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Pharmacological discrimination between enantiomeric germanes by muscarinic receptors: a study on germanium/silicon bioisosterism [1]

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Abstract

The (hydroxymethyl)diorgano(2-piperidinoethyl)germanes *rac*-Ph(*c*-Hex)Ge(CH_2OH)$CH_2CH_2NR_2$ (*rac*-**1a**), $Ph_2Ge(CH_2OH)CH_2$-CH_2NR_2 (**3a**) and (*c*-Hex)$_2$Ge(CH_2OH)$CH_2CH_2NR_2$ (**5a**) (NR_2 = piperidino) were synthesized starting from Cl_3GeCH_2Cl. The (*R*)- and (*S*)-enantiomer of **1a** were obtained by resolution of *rac*-**1a** using the antipodes of *O,O'*-di-*p*-toluoyltartaric acid as resolving agents (resolution by fractional crystallization of diastereomeric salts). The enantiomeric purities of the resolved antipodes of **1a** were shown to be at least 98 (^{1}H NMR) and 97% *ee* (^{13}C NMR) respectively (NMR studies using a chiral shift reagent). Reaction of *rac*-**1a**, (*R*)-**1a**, (*S*)-**1a**, **3a** and **5a** with methyl iodide gave the corresponding methiodides *rac*-**2a**, (*R*)-**2a**, (*S*)-**2a**, **4a** and **6a** (**1a** → **2a**, **3a** → **4a**, **5a** → **6a**). The absolute configuration of (*R*)-**2a** was determined by single-crystal X-ray diffraction. On the basis of the experimentally established absolute configuration of (*R*)-**2a**, the absolute configurations of all the other aforementioned optically active germanium compounds were assigned by chemical and optical correlations. The enantiomerically pure germanium compounds (*R*)-**1a**, (*S*)-**1a**, (*R*)-**2a** and (*S*)-**2a** and their achiral derivatives **3a**–**6a** were studied for their affinities for muscarinic M1, M2, M3 and M4 receptors by functional pharmacological experiments (M1, rabbit vas deferens; M2, guinea-pig atria; M3, guinea-pig ileum) and radioligand binding experiments (M1, human NB-OK 1 cells; M2, rat heart; M3, rat pancreas; M4, rat striatum). The receptor affinities obtained in these studies were compared with those of the related silicon analogues, the (hydroxymethyl)diorgano(2-piperidinoethyl)silanes (*R*)- and (*S*)-Ph(*c*-Hex)Si(CH_2OH)$CH_2CH_2NR_2$ [(*R*)-**1b** and (*S*)-**1b**], $Ph_2Si(CH_2OH)CH_2CH_2NR_2$ (**3b**) and (*c*-Hex)$_2$Si(CH_2OH)$CH_2CH_2NR_2$ (**5b**) (NR_2 = piperidino) and their corresponding methiodides (*R*)-**2b**, (*S*)-**2b**, **4b** and **6b** (**a** → **b**: Ge → Si; studies on Ge/Si bioisosterism). According to these studies, all the germanes and the related silicon analogues behaved as simple competitive antagonists at muscarinic M1–M4 receptors. The pK_i values obtained in binding studies at M1–M3 receptors were similar to the corresponding functional affinities (pA_2 values). The receptor affinities of the respective Ge/Si analogues were found to be very similar, indicating a strongly pronounced Ge/Si bioisosterism. The (*R*)-enantiomers (eutomers) of the Ge/Si pairs **1a**/**1b** and **2a**/**2b** exhibited higher affinities (up to 26-fold) for M1–M4 receptors than their corresponding (*S*)-antipodes (distomers), the stereoselectivity ratios being higher at M1, M3 and M4 than at M2 receptors. In most cases, the diphenyl (**3a**/**3b** and **4a**/**4b**) and dicyclohexyl (**5a**/**5b** and **6a**/**6b**) compounds displayed lower affinities to M1–M4 receptors than the related (*R*)-enantiomers of **1a**/**1b** and **2a**/**2b**, and the sums of the respective affinity differences were very similar to the experimentally established stereoselectivity ratios [(*R*)/(*S*)]. Thus, the stereoselective interaction of the enantiomers of **1a**/**1b** and **2a**/**2b** with muscarinic receptors is best explained in terms of opposite and weaker binding of the phenyl and cyclohexyl ring of the (*S*)-antipodes. The highest receptor selectivity was observed for compound (*R*)-**1b** at M1/M2 receptors (25-fold in binding studies).

Keywords: Silicon; Germanium; Optically active germanes; Bioorganogermanium chemistry; Ge/Si bioisosterism; Muscarinic receptor subtypes

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[1] Dedicated to Professor R.J.P. Corriu in recognition of his outstanding contributions to organosilicon chemistry.

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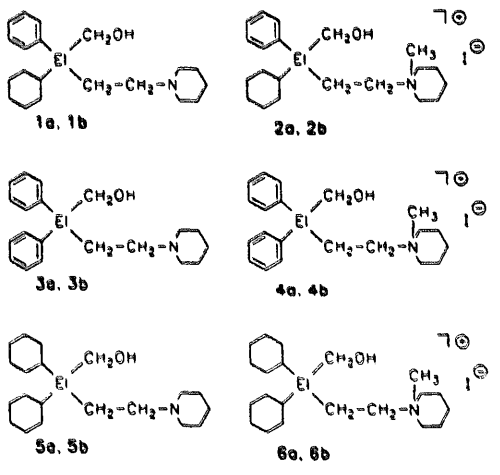
1. Introduction

In contrast to the extensive research activities in bioorganosilicon chemistry (review Ref. [1]; recent publications Refs. [2–9]), there have been few studies on biologically active organogermanium compounds (reviews Refs. [10,11]; recent publication Ref. [12]). Although optically active germanes, with the germanium atom as the centre of chirality, have been described in the literature (see Refs. [13–22]), no studies on optically active organogermanium drugs have been reported up to now. Here we describe the syntheses and some antimuscarinic properties of the enantiomerically pure antipodes of the germanes **1a** and **2a** and their achiral derivatives **3a–6a** (Scheme 1). Preliminary data on the syntheses and functional antimuscarinic activities of the (*R*)- and (*S*)-enantiomers of **1a** and **2a** have been published elsewhere [23]. The receptor affinities of (*R*)-**1a**, (*S*)-**1a**, (*R*)-**2a**, (*S*)-**2a** and **3a–6a** for muscarinic M1, M2, M3 and M4 receptors were compared with those of the corresponding silicon analogues (*R*)-**1b**, (*S*)-**1b**, (*R*)-**2b**, (*S*)-**2b** and **3b–6b** (Scheme 1). The syntheses and antimuscarinic properties of the antipodes of the silanes **1b** and **2b** and their achiral derivatives **3b** and **4b** have been described previously [4,7], whereas the achiral silanes **5b** and **6b** are reported here for the first time. The investigations described in this paper were carried out as a part of our studies on Ge/Si bioisosterism (in this context, see also Refs. [12,24]).

2. Results and discussion

2.1. Syntheses

The preparation of the (*R*)- and (*S*)-enantiomers of compounds **1a** and **2a** is based on the synthesis of the



a: El = Ge; b: El = Si

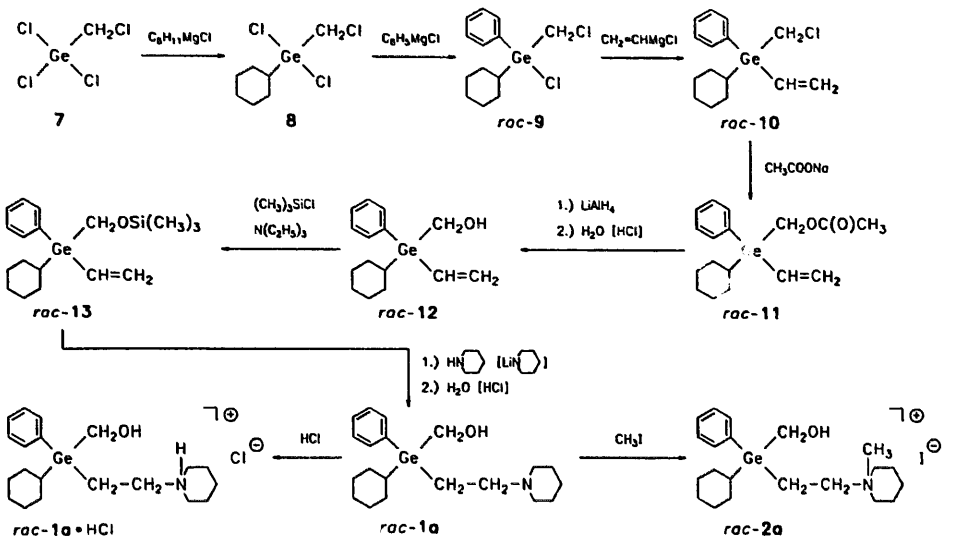
Scheme 1.

racemic germane *rac*-**1a**, followed by its resolution into the antipodes (*R*)-**1a** and (*S*)-**1a** and their subsequent transformation into the enantiomers (*R*)-**2a** and (*S*)-**2a** respectively.

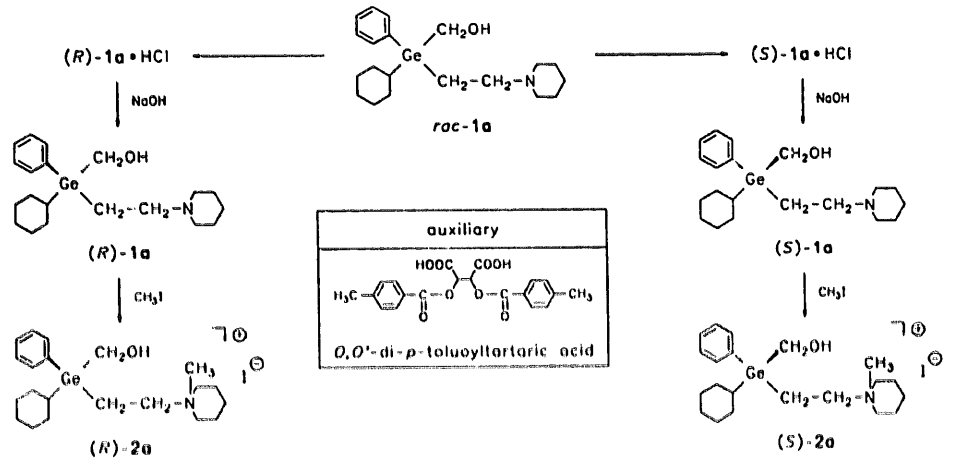
The racemic compound *rac*-**1a** and its quaternary ammonium derivative *rac*-**2a** were synthesized according to Scheme 2, starting from trichloro(chloromethyl)-germane (**7**) [overall yield 28% (*rac*-**1a**) and 26% (*rac*-**2a**)]. In the first step, the chlorogermane **7** [25] was transformed into the cyclohexylgermane **8** by reaction with cyclohexylmagnesium chloride in diethyl ether (yield 56%). Subsequent reaction of **8** with phenylmagnesium chloride in diethyl ether gave the phenylgermane *rac*-**9** (yield 80%), which was converted into the vinylgermane *rac*-**10** by reaction with vinylmagnesium chloride in THF (yield 86%). In the next step, the (chloromethyl)germane *rac*-**10** was transformed into the corresponding (acetoxymethyl)germane *rac*-**11** by reaction with sodium acetate in DMF (yield 91%). The (acetoxymethyl)germane *rac*-**11** was then converted into the corresponding (hydroxymethyl)germane *rac*-**12** by reduction with lithium aluminium hydride in diethyl ether followed by hydrolysis with hydrochloric acid (yield 87%). *O*-Silylation of *rac*-**12** with chlorotrimethylsilane in n-pentane in the presence of triethylamine yielded the corresponding *O*-trimethylsilyl derivative *rac*-**13** (yield 95%). Treatment of the vinylsilane *rac*-**13** with a mixture of piperidine and its lithium amide in THF, followed by hydrolysis with hydrochloric acid and subsequent workup with aqueous KOH solution, gave the corresponding (2-piperidinoethyl)germane *rac*-**1a** (97%), which was then transformed into its hydrochloride *rac*-**1a** · HCl by reaction with hydrogen chloride in diethyl ether (yield 92%). The quaternary ammonium compound *rac*-**2a** was made by reaction of the amine *rac*-**1a** with methyl iodide in acetone (yield 90%).

The enantiomers (*R*)-**1a** · HCl and (*S*)-**1a** · HCl were obtained by resolution of *rac*-**1a** using the antipodes of *O*,*O*′-di-*p*-toluoyltartaric acid as resolving agents, followed by reaction of the enantiomerically pure (*R*)- and (*S*)-enantiomer of **1a** with hydrogen chloride in diethyl ether (yield 8 and 7% respectively; for details, see Experimental section) (Scheme 3). Reaction of the purified antipodes of **1a** · HCl with aqueous NaOH solution gave the pure (*R*)- and (*S*)-enantiomer of **1a** (yield 94 and 93% respectively). The pure (*R*)- and (*S*)-enantiomer of the quaternary ammonium derivative **2a** were obtained by reaction of the antipodes of **1a** with methyl iodide in acetone (yield 82 and 84% respectively).

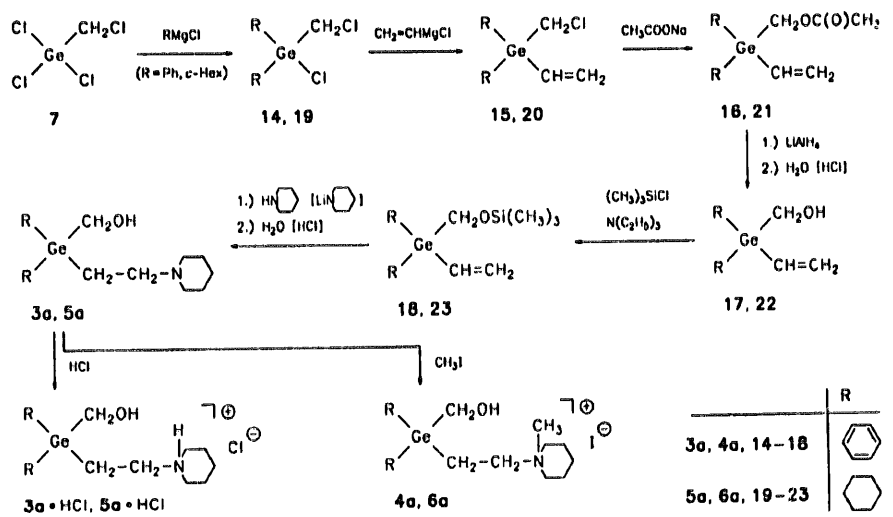
The achiral germanium compounds **3a–6a** were synthesized according to Scheme 4, starting from trichloro(chloromethyl)germane (**7**) [overall yield 37% (**3a**), 32% (**4a**), 29% (**5a**) and 23% (**6a**)]. In the first step, the diphenylgermane **14** [25] and the dicyclohexylgermane **19** were prepared by reaction of **7** with phenyl-



Scheme 2.



