Synthesis of Silaproline, a New Proline Surrogate

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The asymmetric synthesis of a new proline surrogate, incorporating the dimethylsilyl group at position 4 of proline using Schöllkopf's bis-lactim ether method, is described.

Introduction

Knowledge of the active conformation of a given peptide is a major step towards understanding its biological activity. The number of conformational possibilities can be reduced by introducing constraints, such as the incorporation of cyclic amino acid residues. Proline plays a crucial role in peptide structures, especially in reverse-turn formations and therefore it is of great interest to synthesize new proline analogues. As recent examples of modified proline, 3-substituted prolines,[1] azaproline,[2] and racemic imidazolidine-2-carboxylic acids[3] have been synthesized. We now report the synthesis of a new silicon-containing proline surrogate, the 4-(dimethyl)silaproline, denoted silaproline (Sip). In addition, this new residue is expected to promote a higher solubility of silaproline-containing peptides, owing to the high lipophilicity of silyl groups. Indeed, insolubility of fully protected peptides causes difficulties during assembly as a result of internal aggregation of peptide chains. Numerous approaches to overcome this notorious problem have been described. A common solution consists in disrupting secondary structure by using aprotic solvents and chaotropic reagents as additives to the synthesis solvents.[4,5] An interesting alternative has been reported in which reversible *N*-substituted amino acids are introduced into synthetic peptides to eliminate intramolecular hydrogen bonding.[6,7] The incorporation into peptide sequences of serine or threonine as oxazolidine, or cysteine as thiazolidine, offers another possibility of disrupting the internal association of the peptide, thus increasing the solvation of the peptide chain.[8–10] Our new silicon-containing proline surrogate could be expected to contribute to a better solubility of peptide analogues. In addition, replacing proline with this unnatural amino acid, which is presumably stable towards proteolytic enzymatic degradation, may increase the bioavailability of related peptides without affecting conformational and biological properties considering the structural similarity. In this paper we report the successful preparation of protected (*R*)- and (*S*)-silaproline.

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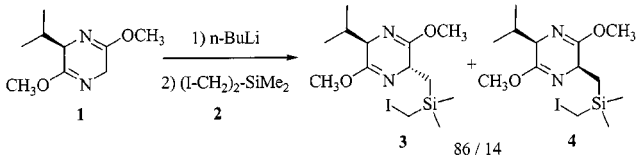
Results and Discussion

A method of synthesizing enantiomerically pure amino acids consists of introducing the side chain by diastereoselective alkylation of chiral glycine anion synthons. One of the most versatile and prolific chiral glycine equivalents is Schöllkopf's bis-lactim ether derived from *cyclo*-(Val–Gly).[11] Although this method has been extensively used to prepare various nonnatural amino acids,[12] only one application concerns a silicon-containing amino acid, the trimethylsilylalanine (TMS–Ala) which is proposed as a substitute for phenylalanine.[13] In this case, TMS–Ala is prepared in both enantiomeric forms by asymmetric synthesis starting from Schöllkopf's reagent and chloromethyltrimethylsilane. Other syntheses of TMS–Ala have been described in the literature,[14–16] and a more recent report concerns γ-silylated amino acids.[17] To the best of our knowledge, the other well-known methods for asymmetric synthesis of amino acids (Williams,[18] Oppolzer,[19] hydroxypinanone[20] methods) have not been applied to silicon-containing amino acids.

To prepare the silaproline, the major difficulty is due to the specificity of the alkylating reagent, which must bear two leaving groups to achieve the cyclization at the nitrogen atom after the *C*-alkylation. Bis(iodomethyl)dimethylsilane is suitable for this purpose.

