Derivatives of (*R*)-1,11-Methyleneaporphine: Synthesis, Structure, and Interactions with G-Protein Coupled Receptors

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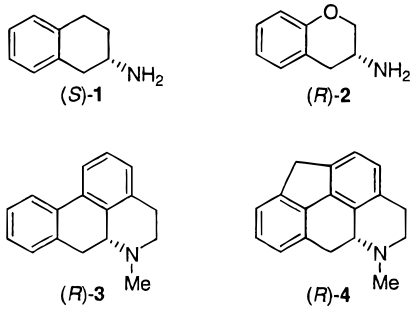
The design and synthesis of a well-characterized novel ring system, (*R*)-λ1,11-methyleneaporphine [(*R*)-**4**], and 15 derivatives thereof are presented. The addition of various nucleophiles to (*R*)-λ1,11-carbonylaporphine [(*R*)-**11**] or to the 1,11-hydroxymethyleneaporphine epimers gave separable mixtures of epimers. The epimeric ratios obtained in most reactions seem to be a result of steric factors directing the nucleophilic attack. The structure of the epimers was determined by a combination of X-ray crystallography (5 derivatives), NMR spectroscopy, and chemical correlation. Interesting and diverse pharmacological profiles of the derivatives were revealed through binding studies at serotonin 5-HT_7 and 5-HT_{1A} receptors as well as at dopamine D_{2A} receptors. Two derivatives appeared to be selective 5-HT_7 receptor antagonists. It is evident from our results that the novel ring system [(*R*)-**4**] provides a useful complement to other scaffolds available to medicinal chemists involved in studies of GPC receptors.

Introduction

Dopamine (DA) and serotonin (5-HT) are neurotransmitters with important central as well as peripheral functions. In the central nervous system (CNS), they are, for example, involved in the regulation of mood, perception, reward mechanisms, memory, behavior, appetite, and sexual function.[1] Hence, molecules which modify dopaminergic or serotonergic brain function may be of interest as drugs in the therapy of diseases related to CNS dysfunction,[1a,2] and the receptors for DA and 5-HT represent targets for novel CNS drugs. Currently, 5 and 14 subtypes have been identified within the DA[1a,b,2a,3] and 5-HT[4] receptor families, respectively. With one exception, the 5-HT_3 receptor, a ligand gated ion channel, these receptors belong to the G-protein coupled (GPC) receptor superfamily.[5]

Detailed structural information providing atomic resolution about these and other GPC receptors is still lacking.[6] Hence, ligands to DA and 5-HT receptors cannot be designed using (direct) structure-based methods, but such efforts have to rely on established indirect methods such as receptor mapping and quantitative structure−activity relationships (QSAR). Alternatively, ligands with suitable properties may be discovered by use of a combination of combinatorial methods and serendipity (screening). The above approaches require access to fairly rigid template moieties which have the potential to give derivatives with diverse pharmacology, which can be readily functionalized and which allow the chemist to explore the properties of the receptor site in three dimensions.

The 2-aminotetralin [(*S*)-**1**],[7] 3-aminochroman [(*R*)-**2**],[8] and aporphine [(*R*)-**3**][9] moieties have served as useful templates for the mapping of the ligand binding sites of certain receptors for DA and 5-HT, primarily the D_1, D_2, D_3, D_4, and 5-HT_{1A} receptors. The aromatic rings of these structures can be readily functionalized allowing well-defined structural extensions in the plane of the ring system.



We have now designed a novel ring system, (*R*)-1,11-methyleneaporphine [(*R*)-**4**], which can be functionalized in space below and above the plane of the ring system, thereby allowing for structural extension into previously unexplored areas of the ligand binding site of the DA and 5-HT receptors. Herein, we present our syntheses of (*R*)-**4** and derivatives thereof, the structures of these derivatives as determined by a combination of X-ray crystallography, NMR spectroscopy, and chemical correlation, and their affinities for selected DA and 5-HT receptors. The compounds are rigid, are feasible to synthesize, and display diverse and interesting pharmacology. This provides support for the use of (*R*)-**4** as

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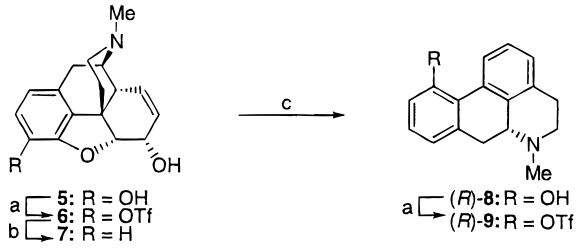
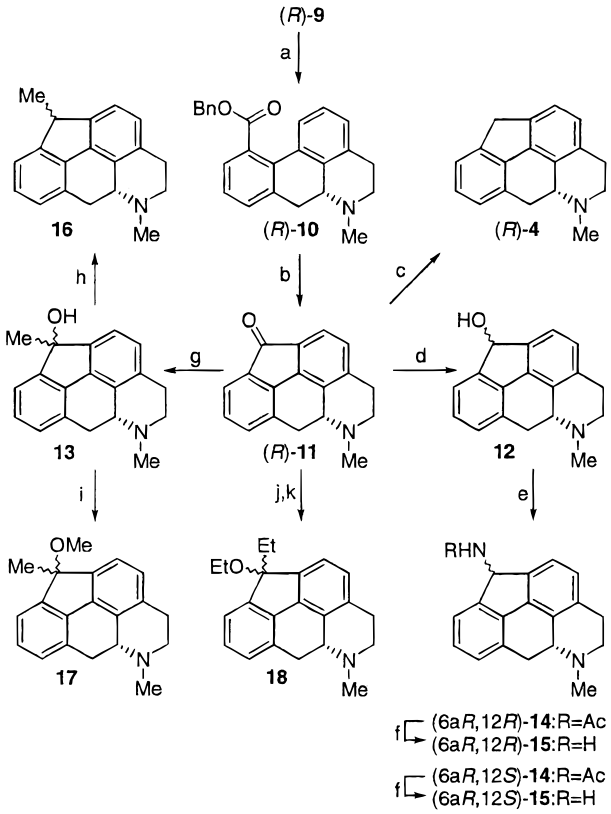
Scheme 1[a]



[a] Reagents: (a) $(CF_3SO_2)_2NPh$, Et_3N, K_2CO_3, CH_2Cl_2; (b) Bu_3N, HCO_2H, $(PPh_3)_2PdCl_2$, dppp, DMF, N_2; (c) $MeSO_3H$, N_2.

Scheme 2[a]



[a] Reagents: (a) BnOH, $Pd(OAc)_2$, dppp, TMEDA, CO, DMF; (b) i. Pd/C (10%), 1,4-dioxane, H_2O, H_2, ii. PPA; (c) Pd/C (10%), HCl (1 M), EtOH, H_2; (d) $NaBH_4$, MeOH/H_2O (1:1); (e) MeCN, H_2SO_4 (concd); (f) HCl (12 M); (g) MeLi, THF; (h) $NaBH_4$, TFA; (i) $(MeO)_3CH$, H_2SO_4 (concd), MeOH; (j) EtMgBr, THF; (k) $(EtO)_3CH$, *p*-TsOH, EtOH.

a scaffold in medicinal chemistry studies of interactions between ligands and GPC receptors.

Synthesis

Synthesis of Key Intermediate (*R*)-11. The synthesis of the (*R*)-1,11-methyleneaporphine derivatives is outlined in Schemes 1 and 2. Our synthetic strategy utilizes the known triflate (*R*)-**9**[9t] to introduce a carboxylic acid function at C11 of (*R*)-aporphine. A subsequent intramolecular electrophilic addition of the carboxylic acid function to the C1 position gave the key intermediate (*R*)-**11**.

Triflate (*R*)-**9** was synthesized from natural morphine in four steps (Scheme 1).[9q,t] Conversion of (*R*)-**9** into the benzyl ester (*R*)-**10** was accomplished by a palladium-catalyzed carbonylative coupling reaction.[10] Various amounts of the reduced byproduct (*R*)-**3** were formed in this reaction, and several reaction conditions were tried in order to minimize the formation of the byproduct. By using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as base in DMF at 70 °C, the amount of the reduced product was suppressed to <1% as indicated by ^{1}H NMR. The benzyl ester was easily converted into the corresponding amino acid by hydrogenolysis (Pd/C, H_2, 1 atm, room temperature). The crude amino acid was treated with polyphosphoric acid (PPA)[11] to give the novel ketone (*R*)-**11** in 72% yield from (*R*)-**9**.

Table 1. Reaction of Ketone (*R*)-**11** with Nucleophiles

entry	reagents	*T* (°C)	products	yield (%)[a]	epimeric ratio[a,b]
1	$NaBH_4$	rt	(6a*R*,12*R*)-**12**/(6a*R*,12*S*)-**12**	90	45:55
2	$LiAlH_4$	−70	(6a*R*,12*R*)-**12**/(6a*R*,12*S*)-**12**	88	35:65
4	MeLi	−70	(6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13**	95	35:65

[a] The mean of 2−4 experiments. [b] The epimeric ratio was determined by HPLC of the crude reaction mixture.

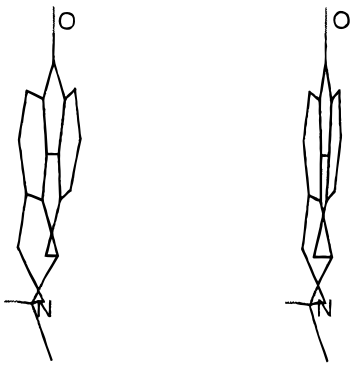


Figure 1. Stereoscopic representation of the lowest energy MM3 conformation of (*R*)-**11** showing the slightly vaulted structure of the 1,11-methyleneaporphine structure. For clarity the psuedoaxial nitrogen lone pair has been added and the hydrogens have been omitted.

