Designing Silylated L -Amino Acids using a Wittig Strategy: Synthesis of Peptide Derivatives and 18 F-Labelling

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Baptiste Rugeri,[a] Hassib Audi,[a] Pawel Jewula,[a] Radouane Koudih,[a] Raluca Malacea-Kabbara,[a]* Delphine Vimont,[b] Jürgen Schulz,[b] Philippe Fernandez[a] and Sylvain Jugé[a]*

Abstract: An efficient hemisynthesis of silylated L-amino acids is described by reaction of silylated benzaldehydes with a phosphonium L-amino acid used as Wittig reagent. The efficiency of the silylated L-amino acids in peptide synthesis was investigated by coupling both carboxylic acid or amino moiety with L-alanine and phenylalanine derivatives, respectively. The silylated derivatives were reacted with KF or TBAF to afford the corresponding fluorosilyl derivatives without racemization. The resistance to hydrolysis of the fluorosilylated derivatives was checked in phosphate buffer at pH 7.2. Finally, the ^{18}F-labeling of the di-*t*-butylsilylated saturated and unsaturated dipeptides was achieved in hot DMSO with a mixture of K[^{18}F]/cryptand (K2.2.2) and acetic acid. The radiolabeled ^{18}F-labeled dipeptides were obtained with radiochemical yields and molar activities up to 27 % (decay uncorrected) and 410 GBq/µmol, respectively. Consequently, the hemisynthesis *via* the Wittig reaction offers a new and efficient route for the design and the ^{18}F-labeling of Si-based amino acids and peptide derivatives, applicable in PET imaging
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Introduction

The use of radioisotopic, optical, fluorescent, electrochemical or nanomaterials tags to label bioactive molecules is now used extensively to explore metabolic pathways, to establish diagnosis and follow diseases progression, to treat pathologies or to guide surgery.[1,2] The development of new methods to track biomolecules like peptides, proteins or antibodies is a constant challenge, because these molecules occupy a prominent position in all living processes. Thus, visualizing and characterizing them in their native environment is essential to understand the biological processes and to focus new diagnostic method.[3]

Usually the labelling of peptides and proteins is achieved using either fluorescent probes or metal radioisotopes such as ^{64}Cu, ^{68}Ga, ^{177}Lu, ^{99m}Tc or ^{186}Re complexed to polydentate chelators.[4] Due to the increasing use of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) for cancer diagnosis *via* positron emission tomography (PET) during the last decades, the ^{18}F-radionuclide has become more accessible for the labeling of amino acids and peptides.[2,4,5]

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Fluorine-18 is a β$^+$-radionuclide with a half-life of 110 min and a size comparable to proton which gives good hydrophilic-lipophilic balance and modestly alters the amino acid or peptide frameworks.[4-6] Among the methods used for labeling amino acid and peptides by the ^{18}F-radionuclide,[7] the formation of Si-^{18}F bond is one of the rare ^{18}F-labeling strategies not employing the carbon-^{18}F bond formation. This method is based on the insertion of prosthetic groups bearing hydrosilane, fluorosilane (via an isotopic exchange), silanol or siloxane groups on the lateral chain of peptides as illustrated by the examples **1-4**. (Figure 1).[8-11]

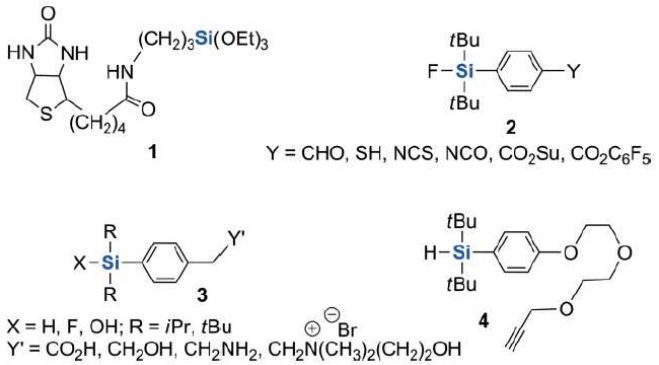


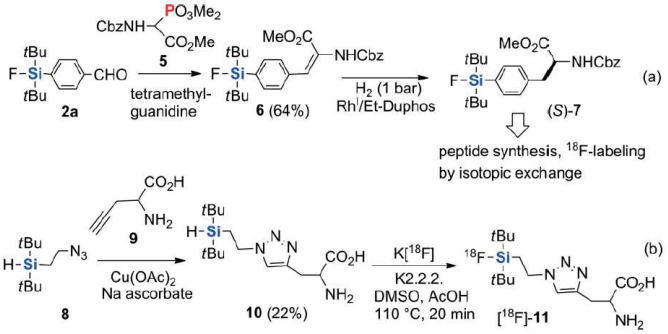
Figure 1. Representative Si-based prosthetic group for ^{18}F-labeling of peptides

The presence of such prosthetic groups usually increase the peptide lipophilicity giving a negative influence on the pharmacokinetics of the labeled peptide and thus a nonspecific binding. Further designing is therefore needed in order to reduce the lipophilicity, for example by introduction of polyethylene glycol (PEG) or charged auxiliaries.

These strategies require multi-step sequences which are often time consuming. This is the reason why it is highly interesting to perform fast direct ^{18}F-labeling of amino acids which could be used in peptide synthesis or as substrates for multi amino acid transport systems in order to improve the specificity with regard to their targets.[6] Such labeling methods offer the possibility to change the position of the modified amino acid inside the sequence in order to reduce the difference with the native peptide.[4,6]

The synthesis of silicon-containing amino acids was intensively developed for maintaining or reinforcing the biological activity of peptides and to enhance their resistance toward enzyme degradation,[12] but very few examples concerning their use in ^{18}F-labeling have been reported. This is explained by *in vivo* hydrolysis of ^{18}F-fluorosilane moiety unless bulky groups such as *i*-propyl or *t*-butyl substitute the silicon center (Figure 1).[9a,10c] In this context, Wängler/Jurkschat *et al* have described the synthesis of (*S*)-4-[(di-*t*-butyl)fluorosilyl]phenylalanine derivative **7** by asymmetric Rh-

catalyzed hydrogenation of dehydroamino acid substrate **6**. The Si-amino acid was then incorporated in Tyr^3-octreotate derivative for radiolabeling study (Scheme 1a).[13] In addition, the (±)-(di-*t*-butyl)hydrosilylated amino acid **10**, obtained by Huisgen cycloaddition of azidoethylsilane **8** with racemic propargyl glycine **9**, has been reported by Ametamey *et al* for the labeling of peptides (Scheme 1b).[14] The ^{18}F-labeling of the silicon-based amino acids **7** and **10** was then achieved either by isotopic exchange according to the SiFA procedure[13] or by direct fluorination of the hydrosilyl moiety,[14,15] respectively (Scheme 1).



