Sila-Substitution of the α-Amino Acid Proline: Synthesis of *rac*- and (*R*)-4,4-Dimethyl-4-sila-proline Ethyl Ester

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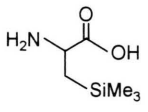
In context with studies on silicon-containing α-amino acids and peptides, a strategy for the synthesis of the 4-sila-proline skeleton was developed. The synthesis of *rac*- and (*R*)-4,4-dimethyl-4-sila-proline ethyl ester [*rac*-**2** and (*R*)-**2**] is described. Compounds *rac*-**2** and (*R*)-**2** (≥ 99% ee) were prepared by two-step syntheses, starting from 3,6-diethoxy-2,5-dihydropyrazine and (*R*)-3,6-diethoxy-2-isopropyl-2,5-dihydropyrazine, respectively.

Introduction

In context with our systematic studies in bioorganosilicon chemistry (for reviews, see refs. [1] and [2]), we have started a research program concerning the synthesis of silicon-containing α-amino acids and peptides and their pharmacological characterization [3, 4] (for further publications dealing with silicon-containing amino acids and their derivatives, see refs. [5 - 14]). β-(Trimethylsilyl)alanine (**1**) [3 - 8, 10, 11, 13] was the first silicon-containing amino acid to be described in the literature. We have now succeeded in synthesizing α-amino acid esters with a 4-sila-proline skeleton. As the cyclic α-amino acid proline plays a crucial role in peptide structures, sila-substitution of the proline framework is of particular interest. Here we report on the synthesis of *rac*- and (*R*)-4,4-dimethyl-4-sila-proline ethyl ester [*rac*-**2** and (*R*)-**2**].



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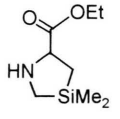

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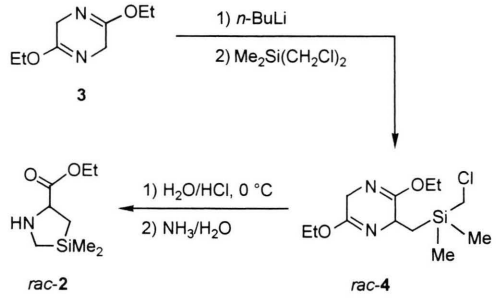
Results and Discussion

The amino acid ester *rac*-**2** was synthesized according to Scheme 1, starting from the 2,5-dihydropyrazine **3**. Metalation of **3** with *n*-butyllithium and subsequent treatment with bis(chloromethyl)dimethylsilane yielded the 2,5-dihydropyrazine *rac*-**4** (yield 50%). Treatment of *rac*-**4** with hydrochloric acid and work-up with aqueous ammonia solution gave glycine ethyl ester (removal by distillation) and *rac*-**2**, which was isolated in 40% yield. The transformation of *rac*-**4** into *rac*-**2** involves hydrolytic opening of the 2,5-dihydropyrazine ring and subsequent cyclization of the resulting intermediate *rac*-β-[(chloromethyl)dimethylsilyl]alanine ethyl ester [*rac*-($ClCH_2$)$Me_2SiCH_2CH(NH_2)COOEt$].



Scheme 1

A crucial step in the preparation of the 2,5-dihydropyrazine *rac*-**4** is its isolation from the reaction mixture. As *rac*-**4** undergoes a thermally induced cyclization reaction to give the sila-

