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Syntheses and pharmacological characterization of achiral and chiral enantiopure C/Si/Ge-analogous derivatives of the muscarinic antagonist cycrimine: a study on C/Si/Ge bioisosterism

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Dedicated to Professor M.G. Voronkov on the occasion of his 80th birthday

Abstract

The C/Si/Ge-analogous compounds *rac*-Ph(*c*-C_5H_9)El(CH_2OH)$CH_2CH_2NR_2$ (NR_2 = piperidino; El = C, *rac*-**3a**; El = Si, *rac*-**3b**; El = Ge, *rac*-**3c**) and (*c*-C_5H_9)$_2$El(CH_2OH)$CH_2CH_2NR_2$ (NR_2 = piperidino; El = C, **5a**; El = Si, **5b**; El = Ge, **5c**) were prepared in multi-step syntheses. The (*R*)- and (*S*)-enantiomers of **3a**–**c** were obtained by resolution of the respective racemates using the antipodes of *O*,*O*′-dibenzoyltartaric acid (resolution of *rac*-**3a**), *O*,*O*′-di-*p*-toluoyltartaric acid (resolution of *rac*-**3b**), or 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (resolution of *rac*-**3c**). The enantiomeric purities of (*R*)-**3a**–**c** and (*S*)-**3a**–**c** were ≥98% ee (determined by ^{1}H-NMR spectroscopy using a chiral solvating agent). Reaction of *rac*-**3a**–**c**, (*R*)-**3a**–**c**, (*S*)-**3a**–**c**, and **5a**–**c** with methyl iodide gave the corresponding methylammonium iodides *rac*-**4a**–**c**, (*R*)-**4a**–**c**, (*S*)-**4a**–**c**, and **6a**–**c** (**3a**–**c** → **4a**–**c**; **5a**–**c** → **6a**–**c**). The absolute configuration of (*S*)-**3a** was determined by a single-crystal X-ray diffraction analysis of its (*R*,*R*)-*O*,*O*′-dibenzoyltartrate. The absolute configurations of the silicon analog (*R*)-**4b** and germanium analog (*R*)-**4c** were also determined by single-crystal X-ray diffraction. The chiroptical properties of the (*R*)- and (*S*)-enantiomers of **3a**–**c**, **3a**–**c**·HCl, and **4a**–**c** were studied by ORD measurements. In addition, the C/Si/Ge analogs (*R*)-**3a**–**c**, (*S*)-**3a**–**c**, (*R*)-**4a**–**c**, (*S*)-**4a**–**c**, **5a**–**c**, and **6a**–**c** were studied for their affinities at recombinant human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors stably expressed in CHO-K1 cells (radioligand binding experiments with [^{3}H]*N*-methylscopolamine as the radioligand). For reasons of comparison, the known C/Si/Ge analogs $Ph_2El(CH_2OH)CH_2CH_2NR_2$ (NR_2 = piperidino; El = C, **7a**; El = Si, **7b**; El = Ge, **7c**) and the corresponding methylammonium iodides **8a**–**c** were included in these studies. According to these experiments, all the C/Si/Ge analogs behaved as simple competitive antagonists at M_1–M_5 receptors. The receptor subtype affinities of the individual carbon, silicon, and germanium analogs **3a**–**8a**, **3b**–**8b**, and **3c**–**8c** were similar, indicating a strongly pronounced C/Si/Ge bioisosterism. The (*R*)-enantiomers (eutomers) of **3a**–**c** and **4a**–**c** exhibited higher affinities (up to 22.4 fold) for M_1–M_5 receptors than their corresponding (*S*)-antipodes (distomers), the stereoselectivity ratios being higher at M_1, M_3, M_4, and M_5 than at M_2 receptors, and higher for the methylammonium compounds (**4a**–**c**) than for the amines (**3a**–**c**). With a few exceptions, compounds **5a**–**c**, **6a**–**c**, **7a**–**c**, and **8a**–**c** displayed lower affinities for M_1–M_5 receptors than the related (*R*)-enantiomers of **3a**–**c** and **4a**–**c**. The stereoselective interaction of the enantiomers of **3a**–**c** and **4a**–**c** with M_1–M_5 receptors is best explained in terms of opposite binding of the phenyl and cyclopentyl ring of the (*R*)- and (*S*)-enantiomers. The highest receptor subtype selectivity was observed for the germanium compound (*R*)-**4c** at M_1/M_2 receptors (12.9-fold).

Keywords: Silicon; Germanium; C/Si/Ge bioisosterism; Chirality; Muscarinic antagonists; ORD

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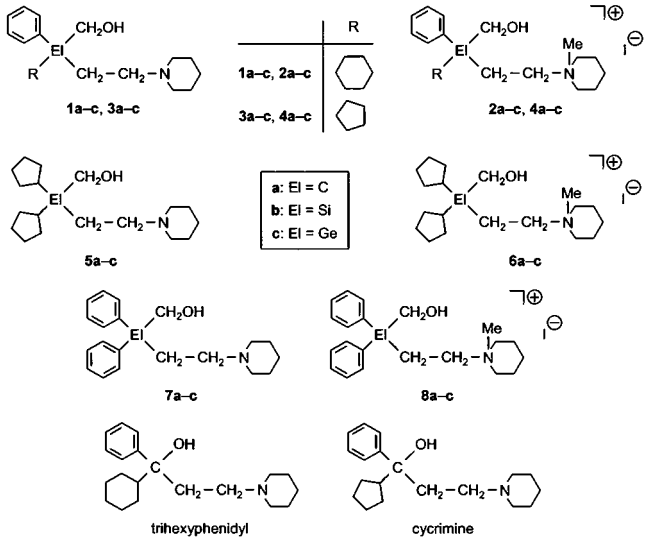
1. Introduction

Some years ago, we reported on the syntheses and antimuscarinic properties of the (*R*)- and (*S*)-enantiomers of the C/Si/Ge analogs **1a**–**c** and **2a**–**c** [1–4]. These compounds are structurally related to the muscarinic antagonist trihexyphenidyl. We have now succeeded in synthesizing the respective cycrimine derivatives, the enantiopure C/Si/Ge analogs (*R*)-**3a**–**c**, (*S*)-**3a**–**c**, (*R*)-**4a**–**c**, and (*S*)-**4a**–**c**. In addition, the related achiral compounds **5a**–**c** and **6a**–**c** were also prepared. The (*R*)- and (*S*)-enantiomers of **3a**–**c** and **4a**–**c** and compounds **5a**–**c** and **6a**–**c** were tested for their affinities at recombinant human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors [5]. For comparison, the known achiral derivatives **7a**–**c** and **8a**–**c** [3,6,7] were included in these studies. Further, the chiroptical properties of the antipodes of **3a**–**c**, **3a**–**c**·HCl, and **4a**–**c** were studied by ORD measurements.



The aim of the studies presented here was: (i) to contribute to the chemistry (stereochemistry) of centrochiral silanes and germanes; (ii) to obtain more information about the stereoselectivity of muscarinic receptor binding; and (iii) to extend our systematic studies on C/Si/Ge bioisosterism [8,9]. Preliminary results of these investigations have already been published elsewhere [8].

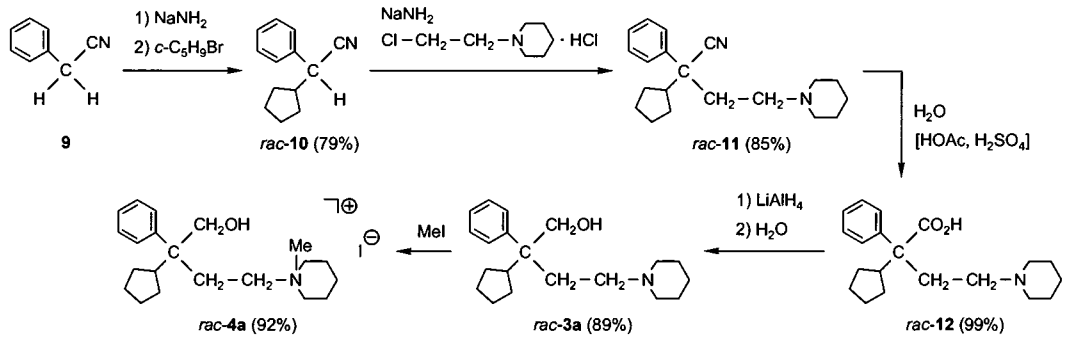
2. Results and discussion

2.1. Syntheses

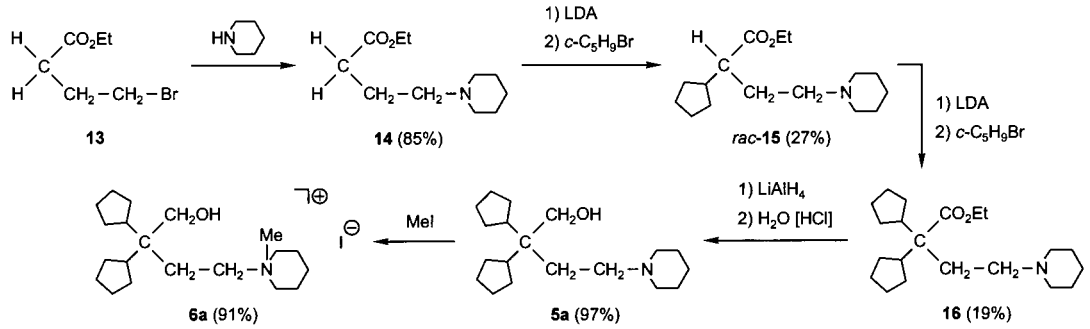
The synthesis of compounds (*R*)-**3a**–**c**, (*S*)-**3a**–**c**, (*R*)-**4a**–**c**, and (*S*)-**4a**–**c** is based on the preparation and resolution of the racemates *rac*-**3a**–**c** and subsequent transformation of the respective enantiopure amines into the corresponding methylammonium iodides.

The racemic compounds *rac*-**3a** and *rac*-**4a** were prepared by a four-step (five-step) synthesis, starting from phenylacetonitrile (**9**) (Scheme 1). Deprotonation of **9** with $NaNH_2$ and subsequent alkylation with cyclopentyl bromide in diethyl ether gave *rac*-**10**, which on deprotonation with $NaNH_2$ and subsequent treatment with 1-(2-chloroethyl)piperidine (generated in situ from its hydrochloride by reaction with $NaNH_2$) in toluene yielded *rac*-**11**. Hydrolysis of *rac*-**11** in a mixture of glacial acetic acid, concentrated sulfuric acid, and water led, after workup with aqueous KOH solution, to *rac*-**12**, which was then converted into *rac*-**3a** by reaction with lithium aluminum hydride in THF and subsequent hydrolysis with hydrochloric acid. Treatment of *rac*-**3a** with saturated ethereal HCl solution gave the corresponding hydrochloride *rac*-**3a**·HCl. The quaternary ammonium derivative *rac*-**4a** was obtained by the reaction of *rac*-**3a** with methyl iodide in acetone.

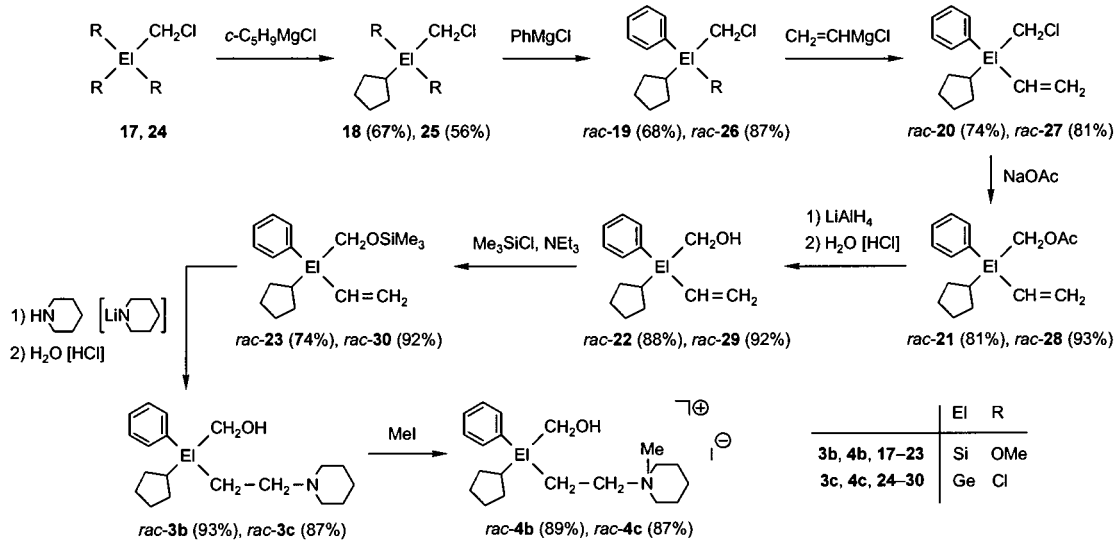
The achiral compound **5a** was obtained by a four-step synthesis, starting from 4-bromobutyric acid ethyl ester (**13**) (Scheme 2) [10]. Reaction of **13** with piperidine in toluene gave **14**, which was treated with lithium diisopropylamide in THF in the presence of HMPTA, followed by alkylation with cyclopentyl bromide to give *rac*-**15**. Deprotonation of *rac*-**15** and subsequent alkylation with cyclopentyl bromide under the same reaction conditions led to **16**, which upon



Scheme 1.



Scheme 2.



Scheme 3.

reduction with lithium aluminum hydride in THF, followed by hydrolysis with hydrochloric acid, gave **5a**. Treatment of **5a** with saturated ethereal HCl solution gave the hydrochloride **5a**·HCl, and reaction with methyl iodide in acetone afforded the quaternary ammonium derivative **6a**.

The syntheses of the silicon and germanium compounds *rac*-**3b** and *rac*-**3c** are quite similar, but differ significantly from that of the carbon analog *rac*-**3a**. Compounds *rac*-**3b** and *rac*-**3c** were prepared by seven-step syntheses, starting from (chloromethyl)trimethoxysilane (**17**) and trichloro(chloromethyl)germane (**24**), respectively (Scheme 3).

For the preparation of the silane *rac*-**3b**, **17** was treated with one molar equivalent of cyclopentylmagnesium chloride in diethyl ether to give **18**, which was then treated with one molar equivalent of phenylmagnesium chloride in THF to afford *rac*-**19**. Subsequent reaction of *rac*-**19** with vinylmagnesium chloride in toluene led to *rac*-**20**, which upon treatment with sodium acetate in DMF gave *rac*-**21**. Reduction of *rac*-**21** with lithium aluminum hydride in diethyl ether, followed by hydrolysis with hydrochloric acid, afforded *rac*-**22**. For the following hydroamination step, the OH group of *rac*-**22** was protected by silylation with chlorotrimethylsilane in *n*-pentane in the presence of triethylamine to give *rac*-**23**. Reaction of *rac*-**23** with piperidine in THF in the presence of 1-lithiopiperidine, followed by hydrolysis with hydrochloric acid, finally yielded *rac*-**3b**. Treatment of *rac*-**3b** with saturated ethereal HCl solution gave the hydrochloride *rac*-**3b**·HCl, and reaction of *rac*-**3b** with methyl iodide in acetone afforded the quaternary ammonium iodide *rac*-**4b**.

For the synthesis of the germane *rac*-**3c**, **24** was treated with one molar equivalent of cyclopentylmagnesium chloride in diethyl ether to give **25**, which upon treatment with one molar equivalent of phenylmagnesium chloride in diethyl ether afforded *rac*-**26**. Subsequent reaction of *rac*-**26** with vinylmagnesium chloride in toluene led to *rac*-**27**, which was treated with sodium acetate in DMF to give *rac*-**28**. Reaction of *rac*-**28** with lithium aluminum hydride in diethyl ether, followed by hydrolysis with hydrochloric acid, afforded *rac*-**29**, which was silylated with chlorotrimethylsilane in *n*-pentane in the presence of triethylamine to give *rac*-**30**.

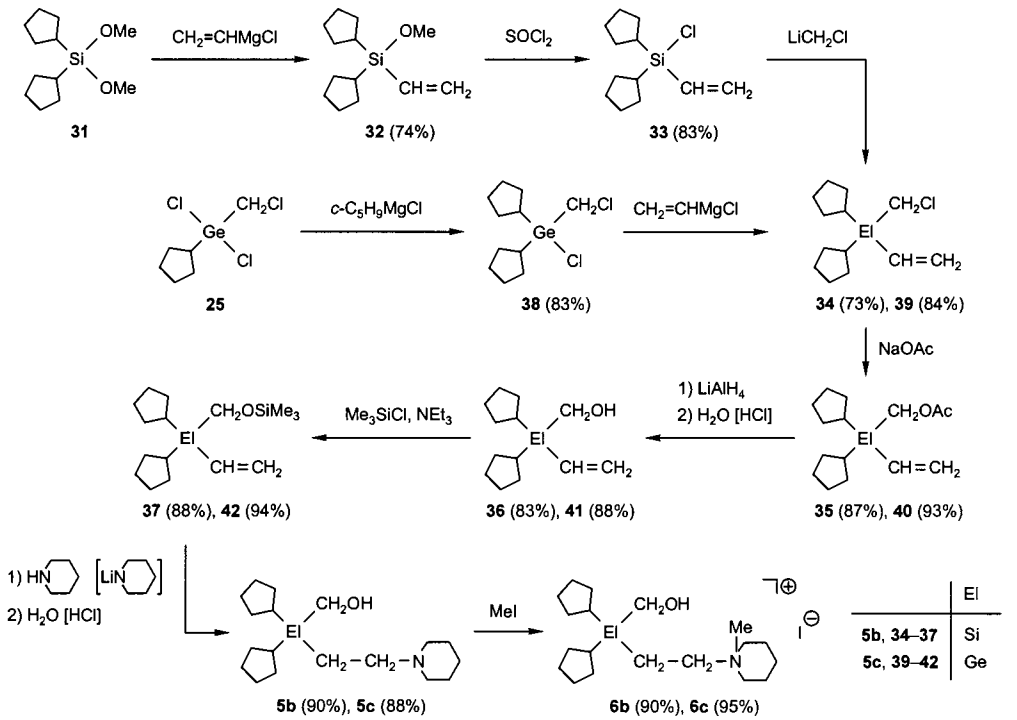
Hydroamination of *rac*-**30** with piperidine in THF in the presence of 1-lithiopiperidine and subsequent hydrolysis with hydrochloric acid finally gave *rac*-**3c**. Treatment of *rac*-**3c** with saturated ethereal HCl solution afforded the hydrochloride *rac*-**3c**·HCl, and reaction of *rac*-**3c** with methyl iodide in acetone led to the quaternary ammonium iodide *rac*-**4c**.

The achiral silane **5b** was prepared by a seven-step synthesis, starting from dicylcopentyldimethoxysilane (**31**) (Scheme 4). Reaction of **31** with one molar equivalent of vinylmagnesium chloride in THF led to **32**, which upon treatment with thionyl chloride gave **33**. Reaction of **33** with $LiCH_2Cl$ (generated in situ from methyllithium and bromochloromethane) in THF afforded **34**. Treatment of **34** with sodium acetate in DMF led to **35**, which was reduced with lithium aluminum hydride in diethyl ether, followed by hydrolysis with hydrochloric acid to give **36**. Silylation of **36** with chlorotrimethylsilane in *n*-pentane in the presence of triethylamine afforded **37**, which upon treatment with piperidine in THF in the presence of 1-lithiopiperidine and subsequent hydrolysis with hydrochloric acid finally gave **5b**. The hydrochloride **5b**·HCl was obtained by treatment of **5b** with saturated ethereal HCl solution, and the quaternary ammonium iodide **6b** was prepared by treatment of **5b** with methyl iodide in acetone.

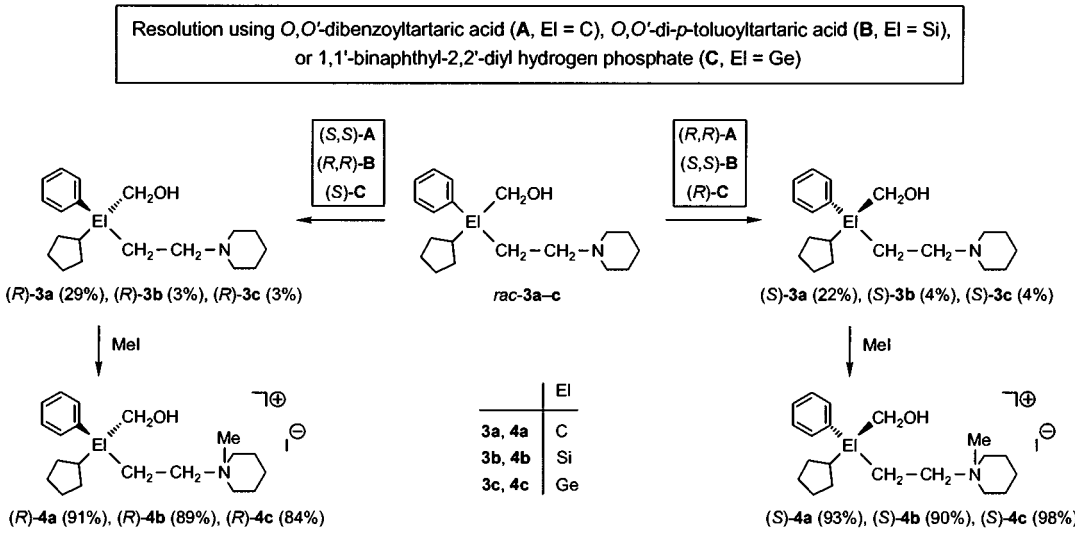
The achiral germane **5c** was prepared by a six-step synthesis, starting from dichloro(chloromethyl)cyclopentylgermane (**25**) (Scheme 4). Treatment of **25** with one molar equivalent of cyclopentylmagnesium chloride in THF gave **38**, which upon reaction with vinylmagnesium chloride yielded **39**. Treatment of **39** with sodium acetate in DMF led to **40**, which was reduced with lithium aluminum hydride in diethyl ether, followed by hydrolysis with hydrochloric acid to afford **41**. Silylation of **41** with chlorotrimethylsilane in *n*-pentane in the presence of triethylamine gave **42**, which was treated with piperidine in the presence of 1-lithiopiperidine, followed by hydrolysis with hydrochloric acid to give finally **5c**. Treatment of **5c** with saturated ethereal HCl solution afforded the hydrochloride **5c**·HCl, and the quaternary ammonium iodide **6c** was obtained by treatment of **5c** with methyl iodide in acetone.

