10-Substituted 11-Oxygenated (*R*)-Aporphines: Synthesis, Pharmacology, and Modeling of 5-HT_{1A} Receptor Interactions

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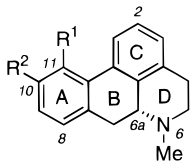
Derivatives of the selective serotonin 5-HT_{1A} receptor agonist (*R*)-11-hydroxy-10-methylaporphine (**2**) having various substituents in the C10-position or at the nitrogen have been synthesized from natural morphine or 6-*O*-acetylcodeine, respectively. The C10-substituents were introduced using efficient Stille or Suzuki cross-coupling reactions. The compounds were evaluated for their affinities to 5-HT_{1A} and dopamine (DA) D_1 and D_{2A} receptors *in vitro*. All compounds tested displayed low (micromolar) affinities to D_1 and D_{2A} receptors. In addition, changes in steric bulk and/or electronic properties of the C10-substituent as compared to a C10-methyl group, as well as substitution of the *N*-methyl group for a hydrogen or a larger *N*-alkyl group, produced a marked decrease in the affinities to 5-HT_{1A} receptors. Selected compounds that displayed moderate to high affinities to 5-HT_{1A} receptors were evaluated for their ability to stimulate 5-HT_{1A} receptors *in vivo*. The evaluated compounds behaved as agonists at 5-HT_{1A} receptors, except for the *N*-propyl analogue of **2**, (*R*)-11-hydroxy-10-methyl-*N*-propylnoraporphine (**23**), which displayed weak DA receptor agonism at the doses tested. Hence, the substitution pattern of **2** (a C10-methyl, a C11-hydroxy, and an *N*-methyl group) appears to be optimal for potent interaction of 10,11-disubstituted (*R*)-aporphines with 5-HT_{1A} receptors. Modeling of ligand−5-HT_{1A} receptor interactions was performed in an attempt to rationalize the observed affinity data. The binding site model suggests the presence of a "methyl pocket" in the 5-HT_{1A} receptor binding site. The C11-methoxy-substituted aporphines appear to have a different binding mode compared to **2**, implying a different accessibility of these compounds to the "methyl pocket".

Introduction

Various analogues of the nonselective dopamine (DA) agonist (*R*)-apomorphine (**1**) have been prepared previously in order to explore structure−activity relationships (SAR) of this class of conformationally rigid DA analogues at D_1 and D_2 receptors.[1] One of these compounds, (*R*)-11-hydroxy-10-methylaporphine (**2**, HYMAP),[2] lacks dopaminergic effects but displays potent and selective serotonin 5-HT_{1A} receptor agonist properties.[2a,c] In addition, the nonselective D_1 receptor antagonist (*R*)-11-hydroxyaporphine (**4**)[1c] is a weak partial 5-HT_{1A} receptor agonist having affinity also to D_{2A} receptors.[2c]



1 R^1=OH; R^2=OH
2 R^1=OH; R^2=Me
3 R^1=OMe; R^2=Me
4 R^1=OH; R^2=H

In order to study the importance of the C10- and *N*-substituents in **2** for serotonergic potency and selectivity, we have now synthesized and tested a series of derivatives of **2** having various substituents in the C10-position or at the nitrogen. The C10-substituents were introduced by use of efficient palladium-catalyzed Stille and Suzuki cross-coupling reactions[3] of triflates **5**[2b,c,4] and **8**.[2b,c] The noraporphines were synthesized from 6-*O*-acetylcodeine (**16**)[5] using a combination of the previously reported sequence for the synthesis of **2**[2b,c] and *N*-demethylation/*N*-alkylation reactions.

The compounds were pharmacologically evaluated *in vitro* for their affinities to 5-HT_{1A}, D_1, and D_{2A} receptors. Selected aporphines having high affinities to 5-HT_{1A} receptors were also evaluated in biochemical and behavioral assays *in vivo*. The difference in 5-HT_{1A} receptor binding profiles were rationalized by modeling of ligand−receptor interactions using a homology-based receptor model of the 5-HT_{1A} receptor binding site.

Chemistry

Synthesis. The novel aporphines **9**−**14** were prepared following the synthetic strategy described recently for compounds **2**−**4** and **7**.[2b,c,6] The methods used are shown in Scheme 1.

The cross-coupling reactions of triflate **8**[2b,c] with stannanes were performed following the recently reported procedure for sterically hindered, electron-rich aryl triflates.[3a] This procedure appeared to be superior to earlier protocols.[3b,c] Compound **9** was prepared from **8** by cross-coupling with tributyl(2-furyl)stannane. Attempts to use (2-furyl)boronic acid[7] as the transmetalating agent in a Suzuki reaction[3d,e] were unsuccessful.

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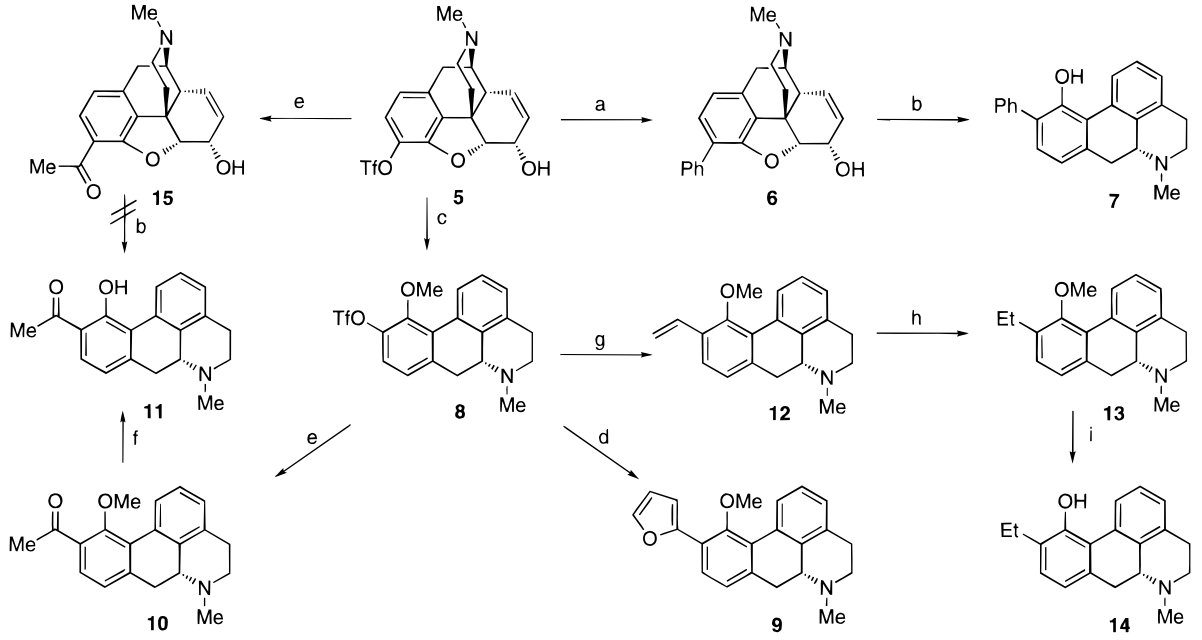
Scheme 1[a]

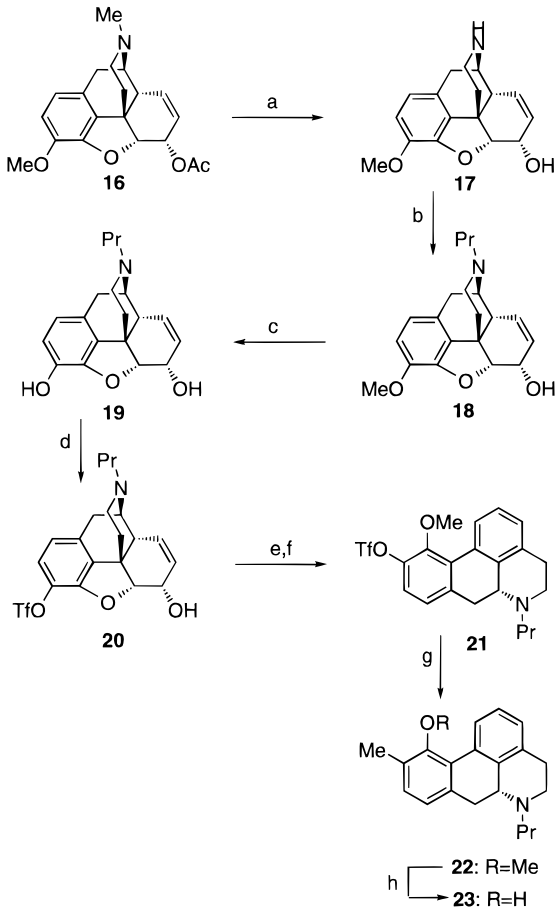


[a] Reagents: (a) $PhB(OH)_2$, $Pd(PPh_3)_4$, LiCl, EtOH, DME, 2 M aqueous Na_2CO_3, reflux; (b) $MeSO_3H$, N_2, 95 °C; (c) i. $MeSO_3H$, N_2, ii. CH_2N_2, Et_2O, $CHCl_3$; (d) tributyl(2-furyl)stannane, $(PPh_3)_2PdCl_2$, PPh_3, LiCl, DMF, 120 °C; (e) i. $(PPh_3)_2PdCl_2$, LiCl, tributyl(1-ethoxyvinyl)stannane, PPh_3, DMF, 120 °C, ii. 1 M HCl, THF; (f) BBr_3, $CHCl_3$, rt; (g) tributylvinylstannane, PPh_3, LiCl, $(PPh_3)_2PdCl_2$, DMF, 120 °C; (h) H_2, 10% Pd(C), THF; (i) 48% HBr, N_2, reflux. Tf = CF_3SO_2−.

