A Practical Synthesis of 4-(Substituted-benzyl)piperidines and (±)-3-(Substituted-benzyl)pyrrolidines via a Wittig Reaction

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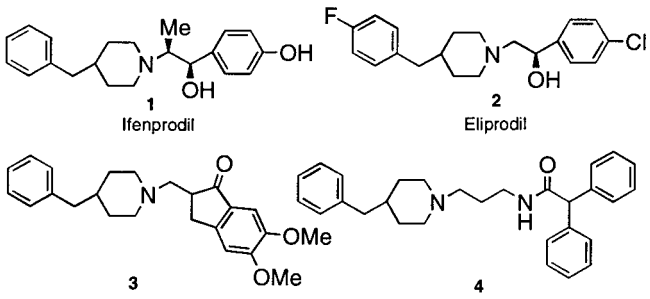
Introduction

4-Benzylpiperidines and their derivatives possess a range of physiological and pharmacological activities. For example, the antihypertensive agent ifenprodil (**1**) exhibits subtype selective NMDA antagonist activity, as well as high affinity for several other central nervous system (CNS) receptors, such as α_1 adrenergic, $5HT_{1A}$, $5HT_2$, and σ receptors.[1] Eliprodil (**2**) is a relative of ifenprodil that has been used for the treatment of stroke in clinical trials.[2] It was recently found that 4-benzyl-1-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidine (**3**) and related compounds exhibit highly potent acetylcholinesterase inhibitor activity.[3] Novel phenylacetamides such as *N*-[3-(4-benzylpiperidin-1-yl)propyl]-2,2-diphenylacetamide (**4**) have been shown to act as sodium channel blockers (Scheme 1).[4]

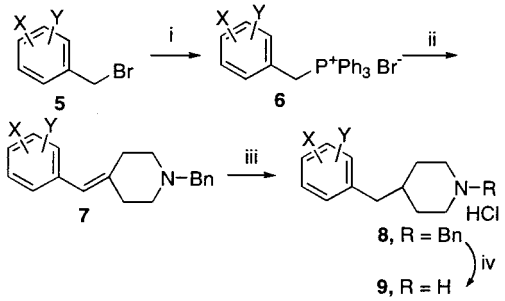
Our research program required a variety of 4-(substituted-benzyl)piperidines in gram quantities. Wick and coworkers[5] reported a four-step procedure for the preparation of 4-benzylpiperidines: (i) preparation of isonicotinic acid chloride; (ii) Friedel−Craft acylation of a substituted benzene to a ketone; (iii) Wolff−Kishner reduction of the ketone to the corresponding benzyl pyridines; and (iv) hydrogenation of the pyridines to the benzyl piperidines. The Friedel−Crafts reaction sometimes gave a mixture of ortho and para acylation products. Meta-substituted acylation products cannot be prepared by this route. In our hands, the yield of the Wolff−Kishner reduction step was highly variable, particularly in the case of 2-fluoro substitution on the phenyl ring. For example, Wolff−Kishner reduction of 2-fluoro-4-methylphenyl- and 2-fluorophenyl 4-pyridyl ketones proceeded in 0−50% yield. Herein, we report a practical approach to 4-(substituted-benzyl)piperidines in multigram amounts via a Wittig olefination reaction (Scheme 2).

The synthesis of 4-(3-fluorobenzyl)piperidine hydrochloride (**9b**) is illustrative. Reaction of commercially available 3-fluorobenzyl bromide (**5b**) with triphenylphosphine in ether at room temperature afforded the corresponding (3-fluorobenzyltriphenyl)phosphonium bromide (**6b**) in 85% yield. Treatment of **6b** with sodium methylsulfinyl carbanion[6] in dimethyl sulfoxide at 80 °C gave the corresponding ylide, which reacted with 1-benzyl-4-piperidone to form 4-(3-fluorobenzylidene)-1-benzylpiperidine (**7b**) in 73% yield. Reduction of **7b** with H_2 in the presence of PtO_2 and 1 M HCl gave 1-benzyl-4-(3-fluorobenzyl)piperidine hydrochloride (**8b**) in 82% yield. Further debenzylation of **8b** by hydrogenation in the presence of 10% Pd/C gave 4-(3-fluorobenzyl)piperidine hydrochloride (**9b**) in quantitative yield.

