Synthesis and Pharmacological Characterization of Sila-panamesine, a Sila-Analogue of the σ Receptor Ligand Panamesine (EMD 57445)

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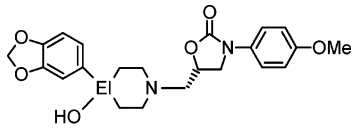
Sila-substitution (C/Si exchange) at the 4-position of the piperidine skeleton of the σ receptor ligand panamesine (**1a**, EMD 57445) leads to sila-panamesine (**1b**). Compounds **1a** and **1b** were synthesized in multistep syntheses, starting from 1-benzyl-4-piperidone and tetramethoxysilane, respectively, and were isolated as the hydrochlorides **1a**·HCl and **1b**·HCl. ESI-MS studies of aqueous solutions of the silanol **1b** and the corresponding disiloxane **14** at different pH values revealed a remarkable stability of **1b**. The identities of **1a**·HCl and **1b**·HCl were established by elemental analyses and multinuclear NMR studies. The σ_1 and σ_2 receptor affinities of the C/Si analogues panamesine (**1a**) and sila-panamesine (**1b**) were determined in competitive radioligand receptor binding studies. It was shown that the C/Si exchange results in a 3-fold enhancement of σ_1 receptor affinity.

Introduction

According to the classical dopamine hypothesis of schizophrenia, classical neuroleptics bind to the dopamine D_2 receptor. However, there are also several neuroleptic drugs, including the "typical" neuroleptic haloperidol and the "atypical" neuroleptic clozapine, that exhibit high affinity for other receptors. Panamesine (EMD 57445, **1a**) has been reported to be a selective σ receptor ligand with the profile of an atypical neuroleptic that shows almost no binding to the dopamine D_2 receptor.[1−3] Panamesine has been studied extensively in animals[4−10] and in clinical trials[11−15] in patients with schizophrenia. As sila-substitution of drugs (carbon/silicon switch) has been demonstrated to affect pharmacological selectivity profiles and thus to be a novel powerful tool for drug design,[16,17] we were interested in the biological properties of the silicon analogue sila-panamesine (**1b**). We report here on the synthesis and pharmacological characterization of the C/Si analogues panamesine hydrochloride (**1a**·HCl) and sila-panamesine hydrochloride (**1b**·HCl).[18]



El = C: Panamesine (**1a**)
El = Si: Sila-panamesine (**1b**)

Results and Discussion

Syntheses. The synthesis of panamesine (**1a**) has been reported in the patent literature;[19,20] however, no experimental details have been given. Thus, for this study a reliable synthesis of **1a** had to be developed.

Panamesine (**1a**) was synthesized in a multistep synthesis, starting from 1-benzyl-4-piperidone (**2**), and was isolated as the hydrochloride **1a**·HCl (Scheme 1). Treatment of **2** with (3,4-methylenedioxyphenyl)magnesium bromide in tetrahydrofuran (THF) gave 1-benzyl-4-hydroxy-4-(3,4-methylenedioxyphenyl)-piperidine (**3**) (yield 62%), which upon reaction with hydrogen in methanol/hydrochloric acid, in the presence of palladium on carbon, yielded 4-hydroxy-4-(3,4-methylenedioxyphenyl)piperidinium chloride (**4**) (yield 68%). Reaction of **4** with (*R*)-(3-(4-methoxyphenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl methanesulfonate (**5**) in acetonitrile, in the presence of potassium carbonate

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(1) Prücher, H.; Gottschlich, R.; Haase, A.; Stohrer, M.; Seyfried, C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 165−170.
(2) Bartoszyk, G. D.; Bender, H. M.; Hellmann, J.; Schnorr, C.; Seyfried, C. A. *CNS Drug Rev.* **1996**, *2*, 175−194.
(3) Van Amsterdam, C. (Merck Patent GmbH, Darmstadt, Germany) PCT Int. Pat. Appl. WO 02/30422 A1 (April 18, 2002).
(4) Dahmen, N.; Fischer, V.; Hödl, P.; Rujescu, D.; Reuss, S.; Bartoszyk, G. D.; Hiemke, C. *Eur. Neuropsychopharmacol.* **1996**, *6*, 237−243.
(5) Maj, J.; Rogóż, Z.; Skuza, G.; Mazela, H. *Eur. J. Pharmacol.* **1996**, *315*, 235−243.
(6) Skuza, G.; Rogóż, Z. *Pol. J. Pharmacol.* **1997**, *49*, 329−335.
(7) Skuza, G.; Rogóż, Z.; Golembiowska, K. *Pol. J. Pharmacol.* **1997**, *49*, 489−493.
(8) Skuza, G.; Golembiowska, K.; Wędzony, K. *Pol. J. Pharmacol.* **1998**, *50*, 61−64.
(9) Skuza, G.; Kolasiewicz, W.; Dziedzicka-Wasylewska, M.; Margas, W. *Pol. J. Pharmacol.* **1998**, *50*, 399−406.
(10) Skuza, G. *Pol. J. Pharmacol.* **1999**, *51*, 477−483.
(11) Frieboes, R.-M.; Murck, H.; Wiedemann, K.; Holsboer, F.; Steiger, A. *Psychopharmacology (Berlin)* **1997**, *132*, 82−88.
(12) Frieboes, R.-M.; Murck, H.; Antonijevic, I.; Kraus, T.; Hinze-Selch, D.; Pollmächer, T.; Steiger, A. *Psychopharmacology (Berlin)* **1999**, *141*, 107−110.
(13) Gründer, G.; Müller, M.-J.; Andreas, J.; Heydari, N.; Wetzel, H.; Schlösser, R.; Schlegel, S.; Nickel, O.; Eissner, D.; Benkert, O. *Psychopharmacology (Berlin)* **1999**, *146*, 81−86.
(14) Huber, M. T.; Gotthardt, U.; Schreiber, W.; Krieg, J.-C. *Pharmacopsychiatry* **1999**, *32*, 68−72.
(15) Müller, M. J.; Gründer, G.; Wetzel, H.; Müller-Siecheneder, F.; Marx-Dannigkeit, P.; Benkert, O. *Psychiatry Res.* **1999**, *89*, 275−280.
(16) Reviews dealing with sila-substituted drugs: (a) Bains, W.; Tacke, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 526−543. (b) Showell, G. A.; Mills, J. S. *Drug Discovery Today* **2003**, *8*, 551−556. (c) Mills, J. S.; Showell, G. A. *Expert Opin. Investig. Drugs* **2004**, *13*, 1149−1157. (d) Englebienne, P.; Van Hoonacker, A.; Herst, C. V. *Drug Design Rev.−Online* **2005**, *2*, 467−483.

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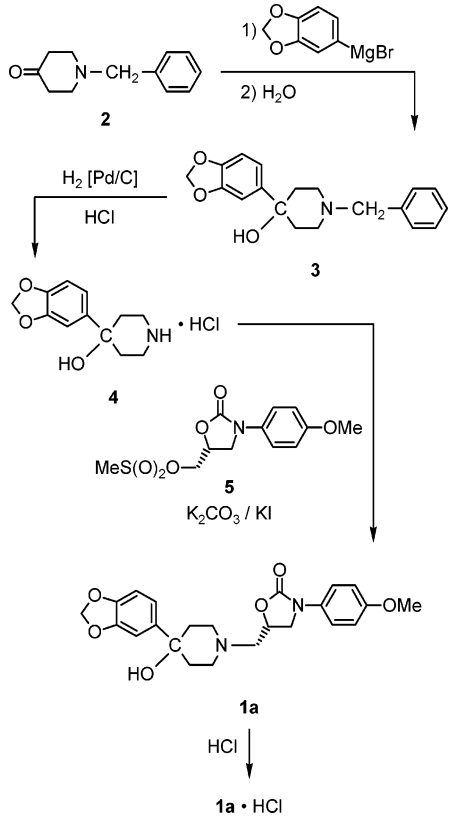
Scheme 1



and potassium iodide, gave (*S*)-5-(4-hydroxy-4-(3,4-methylenedioxyphenyl)piperidin-1-yl)methyl-3-(4-methoxyphenyl)-1,3-oxazolidin-2-one (panamesine, **1a**) (yield 62%), which upon treatment with hydrogen chloride in diethyl ether/dichloromethane finally afforded (*R*)-4-hydroxy-1-(3-(4-methoxyphenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl-4-(3,4-methylenedioxyphenyl)piperidinium chloride (panamesine hydrochloride, **1a**·HCl) (yield 74%).

Due to the significant differences in the chemistry of carbon and silicon, a totally different synthetic strategy for the preparation of sila-panamesine (**1b**) had to be developed. Compound **1b** was synthesized in a multistep synthesis, starting from tetramethoxysilane (**6**), and was isolated as the hydrochloride **1b**·HCl (Scheme 2). Thus, treatment of **6** with (3,4-methylenedioxyphenyl)magnesium bromide in THF gave dimethoxybis(3,4-methylenedioxyphenyl)silane (**7**) (yield 36%), which upon reaction with vinylmagnesium chloride in THF/diethyl ether yielded bis(3,4-methylenedioxyphenyl)divinylsilane (**8**) (yield 71%). Alternatively, compound **8** was obtained from tetramethoxysilane in a one-pot synthesis, without isolation of **7** (yield 47%). Reaction of **8** with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF, followed by sequential treatment with aqueous solutions of sodium hydroxide and hydrogen peroxide, afforded bis(2-hydroxyethyl)bis(3,4-methylenedioxyphenyl)silane (**9**) (yield 69%). Reaction of **9** with *p*-toluenesulfonyl chloride in dichloromethane, in the presence of triethylamine, gave bis(3,4-methylenedioxyphenyl)bis(2-((4-methylphenyl)sulfonyloxy)-ethyl)silane (**10**) (yield 70%), which upon reaction with benzylamine and triethylamine in acetonitrile afforded 1-benzyl-4,4-bis(3,4-methylenedioxyphenyl)-4-silapiperidine (**11**) (yield 71%). Alternatively, compound **11** was obtained from **9** in a one-pot synthesis, without isolation of **10** (yield 59%).[21] Treatment of **11** with 1-chloroethyl chloroformate in dichloromethane, followed by removal of the solvent and reaction with methanol, yielded 4,4-bis(3,4-methylenedioxyphenyl)-4-silapiperidinium chloride (**12**) (yield 85%), which upon reaction with **5** in acetonitrile, in the presence of potassium carbonate and potassium iodide, gave (*S*)-3-(4-methoxyphenyl)-5-(4,4-bis(3,4-methylenedioxyphenyl)-4-silapiperidin-1-yl)methyl-1,3-oxazolidin-2-one (**13**) (yield 50%). Reaction of **13** with trifluoroacetic acid, followed by treatment with water and an ethereal hydrogen chloride solution, finally afforded (*R*)-4-hydroxy-1-(3-(4-methoxyphenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl-4-(3,4-methylenedioxyphenyl)-4-silapiperidinium chloride (sila-panamesine hydrochloride, **1b**·HCl) (yield 40%). (*S*,*S*)-*Si*,*Si*′-Oxybis(3-(4-methoxyphenyl)-5-(4-(3,4-methylenedioxyphenyl)-4-silapiperidin-1-yl)methyl-1,3-oxazolidin-2-one) (**14**) was synthesized by treatment of **13** with trifluoroacetic acid, followed by hydrolysis and subsequent isolation by preparative liquid chromatography (yield 12%; Scheme 3).

Compound **5** was synthesized according to Scheme 4, starting from 4-methoxyaniline (**15**). Treatment of **15** with (*S*)-glycidol in methanol yielded (*R*)-3-((4-methoxyphenyl)amino)propane-1,2-diol (**16**) (yield 41%). Alternatively, compound **16** was obtained by reaction of *N*-benzyl-4-methoxyaniline (**17**) with (*S*)-glycidol in methanol, followed by reaction with hydrogen in ethanol, in the presence of palladium on carbon (yield 80%). Reaction of **16** with diethyl carbonate in toluene, in the presence of potassium *tert*-butoxide, gave (*R*)-5-(hydroxymethyl)-3-(4-methoxyphenyl)-1,3-oxazolidin-2-one (**18**) (yield 88%), which upon treatment with methanesulfonyl chloride and triethylamine in dichloromethane afforded **5** (yield 71%).

All compounds synthesized were isolated as colorless crystalline solids. Their identities were established by elemental analyses and NMR studies (^{1}H, ^{13}C, ^{29}Si), and the silicon compounds **7**, **8**, **10**, **12**, and **13** were additionally characterized by crystal structure analyses.

Crystal Structure Analyses. Compounds **7**, **8**, **10**, **12**, and **13** were structurally characterized by single-crystal X-ray diffraction.[22] The crystal data and the experimental parameters

(17) Original publications dealing with sila-substituted drugs: (a) Tacke, R.; Merget, M.; Bertermann, R.; Bernd, M.; Beckers, T.; Reissmann, T. *Organometallics* **2000**, *19*, 3486-3497. (b) Merget, M.; Günther, K.; Bernd, M.; Günther, E.; Tacke, R. *J. Organomet. Chem.* **2001**, *628*, 183−194. (c) Tacke, R.; Kornek, T.; Heinrich, T.; Burschka, C.; Penka, M.; Pülm, M.; Keim, C.; Mutschler, E.; Lambrecht, G. *J. Organomet. Chem.* **2001**, *640*, 140−165. (d) Tacke, R.; Handmann, V. I.; Kreutzmann, K.; Keim, C.; Mutschler, E.; Lambrecht, G. *Organometallics* **2002**, *21*, 3727−3732. (e) Tacke, R.; Heinrich, T. *Silicon Chem.* **2002**, *1*, 35−39. (f) Tacke, R.; Handmann, V. I.; Bertermann, R.; Burschka, C.; Penka, M.; Seyfried, C. *Organometallics* **2003**, *22*, 916−924. (g) Heinrich, T.; Burschka, C.; Warneck, J.; Tacke, R. *Organometallics* **2004**, *23*, 361−366. (h) Tacke, R.; Heinrich, T.; Bertermann, R.; Burschka, C.; Hamacher, A.; Kassack, M. U. *Organometallics* **2004**, *23*, 4468−4477. (i) Tacke, R.; Schmid, T.; Penka, M.; Burschka, C.; Bains, W.; Warneck, J. *Organometallics* **2004**, *23*, 4915−4923. (j) Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Fleming, I.; Gaudon, C.; Ivanova, D.; Gronemeyer, H.; Tacke, R. *Organometallics* **2005**, *24*, 3192−3199. (k) Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Warneck, J. B. H.; Tacke, R. *Organometallics* **2006**, *25*, 1188−1198. (l) Showell, G. A.; Barnes, M. J.; Daiss, J. O.; Mills, J. S.; Montana, J. G.; Tacke, R.; Warneck, J. B. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2555−2558.