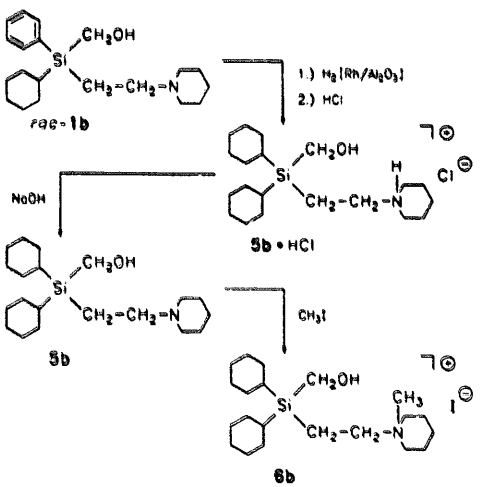
Scheme 3.



Scheme 4.

magnesium chloride and cyclohexylmagnesium chloride respectively in diethyl ether [yield 68% (**14**) and 63% (**19**) respectively]. In the next step, the chlorogermanes **14** and **19** were transformed into the corresponding vinylgermanes **15** (yield 84%) and **20** (yield 67%) by reaction with vinylmagnesium chloride in THF. Subsequent reaction of these (chloromethyl)germanes with sodium acetate in DMF gave the (acetoxymethyl)germanes **16** (yield 83%) and **21** (yield 86%) respectively. These compounds were then converted into the corresponding (hydroxymethyl)germanes **17** (yield 86%) and **22** (yield 88%) by reduction with lithium aluminium hydride in diethyl ether followed by hydrolysis with hydrochloric acid. *O*-Silylation of **17** and **22** with chlorotrimethylsilane in n-pentane in the presence of triethylamine yielded the *O*-trimethylsilyl derivatives **18** (yield 94%) and **23** (yield 94%) respectively. Treatment of the vinylgermanes **18** and **23** with a mixture of piperidine and its lithium amide in THF, followed by hydrolysis with hydrochloric acid and subsequent workup with aqueous KOH solution, gave the corresponding (2-piperidinoethyl)germanes **3a** (yield 96%) and **5a** (yield 95%). These amines were then transformed into their hydrochlorides **3a** · HCl (yield 91%) and **5a** · HCl (yield 92%) respectively by reaction with hydrogen chloride in diethyl ether. The quaternary ammonium compounds **4a** and **6a** were obtained by reaction of the corresponding amines **3a** and **5a** with methyl iodide in acetone [yield 88% (**4a**) and 80% (**6a**)].

The achiral silicon compounds **5b** and **6b** were synthesized according to Scheme 5, starting from *rac*-cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)-silane (*rac*-**1b**) [7]. The dicyclohexylsilane **5b** was prepared by a rhodium-catalyzed hydrogenation of the cyclohexyl(phenyl)silane *rac*-**1b** and then isolated, after reaction with hydrogen chloride in diethyl ether, as the hydrochloride **5b** · HCl (yield 75%). Reaction of the latter compound with aqueous NaOH solution yielded the pure silane **5b** (yield 91%). The quaternary ammonium compound **6b** was obtained by reaction of the amine **5b** with methyl iodide in acetone (yield 91%).



Scheme 5.

Compounds *rac*-**1a**, **8**, *rac*-**9**–*rac*-**13** and **15**–**23** were isolated as colourless liquids, whereas *rac*-**1a** · HCl, *rac*-**2a**, **3a**–**6a**, **3a** · HCl, **5a** · HCl, **5b** · HCl and **6b**, as well as the (*R*)- and (*S*)-enantiomers of **1a**, **1a** · HCl and **2a**, were obtained as colourless crystalline solids. The identity of these hitherto unknown compounds was established by elemental analyses, NMR spectroscopic studies and mass spectrometric investigations. In addition, (*R*)-**2b** was structurally characterized by a single-crystal X-ray diffraction study.

The determination of the absolute configurations and enantiomeric purities of the optically active germanium compounds is described in the following two sections. As the (*R*)- and (*S*)-enantiomers of **1a** and **2a** were found to be configurationally stable under physiological conditions, they could be used to study the stereoselectivity of muscarinic receptor binding (see Section 2.4).

2.2. Determination of the absolute configurations

The absolute configuration of the laevorotatory enantiomer of **2a** was determined by single-crystal X-ray diffraction. The crystal data and experimental parameters used for this study are given in Table 1; the structure of the cation of (−)-**2a** in the crystal is shown in Fig. 1. According to this crystal structure analysis, (−)-**2a** (optical rotation measured for a solution in ethanol at 546 nm) is the (*R*)-enantiomer. The germanium compound (*R*)-**2a** is isostructural to its silicon analogue (*R*)-**2b** (see Ref. [7]).

As the *N*-methylation of **1a** with methyl iodide [(−)-**1a** → (−)-**2a**; (+)-**1a** → (+)-**2a**] and the conversion of **1a** · HCl into **1a** [(+)-**1a** · HCl → (−)-**1a**; (−)-**1a** · HCl → (+)-**1a**] do not affect the configuration at the germanium atom, assignment of the absolute configurations of (−)-**1a** [→ (*R*)], (+)-**1a** [→ (*S*)], (+)-**1a** · HCl[→ (*R*)] and (−)-**1a** · HCl [→ (*S*)] could also be made.

2.3. Determination of the enantiomeric purities

The enantiomeric purities of the (*R*)- and (*S*)-enantiomer of **1a** were determined by NMR experiments using the chiral shift reagent (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol [(−)-TFAE] (^{1}H and ^{13}C NMR). As shown in Fig. 2, the enantiomers of **1a** can be clearly discriminated by NMR spectroscopy and therefore quantitatively determined by integration of their characteristic resonance signals. According to this method, the enantiomeric purities of the resolved antipodes of **1a** were determined to be at least 98 (^{1}H NMR) and 97% *ee* (^{13}C NMR) respectively (in this context, see also Ref. [22]). As the reactions **1a** → **1a** · HCl and **1a** → **2a**

do not affect the absolute configuration at the germanium atom, the same enantiomeric purities can be assumed for the antipodes of **1a** · HCl and **2a**. Thus, the (*R*)- and (*S*)-enantiomers of **1a**, **1a** · HCl and **2a** prepared in this study were almost enantiomerically pure.

2.4. Pharmacological studies

The pure (*R*)- and (*S*)-enantiomers of **1a**, **1b**, **2a** and **2b** and the achiral compounds **3a–6a** and **3b–6b** were studied for their affinities at muscarinic M1, M2, M3 and M4 receptors by functional pharmacological experiments (M1, M2, M3) and radioligand binding experiments (M1, M2, M3, M4). The results of these investigations are summarized in Tables 2–4 and illustrated in Figs. 3–7.

All compounds concentration-dependently antagonized the 4-F-PyMcN$^+$-induced inhibition of the neurogenic twitch contraction in rabbit vas deferens (M1 receptors). Furthermore, they inhibited the negative inotropic responses in guinea-pig atria and ileal contractions (M2 and M3 receptors respectively) induced by arecaidine propargyl ester. All compounds investigated produced parallel shifts of the agonist concentration-response curves without changes in basal tension or maximum agonist responses. Arunlakshana–Schild plots were

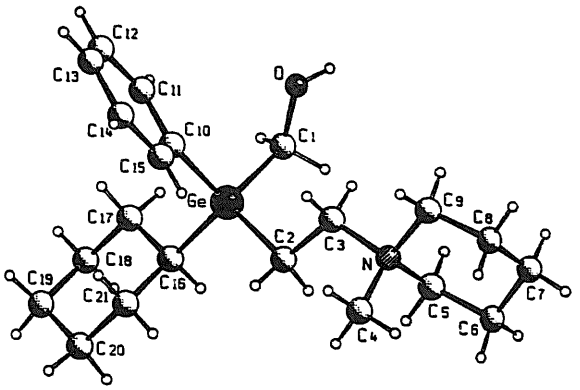


Fig. 1. Structure of the cation of (*R*)-**2a** in the crystal, showing the atomic numbering scheme. Selected bond distances (pm) and angles (deg): Ge–C(1) 196.4(5), Ge–C(2) 198.3(4), Ge–C(10) 195.2(4), Ge–C(16) 196.6(4), C(1)–O 140.7(6), C(1)–Ge–C(2) 109.4(2), C(1)–Ge–C(10) 107.2(2), C(1)–Ge–C(16) 111.2(2), C(2)–Ge–C(10) 111.0(2), C(2)–Ge–C(16) 108.2(2), C(10)–Ge–C(16) 109.9(9), Ge–C(1)–O 112.2(3). The cation and anion of (*R*)-**2a** are connected by a hydrogen bond of the type O–H · · · I [O · · · I 346.5(4) pm].

Table 1
Crystal data and experimental parameters for the crystal structure analysis of (*R*)-**2a**

Empirical formula	$C_{21}H_{36}GeINO$
Formula mass (g mol^{-1})	518.00
Collection *T* (°C)	−100
λ (Mo K α) (pm)	71.073
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a (pm)	892.8(2)
b (pm)	915.1(2)
c (pm)	2748.3(7)
V (nm^3)	2.2454(9)
Z	4
D (calc) (Mg m^{-3})	1.532
μ (Mo K α) (mm^{-1})	2.748
F(000)	1048
Crystal dimensions (mm^3)	0.55×0.55×0.15
θ range (deg)	3.15–27.55
Index ranges	$0 \le h \le 11$, $-11 \le k \le 11$, $0 \le l \le 35$
No. of collected reflections	5584
No. of independent reflections	5182
R_{int}	0.0256
No. of reflections used	5180
No. of parameters	228
Absorption correction	ψ scans, transmissions 0.51–1.00
S [a]	1.066
$R(F)$ [b] [$I > 2\sigma(I)$]	0.0318
$R_w(F^2)$ [c]	0.0410
Max./min. residual electron density (e nm^{-3})	+742/−847

[a] $S = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$; with *n* no. of reflections and *p* no. of parameters.
[b] $R(F) = \Sigma \| F_o | - | F_c \| / \Sigma | F_o |$ (4635 observed reflections).
[c] $R_w(F^2) = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma w(F_o^2)^2\}^{1/2}$ (all reflections).

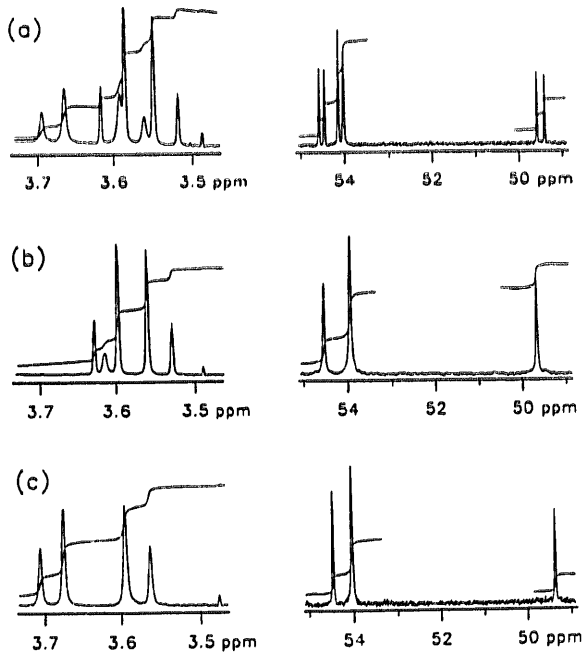


Fig. 2. Quantitative determination of the enantiomeric purities of the antipodes of **1a**: characteristic ^{1}H (left $GeCH_2O$ moiety) and ^{13}C NMR (right GeC_6H_5 moiety) partial spectra of the (*R*)- and (*S*)-enantiomer of **1a** in the presence of (−)-TFAE [(a) racemic mixture; (b) pure (*R*)-enantiomer obtained by preparative resolution; (c) pure (*S*)-enantiomer obtained by preparative resolution]. For details, see Experimental section.

Table 2
Affinities (pA_2 values) and slopes of Arunlakshana–Schild plots (in parentheses) for the (*R*)- and (*S*)-enantiomers of **1a**, **1b**, **2a** and **2b** and for the achiral compounds **3a–6a** and **3b–6b** at muscarinic M1 receptors in rabbit vas deferens (RVD), M2 receptors in guinea-pig atria (GPA) and M3 receptors in guinea-pig ileum (GPI) as well as receptor selectivities of these compounds

Compound	pA_2 values [a]			Selectivity ratios [b]		
	RVD (M1)	GPA (M2)	GPI (M3)	M1/M2	M1/M3	M3/M2
(*R*)-**1a** [c]	7.09 ± 0.05 (1.11 ± 0.10)	6.56 ± 0.05 (0.96 ± 0.08)	7.14 ± 0.03 (1.05 ± 0.04)	3.4	0.9	3.8
(*R*)-**1b** [c,d]	7.39 ± 0.05 (1.14 ± 0.12)	6.76 ± 0.04 (0.85 ± 0.06)	7.32 ± 0.03 (0.91 ± 0.08)	4.3	1.2	3.6
(*R*)-**2a** [c]	9.17 ± 0.07 (0.90 ± 0.12)	8.09 ± 0.03 (0.94 ± 0.05)	8.40 ± 0.04 (1.06 ± 0.07)	12.0	5.9	2.0
(*R*)-**2b** [c,d]	9.09 ± 0.06 (0.98 ± 0.10)	8.21 ± 0.01 (0.98 ± 0.02)	8.65 ± 0.05 (0.98 ± 0.07)	7.6	2.8	2.8
(*S*)-**1a** [c]	6.24 ± 0.09 (1.04 ± 0.22)	6.23 ± 0.05 (1.07 ± 0.13)	6.12 ± 0.04 (0.95 ± 0.11)	1.0	1.3	0.7
(*S*)-**1b** [c,d]	6.53 ± 0.04 (1.18 ± 0.09)	6.26 ± 0.03 (1.11 ± 0.06)	6.15 ± 0.02 (1.03 ± 0.06)	1.9	2.4	0.8
(*S*)-**2a** [c]	7.76 ± 0.05 (1.05 ± 0.09)	7.47 ± 0.04 (0.97 ± 0.07)	7.15 ± 0.04 (1.00 ± 0.08)	2.0	4.1	0.5
(*S*)-**2b** [c,d]	7.74 ± 0.04 (1.12 ± 0.07)	7.57 ± 0.05 (1.01 ± 0.07)	7.36 ± 0.03 (1.03 ± 0.06)	1.5	2.4	0.6
3a	7.07 ± 0.02 (1.01 ± 0.05)	6.68 ± 0.02 (0.98 ± 0.04)	6.62 ± 0.03 (0.90 ± 0.05)	2.5	2.8	0.9
3b [e]	7.04 ± 0.07 (0.98 ± 0.11)	6.72 ± 0.02 (0.94 ± 0.02)	6.81 ± 0.03 (0.96 ± 0.05)	2.1	1.7	1.2
4a	8.73 ± 0.03 (0.97 ± 0.05)	8.06 ± 0.01 (0.96 ± 0.02)	8.09 ± 0.03 (0.95 ± 0.06)	4.7	4.4	1.1
4b [e]	8.72 ± 0.03 (0.99 ± 0.05)	8.24 ± 0.05 (0.93 ± 0.09)	8.19 ± 0.04 (0.97 ± 0.07)	3.0	3.4	0.9
5a	6.74 ± 0.04 (0.98 ± 0.04)	6.04 ± 0.03 (1.05 ± 0.05)	6.62 ± 0.03 (0.93 ± 0.09)	5.0	1.3	3.8
5b	6.76 ± 0.03 (1.05 ± 0.06)	6.23 ± 0.04 (0.94 ± 0.07)	6.77 ± 0.03 (1.01 ± 0.09)	3.4	1.0	3.5
6a	8.24 ± 0.03 (0.95 ± 0.06)	7.03 ± 0.03 (0.94 ± 0.05)	7.71 ± 0.05 (1.05 ± 0.10)	16.2	3.4	4.8
6b	8.30 ± 0.03 (1.01 ± 0.05)	7.25 ± 0.04 (0.96 ± 0.07)	7.75 ± 0.03 (1.02 ± 0.06)	11.2	3.6	3.2

[a] The parameters given represent the means ± s.e. mean ($n = 3$–4).
[b] K_D ratios ($pA_2 = -\log K_D$) are given as a measure of receptor selectivity; these values were calculated from the antilogs of the differences between the respective pA_2 values.
[c] Data taken from Ref. [23].
[d] Data taken from Refs. [7] and [23].
[e] Data taken from Ref. [4].

