Derivatives of *β*-(Trimethylsilyl)alanine with $SiCH_2NH_2$, $SiCH_2OH$, or $SiCH_2SH$ Functionality: Synthesis of the Silicon-Containing α-Amino Acids *rac*- and (*R*)-$Me_2Si(CH_2R)CH_2CH(NH_2)COOH$ (R = NH_2, OH, SH)†

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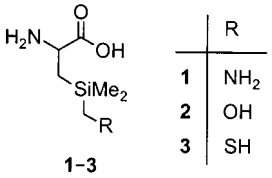
The silicon-containing α-amino acids *rac*- and (*R*)-$Me_2Si(CH_2R)CH_2CH(NH_2)COOH$ (**1**, R = NH_2; **2**, R = OH; **3**, R = SH) were prepared in multistep syntheses and isolated as dihydrochlorides (*rac*-**1**, (*R*)-**1**) and hydrochlorides (*rac*-**2**, (*R*)-**2**, *rac*-**3**, (*R*)-**3**), respectively. 3,6-Diethoxy-2,5-dihydropyrazine (→ racemic compounds) and (*R*)-3,6-diethoxy-2-isopropyl-2,5-dihydropyrazine (→ (*R*)-enantiomers) served as starting materials. The identities of the *β*-(trimethylsilyl)alanine derivatives *rac*-**1**−*rac*-**3** and (*R*)-**1**−(*R*)-**3** were established by elemental analyses and NMR studies.

Introduction

As part of our studies on silicon-based drugs,[1] we have been interested in the synthesis of silicon-containing α-amino acids and peptides.[2] In continuation of these investigations, we have now succeeded in synthesizing *β*-(trimethylsilyl)alanine derivatives with $SiCH_2NH_2$, $SiCH_2OH$, or $SiCH_2SH$ groups. To the best of our knowledge, functionalized *β*-(triorganylsilyl)alanine derivatives have not been described so far in the literature.[3] We report here on the synthesis of the α-amino acids *rac*-**1**−*rac*-**3** and (*R*)-**1**−(*R*)-**3**. Compounds (*R*)-**1**−(*R*)-**3** (L-enantiomers) are promising building blocks for new biologically active peptides.



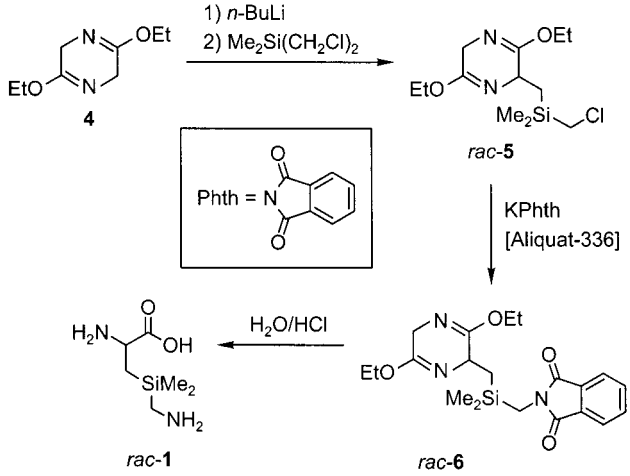
	R
1	NH_2
2	OH
3	SH

1−**3**

Results and Discussion

Synthesis of the Racemic α-Amino Acids. The $SiCH_2NH_2$-functionalized amino acid *rac*-**1** was prepared by a three-step synthesis, starting from 3,6-diethoxy-2,5-dihydropyrazine[4] (**4**) (Scheme 1). In the first step, the dihydropyrazine *rac*-**5** was synthesized according to ref 2a by metalation of **4** with *n*-butyllithium and subsequent treatment with bis(chloro-

Scheme 1



† Dedicated to Professor Hans Bürger on the occasion of his 65th birthday.

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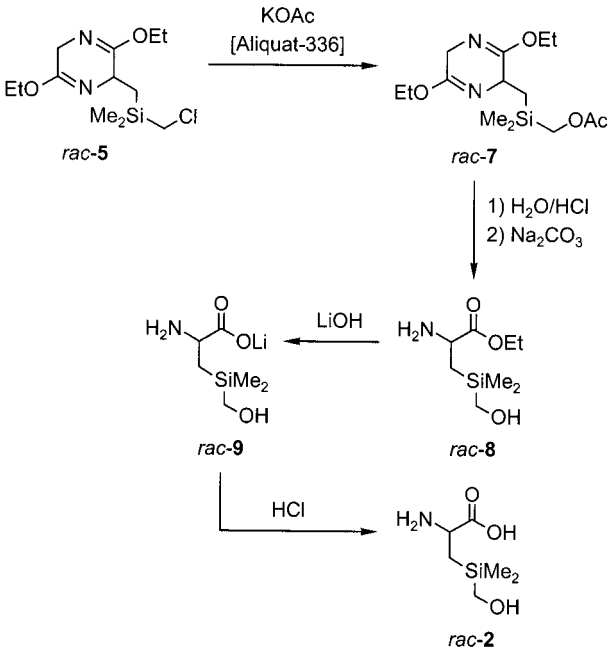
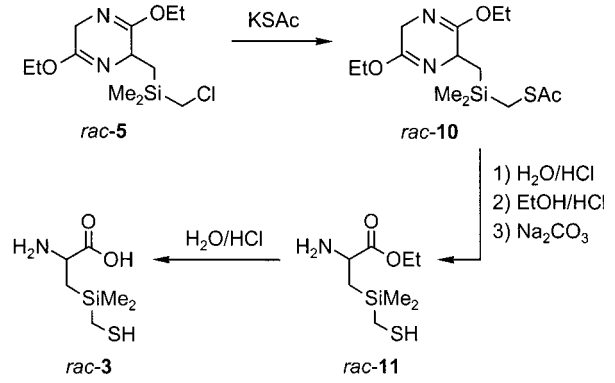
Scheme 2



Scheme 3



methyl)dimethylsilane. Reaction of *rac*-**5** with potassium phthalimide in dimethylformamide in the presence of methyltrioctylammonium chloride (Aliquat-336) led to compound *rac*-**6** (75% yield),[5] which on hydrolysis in boiling hydrochloric acid yielded the amino acid *rac*-**1** (isolated as the dihydrochloride *rac*-**1**·2HCl, 85% yield).

The $SiCH_2OH$-functionalized amino acid *rac*-**2** was prepared by a four-step synthesis, starting from the dihydropyrazine *rac*-**5** (Scheme 2). Thus, treatment of *rac*-**5** with potassium acetate in dimethylformamide in the presence of methyltrioctylammonium chloride (Aliquat-336) afforded compound *rac*-**7** (45% yield), which on hydrolysis with hydrochloric acid at room temperature, followed by workup with aqueous sodium carbonate solution, led to the amino acid ethyl ester *rac*-**8** (81% yield). Attempts to prepare the amino acid *rac*-**2** by hydrolysis of *rac*-**8** in boiling hydrochloric acid failed: under the reaction conditions applied to the hydrolysis of *rac*-**6** (Scheme 1) and *rac*-**10** (Scheme 3), an OH/Cl exchange was observed (formation of $Me_2Si(CH_2Cl)CH_2$-$CH(NH_2)COOH$·HCl). To overcome this problem, the ester cleavage was accomplished by treatment of *rac*-**8** with lithium hydroxide (molar ratio 1:1) in a water/dioxane mixture, followed by treatment with 1 molar equiv of hydrogen chloride in ethanol/diethyl ether, to give the amino acid *rac*-**2**, which on reaction with hydrochloric acid afforded the hydrochloride *rac*-**2**·HCl (60% yield).

The $SiCH_2SH$-functionalized amino acid *rac*-**3** was prepared by a three-step synthesis, again starting from the dihydropyrazine *rac*-**5** (Scheme 3). Thus, treatment of *rac*-**5** with potassium thioacetate in tetrahydrofuran gave compound *rac*-**10** (48% yield), which on hydrolysis with hydrochloric acid at 0 °C and subsequent transesterification in a boiling ethanol/hydrochloric acid mixture, followed by workup with aqueous sodium carbonate solution, led to the amino acid ethyl ester *rac*-**11** (73% yield). Hydrolysis of *rac*-**11** in boiling hydrochloric acid gave *rac*-**3** (isolated as the hydrochloride *rac*-**3**·HCl, 95% yield).

Compounds *rac*-**1**·2HCl, *rac*-**2**·HCl, *rac*-**3**·HCl, *rac*-**6**, and *rac*-**9** were isolated as solids, whereas compounds *rac*-**7**, *rac*-**8**, *rac*-**10**, and *rac*-**11** were obtained as liquids. The identities of all compounds were established by elemental analyses (C, H, N; Li, S) and NMR-spectroscopic studies (^1H, ^{13}C, ^{29}Si).

