizomenon flos-aquae*.[1] It has spawned a virtual explosion of synthetic interest[2] due to its unique structure resembling benzomorphane analgesics such as pentazocine.[3] The potential pharmacological activity should endow aphanorphine and its analogues with great value as lead compounds in new drug development. In all previous syntheses of **1**, ring B was constructed prior to ring C with the following two exceptions: the strategy presented by Ishibashi and co-workers[2b] involved the final formation of ring B via an aryl radical cyclization, and Funk and co-workers[2a] discovered that rings B and C could be simultaneously generated from a substituted ϵ-lactam by an intramolecular mesylate displacement. Remarkably, the majority of the known syntheses of **1** started from either 1,3-disubstituted or 1,2,4-trisubstituted benzenes, but not from those with 1,4-disubstitution, i.e., more highly symmetric molecules.



1: (-)-aphanorphine

SCHEME 1



As a part of our long-term marine natural product program, we recently launched an original asymmetric total synthesis of (−)-aphanorphine (**1**). In our own synthetic strategy, we envisioned that ring B of the tricycle could be effectively constructed with the concomitant stereospecific introduction of the benzylic quaternary carbon center, by an intramolecular Friedel−Crafts alkylation[4] of pyrrolidinol **2** (Scheme 1). Chiral homoallylic alcohol **4**, presumably obtainable from 4-methoxyphenylacetaldehyde[5] (**5**, a highly symmetric 1,4-disubstituted benzene) by Roush methallylation,[6] could be converted to epoxy amine **3** and then to tertiary alcohol **2**, in which rings A and C were both set. If successful, our synthetic studies should provide a general efficient method for rapid assembly of aphanorphine analogues and of other related alkaloids.

Our enantioselective synthesis of (−)-aphanorphine (**1**) is delineated in Scheme 2. Roush reaction[6] of **5**[5] with the enantiopure diisopinocampheyl(methallyl)borane reagent in ether [prepared from methallylmagnesium chloride[7] and commercially available (+)-DIP-chloride] furnished in 85% yield (*R*)-homoallylic alcohol **4** as a colorless oil (95.4% ee, as determined by HPLC analysis: Chiralpak AS column (250 × 4.6 mm), UV detector 254 nm, eluent hexanes/2-propanol (4:1), flow rate 0.7 mL/min). Stereoselective epoxidation[8] with TBHP in the presence of 2 mol % of $VO(acac)_2$ in dichloromethane at room temperature produced epoxy alcohols **6a**/**6b** (96%, dr 2:1) as an inseparable mixture. Surprisingly, reaction of **4** with *m*-CPBA gave **6a**/**6b** in an approximately 1:1 ratio, which was not sufficiently acceptable for our purpose. To eventually form the pyrrolidine ring, the attempt to convert the hydroxyls of **6a**/**6b** to suitable nitrogen-based nucleophilic functional groups was then executed. Displacement of the sulfonates of **6a**/**6b** with NaN_3 or $MeNH_2$ resulted mainly in an elimination product. Reaction of **6a**/**6b** with (BOC)NHTs[9] under typical Mitsunobu[10] conditions (PPh_3, DEAD, THF) led to an amide

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(1) Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 4381.
(2) For most recent synthesis or synthetic studies, see: (a) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923. (b) Tamura, O.; Yangimachi, T.; Kobayashi, T.; Ishibashi, H. *Org. Lett.* **2001**, *3*, 2427. (c) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049. (d) ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Heterocycles* **2002**, *56*, 39. For a list of earlier synthesis or synthetic studies, see the references cited in ref 2a.
(3) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1.
(4) Shapiro, B. L.; Shapiro, M. J. *J. Org. Chem.* **1976**, *41*, 1522.
(5) (a) Eicher, T.; Wobido, M.; Speicher, A. *J. Prakt. Chem.* **1996**, *338*, 706. (b) Firouzabadi, H.; Sharifi, A. *Synthesis* **1992**, *10*, 999.
(6) (a) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (b) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512.
(7) Taber, D. F.; Christos, T. E.; Rahimizadeh, M.; Chen, B. *J. Org. Chem.* **2001**, *66*, 5911.
(8) For stereoselective epoxidation of alkenols, see: Gruttadauria, M.; Meo, P. L.; Noto, R. *Tetrahedron* **1999**, *55*, 14097.
(9) Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379.
(10) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.*Tetrahedron Lett.* **1989**, *30*, 5709.