This can be compared with the successful result reported with triflate **5**[4] in a similar Suzuki reaction and may be due to the increased sterical hindrance in compound **8**.[8] Cross-coupling of **8** with tributyl(1-ethoxyvinyl)stannane followed by acid hydrolysis of the intermediate vinyl ether gave **10**. Attempts to perform a Heck coupling of **8** with butyl vinyl ether[9] were unsuccessful. The vinyl derivative **12** was obtained by cross-coupling of tributylvinylstannane with **8**. The C10-ethyl derivative **13** was obtained by hydrogenation of **12**. Cross-coupling of **8** with tetraethylstannane was not attempted due to the presumed ease of β-hydride elimination from the postulated intermediate *trans*-bis-(triphenylphosphine)ethyl[(*R*)-11-methoxyaporphin-10-yl]palladium(II). This would probably give the hydrogenolysis product (*R*)-11-methoxyaporphine[1c,2] as the main product, in analogy with results reported by Saá *et al.*[3a] Demethylation of **10** and **13** gave **11** and **14**, respectively. In an attempt to synthesize **11** from **15**[4] by an acid-catalyzed rearrangement, we isolated the retro-Friedel−Crafts product **4** (73% yield). Similar reactions have been reported previously for various ketones.[10] The preparation of **8** from triflate **5** has been described previously.[2c]

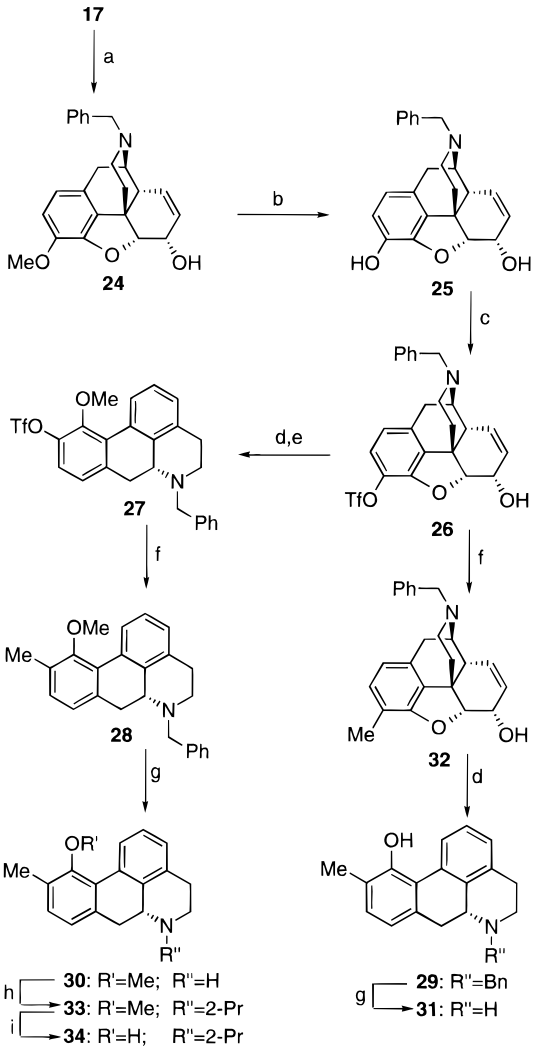
6-*O*-Acetylcodeine (**16**)[5] was utilized as starting material in the synthetic sequence leading to the noraporphine derivatives (Schemes 2 and 3). This approach was attractive because few successful methods for *N*-demethylation of aporphines have been reported in the literature. Cyanogen bromide,[11] chloroformates,[12] or diethyl diazodicarboxylate[13] produce ring opening of the aporphine skeleton, leading to the isolation of (aminoethyl)phenanthrene derivatives. Treatment of an aporphine with hydrogen peroxide, to give the corresponding *N*-oxide, followed by reductive *N*-demethylation with liquid sulfur dioxide as described by Cava and Srinivasan,[14] gave a low yield of the desired noraporphine. The use of electron transfer photooxidation for the

Scheme 2[a]



[a] Reagents: (a) i. $CH_3CHClOCOCl$, $Cl(CH_2)_2Cl$, reflux, ii. MeOH, reflux, iii. HCl (aq), MeOH; (b) propanal, $NaBH_4$, EtOH, H_2O, HOAc, NaOAc, 0 °C; (c) BBr_3, CH_2Cl_2, N_2, −10 to −2 °C; (d) $PhN(Tf)_2$, CH_2Cl_2, Et_3N, N_2, rt or reflux; (e) $MeSO_3H$, N_2, 95 °C; (f) CH_2N_2, $CHCl_3$, ether; (g) Me_4Sn, PPh_3, LiCl, $(PPh_3)_2PdCl_2$, DMF, 120 °C; (h) 48% HBr, N_2, reflux. Tf = CF_3SO_2−.

Scheme 3[a]



[a] Reagents: (a) $PhCH_2Br$, K_2CO_3, DMF, rt; (b) BBr_3, CH_2Cl_2, N_2, −10 to −2 °C; (c) $PhN(Tf)_2$, CH_2Cl_2, Et_3N, N_2, rt or reflux; (d) $MeSO_3H$, N_2, 95 °C; (e) CH_2N_2, $CHCl_3$, ether; (f) Me_4Sn, PPh_3, LiCl, $(PPh_3)_2PdCl_2$, DMF, 120 °C; (g) H_2, 10% Pd(C), HOAc; (h) 2-iodopropane, diisopropylethylamine, K_2CO_3, CH_3CN, 70 °C; (i) 48% HBr, N_2, reflux. Tf = CF_3SO_2−.

N-demethylation of an aporphine as described by Santamaria *et al.*[15] would probably offer a possibility to perform *N*-demethylation at the aporphine stage instead but requires special equipment. In contrast, *N*-demethylation of **16** using 1-chloroethyl chloroformate, as reported by Olofson *et al.*,[12a] gives an excellent yield of the corresponding norcodeine derivative under comparably mild conditions and with a simplified workup procedure in comparison to other methods.[16] *N*-Demethylation[12a] of **16** followed by hydrolysis of the resulting acetate gave **17**[17] (Scheme 2). Reductive amination of propanal[18] with **17** afforded **18**,[19] which was demethylated using a modified version of the protocol reported by Rice[20] to produce **19**.[21] Intermediate **21** was synthesized from **19** using a protocol described previously.[2b,c] Cross-coupling of **21** with tetramethylstannane afforded **22**, which was demethylated to give **23**, the *N*-propyl analogue of **2**.

N-Alkylation of **17** with benzyl bromide afforded **24**,[22] which was demethylated to **25**[23] and further converted to triflate **26** (Scheme 3). Acid-catalyzed rearrangement of **26** followed by *O*-methylation produced **27**. Cross-coupling of **27** with tetramethylstannane afforded **28**, and a subsequent hydrogenolysis gave **30**. Alkylation of **30** with 2-iodopropane using the conditions described by Liu *et al.*[24] gave **33**, which was *O*-demethylated to **34**. Cross-coupling of **26** with tetramethylstannane afforded **32**, which was rearranged in methanesulfonic acid to **29**. Hydrogenolysis of **29** gave **31**, the nor-analogue of **2**. An alternative synthesis of **31** was performed by demethylation of **30**.

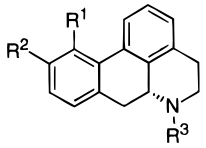
Molecular Modeling. Low-energy conformations of selected nonprotonated (*R*)-aporphines were identified by molecular mechanics MM2(91)[25] calculations using the torsion angle driver procedure as described previously.[2c] When studying intermolecular interactions between the ligand and active site residues, the protonated form of the ligands was used.

A model of the human 5-HT_{1A} receptor, based on a presumed homology in three-dimensional structure between bacteriorhodopsin and the G-protein-coupled receptors,[26,27] has been constructed previously.[2c] This model was adjusted to correct for the revision of the amino acid sequence of the 5-HT_{1A} receptor.[28] Based on results from mutation studies and previous modeling of receptor−ligand interactions,[2c,28,29] Asp116, Ser199, and Phe362 were initially considered as interaction points in the 5-HT_{1A} receptor model. Allowed conformations of these Asp and Ser residues were probed in Sybyl by a systematic search around their side chain torsion angles. Starting orientations of **2** in the resulting 5-HT_{1A} models were obtained by fitting extended N^+-H and O-lone pair points onto the Asp-O and Ser-O; as a third fitting point, an extended normal through the A-ring was used to fit onto the centroid of the Phe residue. The rms value of the fit was used together with the common volume of ligand and active site residues to select complexes for further optimization.

Active site optimization was performed in the pseudoreceptor/minireceptor modeling program Yak[30] in a stepwise manner using high-affinity ligands of increasing size: **4**, **2**, and (*R*)-11-phenylaporphine (**35**).[31] Prior to Yak optimization, two spheres were defined around the ligand(s) of interest by selecting residues that had atoms within 5 and 7.5 Å of ligand atoms, respectively. All residues within the 7.5 Å sphere were transferred to Yak where the residues in the inner 5 Å sphere were optimized; the additional residues in the outer shell served to maintain the overall shape of the binding site. Refinement of the site by optimization of multiple ligands simultaneously was performed with 3 and 5 Å spheres, respectively. Yak minimizations were performed on both ligand(s) and residues simultaneously using the all-atom Yeti force field while keeping the backbone atoms fixed.[32] Translational and rotational degrees of freedom were considered for the ligand(s), whereas only torsional degrees of freedom were considered for the amino acids. Active site complexes resulting from Yak optimization of one ligand were used as the starting point for docking the next high-affinity ligand by fitting that ligand onto the optimized position of the first ligand using the protonated nitrogen, the C11-oxygen (C11 for **35**), and the A-ring centroid.

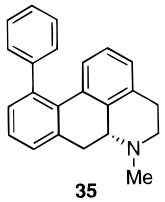
Optimization of **4** in the 5-HT_{1A} site resulted in interactions of this ligand with Asp116 and Ser168. Optimization of **2** in this site gave rise to unfavorable steric interactions between Asp116 and Asn386, as well as an unsatisfactory fit of the ligand. Manual adjust-

Table 1. Physical Data of Novel (*R*)-Aporphines



compd	R^1	R^2	R^3	mp (°C)	yield (%)	recrystn solvents[a]	$[\alpha]^{rt}_D$ (deg) (*c* 1.0, MeOH)	formula
7	OH	Ph	Me	246−250[b]	67	A	−52.0	$C_{23}H_{21}NO\cdot HCl$
9	OMe	2-furyl	Me	133−137	79		−129.7	$C_{22}H_{21}NO_2\cdot H_2C_2O_4\cdot{}^1/_4H_2O$
10	OMe	COMe	Me	209−213[b]	66	A	−179.6	$C_{20}H_{21}NO_2\cdot HCl$
11	OH	COMe	Me	247−251[b]	74	A	−143.3	$C_{19}H_{19}NO_2\cdot HCl$
12	OMe	CH=CH_2	Me	242−246[b]	71	A	−238.5	$C_{20}H_{21}NO\cdot HCl$
13	OMe	Et	Me	247−249[b]	76	B	−201.0	$C_{20}H_{23}NO\cdot HCl$
14	OH	Et	Me	227−230[b]	61	A	−107.4	$C_{19}H_{21}NO\cdot HCl\cdot{}^1/_4H_2O$
21	OMe	OTf	Pr	183−185	71	C	−73.0	$C_{21}H_{22}F_3NO_4S\cdot HCl$
22	OMe	Me	Pr	226−229[b]	86	D	−189.1	$C_{21}H_{25}NO\cdot HCl$
23	OH	Me	Pr	185−188	85	C	−94.9	$C_{20}H_{23}NO\cdot HCl$
27	OMe	OTf	Bn	134−138[b]	84		−33.0	$C_{25}H_{23}F_3NO_4S\cdot HCl$
28	OMe	Me	Bn	218−222	88		−128.0	$C_{25}H_{25}NO\cdot HCl\cdot{}^1/_4H_2O$
29	OH	Me	Bn	206−210[b]	77	A	−45.4[c]	$C_{24}H_{23}NO\cdot HCl\cdot{}^1/_2H_2O$
30	OMe	Me	H	272−276[b]	92	A and D	−222.9	$C_{18}H_{19}NO\cdot HCl$
31	OH	Me	H	313−315[b,d]	71	A	−121.2	$C_{17}H_{17}NO\cdot HCl$
33	OMe	Me	2-Pr	206−210	84	C	−202.2	$C_{21}H_{25}NO\cdot HCl$
34	OH	Me	2-Pr	198−203	94	E and F	−101.0	$C_{20}H_{23}NO\cdot HCl\cdot{}^1/_2H_2O$

[a] A: MeOH/ether. B: 2-PrOH/ether. C: MeCN/ether. D: MeCN. E: $CHCl_3$/ether. F: EtOH/EtOAc. [b] Decomposition. [c] (*c* 0.50, MeOH). [d] Green at 280−282 °C.