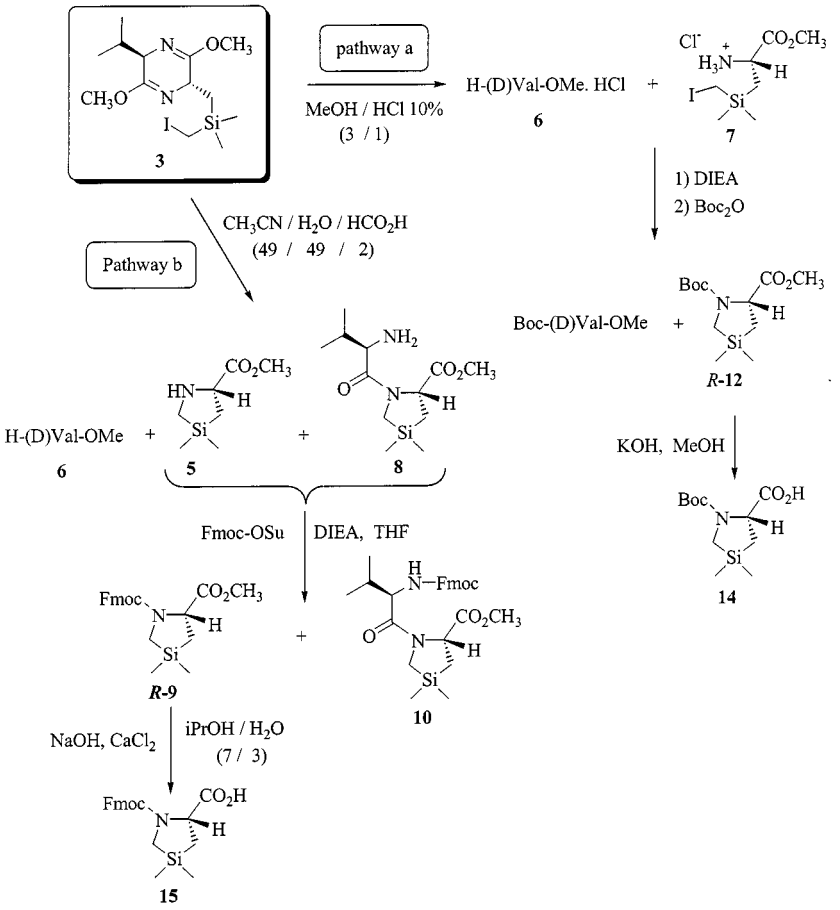
After exploring several unsuccessful chiral glycine enolate equivalents (oxazinone derivatives introduced by Williams, Oppolzer's camphor sultam, hydroxypinanone) for alkylation with bis(iodomethyl)dimethylsilane, we found that Schöllkopf's method enabled the preparation of the silaproline.

Deprotonation with BuLi of the bis-lactim ether **1**, resulting from the D-Val–Gly diketopiperazine,[11] afforded a planar cyclic anion intermediate which reacted with bis(iodomethyl)dimethylsilane **(2)** to give compounds **3** and **4**. Silane **2** was obtained from the corresponding dichloride



Scheme 1. Diastereoselective alkylation

  1434–193X/00/0305–807 $ 17.50+.50/0



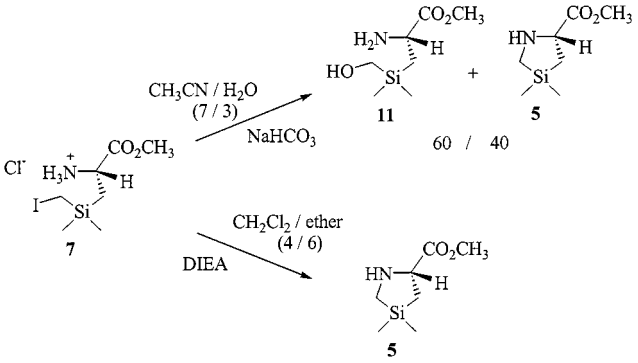
Scheme 2. Pathways to silaproline

on treatment with NaI in acetone. The reagent approached the less sterically hindered face preferentially, yielding the *trans*-disubstituted derivative **3** as the major product (72% diastereomeric excess); compounds **3** and **4** were readily separated by flash column chromatography (FCC) (Scheme 1).

It is worth noting that starting from D-Valine, an amino acid of the L-series [(*S*)-configuration] is obtained.[11] However, in the particular case of L-silaproline, the C_α is of (*R*)-configuration due to changed atom priorities.

To obtain the proline-like ring **5**, we investigated the cyclization step conditions. Distillation of compound **3** did not induce cyclization into silaproline although this method has been successfully applied by Schöllkopf for the synthesis of cyclic amino acids.[21] Acidic conditions (Scheme 2, pathway **a**) did not afford the desired cyclic compound, but hydrolyzed the bis-lactim ether. We established that $CH_3CN/H_2O/HCO_2H$ (49:49:2) were effective conditions to afford the expected silaproline methyl ester **5**, in a mixture along with valine methyl ester **6** and dipeptide **8** (Scheme 2, pathway **b**).

These particular acidic conditions promoted opening of the bis-lactim ether and allowed the nucleophilic amine to yield the expected ring closure reaction in a single step, although the resulting mixture of **5**, **8**, and **6** had to be purified by FCC. The mixture of ester **5** and dipeptide **8** was first derivatized with Fmoc–OSu and the corresponding Fmoc derivatives **9** and **10** were isolated with FCC. Formation of the unwanted dipeptide **8** could be avoided using pathway **a** to hydrolyze the bis-lactim derivative **3** and then cyclize iodide **7** to afford the desired silaproline methyl ester **5** (Scheme 2). However, treatment of iodide **7** with aqueous $NaHCO_3$ gave a mixture of the expected silaproline methyl ester **5** and the corresponding alcohol **11** in the ratio 40:60



Scheme 3. Cyclisation step

(Scheme 3). Hydrolysis of the iodide **7** could be avoided using diisopropylethylamine (DIEA) in an anhydrous environment. In this case, ester **5** was indeed obtained as the sole product.