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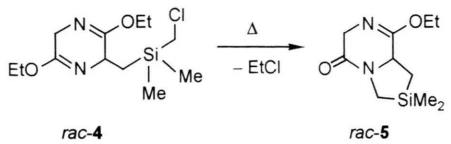
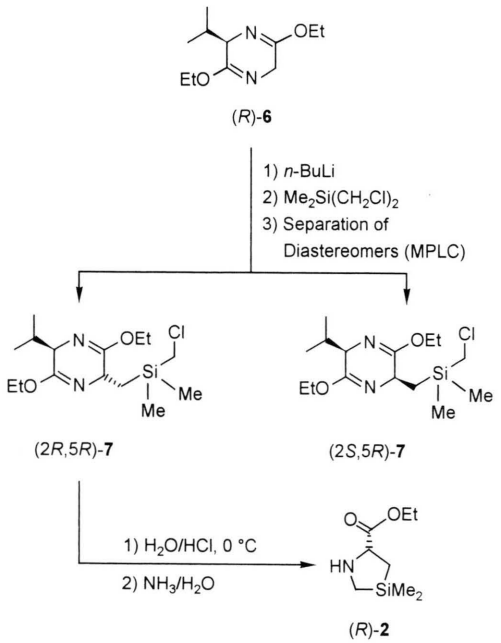
heterocycle *rac*-**5** (structure established by single-crystal X-ray diffraction [15]) and ethyl chloride (Scheme 2), special conditions were necessary for the isolation of *rac*-**4** (see Experimental Section).



Scheme 2



Scheme 3

The amino acid ester (*R*)-**2** (*L*-configuration) was synthesized on the basis of the Schöllkopf approach [16] according to Scheme 3, starting from the 2,5-dihydropyrazine (*R*)-**6**. Metalation of (*R*)-**6** with *n*-butyllithium and subsequent treatment with bis(chloromethyl)dimethylsilane gave a mixture of the diastereomeric 2,5-dihydropyrazines (2*R*,5*R*)-**7** and (2*S*,5*R*)-**7** (molar ratio 85:15; yield 58%). The two diastereomers were separated by medium-pressure liquid chromatography (MPLC; silica gel as stationary phase) (≥ 99% de). Treatment of the major stereoisomer (2*R*,5*R*)-**7** with hydrochloric acid, followed by work-up with aqueous ammonia solution and removal of the valine ethyl ester by distillation, finally gave the enantiomerically pure amino acid ester (*R*)-**2** (≥ 99% ee, yield 41%).

Compounds *rac*-**2**, (*R*)-**2**, *rac*-**4**, (2*R*,5*R*)-**7**, and (2*S*,5*R*)-**7** were isolated as colorless liquids. Their identity was established by elemental analyses (C, H, N), NMR studies (^{1}H, ^{13}C, ^{29}Si), and mass-spectrometric investigations (EI MS). The diastereomeric purity of (2*R*,5*R*)-**7** and (2*S*,5*R*)-**7** was determined by gas-chromatographic studies and ^{1}H NMR experiments [integration of the respective C*H*CH(CH$_3$)$_2$ resonance signals]. The assignment of the absolute configurations of the stereoisomers (2*R*,5*R*)-**7** and (2*S*,5*R*)-**7** is based on the well-established stereochemistry reported for the Schöllkopf approach [16] and is supported by the characteristic ^5J(GK) coupling constants observed in the ^{1}H NMR spectra of (2*R*,5*R*)-**7** (*trans*-isomer, 3.5 Hz) and (2*S*,5*R*)-**7** (*cis*-isomer, 4.1 Hz) (see Experimental Section). As the hydrolytic cleavage of the 2,5-dihydropyrazine (2*R*,5*R*)-**7** does not affect the two centers of chirality, the (*R*)-configuration can be assigned to the resulting amino acid ester **2** [(2*R*,5*R*)-**7** → (*R*)-**2**]. The enantiomeric purity of (*R*)-**2** was determined by ^{1}H NMR studies in the presence of the chiral solvating agent (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol [(*R*)-TFAE] by integration of the respective SiCH$_2$N resonance signals (Fig. 1).

