# 11-Substituted (*R*)-Aporphines: Synthesis, Pharmacology, and Modeling of $D_{2A}$ and 5-$HT_{1A}$ Receptor Interactions

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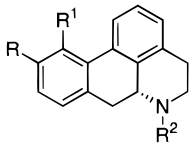
A series of C11-substituted (*R*)-aporphines and C11-oxygenated (*R*)-noraporphines has been synthesized and evaluated for central serotonergic and dopaminergic effects *in vitro* and *in vivo*. The various C11-substituents were introduced using efficient nickel- and palladium-catalyzed reactions of the corresponding triflate (*R*)-11-[[(trifluoromethyl)sulfonyl]oxy]aporphine (**6**). Several compounds display high affinity to serotonin 5-$HT_{1A}$ receptors in spite of major differences in steric bulk and electronic properties of the various C11-substituents. A change of the *N*-methyl group of the nonselective **3** to H [**23**, (*R*)-11-hydroxynoraporphine] or propyl [**2**, (*R*)-11-hydroxy-*N*-propylnoraporphine] increases the selectivity for 5-$HT_{1A}$ receptors (100-fold) and dopamine $D_{2A}$ receptors (3-fold), respectively. Compounds **3** and **23** have similar affinities to 5-$HT_{1A}$ receptors, whereas the propyl substituent of **2** not only enhances the selectivity for $D_{2A}$ receptors but also increases the $D_{2A}$ affinity. Modeling of ligand−receptor binding site interactions yielded an interaction site model for the 5-$HT_{1A}$ receptor that describes a gradual change in binding mode for C11-hydroxy, -methoxy-, and -phenyl-substituted derivatives. Hydrogen bonding is hereby gradually replaced by van der Waals interactions involving a relatively large lipophilic pocket. The derived $D_{2A}$ receptor model can accommodate both the *N*-propyl substituent of **2** and the C11-ethyl substituent of **11** [(*R*)-11-ethylaporphine].

## Introduction

Many aporphines possess the ability to activate dopamine (DA) receptors. Several structural modifications of the nonselective DA receptor agonist (*R*)-apomorphine (**1**) have been performed in order to investigate structure−activity relationships (SAR) primarily at DA $D_1$ and $D_2$ receptors.[1] These studies have shown that the catechol function of **1** is not a prerequisite for a potent interaction of aporphines with DA receptors. (*R*)-11-Hydroxy-*N*-propylnoraporphine (**2**) has been reported by Neumeyer and co-workers[1c] to be equipotent to **1** as a DA receptor agonist. In more recent studies, however, compound **2** appears to be more potent than **1**, reportedly having higher affinity to and efficacy at $D_2$ receptors.[2] The racemic *N*-methyl-substituted analogue (±)-**3** has been reported to be a DA receptor agonist.[1a] However, the pure *R*-enantiomer (**3**) was found to be an antagonist at $D_1$ receptors while also displaying moderate affinity to $D_2$ receptors.[1e] In addition, **3** was shown to have affinity to serotonin 5-$HT_{1A}$ receptors and to possess weak partial 5-$HT_{1A}$ receptor agonist properties.[3] Compound (±)-**4**,[1e,4] the racemic C11-methoxy analogue of **3**, was almost devoid of DA receptor agonist properties.[4] In addition, the C10-methyl analogue of **3**, compound **5** (HYMAP), was recently shown to be a potent and selective 5-$HT_{1A}$ receptor agonist.[3,5]

In the present investigation we have synthesized a series of C11-substituted (*R*)-aporphines and noraporphines in order to investigate the SAR of these compounds at 5-$HT_{1A}$, $D_1$, and $D_{2A}$ receptors. The compounds were evaluated pharmacologically *in vitro* using receptor binding and *in vivo* by use of biochemical and behavioral assays in reserpinized rats. The differences in binding profiles were rationalized by modeling of ligand−receptor interactions using homology-based receptor models of the 5-$HT_{1A}$ and $D_{2A}$ receptor binding sites.




**1** R=OH; $R^1$=OH; $R^2$=Me
**2** R=H; $R^1$=OH; $R^2$=Pr
**3** R=H; $R^1$=OH; $R^2$=Me
**4** R=H; $R^1$=OMe; $R^2$=Me
**5** R=Me, $R^1$=OH; $R^2$=Me

## Chemistry

The syntheses of the novel aporphines and noraporphines presented in Table 1 are shown in Schemes 1−3, and detailed protocols are found in the Experimental Section.

**Synthesis**. Aporphines **7**−**13** were prepared from triflate **6** using efficient palladium- and nickel-catalyzed coupling reactions (Scheme 1). Triflate **6** was synthesized from **3** using a modified version of the procedure reported by Cacchi *et al.*[6] The palladium-catalyzed cross-coupling reactions of **6** with stannanes were performed following the protocol for sterically hindered triflates reported by Saá *et al.*[7] (*R*)-Aporphine (**7**),[5c] synthesized as the racemate in 1924 by Gadamer, Oberlin, and Schoeler,[8] was prepared from **6** by a

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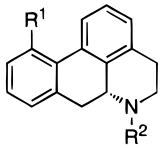
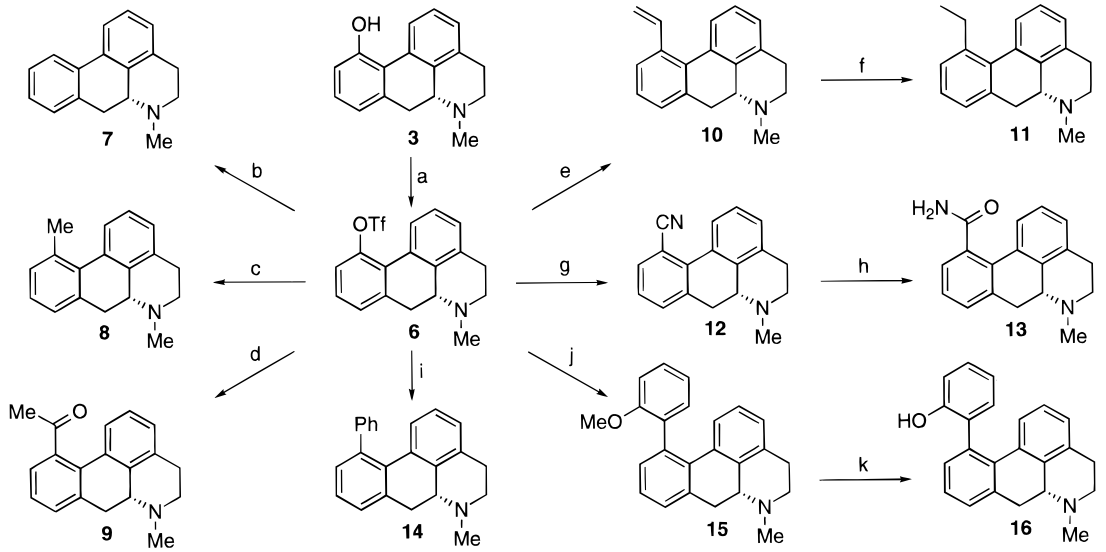
**Table 1.** Physical Data of Novel (*R*)-Aporphines



| compd | $R^1$ | $R^2$ | mp (°C) | yield (%) | recrystn solvents[a] | $[\alpha]^{rt}_D$ (deg) (*c* 1.0, MeOH) | formula |
|---|---|---|---|---|---|---|---|
| **6** | OTf | Me | 233−237[b] | 74 | A | −204.4 | $C_{18}H_{16}F_3NO_3S\cdot HCl$ |
| **8** | Me | Me | 231−234[b] | 70 | B | −51.4 | $C_{18}H_{19}N\cdot HCl$ |
| **9** | COMe | Me | 227−230[b] | 87 | C | −237.7 | $C_{19}H_{19}NO\cdot HCl\cdot{}^1/_4H_2O$ |
| **10** | $CH{=}CH_2$ | Me | 235−236[b] | 57 | D | +88.6 | $C_{19}H_{19}N\cdot HCl$ |
| **11** | Et | Me | 234−238[b] | 56 | B | −44.5 | $C_{19}H_{21}N\cdot HCl\cdot{}^1/_4H_2O$ |
| **12** | CN | Me | 232−234[b] | 66 | E | −170.9 | $C_{18}H_{16}N_2\cdot HCl$ |
| **13** | $CONH_2$ | Me | 230−231[b] | 92 | F | −228.4 | $C_{18}H_{18}N_2O\cdot HCl$ |
| **14** | Ph | Me | 234−237[b] | 60 | G | −111.5 | $C_{23}H_{21}N\cdot HCl$ |
| **15** | 2-OMe-Ph | Me | 233−234[b] | 49 | F | −143.3 | $C_{24}H_{24}NO\cdot HCl$ |
| **16** | 2-OH-Ph | Me | 211−212[b] | 97 | H | −107.3 | $C_{23}H_{22}NO\cdot HCl\cdot{}^1/_2H_2O$ |
| **20** | OMe | Bn | 230−235[b] | 85 | F | −41.4 | $C_{24}H_{23}NO\cdot HCl$ |
| **21** | OH | Bn | 280−283[b] | 77 | I | −24.0[c] | $C_{23}H_{21}NO\cdot HCl$ |
| **22** | OMe | H | 291−292[b,d] | 88 | B and J | −115.3 | $C_{17}H_{17}NO\cdot HCl$ |
| **23** | OH | H | 320−328[b,e] | 94 | H | −90.0[f] | $C_{16}H_{15}NO\cdot HCl$ |
| **24** | OMe | 2-Pr | 230−232 | 86 | F | −103.2 | $C_{20}H_{23}NO\cdot HCl$ |
| **25** | OH | 2-Pr | 267−270[b,g] | 92 | K | −80.9 | $C_{19}H_{21}NO\cdot HCl$ |

[a] A: EtOH. B: MeCN. C: MeCN/*t*-BuOMe. D: EtOH/ether. E: MeCN/EtOH (1:1)/*t*-BuOMe. F: MeCN/ether. G: MeCN/EtOH (1:1)/ether. H: 2-PrOH/ether. I: MeOH. J: MeOH/ether. K: MeCN/MeOH. [b] Decomposition. [c] (*c* 0.10, MeOH). [d] Green at 269−270 °C. [e] Green at 280−285 °C. [f] (*c* 0.25, MeOH). [g] Green at 240 °C.

