Sila-venlafaxine, a Sila-Analogue of the Serotonin/Noradrenaline Reuptake Inhibitor Venlafaxine: Synthesis, Crystal Structure Analysis, and Pharmacological Characterization

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The serotonin/noradrenaline reuptake inhibitor *rac*-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexan-1-ol (*rac*-venlafaxine, *rac*-**1a**) is in clinical use as an antidepressant. The silicon analogue, *rac*-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexan-1-ol (*rac*-sila-venlafaxine, *rac*-**1b**), was synthesized in multistep syntheses, starting from tetrachlorosilane or tetramethoxysilane. The corresponding 1-silacyclopentan-1-ol derivative *rac*-**2** was prepared analogously. The sila-venlafaxine enantiomers (*R*)-**1b** and (*S*)-**1b** were obtained by resolution of *rac*-**1b**, using (+)- or (−)-10-camphorsulfonic acid as the resolving agent. Compounds *rac*-**1b**, (*R*)-**1b**, (*S*)-**1b**, *rac*-**1b**·HCl, (*R*)-**1b**·HCl, (*S*)-**1b**·HCl, (*R*)-**1b**·HBr, *rac*-**2**, and *rac*-**2**·HCl were characterized by multinuclear NMR studies and elemental analyses, and *rac*-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2** were additionally characterized by crystal structure analyses. Compounds *rac*-**1a**, *rac*-**1b**, *rac*-**2**, (*R*)-**1a**, (*S*)-**1a**, (*R*)-**1b**, and (*S*)-**1b** were tested as their hydrochlorides for their efficacy in serotonin, noradrenaline, and dopamine reuptake inhibition assays. Sila-substitution (C/Si switch) of compounds *rac*-**1a**, (*R*)-**1a**, and (*S*)-**1a** (→ *rac*-**1b**, (*R*)-**1b**, (*S*)-**1b**) was found to dramatically influence their pharmacological selectivity profiles with respect to serotonin, noradrenaline, and dopamine reuptake inhibition. (*R*)-Sila-venlafaxine ((*R*)-**1b**) was identified to have a refined selectivity profile consistent with selective noradrenaline reuptake inhibition. Compounds with this profile may provide therapeutic benefit in the treatment of various nervous system disorders.

Introduction

In a series of recently published reviews, silicon chemistry has been demonstrated to be a novel powerful source of chemical diversity in drug design.[1] Sila-substitution of drugs (carbon/silicon switch) is one of the concepts that have been successfully used for the development of new silicon-based drugs (for recent examples, see ref 2). An alternative approach is the development of silicon-containing drugs the carbon analogues of which do not exist (for recent examples, see ref 3).

In context with our systematic studies on sila-substituted drugs,[1a,2] we were interested in the pharmacological properties of sila-venlafaxine (**1b**), a sila-analogue of the serotonin/noradrenaline reuptake inhibitor venlafaxine[4] (**1a**). Racemic venlafaxine hydrochloride (Effexor, Wyeth-Ayerst; Efexor, Wyeth, Wyeth-Lederle; Trevilor, Wyeth) is in clinical use as an antidepressant.[5] As racemic venlafaxine is a well-tolerated and orally dosed drug, it represents a challenging drug-like scaffold to be modified by sila-substitution of the R_3COH carbon atom (→ R_3SiOH), resulting in a silicon compound also containing good drug-like properties. Sila-substitution of **1a** (→ **1b**) was expected to affect the chemical and physicochemical

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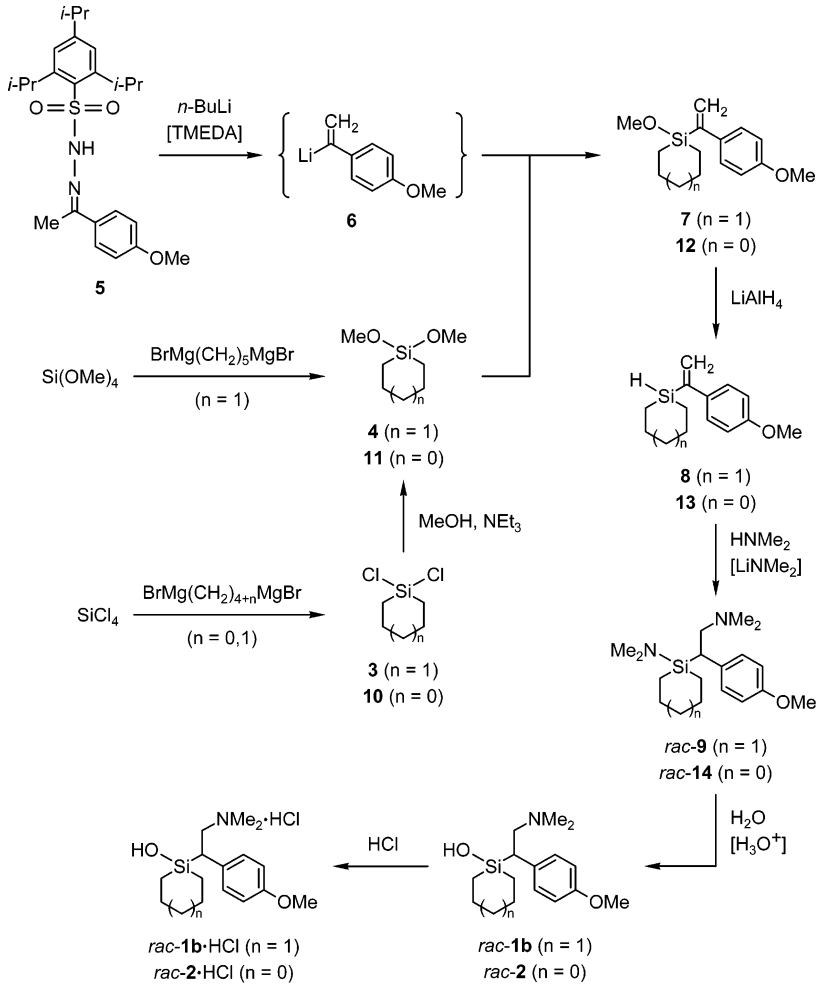
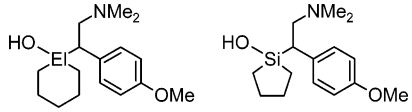
Scheme 1



properties and the structure of **1a** and therefore to alter its biological properties. For example, (i) the higher OH acidity of silanols (compared to analogous carbinols) could increase the strength of hydrogen-bonding interactions with biomolecules (receptors) and thus could enhance receptor binding. (ii) As the covalent radius of silicon is larger than that of carbon, the C/Si analogues **1a** and **1b** are expected to differ in their structure (size and shape) and in their stereodynamics, which may also affect receptor binding. (iii) Furthermore, differences in the lipophilicity of **1a** and **1b** may be assumed, which could alter the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties.

We report here on the synthesis of *rac*-**1b**, (*R*)-**1b**, and (*S*)-**1b**, the preparation of the sila-venlafaxine derivative *rac*-**2**, and the pharmacological characterization of all these compounds. As venlafaxine is a monoamine reuptake inhibitor, serotonin, noradrenaline, and dopamine reuptake inhibition assays were chosen to study if sila-substitution alters the selectivity ratio between the three reuptake transporters. The pharmacological studies were performed with a special emphasis on the comparison of the C/Si pairs *rac*-**1a**/*rac*-**1b**, (*R*)-**1a**/(*R*)-**1b**, and (*S*)-**1a**/(*S*)-**1b**. In addition, compounds *rac*-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2** were structurally characterized by single-crystal X-ray diffraction. Preliminary results of the studies reported here have already been presented elsewhere[6] (for an alternative synthesis of *rac*-**1b**, see ref 7).



Results and Discussion

Syntheses. *rac*-Sila-venlafaxine hydrochloride (*rac*-**1b**·HCl) was prepared in 15% overall yield in a multistep synthesis, starting from tetrachlorosilane (Scheme 1). Thus, treatment of tetrachlorosilane with 1,5-bis(bromomagnesio)pentane gave 1,1-

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dichloro-1-silacyclohexane (**3**) (yield 62%), which upon methanolysis, in the presence of triethylamine, afforded 1,1-dimethoxy-1-silacyclohexane (**4**) (yield 80%). Alternatively, compound **4** was synthesized by reaction of tetramethoxysilane with 1,5-bis(bromomagnesio)pentane (yield 43%). Treatment of 4-methoxyacetophenone 2,4,6-triisopropylbenzenesulfonylhydrazone (**5**) with *n*-butyllithium, in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), gave the intermediate [1-(4-methoxyphenyl)vinyl]lithium (**6**), which upon reaction with **4** afforded 1-methoxy-1-[1-(4-methoxyphenyl)vinyl]-1-silacyclohexane (**7**) (yield 45%), which was then reacted with lithium aluminum hydride to give 1-[1-(4-methoxyphenyl)vinyl]-1-silacyclohexane (**8**) (yield 82%). The lithium dimethylamide-catalyzed reaction of **8** with dimethylamine (→ *rac*-**9**), followed by hydrolysis, yielded *rac*-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexan-1-ol (*rac*-sila-venlafaxine, *rac*-**1b**) (yield 90%). The isolation and purification of the intermediate *rac*-**9** in the transformation **8** → *rac*-**1b** was not necessary. Treatment of *rac*-**1b** with an ethereal hydrogen chloride solution finally afforded the hydrochloride *rac*-**1b**·HCl (yield 90%). To characterize the intermediate *rac*-1-(dimethylamino)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexane (*rac*-**9**), this compound was also isolated and purified (yield 76%).

The sila-venlafaxine hydrochloride analogue *rac*-[2-(1-hydroxy-1-sila-1-cyclopentyl)-2-(4-methoxyphenyl)ethyl]dimethylammonium chloride (*rac*-**2**·HCl) was prepared analogously to the synthesis of *rac*-**1b**·HCl, starting from tetrachlorosilane, and was isolated in 5% overall yield (Scheme 1).

(*R*)-Sila-venlafaxine ((*R*)-**1b**) was prepared by resolution of *rac*-**1b**, using (+)-10-camphorsulfonic acid ((+)-CSA) as the resolving agent (→ (*R*)-**1b**·(+)-CSA; yield 30%, related to *rac*-**1b**). Treatment of the diastereomerically pure salt (*R*)-**1b**·(+)-CSA with an aqueous potassium carbonate solution gave (*R*)-**1b** (yield 99%). The antipode (*S*)-**1b** was prepared analogously, starting from the mother liquor obtained in the preparation of (*R*)-**1b**·(+)-CSA and using (−)-CSA as the resolving agent (→ (*S*)-**1b**·(−)-CSA). The enantiopure hydrochlorides (*R*)-**1b**·HCl and (*S*)-**1b**·HCl were prepared by treatment of (*R*)-**1b** and (*S*)-**1b**, respectively, with an ethereal hydrogen chloride solution (yield 27−28%, related to *rac*-**1b**). Reaction of (*R*)-**1b** with triphenylphosphonium bromide afforded (*R*)-**1b**·HBr (yield 90%), the crystal structure analysis of which allowed the assignment of the absolute configurations of the sila-venlafaxine enantiomers (see below).

Compounds *rac*-**1b**, (*R*)-**1b**, (*S*)-**1b**, *rac*-**1b**·HCl, (*R*)-**1b**·HCl, (*S*)-**1b**·HCl, (*R*)-**1b**·HBr, *rac*-**2**, *rac*-**2**·HCl, and **5** were isolated as colorless crystalline solids, whereas **3**, **4**, **7**, **8**, *rac*-**9**, **10**−**13**, and *rac*-**14** were obtained as colorless liquids. The identities of all these compounds were established by elemental analyses and NMR studies, and *rac*-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2** were additionally characterized by crystal structure analyses.

Determination of Enantiomeric Purities. The ^{1}H NMR resonance signals for the NC*H*$_3$ groups of (*R*)-**1b** and (*S*)-**1b**, in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol ((*R*)-(−)-TFAE), were used as the probe to determine the enantiomeric purities of these enantiomers (for details, see Experimental Section). According to these studies, the resolved antipodes (*R*)-**1b** and (*S*)-**1b** were enantiomerically pure. As salt formation does not affect the stereogenic carbon center, compounds (*R*)-**1b**·HCl, (*S*)-**1b**·HCl, and (*R*)-**1b**·HBr were also enantiomerically pure.