Table 3
Affinities (pK_i values) for the (*R*)- and (*S*)-enantiomers of **1a**, **1b**, **2a** and **2b** and for the achiral compounds **3a–6a** and **3b–6b** obtained in binding studies on homogenates of human NB-OK 1 cells (M1 receptors), rat heart (M2 receptors), rat pancreas (M3 receptors) and rat striatum (M4 receptors) [a]

Compound	pK_i values			
	Human NB-OK 1 (M1)	Rat heart (M2)	Rat pancreas (M3)	Rat striatum (M4)
(*R*)-**1a**/(*S*)-**1a**	7.6/6.6	6.6/6.3	6.6/5.7	7.2/6.4
(*R*)-**1b**/(*S*)-**1b** [b]	7.8/6.9	6.6/6.3	7.4/6.7	7.2/6.5
(*R*)-**2a**/(*S*)-**2a**	8.7/7.7	7.9/7.1	8.1/7.0	8.6/7.2
(*R*)-**2b**/(*S*)-**2b** [b]	8.9/7.9	7.9/7.3	7.9/7.0	8.5/7.4
3a/**3b** [c]	7.1/7.2	6.3/6.3	6.1/6.3	6.8/6.8
4a/**4b** [d]	8.3/8.6	7.6/7.8	7.6/7.8	7.8/8.2
5a/**5b**	7.2/6.9	6.3/6.3	6.1/6.0	6.8/6.8
6a/**6b**	7.9/7.9	7.2/7.2	7.3/7.3	7.7/7.9

[a] All experiments were repeated three times in duplicate. The standard deviations of the pK_i values were generally close to ±0.10, always lower than ±0.15.
[b] Data taken from Ref. [7].
[c] Data for compound **3b** taken from Ref. [4].
[d] Data for compound **4b** taken from Ref. [4].

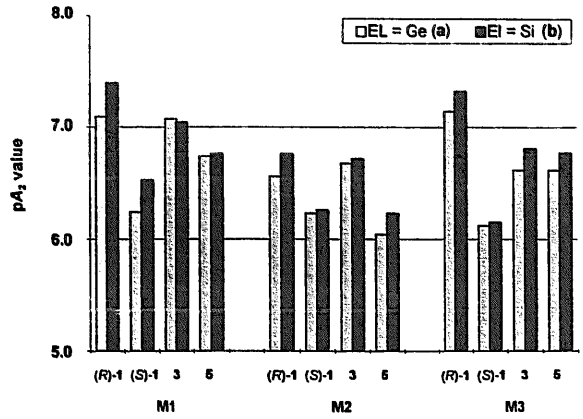


Fig. 3. Affinity profiles (pA_2 values) of the (a) germanium and (b) silicon compounds (*R*)-**1**, (*S*)-**1**, **3** and **5** at muscarinic M1 (rabbit vas deferens), M2 (guinea-pig atria) and M3 receptors (guinea-pig ileum).

linear over the antagonist concentration range examined, and the slopes of the regression lines were not significantly different from unity. In addition, all the competition curves obtained in binding studies were compatible with the existence of a single receptor subtype; the Hill coefficients were not different from unity. Thus, all compounds studied exhibited an apparently competitive antagonism at M1–M3 receptors in functional studies and at M1–M4 receptors in binding experiments.

The pK_i values obtained in binding studies at M1–M3 receptors correspond reasonably to the antimuscarinic potencies (pA_2 values) determined in functional experiments at M1, M2 and M3 receptors (Tables 2 and 3).

Receptor affinities (pA_2 and pK_i values) obtained in both functional and binding studies for the germanes **1a–6a** and for the related silanes **1b–6b** were found to be very similar. In most cases, differences in affinity (Ge vs. Si analogues) were lower than 0.4 log units. Only the pK_i values of the silanes (*R*)-**1b** and (*S*)-**1b** determined at M3 receptors were about ten times higher than those of the related germanium analogues (*R*)-**1a** and (*S*)-**1a**. Thus, in this study most Ge/Si pairs displayed a strongly pronounced Ge/Si bioisosterism (Tables 2 and 3, Figs. 3–6).

In general, the (*R*)-enantiomers (eutomers) of **1a**, **1b**, **2a** and **2b** exhibited higher affinities at all the muscarinic receptor subtypes than the corresponding (*S*)-antipodes (distomers) (Tables 2 and 3, Figs. 3–6). The rank order of the eudismic indices [pA_2(eutomer) – pA_2(distomer)] of compounds **1a** and **1b** obtained in functional experiments was M3 ≥ M1 > M2, whereas the eudismic indices for the (*R*)- and (*S*)-enantiomers of the corresponding *N*-methyl derivatives **2a** and **2b**

Table 4
Comparison of the eudismic indices [a] of the (*R*)- and (*S*)-enantiomers of **1a**, **1b**, **2a** and **2b** with the expected eudismic indices [b] calculated according to the four-binding-site model. These values were obtained from pA_2 or pK_i values determined in functional as well as in binding studies at M1 receptors [rabbit vas deferens (RVD)/human NB-OK 1 cells], at M2 receptors [guinea-pig atria (GPA)/rat heart], at M3 receptors [guinea-pig ileum (GPI)/rat pancreas] and at M4 receptors (rat striatum)

	RVD/NB-OK 1 (M1)	GPA/rat heart (M2)	GPI/rat pancreas (M3)	Rat striatum (M4)
[(*R*)-**1a**] – [**3a**] [c]	0.02/0.5	−0.12/0.3	0.52/0.5	0.4
[(*R*)-**1a**] – [**5a**] [d]	0.35/0.4	0.52/0.3	0.52/0.5	0.4
E.I.: [(*R*)-**1a**] – [(*S*)-**1a**] [a]	0.85/1.0	0.33/0.3	1.02/0.9	0.8
Expected E.I. [b]	0.37/0.9	0.41/0.6	1.04/1.0	0.8
[(*R*)-**1b**] – [**3b**] [c]	0.35/0.4	0.04/0.3	0.51/1.1	0.4
[(*R*)-**1b**] – [**5b**] [d]	0.63/0.9	0.53/0.3	0.55/1.4	0.4
E.I.: [(*R*)-**1b**] – [(*S*)-**1b**] [a]	0.86/0.9	0.50/0.3	1.17/0.7	0.7
Expected E.I. [b]	0.98/1.3	0.57/0.6	1.06/2.5	0.8
[(*R*)-**2a**] – [**4a**] [c]	0.44/0.4	0.03/0.3	0.31/0.5	0.8
[(*R*)-**2a**] – [**6a**] [d]	0.93/0.8	1.06/0.7	0.69/0.8	0.9
E.I.: [(*R*)-**2a**] – [(*S*)-**2a**] [a]	1.41/1.0	0.62/0.8	1.25/1.1	1.4
Expected E.I. [b]	1.37/1.2	1.09/1.0	1.00/1.3	1.7
[(*R*)-**2b**] – [**4b**] [c]	0.37/0.3	−0.03/0.1	0.46/0.1	0.3
[(*R*)-**2b**] – [**6b**] [d]	0.79/1.0	0.96/0.7	0.90/0.6	0.6
E.I.: [(*R*)-**2b**] – [(*S*)-**2b**] [a]	1.34/1.0	0.64/0.6	1.29/0.9	1.1
Expected E.I. [b]	1.17/1.3	0.93/0.8	1.36/0.7	0.9

[a] Eudismic index (E.I.): difference between the pA_2 or pK_i value of the corresponding (*R*)- and (*S*)-enantiomer.
[b] Expected eudismic index (expected E.I.): the sum of the differences obtained according to [c] and [d].
[c] Difference between the pA_2 or pK_i value of the (*R*)-enantiomer and the respective diphenyl analogue.
[d] Difference between the pA_2 or pK_i value of the (*R*)-enantiomer and respective dicyclohexyl analogue.

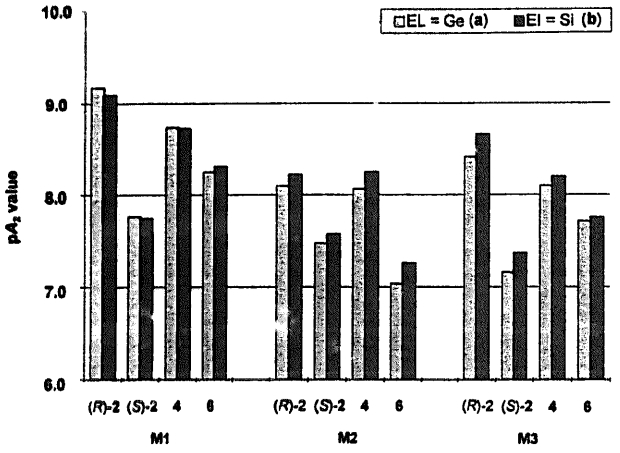


Fig. 4. Affinity profiles (pA_2 values) of the (a) germanium and (b) silicon compounds (*R*)-**2**, (*S*)-**2**, **4** and **6** at muscarinic M1 (rabbit vas deferens), M2 (guinea-pig atria) and M3 receptors (guinea-pig ileum).

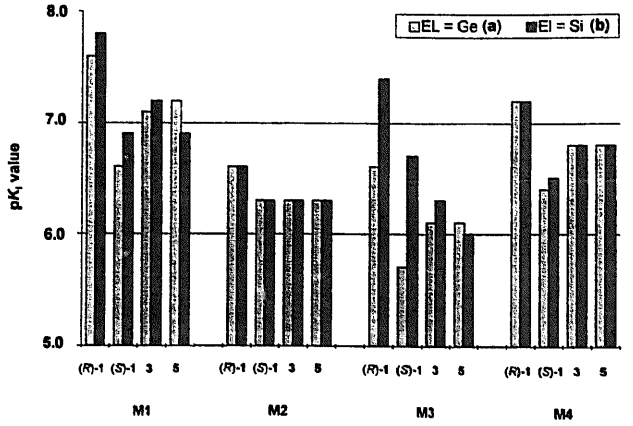


Fig. 5. Affinity profiles (pK_i values) of the (a) germanium and (b) silicon compounds (*R*)-**1**, (*S*)-**1**, **3** and **5** at muscarinic M1 (human NB-OK 1 cells), M2 (rat heart), M3 (rat pancreas) and M4 receptors (rat striatum).

displayed the order M1 ≥ M3 > M2. This is mainly due to the large increase in stereoselectivity at M1 receptors by *N*-methylation (Table 4). The greatest affinity difference between the stereoisomers was found for compound **2a** (26-fold) at functional M1 receptors. In functional studies, receptor affinities of the (*R*)-enantiomers of **1a** and **1b** and of the achiral cyclohexyl analogues **5a** and **5b** obtained at M1 and M3 receptors were always higher than those at M2 receptors (Table 2). The increase in affinity for these compounds and also for the diphenyl derivatives **3a** and **3b** by *N*-methylation [up to 120-fold for (*R*)-**2a** at functional M1 receptors] was consistently highest at M1 receptors. This leads to a receptor selectivity pattern of M1 > M3 ≥ M2 for the *N*-methyl derivatives (*R*)-**2a**, (*R*)-**2b**, **4a**, **4b**, **6a** and **6b**.

In contrast to these results, receptor affinities obtained in binding experiments for most of the compounds studied displayed a receptor selectivity profile of M1 ≥ M4 > M2 = M3. Only (*R*)-**1a** and (*S*)-**1a** showed affinities at M3 receptors, which were comparable with those determined at M1 and M4 receptors. In binding studies, the highest receptor selectivity was observed for compound (*R*)-**1b** (25-fold, M1 over M2).

Replacement of the cyclohexyl group in the (*R*)-enantiomers (eutomers) of **1a**, **1b**, **2a** and **2b** by a phenyl ring (→ diphenyl compounds: **3a**, **3b**, **4a** and **4b**) or replacement of the phenyl group by a cyclohexyl moiety (→ dicyclohexyl compounds: **5a**, **5b**, **6a** and **6b**) decreased the affinities at all muscarinic receptors (M1–M4). Only at functional M2 receptors did the diphenyl derivatives **3a**, **3b**, **4a** and **4b** and the corresponding (*R*)-enantiomers of **1a**, **1b**, **2a** and **2b** display similar pA_2 values.