Synthesis of the (*R*)-α-Amino Acids. The $SiCH_2NH_2$-functionalized amino acid (*R*)-**1** was prepared by a three-step synthesis on the basis of the Schöllkopf approach,[6] starting from (*R*)-3,6-diethoxy-2-isopropyl-2,5-dihydropyrazine[2a,7,8] ((*R*)-**12**) (Scheme 4). In the first step, a mixture of the diastereomeric 2,5-dihydropyrazines (2*R*,5*R*)-**13** and (2*S*,5*R*)-**13** (molar ratio 85:15) was synthesized according to ref 2a. Treatment of this mixture with potassium phthalimide in dimethylformamide in the presence of methyltrioctylammonium chloride (Aliquat-336) afforded compounds (2*R*,5*R*)-**14** and (2*S*,5*R*)-**14** (molar ratio 81:19; 62% de; 77% yield). These diastereomers were separated by medium-pressure liquid chromatography (MPLC) on silica gel using *n*-hexane/ethyl acetate (93:3 (v/v)) as the eluent to yield the diastereomerically pure (≥99% de) dihydropyrazines (2*R*,5*R*)-**14** and (2*S*,5*R*)-**14**. Hydrolysis of the major stereoisomer (2*R*,5*R*)-**14** in boiling hydrochloric acid gave the enantiomerically pure (≥99% ee) amino acid (*R*)-**1** (isolated as the dihydrochloride (*R*)-**1**·2HCl, 83% yield).

The $SiCH_2OH$-functionalized amino acid (*R*)-**2** was prepared by a four-step synthesis, starting from a mixture of the dihydropyrazines (2*R*,5*R*)-**13** and (2*S*,5*R*)-**13** (molar ratio 85:15)[2a] (Scheme 5). Treatment of this mixture with potassium acetate in dimethylformamide in the presence of methyltrioctylammonium chloride (Aliquat-336) afforded compounds (2*R*,5*R*)-**15** and (2*S*,5*R*)-**15** (molar ratio 79:21; 58 de; 47% yield). The diastereomerically pure (≥99% de) dihydropyrazines (2*R*,5*R*)-**15** and (2*S*,5*R*)-**15** were obtained by MPLC separation on silica gel using *n*-hexane/ethyl acetate (98.4:1.6 (v/v)) as the eluent. Hydrolysis of the major stereoisomer (2*R*,5*R*)-**15** with hydrochloric acid at room

(5) As compound *rac*-**5** undergoes a thermally induced cyclization reaction, careful temperature control (maximum temperature 40 °C) is necessary. For the cyclization reaction, see: Handmann, V. I.; Bertermann, R.; Burschka, C.; Tacke, R. *J. Organomet. Chem.* **2000**, *613*, 19−25.

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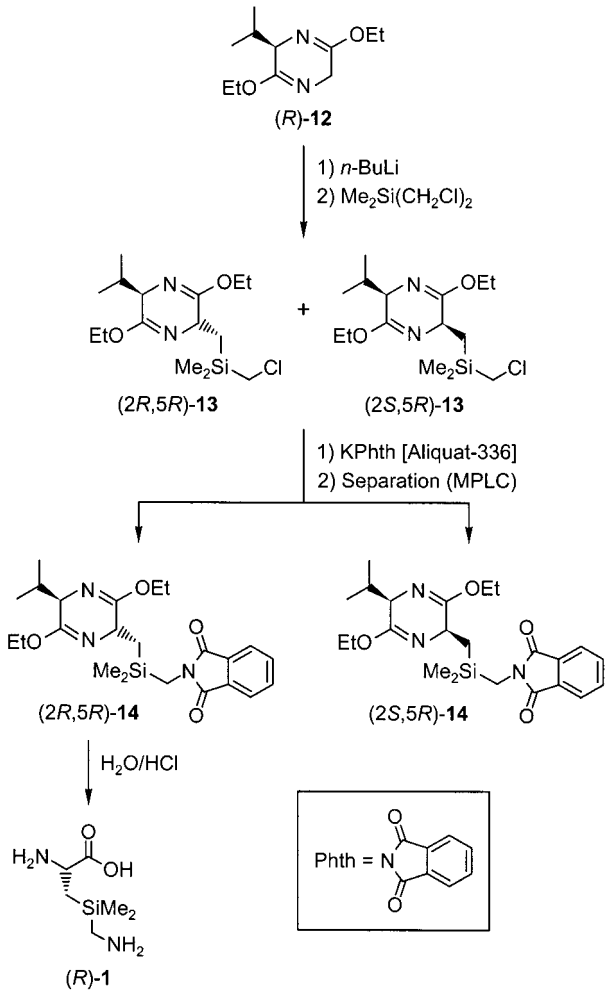
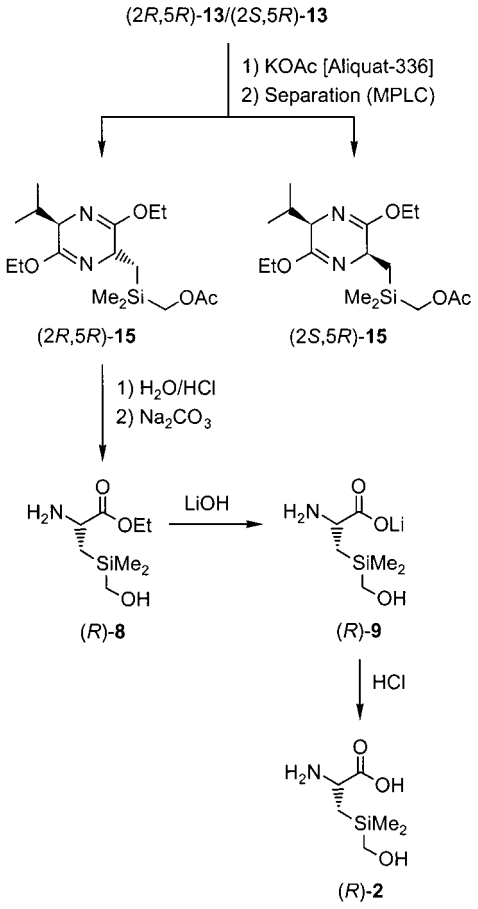
Scheme 4



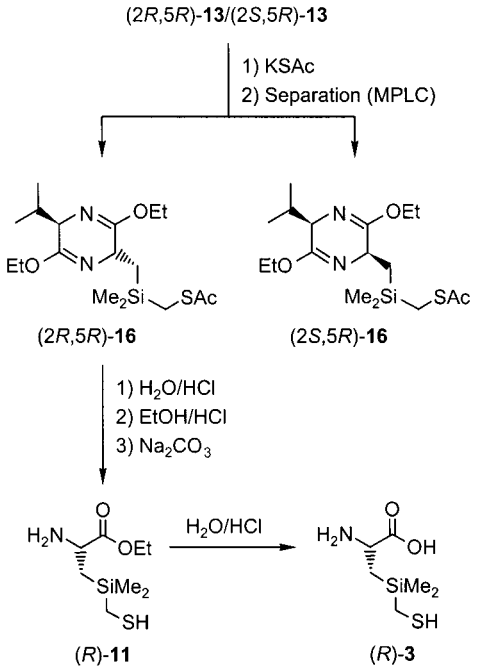
temperature, followed by workup with aqueous sodium carbonate solution, gave the enantiomerically pure (≥99% ee) amino acid ethyl ester (*R*)-**9** (80% yield). Reaction of (*R*)-**9** with lithium hydroxide (molar ratio 1:1) in a water/dioxane mixture and subsequent treatment with 1 molar equiv of hydrogen chloride in ethanol/diethyl ether yielded the amino acid (*R*)-**2**, which on reaction with hydrochloric acid gave the hydrochloride (*R*)-**2**·HCl (62% yield).

The $SiCH_2SH$-functionalized amino acid (*R*)-**3** was prepared by a three-step synthesis, again starting from a mixture of the dihydropyrazines (2*R*,5*R*)-**13** and (2*S*,5*R*)-**13** (molar ratio 85:15)[2a] (Scheme 6). Thus, treatment of this mixture with potassium thioacetate in tetrahydrofuran at room temperature gave compounds (2*R*,5*R*)-**16** and (2*S*,5*R*)-**16** (molar ratio 83:17; 66 de; 65% yield). The diastereomerically pure (≥99% de) dihydropyrazines (2*R*,5*R*)-**16** and (2*S*,5*R*)-**16** were obtained by MPLC separation on silica gel using *n*-hexane/ethyl acetate (98.2:1.8 (v/v)) as the eluent. Hydrolysis of the major stereoisomer (2*R*,5*R*)-**16** with hydrochloric acid at 0 °C and subsequent transesterification in a boiling ethanol/hydrochloric acid mixture, followed by workup with aqueous sodium carbonate solution, led to the enantiomerically pure (≥99% ee) amino acid ethyl ester (*R*)-**10** (78% yield), which on hydrolysis in boiling hydrochloric acid yielded (*R*)-**3** (isolated as the hydrochloride (*R*)-**3**·HCl, 93% yield).

Scheme 5



Scheme 6



Compounds (*R*)-**1**·2HCl, (*R*)-**2**·HCl, (*R*)-**3**·HCl, and (*R*)-**9** were isolated as colorless solids, whereas compounds (*R*)-**8**, (*R*)-**11**, (2*R*,5*R*)-**14**, (2*S*,5*R*)-**14**, (2*R*,5*R*)-**15**, (2*S*,5*R*)-**15**, (2*R*,5*R*)-**16**, and (2*S*,5*R*)-**16** were obtained as liquids. The identities of all compounds were established by elemental analyses (C, H, N; Li, S) and NMR-spectroscopic studies (^{1}H, ^{13}C, ^{29}Si).