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ment of the torsion angles of Asp116, followed by optimization in Yak, relieved the unfavorable interactions and resulted in a better fit of the ligand, again interacting with both Asp116 and Ser168. An additional manual adjustment was made to accomplish a hydrogen bond between Ser199 and Ser168. The subsequent optimization of **35** in the active site resulted in a reorientation of this ligand placing the large C11-substituent in a hydrophobic pocket while maintaining the interaction of the protonated amine with Asp116. In a final step, both **2** and **35** were optimized together to yield the general model used for docking the current series of aporphines (Figure 1).

In our previous modeling study of ligand−5-HT_{1A} receptor interactions,[2c] Ser199 hydrogen bonds to the oxygen-containing moiety at C11 in the aporphines. In the model of the active site optimized to interact with **2**, Ser199 could indeed be rotated to hydrogen bond to the ligand. This interaction was however not compatible with the general model that also includes the nonoxygenated compound **35**. In addition, the hydrogen bond between Ser199 and Ser168 was lost when including **35** in the general model.

Possible binding modes of the different conformations of selected compounds in the 5-HT_{1A} receptor were examined by fitting the protonated N, (C11)O, and A-ring centroid of these structures onto **2** as docked in the active site. The 5 and 3 Å spheres were defined around the whole set of fitted ligands, and the resulting site was used to optimize the orientation of the individual ligands, together with the torsional degrees of freedom of the amino acids in the 3 Å sphere in Yak.

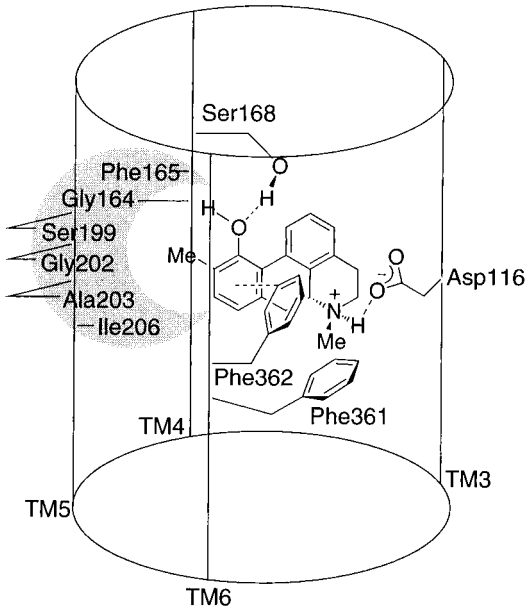

Figure 1. Schematic representation of the interaction between **2** and the 5-HT_{1A} receptor binding site showing only the helices involved in receptor−ligand interactions. A reinforced ionic bond between Asp116 and the protonated nitrogen, a hydrogen bond between Ser168 and the C11-hydroxyl group, and an edge-to-face interaction between Phe362 and the A-ring of **2** represent key interactions. Also indicated is the presence of the "methyl pocket".

Pharmacology

Receptor Binding Studies. The compounds were examined *in vitro* for their ability to displace [^{3}H]-8-OH-DPAT, [^{3}H]SCH23390, and [^{3}H]raclopride binding to rat hippocampal 5-HT_{1A}, rat striatal D_1, and cloned human D_{2A} receptors, respectively (Table 2). The receptor binding assays were performed essentially as described previously.[2c] All compounds tested have a decreased affinity to 5-HT_{1A} receptors as compared to **2**. The noraporphine **31** has the highest selectivity for 5-HT_{1A} sites of the compounds tested. All novel com-

Table 2. Affinities of Selected Aporphines for Rat Brain 5-HT_{1A} and D_1 Receptor Recognition Sites Labeled by [^{3}H]-8-OH-DPAT and [^{3}H]SCH23390, Respectively, and at Cloned Human D_{2A} Receptors Expressed in Ltk$^-$ Cells and Labeled by [^{3}H]Raclopride

	K_i (nM)[a]		
compd	[^{3}H]-8-OH-DPAT (5-HT_{1A})	[^{3}H]SCH23390 (D_1)[b]	[^{3}H]raclopride (D_{2A})[b]
1	296 ± 15[c]	236[d]	41.9 ± 4.7[c]
2	0.45 ± 0.13[c]	382 ± 35[c]	1070 ± 54[c]
3	7.5 ± 1.8	393 ± 15	248 ± 32
4	9.6 ± 3.1[c]	20.4 ± 1.0[c]	58.5 ± 9.5[c]
7	1090 ± 270	9400 ± 270	>1000
8	1621 ± 319	>2000	1040 ± 62
9	995 ± 7	14 000 ± 3200	582 ± 62
10	150 ± 39	4820 ± 900	2980 ± 180
11	1720 ± 300	4620 ± 470	2760 ± 260
12	108 ± 13	1440 ± 92	1750 ± 550
13	17.5 ± 0.2	1030 ± 30	411 ± 38
14	9.2 ± 0.3	782 ± 42	2050 (n = 1)
21	3300 ± 465	>2000	403 ± 106
22	10.8 ± 0.2	>2000	238 ± 32
23	12.3 ± 1.5	>2000	249 ± 46
28	1380 ±36	>5000	>5000
29	772 ± 60	>5000	>1000
30	12.6 ±0.6	>5000	4710 ± 3500
31	3.2 ± 0.2	23 800 ± 2800	>10 000
33	640 ±120	>5000	>1000
34	241 ±14	>10 000	>1000

[a] The K_i values are means ± standard errors of n = 2−3 experiments. [b] None of the compounds tested produced a clear biphasic binding profile at the D_1 and/or D_{2A} receptor. Therefore the results have been interpreted in terms of a one-site model. [c] From ref 2c. [d] From ref 33.

pounds display lower D_1 and D_{2A} receptor affinities as compared to the previously investigated **1**[33] and **4**.[1c,2c] The *N*-propylnoraporphine **23** displays increased affinity to D_{2A} receptors compared to its *N*-methylated analogue **2**.

Biochemistry and Behavior. The rationale for the *in vivo* biochemical experimental protocol is based on the well-established phenomenon of (auto)receptor-mediated feedback inhibition of presynaptic monoaminergic neurons.[34] Thus, the synthesis of 5-HT, DA, and norepinephrine (NA) is inhibited by 5-HT, DA, and α-adrenoceptor agonists, respectively. The *in vivo* effects of single doses of compounds **2**, **23**, and **31** on 5-hydroxytryptophan (5-HTP)/dihydroxyphenylalanine (DOPA) accumulation following decarboxylase inhibition by means of (3-hydroxybenzyl)hydrazine dihydrochloride (NSD1015, 117 mg/kg sc) were investigated in limbic forebrain, striatum, and cortex of reserpine-pretreated rats (Table 3).[35] The accumulation of 5-HTP following decarboxylase inhibition was taken as an indicator of the 5-HT synthesis rate in all three brain parts, whereas the accumulation of DOPA was taken as index of the synthesis rates of DA and NA in DA receptor-rich parts (limbic forebrain, striatum) and NA-predominated regions (cortex), respectively.[36] Compounds **2** (0.33 μmol/kg) and **31** (3.5 μmol/kg) decreased the cerebral 5-HTP levels by 30−40% and 50−60%, respectively. ED_{50} values were determined for these two compounds in all three brain regions to be 0.2, 0.3, and 0.3 μmol/kg for **2** and 1.3, 0.8, and 1.5 μmol/kg for **31** in limbic forebrain, striatum, and cortex, respectively. Compound **23** produced no effect on 5-HTP levels at the dose tested (3.0 μmol/kg). These results indicate that **2** and **31** are agonists at synthesis-controlling 5-HT_{1A} autoreceptors.[34c,d,37] Compound **23** produced a small but significant decrease in the DOPA levels in limbic forebrain and striatum.

Stimulation of postsynaptic 5-HT_{1A} receptors by means of agonists like (*R*)-8-hydroxy-2-(dipropylamino)tetralin [(*R*)-8-OH-DPAT] results in a clear-cut motor behavioral syndrome, the "5-HT syndrome", in rats. Flattened body posture, forepaw treading, and hindlimb abduction are the most prominent features of this syndrome.[35c,39] The ability of compounds **2**, **23**, and **31** to stimulate putative postsynaptic 5-HT_{1A} receptors was thus assessed by rating the occurrence and intensity of these behavioral components in reserpinized rats (Table 4). Immediately after this scoring session the rats were injected with NSD1015 and subsequently used for determination of brain 5-HT and catecholamine synthesis rates as described above. The known 5-HT_{1A} receptor agonist **2** was inactive at the dose tested (0.33 μmol/kg). However, **2** has been shown to induce a clear 5-HT syndrome at a higher dose (13 μmol/kg).[40] Compound **31** (3.5 μmol/kg) induced a clear-cut 5-HT syndrome, whereas **23** (30 μmol/kg) was inactive in this assay. These *in vivo* pharmacological data indicate that **2** and **31** are full agonists at 5-HT_{1A} receptors. The relatively high affinity of **23** to 5-HT_{1A} receptors (Table 2) coupled with its inability to reduce 5-HT synthesis or induce the behavioral 5-HT syndrome might suggest that **23** possesses weak partial agonist or antagonist properties at these sites. However, further work is needed to support this suggestion.