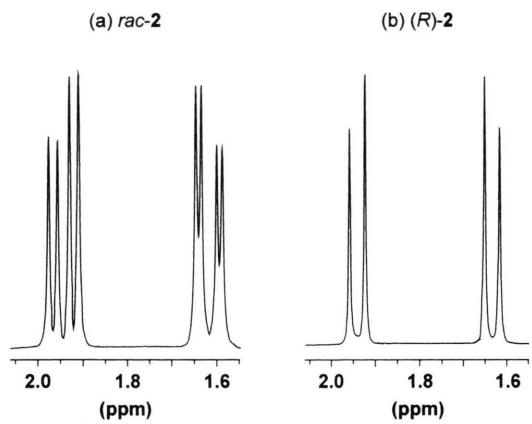


Fig. 1. Quantitative determination of the enantiomeric purity of (*R*)-**2**: ^{1}H NMR partial spectra (SiCH$_2$N protons) of *rac*-**2** (a) and enantiomerically pure (*R*)-**2** (b) in the presence of (*R*)-TFAE [400.1 MHz, 22 °C, CDCl$_3$, molar ratio **2**/(*R*)-TFAE = 1:4].

In conclusion, the almost enantiomerically pure amino acid ester (*R*)-4,4-dimethyl-4-sila-proline

ethyl ester [(*R*)-**2**] and the corresponding racemic compound *rac*-**2** were synthesized. In future studies we will explore the synthetic potential of (*R*)-**2** as a building block for the synthesis of new biologically active peptides containing the unnatural amino acid (*R*)-4,4-dimethyl-4-sila-proline.

Experimental Section

General procedures. The syntheses of *rac*-**4**, (2*R*,5*R*)-**7**, and (2*S*,5*R*)-**7** were carried out under dry nitrogen. Tetrahydrofuran (THF) was dried and purified according to standard procedures and stored under nitrogen. The ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded at room temperature on Bruker DRX-300 (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{29}Si, 59.6 MHz), Bruker AMX-400 (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz), or Bruker DRX-600 NMR spectrometers (^{1}H, 600.1 MHz). $CDCl_3$ was used as solvent. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^{1}H, δ = 7.24), $CDCl_3$ (^{13}C, δ = 77.00), and external TMS (^{29}Si, δ = 0). Assignment of the ^{1}H NMR data of *rac*-**2** was supported by $^{1}H,^{1}H$ COSY experiments, and the ^{1}H spin systems of *rac*-**2**, (*R*)-**2**, *rac*-**4**, (*R*)-**6**, (2*R*,5*R*)-**7**, and (2*S*,5*R*)-**7** were analyzed by simulations using the WIN-DAISY software package (Version 4.0, Bruker). Assignment of the ^{13}C NMR data was supported by DEPT 135 experiments. Mass spectra were obtained with a ThermoQuest mass spectrometer, model TRIO 1000 (EI MS, 70 eV). The selected *m/z* values given refer to the isotopes ^{1}H, ^{12}C, ^{14}N, ^{16}O, ^{28}Si, and ^{35}Cl. IR spectra were obtained with a Bruker Equinox 55 FT-IR spectrometer.