Addition of Nucleophiles to (*R*)-11 (Table 1). Ketone (*R*)-**11** was used as starting material for the synthesis of several novel derivatives as outlined in Scheme 2. The methylene derivative (*R*)-**4** was obtained by using classical conditions for hydrogenolysis of benzylic ketones (Pd/C, HCl, H_2).[12]

Reduction of (*R*)-**11** with $NaBH_4$ consistently gave a 45:55 mixture of the epimeric alcohols (6a*R*,12*R*)-**12** and (6a*R*,12*S*)-**12** (Table 1). Several other reducing agents ($LiAlH_4$, K-selectride, Bu_4NBH_4, *i*-Bu_3BHK, *i*-Bu_2AlH) were tried in attempts to increase the stereoselectivity of the reduction. A slight increase in the stereoselectivity and a high yield were obtained by use of $LiAlH_4$ in THF at −70 °C. Attempts to form the alcohols by catalytic hydrogenation of (*R*)-**11** failed; either no reduction [Ru(C)] or complete reduction [PtO_2 and Pd(C)] to (*R*)-**4** was observed. Addition of MeLi in cumene/THF (9:1) to (*R*)-**11** afforded isomers (6a*R*,12*R*)-**13** and (6a*R*,12*S*)-**13** in a ratio of 35:65.[13]

Nucleophilic addition of a hydride or a methyl anion to (*R*)-**11** consistently gave a higher ratio of the (6a*R*,-12*S*)-isomer. The diastereoselective formation of (6a*R*,-12*S*)-**12** and (6a*R*,12*S*)-**13** might be due to a preferred nucleophilic attack at the least hindered *re*-face of the prochiral carbonyl carbon of (*R*)-**11**; the structure of (*R*)-**11** is slightly vaulted in the direction of the pseudoaxial lone pair of the nitrogen (Figure 1). Hence, the conformation of (*R*)-**11** may make the opposite face of the

Table 2. Acid-Catalyzed Addition of Nucleophiles to Alcohols **12** and **13**

entry	alcohol	reagent	products	yield (%)[a]	epimeric ratio[a,b]
1	(6a*R*,12*R*)-**12**/(6a*R*,12*S*)-**12** (45:55)	$MeCN/H_2SO_4$	(6a*R*,12*R*)-**14**/(6a*R*,12*S*)-**14**	73	65:35
2	(6a*R*,12*R*)-**12**	$MeCN/H_2SO_4$	(6a*R*,12*R*)-**14**/(6a*R*,12*S*)-**14**	nd[c]	65:35
3	(6a*R*,12*S*)-**12**	$MeCN/H_2SO_4$	(6a*R*,12*R*)-**14**/(6a*R*,12*S*)-**14**	nd	65:35
4	(6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13** (40:60)	$NaBH_4$/TFA	(6a*R*,12*R*)-**16**/(6a*R*,12*S*)-**16**	46	35:65
5	(6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13** (40:60)	Et_3SiH/TFA	(6a*R*,12*R*)-**16**/(6a*R*,12*S*)-**16**	23	30:70
6	(6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13** (35:65)	H_2/Pd(C)/HCl/EtOH	(6a*R*,12*R*)-**16**/(6a*R*,12*S*)-**16**	90	2:98
7	(6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13** (40:60)	$(MeO)_3CH/MeOH/H_2SO_4$	(6a*R*,12*R*)-**17**/(6a*R*,12*S*)-**17**	70	55:45
8	(6a*R*,12*R*)-**13**	$(MeO)_3CH/MeOH/H_2SO_4$	(6a*R*,12*R*)-**17**/(6a*R*,12*S*)-**17**	nd	50:50
9	(6a*R*,12*S*)-**13**[d]	$(MeO)_3CH/MeOH/H_2SO_4$	(6a*R*,12*R*)-**17**/(6a*R*,12*S*)-**17**	nd	65:35

[a] The mean of 2−4 experiments. [b] The epimeric ratio was determined by HPLC of the crude reaction mixture. [c] nd = not determined. [d] Contains <5% of (6a*R*,12*R*)-**13**.

molecule more accessible for nucleophilic attack. The small but consistent difference in stereoselectivity obtained with the two nucleophiles, a hydrid and a methyl anion, is probably related to the size of the nucleophile.

Acid-Catalyzed Nucleophilic Addition to Alcohols 12 and 13 (Table 2). The epimeric acetamides **14** were synthesized from a mixture of (6a*R*,12*R*)-**12**/(6a*R*,-12*S*)-**12** (45:55) by a Ritter reaction[14] to give a 65:35 ratio of (6a*R*,12*R*)-**14** and (6a*R*,12*S*)-**14**. This reaction is believed to proceed via a carbocation intermediate,[14] and experiments with the pure isomers (6a*R*,12*R*)-**12** and (6a*R*,12*S*)-**12** as substrates produced a 65:35 mixture of (6a*R*,12*R*)-**12** and (6a*R*,12*S*)-**12**, respectively, supporting the involvment of a common carbocation intermediate. Such an intermediate is probably also involved in the reduction of the mixture of the tertiary alcohols (6a*R*,12*R*)-**13** and (6a*R*,12*S*)-**13** (40:60) by $NaBH_4$/TFA which gave a 35:65 mixture of (6a*R*,12*R*)-**16** and (6a*R*,12*S*)-**16**, i.e., the same ratio (35:65) as the Ritter reaction.[15] Indeed, this reaction is also presumed to proceed via a carbocation intermediate.[16] A similar diastereoselectivity was obtained when (6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13**[15] (40:60) was reduced with triethylsilane in TFA. The epimeric ratio obtained in these reactions seems to be a result of steric factors directing the nucleophilic attack (vide supra), the presumed intermediate cation being more accessible from the *re*-face of C12.

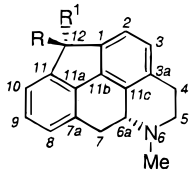
Hydrogenolysis (Pd/C, H_2, HCl, EtOH, 1 atm, room temperature) of (6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13** (35:65) proceeded stereoselectively to give a mixture of (6a*R*,12*R*)-**16**/(6a*R*,12*S*)-**16** in a 2:98 ratio. Addition of sulfuric acid and trimethyl orthoformate to (6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13** (40:60) in methanol gave (6a*R*,12*R*)-**17**/(6a*R*,12*S*)-**17** in a ratio of 55:45. When the pure isomers (6a*R*,12*R*)-**13** and (6a*R*,12*S*)-**13**[17] were reacted under the same conditions, 50:50 and 65:35 mixtures of (6a*R*,12*R*)-**17**/(6a*R*,12*S*)-**17** were formed, respectively. The outcome of these reactions indicates that (6a*R*,12*S*)-**13** probably reacts via a carbocation intermediate while the reaction path of (6a*R*,12*R*)-**13** is different.

Treatment of (*R*)-**11** with EtMgBr in ether gave a 50:50 mixture of unstable epimeric ethyl-substituted alcohols, which were converted into a 50:50 mixture of the ethyl-substituted ethoxy derivatives (6a*R*,12*R*)-**18**/(6a*R*,-12*S*)-**18** by an acid-catalyzed reaction with triethyl orthoformate in ethanol. The conversion of the ethyl alcohols into the ethoxy ethyl derivatives gave a product mixture in agreement with the corresponding methoxy methyl derivatives (**17**) indicating a similar reaction mechanism. Acetamides (6a*R*,12*R*)-**14** and (6a*R*,12*S*)-**14** were converted into the corresponding amines (6a*R*,-12*R*)-**15** and (6a*R*,12*S*)-**15** by acid hydrolysis.

The separation of the epimeric mixtures was in most cases performed by flash column chromatography. The isomers of **17** were, however, separated by straight-phase preparative HPLC using a silica gel column (see Experimental Section). The separation of the epimers of **16** and **18** was difficult and could not be accomplished by the above-mentioned procedures. Instead semipreparative HPLC was performed. Both pairs of epimers were readily chromatographed on a Hypercarb column in the straight-phase mode. Excellent separation was achieved with α-values of 2.89 and 3.88 for (6a*R*,12*R*)-**18**/(6a*R*,-12*S*)-**18** and (6a*R*,12*R*)-**16**/(6a*R*,12*S*)-**16**, respectively.

Structural Studies

The stereochemistry of derivatives **12**−**18** was established by a combination of X-ray crystallography, ^{13}C NMR spectroscopy, and chemical correlation. The relative stereochemistry of (6a*R*,12*R*)-**12**·HCl, (6a*R*,12*S*)-**12**·HCl, (6a*R*,12*S*)-**15**·2HCl·H_2O, (6a*R*,12*S*)-**16**·HCl·MeCN, and (6a*R*,12*R*)-**17**·HCl was determined by X-ray crystallography. ^{13}C NMR chemical shift correlation was used in order to assign the structure of the epimers of **13** and **18**. The stereochemistry of the epimers of **14** was indirectly assigned from the epimers of **15**. The CD spectra of compound **4** and epimers **12**−**17** were also studied in an attempt to determine the stereochemistry



Code	R	R^1
(*R*)-**11**	=O	
(6a*R*,12*R*)-**12**	OH	H
(6a*R*,12*S*)-**12**	H	OH
(6a*R*,12*R*)-**13**	OH	Me
(6a*R*,12*S*)-**13**	Me	OH
(6a*R*,12*R*)-**14**	NHAc	H
(6a*R*,12*S*)-**14**	H	NHAc
(6a*R*,12*R*)-**15**	NH_2	H
(6a*R*,12*S*)-**15**	H	NH_2
(6a*R*,12*R*)-**16**	Me	H
(6a*R*,12*S*)-**16**	H	Me
(6a*R*,12*R*)-**17**	OMe	Me
(6a*R*,12*S*)-**17**	Me	OMe
(6a*R*,12*R*)-**18**	OEt	Et
(6a*R*,12*S*)-**18**	Et	OEt

Table 3. Crystal Data and Details of the Final Structure Refinement Calculation for (6a*R*,12*R*)-**12**·HCl, (6a*R*,12*S*)-**12**·HCl, (6a*R*,12*S*)-**15**·2HCl·H_2O, (6a*R*,12*S*)-**16**·HCl·MeCN, and (6a*R*,12*R*)-**17**·HCl