Scheme 1



Scheme 2[a]



[a] Key: (i) Ph_3P/ether/rt; (ii) NaH/DMSO/80 °C, then 1-benzyl-4-piperidone; (iii) PtO_2/MeOH/H_2, then HCl/MeOH; (iv) 10% Pd/C, 95% EtOH/H_2.

Two observations are noteworthy. Initial attempts to accomplish the Wittig olefination through the usual BuLi/ether gave alkene **7b** in only 13% yield, probably due to the poor solubility of the phosphonium salt in ether. In contrast, the methylsulfinyl carbanion−dimethyl sulfoxide system has been satisfactory for this Wittig reaction in every case investigated. Second, attempts to reduce the double bond and remove the benzyl group in one step resulted in partial reduction of the double bond and partial debenzylation. Stepwise reduction of the double bond and removal of the *N*-benzyl group consistently gave good yields.

Ten different substituted benzyl piperidines were prepared using this methodology (Table 1). Both mono- and disubstituted benzyl bromides including 2,6-difluorobenzyl bromide (**5e**) underwent the four-step procedure to afford the corresponding 4-(substituted-benzyl)piperidine hydrochloride in 58−80% overall yield.

The same methodology can also be successfully employed for the synthesis of the corresponding (±)-3-

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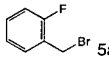
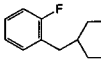
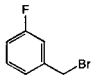
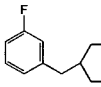
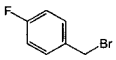
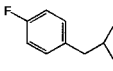
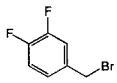
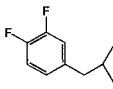
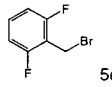
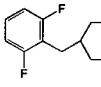
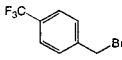
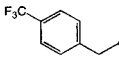
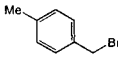
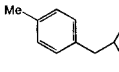
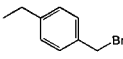
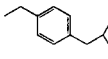
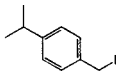
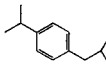
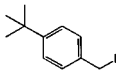
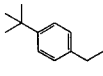
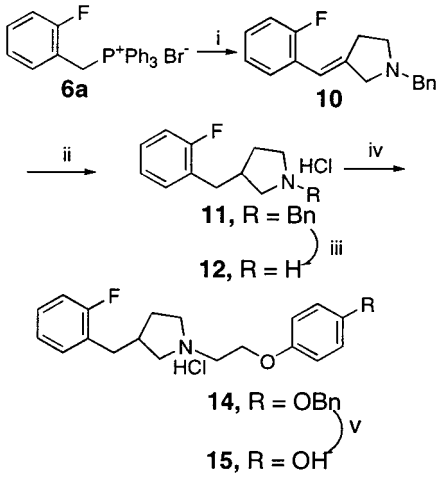
Table 1. Synthesis of 4-(Substituted-benzyl)piperidines via a Wittig Reaction[a]

Entry	Starting bromide 1	4-Benzylpiperidines 5	Overall yield (%)[b]
1	 5a	 9a	62
2	 5b	 9b	58
3	 5c	 9c	65
4	 5d	 9d	80
5	 5e	 9e	62
6	 5f	 9f	58
7	 5g	 9g	78
8	 5h	 9h	78
9	 5i	 9i	62
10	 5j	 9j	62

[a] All intermediates gave satisfactory ^{1}H NMR spectra. [b] Isolated yields based on starting benzyl bromide.

