Synthesis and Dopamine Receptor Affinities of *N*-Alkyl-11-hydroxy-2-methoxynoraporphines: *N*-Alkyl Substituents Determine D1 versus D2 Receptor Selectivity

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We developed a procedure to synthesize a series of *N*-alkyl-2-methoxy-11-hydroxynoraporphines from thebaine and evaluated their binding affinities at dopamine D_1 and D_2 receptors in rat forebrain tissue. At D_2 receptors, the most potent 10,11-catechol-aporphine was (*R*)-(−)-2-methoxy-*N*-*n*-propylnorapomorphine (D_2, K_i = 1.3 nM; D_1, K_i = 6450 nM), and the most selective and potent 11-monohydroxy aporphine was (*R*)-(−)-2-methoxy-11-hydroxy-*N*-*n*-propylnoraporphine (D_2, K_i = 44 nM; D_1, K_i = 1690 nM). In contrast, the *N*-methyl congeners (*R*)-(−)-2-methoxy-11-hydroxy-*N*-methyl-aporphine (D_1 vs D_2, K_i = 46 vs 235 nM) showed higher D_1 than D_2 affinity, indicating that *N*-alkyl substituents have major effects on D_2 affinity and D_2/D_1 selectivity in such 2-methoxy-11-monohydroxy-substituted aporphines.

Introduction

(*R*)-(−)-Apomorphine (APO) is a 10,11-catecholaporphine with dopamine (DA) receptor agonist activity that has been used as a pharmacological probe of DA receptors in a variety of central nervous system disorders. APO has been used successfully in the treatment of Parkinson's disease and erectile dysfunction (Figure 1).[1] For hydroxylated aporphines, the configuration at the 6a asymmetric carbon atom, the number and location of the hydroxyl groups, and the size of *N*-alkyl substituents at the nitrogen atom all appear to contribute to the affinity at D_1 and D_2 DA receptors.[2] The absolute configuration is critically important for interactions at DA receptors. Only the (*R*)-(−) enantiomer of apomorphine, obtained by the acid-catalyzed rearrangement of (−)-morphine, but not the (*S*)-(+)-enantiomer, possesses DA-agonist activity.[3] Total synthesis of racemic *R*,*S*-apomorphine followed by resolution has led to the synthesis and neuropharmacological assessment of a number of dihydroxy noncatechol, masked catecholic, mono- and trihydroxyaporphines, with or without C2 subsituents, as well as aporphines with various *N*-alkyl substituents.[2]

2-Substituted (*R*)-(−)-apomorphine analogues have also been prepared in several laboratories including ours (Figure 1).[4,5] We found that substituents in the 2-position of aporphines modulate dopaminergic receptor potency and D_2/D_1 selectivity and that most of these compounds display relatively high D_2 potency and D_2/D_1 receptor selectivity. DA receptor affinity and functional activity studies found that (*R*)-(−)-2-methoxyapomorphine [(*R*)-(−)-2-OMe-APO, **1d**], (*R*)-(−)-2-methoxy-*N*-*n*-propylnorapomorphine [(*R*)-(−)-2-OMe-NPA, **1c**], and 2-fluoro-*N*-*n*-propylnorapomorphine [(*R*)-(−)-2-F-NPA] were among the most potent and highly selective agonists for the D_2 receptor.[4]

APO has efficacy in the treatment of Parkinson's disease, but its poor oral bioavailability induced by susceptibility to oxidation of the 10,11-catechol moiety greatly limits its clinical utility[6] and encourages development of aporphines with greater oral bioavailability and longer action than are provided by APO. One means of enhancing oral bioavailability without losing DA agonist activity, is to eliminate the 10-hydroxy group in apomorphine to provide active (*R*)-(−)-11-monohydroxyaporphines. Our earlier investigations indicated that the 11-hydroxy group (analogous to the *m*-hydroxy group of DA) plays a crucial role in DA receptor affinity and that 10,11-dihydroxy substitution is not required for dopaminergic activity.[4g] These earlier investigations led to the preparation and neuropharmacological evaluation of (*R*)-(−)-11-hydroxy-*N*-*n*-propylnoraporphine [(*R*)-(−)-11-OH-NPa, **2b**], a compound displaying high affinity and selectivity for the D_2 receptor.[7]

Based on these findings, we investigated the synthesis of a series of 11-monohydroxy (*R*)-(−)-aporphines with a 2-methoxy substituent, and various alkyl groups at the 6N position (compounds **3a**−**d**), and evaluated their DA receptor affinities in rat forebrain tissue.