(18) To avoid any confusion, it should be noted that the stereo descriptors for **1a** and **1b** ((*S*)-configuration) differ from those for the corresponding hydrochlorides **1a**·HCl and **1b**·HCl ((*R*)-configuration).

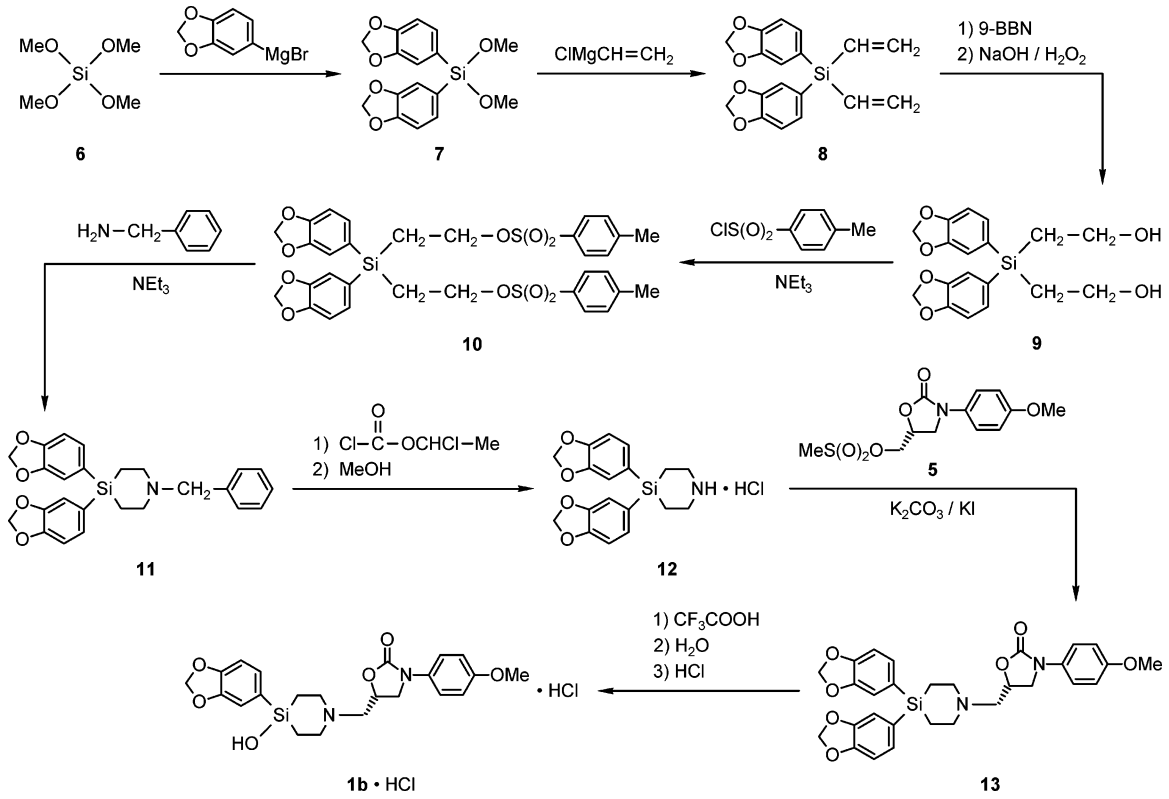
(19) Prücher, H.; Böttcher, H.; Seyfried, C.; Haase, A.; Minck, K.-O.; Gottschlich, R. (Merck Patent GmbH, Darmstadt, Germany) Pat. Appl. DE 4017211 A1 (December 5, 1991).

(20) Heffe, W.; Hunziker, F.; Thoma, K. (Wander AG, Bern, Switzerland) Pat. Appl. DT 2444972 A1 (April 3, 1975).

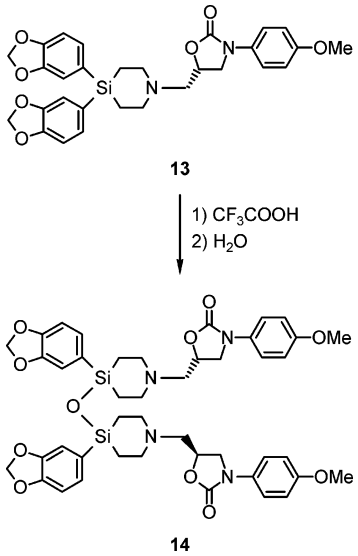
(21) Compound **10** displayed a limited stability; it could be stored at 20 °C for a maximum of 24 h.

(22) All attempts to grow single crystals of **1b**·HCl suitable for X-ray diffraction studies failed.

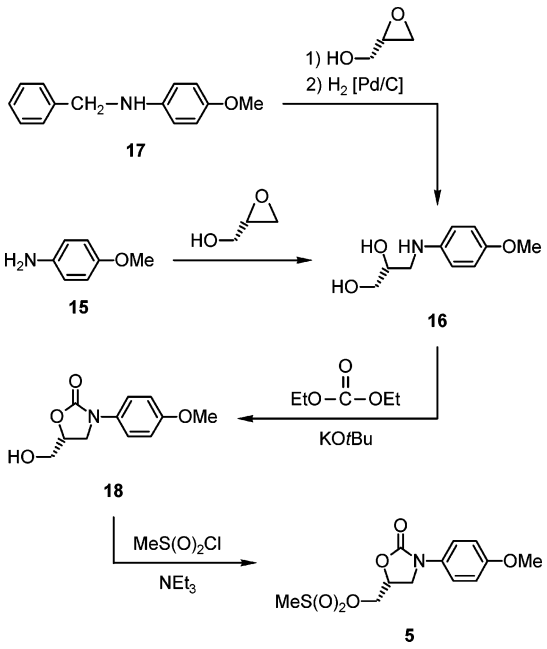
Scheme 2



Scheme 3



Scheme 4



used for these studies are given in Table 1. The molecular structures of the compounds studied are depicted in Figures 1−5; selected interatomic distances and bond angles are given in the respective figure legends.

As can be seen from Figures 4 and 5, the silapiperidinium ring of **12** and the silapiperidine ring of **13** adopt a chair conformation, the structural parameters of these heterocycles being very similar to related silapiperidinium and silapiperidine derivatives.[23] The bond lengths and angles determined for compounds **7**, **8**, **10**, **12**, and **13** are all in the expected range and do not require further discussion.

In the hydrogen-bonding system observed in the crystal of **12**, both NH groups act as proton donors and the chloride anion as proton acceptor. Two neighboring ammonium cations are bridged by one chloride anion via two N−H···Cl hydrogen bonds, forming infinite chains along the direction [010].[24]

Determination of the Enantiomeric Purity. The enantiomeric purity of **13** was determined by ^{1}H NMR experiments using the chiral solvating agent (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol ((*R*)-TFAE). As shown for racemic **13** in Figure 6, the two enantiomers of this compound can be clearly discriminated

(23) Heinrich, T.; Burschka, C.; Penka, M.; Wagner, B.; Tacke, R. *J. Organomet. Chem.* **2005**, *690*, 33−47.

(24) The hydrogen-bonding system was analyzed by using the program system *PLATON*: Spek, A. L. *PLATON*; University of Utrecht: Utrecht, The Netherlands, 1998.

Table 1. Crystal Data and Experimental Parameters for the Crystal Structure Analyses of 7, 8, 10, 12, and 13

	7	8	10	12	13
empirical formula	$C_{16}H_{16}O_6Si$	$C_{18}H_{16}O_4Si$	$C_{32}H_{32}O_{10}S_2Si$	$C_{18}H_{20}ClNO_4Si$	$C_{29}H_{30}N_2O_7Si$
formula mass, g mol^{-1}	332.38	324.40	668.79	377.89	546.64
collection *T*, K	173(2)	173(2)	173(2)	173(2)	293(2)
λ(Mo Kα), Å	0.71073	0.71073	0.71073	0.71073	0.71073
cryst syst	monoclinic	monoclinic	triclinic	orthorhombic	monoclinic
space group (No.)	*C*2/*c* (15)	$P2_1/n$ (14)	$P\bar{1}$ (2)	*Pbca* (61)	*C*2 (5)
a, Å	6.1159(4)	6.3816(6)	9.6792(19)	10.3219(6)	43.378(9)
b, Å	13.2116(14)	18.6027(14)	12.734(3)	11.1170(7)	6.6111(13)
c, Å	19.8763(16)	13.6152(12)	13.605(3)	30.546(2)	9.4509(19)
α, deg	90	90	104.81(3)	90	90
β, deg	94.580(9)	102.442(11)	100.98(3)	90	99.34(3)
γ, deg	90	90	91.51(3)	90	90
V, Å^3	1600.9(2)	1578.4(2)	1586.5(5)	3505.1(4)	2674.4(9)
Z	4	4	2	8	4
D(calcd), g cm^{-3}	1.379	1.365	1.400	1.432	1.358
μ, mm^{-1}	0.175	0.166	0.263	0.310	0.139
F(000)	696	680	700	1584	1152
cryst dimens, mm	0.4 × 0.3 × 0.1	0.5 × 0.4 × 0.3	0.4 × 0.4 × 0.2	0.5 × 0.4 × 0.2	0.5 × 0.3 × 0.1
2θ range, deg	6.16−55.92	5.34−55.96	4.30−53.82	4.76−52.74	4.36−49.46
index ranges	$-7 \le h \le 7$, $17 \le k \le 17$, $26 \le l \le 26$	$-8 \le h \le 8$, $-23 \le k \le 24$, $-17 \le l \le 17$	$-12 \le h \le 12$, $-16 \le k \le 16$, $-17 \le l \le 17$	$-12 \le h \le 12$, $-13 \le k \le 13$, $-38 \le l \le 38$	$-50 \le h \le 50$, $-7 \le k \le 7$, $-11 \le l \le 11$
no. of collected reflns	9861	11910	24838	20979	12860
no. of indep reflns	1840	3519	6305	3567	4513
R_{int}	0.0298	0.0252	0.0450	0.0353	0.0459
no. of reflns used	1840	3519	6305	3567	4513
no. of restraints					24
no. of params	106	208	410	232	431
S[a]	1.085	1.046	1.043	1.023	0.908
wt params *a*/*b*[b]	0.0648/0.7295	0.0524/0.2510	0.0664/0.2797	0.0545/1.4153	0.0268/0.0000
R_1[c] [$I > 2\sigma(I)$]	0.0380	0.0336	0.0421	0.0373	0.0288
wR_2[d] (all data)	0.1110	0.0914	0.1172	0.0998	0.0598
abs struct param					0.13(10)
max./min. residual electron density, e Å^{-3}	+0.263/−0.256	+0.338/−0.258	+0.671/−0.509	+0.469/−0.322	+0.105/−0.128

[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] $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{0.5}$.

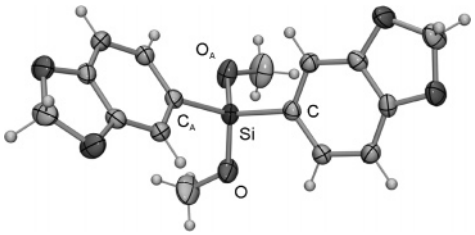


Figure 1. Molecular structure of **7** in the crystal (probability level of displacement ellipsoids 50%). Selected bond distances (Å) and angles (deg): Si−C 1.8593(13), Si−O 1.6279(12), C−Si−C_A 112.73(8), C−Si−O 103.89(6), C−Si−O_A 111.51(6), C_A−Si−O 111.51(6), C_A−Si−O_A 103.89(6), O−Si−O_A 113.59(10).

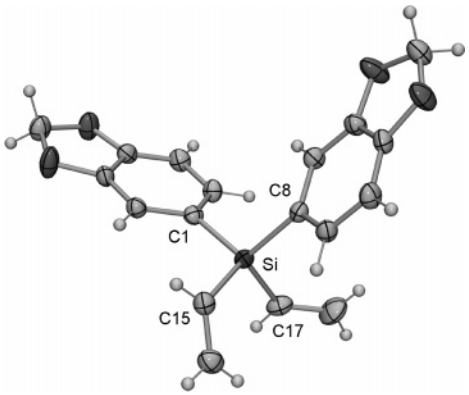


Figure 2. Molecular structure of **8** in the crystal (probability level of displacement ellipsoids 50%). Selected bond distances (Å) and angles (deg): Si−C1 1.8775(14), Si−C8 1.8801(13), Si−C15 1.8594(15), Si−C17 1.8590(14), C1−Si−C8 110.98(6), C1−Si−C15 110.30(6), C1−Si−C17 107.34(6), C8−Si−C15 108.27(6), C8−Si−C17 110.46(6), C15−Si−C17 109.50(7).

by NMR spectroscopy and therefore quantitatively determined by integration of their characteristic resonance signals. According to this method, the enantiomeric purity of **13** was determined to be ≥99% ee. The same enantiomeric purity can also be assumed for **1b**·HCl, as the cleavage of the 3,4-methylenedioxyphenyl substituent does not affect the center of chirality.

NMR Studies. The ^{1}H, ^{13}C, and ^{29}Si NMR spectra of **1b**·HCl revealed the existence of two conformers (molar ratio ca. 2:1) of the cation in solution (solvent [D_6]DMSO). This ratio differs significantly from that found for the carbon analogue **1a**·HCl (ca. 12:1) (Figure 7), indicating considerable differences in the energies of the respective two conformers of the piperidinium and 4-silapiperidinium skeletons. These results are in agreement with those obtained from solution NMR studies on the related C/Si analogues haloperidol hydrochloride and silahaloperidol hydrochloride.[17h] The existence of the two conformers of **1a**·HCl and **1b**·HCl was confirmed by 2D ^{1}H,^{1}H EXSY NMR experiments (for details, see the Experimental Section). Attempts to determine the structures of the two conformers by additional NMR experiments (^{1}H,^{1}H NOESY) failed.