By analogy with the pharmacological results obtained with the (*R*)- and (*S*)-enantiomer of the muscarinic antagonist procyclidine (**24**) and its correspond-

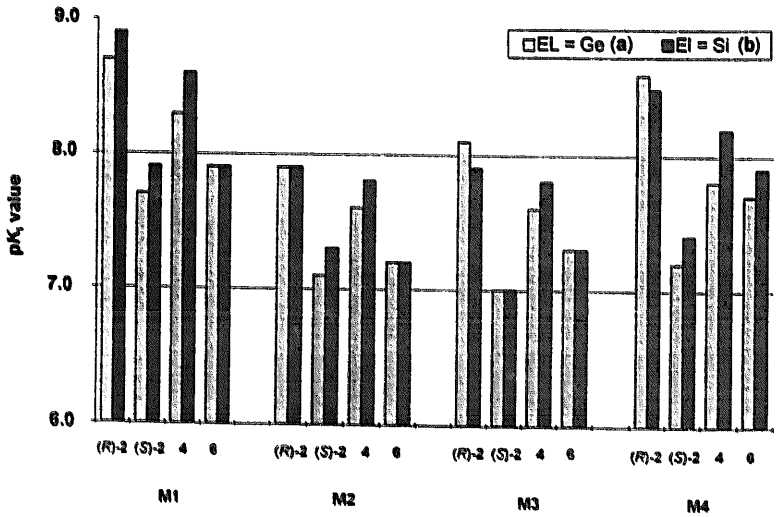


Fig. 6. Affinity profiles (pK_i values) of the (a) germanium and (b) silicon compounds (*R*)-**2**, (*S*)-**2**, **4** and **6** at muscarinic M1 receptors (human NB-OK 1 cells), M2 (rat heart), M3 (rat pancreas) and M4 receptors (rat striatum).

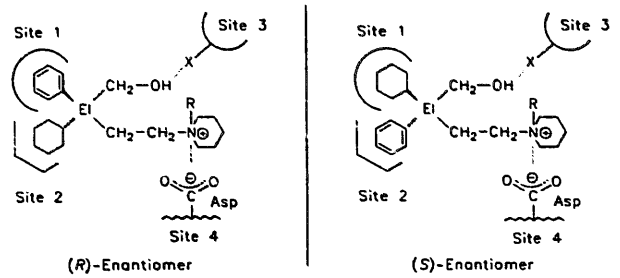


Fig. 7. Model for the interaction of the protonated (*R*)- and (*S*)-enantiomers of compounds **1a** (El = Ge) and **1b** (El = Si) (R = H) and of the (*R*)- and (*S*)-enantiomers of compounds **2a** (El = Ge) and **2b** (El = Si) (R = CH_3) with four subsites of muscarinic receptors: site 1, phenyl-preferring hydrophobic subsite; site 2, cyclohexyl-preferring hydrophobic subsite; site 3, subsite for the hydroxy group, probably forming a hydrogen bond (O–H · · · X); site 4, negatively charged subsite for the ammonium group (Asp = aspartate group).

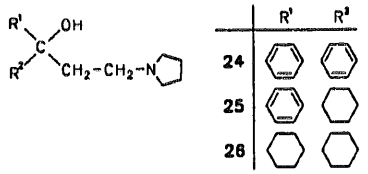
ing diphenyl (**25**) and dicyclohexyl (**26**) analogue [26], the concept of a four-binding-sites model was used in order to explain the differences in binding of the (*R*)- and (*S*)-enantiomers of the Ge/Si pairs **1a/1b** and **2a/2b** at muscarinic receptors (Fig. 5). As can be seen from Table 4, the sums (expected eudismic indices) of the differences observed (i) between the pA_2 (pK_i) values of the (*R*)-enantiomers of **1a**, **1b**, **2a** and **2b** and the related diphenyl analogues **3a**, **3b**, **4a** and **4b** and (ii) between the pA_2 (pK_i) values of the (*R*)-enantiomers and the corresponding dicyclohexyl compounds **5a**, **5b**, **6a** and **6b** were in most cases very similar to the experimentally obtained eudismic indices of the corresponding (*R*)- and (*S*)-enantiomers. These results suggest that the stereoselective interaction of the (*R*)- and (*S*)-enantiomers of the Ge/Si pairs **1a/1b** and **2a/2b** with muscarinic receptors is based on opposite binding to site 1 and site 2 by the phenyl and cyclohexyl ring (Fig. 7).

3. Experimental section

3.1. Syntheses

3.1.1. General procedures

All syntheses were carried out under dry nitrogen. The solvents used were dried by standard procedures and stored under nitrogen. Melting points were determined with a Leitz Laborlux S microscope, equipped with a heater (Leitz, Model M 350). ^1H and ^{13}C NMR



spectra were recorded at room temperature on a Bruker AM-400 (^1H, 400.1 MHz; ^{13}C, 100.6 MHz) or Bruker AC-250 NMR spectrometer (^1H, 250.1 MHz; ^{13}C, 62.9 MHz). ^{29}Si NMR spectra were recorded at room temperature on a Bruker AC-250 NMR spectrometer operating at 49.7 MHz. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^1H, δ 7.25; solvent $CDCl_3$), $CDCl_3$ (^{13}C, δ 77.05; solvent $CDCl_3$), C_6D_5H (^1H, δ 7.16; solvent C_6D_6), C_6D_6 (^{13}C, δ 128.0; solvent C_6D_6) and TMS (^{29}Si, δ 0; solvent $CDCl_3$). Assignment of the ^{13}C NMR data was supported by DEPT experiments. Mass spectra were obtained with a Varian MAT-711 mass spectrometer (EI MS: 70 eV; FI MS: 11 kV; FD MS: 11 kV the solvents used are given in the text); the selected *m/z* values given refer to the isotopes ^1H, ^{12}C, ^{14}N, ^{16}O, ^{28}Si, ^{35}Cl, ^{74}Ge and ^{127}I. Optical rotations were measured with a Perkin-Elmer polarimeter, Model 241; dried ethanol served as solvent. Chromatographic purifications were performed by medium-pressure liquid chromatography (Büchi MPLC system) using a self-packed silica gel column (column length 46 cm, internal diameter 26 mm; silica gel: Europrep 60-20, Eurochrom-Knauer) as the stationary phase; the solvents used as eluent are given in the respective experimental parts (flow rate 30 ml min^{-1}). Catalytic hydrogenations were carried out in a Roth laboratory autoclave.

3.1.2. *rac*-Cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane (*rac*-1a)

A 1.6 M solution of n-butyllithium in n-hexane (19.9 ml, 31.8 mmol of ^{n}BuLi) was added dropwise at 50°C over 15 min to a stirred solution of piperidine (5.41 g, 63.5 mmol) in THF (50 ml). After stirring at 50°C for 30 min, a solution of *rac*-**13** (5.50 g, 15.1 mmol) in THF (50 ml) was added dropwise over 15 min. The resulting mixture was stirred at 50°C for 2 h, cooled to room temperature, and then cautiously added to 6.0 M hydrochloric acid (100 ml). After stirring at room temperature for 30 min, diethyl ether (200 ml) and 6.0 M aqueous KOH solution (110 ml) were added. The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 200 ml). After drying of the combined organic extracts over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue purified by Kugelrohr distillation (160°C/0.01 Torr) to give *rac*-**1a** in 97% yield as an oily liquid (5.53 g, 14.7 mmol). The product crystallized on cooling; m.p. 50–51°C. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.1–1.9 (m, 19H; $GeCH_2C$, $GeCHC_2$, CCH_2C); 2.2–2.6 (m, 6H; NCH_2C); 3.83 (δ_A) and 3.89 (δ_B) (AB system, J_{AB} = 13.1 Hz, 2H; $GeCH_2O$); 6.7 (s, broad, 1H; OH); 7.3–7.5 (m, 5H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 10.6 ($GeCH_2C$); 24.2 (CCH_2C); 25.1 (2C) (CCH_2C); 26.7 (CCH_2C); 26.7 (C-1, GeC_6H_{11}); 28.1 (CCH_2C); 28.2 (CCH_2C); 29.1 (CCH_2C); 29.2

(CCH_2C); 49.9 ($GeCH_2O$); 54.5 (2C) (NCH_2C, NC_5H_{10}); 54.9 ($GeCCH_2N$); 128.0 (C-3/C-5, GeC_6H_5); 128.4 (C-4, GeC_6H_5); 134.3 (C-2/C-6, GeC_6H_5); 137.8 (C-1, GeC_6H_5). EI MS: *m/z* 377 (1%, M^+); 346 (13%, $M^+ - CH_2OH$); 294 (21%, $M^+ - C_6H_{11}$); 151 (27%, $C_6H_5Ge^+$); 98 (100%, $CH_2=NC_5H_{10}^+$). Anal. Found: C, 63.9; H, 8.9; N, 3.7. $C_{20}H_{33}GeNO$ (M_r = 376.1) Calc.: C, 63.88; H, 8.84; N, 3.72%.

3.1.3. *(R)-Cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane [(R)-1a]*

A 2.0 M aqueous NaOH solution (500 μl, 1.00 mmol of NaOH) was added to a mixture of an aqueous solution (20 ml) of (*R*)-**1a** · HCl (200 mg, 485 μmol) and diethyl ether (20 ml). After stirring for 5 min, the organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 20 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure and the residue dried in vacuo to give (*R*)-**1a** in 94% yield as a white crystalline solid (171 mg, 455 μmol); m.p. 41–42°C. The NMR and MS data for the product were identical with those obtained for *rac*-**1a**. $[\alpha]_{546}^{20}$ = −6.5 (EtOH, *c* = 1.0). Anal. Found: C, 64.0; H, 9.0; N, 3.7. $C_{20}H_{33}GeNO$ (M_r = 376.1) Calc.: C, 63.88; H, 8.84; N, 3.72%.

3.1.4. *(S)-Cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane [(S)-1a]*

This compound was prepared from (*S*)-**1a** · HCl (200 mg, 485 μmol) analogously to the synthesis of (*R*)-**1a** and isolated in 93% yield as a white crystalline solid (170 mg, 452 μmol); m.p. 41–42°C. The NMR and MS data for the product were identical with those obtained for *rac*-**1a**. $[\alpha]_{546}^{20}$ = +6.5 (EtOH, *c* = 1.0). Anal. Found: C, 63.9; H, 9.0; N, 3.7. $C_{20}H_{33}GeNO$ (M_r = 376.1) Calc.: C, 63.88; H, 8.84; N, 3.72%.

3.1.5. *rac-1-{2-[Cyclohexyl(hydroxymethyl)phenylgermyl]ethyl}piperidinium chloride (rac-1a · HCl)*

A 3.1 M ethereal HCl solution (1.00 ml, 3.10 mmol of HCl) was added at room temperature to a stirred solution of *rac*-**1a** (500 mg, 1.33 mmol) in diethyl ether (50 ml). After stirring at room temperature for 15 min, the solvent and excess HCl were removed under reduced pressure. The solid residue was dried in vacuo and then recrystallized from acetone/diethyl ether (diffusion of diethyl ether via the gas phase into a saturated solution of the product in acetone at room temperature) to give *rac*-**1a** · HCl in 92% yield as a colourless crystalline solid (504 mg, 1.22 mmol); m.p. 148–149°C. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.0–1.9 and 1.95–2.2 (m, 19H; $GeCH_2C$, $GeCHC_2$, CCH_2C); 2.45–2.7, 2.9–3.1, 3.15–3.3 and 3.35–3.55 (m, 6H; NCH_2C); 3.7 (s, broad, 1H; OH); 4.04 (s, 2H; $GeCH_2O$); 7.25–7.45 (m, 5H; GeC_6H_5); 10.9 (s, broad, 1H; NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 5.6 ($GeCH_2C$); 22.2 (CCH_2C); 22.8 (2C) (CCH_2C); 26.5 (C-1, GeC_6H_{11}); 26.8 (CCH_2C); 27.9 (2C) (CCH_2C); 29.0 (2C) (CCH_2C); 51.6 ($GeCH_2O$); 51.8 (NCH_2C); 52.2 (NCH_2C); 55.3 (NCH_2C); 128.3 (C-3/C-5, GeC_6H_5); 129.0 (C-4, GeC_6H_5); 134.2 (C-2/C-6, GeC_6H_5); 135.4 (C-1, GeC_6H_5). FD MS (DMSO): *m/z* 378 (100%, M_{Cation}^+). Anal. Found: C, 58.2; H, 8.3; N, 3.4; Cl, 8.6. $C_{20}H_{34}ClGeNO$ (M_r = 412.5) Calc.: C, 58.23; H, 8.31; N, 3.40; Cl, 8.59%.

3.1.6. *(R)-1-{2-[Cyclohexyl(hydroxymethyl)phenylgermyl]ethyl}piperidinium chloride [(R)-1a · HCl]*

Except for the mother liquors leading to the crystal crop II [see preparation of (*S*)-**1a** · HCl] all other mother liquors [enriched with (*R*)-**1a**/(*S,S*)-*O,O'*-di-*p*-toluoyltartaric acid] collected in the several steps of the resolution of *rac*-**1a** [see preparation of (*S*)-**1a** · HCl] were combined and then concentrated under reduced pressure. The solid residue was combined with the crystal crop II (7.02 g) and the resulting mixture suspended in water (200 ml). After addition of diethyl ether (200 ml) and 2.0 M aqueous NaOH solution (40 ml), the resulting mixture was stirred at room temperature for 15 min, the organic phase separated, and the aqueous layer extracted with diethyl ether (3 × 150 ml). After drying of the combined organic extracts over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue dried in vacuo to yield an oily mixture of (*R*)-**1a** and (*S*)-**1a** [enriched with (*R*)-**1a**] (7.21 g). A boiling solution of this product in acetone (70 ml) was added to a filtered solution of (*R,R*)-*O,O'*-di-*p*-toluoyltartaric acid (7.41 g, 19.2 mmol) in boiling acetone (250 ml). The mixture was cooled to room temperature and set aside for 60 h, and the crystals formed (7.15 g) were then filtered off and subjected to a four-step fractional crystallization from acetone following the procedure described in Section 3.1.7 to yield 1.43 g of a crystalline product (crop IV). The mother liquors obtained in the four crystallization steps were combined and concentrated under reduced pressure. The resulting residue was dissolved in boiling acetone and the solution was filtered hot and allowed to cool to room temperature during ca. 6 h (slow cooling in a water bath, starting at 55°C) and then set aside for 60 h to yield 6.93 g of a crystalline solid. The crystals were isolated by filtration and then subjected to a four-step fractional crystallization from acetone following the procedure described in Section 3.1.7 to yield 1.12 g of a crystalline solid (crop V). The combined crops IV and V were subjected to a further three-step fractional crystallization from acetone. The product (920 mg) [according to ^{1}H and ^{13}C NMR studies (data not given), this product is the respective *O,O'*-di-*p*-toluoyl hydrogen tartrate containing ca. 1 mol equivalent of acetone]

finally obtained by this method was transformed into crude (*R*)-**1a** (425 mg, 1.13 mmol) and then further into (*R*)-**1a** · HCl by the procedure described for the preparation of (*S*)-**1a** · HCl. Compound (*R*)-**1a** · HCl was isolated in 8% yield [relative to (*R*)-**1a** in the racemic mixture of **1a**] as a colourless crystalline solid (425 mg, 1.03 mmol); m.p. 154–155°C. The NMR and MS data of the product were identical with those obtained for *rac*-**1a** · HCl. $[\alpha]_{546}^{20} = +3.6$ (EtOH, $c = 1.0$). Anal. Found: C, 58.3; H, 8.4; N, 3.4; Cl, 8.6. $C_{20}H_{34}ClGeNO$ ($M_r = 412.5$) Calc.: C, 58.23; H, 8.31; N, 3.40; Cl, 8.59%.