Crystal Structure Analyses. Compounds *rac*-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2** were structurally characterized by single-crystal X-ray diffraction. The crystal data and experimental parameters used for these studies are given in Table 1. The structures of the cations of *rac*-**1b**·HCl and (*R*)-**1b**·HBr and the molecular structure of *rac*-**2** are depicted in Figures 1−3; selected bond distances and angles are given in the respective figure legends.

Table 1. Crystal Data and Experimental Parameters for the Crystal Structure Analyses of *rac*-1b·HCl, (*R*)-1b·HBr, and *rac*-2

	rac-**1b**·HCl	(*R*)-**1b**·HBr	*rac*-**2**
empirical formula	$C_{16}H_{28}ClNO_2Si$	$C_{16}H_{28}BrNO_2Si$	$C_{15}H_{25}NO_2Si$
formula mass, g mol^{-1}	329.93	374.39	279.45
collection *T*, K	173(2)	173(2)	173(2)
λ(Mo Kα), Å	0.71073	0.71073	0.71073
cryst syst	orthorhombic	monoclinic	monoclinic
space group (no.)	*Pca*2$_1$ (29)	*P*2$_1$ (4)	*P*2$_1$/*c* (14)
a, Å	12.8309(16)	6.6309(10)	14.0274(13)
b, Å	14.209(2)	10.3142(11)	10.7234(16)
c, Å	9.8055(11)	13.713(2)	10.7269(17)
β, deg	90	92.637(19)	99.752(14)
V, Å^3	1787.7(4)	936.9(2)	1590.2(4)
Z	4	2	4
D(calcd), g cm^{-3}	1.226	1.327	1.167
μ, mm^{-1}	0.285	2.262	0.147
F(000)	712	392	608
cryst dimens, mm	0.4 × 0.3 × 0.1	0.4 × 0.3 × 0.1	0.3 × 0.3 × 0.2
2θ range, deg	4.28−53.94	4.94−52.94	4.80−56.00
index ranges	$-16 \le h \le 16$, $-18 \le k \le 18$, $-12 \le l \le 12$	$-8 \le h \le 8$, $-12 \le k \le 11$, $-17 \le l \le 17$	$-18 \le h \le 18$, $-14 \le k \le 14$, $-14 \le l \le 14$
no. of collected reflns	20 273	8706	18 884
no. of independent reflns	3853	3648	3738
R_{int}	0.0358	0.0586	0.0411
no. of reflns used	3853	3648	3738
no. of restraints	1	1	14
no. of params	197	201	195
S[a]	1.061	0.986	1.041
weight params *a*/*b*[b]	0.0388/0.1601	0.0502/0.0000	0.0644/0.2725
R_1[c] [$I > 2\sigma(I)$]	0.0257	0.0310	0.0398
wR_2[d] (all data)	0.0627	0.0782	0.1096
absolute struct param	−0.03(4)	−0.018(7)	
max./min. residual electron density, e Å^{-3}	+0.246/−0.134	+0.549/−0.363	+0.293/−0.227

[a] $S = \{\sum[w(F_o^2 - F_c^2)^2]/(n-p)\}^{0.5}$; *n* = no. of reflections; *p* = no. of parameters. [b] $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, with $P = [\max(F_o^2,0) + 2F_c^2]/3$. [c] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [d] $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{0.5}$.

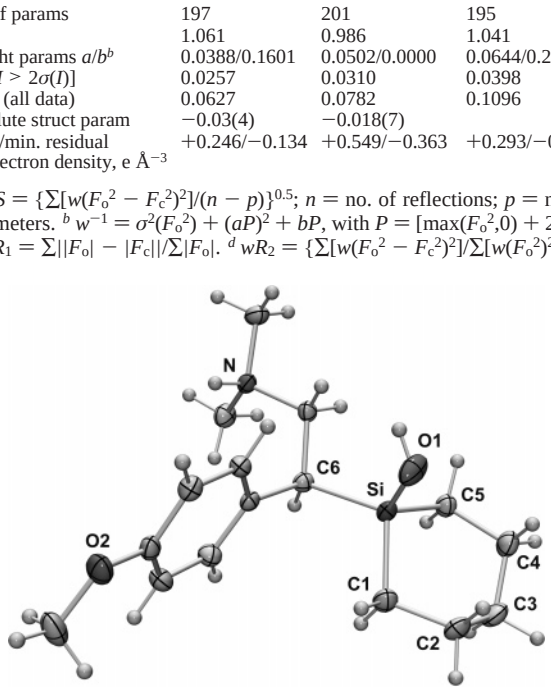

Figure 1. Structure of the cation of *rac*-**1b**·HCl in the crystal (only one enantiomer depicted; probability level of displacement ellipsoids 50%). Selected bond distances (Å) and angles (deg): Si−O1 1.6286(12), Si−C1 1.8549(14), Si−C5 1.8610(14), Si−C6 1.9041-(14), C1−C2 1.539(2), C2−C3 1.529(2), C3−C4 1.526(2), C4−C5 1.5386(19), O1−Si−C1 106.38(7), O1−Si−C5 110.98(7), O1−Si−C6 111.08(6), C1−Si−C5 104.93(7), C1−Si−C6 111.31(7), C5−Si−C6 111.88(6), Si−C1−C2 110.46(10), C1−C2−C3 113.04(12), C2−C3−C4 113.91(13), C3−C4−C5 113.23(12), C4−C5−Si 110.38(10).

As can be seen from Figures 4−6, the crystal structures of *rac*-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2** are governed by hydrogen bonds.[8] Compound *rac*-**1b**·HCl forms O1−H*O*···Cl and N−H*N*···Cl hydrogen bonds, leading to the formation of infinite

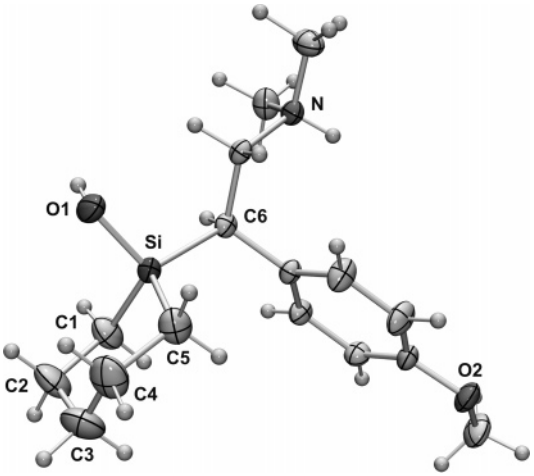

Figure 2. Structure of the cation of (*R*)-**1b**·HBr in the crystal (probability level of displacement ellipsoids 50%). Selected bond distances (Å) and angles (deg): Si−O1 1.637(3), Si−C1 1.845(3), Si−C5 1.854(3), Si−C6 1.909(3), C1−C2 1.534(5), C2−C3 1.510(6), C3−C4 1.506(7), C4−C5 1.525(5), O1−Si−C1 111.38(15), O1−Si−C5 106.75(16), O1−Si−C6 109.18(12), C1−Si−C5 104.72(16), C1−Si−C6 109.49(15), C5−Si−C6 115.26(13), Si−C1−C2 110.3(3), C1−C2−C3 113.6(3), C2−C3−C4 115.1(3), C3−C4−C5 114.0(4), C4−C5−Si 110.1(2).

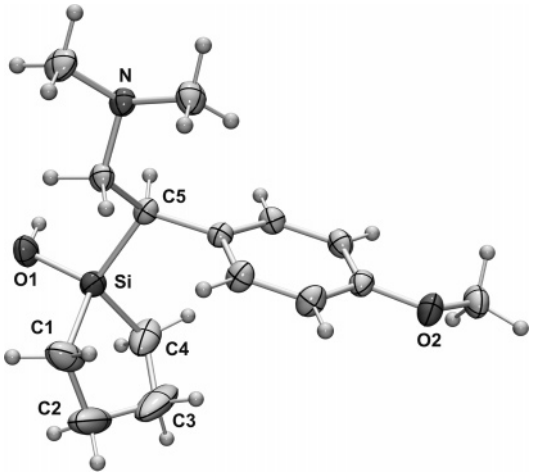

Figure 3. Molecular structure of *rac*-**2** in the crystal (only one enantiomer depicted; probability level of displacement ellipsoids 50%). Due to the presence of two different envelope conformations of the silacyclopentane ring, the crystal structure of *rac*-**2** is characterized by a disorder. The structure shown represents the dominating conformer (occupancy 76%). Selected bond distances (Å) and angles (deg): Si−O1 1.6286(11), Si−C1 1.8834(18), Si−C4 1.8683(17), Si−C5 1.9056(13), C1−C2 1.552(5), C2−C3 1.530(6), C3−C4 1.503(4), O1−Si−C1 109.30(7), O1−Si−C4 115.45(7), O1−Si−C5 108.39(6), C1−Si−C4 96.22(10), C1−Si−C5 114.37(7), C4−Si−C5 112.83(7), Si−C1−C2 101.9(3), C1−C2−C3 109.5(3), C2−C3−C4 107.9(3), C3−C4−Si 104.30(19).

chains along [0 0 1] (Figure 4). These chains are built up by the ammonium cations and chloride anions, the absolute configurations of all the cations in a given chain being identical. Compound (*R*)-**1b** forms O1−H*O*···Br and N−H*N*···Br hydrogen bonds that lead to infinite chains of the ammonium cations and bromide anions along [0 1 0] (Figure 5). Compound *rac*-**2**

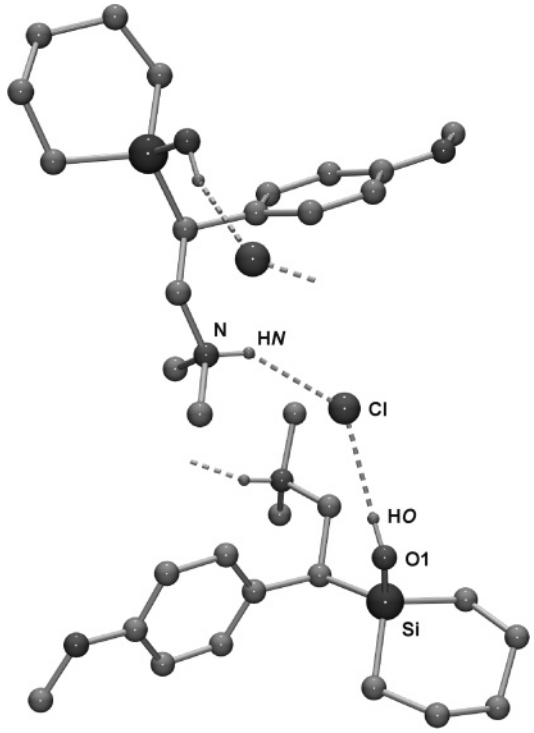

Figure 4. Hydrogen-bonding system in the crystal of *rac*-**1b**·HCl. Selected distances (Å) and angles (deg): O1−H*O* 0.84, H*O*···Cl 2.34, O1···Cl 3.1246(13), O1−H*O*···Cl 156, N···H*N* 0.863(18), H*N*···Cl 2.305(17), N···Cl 3.0680(13), N−H*N*···Cl 147.5(14).[8] The hydrogen atoms (except for the H*O* and H*N* atoms) are omitted for clarity.

forms intermolecular O1−H*O*···N hydrogen bonds, leading to the formation of centrosymmetric dimers (Figure 6).

As would be expected, the silacyclohexane skeletons in *rac*-**1b**·HCl and (*R*)-**1b**·HBr adopt a chair conformation. The silacyclopentane ring in *rac*-**2** adopts two different envelope conformations (disorder of the carbon atoms C2 and C3), with occupancy factors of 0.76 and 0.24. All three structures are characterized by relatively long Si−C6 (Si−C5) distances in the range 1.9041(14) to 1.909(3) Å, the reason for this elongation being unclear. Interestingly, the corresponding C−C distance in (*S*)-**1a**·HBr is less elongated (1.56 Å),[4c] indicating that the steric demand of the equatorial 2-(dimethylammonio)- or 2-(dimethylamino)-1-(4-methoxyphenyl)ethyl substituent is not responsible for the long Si−C6 (Si−C5) distances observed for *rac*-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2**. Despite some significant deviations from the tetrahedral angle in the silacyclopentane skeleton of *rac*-**2**, all the other bond distances and angles of *rac*-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2** are in the expected range and do not need further discussion.