Chemistry. We considered several approaches to the preparation of (*R*)-(−)-*N*-alkyl-11-hydroxy-2-methoxyaporphines[8] and developed a facile procedure using the Pd/C-catalyzed reduction of *N*-alkyl-2-methoxy-10-*O*-[(trifluoromethyl)sulfonyl]-11-hydroxyaporphines **8** with Mg metal in MeOH at room temperature (RT) in the presence of NH_4OAc (Scheme 1). Thebaine **5a** was *O*-demethylated with L-Selectride using the procedure reported by Rice to obtain oripavine **6a**.[9] Thebaine **5a** was also converted to northebaine **4**.[4f] *N*-Alkylnororipavines **6b**−**d** were obtained by *N*-alkylation of northebaine **4**, followed by 3-*O*-demethylation with L-Selectride. 3-*O*-Triflation of oripavine **6a** and its *N*-alkyl derivatives **6b**-**d** with $PhNTf_2$, followed by acid catalyzed rearrangement,[4h] led to the aporphine triflates **8a**−**d**. Further Pd/C-catalyzed reduction with Mg metal in MeOH at RT in the presence of NH_4OAc provided the target *N*-alkyl-11-hydroxy-2-methoxyaporphines **3a**−**d**[8,10] (Scheme 1).

Results and Discussion

We obtained the *in vitro* affinities of compounds **1a**−**d** and **3a**−**d** at DA D_1 and D_2 receptors in rat striatum tissue using competitive binding assays with membrane homogenates of rat striatum tissue, following procedures reported in detail previously.[7] The data show that the 2-methoxy-substituted analogues of (*R*)-(−)-APO and (*R*)-(−)-NPA led to >2857-fold and 4862-fold D_2 over D_1 receptor selectivity, respectively (Table 1). Introduction of a 2-methoxy substituent into (*R*)-(−)-11-OH-NPa increased D_2-over-D_1 selectivity from 24.5-fold to 38.4-

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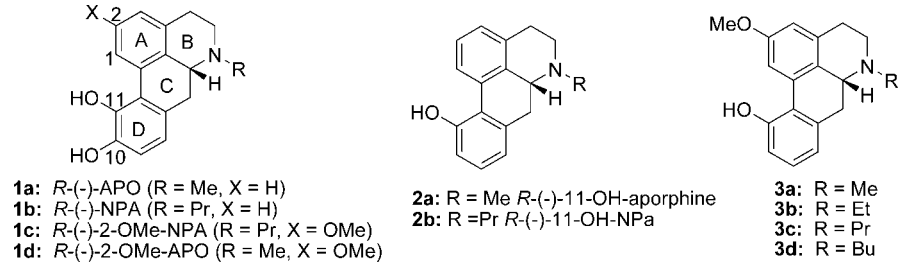


Figure 1. Structures of potent aporphine analogues.