The enantiomers (*R*)-**3a** and (*S*)-**3a** were obtained by resolution of *rac*-**3a** using the antipodes of *O*,*O*′-dibenzoyltartaric acid as resolving agents (Scheme 5). Treatment of (*R*)-**3a** and (*S*)-**3a** with saturated ethereal HCl solution gave the respective hydrochlorides (*R*)-**3a**·HCl and (*S*)-**3a**·HCl, and reaction of (*R*)-**3a** and (*S*)-**3a** with methyl iodide in acetone afforded the respective quaternary ammonium iodides (*R*)-**4a** and (*S*)-**4a**.

The enantiomers (*R*)-**3b** and (*S*)-**3b** (primarily isolated as hydrochlorides and then transformed into the respective amines by treatment with aqueous NaOH solution) were obtained by resolution of *rac*-**3b** using the antipodes of *O*,*O*′-di-*p*-toluoyltartaric acid as resolving agents (Scheme 5). Treatment of (*R*)-**3b** and (*S*)-**3b** with methyl iodide in acetone gave the corre-



Scheme 4.



Scheme 5.

sponding quaternary ammonium iodides (*R*)-**4b** and (*S*)-**4b**.

The enantiomers (*R*)-**3c** and (*S*)-**3c** were obtained by resolution of *rac*-**3c** using the antipodes of 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate as resolving agents (Scheme 5). Treatment of (*R*)-**3c** and (*S*)-**3c** with saturated ethereal HCl solution gave the respective hydrochlorides (*R*)-**3c**·HCl and (*S*)-**3c**·HCl, and reaction of (*R*)-**3c** and (*S*)-**3c** with methyl iodide in acetone afforded the respective quaternary ammonium iodides (*R*)-**4c** and (*S*)-**4c**.

The identities of the hitherto unknown compounds described in this paper were established by elemental analyses (C, H, N) and NMR-spectroscopic studies. In addition, the (*R*,*R*)-*O*,*O*′-dibenzoyltartrate of (*S*)-**3a** and the ammonium iodides (*R*)-**4b** and (*R*)-**4c** were structurally characterized by single-crystal X-ray diffraction studies.

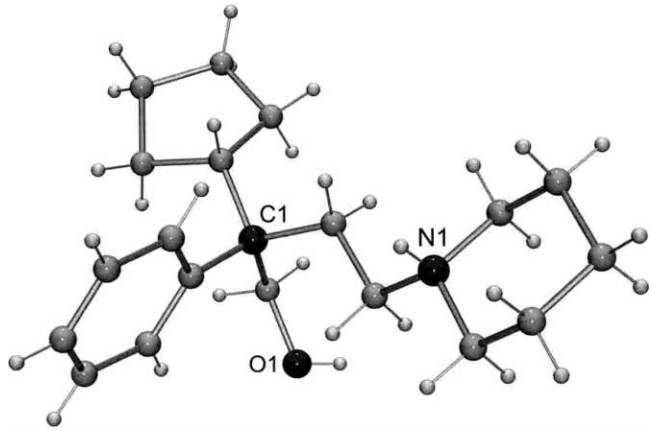


Fig. 1. Structure of one of the two crystallographically independent cations in the crystal of (*R*,*R*)-*O*,*O*′-dibenzoyltartrate of (*S*)-**3a** [2(*S*)-**3a**·(*R*,*R*)-HOOC–CHR–CHR–COOH; R = O–CO–Ph]. The structure of the other cation (not shown) is very similar. The two cations and the anion are connected by two intermolecular N–H···O and two intermolecular O–H···O hydrogen bonds.

2.2. Determination of the absolute configurations

The absolute configurations of the (*R*)- and (*S*)-enantiomers of **3a**–**c**, **3a**–**c**·HCl, and **4a**–**c** were established by crystal structure analyses of the (*R*,*R*)-*O*,*O*′-dibenzoyltartrate of (*S*)-**3a** and the ammonium iodides (*R*)-**4b** and (*R*)-**4c**. The crystal data and the experimental parameters used for these studies are given in Table 1. The crystal structures of the Si/Ge analogs (*R*)-**4b** and (*R*)-**4c** are isotypic. Both compounds crystallize with two cations and two anions in the asymmetric unit. The structures of one of the two crystallographically independent cations each in the crystals of 2(*S*)-**3a**·(*R*,*R*)-HOOC–CHR–CHR–COOH (R = O–CO–Ph), (*R*)-**4b**, and (*R*)-**4c** are shown in Figs. 1–3. The bond distances and bond angles of all three compounds are in the expected range and therefore do

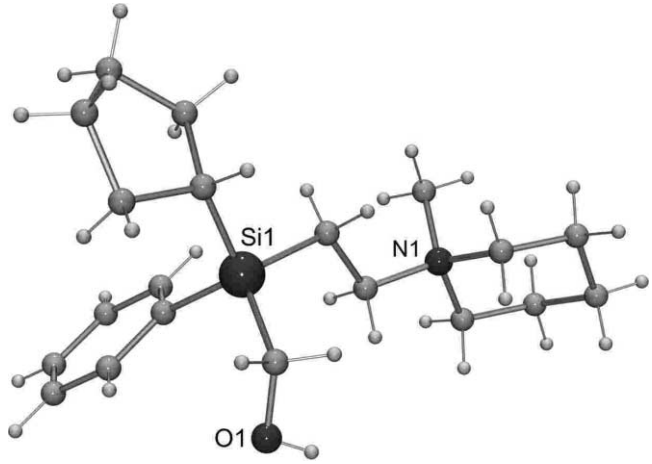


Fig. 2. Structure of one of the two crystallographically independent cations in the crystal of compound (*R*)-**4b**. The structure of the other cation (not shown) is very similar.

Table 1
Crystal data and structure refinement parameters for 2(*S*)-**3a**·(*R*,*R*)-dbta [a], (*R*)-**4b**, and (*R*)-**4c**

	2(*S*)-**3a**·dbta	(*R*)-**4b**	(*R*)-**4c**
Empirical formula	$C_{58}H_{76}N_2O_{10}$	$C_{20}H_{34}INOSi$	$C_{20}H_{34}GeINO$
Formula mass (g mol^{-1})	961.21	459.47	503.97
Temperature (K)	193(2)	173(2)	173(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group (no.)	$P2_12_12_1$ (19)	$P2_12_12_1$ (19)	$P2_12_12_1$ (19)
Unit cell dimensions			
a (Å)	11.4290(2)	8.9504(18)	9.0270(5)
b (Å)	17.8345(3)	9.1231(18)	9.1659(7)
c (Å)	25.7597(5)	51.731(10)	51.441(4)
V (Å^3)	5250.6(2)	4224.1(15)	4256.2(5)
Z	4	8	8
D_{calc} (g cm^{-3})	1.216	1.445	1.573
Absorption coefficient (mm^{-1})	0.082	1.580	2.897
F(000)	2072	1888	2032
Crystal size (mm)	0.8 × 0.3 × 0.1	0.6 × 0.4 × 0.3	0.3 × 0.2 × 0.2
2-Theta range for data collection (°)	3.90–46.38	4.54–43.96	4.52–43.94
Index ranges	$-12 \le h \le 12$, $0 \le k \le 19$, $0 \le l \le 28$	$-9 \le h \le 9$, $-9 \le k \le 9$, $-54 \le l \le 54$	$-9 \le h \le 9$, $-9 \le k \le 9$, $-42 \le l \le 54$
Reflections collected	36 807	24 413	15 027
Independent reflections	7469 [$R_{int} = 0.0412$]	5186 [$R_{int} = 0.0697$]	5139 [$R_{int} = 0.0345$]
No. of reflections used	7469	5186	5139
Restraints	378	0	0
No. of parameters	713	437	438
Absorption correction	Semiempiric	–	–
S [b]	1.135	1.072	1.032
Weight parameters *a*/*b* [c]	0.0297/1.9878	0.0472/3.6805	0.0522/0.1831
Final *R* indices [$I > 2\sigma(I)$]	R_1 [d] = 0.0418	R_1 [d] = 0.0355	R_1 [d] = 0.0257
R indices (all data)	wR_2 [e] = 0.0950	wR_2 [e] = 0.0780	wR_2 [e] = 0.0701
Flack *x* parameter	1.4(9)	−0.05(2)	−0.012(12)
Largest difference peak and hole (e Å^{-3})	+0.440 and −0.168	+0.742 and −0.920	+0.659 and −0.798

[a] (*R*,*R*)-dbta = (*R*,*R*)-HOOC–CHR–CHR–COOH (R = O–CO–Ph).
[b] $S = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{0.5}$; *n* = number of reflections; *p* = number of parameters.
[c] $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, with $P = [\max(F_o^2, 0) + 2F_c^2]/3$.
[d] $R_1 = \Sigma\big||F_o| - |F_c|\big|/\Sigma|F_o|$.
[e] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{0.5}$.

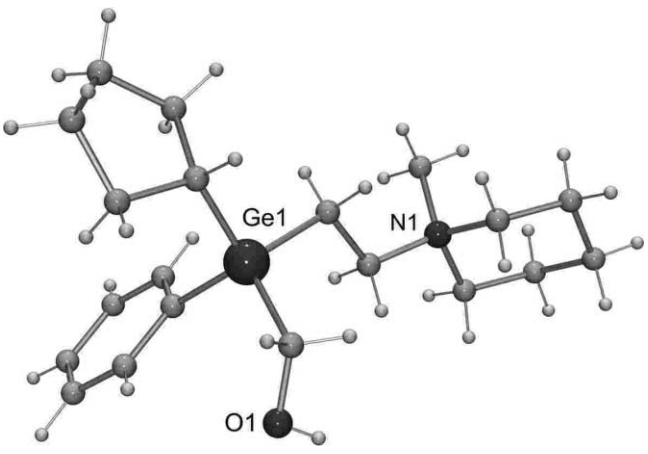


Fig. 3. Structure of one of the two crystallographically independent cations in the crystal of compound (*R*)-**4c**. The structure of the other cation (not shown) is very similar.

not need further comments. As can be seen from the respective torsion angles [11], the El–CH_2–CH_2–N (El = C, Si, Ge) moieties of all cations adopt an *anti*-conformation. All piperidinio groups are characterized by a chair conformation, and all cyclopentyl rings adopt an envelope conformation.

As the conversions **3a**–**c** → **3a**–**c**·HCl and **3a**–**c** → **4a**–**c** do not affect the absolute configurations at the central carbon, silicon, and germanium atoms, assignment of the absolute configurations of all compounds could be made on the basis of these three crystal structure analyses.

2.3. Determination of the enantiomeric purities

The enantiomeric purities of the (*R*)- and (*S*)-enantiomers of **3a**–**c** were determined by ^{1}H-NMR studies using the chiral solvating agent (*R*)-2,2,2-trifluoro-1-(9-

anthryl)ethanol. According to this method, the enantiomeric excess (ee) of the resolved enantiomers of **3a**–**c** was determined to be $\geq 98\%$. As the conversions **3a**–**c** → **3a**–**c**·HCl and **3a**–**c** → **4a**–**c** do not affect the respective centers of chirality, enantiomeric purities of $\geq 98\%$ ee can also be assumed for the antipodes of **3a**–**c**·HCl and **4a**–**c**.

2.4. ORD studies

The (*R*)- and (*S*)-enantiomers of **3a**–**c**, **3a**–**c**·HCl, and **4a**–**c** were studied for their chiroptical properties. For this purpose, the ORD spectra of these compounds were measured using methanol as solvent (Figs. 4–6). As shown for the antipodes of **3a**–**c** in Fig. 4, similar ORD spectra were obtained for the respective C/Si/Ge analogs with the same absolute configuration (→ identical signs for the optical rotations), the specific rotations of these compounds differing only in their absolute values. Analogous results were obtained for the (*R*)- and (*S*)-enantiomers of the hydrochlorides **3a**–**c**·HCl (Fig. 5). Surprisingly, quite a different behavior

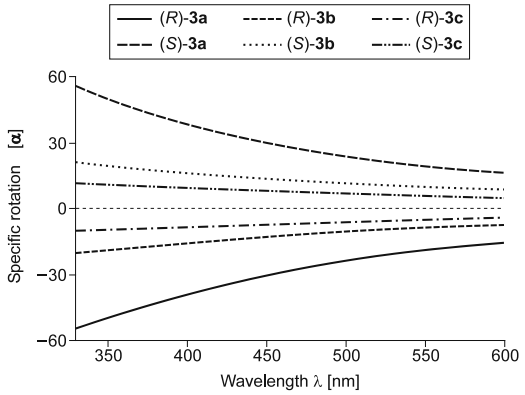


Fig. 4. ORD spectra of the (*R*)- and (*S*)-enantiomers of the C/Si/Ge analogs **3a**–**c** (solvent methanol; $c = 10$ mg ml^{-1}, $d = 10$ cm, $T = 20$ °C).

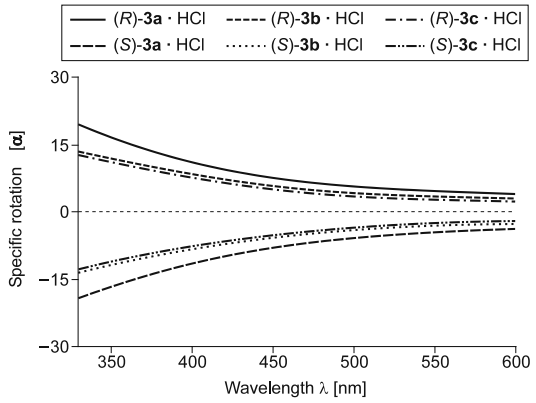


Fig. 5. ORD spectra of the (*R*)- and (*S*)-enantiomers of the C/Si/Ge analogs **3a**–**c**·HCl (solvent methanol; $c = 10$ mg ml^{-1}, $d = 10$ cm, $T = 20$ °C).

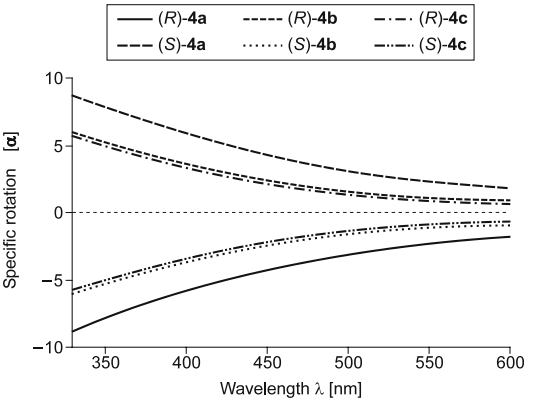


Fig. 6. ORD spectra of the (*R*)- and (*S*)-enantiomers of the C/Si/Ge analogs **4a**–**c** (solvent methanol; $c = 10$ mg ml^{-1}, $d = 10$ cm, $T = 20$ °C).

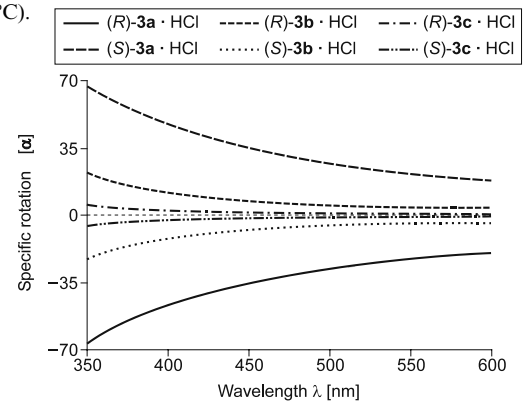


Fig. 7. ORD spectra of the (*R*)- and (*S*)-enantiomers of the C/Si/Ge analogs **3a**–**c**·HCl (solvent trichloromethane; $c = 10$ mg ml^{-1}, $d = 10$ cm, $T = 20$ °C).

was observed for the antipodes of the methylammonium iodides **4a**–**c**, the sign for the optical rotation of the carbon compound (*R*)-**4a** [(*S*)-**4a**] differing from those of its silicon analog (*R*)-**4b** [(*S*)-**4b**] and germanium analog (*R*)-**4c** [(*S*)-**4c**] (Fig. 6). An analogous result was obtained for the (*R*)- and (*S*)-enantiomers of the hydrochlorides **3a**–**c**·HCl in trichloromethane: the sign for the optical rotation of the carbon compound (*R*)-**3a**·HCl [(*S*)-**3a**·HCl] differs from those of its silicon analog (*R*)-**3b**·HCl [(*S*)-**3b**·HCl] and germanium analog (*R*)-**3c**·HCl [(*S*)-**3c**·HCl] (Fig. 7). We do not have a satisfactory explanation for these surprising differences [12]; nevertheless, these different signs for the optical rotations within a series of identically configurated C/Si/Ge analogs clearly indicate that the assignment of absolute configuration via comparison of ORD data of chiral C/Si/Ge analogs is not admissible.

2.5. Pharmacological studies

The (*R*)- and (*S*)-enantiomers of **3a**–**c** and **4a**–**c** and the achiral compounds **5a**–**c**, **6a**–**c**, **7a**–**c**, and **8a**–**c** were studied for their affinities (pK_i values) at recombi-

nant human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors stably expressed in CHO-K1 cells [binding studies with [^{3}H]*N*-methylscopolamine ([^{3}H]NMS) as the radioligand]. The results of these investigations are summarized in Tables 2–4 and illustrated in Figs. 8–13.

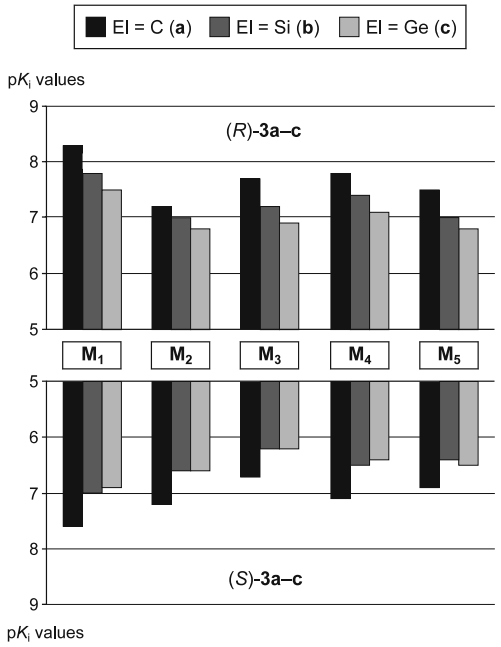


Fig. 8. Affinity profiles (pK_i values) of the (*R*)- and (*S*)-enantiomers of the C/Si/Ge analogs **3a**–**c** at cloned human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors.

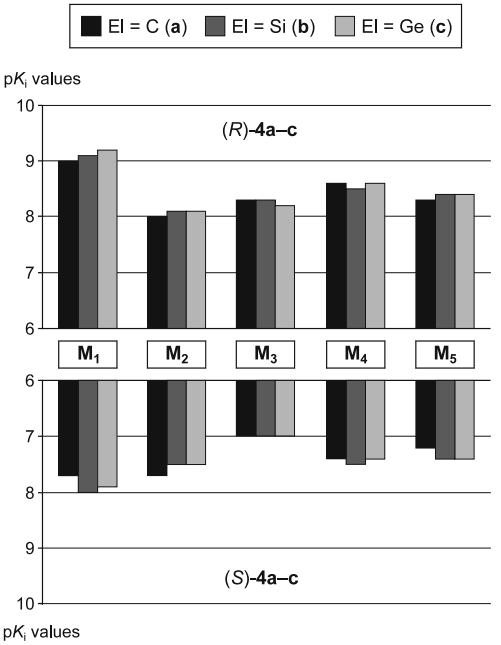


Fig. 9. Affinity profiles (pK_i values) of the (*R*)- and (*S*)-enantiomers of the C/Si/Ge analogs **4a**–**c** at cloned human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors.

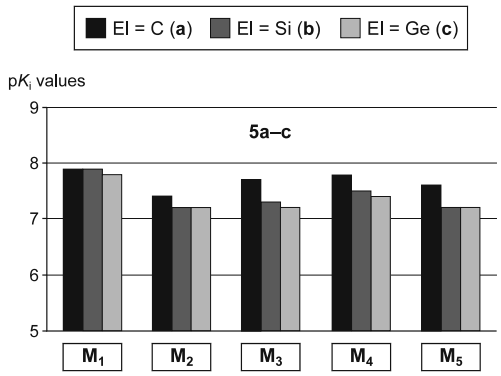


Fig. 10. Affinity profiles (pK_i values) of the C/Si/Ge analogs **5a**–**c** at cloned human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors.

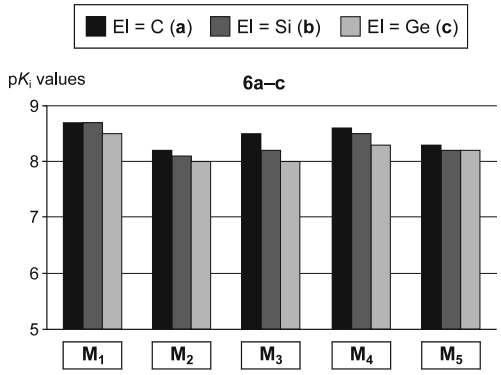


Fig. 11. Affinity profiles (pK_i values) of the C/Si/Ge analogs **6a**–**c** at cloned human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors.