ESI-MS Studies. The stability of **1b** and **14** in aqueous solution at different pH values was investigated at 20 °C by ESI-MS experiments. For this purpose, 10 μM buffered aqueous solutions of **1b**·HCl and **14** at pH 1.0, 5.0, 7.4, and 10.0 were analyzed. Some results of these studies are depicted in Figures 8 and 9. The mass spectra of the aqueous solutions of **1b**·HCl show the characteristic peak for protonated sila-panamesine

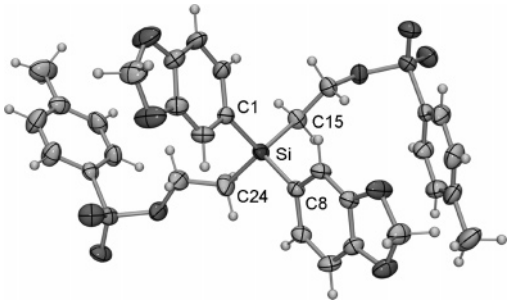


Figure 3. Molecular structure of **10** in the crystal (probability level of displacement ellipsoids 50%). Selected bond distances (Å) and angles (deg): Si−C1 1.870(2), Si−C8 1.870(2), Si−C15 1.886-(2), Si−C24 1.898(2), C1−Si−C8 107.97(10), C1−Si−C15 111.71-(11), C1−Si−C24 111.22(10), C8−Si−C15 109.49(10), C8−Si−C24 110.90(11), C15−Si−C24 105.56(11).

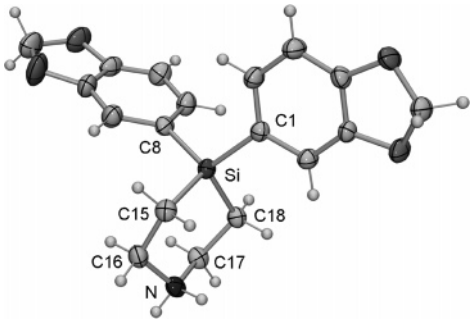


Figure 4. Structure of the cation in the crystal of **12** (probability level of displacement ellipsoids 50%). Selected bond distances (Å) and angles (deg): Si−C1 1.8737(19), Si−C8 1.8715(19), Si−C15 1.8783(19), Si−C18 1.883(2), N−C16 1.499(3), N−C17 1.496-(3), C15−C16 1.526(3), C17−C18 1.532(3), C1−Si−C8 112.34-(8), C1−Si−C15 109.06(8), C1−Si−C18 111.30(9), C8−Si−C15 109.97(8), C8−Si−C18 110.32(8), C15−Si−C18 103.47(9), C16−N−C17 115.59(15), Si−C15−C16 110.97(13), Si−C18−C17 113.10(13), N−C16−C15 112.21(15), N−C17−C18 112.70(16); N−H1 0.90(2), N−H2 0.92(2), H1···Cl 2.24(2), H2···Cl_A 2.22-(2), N···Cl 3.0945(17), N···Cl_A 3.1398(17), N−H1···Cl 157.5(19), N−H2···Cl_A 172.2(18).[24]

Table 2. σ_1 and σ_2 Receptor Affinities of 1a, 1b, and Selected Reference Compounds[a]

compound	σ_1 ([^{3}H]-pentazocine)	σ_2 ([^{3}H]-ditolylguanidine)
panamesine (**1a**)	111 ± 1.2	5%[b]
sila-panamesine (**1b**)	37 ± 4.7	4%[b]
(+)-pentazocine	2.2 ± 1.2	n.d.
haloperidol	1.9 ± 0.4	78.1 ± 2.4
ditolylguanidine	177 ± 6.6	20.2 ± 2.3

[a] Data expressed as K_i values (nM) or percent inhibition of binding. Data represent the mean (±SEM) of three independent determinations, performed in duplicate. [b] Percent inhibition of radioligand binding at a test compound concentration of 1 μM.

(ammonium cation; *m*/*z* 443) at all pH values measured. This holds true for both freshly prepared samples and solutions that were kept at 20 °C for 24 h (Figure 8). When samples of **14** were analyzed, the monoprotonated disiloxane (monoammonium cation; *m*/*z* 867) and the 2-fold protonated disiloxane (diammonium cation; *m*/*z* 434) were detected in the case of freshly prepared solutions at pH 1.0 and 5.0, without any significant amounts of protonated sila-panamesine. After an equilibration period of 24 h at 20 °C, protonated sila-panamesine was found together with the monoprotonated and 2-fold protonated disiloxane (pH 1.0 and 5.0). Under physiological (pH 7.4) and alkaline conditions (pH 10.0), the disiloxane molecule is cleaved to release the corresponding silanol, which was the only detectable

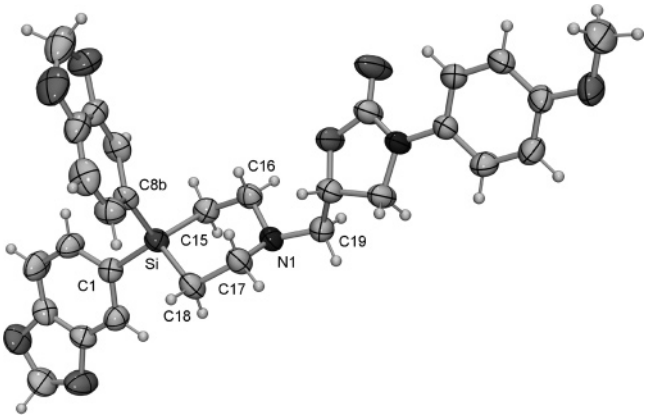


Figure 5. Molecular structure of **13** in the crystal (probability level of displacement ellipsoids 50%). Selected bond distances (Å) and angles (deg): Si−C1 1.8707(19), Si−C8b 1.872(13), Si−C15 1.8697(19), Si−C18 1.859(2), N1−C16 1.463(3), N1−C17 1.474-(3), N1−C19 1.458(2), C15−C16 1.532(3), C17−C18 1.534(3), C1−Si−C8b 111.5(7), C1−Si−C15 112.19(9), C1−Si−C18 112.48-(10), C8b-Si−C15 114.0(6), C8b-Si−C18 104.2(5), C15−Si−C18 101.86(9), C16−N1−C17 114.07(15), C16−N1−C19 112.58(16), C17−N1−C19 110.75(15), Si−C15−C16 109.83(13), Si−C18−C17 110.43(16), N1−C16−C15 112.17(17), N1−C17−C18 112.44-(16). One of the two 3,4-methylenedioxyphenyl substituents is disordered. For details, see Supporting Information.

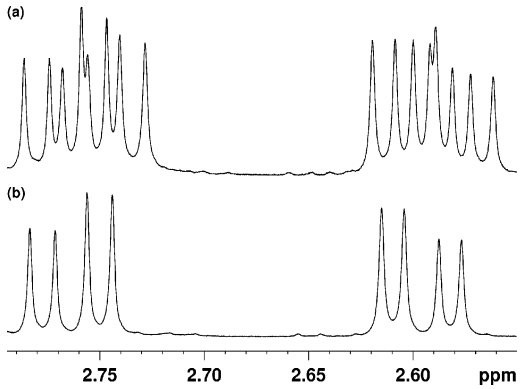


Figure 6. Quantitative NMR spectroscopic determination of the enantiomeric purity of **13**. ^{1}H NMR partial spectra (NCH_2CHCH_2-NC(O) group) of the enantiomers of **13** in the presence of the chiral solvating agent (*R*)-TFAE: (a) *rac*-**13**; (b) **13**. For details, see Experimental Section.

species in aged samples. The stability of the silanol in water could also be confirmed for solutions of **1b**·HCl at higer concentrations (2.5 mM, pH 1.0 and pH 5.0; 1 mM, pH 7.4 and pH 10.0). The disiloxane could not be observed in measurable amounts in any of these samples. In conclusion, the silanol **1b** displays a remarkable stability in aqueous solution. In addition, aqueous solutions of **14** show measurable amounts of the silanol after 24 h at all pH values measured, demonstrating hydrolytic cleavage of the disiloxane.

Pharmacological Studies. The σ receptor affinities of panamesine (**1a**) and sila-panamesine (**1b**) were determined in competitive radioligand binding studies. In the σ_1 assay, homogenates of guinea pig brains were used as the receptor material. [^{3}H]-(+)-Pentazocine was used as the radioligand, which exhibits high affinity and selectivity for the σ_1 receptor. A rat liver membrane preparation served as a source for σ_2 receptors in the σ_2 assay. Since a σ_2-selective radioligand is not commercially available, the nonselective radioligand [^{3}H]-ditolylguanidine was used. The σ_1 receptors were selectively

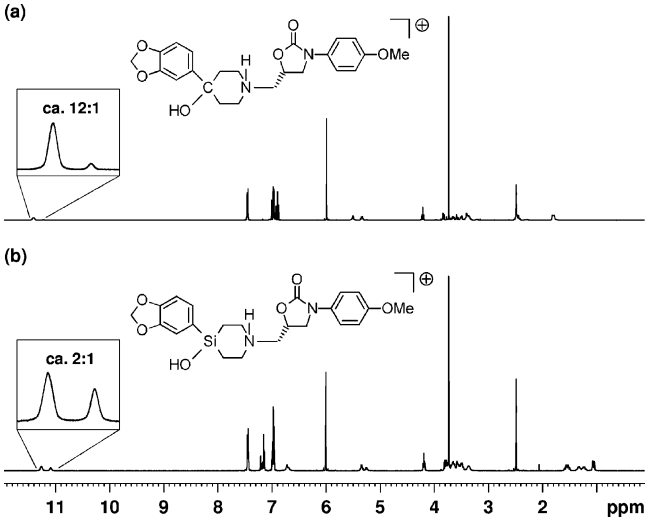


Figure 7. ^{1}H NMR spectra of the C/Si analogues (a) **1a**·HCl and (b) **1b**·HCl, showing the respective pairs of NH protons, which correspond to the two conformers present in solution ([D_6]DMSO, 500.1 MHz, 22 °C).

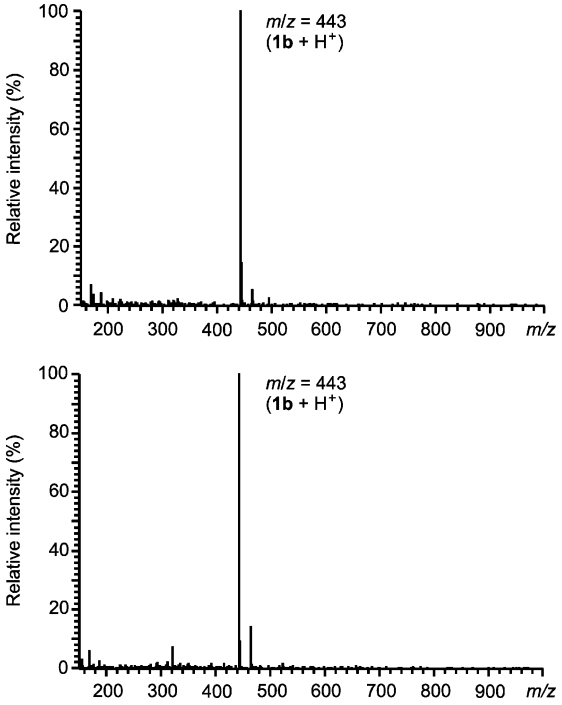


Figure 8. ESI-MS spectra of 10 μM buffered aqueous solutions (pH 5.0) of **1b**·HCl, showing the signal of the ammonium cation (*m*/*z* 443). The spectra were measured 30 min (above) and 24 h (below) after sample preparation at 20 °C (for details, see Experimental Section).

masked by adding an excess of the σ_1-selective compound (+)-pentazocine.[25,26]

The σ receptor affinities of compounds **1a** and **1b** are depicted in Table 2. For comparison, K_i values of the reference compounds haloperidol, (+)-pentazocine, and ditolylguanidine (DTG) are also included.

Table 2 shows that neither panamesine (**1a**) nor its sila-analogue **1b** interacts significantly with σ_2 receptors. However, a remarkable affinity for the σ_1 receptor is observed for both test compounds. Whereas the K_i value of panamesine (**1a**) amounts

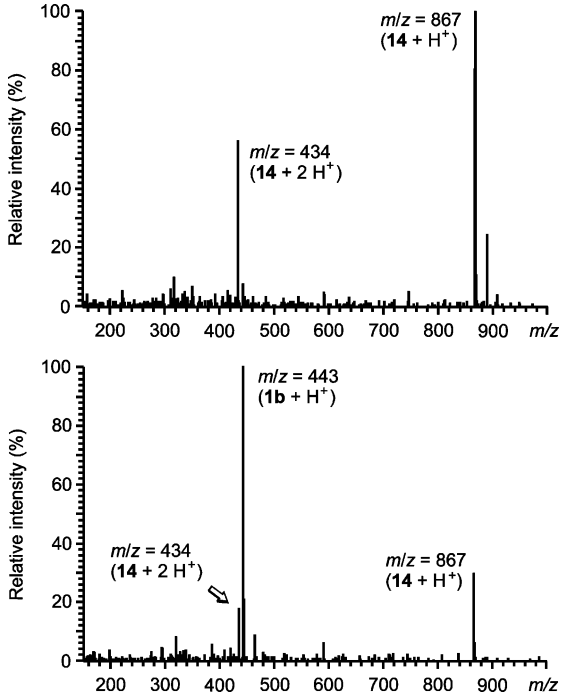


Figure 9. ESI-MS spectra of 10 μM buffered aqueous solutions (pH 5.0) of **14**, showing the signals of the monoammonium cation (*m*/*z* 867) and the diammonium cation (*m*/*z* 434). The signal of protonated **1b** (*m*/*z* 443) is also present, indicating hydrolytic cleavage of the disiloxane. The spectra were measured 30 min (above) and 24 h (below) after sample preparation at 20 °C (for details, see Experimental Section).

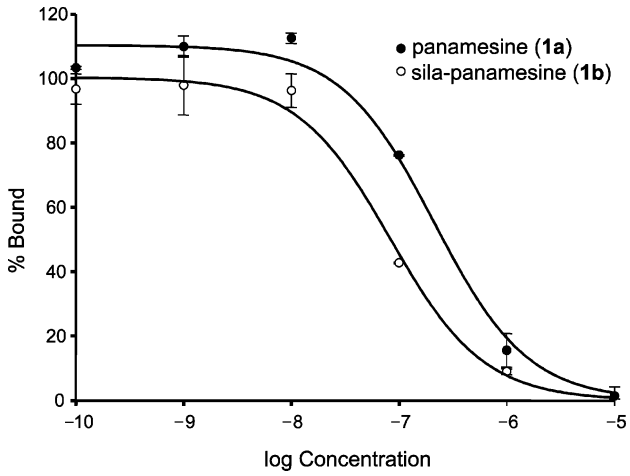


Figure 10. Competition curves obtained for compounds **1a** and **1b** at σ_1 receptors (tissue, guinea pig brain; radioligand, [^{3}H]-pentazocine; for further details, see Experimental Section).

to 111 nM, the K_i value of the sila-analogue **1b** is approximately 3-fold lower (37 nM). These data reveal that the C/Si exchange at the 4-position of the piperidine ring considerably improves the σ_1 receptor affinity (Figure 10). The reason for this enhancement is unclear; however, one might speculate that the different conformational behavior of the C/Si analogues (see NMR Studies) could be partially attributed to this phenomenon.