Cyclization of iodide **7** could be finally realized in an one-pot fashion which involved hydrolysis of the bis-lactim

derivative **3** with a mixture of MeOH and 10% aqueous HCl and then treating this crude mixture of ester **6** and iodide **7** with DIEA. Sequential addition of Boc_2O resulted in the formation of a mixture of Boc–D-Val–OMe and Boc–L-Sip–OMe (***R*-12**) from which compound (***R*)-12** was readily obtained pure through FCC.

Unfortunately all attempts to separate a racemic mixture of Fmoc-(D,L)-silaproline methyl ester failed on chiral columns [Chiraspher (Merck), Chiralsel OD (Daicel), Whelk-01 (Regis)]. After Boc deprotection of (***R*)-12** by treating with TFA, the compound was allowed to react with (*Z*)-L-valine and (*Z*)-(D,L)-valine in the presence of 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) as coupling reagent. HPLC analysis (Waters *m*-Bondasphere C18) of the two diastereoisomeric dipeptides (**13a**, **b**) did not show distinct compounds whatever the conditions used. However, ^{1}H-NMR spectroscopy of the diastereomeric mixture clearly exhibited doubled peaks, which cannot be detected on the spectra resulting from derivatization with (*Z*)-L-valine of compound (***R*)-12** after Boc deprotection, undoubtedly proving the chiral integrity of our derivative.

Whereas saponification of Boc–Sip–OMe led unexceptionally to Boc–Sip–OH (**14**) under classical conditions, saponification of Fmoc–Sip–OMe needed more caution. Saponification was successfully achieved using $CaCl_2$ as an efficient additive to suppress Fmoc cleavage under basic conditions,[22] yielding **15**. In addition, saponification of *C*-terminal Sip methyl ester (both protocols) has been confirmed to induce no racemization. Indeed the analytical HPLC profile (Waters *m*-Bondasphere C18) of the acid-free diastereomeric mixture (*Z*)-(D,L)-Val–L-Sip–OH displayed distinct peaks whereas a single signal characterized the product resulting from saponification of (*Z*)-L-Val–L-Sip–OMe.

The NMR spectral data of compounds **9**, **12**, **14**, and **15** showed two set of signals. Indeed the urethane protection of intracyclic amine led to distinctive conformations.

Following the same procedure but starting from the L-valine derivative of the bis-lactim ether **1**, we have obtained the protected D-silaproline derivatives [Fmoc-D-Sip–OH, Boc-D-Sip–OH and H–Sip–OMe].

In conclusion, we have described the first synthesis of the highly lipophilic silaproline (Sip) in optically pure form in two different *N*-protected versions and as a free amino ester. All three compounds were directly useful for peptide synthesis. The incorporation of this new proline surrogate in several peptides to modulate their conformational, physicochemical, and biological properties is presently under investigation in our laboratory.

Experimental Section

2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), (*Z*)-L-valine and (*Z*)-(D,L)-valine were purchased from Novabiochem, (*R*)-3-isopropyl-2,5-piperazinedione from Fluka, diisopropylethylamine (DIEA), bis(chloromethyl)dimethylsilane, and trimethyloxonium tetrafluoroborate from Aldrich. Tetrahydrofuran (THF) was freshly distilled under argon from sodium and benzophenone. Dichloromethane was dried overnight with $CaCl_2$ then distilled on K_2CO_3 and stored away from bright light in a brown bottle. Water was obtained from a Milli-Q plus system (Millipore). Acetonitrile and trifluoroacetic acid (TFA) were purchased from Merck. – Thin layer chromatography was performed on Merck precoated silica gel $60F_{254}$ plates and spots were visualized by ultraviolet light or by staining with phosphomolybdic acid. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). – Optical rotations were determined with a Perkin–Elmer model 141 polarimeter. – ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker spectrometer AC 250 (250 MHz) or DRX 400 (400 MHz). Chemical shifts are given in δ values referenced to the residual solvent peak: chloroform ($CDCl_3$) at δ_H = 7.26 relative to tetramethylsilane (TMS) and δ_C = 77.6. – The ESI (electrospray ionization) mass spectra were recorded on a Micromass Platform II quadrupole mass spectrometer (Micromass) fitted with an electrospray source coupled with an HPLC Waters or with a Jeol SX 102 apparatus, using xenon in the FAB mode, in glycerol/thioglycerol (50:50, GT) or nitrobenzyl alcohol (NBA). The HPLC analyses were carried out on a Waters Millenium apparatus with a photodiode Array detector 996, length 214 nm, using as column a reversed phase Nucleosil C18, 5μ, (250 × 10 mm), the flow rate: 1 mL/min, eluents: solvent A: 0.1% TFA in H_2O, solvent B: 0.1% TFA in CH_3CN, solvent C: CH_3CN.