Discussion

On the basis of the *in vitro* receptor binding data, it may be concluded that a change of the steric bulk and/or the electronic properties of the C10-substituent in **2** reduces the affinity of the compounds to 5-HT_{1A} receptors. For example, the C10-ethyl derivative **14** displayed a 20-fold decrease in affinity to 5-HT_{1A} receptors as compared to **2**. The effects of various C10-substituents on the 5-HT_{1A} receptor binding affinity support the tentative presence of a lipophilic "methyl pocket" in the 5-HT_{1A} receptor binding site as was previously suggested by modeling studies of ligand−5-HT_{1A} receptor interactions.[2c] In the minireceptor model, the C10-methyl group of **2** is surrounded by Gly164, Phe165, Ser199, Gly202, Ala203, and Ile206 (Figure 1). Although an additional effect of the C10-methyl substituent on the conformational behavior of the C11-hydroxy group cannot be ruled out,[2a] the reduced affinity of the C10-ethyl-substituted **14** may be explained by a combination of steric repulsion and the fact that the conformation of the ethyl substituent most compatible with the site has a relative steric energy of 1.2 kcal/mol. Optimization of C11-hydroxy-, -methoxy-, and -phenyl-substituted aporphines in the active site showed a gradual change in binding orientation as described elsewhere in more detail.[31] This change implies a different position of the C10-substituent in C11-methoxylated vs C11-hydroxylated compounds. Whereas the C10-methyl-substituent of **2** appears to perfectly fit into a lipophilic pocket, the same substituent in the C11-methoxylated compound **3** does not occupy this pocket quite as well and, therefore, does not enhance binding affinity. A change of the C10-substituent from methyl to ethyl has a more dramatic effect on affinity in the C11-hydroxylated series than in the C11-methoxylated

Table 3. Effects of Selected (*R*)-Aporphines on Central 5-HTP and DOPA Accumulation in Reserpine-Pretreated Rats

compd	dose (μmol/kg)	*n*	5-HTP accumulation:[a] percent of saline controls, mean ± SEM			DOPA accumulation:[b] percent of saline controls, mean ± SEM		
			limbic forebrain	striatum	cortex	limbic forebrain	striatum	cortex
2	0.33	2	58 ± 2*	70 ± 8*	72 ± 9*	84 ± 8	90 ± 2	100 ± 6
23	3.0	4	104 ± 11	104 ± 13	102 ± 15	81 ± 9*	72 ± 9*	116 ± 13
31	3.5	3	37 ± 4*	47 ± 5*	40 ± 3*	85 ± 6	78 ± 12	93 ± 7

[a] Shown is the amount of accumulated 5-HTP in percent of saline controls (for **2** and **31**, 100% limbic forebrain 235 ± 33 ng/g, striatum 187 ± 11 ng/g, cortex 95 ± 11 ng/g, $n = 4$; for **23**, 100% limbic forebrain 164 ± 11 ng/g, striatum 158 ± 14 ng/g, cortex 123 ± 15 ng/g, $n = 3$), means ± SEM, $n = 2-4$. Statistical differences were calculated by one-way ANOVA followed by Fischer's protected least-significant-difference test (PLSD): * $p < 0.05$ vs. saline controls. [b] Shown is the amount of accumulated DOPA in percent of saline controls (for **2** and **31**, 100% limbic forebrain 765 ± 50 ng/g, striatum 3526 ± 323 ng/g, cortex 103 ± 11 ng/g, $n = 4$; for **23**, 100% limbic forebrain 674 ± 40 ng/g, striatum 2511 ± 173 ng/g, cortex 100 ± 7 ng/g, $n = 3$, means ± SEM, $n = 2-4$. Statistical differences were calculated by one-way ANOVA followed by Fischer's PLSD: *$p < 0.05$ vs saline controls.

Table 4. Postsynaptic 5-HT_{1A} Receptor-Mediated Behavior[a]

compd	dose (μmol/kg)	$\sum$ scores median (range)	*n*
saline control		0 (0−1)	3
2	0.33	0 (0−0)	3
23	30	0 (0−0)	3
31	3.5	3 (1−5)	3

[a] Behavioral scores according to a 4-point intensity-based rating scale (0 = absent, 1 = equivocal, 2 = clearly present, 3 = intense). Rating period 60 s bin, 30 min after drug administration, just before NSD1015 injection. Rats were pretreated with reserpine (5 mg/kg, sc) 18−20 h before.

series (compare **2** and **14** to **3** and **13**), again indicating a different position of the C10-substituent (Figure 2).

The low affinity of the C10-acetyl derivative **11** to 5-HT_{1A} receptors may be due to an energetically favored, resonance-stabilized intramolecular hydrogen bond between the phenol group and the carbonyl oxygen of this aporphine[41] [IR (CCl_4) 1634 cm^{-1} (C═O_{str}), indicating the presence of an intramolecular hydrogen bond[42b]]. Docking of this conformation into the receptor model results in unfavorable interactions between the carbonyl group of **11** and the carbonyl of Gly164 and between the acetyl-CH_3 and the backbone of Gly202 and Ala203. The methoxy analogue **10** [IR (CCl_4) 1681 cm^{-1} (C═O_{str})] is unable to form this hydrogen bond and displays more than 10-fold higher affinity (Table 2).

Compounds **28**, **29**, **33**, and **34** displayed particularly low affinities to 5-HT_{1A} and DA D_1/D_{2A} receptors, probably due to steric repulsions between the binding sites and the bulky *N*-benzyl and *N*-isopropyl groups. The space available for *N*-alkyl substituents in the 5-HT_{1A} receptor model is limited due to the presence of the Phe361 residue.

The data from the pharmacological evaluations *in vitro* and *in vivo* indicate that **2** and **31** are full agonists at 5-HT_{1A} receptors. Compound **2** has an approximately 7-fold higher affinity for the 5-HT_{1A} receptor *in vitro* than **31** but appears less efficiacious *in vivo* (higher dose to elicit 5-HT_{1A} appropriate behavior). This apparent paradox may be explained by the fact that **2** has not been behaviorally tested over an extended dose range (only 0.33 and 13 μmol/kg). Thus, the discrepancy may well be resolved by performing full behavioral dose−response studies with either agent. None of the novel compounds showed any pronounced affinity to D_1 and D_{2A} receptors in the assays used. In addition, **23** only produced a slight decrease in DOPA accumulation in the dose tested. Introduction of various carbon substituents in the C10-position of the aporphine skeleton appears to unfavorably influence the interaction with DA receptors as was previously rationalized by modeling the interaction of **2** with a homology-based model for the D_{2A} receptor.[2c]

In summary, these results indicate that some of the analogues of **2** presented in this study bind with fair affinity to 5-HT_{1A} receptors and are able to stimulate 5-HT_{1A} receptors in rats. The 10-methyl-11-hydroxy-*N*-methyl substitution pattern in **2** seems to be optimal for a potent interaction between the 5-HT_{1A} receptor and the aporphines, as was suggested by Cannon *et al.*[42] The 5-HT_{1A} receptor affinities may be rationalized by modeling of ligand−receptor interactions using homology-based model building and minireceptor optimization. A slightly different orientation of C11-methoxylated vs C11-hydroxylated aporphines and also the presence of a methyl pocket accommodating the C10-methyl substituent of **2** are crucial elements in the interaction site model.

Experimental Section

Chemistry. General Comments. Melting points (uncorrected) were determined in open glass capillaries using an Electrothermal melting point apparatus. Optical rotation measurements were obtained on a Perkin-Elmer 241 polarimeter. Elemental analyses (C, H, N) were performed at Mikrokemi AB, Uppsala, Sweden, and were within ±0.4% of the theoretical values. Infrared (IR) spectra were recorded on a Perkin-Elmer 298 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 spectrometer at 270 and 64.8 MHz, respectively, and referenced to internal tetramethylsilane. Assignment of signals from the morphine derivatives was done in accordance with previously published material.[2c,43] Thin-layer chromatography (TLC) was performed by using aluminum sheets precoated with either silica gel 60 F_{254} or aluminum oxide 60 F_{254} E neutral (0.2 mm, activity II−III; E. Merck). For preparative TLC, plates precoated with either silica gel F_{254} (2.0 mm) or aluminum oxide F_{254} T (1.5 mm) (E. Merck) were used. Column chromatography was performed on silica gel 60 (230−400 mesh; E. Merck) or aluminum oxide 90 (70−230 mesh; E. Merck). The organostannanes were purchased from Aldrich and used as delivered. Dimethylformamide (DMF) was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen. Physicochemical properties of novel aporphines are also given in Table 1.

(−)-3-Deoxy-3-phenylmorphine (6). A mixture of **5**[2b,c,4] (200 mg, 0.479 mmol), phenylboronic acid (88 mg, 0.72 mmol), $(PPh_3)_4Pd$ (14 mg, 0.012 mmol), and LiCl (41 mg, 0.96 mmol) was dissolved in 4 mL of 1,2-dimethoxyethane (DME) under nitrogen. After stirring for 10 min, EtOH (1 mL) and 2 M aqueous Na_2CO_3 (0.72 mL) were added. The mixture was refluxed under nitrogen at 95 °C for 3 h and then diluted with $CHCl_3$. The organic layer was extracted with 10% aqueous $NaHCO_3$, dried (K_2CO_3), filtered, and concentrated. The brown, oily residue was chromatographed [silica gel; $CHCl_3$/MeOH (19:1) and (9:1) followed by aluminum oxide; $CHCl_3$/MeOH (39:1)] to give, after recrystallization from ether/pentane, 132 mg (80%) of pure **6**:[2b] IR (KBr) 3550 cm^{-1}; ^1H

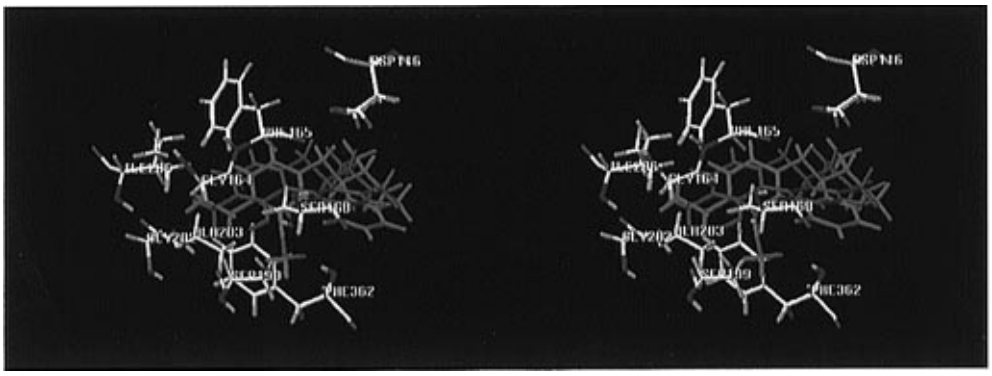

Figure 2. Stereorepresentation of the interaction of **2** (red) and **13** (green) with the 5-HT_{1A} receptor binding site model. The different orientations of the C11-hydroxylated **2** and the C11-methoxylated **13** are shown.

NMR ($CDCl_3$) δ 1.94 (ddd, 1 H), 2.11 (ddd, 1 H), 2.37 (app dd, 1 H), 2.45 (ddd, 1 H), 2.47 (s, 3 H), 2.63 (ddd, 1 H), 2.71−2.73 (m, 1 H), 3.12 (app d, 1 H), 3.38 (dd, 1 H), 4.18−4.22 (m, 1 H), 4.92 (dd, 1 H), 5.33 (ddd, 1 H), 5.66−5.72 (m, 1 H), 6.72 (app d, 1 H), 7.23−7.32 (m, 2 H), 7.36−7.45 (m, 1 H), 7.40 (d, 1 H), 7.68−7.72 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.1, 35.9, 40.9, 42.3, 43.1, 46.4, 58.7, 66.5, 90.7, 119.9, 120.6, 127.0, 127.6, 127.9, 128.3, 128.4, 128.5, 129.0, 130.4, 133.5, 134.6, 136.6, 155.9. Anal. ($C_{23}H_{23}NO_2$) C, H, N.