	(6a*R*,12*R*)-**12**·HCl	(6a*R*,12*S*)-**12**·HCl	(6a*R*,12*S*)-**15**·2HCl·H_2O	(6a*R*,12*S*)-**16**·HCl·MeCN	(6a*R*,12*R*)-**17**·HCl
formula	$C_{18}H_{18}ClNO$	$C_{18}H_{18}ClNO$	$C_{18}H_{22}Cl_2N_2O$	$C_{21}H_{23}ClN_2$	$C_{20}H_{22}ClNO$
formula weight	299.78	299.78	353.28	338.86	327.84
crystal system	orthorhombic	orthorhombic	orthorhombic	orthorhombic	monoclinic
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
a, Å	9.965(3)	8.310(4)	7.071(1)	6.993(1)	10.329(9)
b, Å	12.101(5)	11.833(3)	10.893(1)	14.988(3)	7.109(3)
c, Å	12.209(4)	14.881(3)	23.004(2)	17.269(4)	11.813(7)
β (deg)	90	90	90	90	101.58(9)
V_c, Å^3	1472.3(8)	1463.2(9)	1771.9(3)	1810.0(6)	849.7(10)
Z	4	4	4	4	2
D_c, g·cm^{-1}	1.352(1)	1.361(1)	1.324(1)	1.244(1)	1.281(2)
T, K	150(2)	150(2)	100(2)	150(2)	100(2)
N (measured)	2483	2478	14016	3861	6520
N (unique)	2458	2453	3436	3645	3112
N [$F_o > 4\sigma(F_o)$]	1679	1788	3006	2158	2089
no. of parameters	262	262	275	288	276
R [$F_o > 4\sigma(F_o)$]	0.033	0.031	0.040	0.066	0.041
wR (F^2) for all unique data	0.081	0.079	0.105	0.186	0.091
goodness-of-fit for all unique data	1.04	1.06	1.05	1.05	0.87

at C12. However, no consistent effect of diagnostic value was obtained.

The solid-state conformation and the relative stereochemistry at C12 in the five-membered ring of five epimers were determined using single-crystal X-ray diffraction techniques. Thermal ellipsoid plots of the solid-state conformations are shown in Figure 2, and selected experimental data are collected in Table 3. The solid-state conformations of the studied pentacyclic structures are, as expected, very similar (Figure 2). Derivatives (6a*R*,12*R*)-**12** and (6a*R*,12*S*)-**16** gave the best fit with a root-mean-square (rms) deviation of 0.037 Å between the carbon atoms and the nitrogen atom in the pentacyclic skeleton, while the largest rms deviation, 0.120 Å, was observed between molecules (6a*R*,-12*S*)-**15** and (6a*R*,12*R*)-**17**. The formation of the five-membered ring makes the molecules more rigid and planar as compared to (*R*)-**3**. The two aromatic rings are almost coplanar with a torsion angel τ(C11−C11a−C11b−C1) of about −2° to −3° in the crystal structures (Table 4).

For comparison, a database search for aporphine derivatives, substituted with hydrogen at either C1 or C11, in the Cambridge Structural Database[18] (CSD) was performed. A total number of 13 structures (17 conformations) was found. These structures have noncoplanar aromatic rings and an average τ(C11−C11a−C11b−C1) value of 24(4)°,[19] which is in agreement with results obtained from (*R*)-**3.** A fit between the average structure of the solid-state conformations of (6a*R*,12*R*)-**12**·HCl, (6a*R*,12*S*)-**12**·HCl, (6a*R*,12*S*)-**15**·2HCl·H_2O, (6a*R*,12*S*)-**16**·HCl·MeCN, and (6a*R*,12*R*)-**17**·HCl and an average structure of (*R*)-**3** calculated from the structures obtained in the CSD search clearly shows the difference in the 3D-structure between these two classes of aporphine derivatives (Figure 3).

The conformational distributions of the nonprotonated (6a*R*)-isomers of **11**−**18** and **4** were studied by molecular mechanics MM3 calculations.[20] The results indicate that the 1,11-methyleneaporphine structure mainly adopts four conformations: the most stable conformation has a pseudoequatorial *N*-methyl group and adopts a half-chair conformation of the tetrahydropyridine ring with

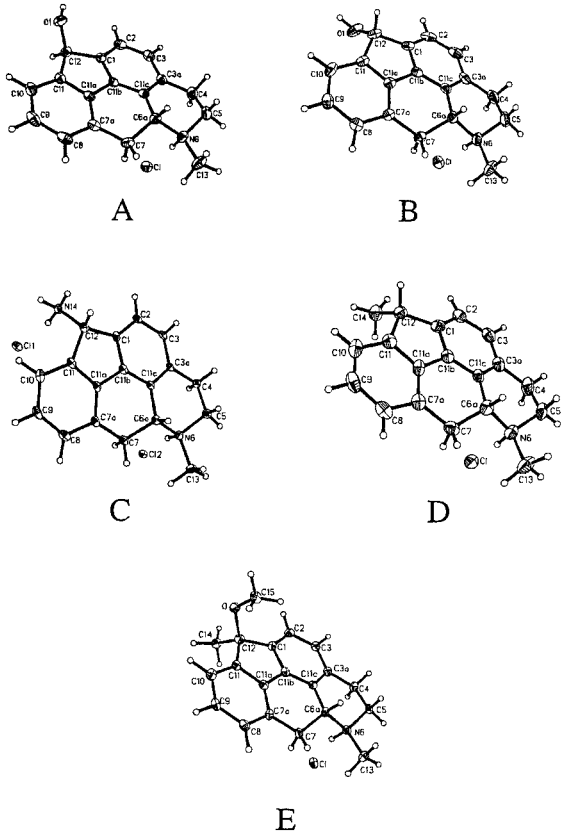


Figure 2. Perspective view (ORTEP) of the solid-state structure of (6a*R*,12*R*)-**12**·HCl (A), (6a*R*,12*S*)-**12**·HCl (B), (6a*R*,12*S*)-**15**·2HCl (C), (6a*R*,12*S*)-**16**·HCl (D), and (6a*R*,12*R*)-**17**·HCl (E). The cocystallized CH_3CN in (6a*R*,12*S*)-**16**·HCl·CH_3CN and H_2O in (6a*R*,12*S*)-**15**·2HCl·H_2O are left out for clarity. Displacement ellipsoids are represented at the 50% probability level.

P-helicity. It constitutes about 90%[21] of the conformations. The conformational distribution of the epimers of **12**−**18** was found to be the same.

Minimization (MM3) of the solid-state conformation of (6a*R*,12*R*)-**12**·HCl, (6a*R*,12*S*)-**12**·HCl, (6a*R*,12*S*)-**15**·2HCl·H_2O, (6a*R*,12*S*)-**16**·HCl·MeCN, and (6a*R*,12*R*)-**17**·HCl in their nonprotonated form resulted in the most

Table 4. Observed and Calculated Values of τ(C11−C11a−C11b−C1) in (6a*R*,12*R*)-**12**·HCl, (6a*R*,12*S*)-**12**·HCl, (6a*R*,12*S*)-**15**·2HCl·H_2O, (6a*R*,12*S*)-**16**·HCl·MeCN, (6a*R*,12*R*)-**17**·HCl, and the (*R*)-Aporphine Skeleton

method	(*R*)-aporphine skeleton	(6a*R*,12*R*)-**12**·HCl	(6a*R*,12*S*)-**13**·HCl	(6a*R*,12*S*)-**15**·2HCl·H_2O	(6a*R*,12*S*)-**16**·HCl·MeCN	(6a*R*,12*R*)-**17**·HCl
crystal structure	−24(4)[a]	−2.5(3)	−2.8(3)	−1.8(5)	−1.8(3)	−2.9(3)
ab initio[b]	−24.4	−3.2	−3.1	−2.9	−3.1	−2.9
MM3[c]	−23.5	−4.1	−4.2	−4.2	−4.2	−4.2

[a] Average value, calculated for crystal structures of aporphine derivatives substituted with hydrogen at either the C1 or C11 position and included in the CSD (see Supporting Information). [b] Ab initio geometry optimization at the RHF/6-31* level of the derivatives in their nonprotonated state. [c] Molecular mechanics MM3 minimization of the derivatives in their nonprotonated state.

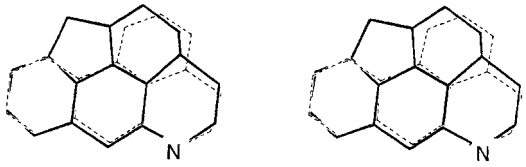
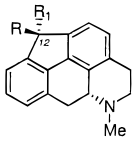


Figure 3. Stereoscopic representation of a rms fit between the average solid-state structure of (6a*R*,12*R*)-**12**·HCl, (6a*R*,12*S*)-**12**·HCl, (6a*R*,12*S*)-**15**·2HCl·H_2O, (6a*R*,12*S*)-**16**·HCl·CH_3CN, and (6a*R*,12*R*)-**17**·HCl (solid lines) and the average aporphine structure calculated from the solid-state structures found in the CSD search (dashed lines). The carbon atoms C7a, C8, C9, C10, C11, and C11a and the nitrogen atom are fitted with unit weight for all atoms.