Bis(iodomethyl)dimethylsilane (2): Bis(chloromethyl)dimethylsilane (1.6 g, 10.18 mmol) was dissolved in dry acetone (45 mL), sodium iodide (6.10 g, 40.73 mmol) was added and the mixture refluxed for 3 h. After filtration, the solvent was removed by distillation. After addition of Et_2O to the remaining oil, the NaCl was filtered. Et_2O was evaporated in vacuo and the residue distilled to give 3.0 g of **2** (88%), oil, b.p. 61 °C/4 mbar. – R_f = 0.8 (EtOAc/hexane 2:8). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.35 [s, 6 H, $Si(CH_3)_2$], 2.15 [s, 4 H, $Si(CH_2I)_2$]. – MS (FAB+); *m*/*z* (%): 340 (100) [M + H].

(2*R*,5*R*)-2,5-Dihydro-5-[(iodomethyl)dimethylsilyl]methyl-3,6-dimethoxy-2-isopropylpyrazine (3) and (2*R*,5*S*)-2,5-Dihydro-5-[(iodomethyl)dimethylsilyl]methyl-3,6-dimethoxy-2-isopropylpyrazine (4): To a solution of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**1**) (0.8 g, 4.35 mmol) in THF (15 mL) was slowly added *n*BuLi (2.5 M in hexane, 1.8 mL) at –70 °C, the mixture was stirred for 15 min at this temperature and then allowed to react with a solution of bis(iodomethyl)dimethylsilane (2.66 g, 7.83 mmol) in THF (4 mL). After 3 h, the mixture was allowed to warm to room temperature. The reaction mixture was diluted with Et_2O, washed with H_2O, dried with $MgSO_4$, and the solvent evaporated. The residue was purified by chromatography on 20 g of silica gel with 1% Et_2O in hexane as eluent, to give 980 mg of **3** (57%) and 160 mg of **4** (10%).

Compound 3: Oil. – R_f = 0.6 (Et_2O/hexane 1:9). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.20 and 0.25 [2s, 6 H, $Si(CH_3)_2$], 0.70 [d, *J* = 6.84 Hz, 3 H, $CH(CH_3)_2$], 0.95–1.05 (dd, *J* = 4.17 Hz, 10.40 Hz, 1 H, SiC*H*HCH), 1.10 [d, *J* = 6.82 Hz, 3 H, $CH(CH_3)_2$], 1.35–1.45 (dd, *J* = 4.17 Hz, 14.14 Hz, 1 H, SiCH*H*CH), 2.15 (s, 2 H, $SiCH_2I$), 2.20–2.35 [m, 1 H, $CH(CH_3)_2$], 3.66 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.90–4.00 (m, 1 H, C*H*α Val), 4.02–4.10 (m, 1 H, $CHCH_2Si$). – MS (FAB+); *m*/*z* (%): 397 (100) [M + H]. – HPLC: t_R = 21.52 min (from 70% to 100% C in a 30 min run).

Compound 4: Oil. – R_f = 0.45 (Et_2O/hexane 1:9). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.15 and 0.20 [2s, 6 H, $Si(CH_3)_2$], 0.70 [d, *J* = 6.84 Hz, 3 H, $CH(CH_3)_2$], 0.75–0.85 (dd, *J* = 4.52 Hz,

11.93 Hz, 1 H, SiC*H*HCH), 1.00 [d, J = 6.86 Hz, 3 H, CH(CH_3)$_2$], 1.30–1.35 (dd, J = 4.52 Hz, 14.56 Hz, 1 H, SiCH*H*CH), 2.10 (s, 2 H, SiCH_2I), 2.10–2.15 [m, 1 H, C*H*(CH$_3$)$_2$], 3.55 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.80–3.90 (m, 1 H, C*Hα* Val), 3.95–4.00 (m, 1 H, C*H*CH$_2$Si). – MS (FAB+); *m/z* (%): 397 (100) [M + H]. – HPLC: t_R = 19.32 min (from 70% to 100% C in a 30 min run).