(−)-(*R*)-11-Hydroxy-10-phenylaporphine (7).[2b] Compound **7** was prepared from **6** following a procedure described previously.[2b] A solution of **6** (71 mg, 0.21 mmol) in $MeSO_3H$ (2 mL) was heated under nitrogen at 95 °C for 15 min. The acidic mixture was added dropwise to a stirred two-phase system of $CHCl_3$ and 10% aqueous $NaHCO_3$ to pH 9. The aqueous layer was extracted with $CHCl_3$, dried (Na_2SO_4), filtered, and concentrated. The black residue was chromatographed [silica gel; $CHCl_3$/MeOH (9:1) and aluminum oxide; ether/hexanes (4:1) followed by $CHCl_3$/MeOH (9:1)] followed by preparative TLC [silica gel; $CHCl_3$/MeOH (9:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeOH/ether to give 50 mg (67%) of pure **7**·HCl: IR (KBr) 2520, 3360 cm^{-1}; ^{1}H NMR (CD_3OD) δ 2.89 (dd, 1 H), 3.08−3.20 (m, 1 H), 3.20 (s, 3 H), 3.33−3.59 (m, 3 H), 3.76−3.85 (m, 1 H), 4.37 (dd, 1 H), 7.01 (app d, 1 H), 7.14 (app d, 1 H), 7.20 (d, 1 H), 7.34−7.53 (m, 5 H), 7.37 (dd, 1 H), 8.39 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 26.9, 33.2, 41.7, 53.5, 63.6, 121.6, 123.2, 128.5, 128.6, 129.0, 129.2, 129.6, 129.8, 130.5, 130.6, 131.5, 132.3, 133.8, 134.8, 139.6, 152.3.

(−)-(*R*)-10-(2-Furyl)-11-methoxyaporphine (9). A solution of **8**[2b,c] (98 mg, 0.236 mmol), $(PPh_3)_2PdCl_2$ (20 mg, 0.028 mmol), PPh_3 (37 mg, 0.14 mmol), and LiCl (82 mg, 1.9 mmol) in DMF (2 mL) was stirred at room temperature under nitrogen. After 5 min, tributyl(2-furyl)stannane (0.17 g, 0.47 mmol) dissolved in 3 mL of DMF and 2 crystals of 2,6-di-*tert*-butyl-4-methylphenol were added. After stirring for 20 min at 120 °C under nitrogen, the mixture was cooled and partitioned between CH_2Cl_2 and 10% aqueous $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed using preparative TLC [aluminum oxide; ether/hexanes (3:2) followed by silica gel; CH_2Cl_2/MeOH (9:1)]. The amine was converted into the oxalate salt, which, after drying at 0.1 mmHg at 55 °C, gave 80 mg (79%) of pure **9**·oxalate: IR (KBr) 2520, 1720 cm^{-1}; ^{1}H NMR (CD_3OD) δ 2.92 (dd, 1 H), 3.05−3.18 (m, 1 H), 3.15 (s, 3 H), 3.34−3.59 (m, 3 H), 3.49 (s, 3 H), 3.76−3.88 (m, 1 H), 4.41 (dd, 1 H), 6.56 (dd, 1 H), 7.03 (app d, 1 H), 7.20 (app d, 1 H), 7.25 (app d, 1 H), 7.41 (1 H, dd), 7.58 (dd, 1 H), 7.74 (d, 1 H), 8.38 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 26.6, 32.7, 41.5, 53.3, 60.1, 63.0, 111.0 , 113.0, 125.8, 126.5, 127.2, 128.0, 129.5, 129.8, 131.2, 132.8, 135.2, 143.1, 151.1, 155.4, 166.6.

(−)-(*R*)-10-Acetyl-11-methoxyaporphine (10). A solution of **8** (323 mg, 0.779 mmol), LiCl (271 mg, 6.39 mmol), PPh_3 (123 mg, 0.467 mmol), and $(PPh_3)_2PdCl_2$ (66 mg, 0.093 mmol) in DMF (10 mL) was stirred under nitrogen at room temperature. After 5 min tributyl(1-ethoxyvinyl)stannane (0.53 mL, 1.56 mmol) and 3 crystals of 2,6-di-*tert*-butyl-4-methylphenol were added. The reaction mixture was stirred for 2 h at 120 °C under nitrogen. The volatiles were evaporated, and the residue was partitioned between ether and water. The ether layer was concentrated, and the residue was dissolved in a mixture of THF (30 mL) and 1 M HCl (10 mL) and stirred until TLC indicated complete hydrolysis of the intermediate vinyl ether (30 min). The volatiles were evaporated, and the residue was partitioned between $CHCl_3$ and 10% aqueous $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered, and concentrated to give a residue, which was chromatographed [aluminum oxide; ether/hexanes (3:2) followed by silica gel; $CHCl_3$/MeOH (39:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeOH/ether to give 90 mg of pure **10**·HCl. The mother liquor from the recrystallization was extracted between $CHCl_3$ and 10% aqueous $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered, and concentrated, and the residue was chromatographed using preparative TLC [aluminum oxide; ether/hexanes (3:2)]. The amine [IR (CCl_4) 1681 cm^{-1}] was converted into the hydrochloride salt, which was recrystallized from MeOH/ether to give 86 mg of pure **10**·HCl (a total yield of 66%): IR (KBr) 2380, 1680 cm^{-1}; ^{1}H NMR (CD_3OD) δ 2.66 (s, 3 H), 2.96 (dd, 1 H), 3.10−3.25 (m, 1 H), 3.21 (s, 3 H), 3.41−3.67 (m, 3 H), 3.57 (s, 3 H), 3.79−3.89 (m, 1 H), 4.50 (app br d, 1 H), 7.27 (app d, 1 H), 7.30 (app d, 1 H), 7.43 (dd, 1 H), 7.55 (d, 1 H), 8.28 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 26.8, 31.2, 32.9, 42.2, 53.4, 62.4, 62.8, 125.7, 128.0, 128.2, 129.7, 129.8, 130.0, 130.3, 131.2, 132.2, 135.6, 140.4, 158.4, 202.3.

(−)-(*R*)-10-Acetyl-11-hydroxyaporphine (11). Compound **11** was prepared using a modified version of the procedure of McOmie *et al.*[44] A solution of **10** (136 mg, 0.442 mmol) in $CHCl_3$ (5 mL) was added dropwise to a stirred solution of BBr_3 (0.25 mL, 2.6 mmol) in $CHCl_3$ (10 mL) at room temperature under nitrogen. After stirring for 15 min, the solution was poured into a stirred two-phase system of $CHCl_3$ and 10% aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed [silica gel; $CHCl_3$ to $CHCl_3$/MeOH (39:1) gradient], and the amine [IR (CCl_4) 1637 cm^{-1}] was converted into the hydrochloride salt. Recrystallization from MeOH/ether gave 108 mg (74%) of pure **11**·HCl: IR (KBr) 2500, 1635 cm^{-1}; ^{1}H NMR (CD_3OD) δ 2.68 (s, 3 H), 2.95 (dd, 1 H), 3.06−3.22 (m, 1 H), 3.18 (s, 3 H), 3.35−3.57 (m, 3 H), 3.74−3.88 (m, 1 H), 4.38 (dd, 1 H), 7.01 (app d, 1 H), 7.23 (app d, 1 H), 7.39 (dd, 1 H), 7.89 (d, 1 H), 8.40 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 26.7, 27.1, 33.4, 41.5, 53.5, 62.7, 120.4, 121.0, 123.0, 128.9, 129.0, 129.2, 129.5, 130.6, 132.2, 132.5, 143.2, 161.1, 207.0.

(−)-(*R*)-11-Methoxy-10-vinylaporphine (12). A solution of **8** (400 mg, 0.965 mmol), LiCl (336 mmol, 7.91 mmol), PPh_3 (152 mg, 0.579 mmol), and $(PPh_3)_2PdCl_2$ (81 mg, 0.12 mmol) in DMF (10 mL) was stirred at room temperature under nitrogen. After 10 min, tributylvinylstannane (612 mg, 1.93 mmol) and 3 crystals of 2,6-di-*tert*-butyl-4-methylphenol were added. After stirring for 1 h at 120 °C under nitrogen, the volatiles were removed *in vacuo* and the residue was partitioned between ether and water. The organic layer was extracted with 10% aqueous KF, dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed [aluminum

oxide; ether/hexanes (3:2)] to give pure amine. The amine was converted into the hydrochloride salt, which was recrystallized from MeOH/ether to give 224 mg (71%) of pure **12**·HCl: IR (KBr) 2500 cm^{-1}; ^1H NMR (CD_3OD) δ 2.87 (dd, 1 H), 3.13−3.63 (m, 4 H), 3.19 (s, 3 H), 3.50 (s, 3 H), 3.77−3.85 (m, 1 H), 4.44 (dd, 1 H), 5.34 (dd, 1 H), 5.82 (dd, 1 H), 7.10 (dd, 1 H), 7.18 (app d, 1 H), 7.26 (app d, 1 H), 7.42 (dd, 1 H), 7.55 (d, 1 H), 8.37 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 26.8, 32.8, 41.8, 53.4, 61.2, 63.3, 115.8, 125.7, 127.3, 127.4, 128.1, 129.4, 129.6, 129.9, 130.9, 132.5, 132.9, 133.3, 135.6, 156.8.

(−)-(*R*)-10-Ethyl-11-methoxyaporphine (13). Palladium on charcoal (10%, 0.10 g) was added to a solution of **12** (113 mg, 0.388 mmol) in THF (20 mL). The resulting slurry was stirred under H_2 (1 atm) at room temperature for 3 h. The mixture was diluted with CH_2Cl_2, and the catalyst was filtered off (Celite). The volatiles were evaporated, and the residue was chromatographed [silica gel; $CHCl_3$/MeOH (39:1) and aluminum oxide; ether/hexanes (1:8−1:1), stepwise gradient]. The amine was converted into the hydrochloride salt, which was recrystallized from 2-PrOH/ether to give 97 mg (76%) of pure **13**·HCl: IR (KBr) 2500 cm^{-1}; ^1H NMR (CD_3OD) δ 1.25 (t, 3 H), 2.59−2.85 (m, 2 H), 2.86 (dd, 1 H), 3.10−3.23 (m, 1 H), 3.19 (s, 3 H), 3.36−3.64 (m, 3 H), 3.50 (s, 3 H), 3.79−3.86 (m, 1 H), 4.42 (app br d, 1 H), 7.12 (app d, 1 H), 7.20 (d, 1 H), 7.25 (app d, 1 H), 7.41 (dd, 1 H), 8.35 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 15.7, 24.1, 27.1, 32.7, 42.3, 53.6, 61.0, 63.6, 125.4, 126.9, 127.9, 129.2, 129.6, 129.9, 130.7, 130.9, 133.4, 133.5, 139.3, 157.4.