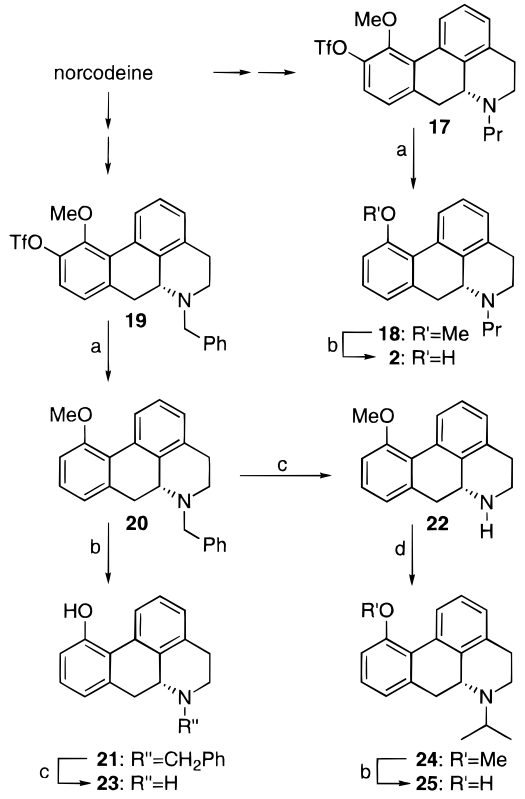
**Scheme 1**[a]




[a] Reagents: (a) $PhN(Tf)_2$, $Et_3N$, $K_2CO_3$, $CH_2Cl_2$, reflux; (b) $(PPh_3)_2PdCl_2$, $Ph_2P(CH_2)_3PPh_2$, $Bu_3N$, $HCO_2H$, DMF, 80 °C; (c) $Me_4Sn$, $(PPh_3)_2PdCl_2$, LiCl, $PPh_3$, 2,6-di-*tert*-butyl-4-methylphenol, DMF, 120 °C; (d) i. $Bu_3SnC(OEt)CH_2$, $(PPh_3)_2PdCl_2$, LiCl, $PPh_3$, 2,6-di-*tert*-butyl-4-methylphenol, DMF, 120 °C, ii. HCl (aq), THF, rt; (e) $Bu_3SnCH{=}CH_2$, $(PPh_3)_2PdCl_2$, LiCl, $PPh_3$, 2,6-di-*tert*-butyl-4-methylphenol, DMF, 120 °C; (f) $H_2$, 10% Pd(C), THF; (g) KCN, $PPh_3$, $(PPh_3)_2NiCl_2$, Zn, DMF, $N_2$, 120 °C; (h) $H_2SO_4$, $H_2O$, 120 °C; (i) $PhSnBu_3$, (2-furyl)$_3$P, $(dba)_3Pd_2$, LiCl, NMP, 100 °C; (j) (2-methoxyphenyl)$SnBu_3$, $(PPh_3)_2PdCl_2$, CuI, LiCl, 2,6-di-*tert*-butyl-4-methylphenol, DMF, 145 °C; (k) 48% HBr (aq), $N_2$, 120 °C. Tf = $CF_3SO_2-$.

palladium-catalyzed hydrogenolysis.[9] Analogues **8**−**10** were synthesized by cross-coupling of **6** with tetramethylstannane, tributyl(1-ethoxyvinyl)stannane, and tributylvinylstannane, respectively. The intermediate vinyl ether formed in the coupling of the 1-ethoxyvinyl group was hydrolyzed to give **9**. Catalytic hydrogenation of **10** afforded **11**. The C11-cyano derivative **12** was prepared by a modified version of the nickel-catalyzed cyanation method reported by Chambers and Widdowson.[10] Longer reaction time and elevated reaction temperature, the use of dimethylformamide as solvent, and additions of extra portions of Ni catalyst and ligand were found to be necessary for the reaction to proceed. Hydrolysis of **12** in acid afforded the amide analogue **13**. In the syntheses of the C11-arylated compounds **14** and **15**, the protocol of Saá *et al.*[7] produced unsatisfactory results. Instead, compound **14** was prepared from **6** using the recently reported method of Farina and coworkers[11] with tri(2-furyl)phosphine as ligand and tris(dibenzylideneacetone)dipalladium [$(dba)_3Pd_2$] as precatalyst in *N*-methylpyrrolidinone (NMP). This latter method, however, failed in the attempted synthesis of the 2-methoxyphenyl-substituted **15** from **6** and (2-methoxyphenyl)stannane even at elevated temperatures and/or using triphenylarsine as ligand. Instead, the use of conditions in which copper(I) cocatalysis was utilized[12] gave the desired **15** in moderate yield. Demethylation of **15** afforded **16**. Compounds **15** and **16** most likely exist as atropisomers[13] as judged by their complicated $^1H$ and $^{13}C$ NMR spectra.

**Scheme 2**[a]

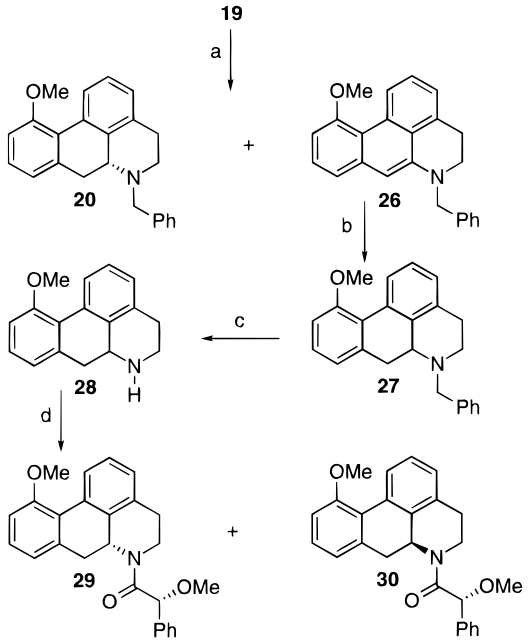



[a] Reagents: (a) $Bu_3N$, $HCO_2H$, $PPh_2(CH_2)_3PPh_2$, $(PPh_3)_2PdCl_2$, DMF, $N_2$, 80 °C; (b) 48% HBr (aq), $N_2$, 120 °C; (c) $H_2$, 10% Pd(C), HOAc, rt; (d) 2-iodopropane, $K_2CO_3$, diisopropylethylamine, $CH_3CN$, 70 °C. Tf = $CF_3SO_2-$.

The (*R*)-noraporphines **2**,[1c,14] **18**,[1c,14] and **20**−**25** were prepared using the synthetic sequences shown in Scheme 2. Palladium-catalyzed hydrogenolysis of triflates **17**[15] and **19**[15] gave the corresponding analogues **18** and **20**, which were further *O*-demethylated to phenols **2** and **21**, respectively. *N*-Debenzylation of **20** and **21** afforded **22** and **23**, respectively. Alkylation of **22** with 2-iodopropane gave **24**, which was *O*-demethylated to **25**.

A 4% yield of derivative **26** was isolated in the synthesis of **20** from **19** (Scheme 3). This byproduct was probably formed by a palladium-catalyzed oxidation of **20** during the workup.[16] Interestingly, Murahashi *et al.* have reported that when treating (*S*)-*N*,*N*,1-trimethylpropylamine with palladium(0) in a palladium-catalyzed oxidation reaction,[17a] in which a palladium hydride−iminium complex is thought to be involved,[17] the recovered starting material is partially racemized. This result, together with the fact that 6a,7-didehydroaporphine analogues of **26** have been reduced to the corresponding aporphines in high yield using metal hydrides (lithium aluminum hydride[18] and sodium cyanoborohydride[16b]), led to the speculation that **20** might have been partially racemized during the workup procedure. Compound **26** was therefore converted to **28**, the racemate of **22**, by reduction[19] followed by hydrogenolysis. Racemic **28** was then used to prepare the diastereomeric *O*-methylmandelic amides[20] **29** and **30**, thus enabling a determination of the optical purity of **22**. The enantiomeric purity of **22** was determined from the corresponding *O*-methylmandelic amide to be 99.8% ee (capillary GC). This result indicates that all aporphines synthesized using the routes presented here

**Scheme 3**[a]




[a] Reagents: (a) $Bu_3N$, $HCO_2H$, $PPh_2(CH_2)_3PPh_2$, $(PPh_3)_2PdCl_2$, DMF, $N_2$, 80 °C; (b) Zn dust, 1 M $H_2SO_4$, EtOH, reflux; (c) $H_2$, 10% Pd(C), HOAc, rt; (d) (*R*)-2-methoxy-2-phenylacetyl chloride, $CH_2Cl_2$, 1 M NaOH, rt.

(Schemes 2 and 3), or by previously reported routes,[3,15,21] are optically pure.

**Molecular Modeling**. Low-energy conformations of selected nonprotonated (*R*)-aporphines were identified by molecular mechanics MM2(91)[22] calculations using the torsion angle driver procedure as described previously.[3,15] When studying intermolecular interactions between the ligands and active site residues, the protonated form of the ligands was used.