Scheme 1. Synthesis of *N*-Alkyl-11-hydroxy-2-methoxynoraporphines **3**

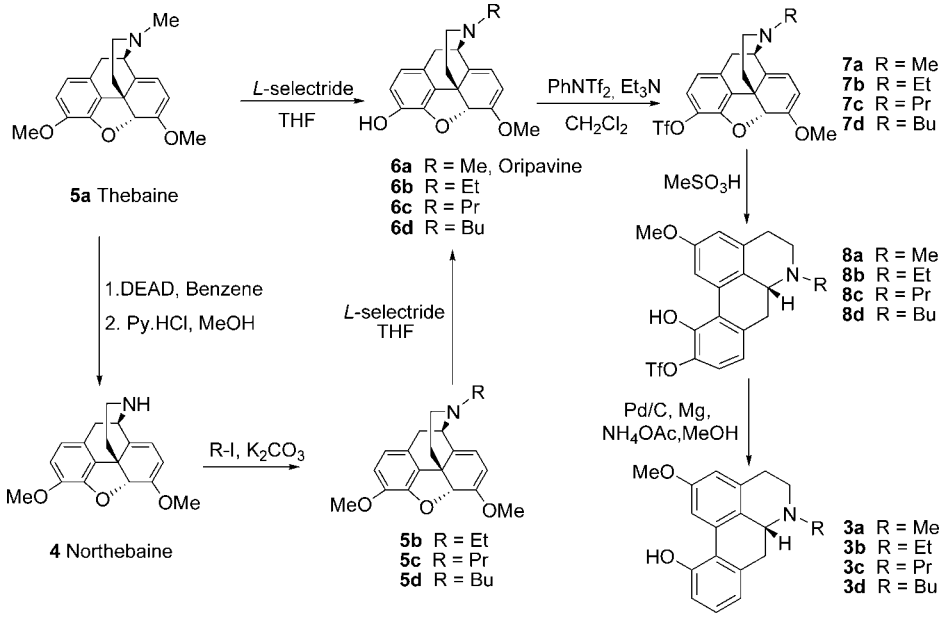
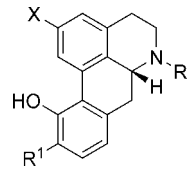


Table 1. Affinities (K_i) for Rat Forebrain D_1 and D_2 Receptors[a]



compd	R	R^1	X	K_i (nM) D_1	K_i (nM) D_2	D_2/D_1 potency ratio
1a APO	Me	OH	H	1010 ± 105	1.9 ± 0.5	532
1b NPA	Pr	OH	H	3410 ± 300	0.9 ± 0.3	3789
1c 2-OMe-NPA	Pr	OH	OMe	6450 ± 130	1.3 ± 0.4	4862
1d 2-OMe-APO	Me	OH	OMe	>10000	3.5 ± 0.8	>2857
2a 11-OH-aporphine	Me	H	H	26.5 ± 1.0[b]	108 ± 11[b]	0.24
2b 11-OH-NPa	Pr	H	H	699 ± 118[b]	28.5 ± 12.8[b]	24.5
3a	Me	H	OMe	46.0 ± 2.8	235 ± 32	0.19
3b	Et	H	OMe	130 ± 20	28.0 ± 6.0	4.60
3c	Pr	H	OMe	1690 ± 130	44.0 ± 8.3	38.4
3d	Bu	H	OMe	>10000	>10000	

[a] Radioligands: D_1, [^{3}H]SCH23390; D_2, [^{3}H]nemonapride. [b] From ref 7b.

fold. As with 10,11-dihydroxy (catechol) aporphines (**1a**−**d**) with or without a 2-methoxy substituent, switching the *N*-methyl to *N*-propyl increased D_2 selectivity. However, *N*-methyl-11-monohydroxyaporphines showed preferential affinity at D_1 over D_2 DA receptors, with or without a 2-methoxy substituent (Table 1). To further understand the affect of *N*-alkyl substituents on D_1/D_2 selectivity, we also synthesized the *N*-ethyl- (**3b**) and *N*-*n*-butyl-2-methoxy-11-hydroxynorapophines (**3d**) and evaluated their D_1 and D_2 receptor binding affinities. The *N*-ethyl analogue (**3b**) was D_2 selective, whereas the *N*-*n*-butyl analogue (**3d**) was inactive at both D_1 and D_2 receptors. Our findings therefore indicate that the *N*-alkyl substituent in 11-monohydroxyaporphines greatly affects their selective interactions at D_1 or D_2 receptors.

Conclusion

The present findings support the following tentative conclusions: (1) The presence of a single hydroxyl group in 11-

hydroxyaporphines is sufficient to confer affinity and activity at DA receptors; (2) introduction of a 2-methoxy moiety on the A-ring of catechol aporphines increases D_2-over-D_1 selectivity; (3) for 11-monohydroxy aporphines, the *N*-substituent determines dopamine receptor selectivity: D_1 is preferred with *N*-methyl, and D_2 is preferred with an *N*-*n*-propyl substituent; (4) the combination of both *N*-propyl or *N*-ethyl and 2-methoxy substituents, as in (*R*)-(−)-2-methoxy-*N*-propyl-11-hydroxynoraporphine **3c** or in (*R*)-(−)-2-methoxy-*N*-ethyl-11-hydroxynoraporphine **3b**, produced high D_2 affinity (44 nM for **3c** and 28 nM for **3b**, Table 1). Such monohydroxy aporphines are expected to have higher chemical stability and oral bioavailability than catechol-aporphines such as apomorphine and *N*-*n*-propylnorapomorphine.

