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Straightforward Synthesis of Chiral Silylated Amino Acids through Hydrosilylation

Damien Marchand,[a,b] Jean Martinez,[a] and Florine Cavelier*[a]

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A method using hydrosilylation of unsaturated amino acids was developed and optimised to obtain silylated amino acids. The platinum $(Bu_4N)_2PtCl_6$ complex was identified as the best catalyst, and the procedure tolerated different unsaturated substrates, silane reagents and protecting groups. Seven silicon-containing α-amino acids were prepared in an enantiomerically pure form under mild conditions in good yields with orthogonal protections for versatile use in peptide synthesis.

Introduction

The pharmaceutical industry has an ongoing need for new safe medicines. During the discovery process that identifies drug development candidates from biologically active hits, the introduction of bioisosteres is a key strategy used by medicinal chemists. Silicon chemistry can be a novel source of chemical diversity in drug design.[1,2] Particularly in the field of amino acids and peptides, unnatural analogues emerge as new compounds with therapeutic potential. As an example, replacement of part of an active peptide with a well-chosen building block may improve their properties and may result in new classes of compounds with better availability. For this purpose, silylated amino acids can be useful to make unconventional biological substrates that are not easily metabolised. Their increased hydrophobic properties will result in improved in vivo half life and enhanced tissue distribution.[3–5]

TMS-Ala was the first silylated amino acid to be described and synthesised as a racemate.[6] It was surprisingly proposed as a phenylalanine isostere.[7] Asymmetric syntheses were reported[7–9] and more recently, enzymatic deracemisation[10,11] and dynamic kinetic resolution[12] were employed to prepare optically active TMS-Ala. Syntheses of derivatives with various triaryl or alkylarylsilyl groups showed difficulties primarily owing to steric hindrance.[13,14]

Some years ago, we reported the asymmetric synthesis of the first silylated proline analogue, silaproline (Sip),[15,16] which can be considered as a cyclic β-silylated amino acid.

[a] Institut des Biomolécules Max Mousseron, UMR-CNRS 5247, Universités de Montpellier I et II,
Place Eugène Bataillon, 34095 Montpellier Cedex 05, France
Fax: +33-4-67144866
E-mail: florine@univ-montp2.fr
[b] CISTIM,
Minderbroedersstraat, 12 Block N, 3000 Leuven, Belgium

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Beside these β-silylated amino acids, there are only few examples of other silylated side chains. A four-step enantioselective synthesis of γ-silylated amino acids was reported by using a procedure based on silylcupration of amino alcohols followed by oxidation into amino acids.[17,18] An amino acid in which the silicon was attached directly to the α carbon has also been prepared as a racemate by a rhodium-catalysed reaction.[19] A single enantiomer was obtained by using an asymmetric reverse-aza-Brook rearrangement.[20] New analogues of homoserine and homomethionine with functionalised silylated side chains are recent additions to this class of compounds.[21–23]

Here we report a new straightforward method based on the hydrosilylation reaction of unsaturated chiral amino acids for the preparation of optically active silylated amino acids.

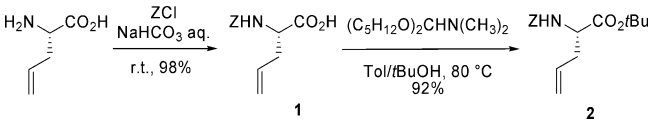
The hydrosilylation reaction[24–26] is a very powerful method to introduce an alkylsilyl group onto a double bond.[27–30] However, this method has never been applied to prepare silicon-containing amino acids, except in one report published as a preliminary note in 1972. The authors obtained a symmetric ε-silylated diamino acid in a siloxane form starting from ethylacetamidomalonate to introduce the unsaturated side chain and the silylated group subsequently.[31] Unsaturated amino acids such as vinyl glycine have also been used as starting materials in a copper-catalysed addition of Grignard reagents to prepare unnatural amino acids, including one with a silylated side chain.[32]

In our strategy based on chiral pool synthesis, the built-in chirality was not affected in the hydrosilylation reaction sequence. The hydrosilylation of the double bond located on the side chain extremity cannot alter the chiral centre issued from the chiral pool. As an example, hydrosilylation on several chiral substrates illustrates that such conditions do not affect pre-existing chiral centres separated from the double bond by one methylene group.[33] Chiral labelling

has also been used to study asymmetric induction during hydrosilylation with a chiral catalyst. The prochiral substrate was derivatised with menthol to observe diastereoisomers, and the optical yield was measured on the created chiral centre. Such results show that pre-existing chiral centres are not affected under hydrosilylation conditions.[34]