Scheme 3[a]



[a] Key: (i) NaH/DMSO/80 °C, then 1-benzyl-3-pyrrolidinone; (ii) PtO_2, MeOH/H_2, then 1 M HCl/MeOH; (iii) 10% Pd/C, 95% EtOH/H_2; (iv) *p*-$BrCH_2CH_2OC_6H_4OBn$ (**13**)/K_2CO_3/CH_3CN/reflux; (v) then 1 M HCl/MeOH, 66%; (v) 20% $Pd(OH)_2$/MeOH, 95%.

(substituted-benzyl)pyrrolidines (Scheme 3), which are otherwise difficult to make.[7] As an example, Wittig reaction of (2-fluorobenzyl)triphenylphosphonium bromide (**6a**) with 1-benzyl-3-pyrrolidinone under similar conditions provided an *E*/*Z* mixture of 3-(2-fluorobenzylidene)-1-benzylpyrrolidine (**10**) in 63% yield. Reduction of the double bond and debenzylation provided the desired (±)-3-(2-fluorobenzyl)pyrrolidine hydrochloride (**12**) in 93% yield as a clear oil. Reaction of **12** with 2-(4-benzyloxyphenoxy)ethyl bromide (**13**) provided the corresponding N-alkylation product (±)-**14** in 50% yield. Debenzylation of **14** gave (±)-3-(2-fluorobenzyl)-1-[2-(4-hydroxyphenoxy)ethyl]pyrrolidine hydrochloride (**15**) in 80% yield. Both compounds **14** and **15** gave satisfactory ^{1}H NMR and elemental analysis.

In summary, we describe herein a practical approach to 4-(substituted-benzyl)piperidines and (±)-3-(substituted-benzyl)pyrrolidines starting from a substituted benzyl bromide via phosphonium salt formation, Wittig olefination, reduction, and N-debenzylation with the advantage of mild reaction conditions, simple workup procedures, and satisfactory yields.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 300 MHz. Chemical shifts are reported in ppm (δ), and *J* coupling constants are reported in Hz. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Mass spectra (MS) were obtained with a VG 12-250 or VG ZAB-2FHF mass spectrometer. Reagent grade solvents were used without further purification unless otherwise specified. Reversed-phase HPLC analyses were monitored at 254 nM on a 4.6 × 250 mM Microsorb-MV C18 column, using as solvents 0.1% trifluoroacetic acid in water (A) and 0.1% trifluoroacetic acid in acetonitrile (B). The linear gradient was 20% B in A to 95% B in A with a flow rate of 1 mL/min.

Typical Procedure: (3-Fluorobenzyl)triphenylphosphonium Bromide (6b). To a solution of triphenylphosphine (31.48 g, 0.12 mol) in 200 mL of ether was added 3-fluorobenzyl bromide (**5b**) (22.68 g, 0.12 mol). The resulting solution was allowed to stir at room temperature overnight. The white solid was collected by filtration and dried to give 46.0 g (85%) of **6b** as a white solid: mp 290−292 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.52 (d, J = 14.7 Hz, 2 H), 6.73 (d, J = 9.6 Hz, 1 H), 6.89 (m, 2 H), 7.08 (m, 2 H), 7.62−7.76 (m, 15 H). Anal. Calcd for $C_{25}H_{21}BrFP$: C, 66.53; H, 4.69. Found: C, 66.30; H, 4.51.