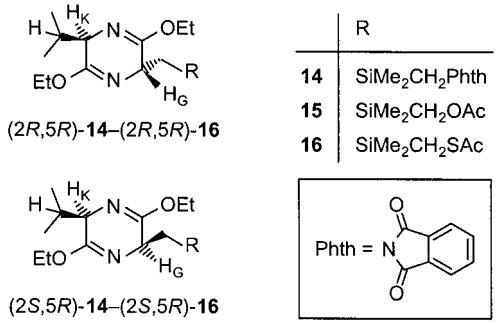


Figure 1. Structures of the *trans*-isomers ((2*R*,5*R*)-configuration) and *cis*-isomers ((2*S*,5*R*)-configuration) of the dihydropyrazines **14**, **15**, and **16**, showing the two coupling protons H_G and H_K.

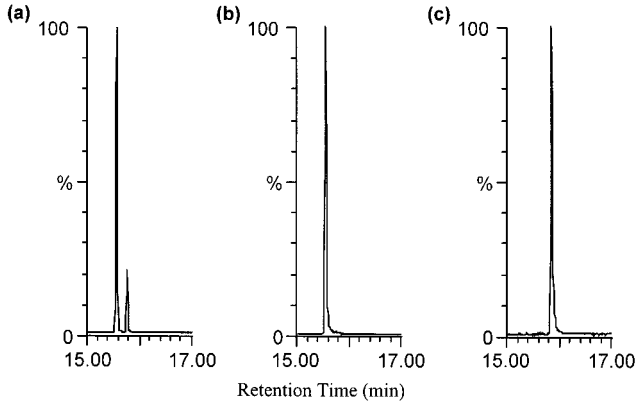


Figure 2. Quantitative gas-chromatographic determination of the molar ratio of the diastereomers of the dihydropyrazine **16**. Gas chromatograms: (a) 83:17 mixture of (2*R*,5*R*)-**16**/(2*S*,5*R*)-**16** obtained by diastereoselective alkylation of (*R*)-**12** with the $CH_2Si(CH_2Cl)Me_2$ group and subsequent reaction with potassium thioacetate; (b) diastereomerically pure (≥99% de) isomer (2*R*,5*R*)-**16** obtained by MPLC separation; (c) diastereomerically pure (≥99% de) isomer (2*S*,5*R*)-**16** obtained by MPLC separation. For details, see Experimental Section.

Determination of the Absolute Configurations. The assignment of the absolute configurations of the diastereomers of **14**, **15**, and **16** is based on the well-established stereochemistry of the Schöllkopf approach[6] and is supported by the characteristic ^5J(GK) coupling constants in the ^{1}H NMR spectra of the (2*R*,5*R*)-isomers (*trans*-isomers of **14**, **15**, and **16**: ^5J(GK) = 3.2−3.4 Hz) and (2*S*,5*R*)-isomers (*cis*-isomers of **14**, **15**, and **16**: ^5J(GK) = 4.2 Hz) (Figure 1). As the hydrolytic cleavage of the dihydropyrazines **14**, **15**, and **16** does not affect the absolute configurations of the two centers of chirality, the absolute configurations of the resulting amino acids can be deduced from the absolute configurations of the respective dihydropyrazines (Schemes 4−6).

Determination of the Diastereomeric Purities. The (2*R*,5*R*)- and (2*S*,5*R*)-diastereomers of the dihydropyrazines **14**, **15**, and **16** could be separated by analytical capillary gas chromatography. This is demonstrated for the diastereomers of **16** in Figure 2. The retention times of the respective stereoisomers of the dihydropyrazines **14**, **15**, and **16** are listed in Table 1. This gas-chromatographic method was used as an analytical tool to determine the molar ratio of the (2*R*,5*R*)- and (2*S*,5*R*)-diastereomers of **14**, **15**, and **16**.

Table 1. Retention Times[a] for the Analytical Gas-Chromatographic Separations of the (2*R*,5*R*)- and (2*S*,5*R*)-Diastereomers of the Dihydropyrazines 14−16

compound	retention time (min)	compound	retention time (min)
(2*R*,5*R*)-**14**	21.6	(2*S*,5*R*)-**14**	21.7
(2*R*,5*R*)-**15**	13.8	(2*S*,5*R*)-**15**	14.1
(2*R*,5*R*)-**16**	15.6	(2*S*,5*R*)-**16**	15.9

[a] For experimental conditions, see Experimental Section.

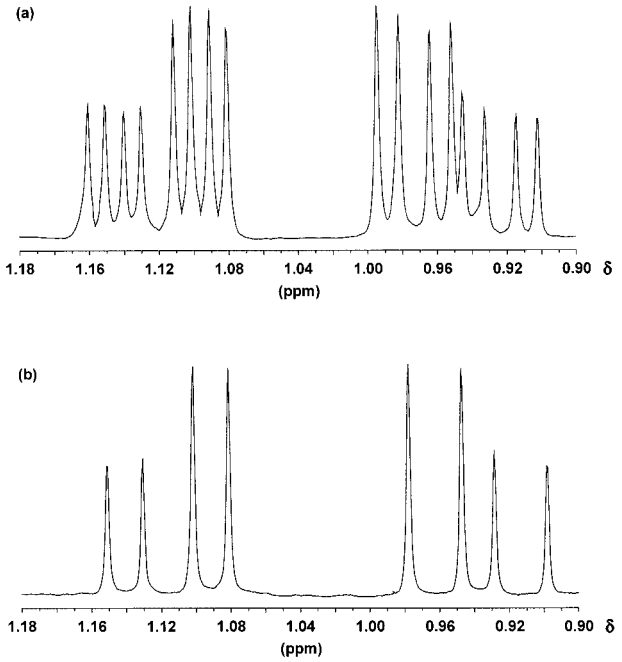


Figure 3. Quantitative NMR-spectroscopic determination of the enantiomeric purity of the amino acid ester (*R*)-**11**. ^{1}H NMR partial spectra ($SiCH_2CH$ group) of the enantiomers of **11** in the presence of the chiral solvating agent (*R*)-TFAE: (a) racemic mixture; (b) (*R*)-enantiomer obtained by hydrolysis of (2*R*,5*R*)-**16**. For details, see Experimental Section.

Determination of the Enantiomeric Purities. The enantiomeric purities of the amino acid ethyl esters (*R*)-**8** and (*R*)-**11** were determined by ^{1}H NMR experiments using the chiral solvating agent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((*R*)-TFAE). As shown for **11** in Figure 3, the two enantiomers of this amino acid ester can be clearly discriminated by NMR spectroscopy and therefore quantitatively determined by integration of their characteristic resonance signals. According to this method, the enantiomeric purities of (*R*)-**8** and (*R*)-**11** were determined to be ≥99% ee. As the hydrolysis of these amino acid esters does not affect the absolute configurations of the centers of chirality, the same enantiomeric purities (≥99% ee) can be assumed for the resulting amino acids (*R*)-**2** ((*R*)-**2**·HCl) and (*R*)-**3** ((*R*)-**3**·HCl). Likewise, an enantiomeric purity of ≥99% ee can also be assumed for the amino acid (*R*)-**1** ((*R*)-**1**·2HCl), which was obtained by hydrolysis of the diastereomerically pure (≥99% de) precursor (2*R*,5*R*)-**14**.

Conclusions

Preparative methods for the synthesis of the silicon-containing α-amino acids *rac*-**1**−*rac*-**3** and (*R*)-**1**−(*R*)-**3**

were developed. The β-(trimethylsilyl)alanine derivatives (*R*)-**1**−(*R*)-**3** (L-configuration), with their bulky triorganylsilyl group and their $SiCH_2NH_2$, $SiCH_2OH$, or $SiCH_2SH$ functionality, are promising building blocks for the synthesis of new biologically active peptides. To the best of our knowledge, analogous *β-tert*-butylalanine derivatives of the formula type $Me_2C(CH_2R)CH_2CH(NH_2)COOH$ (R = NH_2, OH, SH) have not been reported in the literature. It is interesting to note that such compounds, as a matter of principle, cannot be synthesized by using the preparative method developed for the synthesis of β-(triorganylsilyl)alanine derivatives.[9]

Experimental Section

General Procedures. Except for the hydrolyses, all syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. The ^{1}H NMR spectra were recorded at 22 °C on a Bruker DMX-600 (^{1}H, 600.1 MHz), Bruker AMX-400 (^{1}H, 400.1 MHz), or Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz). ^{13}C NMR spectra were recorded at 22 °C on a Bruker AMX-400 (^{13}C, 100.6 MHz) or Bruker DRX-300 NMR spectrometer (^{13}C, 75.5 MHz). ^{29}Si NMR spectra were recorded at 22 °C on a Bruker DRX-300 NMR spectrometer (^{29}Si, 59.6 MHz). Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^{1}H, δ 7.24; solvent $CDCl_3$), internal $CDCl_3$ (^{13}C, δ 77.0; solvent $CDCl_3$), internal HDO (^{1}H, δ 4.82; solvent D_2O), or external TMS (^{13}C, δ 0; solvent D_2O; ^{29}Si, δ 0, solvents $CDCl_3$ and D_2O). Assignment of the ^{1}H NMR data of *rac*-**6**, *rac*-**7**, *rac*-**10**, (2*R*,5*R*)-**14**−(2*R*,5*R*)-**16**, and (2*S*,5*R*)-**14**−(2*S*,5*R*)-**16** was supported by ^{1}H,^{1}H COSY experiments. Assignment of the ^{13}C NMR data was supported by DEPT 135 experiments (all compounds) and by ^{13}C,^{1}H HMQC and ^{13}C,^{1}H HMBC experiments (*rac*-**6**, *rac*-**7**, *rac*-**10**, (2*R*,5*R*)-**14**−(2*R*,5*R*)-**16**, and (2*S*,5*R*)-**14**−(2*S*,5*R*)-**16**). Preparative liquid chromatography (column: 60 mm i.d. × 50 cm) was performed using silica gel as the stationary phase (silica gel 60, 0.015−0.040 mm; Merck 115111).