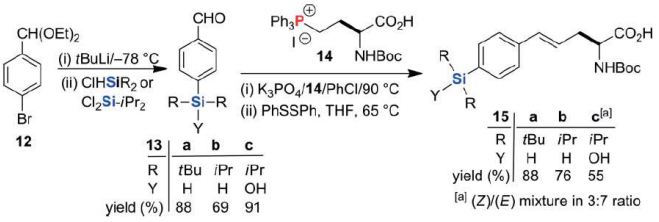
Scheme 1. Synthesis of silylated amino acid applied to ^{18}F-labeling of peptides

In connection with our ongoing investigations in phosphorus- and boron-derivatives useful in ^{18}F-labeling,[16,17] we investigated a new stereoselective synthesis of silylated (Si-)amino acids and studied their efficiency as potential imaging agents. For this, we developed an hemisynthetic approach of Si-amino acids **15** bearing a free carboxylic acid function, by C=C bond forming on the side chain using a key Wittig reaction. This synthesis allows an easy designing of the silyl moiety by changing the substituents R or the living group Y (Scheme 2). The efficiency of the Si-amino acids in peptide synthesis was demonstrated by coupling both acid and amino group with alanine or phenylalanine derivatives (Scheme 3). The fluorination, the kinetics and the resistance to hydrolysis of the Si-amino acids **15** and dipeptide derivatives **18** was then investigated in phosphate buffer (Table 1; Figures 3 and 4). Finally, the ^{18}F-labeling of the Si-peptides **18a** and **20a** was studied. (Table 2).

Results and Discussion

Stereoselective synthesis of silylated amino acid derivatives using a Wittig reaction

The silylated amino acids **15a-c** were synthesized by Wittig reaction of the corresponding aldehydes **13a-c** with the phosphonium salt **14**, in hot chlorobenzene (or dioxane) with K_3PO_4 as base according to the described procedure (Scheme 2).[17] The silylated aldehydes **13a-c** were prepared in yields up to 91% by halogen metal exchange on commercially available 4-bromobenzaldehyde diethyl acetal **12**, and trapping with the appropriate chloro or dichlorosilane, followed by hydrolysis (Scheme 2). The Wittig reagent **14** was prepared in 30% overall yield starting from L-aspartic acid according to a previous established procedure.[17]



Scheme 2. Synthesis of silylated amino acid derivatives **15a-c** by Wittig reaction

The silylated amino acids **15a-c** were initially obtained with a free carboxylic acid group and as a *Z/E* mixture in 3:7 ratio, as shown by the NMR signals of the silane moiety of compound **15a** (Figure 2a). Further heating in THF with diphenyldisulfide trigger isomerization to afford pure (*E*)-**15a** in 88% yield (Figure 2b). While in the same conditions the silylated amino acid **15b** led to the pure (*E*)-isomer, in the case of the silanol derivative *(Z/E)*-**15c** no isomerization was observed under these conditions (Scheme 2).

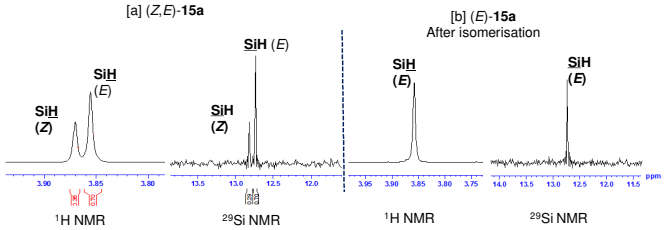
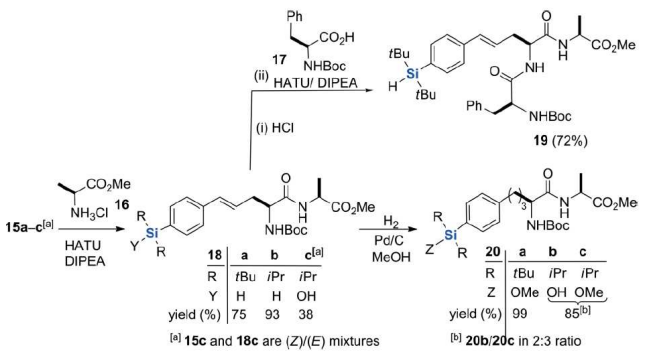


Figure 2. ^{1}H- and ^{29}Si-NMR of compound **15a**: (a) (*Z/E*)-mixture; (b) (*Z*)-mixture after isomerization

Application of silylated amino acids 15a-c in peptide synthesis

The efficiency of silylated amino acids **15a-c** in peptide synthesis *via* both carboxylic acid or amino function was investigated by coupling with L-alanine **16** and L-phenylalanine derivative **17**, respectively (Scheme 3). Silylated compound (*E*)-**15a** (or (*E*)-**15b**) bearing a free carboxylic function was reacted with methyl alaninate **16** at room temperature using HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) as coupling agent,as coupling agent, to afford the corresponding dipeptide **18a** (or **18b**) in yield up to 93%. Under similar conditions the silanol amino acid *(Z/E)*-**15c** led to the peptide **18c** as a (*Z/E*) mixture in 38% yield (Scheme 3). The coupling reaction proceeded without racemisation as shown the NMR spectra of the dipeptide **18a** with an epimeric sample previously prepared starting from racemic Wittig reagent (±)-**14** (see Supporting Information). After deprotection of the Boc group by reaction with HCl 1M in AcOEt, the silyl dipeptide **18a** was coupled with the phenylalanine derivative **17** using the previous HATU procedure, to afford the corresponding tripeptide **19** in 72% yield (Scheme 3). Finally, dipeptide **18a** was quantitatively hydrogenated in MeOH in the presence of Pd/C as catalyst, to give the corresponding saturated methoxysilane **20a**,[18] whereas under the same conditions compound **18c** led to a mixture of silanol **20b** and methoxysilane **20c** in 2:3 ratio (Scheme 3). It is interesting to note that silanol amino acids and peptides are scarcely described in the literature to date.[12,19]