*rac-4,4-Dimethyl-4-sila-proline ethyl ester (rac-***2***)*

3.0 *M* hydrochloric acid (20 ml) was added dropwise at 0 °C within 20 min to a stirred emulsion of *rac*-**4** (2.01 g, 6.91 mmol) in water (14 ml). The resulting mixture was then stirred at 0 °C for 3 h and at room temperature for a further 5 h. The reaction mixture was extracted with diethyl ether (20 ml) and the solvent of the remaining aqueous phase removed under reduced pressure (30 °C, 0.01 Torr), followed by addition of water (0.5 ml) and diethyl ether (20 ml). After the pH value of the aqueous phase was adjusted to pH 8 by addition of concentrated aqueous ammonia solution, the organic phase was separated and the aqueous layer extracted with diethyl ether (5 × 20 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was purified by distillation in a Kugelrohr apparatus (oven temperature 70 °C, 0.01 Torr) to give *rac*-**2** in 40% yield (520 mg, 2.78 mmol) as a colorless liquid (glycine ethyl ester separated at 50 °C, 0.01 Torr). – ^{1}H NMR (300.1 MHz): δ = 0.18 (s, 3 H; $SiCH_3$), 0.19 (s, 3 H; $SiCH_3$), 0.95 (δ_A), 1.10 (δ_B), and 3.69 (δ_X) [^{2}J(AB) = 14.4 Hz, ^{3}J(AX) = 7.4 Hz, ^{3}J(BX) = 7.4 Hz, 3 H; Si-CH_AH_B-CH_X], 1.24 (δ_X) and 4.14 ($\delta_{AA'}$) [^{3}J(AX) = ^{3}J(A'X) = 7.2 Hz, 5 H; O-$CH_AH_{A'}$-CH_{X3}], 2.0 (br. s, 1 H; NH), 2.13 (δ_A) and 2.38 (δ_B) [^{2}J(AB) = 13.2 Hz, 2 H; Si-CH_AH_B-N]. – ^{13}C NMR (75.5 MHz): δ = –2.5 ($SiCH_3$), –2.4 ($SiCH_3$), 14.3 (OCH_2CH_3), 17.2 ($SiCH_2CH$), 34.6 ($SiCH_2N$), 60.7 ($SiCH_2CH$), 60.8 (OCH_2CH_3), 175.0 (C=O). – ^{29}Si NMR: δ = 15.7. – IR (film): ν = 1734 cm^{-1} (C=O). – MS, *m/z* (%): 187 (< 1) [M^+], 172 (< 1) [M^+ - CH_3], 158 (1) [M^+ - CH_2CH_3], 144 (2) [M^+ - CO - CH_3], 114 (100) [M^+ - $CO_2CH_2CH_3$]. $C_8H_{17}NO_2Si$ (187.3): Calcd. C 51.30, H 9.15, N 7.48; Found C 51.2, H 9.1, N 7.6%.

*(R)-4,4-Dimethyl-4-sila-proline ethyl ester [(R)-***2***]*

3.0 *M* hydrochloric acid (30 ml) was added dropwise at 0 °C within 30 min to a stirred emulsion of (2*R*,5*R*)-**7** (3.00 g, 9.01 mmol) in water (20 ml). The resulting mixture was then stirred at 0 °C for 3 h and at room temperature for a further 6 h. The reaction mixture was extracted with diethyl ether (2 × 30 ml) and the solvent of the remaining aqueous phase removed under reduced pressure (30 °C, 0.01 Torr), followed by addition of water (0.5 ml) and diethyl ether (40 ml). After the pH value of the aqueous phase was adjusted to pH 8 by addition of concentrated aqueous ammonia solution, the organic phase was separated and the aqueous layer extracted with diethyl ether (5 × 20 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was purified by distillation in a Kugelrohr apparatus (oven temperature 70 °C, 0.01 Torr) to give (*R*)-**2** in 41% yield (693 mg, 3.70 mmol) as a colorless liquid [(*R*)-valine ethyl ester separated at 50 °C, 0.01 Torr]. - The NMR, IR, and MS data of (*R*)-**2** were identical with those obtained for *rac*-**2**. $C_8H_{17}NO_2Si$ (187.3): Calcd. C 51.30, H 9.15, N 7.48; Found C 51.2, H 9.0, N 7.7%.

*3,6-Diethoxy-2,5-dihydropyrazine (***3***)*

This compound was synthesized according to ref. [17].

*rac-2-{[(Chloromethyl)dimethylsilyl]methyl}-3,6-diethoxy-2,5-dihydropyrazine (rac-***4***)*

A 1.6 *M* solution of *n*-butyllithium in *n*-hexane (2.0 ml, 3.20 mmol *n*-BuLi) was added dropwise at –10 °C within 20 min to a stirred solution of **3** (3.02 g, 17.7 mmol) in THF (80 ml). After cooling the reaction mixture to –70 °C, again a 1.6 *M* solution of *n*-butyllithium in *n*-hexane (9.1 ml, 14.6 mmol *n*-BuLi) was added dropwise over a period of 80 min. The mixture was stirred at –70 °C for 15 min, warmed up to –40 °C, and then