Preparation of *rac*-β-[(Aminomethyl)dimethylsilyl]-alanine Dihydrochloride (*rac*-1·2HCl). Hydrochloric acid (3 M, 6 mL) was added dropwise at 0 °C within 15 min to a stirred solution of *rac*-**6** (350 mg, 872 μmol) in ethanol (4 mL) and the mixture stirred at 0 °C for 3 h. The solvent was removed in vacuo (0.001 mbar, 20 °C), the residue was dissolved in 6 M hydrochloric acid (12 mL), and the resulting solution was heated under reflux for 2 days. After the mixture was cooled to room temperature, the solvent was removed in vacuo (0.001 mbar, 20 °C), and the residue was washed with tetrahydrofuran (3 × 3 mL) and then dried (0.001 mbar, 20 °C, 1 h). This procedure was repeated, starting with the addition of 6 M hydrochloric acid (12 mL) and heating the resulting solution under reflux for 2 days. After the mixture was cooled to room temperature, the solvent was removed in vacuo (0.001 mbar, 20 °C). The residue was washed with tetrahydrofuran (3 × 3 mL) and ethanol (8 × 300 μL) and then dried (0.001 mbar, 20 °C, 9 h) to give *rac*-**1**·2HCl in 85% yield as a colorless solid (185 mg, 742 μmol); mp 143 °C. ^{1}H NMR (300.1 MHz, CD_3OD): δ 0.24 (s, 3 H, $SiCH_3$), 0.25 (s, 3 H, $SiCH_3$), 1.26 (δ_A), 1.32 (δ_B), and 4.03 (δ_X) (^2J(AB) = 14.5 Hz, ^3J(AX) = 6.2 Hz, ^3J(BX) = 10.4 Hz, 3 H, $SiCH_AH_BCH_X$), 2.43 (s, 2 H, $SiCH_2N$). ^{13}C NMR (75.5 MHz, CD_3OD): δ −3.8 ($SiCH_3$), −3.7 ($SiCH_3$), 18.4 ($SiCH_2CH$), 28.8 ($SiCH_2N$), 51.7 ($SiCH_2CH$), 172.2 (C=O). ^{29}Si NMR (59.6 MHz, CD_3OD): δ 1.7. Anal. Calcd for $C_6H_{18}Cl_2N_2O_2Si$: C, 28.92; H, 7.28; N, 11.24. Found: C, 28.7; H, 7.1; N, 11.0.

Preparation of (*R*)-β-[(Aminomethyl)dimethylsilyl]-alanine Dihydrochloride ((*R*)-1·2HCl). This compound was prepared analogously to the synthesis of *rac*-**1**·2HCl, starting from (2*R*,5*R*)-**14** (500 mg, 1.13 mmol). The product was isolated in 83% yield as a colorless solid (233 mg, 935 μmol); mp 153 °C. The NMR data of this compound were identical with those obtained for *rac*-**1**·2HCl. Anal. Calcd for $C_6H_{18}Cl_2N_2O_2Si$: C, 28.92; H, 7.28; N, 11.24. Found: C, 28.7; H, 7.1; N, 11.0.

Preparation of *rac*-β-[(Hydroxymethyl)dimethylsilyl]-alanine Hydrochloride (*rac*-2·HCl). A 1.0 M ethereal HCl solution (550 μL, 550 μmol HCl) was added at 0 °C within 5 min to a solution of *rac*-**9** (100 mg, 546 μmol) in ethanol (2 mL). After the mixture was stirred at 0 °C for 3 h, it was kept undisturbed at −20 °C for 14 days. The resulting solid was isolated by centrifugation and washed with ethanol (2 × 1 mL). Afterward, hydrochloric acid (1 M, 2 mL) was added to the product at 0 °C within 1 min and the solution stirred at 0 °C for 5 min. The solvent was removed in vacuo (0.001 mbar, 20 °C) and the product dried (0.001 mbar, 20 °C, 6 h) to give *rac*-**2**·HCl in 60% yield as a colorless solid (69.5 mg, 325 μmol); mp 125 °C. ^{1}H NMR (300.1 MHz, D_2O): δ 0.12 (s, 3 H, $SiCH_3$), 0.17 (s, 3 H, $SiCH_3$), 1.23 (δ_A), 1.29 (δ_B), and 3.81 (δ_X) (^2J(AB) = 14.5 Hz, ^3J(AX) = 6.8 Hz, ^3J(BX) = 8.7 Hz, 3 H, $SiCH_AH_BCH_X$), 3.44 (s, 2 H, $SiCH_2O$). ^{13}C NMR (75.5 MHz, D_2O): δ −5.5 ($SiCH_3$), −5.3 ($SiCH_3$), 17.7 ($SiCH_2CH$), 51.7 ($SiCH_2CH$), 52.9 ($SiCH_2O$), 172.2 (C=O). ^{29}Si NMR (59.6 MHz, D_2O): δ −0.8. Anal. Calcd for $C_6H_{16}ClNO_3Si$: C, 33.72; H, 7.55; N, 6.55. Found: C, 33.5; H, 7.8; N, 6.5.

Preparation of (*R*)-β-[(Hydroxymethyl)dimethylsilyl]-alanine Hydrochloride ((*R*)-2·HCl). This compound was prepared analogously to the synthesis of *rac*-**2**·HCl, starting from (*R*)-**9** (100 mg, 546 μmol). The product was isolated in 62% yield as a colorless solid (71.8 mg, 336 μmol); mp 136 °C. The NMR data of this compound were identical with those obtained for *rac*-**2**·HCl. Anal. Calcd for $C_6H_{16}ClNO_3Si$: C, 33.72; H, 7.55; N, 6.55. Found: C, 33.6; H, 7.7; N, 6.5.

Preparation of *rac*-β-[(Mercaptomethyl)dimethylsilyl]-alanine Hydrochloride (*rac*-3·HCl). A solution of *rac*-**11** (150 mg, 678 μmol) in 6 M hydrochloric acid (5 mL) was heated under reflux for 5 min. After the mixture was cooled to room temperature, the solvent was removed in vacuo (0.001 mbar, 20 °C), the solid residue was dissolved in 0.3 M hydrochloric acid (4 mL), and the resulting solution was heated under reflux for 3 h.[10] Afterward, the solvent was removed in vacuo (0.001 mbar, 20 °C) and the product dried (0.001 mbar, 20 °C, 9 h) to give *rac*-**3**·HCl in 95% yield as a colorless solid (148 mg, 644 μmol); mp 123 °C. ^{1}H NMR (300.1 MHz, CD_3OD): δ 0.11 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 1.16 (δ_A), 1.17 (δ_B), and 3.92 (δ_X) (^2J(AB) = 14.2 Hz, ^3J(AX) = 6.0 Hz, ^3J(BX) = 10.4 Hz, 3 H, $SiCH_AH_BCH_X$), 1.67 (s, 2 H, $SiCH_2S$). ^{13}C NMR (75.5 MHz, CD_3OD): δ −3.7 ($SiCH_3$), −3.5 ($SiCH_3$), 7.1 ($SiCH_2CH$), 18.4 ($SiCH_2S$), 51.9 ($SiCH_2CH$), 172.2 (C=O). ^{29}Si NMR (59.6 MHz, CD_3OD): δ 3.0. Anal. Calcd for $C_6H_{16}ClNO_2SSi$: C, 31.36; H, 7.02; N, 6.10; S, 13.95. Found: C, 31.4; H, 6.8; N, 6.3; S, 13.7.

Preparation of (*R*)-β-[(Mercaptomethyl)dimethylsilyl]-alanine Hydrochloride ((*R*)-3·HCl). This compound was prepared analogously to the synthesis of *rac*-**3**·HCl, starting from (*R*)-**11** (142 mg, 641 μmol). The product was isolated in 93% yield as a colorless solid (137 mg, 596 μmol); mp 132 °C. The NMR data of this compound were identical with those obtained for *rac*-**3**·HCl. Anal. Calcd for $C_6H_{16}ClNO_2SSi$: C, 31.36; H, 7.02; N, 6.10; S, 13.95. Found: C, 31.3; H, 7.2; N, 6.3; S, 13.7.

(9) Attempts to prepare *rac*-3,6-diethoxy-2-neopentyl-2,5-dihydropyrazine analogously to the synthesis of *rac*-3,6-diethoxy-2-[(trimethylsilyl)methyl]-2,5-dihydropyrazine (see ref 2c) failed. Even treatment of lithiated **4** with neopentyl bromide in tetrahydrofuran (reflux, 24 h) led only to traces of the neopentyl compound.

(10) Treatment of *rac*-**11** with 6 M hydrochloric acid yielded a mixture of *rac*-**3** (main product) and the corresponding cyclic thioester (minor product), which could be transformed again into *rac*-**3** by subsequent treatment with 0.3 M hydrochloric acid.

Preparation of 3,6-Diethoxy-2,5-dihydropyrazine (4). This compound was synthesized according to ref 4.