1-Benzyl-4-(3-fluorobenzylidene)piperidine (7b). To a 250-mL three-necked round-bottom flask was added 1.2 g (60% in mineral oil, 0.03 mol) of NaH and 20 mL of dry DMSO. The mixture was heated at 80 °C for 1 h. The resulting solution was cooled in an ice−water bath. To this solution was added a suspension of (3-fluorobenzyl)triphenylphosphonium bromide (**6b**) (16.98 g, 0.03 mol) in 120 mL of warm DMSO. The resulting mixture was stirred at room temperature for 10 min. Then 1-benzyl-4-piperidone (5.67 g, 0.03 mol) was added dropwise under N_2. The resulting mixture was allowed to stir overnight and then was heated to 80 °C for another 8 h. The mixture was poured over ice and extracted with ether. The combined extract was dried over sodium sulfate. The solvent was evaporated in vacuo to give an oil, which was purified by flash chromatography, giving 6.12 g (73%) of **7b** as pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (m, 2 H), 2.47 (m, 2 H), 2.56 (m, 4 H), 3.56 (s, 2 H), 6.26 (s, 1 H), 6.91 (m, 3 H), 7.28 (m, 6 H); EIMS (*m*/*e*) 281 (M^+, 100), 204 (20), 190 (20), 146 (30), 91 (90). 42 (48); HRMS calcd for $C_{19}H_{20}FN$ 281.1586, found 281.1583 (HPLC 100%).

1-Benzyl-4-(3-fluorobenzyl)piperidine Hydrochloride (8b). To a solution of 1-benzyl-4-(3-fluorobenzylidene)piperidine (**7b**) (2.9 g, 10 mmol) in 100 mL of methanol was added 150 mg of PtO_2. The resulting mixture was hydrogenated at 30 psi for 4 h. The catalyst was removed through a short column of Celite (10 g) and was washed with methanol. To the filtrate was added 20 mL of 1 M HCl in methanol. The resulting mixture was

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stirred for 10 min. Evaporation of the solvent gave a residue to which ether (50 mL) was added. The resulting mixture was allowed to stir overnight. The white solid was collected by filtration and dried in vacuo, giving 4.0 g (96%) of **8b**: mp 153−155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (m, 1 H), 1.78 (m, 2 H), 2.11 (s, 2 H), 2.60 (s, 4 H), 3.45 (s, 2 H), 4.13 (s, 2 H), 6.86 (m, 3 H), 7.26 (m, 1 H), 7.43 (s, 3 H), 7.59 (s, 2 H), 12.40 (brs, 1 H). Anal. Calcd for $C_{19}H_{23}ClFN$: C, 71.35; H, 7.25; N, 4.38. Found: C, 71.33; H, 7.19; N, 4.60.

4-(3-Fluorobenzyl)piperidine Hydrochloride (9b). To a solution of 1-benzyl-4-(3-fluorobenzyl)piperidine hydrochloride (**8b**) (4.0 g, 13 mmol) in 100 mL of 95% ethanol was added 1.0 g of 10% Pd/C. The resulting mixture was hydrogenated at 50 psi for 4 h. The catalyst was removed through a short column of Celite (10 g) and was washed with ethanol. The filtrate was evaporated in vacuo to give a residue to which ether (50 mL) was added. The resulting mixture was allowed to stir overnight. The white solid was collected by filtration and dried in vacuo, giving 2.8 g (98%) of **9b**: mp 173−175 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.61−1.81 (m, 5 H), 2.59 (m, 2 H), 2.79 (m, 2 H), 3.48 (m, 2 H), 6.88 (m, 3 H), 7.25 (m, 1 H), 9.36 (s, 1 H), 9.63 (s, 1 H); EIMS *m/e* 194 ($M^+ + 1$, 15), 193 (M^+, 100), 192 ($M^+ - 1$, 60), 109 (50), 84 (80), 69 (60), 56 (95). Anal. Calcd for $C_{12}H_{17}ClFN$: C, 62.74; H, 7.46; N, 6.10. Found: C, 62.63; H, 7.25; N, 6.01.

4-(2-Fluorobenzyl)piperidine hydrochloride (9a): mp 178−180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.78 (m, 5 H), 2.64 (d, J = 4.3 Hz, 2 H), 3.45 (d, J = 9.0 Hz, 2 H), 7.00−7.09 (m, 3 H), 7.19 (m, 1 H), 9.38 (s, 1 H), 9.62 (s, 1 H). Anal. Calcd for $C_{12}H_{17}ClFN$: C, 62.74; H, 7.46; N, 6.10. Found: C, 62.46; H, 7.36; N, 5.95.