(−)-(*R*)-10-Ethyl-11-hydroxyaporphine (14). A slurry of **13**·HCl (101 mg, 0.306 mmol) in 5 mL of freshly distilled 48% aqueous HBr was refluxed at 120 °C under nitrogen for 3 h. EtOH (99%) was added, and the volatiles were evaporated. The residue was partitioned between $CHCl_3$ and 10% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give a residue which was column chromatographed [silica gel; $CHCl_3$ to $CHCl_3$/MeOH (39:1) gradient] followed by preparative TLC [silica gel; CH_2Cl_2/methanol (9:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeOH/ether to give 59 mg (61%) of pure **14**·HCl: IR (KBr) 3260, 2460 cm^{-1}; ^1H NMR (CD_3OD) δ 1.22 (t, 3 H), 2.69 (q, 2 H), 2.82 (dd, 1 H), 3.10−3.25 (m, 1 H), 3.19 (s, 3 H), 3.29−3.59 (m, 3 H), 3.78−3.83 (m, 1 H), 4.33 (app br d, 1 H), 6.87 (app d, 1 H), 7.07 (d, 1 H), 7.18 (app d, 1 H), 7.37 (dd, 1 H), 8.35 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 14.8, 24.4, 26.8, 33.1, 41.9, 53.4, 63.7, 121.3, 122.5, 128.2, 128.7, 129.2, 129.5, 129.9, 130.4, 132.8, 133.1, 134.1, 153.1.

(−)-*N*-Propylnorcodeine (18).[19] Compound **18** was synthesized from **17** using the conditions for reductive amination reported by Schellenberg.[18] A solution of **17** (3.72 g, 0.0130 mol), NaOAc (2.14 g, 0.0260 mol), and HOAc (11 mL) was added to a stirred mixture of H_2O (120 mL) and absolute EtOH (40 mL) at 0 °C. Propanal (4.7 mL, 0.065 mol) was added followed by 20 mg portions of $NaBH_4$ (2.45 g, 0.065 mol). After 20 min another portion of propanal (4.7 mL, 0.065 mol) and 20 mg portions of $NaBH_4$ (2.45 g, 0.065 mol) were added. The mixture was stirred for 30 min, and 5 M aqueous NaOH was added to pH 12. The basic mixture was extracted with CH_2Cl_2, and the organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed [silica gel; $CHCl_3$/MeOH (19:1)]. The pure amine was converted into the oxalate salt, which was recrystallized from MeOH/ether to give 4.71 g of pure **18**·oxalate: mp 187−189 °C; $[\alpha]^{21}_D$ −97.3° (*c* 1.0, MeOH). Anal. ($C_{20}H_{25}NO_3 \cdot H_2C_2O_4 \cdot {}^1/_4H_2O$) C, H, N.

The residue from the recrystallization was converted to the amine by extraction between CH_2Cl_2 and saturated aqueous Na_2CO_3. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed [silica gel; $CHCl_3$/MeOH (39:1)] to give 0.11 g (total yield 88%) of pure **18**. Data from ^1H NMR for **18** in $CDCl_3$ were identical with previously reported data.[19]

(−)-*N*-Propylnormorphine (19).[21] Compound **19** was prepared from **18** using a modified version of the procedure of Rice.[20] A solution of **18** (1.49 g, 4.55 mmol) in CH_2Cl_2 (0.20 L) was stirred at −30 °C under nitrogen. BBr_3 (15 mL of a 0.91 M solution in CH_2Cl_2) was added dropwise. The temperature was allowed to reach −2 °C, and after stirring for 2 h, the reaction mixture was extracted with 10% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed [silica gel; $CHCl_3$/MeOH (39:1−9:1) gradient], and the amine was recrystallized from absolute EtOH to give 0.96 g (67%) of pure **19**: mp 227−230 °C (lit.[21] mp 225−228 °C).

(−)-*N*-Propyl-3-*O*-[(trifluoromethyl)sulfonyl]normorphine (20). The preparation of compound **20** was performed using a slightly modified version of the procedure reported for the synthesis of **5**.[2b,c] Thus, a solution of **19** (1.30 g, 4.15 mmol) and Et_3N (1.15 mL, 9.30 mmol) in CH_2Cl_2 (0.1 L) was stirred for 10 min at room temperature under nitrogen. K_2CO_3 (0.61 g, 5.0 mmol) and *N*-phenyltrifluoromethanesulfonimide (1.78 g, 4.98 mmol) were added, and the resulting slurry was refluxed for 4.5 h. The crude solution was filtered and concentrated, to give a residue which was chromatographed [silica gel; $CHCl_3$/MeOH (39:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN to give 1.77 g (89%) of pure **20**·HCl: mp 250−253 °C dec; $[\alpha]^{23}_D$ −52.9° (*c* 1.0, MeOH); IR (film) 3554, 2508, 1221, 1140 cm^{-1}. Anal. ($C_{20}H_{23}F_3NO_5S$·HCl) C, H, N.

A small sample of the hydrochloride (0.12 g, 0.25 mmol) was converted to the amine by extraction between $CHCl_3$ and 10% aqueous $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered, and concentrated to give 0.11 g (99%) of pure **20**: IR (film) 3564, 1219, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H), 1.53 (sext, 2 H), 1.88 (ddd, 1 H), 2.09 (ddd, 1 H), 2.31 (ddd, 1 H), 2.33 (dd, 1 H), 2.41−2.51 (m, 2 H), 2.61−2.76 (m, 2 H), 2.53−2.89 (br s, 1 H), 3.03 (app d, 1 H), 3.46 (dd, 1 H), 4.13−4.25 (m, 1 H), 5.01 (dd, 1 H), 5.28 (ddd, 1 H), 5.63−5.75 (m, 1 H), 6.62 (app d, 1 H), 6.88 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.9, 20.9, 21.9, 35.4, 40.6, 44.0, 44.4, 56.5, 57.0, 66.6, 93.7, 118.7 (q), 120.2, 121.0, 128.6, 130.6, 133.5, 134.0, 136.0, 149.5.

(−)-(*R*)-11-Methoxy-*N*-propyl-10-[[(trifluoromethylsulfonyl]oxy]noraporphine (21). Compound **21** was synthesized from **20** (1.38 g, 3.10 mmol) using a procedure described previously.[2b,c] The reaction time was 2 h for the acid-catalyzed rearrangement and 4 h for the etherification of the intermediate phenol with CH_2N_2. Crude **21** was purified by column chromatography [aluminum oxide; ether/hexanes (1:1) and silica gel; ether/hexanes (1:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN/ether to give, after pump-drying at 0.5 mmHg and 60 °C, 1.05 g (71%) of pure **21**·HCl: ^1H NMR (CD_3OD) δ 1.11 (t, 3 H), 1.83−2.03 (m, 2 H), 2.95 (dd, 1 H), 3.14−3.34 (m, 2 H), 3.40−3.69 (m, 4 H), 3.69 (s, 3 H), 3.94−3.99 (m, 1 H), 4.56 (app br d, 1 H), 7.30−7.34 (m, 3 H), 7.43 (dd, 1 H), 8.24 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 11.3, 18.4, 26.9, 32.3, 50.3, 56.9, 61.3, 61.7, 120.2 (q), 122.9, 126.3, 128.0, 129.6, 130.0, 130.3, 130.4, 131.7, 136.7, 144.6, 151.2.

(−)-(*R*)-11-Methoxy-10-methyl-*N*-propylnoraporphine (22). Compound **22** was synthesized from **21** (422 mg, 0.956 mmol) using a procedure described previously.[2c] The reaction time was 6 h. Crude **22** was purified by column chromatography [aluminum oxide; ether/hexanes (1:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN; yield, 254 mg (86%) of pure **22**·HCl: ^1H NMR (CD_3OD) δ 1.11 (t, 3 H), 1.79−2.04 (m, 2 H), 2.32 (s, 3 H), 2.88 (dd, 1 H), 3.08−3.65 (m, 6 H), 3.52 (s, 3 H), 3.87−3.98 (m, 1 H), 4.46 (dd, 1 H), 7.09 (app d, 1 H), 7.17 (d, 1 H), 7.24 (app d, 1 H), 7.40 (dd, 1 H), 8.34 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 12.2, 17.2, 19.1, 27.9, 33.3, 51.0, 57.7, 61.0, 62.7, 126.0, 127.6, 128.6, 129.8, 130.5, 130.7, 132.0, 132.8, 133.8, 134.1, 134.5, 158.4.

(−)-(*R*)-11-Hydroxy-10-methyl-*N*-propylnoraporphine (23). Compound **23** was synthesized from **22**·HCl (192 mg, 0.558 mmol) using the procedure described for the preparation of **14**·HCl. The reaction time was 4 h. Crude **23** was purified by column chromatography [silica gel; $CHCl_3$/MeOH (39:1)] and preparative TLC [silica gel; $CHCl_3$/MeOH (19:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN/ether to give 156 mg (85%) of pure **23**·HCl: ^1H NMR (CD_3OD) δ 1.09 (t, 3 H), 1.73−2.01 (m, 2 H), 2.26 (s, 3 H), 2.83 (dd, 1 H), 2.98−3.62 (m, 6 H), 3.82−3.89 (m, 1 H), 4.30 (app br d, 1 H), 6.80 (app d, 1 H), 7.00 (d, 1 H), 7.13 (app d, 1 H), 7.33 (dd, 1 H), 8.32 (app d, 1

H); ^{13}C NMR (CD_3OD) δ 11.4, 17.0, 18.5, 26.9, 33.0, 50.2, 56.7, 62.3, 121.0, 122.2, 126.7, 128.2, 128.7, 129.1, 129.7, 130.7, 131.5, 133.1, 134.2, 153.7.

(−)-*N*-Benzylnorcodeine (24).[22] A mixture of **17** (18.66 g, 65.4 mmol) and K_2CO_3 (36.15 g, 0.262 mol) in DMF (350 mL) was stirred under nitrogen for 5 min at room temperature. Benzyl bromide (8.16 mL, 68.7 mmol) was added, and the resulting slurry was stirred at room temperature for 2.5 h. The reaction mixture was filtered, and the volatiles were concentrated. The residue was partitioned between ether and H_2O. The ether layer was dried (K_2CO_3), filtered, and concentrated to give the amine. The amine was converted into the hydrochloride salt to give 25.04 g (92.9%) of pure **24**·HCl: mp 171−175 °C; $[\alpha]^{21}_D$ −117.6° (*c* 1.0, MeOH). Anal. ($C_{24}H_{25}NO_3$·HCl) C, H, N.