Models of human 5-$HT_{1A}$[3,15] and $D_{2A}$[3,23,24] receptors based on a presumed homology in three-dimensional structure between bacteriorhodopsin and the G-protein-coupled receptors have been constructed previously according to a strategy first described for modeling of the muscarinic m1 receptor.[25] A combination of this homology-based approach with a systematic side chain search and minireceptor optimization using the pseudoreceptor/minireceptor modeling program Yak[26] resulted in an aporphine-derived binding site model for the 5-$HT_{1A}$ receptor.[15] This same procedure was applied to the homology-based $D_{2A}$ receptor model[3,23] using the side chains of Asp114 and Ser193 in the systematic search and adding Phe390 as a third key residue when fitting **1** in the resulting models. Active site optimization was performed in the pseudoreceptor/minireceptor modeling program Yak[26] using first **1** and then including also **2** to derive a model for examination of putative binding modes of related aporphines in the $D_{2A}$ binding site (Figure 1).

Binding modes in the 5-$HT_{1A}$ and $D_{2A}$ receptor models were examined by fitting the $N^+$-hydrogen, the A-ring centroid, and the C11, or the C11-oxygen, of the different conformations of selected aporphines onto either **5** or **14**, as docked in the active site of the 5-$HT_{1A}$ model,[15] and onto **1**, docked in the $D_{2A}$ site. All Yak minimizations were performed on both ligand(s) and residues simultaneously using the all-atom Yeti force field while keeping the backbone atoms fixed.[27] Translational and

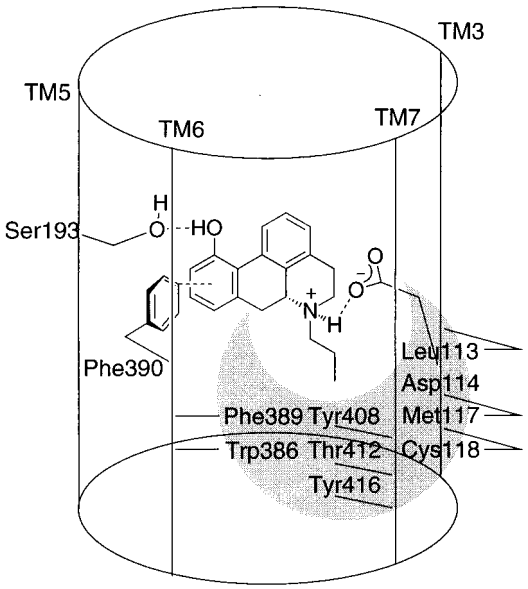



**Figure 1.** Schematic representation of the interaction between **2** and the $D_{2A}$ receptor binding site showing only the helices involved in the receptor−ligand interactions. A reinforced ionic bond between Asp114 and the protonated nitrogen, a hydrogen bond between Ser193 and the C11-hydroxyl group, and an edge-to-face interaction between Phe390 and the A-ring of **2** represent key-interactions. Also indicated is the presence of the "propyl cleft".

rotational degrees of freedom were considered for the ligand(s), whereas only torsional degrees of freedom were considered for the amino acids.

## 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, as described previously.[3] The results are presented in Table 2, and the affinity of (*R*)-apomorphine (**1**) to these receptors is also included. All *N*-methylated compounds, except for **1** and **13**, displayed moderate to high affinity to 5-$HT_{1A}$ receptors. For example, derivatives **3** (OH), **4** (OMe), **6** (OTf), **10** (vinyl) **11** (Et), and **14** (Ph) have affinities < 10 nM to 5-$HT_{1A}$ receptors. Among the noraporphines, only **22** and **23** showed high affinity to and selectivity for 5-$HT_{1A}$ receptors. All compounds tested displayed at least 10-fold lower affinities to $D_1$ receptors compared to the nonselective $D_1$ receptor antagonist **3**.[1e] Several derivatives showed moderate affinity to $D_{2A}$ receptors, the most potent compounds being **1**−**3** and **11**. Interestingly, the C11-ethyl analogue **11** showed only a 2-fold lower affinity to $D_{2A}$ receptors in comparison to **1**. In addition, the previously reported $D_2$ receptor agonist **2**[1c] appeared to have a modest 3-fold selectivity for $D_{2A}$ receptors versus 5-$HT_{1A}$ receptors. In the noraporphine series, the *N*-benzyl- and *N*-isopropyl-substituted derivatives **20**, **21** and **24**, **25** displayed low affinities to all receptors tested.

**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.[28] Thus, the synthesis of 5-HT, DA, and norepinephrine (NA) is inhibited by 5-HT, DA, and

**Table 2.** Affinities of Selected Aporphines to 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** | 39.5 ± 6.1 | 1090 ± 85 | 12.7 ± 1.6 |
| **3** | 9.6 ± 3.1[c] | 20.4 ± 1.0[c] | 58.5 ± 9.5[c] |
| **4** | 5.1 ± 1.2 | 606 ± 21 | 551 ± 31 |
| **6** | 7.7 ± 0.2 | 386 ± 44 | 195 ± 26 |
| **7** | 80.0 ± 2.3 | 717 ± 99 | 527 ± 296 |
| **8** | 14.4 ± 1.5 | 700 ± 137 | 201 ± 91 |
| **9** | 57.1 ± 4.1 | 4690 ± 1100 | 311 ± 28 |
| **10** | 6.0 ± 0.6 | 720 ± 106 | 177 ± 54 |
| **11** | 4.5 ± 0.61 | 270 ± 0.5 | 79.2 ± 32 |
| **12** | 41.1 ± 0.2 | 279 ± 35 | 183 ± 14 |
| **13** | 198 ± 32 | >4000 | >10 000 |
| **14** | 1.8 ± 0.4 | 3630 ± 260 | 233 ± 3 |
| **15** | 26.9 ± 5.4 | >3000 | 1330 ± 130 |
| **16** | 28.5 ± 2.4 | 3750 ± 300 | 1570 ± 590 |
| **18** | 31.3 ± 1.9 | >5000 | 826 ± 319 |
| **20** | 3220 ± 1350 | >10 000 | >1000 |
| **21** | >5000 | >3000 | >1000 |
| **22** | 8.3 ± 1.7 | >5000 | >1000 |
| **23** | 5.7 ± 1.6 | 1097 ± 67 | >1000 |
| **24** | 375 ± 120 | >10 000 | >1000 |
| **25** | 437 ± 240 | >10 000 | 1010 ± 325 |

[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 (see ref 3). [c] From ref 3. [d] From ref 2b.

α-adrenoceptor agonists, respectively. The *in vivo* effects of single doses of **2** (3.2 and 32 μmol/kg), **3** (3.5 μmol/kg), **11** (3.3 μmol/kg), **14** (2.9 μmol/kg), **18** (30 μmol/kg), and **23** (3.7 μmol/kg) on 5-HTP and DOPA accumulation following decarboxylase inhibition by means of (3-hydroxybenzyl)hydrazine dihydrochloride (NSD1015, 117 mg/kg sc) were investigated in the limbic forebrain, striatum, and cortex of reserpine-pretreated rats, as described previously.[15,29−31] None of the compounds was able to decrease the synthesis of 5-HT at the doses tested (Table 3), tentatively suggesting a lack of efficacy/potency at 5-$HT_{1A}$ receptors. As expected, the $D_2$ receptor agonist **2**[1c] significantly decreased the synthesis of DA in limbic forebrain and striatum. Interestingly, derivative **3**, previously reported to lack $D_2$ receptor agonist activity,[1e] and **18** and **23**, which display micromolar affinity to both $D_1$ and $D_{2A}$ receptors, significantly decreased the synthesis of DA 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],[32] results in a clear-cut motor behavioral syndrome, the "5-HT syndrome", in rats (flattened body posture, forepaw treading, and hindlimb abduction).[33,34] The ability of compounds **2**, **3**, **11**, **14**, **18**, and **23** to elicit this behavior was assessed as described previously (Table 4).[15,33,34] None of the compounds tested induced a clear "5-HT syndrome". However, the $D_2$ receptor agonist **2**[1c] (3.2 and 32 μmol/kg) induced an atypical motor stimulation syndrome accompanied by stereotyped behavior in the rat, more akin to dopaminergic overactivation mixed with some 5-$HT_{1A}$ receptor agonist-like effects (see Table 4). Postsynaptic dopaminergic agonists, such as **1**, induce stereotyped behavior (sniffing, licking chewing, etc.) in rats. In addition, they

**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** | 3.2 | 2 | 122 ± 10 | 97 ± 4 | 87 ± 2 | 66 ± 5* | 29 ± 11* | 106 ± 5 |
| | 32 | 2 | 107 ± 6 | 120 ± 23 | 103 ± 8 | 58 ± 4* | 28 ± 6* | 112 ± 1 |
| **3** | 3.5 | 4 | 98 ± 12 | 83 ± 10 | 93 ± 23 | 67 ± 7* | 30 ± 3* | 103 ± 9 |
| **11** | 3.3 | 3 | 83 ± 5 | 95 ± 6 | 104 ± 10 | 87 ± 10 | 92 ± 9 | 100 ± 6 |
| **14** | 2.9 | 3 | 95 ± 2 | 106 ± 7 | 133 ± 7 | 95 ± 6 | 93 ± 4 | 107 ± 14 |
| **18** | 30 | 4 | 96 ± 4 | 87 ± 5 | 89 ± 12 | 66 ± 3* | 43 ± 4* | 82 ± 7 |
| **23** | 3.7 | 3 | 108 ± 10 | 89 ± 6 | 122 ± 11 | 78 ± 1* | 71 ± 4* | 96 ± 6 |