Preparation of *rac*-2-{[(Chloromethyl)dimethylsilyl]methyl}-3,6-diethoxy-2,5-dihydropyrazine (*rac*-5). This compound was synthesized according to ref 2a.

Preparation of *rac*-2-{[Dimethyl(phthalimidomethyl)silyl]methyl}-3,6-diethoxy-2,5-dihydropyrazine (*rac*-6). A mixture of *rac*-**5** (2.89 g, 9.94 mmol), potassium phthalimide (2.00 g, 10.8 mmol), and methyltrioctylammonium chloride (Aliquat-336) (1.73 g, 4.28 mmol) in dimethylformamide (150 mL) was stirred at 40 °C for 9 h, followed by stirring at room temperature for a further 12 h. The solvent was removed under reduced pressure, and water (50 mL) and diethyl ether (100 mL) were added to the oily residue. The organic phase was separated and the aqueous layer extracted with diethyl ether (2 × 100 mL), and the combined organic extracts were dried over anhydrous sodium sulfate and then filtered over silica gel (30 g), followed by elution with diethyl ether (500 mL).[11] The solvent was removed under reduced pressure (rotary evaporator) and the product isolated and purified by liquid chromatography on silica gel (200 g; eluent *n*-hexane/diethyl ether (4:1 (v/v))). The product was recrystallized at −20 °C from *n*-hexane/diethyl ether (3:1 (v/v)) to give *rac*-**6** in 75% yield as a colorless crystalline solid (2.99 g, 7.45 mmol); mp 57−58 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.12 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.94 (δ_A) and 1.29 (δ_B) (^2J(AB) = 14.5 Hz, ^3J(AX) = 10.6 Hz, ^3J(BX) = 5.1 Hz, 2 H, $SiCH_AH_BCH_X$), 1.21 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 1.24 (t, ^3J(HH) = 7.1 Hz, 3 H, OCH_2CH_3), 3.25 (s, 2 H, $SiCH_2N$), 3.98 (t, ^5J(HH) = 3.7 Hz, 2 H, NCH_2C), 3.80−4.16 (m, 5 H, OCH_2CH_3, $SiCH_2CH$), 7.61−7.69 and 7.73−7.81 (m, 4 H, $C(O)C_6H_4C(O)$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −2.7 ($SiCH_3$), −2.6 ($SiCH_3$), 14.2 (OCH_2CH_3), 14.3 (OCH_2CH_3), 21.5 ($SiCH_2CH$), 28.8 ($SiCH_2N$), 46.3 (NCH_2C), 53.1 ($SiCH_2CH$), 61.0 (2 C) (OCH_2CH_3), 122.9 (C-3/C-6, $C(O)C_6H_4C(O)$), 132.3 (C-1/C-2, $C(O)C_6H_4C(O)$), 133.6 (C-4/C-5, $C(O)C_6H_4C(O)$), 161.6 ($CH_2C{=}N$), 166.2 ($CHC{=}N$), 168.5 (2 C) (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 3.6. Anal. Calcd for $C_{20}H_{27}N_3O_4Si$: C, 59.83; H, 6.78; N, 10.46. Found: C, 59.5; H, 6.8; N, 10.2.

Preparation of *rac*-2-{[(Acetoxymethyl)dimethylsilyl]methyl}-3,6-diethoxy-2,5-dihydropyrazine (*rac*-7). A mixture of *rac*-**5** (5.50 g, 18.9 mmol), potassium acetate (2.62 g, 26.7 mmol), and methyltrioctylammonium chloride (Aliquat-336) (4.90 g, 12.1 mmol) in dimethylformamide (250 mL) was stirred at 40 °C for 9 h, followed by stirring at room temperature for a further 36 h. The solvent was removed under reduced pressure, and water (50 mL) and diethyl ether (100 mL) were added to the oily residue. The organic phase was separated and the aqueous layer extracted with diethyl ether (2 × 100 mL), and the combined organic extracts were dried over anhydrous sodium sulfate and then filtered over silica gel (30 g), followed by elution with diethyl ether (500 mL).[11] The solvent was removed under reduced pressure (rotary evaporator) and the crude product purified by distillation in a Kugelrohr apparatus (oven temperature 143 °C/0.001 mbar) to give *rac*-**7** in 45% yield as a yellowish liquid (2.65 g, 8.43 mmol). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.10 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.86 (δ_A) and 1.22 (δ_B) (^2J(AB) = 14.5 Hz, ^3J(AX) = 10.4 Hz, ^3J(BX) = 4.9 Hz, 2 H, $SiCH_AH_BCH_X$), 1.23 (t, ^3J(HH) = 7.1 Hz, 3 H, OCH_2CH_3), 1.25 (t, ^3J(HH) = 7.1 Hz, 3 H, OCH_2CH_3), 2.01 (s, 3 H, $C(O)CH_3$), 3.76 (δ_A) and 3.83 (δ_B) (^2J(AB) = 14.2 Hz, 2 H, $SiCH_AH_BO$), 3.92−3.97 (m, 2 H, NCH_2C), 3.98−4.17 (m, 5 H, OCH_2CH_3, $SiCH_2CH$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −4.0 ($SiCH_3$), −3.8 ($SiCH_3$), 14.2 (OCH_2CH_3), 14.3 (OCH_2CH_3), 20.4 ($SiCH_2CH$), 20.8 ($C(O)CH_3$), 46.4 (NCH_2C), 53.0 ($SiCH_2CH$), 57.5 ($SiCH_2O$), 60.9 (OCH_2CH_3), 61.0 (OCH_2CH_3), 161.5 ($CH_2C{=}N$), 165.9 ($CHC{=}N$), 171.9 (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 0.8. Anal. Calcd for $C_{14}H_{26}N_2O_4Si$: C, 53.47; H, 8.33; N, 8.91. Found: C, 53.8; H, 8.3; N, 9.1.

Preparation of *rac*-β-[(Hydroxymethyl)dimethylsilyl]alanine Ethyl Ester (*rac*-8). Hydrochloric acid (3 M, 10 mL) was added dropwise at 0 °C within 15 min to a stirred solution of *rac*-**7** (1.50 g, 4.77 mmol) in ethanol (15 mL). After the mixture was stirred at 0 °C for 3 h and at room temperature for 5 days, the solvent was removed in vacuo (0.001 mbar, 20 °C) and the residue dissolved in dichloromethane (30 mL), followed by addition of saturated aqueous sodium carbonate solution (7 mL). The organic phase was separated and the aqueous layer extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure (rotary evaporator) and the residue distilled in a Kugelrohr apparatus (oven temperature 80 °C/0.002 mbar, separation of glycine ethyl ester; oven temperature 130 °C/0.002 mbar, purification of the product) to give *rac*-**8** in 81% yield as a colorless liquid (792 mg, 3.86 mmol). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ −0.03 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.89 (δ_A), 1.15 (δ_B), and 3.40 (δ_X) (^2J(AB) = 14.8 Hz, ^3J(AX) = 2.7 Hz, ^3J(BX) = 12.6 Hz, 3 H, $SiCH_AH_BCH_X$), 1.24 (t, ^3J(HH) = 7.1 Hz, 3 H, OCH_2CH_3), 3.0 (br s, 3 H, NH_2, OH), 3.22 (s, 2 H, $SiCH_2O$), 4.14 (q, ^3J(HH) = 7.1 Hz, 2 H, OCH_2CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.7 ($SiCH_3$), −4.3 ($SiCH_3$), 14.1 (OCH_2CH_3), 22.6 ($SiCH_2CH$), 50.5 ($SiCH_2CH$), 53.4 ($SiCH_2O$), 61.1 (OCH_2CH_3), 177.1 (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 0.7. Anal. Calcd for $C_8H_{19}NO_3Si$: C, 46.80; H, 9.33; N, 6.82. Found: C, 47.1; H, 9.2; N, 6.6.

Preparation of (*R*)-β-[(Hydroxymethyl)dimethylsilyl]alanine Ethyl Ester ((*R*)-8). This compound was prepared analogously to the synthesis of *rac*-**8**, starting from (2*R*,5*R*)-**15** (950 mg, 2.66 mmol). After the product was distilled in a Kugelrohr apparatus (oven temperature 85 °C/0.002 mbar, separation of (*R*)-valine ethyl ester; oven temperature 130 °C/0.002 mbar, purification of the product), (*R*)-**8** was isolated in 80% yield as a colorless liquid (439 mg, 2.14 mmol). The NMR data of this compound were identical with those obtained for *rac*-**8**. Anal. Calcd for $C_8H_{19}NO_3Si$: C, 46.80; H, 9.33; N, 6.82. Found: C, 47.0; H, 9.1; N, 6.6.