3.1.7. *(S)-1-{2-[Cyclohexyl(hydroxymethyl)phenylgermyl]ethyl}piperidinium chloride [(S)-1a · HCl]*

(*S,S*)-*O,O'*-Di-*p*-toluoyltartaric acid (10.3 g, 26.7 mmol) was dissolved in boiling acetone (300 ml). The hot solution was filtered and then added to a solution of *rac*-**1a** (10.0 g, 26.6 mmol) in boiling acetone (100 ml). The mixture was cooled to room temperature and then set aside for 60 h to yield 14.9 g of a crystalline solid. The crystals were isolated by filtration and subjected to a five-step fractional crystallization from acetone. For this purpose, the boiling saturated solution of the crystals in acetone was filtered and then allowed to cool slowly to room temperature during ca. 6 h (slow cooling in a water bath, starting at 55°C). The mixture was kept at room temperature for a further 48 h and the crystals formed were filtered off and subjected to the next crystallization step, finally yielding 1.97 g of a crystalline product [crop I, enriched with (*S*)-**1a**/(*S,S*)-*O,O'*-di-*p*-toluoyltartaric acid]. The mother liquors obtained in the five crystallization steps were combined and the solvent removed under reduced pressure. The residue was dissolved in boiling acetone and the hot solution filtered, cooled to room temperature, and then set aside for 96 h to yield 7.02 g of a crystalline solid (crop II) enriched with (*R*)-**1a**/(*S,S*)-*O,O'*-di-*p*-toluoyltartaric acid [for further use of this product, see preparation of (*R*)-**1a** · HCl]. The filtrate from this crystallization was concentrated under reduced pressure and the residue suspended in a mixture of water (150 ml) and diethyl ether (150 ml), to which 2.0 M aqueous NaOH solution (20 ml) was added. After stirring at room temperature for 15 min, the organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 150 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure and the residue dried in vacuo to yield 5.03 g of an oily liquid. A boiling solution of this product in acetone (50 ml) was added to a filtered solution of (*S,S*)-*O,O'*-di-*p*-toluoyltartaric acid (5.17 g, 13.4 mmol) in boiling acetone (150 ml). The mixture was cooled to room temperature and set aside for 60 h, and the crystals formed (6.71 g) were then filtered off and subjected to a three-step fractional crystallization from acetone, as described above, to yield 2.23 g of a crystalline product [crop III, enriched with (*S*)-**1a**/(*S,S*)-*O,O'*-di-*p*-toluoyltartaric acid]. The combined crops I and III were then subjected to a further four-step fractional crystallization from acetone following the procedure described above. The product (781 mg) [according to ^1H and ^{13}C NMR studies (data not given), this product is the respective *O,O'*-di-*p*-toluoyl hydrogen tartrate containing ca. 1 mol equivalent of acetone] finally obtained by this procedure was suspended in a mixture of water (50 ml) and diethyl ether (50 ml), to which 2.0 M aqueous NaOH solution (1.50 ml) was added. After stirring at room temperature for 10 min, the organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 50 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue dried in vacuo to yield crude (*S*)-**1a** as an oily liquid (364 mg, 968 μmol). This was dissolved in diethyl ether (50 ml), 3.1 M ethereal HCl solution (600 μl, 1.86 mmol of HCl) was added at room temperature, and the resulting mixture was stirred for 10 min. The solvent and excess HCl were removed under reduced pressure, and the solid residue was dried in vacuo and then recrystallized from acetone/diethyl ether [diffusion of diethyl ether via the gas phase into a solution of the product in acetone (20 ml) at room temperature] to give (*S*)-**1a** · HCl in 7% yield [relative to (*S*)-**1a** in the racemic mixture of **1a**] as a colourless crystalline solid (367 mg, 890 μmol); m.p. 154–155°C. The NMR and MS data of the product were identical with those obtained for *rac*-**1a** · HCl. $[\alpha]_{546}^{20} = -3.6$ (EtOH, $c = 1.0$). Anal. Found: C, 58.3; H, 8.4; N, 3.4; Cl, 8.6. $C_{20}H_{34}ClGeNO$ ($M_r = 412.5$) Calc.: C, 58.23; H, 8.31; N, 3.40; Cl, 8.59%.

3.1.8. *rac-Cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)silane (rac-1b)*

Synthesis as described in Ref. [7].

3.1.9. *rac-1-{2-[Cyclohexyl(hydroxymethyl)phenylgermyl]ethyl}-1-methylpiperidinium iodide (rac-2a)*

Methyl iodide (378 mg, 2.66 mmol) was added to a solution of *rac*-**1a** (500 mg, 1.33 mmol) in acetone (80 ml) and the resulting mixture stirred at room temperature for 18 h. The solvent and excess methyl iodide were removed under reduced pressure and the solid residue was dried in vacuo and then recrystallized from acetone/diethyl ether (diffusion of diethyl ether via the gas phase into a saturated solution of the product in acetone at room temperature) to give *rac*-**2a** in 90% yield as a colourless crystalline solid (620 mg, 1.20 mmol); m.p. 140–141°C. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.1–2.0 (m, 19H; $GeCH_2C$, $GeCHC_2$, CCH_2C); 3.14 (s, 3H; NCH_3); 3.25–3.3, 3.4–3.65 and 3.9–4.2 (m, 9H; NCH_2C, $GeCH_2O$, OH); 7.3–7.5 (m,

5H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 3.9 ($GeCH_2C$); 20.1 (2C) (CCH_2C); 20.8 (CCH_2C); 26.5 (CCH_2C); 26.9 (C-1, GeC_6H_{11}); 27.9 (2C) (CCH_2C); 29.1 (2C) (CCH_2C); 47.2 (NCH_3); 50.5 ($GeCH_2O$); 59.7 (NCH_2C); 60.2 (NCH_2C); 62.8 (NCH_2C); 128.9 (C-3/C-5, GeC_6H_5); 129.1 (C-4, GeC_6H_5); 134.2 (C-2/C-6, GeC_6H_5); 135.4 (C-1, GeC_6H_5). FD MS (DMSO): *m/z* 392 (100%, M^+_{Cation}). Anal. Found: C, 48.7; H, 7.1; N, 2.7; I, 24.5. $C_{21}H_{36}GeINO$ (M_r = 518.0) Calc.: C, 48.69; H, 7.00; N, 2.70; I, 24.50%.

3.1.10. *(R)-1-{2-[Cyclohexyl(hydroxymethyl)phenylgermyl]ethyl}-1-methylpiperidinium iodide [(R)-2a]*

This compound was prepared analogously to the synthesis of *rac*-**2a** by addition of methyl iodide (91.0 mg, 641 μmol) to a solution of (*R*)-**1a** (120 mg, 319 μmol) in acetone (40 ml). (*R*)-**2a** was isolated in 82% yield as a colourless crystalline solid (135 mg, 261 μmol); m.p. 161–162°C [recrystallization by diffusion of n-pentane via the gas phase into a solution of the product in 2-propanol (15 ml) at room temperature]. The NMR and MS data of the product were identical with those obtained for *rac*-**2a**. $[\alpha]^{20}_{546} = -0.8$ (EtOH, *c* = 1.0). Anal. Found: C, 48.7; H, 7.2; N, 2.7; I, 24.5. $C_{21}H_{36}GeINO$ (M_r = 518.0) Calc.: C, 48.69; H, 7.00; N, 2.70; I, 24.50%.

3.1.11. *(S)-1-{2-[Cyclohexyl(hydroxymethyl)phenylgermyl]ethyl}-1-methylpiperidinium iodide [(S)-2a]*

This compound was prepared analogously to the synthesis of *rac*-**2a** by addition of methyl iodide (91.0 mg, 641 μmol) to a solution of (*S*)-**1** (120 mg, 319 μmol) in acetone (40 ml). (*S*)-**2a** was isolated in 84% yield as a colourless crystalline solid (139 mg, 268 μmol); m.p. 161–162°C [recrystallization by diffusion of n-pentane via the gas phase into a solution of the product in 2-propanol (15 ml) at room temperature]. The NMR and MS data of the product were identical with those obtained for *rac*-**2a**. $[\alpha]^{20}_{546} = +0.8$ (EtOH, *c* = 1.0). Anal. Found: C, 48.7; H, 7.2; N, 2.7; I, 24.5. $C_{21}H_{36}GeINO$ (M_r = 518.0) Calc.: C, 48.69; H, 7.00; N, 2.70; I, 24.50%.

3.1.12. *(Hydroxymethyl)diphenyl(2-piperidinoethyl)germane (3a)*

This compound was prepared analogously to the synthesis of *rac*-**1a** by addition of piperidine to the vinyl group of **18** (2.00 g, 5.60 mmol). After Kugelrohr distillation (170°C/0.01 Torr) and crystallization of the distillate at room temperature, **3a** was isolated in 96% yield as a white crystalline solid (1.98 g, 5.35 mmol); m.p. 73–74°C. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.35–1.75 (m, 8H; $GeCH_2C$, CCH_2C); 2.3–2.65 (m, 6H; NCH_2C); 4.05 (s, 2H; $GeCH_2O$); 6.8 (s, broad, 1H; OH); 7.3–7.6 (m, 10H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.1 ($GeCH_2C$); 23.9 ($NCCCH_2C$); 24.8 ($NCCH_2C$); 51.9 ($GeCH_2O$); 54.3 (NCH_2C, NC_5H_{10}); 54.4 ($GeCCH_2N$); 128.0 (C-3/C-5, GeC_6H_5); 128.6 (C-4, GeC_6H_5); 134.1 (C-2/C-6, GeC_6H_5); 127.2 (C-1, GeC_6H_5). EI MS: *m/z* 371 (5%, M^+); 340 (56%, $M^+ - CH_2OH$); 294 (4%, $M^+ - C_6H_5$); 151 (53%, $C_6H_5Ge^+$); 98 (100%, $CH_2{=}NC_5H^+_{10}$). Anal. Found: C, 65.0; H, 7.5; N, 3.8. $C_{20}H_{27}GeNO$ (M_r = 370.0) Calc.: C, 64.92; H, 7.35; N, 3.79%.

3.1.13. *1-{2-[(Hydroxymethyl)diphenylgermyl]ethyl}-piperidinium chloride (3a · HCl)*

This compound was prepared from **3a** (500 mg, 1.35 mmol) analogously to the synthesis of *rac*-**1a** · HCl and isolated in 91% yield as a colourless crystalline solid (501 mg, 1.23 mmol); m.p. 138–139°C. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.2–1.45 and 1.65–2.2 (m, 8H; $GeCH_2C$, CCH_2C); 2.5–2.7, 3.15–3.3 and 3.4–3.55 (m, 6H; NCH_2C); 4.19 (s, 2H; $GeCH_2O$); 4.2 (s, 1H; OH); 7.25–7.5 (m, 10H; GeC_6H_5); 10.8 (s, broad, 1H; NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.6 ($GeCH_2C$); 21.9 ($NCCCH_2C$); 22.5 ($NCCH_2C$); 51.8 ($GeCH_2O$); 53.2 (NCH_2C, NC_5H_{10}); 54.9 ($GeCCH_2N$); 128.0 (C-3/C-5, GeC_6H_5); 129.1 (C-4, GeC_6H_5); 134.1 (C-2/C-6, GeC_6H_5); 134.9 (C-1, GeC_6H_5). FD MS [$CH_3C(O)CH_3$]: *m/z* 372 (100%, M^+_{Cation}). Anal. Found: C, 59.2; H, 7.0; N, 3.5; Cl, 8.7. $C_{20}H_{28}ClGeNO$ (M_r = 406.5) Calc.: C, 59.10; H, 6.94; N, 3.45; Cl, 8.72%.

3.1.14. *1-{2-[(Hydroxymethyl)diphenylgermyl]ethyl}-piperidinium iodide (4a)*

This compound was prepared from **3a** (500 mg, 1.35 mmol) analogously to the synthesis of *rac*-**2a** and isolated in 88% yield as a colourless crystalline solid (608 mg, 1.19 mmol); m.p. 157–158°C. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.5–1.9 (m, 8H; $GeCH_2C$, CCH_2C); 3.11 (s, 3H; NCH_3); 3.35–3.65 and 3.7–3.85 (m, 7H; NCH_2C, OH); 4.28 (s, 2H; $GeCH_2O$); 7.3–7.55 (m, 10H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 6.4 ($GeCH_2C$); 20.0 ($NCCH_2C$); 20.7 ($NCCCH_2C$); 47.4 (NCH_3); 52.4 ($GeCH_2O$); 60.1 (NCH_2C, NC_5H_{10}); 62.3 ($GeCCH_2N$); 128.6 (C-3/C-5, GeC_6H_5); 129.5 (C-4, GeC_6H_5); 134.3 (C-2/C-6, GeC_6H_5); 134.9 (C-1, GeC_6H_5). FD MS [$CH_3C(O)CH_3$]: *m/z* 386 (100%, M^+_{Cation}). Anal. Found: C, 49.3; H, 6.1; N, 2.7; I, 24.9. $C_{21}H_{30}GeINO$ (M_r = 512.0) Calc.: C, 49.27; H, 5.91; N, 2.74; I, 24.79%.

3.1.15. *Dicyclohexyl(hydroxymethyl)(2-piperidinoethyl)-germane (5a)*

This compound was prepared analogously to the synthesis of *rac*-**1a** by addition of piperidine to the vinyl group of **23** (1.67 g, 4.52 mmol). After Kugelrohr distillation (180°C/0.01 Torr) and crystallization of the distillate at room temperature, **5a** was isolated in 95%

yield as a white crystalline solid (1.64 g, 4.29 mmol); m.p. 70–71°C. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.0–1.95 (m, 30H; $GeCH_2C$, $GeCHC_2$, CCH_2C); 2.25–2.65 (m, 6H; NCH_2C); 3.57 (s, 2H; $GeCH_2O$); 6.5 (s, broad, 1H; OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 8.3 ($GeCH_2C$); 24.3 (CCH_2C); 25.2 (CCH_2C); 25.5 (C-1, GeC_6H_{11}); 27.0 (CCH_2C); 28.4 (CCH_2C); 28.5 (CCH_2C); 29.67 (CCH_2C); 29.71 (CCH_2C); 49.5 ($GeCH_2O$); 54.5 (NCH_2C, NC_5H_{10}); 55.5 ($GeCCH_2N$). EI MS: *m/z* 383 (1%, M^+); 352 (15%, $M^+ - CH_2OH$); 300 (27%, $M^+ - C_6H_{11}$); 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 62.7; H, 10.4; N, 3.7. $C_{20}H_{39}GeNO$ (M_r = 382.1) Calc.: C, 62.86; H, 10.29; N, 3.67%.