Experimental Section

General Synthetic Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent, except compounds **8a**, **8b**, **8c**, and **3d** were in DMSO-d_6, on a Bruker AC300 spectrometer. Chemical shifts are given as δ value (ppm) downfield from tetramethylsilane as an internal reference. Melting points were determined on a Thomas-Hoover capillary tube apparatus and are reported uncorrected. GC−MS analyses were performed with a Hewlett-Packard 5890 (Wilmington, DE) gas chromatograph interfaced with a Hewlett-Packard 5972 mass selective detector. Element analyses, performed by Atlantic Microlabs, Atlanta, GA, were within ± 0.4% of theoretical values. Analytical thin-layer chromatography (TLC) was carried out on 0.2-mm Kieselgel 60F-254 silica gel plastic sheets (EM Science, Newark, NJ). Flash chromatography was used for the routine purification of reaction products.

Northebaine (4). A mixture of thebaine (12 g, 38.5 mmol) and diethyl azodicarboxylate (DEAD) (8.7 g, 7.8 mL, 50 mmol) in dry benzene (80 mL) was refluxed for 3 days. The mixture was evaporated, and MeOH (100 mL) was added to the system followed by pyridine hydrochloride (7.08 g, 61.6 mmol). The mixture was stirred overnight. The solvent was evaporated *in vacuo* to provide a brown gum. MeOH (5 mL) and EtOAc (200 mL) were added to the mixture and stirred for 2 days. The mixture was filtered to yield northebaine hydrochloride as a white solid (4.8g, 37%): mp 270–272 °C (lit.[11] mp 270–272 °C).

General Procedure for the Synthesis of *N*-Alkylnorthebaines 5b−d. A mixture of RI (12 mmol), K_2CO_3 (3.04 g, 22 mmol), and northebaine hydrochloride (3.30 g, 10 mmol) in EtOH (70 mL) was refluxed overnight. Ethanol was removed *in vacuo*. Water (50 mL) was added into the residue and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by chromatography over a short column of silica gel, eluting with CH_3OH/CH_2Cl_2 (1:100, vols).

***N*-Ethylnorthebaine (5b):** oil (74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 5.57 (d, J = 6.5 Hz, 1H), 5.30 (s, 1H), 5.03 (d, J = 6.5 Hz, 1H), 3.85 (s, 3H), 3.77 (d, J = 7.2 Hz, 1H), 3.60 (s, 3H), 3.30 (d, J = 17.7 Hz, 1H), 2.82–2.74 (m, 3H), 2.70–2.62 (m, 2H), 2.19 (m, 1H), 1.74 (dt, J = 12.0 and 2.7 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 144.6, 142.8, 133.4, 131.9, 127.5, 119.2, 112.7, 111.9, 95.8, 89.1, 58.4, 56.3, 54.9, 47.7, 46.4, 43.6, 36.6, 30.3, 12.8.

***N*-Propylnorthebaine (5c):** solid (68%); mp 134–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (d, J = 8.2 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 5.54 (d, J = 6.4 Hz, 1H), 5.29 (s, 1H), 5.03 (d, J = 6.4 Hz, 1H), 3.85 (s, 3H), 3.70 (d, J = 6.9 Hz, 1H), 3.59 (s, 3H), 3.28 (d, J = 18.0 Hz, 1H), 2.81–2.66 (m, 3H), 2.54–2.49 (m, 2H), 2.19 (m, 1H), 1.70 (m, 1H), 1.58–1.50 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 144.6, 142.7, 133.5, 132.7, 127.8, 119.1, 112.7, 111.4, 95.9, 89.2, 58.8, 56.3, 56.2, 54.9, 46.5, 44.2, 36.9, 30.4, 21.0, 12.0.