Preparation of the Lithium Salt of *rac*-β-[(Hydroxymethyl)dimethylsilyl]alanine (*rac*-9). Water (2.5 mL) and a 1.0 M aqueous lithium hydroxide solution (1.22 mL, 1.22 mmol of LiOH) were added to a solution of *rac*-**8** (250 mg, 1.22 mmol) in dioxane (6 mL). After the mixture was stirred at room temperature for 1 day, the solvent was removed in vacuo (0.1 mbar, 30 °C) and the residue washed with *n*-pentane (10 mL) and then dried (0.001 mbar, 20 °C, 3 h) to give *rac*-**9** in quantitative yield as a colorless solid (223 mg, 1.22 mmol); mp 100−102 °C. ^{1}H NMR (400.1 MHz, D_2O): δ 0.12 (s, 3 H, $SiCH_3$), 0.17 (s, 3 H, $SiCH_3$), 1.01 (δ_A), 1.15 (δ_B), and 3.37 (δ_X) (^2J(AB) = 14.7 Hz, ^3J(AX) = 8.8 Hz, ^3J(BX) = 6.2 Hz, 3 H, $SiCH_AH_BCH_X$), 3.38 (s, 2 H, $SiCH_2O$). ^{13}C NMR (100.6 MHz, D_2O): δ −5.6 ($SiCH_3$), −5.2 ($SiCH_3$), 21.6 ($SiCH_2CH$), 53.1 ($SiCH_2CH$), 53.9 ($SiCH_2O$), 185.0 (C=O). ^{29}Si NMR (79.5 MHz, D_2O): δ −0.7. Anal. Calcd for $C_6H_{14}LiNO_3Si$: C, 39.34; H, 7.70; Li, 3.79; N, 7.65. Found: C, 39.4; H, 7.7; Li, 4.0; N, 7.7.

Preparation of the Lithium Salt of (*R*)-β-[(Hydroxymethyl)dimethylsilyl]alanine ((*R*)-9). This compound was prepared analogously to the synthesis of *rac*-**9**, starting from (*R*)-**8** (250 mg, 1.22 mmol). The product was isolated in quantitative yield as a colorless solid (223 mg, 1.22 mmol); mp 102−106 °C. The NMR data of this compound were identical with those obtained for *rac*-**9**. Anal. Calcd for $C_6H_{14}LiNO_3Si$: C, 39.34; H, 7.70; Li, 3.79; N, 7.65. Found: C, 39.0; H, 7.4; Li, 3.9; N, 7.7.

Preparation of *rac*-2-{[(Acetylthiomethyl)dimethylsilyl]methyl}-3,6-diethoxy-2,5-dihydropyrazine (*rac*-10). A mixture of *rac*-**5** (6.39 g, 22.0 mmol) and potassium thioacetate (10.0 g, 87.6 mmol) in tetrahydrofuran (80 mL) was stirred at room temperature for 3 days. The suspension was

(11) This step was performed to separate from Aliquat-336.

filtered and the solvent of the filtrate removed under reduced pressure (rotary evaporator), followed by addition of diethyl ether (150 mL) and water (70 mL) to the residue. 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 sodium sulfate. The solvent was removed under reduced pressure (rotary evaporator) and the product isolated and purified by liquid chromatography on silica gel (200 g; eluent *n*-hexane/ethyl acetate (20:1 (v/v))) to give *rac*-**10** in 48% yield as a yellowish liquid (3.49 g, 10.6 mmol). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.11 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.86 (δ_A) and 1.23 (δ_B) (^2J(AB) = 14.5 Hz, ^3J(AX) = 10.6 Hz, ^3J(BX) = 4.9 Hz, 2 H, $SiCH_AH_BCH_X$), 1.23 (t, ^3J(HH) = 7.1 Hz, 3 H, OCH_2CH_3), 1.24 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 2.13 (δ_A) and 2.19 (δ_B) (^2J(AB) = 13.8 Hz, 2 H, $SiCH_AH_BS$), 2.30 (s, 3 H, $C(O)CH_3$), 3.92−3.99 (m, 2 H, NCH_2C), 4.00−4.20 (m, 5 H, OCH_2CH_3, $SiCH_2CH$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −2.8 ($SiCH_3$), −2.6 ($SiCH_3$), 13.8 ($SiCH_2S$), 14.2 (OCH_2CH_3), 14.3 (OCH_2CH_3), 21.3 ($SiCH_2CH$), 30.1 ($C(O)CH_3$), 46.3 (NCH_2C), 53.1 ($SiCH_2CH$), 61.0 (OCH_2CH_3), 61.3 (OCH_2CH_3), 161.4 ($CH_2C{=}N$), 166.0 ($CHC{=}N$), 196.8 (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 2.9. Anal. Calcd for $C_{14}H_{26}N_2O_3SSi$: C, 50.88; H, 7.93; N, 8.48; S, 9.70. Found: C, 50.7; H, 8.0; N, 8.6; S, 9.8.

Preparation of *rac*-β-[(Mercaptomethyl)dimethylsilyl]-alanine Ethyl Ester (*rac*-11). Hydrochloric acid (3 M, 15 mL) was added dropwise at 0 °C within 15 min to a stirred solution of *rac*-**10** (900 mg, 2.72 mmol) in ethanol (10 mL). After the mixture was stirred at 0 °C for 3 h, the solvent was removed in vacuo (0.001 mbar, 20 °C) and the residue dissolved in ethanol (30 mL), followed by addition of concentrated hydrochloric acid (1.5 mL) at room temperature within 5 min. The resulting solution was heated under reflux for 5 h,[12] the solvent removed in vacuo (0.001 mbar, 20 °C), and the residue dissolved in dichloromethane (30 mL), followed by addition of a saturated aqueous sodium carbonate solution (7 mL). The organic phase was separated and the aqueous layer extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue distilled in a Kugelrohr apparatus (oven temperature 80 °C/0.002 mbar, separation of glycine ethyl ester; oven temperature 110 °C/0.002 mbar, purification of the product) to give *rac*-**11** in 73% yield as a colorless liquid (442 mg, 2.00 mmol). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.12 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.95 (δ_A), 1.13 (δ_B), and 3.48 (δ_X) (^2J(AB) = 14.7 Hz, ^3J(AX) = 9.6 Hz, ^3J(BX) = 5.9 Hz, 3 H, $SiCH_AH_BCH_X$), 1.25 (δ_X), 4.12 (δ_A), and 4.14 (δ_B) (^2J(AB) = 10.8 Hz, ^3J(AX) = 7.1 Hz, ^3J(BX) = 7.1 Hz, 5 H, $OCH_AH_BC(H_X)_3$), 1.7 (br s, 3 H, NH_2, SH), 1.71 (s, 2 H, $SiCH_2S$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −3.5 ($SiCH_3$), −3.4 ($SiCH_3$), 7.5 ($SiCH_2S$), 14.2 (OCH_2CH_3), 20.7 ($SiCH_2CH$), 51.7 ($SiCH_2CH$), 60.9 (OCH_2CH_3), 177.1 (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 3.9. Anal. Calcd for $C_8H_{19}NO_2SSi$: C, 43.40; H, 8.65; N, 6.33; S, 14.48. Found: C, 43.2; H, 8.8; N, 6.5; S, 14.2.

Preparation of (*R*)-β-[(Mercaptomethyl)dimethylsilyl]-alanine Ethyl Ester ((*R*)-11). This compound was prepared analogously to the synthesis of *rac*-**11**, starting from (2*R*,5*R*)-**16** (997 mg, 2.68 mmol). After the product was distilled in a Kugelrohr apparatus (oven temperature 90 °C/0.002 mbar, separation of (*R*)-valine ethyl ester; oven temperature 110 °C/0.002 mbar, purification of the product), (*R*)-**11** was isolated in 78% yield as a colorless liquid (464 mg, 2.10 mmol). The NMR data of this compound were identical with those obtained for *rac*-**11**. Anal. Calcd for $C_8H_{19}NO_2SSi$: C, 43.40; H, 8.65; N, 6.33; S, 14.48. Found: C, 43.2; H, 8.8; N, 6.5; S, 14.2.

Preparation of (*R*)-3,6-Diethoxy-2-isopropyl-2,5-dihydropyrazine ((*R*)-12). This compound was synthesized according to ref 2a. In this context, see also refs 7 and 8.

(12) Treatment with boiling ethanol/hydrochloric acid was necessary to generate the mercapto group of *rac*-**11** via transesterification.

Preparation of (2*R*,5*R*)- and (2*S*,5*R*)-2-{[(Chloromethyl)dimethylsilyl]methyl}-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine ((2*R*,5*R*)-13, (2*S*,5*R*)-13; Molar Ratio 85:15). These compounds were synthesized as a mixture according to ref 2a.

Preparation of (2*R*,5*R*)- and (2*S*,5*R*)-2-{[Dimethyl(phthalimidomethyl)silyl]methyl}-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine ((2*R*,5*R*)-14, (2*S*,5*R*)-14). These compounds were prepared analogously to the synthesis of *rac*-**6**, starting from (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13** (7.00 g, 21.0 mmol; molar ratio 85:15), potassium phthalimide (5.10 g, 27.5 mmol), and methyltrioctylammonium chloride (Aliquat-336) (5.45 g, 13.5 mmol) in dimethylformamide (250 mL). The product was isolated and purified by MPLC on silica gel (200 g; eluent *n*-hexane/diethyl ether (5:1 (v/v))) to give (2*R*,5*R*)-**14**/(2*S*,5*R*)-**14** (molar ratio 81:19, GC analysis) in 77% yield as a colorless liquid (7.17 g, 16.2 mmol). The diastereomerically pure compounds (2*R*,5*R*)-**14** and (2*S*,5*R*)-**14** were obtained by MPLC separation (for the general procedure, see below).