3.1.16. *1-{2-[Dicyclohexyl(hydroxymethyl)germyl]ethyl}piperidinium chloride (5a · HCl)*

This compound was prepared from **5a** (500 mg, 1.31 mmol) analogously to the synthesis of *rac*-**1a** · HCl and isolated in 92% yield as a colourless crystalline solid (506 mg, 1.21 mmol); m.p. 189–190°C. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.0–1.45, 1.5–1.95 and 2.05–2.3 (m, 30H; $GeCH_2C$, $GeCHC_2$, CCH_2C); 2.45–2.95, 3.15–3.3 and 3.4–3.6 (m, 7H; NCH_2C, OH); 3.80 (s, 2H; $GeCH_2O$); 11.1 (s, broad, 1H; NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 4.3 ($GeCH_2C$); 22.4 (CCH_2C); 22.8 (CCH_2C); 25.6 (C-1, GeC_6H_{11}); 26.7 (CCH_2C); 28.19 (CCH_2C); 28.21 (CCH_2C); 29.66 (CCH_2C); 29.70 (CCH_2C); 51.4 ($GeCH_2O$); 51.8 (NCH_2C, NC_5H_{10}); 55.5 ($GeCCH_2N$). FD MS (DMSO): *m/z* 384 (100%, M^+_{Cation}). Anal. Found: C, 57.3; H, 9.7; N, 3.4; Cl, 8.3. $C_{20}H_{40}ClGeNO$ (M_r = 418.6) Calc.: C, 57.39; H, 9.63; N, 3.35; Cl, 8.47%.

3.1.17. *Dicyclohexyl(hydroxymethyl)(2-piperidinoethyl)silane (5b)*

A 2.0 M aqueous NaOH solution (2.00 ml, 4.00 mmol of NaOH) was added to a mixture composed of an aqueous solution (50 ml) of **5b** · HCl (800 mg, 2.14 mmol) and diethyl ether (50 ml). After stirring for 10 min, the organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 50 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, the solvent removed under reduced pressure, and the residue purified by Kugelrohr distillation (170°C/0.01 Torr) to give **5b** in 91% yield as a colourless crystalline solid (658 mg, 1.95 mmol). The product crystallized on cooling; m.p. 105–106°C. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.75–0.95 (m, 4H; $SiCH_2C$, $SiCHC_2$); 1.0–1.3, 1.3–1.5 and 1.5–1.8 (m, 26H; CCH_2C); 2.25–2.5 (m, 6H; NCH_2C); 3.31 (s, 2H; $SiCH_2O$); 6.2 (s, broad, 1H; OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.7 ($SiCH_2C$); 22.6 (C-1, SiC_6H_{11}); 24.3 (CCH_2C); 25.3 (CCH_2C); 27.0 (CCH_2C); 28.1 (CCH_2C); 28.2 (CCH_2C); 28.3 (CCH_2C); 28.4 (CCH_2C); 48.9 ($SiCH_2O$); 54.4 ($SiCCH_2N$); 54.5 (NCH_2C, NC_5H_{10}). ^{29}Si NMR (49.7 MHz, $CDCl_3$): δ −2.0. EI MS: *m/z* 337 (8%, M^+); 306 (1%, $M^+ - CH_2OH$); 254 (9%, $M^+ - C_6H_{11}$); 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 71.2; H, 11.8; N, 4.2. $C_{20}H_{39}NOSi$ (M_r = 337.6) Calc.: C, 71.15; H, 11.64; N, 4.15%.

3.1.18. *1-{2-[Dicyclohexyl(hydroxymethyl)silyl]ethyl}piperidinium chloride (5b · HCl)*

Rhodium on aluminium oxide (300 mg, Rh content 5%) was added to a solution of *rac*-**1b** (1.50 g, 4.52 mmol) in ethanol (50 ml) and the mixture was stirred under hydrogen at 50 bar and 45–50°C for 4 days. After removal of the catalyst by centrifugation, a further portion of rhodium on aluminium oxide (300 mg, Rh content 5%) was added, and the resulting mixture was stirred for a further 4 days under hydrogen at 50 bar and 45–50°C. The catalyst was removed by centrifugation and the solvent evaporated under reduced pressure. The residue was dissolved in diethyl ether (100 ml), 3.1 M ethereal HCl solution (2.00 ml, 6.20 mmol of HCl) was added at room temperature, and the resulting mixture was stirred for 10 min. The precipitate formed was filtered off, washed with diethyl ether, dried in vacuo and then recrystallized from acetone/diethyl ether (diffusion of diethyl ether via the gas phase into a saturated solution of the product in acetone) to give **5b** · HCl in 75% yield as a colourless crystalline solid (1.27 g, 3.40 mmol); m.p. 182–183°C. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.7–0.9, 1.0–1.5, 1.5–1.95 and 2.0–2.25 (m, 30H; $SiCH_2C$, $SiCHC_2$, CCH_2C); 2.55–2.85, 3.0–3.25 and 3.4–3.6 (m, 7H; NCH_2C, OH); 3.48 (s, 2H; $SiCH_2O$); 11.0 (s, broad, 1H; NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 4.5 ($SiCH_2C$); 22.2 (CCH_2C); 22.4 (C-1, SiC_6H_{11}); 22.7 (CCH_2C); 26.7 (CCH_2C); 27.9 (CCH_2C); 28.0 (CCH_2C); 49.8 ($SiCH_2O$); 51.9 (NCH_2C, NC_5H_{10}); 54.6 ($SiCCH_2N$). ^{29}Si NMR (49.7 MHz, $CDCl_3$): δ −1.9. FD MS [$CH_3C(O)CH_3$]: *m/z* 338 (100%, M^+_{Cation}). Anal. Found: C, 64.3; H, 10.8; N, 3.8; Cl, 9.5. $C_{20}H_{40}ClNOSi$ (M_r = 374.1) Calc.: C, 64.22; H, 10.78; N, 3.74; Cl, 9.48%.

3.1.19. *1-{2-[Dicyclohexyl(hydroxymethyl)germyl]ethyl}-1-methylpiperidinium iodide (6a)*

This compound was prepared from **5a** (500 mg, 1.31 mmol) analogously to the synthesis of *rac*-**2a** and isolated after crystallization from acetone (5 ml) at −20°C in 80% yield as a colourless crystalline solid (550 mg, 1.05 mmol); m.p. 140–141°C. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.05–1.45 and 1.6–2.0 (m, 30H; $GeCH_2C$, $GeCHC_2$, CCH_2C); 3.0 (s, broad, 1H; OH); 3.18 (s, 3H; NCH_3); 3.55–3.65 and 3.8–3.95 (m, 8H; NCH_2C, $GeCH_2O$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 2.2 ($GeCH_2C$); 20.3 (CCH_2C); 20.9 (CCH_2C); 25.9 (C-1, GeC_6H_{11}); 26.7 (CCH_2C); 28.2 (CCH_2C); 29.78 (CCH_2C); 29.84 (CCH_2C); 46.8 (NCH_3); 50.2

($GeCH_2O$); 59.9 (NCH_2C, NC_5H_{10}); 63.4 ($GeCCH_2N$). FD MS (DMSO): m/z 398 (100%, M^+_{Cation}). Anal. Found: C, 48.2; H, 8.2; N, 2.8; I, 24.3. $C_{21}H_{42}GeINO$ (M_r = 524.1) Calc.: C, 48.13; H, 8.08; N, 2.67; I, 24.22%.

*3.1.20. 1-{2-[Dicyclohexyl(hydroxymethyl)silyl]ethyl}-1-methylpiperidinium iodide (**6b**)*

Methyl iodide (351 mg, 2.47 mmol) was added to a solution of **5b** (400 mg, 1.18 mmol) in acetone (50 ml) and the mixture stirred at room temperature for 18 h. After removal of the solvent and excess methyl iodide under reduced pressure, the solid residue was dried in vacuo and then recrystallized from acetone/diethyl ether (diffusion of diethyl ether via the gas phase into a saturated solution of the product in acetone) to give **6b** in 91% yield as a colourless crystalline solid (518 mg, 1.08 mmol); m.p. 153–154°C. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.8–1.1, 1.1–1.4 and 1.6–2.0 (m, 30H; $SiCH_2C$, $SiCHC_2$, CCH_2C); 2.8 (s, broad, 1H; OH); 3.13 (s, 3H; NCH_3); 3.45–3.55 and 3.55–3.8 (m, 8H; NCH_2C, $SiCH_2O$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 2.6 ($SiCH_2C$); 20.3 (CCH_2C); 20.9 (CCH_2C); 22.7 (C-1, SiC_6H_{11}); 26.8 (CCH_2C); 28.1 (CCH_2C); 28.2 (CCH_2C); 28.3 (CCH_2C); 46.9 (NCH_3); 48.6 ($SiCH_2O$); 59.9 (NCH_2C, NC_5H_{10}); 62.5 ($SiCCH_2N$). ^{29}Si NMR (49.7 MHz, $CDCl_3$): δ −1.3. FD MS [$CH_3C(O)CH_3$]: m/z 352 (100%, M^+_{Cation}). Anal. Found: C, 52.6; H, 9.0; N, 2.9; I, 26.6. $C_{21}H_{42}INOSi$ (M_r = 479.6) Calc.: C, 52.60; H, 8.83; N, 2.92; I, 26.46%.

*3.1.21. Trichloro(chloromethyl)germane (**7**)*

Synthesis as described in Ref. [25].

*3.1.22. Dichloro(chloromethyl)cyclohexylgermane (**8**)*

A 1.1 M solution of cyclohexylmagnesium chloride in diethyl ether (120 ml, 132 mmol of c-$C_6H_{11}MgCl$) was added dropwise at 0°C over 2.5 h to a stirred solution of **7** (30.2 g, 132 mmol) in diethyl ether (500 ml). The mixture was stirred at room temperature for 15 h and then under reflux for 2 h, and the precipitate was filtered off and the solvent removed by distillation at atmospheric pressure. n-Pentane (200 ml) was added to the resulting residue and the precipitate formed was filtered off. The filtrate was concentrated under reduced pressure and the residue distilled in vacuo (Vigreux column) to give **8** in 56% yield (20.5 g, 74.2 mmol) as a colourless liquid; b.p. 82°C/0.01 Torr. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.3–1.4, 1.5–1.6 and 1.7–2.1 (m, 11H; GeC_6H_{11}); 3.49 (s, 2H; $GeCH_2Cl$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.9 (CCH_2C); 26.9 (CCH_2C); 27.0 (CCH_2C); 33.1 ($GeCH_2Cl$); 37.0 (C-1, GeC_6H_{11}). EI MS: m/z 276 (1%, M^+); 227 (2%, $M^+ - CH_2Cl$); 193 (1%, $M^+ - C_6H_{11}$); 83 (100%, $C_6H_{11}^+$). Anal. Found: C, 30.7; H, 4.6. $C_7H_{13}Cl_3Ge$ (M_r = 276.1) Calc.: C, 30.45; H, 4.75%.

*3.1.23. rac-Chloro(chloromethyl)cyclohexyl(phenyl)germane (rac-**9**)*

A 2.26 M solution of phenylmagnesium chloride in THF (50 ml, 113 mmol of C_6H_5MgCl) was added dropwise at 0°C over 2 h to a stirred solution of **8** (31.2 g, 113 mmol) in diethyl ether (800 ml). After stirring at room temperature for 16 h and heating under reflux for 4 h, the precipitate was filtered off and the solvent removed by distillation at atmospheric pressure. n-Pentane (200 ml) was added to the resulting residue and the precipitate formed was filtered off. The filtrate was concentrated under reduced pressure and the residue distilled in vacuo (Vigreux column) to give *rac*-**9** in 80% yield (28.8 g, 90.6 mmol) as a colourless liquid; b.p. 112°C/0.01 Torr. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.3–1.4, 1.5–1.6, 1.7–1.8 and 1.9–2.0 (m, 11H; GeC_6H_{11}); 3.43 (δ_A) and 3.47 (δ_B) (AB system, J_{AB} = 12.2 Hz, 2H; $GeCH_2Cl$); 7.4–7.5 and 7.6–7.7 (m, 5H; GeC_6H_5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.3 (CCH_2C); 27.5 (2C) (CCH_2C); 27.6 (2C) (CCH_2C); 29.5 ($GeCH_2Cl$); 30.7 (C-1, GeC_6H_{11}); 128.6 (C-3/C-5, GeC_6H_5); 130.5 (C-4, GeC_6H_5); 133.5 (C-2/C-6, GeC_6H_5); 133.6 (C-1, GeC_6H_5). EI MS: m/z 318 (2%, M^+); 269 (75%, $M^+ - CH_2Cl$); 235 (3%, $M^+ - C_6H_{11}$); 151 (12%, $C_6H_5Ge^+$); 83 (100%, $C_6H_{11}^+$). Anal. Found: C, 49.1; H, 5.7. $C_{13}H_{18}Cl_2Ge$ (M_r = 317.8) Calc.: C, 49.14; H, 5.71%.

*3.1.24. rac-(Chloromethyl)cyclohexyl(phenyl)vinylgermane (rac-**10**)*

A 1.0 M solution of vinylmagnesium chloride in THF (195 ml, 195 mmol of $CH_2{=}CHMgCl$) was added dropwise at room temperature over 30 min to a stirred solution of *rac*-**9** (49.7 g, 156 mmol) in toluene (200 ml). The mixture was heated under reflux for 1 h and then cooled to room temperature, and half-saturated aqueous NH_4Cl solution (250 ml) was added at 0°C. The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 200 ml). After drying of the combined organic extracts over anhydrous $MgSO_4$ and removal of the solvent under reduced pressure, the residue was distilled in vacuo (Vigreux column) and the distillate further purified by medium-pressure liquid chromatography on silica gel using n-hexane as the eluent. After removal of the solvent from the eluate under reduced pressure, the residue was subjected to a Kugelrohr distillation (140°C/0.01 Torr) to give *rac*-**10** in 86% yield (41.4 g, 134 mmol) as a colourless liquid; b.p. 127°C/0.01 Torr. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.2–1.55 and 1.65–2.0 (m, 11H; GeC_6H_{11}); 3.32 (δ_A) and 3.37 (δ_B) (AB system, J_{AB} = 12.4 Hz, 2H; $GeCH_2Cl$); 5.87 (dd, J_{gem} = 3.4 Hz, J_{trans} = 19.8 Hz, 1H; GeCH=C*H*H); 6.27 (dd, J_{gem} = 3.4 Hz, J_{cis} = 13.7 Hz, 1H; GeCH=C*H*H); 6.46 (dd, J_{cis} = 13.7 Hz, J_{trans} = 19.8 Hz, 1H; GeC*H*=CH_2); 7.4–7.6 (m, 5H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 26.6 (C-1,

GeC_6H_{11}); 26.7 (CCH_2C); 27.4 ($GeCH_2Cl$); 28.0 (2C) (CCH_2C); 28.88 (CCH_2C); 28.91 (CCH_2C); 128.1 (C-3/C-5, GeC_6H_5); 129.0 (C-4, GeC_6H_5); 132.6 ($GeCH{=}CH_2$); 134.1 ($GeCH{=}CH_2$); 134.4 (C-2/C-6, GeC_6H_5); 135.4 (C-1, GeC_6H_5). EI MS: *m/z* 310 (11%, M^+); 283 (1%, $M^+ - CH{=}CH_2$); 261 (100%, $M^+ - CH_2Cl$); 227 (26%, $M^+ - C_6H_{11}$); 179 (86%, $C_8H_9Ge^+$); 151 (26%, $C_6H_5Ge^+$). Anal. Found: C, 58.2; H, 6.9; Cl, 11.5. $C_{15}H_{21}ClGe$ (M_r = 309.4) Calc.: C, 58.24; H, 6.84; Cl, 11.46%.