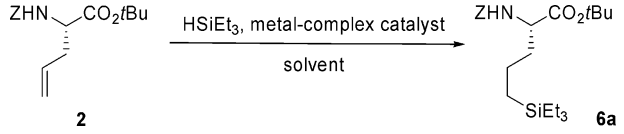
Results and Discussion

Starting from commercially available L-allylglycine,[35] successive protection of the amine and carboxylic acid functionalities with a benzyloxycarbonyl group and a *tert*-butyl ester group, respectively, allowed substrate **2** to be prepared (Scheme 1). We also prepared protected vinylglycine **5** by starting from methionine derivative **3** (Scheme 2).[36]



Scheme 1. Successive protection of allylglycine.

Fully protected L-allylglycine **2** was used in a model reaction with triethylsilane and various metal complexes, solvents and temperatures by using the Quest 210 instrument (Scheme 3).

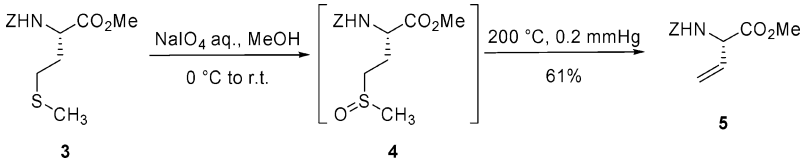


Scheme 3. Model reaction of hydrosilylation.

This preliminary screening allowed us to select platinum catalysts as the most effective (Pd complexes were unsuccessful whatever the solvent used). The results with Pt^0 are summarised in Table 1.

Pt–C (5%) (Table 1, Entries 1 and 2) and *cis*-$(PPh_3)PtCl_2$ (Table 1, Entries 3 and 4) did not afford more than 11% (Table 1, Entry 2) of the expected compound. Speier's catalyst, $H_2PtCl_6{\cdot}6H_2O$, was then targeted for its high reactivity in this type of reaction.[37] The starting material was recovered when the reaction was performed in THF despite a long reaction time (Table 1, Entry 5). Switching to acetonitrile gave the desired compound in moderate yield (Table 1, Entry 6). Increasing temperature did not improve the yield, as reduction as a side reaction appeared (Table 1, Entry 7). Chlorinated solvents also maintained low yields in silylated compounds as a result of unwanted reduced byproducts (Table 1, Entries 8 and 9).

We then tried the platinum complex analogue, tetrabutyl ammonium hexachloroplatinate, $(Bu_4N)_2PtCl_6$.[27,38,39] Again, both THF and acetonitrile proved to be poor solvents in this reaction (Table 1, Entry 10). Increasing temperature improved the yield in silylated compounds, al-



Scheme 2. Synthesis of protected vinylglycine.

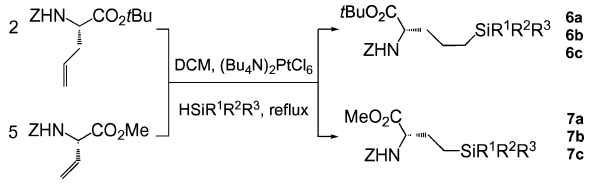
Table 1. Optimisation of the reaction conditions of the hydrosilylation of compound **2** with triethylhydrosilane[a] to synthesise **6a**.