The absolute configuration of (*R*)-**1b**·HBr was reliably determined by refinement of the Flack parameter, leading to a value of 0.000(7) for the reported structure and to a value of 1.018(7) for the inverted structure and thus revealing sufficiently strong inversion distinguishing power of the data set.[9]

Figure 7 shows a superposition of the cyclohexane skeleton of (*S*)-**1a**·HBr[4c] and the 1-silacyclohexane skeleton of the (*S*)-enantiomer of *rac*-**1b**·HCl. Due to the longer covalent radius of the silicon atom, the 1-silacyclohexane ring is more "flattened" than the cyclohexane ring. As a consequence, the OH

(8) The hydrogen-bonding systems were analyzed by using the program system PLATON: Spek, A. L. *PLATON*; University of Utrecht: Utrecht, The Netherlands, 1998. In this context, see also: Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, Germany, 1991; pp 15−24.

(9) (a) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876−881. (b) Flack, H. D.; Bernardinelli, G. *Acta Crystallogr., Sect. A* **1999**, *55*, 908−915. (c) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143−1148.

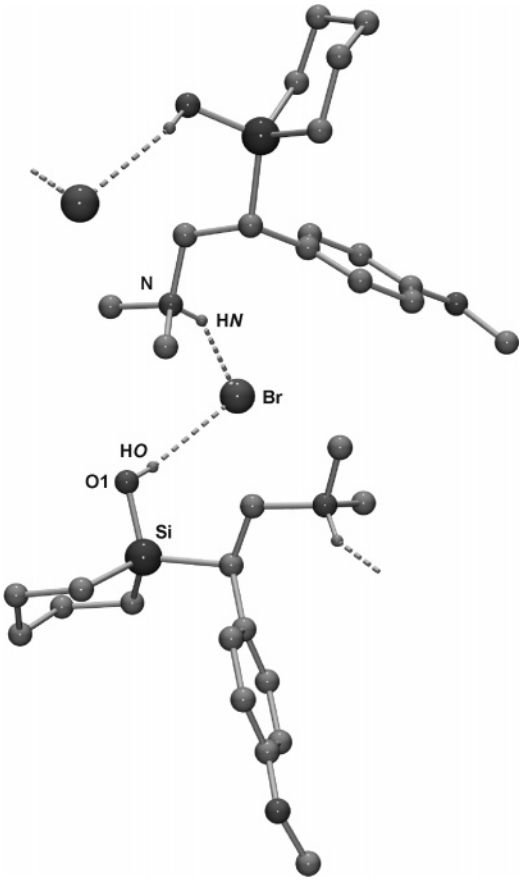

Figure 5. Hydrogen-bonding system in the crystal of (*R*)-**1b**·HBr. Selected distances (Å) and angles (deg): O1−H*O* 0.84, H*O*···Br 2.48, O1···Br 3.261(2), O1−H*O*···Br 154, N···H*N* 0.89(4), H*N*···Br 2.48(4), N···Br 3.290(3), N−H*N*···Br 151(2).[8] The hydrogen atoms (except for the H*O* and H*N* atoms) are omitted for clarity.

group and the ammonio moiety of the C/Si analogues differ in their relative orientation. These structural features might be important for the ligand−receptor interactions of the venlafaxine and sila-venlafaxine enantiomers.

Determination of pK_a, log *P*, and log *D* Values. Compounds *rac*-**1a** and *rac*-**1b** were studied for their pK_a, log *P*, and log *D* (log *P* at pH 7.4) values. As can be seen from Table 2, similar data for the two C/Si analogues were obtained, and therefore it is expected that venlafaxine and sila-venlafaxine would have similar brain penetration profiles. At physiological pH (pH 7.4) both compounds exist predominantly in their protonated form (degree of protonation 89%).

Pharmacological Studies. Compounds *rac*-**1a**, *rac*-**1b**, *rac*-**2**, (*R*)-**1a**, (*S*)-**1a**, (*R*)-**1b**, and (*S*)-**1b** were tested as their hydrochlorides for their efficacy in serotonin, noradrenaline, and dopamine reuptake inhibition assays (Table 3). The data are shown in Table 4 and Figure 8.

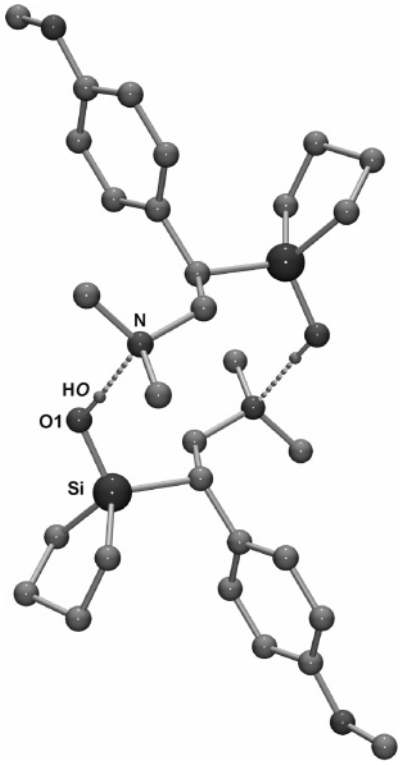

Figure 6. Hydrogen-bonding system in the crystal of *rac*-**2** (dominating conformer). Selected distances (Å) and angles (deg): O1−H*O* 0.84, H*O*···N 1.90, O1···N 2.7338(16), O1−H*O*···N 169.[8] The hydrogen atoms (except for the H*O* atoms) are omitted for clarity.

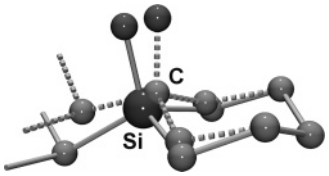

Figure 7. Superposition of the cyclohexane skeleton of (*S*)-**1a**·HBr and the 1-silacyclohexane skeleton of the (*S*)-enantiomer of *rac*-**1b**·HCl. The hydrogen atoms are omitted for clarity.

Table 2. pK_a, log *P*, and log *D* Data for *rac*-1a and *rac*-1b

	pK_a	log *P*	log *D* (log *P* at pH 7.4)
rac-**1a**	9.7	3.13	0.88
rac-**1b**	9.7	3.21	0.92

The sila-venlafaxine enantiomers (*R*)-**1b** and (*S*)-**1b** exhibit a substantially altered monoamine reuptake inhibition profile when compared with their carbon analogues (*R*)-**1a** and (*S*)-**1a**. While activity at the noradrenaline and dopamine transporters is essentially unaffected by sila-substitution (within experimental biological variation), the potency at serotonin transporters is reduced by 2 orders of magnitude. This change in potency is also reflected in the activity profile of *rac*-**1b** when compared with *rac*-**1a**. A similar effect is observed for the silicon

Table 3. Experimental Conditions for the Pharmacological Assays

	SERT	NET	DAT
cell line	human HEK-293	human MDCK	human CHO-K1
radioligand	[^{3}H]serotonin	[^{3}H]noradrenaline	[^{3}H]dopamine
incubation time, min	10	10	10
incubation temp, °C	25	25	25
incubation buffer[a]	5 mM Tris-HCl, 7.5 mM HEPES, 120 mM NaCl, 5.4 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 5 mM glucose, 1 mM ascorbic acid, pH 7.1		
reference	20	21	22, 23

[a] The incubation buffer was identical for all three assays.

Table 4. Monoamine Reuptake Transporter Inhibition Profiles[a]

compound	SERT	NET	DAT
rac-**1a**	0.020	0.149	4.430
(*R*)-**1a**	0.030	0.061	19.600
(*S*)-**1a**	0.006	0.754	6.670
rac-**1b**	1.063	0.109	2.630
(*R*)-**1b**	3.168	0.251	5.270
(*S*)-**1b**	0.791	4.715	36.350
rac-**2**	0.904	0.275	0.707

[a] Data expressed as IC_{50} values (μM). These data represent the mean of at least 2 determinations. SERT = serotonin reuptake transporter, NET = noradrenaline (norepinephrine) reuptake transporter, DAT = dopamine reuptake transporter.

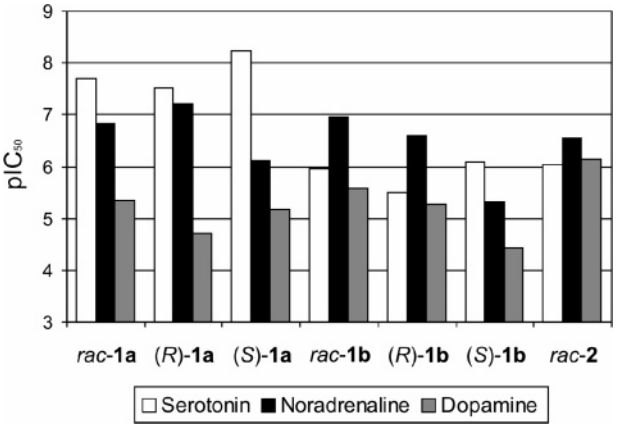

Figure 8. In vitro efficacy of compounds *rac*-**1a**, (*R*)-**1a**, (*S*)-**1a**, *rac*-**1b**, (*R*)-**1b**, (*S*)-**1b**, and *rac*-**2** regarding serotonin, noradrenaline, and dopamine reuptake inhibition. pIC_{50} denotes the negative decadic logarithm of the half-maximum effect concentration [M]. The monoamine reuptake inhibition profiles of *rac*-**1a**, (*R*)-**1a**, (*S*)-**1a**, *rac*-**1b**, (*R*)-**1b**, (*S*)-**1b**, and *rac*-**2** were generated via radioligand transporter assays using recombinant human monoamine transporter proteins. The data represent the mean of at least 2 determinations.

compound *rac*-**2** (a derivative of *rac*-**1b** with a silacyclopentane instead of a silacyclohexane ring), which displays a profile comparable to that of *rac*-**1b**.

The impact of sila-substitution on the activities of the venlafaxine enantiomers (*R*)-**1a** and (*S*)-**1a** dramatically influences their pharmacological selectivity profiles. (*S*)-Venlafaxine ((*S*)-**1a**) is a potent and selective serotonin reuptake inhibitor (SSRI), being about 100-fold and 1000-fold more potent at serotonin transporters than noradrenaline and dopamine transporters, respectively. The reduction in potency of (*S*)-sila-venlafaxine ((*S*)-**1b**) for the serotonin transporter renders this compound a mixed serotonin/noradrenaline reuptake inhibitor with only about 50-fold and 6-fold, respectively, selectivity over dopamine and noradrenaline transporters. (*R*)-Venlafaxine ((*R*)-**1a**) was also found to be a mixed serotonin/noradrenaline reuptake inhibitor, with approximately 500-fold selectivity over dopamine receptors, whereas (*R*)-sila-venlafaxine ((*R*)-**1b**) has a totally different selectivity profile.

These studies have identified (*R*)-**1b** to have a refined selectivity profile consistent with selective noradrenaline reuptake inhibition being approximately 10-fold more potent at noradrenaline transporters than serotonin and dopamine transporters. Compounds with this profile may provide therapeutic benefit in the treatment of various CNS disorders. Comprehensive biological data of (*R*)-sila-venlafaxine, including in vivo data, will be published elsewhere.