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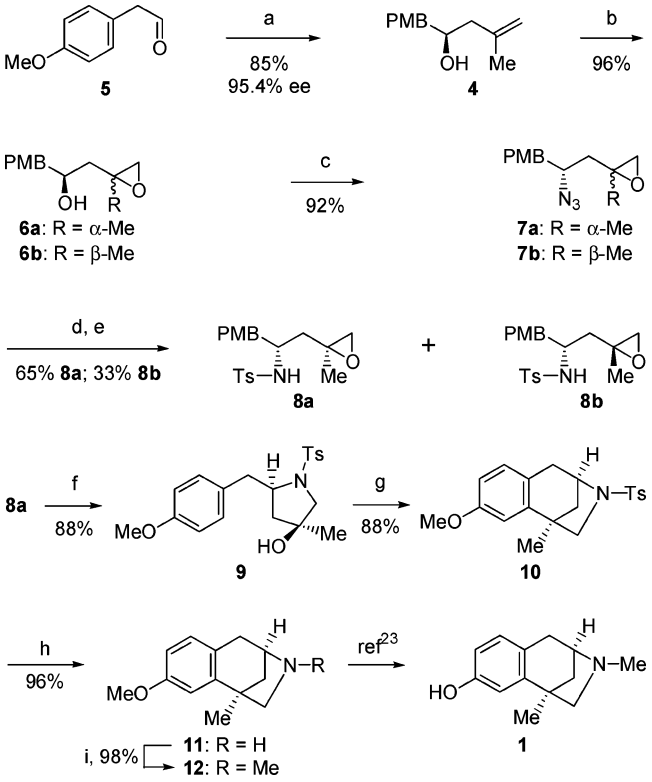
SCHEME 2[a]



[a] Conditions: (a) methallyl-MgCl, (+)-DIP-Cl, ether, −78 °C, 1 h; rt, 4 h; **5**, ether, −78 °C, 4 h; rt 1 h; 3 M NaOH, 30% H_2O_2, reflux, 1 h; (b) $VO(acac)_2$, TBHP, DCM, 0 °C, 10 min; rt, 7.5 h; (c) HN_3, PPh_3, DEAD, PhH, 0 °C; rt 30 min; (d) Lindlar catalyst, H_2, anhyd EtOH, rt, 8.5 h; (e) TsCl, TEA, Et_2O, rt, 1.5 h; (f) NaH, PhH, reflux, 18 h; (g) $AlCl_3$, DCM, rt, 12 h; (h) Red-Al, xylene, reflux, 1 h; (i) HCHO, $NaBH_3CN$, MeOH, rt, 12 h. PMB = *p*-methoxybenzyl.

in only 36% yield; moreover, deprotecting the BOC was comparably unsatisfactory. Replacement of (BOC)NHTs with (CBZ)NHTs[11] yielded nothing but the elimination product. To our delight, by treating **6a**/**6b** with HN_3,[12] PPh_3, and DEAD in benzene, azides **7a**/**7b** were obtained in high yield (92%).[13] Selective azido hydrogenation (while keeping the epoxy groups intact) was realized with the Lindlar catalysis[14] (1 atm of H_2, anhydrous EtOH, room temperature). The homoallylic amines thus obtained were immediately exposed to *p*-toluenesulfonyl chloride and triethylamine in ether at room temperature to produce in excellent yield (98%) the expected sulfonamides **8a** (65%) and **8b** (33%), which were easily separable by silica gel chromatography.[15]