added dropwise at –5 °C within 4 h to a stirred solution of bis(chloromethyl)dimethylsilane (2.79 g, 17.8 mmol) in THF (80 ml). The resulting reaction mixture was allowed to warm up to room temperature over a period of 13 h, followed by addition of diethyl ether (150 ml) and water (150 ml). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 150 ml), and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the oily residue distilled in a Kugelrohr apparatus (oven temperature 125 °C, 0.01 Torr). The distillate was dissolved in *n*-hexane (20 ml) and the resulting solution kept undisturbed at -10 °C for 5 h (crystallization of the by-product *rac*-**5**). After removal of the crystals by filtration, the solvent of the filtrate was removed under reduced pressure at 25 °C to give *rac*-**4** in 50% yield (2.59 g, 8.90 mmol) as a colorless liquid. – ^{1}H NMR (300.1 MHz): δ = 0.16 (s, 3 H; $SiCH_3$), 0.17 (s, 3 H; $SiCH_3$), 0.91 (δ_A), 1.27 (δ_B), 3.94 (δ_L), 3.96 (δ_M), and 4.03 (δ_K) [^2J(AB) = 14.6 Hz, ^3J(AK) = 10.7 Hz, ^3J(BK) = 5.0 Hz, ^5J(KL) = 4.2 Hz, ^5J(KM) = 3.5 Hz, ^2J(LM) = 20.2 Hz, 5 H; Si-CH_AH_B-CH_K-N=C-CH_LH_M], 1.24 (δ_X), 4.02 (δ_A), and 4.05 (δ_B) [^2J(AB) = 10.6 Hz, ^3J(AX) = 7.2 Hz, ^3J(BX) = 7.1 Hz, 5 H; O-CH_AH_B-CH_{X3}], 1.25 (δ_X), 4.02 (δ_A), and 4.10 (δ_B) [^2J(AB) = 10.6 Hz, ^3J(AX) = 7.1 Hz, ^3J(BX) = 7.1 Hz, 5 H; O-CH_AH_B-CH_{X3}], 2.82 (δ_A) and 2.87 (δ_B) [^2J(AB) = 13.4 Hz, 2 H; Si-CH_AH_B-Cl]. – ^{13}C NMR (75.5 MHz): δ = –3.91 ($SiCH_3$), –3.86 ($SiCH_3$), 14.2 (OCH_2CH_3), 14.3 (OCH_2CH_3), 20.3 ($SiCH_2CH$), 31.2 ($SiCH_2Cl$), 46.4 (CCH_2N), 52.9 ($SiCH_2CH$), 60.8 (OCH_2CH_3), 60.9 (OCH_2CH_3), 161.6 (C=N), 165.7 (C=N). – ^{29}Si NMR: δ = 3.5. - MS, *m/z* (%): 290 (4) [M^+], 275 (1) [M^+ - CH_3], 261 (3) [M^+ - CH_2CH_3], 241 (9) [M^+ - CH_2Cl], 169 (100) [M^+ - $CH_2Si(CH_3)_2CH_2Cl$]. $C_{12}H_{23}ClN_2O_2Si$ (290.9): Calcd. C 49.55, H 7.97, N 9.63. Found C 49.3, H 7.8, N 9.5%.