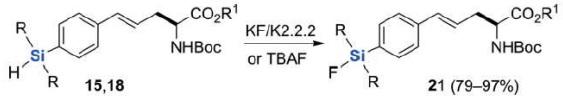


Scheme 3. Synthesis of silylated peptides **18-20**

Fluorination of the hydrosilylated amino acids 15a-b and dipeptides 18a-b

Considering the half-life of ^{18}F (110 min),[10d] both fluorination kinetics and stability are crucial for the development of radiolabeled agents in PET medical imaging.[20] In first attempt, the fluorination of the silylated amino acid derivative **15a** was investigated according to literature conditions,[10c] by reaction with KF in refluxing THF and the presence of cryptand 1,10-diaza-4,7,13,16,21,24-hexa-oxabicyclo[8.8.8] hexacosane (K2.2.2) and a small amount of acetic acid. The Kryptofix® K2.2.2 (2.2.2 cryptand [4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-(8.8.8)-hexacosane]) is a sequestering agent of the potassium counter ion, used in order to enhance the nucleophily of F^-. Under these conditions the fluorosilylated product **21a** was obtained in 97% yield as a stable compound after chromatography on silica gel, exhibiting ^{29}Si and ^{19}F NMR signals at +13.9 ppm (d, $^1J_{Si-F}$ = 298 Hz) and -188 ppm, respectively (Table 1, entry 1).

Table 1. Preparation of fluorosilylated amino acid and dipeptide derivatives **21**



Entry	R_2Si-substrate	R	R^1	Conditions	R_2SiF-Product	Yield [%][a]
1	**15a**	*t*Bu	H	KF/ K2.2.2 AcOH/ THF reflux 48h	**21a**	97 %
2	**15b**	*i*Pr	H	TBAF/ THF rt/ 20 min	**21b**	79 %
3	**18a**	*t*Bu	(*L*)-Ala-OMe	KF/ K2.2.2 AcOH/ THF reflux 24h	**21c**	96 %
4	**18b**	*i*-Pr	(*L*)-Ala-OMe	"	**21d**	92 %

[a] Isolated yields.

On the other hand, the fluorination of the di-*i*-propylsilyl amino acid analogue (**15b**) was achieved by reaction with tetrabutylammonium fluoride (TBAF) in THF at room temperature for 20 min, to afford the fluorosilylated derivative **21b** in 79% isolated yield (entry 2). Finally, under similar conditions as for **15a**, the fluorination of dipeptides **18a** and **18b** led to the corresponding fluorosilylated dipeptides **21c** and **21d** in 96% and 92% yields, respectively (entries 3, 4). These results demonstrate that hydrosilylated amino acids and peptides could be quickly fluorinated under mild conditions which offers an efficient alternative method for the direct ^{18}F-labeling.

Resistance to hydrolysis in phosphate buffer of fluorosilylated dipeptides 21c-d

The aqueous behavior the fluorosilylated dipeptides **21c** and **21d** (chosen as examples) was investigated in an aqueous phosphate buffer (pH 7.2) /acetonitrile-D_3 (8:2) mixture at room temperature. The monitoring was performed using ^{19}F-NMR analysis of the Si-F signal (Figures 3 and 4). Under these conditions, the hydrolysis of **21c** exhibited only traces of the free fluoride F^- ion after 10 days (Figure 3).

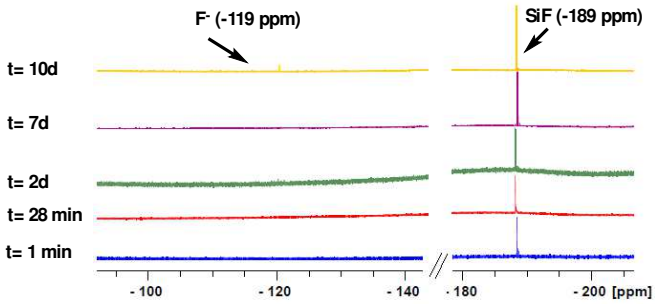


Figure 3. Hydrolysis of fluorosilylated dipeptide **21c** at pH 7 monitored by ^{19}F NMR

By contrast, the di-*i*-propylfluorosilane dipeptide analogue **21d** released 40% of F^- within 5 min, simultanously with the rise of a slightly high field shifted signal at -191.8 ppm (*vs* -191.4 ppm), the intensity of **21d** decreased then steadily with time (Figure 4). This transient signal can be explained by the formation of an solvated hypervalent intermediate such as **22**, in equilibrium with the fluorosilylated precursor **21d**, which leads to the silanol product **18c** and the free fluoride F^- (Figure 4).[9b] It should also be noted that the formation of solvated hypervalent intermediate analogue to **22** has been previously reported by DFT calculations as intermediate in hydrolysis of fluorosilane.[10c]

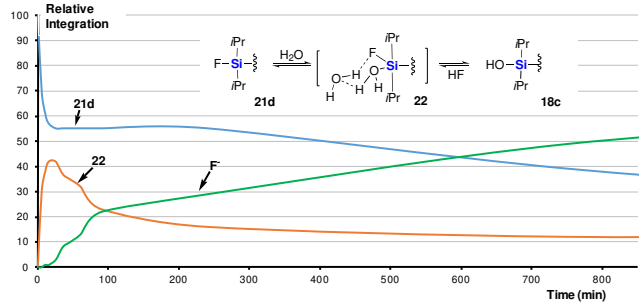


Figure 4. Hydrolysis of fluorosilylated dipeptide **21d** at pH 7.2 monitored by ^{19}F NMR