On reflux with excess sodium hydride in benzene, **8a** was smoothly converted to **9** in 88% yield by forming the pyrrolidine ring through an intramolecular *endo*-epoxy displacement.[16] It is noteworthy that the isomer **8b** remained unreacted under the same condition. Under harsher conditions (e.g., at higher reaction temperatures when using different solvents), a cyclization product could not be isolated and the starting material could not be recovered. Although **8b** could not be utilized directly to synthesize **9**, it could be recycled by a two-step sequence (oxygen extrusion followed by epoxidation) to afford the **8a/8b** mixture. The intramolecular Friedel−Crafts alkylative cyclization[4] of *N*-tosylpyrrolidine **9** was then vigorously investigated. Treating **9** with PPA[17] (at 72, 90 or 100 °C) or 85% H_2SO_4[18] (at 0 °C) failed to form the desired cyclization product. Gratifyingly, agitating **9** with excess $AlCl_3$[19] in dichloromethane at room temperature for 12 h effected the expected transformation to provide **10** (88% yield, 99.7−100% ee[20]), in which the tricyclic framework of aphanorphine **1** had been established. Finally, (+)-8*O*-methylaphanorphine **12** was afforded by reductive desulfurization[21] with Red-Al in refluxing xylene (96%) followed by N-methylation[22] with formaldehyde and $NaBH_3CN$ in MeOH at room temperature (98%). The $[\alpha]^{20}_D$ of **12** was found to be +8.7 (*c* 1.06, $CHCl_3$) [lit.[23] $[\alpha]^{28}_D$ +8.1 (*c* 1.2, $CHCl_3$) [lit.[2b] $[\alpha]^{20}_D$ +9.4 (*c* 0.30, $CHCl_3$)]]. Other spectroscopic data of **12** were also in accord with those disclosed in the literature.[1,2,23] Demethylation of **12** with BBr_3 in dichloromethane has been reported to give tricyclic 3-benzazepine alkaloid (−)-aphanorphine (**1**) in 86% yield.[23]

In summary, we have accomplished a formal asymmetric synthesis of marine alkaloid (−)-aphanorphine (**1**). 8-*O*-methylaphanorphine **12** was synthesized from **5** in nine steps and in 36% overall yield. The present synthesis has the following features. (i) A highly symmetric 1,4-disubstituted (rather than 1,3-disubstituted or 1,2,4-trisubstituted) benzene was utilized as the source of ring A. (2*R*)-1-(4-Methoxyphenyl)-4-methyl-4-penten-2-ol **4** was efficiently synthesized in an enantioselective manner by Roush reaction. (ii) Our unique strategy of sequential cyclizations secured high synthetic efficiency: base-promoted cyclization (via an intramolecular endo epoxy displacement) formed 2-arylmethyl-4-methyl-4-pyrrolidinol **9**, setting the stage for a Lewis acid-effected Friedel−Crafts alkylative cyclization, during which the stereospecific introduction of the benzylic quaternary carbon center was concomitantly realized.

Experimental Section

General Methods. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ or CD_3OD (^1H at 300 MHz and ^{13}C at 75 MHz) using TMS as the internal standard. Column

(11) Moore, J. D.; Harned, A. M.; Henle, J.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 1847.
(12) Wolff, H. *Org. React.* **1946**, *3*, 307.
(13) For conversion of alcohols to azides by Mitsunobu reaction, see: Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546.
(14) For azide reduction with Lindlar catalyst in the presence of epoxides, see: Block, O.; Klein, G.; Altenbach, H. J.; Braner, D. J. *J. Org. Chem.* **2000**, *65*, 716.
(15) For amine sulfonylation, see: Dauban, P.; Ferry, S.; Faure, H.; Ruat, M.; Dodd, R. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2001.
(16) For intramolecular epoxy displacement, see: LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664.
(17) Shiotani, S.; Okada, H.; Yamamoto, T.; Nakamata, K.; Adachi, J.; Nakamoto, H. *Heterocycles* **1996**, *43*, 113.
(18) Bogert, M. T.; Davidson, D. *J. Am. Chem. Soc.* **1934**, *56*, 185.
(19) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 1111.
(20) Determined by HPLC analysis: Chiralpak AD column (250 × 4.6 mm), UV detector 254 nm, eluent hexanes/2-propanol (4: 1), flow rate 0.7 mL/min.
(21) For reductive desulfurization, see: Negash, K.; Nichols, D. E.; Watts, V. J.; Mailman, R. B. *J. Med. Chem.* **1997**, *40*, 2140.
(22) For N-methylation by reductive amination, see: Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
(23) Shimizu, M.; Kamikubo, T.; Ogasawara, K. *Heterocycles* **1997**, *46*, 21.

chromatography was performed on silica gel. Dichloromethane, DMF, and diisopropylamine were distilled over calcium hydride under N_2. Ether, THF, benzene, toluene, and xylene were distilled over sodium benzophenone ketyl under N_2. Ethanol was distilled over magnesium under N_2.