(*R*)-*N*-(9-Fluorenylmethoxycarbonyl)silaproline Methyl Ester (*R*-9) and (*S*)-*N*-(9-fluorenylmethoxycarbonyl)valyl-(*R*)-silaproline Methyl Ester (10): The (*R*,*R*)-isomer **3** (960 mg, 2.42 mmol), freshly purified by chromatography was stirred overnight at 25 °C, in CH$_3$CN/H$_2$O/HCO$_2$H (49:49:2, 10 mL). After evaporation, the residue was distributed between CH$_2$Cl$_2$ and 2 N Na$_2$CO$_3$ solution. The organic layer was carefully concentrated on a rotary evaporator at room temperature and purified by chromatography on silica gel with MeOH/EtOAc (10:90) as eluent. The mixture of **5** and **8** (441 mg), eluted after **6**, was dissolved in THF (15 mL). DIEA (394 µL, 2.26 mmol) and FmocOSu (76 mg, 2.26 mmol) were added. After stirring overnight at room temperature, THF was evaporated in vacuo and the residue was diluted with EtOAc (30 mL). The organic phase was washed with 1 M KHCO$_3$ (2 × 15 mL), dried (MgSO$_4$), and evaporated. The residue was purified by chromatography on silica gel with EtOAc/hexane (20:80) to give 280 mg of **9** (30% from compound **3**) and 420 mg of **10** (35% from compound **3**).

Compound 9: Oil. – $[\alpha]_D^{25}$ = –34.7 (c = 0.98, CH$_2$Cl$_2$). – R_f = 0.5 (EtOAc/hexane 1:9). – ^{1}H NMR (CDCl$_3$, 400 MHz), (two conf.): δ = 0.20 and 0.30 [2s, 6 H, Si(CH_3)$_2$], 1.20–1.40 (m, 2 H, SiCH_2CH), 2.80–3.10 (m, 2 H, SiCH_2N), 3.70 and 3.75 (2s, 3 H, OCH_3), 4.20–4.50 (m, 3 H, CH_2C*H* fluorene), 4.80 and 4.90 (2dd, J = 3.08 Hz, 10.40 Hz, 1 H, C*Hα*), 7.20–7.80 (m, 8 H, aromatic H). – ^{13}C NMR (CDCl$_3$, 100 MHz), (two conf.): δ = –2.09 and –1.92 [2s, Si(*C*H$_3$)$_2$], 16.57 and 17.72 (2s, Si*C*H$_2$CH), 34.63 and 35.14 (2s, Si*C*H$_2$N), 47.69 and 47.77 (2s, *C*HCH$_2$ fluorene), 52.58 (s, O*C*H$_3$), 59.62 and 60.19 (2s, *C*Hα), 68.04 (s, CH*C*H$_2$ fluorene), 120.37, 125.41, 125.62, 127.44, 128.06, 141.72, 144.47, 144.64 (8s, aromatic *C*), 157.46 (s, *C*=O urethane), 174.61 and 174.79 (2s, *C*=O ester). – MS (ESI+); *m/z* (%): 396 (60) [M + H], 418 (100) [M + Na], 813 (45) [2 M + Na]. – HRMS (FAB+): calcd. for C$_{22}$H$_{26}$NO$_4$Si [M + H]: 396.1631; found 396.1631. – HPLC: t_R = 15.88 min (from 50 to 80% B in a 30 min run).

Compound 10: Oil. – R_f = 0.35 (EtOAc/hexane 2:8). – ^{1}H NMR (CDCl$_3$, 250 MHz): δ = 0.20–0.30 [2s, 6 H, Si(CH_3)$_2$], 0.78 [d, J = 6.85 Hz, 3 H, CH(CH_3)$_2$], 0.85 [d, J = 6.88 Hz, 3 H, CH(CH_3)$_2$], 0.85–1.00 (m, 2 H, SiCH_2CH), 2.10 [m, 1 H, C*H*(CH$_3$)$_2$], 2.55–2.65 (d, J = 14.24 Hz, 1 H, SiC*H*HN), 2.95–3.05 (d, J = 14.24 Hz, 1 H, SiCH*H*N), 3.55 (s, 3 H, OCH_3), 4.10–4.40 (m, 4 H, C*Hα* val and CH_2C*H* fluorene), 4.85–4.95 (m, 1 H, C*Hα*, Sip), 6.80 (d, J = 7.64 Hz, 1 H, N*H*), 7.20–7.70 (m, 8 H, aromatic *H*). – MS (ESI+); *m/z* (%): 495 (100) [M + H], 517 (30) [M + Na], 989 (15) [2 M + H], 1011 (20) [2 M + Na]. – HPLC: t_R = 20.45 min (from 10 to 100% B in a 30 min run).