Conclusions

Panamesine (**1a**), a σ receptor ligand, and its silicon analogue sila-panamesine (**1b**) were synthesized in multistep syntheses and isolated as the hydrochlorides **1a**·HCl and **1b**·HCl. ESI-MS studies on aqueous solutions of the silanol **1b** and the

(25) Maier, C. A.; Wünsch, B. *J. Med. Chem.* **2002**, *45*, 438−448.
(26) Bedürftig, S.; Wünsch, B. *Eur. J. Med. Chem.* **2006**, *41*, 387−396.

corresponding disiloxane **14** at different pH values revealed a remarkable stability of the silanol and showed hydrolytic cleavage of the disiloxane at all pH values measured. NMR studies demonstrated the existence of two conformers of the cations of **1a**·HCl and **1b**·HCl in solution ([D$_6$]DMSO), with molar ratios of 12:1 and 2:1, respectively. These different molar ratios indicate considerable differences in the energies of the respective two conformers of the piperidinium and 4-silapiperidinium skeletons. Competitive radioligand binding studies demonstrated a 3-fold higher σ_1 receptor affinity for sila-panamesine (**1b**, K_i = 37 nM) than for panamesine (**1a**, K_i = 111 nM), emphasizing the high potential of the C/Si switch strategy for drug design.

Experimental Section

Chemistry: General Procedures. 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 B-540 melting point apparatus using samples in open glass capillaries. The ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded at 22 °C on a Bruker DRX-300 (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{29}Si, 59.6 MHz; compounds **1a**, **4**, **5**, **7**−**9**, **11**, **12**, and **14**), Bruker Avance 400 (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz; ^{29}Si, 79.5 MHz; compounds **10**, **13**, **16**, and **18**), or Bruker Avance 500 NMR spectrometer (^{1}H, 500.1 MHz; ^{13}C, 125.8 MHz; ^{29}Si, 99.4 MHz; compounds **1a**·HCl, **1b**·HCl, and **3**). $CDCl_3$, CD_2Cl_2, or [D$_6$]DMSO was used as the solvent. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^{1}H, δ 7.24; $CDCl_3$), $CDCl_3$ (^{13}C, δ 77.0; $CDCl_3$), $CHDCl_2$ (^{1}H, δ 5.32; CD_2Cl_2), CD_2Cl_2 (^{13}C, δ 53.8; CD_2Cl_2), [D$_5$]DMSO (^{1}H, δ 2.49; [D$_6$]DMSO), [D$_6$]DMSO (^{13}C, δ 39.5; [D$_6$]DMSO), or external TMS (^{29}Si, δ 0; $CDCl_3$, CD_2Cl_2, [D$_6$]-DMSO). Analysis and assignment of the ^{1}H NMR data were supported by ^{1}H,^{1}H COSY, ^{13}C,^{1}H HMQC, and ^{13}C,^{1}H HMBC experiments and partially by simulations using the *WIN-DAISY* software package (version 4.05, Bruker). Assignment of the ^{13}C NMR data was supported by DEPT 135, ^{13}C,^{1}H HMQC, and ^{13}C,^{1}H HMBC experiments. Optical rotations were measured at 20 °C with a JASCO polarimeter P-1030; DMSO (Aldrich, Art. 276855) served as the solvent.

Preparation of (*S*)-5-(4-Hydroxy-4-(3,4-methylenedioxyphenyl)piperidin-1-yl)methyl-3-(4-methoxyphenyl)-1,3-oxazolidin-2-one (Panamesine, 1a). The synthesis was performed on the basis of ref 19: Compound **5** (5.54 g, 18.4 mmol) was added in one single portion at 20 °C to a stirred suspension of **4** (4.73 g, 18.4 mmol) in acetonitrile (250 mL), followed by sequential addition of potassium carbonate (5.88 g, 42.5 mmol) and potassium iodide (397 mg, 2.39 mmol) in one single portion each. The resulting suspension was stirred under reflux for 2 days, the solvent was removed under reduced pressure, and dichloromethane (400 mL) and water (350 mL) were added one after another. The organic layer was separated, the aqueous phase was extracted with dichloromethane (3 × 150 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on aluminum oxide (column dimensions, 30 × 5 cm; aluminum oxide (neutral, type 507C, Brockmann I, 150 mesh, 58 Å; Aldrich, Art. 19,977-4), 700 g, deactivated with 6% water; eluent, dichloromethane/ethyl acetate (2:1 (v/v))). The resulting solid was recrystallized from boiling ethanol/dichloromethane (99:1 (v/v)) (330 mL; slow cooling and crystallization at 20 °C over a period of 16 h). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 6 h) to give **1a** in 62% yield as a colorless crystalline solid (4.87 g, 11.4 mmol); mp 165 °C; $[\alpha]_D^{20}$ −26.1 (*c* 1.00, DMSO). ^{1}H NMR (CD_2Cl_2): δ 1.66−1.74 (m, 3 H, O*H*, CC*H*$_A$H$_B$CH$_2$N), 2.00−2.13 (m, 2 H, CCH$_A$*H*$_B$CH$_2$N), 2.57−2.85 (m, 6 H, CCH$_2$C*H*$_2$N, NC*H*$_2$CHCH$_2$-NC(O)), 3.74−3.79 and 4.01−4.07 (m, 5 H, OC*H*$_3$, NCH$_2$CHC*H*$_2$-NC(O)), 4.72−4.81 (m, 1 H, NCH$_2$C*H*CH$_2$NC(O)), 5.94 (s, 2 H, OC*H*$_2$O), 6.76−6.79 (m, 1 H, *H*-5, C$_6$H$_3$), 6.89−6.97 (m, 3 H, *H*-6, C$_6$H$_3$, *H*-3/*H*-5, C$_6$H$_4$), 7.01−7.02 (m, 1 H, *H*-2, C$_6$H$_3$), 7.42−7.47 (m, 2 H, *H*-2/*H*-6, C$_6$H$_4$). ^{13}C NMR (CD_2Cl_2): δ 39.01 (C*C*H$_2$-CH$_2$N), 39.04 (CC*H*$_2$CH$_2$N), 49.8 (NCH$_2$CH*C*H$_2$NC(O)), 50.5 (CCH$_2$*C*H$_2$N), 50.9 (CCH$_2$*C*H$_2$N), 55.8 (O*C*H$_3$), 61.8 (N*C*H$_2$-CHCH$_2$NC(O)), 71.0 (*C*OH), 71.5 (NCH$_2$*C*HCH$_2$NC(O)), 101.5 (O*C*H$_2$O), 106.0 (*C*-2, C$_6$H$_3$), 108.0 (*C*-5, C$_6$H$_3$), 114.5 (*C*-3/*C*-5, C$_6$H$_4$), 117.9 (*C*-6, C$_6$H$_3$), 120.4 (*C*-2/*C*-6, C$_6$H$_4$), 132.1 (*C*-1, C$_6$H$_4$), 143.3 (*C*-1, C$_6$H$_3$), 146.8 (*C*-3 or *C*-4, C$_6$H$_3$), 148.0 (*C*-3 or *C*-4, C$_6$H$_3$), 155.2 (*C*═O), 156.6 (*C*-4, C$_6$H$_4$). Anal. Calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.14; N, 6.57. Found: C, 64.8; H, 6.1; N, 6.5.

Preparation of (*R*)-4-Hydroxy-1-(3-(4-methoxyphenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl-4-(3,4-methylenedioxyphenyl)piperidinium Chloride (Panamesine Hydrochloride, 1a·HCl). A 2 M ethereal hydrogen chloride solution (4.15 mL, 8.30 mmol of HCl) was added dropwise at 0 °C within 4 min to a stirred solution of **1a** (3.51 g, 8.23 mmol) in dichloromethane (200 mL), and the resulting mixture was stirred at 0 °C for 50 min. The solvent was removed under reduced pressure, and the resulting solid was recrystallized from boiling methanol (200 mL; slow cooling and crystallization at 20 °C over a period of 1 day). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give 1.62 g of **1a**·HCl. A further 1.21 g of **1a**·HCl was crystallized at 20 °C by vapor diffusion of diethyl ether (150 mL) into the mother liquor of the recrystallization step. The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **1a**·HCl in a total yield of 74% as a colorless crystalline solid (2.83 g, 6.11 mmol); mp 213 °C (dec); $[\alpha]_D^{20}$ −32.3 (*c* 1.00, DMSO). ^{1}H NMR ([D$_6$]DMSO; data for two conformers): δ 1.70−1.82 (m, 2 H, CC*H*$_A$H$_B$CH$_2$N), 2.23−2.36 and 2.42−2.52 (m, 2 H, CCH$_A$*H*$_B$-CH$_2$N; partially overlapped by the [D$_5$]DMSO signal), 3.16−3.26 and 3.35−3.51 (m, 4 H, CCH$_2$C*H*$_2$N), 3.56−3.70 and 3.93−4.02 (m, 2 H, NC*H*$_2$CHCH$_2$NC(O)), 3.74 (s, 3 H, OC*H*$_3$), 3.78−3.85 and 4.20−4.23 (m, 2 H, NCH$_2$CHC*H*$_2$NC(O)), 5.31−5.37 (m, 1 H, NCH$_2$C*H*CH$_2$NC(O)), 5.5 (br s, 1 H, O*H*), 5.99 (s, 2 H, OC*H*$_2$O), 6.89 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, *H*-5, C$_6$H$_3$), 6.93 (dd) and 7.03−7.07 (m) ($^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.8 Hz, 1 H, *H*-6, C$_6$H$_3$), 6.96−6.99 (m, 2 H, *H*-3/*H*-5, C$_6$H$_4$), 7.01 (d) and 7.16−7.19 (m) ($^4J_{HH}$ = 1.8 Hz, 1 H, *H*-2, C$_6$H$_3$), 7.44−7.47 (m, 2 H, *H*-2/*H*-6, C$_6$H$_4$), 11.2 and 11.4 (br s, 1 H, N*H*). ^{13}C NMR ([D$_6$]DMSO; data for the dominating conformer): δ 34.9 (C*C*H$_2$CH$_2$N), 35.1 (C*C*H$_2$CH$_2$N), 48.4 (NCH$_2$CH*C*H$_2$NC(O)), 48.9 (CCH$_2$*C*H$_2$N), 49.4 (CCH$_2$*C*H$_2$N), 55.3 (O*C*H$_3$), 58.2 (N*C*H$_2$CHCH$_2$NC(O)), 67.6 (NCH$_2$*C*HCH$_2$NC-(O)), 67.7 (*C*OH), 100.9 (O*C*H$_2$O), 105.5 (*C*-2, C$_6$H$_3$), 107.7 (*C*-5, C$_6$H$_3$), 114.1 (*C*-3/*C*-5, C$_6$H$_4$), 117.5 (*C*-6, C$_6$H$_3$), 120.4 (*C*-2/*C*-6, C$_6$H$_4$), 131.1 (*C*-1, C$_6$H$_4$), 142.2 (*C*-1, C$_6$H$_3$), 145.9 (*C*-3 or *C*-4, C$_6$H$_3$), 147.1 (*C*-3 or *C*-4, C$_6$H$_3$), 153.6 (*C*═O), 155.9 (*C*-4, C$_6$H$_4$). Anal. Calcd for $C_{23}H_{27}ClN_2O_6$: C, 59.67; H, 5.88; N, 6.05. Found: C, 59.6; H, 5.7; N, 5.8.

Preparation of (*R*)-4-Hydroxy-1-(3-(4-methoxyphenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl-4-(3,4-methylenedioxyphenyl)-4-silapiperidinium Chloride (Sila-panamesine Hydrochloride, 1b·HCl). A solution of **13** (1.09 g, 1.99 mmol) in trifluoroacetic acid (6.14 g, 53.8 mmol) was stirred at 0 °C for 20 h. The excess trifluoroacetic acid was removed under reduced pressure at 0 °C, and the resulting residue was dried in vacuo (0.001 mbar, 0 °C, 30 min). Subsequently, acetonitrile/water (1:1 (v/v)) (230 mL) and a saturated aqueous sodium hydrogencarbonate solution (7.2 mL) were added one after another in one single portion each at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. Dichloromethane (100 mL) and water (200 mL) were added one after another at 20 °C, and the organic phase was separated and extracted

with water (2 × 400 mL). The combined aqueous phases were extracted with dichloromethane (40 mL), the organic solutions were combined, and a 2 M ethereal hydrogen chloride solution (1.1 mL, 2.2 mmol of HCl) was added dropwise at 0 °C within 2 min. The resulting mixture was stirred at 0 °C for 2 min and then extracted with water (4 × 40 mL), and the combined aqueous solutions were washed with dichloromethane (10 mL). The water was removed by freeze-drying, and the resulting solid was crystallized from acetonitrile/water (1:3 (v/v)) (19 mL; crystallization at 4 °C over a period of 3 days). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **1b**·HCl in 40% yield as a colorless crystalline solid (379 mg, 791 μmol); mp 165−166 °C; $[\alpha]_D^{20}$ −30.8 (*c* 1.00, DMSO). ^{1}H NMR ([D$_6$]DMSO; data for two conformers): δ 1.03−1.10, 1.18−1.38, and 1.48−1.60 (m, 4 H, SiC*H*$_2$CH$_2$N), 3.30−3.82 and 4.17−4.21 (m, 11 H, SiCH$_2$C*H*$_2$N, NC*H*$_2$CHC*H*$_2$NC(O), OC*H*$_3$), 5.25−5.37 (m, 1 H, NCH$_2$C*H*CH$_2$NC(O)), 6.007 and 6.013 (s, 2 H, OC*H*$_2$O), 6.70 and 6.73 (s, 1 H, O*H*), 6.96−7.02 (m, 3 H, *H*-5, C$_6$H$_3$, *H*-3/*H*-5, C$_6$H$_4$), 7.14−7.21 (m, 2 H, *H*-2/*H*-6, C$_6$H$_3$), 7.43−7.45 (m, 2 H, *H*-2/*H*-6, C$_6$H$_4$), 11.1 and 11.3 (br s, 1 H, N*H*). ^{13}C NMR ([D$_6$]DMSO; data for two conformers, the dominating conformer being marked with an asterisk [*]): δ 9.5, 9.7, 11.8*, and 12.1* (Si*C*H$_2$CH$_2$N), 48.3 and 48.5* (NCH$_2$*C*HCH$_2$NC(O)), 51.3, 51.9, 52.2*, and 53.3* (SiCH$_2$*C*H$_2$N), 54.8 and 58.7* (N*C*H$_2$-CHCH$_2$NC(O)), 55.3 (OC*H*$_3$), 67.6 and 67.9* (NCH$_2$*C*HCH$_2$NC-(O)), 100.6 (O*C*H$_2$O), 108.68 and 108.72* (*C*-5, C$_6$H$_3$), 112.6* and 112.8 (*C*-2, C$_6$H$_3$), 114.1 (*C*-3/*C*-5, C$_6$H$_4$), 120.3 and 120.4* (*C*-2/*C*-6, C$_6$H$_4$), 127.8 and 128.21* (*C*-1, C$_6$H$_3$), 128.0* and 128.17 (*C*-6, C$_6$H$_3$), 131.1 (*C*-1, C$_6$H$_4$), 147.1* and 147.2 (*C*-3 or *C*-4, C$_6$H$_3$), 148.95* and 149.00 (*C*-3 or *C*-4, C$_6$H$_3$), 153.6 (*C*═O), 155.8 and 155.9* (*C*-4, C$_6$H$_4$). ^{29}Si NMR ([D$_6$]DMSO; data for two conformers, the dominating conformer being marked with an asterisk [*]): δ −11.6* and −11.1. Anal. Calcd for C$_{22}$H$_{27}$ClN$_2$O$_6$-Si: C, 55.16; H, 5.68; N, 5.85. Found: C, 55.1; H, 5.5; N, 5.8.