(2*R*)-1-(4-Methoxyphenyl)-4-methyl-4-penten-2-ol (4). To a dry 100-mL three-necked round-bottomed flask equipped with a thermometer and a dropping funnel were added Mg turnings (4.80 g, 197 mmol), iodine (a grain), and anhydrous ether (25 mL). To this mixture was added dropwise a solution of 3-chloro-2-methylpropene (90%, 4.30 mL, 39.3 mmol) in dry ether (20 mL) over 60 min while maintaining the temperature at 0 °C. The mixture was stirred at 0 °C for 1 h and at rt for 1.5 h and allowed to stand for several hours until the upper layer became clear. The upper clear ether solution contained methallylmagnesium chloride (0.46 M by titration).

To a 25-mL round-bottomed flask containing (+)-DIP-Cl (238 mg, 0.742 mmol) and dry ether (3 mL) at −78 °C was added the above Grignard reagent (0.46 M, 1.46 mL, 0.672 mmol). The mixture was stirred at −78 °C for 1 h and at rt for 4 h and cooled back to −78 °C. A solution of (4-methoxyphenyl)acetaldehyde (100.5 mg, 0.669 mmol) in ether (2 mL) was slowly added to the above mixture at −78 °C. The mixture was stirred at −78 °C for 4 h and at rt for 1 h, quenched with aqueous NaOH solution (3 M, 0.25 mL, 0.75 mmol) and 30% H_2O_2 (0.25 mL, 2.4 mmol), refluxed for 1 h, and cooled to rt. The two layers were separated, and the aqueous layer was extracted with ethyl acetate for three times. The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/hexanes, 1:20) to furnish alcohol **4** (117 mg, 85%). An analytical sample was obtained by converting the above-mentioned alcohol **4** (which could be used directly for the next reaction) to the TBS ether (TBSCl, imidazole, DMF, rt, 16 h), chromatographic separation (EtOAc/hexanes, 1:100) and desilylation (TBAF, THF, rt, 24 h) to remove a tiny amount of the pinenol impurity. **4**: colorless oil: 95.4% ee (determined by HPLC analysis); $[\alpha]^{20}_D$ −19.8 (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.74 (s, 3H, CH_3), 1.91 (br s, 1H, OH), 2.10−2.26 (m, 2H, CH_2), 2.64−2.77 (m, 2H, benzylic CH_2), 3.77 (s, 3H, OCH_3), 3.87−3.93 (m, 1H, OCH), 4.87 (d, J = 0.8 Hz, 1H, 0.5CH_2 (vinyl)), 4.80 (d, J = 0.8 Hz, 1H, 0.5CH_2 (vinyl)), 6.84 (d, J = 8.6 Hz, 2H, 2CH), 7.14 (d, J = 8.6 Hz, 2H, 2CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.3, 42.5, 45.2, 55.0, 69.8, 113.2, 113.7, 130.2, 130.4, 142.6, 158.0; MS (EI) 134 (100), 121 (47), 57 (21). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.59; H, 8.55.

(2*S*)-1-(4-Methoxyphenyl)-3-(1-methyloxiranyl)-2-propanol (6a/6b). To a solution of **4** (1.13 g, 5.48 mmol) in anhydrous dichloromethane (45 mL) at 0 °C were added VO(acac)$_2$ (29 mg, 0.11 mmol) and then TBHP (4.15 M in toluene, 2.64 mL, 11.0 mmol, dropwise). The reaction mixture was stirred at 0 °C for 10 min, allowed to warm to rt, stirred for further 7.5 h, quenched with saturated aqueous sodium thiosulfate solution, and extracted with EtOAc. The organic layers were combined, washed with water and brine successively, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (EtOAc/hexanes, 1:6) to give a mixture of oxiranes **6a**/**6b** (1.17 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) diastereomers, 2:1, δ 1.37 (s, 2H, 0.67CH_3), 1.38 (s, 1H, 0.33CH_3), 1.50−1.97 (m, 3H, CH_2 + OH), 2.50−2.94 (m, 4H, oxiranyl CH_2 + benzylic CH_2), 3.81 (s, 3H, OCH_3), 3.82−3.88 (m, 0.33H, 0.33OCH), 4.05−4.14 (m, 0.67H, 0.67OCH), 6.87 (d, J = 8.7 Hz, 2H, 2CH), 7.15 (d, J = 8.7 Hz, 2H, 2CH); MS (EI) 222 (M^+, 2), 204 (9), 150 (20), 121 (100). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.80; H, 7.88.