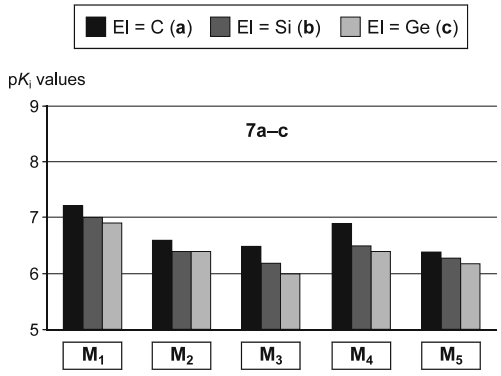


Fig. 12. Affinity profiles (pK_i values) of the C/Si/Ge analogs **7a**–**c** at cloned human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors.

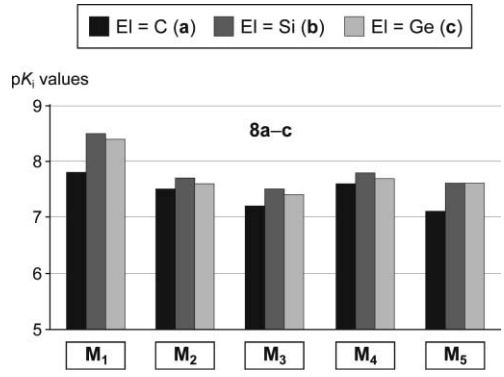


Fig. 13. Affinity profiles (pK_i values) of the C/Si/Ge analogs **8a**–**c** at cloned human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors.

Table 2
Affinities (pK_i values) for the (*R*)- and (*S*)-enantiomers of **3a–c** and **4a–c** and for the achiral compounds **5a–c**, **6a–c**, **7a–c**, and **8a–c** obtained in radioligand binding studies at recombinant human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors stably expressed in CHO-K1 cells[a]

Compound	pK_i values				
	M_1	M_2	M_3	M_4	M_5
(*R*)-**3a**	8.25 ± 0.02	7.22 ± 0.08	7.67 ± 0.03	7.83 ± 0.03	7.47 ± 0.03
(*S*)-**3a**	7.58 ± 0.03	7.15 ± 0.01	6.74 ± 0.01	7.07 ± 0.01	6.84 ± 0.02
(*R*)-**3b**	7.81 ± 0.05	6.95 ± 0.08	7.21 ± 0.01	7.36 ± 0.07	7.03 ± 0.02
(*S*)-**3b**	7.02 ± 0.19	6.57 ± 0.18	6.22 ± 0.16	6.53 ± 0.20	6.40 ± 0.18
(*R*)-**3c**	7.53 ± 0.02	6.78 ± 0.03	6.90 ± 0.04	7.06 ± 0.03	6.79 ± 0.05
(*S*)-**3c**	6.92 ± 0.03	6.62 ± 0.08	6.19 ± 0.03	6.43 ± 0.03	6.46 ± 0.01
(*R*)-**4a**	8.99 ± 0.03	8.01 ± 0.05	8.34 ± 0.02	8.59 ± 0.03	8.31 ± 0.05
(*S*)-**4a**	7.70 ± 0.06	7.65 ± 0.08	6.99 ± 0.09	7.40 ± 0.09	7.23 ± 0.01
(*R*)-**4b**	9.12 ± 0.04	8.05 ± 0.06	8.25 ± 0.06	8.53 ± 0.05	8.35 ± 0.04
(*S*)-**4b**	7.98 ± 0.03	7.52 ± 0.02	7.03 ± 0.09	7.51 ± 0.08	7.37 ± 0.07
(*R*)-**4c**	9.22 ± 0.04	8.11 ± 0.03	8.23 ± 0.04	8.63 ± 0.05	8.40 ± 0.03
(*S*)-**4c**	7.94 ± 0.02	7.51 ± 0.02	6.98 ± 0.06	7.40 ± 0.02	7.38 ± 0.02
5a	7.94 ± 0.11	7.37 ± 0.03	7.65 ± 0.04	7.79 ± 0.03	7.56 ± 0.04
5b	7.89 ± 0.01	7.16 ± 0.03	7.30 ± 0.02	7.50 ± 0.02	7.24 ± 0.01
5c	7.79 ± 0.03	7.19 ± 0.02	7.21 ± 0.03	7.37 ± 0.02	7.17 ± 0.03
6a	8.73 ± 0.06	8.17 ± 0.07	8.46 ± 0.07	8.56 ± 0.11	8.31 ± 0.05
6b	8.70 ± 0.05	8.12 ± 0.04	8.17 ± 0.05	8.46 ± 0.05	8.24 ± 0.08
6c	8.53 ± 0.04	8.00 ± 0.06	8.03 ± 0.06	8.28 ± 0.10	8.15 ± 0.01
7a	7.15 ± 0.10	6.63 ± 0.06	6.53 ± 0.10	6.89 ± 0.05	6.38 ± 0.05
7b	7.00 ± 0.03	6.43 ± 0.06	6.20 ± 0.07	6.51 ± 0.03	6.29 ± 0.04
7c	6.94 ± 0.05	6.41 ± 0.07	6.03 ± 0.04	6.35 ± 0.03	6.18 ± 0.03
8a	7.84 ± 0.07	7.48 ± 0.02	7.20 ± 0.02	7.58 ± 0.06	7.11 ± 0.03
8b	8.49 ± 0.03	7.70 ± 0.05	7.51 ± 0.04	7.81 ± 0.05	7.61 ± 0.03
8c	8.42 ± 0.06	7.62 ± 0.02	7.39 ± 0.04	7.73 ± 0.06	7.56 ± 0.03

[a] Data are presented as means ± SD of at least three experiments performed in duplicate.

The Hill coefficients (0.89 ± 0.09–1.10 ± 0.19) of all saturation and competition curves were not significantly different from unity, indicating the presence of a single recombinant muscarinic receptor subtype (M_1, M_2, M_3, M_4, or M_5) in the five CHO-K1 cell lines, and a competitive antagonism by compounds **3a–c**, **4a–c**, **5a–c**, **6a–c**, **7a–c**, and **8a–c** at M_1–M_5 receptors. It is interesting to note that the binding affinities of the diphenyl compounds **7a–c** and **8a–c** obtained in the present study at cloned human M_1–M_4 receptors (Table 2) were found to be very similar to those obtained in binding studies at native muscarinic receptors present in human NB-OK1 neuroblastoma cells (M_1), rat heart (M_2), rat pancreas (M_3), and rat striatum (M_4) [3,4; and unpublished results].

The affinities of compounds **3a–c**, **4a–c**, **5a–c**, **6a–c**, **7a–c**, and **8a–c** for the different muscarinic receptor subtypes were found to be controlled by the following structural parameters: (i) the nature of the central atom 'El' (C, Si, or Ge); (ii) the nature of the ring substituent at 'El' (phenyl/cyclopentyl, phenyl/phenyl, or cyclopentyl/cyclopentyl; (iii) the structure of the cationic head [tertiary amino group (protonated under physiological conditions) or quaternary ammonium moiety]; and (iv) the absolute configuration in the case of chiral compounds **3a–c** and **4a–c**.

In most cases, the muscarinic receptor affinities for the individual carbon (**3a–8a**), silicon (**3b–8b**), and germanium analogs (**3c–8c**) were found to be very similar, displaying a strongly pronounced C/Si/Ge bioisosterism. The greatest differences in affinity (C vs. Si vs. Ge analogs) were observed for the enantiomers of **3a–c** (C ≥ Si ≥ Ge, up to 5.2-fold) (Fig. 8).

N-Methylation increased the affinities for M_1–M_5 receptors, this increase being consistently lower among the carbon compounds (**3a**, **5a**, **7a** → **4a**, **6a**, **8a**) than among the silicon (**3b**, **5b**, **7b** → **4b**, **6b**, **8b**) and germanium compounds (**3c**, **5c**, **7c** → **4c**, **6c**, **8c**) and amounting to 49-fold for (*R*)-**3c** → (*R*)-**4c** at M_1 receptors.

In general, the (*R*)-enantiomers (eutomers) of **3a–c** and **4a–c** exhibited higher affinities at all muscarinic receptor subtypes than the corresponding (*S*)-enantiomers (distomers). However, this stereoselectivity [up to 22.4-fold; (*R*)-**4a**/(*S*)-**4a** at M_3 receptors, Fig. 9] was not the same for all receptor subtypes ($M_3 \geq M_1 \geq M_4 \geq M_5 > M_2$), being lower for the tertiary amines (**3a–c**, 1.2- to 9.8-fold) than for the corresponding quaternary ammonium derivatives (**4a–c**, 2.3- to 22.4-fold) (Table 4). Notably, there were no significant differences between the stereoselectivity ratios (eudismic indices; Table 4) of the individual (*R*)- and

Table 3
Pharmacological selectivity ratios for the (*R*)- and (*S*)-enantiomers of **3a–c** and **4a–c** and for the achiral compounds **5a–c**, **6a–c**, **7a–c**, and **8a–c**

Compound	Selectivity ratios [a]									
	M_1/M_2	M_1/M_3	M_1/M_4	M_1/M_5	M_2/M_3	M_2/M_4	M_2/M_5	M_3/M_4	M_3/M_5	M_4/M_5
(*R*)-**3a**	10.7	3.8	2.6	6.0	0.4	0.2	0.6	0.7	1.6	2.3
(*S*)-**3a**	2.7	6.9	3.2	5.5	2.6	1.2	2.0	0.5	0.8	1.7
(*R*)-**3b**	7.2	4.0	2.8	6.0	0.5	0.4	0.8	0.7	1.5	2.1
(*S*)-**3b**	2.9	6.3	3.1	4.2	2.2	1.1	1.4	0.5	0.7	1.3
(*R*)-**3c**	5.6	4.3	3.0	5.5	0.8	0.5	1.0	0.7	1.3	1.9
(*S*)-**3c**	2.0	5.4	3.1	2.9	2.7	1.5	1.4	0.6	0.5	0.9
(*R*)-**4a**	9.5	4.5	2.5	4.8	0.5	0.3	0.5	0.6	1.1	1.9
(*S*)-**4a**	1.1	5.1	2.0	3.0	4.6	1.8	2.6	0.4	0.6	1.5
(*R*)-**4b**	11.7	7.4	3.9	5.9	0.6	0.3	0.5	0.5	0.8	1.5
(*S*)-**4b**	2.9	8.9	3.0	4.1	3.1	1.0	1.4	0.3	0.5	1.4
(*R*)-**4c**	12.9	9.8	3.9	6.6	0.8	0.3	0.5	0.4	0.7	1.7
(*S*)-**4c**	2.7	9.1	3.5	3.6	3.4	1.3	1.3	0.4	0.4	1.0
5a	3.7	2.1	1.4	2.4	0.5	0.4	0.6	0.7	1.2	1.7
5b	5.4	3.9	2.5	4.5	0.7	0.5	0.8	0.6	1.1	1.8
5c	4.0	3.8	2.6	4.2	1.0	0.7	1.0	0.7	1.1	1.6
6a	3.6	1.9	1.5	2.6	0.5	0.4	0.7	0.8	1.4	1.8
6b	3.8	3.4	1.7	2.9	0.9	0.5	0.8	0.5	0.9	1.7
6c	3.4	3.2	1.8	2.4	0.9	0.5	0.7	0.6	0.8	1.3
7a	3.3	4.2	1.8	5.9	1.3	0.5	1.8	0.4	1.4	3.2
7b	3.7	6.3	3.1	5.1	1.7	0.8	1.4	0.5	0.8	1.7
7c	3.4	8.1	3.9	5.8	2.4	1.1	1.7	0.5	0.7	1.5
8a	2.3	4.4	1.8	5.4	1.9	0.8	2.3	0.4	1.2	3.0
8b	6.2	9.5	4.8	7.6	1.5	0.8	1.2	0.5	0.8	1.6
8c	6.3	10.7	4.9	7.2	1.7	0.8	1.1	0.5	0.7	1.5

[a] K_i ratios ($pK_i = -\log K_i$) are given as a measure of receptor selectivity; these values were calculated from the antilogs of the differences between the respective pK_i values.

(*S*)-enantiomers of the carbon (**3a**, **4a**), silicon (**3b**, **4b**), and germanium analogs (**3c**, **4c**) at M_1–M_5 receptors, again confirming the C/Si/Ge bioisosterism.

Replacement of the cyclopentyl moiety in the (*R*)-enantiomers (eutomers) of the C/Si/Ge analogs **3a–c** and **4a–c** by a phenyl ring (→ achiral diphenyl compounds **7a–c** and **8a–c**) decreased the affinities at M_1–M_5 receptors up to 16-fold [(*R*)-**4a** vs. **8a** at M_5 receptors; Table 4]. In contrast, the differences in affinity for M_1–M_5 receptors between the (*R*)-enantiomers of **3a–c** and **4a–c** and the corresponding achiral dicyclopentyl compounds **5a–c** and **6a–c** (the latter being in all cases more potent than the diphenyl analogs **7a–c** and **8a–c**) varied: (*R*)-**3a–c**/(*R*)-**4a–c** ≥ ≤ **5a–c**/**6a–c**. Analogous with the pharmacological results obtained with the (*R*)- and (*S*)-enantiomers of the muscarinic antagonists procyclidine [13] and hexahydro-difenidol [14] and their corresponding diphenyl and dicyclohexyl derivatives, the concept of the 'four-binding-sites model' [3,13,14] was used in the present study to explain the differences in binding of the (*R*)- and (*S*)-enantiomers of the C/Si/Ge analogs **3a–c** and **4a–c** at muscarinic M_1–M_5 receptors. As can be seen from Table 4, in most cases the sums (expected eudismic indices) of the differences observed (i) between the pK_i values of the (*R*)-enantiomers of **3a–c** and **4a–c** and the related diphenyl analogs **7a–c** and **8a–c** and (ii) between the pK_i values of the (*R*)-enantiomers of **3a–c** and **4a–c** and the corresponding dicyclopentyl derivatives **5a–c** and **6a–c** were 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 C/Si/Ge analogs **3a–c** and **4a–c** with muscarinic M_1–M_5 receptors is mainly based on the opposite binding of the phenyl and cyclopentyl ring to their individual binding sites. Similar results have been obtained with cyclohexyl-substituted (instead of cyclopentyl) C/Si/Ge analogs [3,4].

As far as the muscarinic receptor subtype selectivity is concerned, most compounds showed a slight preference for M_1 receptors with similar affinities for M_2–M_5 subtypes (Table 3). The highest M_1 receptor selectivity was observed for the potent germanium compound (*R*)-**4c** (12.9-fold, M_1 over M_2; affinity profile: $M_1 > M_4 \geq M_5 \geq M_3 \geq M_2$).

Table 4
Comparison of the eudismic indices [a] of the (*R*)- and (*S*)-enantiomers of **3a–c** and **4a–c** with the expected eudismic indices [b] calculated according to the 'four-binding-site model'

Compound	M_1	M_2	M_3	M_4	M_5
[(*R*)-**3a**]−[**5a**] [c]	0.31	−0.15	0.02	0.04	−0.09
[(*R*)-**3a**]−[**7a**] [d]	1.10	0.59	1.14	0.94	1.09
E.I.: [(*R*)-**3a**]−[(*S*)-**3a**] [a]	0.67	0.07	0.93	0.76	0.63
Expected E.I. [b]	1.41	0.44	1.16	0.98	1.00
[(*R*)-**3b**]−[**5b**] [c]	−0.08	−0.21	−0.09	−0.14	−0.21
[(*R*)-**3b**]−[**7b**] [d]	0.81	0.52	1.01	0.85	0.74
E.I.: [(*R*)-**3b**]−[(*S*)-**3b**] [a]	0.79	0.39	0.99	0.83	0.63
Expected E.I. [b]	0.73	0.31	0.92	0.71	0.53
[(*R*)-**3c**]−[**5c**] [c]	−0.26	−0.41	−0.31	−0.31	−0.38
[(*R*)-**3c**]−[**7c**] [d]	0.59	0.37	0.87	0.71	0.61
E.I.: [(*R*)-**3c**]−[(*S*)-**3c**] [a]	0.61	0.16	0.71	0.63	0.33
Expected E.I. [b]	0.33	−0.04	0.56	0.40	0.23
[(*R*)-**4a**]−[**6a**] [c]	0.26	−0.16	−0.12	0.03	0.00
[(*R*)-**4a**]−[**8a**] [d]	1.15	0.53	1.14	1.01	1.20
E.I.: [(*R*)-**4a**]−[(*S*)-**4a**] [a]	1.29	0.36	1.35	1.19	1.08
Expected E.I. [b]	1.41	0.37	1.02	1.04	1.20
[(*R*)-**4b**]−[**6b**] [c]	0.42	−0.07	0.08	0.07	0.11
[(*R*)-**4b**]−[**8b**] [d]	0.63	0.35	0.74	0.72	0.74
E.I.: [(*R*)-**4b**]−[(*S*)-**4b**] [a]	1.14	0.53	1.22	1.02	0.98
Expected E.I. [b]	1.05	0.28	0.82	0.79	0.85
[(*R*)-**4c**]−[**6c**] [c]	0.69	0.11	0.20	0.35	0.25
[(*R*)-**4c**]−[**8c**] [d]	0.80	0.49	0.84	0.90	0.84
E.I.: [(*R*)-**4c**]−[(*S*)-**4c**] [a]	1.28	0.60	1.25	1.23	1.02
Expected E.I. [b]	1.49	0.60	1.04	1.25	1.09

These values were obtained from pK_i values determined in radioligand binding studies at cloned human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors stably expressed in CHO-K1 cells.

[a] Eudismic index (E.I.): difference between the pK_i values 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 pK_i values of the (*R*)-enantiomer and the respective dicyclopentyl analog.

[d] Difference between the pK_i values of the (*R*)-enantiomer and the respective diphenyl analog.

3. Experimental

3.1. Syntheses

3.1.1. General procedures

All syntheses were carried out under dry nitrogen. The solvents used were dried and purified according to standard procedures and stored under nitrogen. Melting points (m.p.) (uncorrected) were determined with a Leitz Biomed microscope equipped with a heater (Leitz, Model M 350). The ^{1}H-, ^{13}C-, and ^{29}Si-NMR spectra were recorded at 22 °C on a Bruker AMX-400 (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz; ^{29}Si, 79.5 MHz) or Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{29}Si, 59.6 MHz). Chemical shifts (ppm) were determined relative to the internal $CHCl_3$ (^{1}H, δ 7.24; solvent $CDCl_3$), $CDCl_3$ (^{13}C, δ 77.0; solvent $CDCl_3$), C_6D_5H (^{1}H, δ 7.28; solvent C_6D_6), C_6D_6 (^{13}C, δ 128.0; solvent C_6D_6), CD_2HOD (^{1}H, δ 3.30; solvent CD_3OD), CD_3OD (^{13}C, δ 49.0; solvent CD_3OD), [D_5]acetone (^{1}H, δ 2.04; solvent [D_6]acetone), [D_6]acetone (^{13}C, δ 29.8, 206.3; solvent [D_6]acetone), or external Me_4Si (^{29}Si, δ 0; solvent $CDCl_3$). Analysis and assignment of the ^{1}H-NMR data were partially supported by simulations using the WIN-DAISY software package (version 4.05, Bruker). Assignment of the ^{13}C-NMR data was supported by DEPT 135 experiments. Optical rotations were measured at 20 °C with a JASCO polarimeter, Model P-1030; CH_3OH (purified by drying over Mg and subsequent distillation), acetone (purified by distillation), or $CHCl_3$ [purified by dynamic drying over an Al_2O_3 column (50 g of Al_2O_3 (Merck, 1077) per 100 ml of $CHCl_3$) and subsequent distillation] served as solvents.

3.1.2. *rac*-2-Cyclopentyl-2-phenyl-4-(piperidin-1-yl)-butan-1-ol (*rac*-**3a**)

Compound *rac*-**12** (10.0 g, 31.7 mmol) was added in small portions to a stirred suspension of lithium aluminum hydride (5.00 g, 132 mmol) in THF (200 ml) at room temperature (r.t.). After the mixture was stirred at r.t. for 1 h and heated under reflux for 2 h, saturated aqueous Na_2SO_4 solution was added dropwise until the evolution of hydrogen was completed. The mixture was

then kept at r.t. for 18 h, and the precipitate was filtered off and washed with Et_2O (5×40 ml). The combined organic solutions were dried over anhydrous Na_2SO_4 and the solvents removed under reduced pressure. The residue was recrystallized from *n*-hexane to give *rac*-**3a** in 89% yield as a colorless crystalline solid (8.52 g, 28.3 mmol); m.p. 108 °C. ^{1}H-NMR (400.1 MHz, C_6D_6): δ 1.2–1.7, 1.9–2.2, and 2.3–2.5 (m, 23H, CCH_2C, C_3CH, CCH_2N), 4.07 (δ_A) and 4.27 (δ_B) (AB system, $J_{AB} = 12.0$ Hz, 2H, CCH_2O), 7.1–7.5 (m, 5H, C_6H_5), OH resonance not detected. ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 24.2 (C-4, NC_5H_{10}), 24.5 (CCH_2C, C_5H_9), 24.6 (CCH_2C, C_5H_9), 25.7 (C-3/C-5, NC_5H_{10}), 27.1 (2 C, CCH_2C, C_5H_9), 32.4 (CCH_2CH_2N), 48.9 (CCH_2O), 50.2 (C-1, C_5H_9), 54.5 (CCH_2CH_2N), 54.8 (C-2/C-6, NC_5H_{10}), 66.3 (CCH_2O), 125.4 (C-4, C_6H_5), 127.7 (C-2/C-6, C_6H_5), 128.4 (C-3/C-5, C_6H_5), 142.5 (C-1, C_6H_5). Anal. Found: C, 79.7; H, 10.3; N, 4.8. Calc. for $C_{20}H_{31}NO$ ($M_r = 301.5$): C, 79.68; H, 10.36; N, 4.65%.