1-Benzyl-4-piperidone (2). This compound was commercially available (Aldrich, Art. B29806).

Preparation of 1-Benzyl-4-hydroxy-4-(3,4-methylenedioxyphenyl)piperidine (3). The synthesis was performed on the basis of ref 20: A mixture of magnesium turnings (1.40 g, 57.6 mmol) and iodine (50 mg, 197 μmol of I$_2$) was heated in a sealed flask at 80 °C for 30 min and then cooled to 20 °C, followed by addition of THF (8 mL). A solution of 1-bromo-3,4-methylenedioxybenzene (10.5 g, 52.2 mmol) in THF (30 mL) was added dropwise in such a way that, after the reaction had started, the solvent refluxed permanently. The mixture was stirred under reflux for a further 1.5 h and then cooled to 20 °C. A mixture of **2** (9.50 g, 50.2 mmol) in THF (30 mL) was added dropwise at 20 °C within 1 h, and the resulting mixture was stirred at 20 °C for 90 min and then at 35−40 °C for a further 3.5 h. The solvent was removed under reduced pressure, diethyl ether (200 mL) and a saturated aqueous ammonium chloride solution (130 mL) were added successively, the organic layer was separated, and the aqueous phase was extracted with diethyl ether (6 × 200 mL). The combined organic extracts were washed with water (2 × 150 mL) and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was crystallized from boiling 2-propanol (80 mL; slow cooling and crystallization at 20 °C over a period of 1 day). The product was isolated by suction filtration, washed with cold 2-propanol (25 mL, −20 °C), recrystallized from boiling 2-propanol (120 mL; slow cooling and crystallization at 20 °C over a period of 1 day), isolated by suction filtration, washed with cold 2-propanol (25 mL, −20 °C), and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **3** in 62% yield as a colorless crystalline solid (9.68 g, 31.1 mmol); mp 143 °C. ^{1}H NMR (CD$_2$Cl$_2$): δ 1.66−1.70 and 2.03−2.09 (m, 5 H, O*H*, CC*H*$_2$CH$_2$N), 2.40−2.46 and 2.72−2.74 (m, 4 H, CCH$_2$C*H*$_2$N), 3.55 (s, 2 H, NC*H*$_2$C$_6$H$_5$), 5.93 (s, 2 H, OC*H*$_2$O), 6.77 (dd, 1 H, *H*-5, C$_6$H$_3$), 6.97 (dd, 1 H, *H*-6, C$_6$H$_3$), and 7.03 (dd, 1 H, *H*-2, C$_6$H$_3$) ($^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.9 Hz, $^5J_{HH}$ = 0.4 Hz), 7.23−7.37 (m, 5 H, C$_6$H$_5$). ^{13}C NMR (CD$_2$Cl$_2$): δ 39.1 (C*C*H$_2$CH$_2$N), 49.9 (CCH$_2$*C*H$_2$N), 63.4 (N*C*H$_2$C$_6$H$_5$), 71.4 (*C*OH), 101.5 (O*C*H$_2$O), 106.1 (*C*-2, C$_6$H$_3$), 108.0 (*C*-5, C$_6$H$_3$), 118.0 (*C*-6, C$_6$H$_3$), 127.2 (*C*-4, C$_6$H$_5$), 128.5 (*C*-2/*C*-6 or *C*-3/*C*-5, C$_6$H$_5$), 129.4 (*C*-2/*C*-6 or *C*-3/*C*-5, C$_6$H$_5$), 139.4 (*C*-1, C$_6$H$_5$), 143.6 (*C*-1, C$_6$H$_3$), 146.7 (*C*-3 or *C*-4, C$_6$H$_3$), 148.0 (*C*-3 or *C*-4, C$_6$H$_3$). Anal. Calcd for C$_{19}$H$_{21}$NO$_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.4; H, 6.9; N, 4.4.

Preparation of 4-Hydroxy-4-(3,4-methylenedioxyphenyl)piperidinium Chloride (4). The synthesis was performed on the basis of ref 20: Palladium on carbon (470 mg; Merck, Art. 807104) was added in one single portion at 20 °C to a stirred solution of **3** (6.20 g, 19.9 mmol) and hydrochloric acid (4 M, 4.7 mL) in methanol (75 mL), and the resulting mixture was stirred under a hydrogen atmosphere (4 bar) at 40 °C for 48 h, followed by filtration. The solvent of the filtrate was removed under reduced pressure, charcoal (1.44 g) and methanol (44 mL) were added, and the resulting mixture was stirred under reflux for 10 min, followed by filtration in the heat. The filter cake was washed with hot methanol (50 mL, 65 °C), the wash solution and the filtrate were combined, and the solvent was removed under reduced pressure. The resulting solid was dissolved in boiling methanol (50 mL), 2-propanol (68 mL, 20 °C) was added, and the product was then crystallized at 20 °C over a period of 1 day. The solvent was removed via a syringe, and the product was dried in vacuo (0.001 mbar, 20 °C, 48 h) to give **4** in 68% yield as a colorless crystalline solid (3.51 g, 13.6 mmol); mp 189 °C. ^{1}H NMR ([D$_6$]DMSO): δ 1.68−1.72 and 2.15−2.25 (m, 4 H, CC*H*$_2$CH$_2$N), 3.12−3.15 (m, 4 H, CCH$_2$C*H*$_2$N), 5.41 (s, 1 H, O*H*), 5.98 (s, 2 H, OC*H*$_2$O), 6.85−6.92 (m, 2 H, *H*-5, *H*-6, C$_6$H$_3$), 6.98−6.99 (m, 1 H, *H*-2, C$_6$H$_3$), 9.1 (br s, 2 H, N*H*$_2$). ^{13}C NMR ([D$_6$]DMSO): δ 34.4 (C*C*H$_2$CH$_2$N), 39.8 (CCH$_2$*C*H$_2$N), 68.3 (*C*OH), 100.9 (O*C*H$_2$O), 105.5 (*C*-2, C$_6$H$_3$), 107.7 (*C*-5, C$_6$H$_3$), 117.5 (*C*-6, C$_6$H$_3$), 142.7 (*C*-1, C$_6$H$_3$), 145.9 (*C*-3 or *C*-4, C$_6$H$_3$), 147.1 (*C*-3 or *C*-4, C$_6$H$_3$). Anal. Calcd for C$_{12}$H$_{16}$ClNO$_3$: C, 55.93; H, 6.26; N, 5.43. Found: C, 55.7; H, 6.3; N, 5.3.

Preparation of (*R*)-(3-(4-Methoxyphenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl Methanesulfonate (5). The synthesis was performed on the basis of ref 27: Triethylamine (3.04 g, 30.0 mmol) was added in one single portion at 20 °C to a stirred mixture of **18** (4.40 g, 19.7 mmol) in dichloromethane (100 mL), the resulting mixture was cooled to 0 °C, and methanesulfonyl chloride (2.49 g, 21.7 mmol) was added dropwise within 3 min. The resulting mixture was stirred at 0 °C for 1 h and then at 20 °C for a further 3 h. Dichloromethane (400 mL) and water (200 mL) were added one after another, and the organic layer was separated and washed successively with water (100 mL), hydrochloric acid (2 M, 2 × 100 mL), and a saturated aqueous sodium hydrogencarbonate solution (100 mL). The solvent was removed under reduced pressure, and the resulting residue was crystallized from boiling methanol (400 mL; slow cooling and crystallization at 20 °C over a period of 1 day). The product was isolated by suction filtration and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **5** in 71% yield as a colorless crystalline solid (4.24 g, 14.1 mmol); mp 152 °C. ^{1}H NMR ([D$_6$]DMSO): δ 3.25 (s, 3 H, SC*H*$_3$), 3.73 (s, 3 H, OC*H*$_3$), 3.79 (δ_A), 4.14 (δ_B), 4.45 (δ_X), 4.50 (δ_Y), and 4.96 (δ_M) ($^2J_{AB}$ = 9.2 Hz, $^2J_{XY}$ = 11.5 Hz, $^3J_{AM}$ = 6.3 Hz, $^3J_{BM}$ = −9.3 Hz, $^3J_{MX}$ = 5.5 Hz, $^3J_{MY}$ = 2.7 Hz, 5 H, OC*H*$_X$*H*$_Y$C*H*$_M$C*H*$_A$*H*$_B$N), 6.93−6.99 (m, 2 H, *H*-3/*H*-5, C$_6$H$_4$), 7.42−7.47 (m, 2 H, *H*-2/*H*-6, C$_6$H$_4$). ^{13}C NMR ([D$_6$]DMSO): δ 36.8 (S*C*H$_3$), 46.3 (OCH$_2$-CH*C*H$_2$N), 55.3 (O*C*H$_3$), 69.81 (OCH$_2$*C*HCH$_2$N), 69.84 (O*C*H$_2$-CHCH$_2$N), 114.1 (*C*-3/*C*-5, C$_6$H$_4$), 120.1 (*C*-2/*C*-6, C$_6$H$_4$), 131.2 (*C*-1, C$_6$H$_4$), 153.9 (*C*═O), 155.7 (*C*-4, C$_6$H$_4$). Anal. Calcd for C$_{12}$H$_{15}$NO$_6$S: C, 47.83; H, 5.02; N, 4.65; S, 10.64. Found: C, 47.7; H, 4.9; N, 4.6; S, 10.7.

(27) Gates, K. S.; Silverman, R. B. *J. Am. Chem. Soc.* **1990**, *112*, 9364−9372.

Preparation of *rac*-(3-(4-Methoxyphenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl Methanesulfonate (*rac*-5). This compound was prepared analogously to the synthesis of **5**, starting from *rac*-**18** (4.15 g, 18.6 mmol). Compound *rac*-**5** was isolated in 89% yield as a colorless crystalline solid (4.98 g, 16.5 mmol); mp 129 °C. The NMR data of this compound were identical with those obtained for **5**. Anal. Calcd for $C_{12}H_{15}NO_6S$: C, 47.83; H, 5.02; N, 4.65; S, 10.64. Found: C, 47.7; H, 5.0; N, 4.5; S, 10.4.

Tetramethoxysilane (6). This compound was commercially available (Fluka, Art. 87680).

Preparation of Dimethoxybis(3,4-methylenedioxyphenyl)silane (7). A mixture of magnesium turnings (2.80 g, 115 mmol) and iodine (100 mg, 394 μmol of I_2) was heated in a sealed flask at 80 °C for 30 min and then cooled to 20 °C, followed by addition of THF (15 mL). A solution of 1-bromo-3,4-methylenedioxybenzene (21.0 g, 104 mmol) in THF (60 mL) was added dropwise in such a way that, after the reaction had started, the solvent refluxed permanently. The mixture was stirred under reflux for a further 1.5 h, cooled to 20 °C, and then added dropwise at 20 °C within 40 min to a stirred solution of **6** (7.95 g, 52.2 mmol) in THF (85 mL), and the resulting mixture was stirred at 20 °C for 15 h. The solvent was removed under reduced pressure, water (1 L) and diethyl ether (1 L) were added one after another, the organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 × 300 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, the residue was distilled in a Kugelrohr apparatus (oven temperature 180 °C, 0.01 mbar), and the resulting solid was recrystallized from boiling diethyl ether (12 mL; slow cooling and crystallization at −20 °C over a period of 9 days). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 2 h) to give **7** in 36% yield as a colorless crystalline solid (6.18 g, 18.6 mmol); mp 60 °C. ^{1}H NMR (CD_2Cl_2): δ 3.57 (s, 6 H, OCH_3), 5.95 (s, 4 H, OCH_2O), 6.86 (dd, 2 H, *H*-5, C_6H_3), 7.05 (dd, 2 H, *H*-2, C_6H_3), and 7.12 (dd, 2 H, *H*-6, C_6H_3) ($^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.1 Hz, $^5J_{HH}$ = 0.5 Hz). ^{13}C NMR (CD_2Cl_2): δ 51.0 (O*C*H$_3$), 101.3 (O*C*H$_2$O), 108.9 (*C*-5, C_6H_3), 114.1 (*C*-2, C_6H_3), 125.8 (*C*-1, C_6H_3), 129.7 (*C*-6, C_6H_3), 147.9 (*C*-3 or *C*-4, C_6H_3), 149.9 (*C*-3 or *C*-4, C_6H_3). ^{29}Si NMR (CD_2Cl_2): δ −29.2. Anal. Calcd for $C_{16}H_{16}O_6Si$: C, 57.82; H, 4.85. Found: C, 57.8; H, 4.9.