Table 5. Selected ^{13}C NMR Spectral Data[a] of Diagnostic Value for Assignment of the Stereochemistry at C12 of the 1,11-Methyleneaporphine Derivatives



			δ (ppm)	
compd	R	R^1	C1	C11
(6a*R*,12*R*)-**12**	OH	H	139.5	143.3
(6a*R*,12*S*)-**12**	H	OH	140.6	144.2
(6a*R*,12*R*)-**13**	OH	Me	143.8[b]	147.4[b]
(6a*R*,12*S*)-**13**	Me	OH	144.6[b]	148.6[b]
(6a*R*,12*R*)-**14**	NHAc	H	138.1	141.9
(6a*R*,12*S*)-**14**	H	NHAc	139.3	142.4
(6a*R*,12*R*)-**15**	NH_2	H	141.0	144.6
(6a*R*,12*S*)-**15**	H	NH_2	142.1	145.3
(6a*R*,12*R*)-**16**	Me	H	143.3	146.6
(6a*R*,12*S*)-**16**	H	Me	143.6	146.9
(6a*R*,12*R*)-**17**	OMe	Me	140.0	143.9
(6a*R*,12*S*)-**17**	Me	OMe	141.2	144.2
(6a*R*,12*R*)-**18**	OEt	Et	139.7[b]	143.6[b]
(6a*R*,12*S*)-**18**	Et	OEt	141.2[b]	144.2[b]
(*R*)-**4**	H	H	139.1	141.0

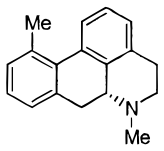
[a] Unambiguously assigned by ^{1}H−^{1}H, ^{1}H−^{13}C, and COLOC correlation experiments. [b] Assigned by ^{13}C NMR chemical shift correlation.

stable conformation as identified by the molecular mechanics MM3 calculations. Ab initio geometry optimization at the RHF/6-31* level confirmed the MM3 minimizations. Consequently, both experimental and computational methods give the same preferred conformation of these rigid structures (Table 4).

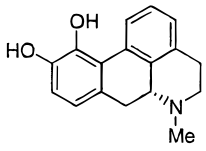
The ^{13}C NMR chemical shifts of the pentacyclic derivatives **12** and **14**−**17** have unambiguously been assigned by a combination of ^{1}H−^{1}H, ^{1}H−^{13}C, and long-range ^{1}H−^{13}C (COLOC[22]) correlation experiments. Throughout, a downfield shift of C1 and C11 was obtained for the (12*S*)-isomer (Table 5). Therefore, the observed chemical shift difference between the epimers of **13** and **18** was used to assign their respective stereochemistry.

Interactions with GPC Receptors

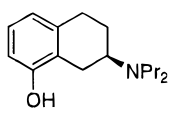
The compounds were examined in vitro for their ability to displace [^{3}H]5-HT, [^{3}H]8-OH-DPAT, and [^{3}H]-raclopride binding to cloned rat 5-HT_7 receptors and to cloned human 5-HT_{1A} and D_{2A} receptors, respectively, as described in the Experimental Section. The results are presented in Table 6, and the affinities of (*R*)-**3**, (*R*)-**19**, (*R*)-apomorphine, (*R*)-8-OH-DPAT, (*S*)-UH301, and 5-CT to some of these receptors are also included.



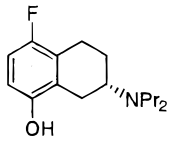
(*R*)-**19**



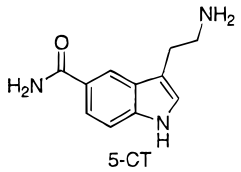
(*R*)-apomorphine



(*R*)-8-OH-DPAT



(*S*)-UH301

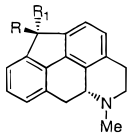


5-CT

The methylene derivative (*R*)-**4** and the unsubstituted aporphine (*R*)-**3** exhibit similar affinities to 5-HT_{1A} and D_{2A} receptors, (*R*)-**4** being slightly more potent (Table 6). At 5-HT_7 receptors, however, the affinity of (*R*)-**4** is about 12 times higher than that of (*R*)-**3.** Hence, the added bulk of the methylene group in (*R*)-**4** and the geometrical difference between the two ring systems, which is a consequence of the ring strain imposed by the fusion of a five-membered ring onto (*R*)-**4**, do not appear to lead to a major difference in the interaction with the 5-HT_{1A} and D_{2A} receptors. However, it seems to be beneficial for the interaction with 5-HT_7 receptors.

The introduction of substituents at C12 in (*R*)-**4**, i.e., above and/or below the plane of the ring system, produces ligands with great variations in pharmacological profiles: a C12-acetamido group [(6a*R*,12*S*)-**14**] reduces affinity to 5-HT_7 receptors 190-fold whereas the simultaneous introduction of methyl and methoxy groups [(6a*R*,12*R*)-**17** and (6a*R*,12*S*)-**17**] leads to a 6-fold increase in 5-HT_7 receptor affinity. Similarly, the affinities for 5-HT_{1A} and D_{2A} receptors are affected by the

Table 6. Affinities of 1,11-Methyleneaporphine Derivatives for Cloned Rat 5-HT_7 and Cloned Human 5-HT_{1A} and D_{2A} Receptors Labeled by [^{3}H]5-HT, [^{3}H]8-OH-DPAT, and [^{3}H]Raclopride, Respectively



			K_i (nM)[a]		
compd	R	R^1	[^{3}H]5-HT (5-HT_7)	[^{3}H]8-OH-DPAT (5-HT_{1A})	[^{3}H]raclopride (D_{2A})
(*R*)-**4**	H	H	6.9 ± 0.3	40.7 ± 12	83.2 ± 9.9
(*R*)-**11**	=O		291 ± 110	140 ± 33[b]	317 ± 170
(6a*R*,12*R*)-**12**	OH	H	13.5 ± 3.2	31.0 ± 3.5[b]	23.8 ± 1.7
(6a*R*,12*S*)-**12**	H	OH	103 ± 16	1210 ± 91[b]	215 ± 12
(6a*R*,12*R*)-**13**	OH	Me	27.7 ± 2.9	315 ± 110[b]	182 ± 6.0
(6a*R*,12*S*)-**13**	Me	OH	4.3 ± 0.9	61.5 ± 9.9[b]	26.0 ± 2.0
(6a*R*,12*R*)-**14**	NHAc	H	538 ± 8.5	204 ± 12	3650 ± 660
(6a*R*,12*S*)-**14**	H	NHAc	1320 ± 31	716 ± 12	7980 ± 1200
(6a*R*,12*R*)-**15**	NH_2	H	13.4 ± 2.9	142 ± 72	261 ± 53
(6a*R*,12*S*)-**15**	H	NH_2	18.0 ± 1.2	355 ± 32	2250 ± 550
(6a*R*,12*R*)-**16**	Me	H	3.36 ± 1.1	5.05 ± 1.2	19.4 (n = 1)
(6a*R*,12*S*)-**16**	H	Me	5.6 ± 1.0	31.0 ± 8.0	39.2 ± 1.6
(6a*R*,12*R*)-**17**	OMe	Me	1.1 ± 0.03	17.3 ± 2.3	7.1 ± 0.3
(6a*R*,12*S*)-**17**	Me	OMe	1.1 ± 0.04	16.9 ± 6.9	71.0 ± 7.5
(6a*R*,12*R*)-**18**	OEt	Et	25.7 ± 0.66	1.84 ± 0.2	70.8 (n = 1)
(6a*R*,12*S*)-**18**	Et	OEt	3.05 ± 0.7	19.1 ± 0.1	24.5 ± 0.8
(*R*)-**3**			88.0 ± 3.7	80.0 ± 2.3[b,c]	527 ± 296[c]
(*R*)-**19**			38.3 ± 0.03	14.4 ± 1.5[b,c]	201 ± 91[c]
(*R*)-apomorphine			188 ± 17	296 ± 15[b,d]	41.6 ± 4.7[d]
(*R*)-8-OH-DPAT			8.81 ± 0.02	1.30	819
(*S*)-UH301			3180 ± 50	87	3760
5-CT			0.029 ± 0.01	<0.3	

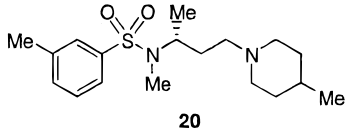
[a] The K_i values are means ± standard errors of 2−3 experiments. [b] Data obtained from competition experiments with rat brain 5-HT_{1A} receptor recognition site. [c] From ref 9t. [d] From ref 9q.

introduction of C12 substituents in (*R*)-**4**: the affinity to D_{2A} receptors can be decreased 95-fold [(6a*R*,12*S*)-**14**] or increased almost 12-fold [(6a*R*,12*R*)-**17**] and the affinity to 5-HT_{1A} receptors can be reduced 30-fold [(6a*R*,12*S*)-**12**] or increased 22-fold [(6a*R*,12*R*)-**18**] by the introduction of the proper substituents.

As mentioned above, the unsubstituted (*R*)-**4** has a higher affinity for 5-HT_7 receptors than for 5-HT_{1A} and D_{2A} receptors. This receptor selectivity may be increased by introducing an amino group at C12 [(6a*R*,12*S*)-**15**] or partially reversed by substituting C12 with ethyl and ethoxy groups [(6a*R*,12*R*)-**18**], the latter compound exhibiting selectivity for 5-HT_{1A} receptors. Whereas (6a*R*,12*S*)-**15** and (6a*R*,12*R*)-**18** displayed selectivity for 5-HT_7 and 5-HT_{1A} receptors, respectively, no derivative within the present series of compounds displayed D_{2A} receptor selectivity. However, several of the derivatives exhibit selectivity for two of the three receptor subtypes studied: for example, (6a*R*,12*S*)-**12** and (6a*R*,12*R*)-**17** have higher affinity for the 5-HT_7 and D_{2A} receptors than for the 5-HT_{1A} receptor. Only one epimer, (6a*R*,-12*R*)-**12**, has a similar affinity for the three receptors studied.

Throughout, the epimers generated by the introduction of substituents at C12 in the 1,11-methyleneaporphine ring system interacted with at least one of the three receptors in a stereoselective fashion. The highest stereoselectivity and the largest variation in stereoselectivity were observed in the interaction with the 5-HT_{1A} receptor: the affinity of the epimers of **12** differed 39-fold whereas the epimers of **17** had equal affinity at this receptor. The most pronounced stereoselectivity at the D_{2A} receptor was displayed by the epimers of **12**, **15**, and **17**. In general, the stereoselectivity of interaction of the epimers with the 5-HT_7 receptor was smaller than that observed with the other two receptors.