3.1.25. *rac*-(Acetoxymethyl)cyclohexyl(phenyl)vinylgermane (*rac*-11)

A mixture of *rac*-**10** (39.8 g, 129 mmol) and sodium acetate (13.2 g, 161 mmol) in DMF (200 ml) was stirred under reflux for 8 h. The mixture was cooled to room temperature, the precipitate filtered off, and the solvent removed under reduced pressure. The residue was distilled in vacuo (Vigreux column) and the distillate further purified by medium-pressure liquid chromatography on silica gel using diethyl ether/n-hexane [1 : 10 (v : v)] as eluent. After removal of the solvent from the eluate under reduced pressure, the residue was subjected to a Kugelrohr distillation (140°C/0.01 Torr) to give *rac*-**11** in 91% yield as a colourless liquid (39.1 g, 117 mmol); b.p. 133°C/0.01 Torr. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.2–1.9 (m, 11H; GeC_6H_{11}); 2.00 (s, 3H; CCH_3); 4.38 (s, 2H; $GeCH_2O$); 5.79 (dd, J_{gem} = 3.5 Hz, J_{trans} = 19.8 Hz, 1H; $GeCH{=}CHH$); 6.19 (dd, J_{gem} = 3.5 Hz, J_{cis} = 13.5 Hz, 1H; $GeCH{=}CHH$); 6.38 (dd, J_{cis} = 13.5 Hz, J_{trans} = 19.8 Hz, 1H; $GeCH{=}CH_2$); 7.3–7.55 (m, 5H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.7 (CCH_3); 26.6 (CCH_2C); 26.8 (C-1, GeC_6H_{11}); 28.0 (2C) (CCH_2C); 28.91 (CCH_2C); 28.94 (CCH_2C); 54.8 ($GeCH_2O$); 128.0 (C-3/C-5, GeC_6H_5); 128.7 (C-4, GeC_6H_5); 132.9 ($GeCH{=}CH_2$); 133.6 ($GeCH{=}CH_2$); 134.4 (C-2/C-6, GeC_6H_5); 135.6 (C-1, GeC_6H_5); 171.4 (CO). EI MS: *m/z* 307 (9%, $M^+ - CH{=}CH_2$); 251 (100%, $M^+ - C_6H_{11}$); 179 (49%, $C_8H_9Ge^+$); 151 (44%, $C_6H_5Ge^+$). Anal. Found: C, 61.3; H, 7.3. $C_{17}H_{24}GeO_2$ (M_r = 333.0) Calc.: C, 61.32; H, 7.26%.

3.1.26. *rac*-Cyclohexyl(hydroxymethyl)phenyl(vinyl)germane (*rac*-12)

A solution of *rac*-**11** (22.6 g, 67.9 mmol) in diethyl ether (150 ml) was added dropwise at 0°C over 45 min to a stirred suspension of lithium aluminium hydride (5.41 g, 143 mmol) in diethyl ether (300 ml). The mixture was stirred at 0°C for 1 h and water (150 ml) and 6.0 M hydrochloric acid (150 ml) were then added dropwise. The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 250 ml). After drying of the combined organic extracts over anhydrous Na_2SO_4 and removal of the solvent under reduced pressure, the residue was distilled in vacuo (Vigreux column) to give *rac*-**12** in 87% yield as a colourless liquid (17.2 g, 59.1 mmol); b.p. 118°C/0.01 Torr. ^{1}H NMR (250.1 MHz, C_6D_6): δ 1.1–1.9 (m, 12H; GeC_6H_{11}, OH); 3.86 (s, 2H; $GeCH_2O$); 5.78 (dd, J_{gem} = 3.4 Hz, J_{trans} = 20.0 Hz, 1H; $GeCH{=}CHH$); 6.09 (dd, J_{gem} = 3.4 Hz, J_{cis} = 13.8 Hz, 1H; $GeCH{=}CHH$); 6.37 (dd, J_{cis} = 13.8 Hz, J_{trans} = 20.0 Hz, 1H; $GeCH{=}CH_2$); 7.1–7.3 and 7.5–7.6 (m, 5H; GeC_6H_5). ^{13}C NMR (62.9 MHz, C_6D_6): δ 26.6 (C-1, GeC_6H_{11}); 26.7 (CCH_2C); 28.1 (2C) (CCH_2C); 29.2 (2C) (CCH_2C); 53.2 ($GeCH_2O$); 128.1 (C-3/C-5, GeC_6H_5); 127.8 (C-4, GeC_6H_5); 133.4 ($GeCH{=}CH_2$); 133.9 ($GeCH{=}CH_2$); 134.6 (C-2/C-6, GeC_6H_5); 136.1 (C-1, GeC_6H_5). EI MS: *m/z* 292 (1%, M^+); 261 (61%, $M^+ - CH_2OH$); 209 (9%, $M^+ - C_6H_{11}$); 179 (100%, $C_8H_9Ge^+$); 151 (48%, $C_6H_5Ge^+$). Anal. Found: C, 61.9; H, 7.7. $C_{15}H_{22}GeO$ (M_r = 290.9) Calc.: C, 61.93; H, 7.62%.

3.1.27. *rac*-Cyclohexyl(phenyl)[(trimethylsilyloxy)methyl]vinylgermane (*rac*-13)

A solution of chlorotrimethylsilane (14.1 g, 130 mmol) in n-pentane (200 ml) was added dropwise at 0°C over 90 min to a stirred solution of *rac*-**12** (17.2 g, 59.1 mmol) and triethylamine (6.59 g, 65.1 mmol) in n-pentane (300 ml). The solution was allowed to warm to room temperature and then stirred for 18 h. The precipitate was filtered off, the solvent removed under reduced pressure, and the residue distilled in vacuo (Vigreux column) to give *rac*-**13** in 95% yield as a colourless liquid (20.4 g, 56.2 mmol); b.p. 120°C/0.01 Torr. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.12 (s, 9H; $SiCH_3$); 1.2–1.9 (m, 11H; GeC_6H_{11}); 3.96 (s, 2H; $GeCH_2O$); 5.80 (dd, J_{gem} = 3.5 Hz, J_{trans} = 20.0 Hz, 1H; $GeCH{=}CHH$); 6.19 (dd, J_{gem} = 3.5 Hz, J_{cis} = 13.8 Hz, 1H; $GeCH{=}CHH$); 6.43 (dd, J_{cis} = 13.8 Hz, J_{trans} = 20.0 Hz, 1H; $GeCH{=}CH_2$); 7.35–7.65 (m, 5H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −0.8 ($SiCH_3$); 26.7 (C-1, GeC_6H_{11}); 26.9 (CCH_2C); 28.3 (2C) (CCH_2C); 29.16 (CCH_2C); 29.19 (CCH_2C); 53.1 ($GeCH_2O$); 127.9 (C-3/C-5, GeC_6H_5); 128.5 (C-4, GeC_6H_5); 133.1 ($GeCH{=}CH_2$); 134.3 ($GeCH{=}CH_2$); 134.7 (C-2/C-6, GeC_6H_5); 137.4 (C-1, GeC_6H_5). EI MS: *m/z* 364 (1%, M^+); 349 (3%, $M^+ - CH_3$); 337 (2%, $M^+ - CH{=}CH_2$); 281 (26%, $M^+ - C_6H_{11}$); 261 [70%, $M^+ - CH_2OSi(CH_3)_3$]; 179 (100%, $C_8H_9Ge^+$); 151 (54%, $C_6H_5Ge^+$). Anal. Found: C, 59.5; H, 8.5. $C_{18}H_{30}GeOSi$ (M_r = 363.1) Calc.: C, 59.54; H, 8.33%.

3.1.28. Chloro(chloromethyl)diphenylgermane (14)

Synthesis as described in Ref. [25].

3.1.29. (Chloromethyl)diphenyl(vinyl)germane (15)

This compound was prepared from **14** (15.2 g, 48.8 mmol) analogously to the synthesis of *rac*-**10** and isolated in 84% yield as a colourless liquid (12.4 g, 40.9 mmol); b.p. 129°C/0.01 Torr. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 3.54 (s, 2H; $GeCH_2Cl$); 5.92 (dd, J_{gem} = 2.9

Hz, J_{trans} = 19.9 Hz, 1H; GeCH=CHH); 6.37 (dd, J_{gem} = 2.9 Hz, J_{cis} = 13.5 Hz, 1H; GeCH=CHH); 6.66 (dd, J_{cis} = 13.5 Hz, J_{trans} = 19.9 Hz, 1H; GeCH=CH_2); 7.4–7.6 (m, 10H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 28.3 ($GeCH_2Cl$); 128.4 (C-3/C-5, GeC_6H_5); 129.5 (C-4, GeC_6H_5); 132.3 (GeCH=CH_2); 134.6 (3C) (C-1, C-2/C-6, GeC_6H_5); 135.1 (GeCH=CH_2). EI MS: *m/z* 304 (1%, M^+); 277 (3%, $M^+ - CH{=}CH_2$); 269 (2%, $M^+ - Cl$); 255 (100%, $M^+ - CH_2Cl$). Anal. Found: C, 59.4; H, 5.0; Cl, 11.7. $C_{15}H_{15}ClGe$ (M_r = 303.3) Calc.: C, 59.40; H, 4.98; Cl, 11.69%.

3.1.30. (Acetoxymethyl)diphenyl(vinyl)germane (16)

This compound was prepared from **15** (12.3 g, 40.6 mmol) analogously to the synthesis of *rac*-**11** and isolated in 83% yield as a colourless liquid (11.0 g, 33.6 mmol); b.p. 131°C/0.01 Torr. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.97 (s, 3H; CCH_3); 4.58 (s, 2H; $GeCH_2O$); 5.84 (dd, J_{gem} = 3.0 Hz, J_{trans} = 19.9 Hz, 1H; GeCH=CHH); 6.29 (dd, J_{gem} = 3.0 Hz, J_{cis} = 13.5 Hz, 1H; GeCH=CHH); 6.58 (dd, J_{cis} = 13.5 Hz, J_{trans} = 19.9 Hz, 1H; GeCH=CH_2); 7.35–7.65 (m, 10H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.6 (CCH_3); 56.1 ($GeCH_2O$); 128.3 (C-3/C-5, GeC_6H_5); 129.2 (C-4, GeC_6H_5); 132.9 (GeCH=CH_2); 134.6 (3C) (C-1, C-2/C-6, GeC_6H_5); 134.9 (GeCH=CH_2); 171.4 (CO). EI MS: *m/z* 328 (2%, M^+); 301 (25%, $M^+ - CH{=}CH_2$); 255 [100%, $M^+ - CH_2OC(O)CH_3$]; 251 (97%, $M^+ - C_6H_5$); 151 (75%, $C_6H_5Ge^+$). Anal. Found: C, 62.5; H, 5.7. $C_{17}H_{18}GeO_2$ (M_r = 326.9) Calc.: C, 62.46; H, 5.55%.

3.1.31. (Hydroxymethyl)diphenyl(vinyl)germane (17)

This compound was prepared from **16** (12.4 g, 37.9 mmol) analogously to the synthesis of *rac*-**12** and isolated in 86% yield as a colourless liquid (9.30 g, 32.6 mmol); b.p. 115°C/0.01 Torr. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.5 (s, broad, 1H; OH); 4.21 (s, 2H; $GeCH_2O$); 5.88 (dd, J_{gem} = 3.1 Hz, J_{trans} = 20.0 Hz, 1H; GeCH=CHH); 6.31 (dd, J_{gem} = 3.1 Hz, J_{cis} = 13.5 Hz, 1H; GeCH=CHH); 6.60 (dd, J_{cis} = 13.5 Hz, J_{trans} = 20.0 Hz, 1H; GeCH=CH_2); 7.35–7.65 (m, 10H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 54.7 ($GeCH_2O$); 128.6 (C-3/C-5, GeC_6H_5); 129.2 (C-4, GeC_6H_5); 133.2 (GeCH=CH_2); 134.7 (3C) (GeCH=CH_2; C-2/C-6, GeC_6H_5); 135.4 (C-1, GeC_6H_5). EI MS: *m/z* 286 (2%, M^+); 255 (100%, $M^+ - CH_2OH$); 151 (44%, $C_6H_5Ge^+$). Anal. Found: C, 63.3; H, 5.7. $C_{15}H_{16}GeO$ (M_r = 284.9) Calc.: C, 63.24; H, 5.66%.

3.1.32. Diphenyl[(trimethylsilyloxy)methyl]vinylgermane (18)

This compound was prepared from **17** (6.48 g, 22.7 mmol) analogously to the synthesis of *rac*-**13** and isolated in 94% yield as a colourless liquid (7.63 g, 21.4 mmol); b.p. 98°C/0.01. ^1H NMR (250.1 MHz, $CDCl_3$): δ 0.13 (s, 9H; $SiCH_3$); 4.20 (s, 2H; $GeCH_2O$); 5.88 (dd, J_{gem} = 3.2 Hz, J_{trans} = 20.0 Hz, 1H; GeCH=CHH); 6.31 (dd, J_{gem} = 3.2 Hz, J_{cis} = 13.5 Hz, 1H; GeCH=CHH); 6.63 (dd, J_{cis} = 13.5 Hz, J_{trans} = 20.0 Hz, 1H; GeCH=CH_2); 7.4–7.7 (m, 10H; GeC_6H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −0.8 ($SiCH_3$); 54.5 ($GeCH_2O$); 128.1 (C-3/C-5, GeC_6H_5); 128.9 (C-4, GeC_6H_5); 134.0 (GeCH=CH_2); 134.2 (GeCH=CH_2); 134.9 (C-2/C-6, GeC_6H_5); 136.4 (C-1, GeC_6H_5). EI MS: *m/z* 358 (1%, M^+); 255 [100%, $M^+ - CH_2OSi(CH_3)_3$]; 151 (28%, $C_6H_5Ge^+$). Anal. Found: C, 60.6; H, 6.9. $C_{18}H_{24}GeOSi$ (M_r = 357.1) Calc.: C, 60.55; H, 6.77%.