^{18}F-Labeling of dipeptides derivatives 18a and 20a

The ^{18}F-labeling of organosilylated compounds is currently achieved using K[^{18}F] in the presence of cryptand K2.2.2.[21] The fluorination of the hydrosilylated "prosthetic compounds" such as **3** (X= H) or **4**, has been carried out by heating between 30 and 100°C in the presence of a small quantity of acid such as AcOH.[10,11] Under these conditions ^{18}F-incorporation (73%) was achieved and specific activities up to 62 GBq/µmol were observed.[10d,22] In this study, the direct radiofluorination was investigated with the di-*t*-butylsilylated dipeptides **18a** and **20a** bearing hydrosilane and methoxysilane moieties, respectively (Table 2). The labeling was performed by heating the dipeptide for 15 min with a mixture of K[^{18}F], cryptand K2.2.2 and AcOH in DMSO. The initial activity of the ^{18}F solution at cyclotron output was in the range 103-127 Gbq

and the radiolabeling conditions and results are reported in Table 2. **[^{18}F]-21**c was obtained in 18% radiochemical yield (Decay uncorrected RCY/ radiochemical purity > 97%) and with a molar activity (A_m) of 410 GBq/µmol when the radiolabeling of the unsaturated dipeptide **18a** was performed by heating at 100°C with 120 GBq as starting ^{18}F (Table 2, entry 1). Different RCY and molar activities of **[^{18}F]-21c** were obtained by changing the quantities of acetic acid and the heating conditions (entries 2-4). (the measurement time for the molar activity determination must be stated)

Table 2. ^{18}F-labeling of dipeptide derivatives **18a** and **20a**

Entry	Dipeptide	Y	Initial activity [GBq]	Conditions T[°C]	^{18}F-Labeled dipeptide	RCY[a,b] [%]	A_m[c] [GBq/µmol]
1	**18a**	H	120	100	**[^{18}F]-21c**	18	410
2	**18a**	H	103	80	**[^{18}F]-21c**	27	260
3	**18a**	H	122	80[d]	**[^{18}F]-21c**	13	117
4	**18a**	H	117	60	**[^{18}F]-21c**	19	158
5	**20a**	MeO	111	100	**[^{18}F]-21e**	10	82
6	**20a**	MeO	127	80	**[^{18}F]-21e**	9	104

[a] Decay uncorrected radiochemical yield. [b] Radiochemical purity > 97%. [c] Molar activity. [d] 50 µL AcOH instead of 3 µL

Results showed that performing the radiolabeling at 80°C afforded a lower SA but a slightly higher RCY (entry 4 *vs* entry 1). It was also shown that the radiolabeling was not facilitated by higher acidic conditions (entry 3), possibly because the dipeptide was partially degraded either by reaction of the unsaturation or by deprotection of the Boc group.

However contrary to **21c**, **[^{18}F]-21c** evolved toward a new radiolabeled species with similar HPLC retention time. This unexpected reaction was slowed down by diluting **[^{18}F]-21c** in saline solution (NaCl, 0.9%) and nearly stopped using aqueous ascorbic acid (0.1%). It was identified as resulting from an addition reaction on the C=C double bond with radical intermediates due to ionizing conditions (see Supporting Information).[23]

Since stability over time is mandatory for potential PET imaging, the radiolabeling was considered in a second instance with the saturated methoxysilylated dipeptide **20a**, obtained by hydrogenation of **18a** (Scheme 3). When the radiolabeling of the saturated dipeptide **20a** was performed by heating at 100°C for 15 min with 111 GBq as starting K[^{18}F], the labeled product **[^{18}F]-21e** was obtained in 10% RCY and with a SA of 82 GBq/µmol (entry 5). By heating at 80°C, the radiolabelled dipeptide **[^{18}F]-21e** was obtained in only 9% RCY and with a SA of 104 GBq/µmol (entry 6). HPLC analyses of dipeptide **[^{18}F]-21c** and **[^{18}F]-21e** were compared to those of corresponding non-radioactive references **21c** and **21e**, the latter prepared by hydrogenation of **21c**. This proved that no degradation was observed in the case of the saturated dipeptide **[^{18}F]-21e** for at least 5h40 (see Supporting Information). While RCY are moderate, it should be pointed out that high specific activities are requested for receptor binding studies in order to avoid receptor saturation.[24]

Conclusions

In this manuscript we have demonstrated that unsaturated silylated L-amino acids can be synthesized based on the Wittig reaction between silylated benzaldehydes with a phosphonium L-amino acid reagent. The silane fragment tolerates the conditions of peptide coupling allowing synthesis of several dipeptides. Although *t*Bu$_2$SiH compounds are more difficult to fluorinate than the corresponding *i*Pr derivatives, the resulting fluorinated *t*Bu$_2$SiF dipeptides are more resistant in aqueous conditions. Dipeptides carrying silane and methoxysilane moieties were easily labeled with ^{18}F, however better radiochemical yields and specific activities were obtained for the SiH fluorination. Whereas the radiolabeled unsaturated dipeptide turned out to be radiosensitive, this was not the case of the corresponding saturated analogue.