***N*-Butylnorthebaine (5d):** oil (65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (d, J = 8.2 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 5.54 (d, J = 6.4 Hz, 1H), 5.29 (s, 1H), 5.03 (d, J = 6.4 Hz, 1H), 3.84 (s, 3H), 3.71 (d, J = 6.9 Hz, 1H), 3.59 (s, 3H), 3.28 (d, J = 18.0 Hz, 1H), 2.85–2.66 (m, 3H), 2.57–2.52 (m, 2H), 2.18 (m, 1H), 1.70 (dt, J = 12.3 and 2.7 Hz, 1H), 1.56–1.46 (m, 2H), 1.42–1.27 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 144.6, 142.7, 133.5, 132.6, 127.8, 119.1, 112.7, 111.5, 95.9, 89.2, 58.8, 56.3, 54.9, 53.9, 46.5, 44.2, 36.9, 30.4, 30.0, 20.8, 14.1.

General Procedure for the Synthesis of Oripavine (6a) and *N*-Alkylnororipavines 6b−d. A mixture of thebaine (or *N*-alkylnorthebaine, 9 mmol) and 18 mL L-Selectride (1.0 M in THF) were heated under reflux for 30 min. After cooling to rt, the mixture was poured into 50 mL of ice–water, and 10 mL of 1 N NaOH was added. The mixture was extracted with CH_2Cl_2 (50 mL × 3). At 0–5 °C, the aqueous phase was acidified to pH = 1–2 with 10% (vol) HCl and then made basic to pH 9–10 with NH_4OH. The mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with brine (100 mL), dried with sodium sulfate, and concentrated in vacuo. The residue was purified by chromatography over a short column of silica gel eluting with CH_3OH/CH_2Cl_2 (1:20, vol) to provide *N*-alkylnororipavine.

Oripavine (6a): solid (28%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 5.58 (d, J = 6.4 Hz, 1H), 5.27 (s, 1H), 5.06 (d, J = 6.4 Hz, 1H), 3.73 (d, J = 7.2 Hz, 1H), 3.59 (s, 3H), 3.33 (d, J = 18.3 Hz, 1H), 2.98–2.89 (m, 1H), 2.77–2.69 (m, 2H), 2.48 (s, 3H), 2.24 (m, 1H), 1.72 (dd, J = 12.6 and 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 143.1, 139.0, 132.7, 131.8, 126.2, 119.7, 116.6, 112.1, 96.2, 89.0, 60.6, 54.9, 46.2, 45.6, 41.6, 36.0, 30.4.

***N*-Ethylnororipavine (6b):** solid (25%); mp 130–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 5.57 (d, J = 6.4 Hz, 1H), 5.27 (s, 1H), 5.05 (d, J = 6.4 Hz, 1H), 3.83 (d, J = 6.9 Hz, 1H), 3.59 (s, 3H), 3.29 (d, J = 18.3 Hz, 1H), 2.88–2.66 (m, 5H), 2.20 (m, 1H), 1.70 (d, J = 12.3 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 143.0, 138.8, 133.0, 132.3, 126.5, 119.7, 116.5, 111.9, 96.2, 89.2, 58.3, 54.9, 47.4, 46.7, 43.3, 36.1, 30.9, 12.5.

***N*-Propylnororipavine (6c):** foam (37%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 8.1 Hz, 1H), 5.59 (d, J = 6.4 Hz, 1H), 5.28 (s, 1H), 5.03 (d, J = 6.4 Hz, 1H), 3.86 (d, J = 6.9 Hz, 1H), 3.56 (s, 3H), 3.39 (d, J = 18.3 Hz, 1H), 3.02–2.63 (m, 5H), 2.22 (m, 1H), 1.70–59 (m, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 143.5, 139.4, 133.0, 126.2, 119.9, 117.1, 113.3, 96.3, 89.0, 59.4, 55.4, 55.1, 53.6, 46.7, 43.7, 31.9, 28.6, 20.3, 12.2.

***N*-Butylnororipavine (6d):** oil (15%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 5.57 (d, J = 6.4 Hz, 1H), 5.27 (s, 1H), 5.05 (d, J = 6.4 Hz, 1H), 3.80 (d, J = 6.6 Hz, 1H), 3.59 (s, 3H), 3.31 (d, J = 18.0 Hz, 1H), 2.90–2.58 (m, 5H), 2.21 (m, 1H), 1.70 (d, J = 12.6 Hz, 1H), 1.58–1.48 (m, 2H), 1.39–1.27 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 143.0, 138.6, 132.9, 132.1, 126.6, 119.8, 116.4, 112.0, 96.3, 89.3, 58.9, 54.9, 53.5, 46.7, 43.8, 36.1, 31.0, 29.5, 20.8, 14.0.