Experimental Section

Chemistry: General Procedures. Except for the hydrolyses *rac*-**9** → *rac*-**1b** and *rac*-**14** → *rac*-**2**, all syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. A Büchi GKR 50 apparatus was used for the bulb-to-bulb distillations. Melting points were determined with a Büchi Melting Point B-540 apparatus in open glass capillaries. The ^{1}H, ^{13}C, ^{15}N, and ^{29}Si NMR spectra were recorded on a Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{15}N, 30.4 MHz; ^{29}Si, 59.6 MHz). $CDCl_3$, CD_2Cl_2, [D_8]THF, or [D_6]DMSO were used as the solvent. Unless otherwise stated, spectra were recorded at 22 °C. Chemical shifts were determined relative to internal $CHCl_3$ (^{1}H, δ 7.24; $CDCl_3$), internal $CDCl_3$ (^{13}C, δ 77.0; $CDCl_3$), internal $CHDCl_2$ (^{1}H, δ 5.32; CD_2Cl_2), internal CD_2Cl_2 (^{13}C, δ 53.8; CD_2Cl_2), internal [D_7]THF (^{1}H, δ 1.73; [D_8]THF), internal [D_8]THF (^{13}C, δ 25.3; [D_8]THF), internal [D_5]DMSO (^{1}H, δ 2.49; [D_6]DMSO), internal [D_6]DMSO (^{13}C, δ 39.5; [D_6]DMSO), external formamide (^{15}N, δ −268.0; $CDCl_3$, [D_6]DMSO), or external TMS (^{29}Si, δ 0; $CDCl_3$, CD_2Cl_2, [D_6]DMSO, [D_8]THF). Analysis and assignment of the ^{1}H NMR data were supported by $^{1}H,^{1}H$ and $^{13}C,^{1}H$ correlation experiments and partially by simulations using the *WIN-DAISY* software package (version 4.05, Bruker).[10] Assignment of the ^{13}C NMR data was supported by DEPT 135 and $^{13}C,^{1}H$ correlation experiments. The $^{2}J_{HH}$ coupling constants reported for the C=CH_2 groups represent absolute values. Specific optical rotations were determined with a Jasco P-1030 polarimeter using a 10 cm cuvette; dichloromethane (spectroscopy grade, stabilized with amylene (25 mg/L); Riedel-deHaën, art. no. 34908) was used as the solvent.

Preparation of *rac*-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexan-1-ol (*rac*-Sila-venlafaxine, *rac*-1b). A 2.7 M solution of *n*-butyllithium in *n*-heptane (35 mL, 94.5 mmol of *n*-BuLi) was added dropwise at −50 °C within 10 min to a stirred solution of dimethylamine (21.6 g, 479 mmol) in tetrahydrofuran (THF) (100 mL). The resulting mixture was warmed to −10 °C within 2 h and then cooled to −40 °C, followed by dropwise addition of **8** (20.0 g, 86.1 mmol) within a period of 15 min (evolution of hydrogen; rise in temperature from −40 to −35 °C). The resulting stirred yellow solution was warmed to −20 °C within 2 h and then kept undisturbed at −26 °C for 16 h. Subsequently, the solvent was removed under reduced pressure in a water bath (5−15 °C) until a residual volume of 50 mL was obtained. This solution was diluted with diethyl ether (200 mL) and then added in one single portion at 0 °C to a stirred two-phase mixture of diethyl ether (50 mL) and 2 M potassium acetate/acetic acid buffer (pH 4.5) (300 mL). The pH of the aqueous phase changed to pH 7.2 within 10 min and was readjusted to pH 5.0 by addition of small portions of glacial acetic acid. The mixture was stirred for a further 1 h at 0 °C, with the pH of the aqueous phase remaining constant at pH 5.0 during this time. The aqueous layer was separated, the organic phase was extracted with 1 M potassium acetate/acetic acid buffer (pH 5.0) (3 × 100 mL), and the aqueous solutions were combined. Diethyl ether (150 mL) was added, and the pH of the aqueous phase was adjusted to pH 10.5 by addition of small portions of a saturated aqueous potassium carbonate solution. The organic layer was separated, the aqueous phase was extracted with diethyl ether (5 × 100 mL), and the organic extracts were combined, followed by addition of *n*-hexane (200 mL). The solvent was removed under reduced pressure in a water bath (5−15 °C) until a residual volume of 100 mL was obtained, whereupon residual water separated from the organic phase (formation of a two-phase system). The organic layer was separated, the aqueous

(10) (a) *WIN-DAISY* 4.05, Bruker-Franzen GmbH: Bremen, Germany, 1998. (b) Weber, U.; Germanus, A.; Thiele, H. *Fresenius J. Anal. Chem.* **1997**, *359*, 46−49.

phase was extracted with *n*-hexane (2 × 100 mL), and the organic solutions were combined. The solvent was removed completely under reduced pressure in a water bath (5−15 °C) to give a colorless oil. Crystallization of this oil from *n*-pentane (400 mL) at −26 °C using seed crystals (obtained by cooling of a solution of oily *rac*-**1b** (3.20 g) in *n*-pentane (5 mL) to −26 °C) afforded *rac*-**1b** in 90% yield as a colorless crystalline solid (22.8 g, 77.7 mmol) (isolated by quick decantation of the cold solvent, followed by drying in vacuo (0.001 mbar, 20 °C, 6 h)); mp 33 °C. ^{1}H NMR ($CDCl_3$): δ 0.44−0.78, 1.00−1.15, and 1.19−1.69 (m, 10 H, Si-(CH_2)$_5$), 2.29 (s, 6 H, NCH_3), 2.44 (δ_C), 2.52 (δ_A), and 3.12 (δ_B) (3 H, $^2J_{AB}$ = −12.1 Hz, $^3J_{AC}$ = 5.0 Hz, $^3J_{BC}$ = 12.1 Hz, SiCH_CCH_AH_BN), 3.75 (s, 3 H, OCH_3), 5.6 (br s, 1 H, SiO*H*), 6.75−6.83 (m, 2 H, *H*-3/*H*-5, Aryl), 6.91−6.98 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR ($CDCl_3$): δ 12.1 (Si*C*H$_2$C), 14.2 (Si*C*H$_2$C), 24.06 (SiCH$_2$*C*H$_2$C), 24.13 (SiCH$_2$*C*H$_2$C), 29.4 (Si(CH$_2$)$_2$*C*H$_2$C), 32.6 (Si*C*HC$_2$), 45.4 (N*C*H$_3$), 55.2 (O*C*H$_3$), 61.8 (N*C*H$_2$C), 113.8 (*C*-3/*C*-5, Aryl), 128.2 (*C*-2/*C*-6, Aryl), 133.0 (*C*-1, Aryl), 157.1 (*C*-4, Aryl). ^{15}N NMR ($CDCl_3$): δ −353. ^{29}Si NMR ($CDCl_3$): δ 10.3. Anal. Calcd for $C_{16}H_{27}NO_2Si$: C, 65.48; H, 9.27; N, 4.77. Found: C, 65.5; H, 9.3; N, 4.8.

Preparation of (*R*)-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexan-1-ol ((*R*)-Sila-venlafaxine, (*R*)-1b). (a) Preparation of Seed Crystals of (*R*)-Sila-venlafaxine·(+)-10-Camphorsulfonic Acid ((*R*)-1b·(+)-CSA). A solution of (+)-10-camphorsulfonic acid ((+)-CSA) (792 mg, 3.41 mmol) in acetone (25 mL) was added at 0 °C to a solution of *rac*-**1b** (1.00 g, 3.41 mmol) in acetone (25 mL). After the mixture was shaken briefly, it was kept undisturbed at 0 °C. After ca. 10 min, thin needle-shaped crystals precipitated. A further 40 mL of acetone was added immediately, and the mixture was then kept undisturbed at 4 °C for 2 days. The precipitate was isolated by filtration, washed with acetone (20 mL), and then recrystallized twice from boiling acetone (45 mL; crystallization at 4 °C over a period of 2 days). (To leave a few seed crystals, the solid was not allowed to dissolve completely in both recrystallization steps.) The product was finally isolated by filtration, washed with acetone (3 mL), and dried in vacuo (0.001 mbar, 20 °C, 6 h) to give 629 mg of a colorless crystalline solid. This material (long, very thin needles) was used as seed crystals in the following protocol.

(b) Preparation of (*R*)-Sila-venlafaxine·(+)-10-Camphorsulfonic Acid ((*R*)-1b·(+)-CSA). A solution of (+)-CSA (4.55 g, 19.6 mmol) in acetone (120 mL) was added at 20 °C to a solution of *rac*-**1b** (5.75 g, 19.6 mmol) in acetone (375 mL). After the mixture was shaken briefly, it was kept undisturbed at 4 °C for 2 h. Subsequently, a few seed crystals (see above) were added, and the mixture was then kept undisturbed at 4 °C for 2 days. The resulting precipitate was isolated by filtration, washed with acetone (2 × 20 mL), and then recrystallized twice from boiling acetone (280 mL; crystallization at 4 °C over a period of 2 days). (To leave a few seed crystals, the solid was not allowed to dissolve completely in these recrystallization steps.) The product was isolated and washed as described above and finally dried in vacuo (0.001 mbar, 20 °C, 6 h) to give (*R*)-**1b**·(+)-CSA in 30% yield (related to *rac*-**1b**) as a colorless crystalline solid (3.10 g, 5.90 mmol); mp 164 °C; $[\alpha]_{589}^{20}$ +7.7 (*c* 2.50, CH_2Cl_2). Anal. Calcd for $C_{26}H_{43}NO_6SSi$: C, 59.39; H, 8.24; N, 2.66; S, 6.10. Found: C, 59.4; H, 8.2; N, 2.7; S, 6.0.

(c) Preparation of (*R*)-Sila-venlafaxine ((*R*)-1b). Diethyl ether (5 mL) was added at 20 °C to a stirred solution of (*R*)-**1b**·(+)-CSA (3.05 g, 5.80 mmol) in water (85 mL), and the pH of the aqueous phase was adjusted to pH 10.5 by addition of a saturated aqueous potassium carbonate solution. The resulting mixture was extracted with diethyl ether (4 × 100 mL), and the organic layers were combined, followed by addition of *n*-hexane (200 mL). The solvent was removed under reduced pressure in a water bath (5−15 °C) until a residual volume of 50 mL was obtained. The mixture was then kept at −20 °C for 3 h (crystallization of the residual water), and the organic supernatant was quickly isolated by decantation and stored separately. The ice was allowed to melt, the resulting aqueous phase was shaken with *n*-hexane (60 mL), and the two-phase system was again kept at −20 °C for 3 h. The decantation procedure was repeated, the organic solutions were combined, and the solvent was removed under reduced pressure in a water bath (5−15 °C). The resulting colorless oil was dissolved in *n*-pentane (35 mL), and the solution was kept undisturbed at −20 °C. After a period of ca. 2−3 h, an oil separated, and a few crystals grew within the oil drops. The mixture was then warmed to 20 °C, whereupon the oil dissolved rapidly, whereas the crystals dissolved only slowly. After most of the crystals were dissolved (except for a few seed crystals), the mixture was again kept undisturbed at −20 °C for 3 days. The resulting product was isolated by decantation and then dried in vacuo (0.001 mbar, 20 °C, 6 h) to give (*R*)-**1b** in 99% yield as a colorless crystalline solid (1.68 g, 5.72 mmol; including workup of the mother liquor by concentrating it to a volume of 10 mL and using the crystallization protocol described above); mp 64−65 °C; $[\alpha]_{589}^{20}$ −40.3 (*c* 2.50, CH_2Cl_2). The NMR data of the product were identical with those obtained for *rac*-**1b**. Anal. Calcd for $C_{16}H_{27}NO_2Si$: C, 65.48; H, 9.27; N, 4.77. Found: C, 65.2; H, 9.1; N, 4.7.

Preparation of (*S*)-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexan-1-ol ((*S*)-Sila-venlafaxine, (*S*)-1b). (a) Preparation of (*S*)-Sila-venlafaxine·(−)-10-Camphorsulfonic Acid ((*S*)-1b·(−)-CSA). The combined mother liquors obtained in the preparation of (*R*)-**1b**·(+)-CSA (see above) were used to prepare (*S*)-**1b**·(−)-CSA. For this purpose, the mother liquors were concentrated under reduced pressure, treated with potassium carbonate as described for the preparation of (*R*)-**1b**, and concentrated again, and the oily residue was then reacted with (−)-CSA analogously to the protocol described for the preparation of (*R*)-**1b**·(+)-CSA. Compound (*S*)-**1b**·(−)-CSA was obtained in 32% yield (related to *rac*-**1b**) as a colorless crystalline solid (3.29 g, 6.26 mmol); mp 164 °C; $[\alpha]_{589}^{20}$ −7.6 (*c* 2.50, CH_2Cl_2). Anal. Calcd for $C_{26}H_{43}NO_6SSi$: C, 59.39; H, 8.24; N, 2.66; S, 6.10. Found: C, 59.3; H, 7.9; N, 2.4; S, 5.9.