Preparation of Bis(3,4-methylenedioxyphenyl)divinylsilane (8). Protocol A. A 1.7 M solution of vinylmagnesium chloride in THF (67 mL, 114 mmol of CH_2═CHMgCl) was added dropwise at 20 °C within 2 h to a stirred solution of **7** (17.0 g, 51.1 mmol) in diethyl ether (200 mL), and the resulting mixture was stirred at 20 °C for 1 h. The precipitate was isolated by filtration and washed with diethyl ether (2 × 250 mL), the filtrate and the wash solutions were combined, and the resulting precipitate was removed by filtration and then discarded. The solvent of the filtrate was removed under reduced pressure, the residue was distilled in a Kugelrohr apparatus (oven temperature 160 °C, 0.02 mbar), and the resulting solid was recrystallized from boiling acetone (13 mL; slow cooling and crystallization at −20 °C over a period of 5 days). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **8** in 71% yield as a colorless crystalline solid (11.8 g, 36.4 mmol); mp 70−71 °C. Anal. Calcd for $C_{18}H_{16}O_4Si$: C, 66.64; H, 4.97. Found: C, 66.4; H, 5.1.

Protocol B. A mixture of magnesium turnings (13.3 g, 547 mmol) and iodine (350 mg, 1.38 mmol of I_2) was heated in a sealed flask at 80 °C for 30 min and then cooled to 20 °C, followed by addition of THF (20 mL). A solution of 1-bromo-3,4-methylenedioxybenzene (100 g, 497 mmol) in THF (250 mL) was added dropwise in such a way that, after the reaction had started, the solvent refluxed permanently. The mixture was stirred under reflux for a further 1.5 h, cooled to 20 °C, and then added dropwise at 20 °C within 2 h to a stirred solution of **6** (37.8 g, 248 mmol) in THF (400 mL), and the resulting mixture was stirred at 20 °C for 15 h. A 1.7 M solution of vinylmagnesium chloride in THF (310 mL, 527 mmol of CH_2═CHMgCl) was added dropwise at 20 °C within 3.5 h, and the resulting mixture was stirred at 20 °C for 18 h. The precipitate was isolated by filtration and washed with diethyl ether (3 × 100 mL), the filtrate and the wash solutions were combined, and water (10 mL) was added dropwise at 20 °C to quench the excess Grignard reagent (exothermic reaction). The organic solvent was removed under reduced pressure, water (1 L) and diethyl ether (2 L) were added one after another, the organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 × 250 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, the residue was distilled in a Kugelrohr apparatus (oven temperature <130 °C, 0.2 mbar (byproduct, discarded); oven temperature 160 °C, 0.02 mbar (product)), and the resulting solid was recrystallized from boiling acetone (40 mL; slow cooling and crystallization at −20 °C over a period of 5 days). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **8** in 47% yield as a colorless crystalline solid (38.2 g, 118 mmol); mp 70−71 °C. ^{1}H NMR (CD_2Cl_2): δ 5.79 (δ_A), 6.25 (δ_B), and 6.45 (δ_G) ($^2J_{AB}$ = 4.0 Hz, $^3J_{AG,trans}$ = 20.0 Hz, $^3J_{BG,cis}$ = 14.6 Hz, 6 H, SiCH_GC$H_A$$H_B$), 5.94 (s, 4 H, OC$H_2$O), 6.86 (dd, 2 H, *H*-5, C_6H_3), 6.95 (dd, 2 H, *H*-2, C_6H_3), and 7.01 (dd, 2 H, *H*-6, C_6H_3) ($^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.1 Hz, $^5J_{HH}$ = 0.5 Hz). ^{13}C NMR (CD_2Cl_2): δ 101.2 (O*C*H$_2$O), 108.9 (*C*-5, C_6H_3), 114.8 (*C*-2, C_6H_3), 127.5 (*C*-1, C_6H_3), 130.1 (*C*-6, C_6H_3), 134.4 (*C*HCH$_2$), 136.6 (CH*C*H$_2$), 147.9 (*C*-3 or *C*-4, C_6H_3), 149.3 (*C*-3 or *C*-4, C_6H_3). ^{29}Si NMR (CD_2Cl_2): δ −19.8. Anal. Calcd for $C_{18}H_{16}O_4Si$: C, 66.64; H, 4.97. Found: C, 66.4; H, 5.0.

Preparation of Bis(2-hydroxyethyl)bis(3,4-methylenedioxyphenyl)silane (9). 9-Borabicyclo[3.3.1]nonane (54.9 g, 450 mmol) was added in one single portion at 20 °C to a stirred solution of **8** (48.7 g, 150 mmol) in THF (220 mL), and the resulting solution was stirred at 20 °C for 44 h. Subsequently, water (30 mL) was added dropwise to the stirred mixture at 20 °C within 30 min, and stirring was continued at 20 °C for a further 20 min. After that a 3 M aqueous sodium hydroxide solution (120 mL) was added dropwise to the stirred mixture at 20 °C within 45 min, and stirring was continued at 20 °C for a further 20 min. Subsequently, an aqueous hydrogen peroxide solution (30%, 120 mL) was added dropwise at 0 °C within 1 h while stirring, and the resulting mixture was stirred at 0 °C for 20 min, heated under reflux for 4.5 h, and then stirred at 20 °C for a further 15 h. The organic layer was separated, the solvent was removed under reduced pressure, and the residue and the aqueous phase were combined, followed by extraction with dichloromethane (4 × 400 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the byproduct cyclooctane-1,5-diol was removed by distillation in a Kugelrohr apparatus (oven temperature 130 °C, 0.03 mbar). The residue was crystallized from boiling *n*-hexane/ethyl acetate/ethanol (10:10:1 (v/v/v)) (550 mL; slow cooling and crystallization at 20 °C over a period of 2 days), and the product was isolated by suction filtration and then dried in vacuo (0.001 mbar, 20 °C, 20 h) to give **9** in 69% yield as a colorless crystalline solid (37.5 g, 104 mmol); mp 106 °C. ^{1}H NMR ($CDCl_3$): δ 1.46 (t, $^3J_{HH}$ = 7.6 Hz, 4 H, SiCH_2C), 2.1 (br s, 2 H, O*H*), 3.77 (t, $^3J_{HH}$ = 7.6 Hz, 4 H, CCH_2O), 5.92 (s, 4 H, OCH_2O), 6.82 (dd, 2 H, *H*-5, C_6H_3), 6.91 (dd, 2 H, *H*-2, C_6H_3), and 6.96 (dd, 2 H, *H*-6, C_6H_3) ($^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.1 Hz, $^5J_{HH}$ = 0.5 Hz). ^{13}C NMR ($CDCl_3$): δ 18.4 (Si*C*H$_2$C), 59.3 (C*C*H$_2$O), 100.7 (O*C*H$_2$O), 108.8 (*C*-5, C_6H_3), 113.8 (*C*-2, C_6H_3), 127.8 (*C*-1, C_6H_3), 128.9 (*C*-6, C_6H_3), 147.5 (*C*-3 or *C*-4, C_6H_3), 148.8 (*C*-3 or *C*-4, C_6H_3). ^{29}Si NMR ($CDCl_3$): δ −8.9. Anal. Calcd for $C_{18}H_{20}O_6Si$: C, 59.98; H, 5.59. Found: C, 60.0; H, 5.6.

Preparation of Bis(3,4-methylenedioxyphenyl)bis(2-((4-methylphenyl)sulfonyloxy)ethyl)silane (10). *p*-Toluenesulfonyl chlo-

ride (4.04 g, 21.2 mmol) was added in one single portion at 20 °C to a stirred solution of **9** (3.46 g, 9.60 mmol) in dichloromethane (50 mL), followed by addition of triethylamine (2.15 g, 21.2 mmol) in one single portion at 20 °C and stirring of the resulting mixture at 20 °C for 15 h. Water (50 mL) and dichloromethane (50 mL) were added, the organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (column dimensions, 32 × 5.5 cm; silica gel (32−63 μm, ICN 02826), 290 g; eluent, *n*-hexane/ethyl acetate (2:1 (v/v))) and then crystallized from boiling *n*-hexane/ethyl acetate (2:1 (v/v)) (75 mL; slow cooling and crystallization at 20 °C over a period of 15 h and then at −20 °C over a period of 3 days). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **10** in 70% yield as a colorless crystalline solid (4.50 g, 6.73 mmol); mp 93 °C. ^{1}H NMR (CD_2Cl_2): δ 1.48 (AA′ part of an AA′XX′ system, $^2J_{AA'} = 10.1$ Hz, $^2J_{XX'} = 14.2$ Hz, $^3J_{AX} = {}^3J_{A'X'} = 11.1$ Hz, $^3J_{A'X} = {}^3J_{AX'} = 5.7$ Hz, 4 H, SiCH_2C), 2.44 (s, 6 H, CCH_3), 4.05 (XX′ part of an AA′XX′ system, 4 H, CCH_2O), 5.96 (s, 4 H, OCH_2O), 6.71−6.72 and 6.78−6.82 (m, 6 H, *H*-2/*H*-5/*H*-6, C_6H_3), 7.31−7.35 (m, 4 H, *H*-3/*H*-5, C_6H_4), 7.65−7.68 (m, 4 H, *H*-2/*H*-6, C_6H_4). ^{13}C NMR (CD_2Cl_2): δ 15.3 (SiCH_2C), 21.7 (CCH_3), 68.7 (CCH_2O), 101.4 (OCH_2O), 109.2, 113.8, and 129.3 (*C*-2/*C*-5/*C*-6, C_6H_3), 125.4 (*C*-1, C_6H_3), 128.0 (*C*-2/*C*-6, C_6H_4), 130.2 (*C*-3/*C*-5, C_6H_4), 133.5 (*C*-1, C_6H_4), 145.3 (*C*-4, C_6H_4), 148.2 (*C*-3 or *C*-4, C_6H_3), 149.8 (*C*-3 or *C*-4, C_6H_3). ^{29}Si NMR (CD_2Cl_2): δ −10.1. Anal. Calcd for $C_{32}H_{32}O_{10}S_2Si$: C, 57.47; H, 4.82; S, 9.59. Found: C, 57.3; H, 4.8; S, 9.6.

Preparation of 1-Benzyl-4,4-bis(3,4-methylenedioxyphenyl)-4-silapiperidine (11). Protocol A. Benzylamine (7.05 g, 65.8 mmol) was added in one single portion at 20 °C to a stirred solution of **10** (4.40 g, 6.58 mmol) in acetonitrile (65 mL), followed by addition of triethylamine (1.33 g, 13.1 mmol) in one single portion at 20 °C and stirring of the resulting mixture under reflux for 21 h. The solvent was removed under reduced pressure, diethyl ether (130 mL) and water (80 mL) were added one after another, the organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, the excess benzylamine was removed by distillation in a Kugelrohr apparatus (oven temperature 130 °C, 0.001 mbar), and the oily residue was purified by crystallization from boiling acetonitrile (5 mL; slow cooling and crystallization at 4 °C over a period of 6 days). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 30 h) to give **11** in 71% yield as a colorless crystalline solid (2.02 g, 4.68 mmol); mp 91 °C. Anal. Calcd for $C_{25}H_{25}NO_4Si$: C, 69.58; H, 5.84; N, 3.25. Found: C, 69.7; H, 5.8; N, 3.2.

Protocol B. *p*-Toluenesulfonyl chloride (91.8 g, 482 mmol) was added in one single portion at 20 °C to a stirred solution of **9** (82.7 g, 229 mmol) in dichloromethane (1.24 L), followed by addition of triethylamine (51.1 g, 505 mmol) in one single portion. The resulting mixture was stirred at 20 °C for 40 h, water (900 mL) and dichloromethane (500 mL) were added one after another, the organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 450 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the resulting residue was dried in vacuo (0.001 mbar, 20 °C, 1 h) and then dissolved in acetonitrile (1 L). Benzylamine (244 g, 2.28 mol) and triethylamine (46.3 g, 458 mmol) were added one after another in one single portion each at 20 °C, and the resulting mixture was stirred under reflux for 4 days. The solvent was removed under reduced pressure, diethyl ether (2.4 L) and water (1.2 L) were added one after another, the organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 × 600 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, the excess benzylamine was removed by distillation under reduced pressure, and the oily residue was purified by crystallization from boiling acetonitrile (400 mL; slow cooling and crystallization at −20 °C over a period of 2 days). The precipitate was isolated by filtration, washed with cold acetonitrile (70 mL, −20 °C), dried in vacuo (0.001 mbar, 20 °C, 4 h), and then further purified by recrystallization from boiling acetonitrile (260 mL; slow cooling and crystallization at −20 °C over a period of 1 day). The product was isolated by filtration, washed with cold acetonitrile (80 mL, −20 °C), and then dried in vacuo (0.001 mbar, 20 °C, 4 h) to give **11** in 59% yield (58.2 g, 135 mmol) as a colorless crystalline solid; mp 91 °C. ^{1}H NMR (CD_2Cl_2): δ 1.24−1.32 (m, 4 H, SiCH_2C), 2.72−2.80 (m, 4 H, CCH_2N), 3.55 (s, 2 H, N$CH_2C_6H_5$), 5.94 (s, 4 H, OCH_2O), 6.86 (dd, 2 H, *H*-5, C_6H_3), 6.97 (dd, 2 H, *H*-2, C_6H_3), and 7.03 (dd, 2 H, *H*-6, C_6H_3) ($^3J_{HH} = 7.6$ Hz, $^4J_{HH} = 1.1$ Hz, $^5J_{HH} = 0.5$ Hz), 7.20−7.36 (m, 5 H, C_6H_5). ^{13}C NMR (CD_2Cl_2): δ 12.1 (SiCH_2C), 52.6 (CCH_2N), 62.9 (N$CH_2C_6H_5$), 101.2 (OCH_2O), 109.0 (*C*-5, C_6H_3), 114.0 (*C*-2, C_6H_3), 127.1 (*C*-4, C_6H_5), 128.5 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_5), 129.0 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_5), 129.1 (*C*-6, C_6H_3), 129.3 (*C*-1, C_6H_3), 140.2 (*C*-1, C_6H_5), 147.9 (*C*-3 or *C*-4, C_6H_3), 149.1 (*C*-3 or *C*-4, C_6H_3). ^{29}Si NMR (CD_2Cl_2): δ −14.3. Anal. Calcd for $C_{25}H_{25}NO_4Si$: C, 69.58; H, 5.84; N, 3.25. Found: C, 69.6; H, 5.9; N, 3.3.