3.1.3. *rac*-1-(3-Cyclopentyl-4-hydroxy-3-phenylbutyl)-piperidinium chloride (*rac*-**3a**·HCl)

A saturated solution of HCl in Et_2O (2 ml) was added to a stirred solution of *rac*-**3a** (500 mg, 1.66 mmol) in Et_2O (20 ml) at r.t. The mixture was stirred at r.t. for 15 h, and the precipitate was filtered off, washed with Et_2O (2×20 ml), and dried in vacuo to give *rac*-**3a**·HCl in 99% yield as a colorless crystalline solid (557 mg, 1.65 mmol); m.p. 189 °C. ^{1}H-NMR (400.1 MHz, CD_3OD): δ 1.0–3.7 (m, 23H, CCH_2C, C_3CH, CCH_2N), 3.93 (δ_A) and 4.00 (δ_B) (AB system, $J_{AB} = 11.4$ Hz, 2H, CCH_2O), 7.1–7.4 (m, 5H, C_6H_5), OH resonance not detected. ^{13}C-NMR (100.6 MHz, CD_3OD): δ 23.0 (C-4, NC_5H_{10}), 24.7 (C-3/C-5, NC_5H_{10}), 25.86 (CCH_2C, C_5H_9), 25.93 (CCH_2C, C_5H_9), 28.1 (CCH_2C, C_5H_9), 28.3 (CCH_2C, C_5H_9), 30.6 (CCH_2CH_2N), 48.5 (CCH_2O), 50.0 (C-1, C_5H_9), 54.7 (C-2/C-6, NC_5H_{10}), 55.8 (CCH_2CH_2N), 65.7 (CCH_2O), 127.8 (C-4, C_6H_5), 129.2 (C-2/C-6 or C-3/C-5, C_6H_5), 129.6 (C-2/C-6 or C-3/C-5, C_6H_5), 142.2 (C-1, C_6H_5). Anal. Found: C, 70.9; H, 9.8; N, 4.1. Calc. for $C_{20}H_{32}ClNO$ ($M_r = 337.9$): C, 71.09; H, 9.54; N, 4.14%.

3.1.4. (*R*)-2-Cyclopentyl-2-phenyl-4-(piperidin-1-yl)-butan-1-ol [(*R*)-**3a**]

A solution of (*S*,*S*)-*O*,*O*′-dibenzoyltartaric acid (35.8 g, 100 mmol) in acetone (80 ml) was added to a stirred solution of *rac*-**3a** (29.8 g, 98.8 mmol) in boiling acetone (150 ml), and the mixture was stirred under reflux for 1 h and at r.t. for another 15 h. The resulting crystalline precipitate (20.5 g) was isolated by filtration and subjected to a four-step fractional crystallization from EtOH. For this purpose, a boiling saturated solution of the crystals in EtOH was filtered and the clear hot filtrate then allowed to cool to r.t. over a period of ca. 10 h (slow cooling in a water bath, starting at 80 °C). The mixture was kept at r.t. for additional 48 h, and the crystals formed were isolated by filtration and then subjected to the next crystallization step, finally yielding 6.92 g of the (*S*,*S*)-*O*,*O*′-dibenzoyltartrate of (*R*)-**3a** (characterized by ^{1}H- and ^{13}C-NMR studies; data not given). The crystals were added to a mixture of 1.0 M aqueous NaOH solution (100 ml) and Et_2O (200 ml). After the mixture was stirred at r.t. for 18 h, the organic phase was separated and the aqueous layer extracted with Et_2O (3×100 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*)-**3a** in 29% yield [relative to (*R*)-**3a** in the racemic mixture of **3a**] as a colorless crystalline solid (4.39 g, 14.6 mmol); m.p. 131 °C. The NMR data of the product were identical to those obtained for *rac*-**3a**. $[\alpha]^{25}_{366} = -68.4$, $[\alpha]^{25}_{436} = -50.3$, $[\alpha]^{25}_{546} = -32.4$, $[\alpha]^{25}_{578} = -29.1$, $[\alpha]^{25}_{589} = -28.2$ (acetone, $c = 1.50$). Anal. Found: C, 79.7; H, 10.3; N, 4.8. Calc. for $C_{20}H_{31}NO$ ($M_r = 301.5$): C, 79.68; H, 10.36; N, 4.65%.

3.1.5. (*R*)-1-(3-Cyclopentyl-4-hydroxy-3-phenylbutyl)-piperidinium chloride [(*R*)-**3a**·HCl]

This compound was prepared from (*R*)-**3a** (300 mg, 995 μmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated in 94% yield as a colorless crystalline solid (317 mg, 938 μmol); m.p. 193 °C. The NMR data of the product were identical to those obtained for *rac*-**3a**·HCl. $[\alpha]^{20}_{365} = 16.4$, $[\alpha]^{20}_{405} = 11.4$, $[\alpha]^{20}_{435} = 9.1$, $[\alpha]^{20}_{546} = 5.0$, $[\alpha]^{20}_{589} = 4.2$ (MeOH, $c = 1.00$). Anal. Found: C, 70.9; H, 9.3; N, 4.0. Calc. for $C_{20}H_{32}ClNO$ ($M_r = 337.9$): C, 71.09; H, 9.54; N, 4.14%.

3.1.6. (*S*)-2-Cyclopentyl-2-phenyl-4-(piperidin-1-yl)-butan-1-ol [(*S*)-**3a**]

All mother liquors collected in the several steps of the resolution of *rac*-**3a** [see preparation of (*R*)-**3a**] were combined. The solvent was removed under reduced pressure and the solid residue added to a mixture of 2.0 M aqueous NaOH solution (150 ml) and Et_2O (250 ml). The resulting mixture was stirred at r.t. for 30 min, the organic phase separated, and the aqueous layer extracted with Et_2O (3×80 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 an oily mixture consisting of (*R*)-**3a** and (*S*)-**3a** [14.7 g, 48.8 mmol; enriched with (*S*)-**3a**]. A solution of (*R*,*R*)-*O*,*O*′-dibenzoyltartaric acid monohydrate (18.3 g, 48.6 mmol) in acetone (50 ml) was added to a solution of this mixture in boiling acetone (150 ml). The resulting mixture was stirred under reflux for 1 h and at r.t. for another 15 h. The crystalline precipitate was isolated by filtration and then subjected to a four-step fractional crystallization

from EtOH as described for the preparation of (*R*)-**3a**. Treatment of the resulting salt with NaOH following the procedure described for the preparation of (*R*)-**3a** afforded (*S*)-**3a** in 22% yield [relative to (*S*)-**3a** in the racemic mixture of **3a**] as a colorless crystalline solid (3.24 g, 10.7 mmol); m.p. 131 °C. The NMR data of the product were identical to those obtained for *rac*-**3a**. $[\alpha]_{366}^{25} = 68.0$, $[\alpha]_{436}^{25} = 50.1$, $[\alpha]_{546}^{25} = 32.6$, $[\alpha]_{578}^{25} = 29.2$, $[\alpha]_{589}^{25} = 28.0$ (acetone, $c = 1.50$). Anal. Found: C, 79.7; H, 10.4; N, 4.8. Calc. for $C_{20}H_{31}NO$ ($M_r = 301.5$): C, 79.68; H, 10.36; N, 4.65%.

3.1.7. (S)-1-(3-Cyclopentyl-4-hydroxy-3-phenylbutyl)-piperidinium chloride [(S)-3a·HCl]

This compound was prepared from (*S*)-**3a** (300 mg, 995 μmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated in 97% yield as a colorless crystalline solid (326 mg, 965 μmol); m.p. 193 °C. The NMR data of the product were identical to those obtained for *rac*-**3a**·HCl. $[\alpha]_{365}^{20} = -16.4$, $[\alpha]_{405}^{20} = -11.4$, $[\alpha]_{435}^{20} = -9.1$, $[\alpha]_{546}^{20} = -5.0$, $[\alpha]_{589}^{20} = -4.2$ (MeOH, $c = 1.00$). Anal. Found: C, 71.2; H, 9.5; N, 4.0. Calc. for $C_{20}H_{32}ClNO$ ($M_r = 337.9$): C, 71.09; H, 9.54; N, 4.14%.

3.1.8. rac-Cyclopentyl(hydroxymethyl)phenyl-[2-(piperidin-1-yl)ethyl]silane (rac-3b)

A 1.6 M solution of *n*-butyllithium in *n*-hexane (13.0 ml, 20.8 mmol of *n*-BuLi) was added dropwise at 40 °C within 15 min to a stirred solution of piperidine (4.50 g, 52.8 mmol) in THF (50 ml). After the mixture was stirred at 40 °C for 30 min, a solution of *rac*-**23** (6.00 g, 19.7 mmol) in THF (30 ml) was added dropwise over a period of 30 min. The resulting mixture was stirred at 40 °C for 2 h and at r.t. for another 16 h, followed by the cautious addition of 2.0 M hydrochloric acid (150 ml). After the mixture was stirred at r.t. for 30 min, Et_2O (150 ml) and 6.0 M aqueous KOH solution (70 ml) were added. The organic phase was separated and the aqueous layer extracted with Et_2O (3 × 100 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure and the residue purified by Kugelrohr distillation (200 °C/0.01 mbar) to give *rac*-**3b** in 93% yield as an oily liquid (5.80 g, 18.3 mmol). ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.0–1.9 (m, 17H, $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.1–2.6 (m, 6H, CCH_2N), 3.59 (δ_A) and 3.66 (δ_B) (AB system, $J_{AB} = 14.7$ Hz, 2H, $SiCH_2O$), 7.2–7.4 and 7.5–7.7 (m, 5H, SiC_6H_5), OH resonance not detected. ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 10.8 ($SiCH_2C$), 23.1 (C-1, SiC_5H_9), 24.2 (C-4, NC_5H_{10}), 25.2 (C-3/C-5, NC_5H_{10}), 26.7 (CCH_2C, SiC_5H_9), 26.8 (CCH_2C, SiC_5H_9), 28.2 (2 C, CCH_2C, SiC_5H_9), 49.9 ($SiCH_2O$), 54.0 ($SiCH_2CH_2N$), 54.5 (C-2/C-6, NC_5H_{10}), 127.8 (C-3/C-5, SiC_6H_5), 129.1 (C-4, SiC_6H_5), 134.6 (C-1, SiC_6H_5), 135.1 (C-2/C-6, SiC_6H_5). ^{29}Si-NMR (79.5 MHz, $CDCl_3$): δ −4.6. Anal. Found: C, 71.5; H, 10.0; N, 4.3. Calc. for $C_{19}H_{31}NOSi$ ($M_r = 317.5$): C, 71.87; H, 9.84; N, 4.41%.

3.1.9. rac-1-{2-[Cyclopentyl(hydroxymethyl)phenylsilyl]ethyl}piperidinium chloride (rac-3b·HCl)

This compound was prepared from *rac*-**3b** (600 mg, 1.89 mmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated, after crystallization from acetone–Et_2O [diffusion of Et_2O via the gas phase into a solution of the product in acetone (15 ml) at r.t.], in 91% yield as a colorless crystalline solid (609 mg, 1.72 mmol); m.p. 124–125 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.1–1.3, 1.3–2.2, 1.8–2.0, and 2.0–2.2 (m, 17H, $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.4–2.7, 2.9–3.1, 3.1–3.3, and 3.4–3.6 (m, 6H, CCH_2N), 2.8 (br s, 1H, OH), 3.84 (δ_A) and 3.79 (δ_B) (AB system, $J_{AB} = 14.6$ Hz, 2H, $SiCH_2O$), 7.2–7.5 and 7.5–7.7 (m, 5H, SiC_6H_5), 10.8 (br s, 1H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 6.7 ($SiCH_2C$), 22.3 (C-4, NC_5H_{10}), 22.6 (C-1, SiC_5H_9), 22.8 (C-3/C-5, NC_5H_{10}) 26.68 (CCH_2C, SiC_5H_9), 26.71 (CCH_2C, SiC_5H_9), 28.06 (CCH_2C, SiC_5H_9), 28.11 (CCH_2C, SiC_5H_9), 50.9 ($SiCH_2O$), 51.8 (C-2 or C-6, NC_5H_{10}), 52.4 (C-2 or C-6, NC_5H_{10}), 54.6 ($SiCH_2CH_2N$), 128.2 (C-3/C-5, SiC_6H_5), 129.8 (C-4, SiC_6H_5), 132.9 (C-1, SiC_6H_5), 134.5 (C-2/C-6, SiC_6H_5). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ −5.8. Anal. Found: C, 64.3; H, 9.0; N, 4.0. Calc. for $C_{19}H_{32}ClNOSi$ ($M_r = 354.0$): C, 64.46; H, 9.11; N, 3.96%.

3.1.10. (R)-Cyclopentyl(hydroxymethyl)-phenyl[2-(piperidin-1-yl)ethyl]silane [(R)-3b)]

A 2.0 M aqueous NaOH solution (250 μl, 500 μmol of NaOH) was added to a mixture of an aqueous solution (10 ml) of (*R*)-**3b**·HCl (100 mg, 282 μmol) and Et_2O (10 ml). After the resulting mixture was stirred at r.t. for 5 min, the organic phase was separated and the aqueous layer extracted with Et_2O (3 × 10 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*)-**3b** in 91% yield as an oily liquid (81.5 mg, 257 μmol). The NMR data of the product were identical to those obtained for *rac*-**3b**. $[\alpha]_{365}^{20} = -19.8$, $[\alpha]_{405}^{20} = -16.8$, $[\alpha]_{435}^{20} = -15.0$, $[\alpha]_{546}^{20} = -9.2$, $[\alpha]_{589}^{20} = -8.4$ (MeOH, $c = 1.00$). Anal. Found: C, 71.6; H, 9.9; N, 4.3. Calc. for $C_{19}H_{31}NOSi$ ($M_r = 317.5$): C, 71.87; H, 9.84; N, 4.41%.

3.1.11. (R)-1-{2-[Cyclopentyl(hydroxymethyl)phenylsilyl]ethyl}piperidinium chloride [(R)-3b·HCl]

The mother liquors collected in the first six crystallization steps of the resolution of *rac*-**3b** [see preparation of (*S*)-**3b**·HCl] were combined. The solvent was removed under reduced pressure and the solid residue suspended in water (200 ml). EtO_2 (200 ml) and 2.0 M aqueous NaOH solution (20 ml) were added, and the

resulting mixture was stirred at r.t. for 15 min. The organic phase was separated and the aqueous layer extracted with Et_2O (2 × 100 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 an oily mixture consisting of (*S*)-**3b** and (*R*)-**3b** [7.00 g, 22.0 mmol; enriched with (*R*)-**3b**]. A solution of this product in boiling acetone (150 ml) was added to a filtered solution of (*R*,*R*)-*O*,*O*′-di-*p*-toluoyltartaric acid (8.40 g, 21.7 mmol) in boiling acetone (150 ml). The resulting mixture was stirred for 10 min, cooled to r.t., and then kept undisturbed for 40 h. The crystalline solid formed was isolated by filtration and subjected to a nine-step fractional crystallization from acetone following the procedure described for the preparation of (*S*)-**3b**·HCl. The product (450 mg) finally obtained was added to a mixture of water (50 ml) and Et_2O (50 ml), followed by the addition of 2.0 M aqueous NaOH solution (2.0 ml). After the mixture was stirred at r.t. for 15 min, the organic phase was separated and the aqueous layer extracted with Et_2O (2 × 50 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 (*R*)-**3b** as an oily liquid (190 mg, 598 μmol). This product was dissolved in Et_2O (50 ml), followed by the addition of a saturated solution of HCl in Et_2O (500 μl). After the mixture was stirred at r.t. 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–Et_2O [diffusion of Et_2O via the gas phase into a solution of the product in acetone (15 ml) at r.t.] to give (*R*)-**3b**·HCl in 3% yield [relative to (*R*)-**3b** in the racemic mixture of **3b**] as a colorless crystalline solid (196 mg, 554 μmol); m.p. 125 °C. The NMR data of the product were identical to those obtained *rac*-**3b**·HCl. $[\alpha]_{365}^{20} = 11.0$, $[\alpha]_{405}^{20} = 7.8$, $[\alpha]_{435}^{20} = 6.4$, $[\alpha]_{546}^{20} = 3.9$, $[\alpha]_{589}^{20} = 3.5$ (MeOH, $c = 1.00$). Anal. Found: C, 64.3; H, 9.1; N, 4.0. Calc. for $C_{19}H_{32}ClNOSi$ ($M_r = 354.0$): C, 64.46; H, 9.11; N, 3.96%.

*3.1.12. (S)-Cyclopentyl(hydroxymethyl)-phenyl[2-(piperidin-1-yl)ethyl]silane [(S)-**3b**)]*

This compound was prepared from (*S*)-**3b**·HCl (100 mg, 282 μmol) analogous to the synthesis of (*R*)-**3b** and isolated in 92% yield as an oily liquid (82.5 mg, 260 μmol). The NMR data of the product were identical to those obtained for *rac*-**3b**. $[\alpha]_{365}^{20} = 19.8$, $[\alpha]_{405}^{20} = 16.8$, $[\alpha]_{435}^{20} = 15.0$, $[\alpha]_{546}^{20} = 9.2$, $[\alpha]_{589}^{20} = 8.4$ (MeOH, $c = 1.00$). Anal. Found: C, 71.6; H, 10.0; N, 4.3. Calc. for $C_{19}H_{31}NOSi$ ($M_r = 317.5$): C, 71.87; H, 9.84; N, 4.41%.

*3.1.13. (S)-1-{2-[Cyclopentyl(hydroxymethyl)phenylsilyl]ethyl}piperidinium chloride [(S)-**3b**·HCl]*

(*S*,*S*)-*O*,*O*′-Di-*p*-toluoyltartaric acid (13.0 g, 33.6 mmol) was dissolved in boiling acetone (200 ml). The hot solution was filtered and then added to a solution of *rac*-**3b** (10.8 g, 34.0 mmol) in boiling acetone (100 ml). The resulting mixture was stirred for 30 min, cooled to r.t., and then kept undisturbed for 16 h. The crystalline solid formed was isolated by filtration and then subjected to an 11-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 r.t. over a period of ca. 4 h (slow cooling in a water bath, starting at 60 °C). The mixture was kept undisturbed at r.t. for another 48 h, and the crystalline product was isolated by filtration and then subjected to the next crystallization step to yield finally 540 mg of a crystalline solid. [The mother liquors of the first six crystallization steps were combined and used for the preparation of (*R*)-**3b**·HCl.] This product was added to a mixture of water (60 ml) and Et_2O (60 ml), followed by the addition of 2.0 M aqueous NaOH solution (2.0 ml). After the resulting mixture was stirred at r.t. for 15 min, the organic phase was separated and the aqueous layer extracted with Et_2O (2 × 50 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 (*S*)-**3b** as an oily liquid (220 mg, 683 μmol). This product was dissolved in Et_2O (50 ml), followed by the addition of a saturated solution of HCl in Et_2O (500 μl). After the mixture was stirred at r.t. 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–Et_2O [diffusion of Et_2O via the gas phase into a solution of the product in acetone (15 ml) at r.t.] to give (*S*)-**3b**·HCl in 4% yield [relative to (*S*)-**3b** in the racemic mixture of **3b**] as a colorless crystalline solid (225 mg, 636 μmol); m.p. 125 °C. The NMR data of the product were identical to those obtained for *rac*-**3b**·HCl. $[\alpha]_{365}^{20} = -11.0$, $[\alpha]_{405}^{20} = -7.8$, $[\alpha]_{435}^{20} = -6.4$, $[\alpha]_{546}^{20} = -3.9$, $[\alpha]_{589}^{20} = -3.5$ (MeOH, $c = 1.00$). Anal. Found: C, 64.3; H, 9.1; N, 4.0. Calc. for $C_{19}H_{32}ClNOSi$ ($M_r = 354.0$): C, 64.46; H, 9.11; N, 3.96%.

*3.1.14. rac-Cyclopentyl(hydroxymethyl)phenyl[2-(piperidin-1-yl)ethyl]germane (rac-**3c**)*

A 1.35 M solution of *n*-butyllithium in *n*-hexane (109 ml, 147 mmol of *n*-BuLi) was added dropwise at 50 °C within 15 min to a stirred solution of piperidine (25.1 g, 295 mmol) in THF (230 ml). After the mixture was stirred at 50 °C for 30 min, a solution of *rac*-**30** (24.5 g, 70.2 mmol) in THF (230 ml) was added dropwise over a period of 35 min. The resulting mixture was stirred at 50 °C for 2 h, cooled to r.t., and then added cautiously

to 6.0 M hydrochloric acid (450 ml). After the mixture was stirred at r.t. for 30 min, Et_2O (500 ml) and 6.0 M aqueous KOH solution (500 ml) were added. The organic phase was separated and the aqueous layer extracted with Et_2O (3 × 300 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure and the residue purified by Kugelrohr distillation (180 °C/0.01 mbar) to give *rac*-**3c** in 87% yield as an oily liquid (22.0 g, 60.8 mmol). ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.2–1.9 and 2.1–2.6 (m, 23H, $GeCH_2C$, $GeCHC_2$, CCH_2C, CCH_2N), 3.78 (δ_A) and 3.89 (δ_B) (AB system, J_{AB} = 12.5 Hz, 2H, $GeCH_2O$), 6.7 (br s, 1H, OH), 7.2–7.3 and 7.4–7.5 (m, 5H, GeC_6H_5). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 11.6 ($GeCH_2C$), 24.0 (C-4, NC_5H_{10}), 25.0 (C-3/C-5, NC_5H_{10}), 25.4 (C-1, GeC_5H_9), 26.03 (CCH_2C, GeC_5H_9), 26.10 (CCH_2C, GeC_5H_9), 28.9 (2 C, CCH_2C, GeC_5H_9), 50.5 ($GeCH_2O$) 54.4 (C-2/C-6, NC_5H_{10}), 54.8 ($GeCH_2CH_2N$), 127.9 (C-3/C-5, GeC_6H_5), 128.3 (C-4, GeC_6H_5), 134.1 (C-2/C-6, GeC_6H_5), 138.1 (C-1, GeC_6H_5). Anal. Found: C, 63.2; H, 8.8; N, 3.9. Calc. for $C_{19}H_{31}GeNO$ (M_r = 362.1): C, 63.03; H, 8.63; N, 3.87%.