*(R)-3,6-Diethoxy-2-isopropyl-2,5-dihydropyrazine [(R)-**6**]*

This compound was synthesized in analogy to (*R*)-3,6-dimethoxy-2-isopropyl-2,5-dihydropyrazine according to ref. [18] (in this context, see also ref. [19]): A mixture of (*R*)-3-isopropylpiperazine-2,5-dione (9.40 g, 60.2 mmol) and triethyloxonium tetrafluoroborate (28.5 g, 150 mmol) in dichloromethane (200 ml) was stirred at room temperature for 24 h. After addition of another portion of triethyloxonium tetrafluoroborate (11.4 g, 60.0 mmol), the resulting mixture was stirred at room temperature for 48 h, followed by addition of a solution of $NaH_2PO_4 \cdot H_2O$ (24.9 g, 180 mmol) and $Na_2HPO_4 \cdot 7\,H_2O$ (161 g, 601 mmol) in water (500 ml). The organic phase was separated and the aqueous layer extracted with dichloromethane (3 × 150 ml). The combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by distillation (82 °C, 4 Torr) to give (*R*)-**6** in 77% yield (9.80 g, 46.2 mmol) as a colorless liquid. – ^{1}H NMR (300.1 MHz): δ = 0.74 (δ_Q), 1.10 (δ_T), 2.20 (δ_N), 3.916 (δ_A), 3.921 (δ_K), and 3.97 (δ_B) [^2J(AB) = 20.4 Hz, ^5J(AK) = 3.7 Hz, ^5J(BK) = 3.8 Hz, ^3J(KN) = 3.6 Hz, ^3J(NQ) = 6.9 Hz, ^3J(NT) = 6.9 Hz, 10 H; CH_AH_B-N=C-CH_K-$CH_N(CH_{Q3})(CH_{T3})$], 1.24 (δ_X), 4.04 (δ_A), and 4.07 (δ_B) [^2J(AB) = 10.6 Hz, ^3J(AX) = 7.2 Hz, ^3J(BX) = 7.0 Hz, 5 H; O-CH_AH_B-CH_{X3}], 1.25 (δ_X), 4.06 (δ_A), and 4.16 (δ_B) [^2J(AB) = 10.6 Hz, ^3J(AX) = 7.2 Hz, ^3J(BX) = 7.0 Hz, 5 H; O-CH_AH_B-CH_{X3}]. – ^{13}C NMR (75.5 MHz): δ = 14.3 (2 C, OCH_2CH_3), 17.0 ($CHCH_3$), 19.0 ($CHCH_3$), 32.5 [$CHCH(CH_3)_2$], 46.8 (CCH_2N), 60.7 (2 C, OCH_2CH_3), 61.0 [$CHCH(CH_3)_2$], 161.8 (C=N), 164.3 (C=N). - MS, *m/z* (%): 212 (7) [M^+], 197 (3) [M^+ - CH_3], 169 (86) [M^+ - $CH(CH_3)_2$], 85 (100). $C_{11}H_{20}N_2O_2$ (212.3): Calcd. C 62.24, H 9.50, N 13.20. Found C 62.0, H 9.6, N 13.2%.

*(2R,5R)- and (2S,5R)-2-{[(Chloromethyl)dimethylsilyl]-methyl}-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine [(2R,5R)-**7** and (2S,5R-**7**)]*

A 2.5 *M* solution of *n*-butyllithium in *n*-hexane (2.0 ml, 5.00 mmol *n*-BuLi) was added dropwise at –10 °C within 20 min to a stirred solution of (*R*)-**6** (8.00 g, 37.7 mmol) in THF (100 ml). After cooling the reaction mixture to –70 °C, again a 2.5 *M* solution of *n*-butyllithium in *n*-hexane (13.1 ml, 32.8 mmol *n*-BuLi) was added dropwise over a period of 1 h. The mixture was stirred at –70 °C for 10 min, warmed up to –40 °C, and then added dropwise at –5 °C within 4 h to a stirred solution of bis(chloromethyl)dimethylsilane (5.92 g, 37.7 mmol) in THF (110 ml). The resulting mixture was allowed to warm up to room temperature within 2 h, followed by addition of diethyl ether (300 ml) and water (300 ml). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 250 ml), and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the oily residue distilled in a Kugelrohr apparatus (oven temperature 125 °C, 0.01 Torr) to give 7.29 g (21.9 mmol, yield 58%) of a mixture consisting of (2*R*,5*R*)-**7** and (2*S*,5*R*)-**7** (molar ratio 85:15; GC and ^{1}H NMR analysis). The diastereomerically pure compounds (2*R*,5*R*)-**7** and (2*S*,5*R*)-**7** were obtained by liquid-chromatographic separation (see below).