4-(4-Fluorobenzyl)piperidine hydrochloride (9c): mp 158−160 °C (lit.[5] mp 158−160 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.79 (m, 2 H), 1.96 (m, 2 H), 2.54 (d, J = 5.4 Hz, 2 H), 2.37 (m, 2 H), 3.42 (d, J = 14.7 Hz, 2 H), 6.98 (m, 2 H), 7.05 (m, 2 H), 9.50 (brs, 2 H).

4-(3,4-Difluorobenzyl)piperidine hydrochloride (9d): mp 174−175 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70−1.83 (m, 5 H), 2.56 (m, 2 H), 2.80 (m, 2 H), 3.46 (d, J = 8.1 Hz, 2 H), 6.83 (m, 1 H), 6.89 (m, 1 H), 7.05 (m, 1 H), 9.38 (s, 1 H), 9.60 (s, 1 H). Anal. Calcd for $C_{12}H_{16}ClF_2N$: C, 58.18; H, 6.51; N, 5.65. Found: C, 57.89; H, 6.43; N, 5.59.

4-(2,6-Difluorobenzyl)piperidine hydrochloride (9e): mp 216−218 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.83 (m, 5 H), 2.68 (s, 2 H), 2.81 (m, 2 H), 3.46 (d, J = 11.1 Hz, 2 H), 6.86 (m, 2 H), 7.18 (m, 1 H), 9.40 (s, 1 H), 9.62 (s, 1 H). Anal. Calcd for $C_{12}H_{16}ClF_2N\cdot 0.2H_2O$: C, 57.35; H, 6.58; N, 5.57. Found: C, 57.50; H, 6.62; N, 5.36.

4-(4-Trifluoromethylbenzyl)piperidine hydrochloride (9f): mp 208−210 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.76−1.85 (m, 5 H), 2.66 (s, 2 H), 2.79 (m, 2 H), 3.45 (d, J = 11.7 Hz, 2 H), 7.23 (d, J = 7.8 Hz, 2 H), 7.54 (d, J = 7.8 Hz, 2 H), 9.41 (s, 1 H), 9.66 (s, 1 H). Anal. Calcd for $C_{13}H_{17}ClF_3N\cdot 0.1H_2O$: C, 55.46; H, 6.16; N, 4.98. Found: C, 55.46; H, 6.00; N, 5.07.

4-(4-Methylbenzyl)piperidine hydrochloride (9g): mp 209−211 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70 (m, 3 H), 1.82 (m, 2 H), 2.32 (s, 3 H), 2.55 (m, 2 H), 2.78 (m, 2 H), 3.44 (d, J = 8.7 Hz, 2 H), 6.99 (d, J = 7.8 Hz, 2 H), 7.05 (d, J = 7.8 Hz, 2 H), 9.30 (s, 1 H), 9.60 (s, 1 H). Anal. Calcd for $C_{13}H_{20}ClN$: C, 69.16; H, 8.93; N, 6.20. Found: C, 69.02; H, 9.12; N, 6.10.

4-(4-Ethylbenzyl)piperidine hydrochloride (9h): mp 175−177 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J = 7.8 Hz, 3 H), 1.71 (m, 2 H), 1.83 (m, 3 H), 2.55−2.65 (m, 4 H), 2.78 (m, 2 H), 3.44 (d, J = 8.7 Hz, 2 H), 7.02 (d, J = 7.8 Hz, 2 H), 7.11 (d, J = 7.8 Hz, 2 H), 9.30 (s, 1 H), 9.60 (s, 1 H). Anal. Calcd for $C_{14}H_{22}ClN$: C, 70.13; H, 9.25; N, 5.84. Found: C, 69.78; H, 9.48; N, 5.71.