(b) Preparation of (*S*)-Sila-venlafaxine ((*S*)-1b). Compound (*S*)-**1b** was prepared from (*S*)-**1b**·(−)-CSA (3.23 g, 6.14 mmol) analogously to the synthesis of (*R*)-**1b** and was isolated in 94% yield as a colorless crystalline solid (1.70 g, 5.79 mmol); mp 64−65 °C; $[\alpha]_{589}^{20}$ +40.3 (*c* 2.50, CH_2Cl_2). The NMR data of the product were identical with those obtained for *rac*-**1b**. Anal. Calcd for $C_{16}H_{27}NO_2Si$: C, 65.48; H, 9.27; N, 4.77. Found: C, 65.2; H, 9.1; N, 4.8.

Preparation of *rac*-[2-(1-Hydroxy-1-sila-1-cyclohexyl)-2-(4-methoxyphenyl)ethyl]dimethylammonium Chloride (*rac*-Sila-venlafaxine Hydrochloride, *rac*-1b·HCl). A 2 M ethereal hydrogen chloride solution (23 mL, 46.0 mmol of HCl) was added in one single portion at 20 °C to a stirred solution of *rac*-**1b** (12.9 g, 44.0 mmol) in dichloromethane (200 mL). The resulting solution was cooled to −11 °C, and a few seed crystals (obtained from 20 μL of the reaction mixture by slow evaporation of the solvent at 20 °C) were added. The mixture was kept undisturbed for 1 day at −11 °C and then for a further 1 day at −27 °C. The resulting precipitate was isolated by filtration at −27 °C, washed with ice-cold acetone (20 mL), and dried in vacuo (0.001 mbar, 20 °C, 6 h) to give *rac*-**1b**·HCl in 90% yield (including workup of the mother liquor) as a colorless crystalline solid (13.0 g, 39.4 mmol); mp 160 °C. ^{1}H NMR ([D$_6$]DMSO):[11] δ 0.25−0.41, 0.50−0.69, and 1.13−

(11) The ^{1}H NMR data of *rac*-**1b**·HCl, (*R*)-**1b**·HCl, (*S*)-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2**·HCl depend significantly on the concentration of these compounds, especially for the SiCH_CCH_AH_BNH_G(C(H_M)$_3$(C(H_N)$_3$) moiety. The data given were obtained at a concentration of 80 mM. The $^3J_{AG}$ and $^3J_{BG}$ couplings are not resolved, but recognizable by line broadening of the signals for the CH_AH_BN protons.

1.70 (m, 10 H, Si(CH_2)$_5$), 2.56 (δ_M), 2.61 (δ_N), 2.74 (δ_C), 3.38 (δ_A), 3.73 (δ_B), and 9.6 (br, δ_G) (10 H, $^2J_{AB}$ = −13.8 Hz, $^3J_{AC}$ = 2.5 Hz, $^3J_{BC}$ = 12.7 Hz, $^3J_{GM}$ = 3.2 Hz, $^3J_{GN}$ = 3.5 Hz, SiCH_CCH_ACH_BNH_G(C(H_M)$_3$)(C(H_N)$_3$)), 3.71 (s, 3 H, OCH_3), 6.01 (s, 1 H, SiO*H*), 6.83−6.91 (m, 2 H, *H*-3/*H*-5, Aryl), 7.14−7.22 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR ([D$_6$]DMSO): δ 12.4 (SiCH_2C), 13.2 (SiCH_2C), 23.6 (SiCH$_2$CH_2C), 23.7 (SiCH$_2$CH_2C), 29.2 (Si(CH$_2$)$_2$CH_2C), 30.8 (SiCHCH_2), 41.4 (NCH_3), 43.0 (NCH_3), 54.9 (OCH_3), 57.6 (CCH_2N), 114.0 (*C*-3/*C*-5, Aryl), 128.7 (*C*-2/*C*-6, Aryl), 130.5 (*C*-1, Aryl), 157.2 (*C*-4, Aryl). ^{15}N NMR ([D$_6$]DMSO): δ −338. ^{29}Si NMR ([D$_6$]DMSO): δ 2.8. Anal. Calcd for $C_{16}H_{28}ClNO_2Si$: C, 58.25; H, 8.55; N, 4.25. Found: C, 58.1; H, 8.4; N, 4.3.

Preparation of (*R*)-[2-(1-Hydroxy-1-sila-1-cyclohexyl)-2-(4-methoxyphenyl)ethyl]dimethylammonium Chloride ((*R*)-Sila-venlafaxine Hydrochloride, (*R*)-1b·HCl). Method A. A 2 M ethereal hydrogen chloride solution (1.8 mL, 3.6 mmol of HCl) was added at 20 °C to a solution of (*R*)-**1b** (1.00 g, 3.41 mmol) in dichloromethane (19 mL), and the resulting mixture was shaken briefly. Upon vapor diffusion of diethyl ether into this mixture at 20 °C over a period of 6 days, a crystalline product was obtained, which was isolated by filtration, washed with diethyl ether (40 mL), and finally dried in vacuo (0.001 mbar, 20 °C, 6 h) to give (*R*)-**1b**·HCl in 93% yield as a colorless crystalline solid (1.04 g, 3.15 mmol); mp 174 °C; $[\alpha]_{589}^{20}$ −29.3 (*c* 1.00, CH_2Cl_2). ^{1}H NMR ([D$_6$]-DMSO):[11,12] δ 0.25−0.41, 0.50−0.69, and 1.13−1.70 (m, 10 H, Si(CH_2)$_5$), 2.56 (br, δ_M), 2.61 (br, δ_N), 2.74 (δ_C), 3.38 (δ_A), 3.73 (δ_B), and 9.6 (br, δ_G) (10 H, $^2J_{AB}$ = −14.2 Hz, $^3J_{AC}$ = 2.6 Hz, $^3J_{BC}$ = 12.7 Hz, $^3J_{GM}$ and $^3J_{GN}$ not resolved, SiCH_CCH_ACH_BNH_G-(C(H_M)$_3$)(C(H_N)$_3$)), 3.71 (s, 3 H, OCH_3), 6.01 (s, 1 H, SiO*H*), 6.83−6.91 (m, 2 H, *H*-3/*H*-5, Aryl), 7.14−7.22 (m, 2 H, *H*-2/*H*-6, Aryl). The ^{13}C and ^{29}Si NMR data were identical with those obtained for *rac*-**1b**·HCl. Anal. Calcd for $C_{16}H_{28}ClNO_2Si$: C, 58.25; H, 8.55; N, 4.25. Found: C, 58.4; H, 8.4; N, 4.4. **Method B.** A 2.1 M ethereal hydrogen chloride solution (17.5 mL, 36.8 mmol of HCl) was added at 20 °C (water bath) to a stirred solution of (*R*)-**1b** (10.2 g, 34.8 mmol) in THF/dichloromethane (9:1, v/v) (228 mL), and the resulting mixture was stirred moderately for 5 s and then cooled to 0 °C (spontaneous crystallization). The mixture was kept undisturbed at 0 °C for 1 h and then at 4 °C for 16 h. The precipitate was isolated by suction filtration, washed with diethyl ether (2 × 40 mL), and dried in vacuo (0.001 mbar, 20 °C, 4 h) to give (*R*)-**1b**·HCl in 95% yield as a colorless crystalline solid (10.9 g, 33.0 mmol); mp 180−181 °C; $[\alpha]_{589}^{20}$ −29.3 (*c* 1.00, CH_2Cl_2). The NMR data of the product were identical with those obtained for (*R*)-**1b**·HCl synthesized according to Method A. Anal. Calcd for $C_{16}H_{28}ClNO_2Si$: C, 58.25; H, 8.55; N, 4.25. Found: C, 58.1; H, 8.5; N, 4.3.

Preparation of (*R*)-[2-(1-Hydroxy-1-sila-1-cyclohexyl)-2-(4-methoxyphenyl)ethyl]dimethylammonium Bromide ((*R*)-Sila-venlafaxine Hydrobromide, (*R*)-1b·HBr). A solution of triphenylphosphonium bromide (586 mg, 1.71 mmol) in dichloromethane (10 mL) was added at 20 °C in one single portion to a solution of (*R*)-**1b** (501 mg, 1.71 mmol) in dichloromethane (5 mL). The resulting mixture was stirred at 20 °C for 10 min, ethyl acetate was added (30 mL), and the solvent was removed under reduced pressure in a water bath (5−15 °C) until a residual volume of 15 mL was obtained (partial precipitation of (*R*)-**1b**·HBr). A further 30 mL of ethyl acetate was added, and the solution was concentrated again under reduced pressure (water bath, 5−15 °C) until a residual volume of 15 mL was obtained (almost quantitative precipitation of (*R*)-**1b**·HBr). The solvent was removed by decantation, and the precipitate was washed with diethyl ether (2 × 10 mL; separation by decantation), dried in vacuo (0.001 mbar, 20 °C, 1 h), and then redissolved in dichloromethane (6 mL). Upon vapor diffusion of diethyl ether into the resulting solution at 20 °C, crystals precipitated, which were isolated by filtration to give (*R*)-**1b**·HBr in 90% yield as a colorless crystalline solid (573 mg, 1.53 mmol); mp 152−153 °C; $[\alpha]_{589}^{20}$ −20.8 (*c* 2.50, CH_2Cl_2). ^{1}H NMR ([D$_6$]DMSO):[11] δ 0.26−0.43, 0.50−0.70, and 1.13−1.70 (m, 10 H, Si(CH_2)$_5$), 2.65 (br s, 6 H, NCH_3), 2.68 (δ_C), 3.36 (δ_A), and 3.79 (δ_B) (3 H, $^2J_{AB}$ = −13.6 Hz, $^3J_{AC}$ = 2.9 Hz, $^3J_{BC}$ = 13.3 Hz, SiCH_CCH_ACH_BN), 3.72 (s, 3 H, OCH_3), 5.9 (br s, 1 H, SiO*H*), 6.84−6.92 (m, 2 H, *H*-3/*H*-5, Aryl), 7.15−7.23 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR ([D$_6$]-DMSO): δ 12.4 (SiCH_2C), 13.2 (SiCH_2C), 23.5 (SiCH$_2$CH_2C), 23.7 (SiCH$_2$CH_2C), 29.1 (Si(CH$_2$)$_2$CH_2C), 30.7 (SiCHCH_2), 40.8 (NCH_3), 43.8 (NCH_3), 55.0 (OCH_3), 57.7 (CCH_2N), 114.1 (*C*-3/*C*-5, Aryl), 128.8 (*C*-2/*C*-6, Aryl), 129.7 (*C*-1, Aryl), 157.3 (*C*-4, Aryl). ^{29}Si NMR ([D$_6$]DMSO): δ 2.9. Anal. Calcd for $C_{16}H_{28}BrNO_2Si$: C, 51.33; H, 7.54; N, 3.74. Found: C, 51.0; H, 7.3; N, 3.8.

Preparation of (*S*)-[2-(1-Hydroxy-1-sila-1-cyclohexyl)-2-(4-methoxyphenyl)ethyl]dimethylammonium Chloride ((*S*)-Sila-venlafaxine Hydrochloride, (*S*)-1b·HCl). This compound was prepared from (*S*)-**1b** analogously to the protocols used for the preparation of (*R*)-**1b**·HCl. **Method A.** Compound (*S*)-**1b**·HCl was synthesized from (*S*)-**1b** (1.00 g, 3.41 mmol) and isolated in 92% yield as a colorless crystalline solid (1.03 g, 3.12 mmol); mp 174 °C; $[\alpha]_{589}^{20}$ +29.3 (*c* 1.00, CH_2Cl_2). The NMR data of the product were identical with those obtained for (*R*)-**1b**·HCl. Anal. Calcd for $C_{16}H_{28}ClNO_2Si$: C, 58.25; H, 8.55; N, 4.25. Found: C, 58.0; H, 8.2; N, 4.0. **Method B.** Compound (*S*)-**1b**·HCl was synthesized from (*S*)-**1b** (8.95 g, 30.5 mmol) and isolated in 89% yield as a colorless crystalline solid (8.93 g, 27.1 mmol); mp 180−181 °C; $[\alpha]_{589}^{20}$ +29.3 (*c* 1.00, CH_2Cl_2). The NMR data of the product were identical with those obtained for (*R*)-**1b**·HCl. Anal. Calcd for $C_{16}H_{28}ClNO_2Si$: C, 58.25; H, 8.55; N, 4.25. Found: C, 58.0; H, 8.3; N, 4.3.