Experimental Section

General

All reactions were carried out using standard Schlenk techniques under inert atmosphere. Solvents were dried and purified by conventional methods prior to use. The chlorobenzene, toluene, diethyl ether, *n*-hexane, ethyl acetate, petroleum ether (EP), methanol, dimethylsulfoxyde (DMSO) and acetic acid were purchased in anhydrous form. The reagents *t*-butyllithium, 4-bromobenzaldehyde diethylacetal, di-*t*-butylchlorosilane, chloro-di-*i*-propylsilane, dichloro-di-*t*-butylsilane, cryptand K2.2.2 (Kryptofix®), diphenyldisufide, ethyl-di-*i*-propylamine (DIPEA), O-(7-Aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU), L-Boc-Phe-OH, L-Alanine methyl ester hydrochloride, hydrogen chloride 1M in AcOEt, tetrabutylammonium fluoride 1M in THF, were purchased from commercial sources. The iodide (S)-2-(*t*-butyloxycarbonyl)amino]-4-triphenylphosphonium-butanoic acid **14** was prepared according to the published procedure.[17] The flash chromatography was performed with the indicated solvents using silica gel 60 (60AAC, 35-70 µm; SDS). The ^{1}H, ^{13}C, ^{19}F and ^{29}Si NMR spectra were recorded on Bruker Avance 600, 500 or 300 MHz spectrometers at ambient temperature using TMS as internal reference for ^{1}H, ^{13}C and ^{29}Si NMR, and CCl_3F for ^{19}F NMR. Data are reported in ppm as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad signal, coupling constants in Hertz, integration. The mass spectra and accurate mass measurements (HRMS) were performed under (ESI) conditions with a Bruker micro Q-TOF detector or Thermo Orbitrap detector. HPLC analyses were performed either on a Shimadzu chromatograph equipped with a UV detector at λ = 210 nm and λ = 254 nm, or a JASCO system equipped a MD-2010 Plus photodiode array detector, or a Dionex P680 system equipped with UV multiwavelength and Raytest Gabi Star detectors. High-performance liquid chromatography (HPLC) analyses were performed using a Phenomenex Luna C_{18} column (250 × 4.6 mm, 5 µm, flow 1 mL/ min) and the indicated conditions. The infra-red spectra were recorded on a FT-IR Bruker Vector 22 or Vertex 70v instruments and the data are given in cm^{-1}. The buffer solution pH = 7.2 (0.2M) was prepared by mixing in 100 mL H_2O, $Na_2HPO_4{\cdot}7H_2O$ (5.3 g) and $NaH_2PO_4{\cdot}H_2O$ (40 mg). Melting points were measured on a Kofler melting point apparatus and are uncorrected. Optical rotation values were measured on Perkin Elmer 241 polarimeter at 589 nm (sodium lamp). All radiofluorination experiments were run on a commercial TRACERLab FxF-N® (Ge Healthcare).

4-[Hydro(di-*t*-butyl)silyl]benzaldehyde 13a.

*t*BuLi in hexane (1.84M, 11 mL, 20.2 mmol) was added dropwise at -78°C under argon to a solution of 4-bromobenzaldehyde diethylacetal **12** (2 mL, 10 mmol) in 20 mL of dry THF in a Schlenk tube. After 30 min, di-*t*-butylchlorosilane (1.8 mL, 11.4 mmol) was added. The mixture was stirred 2h at -78°C and then let warm up to room temperature overnight. After

addition of HCl 1M until pH = 3 and stirring at room temperature for 1 h, the reaction mixture was extracted with 3 x 50 mL of CH_2Cl_2. The organic phases were gathered, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture petroleum ether/ AcOEt (19:1) as eluent. After removing the solvent under vacuum the 4-[hydro(di-*t*-butyl)silyl] benzaldehyde **13a** was obtained as a colorless oil with an intense almond-like smell (2.2 g, 8.83 mmol, 88% yield) which crystallizes as a white solid; m.p. 60-61°C; R_f: 0.58 (petroleum ether/Et_2O 9:1); FTIR (neat): 2959-2856 (CH,CHO), 2105 (SiH), 1701 (C=O), 1592 (C=C), 1466, 1207, 793, 686; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.05 (s, 18 H; C(C*H*$_3$)$_3$), 3.92 (s, 1 H; Si*H*), 7.76 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 7.83 (d, ^3J(H,H) = 8.0 Hz, 2H; Ar*H*), 10.03 ppm (s, 1 H; C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (*C*(CH$_3$)$_3$), 29.0 (C(*C*H$_3$)$_3$), 128.5 (*C*arom), 136.4 (*C*arom), 136.7 (*C*arom), 144.6 (*C*arom), 192.7 ppm (*C*HO); ^{29}Si NMR (99 MHz, $CDCl_3$): δ= +12.9 ppm; HRMS (ESI-Q-TOF) calcd. for $C_{15}H_{24}OSiNa$ [M+Na]$^+$: 271.14833; found: 271.14940.

4-[Hydro(di-*i*-propyl)silyl]benzaldehyde 13b.

This compound was prepared according to a new procedure with regard to the literature.[25] *t*BuLi in hexane (2.23M, 1.8 mL, 4 mmol) was added dropwise at -78°C under argon to a solution of 4-bromobenzaldehyde diethyl acetal **12** (0.5 mL, 2 mmol) in 5 mL of dry THF in a Schlenk tube. After 30 min, chloro(di-*i*-propyl)silane (2 mL, 2.2 mmol) was added. The mixture was stirred for 2h at -78°C and then let warm up to room temperature overnight. The mixture was acidified to pH = 3 with HCl 1M and stirred at room temperature for 1h. The reaction mixture was extracted with 3 x 30 mL of CH_2Cl_2, the organic phases were gathered, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using a mixture petroleum ether/AcOEt (9:1) as eluent. The 4-[hydro(di-*i*-propyl)silyl]benzaldehyde **13b** was obtained as a colorless liquid with an intense almond-like smell (365 mg, 1.37 mmol, 69% yield); R_f: 0.40 (petroleum ether/Et_2O 19:1); FTIR (neat): 2944-2864 (CH, CHO), 2107 (SiH), 1702 (C=O), 783; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.00 (d, ^3J(H,H) = 7.4 Hz, 6 H; CH(C*H*$_3$)$_2$), 1.08 (d, ^3J(H,H) = 7.4 Hz, 6 H; CH(C*H*$_3$)$_2$), 1.24 (hept d, ^3J(H,H) = 7.4 Hz, ^3J(H,H) = 3.3 Hz, 2 H; 2 C*H*(CH$_3$)$_2$), 4.00 (t, ^3J(H,H) = 3.3 Hz, 1 H; Si*H*), 7.70 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 7.84 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 10.03 ppm (s, 1 H; C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.8 (*C*H(CH$_3$)$_2$), 18.6 (CH(*C*H$_3$)$_2$), 18.7 (CH(*C*H$_3$)$_2$), 128.6 (*C*arom), 136.1 (*C*arom), 136.9 (*C*arom), 143.4 (*C*arom), 192.7 ppm (*C*HO); HRMS (ESI-Q-TOF) calcd. for $C_{13}H_{21}OSi$ [M+H]$^+$: 221.13562; found: 221.13478.

4-[Hydroxy(di-*i*-propyl)silyl]benzaldehyde 13c.