(*S*)-*N*-(9-Fluorenylmethoxycarbonyl)silaproline Methyl Ester (*S*-9): Same procedure as for ***R*-9**, but with the (*R*,*S*)-isomer **4**.The product was obtained as an oil. – $[\alpha]_D^{25}$ = +34.9 (c = 0.98, CH$_2$Cl$_2$). All the other spectral data are identical to those obtained for compound ***R*-9**.

(*R*)-*N*-(*tert*-Butoxycarbonyl)silaproline Methyl Ester (*R*-12): The (*R*,*R*)-isomer **3** (930 mg, 2.35 mmol), freshly purified by chromatography was stirred for 2 h at 25 °C, in MeOH/10% HCl (3:1, 7 mL). After evaporation, the residue was coevaporated three times with MeOH (10 mL). The mixture of **6** and **7** (710 mg) thus obtained was dissolved in CH$_2$Cl$_2$/Et$_2$O (4:6, 10 mL) and DIEA (0.9 mL, 5.2 mmol) was added. After stirring for 4 h, Boc$_2$O (113 mg, 5.12 mmol) was added and the solution was stirred overnight at room temperature. The mixture was evaporated in vacuo and the residue diluted with EtOAc (40 mL). The organic phase was washed with 1 M KHSO$_4$ (3 × 15 mL), H$_2$O (15 mL), dried with MgSO$_4$, and then concentrated in vacuo. The product was purified by chromatography on silica gel in EtOAc/hexane (10:90) to give 465 mg of **12** (70%), oil. $[\alpha]_D^{25}$ = –36.2 (c = 1.0, CH$_2$Cl$_2$). – R_f = 0.24 (EtOAc/hexane 1:9) – ^{1}H NMR (CDCl$_3$, 400 MHz), (two conf.): δ = 0.20 [s, 6 H, Si(CH_3)$_2$], 1.00–1.05 (dd, 1 H, J = 3.31 Hz, 15.14 Hz, SiCH*H*CH), 1.10–1.20 (dd, 1 H, J = 10.15 Hz, 15.14 Hz, SiC*H*HCH), 1.30 and 1.40 (2s, 9 H, Boc), 2.70–2.90 (m, 2 H, SiCH_2N), 3.60 (s, 3 H, OCH_3), 4.55 and 4.70 (2dd, J = 3.31 Hz, 10.15 Hz, 1 H, C*Hα*); ^{13}C NMR (CDCl$_3$, 100 MHz), (two conf.): δ = –2.27 and –1.96 [2s, Si(*C*H$_3$)$_2$], 16.58 and 17.53 (2s, Si*C*H$_2$CH), 28.72 and 28.80 [2s, C(*C*H$_3$)$_3$], 34.60 and 34.89 (2s, Si*C*H$_2$N), 52.22 and 52.36 (2s, O*C*H$_3$), 59.64 and 60.03 (2s, *C*Hα), 80.02 and 80.27 [2s, *C*(CH$_3$)$_3$], 156.23 and 157.09 (2s, *C*=O urethane), 175.14 and 175.33 (2s, *C*=O ester). – MS (ESI+); *m/z* (%): 274 (50) [M + H], 296 (25) [M + Na], 312 (8) [M + K], 174 (40) [M + H – Boc], 218 (100) [M + H – CH$_2$=CMe$_2$], 547 (20) [2 M + H], 569 (50) [2 M + Na], 842 (4) [3 M + Na]. – HRMS (FAB+): calcd. for C$_{12}$H$_{24}$NO$_4$Si [M + H]: 274.1475; found 274.1478.

(*S*)-*N*-(*tert*-Butoxycarbonyl)silaproline Methyl Ester (*S*-12): Same procedure as for ***R*-12**, but with the (*R*,*S*)-isomer **4**. The product was obtained as an oil. – $[\alpha]_D^{25}$= +36.1 (c = 0.98, CH$_2$Cl$_2$). All the other spectral data are identical to those obtained for compound ***R*-12**.