(2*R*)-2-Azido-1-(4-methoxyphenyl)-3-(1-methyloxiranyl)-propane (7a/7b). Hydrazoic acid (2.29 M in benzene, 0.17 mL, 0.39 mmol) was added to a solution of epoxy alcohol **6a**/**6b** (44 mg, 0.20 mmol) and triphenylphosphine (78 mg, 0.30 mmol) in benzene (1 mL). The resultant mixture was cooled to 0 °C, and DEAD (40% in toluene, 0.14 mL, 0.31 mmol) was added in a dropwise fashion. The solution was allowed to slowly warm to rt. After 0.5 h, the mixture was concentrated and the crude product was purified by column chromatography (EtOAc/hexanes, 1:40) to give a mixture of azides **7a**/**7b** (45 mg, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) diastereomers, 2:1, δ 1.26 (s, 1H, 0.33CH_3), 1.36 (s, 2H, 0.67CH_3), 1.51−1.73 (m, 1H, 0.5CH_2), 1.77−1.93 (m, 1H, 0.5CH_2), 2.58−2.70 (m, 2H, oxiranyl CH_2), 2.78−2.83 (m, 2H, benzylic CH_2), 3.50−3.56 (m, 0.33H, 0.33N_3CH), 3.59−3.70 (m, 0.67H, 0.67N_3CH), 3.80 (s, 3H, OCH_3), 6.86 (d, J = 8.1 Hz, 2H, 2CH), 7.13 (d, J = 8.4 Hz, 2H, 2CH). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.10; H, 6.94; N, 17.15.

(2*R*,4*R*)-*N*-[(1-(4-Methoxyphenyl)-4-methyl-4,5-epoxy)-pentyl]-4-toluenesulfonamide (8a) and (2*R*,4*S*)-*N*-[(1-(4-Methoxyphenyl)-4-methyl-4,5-epoxy)pentyl]-4-toluenesulfonamide (8b). A solution of **7a**/**7b** (34.0 mg, 0.137 mmol) in dry EtOH (2 mL) was stirred with Lindlar catalyst (Pd/$CaCO_3$/Pb, 5% Pd, 11 mg) under H_2 (1 atm) at rt for 8.5 h and filtered (through folded filters). The solid bed was washed with EtOH, and the filtrate was concentrated to give the crude amines, which could be used directly for the next reaction. An analytical sample of the diastereomeric amines was obtained by column chromatograph (CH_2Cl_2/MeOH/Et_3N, 100:2:1) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) diastereomers, 2:1, δ 1.34 (s, 2H, 0.67CH_3), 1.36 (s, 1H, 0.33CH_3), 1.37−1.55 (m, 1H, 0.5CH_2), 1.70−2.10 (m, 3H, NH_2 + 0.5CH_2), 2.40−2.80 (m, 4H, oxiranyl CH_2 + benzylic CH_2), 3.03−3.15 (m, 0.33H, 0.33NCH), 3.15−3.28 (m, 0.67H, 0.67NCH), 3.79 (s, 3H, OCH_3), 6.85 (d, J = 8.0 Hz, 2H, 2CH), 7.11 (d, J = 8.0 Hz, 2H, 2CH).

To a solution of the above-mentioned crude amines in dry Et_2O (1 mL) were added Et_3N (0.10 mL, 0.72 mmol) and TsCl (52 mg, 0.27 mmol, in one portion). The mixture was stirred at rt for 1.5 h, quenched with saturated aqueous $NaHCO_3$, and extracted three times with EtOAc. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/hexanes, 1:5) to give **8a** (33.5 mg, 65%) as a colorless crystal and **8b** (17 mg, 33%) as a colorless oil.