[a] Shown is the amount of accumulated 5-HTP in percent of saline controls (for **11**, **14** and **23**, 100% limbic forebrain 235 ± 33 ng/g, striatum 187 ± 11 ng/g, cortex 95 ± 11 ng/g, $n = 4$; for **2**, **3** and **18**, 100% limbic forebrain 164 ± 11 ng/g, striatum 158 ± 14 ng/g, cortex 123 ± 15,$n = 3$), 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 **11**, **14** and **23**, 100% limbic forebrain 765 ± 50 ng/g, striatum 3526 ± 323 ng/g, cortex 103 ± 11 ng/g, $n = 4$; for **2**, **3** and **18**, 100% limbic forebrain 674 ± 40 ng/g, striatum 2511 ± 173 ng/g, cortex 100 ± 7, $n = 3$), 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) | Σ, scores median (range) | n |
|---|---|---|---|
| saline control | | 0 (0−1) | 3 |
| **2** | 3.2 | 1 (0−2)[b] | 2 |
| | 32 | 3 (3−3)[b] | 2 |
| **3** | 3.5 | 0 (0−1) | 3 |
| **11** | 3.3 | 0 (0−1) | 3 |
| **14** | 2.9 | 0 (0−1) | 3 |
| **18** | 30 | 0 (0−0) | 3 |
| **23** | 3.7 | 0 (0−0) | 3 |

[a] Behavioral scores according to a 3-item, 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. [b] Compound **2** (32 μmol/kg) induced an atypical motor stimulation syndrome: sudden jerks and movement "explosions", running around, aggression, strong stereotyped sniffing, licking and chewing, clear-cut to intense hindlimb extension, tremor to almost convulsive extent. The lower dose of **2** resulted in milder but still mixed DA and 5-$HT_{1A}$ agonist-like behavioral activation.

induce locomotor activity and rearing.[35,36] The other compounds were inactive at the dose tested.

## Discussion

The pharmacological evaluation of the present series of derivatives (Tables 2−4) reveals some interesting SAR of C11-substituted (*R*)-aporphines. High affinities to 5-$HT_{1A}$ receptors are displayed by a number of aporphines carrying sterically and electronically different C11-substituents. As was shown previously,[23] a hydrogen bond-donating group in the C11-position of the aporphines seems to be required for an optimal interaction with $D_{2A}$ receptors. However, hydrogen bonding to a C11-substituent does not seem to be essential for an interaction of C11-substituted aporphines with 5-$HT_{1A}$ receptors.[37] This behavior can be rationalized using a previously described binding site model for the 5-$HT_{1A}$ receptor. In this model **5** interacts with Asp116 (a reinforced ionic bond), Ser168 (a hydrogen bond), and Phe362 (an aromatic edge-to-face interaction).[15] Compound **14** has to bind in a different orientation compared to **5** in order to fit in the binding site and to maintain an interaction with Asp116.[15] The C11-phenyl substituent of **14** then fits into a pocket lined by Ser168, Met172, Thr196, Ser199, Thr200, Phe362, Ala365, and Leu366. Optimization of **3** and **4** in the derived binding site indicates that **3** assumes an orientation similar to **5**[15] while **4** appears to accept an intermediate orientation. Figure 2 shows the gradual change in binding mode when **3**, **4**, and **14** were optimized simultaneously. The C11-oxygenated compounds **3** and **4** interact through hydrogen bonding with Ser168 and differ from the C11-arylated **14** in their position of the protonated nitrogen and therefore also in the oxygen atom at Asp116 with which they interact. Interestingly, the C11-ethyl and C11-phenyl derivatives **11** and **14** had high affinities to 5-$HT_{1A}$ receptors and moderate to low affinities to $D_{2A}$, but neither produced any effects *in vivo* in the doses tested (Table 2−4). Thus, both **11** and **14** seem to behave as weak partial agonists or antagonists, although further work is needed to examine this possibility.

The $D_{2A}$ binding site model obtained after optimization in Yak confirms the previously described interactions: a reinforced ionic bond between the protonated nitrogen and Asp114, a hydrogen bond from the phenolic hydrogen to Ser193, an aromatic edge-to-face interaction between the A-ring and Phe390, and a "propyl cleft" accommodating the *N*-propyl substituent of high-affinity $D_{2A}$ receptor ligands (Figure 1).[3] The propyl cleft is lined by Leu113, Asp114, Met117, Cys118, Trp386, Phe389, Tyr408, Thr412, and Tyr416 (Figures 1 and 3). Optimization of C11-substituted aporphines in the obtained binding site of the $D_{2A}$ receptor model indicated that in accordance with the moderate affinity of **11** to $D_{2A}$ receptors, there is space available for a C11-ethyl substituent when Ser193 and His393 are rotated. Residues in close contact with the ethyl moiety (*i.e.*, those that have atoms within 3 Å of the substituent) are Leu171, Ser193, Ser197, Phe390, and His393 (Figure 3); those residues could be considered to contribute to the slight enhancement of $D_{2A}$ affinity when comparing **11** to **7** and **8**. The reduction in affinity when ethyl is substituted with methoxy (**11** vs **4**) is probably due to unfavorable electrostatic interactions of the methoxy moiety with several of these residues.

The influence of the *N*-substituent on the affinity to 5-$HT_{1A}$ and $D_{2A}$ receptors is evident by a comparison of derivatives **23** (H), **3** (Me), **2** (Pr), **25** (2-Pr), and **21** (Bn). An increase in affinity and selectivity for 5-$HT_{1A}$ receptors was observed when the size of the *N*-substituent was decreased to methyl (**3**) or hydrogen (**23**), whereas an *N*-propyl group as in **2** seemed to be optimal for a potent interaction with $D_{2A}$ receptors.[23] The propyl cleft described above for the $D_{2A}$ binding site accommodates a low-energy conformation of the *N*-propyl substituent

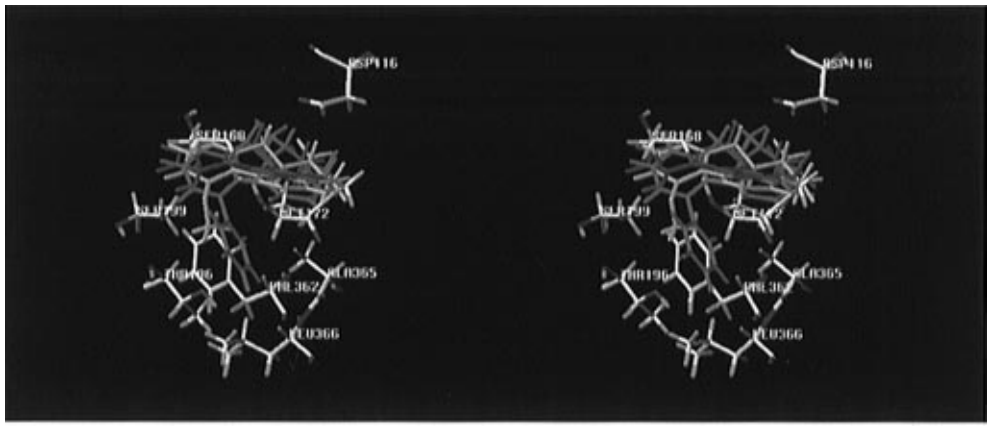


**Figure 2.** Stereoscopic representation of a 5-$HT_{1A}$ receptor binding site model obtained by simultaneous optimization of **3** (red), **4** (yellow), and **14** (green) showing a gradual change in binding mode which is dependent on the C11-substituent.

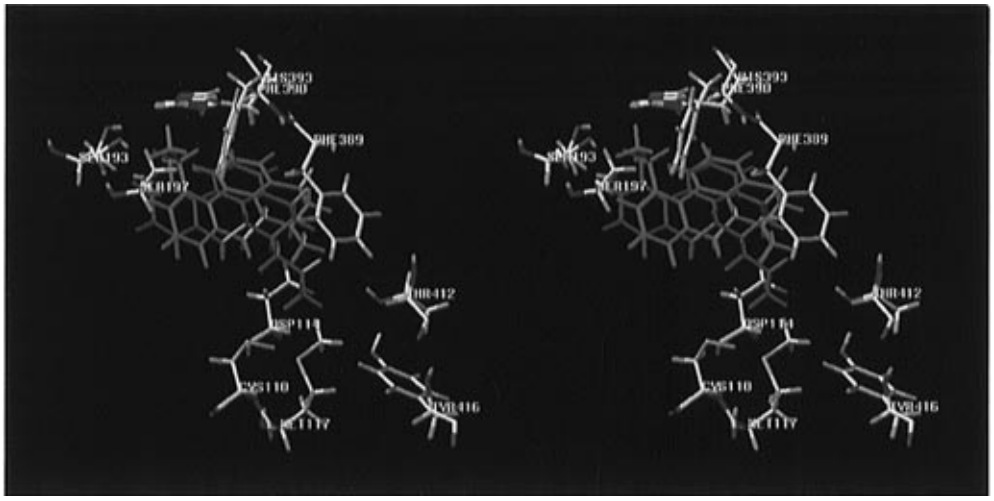


**Figure 3.** Stereoscopic representation of a $D_{2A}$ receptor binding site model interacting with **2** (red) and **11** (green). The residues responsible for key interactions (Asp114, Ser193, and Phe390) and some of the residues lining the *N*-propyl cleft and the site accommodating the C11-ethyl substituent are shown. The two orientations shown for Ser193 and His393 correspond to those obtained after individually optimizing the site for either ligand.

of **2** ($\Delta E_s$ = 0.3 kcal/mol). Docking all 11 minimum energy conformations of **2** into the 5-$HT_{1A}$ binding site revealed that none of the low-energy conformations could bind to both Asp116 and Ser168 without undergoing steric repulsion. The lowest energy conformation that could be docked had a relative steric energy of 2.5 kcal/mol which may explain the drop in 5-$HT_{1A}$ receptor affinity observed for **2** compared to **3**.