A small sample of the hydrochloride **24**·HCl (0.20 g, 0.49 mmol) was extracted between $CHCl_3$ and 10% aqueous $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered, and concentrated to give 0.18 g (99%) of pure **24**: ^{1}H NMR ($CDCl_3$) δ 1.85 (ddd, 1 H), 2.06 (ddd, 1 H), 2.31 (app dd, 1 H), 2.46 (ddd, 1 H), 2.63 (ddd, 1 H), 2.68−2.74 (m, 1 H), 3.08 (app br s, 1 H), 3.09 (app d, 1 H), 3.38 (dd, 1 H), 3.64−3.77 (m, 2 H), 3.81 (s, 3 H), 4.08−4.25 (m, 1 H), 4.89 (dd, 1 H), 5.24 (ddd, 1 H), 5.60−5.74 (m, 1 H), 6.58 (app d, 1 H), 6.67 (d, 1 H), 7.21−7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.3, 35.8, 40.8, 43.4, 44.5, 56.1, 56.2, 59.2, 66.4, 91.4, 112.6, 119.4, 126.9, 127.2, 128.2, 128.5, 128.6, 131.2, 133.1, 138.9, 142.0, 146.2.

(−)-*N*-Benzylnormorphine (25).[23] Compound **25** was prepared from **24** (10.37 g, 0.0252 mol) using the protocol for the synthesis of **19**. The reaction temperature was −10 °C, and the reaction time was 1 h and 15 min. Crude **25** was purified by column chromatography [silica gel; $CHCl_3$ to $CHCl_3$/MeOH (19:1) gradient]. The free amine was recrystallized from absolute EtOH to give 6.34 g (70%) of pure **25**: mp 227−229 °C (lit.[23] mp 230−231 °C); $[\alpha]^{21}_D$ −132.6° (*c* 0.50, MeOH) (lit.[23] $[\alpha]^{23}_D$ −130°, no concentration given).

(−)-*N*-Benzyl-3-*O*-[(trifluoromethylsulfonyl]normorphine (26). Compound **26** was synthesized from **25** (5.21 g, 0.014 mol) using the procedure described for the preparation of **5**.[2b,c] The reaction time was 3.5 h. Crude **26** was treated with HCl in ether, and the hydrochloride salt formed was partitioned between $CHCl_3$ and 10% aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the amine. Recrystallization of the amine from ether yielded 6.00 g of pure **26**. The mother liquor was concentrated, and the residue was chromatographed [aluminum oxide; $CHCl_3$]. Recrystallization from ether afforded 0.32 g (a total yield of 89%) of pure **26**: mp 166−168 °C; $[\alpha]^{21}_D$ −80.8° (*c* 0.50, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.87 (ddd, 1 H), 2.11 (ddd, 1 H), 2.33 (app dd, 1 H), 2.41 (ddd, 1 H), 2.66 (ddd, 1 H), 2.69−2.76 (m, 1 H), 2.91 (app br d, 1 H), 3.12 (app d, 1 H), 3.42 (dd, 1 H), 3.63−3.77 (m, 2 H), 4.10−4.27 (m, 1 H), 5.02 (dd, 1 H), 5.22 (ddd, 1 H), 5.61−5.73 (m, 1 H), 6.65 (app d, 1 H), 6.90 (d, 1 H), 7.18−7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 35.4, 40.6, 44.0, 44.3, 56.0, 59.3, 66.6, 93.8, 118.7 (q), 120.3, 121.0, 127.2, 128.4, 128.6, 128.7, 130.6, 133.5, 134.1, 135.9, 138.7, 149.6. Anal. ($C_{24}H_{22}F_3NO_5S$) C, H, N.

(−)-(*R*)-*N*-Benzyl-11-methoxy-10-[[(trifluoromethyl)-sulfonyl]oxy]noraporphine (27). Compound **27** was synthesized from **26** (17.63 g, 35.7 mmol) using the procedure for the synthesis of **21**. The amount of $MeSO_3H$ was 45 mL, and the reaction time was 2 h for the acid-catalyzed rearrangement. The subsequent reaction with CH_2N_2 was run overnight. Crude **27** was purified by column chromatography [aluminum oxide; ether/hexanes (1:1) followed by ether/hexanes (1:7−1:4−1:1) gradient]. The amine was converted into the hydrochloride salt, to give 15.9 g (84%) of pure **27**·HCl: ^{1}H NMR (CD_3OD) δ 3.00−3.18 (m, 2 H), 3.20−3.44 (m, 2 H), 3.69 (s, 3 H), 3.72−3.94 (m, 2 H), 4.42 (br d, 1 H), 4.58 (app br d, 1 H), 5.10 (br d, 1 H), 7.28 (app d, 1 H), 7.34 (app d, 1 H), 7.39 (app d, 1 H), 7.42 (dd, 1 H), 7.49−7.57 (m, 3 H), 7.60−7.70 (m, 2 H), 8.24 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 27.0, 32.9, 49.4, 59.0, 61.7, 61.9, 120.2 (q), 122.9, 126.2, 127.9, 129.7, 129.9, 130.3, 130.5, 131.1, 131.2, 131.7, 132.0, 132.5, 137.0, 144.6, 151.2.

(−)-(*R*)-*N*-Benzyl-11-methoxy-10-methylnoraporphine (28). Compound **28** was prepared from **27** (3.92 g, 7.99 mmol) using a procedure described previously.[2c] The reaction time was 6 h. Crude **28** was purified by column chromatography [alumina; ether/hexanes (1:7−1:4−1:1) gradient]. The amine was converted into the hydrochloride salt to give 2.74 g (88%) of pure **28**·HCl: ^{1}H NMR (CD_3OD) δ 2.32 (s, 3 H), 2.96−3.15 (m, 2 H), 3.22−3.52 (m, 2 H), 3.50 (s, 3 H), 3.60−3.87 (m, 2 H), 4.36−4.56 (m, 2 H), 5.06 (app br d, 1 H), 7.13 (app d, 1 H), 7.16−7.23 (m, 2 H), 7.37 (dd, 1 H), 7.46−7.75 (m, 5 H), 8.34 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 16.4, 27.1, 32.8, 49.5, 59.0, 60.2, 62.4, 125.2, 126.9, 127.9, 129.0, 129.7, 129.9, 130.2, 130.5, 131.1, 131.4, 132.1, 132.8, 133.2, 133.4, 133.7, 157.7.

(−)-(*R*)-*N*-Benzyl-11-hydroxy-10-methylnoraporphine (29). Compound **29** was synthesized from **32** (0.33 g, 0.92 mmol) using the procedure described for the synthesis of **8**. The amount of $MeSO_3H$ was 2 mL, and the reaction time was 1 h. Crude **29** was purified by column chromatography [silica gel; $CHCl_3$ to $CHCl_3$/MeOH (39:1) gradient]. The amine was converted into the hydrochloride salt, which was recrystallized from MeOH/ether to give 0.27 g (77%) of pure **29**·HCl: ^{1}H NMR (CD_3OD, 50 °C) δ 2.30 (s, 3 H), 2.89−3.44 (m, 4 H), 3.57−3.86 (m, 2 H), 4.31−4.49 (m, 2 H), 5.04 (d, 1 H), 6.90 (app d, 1 H), 7.08 (d, 1 H), 7.14 (app d, 1 H), 7.36 (dd, 1 H), 7.44−7.70 (m, 5 H), 8.36 (app d, 1 H); ^{13}C NMR (CD_3OD, 50 °C) δ 16.9, 27.0, 33.4, 49.9, 59.2, 62.9, 121.1, 122.4, 127.1, 128.2, 128.9, 129.2, 129.7, 130.2, 130.7, 131.57, 131.64, 132.8, 133.0, 134.3, 153.8.

(−)-(*R*)-11-Methoxy-10-methylnoraporphine (30). A mixture of **28**·HCl (1.27 g, 7.99 mmol) and Pd(C) (10%, 0.24 g) in HOAc (20 mL) was stirred at room temperature under H_2 (1 atm) for 7 h. The mixture was diluted with $CHCl_3$/MeOH (4:1) and filtered through Celite. Crude **30**·HCl was purified by recrystallization from MeCN followed by MeOH/ether. The crystals were dried at 0.1 mmHg and 150 °C to give 0.90 g (92%) of pure **30**·HCl: ^{1}H NMR (CD_3OD) δ 2.32 (s, 3 H), 2.89 (dd, 1 H), 3.06−3.18 (m, 2 H), 3.25−3.36 (m, 1 H), 3.36−3.52 (m, 1 H), 3.51 (s, 3 H), 3.71−3.80 (m, 1 H), 4.45 (dd, 1 H), 7.03 (app d, 1 H), 7.16 (d, 1 H), 7.24 (app d, 1 H), 7.40 (dd, 1 H), 8.37 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 16.4, 26.3, 34.6, 42.5, 54.3, 60.1, 125.1, 127.0, 127.8, 129.3, 129.76, 129.85, 131.3, 132.1, 133.1, 133.6, 157.9.

(−)-(*R*)-11-Hydroxy-10-methylnoraporphine (31). Method A. Compound **31** was prepared from **29**·HCl (0.15 g, 0.40 mmol) using the procedure for the preparation of **30**·HCl. The reaction time was 10 h. Crude **31**·HCl was recrystallized twice from MeOH/ether to give 82 mg (71%) of pure **31**·HCl: ^{1}H NMR (CD_3OD) δ 2.27 (s, 3 H), 2.87 (dd, 1 H), 3.01−3.14 (m, 2 H), 3.21−3.44 (m, 2 H), 3.64−3.80 (m, 1 H), 4.37 (dd, 1 H), 6.78 (app d, 1 H), 7.03 (d, 1 H), 7.16 (app d, 1 H), 7.35 (dd, 1 H), 8.36 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 17.0, 26.3, 34.9, 42.4, 54.4, 120.9, 122.4, 126.7, 128.4, 128.7, 129.1, 129.6, 130.7, 131.4, 133.0, 133.9, 153.9.

Method B. Compound **31** was synthesized from **30**·HCl (155 mg, 0.514 mmol) using the procedure described for the preparation of **14**·HCl. The reaction time was 6 h. Crude **31** was converted into the hydrochloride salt, which was recrystallized from MeOH/ether, to give 142 mg (96%) of pure **31**·HCl.