The observed preferences in affinity of the novel derivatives at 5-HT_7, 5-HT_{1A}, and D_{2A} receptors are interesting. The selectivity of compounds (6a*R*,12*S*)-**15** and (6a*R*,12*S*)-**17** for 5-HT_7 receptors is especially intriguing since only two ligands with selectivity for 5-HT_7 receptors, **20** and **21**, have been published so far.[23] These two ligands are antagonists and preliminary data obtained in second-messenger studies indicate that also (6a*R*,12*S*)-**15** and (6a*R*,12*S*)-**17** are 5-HT_7 receptor antagonists. In a preliminary profiling effort of (6a*R*,-12*S*)-**15** the following affinities were obtained: serotonin 5-HT_{2A} 469 ± 102 nM ([^{3}H]ketanserine, n = 3); adrenergic α_1 373 ± 25 nM ([^{3}H]prazocin, n = 2); adrenergic α_2 92.8 ± 3 nM ([^{3}H]RX821002, n = 2); adrenergic β >1000 nM ([^{3}H]DHA, n = 1); muscarinic M >1000 nM ([^{3}H]QNB, n = 2); and dopamine D_1 >1000 nM ([^{3}H]-SCH23390, n = 2). Hence, (6a*R*,12*S*)-**15** in particular and also (6a*R*,12*S*)-**17** may be considered as valuable



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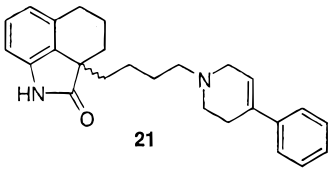

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structural leads in future efforts to obtain selective 5-HT_7 receptor drugs.

It is evident that the pharmacology displayed by the 1,11-methyleneaporphine derivatives exhibits a large variation and, hence, a large information content. The pharmacology of the present series has not been sufficiently studied, and the series is not large enough to allow us to derive final conclusions regarding SAR. Nevertheless, it is apparent that the novel ring system presented herein provides a useful complement to the arsenal of scaffolds used in medicinal chemistry studies of GPC receptors. Its well-defined structure and relative ease of synthesis add to its potential value in this context.

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 polarimeter. Elemental analyses (C, H, N) were performed at Mikrokemi AB, Uppsala, Sweden, and were within ±0.4% of the theoretical values. Accurate mass determination was perfomed on a quadrupole time-of-flight hybrid instrument equipped with electrospray ionization. The ^{1}H and ^{13}C NMR spectra of the amines were recorded at 399.8 and 100.5 MHz, respectively, and were referenced to internal tetramethylsilane. Spectra were recorded using a mixture of $CDCl_3$ and CD_3OD (90:10 v/v) at 25 °C. Infrared (IR) spectra were recorded on a FTIR spectrophotometer. Thin-layer chromatography (TLC) was performed by using aluminum sheets precoated (0.2 mm) with either silica gel 60 F_{254} (Riedel-de Haën) or aluminum oxide 60 F_{254} neutral (E. Merck). Column chromatography was performed on silica gel 60 (0.040−0.063 mm; Riedel-de Haën or E. Merck) or aluminum oxide 90 (0.063−0.2 mm, deactivated with 5% water; E. Merck). In preparative HPLC a Dynamax 60-A column (21.4 × 250 mm, 8-μm silica gel, flow 13 mL/min) was used, and in semipreparative HPLC a Hypercarb S column (100 × 10 mm, 7-μm particles, flow 1.5 mL/min) guarded with a Hypercarb S stationary-phase precolumn was used. Diastereoselectivities were determined by analytical HPLC using LiChrospher C_{18} (4 × 250 mm, 5-μm particles, flow 0.7 mL/min) or Nucleosil C_{18} (4.6 × 100 mm, 5-μm particles, flow 0.7 mL/min) columns. The eluent was either 0.1 M phosphate buffer (pH 3.2)/MeOH/acetonitrile/*N*,*N*-dimethyloctylamine (DMOA) (500:350:150:1) or 0.05 M phosphate buffer (pH 6.0)/acetonitrile/DMOA (400:600:1 or 600:400:1).

(−)-(*R*)-11-Benzyloxycarbonylaporphine [(*R*)-10]. A mixture of $Pd(OAc)_2$ (171 mg, 0.76 mmol) and 1,3-bis(diphenylphosphine)propane (348 mg, 0.84 mmol) in DMF (25 mL) was stirred under N_2 for 30 min. Half of the catalyst−ligand mixture was added to a solution of (*R*)-**9**^{9t} (2.92 g, 7.6 mmol), TMEDA (3.4 mL, 20 mmol) and benzyl alcohol (10 mL) in DMF (25 mL). The reaction mixture was heated at 70 °C and CO was bubbled through the mixture. After 2 h the other half of the catalyst−ligand mixture was added to the reaction mixture. After another 2 h at 70 °C the volatiles were evaporated and the oily residue was chromatographed [Al_2O_3; EtOAc followed by Al_2O_3; EtOAc/hexanes (1:4)]. The amine was converted into the hydrochloride salt to give 2.45 g (79%) of pure (*R*)-**10**·HCl: IR (KBr) 1718 cm^{-1} (C═O); mp 132−134 °C; $[\alpha]_D^{22}$ −164° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{21}H_{23}NO_2$·HCl) H, C, N.

(*R*)-10: ^{1}H NMR δ 2.49−2.70 (m, 2H), 2.58 (s, 3H), 2.80 (dd, *J* = 16, 3.5 Hz, 1H), 3.03−3.33 (m, 4H), 5.18, (d, *J* = 12 Hz, 1H), 5.34 (d, *J* = 12 Hz, 1H), 6.96−7.11 (m, 3H), 7.20−7.35 (m, 6H), 7.39 (ddd, *J* = 7.5, 1.0, 1.0 Hz, 1H), 7.55 (ddd, *J* = 7.5, 1.0, 1.0 Hz, 1H); ^{13}C NMR δ 28.6, 34.5, 43.9, 52.9, 61.6, 67.3, 125.8, 126.4, 127.1 128.3, 128.4, 128.5, 128.6,128.7, 130.1, 130.7, 131.8, 132.8, 134.0, 134.3, 135.3, 137.0, 170.7.

(−)-(*R*)-1,11-Carbonylaporphine [(*R*)-11]. A mixture of (*R*)-**10** (4.34 g, 10.7 mmol), Pd/C (10%, 1.23 g, 1.2 mmol Pd), 1,4-dioxane (40 mL) and water (8 mL) was vigorously stirred under an atmosphere of H_2 at room temperature for 5 h. The catalyst was filtered off and the volatiles were evaporated. Polyphosphoric acid (25 g) was added to the residue and the slurry was mechanically stirred at 90 °C for 30 min. H_2O (300 mL) was added and the pH of the mixture was brought to pH 8−9 by addition of NaOH(s). The aqueous phase was extracted with CH_2Cl_2. The combined organic layers was dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed [silica; $CHCl_3$/MeOH (95:5)]. The amine was converted into the hydrochloride salt, which was recrystallized (MeOH/Et_2O) to give 2.64 g (83%) of pure (*R*)-**11**·HCl: IR (KBr) 1712 cm^{-1} (C═O); mp 231−234 °C; $[\alpha]_D^{23}$ −98° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{18}H_{15}NO$·HCl) C, H, N.

(*R*)-11: ^{1}H NMR δ 2.52 (s, 3H), 2.65 (ddd, *J* = 12, 12, 4 Hz, 1H), 2.73−2.92 (m, 2H), 3.08 (ddd, *J* = 17.5, 12, 6 Hz, 1H), 3.18 (dd, *J* = 12, 6 Hz, 1H), 3.30 (dd, *J* = 16, 7 Hz, 1H), 3.57 (dd, *J* = 13, 7 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 7.15 (dd, *J* = 7.5, 7 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 7 Hz, 1H); ^{13}C NMR δ 28.0, 31.0, 43.3, 55.1, 60.9, 123.0, 123.5, 126.7, 128.5, 129.2, 129.3, 130.1, 132.2, 133.3, 140.8, 141.2, 194.4. One ^{13}C-signal is missing due to overlapping resonances.

(−)-(*R*)-1,11-Methyleneaporphine [(*R*)-4]. A mixture of (*R*)-**11** (116 mg, 0.44 mmol), Pd/C (10%, 56 mg, 0.053 mmol Pd), aqueous 1 M HCl (10 mL) and EtOH (20 mL) was vigorously stirred under an atmosphere of H_2 at room temperature for 8 h. The catalyst was filtered off and the volatiles were evaporated. Aqueous saturated $NaHCO_3$ was added to the residue and the mixture was extracted with CH_2Cl_2. The combined organic layers was dried (K_2CO_3), filtered and concentrated. The amine was converted into the hydrochloride salt, which was recrystallized (acetonitrile/Et_2O) to give 93 mg (84%) of (*R*)-**4**·HCl: mp 246−249 °C dec; $[\alpha]_D^{22}$ −25° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{18}H_{17}N$·HCl·1/4H_2O) C, H, N.

(*R*)-4: ^{1}H NMR δ 2.56 (s, 3H), 2.66−2.86 (m, 2H), 2.93 (dd, *J* = 14.5, 14.5 Hz, 1H), 3.12−3.25 (m, 2H), 3.41 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.77 (dd, *J* = 13, 6.5 Hz, 1H), 3.95 (d, *J* = 21 Hz, 1H), 3.83 (d, *J* = 21 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR δ 27.4, 32.1, 37.9, 43.6, 55.8, 62.4, 123.4, 123.6, 125.2 126.4 (2C), 127.5, 129.1, 131.5, 137.6, 137.9, 139.1, 141.0.