A moderate to high affinity of **2**, **18**, and **23** to 5-$HT_{1A}$ receptors, together with their inability to decrease the 5-HT synthesis rate and to induce the 5-$HT_{1A}$ syndrome *in vivo* at the doses tested, may indicate antagonistic properties or lack of efficacy of these analogues at 5-$HT_{1A}$ receptors. As expected, the $D_2$ receptor agonist **2**[1c] decreased the DA synthesis rate, induced stereotyped behavior, and displayed high affinity to $D_{2A}$ receptors. Surprisingly, **18** and **23** also produced $D_2$ agonistic effects by decreasing the DA synthesis *in vivo*, although they only displayed micromolar affinity to $D_{2A}$ receptors. These results indicate mixed agonist/antagonist effects of **2**, **18**, and **23** at 5-$HT_{1A}$ and $D_{2A}$ receptors. It is also possible that pharmacokinetic factors could contribute to the complex profile observed *in vivo* with these compounds,[38] and further work is needed to clarify these issues.

Compound **3** was recently reported to have antagonistic properties at $D_1$ receptors[1e] and to be a partial 5-$HT_{1A}$ receptor agonist.[3] The moderate affinity to $D_{2A}$ receptors together with the ability to decrease the DOPA accumulation indicates that **3** may also have agonistic properties at $D_2$ receptors.

The present series of compounds clearly shows how small structural changes significantly influence the receptor binding profile and the *in vivo* pharmacological activity. Although the complex *in vivo* pharmacological profiles are not fully understood yet, the *in vitro* binding data could be rationalized using models of the 5-$HT_{1A}$ and $D_{2A}$ receptor binding sites.

## Experimental Section

**Chemistry. General Comments**. Melting points (uncorrected) were determined in open glass capillaries on 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 determined within ±0.4% of the theoretical values. The $^1$H and $^{13}$C NMR spectra of the amines were recorded on a JEOL JNM-EX270 spectrometer at 270 and 67.8 MHz, respectively, and are referenced to internal tetramethylsilane. In the $^1$H and $^{13}$C NMR spectra of the hydrochloride salts of **6**−**13** in $CD_3OD$, diastereomeric conformations at or below the slow exchange limit (SEL) were present.[39] The spectra could not be simplified by heating the $CD_3OD$ sample to 50 °C. Therefore, the NMR data reported for compounds **6**−**16** were recorded for the amines in $CDCl_3$, whereas for the 11-oxygenated analogues **2, 18**, and **20**−**25**,

the data for the hydrochlorides in $CD_3OD$ are reported. Compounds **15** and **16** most likely exist as mixtures of atropisomers,[13] as judged by their complicated $^1H$ and $^{13}C$ NMR spectra. Infrared (IR) spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. 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; E. Merck). For preparative TLC, plates precoated with either silica gel 60 $F_{254}$ (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, activity II−III; E. Merck). Capillary GC was performed on a Carlo Erba 6000 instrument, equipped with a SE 54 fused silica gel capillary column (25 m). Dimethylformamide (DMF) was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen. *N*-methyl-2-pyrrolidinone (NMP) was used as received. Physicochemical properties of the novel compounds are also shown in Table 1.

**Syntheses. (−)-(*R*)-11-[[(Trifluoromethyl)sulfonyl]oxy]-aporphine (6)**. *N*-Phenyltrifluoromethanesulfonimide (3.41 g, 9.54 mmol) and $K_2CO_3$ (1.12 g, 8.10 mmol) were added to a refluxed (15 min) slurry of **3** (2.01 g, 8.00 mmol) and $Et_3N$ (3.40 mL, 24.5 mmol) in $CH_2Cl_2$ (100 mL), kept under nitrogen. Additional portions of *N*-phenyltrifluoromethanesulfonimide (400 mg, 1.11 mmol and 330 mg, 0.92 mmol) were added after 24 and 43 h. After 70 h, the heating was interrupted, and the reaction mixture was extracted with 10% aqueous $NaHCO_3$. The organic layer was dried ($K_2CO_3$), filtered, and concentrated *in vacuo*. The oily residue was chromatographed [silica gel; $CHCl_3$/MeOH (9:1) and aluminum oxide (deactivated with 5% $H_2O$); ether]. The pure amine was converted into the hydrochloride salt, which was recrystallized from EtOH to give 2.49 g (74%) of pure **6**·HCl: IR (KBr) 2369, 1212, 1142 $cm^{-1}$.

**6**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.51−2.63 (m, 2 H), 2.56 (s, 3 H), 2.77 (dd, 1 H), 3.05 (ddd, 1 H), 3.13−3.25 (m, 3 H), 7.14 (app d, 1 H), 7.13−7.16 (m, 4 H), 7.79 (app d, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.1, 35.0, 44.1, 52.8, 61.5, 118.5 (q), 121.4, 126.0, 126.6, 128.1, 128.3, 128.7, 128.3, 129.2, 133.3, 135.2, 139.7, 146.4; $^{19}F$ NMR ($CDCl_3$) $\delta$ −73.6.

**(−)-(*R*)-Aporphine (7)**.[5c] A mixture of **6** (223 mg, 0.58 mmol), (diphenylphosphino)propane (dppp; 37 mg, 0.089 mmol), $(PPh_3)_2PdCl_2$ (25 mg, 0.035 mmol), $Bu_3N$ (0.55 mL, 2.31 mmol), and formic acid (66 $\mu$L, 1.8 mmol) in dry DMF (5 mL) was stirred at 80 °C for 15 h. The volatiles were evaporated *in vacuo*, and the residue was 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 [silica gel; $CHCl_3$/MeOH (gradient 1:0−9:1) and aluminum oxide ether/hexanes (gradient 1:1−6:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN to give 80 mg (51%) of pure **7**·HCl: mp 233−234 °C (lit.[5c] mp 229−232 °C); $[\alpha]^{23}_D$ −108.2° (*c* 1.0, MeOH) [lit.[5c] $[\alpha]^{28.5}_D$ −109.4° (*c* 0.0019, MeOH)].

**7**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.55 (ddd, 1 H), 2.57 (s, 3 H), 2.63−2.81 (m, 2 H), 3.07 (ddd, 1 H), 3.14−3.26 (m, 3 H), 7.08 (app d, 1 H), 7.20−7.35 (m, 4 H), 7.56 (app d, 1 H), 7.72 (app d, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.1, 34.1, 43.8, 53.4, 62.0, 121.2, 123.7, 126.8, 127.3, 127.5, 128.0, 128.3, 133.4, 133.5, 133.8, 134.4, 135.3.

**(−)-(*R*)-11-Methylaporphine (8)**. A mixture of **6** (233 mg, 0.61 mmol), LiCl (130 mg, 3.07 mmol), $PPh_3$ (98 mg, 0.37 mmol), $(PPh_3)_2PdCl_2$ (52 mg, 0.074 mmol), $Me_4Sn$ (0.34 mL, 2.5 mmol), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol in dry DMF (5 mL) was stirred in a closed vessel at 120 °C for 7 h. The volatiles were evaporated *in vacuo*, and the residue was partitioned between ether and 10% aqueous $NaHCO_3$. The ether layer was dried ($K_2CO_3$), filtered, and concentrated. The residue was dissolved in $CHCl_3$, filtered through a pad of silica gel, concentrated, and chromatographed [aluminum oxide; ether/hexanes (gradient 1:1−1:0)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN to give 121 mg (70%) of pure **8**·HCl.

**8**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.48−2.60 (m, 2 H), 2.55 (s, 3 H), 2.60 (s, 3 H), 2.77 (dd, 1 H), 2.92−3.06 (m, 3 H), 3.15 (ddd, 1 H), 6.97−7.17 (m, 5 H), 7.38 (app d, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 22.6, 29.2, 35.7, 44.1, 52.8, 62.3, 125.6, 125.7, 126.0, 126.8, 127.4, 130.8, 132.7, 133.4, 133.9, 134.3, 136.0, 137.1.

**(−)-(*R*)-11-Acetylaporphine (9)**. A mixture of **6** (154 mg, 0.40 mmol), LiCl (75 mg, 1.8 mmol), $PPh_3$ (180 mg, 0.69 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.050 mmol), and tributyl(1-ethoxyvinyl)-stannane (293 mg, 0.85 mmol) in dry DMF (10 mL) was stirred in a closed vessel at 120 °C for 18 h. The volatiles were evaporated *in vacuo*. The residue was diluted with ether, filtered through a pad of aluminum oxide, and concentrated. THF (10 mL) and concentrated aqueous HCl (10 mL) were added to the residue, and the mixture was stirred for 2 min. The volatiles were evaporated, and the residue was partitioned between 10% aqueous $NaHCO_3$ and $CH_2Cl_2$. The combined organic extracts were dried ($K_2CO_3$), filtered, and concentrated to give an oil which was chromatographed [silica gel; $CH_2Cl_2$/MeOH (gradient 39:1−9:1) and aluminum oxide; ether/hexanes (gradient 1:1−1:0)]. The amine was converted into the hydrochloride, which was recrystallized from MeCN/*tert*-butyl methyl ether to give 109 mg (87%) of pure **9**·HCl.