*Preparative liquid-chromatographic separation of the diastereomers (2R,5R)-**7** and (2S,5R)-**7***

The diastereomers (2*R*,5*R*)-**7** and (2*S*,5*R*)-**7** were separated by liquid chromatography on silica gel (30-60 μm; Baker, 7024). The experimental conditions were as follows: LC pump, Büchi Pump 688; detector, differential

refractometer Knauer K-2300; column, 20 mm i.d. × 250 mm; pressure, 5 bar; eluent, *n*-hexane/diethyl ether (60:1, v/v); injection volume, 1 ml (250 mg of the sample material dissolved in 750 μl of diethyl ether); flow rate, 8.0 ml/min. The solvent of the respective fractions obtained [(2*R*,5*R*)-**7**, first fraction; (2*S*,5*R*)-**7**, second fraction] was removed (rotary evaporator; 40 °C, 350 Torr) and the residues [(2*R*,5*R*)-**7** or (2*S*,5*R*)-**7**] were purified by Kugelrohr distillation (oven temperature 125 °C, 0.01 Torr).

(2R,5R)-2-{[(Chloromethyl)dimethylsilyl]methyl}-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine [(2R,5R)-7]

200 mg (601 μmol, 80%) of compound (2*R*,5*R*)-**7** were isolated by liquid-chromatographic separation of 250 mg of (2*R*,5*R*)-**7**/(2*S*,5*R*)-**7** (see above) with a diastereomeric purity of ≥ 99% de. – ^{1}H NMR (600.1 MHz): δ = 0.15 (s, 3 H; $SiCH_3$), 0.16 (s, 3 H; $SiCH_3$), 0.69 (δ_Q), 0.93 (δ_A), 0.99 (δ_T), 1.35 (δ_B), 2.22 (δ_N), 3.89 (δ_K), and 3.98 (δ_G) [^2J(AB) = 14.6 Hz, ^3J(AG) = 10.5 Hz, ^3J(BG) = 4.6 Hz, ^5J(GK) = 3.5 Hz, ^3J(KN) = 3.5 Hz, ^3J(NQ) = 6.8 Hz, ^3J(NT) = 6.9 Hz, 11 H; Si-CH_AH_B-CH_G-N=C-CH_K-$CH_N(CH_{Q3})(CH_{T3})$], 1.24 (δ_X), 4.00 (δ_A), and 4.11 (δ_B) [^2J(AB) = 10.5 Hz, ^3J(AX) = 7.0 Hz, ^3J(BX) = 7.0 Hz, 5 H; O-CH_AH_B-CH_{X3}], 1.25 (δ_X), 4.04 (δ_A), and 4.15 (δ_B) [^2J(AB) = 10.7 Hz, ^3J(AX) = 7.0 Hz, ^3J(BX) = 7.1 Hz, 5 H; O-CH_AH_B-CH_{X3}], 2.82 (δ_A) and 2.86 (δ_B) [^2J(AB) = 13.4 Hz, 2 H; Si-CH_AH_B-Cl]. – ^{13}C NMR (100.6 MHz): δ = –3.79 ($SiCH_3$), –3.75 ($SiCH_3$), 14.3 (OCH_2CH_3), 14.4 (OCH_2CH_3), 16.8 ($CHCH_3$), 19.0 ($CHCH_3$), 20.6 ($SiCH_2CH$), 31.5 ($SiCH_2Cl$), 32.0 [$CHCH(CH_3)_2$], 52.8 ($SiCH_2CH$), 60.5 (OCH_2CH_3), 60.6 (OCH_2CH_3), 60.8 [$CHCH(CH_3)_2$], 162.7 (C=N), 164.5 (C=N). – ^{29}Si NMR: δ = 3.6. – MS, *m/z* (%): 332 (10) [M^+], 317 (7) [M^+ - CH_3], 303 (2) [M^+ - CH_2CH_3], 289 (19) [M^+ - $CH(CH_3)_2$], 211 (100) [M^+ - $CH_2Si(CH_3)_2CH_2Cl$]. $C_{15}H_{29}ClN_2O_2Si$ (332.9): Calcd. C 54.11, H 8.78, N 8.41. Found C 54.4, H 8.6, N 8.6%.