Entry	Catalyst[b]	Solvent	*T* [°C]	Reaction time[c] [h]	**6a** Yield[d]
1	Pt–C (5 mol-%)	THF, ACN or DCM	r.t.	>72	0
2	Pt-C (5 mol-%)	DCE	reflux	12	11
3	*cis*-$(PPh_3)PtCl_2$	THF, ACN or DCM	r.t.	>72	0
4	*cis*-$(PPh_3)PtCl_2$	DCE	reflux	12	<3[e]
5	$H_2PtCl_6{\cdot}6H_2O$	THF	r.t.	>72	0
6	$H_2PtCl_6{\cdot}6H_2O$	ACN	r.t.	>72	57
7	$H_2PtCl_6{\cdot}6H_2O$	ACN	reflux	12	40[e]
8	$H_2PtCl_6{\cdot}6H_2O$	DCM	r.t.	24	45[e]
9	$H_2PtCl_6{\cdot}6H_2O$	DCE	reflux	12	36[e]
10	$(Bu_4N)_2PtCl_6$	THF or ACN	r.t.	>72	0
11	$(Bu_4N)_2PtCl_6$	ACN	reflux	12	50[e]
12	$(Bu_4N)_2PtCl_6$	DCE	reflux	12	54[e]
13	$(Bu_4N)_2PtCl_6$	DCM	r.t.	24	65[e]
14	$(Bu_4N)_2PtCl_6$	DCM	reflux	2	85

[a] Compound **2** (100 mg, 0.33 mmol), $HSiEt_3$ (107 μL, 0.66 mmol). [b] Catalyst (5 mol-% per mol of unsaturated substrate). [c] Monitored by TLC and HPLC analysis. [d] After purification on silica gel column. [e] Remaining products is a mixture of starting material and hydrogenated byproduct.

though the hydrogenated side product was always formed (Table 1, Entries 11 and 12). Finally, dichloromethane at room temperature gave the best ratio between the desired compound and the side product (Table 1, Entry 13). Gently increasing the temperature was the best compromise, as the silylated compound was obtained in 85% yield contaminated by only 2% of side product (Table 1, Entry 14). This result suggested that the rate of hydrosilylation, which depends heavily on the solvent and on the temperature, was higher under these conditions than the rate of reduction.

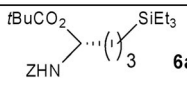
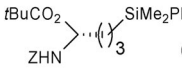
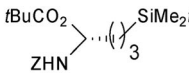
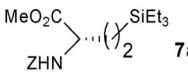
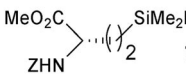
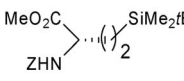
With these optimised conditions of hydrosilylation in hands, we generalised this methodology with different commercially available hydrosilanes to obtain δ-silylated amino acids **6** and γ-silylated amino acids **7** starting from allylglycine derivative **2** and from vinylglycine derivative **5**, respectively (Scheme 4).



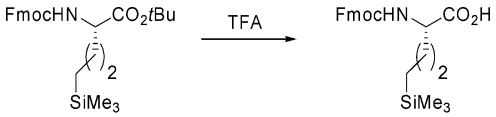
Scheme 4. Hydrosilylation to obtain six silylated amino acids; R^1, R^2 and R^3 are defined in Table 2.

The yields were closely dependent on the steric hindrance of the alkylsilane and range from 45–55% with a *tert*-butyl substitution (Table 2, Entries 2 and 6) to about 85% for all other silane derivatives. In accordance with results obtained in a platinum-catalysed system,[40] the HPLC and the NMR spectroscopic analysis displayed only one regioisomer.

Table 2. Silylated amino acids obtained by hydrosilylation under optimised reaction conditions.

Entry	Substrate	Product	Reaction time [h]	Yield [%]
1	2	 **6a**	2	85
2	2	 **6b**	2	87
3	2	 **6c**	3	55
4	5	 **7a**	2	87
5	5	 **7b**	2	88
6	5	 **7c**	3	45

To increase the scope of the reaction and to show that protection did not alter the reactivity of the side chain, we also prepared Fmoc/*t*Bu derivative **8** as an example. Removal of the *t*Bu group gave compound **9** ready for solid-phase peptide synthesis (SPPS) use (Scheme 5).



8 **9**

Scheme 5. Fmoc-protected example of silylated amino acid for SPPS.

Conclusions

We found the platinum $(Bu_4N)_2PtCl_6$ complex to be the best catalyst in the hydrosilylation reaction, and we established optimised conditions for this reaction. The procedure tolerated different unsaturated substrates and a range of substitution on the silane reagent, although a cumulative bulkiness may represent a limitation of this new methodology. Seven silicon-containing amino acids were synthesised under mild conditions in an enantiomerically pure form in good yields. Different urethane protecting groups on the amine and ester functionalities were used without any difficulty. Orthogonal protections allow versatile use in peptide synthesis.