Preparation of *rac*-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclopentan-1-ol (*rac*-2). This compound was prepared analogously to the synthesis of *rac*-**1b** (**13** (2.54 g, 11.6 mmol), dimethylamine (8.07 g, 179 mmol), a 1.6 M solution of *n*-butyllithium in *n*-hexane (8.0 mL, 12.8 mmol of *n*-BuLi), THF (65 mL)). The oily crude product crystallized from *n*-pentane (45 mL; −11 °C (1 h) → −26 °C (1 day)), and compound *rac*-**2** was isolated in 54% yield as a colorless crystalline solid (1.77 g, 6.33 mmol); mp 37 °C. ^{1}H NMR ($CDCl_3$):[13] δ 0.32−0.65 (m, 4 H, SiCH_2C), 0.70−0.88, 0.95−1.11, and 1.31−1.49 (m, 4 H, SiCH$_2$CH_2C), 2.32 (s, 6 H, NCH_3), 2.52−2.68 (m, 2 H, SiC*H*-C*H*HN), 3.12−3.28 (m, 1 H, SiCHCH*H*N), 3.75 (s, 3 H, OCH_3), 6.3 (br s, 1 H, SiO*H*), 6.74−6.81 (m, 2 H, *H*-3/*H*-5, Aryl), 6.91−6.98 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR ($CDCl_3$):[13] δ 9.8 (SiCH_2C), 11.0 (SiCH_2C), 25.56 (SiCH$_2$CH_2C), 25.60 (SiCH$_2$CH_2C), 31.1 (SiCHCH_2), 45.4 (NCH_3), 55.1 (OCH_3), 61.9 (CCH_2N), 113.5 (*C*-3/*C*-5, Aryl), 128.0 (*C*-2/*C*-6, Aryl), 132.0 (*C*-1, Aryl), 156.6 (*C*-4, Aryl). ^{29}Si NMR ($CDCl_3$):[13] δ 34.4. Anal. Calcd for $C_{15}H_{25}NO_2Si$: C, 64.47; H, 9.02; N, 5.01. Found: C, 64.6; H, 9.1; N, 5.1.

Preparation of [2-(1-Hydroxy-1-sila-1-cyclopentyl)-2-(4-methoxyphenyl)ethyl]dimethylammonium Chloride (*rac*-2·HCl). A 2 M ethereal hydrogen chloride solution (2.0 mL, 4.0 mmol of HCl) was added at 20 °C in one single portion to a stirred solution of *rac*-**2** (1.02 g, 3.65 mmol) in dichloromethane (16 mL). The mixture was kept undisturbed at −27 °C for 2 h, and a few seed crystals (obtained from 20 μL of the reaction mixture by slow evaporation of the solvent at 20 °C, followed by cooling of the resulting oil to −27 °C) were added. The resulting mixture was kept undisturbed at −27 °C for 3 days, and the precipitate was isolated by filtration at −27 °C, washed with ice-cold acetone (10 mL), and then dried

(12) The ^{1}H NMR spectra of (*R*)-**1b**·HCl and (*S*)-**1b**·HCl differ slightly from the ^{1}H NMR spectrum of *rac*-**1b**·HCl in the SiCH$_C$CH$_A$H$_B$NH$_G$-(C(H_M)$_3$)(C(H_N)$_3$) region. This could be explained by the existence of different aggregates in solution ((*R*)-**1b**·HCl and (*S*)-**1b**·HCl, exclusively (*R*,*R*)- or (*S*,*S*)-aggregates; *rac*-**1b**·HCl, (*R*,*R*)-, (*S*,*S*)-, and (*R*,*S*)-aggregates).

(13) As significant disiloxane formation was observed at 22 °C in $CDCl_3$, the NMR spectra of *rac*-**2** were recorded at −20 °C.

in vacuo (0.001 mbar, 20 °C, 6 h) to give *rac*-**2**·HCl in 52% yield as a colorless crystalline solid (598 mg, 1.89 mmol); mp 153−154 °C. ^{1}H NMR ([D$_6$]DMSO):[11] δ 0.18−0.62 (m, 4 H, SiCH_2C), 1.06−1.27 and 1.32−1.55 (m, 4 H, SiCH$_2$CH_2C), 2.6 (br s, 6 H, NCH_3), 2.82 (δ_C), 3.43 (δ_A), and 3.82 (δ_B) (3 H, $^2J_{AB}$ = −13.5 Hz, $^3J_{AC}$ = 2.6 Hz, $^3J_{BC}$ = 12.7 Hz, SiCH_CC$H_A$$H_B$N), 3.71 (s, 3 H, OC$H_3$), 6.2 (br s, 1 H, SiO*H*), 6.82−6.90 (m, 2 H, *H*-3/*H*-5, Aryl), 7.17−7.25 (m, 2 H, *H*-2/*H*-6, Aryl), 9.5 (br s, 1 H, N*H*). ^{13}C NMR ([D$_6$]-DMSO): δ 10.4 (SiCH$_2$C), 10.9 (SiCH$_2$C), 25.36 (SiCH$_2$$CH_2$C), 25.43 (SiCH$_2$$CH_2$C), 31.7 (Si$CHC_2$), 41.5 (N$CH_3$), 43.1 (N$CH_3$), 55.0 (O$CH_3$), 57.5 (C$CH_2$N), 114.1 (*C*-3/*C*-5, Aryl), 128.9 (*C*-2/*C*-6, Aryl), 130.0 (*C*-1, Aryl), 157.3 (*C*-4, Aryl). ^{29}Si NMR ([D$_6$]-DMSO): δ 25.1. Anal. Calcd for $C_{15}H_{26}ClNO_2Si$: C, 57.03; H, 8.30; N, 4.43. Found: C, 56.6; H, 7.9; N, 4.4.

Preparation of 1,1-Dichloro-1-silacyclohexane (3).[14] A portion of 50 mL of a solution of 1,5-dibromopentane (161 g, 700 mmol) in diethyl ether (300 mL) was added to a stirred suspension of magnesium turnings (37.4 g, 1.54 mol) in diethyl ether (400 mL), and the reaction was started by gentle heating. Subsequently, the remaining 1,5-dibromopentane solution was added within 2 h, causing the mixture to boil under reflux. After the addition was complete, the mixture was heated under reflux for a further 90 min and then cooled to 20 °C within 1 h. The resulting two-phase Grignard reagent (which was separated from residual magnesium turnings by decantation, followed by washing of the magnesium with diethyl ether (2 × 50 mL)) was added dropwise within 2 h to a solution of tetrachlorosilane (131 g, 771 mmol) in diethyl ether (300 mL), causing the mixture to boil under reflux. During the addition, the mixture was stirred vigorously with a mechanical stirrer (formation of a precipitate). The mixture was stirred at 20 °C for 16 h, and the precipitate was separated by filtration and washed with diethyl ether (2 × 200 mL). The filtrate and the wash solutions were combined, and the solvent was removed by distillation under atmospheric pressure, causing a postprecipitation. The precipitate was separated by decantation and washed with *n*-pentane (2 × 50 mL), and the organic solutions were combined. The solvent was removed as described above, and the crude product was isolated by distillation under atmospheric pressure; bp 166−178 °C. Redistillation (Vigreux column, 30 cm) under reduced pressure afforded **3** in 62% yield (related to 1,5-dibromopentane) as a colorless liquid (72.9 g, 431 mmol); bp 70−71 °C/37 mbar. ^{1}H NMR ($CDCl_3$): δ 1.13−1.22 (m, 4 H, SiCH_2C), 1.43−1.52 (m, 2 H, Si(CH$_2$)$_2$CH_2C), 1.77−1.87 (m, 4 H, SiCH$_2$CH_2C). ^{13}C NMR ($CDCl_3$): δ 20.2 (SiCH$_2$C), 24.0 (SiCH$_2$$CH_2$C), 28.6 (Si(CH$_2$)$_2$$CH_2$C). ^{29}Si NMR ($CDCl_3$): δ 28.8. Anal. Calcd for $C_5H_{10}Cl_2Si$: C, 35.51; H, 5.96; Cl, 41.92. Found: C, 35.8; H, 6.1; Cl, 42.2.

Preparation of 1,1-Dimethoxy-1-silacyclohexane (4). Method A.[14] Methanol (34.8 g, 1.09 mol) was added dropwise within 10 min to a stirred solution of **3** (83.2 g, 492 mmol) and triethylamine (110 g, 1.09 mol) in *n*-hexane (500 mL), causing the mixture to boil under reflux (formation of a precipitate). After the addition was complete, the mixture was heated under reflux for a further 2 h and was then cooled to 20 °C within 1 h and left undisturbed at this temperature for 16 h. The precipitate was separated by suction filtration and washed thoroughly with *n*-hexane (1.5 L). The filtrate and the wash solutions were combined, the solvent was removed by distillation under atmospheric pressure (Vigreux column, 20 cm), and the residue was distilled in vacuo (Vigreux column, 20 cm) to give **4** as a crude product (69 g; bp 70−75 °C/30 mbar) that contained small amounts of a solid. The distillate was diluted with *n*-pentane (150 mL), the mixture was kept undisturbed at 4 °C for 16 h, the resulting precipitate was separated by filtration, the filter cake was washed with *n*-pentane (20 mL), and the filtrate and the wash solution were combined. The solvent was removed by distillation under atmospheric pressure (Vigreux column, 30 cm), and the residue was distilled in vacuo (Vigreux column, 30 cm) to give **4** in 80% yield as a colorless liquid (62.8 g, 392 mmol); bp 62 °C/20 mbar. ^{1}H NMR ($CDCl_3$): δ 0.63−0.72 (m, 4 H, SiCH_2C), 1.32−1.43 (m, 2 H, Si(CH$_2$)$_2$CH_2C), 1.62−1.75 (m, 4 H, SiCH$_2$CH_2C), 3.50 (s, 6 H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 11.0 (SiCH$_2$C), 24.6 (SiCH$_2$$CH_2$C), 29.6 (Si(CH$_2$)$_2$$CH_2$C), 50.1 (O$CH_3$). ^{29}Si NMR ($CDCl_3$): δ −5.1. Anal. Calcd for $C_7H_{16}O_2Si$: C, 52.45; H, 10.06. Found: C, 52.6; H, 9.9. **Method B.**[14] A 1,5-bis-(bromomagnesio)pentane reagent was prepared from magnesium turnings (22.0 g, 905 mmol), 1,5-dibromopentane (46.0 g, 200 mmol), and diethyl ether (200 mL) analogously to Method A (see above). The two-phase Grignard reagent was then added at 0 °C over a period of 1 h to a vigorously stirred solution of tetramethoxysilane (45.7 g, 300 mmol) in diethyl ether (500 mL) (formation of a precipitate). After the addition was complete, the mixture was heated under reflux for 16 h and was then cooled to 20 °C within 1 h. The precipitate was separated by filtration and washed with diethyl ether (3 × 50 mL), the filtrate and the wash solutions were combined, the solvent was removed under reduced pressure, and the residue was distilled and then redistilled in vacuo to give **4** in 43% yield (related to 1,5-dibromopentane) as a colorless liquid (13.9 g, 86.7 mmol); bp 75 °C/36 mbar. The NMR data of the product were identical with those obtained for **4** synthesized according to Method A. Anal. Calcd for $C_7H_{16}O_2Si$: C, 52.45; H, 10.06. Found: C, 51.7; H, 9.9.