(2S,5R)-2-{[(Chloromethyl)dimethylsilyl]methyl}-3,6-diethoxy-5-isopropy l-2,5-dihydropyrazine [(2S,5R)-7]

30.0 mg (90.1 μmol, 12%) of compound (2*S*,5*R*)-**7** were isolated by liquid-chromatographic separation of 250 mg of (2*R*,5*R*)-**7**/(2*S*,5*R*)-**7** (see above) with a diastereomeric purity of ≥ 99% de. – ^{1}H NMR (600.1 MHz): δ = 0.18 (s, 3 H; $SiCH_3$), 0.19 (s, 3 H; $SiCH_3$), 0.74 (δ_Q), 0.81 (δ_A), 1.03 (δ_T), 1.37 (δ_B), 2.17 (δ_N), 3.84 (δ_K), and 3.98 (δ_G) [^2J(AB) = 14.6 Hz, ^3J(AG) = 11.9 Hz, ^3J(BG) = 4.5 Hz, ^5J(GK) = 4.1 Hz, ^3J(KN) = 4.1 Hz, ^3J(NQ) = 6.8 Hz, ^3J(NT) = 6.9 Hz, 11 H; Si-CH_AH_B-CH_G-N=C-CH_K-$CH_N(CH_{Q3})(CH_{T3})$], 1.24 (δ_X), 4.01 (δ_A), and 4.09 (δ_B) [^2J(AB) = 10.6 Hz, ^3J(AX) = 7.1 Hz, ^3J(BX) = 7.2 Hz, 5 H; O-CH_AH_B-CH_{X3}], 1.25 (δ_X), 4.04 (δ_A), and 4.13 (δ_B) [^2J(AB) = 10.7 Hz, ^3J(AX) = 7.2 Hz, ^3J(BX) = 7.1 Hz, 5 H; O-CH_AH_B-CH_{X3}], 2.86 (δ_A) and 2.90 (δ_B) [^2J(AB) = 13.3 Hz, 2 H; Si-CH_AH_B-Cl]. – ^{13}C NMR (100.6 MHz): δ = –3.9 ($SiCH_3$), –3.8 ($SiCH_3$), 14.3 (OCH_2CH_3), 14.4 (OCH_2CH_3), 17.6 ($CHCH_3$), 19.5 ($CHCH_3$), 21.3 ($SiCH_2CH$), 31.4 ($SiCH_2Cl$), 31.5 [$CHCH(CH_3)_2$], 52.9 ($SiCH_2CH$), 60.3 (OCH_2CH_3), 60.4 (OCH_2CH_3), 61.0 [$CHCH(CH_3)_2$], 162.6 (C=N), 164.3 (C=N). – ^{29}Si NMR: δ = 3.6. – MS, *m/z* (%): 332 (< 1) [M^+], 317 (2) [M^+ - CH_3], 303 (2) [M^+ - CH_2CH_3], 289 (69) [M^+ - $CH(CH_3)_2$], 211 (29) [M^+ - $CH_2Si(CH_3)_2CH_2Cl$], 55 (100). $C_{15}H_{29}ClN_2O_2Si$ (332.9): Calcd. C 54.11, H 8.78, N 8.41. Found C 54.4, H 8.8, N 8.6%.

Separation of the diastereomers (2R,5R)-7 and (2S,5R)-7 by analytical capillary gas chromatography

The diastereomers (2*R*,5*R*)-**7** and (2*S*,5*R*)-**7** were separated by analytical capillary gas chromatography [gas chromatograph, Shimadzu GC-14A; SE-30 column (0.32 mm i.d. × 10 m), Macherey-Nagel; carrier gas, nitrogen; temperature program, 80 °C (2 min) to 280 °C (15 min) with 10 °C/min; injector temperature, 200 °C; split 1:45; detector, FID; detector temperature, 320 °C]. Retention times of the diastereomers: 14.70 [(2*R*,5*R*)-**7**] and 14.95 min [(2*S*,5*R*)-**7**].

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