Experimental Section

L-Allylglycine and L-methionine methyl ester were purchased from Novabiochem and the metal complex catalysts from Aldrich. Tetrahydrofuran (THF) was freshly distilled under argon from sodium and benzophenone. Dichloromethane and dichloroethane were 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 Milli-Q plus system (Millipore) and acetonitrile from Merck. Thin-layer chromatography was performed on Merck precoated silica gel $60F_{254}$ plates and spots were visualised by ultraviolet light or by staining with phosphomolybdic acid. Flash chromatography was performed by using Merck silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded with a Bruker spectrometer AC 300 (300 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 ppm relative to tetramethylsilane (TMS) and δ_C = 77.6 ppm. The ESI (electrospray ionisation) mass spectra were recorded with a Micromass Platform II quadrupole mass spectrometer (Micromass) fitted with an electrospray source coupled with an HPLC Waters.

(*S*)-2-(Benzyloxycarbonylamino)pent-4-enoic Acid (1): To a suspension of L-allylglycine (500 mg, 4.35 mmol) in water (20 mL) was first added sodium hydrogen carbonate (1.1 g, 13.05 mmol) and then benzyl chloroformate (932 μL, 6.52 mmol) was added dropwise for 2 h. The mixture was stirred at room temperature for 3 h. The reaction mixture was washed with diethyl ether then acidified with HCl (12 N) until pH 1–2. The aqueous layer was extracted with ethyl acetate, dried with magnesium sulfate and concentrated under reduced pressure to give **1** as a pure colourless oil (1.06 g,

98%). R_f = 0.75 ($CHCl_3$/CH_3OH/AcOH, 120:10:5). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50–2.75 (m, 2 H, CH_2-CH_α), 4.40–4.55 (m, 1 H, CH_α), 5.10 (s, 2 H, CH_2Ar), 5.20 (d, J = 2.9 Hz, 2 H, CH_2=CH), 5.25 (d, J = 7.8 Hz, 1 H, N*H*), 5.60–5.85 (m, 1 H, C*H*=CH_2), 7.35–7.50 (m, 5 H, H_{arom}), 9.25–9.75 (sl, 1 H, CO_2H) ppm. MS (ESI): m/z = 250 $[M + H]^+$, 272 $[M + Na]^+$, 499 $[2M + H]^+$.

***tert*-Butyl (*S*)-2-(Benzyloxycarbonylamino)pent-4-enoate (2):** To a solution of **1** (1 g, 4.02 mmol) in a mixture of toluene (20 mL) and *tert*-butyl alcohol (4.46 g, 60.30 mmol) at 80 °C and under nitrogen was added *N*,*N*′-dimethylformamide dineopentyl acetal (3.36 mL, 12.06 mmol) with a flow of 20 mL/h. The reaction mixture was stirred for 3 h and then cooled to room temperature. The organic layer was washed with a saturated sodium hydrogen carbonate solution (2×). The organic phase was dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude oil was purified by flash chromatography (silica gel; EtOAc/hexane, 1:9) to give **2** as a colourless oil (1.13 g, 92%). R_f = 0.6 (EtOAc/hexane, 2:8). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, *tBu*), 2.50–2.70 (m, 2 H, CH_2-CH_α), 4.35–4.50 (m, 1 H, CH_α), 5.10 (s, 2 H, CH_2Ar), 5.20 (d, J = 2.9 Hz, 2 H, CH_2=CH), 5.25 (d, J = 7.8 Hz, 1 H, N*H*), 5.60–5.85 (m, 1 H, C*H*=CH_2), 7.35–7.50 (m, 5 H, H_{arom}) ppm. MS (ESI): m/z = 306 $[M + H]^+$, 328 $[M + Na]^+$, 611 $[2M + H]^+$, 250 $[M + H - t\text{Bu}]^+$.