3.1.33. Chloro(chloromethyl)dicyclohexylgermane (19)

A 920 mM solution of cyclohexylmagnesium chloride in diethyl ether (150 ml, 138 mmol of *c*-$C_6H_{11}MgCl$) was added dropwise at 0°C over 50 min to a stirred solution of **7** (15.7 g, 68.7 mmol) in THF (300 ml). The mixture was stirred at room temperature for 18 h and then under reflux for 8 h and the precipitate was filtered off and the solvent removed under reduced pressure. n-Pentane (500 ml) was added to the residue and the precipitate formed was filtered off. The filtrate was concentrated under reduced pressure and the residue distilled in vacuo (Vigreux column) to give **19** in 63% yield as a colourless liquid (14.0 g, 43.2 mmol); b.p. 122°C/0.01 Torr. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.1–2.0 (m, 22H; GeC_6H_{11}); 3.22 (s, 2H; $GeCH_2Cl$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 26.4 ($GeCH_2Cl$); 27.67 (CCH_2C); 27.74 (CCH_2C); 27.9 (CCH_2C); 28.08 (CCH_2C); 28.1 (CCH_2C); 30.1 (C-1, GeC_6H_{11}). EI MS: *m/z* 324 (3%, M^+); 289 (1%, $M^+ - Cl$); 275 (56%, $M^+ - CH_2Cl$); 241 (2%, $M^+ - C_6H_{11}$); 83 (100%, $C_6H_{11}^+$). Anal. Found: C, 48.2; H, 7.6; Cl, 22.0. $C_{13}H_{24}Cl_2Ge$ (M_r = 323.8) Calc.: C, 48.22; H, 7.47; Cl, 21.90%.

3.1.34. (Chloromethyl)dicyclohexyl(vinyl)germane (20)

This compound was prepared from **20** (13.8 g, 42.6 mmol) analogously to the synthesis of *rac*-**10** and isolated in 67% yield as a colourless liquid (9.04 g, 28.7 mmol); b.p. 125°C/0.01 Torr. ^1H NMR (250.1 MHz, $CDCl_3$): δ 1.1–1.45 and 1.55–1.85 (m, 22H; GeC_6H_{11}); 3.08 (s, 2H; $GeCH_2Cl$); 5.65 (dd, J_{gem} = 4.7 Hz, J_{trans} = 18.8 Hz, 1H; GeCH=CHH); 6.05 (dd, J_{gem} = 4.7 Hz, J_{cis} = 13.9 Hz, 1H; GeCH=CHH); 6.16 (dd, J_{cis} = 13.9 Hz, J_{trans} = 18.8 Hz, 1H; GeCH=CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 25.7 (C-1, GeC_6H_{11}); 26.4 ($GeCH_2Cl$); 26.9 (CCH_2C); 28.3 (CCH_2C); 29.3 (CCH_2C); 29.4 (CCH_2C); 132.7 (GeCH=CH_2); 133.6 (GeCH=CH_2). EI MS: *m/z* 316 (2%, M^+); 289 (1%, $M^+ - CH{=}CH_2$); 267 (56%, $M^+ - CH_2Cl$); 233 (20%, $M^+ - C_6H_{11}$); 81 (100%). Anal. Found: C, 57.0; H,

8.6; Cl, 11.3. $C_{15}H_{27}ClGe$ (M_r = 315.4) Calc.: C, 57.12; H, 8.63; Cl, 11.24%.

3.1.35. (Acetoxymethyl)dicyclohexyl(vinyl)germane (21)

This compound was prepared from **20** (5.20 g, 16.5 mmol) analogously to the synthesis of *rac*-**11** and isolated in 86% yield as a colourless liquid (4.81 g, 14.2 mmol); b.p. 136°C/0.01 Torr. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.1–1.45 and 1.6–1.85 (m, 22H; GeC_6H_{11}); 2.01 (s, 3H; CCH_3); 4.11 (s, 2H; $GeCH_2O$); 5.61 (dd, J_{gem} = 5.0 Hz, J_{trans} = 18.6 Hz, 1H; GeCH=C*H*H); 6.01 (dd, J_{gem} = 5.0 Hz, J_{cis} = 13.8 Hz, 1H; GeCH=C*H*H); 6.11 (dd, J_{cis} = 13.8 Hz, J_{trans} = 18.6 Hz, 1H; GeC*H*=CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.9 (CCH_3); 25.7 (C-1, GeC_6H_{11}); 26.9 (CCH_2C); 28.3 (CCH_2C); 29.3 (CCH_2C); 29.4 (CCH_2C); 53.9 ($GeCH_2O$); 132.5 (GeCH=CH_2); 133.6 (Ge*C*H=CH_2); 171.9 (CO). EI MS: *m/z* 313 (4%, $M^+ - CH{=}CH_2$); 267 [1%, $M^+ - CH_2OC(O)CH_3$], 257 (100%, $M^+ - C_6H_{11}$). Anal. Found: C, 60.3; H, 9.0. $C_{17}H_{30}GeO_2$ (M_r = 339.0) Calc.: C, 60.23; H, 8.92%.

3.1.36. Dicyclohexyl(hydroxymethyl)vinylgermane (22)

This compound was prepared from **21** (4.52 g, 13.3 mmol) analogously to the synthesis of *rac*-**12** and isolated in 88% yield as a colourless liquid (3.48 g, 11.7 mmol); b.p. 128°C/0.01 Torr. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 1.05–1.45 and 1.55–1.85 (m, 23H; GeC_6H_{11}, OH); 3.80 (s, 2H; $GeCH_2O$); 5.67 (dd, J_{gem} = 5.2 Hz, J_{trans} = 18.6 Hz, 1H; GeCH=C*H*H); 6.09 (dd, J_{gem} = 5.2 Hz, J_{cis} = 13.7 Hz, 1H; GeCH=C*H*H); 6.37 (dd, J_{cis} = 13.7 Hz, J_{trans} = 18.6 Hz, 1H; GeC*H*=CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 25.4 (C-1, GeC_6H_{11}); 26.9 (CCH_2C); 28.3 (CCH_2C); 29.5 (CCH_2C); 29.6 (CCH_2C); 52.2 ($GeCH_2O$); 132.7 (GeCH=CH_2); 134.2 (Ge*C*H=CH_2). EI MS: *m/z* 298 (1%, M^+); 267 (39%, $M^+ - CH_2OH$); 215 (8%, $M^+ - C_6H_{11}$); 81 (100%). Anal. Found: C, 60.6; H, 9.6. $C_{15}H_{28}GeO$ (M_r = 297.0) Calc.: C, 60.67; H, 9.50%.

3.1.37. Dicyclohexyl[(trimethylsilyloxy)methyl]vinylgermane (23)

This compound was prepared from **22** (3.03 g, 10.2 mmol) analogously to the synthesis of *rac*-**13** and isolated in 94% yield as a colourless liquid (3.54 g, 9.59 mmol); b.p. 124°C/0.01 Torr. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 0.07 (s, 9H; $SiCH_3$); 1.15–1.45 and 1.65–1.85 (m, 22H; GeC_6H_{11}); 3.69 (s, 2H; $GeCH_2O$); 5.62 (dd, J_{gem} = 4.2 Hz, J_{trans} = 19.7 Hz, 1H; GeCH=C*H*H); 6.00 (dd, J_{gem} = 4.2 Hz, J_{cis} = 13.9 Hz, 1H; GeCH=C*H*H); 6.16 (dd, J_{cis} = 13.9 Hz, J_{trans} = 19.7 Hz, 1H; GeC*H*=CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −0.8 ($SiCH_3$); 25.5 (C-1, GeC_6H_{11}); 27.1 (CCH_2C); 28.4 (CCH_2C); 29.4 (CCH_2C); 29.5 (CCH_2C); 51.5 ($GeCH_2O$); 131.7 (GeCH=CH_2); 135.3 (Ge*C*H=CH_2). FI MS: *m/z* 370 (5%, M^+); 343 (1%, $M^+ - CH{=}CH_2$); 329 (100%, $C_{15}H_{31}OSiGe^+$); 287 (1%, $M^+ - C_6H_{11}$); 267 [1%, $M^+ - CH_2OSi(CH_3)_3$]. Anal. Found: C, 58.5; H, 9.9. $C_{18}H_{36}GeOSi$ (M_r = 369.2) Calc.: C, 58.57; H, 9.83%.

3.2. NMR spectroscopic determination of the enantiomeric purities of the antipodes of ***1a***

The enantiomeric purities of the (*R*)- and (*S*)-enantiomer of **1a** were determined by ^{1}H and ^{13}C NMR studies using the chiral shift reagent (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol [(−)-TFAE; Sigma]. The NMR spectra were recorded at room temperature on a Bruker AM-400 NMR spectrometer operating at 400.1 (^{1}H) and 100.6 MHz (^{13}C) respectively. The composition of the samples used for the NMR experiments was as follows: 31.9 μmol **1a**, 192 μmol (−)-TFAE, 0.5 ml $CDCl_3$.

3.3. Crystal structure analysis of (R)-2a

Crystal data and refinement details are presented in Table 1. Data were collected on a Siemens R3 diffractometer with an LT-2 low temperature attachment. The structure was solved by assuming the coordinates of the isostructural silicon analogue (*R*)-**2b** [7] and refined anisotropically on F^2 (program SHELXL-93, G.M. Sheldrick, University of Göttingen, Germany). H atoms were included in rigid groups (OH, CH_3) or with a riding model. The weighting scheme was $w^{-1} = \sigma^2(F^2) + (aP)^2 + bP$, where $3P = (2F_c^2 + F_o^2)$ and *a* and *b* are constants optimized by the program. The absolute configuration was confirmed by an *x* refinement [27]; *x* refined to −0.01(2). Final atomic coordinates are presented in Table 5. Further details of the structure determination may be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany, on quoting the reference number CSD-491548, the names of the authors and the journal citation.

3.4. Pharmacological studies

3.4.1. Functional pharmacological studies

As a measure of affinity, pA_2 values of the pure (*R*)- and (*S*)-enantiomers of **1a**, **1b**, **2a** and **2b** and of the achiral compounds **3a–6a** and **3b–6b** were determined at muscarinic M1 receptors in rabbit vas deferens [1-[4-[[(4-fluorophenyl)carbamoyl]oxy]-2-butyn-1-yl]-1-methylpyrrolidinium tosylate (4-F-PyMcN$^+$) as agonist], M2 receptors in guinea-pig atria and M3 receptors in guinea-pig ileum (arecaidine propargyl ester as agonist) according to published procedures [3].

Concentration-response curves of the agonists were constructed in the absence and in the presence of the

Table 5
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($pm^2 \times 10^{-1}$) (*R*)-**2a**

Atom	x	y	z	U_{eq} [a]
I	2944.7(3)	9307.6(3)	4784.1(1)	36.1(1)
Ge	2249.5(5)	5187.1(4)	3866.6(2)	23.4(1)
O	−865(4)	5277(5)	4024.0(15)	59.9(11)
N	2694(3)	4019(3)	5380.5(10)	19.5(6)
C(1)	358(5)	6235(6)	3973(2)	40.8(11)
C(2)	3234(4)	4827(4)	4502.0(14)	25.2(8)
C(3)	2192(4)	4042(4)	4849.5(12)	22.5(7)
C(4)	4219(4)	3347(5)	5414(2)	27.3(8)
C(5)	2689(5)	5561(4)	5572.8(13)	26.7(8)
C(6)	2968(5)	5611(5)	6122.2(14)	35.3(9)
C(7)	1823(6)	4695(5)	6394(2)	38.4(10)
C(8)	1815(5)	3143(5)	6204.6(15)	32.1(9)
C(9)	1567(4)	3107(4)	5659.0(15)	25.7(8)
C(10)	1760(4)	3351(4)	3541.7(14)	25.5(8)
C(11)	736(5)	3336(5)	3159(2)	35.9(10)
C(12)	402(6)	2058(6)	2911(2)	45.1(12)
C(13)	1048(6)	750(6)	3051(2)	41.8(11)
C(14)	2051(5)	733(5)	3434(2)	34.9(8)
C(15)	2398(5)	2024(4)	3675.5(15)	28.9(9)
C(16)	3627(4)	6336(4)	3460.1(14)	23.0(7)
C(17)	2877(5)	6765(4)	2979.2(14)	28.9(8)
C(18)	3914(5)	7657(5)	2657(2)	33.4(9)
C(19)	5372(5)	6862(5)	2562(2)	36.7(10)
C(20)	6134(5)	6413(5)	3032(2)	36.4(10)
C(21)	5101(5)	5546(5)	3365(2)	30.3(8)

[a] The equivalent isotropic displacement parameter U_{eq} is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

antagonists. Dose ratios calculated from the respective EC_{50} values of the agonists were used to perform a Schild analysis [28]. Since the Arunlakshana–Schild plots of all compounds investigated were linear and the slopes of the regression lines were not significantly different from unity ($P < 0.05$), pA_2 values were estimated as the intercept on the abscissa scale by fitting to the data the best straight line with a slope of unity (constrained plot) [29]. The pA_2 values given in Table 2 correspond to $-\log K_D$ values (where K_D is the dissociation constant of the antagonist–receptor complex).

3.4.2. Radioligand binding studies

Radioligand binding studies of the pure (*R*)- and (*S*)-enantiomers of **1a**, **1b**, **2a** and **2b** and of the achiral compounds **3a–6a** and **3b–6b** were carried out with homogenates of human NB-OK 1 neuroblastoma cells (M1 receptors) as well as with homogenates of rat heart (M2 receptors), rat pancreas (M3 receptors) and rat striatum (M4 receptors). The radioligand was [^{3}H]-*N*-methylscopolamine (0.24–1.0 nM). Data of the binding experiments were analyzed by an iterative curve fitting procedure. Dissociation constants (K_i values) of all compounds studied were determined from IC_{50} values obtained from competition curves. The pK_i values given in Table 3 correspond to $-\log K_i$ values. For more experimental details, see Refs. [3,30].

3.4.3. Data analysis

All pharmacological data are presented as arithmetic means of the indicated number of experiments (see Tables 2 and 3). Linear regression analyses were carried out by the method of least-squares. Differences between mean values were tested for statistical significance by Student's *t* test; $P < 0.05$ was accepted as being significant.

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