General Procedure for the Synthesis of *N*-Alkyl-3-*O*-[(trifluoromethyl)sulfonyl]oripavines 7a–d. Under nitrogen, *N*-phenyltrifluoromethanesulfonimide (11 mmol) was added to a mixture of *N*-alkylnororipavine (10 mmol) and triethylamine (2.1 mL, 15 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at rt for 3 h. The reaction mixture was washed with 30 mL of water and 30 mL of brine. The organic layer was dried with anhydrous Na_2SO_4, and the solvent was evaporated. The residue was dissolved in ether (60 mL) and extracted with 1 M HCl (4 × 50 mL). The combined acidic layer was basified with ammonium hydroxide, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine (80 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated. The residue was purified by chromatography over a short column of silica gel, eluting with CH_2Cl_2/MeOH (20:1) to yield the product.

3-*O*-[(Trifluoromethyl)sulfonyl]oripavine (7a): solid (75%); mp 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 8.6 Hz, 1H), 6.66 (d, J = 8.6 Hz, 1H), 5.59 (d, J = 6.4 Hz, 1H), 5.39 (s, 1H), 5.06 (d, J = 6.4 Hz, 1H), 3.64 (d, J = 6.9 Hz, 1H), 3.61 (s, 3H), 3.34 (d, J = 18.6 Hz, 1H),2.82–2.63 (m, 3H), 2.46 (s, 3H), 2.24 (ddd, J = 12.6, 5.1 and 5.1 Hz, 1H), 1.75 (dd, J = 12.6 and 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 147.85, 136.0, 135.7, 131.2, 131.1, 121.5, 119.7, 118.7 (q, J = 318 Hz), 112.2, 96.3, 90.8, 60.3, 55.0, 45.9, 45.7, 42.3, 36.6, 29.8.

***N*-Ethyl-3-*O*-[(trifluoromethyl)sulfonyl]nororipavine (7b):** oil (73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J = 8.6 Hz, 1H), 6.65 (d, J = 8.6 Hz, 1H), 5.56 (d, J = 6.5 Hz, 1H), 5.38 (s, 1H), 5.06 (d, J = 6.5 Hz, 1H), 3.72 (d, J = 7.2 Hz, 1H), 3.61 (s, 3H), 3.30 (d, J = 18.6 Hz, 1H), 2.77–2.68 (m, 3H), 2.53–2.49 (m, 2H), 2.23 (m, 1H), 1.74–1.68 (m, 1H), 1.58–1.51 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 147.8, 136.1, 135.9, 131.2, 131.2 121.4, 119.7, 118.6 (J = 319 Hz), 112.4, 96.3, 90.8, 58.0, 55.0, 47.7, 46.5, 43.4, 36.3, 30.7, 12.9.

***N*-Propyl-3-*O*-[(trifluoromethyl)sulfonyl]nororipavine (7c):** solid (72%); mp 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J = 8.2 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.56 (d, J = 6.5 Hz, 1H), 5.38 (s, 1H), 5.06 (d, J = 6.5 Hz, 1H), 3.72 (d, J = 7.2 Hz, 1H), 3.61 (s, 3H), 3.30 (d, J = 18.6 Hz, 1H), 2.77–2.68 (m, 3H), 2.53–2.49 (m, 2H), 2.23 (m, 1H), 1.74–1.68 (m, 1H), 1.58–1.51 (m, 2H), 0.94 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 147.8, 136.2, 136.0, 131.6, 131.2, 121.4, 119.7, 118.6 (J = 319 Hz), 112.1, 96.3, 90.8, 58.5, 56.1, 55.0, 46.5, 43.8, 36.5, 31.0, 21.0, 11.9.