4-(4-Isopropylbenzyl)piperidine hydrochloride (9i): mp 183−185 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (d, J = 7.2 Hz, 6 H), 1.71 (m, 2 H), 1.83 (m, 3 H), 2.55 (m, 2 H), 2.78−2.88 (m, 3 H), 3.43 (d, J = 11.7 Hz, 2 H), 7.03 (d, J = 7.8 Hz, 2 H), 7.14 (d, J = 7.8 Hz, 2 H), 9.30 (s, 1 H), 9.60 (s, 1 H). Anal. Calcd for $C_{15}H_{24}ClN\cdot 0.2H_2O$: C, 69.98; H, 9.55; N, 5.44. Found: C, 70.06; H, 9.30; N, 5.29.

4-(4-*tert*-Butylbenzyl)piperidine hydrochloride (9j): mp 208−210 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 9 H), 1.68 (m, 3 H), 1.84 (m, 2 H), 2.55 (m, 2 H), 2.80 (m, 2 H), 3.44 (d, J = 12.3 Hz, 2 H), 7.04 (d, J = 8.1 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 9.30 (brs, 1 H), 9.61 (brs, 1 H). Anal. Calcd for $C_{15}H_{26}ClN\cdot 0.3H_2O$: C, 70.33; H, 9.81; N, 5.13. Found: C, 70.20; H, 9.62; N, 5.03.

(*E*/*Z*)-1-Benzyl-3-(2-fluorobenzylidene)pyrrolidine Hydrochloride (10). To a 250-mL three-necked round-bottom flask was added 0.64 g (60% in mineral oil) of sodium hydride and 15 mL of dry DMSO under N_2. The mixture was heated at 80 °C for 1 h. The resulting solution was cooled in an ice−water bath. To this solution was added a suspension of (2-fluorobenzyl)-triphenylphosphonium bromide (**6a**) (8.2 g, 0.018 mol) in 80 mL of warm DMSO. The resulting solution was stirred at 0 °C for 10 min and at room temperature for 15 min. Then 1-benzyl-3-pyrrolidinone (2.63 g, 15 mol) was added dropwise under N_2. The resulting mixture was allowed to stir at 80 °C overnight. Then the mixture was poured into ice and extracted with ether. The combined extracts were dried over sodium sulfate. The solvent was evaporated in vacuo to give a residue, which was purified by flash chromatography (eluent 5% EtOAc in hexanes), giving 2.5 g (63%) of the product as a pale yellow oil, 200 mg of which was dissolved into 10 mL of methanol and 2 mL of 1 M HCl in methanol was added. Evaporation of methanol gave a residue to which was added 30 mL of ether. A white solid was collected by filtration and dried to give 230 mg (100%) of the title compound: mp 187−189 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.90−3.17 (m, 3 H), 3.68 (m, 2 H), 4.15−4.43 (m, 3 H), 6.65 (s, 1 H), 7.14 (m, 3 H), 7.28 (m,1 H), 7.15 (m, 3 H), 7.62 (m, 2H), 13.30 (brs, 1 H).

(±)-1-Benzyl-3-(2-fluorobenzyl)pyrrolidine Hydrochloride (11). To a solution of 1-benzyl-3-(2-fluorobenzylidene)-pyrrolidine (**10**) (1.34 g, 5.0 mmol) in 50 mL of methanol was added 100 mg of PtO_2. The resulting mixture was hydrogenated at 40 psi for 8 h. The catalyst was removed through a short column of Celite and was washed with methanol. The filtrate was evaporated in vacuo and dissolved into 20 mL of methanol, to which was added 24 mL of 1 M HCl in methanol. The resulting solution was stirred for 10 min. Evaporation of methanol gave a residue, to which ether (60 mL) was added, and the mixture was stirred overnight. Evaporation of solvent gave **11** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62 (m, 3 H), 2.73 (m, 2 H), 2.93 (m, 2 H), 3.49 (m, 2 H), 3.65 (m, 2 H), 7.13 (m, 3 H), 7.26 (m, 2 H), 7.36 (m, 2 H), 7.62 (m, 2 H), 12.80 (brs, 1 H).