Data for (2*R*,5*R*)-14. Yield: 58% (5.38 g, 12.1 mmol), relative to (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13**; diastereomeric purity ≥ 99% de. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.11 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$), 0.69 (d, ^3J(HH) = 6.8 Hz, 3 H, $CHCH_3$), 0.95 (δ_A) and 1.38 (δ_B) (^2J(AB) = 14.5 Hz, ^3J(AX) = 10.8 Hz, ^3J(BX) = 4.7 Hz, 2 H, $SiCH_AH_BCH_X$), 0.99 (d, ^3J(HH) = 6.8 Hz, 3 H, $CHCH_3$), 1.21 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 1.24 (t, ^3J(HH) = 7.1 Hz, 3 H, OCH_2CH_3), 2.23 (dsept, ^3J(HH) = 3.3 Hz, ^3J(HH) = 6.8 Hz, ^3J(HH) = 6.8 Hz, 1 H, $CHCH(CH_3)_2$), 3.24 (δ_A) and 3.29 (δ_B) (^2J(AB) = 15.3 Hz, 2 H, $SiCH_AH_BN$), 3.91 (t, ^2J(HH) = 3.3 Hz, ^5J(HH) = 3.3 Hz, 1 H, $CHCH(CH_3)_2$), 3.94−4.24 (m, 5 H, OCH_2CH_3, $SiCH_2CH$), 7.60−7.69 and 7.73−7.81 (m, 4 H, $C(O)C_6H_4C(O)$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −2.5 ($SiCH_3$), −2.4 ($SiCH_3$), 14.29 (OCH_2CH_3), 14.34 (OCH_2CH_3), 16.9 ($CHCH_3$), 19.0 ($CHCH_3$), 21.6 ($SiCH_2CH$), 29.0 ($SiCH_2N$), 32.0 ($CHCH_3$), 52.8 ($SiCH_2CH$), 60.7 ($CHCH(CH_3)_2$), 61.0 (2 C) (OCH_2CH_3), 122.8 (C-3/C-6, $C(O)C_6H_4C(O)$), 132.3 (C-1/C-2, $C(O)C_6H_4C(O)$), 133.5 (C-4/C-5, $C(O)C_6H_4C(O)$), 162.7 (C=N), 164.8 (C=N), 168.6 (2 C) (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 3.7. Anal. Calcd for $C_{23}H_{33}N_3O_4Si$: C, 62.27; H, 7.50; N, 9.47. Found: C, 61.8; H, 7.5; N, 9.4.

Data for (2*S*,5*R*)-14. Yield: 12% (1.08 g, 2.43 mmol), relative to (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13**; diastereomeric purity ≥ 99% de. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.14 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.75 (d, ^3J(HH) = 6.8 Hz, 3 H, $CHCH_3$), 0.82 (δ_A) and 1.40 (δ_B) (^2J(AB) = 14.5 Hz, ^3J(AX) = 11.8 Hz, ^3J(BX) = 4.7 Hz, 2 H, $SiCH_AH_BCH_X$), 1.02 (d, ^3J(HH) = 7.0 Hz, 3 H, $CHCH_3$), 1.20 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 1.23 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 2.23 (dsept, ^3J(HH) = 4.2 Hz, ^3J(HH) = 6.8 Hz, ^3J(HH) = 6.8 Hz, 1 H, $CHCH(CH_3)_2$), 3.25 (δ_A) and 3.31 (δ_B) (^2J(AB) = 15.1 Hz, 2 H, $SiCH_AH_BN$), 3.84 (t, ^3J(HH) = 4.2 Hz, ^5J(HH) = 4.2 Hz, 1 H, $CHCH(CH_3)_2$), 3.93−4.20 (m, 5 H, OCH_2CH_3, $SiCH_2CH$), 7.60−7.69 and 7.72−7.82 (m, 4 H, $C(O)C_6H_4C(O)$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −2.6 ($SiCH_3$), −2.4 ($SiCH_3$), 14.3 (OCH_2CH_3), 14.4 (OCH_2CH_3), 17.7 ($CHCH_3$), 19.5 ($CHCH_3$), 22.6 ($SiCH_2CH$), 28.8 ($SiCH_2N$), 31.5 ($CHCH_3$), 52.9 ($SiCH_2CH$), 60.4 (2 C) (OCH_2CH_3), 60.9 ($CHCH(CH_3)_2$), 122.8 (C-3/C-6, $C(O)C_6H_4C(O)$), 132.3 (C-1/C-2, $C(O)C_6H_4C(O)$), 133.5 (C-4/C-5, $C(O)C_6H_4C(O)$), 162.4 (C=N), 164.5 (C=N), 168.6 (2 C) (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 3.8. Anal. Calcd for $C_{23}H_{33}N_3O_4Si$: C, 62.27; H, 7.50; N, 9.47: Found: C, 61.8; H, 7.6; N, 9.3.

Preparation of (2*R*,5*R*)- and (2*S*,5*R*)-2-{[(Acetoxymethyl)dimethylsilyl]methyl}-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine ((2*R*,5*R*)-15, (2*S*,5*R*)-15). These compounds were prepared analogously to the synthesis of *rac*-**7**, starting from (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13** (7.00 g, 21.0 mmol; molar ratio 85:15), potassium acetate (3.50 g, 35.7 mmol), and methyltrioctylammonium chloride (Aliquat-336) (6.62 g, 16.4 mmol) in dimethylformamide (350 mL). The crude product was distilled in a Kugelrohr apparatus (oven temperature 165 °C/0.001 mbar) and then further purified by liquid chrom-

atography on silica gel (200 g; eluent *n*-hexane/ethyl acetate (20:1 (v/v))) to give (2*R*,5*R*)-**15**/(2*S*,5*R*)-**15** (molar ratio 79:21, GC analysis) in 47% yield as a colorless liquid (3.52 g, 9.87 mmol). The diastereomerically pure compounds (2*R*,5*R*)-**15** and (2*S*,5*R*)-**15** were obtained by MPLC separation (for the general procedure, see below).

Data for (2*R*,5*R*)-15. Yield: 31% (2.29 g, 6.42 mmol), relative to (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13**; diastereomeric purity ≥ 99% de. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.09 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.69 (d, ^3J(HH) = 6.8 Hz, 3 H, $CHCH_3$), 0.91 (δ_A) and 1.31 (δ_B) (^2J(AB) = 14.5 Hz, ^3J(AX) = 10.6 Hz, ^3J(BX) = 4.9 Hz, 2 H, $SiCH_AH_BCH_X$), 0.99 (d, ^3J(HH) = 6.8 Hz, 3 H, $CHCH_3$), 1.24 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 1.26 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 2.01 (s, 3 H, $C(O)CH_3$), 2.23 (dsept, ^3J(HH) = 3.2 Hz, ^3J(HH) = 6.8 Hz, ^3J(HH) = 6.8 Hz, 1 H, $CHCH(CH_3)_2$), 3.77 (δ_A) und 3.85 (δ_B) (^2J(AB) = 14.2 Hz, 2 H, $SiCH_AH_BO$), 3.89 (t, ^3J(HH) = 3.2 Hz, ^5J(HH) = 3.2 Hz, 1 H, $CHCH(CH_3)_2$), 3.94−4.25 (m, 5 H, OCH_2CH_3, $SiCH_2CH$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −3.9 ($SiCH_3$), −3.7 ($SiCH_3$), 14.33 (OCH_2CH_3), 14.34 (OCH_2CH_3), 16.8 ($CHCH_3$), 19.0 ($CHCH_3$), 20.5 ($SiCH_2CH$), 20.8 ($C(O)CH_3$), 32.0 ($CHCH_3$), 52.8 ($SiCH_2CH$), 57.7 ($SiCH_2O$), 60.6 (2 C) (OCH_2CH_3), 60.7 ($CHCH(CH_3)_2$), 162.5 (C=N), 164.7 (C=N), 172.0 (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 0.8. Anal. Calcd for $C_{17}H_{32}N_2O_4Si$: C, 57.27; H, 9.05; N, 7.86. Found: C, 57.1; H, 8.8; N, 7.8.

Data for (2*S*,5*R*)-15. Yield: 7% (531 mg, 1.49 mmol), relative to (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13**; diastereomeric purity ≥ 99% de. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.12 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$), 0.74 (d, ^3J(HH) = 7.0 Hz, 3 H, $CHCH_3$), 0.80 (δ_A) and 1.32 (δ_B) (^2J(AB) = 14.4 Hz, ^3J(AX) = 11.6 Hz, ^3J(BX) = 4.7 Hz, 2 H, $SiCH_AH_BCH_X$), 1.02 (d, ^3J(HH) = 7.0 Hz, 3 H, $CHCH_3$), 1.23 (t, ^3J(HH) = 7.0 Hz, 3 H, OCH_2CH_3), 1.25 (t, ^3J(HH) = 7.0 Hz, 3 H, OCH_2CH_3), 2.01 (s, 3 H, $C(O)CH_3$), 2.16 (dsept, ^3J(HH) = 4.2 Hz, ^3J(HH) = 7.0 Hz, ^3J(HH) = 7.0 Hz, 1 H, $CHCH(CH_3)_2$), 3.79 (δ_A) and 3.86 (δ_B) (^2J(AB) = 14.2 Hz, 2 H, $SiCH_AH_BO$), 3.86 (t, ^3J(HH) = 4.2 Hz, ^5J(HH) = 4.2 Hz, 1 H, $CHCH(CH_3)_2$), 3.93−4.26 (m, 5 H, OCH_2CH_3, $SiCH_2CH$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −3.9 ($SiCH_3$), −3.8 ($SiCH_3$), 14.3 (OCH_2CH_3), 14.4 (OCH_2CH_3), 17.7 ($CHCH_3$), 19.5 ($CHCH_3$), 20.8 ($SiCH_2CH$), 21.5 ($C(O)CH_3$), 31.4 ($CHCH_3$), 52.9 ($SiCH_2CH$), 57.7 ($SiCH_2O$), 60.4 (OCH_2CH_3), 60.6 (OCH_2CH_3), 60.9 ($CHCH(CH_3)_2$), 162.2 (C=N), 164.4 (C=N), 172.0 (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 0.9. Anal. Calcd for $C_{17}H_{32}N_2O_4Si$: C, 57.27; H, 9.05; N, 7.86. Found: C, 57.1; H, 8.8; N, 7.8.