*3.1.15. rac-1-{2-[Cyclopentyl(hydroxymethyl)phenylgermyl]ethyl}piperidinium chloride (rac-**3c**·HCl)*

This compound was prepared from *rac*-**3c** (453 mg, 1.25 mmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated in 94% yield as a colorless crystalline solid (470 mg, 1.18 mmol); m.p. 119 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.2–2.3 and 2.4–2.7 (m, 18H, $GeCH_2C$, $GeCHC_2$, CCH_2C), 2.9–3.6 (m, 6H, CCH_2N), 4.00 (δ_A) and 4.05 (δ_B) (AB system, J_{AB} = 12.8 Hz, 2 H $GeCH_2O$), 7.2–7.5 (m, 5H, GeC_6H_5), 10.9 (br s, 1H, NH), OH resonance not detected. ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 6.5 ($GeCH_2CH_2N$), 22.2 (C-4, NC_5H_{10}), 22.7 (C-3/C-5, NC_5H_{10}), 25.2 (C-1, GeC_5H_9), 26.00 (CCH_2C, GeC_5H_9), 26.05 (CCH_2C, GeC_5H_9), 28.93 (CCH_2C, GeC_5H_9), 28.98 (CCH_2C, GeC_5H_9), 51.7 ($GeCH_2O$), 52.3 (C-2/C-6, NC_5H_{10}), 55.4 ($GeCH_2CH_2N$), 128.3 (C-3/C-5, GeC_6H_5), 128.9 (C-4, GeC_6H_5), 134.1 (C-2/C-6, GeC_6H_5), 135.9 (C-1, GeC_6H_5). Anal. Found: C, 57.2; H, 8.2; N, 3.5. Calc. for $C_{19}H_{32}ClGeNO$ (M_r = 398.5): C, 57.26; H, 8.09; N, 3.51%.

*3.1.16. (R)-Cyclopentyl(hydroxymethyl)phenyl[2-(piperidin-1-yl)ethyl]germane [(R)-**3c**]*

A solution of (*S*)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (8.60 g, 24.7 mmol) in boiling EtOH (180 ml) was added to a solution of *rac*-**3c** (8.94 g, 24.7 mmol) in EtOH (100 ml). After the mixture was stirred under reflux for 30 min, water (ca. 100 ml) was added until the formation of a white precipitate was observed. Ethanol was added to the boiling solution until the precipitate just disappeared, and the hot solution was filtered, cooled to r.t. within 10 h (slow cooling in a water bath, starting at 80 °C), and the mixture then kept undisturbed for 48 h. The resulting precipitate was isolated by filtration and then subjected to a 13-step fractional crystallization from EtOH–water as described above. For this purpose, the boiling saturated solution of the precipitate in EtOH–water was filtered, cooled to r.t. within 10 h, and the mixture then kept undisturbed for 48 h. The crystalline product was isolated by filtration and subjected to the next crystallization step to yield finally 686 mg of a crystalline solid. This product was added to a mixture of 2.0 M aqueous NaOH solution (30 ml) and Et_2O (40 ml), and the mixture was stirred at r.t. for 30 min. The organic phase was separated and the aqueous layer extracted with Et_2O (3 × 30 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*)-**3c** in 8% yield [relative to (*R*)-**3c** in the racemic mixture of **3c**] as an oily liquid (340 mg, 939 μmol). The NMR data of the product were identical to those obtained for *rac*-**3c**. $[\alpha]^{20}_{365}$ = −11.5, $[\alpha]^{20}_{405}$ = −11.0, $[\alpha]^{20}_{435}$ = −10.1, $[\alpha]^{20}_{546}$ = −7.3, $[\alpha]^{20}_{589}$ = −6.3 (MeOH, *c* = 1.00). Anal. Found: C, 63.0; H, 8.6; N, 3.7. Calc. for $C_{19}H_{31}GeNO$ (M_r = 362.1): C, 63.03; H, 8.63; N, 3.87%.

*3.1.17. (R)-1-{2-[Cyclopentyl(hydroxymethyl)phenylgermyl]ethyl}piperidinium chloride [(R)-**3c**·HCl]*

This compound was prepared from (*R*)-**3c** (50.0 mg, 138 μmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated in 94% yield as a colorless crystalline solid (52.0 mg, 130 μmol); m.p. 127 °C. The NMR data of the product were identical to those obtained for *rac*-**3c**·HCl. $[\alpha]^{20}_{365}$ = 10.9, $[\alpha]^{20}_{405}$ = 7.0, $[\alpha]^{20}_{435}$ = 5.6, $[\alpha]^{20}_{546}$ = 2.6, $[\alpha]^{20}_{589}$ = 2.3 (MeOH, *c* = 1.00). Anal. Found: C, 56.9; H, 8.3; N, 3.7. Calc. for $C_{19}H_{32}ClGeNO$ (M_r = 398.5): C, 57.26; H, 8.09; N, 3.51%.

*3.1.18. (S)-Cyclopentyl(hydroxymethyl)phenyl[2-(piperidin-1-yl)ethyl]germane [(S)-**3c**]*

All mother liquors collected in the several steps of the resolution of *rac*-**3c** [see preparation of (*R*)-**3c**] were combined. The solvent was removed under reduced pressure and the solid residue added to a mixture of 2.0 M aqueous NaOH solution (100 ml) and Et_2O (300 ml). The resulting mixture was stirred at r.t. for 30 min, the organic phase separated, and the aqueous layer extracted with Et_2O (2 × 80 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 an oily mixture consisting of (*R*)-**3c** and (*S*)-**3c** [6.44 g, 17.8 mmol; enriched with (*S*)-**3c**]. A solution of this product in EtOH (70 ml) was added to a solution of (*R*)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (6.20 g, 17.8 mmol) in boiling EtOH

(140 ml). After the mixture was stirred under reflux for 30 min, water (ca. 80 ml) was added until the formation of a white precipitate was observed. EtOH was added to the boiling solution until the precipitate just disappeared, and the hot solution was filtered, cooled to r.t. within 10 h, and the mixture then kept undisturbed for 48 h. The resulting precipitate was isolated by filtration and subjected to a 17-step fractional crystallization from EtOH–water as described above. For this purpose, the boiling saturated solution of the precipitate in EtOH–water was filtered, cooled to r.t. within 10 h, and the mixture then kept undisturbed for 48 h. The crystalline product was isolated by filtration and subjected to the next crystallization step to yield finally 330 mg of a crystalline solid. This product was added to a mixture of 2.0 M aqueous NaOH solution (20 ml) and Et_2O (30 ml), and the resulting mixture was stirred at r.t. for 30 min. The organic phase was separated and the aqueous layer extracted with Et_2O (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 (*S*)-**3c** in 4% yield [relative to (*S*)-**3c** in the racemic mixture of **3c**] as an oily liquid (164 mg, 453 μmol). The NMR data of the product were identical to those obtained for *rac*-**3c**. $[\alpha]_{365}^{20} = 11.5$, $[\alpha]_{405}^{20} = 11.0$, $[\alpha]_{435}^{20} = 10.1$, $[\alpha]_{546}^{20} = 7.3$, $[\alpha]_{589}^{20} = 6.3$ (MeOH, $c = 1.00$). Anal. Found: C, 63.1; H, 8.8; N, 3.9. Calc. for $C_{19}H_{31}GeNO$ ($M_r = 362.1$): C, 63.03; H, 8.63; N, 3.87%.

*3.1.19. (S)-1-{2-[Cyclopentyl(hydroxymethyl)phenylgermyl]ethyl}piperidinium chloride [(S)-**3c**·HCl]*

This compound was prepared from (*S*)-**3c** (45.0 mg, 124 μmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated in 97% yield as a colorless crystalline solid (48.0 mg, 120 μmol); m.p. 127 °C. The NMR data of the product were identical to those obtained for *rac*-**3c**·HCl. $[\alpha]_{365}^{20} = -10.9$, $[\alpha]_{405}^{20} = -7.0$, $[\alpha]_{435}^{20} = -5.6$, $[\alpha]_{546}^{20} = -2.6$, $[\alpha]_{589}^{20} = -2.3$ (MeOH, $c = 1.00$). Anal. Found: C, 56.9; H, 8.3; N, 3.7. Calc. for $C_{19}H_{32}ClGeNO$ ($M_r = 398.5$): C, 57.26; H, 8.09; N, 3.51%.

*3.1.20. rac-1-(3-Cyclopentyl-4-hydroxy-3-phenylbutyl)-1-methylpiperidinium iodide (rac-**4a**)*

Methyl iodide (4.70 g, 33.1 mmol) was added to a solution of *rac*-**3a** (1.00 g, 3.32 mmol) in acetone (50 ml) and the resulting mixture stirred at r.t. for 21 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–Et_2O (diffusion of Et_2O via the gas phase into a saturated solution of the product in acetone at r.t.) to give *rac*-**4a** in 92% yield as a colorless crystalline solid (1.36 g, 3.07 mmol); m.p. 138 °C. ^{1}H-NMR (400.1 MHz, [D$_6$]acetone): δ 1.1–2.0, 2.2–2.6, 3.1–3.2, and 3.6–4.2 (m, 25H, CCH_2C, C_3CH, CCH_2N, CCH_2O), 3.34 (s, 3H, NCH_3), 7.1–7.4 (m, 5H, C_6H_5), OH resonance not detected. ^{13}C-NMR (100.6 MHz, [D$_6$]acetone): δ 20.65 (CCH_2C), 20.71 (CCH_2C), 21.6 (CCH_2C), 25.0 (CCH_2C), 25.1 (CCH_2C), 26.8 (CCH_2C), 27.55 (CCH_2C), 27.62 (CCH_2C), 47.4 (CCH_2O), 47.8 (C-1, C_5H_9, or NCH_3), 49.3 (C-1, C_5H_9, or NCH_3), 61.5 (2 C), 63.3, and 63.4 (C-2/C-6, NC_5H_{10}, CCH_2CH_2N, CCH_2O), 126.9 (C-4, C_6H_5), 128.2 (C-2/C-6 or C-3/C-5, C_6H_5), 128.5 (C-2/C-6 or C-3/C-5, C_6H_5) 142.4 (C-1, C_6H_5). Anal. Found: C, 56.6; H, 7.7; N, 3.1. Calc. for $C_{21}H_{34}INO$ ($M_r = 443.4$): C, 56.88; H, 7.73; N, 3.16%.

*3.1.21. (R)-1-(3-Cyclopentyl-4-hydroxy-3-phenylbutyl)-1-methylpiperidinium iodide [(R)-**4a**]*

This compound was prepared from (*R*)-**3a** (500 mg, 1.66 mmol) analogous to the synthesis of *rac*-**4a** and isolated in 91% yield as a colorless crystalline solid (667 mg, 1.50 mmol); m.p. 177 °C. The NMR data of the product were identical to those obtained for *rac*-**4a**. $[\alpha]_{546}^{20} = -18.6$, $[\alpha]_{589}^{20} = -16.4$ ($CHCl_3$, $c = 1.00$). Anal. Found: C, 56.6; H, 7.7; N, 3.2. Calc. for $C_{21}H_{34}INO$ ($M_r = 443.4$): C, 56.88; H, 7.73; N, 3.16%.

*3.1.22. (S)-1-(3-Cyclopentyl-4-hydroxy-3-phenylbutyl)-1-methylpiperidinium iodide [(S)-**4a**]*

This compound was prepared from (*S*)-**3a** (500 mg, 1.66 mmol) analogous to the synthesis of *rac*-**4a** and isolated in 93% yield as a colorless crystalline solid (684 mg, 1.54 mmol); m.p. 177 °C. The NMR data of the product were identical to those obtained for *rac*-**4a**. $[\alpha]_{546}^{20} = 18.6$, $[\alpha]_{589}^{20} = 16.4$ ($CHCl_3$, $c = 1.00$). Anal. Found: C, 56.6; H, 7.7; N, 3.2. Calc. for $C_{21}H_{34}INO$ ($M_r = 443.4$): C, 56.88; H, 7.73; N, 3.16%.

*3.1.23. rac-1-{2-[Cyclopentyl(hydroxymethyl)phenylsilyl]ethyl}-1-methylpiperidinium iodide (rac-**4b**)*

This compound was prepared from *rac*-**3b** (600 mg, 1.89 mmol) analogous to the synthesis of *rac*-**4a** and isolated in 89% yield as a colorless crystalline solid (773 mg, 1.68 mmol); m.p. 159–160 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.2–1.6 and 1.6–2.0 (m, 17H, $SiCH_2C$, $SiCHC_2$, CCH_2C), 3.0 (br s, 1H, OH), 3.15 (s, 3H, NCH_3), 3.4–3.7 and 3.9–4.1 (m, 6H, CCH_2N), 3.89 (δ_A) and 3.84 (δ_B) (AB system, $J_{AB} = 13.7$ Hz, 2H, $SiCH_2O$), 7.3–7.5 and 7.5–7.6 (m, 5H, SiC_6H_5). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 5.3 ($SiCH_2C$), 20.2 (C-3/C-5, NC_5H_{10}), 20.8 (C-4, NC_5H_{10}), 22.6 (C-1, SiC_5H_9), 26.7 (CCH_2C, SiC_5H_9), 26.8 (CCH_2C, SiC_5H_9), 28.1 (CCH_2C, SiC_5H_9), 28.2 (CCH_2C, SiC_5H_9), 47.1 (NCH_3), 49.4 ($SiCH_2O$), 59.8 (C-2 or C-6, NC_5H_{10}), 60.3 (C-2 or C-6, NC_5H_{10}), 62.0 ($SiCH_2CH_2N$), 128.3 (C-3/C-5, SiC_6H_5), 130.0 (C-4, SiC_6H_5), 133.0 (C-1, SiC_6H_5), 134.4 (C-2/C-6, SiC_6H_5). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ −5.1. Anal. Found: C, 52.4; H, 7.4;

N, 3.1. Calc. for $C_{20}H_{34}INOSi$ ($M_r = 459.5$): C, 52.28; H, 7.46; N, 3.05%.

*3.1.24. (R)-1-{2-[Cyclopentyl(hydroxymethyl)phenylsilyl]ethyl}-1-methylpiperidinium iodide [(R)-**4b**]*

This compound was prepared from (*R*)-**3b** (100 mg, 315 μmol) analogous to the synthesis of *rac*-**4a** and isolated in 89% yield as a colorless crystalline solid (128 mg, 279 μmol); m.p. 160 °C. The NMR data of the product were identical to those obtained for *rac*-**4b**. $[\alpha]_{365}^{20} = 5.0$, $[\alpha]_{405}^{20} = 3.7$, $[\alpha]_{435}^{20} = 3.2$, $[\alpha]_{546}^{20} = 2.5$, $[\alpha]_{589}^{20} = 2.2$ (MeOH, $c = 1.00$). Anal. Found: C, 52.4; H, 7.3; N, 3.1. Calc. for $C_{20}H_{34}INOSi$ ($M_r = 459.5$): C, 52.28; H, 7.46; N, 3.05%.

*3.1.25. (S)-1-{2-[Cyclopentyl(hydroxymethyl)phenylsilyl]ethyl}-1-methylpiperidinium iodide [(S)-**4b**]*

This compound was prepared from (*S*)-**3b** (100 mg, 315 μmol) analogous to the synthesis of *rac*-**4a** and isolated in 90% yield as a colorless crystalline solid (130 mg, 283 μmol); m.p. 160 °C. The NMR data of the product were identical to those obtained for *rac*-**4b**. $[\alpha]_{365}^{20} = -5.0$, $[\alpha]_{405}^{20} = -3.7$, $[\alpha]_{435}^{20} = -3.2$, $[\alpha]_{546}^{20} = -2.5$, $[\alpha]_{589}^{20} = -2.2$ (MeOH, $c = 1.00$). Anal. Found: C, 52.4; H, 7.4; N, 3.0. Calc. for $C_{20}H_{34}INOSi$ ($M_r = 459.5$): C, 52.28; H, 7.46; N, 3.05%.

*3.1.26. rac-1-{2-[Cyclopentyl(hydroxymethyl)phenylgermyl]ethyl}-1-methylpiperidinium iodide (rac-**4c**)*

This compound was prepared from *rac*-**3c** (360 mg, 994 μmol) analogous to the synthesis of *rac*-**4a** and isolated, after crystallization from acetone–water [10:1 (v/v)], in 87% yield as a colorless crystalline solid (436 mg, 865 μmol); m.p. 152 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.3–2.0 (m, 17H, $GeCH_2C$, $GeCHC_2$, CCH_2C), 3.15 (s, 3H, NCH_3), 3.2–3.6 (m, 6H, CCH_2N), 3.8–4.2 (m, 3H, $GeCH_2O$, OH), 7.3–7.5 (m, 5H, GeC_6H_5). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 5.0 ($GeCH_2CH_2N$), 20.1 (C-3 or C-5, NC_5H_{10}), 20.7 (C-3 or C-5, NC_5H_{10}), 25.3 (C-1, GeC_5H_9), 26.0 (CCH_2C, GeC_5H_9), 26.1 (CCH_2C, GeC_5H_9), 28.98 (CCH_2C, GeC_5H_9), 29.03 (CCH_2C, GeC_5H_9), 47.1 (NCH_3), 51.1 ($GeCH_2O$), 59.7 (C-2 or C-6, NC_5H_{10}), 60.1 (C-2 or C-6, NC_5H_{10}), 62.7 ($GeCH_2CH_2N$), 128.4 (C-3/C-5, GeC_6H_5), 129.1 (C-4, GeC_6H_5), 134.1 (C-2/C-6, GeC_6H_5), 135.8 (C-1, GeC_6H_5). Anal. Found: C, 47.4; H, 7.1; N, 2.7. Calc. for $C_{20}H_{34}GeINO$ ($M_r = 504.0$): C, 47.66; H, 6.80; N, 2.78%.

*3.1.27. (R)-1-{2-[Cyclopentyl(hydroxymethyl)phenylgermyl]ethyl}-1-methylpiperidinium iodide [(R)-**4c**]*

This compound was prepared from (*R*)-**3c** (87.0 mg, 240 μmol) analogous to the synthesis of *rac*-**4a** and isolated in 84% yield as a colorless crystalline solid (102 mg, 202 μmol); m.p. 167 °C. The NMR data of the product were identical to those obtained for *rac*-**4c**. $[\alpha]_{365}^{20} = 4.9$, $[\alpha]_{405}^{20} = 3.1$, $[\alpha]_{435}^{20} = 2.2$, $[\alpha]_{546}^{20} = 0.9$, $[\alpha]_{589}^{20} = 0.8$ (MeOH, $c = 1.00$). Anal. Found: C, 47.7; H, 6.9; N, 2.8. Calc. for $C_{20}H_{34}GeINO$ ($M_r = 504.0$): C, 47.66; H, 6.80; N, 2.78%.

*3.1.28. (S)-1-{2-[Cyclopentyl(hydroxymethyl)phenylgermyl]ethyl}-1-methylpiperidinium iodide [(S)-**4c**]*

This compound was prepared from (*S*)-**3c** (47.0 mg, 130 μmol) analogous to the synthesis of *rac*-**4a** and isolated in 98% yield as a colorless crystalline solid (64.0 mg, 127 μmol); m.p. 167 °C. The NMR data of the product were identical to those obtained for *rac*-**4c**. $[\alpha]_{365}^{20} = -4.9$, $[\alpha]_{405}^{20} = -3.1$, $[\alpha]_{435}^{20} = -2.2$, $[\alpha]_{546}^{20} = -0.9$, $[\alpha]_{589}^{20} = -0.8$ (MeOH, $c = 1.00$). Anal. Found: C, 47.9; H, 6.9; N, 2.8. Calc. for $C_{20}H_{34}GeINO$ ($M_r = 504.0$): C, 47.66; H, 6.80; N, 2.78%.

*3.1.29. 2,2-Dicyclopentyl-4-(piperidin-1-yl)butan-1-ol (**5a**)*

This compound was prepared analogous to the synthesis of *rac*-**3a** by the treatment of **16** (1.06 g, 3.16 mmol) with a suspension of lithium aluminum hydride (482 mg, 12.7 mmol) in THF (20 ml) and isolated in 97% yield as a colorless solid (900 mg, 3.07 mmol); m.p. 79 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.2–1.7, 1.9–2.1, and 2.2–2.6 (m, 32H, CCH_2C, C_3CH, CCH_2N), 3.37 (s, 2H, CCH_2O), OH resonance not detected. ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 24.2 (C-4, NC_5H_{10}), 24.82 (CCH_2C, C_5H_9), 24.87 (CCH_2C, C_5H_9), 25.5 (C-3/C-5, NC_5H_{10}), 27.0 (CCH_2C, C_5H_9), 27.11 (CCH_2C, C_5H_9), 29.1 (CCH_2CH_2N), 42.9 (CCH_2O), 44.0 (C-1, C_5H_9), 54.3 (C-2/C-6, NC_5H_{10}), 54.5 (CCH_2CH_2N), 68.1 (CCH_2O). Anal. Found: C, 77.7; H, 11.9; N, 4.8. Calc. for $C_{19}H_{35}NO$ ($M_r = 293.5$): C, 77.76; H, 12.02; N, 4.77%.