***N*-Butyl-3-*O*-[(trifluoromethyl)sulfonyl]nororipavine (7d):** oil (75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 5.57 (d, J = 6.6 Hz, 1H), 5.38 (s, 1H), 5.06 (d, J = 6.6 Hz, 1H), 3.73 (d, J = 7.2 Hz, 1H), 3.61 (s, 3H), 3.30 (d, J = 18.6 Hz, 1H), 2.77–2.68 (m, 3H), 2.57–2.52 (m, 2H), 2.23 (m, 1H), 1.74–1.69 (m, 1H), 1.56–1.46 (m, 2H), 1.42–1.28 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ151.9, 147.8, 136.2, 136.0, 131.5, 131.2, 121.4, 119.7, 118.7 (J = 322.5 Hz), 112.2, 96.3, 90.8, 58.4, 54.9, 53.9, 46.5, 43.9, 36.4, 30.9, 29.9, 20.7, 14.0.

General Procedure for the Synthesis of *N*-Alkyl-2-methoxy-10-*O*-[(trifluoromethyl)sulfonyl]-11-hydroxynoraporphines 8a–d. The triflates **7a–d** (5.6 mmol) were dissolved in 99% (vol) methanesulfonic acid (15 mL, 232 mmol) under nitrogen at rt. The resulting mixture was stirred for 30 min at 90 °C and then cooled to rt. Ice–water (50 mL) was added, and the mixture was made basic with ammonium hydroxide and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine (50 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated. The residue was purified by chromatography over a short column of silica gel, eluting with CH_2Cl_2/MeOH (50:1, vol), and recrystalized from methanol to yield compounds **8a−d**.

(*R*)-(−)-2-Methoxy-10-*O*-[(trifluoromethyl)sulfonyl]-11-hydroxyaporphine (8a): solid (56%); mp 168–170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (br, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 2.7 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.71 (dd, J = 12.9 and 2.7 Hz, 1H), 3.75 (s, 3H), 3.25–2.67 (m, 6H), 2.44 (s, 3H), 2.38–2.16 (m, 1H). Anal. ($C_{19}H_{18}NF_3O_5S$) C, H, N.

(*R*)-(−)-*N*-Ethyl-2-methoxy-10-*O*-[(trifluoromethyl)sulfonyl]-11-hydroxynoraporphine (8b): solid (42%); mp 178–180 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.64 (s, br, 1H), 7.24 (dd, J = 8.1 and 5.1 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.70 (dd, J = 12.9 and 2.4 Hz, 1H), 3.74 (s, 3H), 3.23–2.88 (m, 6H), 2.70 (m, 1H), 2.38–2.11 (m, 2H), 1.05 (t, J = 5.7 Hz, 3H). Anal. ($C_{20}H_{20}NF_3O_5S$) C, H, N.

(*R*)-(−)-*N*-Propyl-2-methoxy-10-*O*-[(trifluoromethyl)sulfonyl]-11-hydroxynoraporphine (8c): solid (44%); mp 173–175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (br, 1H), 7.25 (t, J = 8.1 Hz, 1H), 7.18 (d, J = 2.7 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.72 (dd, J = 12.3 and 2.7 Hz, 1H), 3.76 (s, 3H), 3.19–3.11 (m, 3H), 3.00–2.65 (m, 3H), 2.35–2.26 (m, 3H), 1.52 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H).

(*R*)-(−)-*N*-Butyl-2-methoxy-10-*O*-[(trifluoromethyl)sulfonyl]-11-hydroxynoraporphine (8d): solid (45%); mp 165–167 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 2.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 3.75 (s, 3H), 3.29–2.85 (m, 5H), 2.67 (m, 1H), 2.53–2.41 (m, 3H), 1.58–1.48 (m, 2H), 1.40–1.32 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ158.0, 138.0, 135.0, 131.5, 130.6, 127.0, 126.6, 124.3, 120.3, 120.1, 118.3 (J = 270.8 Hz), 112.6, 111.1, 58.6, 55.2, 53.4, 48.5, 34.5, 28.8, 27.9, 20.7, 14.0. Anal. ($C_{22}H_{24}NF_3O_5S$) C, H, N.