(−)-*N*-Benzyl-3-deoxy-3-methylnormorphine (32). Compound **32** was synthesized from **26** (0.58 g, 1.2 mmol) using the procedure reported for the synthesis of **22**. The reaction time was 3 h. Crude **32** was purified by column chromatography [silica gel; $CHCl_3$/MeOH (39:1) and aluminum oxide; ether to $CHCl_3$ followed by silica; hexane/EtOAc/acetone (1:9:3)] to give 0.34 g (80%) of pure **32**: ^{1}H NMR ($CDCl_3$) δ 1.82 (ddd, 1 H), 2.05 (ddd, 1 H), 2.18 (s, 3 H), 2.30 (app dd, 1 H), 2.45 (ddd, 1 H), 2.62 (ddd, 1 H), 2.67−2.73 (m, 1 H), 2.85 (app br d, 1 H), 3.09 (app d, 1 H), 3.36 (dd, 1 H), 3.62−3.78 (m, 2 H), 4.05−4.24 (m, 1 H), 4.83 (dd, 1 H), 5.23 (ddd, 1 H), 5.57−5.70 (m, 1 H), 6.55 (app d, 1 H), 6.82 (d, 1 H), 7.18−7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.6, 21.9, 35.9, 41.0, 43.0, 44.6, 56.3, 59.4, 66.4, 90.4, 116.1, 119.0, 127.0, 128.3, 128.6, 128.7, 129.1, 129.7, 132.6, 133.1, 139.0, 156.9.

A small sample of **32** was converted into the hydrochloride salt, which was recrystallized from MeCN/ether to give pure **32**·HCl: mp 190−193 °C; $[\alpha]^{23}_{D}$ −143.4° (*c* 0.50, MeOH). Anal. ($C_{24}H_{25}NO_2$·HCl·$^3/_4H_2O$) C, H, N.

(−)-(*R*)-*N*-Isopropyl-11-methoxy-10-methylnoraporphine (33). Compound **33** was prepared from **30** according to a method previously described by Liu *et al.*[24] A mixture of **30** (0.32 g, 1.2 mmol), K_2CO_3 (0.18 g, 1.3 mmol), and diisopropylethylamine (0.22 mL, 1.3 mmol) in MeCN (1.2 mL) was stirred at room temperature. After 20 min 2-iodopropane (0.13 mL, 1.3 mmol) was added. The flask was sealed, and the reaction mixture was stirred at 70 °C for 67 h. The crude mixture was partitioned between CH_2Cl_2 and H_2O, and the organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed [silica gel; $CHCl_3$/MeOH (39:1) and aluminum oxide; ether/hexanes (1:8)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN/ether to give 0.35 g (84%) of pure **33**·HCl: ^{1}H NMR (CD_3OD) δ 1.34 (d, 3 H), 1.56 (d, 3 H), 2.31 (s, 3 H), 2.91 (dd, 1 H), 3.12−3.24 (m, 1 H), 3.25−3.52 (m, 3 H), 3.51 (s, 3 H), 3.79−3.89 (m, 1 H), 4.30 (sept, 1 H), 4.59 (dd, 1 H), 7.08 (app d, 1 H), 7.16 (d, 1 H), 7.23 (app d, 1 H), 7.38 (dd, 1 H), 8.34 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 14.3, 16.4, 18.8, 27.3, 32.3, 43.5, 54.6, 59.9, 60.2, 125.3, 126.9, 127.8, 129.1, 129.6, 130.4, 131.6, 132.0, 133.1, 133.56, 133.60, 157.6.

(−)-(*R*)-11-Hydroxy-*N*-isopropyl-10-methylnoraporphine (34). Compound **34** was synthesized from **33**·HCl (156 mg, 0.454 mmol) using the procedure described for the preparation of **14**·HCl. The reaction time was 4 h. Crude **34** was purified by column chromatography [silica gel; $CHCl_3$/MeOH (39:1) and toluene/MeCN (2:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from $CHCl_3$/ether and then EtOH/EtOAc. The crystalline powder was dried at 0.5 mmHg and 60 °C to give 0.14 g (94%) of pure **34**·HCl: ^{1}H NMR (CD_3OD) δ 1.34 (d, 3 H), 1.54 (d, 3 H), 2.27 (s, 3 H), 2.84 (dd, 1 H), 3.08−3.45 (m, 4 H), 3.72−3.87 (m, 1 H), 4.28 (sept, 1 H), 4.48 (dd, 1 H), 6.83 (app d, 1 H), 7.03 (d, 1 H), 7.17 (app d, 1 H), 7.35 (dd, 1 H), 8.34 (app d, 1 H); ^{13}C NMR (CD_3OD) δ 14.2, 17.1, 18.7, 27.3, 32.7, 43.5, 54.5, 60.2, 121.1, 122.2, 126.7, 128.2, 128.7, 129.1, 130.2, 131.1, 131.5, 133.0, 134.4, 153.6.

Computational Methods. MacMimic version 2.1 (InStar Software, IDEON Research Park, S-233 70 Lund, Sweden) was used as graphical interface for MM2(91).[25] Torsion angle drivers on aromatic and *N*-alkyl substituents were performed from 0° to 360° with a 10° increment and full energy minimization except for the dihedral angles used as driving angle(s). The resulting local minima were built and subjected to unrestricted energy minimization. Conformational preferences of compounds **12** and **13** were examined by driving simultaneously around C11−O (90° increments) and C10−C(ethyl/vinyl) (30° increments). The most stable conformation of the aporphine skeleton was used. It has a pseudoequatorial *N*-alkyl substituent and adopts a half-chair conformation of the tetrahydropyridine ring with P-helicity. Conformations with P-helicity and a pseudoaxial *N*-substituent, M-helicity and a pseudoequatorial *N*-substituent, and M-helicity with a pseudoaxial *N*-substituent have relative steric energies of 0.8, 3.1, and 3.6 kcal/mol, respectively (compound **2**). Compounds with a C11-OH substituent were modeled with C10−C11−O−H in an eclipsed orientation as selected previously for hydrogen bonding to active site residues.[2c]

Receptor Modeling. The adjusted 5-HT_{1A} model[28] was further minimized in Sybyl 6.0.3 (Tripos Associates Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO) using the following parameters: AMBER force field (Kollman_all_atoms, Kollman charges) with conjugate gradient minimizer, a distance dielectric constant of 4, nonbonded cut-off 9.0. All other parameters were Sybyl default.

Active Site Definition. Amino acids having atoms within a 10 Å sphere around the centroid of the Cα atoms of Asp116, Ser199, and Phe362 were considered in the initial active site definition. A systematic search around $\chi(1)$ and $\chi(2)$ of the Asp residue and around $\chi(1)$ of the Ser residue was performed in Sybyl to probe allowed orientations of these functional groups (resolution 15°, default VDW cut-off values). The resulting sites were filtered to retain those that were compatible with the distance between the ligand −OH and $-N^+$-H functional groups. The ligand N^+-H was therefore extended to a distance of 2.6 Å, and both O-lone pairs of the ligand were extended to 2.75 Å. The distance between these extended points in **2** was 7.96/7.83 Å. When using Ser199, the minimum distance between Asp-O and Ser-O was 8.84 Å, and the 10 sites with the smallest distance between Asp-O and Ser-O were used. Visual inspection revealed that Ser168 came closer to Asp116, and a systematic search using this Ser residue yielded a minimum distance in allowed sites of 7.79 Å. From this Asp116/Ser168 search, also the 10 sites with the smallest distance between Asp-O and Ser-O were considered. In the selected sites, the ligand was fitted to the Asp, Ser, and Phe, and the rms and the common volume were recorded. The extended points defined above (N^+-H and O-lone pairs) were used to fit onto the Asp-O and Ser-O. For the third fitting point a normal was defined through the A-ring, extending 6 Å toward the Phe residue. The end point of this normal was fitted onto the centroid of the phenyl ring of the Phe residue. The weight of this last fitting point was 1/10th of the weight of the other two points.

Minireceptor modeling. Active site optimization was performed in Yak version 3.9 (SIAT Biographics Laboratory, Missionsstrasse 60, CH-4055 Basel, Switzerland). Atomic charges of ligands transferred to Yak were obtained from a single-point MNDO calculation (MOPAC version 5.0, implemented in Sybyl 6.0.3). The necessary free energies of binding and of ligand solvation were obtained from the K_i values and the program ESOLV (supplied with Yak and based on an algorithm developed by Still *et al.*[45]), respectively. Minimizations started with 25 steps of the steepest-descent minimizer followed by 25 steps of the conjugate gradient minimizer. When convergence was not achieved after these 50 steps, a new 50-step minimization was performed.

Pharmacology. Receptor Binding Assays. The 5-HT_{1A} receptor binding assay was performed essentially as described previously.[2c] The modifications compared with the assay in ref 2c were as follows: (a) the composition of the Tris-HCl buffer used for the incubation mixtures (50 mM containing 2.0 mM $CaCl_2$, 1.0 mM $MgCl_2$, 1.0 mM $MnCl_2$, 5.7 mM ascorbic acid, pH 7.4), (b) nonspecific binding measured by the addition of 100 μM 5-HT·HCl to the reaction mixture, and (c) the time for the incubation at 37 °C as 45 min. The DA D_1 and D_{2A} receptor binding assays were performed as previously reported,[2c] by measuring the ability of the compounds to displace [^{3}H]-SCH23390 from rat striatal tissue and [^{3}H]raclopride from cloned human D_{2A} receptors expressed in mouse fibroblast (Ltk^-) cells, respectively.

Biochemistry. The 5-HT and catecholamine synthesis rates were estimated by measuring the accumulation of 5-hydroxytryptophan (5-HTP) and 3,4-dihydroxy phenylalanine (DOPA), respectively, after pretreatment with the aromatic L-amino acid decarboxylase inhibitor NSD1015 (117 mg/kg).[36] Male Sprague−Dawley rats (B&K Universal, Sollentuna, Sweden), weighing 250−300 g, were used. Reserpine pretreatment (5 mg/kg, sc) was given 18−20 h before the start of the experiments. The compounds to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial HOAc to obtain complete dissolution. Reserpine (Ciba, Basel, Switzerland) was dissolved in a few drops of glacial HOAc and made up to volume with 5.5% aqueous glucose (w/v). All compounds, including reserpine and NSD1015 (Sigma, St. Louis, MO), were subcutaneously injected in the neck region in a volume of 5 mL/kg. The biochemical experiments, including brain dissections and HPLC determinations (electrochemical detection) of tissue contents of DOPA and 5-HTP, were carried out essentially according to methods detailed elsewhere.[35a,b] Empirically, the maximum decrease of cerebral 5-HTP values obtained with a direct-acting 5-HT_{1A} receptor agonist, like 8-OH-DPAT, is about 50% from control values under conditions equivalent to those used in the present experiments.[35c]

Behavior. The occurrence and intensity of flattened body posture, forepaw treading, and hindlimb abduction were scored for 60 s 30 min after test compound administration, using an

intensity-based rating scale, where 0 = absent, 1 = equivocal, 2 = definite, and 3 = intense.[46] The maximum score for the total set of behavioral items was 9. For reference, a subcutaneous dose of 0.1 μmol/kg (*R*)-8-OH-DPAT, which causes near maximal postsynaptic 5-HT_{1A} receptor activation, yields summed scores of 8−9 under similar conditions.[46]

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Supporting Information Available: Assigned ^{1}H NMR data (7 pages). Ordering information is given on any current masthead page.

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