Methyl (*S*)-2-(Benzyoxycarbonylamino)-4-methylmercaptobutanoate (3): HCl·Met-OMe (5 g, 25 mmol) was dissolved in a mixture of H_2O/Et_2O (1:1, 75 mL) with potassium hydrogen carbonate (17.2 g, 125 mmol). The reaction was stirred vigorously and cooled to 0 °C and then benzyl chloroformate (4 mL, 27.5 mmol) was added dropwise. The stirring was continued for another 5 h at room temperature. The different layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic phase was with magnesium sulfate, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel; EtOAc/hexane, 3:7) to give the expected product as a colourless oil (7.35 g, 99%). R_f = 0.5 (EtOAc/hexane, 3:7). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.90–2.25 (m, 2 H, C$H_{\beta\beta'}$), 2.10 (s, 3 H, SCH_3), 2.55 (t, 2 H, C$H_{\gamma\gamma'}$), 3.80 (s, 3 H, OCH_3), 4.55 (m, 1 H, CH_α), 5.15 (s, 2 H, CH_2Ar), 5.45 (dl, J = 7.7 Hz, 1 H, N*H*), 7.30–7.45 (m, 5 H, H_{arom}) ppm. MS (ESI): m/z = 298 $[M + H]^+$, 595 $[2M + H]^+$.

Methyl (*S*)-2-(Benzyloxycarbonylamino)but-3-enoate (5): A solution of protected methionine **3** (7.3 g, 24.5 mmol) in methanol (66 mL) was cooled to 0 °C, and a solution of sodium periodate (6.3 g, 27 mmol) in water (88 mL) was added dropwise over 1 h. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. The resulting suspension was filtered through a pad of Celite, and the filtrate was extracted with dichloromethane. The combined organic layer was washed with water and brine and then dried with magnesium sulfate, filtered and evaporated under reduced pressure to give intermediate product **4** as a slurry yellow oil (99%). The last crude was directly heated at 200 °C under 0.2 Torr in a Kugelrohr apparatus. The mixture became dark and a light yellow liquid was slowly distilled. The distilled product was purified by chromatography (silica gel; EtOAc/hexane, 2:8) to give the product of elimination **5** as an oil, which crystallised in the refrigerator (3.72 g, 61%). R_f = 0.45 (EtOAc/hexane, 2:8). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OCH_3), 4.95 (m, 1 H, CH_α), 5.15 (s, 2 H, CH_2Ar), 5.30 (dd, J = 10.3 and 1.4 Hz, 1 H, CHH_{cis}=CH), 5.40 (dd, J = 17.1 and 1.4 Hz, 1 H, CHH_{trans}=CH), 5.55 (dl, J = 7.8 Hz, 1 H, N*H*), 5.85–6.00 (m, 1 H, C*H*=CH_2), 7.30–7.45 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.76 (O*C*H_3), 56.14 (C_α), 67.15 (*C*H_2-Ar), 117.80 (CH=*C*H_2), 128.15 (*C*H=CH_2), 128.55, 132.32, 136.16 (C_{arom}), 155.57 (*C*=O carbamate), 170.91 (*C*=O ester) ppm. MS (ESI): m/z = 250 $[M + H]^+$, 499 $[2M + H]^+$, 194 $[M + H - t\text{Bu}]^+$.

General Procedure for the Hydrosilylation Reaction: The unsaturated compound (1 equiv.) was dissolved in dry dichloromethane (2.5 mL/mmol) under argon and then the catalyst (0.05 equiv.) and trialkylhydrosilane (2 equiv.) were added successively. The stirred mixture was heated at reflux for 2–3 h (TLC and HPLC controls). The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography column to give the hydrosilylated product.

***tert*-Butyl (*S*)-2-(Benzyloxycarbonylamino)-5-(triethylsilyl)pentanoate (6a):** Following the general procedure for the hydrosilylation reaction of **2** (100 mg, 0.33 mmol), compound **6a** (118 mg, 85% yield) was obtained as a colourless oil. R_f = 0.5 (EtOAc/hexane, 1:9). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.50 [q, J = 7.9 Hz, 8 H, Si(CH_2CH$_3$)$_3$ and C$H_{\delta\delta'}$-Si], 0.90 [t, J = 7.9 Hz, 9 H, Si(CH$_2$CH_3)$_3$], 1.25–1.45 (m, 2 H, CH$_{\gamma\gamma'}$), 1.45 (s, 9 H, *tBu*), 1.60–1.75 (m, 1 H, CH_β), 1.75–1.90 (m, 1 H, C$H_{\beta'}$), 4.20–4.35 (m, 1 H, CH_α), 5.10 (s, 2 H, CH_2Ar), 5.20 (dl, 1 H, N*H*), 7.20–7.40 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.26 [Si(*C*H$_2$CH$_3$)$_3$], 7.41 [Si(CH$_2$*C*H$_3$)$_3$], 11.17 (C_δ), 19.53 (C_γ), 27.99 [OC(*C*H$_3$)$_3$], 36.95 (C_β), 54.19 (*C*H$_2$-Ar), 66.79 (C_α), 81.83 [O*C*(CH$_3$)$_3$], 128.08, 128.49, 136.42 (*C*arom.), 155.80 (*C*=O carbamate), 171.79 (*C*=O ester) ppm. MS (ESI): m/z = 422 $[M + H]^+$, 843 $[2M + H]^+$, 366 $[M + H - t\text{Bu}]^+$. HRMS (Q-TOF): calcd. for $C_{23}H_{40}NO_4Si$ 422.2727; found 422.2696.