(*R*)-*N*-(Benzyloxycarbonyl)valyl-(*R*)-silaproline Methyl Ester (13a): A solution of ***R*-12** (50 mg, 183 µmol) in CH$_2$Cl$_2$ (2 mL) was stirred for 1 h at room temperature with TFA (2 mL). The mixture was evaporated in vacuo and the residue was coevaporated three times with hexane/Et$_2$O (4:2, 10 mL) to remove TFA. The trifluoroacetate salt (53 mg, 183 µmol) was dissolved in CH$_2$Cl$_2$ (8 mL). HBTU (69 mg, 183 µmol), (*Z*)-L-Val–OH (46 mg, 183 µmol) and DIEA (73 µL, 421 µmol) were added. After stirring for 3 h at room temperature, the reaction mixture was evaporated in vacuo and the resulting residue dissolved in EtOAc (25 mL). The organic phase was successively washed with aqueous 0.1 N KHSO$_4$ (3 × 10 mL) and saturated NaHCO$_3$ (3 × 10 mL). Evaporation of the dried (MgSO$_4$) organic phase gave 70 mg of **13a** (90%), oil. – R_f = 0.23 (EtOAc/hexane 3:7). – ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.30 [s, 6 H, Si(CH_3)$_2$], 0.90 [d, J = 6.77 Hz, 3 H, CH(CH_3)$_2$], 1.05 [d, J = 6.77 Hz, 3 H, CH(CH_3)$_2$], 1.10–1.20 (dd, J = 4.33 Hz, 15.10 Hz, 1 H, SiCH*H*CH), 1.20–1.35 (dd, J = 10.08 Hz, 15.10 Hz, 1 H, SiC*H*HCH), 2.10 [m, 1 H, C*H*(CH$_3$)$_2$], 2.90–2.95 (d, J = 13.37 Hz, 1 H, SiC*H*HN), 3.15–3.20 (d, J = 13.37 Hz, 1 H, SiCH*H*N), 3.70 (s, 3 H, OCH_3), 4.60–4.70 (dd, J = 5.63 Hz, 9.29 Hz, 1 H, C*Hα*, val), 5.00–5.05 (dd, J = 4.33 Hz, 10.08 Hz, 1 H, C*Hα*, Sip), 5.10 (s, 2 H, CH_2O), 5.60 (d, J = 9.25 Hz, 1 H, N*H*), 7.30–7.45 (m, 5 H, aromatic *H*). – MS (ESI+); *m/z* (%): 407 (100) [M + H], 429 (50) [M + Na], 445 (8) [M + K], 813 (10) [2 M + H], 835 (15) [2 M + Na]. – HPLC: t_R = 26.31 min (from 10 to 100% B in a 30 min run).

(*R*,*S*)-*N*-(Benzyloxycarbonyl)valyl-(*R*)-silaproline Methyl Ester (13a, b): Same procedure as for **13a**, but with the (*Z*)-(D,L)-Val–OH. The product was obtained as an oil, 70 mg (90%). – R_f = 0.23 (EtOAc/hexane 3:7). – ^{1}H NMR (CDCl$_3$, 400 MHz), (two diast.): δ = 0.20 {m, 12 H, 2 × [Si(CH_3)$_2$]}, 0.80 and 0.85 [2d, J = 6.77 Hz, 6 H, CH(CH_3)$_2$], 0.9 and 0.95 [2d, J = 6.77 Hz, 6 H, CH(CH_3)$_2$], 1.00–1.25 [m, 4 H, 2 × (SiCH_2CH)], 1.8–1.95 [m, 1

H, C*H*$(CH_3)_2$], 2.00–2.10 [m, 1 H, C*H*$(CH_3)_2$], 2.80–2.90 [2d, J = 13.37 Hz, 13.43 Hz, 2 H, 2 × (SiC*H*HN)], 3.00–3.10 [2d, J = 13.37 Hz, 13.43 Hz, 2 H, 2 × (SiCH*H*N)], 3.60 [2s, 6 H, 2 × (OCH_3)], 4.50–4.65 [2dd, J = 5.63 Hz, 9.29 Hz, 2 H, 2 × (C*H*α val)], 4.80–5.00 [2dd, J = 4.33 Hz, 10.08 Hz, 2 H, 2 × (C*H*α, Sip)], 5.00–5.10 [m, 4 H, 2 × (CH_2O)], 5.45–5.50 (m, 2 H, N*H*), 7.20–7.30 (m, 10 H, aromatic *H*). – MS (ESI+); *m*/*z* (%): 407 (100) [M + H], 429 (50) [M + Na], 445 (8) [M + K], 813 (10) [2 M + H], 835 (15) [2 M + Na]. – HPLC: t_R = 26.31 min (from 10 to 100% B in a 30 min run).