**9**: IR (film) 1684, 1463, 1374 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.27 (s, 3 H), 2.50−2.67 (m, 2 H), 2.60 (s, 3 H), 2.80 (dd, 1 H), 3.08 (ddd, 1 H), 3.12−3.28 (m, 3 H), 7.07−7.65 (m, 6 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.2, 31.0, 34.6, 44.1, 52.9, 61.7, 126.47, 126.48, 126.8, 127.4, 128.7, 130.1, 131.7, 133.0 133.5, 135.0, 137.2, 139.9, 206.4.

**(+)-(*R*)-11-Vinylaporphine (10)**. A mixture of **6** (429 mg, 1.11 mmol), LiCl (384 mg, 8.95 mmol), $PPh_3$ (180 mg, 0.69 mmol), $(PPh_3)_2PdCl_2$ (94 mg, 0.13 mmol), tributylvinylstannane (720 mg, 2.3 mmol), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol in dry DMF (10 mL) was stirred in a closed vessel at 120 °C for 5 h. The volatiles were evaporated *in vacuo*, and the residue was partioned between $CHCl_3$ and 10% aqueous $NaHCO_3$. The combined organic layers were dried ($K_2CO_3$), filtered, and concentrated. The residue was chromatographed [silica gel; $CHCl_3$/MeOH (gradient 39:1−9:1) and aluminum oxide (deactivated with 3.5% $H_2O$); ether/hexanes (gradient 1:1−3:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from EtOH/ether to give 191 mg (57%) of pure **10**·HCl.

**10**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.49−2.61 (m, 2 H), 2.56 (s, 3 H), 2.77 (dd, 1 H), 3.01−3.27 (m, 4 H), 5.71 (dd, 1 H), 5.77 (dd, 1 H), 7.03 (dd, 1 H), 7.09 (app d, 1 H), 7.18−7.26 (m, 3 H), 7.45−7.50 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.1, 35.3, 44.1, 52.9, 62.0, 114.6, 125.6, 126.9, 127.1, 127.3, 127.4, 127.7, 132.5, 132.8, 132.9, 135.3, 135.7, 136.9, 138.3.

**(−)-(*R*)-11-Ethylaporphine (11)**. A slurry of **10** (93 mg, 0.36 mmol) and Pd(C) (10%, 90 mg) in THF was hydrogenated at atmospheric pressure for 5 h. The catalyst was filtered off (aluminum oxide), and the volatiles were evaporated *in vacuo*. The residue was chromatographed [silica gel; $CH_2Cl_2$/MeOH (gradient 1:0−9:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN to give 57 mg (56%) of pure **11**·HCl.

**11**: $^1H$ NMR ($CDCl_3$) $\delta$ 1.34 (t, 3 H), 2.47−2.61 (m, 2 H), 2.55 (s, 3 H), 2.77 (dd, 1 H), 2.83−3.14 (m, 5 H), 3.21 (ddd, 1 H), 7.09 (app d, 1 H), 7.12 (app d, 1 H), 7.19 (app t, 1 H), 7.23 (app t, 1 H), 7.27 (app d, 1 H), 7.42 (app d, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 15.3, 26.7, 29.2, 36.0, 44.1, 52.8, 62.2, 125.5, 125.7, 125.9, 127.0, 127.4, 128.8, 132.8, 133.3, 133.7, 136.1, 137.1, 140.6.

**(−)-(*R*)-11-Cyanoaporphine (12)**. Dry nitrogen gas was passed through a mixture of **6** (588 mg, 1.53 mmol), KCN (123 mg, 1.89 mmol), $PPh_3$ (208 mg, 0.79 mmol), Zn (152 mg, 2.33 mmol), and $(PPh_3)_2NiCl_2$ (255 mg, 0.39 mmol) in dry DMF (5 mL). The vessel was sealed, and the mixture was stirred at 120 °C for 48 h. Additional portions of $PPh_3$ (78.0 mg, 0.30 mmol) and $(PPh_3)_2NiCl_2$ (97 mg, 0.15 mmol) were added, and after an additional 24 h, the mixture was diluted with $CH_2Cl_2$ and filtered through a pad of aluminum oxide. The volatiles were evaporated *in vacuo*, and the residue was chromatographed [silica gel; $CHCl_3$/MeOH (gradient 39:1−9:1) and aluminum oxide; ether/hexanes/methanol (gradient 1:2:0−97:0:3)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN/EtOH (1:1)/*tert*-butyl methyl ether to give 299 mg (66%) of pure **12**·HCl.

**12**: IR (film) 2225 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.47−2.65 (m, 2 H), 2.55 (s, 3 H), 2.77 (dd, 1 H), 3.02−3.26 (m, 4 H), 7.19 (app d, 1 H), 7.29 (app t, 1 H), 7.33 (app t, 1 H), 7,49 (app d, 1 H), 7.65 (app d, 1 H), 8.11 (app d, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 28.9, 34.6, 44.0, 52.9, 61.4, 108.0, 119.9, 124.7, 126.8, 127.3, 129.8, 130.3, 132.6, 133.4, 133.9, 135.1, 137.4, 137.7.

**(−)-(*R*)-11-Carbamoylaporphine (13)**. A mixture of **12**·HCl (74 mg, 0.25 mmol), $H_2O$ (7 mL), and concentrated $H_2SO_4$ (3 mL) was stirred at 120 °C for 4 h. The mixture was partitioned between 2 M aqueous NaOH and $CHCl_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN/ether to give 72 mg (92%) of pure **13**·HCl: IR (KBr) 1664 $cm^{-1}$.

**13**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.43−2.60 (m, 2 H), 2.54 (s, 3 H), 2.73 (dd, 1 H), 3.03 (dd, 1 H), 3.07−3.24 (m, 3 H), 5.97 (s, 1 H), 6.35 (s, 1 H), 7.07 (app d, 1 H), 7.16 (app t, 1 H), 7.21 (app t, 1 H), 7.31 (app d, 1 H), 7.41 (app d, 1 H), 7.51 (app d, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 28.9, 34.8, 44.0, 52.8, 61.6, 125.8, 126.3, 127.2, 127.6, 128.5, 129.9, 131.2, 132.0, 133.0, 133.7, 134.9, 137.2, 173.6.

**(−)-(*R*)-11-Phenylaporphine (14)**. A solution of **6** (100 mg, 0.26 mmol) in NMP (2.5 mL) was added to a mixture of (2-furyl)$_3$P (12.2 mg, 0.053 mmol), LiCl (33.2 mg, 0.78 mmol), $PhSnBu_3$ (196 mg, 0.53 mmol), and tris(dibenzylideneacetone-)dipalladium(0) [$(dba)_3Pd_2$; 12 mg, 0.014 mmol]. The mixture was stirred at 100 °C for 5 h. Ether was added, the mixture was filtered through a pad of alumina, and the volatiles were evaporated *in vacuo*. The residue was chromatographed [silica gel; EtOAc/MeOH (9:1)], and the amine was converted into the hydrochloride, which was recrystallized from acetonitrile/EtOH/ether to give 54 mg (60%) of pure **14**·HCl.

**14**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.51−2.66 (m, 2 H), 2.58 (s, 3 H), 2.75 (dd, 1 H), 3.06 (dd, 1 H), 3.10−3.33 (m, 3 H), 6.65 (d, 1 H), 6.75 (dd, 1 H), 6.91 (d, 1 H), 7.20−7.37 (m, 8 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.2, 36.0, 44.1, 52.8, 62.2, 125.2, 126.7, 127.1, 127.4, 127.8, 128.4, 128.4, 129.5, 129.5, 130.6, 132.56, 132.56, 132.61, 132.7, 135.7, 137.6, 139.7, 143.0.

**(−)-(*R*)-11-(2-Methoxyphenyl)aporphine (15)**. A mixture of **6** (630 mg, 1.64 mmol), LiCl (560 mg, 13 mmol), CuI (127 mg, 0.67 mmol), $(PPh_3)_2PdCl_2$ (183 mg 0.26 mmol), (2-methoxyphenyl)$SnBu_3$ (720 $\mu$L, 1.9 mmol), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol were suspended in DMF (5 mL). The mixture was stirred at 145 °C for 3 h. A second portion of (2-methoxyphenyl)$SnBu_3$ (720 $\mu$L, 1.9 mmol) was added, and the heating was continued at 145 °C for an additional 9 h. The volatiles were evaporated, and the residue was partioned between 10% aqueous $NaHCO_3$ and $CH_2Cl_2$. The combined organic extracts were dried ($K_2CO_3$), filtered, and concentrated. The residue was chromatographed [alumina (deactivated with 7.5% $H_2O$); EtOAc/hexanes (5:1)]. Two presumed atropisomers[13] were separated. The main isomer was converted into the hydrochloride, which was recrystallized from acetonitrile/ether to give 300 mg (49%) of pure **15**·HCl.

**15**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.27 (s, 3 H), 2.50−2.67 (m, 2 H), 2.60 (s, 3 H), 2.80 (dd, 1 H), 3.08 (ddd, 1 H), 3.12−3.28 (m, 3 H), 7.07−7.65 (m, 10 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.2, 35.2, 35.7, 43.9, 52.7, 53.0, 54.9, 55.5, 62.0, 62.2, 111.1, 111.7, 120.5, 121.3, 124.1, 125.0, 125.2, 126.1, 126.8, 126.9, 127.1, 127.2, 128.3, 128.5, 130.3, 130.4, 131.3, 131.5, 131.7, 132.0, 132.2, 132.6, 133.1, 134.2, 134.6, 135.4, 135.4, 135.6, 136.0, 137.2, 155.8, 156.8.