Preparation of 4,4-Bis(3,4-methylenedioxyphenyl)-4-silapiperidinium Chloride (12). 1-Chloroethyl chloroformate (7.26 g, 50.8 mmol) was added dropwise at 0 °C within 5 min to a stirred solution of **11** (17.7 g, 41.0 mmol) in dichloromethane (300 mL), and the resulting mixture was warmed to 20 °C within 20 min and then stirred under reflux for 80 min. The solvent was removed under reduced pressure, and the resulting residue was dried in vacuo (0.001 mbar, 20 °C, 30 min), followed by addition of methanol (180 mL) in one single portion at 20 °C. The resulting mixture was heated under reflux for 1 h (formation of a precipitate), the precipitate was dissolved by addition of methanol (450 mL) at reflux temperature, and **12** was then crystallized by slow cooling of the solution (crystallization at 20 °C over a period of 24 h and then at −20 °C over a period of 6 days). The product was isolated by suction filtration and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **12** in 85% yield as a colorless crystalline solid (13.1 g, 34.7 mmol); mp 262 °C (dec). ^{1}H NMR ([D_6]DMSO): δ 1.50−1.60 (m, 4 H, SiCH_2C), 3.11−3.21 (m, 4 H, CCH_2N), 6.01 (s, 4 H, OCH_2O), 6.96−7.00 (m, 2 H, *H*-5, C_6H_3), 7.00−7.04 (m, 2 H, *H*-6, C_6H_3), 7.11−7.13 (m, 2 H, *H*-2, C_6H_3), 9.2 (br s, 2 H, NH_2). ^{13}C NMR ([D_6]DMSO): δ 8.3 (SiCH_2C), 43.4 (CCH_2N), 100.8 (OCH_2O), 108.9 (*C*-5, C_6H_3), 113.4 (*C*-2, C_6H_3), 125.9 (*C*-1, C_6H_3), 128.8 (*C*-6, C_6H_3), 147.5 (*C*-3 or *C*-4, C_6H_3), 149.0 (*C*-3 or *C*-4, C_6H_3). ^{29}Si NMR ([D_6]DMSO): δ −16.0. Anal. Calcd for $C_{18}H_{20}ClNO_4Si$: C, 57.21; H, 5.33; N, 3.71. Found: C, 57.5; H, 5.4; N, 3.6.

Preparation of (*S*)-3-(4-Methoxyphenyl)-5-(4,4-bis(3,4-methylenedioxyphenyl)-4-silapiperidin-1-yl)methyl-1,3-oxazolidin-2-one (13). Compound **5** (10.2 g, 33.9 mmol) was added in one single portion at 20 °C to a stirred suspension of **12** (12.8 g, 33.9 mmol) in acetonitrile (270 mL), followed by addition of potassium carbonate (10.8 g, 78.1 mmol) and potassium iodide (730 mg, 4.40 mmol) in one single portion each. The resulting mixture was stirred under reflux for 20 h, the solvent was removed under reduced pressure, and dichloromethane (660 mL) and water (440 mL) were added successively. The organic layer was separated, the aqueous phase was extracted with dichloromethane (2 × 440 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the oily residue was crystallized from boiling ethanol (1.25 L; slow cooling and crystallization at 20 °C over a period of 1 day and then at −20 °C over a period of 3 days). The product was isolated

by suction filtration, washed with ethanol (3 × 10 mL), and then further purified by column chromatography on aluminum oxide (column dimensions, 39 × 8 cm; aluminum oxide (neutral, type 507C, Brockmann I, 150 mesh, 58 Å; Aldrich, Art. 19,977-4), 2.30 kg, deactivated with 6% water; eluent, dichloromethane/*n*-hexane/ethyl acetate (2:1:1 (v/v/v))). The resulting solid was finally recrystallized from boiling ethanol/dichloromethane (24:1 (v/v)) (1.25 L; slow cooling and crystallization at 20 °C over a period of 3 days and then at −20 °C over a period of 9 days). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **13** in 50% yield as a colorless crystalline solid (9.29 g, 17.0 mmol); mp 152 °C. ^{1}H NMR (CD_2Cl_2): δ 1.22−1.33 (m, 4 H, SiCH_2C), 2.70 (δ_A), 2.85 (δ_B), 3.76 (δ_X), 4.01 (δ_Y), and 4.68 (δ_M) ($^2J_{AB}$ = 13.6 Hz, $^2J_{XY}$ = 8.8 Hz, $^3J_{AM}$ = 6.0 Hz, $^3J_{BM}$ = 5.5 Hz, $^3J_{MX}$ = 6.6 Hz, $^3J_{MY}$ = −8.6 Hz, 5 H, NC$H_A$$H_BCH_MCH_X$$H_Y$NC(O)), 2.86−2.96 (m, 4 H, SiCH$_2$CH_2N), 3.79 (s, 3 H, OCH_3), 5.94 (s, 4 H, OCH_2O), 6.85 (dd, 2 H, *H*-5, C_6H_3), 6.95 (dd, 2 H, *H*-2, C_6H_3), and 7.00 (dd, 2 H, *H*-6, C_6H_3) ($^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.1 Hz, $^5J_{HH}$ = 0.5 Hz), 6.89−6.93 (m, 2 H, *H*-3/*H*-5, C_6H_4), 7.42−7.47 (m, 2 H, *H*-2/*H*-6, C_6H_4). ^{13}C NMR (CD_2Cl_2): δ 11.9 (Si*C*H$_2$C), 49.7 (NCH$_2$CH*C*H$_2$NC(O)), 53.6 (SiCH$_2$*C*H$_2$N), 55.8 (O*C*H$_3$), 60.8 (N*C*H$_2$CHCH$_2$NC(O)), 71.8 (NCH$_2$*C*HCH$_2$NC(O)), 101.2 (O*C*H$_2$O), 109.0 (*C*-5, C_6H_3), 113.9 (*C*-2, C_6H_3), 114.4 (*C*-3/*C*-5, C_6H_4), 120.4 (*C*-2/*C*-6, C_6H_4), 128.9 (*C*-1, C_6H_3), 129.1 (*C*-6, C_6H_3), 132.2 (*C*-1, C_6H_4), 148.0 (*C*-3 or *C*-4, C_6H_3), 149.2 (*C*-3 or *C*-4, C_6H_3), 155.3 (*C*═O), 156.6 (*C*-4, C_6H_4). ^{29}Si NMR (CD_2Cl_2): δ −15.0. Anal. Calcd for $C_{29}H_{30}N_2O_7Si$: C, 63.72; H, 5.53; N, 5.12. Found: C, 63.8; H, 5.5; N, 5.1.

Preparation of *rac*-3-(4-Methoxyphenyl)-5-(4,4-bis(3,4-methylenedioxyphenyl)-4-silapiperidin-1-yl)methyl-1,3-oxazolidin-2-one (*rac*-13). This compound was prepared analogously to the synthesis of **13**, starting from *rac*-**5** (2.23 g, 7.40 mmol). Compound *rac*-**13** was isolated in 60% yield as a colorless crystalline solid (2.44 g, 4.46 mmol); mp 141−142 °C. The NMR data of this compound were identical with those obtained for **13**. Anal. Calcd for $C_{29}H_{30}N_2O_7Si$: C, 63.72; H, 5.53; N, 5.12. Found: C, 63.7; H, 5.5; N, 5.0.

Preparation of (*S*,*S*)-*Si*,*Si*′-Oxybis(3-(4-methoxyphenyl)-5-(4-(3,4-methylenedioxyphenyl)-4-silapiperidin-1-yl)methyl-1,3-oxazolidin-2-one) (14). A solution of **13** (317 mg, 580 μmol) in trifluoroacetic acid (1.54 g, 13.5 mmol) was stirred at 0 °C for 20 h. The excess trifluoroacetic acid was removed under reduced pressure at 0 °C, and the residue was dried in vacuo (0.001 mbar, 0 °C, 30 min). Subsequently, acetonitrile/water (4:1 (v/v)) (15 mL) and a saturated aqueous sodium hydrogencarbonate solution (1.6 mL) were added one after another in one single portion each at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure, ethyl acetate (10 mL) and water (5 mL) were added one after another, the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the resulting residue was purified by preparative liquid chromatography (HPLC; for experimental details, see below) to give **14** in 12% yield as a colorless liquid (31.0 mg, 35.8 μmol), which crystallized at 20 °C; mp 105−106 °C (dec); $[\alpha]_D^{20}$ −34.0 (*c* 0.10, DMSO). ^{1}H NMR (CD_2Cl_2): δ 0.92−1.12 (m, 8 H, SiCH_2C), 2.65−2.86 (m, 4 H, NCH_2CHCH$_2$NC(O)), 2.86−2.90 (m, 8 H, SiCH$_2$CH_2N), 3.72−4.03 (m, 10 H, NCH$_2$CHCH_2NC(O), OCH_3), 4.61−4.70 (m, 2 H, NCH$_2$C*H*CH$_2$NC(O)), 5.94 (s, 4 H, OCH_2O), 6.85 (dd, 2 H, *H*-5, C_6H_3), 6.95 (dd, 2 H, *H*-2, C_6H_3), and 7.02 (dd, 2 H, *H*-6, C_6H_3) ($^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.1 Hz, $^5J_{HH}$ = 0.4 Hz), 6.88−6.94 (m, 4 H, *H*-3/*H*-5, C_6H_4), 7.41−7.47 (m, 4 H, *H*-2/*H*-6, C_6H_4). ^{13}C NMR (CD_2Cl_2): δ 15.0 (Si*C*H$_2$C), 49.6 (NCH$_2$CH*C*H$_2$NC(O)), 53.5 (SiCH$_2$*C*H$_2$N), 55.7 (O*C*H$_3$), 60.5 (NCH$_2$CHCH$_2$NC(O)), 71.8 (NCH$_2$*C*HCH$_2$NC(O)), 101.2 (O*C*H$_2$O), 108.9 (*C*-5, C_6H_3), 112.9 (*C*-2, C_6H_3), 114.4 (*C*-3/*C*-5, C_6H_4), 120.3 (*C*-2/*C*-6, C_6H_4), 128.1 (*C*-6, C_6H_3), 130.2 (*C*-1, C_6H_3), 132.2 (*C*-1, C_6H_4), 147.8 (*C*-3 or *C*-4, C_6H_3), 149.4 (*C*-3 or *C*-4, C_6H_3), 155.2 (*C*═O), 156.5 (*C*-4, C_6H_4). ^{29}Si NMR (CD_2Cl_2): δ −9.0. Anal. Calcd for $C_{44}H_{50}N_4O_{11}Si_2$: C, 60.95; H, 5.81; N, 6.46. Found: C, 60.6; H, 5.8; N, 6.1.

4-Methoxyaniline (15). This compound was commercially available (ABCR, Art. A10946).

Preparation of (*R*)-3-((4-Methoxyphenyl)amino)propane-1,2-diol (16). Protocol A. (*S*)-Glycidol (3.79 g, 51.2 mmol) was added in one single portion at 20 °C to a stirred solution of **17** (9.79 g, 45.9 mmol) in methanol (100 mL), and the resulting mixture was stirred under reflux for 4 days. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (column dimensions, 30 × 5.5 cm; silica gel (32−63 μm, ICN 02826), 290 g; eluent, ethyl acetate/*n*-hexane (2:1 (v/v))) to afford an oily product. Ethanol (130 mL) and palladium on carbon (2.40 g) (Aldrich, 33.010-8, Degussa type E101 NE/W) were added, and the resulting suspension was stirred under a hydrogen atmosphere (3 bar) at 20 °C for 40 h, followed by filtration. The solvent of the filtrate was removed under reduced pressure, and the residue was purified by distillation in a Kugelrohr apparatus (oven temperature 150 °C, 0.02 mbar). The resulting solid was recrystallized from boiling *n*-hexane/ethyl acetate (1:1 (v/v)) (50 mL; slow cooling and crystallization at 20 °C over a period of 2 days). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **16** in 80% yield as a colorless crystalline solid (7.21 g, 36.6 mmol); mp 67 °C. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.7; H, 7.6; N, 7.1.

Protocol B. The synthesis was performed on the basis of ref 27: A solution of (*S*)-glycidol (22.2 g, 300 mmol) in methanol (250 mL) was added dropwise at 50 °C within 5 h to a stirred solution of **15** (74.2 g, 602 mmol) in methanol (250 mL), and the resulting mixture was stirred at 50 °C for 24 h and then under reflux for 9 h. The solvent was removed under reduced pressure, and the resulting residue was purified by distillation in a Kugelrohr apparatus (oven temperature <110 °C, 0.02 mbar (byproduct, discarded); oven temperature 160 °C, 0.005 mbar (product)). The resulting oily product was crystallized from boiling *n*-hexane/ethyl acetate (1:1 (v/v)) (770 mL; decantation from the black oily residue, followed by slow cooling and crystallization at 0 °C over a period of 2 h), the solvent was removed via a syringe, and the resulting solid was recrystallized from boiling *n*-hexane/ethyl acetate (1:1 (v/v)) (660 mL; slow cooling and crystallization at 20 °C over a period of 24 h and then at 0 °C over a period of 2 h). The product was isolated by removal of the solvent via a syringe and then dried in vacuo (0.001 mbar, 20 °C, 24 h) to give **16** in 41% yield as a colorless crystalline solid (24.1 g, 122 mmol); mp 67 °C. ^{1}H NMR ([D$_6$]DMSO): δ 2.82 (δ_A), 3.08 (δ_B), 3.37 (δ_C), 3.61 (δ_D), 4.55 (δ_E), and 4.70 (δ_F) ($^2J_{AB}$ = −12.6 Hz, $^3J_{AD}$ = 7.0 Hz, $^3J_{BD}$ = 4.7 Hz, $^3J_{CD}$ = 5.5 Hz, $^3J_{CE}$ = 5.6 Hz, $^3J_{DF}$ = 5.0 Hz, 7 H, H_EOC(H_C)$_2$C(OH_F)H_DC$H_A$$H_B$N), 3.62 (s, 3 H, OC$H_3$), 4.9 (br s, 1 H, N*H*), 6.52−6.56 (m, 2 H, *H*-3/*H*-5, C_6H_4), 6.67−6.71 (m, 2 H, *H*-2/*H*-6, C_6H_4). ^{13}C NMR ([D$_6$]DMSO): δ 47.3 (OCH$_2$CHCH$_2$N), 55.3 (O*C*H$_3$), 64.1 (O*C*H$_2$CHCH$_2$N), 70.1 (OCH$_2$*C*HCH$_2$N), 113.2 (*C*-2/*C*-6, C_6H_4), 114.6 (*C*-3/*C*-5, C_6H_4), 143.3 (*C*-1, C_6H_4), 150.6 (*C*-4, C_6H_4). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.1; H, 7.6; N, 7.1.