*3.1.30. 1-(3,3-Dicyclopentyl-4-hydroxybutyl)piperidinium chloride (**5a**·HCl)*

This compound was prepared from **5a** (200 mg, 681 μmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated in 97% yield as a colorless crystalline solid (218 mg, 661 μmol); m.p. 202 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.2–2.2 (m, 26H, CCH_2C, C_3CH), 2.6–2.8 (m, 2H, CCH_2N), 3.1–3.3 and 3.4–3.6 (m, 6H, CCH_2N, CCH_2O), 3.8 (br s, 1H, OH), 11.0 (br s, 1H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 22.1 (C-4, NC_5H_{10}), 22.8 (C-3/C-5, NC_5H_{10}), 24.68 (CCH_2C, C_5H_9), 24.69 (CCH_2C, C_5H_9), 27.3 (CCH_2CH_2N), 27.5 (CCH_2C, C_5H_9), 27.6 (CCH_2C, C_5H_9), 42.3 (CCH_2O), 44.8 (C-1, C_5H_9), 52.9 (C-2/C-6, NC_5H_{10}), 54.3 (CCH_2CH_2N), 66.7 (CCH_2O). Anal. Found: C, 68.8; H, 10.8; N, 4.2. Calc. for $C_{19}H_{36}ClNO$ ($M_r = 330.0$): C, 69.16; H, 11.00; N, 4.25%.

*3.1.31. Dicyclopentyl(hydroxymethyl)[2-(piperidin-1-yl)ethyl]silane (**5b**)*

This compound was prepared from **37** (3.00 g, 10.1 mmol) analogous to the synthesis of *rac*-**3b** and isolated in 90% yield as a colorless oily liquid (2.80 g, 9.04 mmol); b.p. 210 °C/0.01 mbar (oven temperature of the Kugelrohr distillation apparatus). ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 0.8–1.9 (m, 26H, $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.2–2.7 (m, 6H, CCH_2N), 3.31 (s, 2H, $SiCH_2O$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 9.2 ($SiCH_2CH_2N$), 22.2 (C-1, SiC_5H_9), 24.2 (C-4, NC_5H_{10}), 25.2 (C-3/C-5, NC_5H_{10}), 26.8 (CCH_2C, SiC_5H_9), 28.4 (CCH_2C, SiC_5H_9), 28.5 (CCH_2C, SiC_5H_9), 50.0 ($SiCH_2O$), 54.4 ($SiCH_2CH_2N$), 54.5 (C-2/C-6, NC_5H_{10}). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ 2.1. Anal. Found: C, 69.5; H, 11.1; N, 4.3. Calc. for $C_{18}H_{35}NOSi$ (M_r = 309.6): C, 69.84; H, 11.40; N, 4.52%.

*3.1.32. 1-{2-[Dicyclopentyl(hydroxymethyl)silyl]ethyl}-piperidinium chloride (**5b**·HCl)*

This compound was prepared from **5b** (700 mg, 2.26 mmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated, after crystallization from acetone–Et_2O [diffusion of Et_2O via the gas phase into a solution of the product in acetone (15 ml) at r.t.], in 93% yield as a colorless crystalline solid (727 mg, 2.10 mmol); m.p. 165–166 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 0.9–1.1, 1.2–1.7, 1.7–2.0, and 2.1–2.3 (m, 26H, $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.4–2.7, 3.1–3.3, and 3.4–3.6 (m, 6H, CCH_2N), 2.9 (br s, 1H, OH), 3.55 (s, 2H, $SiCH_2O$), 11.3 (br s, 1H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 5.8 ($SiCH_2CH_2N$), 22.0 (C-1, SiC_5H_9), 22.3 (C-4, NC_5H_{10}), 22.7 (C-3/C-5, NC_5H_{10}), 26.6 (CCH_2C, SiC_5H_9), 26.7 (CCH_2C, SiC_5H_9), 28.4 (CCH_2C, SiC_5H_9), 28.5 (CCH_2C, SiC_5H_9), 51.1 ($SiCH_2O$), 51.9 (C-2/C-6, NC_5H_{10}), 54.7 ($SiCH_2CH_2N$). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ 0.9. Anal. Found: C, 62.1; H, 10.2; N, 4.1. Calc. for $C_{18}H_{36}ClNOSi$ (M_r = 346.0): C, 62.48; H, 10.49; N, 4.06%.

*3.1.33. Dicyclopentyl(hydroxymethyl)[2-(piperidin-1-yl)ethyl]germane (**5c**)*

This compound was prepared from **42** (10.5 g, 30.8 mmol) analogous to the synthesis of *rac*-**3c** and isolated in 88% yield as a colorless oily liquid (9.55 g, 27.0 mmol); b.p. 152 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.0–1.8 (m, 26H, $GeCH_2C$, $GeCHC_2$, CCH_2C), 2.1–2.5 (m, 6H, CCH_2N), 3.49 (s, 2H, $GeCH_2O$), 6.4 (br s, 1H, OH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 9.9 ($GeCH_2CH_2N$), 24.1 (C-4, NC_5H_{10}), 24.3 (C-1, GeC_5H_9), 25.0 (C-3/C-5, NC_5H_{10}), 26.1 (4C, CCH_2C, GeC_5H_9), 29.15 (CCH_2C, GeC_5H_9), 29.22 (CCH_2C, GeC_5H_9), 50.3 ($GeCH_2O$), 54.3 (C-2/C-6, NC_5H_{10}), 55.3 ($GeCH_2CH_2N$). Anal. Found: C, 60.9; H, 9.9; N, 4.2. Calc. for $C_{18}H_{35}GeNO$ (M_r = 354.1): C, 61.06; H, 9.96; N, 3.96%.

*3.1.34. 1-{2-[Dicyclopentyl(hydroxymethyl)germyl]-ethyl}piperidinium chloride (**5c**·HCl)*

This compound was prepared from **5c** (453 mg, 1.28 mmol) analogous to the synthesis of *rac*-**3a**·HCl and isolated, after crystallization from acetone–Et_2O [diffusion of Et_2O via the gas phase into a solution of the product in acetone (10 ml) at r.t.], in 93% yield as a colorless crystalline solid (465 mg, 1.19 mmol); m.p. 165 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.1–2.2 and 2.5–2.7 (m, 27H, $GeCH_2C$, $GeCHC_2$, CCH_2C, OH), 3.1–3.3 and 3.4–3.6 (m, 6H, CCH_2N), 3.74 (s, 2H, $GeCH_2O$); 10.7 (br s, 1H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 5.5 ($GeCH_2CH_2N$), 22.1 (C-4, NC_5H_{10}), 22.7 (C-3/C-5, NC_5H_{10}), 24.3 (C-1, GeC_5H_9), 26.01 (CCH_2C, GeC_5H_9), 26.05 (CCH_2C, GeC_5H_9), 29.2 (CCH_2C, GeC_5H_9), 29.3 (CCH_2C, GeC_5H_9), 51.76 (C-2/C-6, NC_5H_{10}), 51.84 ($GeCH_2CH_2N$), 55.6 ($GeCH_2O$). Anal. Found: C, 55.7; H, 9.5; N, 3.7. Calc. for $C_{18}H_{36}ClGeNO$ (M_r = 390.6): C, 55.36; H, 9.29; N, 3.59%.

*3.1.35. 1-(3,3-Dicyclopentyl-4-hydroxybutyl)-1-methylpiperidinium iodide (**6a**)*

This compound was prepared from **5a** (200 mg, 681 μmol) analogous to the synthesis of *rac*-**4a** and isolated in 91% yield as a colorless crystalline solid (269 mg, 618 μmol); m.p. 146 °C. ^{1}H-NMR (300.1 MHz, CD_3OD): δ 1.3–2.1 (m, 26H, CCH_2C, C_3CH), 3.06 (s, 3H, NCH_3), 3.3–3.6 (m, 9H, CCH_2N, CCH_2O, OH). ^{13}C-NMR (75.5 MHz, CD_3OD): δ 21.4 (C-3/C-5, NC_5H_{10}), 22.4 (C-4, NC_5H_{10}), 26.12 (CCH_2C, C_5H_9), 26.13 (CCH_2C, C_5H_9), 26.4 (CCH_2CH_2N), 28.86 (CCH_2C, C_5H_9), 29.01 (CCH_2C, C_5H_9), 43.9 (CCH_2O), 46.9 (C-1, C_5H_9), 48.0 (NCH_3), 62.4 (C-2/C-6, NC_5H_{10}), 63.1 (CCH_2CH_2N), 67.6 (CCH_2O). Anal. Found: C, 55.0; H, 8.6; N, 3.2. Calc. for $C_{20}H_{38}INO$ (M_r = 435.4): C, 55.17; H, 8.80; N, 3.22%.

*3.1.36. 1-{2-[Dicyclopentyl(hydroxymethyl)silyl]ethyl}-1-methylpiperidinium iodide (**6b**)*

This compound was prepared from **5b** (700 mg, 2.26 mmol) analogous to the synthesis of *rac*-**4a** and isolated in 90% yield as a colorless crystalline solid (917 mg, 2.03 mmol); m.p. 95–96 °C. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 0.9–1.2, 1.2–1.7, and 1.7–2.0 (m, 26H, $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.7 (br s, 1H, OH), 3.18 (s, 3H, NCH_3), 3.58 (s, 2H, $SiCH_2O$), 3.5–3.7 and 3.7–3.9 (m, 6H, CCH_2N). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 4.3 ($SiCH_2CH_2N$), 20.3 (C-3/C-5, NC_5H_{10}), 20.9 (C-4, NC_5H_{10}), 22.2 (C-1, SiC_5H_9), 26.72 (CCH_2C, SiC_5H_9), 26.75 (CCH_2C, SiC_5H_9), 28.5 (CCH_2C, SiC_5H_9), 28.6 (CCH_2C, SiC_5H_9), 47.1 (NCH_3), 49.6 ($SiCH_2O$), 60.0 (C-2/C-6, NC_5H_{10}), 62.3 ($SiCH_2CH_2N$). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ 2.1. Anal. Found: C, 50.3; H, 8.3; N, 3.1. Calc. for $C_{19}H_{38}INOSi$ (M_r = 451.5): C, 50.54; H, 8.48; N, 3.10%.

*3.1.37. 1-{2-[Dicyclopentyl(hydroxymethyl)germyl]-ethyl}-1-methylpiperidinium iodide (**6c**)*

This compound was prepared from **5c** (1.50 g, 4.24 mmol) analogous to the synthesis of *rac*-**4a** and isolated, after crystallization from EtOAc, in 95% yield as a colorless crystalline solid (2.00 g, 4.03 mmol); m.p. 93 °C. ^{1}H-NMR (300.1 MHz, [D$_6$]acetone): δ 1.3–2.1 (m, 26H, $GeCH_2C$, $GeCHC_2$, CCH_2C), 3.25 (s, 3H, NCH_3), 3.5–4.0 (m, 9H, CCH_2N, $GeCH_2O$, OH). ^{13}C-NMR (75.5 MHz, [D$_6$]acetone): δ 4.2 ($GeCH_2CH_2N$), 20.7 (C-3/C-5, NC_5H_{10}), 21.6 (C-4, NC_5H_{10}), 25.2 (C-1, GeC_5H_9), 26.67 (CCH_2C, GeC_5H_9), 26.72 (CCH_2C, GeC_5H_9), 29.84 (CCH_2C, GeC_5H_9), 29.89 (CCH_2C, GeC_5H_9), 46.5 (NCH_3), 51.1 ($GeCH_2O$), 60.0 (C-2/C-6, NC_5H_{10}), 63.8 ($GeCH_2CH_2N$). Anal. Found: C, 46.2; H, 8.0; N, 2.9. Calc. for $C_{19}H_{38}GeINO$ ($M_r = 496.0$): C, 46.01; H, 7.72; N, 2.82%.

*3.1.38. 2,2-Diphenyl-4-(piperidin-1-yl)butan-1-ol (**7a**)*

Synthesis as described in Ref. [6].

*3.1.39. (Hydroxymethyl)diphenyl[2-(piperidin-1-yl)-ethyl]silane (**7b**)*

Synthesis as described in Ref. [7].

*3.1.40. (Hydroxymethyl)diphenyl[2-(piperidin-1-yl)-ethyl]germane (**7c**)*

Synthesis as described in Ref. [3].

*3.1.41. 1-(4-Hydroxy-3,3-diphenylbutyl)piperidinium chloride (**7a**·HCl)*

Synthesis as described in Ref. [6].

*3.1.42. 1-{2-[(Hydroxymethyl)diphenylsilyl]ethyl}-piperidinium chloride (**7b**·HCl)*

Synthesis as described in Ref. [7].

*3.1.43. 1-{2-[(Hydroxymethyl)diphenylgermyl]ethyl}-piperidinium chloride (**7c**·HCl)*

Synthesis as described in Ref. [3].

*3.1.44. 1-(4-Hydroxy-3,3-diphenylbutyl)-1-methyl-piperidinium iodide (**8a**)*

Synthesis as described in Ref. [6].

*3.1.45. 1-{2-[(Hydroxymethyl)diphenylsilyl]ethyl}-1-methylpiperidinium iodide (**8b**)*

Synthesis as described in Ref. [7].

*3.1.46. 1-{2-[(Hydroxymethyl)diphenylgermyl]ethyl}-1-methylpiperidinium iodide (**8c**)*

Synthesis as described in Ref. [3].

*3.1.47. Phenylacetonitrile (**9**)*

This compound was commercially available (Aldrich).

*3.1.48. rac-Cyclopentyl(phenyl)acetonitrile (rac-**10**)*

Freshly distilled **9** (62.7 g, 535 mmol) was added dropwise at 0 °C within 10 min to a stirred suspension of $NaNH_2$ (21.6 g, 554 mmol) in Et_2O (250 ml) and the resulting mixture heated under reflux for 2 h. After cooling to 0 °C, cyclopentyl bromide (79.7 g, 535 mmol) was added and the mixture heated under reflux for 1 h, followed by the addition of water (250 ml) at r.t.. The organic phase was separated and the aqueous layer extracted with Et_2O (2×100 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure and the residue distilled in vacuo (Vigreux column) to give *rac*-**10** in 79% yield as a colorless liquid (78.8 g, 425 mmol); b.p. 84 °C/0.01 mbar. The product crystallized on cooling; m.p. 45–46 °C. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.2–1.9 and 2.2–2.3 (m, 9H, C_5H_9), 3.63 (d, $^3J_{HH} = 7.6$ Hz, 1H, CHCN), 7.2–7.4 (m, 5H, C_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 24.8 (CCH_2C, C_5H_9), 24.9 (CCH_2C, C_5H_9), 30.2 (CCH_2C, C_5H_9), 30.9 (CCH_2C, C_5H_9), 42.5 (C-1, C_5H_9, or *C*CN), 45.2 (C-1, C_5H_9, or *C*CN), 120.5 (C*C*N), 127.6 (C-2/C-6, C_6H_5), 127.9 (C-4, C_6H_5), 128.9 (C-3/C-5, C_6H_5), 135.9 (C-1, C_6H_5). Anal. Found: C, 84.1; H, 8.1; N, 7.6. Calc. for $C_{13}H_{15}N$ ($M_r = 185.3$): C, 84.28; H, 8.16; N, 7.56%.

*3.1.49. rac-2-Cyclopentyl-2-phenyl-4-(piperidin-1-yl)-butyronitrile (rac-**11**)*

A stirred mixture of *rac*-**10** (78.8 g, 425 mmol), 1-(2-chloroethyl)piperidinium chloride (78.3 g, 425 mmol), $NaNH_2$ (33.2 g, 851 mmol), and toluene (1 l) was heated until NH_3 was evolved (60–65 °C) and the temperature was then maintained at 60 °C. After the evolution of NH_3 was complete, the mixture was stirred for another 2 h at 65 °C and then heated under reflux for 4 h. After cooling to 0 °C, water (500 ml) was added and the mixture stirred for 5 min. The organic phase was separated and the aqueous layer extracted with toluene (3×170 ml). The combined organic phases were extracted with 2.0 M hydrochloric acid (3×300 ml), and the pH of the combined aqueous solutions was adjusted to 10–12 by the addition of a 2.0 M aqueous NaOH solution. This mixture was extracted with Et_2O (3×400 ml), and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue distilled in vacuo to give *rac*-**11** in 85% yield as a colorless oily liquid (107 g, 361 mmol); b.p. 148 °C/0.01 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.1–2.3 (m, 23H, CCH_2C, $CCHC_2$, CCH_2N), 7.1–7.3 (m, 5H, C_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 24.2 (CCH_2C), 24.7 (CCH_2C), 25.3 (CCH_2C), 25.8 (C-3/C-5, NC_5H_{10}), 29.1 (CCH_2C), 29.2 (CCH_2C), 36.4 (CCH_2C), 50.3 (C-1, C_5H_9), 51.2 (*C*CN), 54.7 (C-2/C-6, NC_5H_{10}), 55.2 (CCH_2CH_2N), 121.2 (C*C*N), 126.0 (C-2/

C-6, C_6H_5), 127.4 (C-4, C_6H_5), 128.6 (C-3/C-5, C_6H_5), 138.5 (C-1, C_6H_5). Anal. Found: C, 80.6; H, 9.8; N, 9.3. Calc. for $C_{20}H_{28}N_2$ ($M_r = 296.5$): C, 81.03; H, 9.52; N, 9.45%.

3.1.50. *rac*-2-Cyclopentyl-2-phenyl-4-(piperidin-1-yl)-butyric acid (*rac*-**12**)

A solution of *rac*-**11** (29.7 g, 100 mmol) in a mixture of sulfuric acid, AcOH, and water [1:1:1 (v/v/v)] (150 ml) was stirred under reflux for seven days. After the hydrolysis was complete (GC control), the mixture was cooled to 0 °C and the pH adjusted to 5–6 by the addition of 2.0 M aqueous NaOH solution. The resulting precipitate was isolated by filtration, washed with water (3 × 500 ml), and then dried in vacuo to give *rac*-**12** in 99% as a colorless crystalline solid (31.2 g, 98.9 mmol); m.p. 251 °C. Owing to the insolubility of *rac*-**12** in acetone, MeOH, toluene, Et_2O, $CHCl_3$, Me_2SO, and water, NMR data could not be obtained. Anal. Found: C, 75.9; H, 9.4; N, 4.4. Calc. for $C_{20}H_{29}NO_2$ ($M_r = 315.5$): C, 76.15; H, 9.27; N, 4.44%.

3.1.51. Ethyl 4-bromobutyrate (**13**)

This compound was commercially available (Aldrich).

3.1.52. Ethyl 4-(piperidin-1-yl)butyrate (**14**)

A stirred solution of **13** (51.7 g, 265 mmol) and piperidine (89.2 g, 1.05 mol) in toluene (300 ml) was heated under reflux for 4 h. After cooling to r.t., the resulting precipitate was filtered off and washed with Et_2O (100 ml). The filtrate and the wash solutions were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue distilled in vacuo (Vigreux column) to give **14** in 85% yield as a colorless liquid (45.0 g, 226 mmol); b.p. 68 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.18 (t, $^3J_{HH} = 7.2$ Hz, 3H, CCH_3), 1.3–1.6, 1.7–1.8, and 2.2–2.4 (m, 16H, CCH_2C, CCH_2N), 4.04 (q, $^3J_{HH} = 7.2$ Hz, 2H, CCH_2O). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 14.1 (CCH_3), 22.1 (C-4, NC_5H_{10}), 24.3 ($CCH_2CH_2CH_2N$), 25.9 (C-3/C-5, NC_5H_{10}), 32.3 ($CCH_2CH_2CH_2N$), 54.4 (C-2/C-6, NC_5H_{10}), 58.4 ($CCH_2CH_2CH_2N$), 60.1 (CCH_2O), 173.5 (C=O). Anal. Found: C, 66.4; H, 10.8; N, 7.1. Calc. for $C_{11}H_{21}NO_2$ ($M_r = 199.3$): C, 66.29; H, 10.62; N, 7.03%.

3.1.53. Ethyl *rac*-2-cyclopentyl-4-(piperidin-1-yl)-butanoate (*rac*-**15**)

Compound **14** (26.8 g, 134 mmol) was added at −78 °C within 5 min to a stirred solution of lithium diisopropylamide in THF–*n*-hexane [prepared from a solution of diisopropylamine (14.3 g, 141 mmol) in THF (350 ml) and a 1.6 M solution of *n*-butyllithium (88.6 ml, 142 mmol of *n*-BuLi) in *n*-hexane]. After the mixture was stirred for 1 h at −78 °C, a solution of cyclopentyl bromide (21.1 g, 142 mmol) in HMPTA (25.4 g, 142 mmol) was added within 5 min. After the mixture was stirred for 18 h at r.t., Et_2O (200 ml) and a saturated aqueous NH_4Cl solution (60 ml) was added. The organic phase was separated and the aqueous layer extracted with Et_2O (2 × 100 ml). After drying the combined organic extracts over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue distilled in vacuo (Vigreux column) to give *rac*-**15** in 27% yield as a colorless liquid (9.67 g, 36.2 mmol); b.p. 125 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.0–2.5 (m, 24H, CCH_2C, C_3CH, CCH_2N), 1.22 (t, 3H, $^3J_{HH} = 7.1$ Hz, CCH_3), 4.0–4.2 (m, 2H, CCH_2O). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 14.3 (CCH_3), 24.3 (C-4, NC_5H_{10}), 25.0 (C-3/C-5, NC_5H_{10}), 25.8 (2C, CCH_2C, C_5H_9), 28.7 [$CHCH_2CH_2N$], 30.6 (CCH_2C, C_5H_9), 30.8 (CCH_2C, C_5H_9), 42.9 (C-1, C_5H_9), 50.0 (CC=O), 54.6 (C-2/C-6, NC_5H_{10}), 57.5 [$CHCH_2CH_2N$], 60.0 (CCH_2O), 175.8 (C=O). Anal. Found: C, 71.8; H, 10.8; N, 5.1. Calc. for $C_{16}H_{29}NO_2$ ($M_r = 267.4$): C, 71.87; H, 10.93; N, 5.24%.