**(−)-(*R*)-11-(2-Hydroxyphenyl)aporphine (16)**. A mixture of **15**·HCl (90 mg, 0.24 mmol) and 48% aqueous HBr (10 mL) kept under nitrogen was stirred at 110 °C. After 2 h the volatiles were evaporated, and the residue was partitioned between $CH_2Cl_2$ and 10% aqueous $NaHCO_3$. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed [silica gel; $CHCl_3$/MeOH (9:1)], and the amine was converted into the hydrochloride, which was recrystallized from 2-PrOH/ether to give 73 mg (97%) of pure **16**·HCl.

**16**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.44−2.80 (m, 3 H), 2.54 (s, 3 H), 2.97 (dd, 1 H), 3.03−3.30 (m, 3 H), 6.58−7.50 (m, 10 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.0, 35.3, 35.6, 44.0, 52.76, 52.79, 61.9, 62.0, 115.9, 120.5, 121.1, 124.8, 125.6, 125.8, 126.8, 127.2, 127.5, 128.1, 128.2, 128.4, 128.8, 128.9, 129.0, 129.6, 130.4, 130.5, 130.8, 131.8, 132.2, 132.4, 132.5, 132.7, 133.1, 133.5, 134.1, 134.4, 134.8, 135.8, 137.1, 138.5, 151.8, 153.4.

**(−)-(*R*)-11-Methoxy-*N*-propylnoraporphine (18)**.[1c,14] Compound **18** was synthesized from **17**[15] (0.34 g, 0.78 mmol) using the procedure described for the preparation of **4**.[3,21] The reaction time was 18 h. Crude **18** was chromatographed [silica gel; $CHCl_3$/MeOH (39:1) and ether/hexanes (1:1) followed by aluminum oxide; ether/hexanes (1:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN to yield 0.21 g (82%) of pure **18**·HCl: mp 231−234 °C dec (lit.[14] mp 227−229 °C); $[\alpha]^{23}_D$ −81.1° (*c* 1.0, MeOH) [lit.[14] $[\alpha]^{26}_{578}$ −69.9°, $[\alpha]^{26}_{546}$ −89.32° (*c* 0.0515, MeOH)]; $^1H$ NMR ($CD_3OD$) $\delta$ 1.10 (t, 3 H), 1.75−2.04 (m, 2 H), 2.95 (dd, 1 H), 3.04−3.32 (m, 2 H), 3.32−3.69 (m, 4 H), 3.89 (s, 3 H), 3.81−3.92 (m, 1 H), 4.37 (app br d, 1 H), 7.01 (app d, 1 H), 7.06 (app d, 1 H), 7.17 (app d, 1 H), 7.27 (dd, 1 H), 7.34 (dd, 1 H), 8.22 (app d, 1 H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 12.1, 19.2, 27.7, 33.8, 51.0, 57.0, 57.5, 62.9, 113.7, 122.9, 123.9, 129.3, 129.7, 129.9, 130.4, 131.1, 131.5, 134.1, 136.5, 159.2.

**(−)-(*R*)-11-Hydroxy-*N*-propylnoraporphine (2)**.[1c,14] A slurry of **18**·HCl (167 mg, 0.506 mmol) in 48% HBr (8 mL) was refluxed for 4 h at 120 °C under nitrogen. Absolute ethanol was added, and the volatiles were removed *in vacuo*. The residue was partitioned between ether/10% aqueous $NaHCO_3$, and the combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. Crude **2** was purified by chromatography [silica gel; $CHCl_3$/MeOH (39:1 and 9:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN/ether to give 123 mg (77%) of pure **2**·HCl: mp 260−263 °C dec (lit.[1c] mp 257−258 °C); $[\alpha]^{23}_D$ −67.4° (*c* 1.0, MeOH) [lit.[1c] $[\alpha]^{25}_{578}$ −64.0° (*c* 0.289, MeOH)]; $^1H$ NMR ($CD_3OD$) $\delta$ 1.07 (t, 3 H), 1.71−2.07 (m, 2 H), 2.89 (dd, 1 H), 3.00−3.70 (m, 6 H), 3.81−3.97 (m, 1 H), 4.37 (app br d, 1 H), 6.86 (app d, 1 H), 6.87 (app d, 1 H), 7.10 (dd, 1 H), 7.15 (app d, 1 H), 7.34 (dd, 1 H), 8.38 (app d, 1 H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 11.3, 18.4, 27.1, 33.0, 50.3, 56.8, 62.2, 117.2, 120.8, 121.2, 128.2, 128.8, 129.1, 129.3, 130.0, 130.5, 134.0, 135.6, 156.2.

**(−)-(*R*)-*N*-Benzyl-11-methoxynoraporphine (20)**. Compound **20** was synthesized from **19**[15] (5.37 g, 0.0109 mol) using the procedure described for the preparation of **18**. The reaction time was 18 h. The crude mixture was concentrated *in vacuo*, and the residue was partitioned between ether and 10% aqueous $Na_2CO_3$. The organic layer was dried ($Na_2SO_4$), filtered, and concentrated. Excess $Bu_3N$ was removed by vacuum distillation at 80 °C and 2 mmHg. The crude mixture was chromatographed [aluminum oxide; ether/hexanes (1:8−1:3) and silica gel; toluene to toluene/MeCN (20:1)] to give 3.60 g of pure **20** and 0.16 g of the oxidized analogue *N*-benzyl-6a,7-didehydro-11-methoxynoraporphine (**26**). The amine **20** was converted into the hydrochloride salt, which was recrystallized from MeCN/ether to give 3.52 g (85%) of pure **20**·HCl: $^1H$ NMR ($CD_3OD$) $\delta$ 2.97−3.14 (m, 2 H), 3.18−3.65 (m, 2 H), 3.64−3.82 (m, 2 H), 3.88 (s, 3 H), 4.42 (m, 2 H), 5.07 (br d, 1 H), 7.07 (app d, 1 H), 7.09 (app d, 1 H), 7.15 (app d, 1 H), 7.31 (dd, 1 H), 7.34 (dd, 1 H), 7.49−7.56 (m, 3 H), 7.58−7.65 (m, 2 H), 8.21 (app d, 1 H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 26.9, 33.2, 49.5, 56.2, 58.9, 62.4, 112.8, 122.1, 123.1, 128.5, 128.9, 129.1, 129.6, 130.2, 130.4, 130.5, 130.7, 131.4, 132.8, 133.3, 135.7, 158.3.

Compound **26** was chromatographed [aluminum oxide; ether/hexanes (1:8−1:1)] and recrystallized (ether) to give 0.14 g (3.8%) of pure **26**: mp 126−127 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 3.29 (app dd, 2 H), 3.47 (app dd, 2 H), 4.05 (s, 3 H), 4.65 (s, 2 H), 6.72 (app s, 1 H), 6.83 (dd, 1 H), 7.12−7.41 (m, 8 H), 7.53 (dd, 1 H), 9.57 (app d, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 31.3, 48.1, 55.6, 55.9, 102.9, 104.7, 115.2, 119.8, 123.7, 124.3, 125.9, 126.5, 126.6, 126.9, 127.3, 128.6, 131.5, 132.2, 136.2, 138.4, 142.5, 158.7. Anal. ($C_{24}H_{21}NO$) C, H, N.

**(−)-(*R*)-*N*-Benzyl-11-hydroxynoraporphine (21)**. Compound **21** was synthesized from **20**·HCl (0.60 g, 1.6 mmol) using the procedure described for the preparation of **2**·HCl. The reaction time was 6 h. Crude **21**·HCl was partitioned between $CH_2Cl_2$/EtOH (9:1) and 10% aqueous $NaHCO_3$. The organic layer was dried ($Na_2SO_4$), filtered, and concentrated.

The residue was chromatographed [silica gel; $CHCl_3$ to $CHCl_3$/MeOH (39:1)] to give 0.050 g of recovered **20** and pure **21**. The amine **21** was converted into the hydrochloride salt, which was recrystallized from MeOH to give 0.39 g (total yield 77%) of pure **21**·HCl: $^1$H NMR ($CD_3OD$, 50 °C) $\delta$ 2.94−3.44 (m, 4 H), 3.64−3.83 (m, 2 H), 4.36−4.51 (m, 2 H), 5.06 (br d, 1 H), 6.90 (app d, 1 H), 6.93 (app d, 1 H), 7.13 (app d, 1 H), 7.14 (dd, 1 H), 7.36 (dd, 1 H), 7.50−7.64 (m, 5 H), 8.41 (app d, 1 H); $^{13}$C NMR ($CD_3OD$, 50 °C) $\delta$ 27.0, 33.5, 50.0, 59.3, 62.9, 117.5, 120.8, 128.2, 129.0, 129.3, 130.15, 130.24, 130.5, 130.7, 131.6, 132.7, 134.0, 135.5, 156.4.

**(−)-(*R*)-11-Methoxynoraporphine (22)**. A mixture of **20**·HCl (1.12 g, 2.96 mmol) and Pd(C) (10%, 0.20 g) in HOAc (30 mL) was stirred under $H_2$ (1 atm). After stirring for 4 h, the volatiles were removed *in vacuo*. Crude **22**·HCl was purified by recrystallization from MeCN and MeOH/ether to give 0.75 g (88%) of pure **22**·HCl: $^1$H NMR ($CD_3OD$) $\delta$ 2.93 (dd, 1 H), 3.04−3.19 (m, 2 H), 3.25−3.48 (m, 2 H), 3.70−3.79 (m, 1 H), 3.90 (s, 3 H), 4.39 (dd, 1 H), 6.96 (app d, 1 H), 7.06 (app d, 1 H), 7.18 (app d, 1 H), 7.27 (dd, 1 H), 7.34 (dd, 1 H), 8.24 (app d, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 26.3, 35.0, 42.5, 54.3, 56.2, 112.8, 121.9, 123.2, 128.8, 128.9, 129.1, 129.6, 130.3, 130.8, 133.0, 135.6, 158.6.