*t*BuLi in hexane (1.7M, 5.9 mL, 10 mmol) was added dropwise at -78°C under argon to a solution of 4-bromobenzaldehyde diethyl acetal **12** (1.0 mL, 5 mmol) in 5 mL of dry THF in a Schlenk tube. After 30 min, the mixture was cannulated over a solution of dichloro(di-*i*-propyl)silane (1.2 mL, 6.6 mmol) in 5 mL of dry THF. The mixture was stirred 2h at -78°C then let warm up to room temperature overnight. The reaction mixture was quenched with 10 mL of water and extracted with 3 x 30 mL of CH_2Cl_2, the organic phases were then gathered, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by chromatography on column using petroleum ether/AcOEt (6:4) as eluent, to afford the 4-[hydroxy(di-*t*-butyl)silyl]benzaldehyde **13c** as a pale yellow liquid (1.07 g, 4.52 mmol, 91% yield); R_f: 0.60 (petroleum ether/AcOEt 6:4); FTIR (neat): 3442 (OH), 2946-2864 (CH, CHO), 1683 (C=O), 810; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 090 (d, ^3J(H,H) = 7.2 Hz, 6 H; CH(C*H*$_3$)$_2$), 0.99(d, ^3J(H,H) = 7.2 Hz, 6 H; CH(C*H*$_3$)$_2$), 1.17 (hept, ^3J(H,H) = 7.4 Hz, 2 H; C*H*(CH$_3$)$_2$), 2.16 (brs, 1 H; SiO*H*), 7.67 (d, ^3J(H,H)= 7.8 Hz, 2 H; Ar*H*), 7.88 (d, ^3J(H,H) = 7.8 Hz, 2 H; Ar*H*), 9.95 ppm (s, 1 H; C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4 (*C*H(CH$_3$)$_2$), 16.8 (CH(*C*H$_3$)$_2$), 17.1 (CH(*C*H$_3$)$_2$), 128.6 (*C*arom), 134.6 (*C*arom), 136.8 (*C*arom), 144.2 (*C*arom), 192.8 ppm (*C*HO); HRMS (ESI-Q-TOF) calcd. for $C_{13}H_{21}O_2Si$ [M-H]$^-$: 235.11598; found: 235.11528.

(2*S*)-2-(*t*-Butoxycarbonyl)amino-5-[4-(di-*t*-butylhydrosilyl)phenyl]pent-4-enoique acid 15a.

Mixture (*Z,E*): Aldehyde **13a** (500 mg, 2.0 mmol) and K_3PO_4 (1,08 g, 5.1 mmol) previously dried by heating under vacuum, were added to a solution of phosphonium salt **14 (**500 mg, 0.85 mmol) in chlorobenzene (6.5 mL). The reaction mixture was stirred for 16h at 90°C, then hydrolyzed with distilled water (5 mL) and extracted with diethyl ether (3 x 5 mL). The resulting aqueous phase was acidified with $KHSO_4$ (1M) to pH = 3 and extracted with ethyl acetate (3 x 5 mL). The organic phase was then dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using petroleum ether/AcOEt (8:2 + 1% AcOH) as eluent, to afford the silylated amino acid **15a** (330 mg, 0.76 mmol, 90% yield) as a (*Z*/E) mixture in the ratio 3:7. Colorless solid; R_f: 0.39 (petroleum ether/AcOEt 8:2 + 1% AcOH); $[\alpha]_D^{20}$ = +17.1 (c = 0.2 in $CHCl_3$); FTIR (neat): 3346 (OH), 2981-2881 (CH), 2105 (SiH), 1714 (C=O), 1400, 1356, 1160; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.05 (s, 18 H; C(C*H*$_3$)$_3$), 1.43 (s, 9 H; OC(C*H*$_3$)$_3$), 2.61-2.99 (m, 2 H; C*H*$_2$), 3.86 (s, 0.6 H; Si*H*), 3.87 (s, 0.4 H; Si*H*), 4.26 (brs, 0.4 H; C*H*N), 4.49 (brs, 0.6 H; C*H*N), 5.09-5.13 (m, 1 H; N*H*), 5.65 (m, 0.3 H; ArCH=C*H*), 6.15-6.19 (m, 0.7 H; ArCH=C*H*), 6.49 (d, ^3J(H,H) = 16 Hz, 0.7 H; ArC*H*=CH), 6.58 (d, ^3J(H,H) = 11.5 Hz, 0.3 H; ArC*H*=CH), 7.22-7.55 (m, 4 H; Ar*H*), 11.03 ppm (s, 1 H; CO_2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 19.1 (*C*(CH$_3$)$_3$, *trans*), 19.2 (*C*(CH$_3$)$_3$, *cis*), 28.4 (C(*C*H$_3$)$_3$), 29.0 (C(*C*H$_3$)$_3$), *trans*), 29.1 (C(*C*H$_3$)$_3$), *cis*), 36.0 (*C*H$_2$, *trans*), 36.2 (*C*H$_2$, *cis*), 53.2 (*C*HN, *trans*), 53.4 (*C*HN, *cis*), 80.5 (O*C*(CH$_3$)$_3$), 124.0 (*C*H=), 125.6 (*C*arom, *trans*), 125.9 (*C*H=), 128.0 (*C*arom, *cis*), 134.4 (*C*H=), 135.1 (*C*arom), 135.9 (*C*arom, cis), 136.2 (*C*arom, *trans*), 137.4 (*C*arom), 155.7 (N*C*O$_2$), 176.7 (*C*O$_2$H, cis), 176.9 ppm (*C*O$_2$H, *trans*); ^{29}Si NMR (99 MHz, $CDCl_3$): δ= +12.7 (s, *trans*), +12.8 ppm (s, *cis*). HRMS (ESI-Q-TOF) calcd. for $C_{24}H_{38}NO_4Si$ [M-H]$^-$: 432.25646; found: 432.25790.