3.1.54. Ethyl 2,2-dicyclopentyl-4-(piperidin-1-yl)-butyrate (**16**)

This compound was prepared analogous to the synthesis of *rac*-**15** from *rac*-**15** (9.57 g, 35.8 mmol), a solution of lithium diisopropylamide in THF–*n*-hexane [prepared from a solution of diisopropylamine (3.83 g, 37.8 mmol) in THF (80 ml) and a 1.5 M solution of *n*-butyllithium (25.2 ml, 37.8 mmol of *n*-BuLi) in *n*-hexane], and a solution of cyclopentyl bromide (5.63 g, 37.8 mmol) in HMPTA (6.77 g, 37.8 mmol). Compound **16** was isolated in 19% yield as a colorless liquid (2.33 g, 6.94 mmol); b.p. 152 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.21 (t, 3H, $^3J_{HH} = 7.0$ Hz, CCH_3), 1.3–2.7 (m, 32H, CCH_2C, C_3CH, CCH_2N), 4.07 (q, $^3J_{HH} = 7.0$ Hz, 2H, CCH_2O). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 14.3 (CCH_3), 24.4 (C-4, NC_5H_{10}) 25.1 (C-3/C-5, NC_5H_{10}), 25.5 (CCH_2C, C_5H_9), 25.9 (CCH_2C, C_5H_9), 28.3 (CCH_2C, C_5H_9), 28.5 (CCH_2C, C_5H_9), 30.2 (CCH_2CH_2N), 45.9 (C-1, C_5H_9), 52.2 (CC=O), 54.8 (C-2/C-6, NC_5H_{10}), 56.0 (CCH_2CH_2N), 59.6 (CCH_2O), 175.8 (C=O). Anal. Found: C, 74.9; H, 11.3; N, 4.1. Calc. for $C_{21}H_{37}NO_2$ ($M_r = 335.5$): C, 75.17; H, 11.11; N, 4.17%.

3.1.55. (Chloromethyl)trimethoxysilane (**17**)

Synthesis as described in Ref. [15].

3.1.56. (Chloromethyl)cyclopentyldimethoxysilane (**18**)

A 1.9 M solution of cyclopentylmagnesium chloride in Et_2O (225 ml, 428 mmol of *c*-C_5H_9MgCl) was added dropwise at r.t. within 100 min to a stirred solution of **17** (68.3 g, 400 mmol) in Et_2O (400 ml). The mixture was stirred at r.t. for 16 h and then heated under reflux

for 6 h. The precipitate was filtered off and washed with Et_2O (3 × 200 ml), and the filtrate and wash solutions were combined. The solvent was removed by distillation at atmospheric pressure and *n*-pentane (300 ml) added to the residue. The resulting precipitate was filtered off, the filtrate concentrated under reduced pressure, and the residue distilled in vacuo (Vigreux column) to give **18** in 67% yield as a colorless liquid (55.8 g, 267 mmol); b.p. 65 °C/1 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.1–1.3, 1.4–1.7, and 1.7–1.8 (m, 9H, SiC_5H_9), 2.81 (s, 2H, $SiCH_2Cl$), 3.59 (s, 6H, OCH_3). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 22.2 (C-1, SiC_5H_9), 24.9 ($SiCH_2Cl$), 26.8 (CCH_2C), 27.1 (CCH_2C), 51.2 (OCH_3). Anal. Found: C, 45.4; H, 8.3. Calc. for $C_8H_{17}ClO_2Si$ (M_r = 208.8): C, 46.03; H, 8.21%.

3.1.57. *rac*-(Chloromethyl)cyclopentyl(methoxy)-phenylsilane (*rac*-**19**)

A 2.0 M solution of phenylmagnesium chloride in Et_2O (140 ml, 280 mmol of C_6H_5MgCl) was added dropwise at r.t. within 2 h to a stirred solution of **18** (54.4 g, 261 mmol) in Et_2O (200 ml). The mixture was stirred at r.t. for 14 h and then heated under reflux for 5 h. The precipitate was filtered off and washed with Et_2O (3 × 200 ml), and the filtrate and wash solutions were combined. The solvent was removed by distillation at atmospheric pressure and *n*-pentane (300 ml) added to the residue. The resulting precipitate was filtered off, the filtrate concentrated under reduced pressure, and the residue distilled in vacuo (Vigreux column) to give **19** in 68% yield as a colorless liquid (44.9 g, 176 mmol); b.p. 90 °C/0.05 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.4–2.0 (m, 9H, SiC_5H_9), 3.12 (δ_A) and 3.14 (δ_B) (AB system, J_{AB} = 14.1 Hz, 2H, $SiCH_2Cl$), 3.63 (s, 3H, OCH_3), 7.3–7.7 (m, 5H, SiC_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 23.1 (C-1, SiC_5H_9), 26.83 (CCH_2C) 26.85 (CCH_2C), 26.9 ($SiCH_2Cl$), 27.5 (2C, CCH_2C), 52.0 (OCH_3), 128.0 (C-3/C-5, SiC_6H_5), 130.2 (C-4, SiC_6H_5), 132.9 (C-1, SiC_6H_5), 134.3 (C-2/C-6, SiC_6H_5). $C_{13}H_{19}ClOSi$ (M_r = 254.8). For an alternative synthesis of compound *rac*-**19**, see Ref. [15].

3.1.58. *rac*-(Chloromethyl)cyclopentyl(phenyl)vinylsilane (*rac*-**20**)

A 1.7 M solution of vinylmagnesium chloride in THF (115 ml, 196 mmol of CH_2=CHMgCl) was added dropwise at r.t. within 1.5 h to a stirred solution of *rac*-**19** (44.2 g, 173 mmol) in THF (300 ml). After the mixture was stirred at r.t. for 16 h and heated under reflux for 6 h, a saturated aqueous NH_4Cl solution (500 ml) was added to the reaction mixture at 0 °C. The organic phase was separated and the aqueous layer extracted with Et_2O (3 × 350 ml), and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue distilled in vacuo (Vigreux column) to give *rac*-**20** in 74% yield as a colorless liquid (32.0 g, 128 mmol); b.p. 92 °C/0.02 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.4–2.0 (m, 9H, SiC_5H_9), 3.14 (s, 2H, $SiCH_2Cl$), 5.92 (δ_A), 6.25 (δ_B), and 6.29 (δ_C) (ABC system, J_{AB} = 15.0 Hz, J_{AC} = 20.6 Hz, J_{BC} = 3.4 Hz, 3H, $SiCH_A$=CH_BH_C), 7.3–7.5 and 7.5–7.7 (m, 5H, SiC_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 22.1 (C-1, SiC_5H_9), 26.9 (CCH_2C, SiC_5H_9), 27.0 (CCH_2C), 27.9 ($SiCH_2Cl$), 28.1 (CCH_2C), 28.2 (CCH_2C), 127.9 (C-3/C-5, SiC_6H_5), 129.7 (C-4, SiC_6H_5), 132.0 (SiCH=CH_2), 133.3 (C-1, SiC_6H_5), 135.0 (C-2/C-6, SiC_6H_5), 136.5 (SiCH=CH_2). ^{29}Si-NMR (79.5 MHz, $CDCl_3$): δ −10.9. Anal. Found: C, 67.2; H, 7.9. Calc. for $C_{14}H_{19}ClSi$ (M_r = 250.8): C, 67.04; H, 7.63%.

3.1.59. *rac*-(Acetoxymethyl)cyclopentyl(phenyl)-vinylsilane (*rac*-**21**)

A mixture of *rac*-**20** (37.6 g, 150 mmol) and AcONa (15.6 g, 190 mmol) in DMF (200 ml) was stirred under reflux for 5 h. After cooling to r.t., the precipitate was filtered, the solvent of the filtrate was removed under reduced pressure, and the residue distilled in vacuo (Vigreux column) to give *rac*-**21** in 81% yield as a colorless liquid (33.3 g, 121 mmol); b.p. 106–108 °C/0.01 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.3–1.9 (m, 9H, SiC_5H_9), 2.01 (s, 3H, CCH_3), 4.15 (s, 2H, $SiCH_2O$), 5.87 (δ_A), 6.20 (δ_B), and 6.22 (δ_C) (ABC system, J_{AB} = 15.0 Hz, J_{AC} = 20.5 Hz, J_{BC} = 3.4 Hz, 3H, $SiCH_A$=CH_BH_C), 7.3–7.4 and 7.5–7.6 (m, 5H, SiC_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 20.9 (CCH_3), 22.3 (C-1, SiC_5H_9), 26.9 (CCH_2C), 27.0 (CCH_2C), 28.1 (CCH_2C), 28.2 (CCH_2C), 54.2 ($SiCH_2O$), 127.9 (C-3/C-5, SiC_6H_5), 129.6 (C-4, SiC_6H_5), 132.2 (SiCH=CH_2), 133.6 (C-1, SiC_6H_5), 134.9 (C-2/C-6, SiC_6H_5), 136.1 (SiCH=CH_2), 171.8 (C=O). ^{29}Si-NMR (79.5 MHz, $CDCl_3$): δ −12.8. Anal. Found: C, 69.7; H, 8.3. Calc. for $C_{16}H_{22}O_2Si$ (M_r = 274.4): C, 70.03; H, 8.08%.

3.1.60. *rac*-(Hydroxymethyl)cyclopentyl(phenyl)-vinylsilane (*rac*-**22**)

A solution of *rac*-**21** (33.2 g, 121 mmol) in Et_2O (250 ml) was added dropwise at −30 °C within 2 h to a stirred suspension of lithium aluminum hydride (9.60 g, 253 mmol) in Et_2O (400 ml). The mixture was stirred at −30 °C for 1 h and then added in 20 ml portions to ice-cold hydrochloric acid (18%, 1 l). The organic phase was separated and the aqueous layer extracted with Et_2O (3 × 400 ml), and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue distilled in vacuo (Vigreux column) to give *rac*-**22** in 88% yield as a colorless liquid (24.7 g, 106 mmol); b.p. 99 °C/0.005 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.1 (br s, 1H, OH), 1.3–2.0 (m, 9H, SiC_5H_9), 3.78 (s, 2H, $SiCH_2O$), 5.93 (δ_A), 6.23 (δ_B), and 6.28 (δ_C) (ABC

system, $J_{AB} = 15.0$ Hz, $J_{AC} = 20.6$ Hz, $J_{BC} = 3.5$ Hz, 3H, $SiCH_A{=}CH_BH_C$), 7.3–7.4 and 7.5–7.7 (m, 5H, SiC_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 22.1 (C-1, SiC_5H_9), 26.9 (CCH_2C), 27.0 (CCH_2C), 28.2 (CCH_2C), 28.3 (CCH_2C), 52.6 ($SiCH_2O$), 127.0 (C-3/C-5, SiC_6H_5), 129.6 (C-4, SiC_6H_5), 132.7 ($SiCH{=}CH_2$), 134.0 (C-1, SiC_6H_5), 135.0 (C-2/C-6, SiC_6H_5), 136.2 ($SiCH{=}CH_2$). ^{29}Si-NMR (79.5 MHz, $CDCl_3$): δ −12.1. Anal. Found: C, 71.8; H, 8.6. Calc. for $C_{14}H_{20}OSi$ ($M_r = 232.4$): C, 72.36; H, 8.67%.

3.1.61. *rac*-Cyclopentyl(phenyl)[(trimethylsilyloxy)methyl]vinylsilane (*rac*-**23**)

A solution of chlorotrimethylsilane (36.0 g, 331 mmol) in *n*-pentane (200 ml) was added dropwise at −40 °C within 1 h to a stirred solution of *rac*-**22** (24.5 g, 105 mmol) and Et_3N (12.5 g, 124 mmol) in *n*-pentane (350 ml). The mixture was warmed to r.t. and then stirred for 16 h. The precipitate was filtered off, the solvent of the filtrate removed under reduced pressure, and the residue distilled in vacuo (Vigreux column) to give *rac*-**23** in 74% yield as a colorless liquid (23.9 g, 78.5 mmol); b.p. 88–90 °C/0.01 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 0.06 (s, 9H, $SiCH_3$), 1.3–2.0 (m, 9H, SiC_5H_9), 3.66 (s, 2H, $SiCH_2O$), 5.86 (δ_A), 6.16 (δ_B), and 6.27 (δ_C) (ABC system, $J_{AB} = 15.0$ Hz, $J_{AC} = 20.6$ Hz, $J_{BC} = 3.8$ Hz, 3H, $SiCH_A{=}CH_BH_C$), 7.3–7.5 and 7.5–7.7 (m, 5H, SiC_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ −0.9 ($SiCH_3$), 22.3 (C-1, SiC_5H_9), 27.0 (CCH_2C), 27.1 (CCH_2C), 28.2 (CCH_2C), 28.3 (CCH_2C), 52.2 ($SiCH_2O$), 127.6 (C-3/C-5, SiC_6H_5), 129.2 (C-4, SiC_6H_5), 133.5 ($SiCH{=}CH_2$), 135.1 (C-1, SiC_6H_5), 135.2 (C-2/C-6, SiC_6H_5), 135.3 ($SiCH{=}CH_2$). ^{29}Si-NMR (79.5 MHz, $CDCl_3$): δ −13.9 (SiC_5H_9), 19.2 ($SiCH_3$). Anal. Found: C, 66.4, H, 9.5. Calc. for $C_{17}H_{28}OSi_2$ ($M_r = 304.6$): C, 67.04; H, 9.27%.

3.1.62. Trichloro(chloromethyl)germane (**24**)

Synthesis as described in Ref. [16].

3.1.63. Dichloro(chloromethyl)cyclopentylgermane (**25**)

A 3.05 M solution of cyclopentylmagnesium chloride in Et_2O (119 ml, 363 mmol of *c*-C_5H_9MgCl) was added dropwise at −20 °C within 1.5 h to a stirred solution of **24** (83.0 g, 363 mmol) in Et_2O (1.5 l). The mixture was stirred at r.t. for 16 h and then heated under reflux for 4 h. The precipitate was filtered off and washed with Et_2O (5 × 200 ml), and the filtrate and wash solutions were combined. The solvent was removed by distillation at atmospheric pressure and *n*-pentane (200 ml) added to the residue. The resulting precipitate was filtered off, the filtrate concentrated under reduced pressure, and the residue distilled in vacuo (Vigreux column) to give **25** in 56% yield as a colorless liquid (53.3 g, 203 mmol); b.p. 115 °C/12 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.4–2.3 (m, 9H, GeC_5H_9), 3.50 (s, 2H, $GeCH_2Cl$). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 25.9 (CCH_2C), 27.4 (CCH_2C), 33.8 ($GeCH_2Cl$), 34.9 (C-1, GeC_5H_9). Anal. Found: C, 27.8; H, 4.1. Calc. for $C_6H_{11}Cl_3Ge$ ($M_r = 262.1$): C, 27.49; H, 4.23%.

3.1.64. *rac*-Chloro(chloromethyl)cyclopentyl(phenyl)germane (*rac*-**26**)

A 2.23 M solution of phenylmagnesium chloride in THF (60.1 ml, 134 mmol of C_6H_5MgCl) was added dropwise at 0 °C within 2 h to a stirred solution of **25** (35.0 g, 134 mmol) in Et_2O (1 l). After the mixture was stirred at r.t. for three days and heated under reflux for 4 h, the precipitate was filtered off and the solvent removed by distillation at atmospheric pressure. The residue was distilled in vacuo (Vigreux column) to give *rac*-**26** in 87% yield as a colorless liquid (35.4 g, 117 mmol); b.p. 114 °C/0.01 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.6–2.2 (m, 9H, GeC_5H_9), 3.46 (δ_A) and 3.49 (δ_B) (AB system, $J_{AB} = 14.4$ Hz, 2H, $GeCH_2Cl$), 7.4–7.5 and 7.6–7.8 (m, 5H, GeC_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 26.0 (CCH_2C), 26.1 (CCH_2C), 27.9 (CCH_2C), 28.0 (CCH_2C), 28.9 (C-1, GeC_5H_9), 30.2 ($GeCH_2Cl$), 128.5 (C-3/C-5, GeC_6H_5), 130.4 (C-4, GeC_6H_5), 133.3 (C-1, GeC_6H_5), 134.3 (C-2/C-6, GeC_6H_5). Anal. Found: C, 47.3; H, 5.1. Calc. for $C_{12}H_{16}Cl_2Ge$ ($M_r = 303.8$): C, 47.45; H, 5.31%.

3.1.65. *rac*-(Chloromethyl)cyclopentyl(phenyl)vinylgermane (*rac*-**27**)

A 1.7 M solution of vinylmagnesium chloride in THF (84.7 ml, 144 mmol of $CH_2{=}CHMgCl$) was added dropwise at r.t. within 1.5 h to a stirred solution of *rac*-**26** (35.0 g, 115 mmol) in toluene (150 ml) and the mixture heated under reflux for 1 h. After cooling to 0 °C, a half-saturated aqueous NH_4Cl solution (190 ml) was added. The organic phase was separated and the aqueous layer extracted with Et_2O (3 × 150 ml), and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue distilled in vacuo (Vigreux column) to give *rac*-**27** in 81% yield as a colorless liquid (27.7 g, 93.8 mmol); b.p. 110 °C/0.01 mbar. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 1.5–2.1 (m, 9H, GeC_5H_9), 3.30 (δ_A) and 3.34 (δ_B) (AB system, $J_{AB} = 12.8$ Hz, 2H, $GeCH_2Cl$), 5.85 (δ_A), 6.24 (δ_B), and 6.41 (δ_C) (ABC system, $J_{AB} = 13.6$ Hz, $J_{AC} = 20.0$ Hz, $J_{BC} = 3.0$ Hz, 3H, $GeCH_A{=}CH_BH_C$), 7.3–7.5 and 7.5–7.6 (m, 5H, GeC_6H_5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 25.1 (C-1, GeC_5H_9), 26.1 (CCH_2C), 26.2 (CCH_2C) 28.0 ($GeCH_2Cl$), 28.8 (CCH_2C), 28.9 (CCH_2C), 128.1 (C-3/C-5, GeC_6H_5), 129.0 (C-4, GeC_6H_5), 132.9 ($GeCH{=}CH_2$), 134.1 ($GeCH{=}CH_2$), 134.3 (C-2/C-6, GeC_6H_5), 135.8 (C-1, GeC_6H_5). Anal. Found: C, 56.6; H, 6.6. Calc. for $C_{14}H_{19}ClGe$ ($M_r = 295.4$): C, 56.93; H, 6.48%.

*3.1.66. rac-(Acetoxymethyl)cyclopentyl(phenyl)vinylgermane (rac-**28**)*

This compound was prepared from *rac*-**27** (27.5 g, 93.1 mmol) analogous to the synthesis of *rac*-**21** and isolated in 93% yield as a colorless liquid (27.6 g, 86.5 mmol); b.p. 120 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.4–2.0 (m, 9H, GeC_5H_9), 1.98 (s, 3H, CCH_3), 4.34 (s, 2H, $GeCH_2O$), 5.77 (δ_A), 6.16 (δ_B), and 6.35 (δ_C) (ABC system, $J_{AB} = 13.6$ Hz, $J_{AC} = 20.0$ Hz, $J_{BC} = 3.4$ Hz, 3H, $GeCH_A{=}CH_BH_C$), 7.3–7.4 and 7.4–7.5 (m, 5H, GeC_6H_5). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 20.8 (CCH_3), 25.2 (C-1, GeC_5H_9), 26.17 (CCH_2C), 26.22 (CCH_2C), 28.8 (CCH_2C), 28.9 (CCH_2C), 55.6 ($GeCH_2O$), 128.0 (C-3/C-5, GeC_6H_5), 128.8 (C-4, GeC_6H_5), 133.3 ($GeCH{=}CH_2$), 133.7 ($GeCH{=}CH_2$), 134.4 (C-2/C-6, GeC_6H_5), 136.1 (C-1, GeC_6H_5), 171.6 (CCH_3). Anal. Found: C, 59.9; H, 7.0. Calc. for $C_{16}H_{22}GeO_2$ ($M_r = 319.0$): C, 60.25; H, 6.95%.