8a: mp 102−103 °C; $[\alpha]^{20}_D$ −22.2 (*c* 0.911, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21 (s, 3H, CH_3), 1.59 (dd, J = 14.4, 8.5 Hz, 1H, 0.5 CH_2), 1.77 (dd, J = 14.4, 5.3 Hz, 1H, 0.5 CH_2), 2.41 (s, 3H, benzylic CH_3), 2.47 (d, J = 4.5 Hz, 1H, 0.5CH_2 (oxiranyl)), 2.52 (d, J = 4.5 Hz, 1H, 0.5CH_2 (oxiranyl)), 2.62−2.75 (m, 2H, benzylic CH_2), 3.48−3.57 (m, 1H, NCH), 3.77 (s, 3H, OCH_3), 4.91 (d, J = 7.4 Hz, 1H, NH), 6.72 (d, J = 8.4 Hz, 2H, 2CH), 6.91 (d, J = 8.4 Hz, 2H, 2CH), 7.24 (d, J = 8.1 Hz, 2H, 2CH), 7.65 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 21.4, 40.5, 41.2, 52.7, 53.8, 55.1, 55.4, 113.8, 126.9, 128.5, 129.5, 130.4, 137.5, 143.2, 158.3; MS (EI) 375 (M^+, 2), 358 (M − 17, 1), 254 (80), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73. Found: C, 64.23; H, 6.70; N, 3.61.

8b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (s, 3H, CH_3), 1.20−1.35 (m, 1H, 0.5CH_2), 1.80 (dd, J = 14.7, 4.1 Hz, 1H, 0.5 CH_2), 2.40 (s, 3H, benzylic CH_3), 2.42 (d, J = 4.8 Hz, 1H, 0.5CH_2 (oxiranyl)), 2.45 (d, J = 4.7 Hz, 1H, 0.5CH_2 (oxiranyl)), 2.69 (dd, J = 13.8, 7.9 Hz, 1H, 0.5CH_2 (benzylic)), 2.94 (dd, J = 13.8, 4.5 Hz, 1H, 0.5CH_2 (benzylic)), 3.40−3.51 (m, 1H, NCH), 3.76 (s, 3H, OCH_3), 5.32 (d, J = 4.3 Hz, 1H, NH), 6.77 (d, J = 8.5 Hz, 2H, 2CH), 7.01 (d, J = 8.4 Hz, 2H, 2CH), 7.28 (d, J = 8.1 Hz, 2H, 2CH), 7.79 (d, J = 8.1 Hz, 2H, 2CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 21.4, 39.7, 41.2, 53.0, 53.1, 55.1, 55.3, 113.7, 127.3, 129.1, 129.5, 130.4, 137.0, 143.2, 158.2.

(2*R*,4*S*)-4-Hydroxy-2-(4-methoxybenzyl)-4-methyl-1-(4-toluenesulfonyl)pyrrolidine (9). To a suspension of NaH (60% in mineral oil, 34 mg, 0.85 mmol) in dry benzene (3 mL) was added a solution of **8a** (40.0 mg, 0.106 mmol) in benzene (2 mL) under N_2. The mixture was refluxed for 18 h, cooled to rt, poured into crushed ice, and adjusted to pH 4.0 with 25% H_2SO_4. The benzene layer was separated, and the aqueous phase was extracted repeatedly with CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/hexanes, 1:4) to provide the cyclization product **9** (35 mg, 88%) as colorless crystals: mp 105−107 °C; $[\alpha]^{20}_D$ −63.6 (*c* 0.759, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (s, 3H, CH_3), 1.58 (dd, J = 13.6, 9.2 Hz, 1H, 0.5CH_2), 1.82 (ddd, J = 13.6, 3.6, 1.2 Hz, 1H, 0.5CH_2), 2.44 (s, 3H, benzylic CH_3), 3.04 (d, J = 10.2 Hz, 1H, 0.5CH_2N), 3.11 (dd, J = 13.4, 9.4 Hz, 1H, 0.5CH_2 (benzylic)), 3.24 (dd, J = 13.4, 4.0 Hz, 1H, 0.5CH_2 (benzylic)), 3.41 (dd, J = 10.5, 1.2 Hz, 1H, 0.5CH_2N),

3.74−3.84 (m, 1H, NCH), 3.79 (s, 3H, OCH_3), 6.86 (d, J = 8.7 Hz, 2H, 2CH), 7.21 (d, J = 8.4 Hz, 2H, 2CH), 7.35 (d, J = 8.4 Hz, 2H, 2CH), 7.77 (d, J = 8.1 Hz, 2H, 2CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 25.4, 41.2, 43.1, 55.2, 61.5, 61.6, 76.0, 113.9, 127.6, 129.7, 130.0, 130.9, 133.7, 143.7, 158.2; MS (EI) 358 (M −17, 3), 254 (43), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73. Found: C, 63.83; H, 6.76; N, 3.73.