Preparation of (2*R*,5*R*)- and (2*S*,5*R*)-2-{[(Acetylthiomethyl)dimethylsilyl]methyl}-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine ((2*R*,5*R*)-16, (2*S*,5*R*)-16). These compounds were prepared analogously to the synthesis of *rac*-**10**, starting from (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13** (8.00 g, 24.0 mmol; molar ratio 85:15) and potassium thioacetate (13.0 g, 114 mmol) in tetrahydrofuran (100 mL). The product was isolated and purified by liquid chromatography on silica gel (350 g; eluent *n*-hexane/ethyl acetate (20:1 (v/v))) to give (2*R*,5*R*)-**16**/(2*S*,5*R*)-**16** (molar ratio 83:17, GC analysis) in 65% yield as a colorless liquid (5.82 g, 15.6 mmol). The diastereomerically pure compounds (2*R*,5*R*)-**16** and (2*S*,5*R*)-**16** were obtained by MPLC separation (for the general procedure, see below).

Data for (2*R*,5*R*)-16. Yield: 53% (4.77 g, 12.8 mmol), relative to (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13**; diastereomeric purity ≥ 99% de. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.09 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.68 (d, ^3J(HH) = 6.8 Hz, 3 H, $CHCH_3$), 0.89 (δ_A) and 1.32 (δ_B) (^2J(AB) = 14.9 Hz, ^3J(AX) = 10.6 Hz, ^3J(BX) = 4.5 Hz, 2 H, $SiCH_AH_BCH_X$), 0.99 (d, ^3J(HH) = 6.8 Hz, 3 H, $CHCH_3$), 1.23 (t, ^3J(HH) = 7.1 Hz, 3 H, OCH_2CH_3), 1.26 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 2.13 (δ_A) and 2.19 (δ_B) (^2J(AB) = 13.8 Hz, 2 H, $SiCH_AH_BS$), 2.23 (dsept, ^3J(HH) = 3.4 Hz, ^3J(HH) = 6.8 Hz, ^3J(HH) = 6.8 Hz, 1 H, $CHCH(CH_3)_2$), 2.34 (s, 3 H, $C(O)CH_3$), 3.89 (t, ^3J(HH) = 3.4 Hz, ^5J(HH) = 3.4 Hz, 1 H, $CHCH(CH_3)_2$), 3.93−4.24 (m, 5 H, OCH_2CH_3, $SiCH_2CH$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −2.7 ($SiCH_3$), −2.5 ($SiCH_3$), 14.0 ($SiCH_2S$), 14.3 (OCH_2CH_3), 14.4 (OCH_2CH_3), 16.8 ($CHCH_3$), 19.0 ($CHCH_3$), 21.4 ($SiCH_2CH$), 30.1 ($C(O)CH_3$), 32.0 ($CHCH_3$), 52.8 ($SiCH_2CH$), 60.7 ($CHCH(CH_3)_2$), 60.8 (2 C) (OCH_2CH_3), 162.6 (C=N), 164.6 (C=N), 197.0 (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 2.9. Anal. Calcd for $C_{17}H_{32}N_2O_3SSi$: C, 54.80; H, 8.66; N, 7.52; S, 8.61. Found: C, 54.7; H, 8.5; N, 7.6; S, 8.7.

Data for (2*S*,5*R*)-16. Yield: 9% (845 mg, 2.27 mmol), relative to (2*R*,5*R*)-**13**/(2*S*,5*R*)-**13**; diastereomeric purity ≥ 99% de. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.12 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.74 (d, ^3J(HH) = 6.8 Hz, 3 H, $CHCH_3$), 0.75 (δ_A) and 1.31 (δ_B) (^2J(AB) = 14.5 Hz, ^3J(AX) = 11.9 Hz, ^3J(BX) = 4.5 Hz, 2 H, $SiCH_AH_BCH_X$), 1.02 (d, ^3J(HH) = 7.0 Hz, 3 H, $CHCH_3$), 1.23 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 1.25 (t, ^3J(HH) = 7.2 Hz, 3 H, OCH_2CH_3), 2.16 (δ_A) and 2.22 (δ_B) (^2J(AB) = 13.8 Hz, 2 H, $SiCH_AH_BS$), 2.17 (dqq, ^3J(HH) = 3.4 Hz, ^3J(HH) = 6.8 Hz, ^3J(HH) = 7.0 Hz, 1 H, $CHCH(CH_3)_2$), 2.30 (s, 3 H, $C(O)CH_3$), 3.85 (t, ^3J(HH) = 4.2 Hz, ^5J(HH) = 4.2 Hz, 1 H, $CHCH(CH_3)_2$), 3.92−4.21 (m, 5 H, OCH_2CH_3, $SiCH_2CH$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −2.8 ($SiCH_3$), −2.6 ($SiCH_3$), 13.9 ($SiCH_2S$), 14.3 (OCH_2CH_3), 14.4 (OCH_2CH_3), 17.7 ($CHCH_3$), 19.5 ($CHCH_3$), 22.4 ($SiCH_2CH$), 30.1 ($C(O)CH_3$), 31.5 ($CHCH_3$), 53.0 ($SiCH_2CH$), 60.5 (2 C) (OCH_2CH_3), 60.9 ($CHCH(CH_3)_2$), 162.4 (C=N), 164.5 (C=N), 196.9 (C=O). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 3.0. Anal. Calcd for $C_{17}H_{32}N_2O_3SSi$: C, 54.80; H, 8.66; N, 7.52; S, 8.61. Found: C, 54.8; H, 8.9; N, 7.7; S, 8.7.

Preparative Separation of (2*R*,5*R*)-14/(2*S*,5*R*)-14, (2*R*,5*R*)-15/(2*S*,5*R*)-15, and (2*R*,5*R*)-16/(2*S*,5*R*)-16 by Medium-Pressure Liquid Chromatography (MPLC). The (2*R*,5*R*)- and (2*S*,5*R*)-isomers of **14**, **15**, and **16** were separated by medium-pressure liquid chromatography (MPLC) on silica gel (5−15 μm; YMC-GEL, 2778). The experimental conditions were as follows: LC pump, LEWA FL1; detector, spectral photometer 87.00, Knauer; column, 25 mm i.d. × 500 mm; pressure, 15−17 bar; eluent, *n*-hexane/ethyl acetate ((2*R*,5*R*)-**14**/(2*S*,5*R*)-**14**: 97:3 (v/v); (2*R*,5*R*)-**15**/(2*S*,5*R*)-**15**: 98.4:1.6 (v/v); (2*R*,5*R*)-**16**/(2*S*,5*R*)-**16**: 98.2:1.8 (v/v)); injection volume, 1.0 mL (ca. 500 mg of the sample material dissolved in 0.5 mL of the eluent); flow rate, 50 mL/min. The solvent of the respective fractions obtained ((2*R*,5*R*)-isomers, first fraction; (2*S*,5*R*)-isomers, second fraction) was removed under reduced pressure (rotary evaporator) at room temperature, and the respective diastereomerically products were then dried in vacuo (0.001 mbar, 20 °C, 3 h).

Analytical Separation of (2*R*,5*R*)-14/(2*S*,5*R*)-14, (2*R*,5*R*)-15/(2*S*,5*R*)-15, and (2*R*,5*R*)-16/(2*S*,5*R*)-16 by Capillary Gas Chromatography: Determination of Diastereomeric Purities. The (2*R*,5*R*)- and (2*S*,5*R*)-isomers of **14**, **15**, and **16** were separated by capillary gas chromatography (gas chromatograph, ThermoQuest MS-8060; DB-5M column (0.32 mm i.d. × 30 m), Ziemer; carrier gas, helium; temperature program, 80 °C (2 min) to 280 °C (20 min) with 10 °C/min; injector temperature, 225 °C; split 1:10; detector temperature, 225 °C). The retention times of the diastereomers of **14**, **15**, and **16** are listed in Table 1.

Determination of the Enantiomeric Purities of the Amino Acid Ethyl Esters (*R*)-8 and (*R*)-11 by ^{1}H NMR Spectroscopy. The enantiomeric purities of (*R*)-**8** and (*R*)-**11** were determined by ^{1}H NMR experiments using the chiral solvating agent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((*R*)-TFAE; Aldrich). The NMR spectra were recorded at 22 °C on a Bruker DRX-300 NMR spectrometer operating at 300.1 MHz. The composition of the samples (molar ratio) used for the ^{1}H NMR experiments was as follows: (*R*)-**8**/(*R*)-TFAE, 1:6; (*R*)-**11**/(*R*)-TFAE, 2.4:1; $CDCl_3$, 550 μL.

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