***tert*-Butyl (*S*)-2-(Benzyloxycarbonylamino)-5-(dimethylphenylsilyl)-pentanoate (6b):** Following the general procedure for the hydrosilylation reaction of **2** (100 mg, 0.33 mmol), compound **6b** (127 mg, 87% yield) was obtained as a colourless oil. R_f = 0.5 (EtOAc/hexane, 1:9). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.30 [s, 6 H, Si(CH$_3$)$_2$], 0.75–0.85 (m, 2 H, C$H_{\delta\delta'}$), 1.35–1.50 (m, 2 H, CH$_{\gamma\gamma'}$), 1.45 (s, 9 H, *tBu*), 1.65–1.75 (m, 1 H, CH_β), 1.75–1.90 (m, 1 H, C$H_{\beta'}$), 4.20–4.35 (m, 1 H, CH_α), 5.10 (s, 2 H, CH_2Ar), 5.30 (d, J = 7.7 Hz, 1 H, N*H*), 7.35–7.50 (m, 10 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –1.31 [Si(*C*H$_3$)$_2$], 15.50 (C_δ), 19.62 (C_γ), 28.02 [OC(*C*H$_3$)$_3$], 36.63 (C_β), 54.15 (*C*H$_2$-Ar), 66.82 (C_α), 81.85 [O*C*(CH$_3$)$_3$], 127.80, 128.11, 128.52, 128.91, 133.53, 136.49, 139.07 (C_{arom}), 155.83 (*C*=O carbamate), 171.74 (*C*=O ester) ppm. MS (ESI): m/z = 442 $[M + H]^+$, 883 $[2M + H]^+$, 905 $[2M + Na]^+$, 386 $[M + H - t\text{Bu}]^+$. HRMS (Q-TOF): calcd. for $C_{25}H_{36}NO_4Si$ 442.2414; found 422.2382.

***tert*-Butyl (*S*)-2-(Benzyloxycarbonylamino)-5-(*tert*-butyldimethylsilyl)pentanoate (6c):** Following the general procedure for the hydrosilylation reaction of **2** (90 mg, 0.30 mmol), compound **6c** (69 mg, 55% yield) was obtained as a colourless oil. R_f = 0.55 (EtOAc/hexane, 1:9). ^1H NMR (400 MHz, $CDCl_3$): δ = –0.05 [s, 6 H, Si(CH$_3$)$_2$], 0.45–0.60 (m, 2 H, C$H_{\delta\delta'}$), 0.90 (s, 9 H, Si*tBu*), 1.30–1.50 (m, 2 H, CH$_{\gamma\gamma'}$), 1.45 (s, 9 H, *tBu*), 1.60–1.75 (m, 1 H, CH_β), 1.75–1.90 (m, 1 H, C$H_{\beta'}$), 4.25–4.35 (m, 1 H, CH_α), 5.10 (s, 2 H, CH_2Ar), 5.30 (d, J = 7.7 Hz, 1 H, N*H*), 7.30–7.40 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –6.29 [Si(*C*H$_3$)$_2$], 12.26 (C_δ), 16.48 [Si*C*(CH$_3$)$_3$], 19.99 (C_γ), 26.56 [SiC(*C*H$_3$)$_3$], 28.01 [OC(*C*H$_3$)$_3$], 36.97 (C_β), 54.21 (*C*H$_2$-Ar), 66.80 (C_α), 81.84 [O*C*(CH$_3$)$_3$], 128.09, 128.50, 136.47 (C_{arom}), 155.80 (*C*=O carbamate), 171.78 (*C*=O ester) ppm. MS (ESI): m/z = 422 $[M + H]^+$, 843 $[2M + H]^+$, 366 $[M + H - t\text{Bu}]^+$. HRMS (Q-TOF): calcd. for $C_{23}H_{40}NO_4Si$ 422.2727; found 422.2697.