(1*R*,4*S*)-1-Methyl-8-methoxy-3-(4-tosyl)-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine (10). Aluminum chloride (2.24 g, 16.8 mmol) was added to a solution of **9** (0.63 g, 1.68 mmol) in dry CH_2Cl_2 (30 mL). The mixture was stirred at rt for 12 h, poured into saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine successively, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/hexane, 1:10) to give, after one recrystallization, tricycle **10** (525 mg, 88%) as a colorless solid: mp 137−138 °C; 100% ee (determined by HPLC analysis); $[\alpha]^{20}_D$ −13.4 (*c* 0.969, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 3H, CH_3), 1.46 (ddd, J = 11.1, 6.3, 1.5 Hz, 1H, 0.5CH_2), 1.79 (d, J = 11.1 Hz, 1H, 0.5CH_2), 2.43 (s, 3H, benzylic CH_3), 2.93 (dd, J = 16.6, 2.8 Hz, 1H, 0.5CH_2), 3.02 (d, J = 8.7 Hz, 1H, 0.5CH_2), 3.12 (d, J = 16.8 Hz, 1H, 0.5CH_2), 3.40 (dd, J = 8.6, 1.4 Hz, 1H, 0.5CH_2), 3.79 (s, 3H, OCH_3), 4.39−4.45 (m, 1H. NCH), 6.72 (dd, J = 8.6, 2.8 Hz, 1H, CH), 6.78 (d, J = 2.1 Hz, 1H, CH),6.98 (d, J = 8.1 Hz, 1H, CH), 7.28 (d, J = 8.1 Hz, 2H, 2CH), 7.69 (d, J = 8.4 Hz, 2H, 2CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7, 21.5, 38.2, 41.7, 42.3, 55.3, 57.8, 62.9, 110.0, 111.7, 125.2, 127.1, 129.6, 130.4, 135.6, 143.1, 144.9, 157.9; MS (EI) 357 (M^+, 18), 202 (15), 173 (100). Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.18; H, 6.55; N, 3.80.

(1*R*,4*S*)-1-Methyl-8-methoxy-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine (11). To a solution of **10** (103 mg, 0.288 mmol) in xylene (3 mL) was added Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride in toluene, 65%, 0.32 mL, 1.07 mmol). The resultant mixture was heated at reflux for 1 h, cooled to rt, and poured onto wet Na_2SO_4. After filtration and washing with CH_2Cl_2/IPA (3:1), the filtrate was dried ($MgSO_4$) and concentrated. The residue was chromatographed (CH_2Cl_2/MeOH/Et_3N, 80:2:1) to give **11** (56 mg, 96%) as a colorless oil: $[\alpha]^{20}_D$ −54.6 (*c* 0.471, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.49 (s, 3H, CH_3), 1.85 (d, J = 11.2 Hz, 1H, 0.5CH_2), 1.92 (ddd, J = 11.2, 5.5, 1.0 Hz, 1H, 0.5CH_2), 2.37 (br s, 1H, NH), 2.73 (d, J = 16.9 Hz, 1H, 0.5CH_2), 2.90 (d, J = 10.0 Hz, 1H, 0.5CH_2), 3.02 (dd, J = 10.2, 0.8 Hz, 1H, 0.5CH_2), 3.09 (dd, J = 16.8, 2.7 Hz, 1H, 0.5CH_2), 3.75−3.90 (m, 1H, NCH), 3.79 (s, 3H, OCH_3), 6.71 (dd, J = 8.3, 2.6 Hz, 1H, CH), 6.83 (d, J = 2.6 Hz, 1H, CH), 7.02 (d, J = 8.3 Hz, 1H, CH). The HCl salt of **11**: mp 240−241 °C; ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.58 (s, 3H, CH_3), 2.14 (s, 2H, CH_2), 3.05−3.33 (m, 4H, 2CH_2), 3.75 (s, 3H, OCH_3), 4.34 (s, 1H, NCH), 6.80 (d, J = 8.1 Hz, 1H, CH), 6.84 (s, 1H, CH), 7.08 (d, J = 8.1 Hz, 1H, CH); ^{13}CNMR (MeOH-d_4, 75 MHz) δ 20.1, 35.7, 42.1, 43.3, 55.8, 58.5, 61.0, 110.5, 114.2, 123.5, 131.7, 145.4, 160.2. Anal. Calcd for $C_{13}H_{17}NO\cdot HCl\cdot{}^1/_2H_2O$: C, 62.77; H, 7.70; N, 5.63. Found: C, 62.66; H, 7.98; N, 5.58.