(−)-(6a*R*,12*R*)-1,11-(Hydroxymethylene)aporphine [(6a*R*,12*R*)-12] and (−)-(6a*R*,12*S*)-1,11-(Hydroxymethylene)aporphine [(6a*R*,12*S*)-12]. A mixture of (*R*)-**11**·HCl (168 mg, 0.56 mmol), $NaBH_4$ (250 mg, 6.6 mmol) and 50% aqueous MeOH (10 mL) was stirred at room temperature for 5 min. Aqueous HCl (5 M) was added until no more H_2 evolution occurred. The mixture was alkalinized with aqueous saturated $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$ and the combined organic layers was dried (K_2CO_3), filtered and concentrated to give a mixture of (6a*R*,12*R*)-**12** and (6a*R*,12*S*)-**12** (45:55). The epimers (6a*R*,12*R*)-**12** and (6a*R*,12*S*)-**12** were separated by chromatography [Al_2O_3; EtOAc/$CHCl_3$/EtOH (90:10:0 followed by 89:10:1)]. The amines were converted into the hydrochloride salts and recrystallized from MeOH to give 75 mg (44%) of (6a*R*,12*S*)-**12**·HCl and 54 mg (32%) of (6a*R*,12*R*)-**12**·HCl.

(6a*R*,12*R*)-12·HCl: mp 274−277 °C dec; $[\alpha]_D^{23}$ −21° [*c* 0.2, MeOH/H_2O (1:1)]. Anal. ($C_{18}H_{17}NO$·HCl) C, H, N.

(6a*R*,12*R*)-12: ^{1}H NMR δ 2.44 (s, 3H), 2.39−2.78 (m, 3H), 2.96−3.13 (m, 2H), 3.18 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.51 (dd, *J* = 13, 6.5 Hz, 1H), 5.62 (s, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.12 (dd, *J* = 7.5, 7 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR δ 27.2, 31.3, 43.3, 55.6, 62.1, 77.1, 123.4, 123.7, 126.0 127.1, 127.3, 128.3, 128.9, 133.7, 136.1, 137.0, 139.5, 143.3.

(6a*R*,12*S*)-12·HCl: mp 310−311 °C dec; $[\alpha]_D^{23}$ −44° [*c* 0.2, MeOH/H_2O (1:1)]. Anal. ($C_{18}H_{17}NO$·HCl) C, H, N.

(6a*R*,12*S*)-12: ^{1}H NMR δ 0.99 (dd, *J* = 14, 14.5 Hz, 1H), 2.26 (s, 3H), 2.35−2.59 (m, 2H), 2.65 (dd, *J* = 16, 7 Hz, 1H), 2.88−3.07 (m, 2H), 3.27 (dd, *J* = 13.5, 7 Hz, 1H), 5.62 (s, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 7.13 (dd, *J*

= 7.5, 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR *δ* 27.0, 30.3, 43.0, 55.4, 61.0, 77.8, 122.4, 122.7, 125.4 127.1, 127.2, 128.0 129.2, 132.9, 135.0, 137.0 140.6, 144.2.

(−)-(6a*R*,12*R*)-1,11-(1-Hydroxyethylidene)aporphine [(6a*R*,12*R*)-13] and (−)-(6a*R*,12*S*)-1,11-(1-Hydroxyethylidene)aporphine [(6a*R*,12*S*)-13]. A solution of (*R*)-**11** (189 mg, 0.72 mmol) in dry THF (20 mL) under an atmosphere of N_2 was cooled to −70 °C. MeLi (0.80 M,[24] 0.94 mL, 0.75 mmol) in THF/cumene (1:9) was added during 5 min. The reaction temperature was allowed to rise to room temperature and aqueous saturated $NaHCO_3$ was added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers was dried (Na_2SO_4), filtered and concentrated to give a mixture of (6a*R*,12*R*)-**13** and (6a*R*,12*S*)-**13** (35:65). The epimers were separated by column chromatography [silica; isohexanes/$CHCl_3$/MeOH/Et_2NH (200:189:10:1)]. The amines were converted into the oxalate salts to give 77 mg (38%) of (6a*R*,12*S*)-**13**·oxalate and 40 mg (20%) of (6a*R*,12*R*)-**13**·oxalate. The isomer (6a*R*,12*R*)-**13**·oxalate contains <5% of (6a*R*,12*S*)-**13** as determined by ^{1}H NMR.

(6a*R*,12*R*)-13·oxalate: 95% pure; mp 178−182 °C dec; $[\alpha]_D^{23}$ −11° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{19}H_{19}NO{\cdot}C_2H_2O_4{\cdot}1/2H_2O$) C, H, N.

(6a*R*,12*R*)-13: 95% pure; ^{1}H NMR *δ* 1.60 (s, 3H), 2.30 (s, 3H), 2.37−2.67 (m, 3H), 2.83−3.03 (m, 2H), 3.08 (dd, *J* = 16, 7 Hz, 1H), 3.41 (dd, *J* = 13, 6 Hz,1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 7.02 (dd, *J* = 7.5, 7 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7 Hz, 1H); ^{13}C NMR *δ* 25.4, 27,1, 31.3, 43.2, 55.5, 61.9, 83.1, 121.4, 121.7, 126.0, 127.2, 127.3, 128.5, 128.9, 133.5, 134.8, 135.8, 143.8, 147.4.

(6a*R*,12*S*)-13·oxalate: mp 232−234 °C dec; $[\alpha]_D^{23}$ −18° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{19}H_{19}NO{\cdot}C_2H_2O_4$) C, H, N.

(6a*R*,12*S*)-13: ^{1}H NMR *δ* 0.75 (dd, *J* = 14.5, 14.5 Hz, 1H), 1.68 (s, 3H), 2.21 (s, 3H), 2.31−2.63 (m, 3H), 2.82−3.05 (m, 2H), 3.24 (dd, *J* = 13, 7 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR *δ* 26.0, 27.1, 29.9, 43.1, 55.4, 61.1, 83.0, 120.5 120.9, 125.4 127.1, 127.1, 128.2, 129.4, 132.7, 133.6, 135.8, 144.6, 148.6.

(+)-(6a*R*,12*R*)-1,11-(Acetamidomethylene)aporphine [(6a*R*,12*R*)-14] and (−)-(6a*R*,12*S*)-1,11-(Acetamidomethylene)aporphine [(6a*R*,12*S*)-14]. A mixture of (6a*R*,12*R*)-**12**/(6a*R*,12*S*)-**12** (45:55) was synthesized using the same method as described for the synthesis of (6a*R*,12*R*)-**12** and (6a*R*,12*S*)-**12**. Acetonitrile (2 mL, 49 mmol) and concentrated H_2SO_4 (0.7 mL, 10 mmol) were added to (6a*R*,12*R*)-**12**/(6a*R*,-12*S*)-**12** [(45:55) 336 mg, 1.3 mmol] and the reaction mixture was stirred at 70 °C for 5 min. Aqueous saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic layers was dried (K_2CO_3), filtered and concentrated to give a mixture of (6a*R*,12*R*)-**14** and (6a*R*,12*S*)-**14** (65:35). The epimers were separated by chromatography [silica; $CHCl_3$/MeOH (100:0 followed by 90:10) and silica; $CHCl_3$/isohexanes/MeOH (45:45:10)]. The amines were converted into the hydrochloride salts and recrystallized (EtOH/Et_2O) to give 91 mg (19%) of (6a*R*,12*S*)-**14**·HCl and 189 mg (40%) of (6a*R*,12*R*)-**14**·HCl.

(6a*R*,12*R*)-14·HCl: IR (KBr) 1635 cm^{-1} (C=O); mp 234−237 °C; $[\alpha]_D^{23}$ +19° (*c* 1.0, MeOH). Anal. ($C_{20}H_{20}N_2O{\cdot}HCl{\cdot}5/4H_2O$) C, H, N.

(6a*R*,12*R*)-14: ^{1}H NMR *δ* 2.05 (s, 3H), 2.51 (s, 3H), 2.61 (ddd, *J* = 11, 9.5, 4 Hz, 1H), 2.74 (dd, *J* = 15.5, 5 Hz, 1H), 2.85 (dd, *J* = 13, 13 Hz, 1H) 3.04−3.23 (m, 2H), 3.32 (dd, *J* = 15.5, 7 Hz, 1H), 3.62 (dd, *J* = 13, 7 Hz, 1H), 6.10 (app.d, 1H), 6.85 (app d, 0.6H), 6.97 (d, *J* = 7.5 Hz, 1H), 7.11−7.21 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.31−7.37 (m, 1.4H); ^{13}C NMR *δ* 22.9, 27.4, 31.6, 43.5, 55.6, 56.9 (2C), 62.2, 123.6, 123.9, 126.3, 127.2, 127.3, 128.4, 129.1, 133.6, 136.7, 137.6, 138.1, 141.9, 171.6 (2C).

(6a*R*,12*S*)-14·HCl: IR (KBr) 1636 cm^{-1} (C=O); mp 222−226 °C dec; $[\alpha]_D^{23}$ −37° (*c* 1.0, MeOH). Anal. ($C_{20}H_{20}N_2O{\cdot}HCl{\cdot}5/4H_2O$) C, H, N.

(6a*R*,12*S*)-14: ^{1}H NMR *δ* 2.04 (s, 3H), 2.52 (s, 3H), 2.62−2.84 (m, 3H), 3.02−3.32 (m, 2H), 3.35 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.69 (dd, *J* = 13, 6.5 Hz, 1H), 6.28 (s, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 7.05 (app d, 0.3H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 7.5, 7 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7 Hz, 1H); ^{13}C NMR *δ* 22.9, 27.4, 31.9, 43.6, 55.6, 57.3 (2C), 61.7, 123.2, 123.4, 126.4, 126.9, 127.1, 128.4, 129.0, 133.5, 136.5, 137.9, 139.3, 142.4, 171.7 (2C).

(−)-(6a*R*,12*R*)-1,11-(Aminomethylene)aporphine [(6a*R*,-12*R*)-15]. A solution of (6a*R*,12*R*)-**14** (95.7 mg, 0.32 mmol) in concentrated aqueous HCl (15 mL) was heated in a closed vial at 120 °C for 80 h. Aqueous saturated $NaHCO_3$ was added and the aqueous phase was extracted with $CHCl_3$. The combined organic layers was dried (K_2CO_3), filtered and concentrated. The residue was chromatographed [silica; $CHCl_3$/MeOH/aqueous NH_3 (900:95:5)] and the diamine was converted into the dihydrochloride salt, which was recrystallized [acetonitrile/EtOH (1:1)] to give 43 mg (52%) of (6a*R*,12*R*)-**15**·2HCl: mp 239−242 °C dec; $[\alpha]_D^{23}$ −16° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{18}H_{17}N_2{\cdot}2HCl{\cdot}1/2H_2O$) C, H, N.