**(−)-(*R*)-11-Hydroxynoraporphine (23)**. Compound **23** was prepared from **21**·HCl (0.17 g, 0.47 mmol) using the procedure for the synthesis of **22**·HCl. Absolute EtOH (40 mL) was added to dissolve the starting material. The reaction time was 6 h. Crude **23**·HCl was purified by recrystallization from MeOH/ether to give 0.12 g (94%) of pure **23**·HCl: $^1$H NMR ($CD_3OD$) $\delta$ 2.92 (dd, 1 H), 3.03−3.17 (m, 2 H), 3.13−3.48 (m, 2 H), 3.69−3.81 (m, 1 H), 4.39 (dd, 1 H), 6.82 (app d, 1 H), 6.86 (app d, 1 H), 7.10 (dd, 1 H), 7.15 (app d, 1 H), 7.34 (dd, 1 H), 8.40 (app d, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 26.4, 35.2, 42.7, 54.6, 117.4, 120.7, 121.5, 128.4, 128.9, 129.2, 129.3, 130.0, 130.7, 133.7, 135.6, 156.5.

**(−)-(*R*)-*N*-Isopropyl-11-methoxynoraporphine (24)**. Compound **24** was synthesized from **22** according to a method previously described by Liu *et al*.[24] A suspension of **22** (0.31 g, 1.2 mmol), $K_2CO_3$ (0.19 g, 1.4 mmol), diisopropylethylamine (0.23 mL, 1.4 mmol), and 2-iodopropane (0.14 mL, 1.4 mmol) in MeCN (1.5 mL) was stirred at 70 °C for 89 h. The crude mixture was diluted with $CH_2Cl_2$, filtered, and concentrated. The residue was chromatographed [aluminum oxide; ether/hexanes (1:8)], and the amine was converted into the hydrochloride salt. Recrystallization from MeCN/ether gave 0.35 g (86%) of pure **24**·HCl: $^1$H NMR ($CD_3OD$) $\delta$ 1.33 (d, 3 H), 1.55 (d, 3 H), 2.93 (dd, 1 H), 3.08−3.33 (m, 2 H), 3.33−3.52 (m, 2 H), 3.75−3.88 (m, 1 H), 3.88 (s, 3 H), 4.30 (sept, 1 H), 4.49 (dd, 1 H), 7.01 (app d, 1 H), 7.05 (app d, 1 H), 7.18 (app d, 1 H), 7.27 (dd, 1 H), 7.34 (dd, 1 H), 8.21 (app d, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 14.2, 18.7, 27.3, 32.6, 43.5, 54.6, 56.2, 60.0, 112.8, 122.2, 123.2, 128.6, 128.9, 129.0, 130.1, 130.3, 131.1, 133.5, 135.6, 158.3.

**(−)-(*R*)-11-Hydroxy-*N*-isopropylnoraporphine (25)**. Compound **25** was synthesized from **24**·HCl (0.17 g, 0.52 mmol) using the procedure for the synthesis of **2**·HCl. The reaction time was 4 h and 30 min. Crude **25**·HBr was partitioned between $CH_2Cl_2$/EtOH (5:1) and 10% aqueous $NaHCO_3$. The organic layer was dried ($Na_2SO_4$), filtered, and concentrated. The amine was converted into the hydrochloride salt, which was recrystallized from MeCN/MeOH followed by MeOH/ether to give 0.15 g (92%) of pure **25**·HCl: $^1$H NMR ($CD_3OD$) $\delta$ 1.35 (d, 3 H), 1.54 (d, 3 H), 2.87 (dd, 1 H), 3.13−3.40 (m, 3 H), 3.46 (dd, 1 H), 3.78−3.89 (m, 1 H), 4.32 (sept, 1 H), 4.59 (dd, 1 H), 6.88 (app d, 2 H), 7.12 (dd, 1 H), 7.18 (app d, 1 H), 7.36 (dd, 1 H), 8.40 (app d, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 14.1, 18.7, 27.3, 32.7, 43.6, 54.5, 60.1, 117.2, 120.8, 121.2, 128.2, 128.7, 129.1, 129.8, 130.0, 130.9, 134.1, 135.4, 156.1.

**(±)-*N*-Benzyl-11-methoxynoraporphine (27)**.[1a] Compound **27** was prepared from **26** according to a method previously described by Gerecke *et al*.[19] A suspension of **26** (71 mg, 0.21 mmol) and zink (0.20 g, 3.1 mmol) in 1 M aqueous $H_2SO_4$ (5 mL) was stirred at 75 °C for 29 h. Due to lack of further progress of the reaction, it was restarted using the following procedure: The mixture was partitioned between $CHCl_3$ and 10% $NaHCO_3$, and the organic layer was dried ($Na_2SO_4$), filtered, and concentrated. The residue was suspended in a mixture of absolute EtOH and 1 M aqueous $H_2SO_4$ (1:3). Zink dust (0.35 g, 5.4 mmol) was added, and the mixture was stirred at 75 °C for 42 h. Crude **27** was purified by preparative TLC [silica gel; toluene/MeCN (10:1)]. The amine was converted into the hydrochloride salt, which was recrystallized from MeOH/ether to give 18 mg of recovered **26** and 58 mg of pure **27**·HCl (total yield 91%): mp 232−236 °C. Anal. ($C_{24}H_{24}ClNO$) C, H, N. Racemic **27**·HCl was used for determination of the optical purity of **22** as described below.

**Determination of Optical Purity of Compound 22**. The optical purity of **22** was determined as follows: **22**·HCl (32 mg, 85 mmol) was partitioned between $CH_2Cl_2$ and 10% aqueous $Na_2CO_3$, and the organic layer was dried ($K_2CO_3$), filtered, and concentrated. The residue was stirred with (*R*)-*O*-methylmandelic chloride as described previously[20] to give **29**. Compound **28** was synthesized from **27**·HCl (25 mg, 66 mmol) using the procedure for the synthesis of **22**. Treatment of **28** with (*R*)-*O*-methylmandelic chloride as described previously[20] afforded a 1:1 mixture of **29** and **30** (capillary GC). The enantiomeric excess of **22** was determined to be >99.8% ee, which was shown by comparison with a sample of **29** to which 0.2% of the 1:1 mixture of **29** and **30** had been added (capillary GC).

**Computational Methods**. MacMimic version 2.1 (InStar Software, IDEON Research Park, S-233 70 Lund, Sweden) was used as graphical interface for MM2(91).[22] 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. The most stable conformation of the aporphine skeleton was used having a pseudoequatorial *N*-alkyl substituent and adopting 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.[15] Compounds with a C11-OH-substituent were modeled with C10−C11−O−H in an eclipsed orientation as selected previously for H-bonding to active site residues.[3]

**Active Site Definition**. The definition of the 5-$HT_{1A}$ receptor active site has been described elsewhere.[15] Amino acids having atoms within a 10 Å sphere around the centroid of the Cα atoms of Asp114, Ser193, and Phe390 were considered in the initial active site definition for the $D_{2A}$ receptor model. 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 6.0.3 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 the ligand OH was extended to 2.75 Å. The distance between these extended points in **1** was 10.16 Å, and the sites selected from the systematic search output were those that had the Asp-O and the Ser-O at distances between 9.91 and 10.41 Å. Compound **1** was fitted to the Asp-O and Ser-O using the $N^+$-H and OH extended points defined above. For the third fitting point a normal was defined through the A-ring extending 6 Å toward the aromatic ring of Phe390. The end point of this normal was fitted onto the centroid of Phe390. The weight of this last fitting point was 1/10th of the weight of the other two points. The rms value of the fit was used together with the common volume of ligand and active site residues to select complexes for futher optimization.

**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, Tripos Associates Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO). The necessary free energies of binding and 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.*[40]), 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.

An active site model for the $D_{2A}$ receptor was derived from the systematically generated sites in a stepwise manner using the high-affinity ligands **1** and **2**. Prior to optimization, two spheres were defined around the ligand 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. The active site complex resulting from Yak optimization of **1** was used as the starting point for docking **2** by fitting that ligand onto the optimized position of **1** (using the nitrogen, the C11-oxygen and the A-ring centroid). The model was obtained by optimization of **1** and **2** simultaneously using 3 and 5 Å spheres, respectively. The 5-$HT_{1A}$[15] and $D_{2A}$ models were used to dock the different conformations of selected compounds, grouped into sets that differ only in the substitution on one position of the aporphine skeleton. The 5 and 3 Å spheres were defined around the whole set of those ligands fitted onto **1** ($D_{2A}$) and either **5** or **14** (5-$HT_{1A}$). 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.

**Pharmacology. Receptor Binding Assays**. The serotonin 5-$HT_{1A}$[3,15] and the dopamine $D_{2A}$[41] and $D_1$[42] receptor binding assays were performed as described previously, using [$^3$H]-8-OH-DPAT·HBr, [$^3$H]raclopride, and [$^3$H]SCH23390, respectively, as radioligands.

**Biochemistry and Behavior**. The monitoring and scoring of the behavior produced by the compounds and the estimation of their effects on central 5-HT, DA, and NA synthesis rates by measuring the accumulation of 5-hydroxytryptophan (5-HTP) and 3,4-dihydroxyphenylalanine (DOPA), respectively, were performed in reserpinized rats as previously described.[15,34b]

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**Supporting Information Available:** Assigned $^1$H NMR data (4 pages). Ordering information is given on any current masthead page.

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