*3.1.67. rac-Cyclopentyl(hydroxymethyl)phenyl(vinyl)germane (rac-**29**)*

This compound was prepared from *rac*-**28** (27.0 g, 84.7 mmol) analogous to the synthesis of *rac*-**22** and isolated in 92% yield as a colorless liquid (21.6 g, 78.0 mmol); b.p. 107 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.4–2.0 (m, 9H, GeC_5H_9), 3.99 (s, 2H, $GeCH_2O$), 5.83 (δ_A), 6.21 (δ_B), and 6.41 (δ_C) (ABC system, $J_{AB} = 13.6$ Hz, $J_{AC} = 20.0$ Hz, $J_{BC} = 3.4$ Hz, 3H, $GeCH_A{=}CH_BH_C$), 7.3–7.4 and 7.5–7.6 (m, 5H, GeC_6H_5). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 24.8 (C-1, GeC_5H_9), 26.10 (CCH_2C), 26.15 (CCH_2C), 28.95 (CCH_2C), 29.00 (CCH_2C), 53.7 ($GeCH_2O$), 128.0 (C-3/C-5, GeC_6H_5), 128.7 (C-4, GeC_6H_5), 133.7 (2C, $GeCH{=}CH_2$), 134.4 (C-2/C-6, GeC_6H_5), 136.6 (C-1, GeC_6H_5). Anal. Found: C, 60.9; H, 7.5. Calc. for $C_{14}H_{20}GeO$ ($M_r = 276.9$): C, 60.72; H, 7.28%.

*3.1.68. rac-Cyclopentyl(phenyl)[(trimethylsilyloxy)methyl]vinylgermane (rac-**30**)*

This compound was prepared from *rac*-**29** (21.3 g, 76.9 mmol) analogous to the synthesis of *rac*-**23** and isolated in 92% yield as a colorless liquid (24.7 g, 70.8 mmol); b.p. 91 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 0.08 (s, 9H, $SiCH_3$), 1.4–2.0 (m, 9H, GeC_5H_9), 3.92 (s, 2H, $GeCH_2O$), 5.77 (δ_A), 6.15 (δ_B), and 6.39 (δ_C) (ABC system, $J_{AB} = 13.6$ Hz, $J_{AC} = 20.0$ Hz, $J_{BC} = 3.4$ Hz, 3H, $GeCH_A{=}CH_BH_C$), 7.3–7.4 and 7.5–7.6 (m, 5H, GeC_6H_5). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ −0.9 ($SiCH_3$), 25.1 (C-1, GeC_5H_9), 26.28 (CCH_2C), 26.33 (CCH_2C), 29.0 (CCH_2C), 29.1 (CCH_2C), 53.6 ($GeCH_2O$), 127.8 (C-3/C-5, GeC_6H_5), 128.5 (C-4, GeC_6H_5), 133.1 ($GeCH{=}CH_2$), 134.6 (C-2/C-6, GeC_6H_5), 134.7 ($GeCH{=}CH_2$), 137.9 (C-1, GeC_6H_5). Anal. Found: C, 58.8; H, 8.3. Calc. for $C_{17}H_{28}GeOSi$ ($M_r = 349.1$): C, 58.49; H, 8.08%.

*3.1.69. Dicyclopentyldimethoxysilane (**31**)*

This compound was commercially available (Wacker-Chemie).

*3.1.70. Dicyclopentyl(methoxy)vinylsilane (**32**)*

A 1.7 M solution of vinylmagnesium chloride in THF (110 ml, 187 mmol of $CH_2{=}CHMgCl$) was added dropwise at r.t. within 1.5 h to a stirred solution of **31** (40.0 g, 175 mmol) in THF (300 ml). The mixture was stirred at r.t. for 16 h and then heated under reflux for 6 h. The precipitate was filtered off and washed with Et_2O (3 × 200 ml), and the filtrate and wash solutions were combined. The solvent was removed by distillation at atmospheric pressure and *n*-pentane (300 ml) added to the residue. The resulting precipitate was filtered off, the filtrate concentrated under reduced pressure, and the residue distilled in vacuo (Vigreux column) to give *rac*-**32** in 74% yield as a colorless liquid (29.0 g, 129 mmol); b.p. 75 °C/0.03 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.0–1.2 (m, 2H, $SiCHC_2$), 1.3–1.6 and 1.7–1.9 (m, 16H, CCH_2C), 3.50 (s, 3H, OCH_3), 5.84 (δ_A), 6.04 (δ_C), and 6.08 (δ_B) (ABC system, $J_{AB} = 15.2$ Hz, $J_{AC} = 21.1$ Hz, $J_{BC} = 3.5$ Hz, 3H, $SiCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 23.9 (C-1, SiC_5H_9), 26.96 (CCH_2C), 27.00 (CCH_2C), 27.75 (CCH_2C), 27.77 (CCH_2C), 51.6 (OCH_3), 133.7 ($SiCH{=}CH_2$), 134.5 ($SiCH{=}CH_2$). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ 5.56. Anal. Found: C, 69.6; H, 10.5. Calc. for $C_{13}H_{24}OSi$ ($M_r = 224.4$): C, 69.58; H, 10.78%.

*3.1.71. Chlorodicyclopentyl(vinyl)silane (**33**)*

A mixture of **32** (10.0 g, 44.6 mmol) and thionyl chloride (40.0 g, 336 mmol) was heated under reflux for 6 h. The excess $SOCl_2$ was removed under reduced pressure and the residue distilled in vacuo (Vigreux column) to give **33** in 83% yield as a colorless liquid (8.50 g, 37.1 mmol); b.p. 75 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.2–1.3 (m, 2H, $SiCHC_2$), 1.3–1.7 and 1.7–1.9 (m, 16H, CCH_2C), 5.94 (δ_A), 6.08 (δ_C), and 6.12 (δ_B) (ABC system, $J_{AB} = 14.8$ Hz, $J_{AC} = 20.3$ Hz, $J_{BC} = 3.4$ Hz, 3H, $SiCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 25.6 (C-1, SiC_5H_9), 26.9 (CCH_2C), 27.66 (CCH_2C), 27.71 (CCH_2C), 132.5 ($SiCH{=}CH_2$), 135.7 ($SiCH{=}CH_2$). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ 4.88. Anal. Found: C, 62.6; H, 9.1. Calc. for $C_{12}H_{21}ClSi$ ($M_r = 228.8$): C, 62.98; H, 9.25%.

*3.1.72. (Chloromethyl)dicyclopentyl(vinyl)silane (**34**)*

A cooled (−78 °C) 1.6 M solution of *n*-butyllithium in *n*-hexane (28.0 ml, 44.8 mmol of *n*-BuLi) was added dropwise at −75 °C (internal temperature) within 30 min to a stirred solution of **33** (10.0 g, 43.7 mmol) and bromochloromethane (5.80 g, 44.8 mmol) in THF (150 ml) (careful temperature control). After the addition was complete, the reaction mixture was stirred at −75 °C for 30 min and then allowed to warm to r.t.

within 15 h. Et_2O (100 ml) and a half-saturated aqueous NH_4Cl solution (75 ml) were added, and the organic phase was separated and the aqueous layer extracted with Et_2O (2 × 75 ml). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure and the residue distilled in vacuo (Vigreux column). The distillate (b.p. 82–89 °C/0.03 mbar) was purified further by column chromatography on silica gel using Et_2O–*n*-hexane [1:20 (v/v)] as the eluent to give **34** in 73% yield as a colorless liquid (7.75 g, 31.9 mmol); b.p. 82–84 °C/0.02 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.1–1.3 (m, 2H, $SiCHC_2$), 1.3–1.7 and 1.7–1.9 (m, 16H, CCH_2C), 2.93 (s, 2H, $SiCH_2Cl$), 5.78 (δ_A), 6.05 (δ_C), and 6.08 (δ_B) (ABC system, $J_{AB} = 15.1$ Hz, $J_{AC} = 20.7$ Hz, $J_{BC} = 3.5$ Hz, 3H, $SiCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 22.5 (C-1, SiC_5H_9), 27.2 (CCH_2C), 27.3 (CCH_2C), 27.6 ($SiCH_2Cl$), 28.65 (CCH_2C), 28.66 (CCH_2C), 133.0 ($SiCH{=}CH_2$), 135.3 ($SiCH{=}CH_2$). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ −4.3. Anal. Found: C, 64.4; H, 9.3. Calc. for $C_{13}H_{23}ClSi$ ($M_r = 242.9$): C, 64.29; H, 9.55%.

3.1.73. (Acetoxymethyl)dicyclopentyl(vinyl)silane (35)

This compound was prepared from **34** (20.0 g, 82.4 mmol) analogous to the synthesis of *rac*-**21** and isolated in 87% yield as a colorless liquid (19.1 g, 71.7 mmol); b.p. 81 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.0–1.2 (m, 2H, $SiCHC_2$), 1.3–1.7 and 1.7–1.9 (m, 16H, CCH_2C), 2.01 (s, 3H, CCH_3), 3.92 (s, 2H, $SiCH_2O$), 5.77 (δ_A), 6.03 (δ_C), and 6.05 (δ_B) (ABC system, $J_{AB} = 15.1$ Hz, $J_{AC} = 20.6$ Hz, $J_{BC} = 3.6$ Hz, 3H, $SiCH_A{=}CH_BH_C$). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 21.0 (CCH_3), 22.1 (C-1, SiC_5H_9), 26.9 (CCH_2C), 28.25 (CCH_2C), 28.31 (CCH_2C), 53.8 ($SiCH_2O$), 132.7 ($SiCH{=}CH_2$), 134.7 ($SiCH{=}CH_2$), 172.0 (C=O). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ −6.3. Anal. Found: C, 67.8; H, 9.5. Calc. for $C_{15}H_{26}O_2Si$ ($M_r = 266.5$): C, 67.62; H, 9.84%.

3.1.74. Dicyclopentyl(hydroxymethyl)vinylsilane (36)

This compound was prepared from **35** (15.0 g, 56.3 mmol) analogous to the synthesis of *rac*-**22** and isolated in 83% yield as a colorless liquid (10.5 g, 46.8 mmol); b.p. 86 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.0–1.2 (m, 2H, $SiCHC_2$), 1.3–1.7 and 1.7–1.9 (m, 16H, CCH_2C), 3.57 (s, 2H, $SiCH_2O$), 5.82 (δ_A), 6.07 (δ_C), and 6.09 (δ_B) (ABC system, $J_{AB} = 15.0$ Hz, $J_{AC} = 20.8$ Hz, $J_{BC} = 3.6$ Hz, 3H, $SiCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 22.0 (C-1, SiC_5H_9), 26.86 (CCH_2C), 26.89 (CCH_2C), 28.4 (CCH_2C), 28.5 (CCH_2C), 52.2 ($SiCH_2O$), 133.3 ($SiCH{=}CH_2$), 134.8 ($SiCH{=}CH_2$). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ −5.8. Anal. Found: C, 69.4; H, 10.3. Calc. for $C_{13}H_{24}OSi$ ($M_r = 224.4$): C, 69.58; H, 10.78%.

3.1.75. Dicyclopentyl[(trimethylsilyloxy)methyl]vinylsilane (37)

This compound was prepared from **36** (11.5 g, 51.2 mmol) analogous to the synthesis of *rac*-**23** and isolated in 88% yield as a colorless liquid (13.4 g, 45.2 mmol); b.p. 80–82 °C/0.04 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 0.05 (s, 9H, $SiCH_3$), 1.0–1.2 (m, 2H, $SiCHC_2$), 1.3–1.7 and 1.7–1.9 (m, 16H, CCH_2C), 3.42 (s, 2H, $SiCH_2O$), 5.75 (δ_A), 6.01 (δ_B), and 6.05 (δ_C) (ABC system, $J_{AB} = 15.0$ Hz, $J_{AC} = 20.7$ Hz, $J_{BC} = 3.9$ Hz, 3H, $SiCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ −0.9 ($SiCH_3$), 22.2 (C-1, SiC_5H_9), 26.96 (CCH_2C), 26.98 (CCH_2C), 28.3 (CCH_2C), 28.4 (CCH_2C), 51.3 ($SiCH_2O$), 133.7 ($SiCH{=}CH_2$), 134.3 ($SiCH{=}CH_2$). ^{29}Si-NMR (59.6 MHz, $CDCl_3$): δ −7.0 (SiC_5H_9), 18.5 ($SiCH_3$). Anal. Found: C, 64.5; H, 10.4. Calc. for $C_{16}H_{32}OSi_2$ ($M_r = 296.6$): C, 64.79; H, 10.87%.

3.1.76. Chloro(chloromethyl)dicyclopentylgermane (38)

This compound was prepared from **25** (18.3 g, 69.8 mmol) by treatment with a 1.7 M solution of cyclopentylmagnesium chloride in THF (41.1 ml, 69.9 mmol of *c*-C_5H_9MgCl) analogous to the synthesis of *rac*-**26** and isolated in 83% yield as a colorless liquid (17.2 g, 58.1 mmol); b.p. 100 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.4–2.1 (m, 18H, GeC_5H_9), 3.28 (s, 2H, $GeCH_2Cl$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 25.9 (CCH_2C), 26.2 (CCH_2C), 28.2 (CCH_2C), 28.3 (CCH_2C), 28.8 (C-1, GeC_5H_9), 29.4 ($GeCH_2Cl$). Anal. Found: C, 44.5; H, 6.7. Calc. for $C_{11}H_{20}Cl_2Ge$ ($M_r = 295.8$): C, 44.67; H, 6.82%.

3.1.77. (Chloromethyl)dicyclopentyl(vinyl)germane (39)

This compound was prepared from **38** (16.9 g, 57.1 mmol) analogous to the synthesis of *rac*-**27** and isolated in 84% yield as a colorless liquid (13.8 g, 48.0 mmol); b.p. 100 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.3–2.0 (m, 18H, GeC_5H_9), 3.07 (s, 2H, $GeCH_2Cl$), 5.68 (δ_A), 6.05 (δ_B), and 6.18 (δ_C) (ABC system, $J_{AB} = 13.6$ Hz, $J_{AC} = 20.0$ Hz, $J_{BC} = 3.4$ Hz, 3H, $GeCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 24.7 (C-1, GeC_5H_9), 26.15 (CCH_2C), 26.23 (CCH_2C), 27.6 ($GeCH_2Cl$), 29.1 (CCH_2C), 132.7 ($GeCH{=}CH_2$), 134.0 ($GeCH{=}CH_2$). Anal. Found: C, 54.2; H, 8.0. Calc. for $C_{13}H_{23}ClGe$ ($M_r = 287.4$): C, 54.33; H, 8.07%.

3.1.78. (Acetoxymethyl)dicyclopentyl(vinyl)germane (40)

This compound was prepared from **39** (13.3 g, 46.3 mmol) analogous to the synthesis of *rac*-**21** and isolated in 93% yield as a colorless liquid (13.4 g, 43.1 mmol); b.p. 109 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.2–1.9 (m, 18H, GeC_5H_9), 1.96 (s, 3H, CCH_3), 4.09 (s, 2H, $GeCH_2O$), 5.63 (δ_A), 5.98 (δ_B), and 6.13 (δ_C) (ABC system, $J_{AB} = 13.6$ Hz, $J_{AC} = 20.0$ Hz, $J_{BC} = 3.8$ Hz, 3H, $GeCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 20.8 (CCH_3), 24.6 (C-1, GeC_5H_9), 26.2

(CCH_2C), 29.0 (CCH_2C), 29.1 (CCH_2C), 54.9 ($GeCH_2O$), 132.4 ($GeCH{=}CH_2$), 134.1 ($GeCH{=}CH_2$), 171.7 (C=O). Anal. Found: C, 57.8; H, 8.5. Calc. for $C_{15}H_{26}GeO_2$ ($M_r = 311.0$): C, 57.93; H, 8.43%.

*3.1.79. Dicyclopentyl(hydroxymethyl)vinylgermane (**41**)*

This compound was prepared from **40** (13.0 g, 41.8 mmol) analogous to the synthesis of *rac*-**22** and isolated in 88% yield as a colorless liquid (9.91 g, 36.8 mmol); b.p. 112 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 1.1–2.0 (m, 18H, GeC_5H_9), 3.76 (s, 2H, $GeCH_2O$), 5.69 (δ_A), 6.05 (δ_B), and 6.18 (δ_C) (ABC system, $J_{AB} = 13.6$ Hz, $J_{AC} = 20.0$ Hz, $J_{BC} = 3.8$ Hz, 3H, $GeCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 24.3 (C-1, GeC_5H_9), 26.16 (CCH_2C), 26.18 (CCH_2C), 29.23 (CCH_2C), 29.27 (CCH_2C), 53.2 ($GeCH_2O$), 132.7 ($GeCH{=}CH_2$), 134.7 ($GeCH{=}CH_2$). Anal. Found: C, 57.8; H, 8.9. Calc. for $C_{13}H_{24}GeO$ ($M_r = 268.9$): C, 58.06; H, 8.99%.

*3.1.80. Dicyclopentyl[(trimethylsilyloxy)methyl]-vinylgermane (**42**)*

This compound was prepared from **41** (9.50 g, 35.3 mmol) analogous to the synthesis of *rac*-**23** and isolated in 94% yield as a colorless liquid (11.3 g, 33.1 mmol); b.p. 81 °C/0.01 mbar. ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ 0.05 (s, 9H, $SiCH_3$), 1.2–1.9 (m, 18H, GeC_5H_9), 3.68 (s, 2H, $GeCH_2O$), 5.65 (δ_A), 6.00 (δ_B), and 6.20 (δ_C) (ABC system, $J_{AB} = 14.0$ Hz, $J_{AC} = 20.0$ Hz, $J_{BC} = 3.8$ Hz, 3H, $GeCH_A{=}CH_BH_C$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ −0.9 ($SiCH_3$), 24.6 (C-1, GeC_5H_9), 26.4 (CCH_2C), 29.2 (CCH_2C), 29.3 (CCH_2C), 52.6 ($GeCH_2O$), 131.7 ($GeCH{=}CH_2$), 135.9 ($GeCH{=}CH_2$). Anal. Found: C, 56.1; H, 9.4. Calc. for $C_{16}H_{32}GeOSi$ ($M_r = 341.1$): C, 56.34; H, 9.46%.

3.2. Single-crystal X-ray diffraction studies

Suitable single crystals of 2(*S*)-**3a**·(*R*,*R*)-HOOC–CHR–CHR–COOH (R = O–CO–Ph), (*R*)-**4b**, and (*R*)-**4c** were obtained by crystallization from solutions in acetone at 20 °C. 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 [2(*S*)-**3a**·(*R*,*R*)-HOOC–CHR–CHR–COOH (R = O–CO–Ph), Stoe–Huber–Siemens CCD; (*R*)-**4b** and (*R*)-**4c**, Stoe IPDS; graphite-monochromated Mo–K_α radiation ($\lambda = 0.71073$ Å)]. The structures were solved using direct methods [17,18]. All non-hydrogen atoms were refined anisotropically [19]. A riding model was employed in the refinement of the hydrogen atoms.

3.3. Determination of the enantiomeric purities

The enantiomeric purities of the (*R*)- and (*S*)-enantiomers of **3a**–**c** were determined by ^{1}H-NMR studies using the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol [(−)-TFAE); Aldrich]. The ^{1}H-NMR spectra were recorded at 22 °C on a Bruker AMX-400 (400.1 MHz) or Bruker DRX-300-NMR spectrometer (300.1 MHz). The compositions of the samples used for the NMR experiments were as follows: (a) **3a**, 55 μmol; (−)-TFAE, 110 μmol; C_6D_6, 0.5 ml. (b) **3b**, 57 μmol; (−)-TFAE, 170 μmol; $CDCl_3$, 0.5 ml. (c) **3c**, 55 μmol; (−)-TFAE, 110 μmol; $CDCl_3$, 0.5 ml.

3.4. ORD studies

The ORD spectra of **3a**–**c**, **3a**–**c**·HCl, and **4a**–**c** were measured at 20 °C with a JASCO spectropolarimeter, Model J-710; CH_3OH (purified by drying over Mg and subsequent distillation) or $CHCl_3$ [purified by dynamic drying over an Al_2O_3 column (50 g of Al_2O_3 (Merck, 1077) per 100 ml of $CHCl_3$) and subsequent distillation] served as solvents. The concentrations of the samples were 10 mg ml^{-1}.

3.5. Pharmacological studies

Radioligand binding studies were performed according to the methods outlined in the literature [20,21]. Briefly, [^{3}H]NMS (80–85 Ci mmol^{-1}; Amersham International, Bucks, England) binding to membranes of CHO-K1 cells stably transfected with human M_1–M_5 receptors was measured in a buffer containing 20 mM HEPES (pH 7.4) enriched with 100 mM NaCl and 10 mM $MgCl_2$. Final membrane protein concentrations were (μg ml^{-1}): M_1, 2; M_2, 6; M_3, 2; M_4, 2; M_5, 5. The incubation of tracer (0.2 nM) and different concentrations of competitors (**3a**–**c**, **4a**–**c**, **5a**–**c**, **6a**–**c**, **7a**–**c**, and **8a**–**c**) was 2 h at 25 °C and terminated by filtration over Whatman GF/B filters presoaked in 0.5% polyethylenimine (1–2 h) using a Brandel cell harvester. Non-specific binding was measured in the presence of 1 μM atropine. Previously estimated [^{3}H]NMS K_D values, obtained in saturation experiments, were 0.19 (M_1), 0.33 (M_2), 0.17 (M_3), 0.10 (M_4), and 0.48 nM (M_5).

Data of the binding experiments were analyzed by a non-linear, iterative curve fitting procedure (GraphPad Software, San Diego, CA, USA). K_i values of compounds **3a**–**c**, **4a**–**c**, **5a**–**c**, **6a**–**c**, **7a**–**c**, **8a**–**c** were calculated from IC_{50} values obtained from competition curves using the Cheng–Prusoff equation [22]. All data are presented as arithmetic means ± SD of at least three experiments performed in duplicate. Differences between mean values were tested for statistical significance by Student's *t* test; $P < 0.05$ was accepted as being significant.

4. Supplementary material

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 166211, 166212, 166213 for compounds [2(*S*)-**3a**·(*R*,*R*)-HOOC–CHR–CHR–COOH (R = O–CO–Ph], and [(*R*)-**4b**], [(*R*)-**4c**], respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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