General Procedure for the Synthesis of *N*-Alkyl-2-methoxy-11-hydroxynoraporphine 3a–d. Metallic Mg (36 mg, 1.5 mmol) and NH_4OAc (193 mg, 2.5 mmol) were added to a mixture of the triflates **8a–d** (0.5 mmol) and 10% (wt) Pd/C (44 mg) in MeOH (15 mL) at rt under nitrogen. The resulting mixture was stirred at rt for 24 h and filtered with Celite. The residue was washed with MeOH (2 × 20 mL). The filtrate was evaporated to dryness and dissolved in 100 mL of CH_2Cl_2. The solution was washed with 30 mL of 10% (wt) ammonium hydroxide and 50 mL of brine. The organic layer was dried with anhydrous Na_2SO_4 and evaporated *in vacuo* to dryness. The residue was purified by chromatography over a short column of silica gel, eluting with CH_2Cl_2/MeOH (100:1, vol), and recrystallized from CH_2Cl_2 to yield a colorless solid. The free base was converted to HCl salt with 1 N HCl−ether.

(*R*)-(−)-2-Methoxy-11-hydroxyaporphine (3a): solid (75%); mp (base) 214–215 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.61 (d, J = 2.7 Hz, 1H), 7.08 (dd, J = 7.2 and 7.8 Hz, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 3.80 (s, 3H), 3.25–3.02 (m, 4H), 2.76–2.49 (m, 3H), 2.55 (s, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 158.0, 152.8, 138.5, 134.5, 132.4, 128.2, 127.4, 121.1, 120.7, 115.6, 111.9, 111.1, 61.8, 55.2, 53.1, 43.9, 35.3, 29.4; MS (EI): m/z 281 (M^+). Anal. ($C_{18}H_{19}NO_2$) C, H, N.

(*R*)-(−)-*N*-Ethyl-2-methoxy-11-hydroxynoraporphine (3b): solid (66%); mp (HCl salt) 214–215 °C; ^{1}H NMR (base) (300 MHz, $CDCl_3$) δ 7.68 (d, J = 2.5 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 6.79 (d, J = 7.2 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 3.78 (s, 3H), 3.35 (d, J = 13.5 Hz, 1H), 3.21–3.05 (m, 4H), 2.76–2.50 (m, 4H), 1.18 (t, J = 6.9 Hz, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 157.8, 153.0, 138.3, 134.4, 132.8, 128.1, 127.3, 121.2, 120.3, 115.6, 111.9, 111.4, 58.6, 55.2, 48.0, 47.7, 34.9, 29.1, 10.5; MS (EI) m/z 296 $(M + H)^+$. Anal. ($C_{19}H_{21}NO_2 \cdot HCl \cdot 0.9H_2O$) C, H, N.

(*R*)-(−)-*N*-Propyl-2-methoxy-11-hydroxynoraporphine (3c): solid (76%); mp (HCl salt) 188–190 °C dec; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.68 (d, J = 2.7 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 2.7 Hz, 1H), 3.78 (s, 3H), 3.35 (d, J = 13.5 Hz, 1H), 3.21–3.05 (m, 3H), 2.92–2.89 (m, 1H), 2.74–2.68 (m, 1H), 2.59–2.43 (m, 3H), 1.65–1.57 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 157.8, 153.1, 138.5, 134.5, 132.8, 128.1, 127.6, 121.2, 120.3, 115.6, 111.9, 111.4, 59.2, 56.3, 55.2, 48.9, 35.1, 29.2, 19.0, 12.1; MS (EI) m/z 310 $(M + H)^+$. Anal. ($C_{20}H_{23}NO_2 \cdot HCl \cdot 1.25H_2O$) C, H, N.

(*R*)-(−)-*N*-Butyl-2-methoxy-11-hydroxynoraporphine (3d). solid (55%); mp (HCl salt) 218–220 °C dec; ^{1}H NMR (HCl salt, 300 MHz, DMSO-d_6) δ 11.02 (br, 1H), 10.16 (s, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.86 (d, J = 7.2 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 4.29 (m, 1H), 3.82 (m, 1H), 3.77 (s, 3H), 3.53–3.27 (m, 3H), 3.16–2.88 (m, 4H), 1.80–1.72 (m, 2H), 1.45–1.33 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (HCl salt, 75 MHz, DMSO-d_6) δ158.2, 154.8, 135.3, 133.2, 131.4, 128.7, 121.1, 119.5, 119.3, 115.9, 113.7, 110.7, 59.0, 55.1, 52.6, 47.9, 31.1, 25.9, 24.7, 19.6, 13.6; MS (EI) m/z 324 $(M + H)^+$. Anal. ($C_{21}H_{25}NO_2 \cdot HCl \cdot 1.25H_2O$) C, H, N.

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Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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