(*R*)-*N*-(*tert*-Butoxycarbonyl)silaproline (14): A solution of ***R*-12** (240 mg, 0.879 mmol) in MeOH (3 mL), cooled to 0–5 °C was slowly treated with a solution of KOH 2 N (1.3 mL, 2.637 mmol). After 4 h at room. temperature, MeOH was evaporated, and the resulting residue was diluted with H_2O (10 mL) and the aqueous phase was extracted with Et_2O, acidified with a solution of 1 N HCl (pH = 4) and again extracted with Et_2O (2 × 15 mL). The second extract was dried ($MgSO_4$) and evaporated in vacuo to give 220 mg of **14** (97%), oil. $[\alpha]_D^{25}$ = –40.8 (c = 4.8, $CHCl_3$). – R_f = 0.65 ($CHCl_3$/MeOH/AcOH 120:10:5) – ^{1}H NMR ($CDCl_3$, 400 MHz), (two conf.): δ = 0.20 [s, 6 H, Si(CH_3)$_2$], 0.80–1.20 (m, 2 H, SiCH_2CH), 1.30 and 1.40 (2s, 9 H, Boc), 2.60–2.90 (m, 2 H, SiCH_2N), 4.55 and 4.70 (2dd, J = 3.52 Hz, 10.26 Hz, 1 H, C*H*α), 9.50 (s, 1 H, CO_2H) – ^{13}C NMR ($CDCl_3$, 100 MHz), (two conf.): δ = –2.23 and –2.09 [2s, Si(*C*H_3)$_2$], 16.13 and 17.39 (2s, Si*C*H_2CH), 28.66 and 28.78 [2s, C(*C*H_3)$_3$], 34.61 and 34.91 (2s, Si*C*H_2N), 59.75 and 59.86 (2s, *C*Hα), 80.27 and 80.62 [2s, *C*$(CH_3)_3$], 156.38 and 157.69 (2s, *C*=O urethane), 177.07 and 179.06 (2s, *C*=O acid). – MS (ESI+); *m*/*z* (%): 260 (50) [M + H], 282 (25) [M + Na], 160 (10) [M + H – Boc], 204 (100) [M + H – CH_2=CMe_2], 519 (25) [2 M + H], 541 (20) [2 M + Na]. – HRMS (FAB+): calcd. for $C_{11}H_{22}NO_4Si$ [M + H]: 260.1318; found 260.1350.

(*R*)-*N*-(9-Fluorenylmethoxycarbonyl)silaproline (15): To a solution of ***R*-9** (230 mg, 0.582 mmol) in a solution (0.8 M) of $CaCl_2$ in *i*PrOH/H_2O (7:3, 6 mL), was added 1.5 equiv. of NaOH (35 mg, 0.873 mmol). After stirring at room temperature overnight, the solvent was evaporated and the residue obtained was diluted with H_2O (10 mL). The aqueous phase was extracted with Et_2O, acidified with a solution of 1 N HCl and extracted with Et_2O (2 × 15 mL). The second extract was dried ($MgSO_4$) and evaporated in vacuo to give 168 mg of **15** (76%), oil. – $[\alpha]_D^{25}$ = –33.8 (c = 3.1, $CHCl_3$). – R_f = 0.5 ($CHCl_3$/MeOH/AcOH 120:10:5). – ^{1}H NMR ($CDCl_3$, 250 MHz), (two conf.): δ = 0.20 and 0.30 [2s, 6 H, Si(CH_3)$_2$], 0.9 –1.40 (m, 2 H, SiCH_2CH), 2.80–3.10 (m, 2 H, SiCH_2N), 4.20–4.60 (m, 3 H, CH_2C*H* fluorene), 4.80 and 4.90 (2dd, J = 4.01 Hz, 9.63 Hz, 1 H, C*H*α), 7.20–7.80 (m, 8 H, aromatic H), 10.50 (s, 1 H, CO_2H). – ^{13}C NMR ($CDCl_3$, 100 MHz), (two conf.): δ = –2.35 and –2.05 [2s, Si(*C*H_3)$_2$], 16.22 and 17.55 (2s, Si*C*H_2CH), 34.68 and 35.18 (2s, Si*C*H_2N), 47.67 (1s, *C*HCH_2 fluorene), 59.43 and 60.23 (2s, *C*Hα), 68.28 (s, CH*C*H_2 fluorene), 120.39, 125.40, 125.60, 127;47, 128.05, 141.67, 144.29, 144.51 (8s, aromatic *C*), 156.87 and 157.91 (2s, *C*=O urethane), 179.10 and 179.80 (2s, *C*=O acid). – MS (ESI+); *m*/*z* (%): 382 (60) [M + H], 404 (100) [M + Na], 785 (5) [2 M + Na]. – HRMS (FAB+): calcd for $C_{21}H_{24}NO_4Si$ [M + H]: 382.1475; found 382.1495. – HPLC: t_R = 27.91 min (from 10 to 100% B in a 30 min run).

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