(6a*R*,12*R*)-15: ^{1}H NMR *δ* 2.55 (s, 3H), 2.70 (ddd, *J* = 11.5, 10.5, 4.5 Hz, 1H), 2.80 (dd, *J* = 17, 4 Hz, 1H), 2.84 (dd, *J* = 14.5, 14.5 Hz, 1H), 3.08−3.24 (m, 2H), 3.36−3.40 (m, 1H), 3.72 (dd, *J* = 13.5, 6.5 Hz, 1H), 4.98 (s, 1H), 7.02, (d, *J* = 7.5 Hz, 1H), 7.16, (d, *J* = 7.5 Hz, 1H), 7.22 (dd, *J* = 7.5, 7 Hz, 1H), 7.32−7.38 (m, 1H), 7.40 (d, *J* = 7 Hz, 1H); ^{13}C NMR *δ* 27.3, 31.6, 43.5, 55.7, 60.3, 62.3, 122.8, 123.2, 126.4, 127.0, 127.3, 128.3, 129.2, 133.4, 136.2, 137.2, 141.0, 144.6.

(−)-(6a*R*,12*S*)-1,11-(Aminomethylene)aporphine [(6a*R*,-12*S*)-15]. Compound (6a*R*,12*S*)-**15** was synthesized from (6a*R*,12*S*)-**14** (60.3 mg, 0.18 mmol) using the same method as described for the synthesis of (6a*R*,12*R*)-**15** to give 52 mg (88%) of (6a*R*,12*S*)-**15**·2HCl: mp 244−248 °C dec; $[\alpha]_D^{23}$ −36° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{18}H_{17}N_2{\cdot}2HCl{\cdot}1H_2O$) C, H, N.

(6a*R*,12*S*)-15: ^{1}H NMR *δ* 2.55 (s, 3H), 2.70 (ddd, *J* = 12, 11, 4 Hz, 1H), 2.80 (dd, *J* = 16, 4.5 Hz, 1H), 2.88 (dd, *J* = 14.5, 14.5 Hz, 1H), 3.09−3.23 (m, 2H), 3.39−3.49 (m, 1H), 3.73 (dd, *J* = 13, 6.5 Hz, 1H), 5.09 (s, 1H), 7.01, (d, *J* = 7.5 Hz, 1H), 7.15, (d, *J* = 7.5 Hz, 1H), 7.23 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.31−7.37 (m, 1H), 7.39 (d, *J* = 7 Hz, 1H); ^{13}C NMR *δ* 27.4, 32.1, 43.6, 55.6, 60.6, 61.8, 122.5, 122.9, 126.5, 126.7, 127.1, 128.5, 129.2, 133.3, 136.1, 137.5, 142.1, 145.3.

(−)-(6a*R*,12*S*)-1,11-Ethylideneaporphine [(6a*R*,12*S*)-16]. A mixture of (6a*R*,12*R*)-**13**·oxalate/(6a*R*,12*S*)-**13**·oxalate (40:60) was synthesized using the same method as described above for the synthesis of (6a*R*,12*R*)-**13** and (6a*R*,12*S*)-**13**. Pd/C (10%, 62 mg, 0.057 mmol Pd) and aqueous 1 M HCl (15 mL) was added to (6a*R*,12*R*)-**13**/(6a*R*,12*S*)-**13**·oxalate [(40:60), 213 mg, 0.58 mmol] in EtOH (30 mL). The reaction mixture was vigorously stirred under an atmosphere of H_2 for 8 h. The catalyst was filtered off and the volatiles were evaporated. Aqueous saturated $NaHCO_3$ was added to the residue and the mixture was extracted with CH_2Cl_2. The combined organic layers was dried (K_2CO_3), filtered through Al_2O_3 and concentrated. The amine was converted into the hydrochloride salt and recrystallized (acetonitrile/Et_2O) to give 155 mg (90%) of (6a*R*,12*S*)-**16**·HCl: mp 198−200 °C; $[\alpha]_D^{23}$ −18° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{19}H_{19}N{\cdot}HCl{\cdot}1/4H_2O$) C, H, N.

(6a*R*,12*S*)-16: ^{1}H NMR *δ* 1.48 (d, *J* = 7.5 Hz, 3H), 2.56 (s, 3H), 2.64−2.84 (m, 2H), 2.92 (dd, *J* = 14.5, 14.5 Hz, 1H), 3.09−3.24 (m, 2H), 3.40 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.76, (dd, *J* = 13, 6.5 Hz, 1H), 4.11 (q, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.21 (dd. *J* = 7.5, 7.5 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR *δ* 17.1, 27.4, 32.2, 43.6, 44.9, 55.8, 62.2, 122.3, 122.5, 125.4 126.3, 126.5, 127.8 129.0, 131.6, 136.6, 137.9, 143.6, 146.9.

(−)-(6a*R*,12*R*)-1,11-Ethylideneaporphine [(6a*R*,12*R*)-16]. An ice-cold solution of trifluoroacetic acid (2 mL) and $NaBH_4$ (81 mg, 2.1 mmol) was added to (6a*R*,12*R*)-**13**·oxalate/(6a*R*,12*S*)-**13**·oxalate [(40:60), 137 mg, 0.37 mmol]. The reaction mixture was stirred at 0 °C for 5 min. Aqueous saturated $NaHCO_3$ was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers was dried (K_2CO_3), filtered and concentrated. The amine was converted into the hydrochloride salt, which was recrystallized (acetonitrile/Et_2O)

to give 51 mg (46%) of a 35:65 mixture of (6a*R*,12*R*)-**16**·HCl/(6a*R*,12*S*)-**16**·HCl. The epimeric amines (6a*R*,12*R*)-**16**·HCl and (6a*R*,12*S*)-**16**·HCl (39 mg) were separated by semipreparative HPLC [Hybercarb S; MeOH/CH_2Cl_2/Et_2NH (2000:8000:1)]. The amines were converted into the hydrochloride salts to give 10 mg of (6a*R*,12*R*)-**16**·HCl and 20 mg of (6a*R*,12*S*)-**16**·HCl.

(6a*R*,12*R*)-16·HCl: mp 206−213 °C dec; $[\alpha]_D^{23}$ −3° [*c* 1.0, MeOH/H_2O 1.1)]; HRMS *m*/*z* ($M^+ + 1$) calcd 262.1596, obsd 262.1591; ^{1}H NMR (CD_3OD) δ 1.53 (d, J = 7.5 Hz, 3H), 3.00−3.28 (m, 2H), 3.20 (s, 3H), 3.29−3.51 (m, 1H) 3.68−3.82 (m, 2H), 3.96 (ddd, J = 12.5, 6, 1.5 Hz, 1H) 4.04−4.16 (m, 1H), 5.00 (dd, J = 13, 6.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.28 (dd, J = 7.5, 7.5 Hz, 1H),7.40 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 18.0, 26.4, 30.2, 41.7, 46.6, 56.8, 64.0, 121.7, 124.4, 126.2, 126.8, 127.8, 128.1, 130.3, 130.5, 137.6, 138.2, 146.0, 148.4.

(−)-(6a*R*,12*R*)-1,11-(1-Methoxyethylidene)aporphine [(6a*R*,12*R*)-17] and (−)-(6a*R*,12*S*)-1,11-(1-Methoxyethylidene)aporphine [(6a*R*,12*S*)-17]. Concentrated H_2SO_4 (520 mg, 5.3 mmol) in MeOH (2 mL) was added dropwise to a solution of (6a*R*,12*R*)-**13**·oxalate/(6a*R*,12*S*)-**13**·oxalate [(40:60), 301 mg, 0.82 mmol] and $(MeO)_3CH$ (2 mL) in MeOH (4 mL). The reaction mixture was stirred at room temperature for 2 min, aqueous saturated $NaHCO_3$ was added and the volatiles were evaporated. The aqueous phase was extracted with $CHCl_3$ and the combined organic layers was dried (K_2CO_3), filtered and concentrated to give a mixture of (6a*R*,12*R*)-**17** and (6a*R*,12*S*)-**17** (55:45). The epimeric mixture was chromatographed [silica; $CHCl_3$/MeOH (95:5)] and the epimers were separated by preparative HPLC [silica; isohexanes/EtOH/Et_3N (898:100:2)]. The amines were converted into the hydrochloride salts and recrystallized (acetonitrile/Et_2O) to give 72 mg (27%) of (6a*R*,12*S*)-**17**·HCl and 80 mg (30%) of (6a*R*,12*R*)-**17**·HCl.

(6a*R*,12*R*)-17·HCl: mp 246−250 °C dec; $[\alpha]_D^{23}$ −14° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{20}H_{21}NO$·HCl) C, H, N.

(6a*R*,12*R*)-17: ^{1}H NMR δ 1.68 (s, 3H), 2.55 (s, 3H), 2.67−2.90 (m, 3H), 2.94 (s, 3H), 3.07−3.23 (m, 2H), 3.36 (dd, J = 15.5, 6.5 Hz, 1H), 3.75 (dd, J = 13, 6.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.20 (dd, J = 7.5, 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 25.3, 27.5, 31.7 43.5, 52.3, 55.6, 62.0, 89.2, 122.3, 122.5, 126.2, 127.4, 127.5, 128.6, 129.1, 134.0, 135.9, 136.9, 140.0 143.9.

(6a*R*,12*S*)-17·HCl: mp 235−237 °C dec; $[\alpha]_D^{23}$ −19° [*c* 1.0, MeOH/H_2O (1:1)]. Anal. ($C_{20}H_{21}NO$·HCl) C, H, N.