4-Methoxyacetophenone 2,4,6-Triisopropylbenzenesulfonylhydrazone (5). This compound was synthesized according to ref 15 and was isolated, after recrystallization from boiling methanol (crystallization at 4 °C over a period of 16 h), as a colorless crystalline solid; mp 152−153 °C (dec). ^{1}H NMR (CD_2Cl_2): δ 1.25 (d, $^3J_{HH}$ = 6.8 Hz, 6 H, *p*-CH(CH_3)$_2$), 1.30 (d, $^3J_{HH}$ = 6.8 Hz, 12 H, *o*-CH(CH_3)$_2$), 2.16 (s, 3 H, C(=N)CH_3), 2.92 (septett, $^3J_{HH}$ = 6.8 Hz, 1 H, *p*-CH(CH$_3$)$_2$), 3.80 (s, 3 H, OCH_3), 4.31 (septett, $^3J_{HH}$ = 6.8 Hz, 2 H, *o*-CH(CH$_3$)$_2$), 6.81−6.89 (m, 2 H, *H*-3/*H*-5, C(=N)-Aryl), 7.22 (s, 2 H, S-Aryl), 7.56−7.64 (m, 2 H, *H*-2/*H*-6, C(=N)-Aryl), 7.7 (br s, 1 H, N*H*). ^{13}C NMR (CD_2Cl_2): δ 13.3 (C(=N)CH$_3$), 23.6 (*p*-CH(*C*H$_3$)$_2$), 24.9 (*o*-CH(*C*H$_3$)$_2$), 30.4 (*o*-*C*H(CH$_3$)$_2$), 34.6 (*p*-*C*H(CH$_3$)$_2$), 55.6 (OCH$_3$), 113.9 (*C*-3/*C*-5, C(=N)-Aryl), 124.2 (*C*-3/*C*-5, S-Aryl), 128.0 (*C*-2/*C*-6, C(=N)-Aryl), 130.2 (*C*-1, C(=N)-Aryl), 131.9 (*C*-1, S-Aryl), 151.5 (*C*(=N)CH$_3$), 151.6 (*C*-2/*C*-6, S-Aryl), 153.9 (*C*-4, S-Aryl), 161.2 (*C*-4, C(=N)-Aryl). Anal. Calcd for $C_{24}H_{34}N_2O_3S$: C, 66.94; H, 7.96; N, 6.51; S, 7.45. Found: C, 67.0; H, 8.0; N, 6.6; S, 7.6.

Preparation of 1-Methoxy-1-[1-(4-methoxyphenyl)vinyl]-1-silacyclohexane (7). A 2.7 M solution of *n*-butyllithium in *n*-heptane (70 mL, 189 mmol of *n*-BuLi) was added dropwise at −78 °C within 50 min to a stirred mixture of finely ground **5** (40.0 g, 92.9 mmol), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (40 mL), and *n*-hexane (360 mL). The resulting yellow mixture was stirred at −78 °C for 2 h and then warmed to 0 °C within 90 min (evolution of nitrogen; change of color to orange; formation of [1-(4-methoxyphenyl)vinyl]lithium (**6**)). After the nitrogen evolution was finished, the mixture was stirred for a further 10 min at 20 °C and then added dropwise at 0 °C within 30 min to a stirred solution of **4** (15.0 g, 93.6 mmol) in *n*-hexane (100 mL). The resulting mixture was warmed to 20 °C within 1 h (change of color from orange to yellow within ca. 12 h) and stirred at this temperature for 3 days. The resulting clear yellow solution was cooled in an ice bath, and iodomethane (125 g, 881 mmol) was added (formation of a precipitate). After a period of 2 h, the ice bath was removed and stirring was continued at 20 °C for 1 day. The precipitate was separated by filtration and washed with *n*-hexane (4 × 250 mL), and the filtrate and the wash solutions

(14) For a similar method, see: West, R. *J. Am. Chem. Soc.* **1954**, *76*, 6012−6014.

(15) This procedure follows a general protocol described in: Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147−154 (there referred to as Method A). In this context, see also: Yu, W.-Y.; Bensimon, C.; Alper, H. *Chem. Eur. J.* **1997**, *3*, 417−423.

were combined. The solvent was removed under reduced pressure, and the residue was distilled in vacuo (Kugelrohr apparatus; first fraction, ≤90 °C/0.001 mbar, discarded; second fraction, 90−145 °C/0.001 mbar, crude product). The crude products of three identical runs of this preparation were combined (→ 43.0 g) and distilled in vacuo (Vigreux column, 15 cm) to give **7** in 45% yield (related to **4**) as a colorless oily liquid (33.2 g, 127 mmol); bp 105 °C/0.001 mbar. ^{1}H NMR (CD_2Cl_2): δ 0.71−0.98 (m, 4 H, SiCH_2C), 1.34−1.58 (m, 2 H, Si$(CH_2)_2$CH_2C), 1.62−1.82 (m, 4 H, SiCH_2CH_2C), 3.44 (s, 3 H, SiOCH_3), 3.79 (s, 3 H, COCH_3), 5.64 (δ_A) and 6.02 (δ_B) (2 H, $^2J_{AB}$ = 2.7 Hz, C=C$H_A H_B$), 6.83−6.90 (m, 2 H, *H*-3/*H*-5, Aryl), 7.26−7.33 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR (CD_2Cl_2): δ 12.6 (Si*C*H$_2$C), 24.7 (SiCH$_2$*C*H$_2$C), 30.2 (Si$(CH_2)_2$*C*H$_2$C), 50.6 (SiO*C*H$_3$), 55.5 (CO*C*H$_3$), 114.0 (*C*-3/*C*-5, Aryl), 128.00 (C=*C*H$_2$), 128.05 (*C*-2/*C*-6, Aryl), 135.9 (*C*-1, Aryl), 147.8 (*C*=CH$_2$), 159.1 (*C*-4, Aryl). ^{29}Si NMR (CD_2Cl_2): δ 3.7. Anal. Calcd for $C_{15}H_{22}O_2Si$: C, 68.65; H, 8.45. Found: C, 68.8; H, 8.5.

Preparation of 1-[1-(4-Methoxyphenyl)vinyl]-1-silacyclohexane (8). A solution of **7** (32.0 g, 122 mmol) in diethyl ether (50 mL) was added at 20 °C within 10 min to a stirred suspension of lithium aluminum hydride (LAH) (2.48 g, 65.3 mmol) in diethyl ether (200 mL). The mixture was heated under reflux for 2 h and then added carefully at 0 °C to a stirred mixture of 4 M hydrochloric acid (210 mL) and diethyl ether (100 mL). The organic phase was separated, the aqueous layer was extracted with diethyl ether (3 × 100 mL), and the organic solutions were combined and dried over anhydrous magnesium sulfate in an ice bath, followed by an additional thorough dynamic drying using a chromatographic column densely packed with anhydrous magnesium sulfate (column diameter, 3.5 cm; column length, 15 cm). The magnesium sulfate was finally washed with diethyl ether (500 mL), the organic solutions were combined, the solvent was removed under reduced pressure, and the residue was distilled in vacuo (Vigreux column, 15 cm) to give **8** in 82% yield as a colorless oily liquid (23.3 g, 100 mmol); bp 91−92 °C/0.001 mbar. ^{1}H NMR (CD_2Cl_2): δ 0.68−0.85 and 0.92−1.05 (m, 4 H, SiCH_2C), 1.25−1.41, 1.51−1.72, and 1.80−1.96 (m, 6 H, SiCH_2CH_2CH_2C), 3.80 (s, 3 H, OCH_3), 4.26−4.33 (δ_X), 5.60 (δ_A), and 6.00 (δ_B) (3 H, $^2J_{AB}$ = 2.6 Hz, $^4J_{BX}$ = 0.5 Hz, H_XSiC=C$H_A H_B$), 6.83−6.90 (m, 2 H, *H*-3/*H*-5, Aryl), 7.24−7.31 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR (CD_2Cl_2): δ 10.8 (Si*C*H$_2$C), 25.2 (SiCH$_2$*C*H$_2$C), 30.1 (Si$(CH_2)_2$*C*H$_2$C), 55.5 (O*C*H$_3$), 114.1 (*C*-3/*C*-5, Aryl), 126.9 (C=*C*H$_2$), 127.8 (*C*-2/*C*-6, Aryl), 136.1 (*C*-1, Aryl), 147.6 (*C*=CH$_2$), 159.2 (*C*-4, Aryl). ^{29}Si NMR (CD_2Cl_2): δ −20.1. Anal. Calcd for $C_{14}H_{20}OSi$: C, 72.36; H, 8.67. Found: C, 72.1; H, 8.7.

Preparation of *rac*-1-(Dimethylamino)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexane (*rac*-9). A 1.6 M solution of *n*-butyllithium in *n*-hexane (9.5 mL, 15.2 mmol of *n*-BuLi) was added dropwise at −50 °C within 5 min to a stirred solution of dimethylamine (5.51 g, 122 mmol) in THF (150 mL). The resulting mixture was warmed to −15 °C within 4 h and then cooled to −35 °C, followed by dropwise addition of **8** (3.20 g, 13.8 mmol) within 10 min (evolution of hydrogen; rise in temperature from −35 to −30 °C). The resulting yellow solution was stirred at −30 °C for 3 h and then kept undisturbed at −26 °C for 16 h. Subsequently, the solution was placed in an ice bath and stirred again, followed by addition of chlorotrimethylsilane (1.72 g, 15.8 mmol) in one single portion (change of color from yellow to colorless). The mixture was stirred at 0 °C for 30 min, and the solvent was removed completely under reduced pressure in a water bath (5−15 °C), followed by addition of *n*-hexane (40 mL). The mixture was stirred at 20 °C for 30 min, the resulting precipitate was separated by filtration, and the filter cake was washed with *n*-hexane (20 mL). The filtrate and the wash solution were combined, the solvent was removed completely under reduced pressure in a water bath (5−15 °C), and the residue was distilled in vacuo (Vigreux column, 5 cm) to give *rac*-**9** in 76% yield as a colorless oily liquid (3.37 g, 10.5 mmol); bp 115−118 °C/0.003 mbar. ^{1}H NMR ([D$_8$]THF): δ 0.35−0.75, 0.84−0.97, and 1.12−1.79 (m, 10 H, Si$(CH_2)_5$), 2.12 (s, 6 H, CNCH_3), 2.34 (δ_C), 2.618 (δ_A), and 2.623 (δ_B) (3 H, $^2J_{AB}$ = 0.0 Hz, $^3J_{AC}$ = 7.8 Hz, $^3J_{BC}$ = 9.2 Hz, SiCH_CC$H_A H_B$N), 2.44 (s, 6 H, SiNCH_3), 3.71 (s, 3 H, OCH_3), 6.71−6.78 (m, 2 H, *H*-3/*H*-5, Aryl), 6.89−6.96 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR ([D$_8$]THF): δ 12.0 (Si*C*H$_2$C), 12.8 (Si*C*H$_2$C), 24.9 (SiCH$_2$*C*H$_2$C), 25.0 (SiCH$_2$*C*H$_2$C), 31.1 (Si$(CH_2)_2$*C*H$_2$C), 36.1 (Si*C*HC$_2$), 38.7 (SiN*C*H$_3$), 45.7 (CN*C*H$_3$), 55.1 (O*C*H$_3$), 61.6 (C*C*H$_2$N), 114.0 (*C*-3/*C*-5, Aryl), 129.4 (*C*-2/*C*-6, Aryl), 135.4 (*C*-1, Aryl), 159.2 (*C*-4, Aryl). ^{29}Si NMR ([D$_8$]THF): δ 0.8. Anal. Calcd for $C_{18}H_{32}N_2OSi$: C, 67.45; H, 10.06; N, 8.74. Found: C, 67.3; H, 9.8; N, 8.6.