(+)-8*O*-Methylaphanorphine (12). A mixture of amine **11** (114 mg, 0.561 mmol), aqueous HCHO solution (37%, 0.50 mL, 6.71 mmol), and $NaCNBH_3$ (95%, 371 mg, 5.61 mmol) in methanol (8 mL) was stirred overnight at rt. After evaporation of the volatiles, the residue was partitioned between 5% HCl and ether, and the two layers were separated. The aqueous layer was washed one more time with ether, and the organic phase was discarded. The aqueous phase was made basic with concentrated NH_4OH, extracted with CH_2Cl_2/IPA (3:1), dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (CH_2Cl_2/MeOH/Et_3N, 100:2:1) to give aphanorphine methyl ether **12** (120 mg, 98%) as a colorless oil: $[\alpha]^{20}_D$ +8.7 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 Hz) δ 1.48 (s, 3H, CH_3), 1.86 (d, J = 10.8 Hz, 1H, 0.5CH_2), 2.01 (ddd, J = 11.0, 5.7, 1.6 Hz, 1H, 0.5CH_2), 2.47 (s, 3H, NCH_3), 2.72 (d, J = 9.3 Hz, 1H, 0.5CH_2), 2.81−2.84 (m, 1H, 0.5CH_2), 2.86−2.89 (m, 1H, 0.5CH_2), 3.02 (d, J = 16.5 Hz, 1H, 0.5CH_2), 3.37−3.43 (m, 1H, NCH), 3.79 (s, 3H, OCH_3), 6.70 (dd, J = 8.2, 2.6 Hz, 1H, CH), 6.79 (d, J = 2.7 Hz, 1H, CH), 7.03 (d, J = 8.1, Hz, 1H, CH). The HCl salt of **12**: mp 206−208 °C; ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.51 (s, 3H, CH_3), 2.07 (dd, J = 12.6, 1.2 Hz, 1H, 0.5CH_2), 2.36 (dd, J = 12.8, 6.2 Hz, 1H, 0.5CH_2), 2.88 (s, 3H, NCH_3), 3.06 (d, J = 11.4 Hz, 1H, 0.5CH_2), 3.14−3.20 (m, 2H, CH_2), 3.49 (d, J = 11.1 Hz, 1H, 0.5CH_2), 3.69 (s, 3H, OCH_3), 4.08−4.16 (m, 1H, NCH), 6.76 (d, J = 9.0 Hz, 1H, CH), 6.77 (s, 1H, CH), 7.04 (d, J = 9.0, Hz, 1H, CH); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 20.1, 35.0, 40.5, 43.3, 44.6, 55.8, 68.3, 71.9, 110.6, 114.4, 123.1, 131.7, 145.0, 160.3. Anal. Calcd for $C_{14}H_{19}NO\cdot HCl\cdot{}^1/_3H_2O$: C, 64.73; H, 8.02; N, 5.39. Found: C, 64.71; H, 7.76; N, 5.23.

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Supporting Information Available: ^{1}H NMR spectra of **4**, **6a**/**6b**, **7a**/**7b**, and their hydrogenation products, **8a**,**b**, **9**−**11**, **11**·HCl, **12**, and **12**·HCl as well as ^{13}C NMR spectra of **4**, **8a**,**b**, **9**, **10**, **11**·HCl, and **12**·HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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