(6a*R*,12*S*)-17: ^{1}H NMR δ 1.76 (s, 3H), 2.55 (s, 3H), 2.65−2.85 (m, 2H), 2.76 (s, 3H), 2.90 (dd, J = 14, 14 Hz, 1H), 3.08−3.23 (m, 2H), 3.37 (dd, J = 15.5, 7 Hz, 1H), 3.71 (dd, J = 13, 7 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7 Hz, 1H), 7.20 (dd, J = 7.5, 8 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 7 Hz, 1H); ^{13}C NMR δ 25.6, 27.5, 31.7 43.5, 51.2, 55.6, 61.8, 89.9, 121.9, 122.4, 126.5, 127.2, 127.3, 128.5, 129.0, 134.0, 135.8, 137.0, 141.2, 144.2.

(−)-(6a*R*,12*R*)-1,11-(1-Ethoxypropylidene)aporphine [(6a*R*,12*R*)-18] and (−)-(6a*R*,12*S*)-1,11-(1-Ethoxypropylidene)aporphine [(6a*R*,12*S*)-18]. EtMgBr in THF (5.5 M, 0.40 mL, 2.2 mmol) was added to a solution of (*R*)-**11** (284 mg, 1.1 mmol) in dry THF (10 mL) kept at −70 °C and under an atmosphere of N_2. After one min at −70 °C, H_2O (2 mL) was added and the reaction temperature was allowed to rise to 0 °C. Aqueous saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic layers was filtered through a pad of K_2CO_3 and concentrated to give a mixture of epimeric ethyl substituted alcohols (50:50). $(EtO)_3CH$ (1.5 mL), EtOH (4.5 mL) and *p*-toluenesulfonic acid (120 mg, 0.70 mmol) were added to the residue and after stirring for 1 h at room temperature additional *p*-toluenesulfonic acid (120 mg, 0.70 mmol) and $(EtO)_3CH$ (1.5 mL) were added. After 5 h aqueous saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 The combined organic layers was dried (K_2CO_3), filtered and concentrated to give a mixture of (6a*R*,-12*R*)-**18** and (6a*R*,12*S*)-**18** (50:50). The residue was chromatographed [silica; $CHCl_3$/MeOH (98:2)] and the mixture of amines was converted into the hydrochloride salt and recrystallized (acetonitrile/Et_2O) to give 89 mg (23%) of a 50:50 mixture of (6a*R*,12*R*)-**18**·HCl/(6a*R*,12*S*)-**18**·HCl. The epimeric amines (6a*R*,12*R*)-**18**·HCl and (6a*R*,12*S*)-**18**·HCl (40 mg) were separated by semipreparative HPLC [Hypercarb S; MeOH/CH_2Cl_2/Et_2NH (8000:2000:1)]. The amines were converted into the hydrochloride salts to give 16 mg of (6a*R*,12*R*)-**18**·HCl and 12 mg of (6a*R*,12*S*)-**18**·HCl.

(6a*R*,12*R*)-18·HCl: mp 188−192 °C; $[\alpha]_D^{22}$ −1° [*c* 1.0, MeOH/H_2O (50:50)]; HRMS *m*/*z* ($M^+ + 1$) calcd 320.2014, obsd 320.2012.

(6a*R*,12*R*)-18: ^{1}H NMR δ 0.58 (t, J = 7.5 Hz, 3H), 1.06 (t, J = 7 Hz, 3H), 2.01−2.18 (m, 2H), 2.59 (s, 3H), 2.73−2.97 (m, 2H), 3.01−3.31 (m, 3H), 3.36 (dd, J = 15, 6.5 Hz, 1H), 3.66 (q, J = 7 Hz, 2H), 3.82 (dd, J = 13, 6.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.16−7.22 (m, 2H), 7.24 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 8.2, 15.7, 27.2, 31.4, 32.0, 43.1, 55.6, 60.0, 62.0, 92.7, 122.7, 123.2, 125.6, 127.3, 127.3, 128.4, 128.6, 133.5, 136.5, 137.2, 139.7, 143.6.

(6a*R*,12*S*)-18·HCl: mp 221−223 °C dec; $[\alpha]_D^{22}$ −12° [*c* 1.0, MeOH/H_2O (1:1)]; HRMS *m*/*z* ($M^+ + 1$) calcd 320.2014, obsd 320.2016.

(6a*R*,12*S*)-18: ^{1}H NMR δ 0.82 (t, J = 7.5 Hz, 3H), 1.01 (t, J = 7 Hz, 3H), 2.11 (q, J = 7.5 Hz, 2H), 2.60 (s, 3H), 2.72−2.97 (m, 3H), 3.10−3.31 (m, 2H), 3.39 (dd, J = 14.5, 6.5 Hz, 1H), 3.47 (q, J = 7 Hz, 2H), 3.82 (dd, J = 12.5, 6.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 7.16−7.22 (m, 2H), 7.24 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 8.6, 15.6, 27.2, 31.6, 32.3, 43.2, 55.5, 59.9, 61.7, 93.2, 122.6, 123.2, 125.7, 127.0, 127.1, 128.4, 128.7, 133.4, 136.2, 137.4, 141.2, 144.2.

X-ray Crystallography. The reflection intensities for (6a*R*,12*R*)-**12**·HCl, (6a*R*,12*S*)-**12**·HCl, and (6a*R*,12*S*)-**16**·HCl·CH_3CN were measured with a STOE/AED2 diffractometer and $\omega - 2\theta$ scan technique, and the intensity data for (6a*R*,12*S*)-**15**·2HCl·H_2O and (6a*R*,12*R*)-**17**·HCl were collected using a STOE image plate detector system and ϕ oscillation technique. Data reductions included corrections for background and Lorentz and polarization effects. The structures were solved by application of direct methods (SHELXS[25]) and refined with full-matrix least-squares technique based on F^2 for all observations (SHELXL-93[26]). The non-hydrogen atoms were refined as vibrating anisotropic. The hydrogen atoms were located in difference electron density maps and their positions were refined, whereas their isotropic vibration parameters U_{iso} were set to 1.2·U_{eq} (methyl groups 1.5·U_{eq}) of the parent non-hydrogen atom. The geometric calculations were performed using the programs SHELXL-93[26] and PLATON.[27] Crystal data and selected details of the refinement calculations are listed in Table 3.

Computational Methods. An automated conformational analysis (MM3) of the novel pentacyclic derivatives in their nonprotonated state was performed using the BatchMin program included in the MacroModel v5.5 package.[28] A 2000-step Monte Carlo search was performed on each compound. Geometry optimizations of the solid-state conformations of the nonprotonated (6a*R*,12*R*)-**12**, (6a*R*,12*S*)-**12**, (6a*R*,12*S*)-**15**, (6a*R*,-12*S*)-**16,** and (6a*R*,12*R*)-**17** and of the (*R*)-aporphine skeleton were performed in SPARTAN[29] at the RHF/6-31G* level with a net charge of zero and by molecular mechanics calculations using the MM3 force field included in MacroModel.

Pharmacology: Receptor Binding Assays. The DA D_{2A} receptor binding assay was performed as described previously[30] by measuring the ability of the compounds to displace [^{3}H]-raclopride binding from cloned human D_{2A} receptors expressed in mouse fibroblast (Ltk^-) cells. The 5-HT_{1A} receptor binding assay was performed using cloned human 5-HT_{1A} receptors expressed in Chinese hamster ovary (CHO) cells or as described earlier using rat hippocampus.[31] The same K_d-value of the radioligand [^{3}H]8-OH-DPAT was obtained both in hippocampus and in the cell line. The CHO cells expressing human 5-HT_{1A} receptors were obtained from Dr. P. G. Strange (University of Reading, Reading, U.K.). Membranes were prepared as described previously,[30] resuspended in binding buffer (in mM: 50 Tris-HCl, 4 $MgCl_2$, pH 7.4) and stored in

aliquots at −70 °C. The frozen cell membranes were thawed, homogenized with Ultra Turrax, and suspended in binding buffer. The binding assays were performed in a total volume of 0.5 mL with a receptor concentration of about 40 pM. 1 nM [^{3}H]8-OH-DPAT (127 Ci/mmol) was incubated with nonlabeled ligand for 60 min at 30 °C. Binding in the presence of WAY-100635 (10 μM) was defined as nonspecific. The incubations were terminated by rapid filtration through Whatman GF/B glass fiber filters (Maidstone, England) using a Tomtec cell harvester. The filters were washed with ice-cold buffer (5 mM Tris-HCl, pH 7.4), and the radioactivity was determined in a Packard 2500TR liquid scintillation analyzer or in a Wallac Betaplate counter. The serotonin 5-HT$_7$ receptor binding assay was performed using cloned rat 5-HT$_7$ receptors expressed in CHO cells or Sf9 cells. The same K_d-value of the radioligand, [^{3}H]5-HT, was obtained in both cell lines. The CHO cell membranes were prepared as described previously[30] and above for the 5-HT$_{1A}$ receptor binding. The Sf9 cell membranes were used as obtained from BioSignal (Montreal, Canada). The 5-HT$_7$ receptor binding assay was performed essentially as the 5-HT$_{1A}$ receptor binding assay described above, with the following modifications: Membranes were suspended in binding buffer (in mM: 50 Tris-HCl, 4 $MgCl_2$, 1 EDTA, pH 7.4). The binding assays were performed in a total volume of 1 mL with a receptor concentration of 30−40 pM. [^{3}H]5-HT (0.8 nM, 103 Ci/mmol) was incubated with nonlabeled ligand for 60 min at 30 °C. Binding in the presence of methiothepin (10 μM) was defined as nonspecific. The binding data were analyzed by nonlinear regression using the LIGAND program.[32]

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Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, and anisotropic displacement parameters for (6a*R*,12*R*)-**12**·HCl, (6a*R*,12*S*)-**12**·HCl, (6a*R*,12*S*)-**15**·2HCl·H_2O, (6a*R*,12*S*)-**16**·HCl·MeCN, and (6a*R*,12*R*)-**17**·HCl; also conformational features of selected aporphine derivatives included in the CSD. This material is available free of charge via the Internet at http://pubs.acs.org.

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