(2*S*,4*E*)-*Isomer* **15a**. The isomerization of the *Z*/*E* mixture **15a** (275 mg, 0.63 mmol) in THF (10 mL) was performed by heating under argon for 15h with diphenyldisulfide (27.7 mg, 0.127 mmol) according to a described procedure.[17] After cooling and removing the solvent, the crude product was purified by chromatography on silica gel using a mixture petroleum ether/AcOEt (7:3) + 1% AcOH as eluent to afford the *trans*-**15a** (270 mg, 0.62 mmol, 98% yield) as a colorless solid; m.p. 60-61°C; R_f: 0.46 (petroleum ether/AcOEt 7:3 + 1% AcOH); $[\alpha]_D^{20}$ = +19 (c = 0.2 in $CHCl_3$); FTIR (neat): 3368 (OH), 2929-2855 (CH), 2096 (SiH), 1715 (C=O), 1501 (CC), 1248 (C-O), 1104, 796, 669; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.04 (s, 18 H; C(C*H*$_3$)$_3$), 1.43 (s, 9 H; OC(C*H*$_3$)$_3$), 2.67-2.77 (m, 2 H; C*H*$_2$), 3.86 (s, 1 H; Si*H*), 4.50 (m, 1 H; C*H*N), 5.15 (brs, 1 H; N*H*), 6.15-6.18 (m, 1 H; ArCH=C*H*), 6.49 (d, ^3J(H,H) = 16.0 Hz, 1 H; ArC*H*=CH), 7.32 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 7.52 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 10.76 ppm (brs, 1 H; CO_2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.0 (*C*(CH$_3$)$_3$), 28.3 (C(*C*H$_3$)$_3$), 28.9 (C(*C*H$_3$)$_3$), 35.9 (*C*H$_2$), 53.1 (*C*HN), 80.4 (O*C*(CH$_3$)$_3$, 123.9 (*C*H=), 125.5 (*C*arom), 134.3 (*C*H=), 134.9 (*C*arom), 136.0 (*C*arom), 137.3 (*C*arom), 155.5 (*C*O$_2$*t*Bu), 176.8 ppm (*C*O$_2$H); ^{29}Si NMR (99 MHz, $CDCl_3$): δ= +12.7 ppm (s).

(±)-(4*E*)-*Isomer* **15a.** The racemic silylated amino acid *trans*-**15a** was synthesized from (±)-amino acid Wittig reagent **14,** previously prepared from (±)-aspartic acid, according to the procedure described above.

(2*S*)-2-(*t*-Butoxycarbonyl)amino-5-[4-hydro(di-*i*-propyl)silylphenyl] pent-4-enoique acid 15b.

Mixture (*Z,E*). Aldehyde **13b** (240 mg, 1.09 mmol) and K_3PO_4 (600 mg, 2.83 mmol) previously dried by heating under vacuum, were added to a solution of phosphonium salt **14** (260 mg, 0.44 mmol) in dry dioxane (5 mL). The reaction mixture was heated at 80°C under stirring for 12h. After cooling and filtration on a celite pad, the residue was washed with CH_2Cl_2 (10 mL). The filtrate was concentrated under reduced pressure. The crude product was then purified by chromatography on silica gel using a mixture petroleum ether/AcOEt (9:1) + 1% AcOH as eluent, to afford the amino acid **15b** (158 mg, 0.39 mmol, 89% yield) as a *Z*/*E* mixture in 3:7 ratio. Colorless uncrystallized solid; R_f: 0.23 (petroleum ether/AcOEt 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.98 (d, ^3J(H,H) = 7.2 Hz, 4.2 H; CH(C*H*$_3$)$_2$ *trans*), 1.00 (d, ^3J(H,H) = 7.1 Hz, 1.8 H; CH(C*H*$_3$)$_2$ *cis*), 1.06 (d, ^3J(H,H) = 7.2 Hz, 4.2 H; CH(C*H*$_3$)$_2$ *trans*), 1.07 (d, ^3J(H,H) = 7.1 Hz, 1.8 H; CH(C*H*$_3$)$_2$ *cis*), 1.21 (m, 2 H; C*H*(CH$_3$)$_2$ *Z*, *E* overlapping), 1.42 (s, 9 H; OC(C*H*$_3$)$_3$), 2.50-3.03 (m, 2 H; C*H*$_2$), 3.92 (t, ^3J(H,H) = 3.1 Hz, 0.7 H; Si*H trans*), 3.93 (t, ^3J(H,H) = 3.1 Hz, 0.3 H; Si*H cis*), 4.17-4.57 (brs, 1 H; C*H*N), 4.92-5.09 (brs, 1 H; N*H*), 5.64 (m, 0.3 H; ArCH=C*H*), 6.17 (m, 0.7 H; ArCH=C*H*), 6.49 (d, ^3J(H,H) = 15.8 Hz, 0.7 H; ArC*H*=CH *trans*), 6.58 (d, ^3J(H,H) = 11.7 Hz, 0.3 H; ArC*H*=CH *cis*), 7.23 (d, 0.7 H, ^3J(H,H) = 8.1 Hz; Ar*H cis*), 7.32 (d, 1.3 H, ^3J(H,H) = 8.1 Hz, 1.3 H; Ar*H trans*), 7.45 (d, ^3J(H,H) = 8 Hz, 1.3 H; Ar*H trans*), 7.58 (d, 0.7 H, ^3J(H,H) = 8.1 Hz, Ar*H cis*), 9.50 ppm (brs, 1 H; CO_2H).