Methyl (*S*)-2-(Benzyloxycarbonylamino)-4-(triethylsilyl)butanoate (7a): Following the general procedure for the hydrosilylation reac-

tion of **5** (100 mg, 0.40 mmol), compound **7a** (127 mg, 87%) was obtained as a colourless oil. R_f = 0.3 (EtOAc/hexane, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.50 [m, 8 H, Si(CH_2CH$_3$)$_3$ and C$H_{\gamma\gamma'}$-Si], 0.90 [t, J = 7.9 Hz, 9 H, Si(CH$_2$CH_3)$_3$], 1.65–1.80 (m, 1 H, CH_β), 1.80–1.95 (m, 1 H, C$H_{\beta'}$), 3.75 (s, 3 H, OCH_3), 4.35–4.45 (m, 1 H, CH_α), 5.15 (s, 2 H, CH_2Ar), 5.40 (d, J = 8 Hz, 1 H, NH), 7.25–7.40 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 2.35 [Si(CH$_2$CH$_3$)$_3$], 5.24 (C_γ), 6.62 [Si(CH$_2$$CH_3$)$_3$], 26.36 ($C_\beta$), 51.53 (O$CH_3$), 55.32 ($C_\alpha$), 66.23 ($CH_2$-Ar), 127.39, 127.81, 135.64 (C_{arom}), 155.14 (C=O carbamate), 172.12 (C=O ester) ppm. MS (ESI): m/z = 366 [M + H]$^+$, 731 [2M + H]$^+$. HRMS (Q-TOF): calcd. for $C_{19}H_{32}NO_4Si$ 366.2101; found 366.2072.

Methyl (*S*)-2-(Benzyloxycarbonylamino)-4-(dimethylphenylsilyl)butanoate (7b): Following the general procedure for the hydrosilylation reaction of **5** (200 mg, 0.80 mmol), compound **7b** (271 mg, 88%) was obtained as a colourless oil. R_f = 0.3 (EtOAc/hexane, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.35 (s, 6 H, SiCH$_3$), 0.70–0.90 (m, 2 H, C$H_{\gamma\gamma'}$), 1.65–1.80 (m, 1 H, CH_β), 1.80–1.95 (m, 1 H, C$H_{\beta'}$), 3.75 (s, 3 H, OCH_3), 4.40–4.50 (m, 1 H, CH_α), 5.15 (s, 2 H, CH_2Ar), 5.50 (d, J = 8.4 Hz, 1 H, NH), 7.30–7.50 (m, 10 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.02 [Si(CH$_3$)$_2$], 10.07 (C_γ), 26.50 (C_β), 51.58 (OCH$_3$), 55.29 (C_α), 66.26 (CH$_2$-Ar), 127.12, 127.44, 127.86, 128.45, 132.85, 135.69, 137.62 (C_{arom}), 155.26 (C=O carbamate), 172.15 (C=O ester) ppm. MS (ESI): m/z = 386 [M + H]$^+$, 771 [2M + H]$^+$. HRMS (Q-TOF): calcd. for $C_{21}H_{28}NO_4Si$ 386.1788; found 386.1760.

Methyl (*S*)-2-(Benzyloxycarbonylamino)-4-(*tert*-butyldimethylsilyl)-butanoate (7c): Following the general procedure for the hydrosilylation reaction of **5** (200 mg, 0.80 mmol), compound **7c** (131 mg, 45%) was obtained as a colourless oil. R_f = 0.3 (EtOAc/hexane, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.10 [s, 6 H, Si(CH_3)$_2$], 0.35–0.60 (m, 2 H, C$H_{\gamma\gamma'}$), 0.85 (s, 9 H, SitBu), 1.60–1.80 (m, 1 H, CH_β), 1.80–1.95 (m, 1 H, C$H_{\beta'}$), 3.75 (s, 3 H, OCH_3), 4.35–4.45 (m, 1 H, CH_α), 5.15 (s, 2 H, CH_2Ar), 5.40 (d, J = 8 Hz, 1 H, NH), 7.25–7.40 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –7.12 [Si(CH$_3$)$_2$], 6.58 (C_γ), 15.83 [SiC(CH$_3$)$_3$], 25.82 [SiC(CH$_3$)$_3$], 26.90 (C_β), 51.56 (OCH$_3$), 55.38 (C_α), 66.25 (CH$_2$-Ar), 127.40, 127.83, 135.62 (C_{arom}), 155.17 (C=O carbamate), 172.16 (C=O ester) ppm. MS (ESI): m/z = 366 [M + H]$^+$, 731 [2M + H]$^+$. HRMS (Q-TOF): calcd. for $C_{19}H_{32}NO_4Si$ 366.2101; found 366.2072.