Preparation of 1,1-Dichloro-1-silacyclopentane (10).[14] This compound was prepared analogously to the synthesis of **3** (1,4-dibromobutane (151 g, 699 mmol), magnesium turnings (37.4 g, 1.54 mol), tetrachlorosilane (131 g, 771 mmol)). After distillation under atmospheric pressure (Vigreux column, 15 cm; 71 g of isolated crude product; bp 141−145 °C) and redistillation in vacuo (Vigreux column, 30 cm), compound **10** was obtained in 61% yield (related to 1,4-dibromobutane) as a colorless liquid (66.2 g, 427 mmol); bp 71−73 °C/100 mbar. ^{1}H NMR ($CDCl_3$): δ 1.09−1.17 (m, 4 H, SiCH_2C), 1.69−1.81 (m, 4 H, SiCH_2CH_2C). ^{13}C NMR ($CDCl_3$): δ 17.9 (Si*C*H$_2$C), 24.8 (SiCH$_2$*C*H$_2$C). ^{29}Si NMR ($CDCl_3$): δ 45.5. Anal. Calcd for $C_4H_8Cl_2Si$: C, 30.98; H, 5.20; Cl, 45.72. Found: C, 31.3; H, 5.2; Cl, 45.5.

Preparation of 1,1-Dimethoxy-1-silacyclopentane (11).[14] This compound was prepared analogously to the synthesis of **4**, Method A (**10** (66.2 g, 427 mmol), methanol (30.4 g, 949 mmol), triethylamine (96.1 g, 950 mmol)). After distillation under atmospheric pressure (Vigreux column, 15 cm; 53 g of isolated crude product; bp 136−144 °C) and redistillation in vacuo, compound **11** was isolated in 74% yield as a colorless liquid (46.2 g, 316 mmol); bp 73 °C/100 mbar. ^{1}H NMR ($CDCl_3$): δ 0.48−0.56 (m, 4 H, SiCH_2C), 1.53−1.62 (m, 4 H, SiCH_2CH_2C), 3.52 (s, 6 H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 7.4 (Si*C*H$_2$C), 24.7 (SiCH$_2$*C*H$_2$C), 50.7 (O*C*H$_3$). ^{29}Si NMR ($CDCl_3$): δ 16.4. Anal. Calcd for $C_6H_{14}O_2Si$: C, 49.27; H, 9.65. Found: C, 49.1; H, 9.6.

Preparation of 1-Methoxy-1-[1-(4-methoxyphenyl)vinyl]-1-silacyclopentane (12). A 2.7 M solution of *n*-butyllithium in *n*-heptane (70 mL, 189 mmol of *n*-BuLi) was added dropwise at −78 °C within 50 min to a stirred mixture of **5** (40.0 g, 92.9 mmol), TMEDA (40 mL), and *n*-hexane (360 mL). The resulting yellow solution was stirred at −78 °C for 2 h and then warmed to 0 °C within 90 min (evolution of nitrogen; change of color to orange; formation of [1-(4-methoxyphenyl)vinyl]lithium (**6**)). After the nitrogen evolution was finished, the mixture was stirred for a further 10 min at 20 °C and then added dropwise at −55 ±5 °C within 30 min to a solution of **11** (14.3 g, 97.8 mmol) in *n*-hexane (200 mL). The resulting mixture was warmed to −30 °C within 2 h and then to 10 °C within a further 15 h, and was finally stirred at 20 °C for 1 day. The resulting clear yellow solution was cooled in an ice bath, and iodomethane (125 g, 881 mmol) was added (formation of a precipitate). After a period of 2 h, the ice bath was removed and stirring was continued at 20 °C for 1 day. The precipitate was separated by filtration and washed with *n*-hexane (4 × 250 mL), and the filtrate and the wash solutions were combined. The solvent was removed under reduced pressure, and the residue was distilled in vacuo (Kugelrohr apparatus; first fraction, ≤90 °C/0.001 mbar, discarded; second fraction, 90−140 °C/0.001 mbar, crude product (15.8 g)). Distillation of this crude product in vacuo (Vigreux column, 15 cm) gave **12** in 45% yield (related to **11**) as a colorless oily liquid (10.9 g, 43.9 mmol); bp 90 °C/0.001 mbar. ^{1}H NMR ($CDCl_3$): δ 0.66−0.89 (m, 4 H, SiCH_2C), 1.52−1.79 (m, 4 H, SiCH_2CH_2C), 3.42 (s, 3 H, SiOCH_3), 3.79 (s, 3 H, COCH_3), 5.70 (δ_A) and 6.05 (δ_B) (2 H, $^2J_{AB}$ = 2.5 Hz, C=C$H_A H_B$), 6.83−6.89 (m, 2 H, *H*-3/*H*-5, Aryl), 7.28−7.35 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C

NMR ($CDCl_3$): δ 10.8 (Si*C*H_2C), 26.1 (SiCH$_2$*C*H_2C), 51.0 (SiO*C*H_3), 55.2 (CO*C*H_3), 113.8 (*C*-3/*C*-5, Aryl), 127.4 (C=*C*H_2), 127.6 (*C*-2/*C*-6, Aryl), 134.9 (*C*-1, Aryl), 147.0 (*C*=CH$_2$), 158.8 (*C*-4, Aryl). ^{29}Si NMR ($CDCl_3$): δ 26.8. Anal. Calcd for $C_{14}H_{20}O_2Si$: C, 67.70; H, 8.12. Found: C, 67.8; H, 8.0.

Preparation of 1-[1-(4-Methoxyphenyl)vinyl]-1-silacyclopentane (13). This compound was prepared analogously to the synthesis of **8** (**12** (10.7 g, 43.1 mmol), LAH (820 mg, 21.6 mmol), diethyl ether (100 mL)) and was isolated in 79% yield as a colorless oily liquid (7.45 g, 34.1 mmol); bp 77 °C/0.001 mbar. ^{1}H NMR (CD_2Cl_2): δ 0.72−1.04 (m, 4 H, SiCH_2C), 1.61−1.73 (m, 4 H, SiCH$_2$CH_2C), 3.80 (s, 3 H, OCH_3), 4.39−4.46 (δ_X), 5.67 (δ_A), and 6.02 (δ_B) (3 H, $^2J_{AB}$ = 2.4 Hz, $^4J_{BX}$ = 0.7 Hz, 2 H, H_XSiC=C$H_A$$H_B$), 6.84−6.91 (m, 2 H, *H*-3/*H*-5, Aryl), 7.25−7.32 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR (CD_2Cl_2): δ 10.2 (Si*C*H_2C), 27.6 (SiCH$_2$*C*H_2C), 55.6 (O*C*H_3), 114.1 (*C*-3/*C*-5, Aryl), 126.6 (C=*C*H_2), 127.8 (*C*-2/*C*-6, Aryl), 135.9 (*C*-1, Aryl), 147.3 (*C*=CH$_2$), 159.3 (*C*-4, Aryl). ^{29}Si NMR (CD_2Cl_2): δ −3.2. Anal. Calcd for $C_{13}H_{18}OSi$: C, 71.50; H, 8.31. Found: C, 71.8; H, 8.3.

Preparation of *rac*-1-(Dimethylamino)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclopentane (*rac*-14). This compound was prepared analogously to the synthesis of *rac*-**9** (**13** (2.52 g, 11.5 mmol), dimethylamine (7.07 g, 157 mmol), a 1.6 M solution of *n*-butyllithium in *n*-hexane (7.9 mL, 12.6 mmol of *n*-BuLi), chlorotrimethylsilane (1.46 g, 13.4 mmol), THF (45 mL)) and was isolated in 60% yield as a colorless oily liquid (2.13 g, 6.95 mmol); bp 112−113 °C/0.001 mbar. ^{1}H NMR ([D$_8$]THF): δ 0.48−0.67 (m, 4 H, SiCH_2C), 1.29−1.59 (m, 4 H, SiCH$_2$CH_2C), 2.12 (s, 6 H, CNCH_3), 2.42 (s, 6 H, SiNCH_3), 2.51 (δ_C), 2.60 (δ_A), and 2.71 (δ_B) (3 H, $^2J_{AB}$ = −12.0 Hz, $^3J_{AC}$ = 6.7 Hz, $^3J_{BC}$ = 9.6 Hz, SiCH_CC$H_A$$H_B$N), 3.70 (s, 3 H, OC$H_3$), 6.71−6.78 (m, 2 H, *H*-3/*H*-5, Aryl), 6.95−7.01 (m, 2 H, *H*-2/*H*-6, Aryl). ^{13}C NMR ([D$_8$]-THF): δ 10.6 (Si*C*H$_2$C), 11.1 (Si*C*H$_2$C), 27.3 (SiCH$_2$*C*H$_2$C), 27.5 (SiCH$_2$*C*H$_2$C), 35.8 (Si*C*HC$_2$), 39.4 (SiN*C*H$_3$), 45.7 (CN*C*H$_3$), 55.1 (O*C*H$_3$), 61.7 (C*C*H$_2$N), 114.1 (*C*-3/*C*-5, Aryl), 129.5 (*C*-2/*C*-6, Aryl), 135.4 (*C*-1, Aryl), 158.1 (*C*-4, Aryl). ^{29}Si NMR ([D$_8$]THF): δ 23.8. Anal. Calcd for $C_{17}H_{30}N_2OSi$: C, 66.61; H, 9.86; N, 9.14. Found: C, 66.2; H, 9.6, N, 8.8.

Determination of Enantiomeric Purities. Compounds *rac*-**1b**, (*R*)-**1b**, or (*S*)-**1b** (10.0 mg, 34.1 μmol) and (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol ((*R*)-(−)-TFAE; 26.4 mg, 95.6 μmol; 2.8 molar equiv) were dissolved in $CDCl_3$ (700 μL), and the solutions were studied at 22 °C by ^{1}H NMR spectroscopy (300.1 MHz). The ^{1}H NMR resonance signals for the NCH_3 groups were used as the probe to determine the enantiomeric purities of (*R*)-**1b** and (*S*)-**1b**. When measuring a sample of *rac*-**1b**, baseline separation for the NCH_3 signals was found for the diastereomeric solvates (*R*)-**1b**·(*R*)-(−)-TFAE (δ 2.13 ppm) and (*S*)-**1b**·(*R*)-(−)-TFAE (δ 2.10 ppm).

Crystal Structure Analyses. Suitable single crystals of *rac*-**1b**·HCl were obtained by cooling of a boiling saturated solution of *rac*-**1b**·HCl in dichloromethane to 4 °C. Single crystals of *rac*-**2** were grown by cooling of a solution of *rac*-**2** (934 mg) in *n*-pentane (3 mL) to 4 °C. Suitable single crystals of (*R*)-**1b**·HBr were obtained directly from the preparation of this compound (see above). The crystals were mounted in inert oil on a glass fiber and then transferred to the cold nitrogen gas stream of the diffractometer (Stoe IPDS; graphite-monochromated Mo Kα radiation (λ = 0.71073 Å)). The structures were solved by direct methods.[16,17] All non-hydrogen atoms were refined anisotropically.[18] A riding model was employed in the refinement of the C*H* and O*H* hydrogen atoms.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-293029 (*rac*-**1b**·HCl), CCDC-293030 ((*R*)-**1b**·HBr), and CCDC-293031 (*rac*-**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223/336033; e-mail: deposit@ccdc.cam.ac.uk).

Determination of pK_a, log *P*, and log *D* Values. All physicochemical measurements were performed on a Sirius GlpKa instrument (Sirius Analytical Instruments Ltd., UK). The pK_a data were measured by a combination of pH-metric and UV titrations in water/methanol mixtures to ensure complete dissolution. The pK_a values found were calculated at 0% cosolvent using a Yasuda-Shedlovsky extrapolation (in this context, see ref 19). The log *P* measurements were performed using *n*-octanol/aqueous buffer mixtures. The log *P* value is calculated from the ratio of *n*-octanol to water and the difference between the aqueous and the apparent pK_a value. The log *D* values are calculated from data measured in different ratios of *n*-octanol to water.

Pharmacological Studies. Receptor binding activities were determined using radioligand cellular uptake inhibition assays using contract research services (MDS Pharma Services, Taipei, Taiwan). Radioactivity levels were detected by scintillation counting. The experimental conditions for each assay are given in Table 4.

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Supporting Information Available: Tables of atomic coordinates and equivalent isotropic displacement parameters, anisotropic displacement parameters, experimental details of the X-ray diffraction studies, and bond lengths and angles for *rac*-**1b**·HCl, (*R*)-**1b**·HBr, and *rac*-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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