Preparation of *rac*-3-((4-Methoxyphenyl)amino)propane-1,2-diol (*rac*-16). This compound was prepared analogously to the synthesis of **16** (protocol B), starting from *rac*-glycidol (4.07 g, 54.9 mmol). Compound *rac*-**16** was isolated in 38% yield as a colorless crystalline solid (4.10 g, 20.8 mmol); mp 76 °C. The NMR data of this compound were identical with those obtained for **16**. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.8; H, 7.3; N, 6.9.

***N*-Benzyl-4-methoxyaniline (17).** This compound was commercially available (Lancaster, Art. 11158).

Preparation of (*R*)-5-(Hydroxymethyl)-3-(4-methoxyphenyl)-1,3-oxazolidin-2-one (18). The synthesis was performed on the basis of ref 27: Potassium *tert*-butoxide (415 mg, 3.70 mmol) and diethyl carbonate (17.5 g, 148 mmol) were added one after another in one single portion each at 20 °C to a stirred suspension of **16** (14.6 g, 74.0 mmol) in toluene (100 mL), and the resulting mixture was stirred under reflux for 1 h. The solvent was removed under reduced pressure, and the residue was crystallized from boiling ethanol (310 mL; slow cooling and crystallization at −20 °C over a period of 1 day). The product was isolated by suction filtration, washed with cold ethanol (20 mL, −20 °C), and then dried in vacuo (0.001 mbar, 20 °C, 12 h) to give **18** in 88% yield as a colorless crystalline solid (14.5 g, 65.0 mmol); mp 164 °C. ^{1}H NMR ([D$_6$]-DMSO): δ 3.55 (δ_A), 3.65 (δ_B), 3.78 (δ_C), 4.03 (δ_D), 4.65 (δ_E), and 5.19 (δ_F) ($^2J_{AB}$ = 12.3 Hz, $^2J_{CD}$ = 8.8 Hz, $^3J_{AE}$ = 4.2 Hz, $^3J_{AF}$ = 5.8 Hz, $^3J_{BE}$ = 3.5 Hz, $^3J_{BF}$ = 5.6 Hz, $^3J_{CE}$ = 6.4 Hz, $^3J_{DE}$ = −9.1 Hz, 6 H, H_FOC$H_A$$H_BCH_ECH_C$$H_D$N), 3.73 (s, 3 H, OC$H_3$), 6.92−6.96 (m, 2 H, *H*-3/*H*-5, C$_6$H$_4$), 7.44−7.48 (m, 2 H, *H*-2/*H*-6, C$_6$H$_4$). ^{13}C NMR ([D$_6$]DMSO): δ 46.4 (OCH$_2$C*H*CH$_2$N), 55.2 (O*C*H$_3$), 61.7 (O*C*H$_2$CHCH$_2$N), 73.0 (OCH$_2$*C*HCH$_2$N), 114.0 (*C*-3/*C*-5, C$_6$H$_4$), 119.7 (*C*-2/*C*-6, C$_6$H$_4$), 131.8 (*C*-1, C$_6$H$_4$), 154.6 (*C*═O), 155.4 (*C*-4, C$_6$H$_4$). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.0; H, 5.8; N, 6.2.

Preparation of *rac*-5-(Hydroxymethyl)-3-(4-methoxyphenyl)-1,3-oxazolidin-2-one (*rac*-18). This compound was prepared analogously to the synthesis of **18**, starting from *rac*-**16** (4.00 g, 20.3 mmol). Compound *rac*-**18** was isolated in 96% yield as a colorless crystalline solid (4.35 g, 19.5 mmol); mp 139−140 °C. The NMR data of this compound were identical with those obtained for **18**. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.0; H, 5.8; N, 6.1.

Preparative Isolation of 14 by HPLC. The experimental conditions were as follows: LC pump, SunChrom SunFlow 100; detector, SunChrom SpectraFlow 600 (λ = 210 nm); column thermostat, Spark Mistral; column temperature, 10 °C; column (25 cm, i.d. 8 mm), GROM-SIL 120 ODS-5 ST (particle size, 5 μm); injection volumes, 40 μL (stock solution, 330 mg of the sample material dissolved in 8.0 mL of acetonitrile; sample loop, 200 μL); flow rate, 4.0 mL/min; solvent, water/acetonitrile (1:1 (v/v)), using an increase of 2% acetonitrile/min gradient. The solvent of the respective fractions obtained (byproduct, first fractions; **14**, following fractions) was removed under reduced pressure.

Crystal Structure Analyses. Suitable single crystals of **7**, **10**, and **13** resulted directly from the preparation. Single crystals of **8** were obtained from a solution of **8** (983 mg, 3.03 mmol) in acetone (5 mL) by slow evaporation of the solvent at 20 °C. Suitable single crystals of **12** resulted from vapor diffusion of diethyl ether (215 mL) into a solution of **12** (1.84 g, 4.87 mmol) in methanol (93 mL) at 20 °C over a period of 6 days. The crystals were mounted in inert oil (perfluoroalkyl ether, ABCR) 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.[28] All non-hydrogen atoms were refined anisotropically.[29] A riding model was employed in the refinement of the 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-612822 (**7**), CCDC-612823 (**8**), CCDC-612824 (**10**), CCDC-612825 (**12**), and CCDC-612826 (**13**). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax, (+44)1223/336033; e-mail, deposit@ccdc.cam.ac.uk).

Determination of the Enantiomeric Purity of 13 by ^{1}H NMR Spectroscopy. The enantiomeric purity of **13** was determined by ^{1}H NMR experiments using the chiral solvating agent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((*R*)-TFAE; Aldrich, Art. 211354). The NMR spectra were recorded at 22 °C on a Bruker Avance 500 NMR spectrometer operating at 500.1 MHz. The compositions of the samples used for the ^{1}H NMR experiments were as follows: **13** (*rac*-**13**), 27.4 μmol; (*R*)-TFAE, 41.2 μmol; CD_2Cl_2, 750 μL.

2D ^{1}H,^{1}H EXSY NMR Studies. ^{1}H, ^{13}C, and ^{29}Si NMR studies of the C/Si analogues **1a**·HCl and **1b**·HCl demonstrated the existence of two conformers of the respective ammonium cations (**1a**·HCl, molar ratio ca. 12:1; **1b**·HCl, molar ratio ca. 2:1) in solution (solvent [D$_6$]DMSO). These conformers are configurationally stable on the NMR time scale under the experimental conditions used. To prove the existence of the two conformers, 2D ^{1}H,^{1}H EXSY experiments were carried out at 22 °C (solvent [D$_6$]DMSO) using a Bruker Avance 500 NMR spectrometer. In the case of **1a**·HCl, the site exchange for the CCH_AH$_B$CH$_2$N and CCH$_2$CH_2N protons of the piperidinium skeleton and the *H*-2/*H*-6 protons of the 3,4-methylenedioxyphenyl substituent was observed in this study, showing strong cross-peaks between the respective signals of the two conformers. In the case of **1b**·HCl, the SiCH_2CH$_2$N and SiCH$_2$CH_2N protons of the 4-silapiperidinium skeleton were monitored. The mixing time was on the order of the spin−lattice relaxation time T_1, calculated by a standard 1D T_1-inversion recovery experiment.

ESI-MS Studies. (a) Chemicals. Water (HPLC gradient grade) was purchased from Acros. Acetic acid (98%, analytical reagent grade), ammonium hydroxide solution (25%, analytical reagent grade), and ammonium acetate (analytical reagent grade) were purchased from Fluka.

(b) Sample Preparations. A 10 mM aqueous ammonium acetate buffer was prepared from a 1.0 M stock solution by dilution with water and adjusting the pH with 98% acetic acid (pH 5), 0.25% ammonium hydroxide solution (pH 7.4), or 2.5% ammonium hydroxide solution (pH 10). For measurements at pH 1, 0.1 M hydrochloric acid was used as the solvent.

Sample solutions with a concentration of 10 μM were prepared from a 2.1 mM stock solution of **1b**·HCl in water/acetonitrile (2.5:1 (v/v)) or from a 1.2 mM stock solution of **14** in acetonitrile by dilution with the respective buffer (pH 5, pH 7.4, pH 10) or 0.1 M hydrochloric acid (pH 1) and were analyzed by ESI-MS (i) 30 min and (ii) 24 h after preparation.

Sample solutions with concentrations of 2.5 mM (pH 1, pH 5) or 1 mM (pH 7.4, pH 10) of **1b**·HCl were prepared by dissolving the appropriate amount of **1b**·HCl in 0.1 M hydrochloric acid (pH 1) or in the respective buffer solution (pH 5, pH 7.4, pH 10). At pH 7.4 and pH 10, acetonitrile was used as a cosolvent (buffer/acetonitrile (3:1 (v/v)) and buffer/acetonitrile (3:2 (v/v)), respectively) for reasons of solubility. These samples were stored for 24 h after preparation, were then diluted to a concentration of 0.1 mM by addition of water, and were analyzed instantaneously by ESI-MS.

(c) ESI-MS Analyses. The measurements were performed with a Finnigan MAT triple-stage quadrupole TSQ 7000 mass spectrometer with an ESI interface. Data acquisition and evaluation were conducted on a Digital Equipment personal DEC-station 5000/33 using Finnigan MAT ICIS 8.1 software. Nitrogen served both as sheath and auxiliary gas. The electrospray ionization parameters were as follows: temperature of the heated capillary, 200 °C; electrospray capillary voltage, 2.6 kV; sheath gas, 70 psi (1 psi = 6894.74 Pa); auxiliary gas, 10 units. For measurement, the sample solutions were continuously delivered at a flow rate of 20 μL min^{-1} by means of a syringe pump system (Harvard apparatus, No. 22,

(28) (a) Sheldrick, G. M. *SHELXS-97*; University of Göttingen: Göttingen, Germany, 1997. (b) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467−473.

(29) Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Göttingen, Germany, 1997.

South Natick, MA). Positive ions were detected by scanning from 150 to 1000 u with a total scan duration of 1.0 s; 60 scans were collected within 1 min. The multiplier voltage was set to 1.3 kV.

Pharmacological Studies: Materials and General Procedures. Homogenizer: Elvehjem Potter (B. Braun Biotech International). Centrifuge: High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Finnigan). Filter: Printed Filtermat Type B (Perkin-Elmer), presoaked in 0.5% aqueous polyethylenimine for 2 h at room temperature before use. The filtration was carried out with an Unifilter 96 Harvester (Perkin-Elmer). The scintillation analysis was performed using a Meltilex (Type A) solid scintillator (Perkin-Elmer). The solid scintillator was melted on the filter mat at a temperature of 95 °C for 5 min. After solidifying of the scintillator at room temperature, the scintillation was measured using a MicroBeta Trilux scintillation analyzer (Perkin-Elmer). The counting efficiency was 40%. All experiments were carried out in duplicate using standard 96-well multiplates (Diagonal). The IC_{50} values were determined in competition experiments with six concentrations of the test compounds and were calculated with the program GraphPad Prism 3.0 (GraphPad Software) by nonlinear regression analysis. The K_i values were calculated according to ref 30. The K_i values are given as mean value ± SEM from three independent experiments.

Preparation of the Tissue for the σ_1 Assay (modified according to refs 25 and 26). Five guinea pig brains were homogenized with a potter (500−800 rpm, 10 up-and-down strokes) in a 6-fold volume of cold 0.32 M sucrose. The suspension was centrifuged at 1200*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23500*g* for 20 min at 4 °C. The pellet was separated and resuspended in ca. 10 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23500*g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in buffer, and the protein concentration was determined according to ref 31 using bovine serum albumin as standard. Subsequently, the preparation was frozen (−80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

Preparation of the Tissue for the σ_2 Assay (modified according to refs 25 and 26). Two rat livers were cut into small pieces and homogenized with a potter (500−800 rpm, 10 up-and-down strokes) in a 6-fold volume of cold 0.32 M sucrose. The suspension was centrifuged at 1200*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 31000*g* for 20 min at 4 °C. The pellet was separated, resuspended in ca. 10 volumes of buffer (50 mM TRIS, pH 8.0), and incubated at room temperature for 30 min. After the incubation, the suspension was centrifuged again at 31000*g* for 20 min at 4 °C. The final pellet was resuspended in buffer, and the protein concentration was determined according to ref 31 using bovine serum albumin as standard. Subsequently, the preparation was frozen (−80 °C) in 1.5 mL portions containing about 2 mg protein/mL.

Performance of the σ_1 Assay (modified according to refs 25 and 26). The test was performed with the radioligand [^{3}H]-(+)-pentazocine (42.5 Ci/mmol, Perkin-Elmer). The thawed membrane preparation (about 75 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-pentazocine, and buffer (50 mM TRIS, pH 7.4) in a total volume of 200 μL for 180 min at 37 °C. The incubation was terminated by rapid filtration through presoaked filter mats using a cell harvester. After washing each well five times with 300 μL of water, the filter mats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filter mat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temperature. The bound radioactivity trapped on the filters was counted in a scintillation analyzer. The nonspecific binding was determined with 10 μM nonlabeled (+)-pentazocine.

Performance of the σ_2 Assay (modified according to refs 25 and 26). The test was performed with the radioligand [^{3}H]-ditolylguanidine (5 Ci/mmol, ARC). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 3 nM [^{3}H]-ditolylguanidine, and buffer containing (+)-pentazocine (2 μM (+)-pentazocine in 50 mM TRIS, pH 8.0) in a total volume of 200 μL for 180 min at 25 °C. The incubation was terminated by rapid filtration through presoaked filter mats using a cell harvester. After washing each well five times with 300 μL of water, the filter mats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filter mat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temperature. The bound radioactivity trapped on the filters was counted in a scintillation analyzer. The nonspecific binding was determined with 10 μM ditolylguanidine.

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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 **7**, **8**, **10**, **12**, and **13** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

(31) Bradford, M. M. *Anal. Biochem.* **1976**, *72*, 248−254.