(±)-3-(2-Fluorobenzyl)pyrrolidine Hydrochloride (12). A mixture of 1-benzyl-3-(2-fluorobenzyl)pyrrolidine hydrochloride (**11**) (1.53 g, 5.0 mmol) and 0.66 g of 10% Pd/C in 50 mL of 95% ethanol was hydrogenated at 50 psi for 12 h. The catalyst was removed through a short column of Celite (10 g) and was washed with methanol. The filtrate was evaporated in vacuo to give a residue, to which ether (50 mL) was added, and the resulting mixture was stirred overnight. Evaporation of the solvent gave **12** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.77 (m, 2 H), 2.11 (m, 1 H), 2.660−2.96 (m, 4 H), 3.39 (m, 2 H), 6.99−7.20 (m, 4 H), 9.80 (s, 2 H).

(±)-1-[2-(4-Benzoxyphenoxy)ethyl]-3-(2-fluorobenzyl)-pyrrolidine Hydrochloride (14). A mixture of 2-(4-benzoxyphenoxy)ethyl bromide (**13**) (0.46 g, 1.50 mmol), 3-(2-fluorobenzyl)pyrrolidine hydrochloride (**12**) (0.323 g, 1.50 mmol), and potassium carbonate (0.518 g, 3.8 mmol) in 30 mL of acetonitrile was allowed to reflux for 12 h. The inorganic salt was removed through a short column of silica gel and washed with ethyl acetate. The combined filtrate was evaporated in vacuo to give a crude mixture, which was purified by flash chromatography (20% methanol in ethyl acetate) to give an oil, to which was added 3 mL of 1 M HCl in methanol. Evaporation of methanol gave a residue, to which ether (30 mL) was added, and then the mixture was allowed to stir overnight. An off-white solid was collected by filtration and dried in vacuo to give 0.25 g (38%) of the title compound: mp 116−118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82−2.30 (m, 3 H), 2.82 (m, 1 H), 2.94 (m, 3 H), 3.42 (m, 2 H), 3.86 (m, 2 H), 4.44 (m, 2 H), 5.02 (s, 2 H), 6.82−6.88 (m, 4 H), 7.06 (m, 2 H), 7.26 (m, 2 H), 7.41 (m, 5 H), 12.87 (brs, 1 H). Anal. Calcd for $C_{26}H_{29}ClFNO_2\cdot 0.5H_2O$: C, 69.24; H, 6.70; N, 3.11. Found: C, 69.15; H, 6.45; N, 3.11.

(±)-1-[2-(4-Hydroxyphenoxy)ethyl]-3-(2-fluorobenzyl)-pyrrolidine Hydrochloride (15). To a solution of 1-[2-(4-benzoxyphenyl)ethoxy]-3-(2-fluorobenzyl)pyrrolidine hydrochloride (**14**) (0.2 g, 0.45 mmol) in 30 mL of methanol was added 0.050 g of 20% $Pd(OH)_2$. The resulting mixture was hydroge-

nated at 30 psi of hydrogen for 4 h. The catalyst was removed through a short column of Celite (5 g) and washed with methanol. Evaporation of methanol gave a residue, to which ether (100 mL) was added, and the mixture was allowed to stir at room temperature overnight. The off-white solid was collected by filtration and dried in vacuo, giving 0.125 g (79%) of the title product: mp 75−77 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.70 (m, 2 H), 2.00(m, 2 H), 2.67 (m, 3 H), 3.42 (m, 4 H), 4.03 (m, 2 H), 6.52 (d, J = 9.0 Hz, 2 H), 6.64 (d, J = 9.0 Hz, 2 H), 6.94 (m, 2 H), 7.09 (m, 2 H). Anal. Calcd for $C_{19}H_{23}ClFNO_2 \cdot 0.7H_2O$: C, 62.61; H, 6.75; N, 3.84. Found: C, 62.60; H, 6.51; N, 4.19. (HPLC 100%).

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