***tert*-Butyl (*S*)-2-(Fluorenyloxycarbonylamino)-5-(trimethylsilyl)-pentanoate (8):** Following the general procedure of hydrosilylation reaction, from *N*-Fmoc-allylglycine butyl ester (100 mg, 0.25 mmol), compound **8** (106 mg, 89%) was obtained as a colorless oil. R_f = 0.4 (EtOAc/hexane, 1:9). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.0 [s, Si(CH_3)$_3$], 0.45–0.55 (m, 2 H, C$H_{\delta\delta'}$-Si), 1.25–1.45 (m, 2 H, CH$_{\gamma\gamma'}$), 1.50 (s, 9 H, tBu), 1.60–1.75 (m, 1 H, CH_β), 1.75–1.90 (m, 1 H, C$H_{\beta'}$), 4.20–4.35 [m, 2 H, CH(Fmoc) and CH_α], 4.40 [d, J = 7 Hz, 2 H, CH_2(Fmoc)], 5.35 (dl, 1 H, NH), 7.30–7.50 (m, 8 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.0 [Si(CH$_3$)$_3$], 18.03 (C_δ), 21.27 (C_γ), 29.70 [OC(CH$_3$)$_3$], 38.27 (C_β), 48.87 (CH Fmoc), 55.82 (C_α), 68.61 (CH$_2$ Fmoc), 83.63 [OC-(CH$_3$)$_3$], 121.64, 126.81, 128.73, 129.35, 142.97, 145.55, 145.65 (C_{arom}), 157.50 (C=O carbamate), 173.59 (C=O ester) ppm. MS (ESI): m/z = 468 [M + H]$^+$, 490 [M + Na]$^+$, 412 [M + H – tBu]$^+$. HRMS (Q-TOF): calcd. for $C_{27}H_{38}NO_4Si$ 468.2570; found 468.2547.

(*S*)-2-(Fluorenyloxycarbonylamino)-5-(trimethylsilyl)pentanoic Acid (9): After a standard treatment of compound **8** with TFA, compound **9** was obtained almost quantitatively (93 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.0 [s, Si(CH_3)$_3$], 0.45–0.55 (m, 2 H, C$H_{\delta\delta'}$-Si), 1.25–1.45 (m, 2 H, CH$_{\gamma\gamma'}$), 1.65–1.80 (m, 1 H, CH_β), 1.80–1.95 (m, 1 H, C$H_{\beta'}$), 4.15–4.25 [m, 2 H, CH(Fmoc) and CH_α], 4.40 [d, J = 6.8 Hz, 2 H, CH_2(Fmoc)], 5.35 (dl, 1 H, NH), 7.30–7.50 (m, 8 H, H_{arom}), 10.6 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.0 [Si(CH$_3$)$_3$], 16.47 (C_δ), 21.62 (C_γ), 37.59 (C_β), 48.81 (CH Fmoc), 55.32 (C_α), 67.81 (CH$_2$ Fmoc), 121.78, 126.44, 128.86, 129.53, 143.07, 145.32, 145.43 (C_{arom}), 158.18 (C=O carbamate), 179.44 (C=O acid) ppm. MS (ESI): m/z = 412 [M + H]$^+$, 823 [2M + H]$^+$. HRMS (Q-TOF): calcd. for $C_{23}H_{30}NO_4Si$ 412.1944; found 412.1928.

Supporting Information (see footnote on the first page of this article): HPLC profiles, mass spectra, ^{1}H and ^{13}C NMR spectra of six new silylated amino acids.

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