(2*S*,4*E*)-*Isomer* **15b**. The isomerization of the *Z*/*E* mixture **15b** (172 mg, 0.42 mmol) was achieved by heating in THF under argon for 15h with diphenyldisulfide, according to the procedure described above, to afford 147 mg of (*E*)-isomer **15b** (0.36 mmol, 86% yield). Colorless solid; R_f: 0.23 (petroleum ether/AcOEt (9:1) + 1% AcOH); $[\alpha]_D^{20}$ = +9.6 (c = 4.1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (d, ^3J(H,H) = 7.4 Hz, 6 H; CH(CH_3)$_2$), 1.06 (d, ^3J(H,H) = 7.4 Hz, 6 H; CH(CH_3)$_2$), 1.24 (d, ^3J(H,H) = 7.3 Hz, ^3J(H,H) = 3.2 Hz, 2 H; CH(CH$_3$)$_2$), 1.43 (s, 9 H; OC(CH_3)$_3$), 2.70-2.78 (m, 2 H; CH_2), 3.93 (t, ^3J(H,H) = 3.2 Hz, 1 H; SiH), 4.49 (brs, 1 H, CHN), 5.07 (d, ^3J(H,H) = 6.0 Hz, 1 H; NH), 6.17 (m, 1 H; ArCH=CH), 6.5 (d, ^3J(H,H) = 16 Hz, 1 H; ArCH=CH), 7.33 (d, ^3J(H,H) = 8.0 Hz, 2 H; ArH), 7.47 (d, ^3J(H,H) = 8.1 Hz, 2 H; ArH), 9.26 ppm (brs, 1 H; CO_2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ= 10.7 (*C*H(CH$_3$)$_2$), 18.5 (CH(*C*H$_3$)$_2$), 18.6 (CH(*C*H$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 35.8 (*C*H$_2$), 53.1 (*C*HN), 80.4 (O*C*(CH$_3$)$_3$), 123.9 (*C*H=), 125.6 (Carom), 133.7 (*C*H=), 134.3 (*C*arom), 135.7 (*C*arom), 137.5 (*C*arom), 155.6 (N*C*O$_2$), 176.5 ppm (*C*O$_2$H); HRMS (ESI-Q-TOF) calcd. for $C_{22}H_{35}NO_4SiNa$ [M+Na]$^+$: 428.22276; found: 428.22214.

(2*S*)-2-(*t*-Butoxycarbonyl)amino-5-[4-(hydroxy-di-*i*-propylsilyl) phenyl]pent-4-enoique acid 15c.

This amino acid was prepared using the same procedure described above for **15a**. The reaction of aldehyde **13c** (850 mg, 3.6 mmol) with the phosphonium salt **14** (1.55 g, 2.6 mmol) and K_3PO_4 (3.4 g, 15.8 mmol) in chlorobenzene (24 mL) lead after purification by column chromatography to the amino acid **15c** as a *Z*/*E* mixture in 3:7 ratio (750 mg, 80% chemical purity by ^{1}H NMR, 1.42 mmol, 55% yield). For analytical purposes a sample (100 mg) was purified using preparative HPLC giving a colorless uncrystallized product (*Z*/*E* mixture in 1:9 ratio); R_f: 0.4 (petroleum ether/AcOEt 1:1 + 1% AcOH); ^{1}H NMR (300 MHz, CD_3CN): δ = 0.92 (d, ^3J(H,H) = 7.1 Hz, 6 H; CH(CH_3)$_2$)), 1.00 (d, ^3J(H,H) = 7.1 Hz, 6 H; CH(CH_3)$_2$), 1.15 (m, 2 H; CH(CH$_3$)$_2$), 1.38 (s, 9 H; C(CH_3)$_3$), 2.77 (m, 2 H; CH_2), 4.19 (m, 1 H; CHN), 5.63 (m, 2 H; ArCH=CH, NH), 6.56 (d, ^3J(H,H) = 11.8 Hz, 1 H; ArCH=CH), 7.29 (d, ^3J(H,H) = 7.9 Hz, 2 H; ArH), 7.52 ppm (d, ^3J(H,H) = 7.9 Hz, 2 H; ArH); ^{13}C NMR (75 MHz, CD_3CN): δ = 12.9 (*C*H(CH$_3$)$_2$), 16.9 (CH(*C*H$_3$)$_2$), 17.2 (CH(*C*H$_3$)$_2$), 28.1 (C(*C*H$_3$)$_3$), 127.8 (*C*H=), 128.3 (*C*arom), 132.0 (*C*H=), 134.8(*C*arom), 135.6 (*C*arom), 138.2 ppm (*C*arom), 5C not observed; HRMS (ESI-Q-TOF) calcd. for $C_{22}H_{35}NO_5SiNa$ [M+Na]$^+$: 444.21767; found: 444.21698.

(*S*,*S*)-di-*t*-Butylhydrosilylated dipeptide 18a.

DIPEA (0.95 mL, 5.5 mmol) was added to a solution of methyl L-alaninate.HCl **16** (460 mg, 3.3 mmol) in dry DMF (14 mL). The reaction mixture was stirred for 30 min at room temperature. Meanwhile in another flask, HATU (1 g, 2.63 mmol) and DIPEA (0.95 mL, 5.5 mmol) were successively added to a solution of *trans*-**15a** (950 mg, 2.2 mmol) in dry DMF (22 mL) at 0°C under argon. This reaction mixture was stirred for 10 min and the methyl L-alaninate **16** (prepared in the first flask) was added to the mixture. After 4h stirring at room temperature, the solvent was removed under vacuum and the residue was purified by chromatography on silica gel using a mixture petroleum ether/Et_2O (1:1) as eluent to afford the silylated dipeptide **18a** (850 mg, 1.64 mmol, 74.5% yield); Colorless foam; R_f: 0.30 (petroleum ether/Et_2O 1:1); $[\alpha]_D^{20}$ = +13.3 (c = 0.6 in $CHCl_3$)**;** FTIR (neat): 3302 (NH), 2929-2855 (CH), 2095 (SiH), 1747 (C=O), 1658 (C=O), 1596 (C=C), 1525 (C=C), 1364 (CC), 1248 (C-O), 1160 (C-O), 797, 668; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (s, 18 H; C(CH_3)$_3$), 1.41 (d, ^3J(H,H) = 8.5 Hz, 3 H; CH_3), 1.42 (s, 9 H; C(CH_3)$_3$), 2.67 (m, 2 H; CH_2), 3.70 (s, 3 H; OCH_3), 3.84 (s, 1 H; SiH), 4.24 (m, 1 H; CHN), 4.56-4.61 (m, 1 H; CHN), 5.08 (m, 1 H; NH), 6.16-6.23 (m, 1 H; ArCH=CH), 6.48 (d, ^3J(H,H) = 16.0 Hz, 1 H; ArCH=CH), 6.68 (d, ^3J(H,H) = 7.0 Hz, 1 H; NCH(CH$_3$)), 7.31 (d, ^3J(H,H) = 8.0 Hz , 2 H; ArH), 7.50 ppm (d, ^3J(H,H) = 8.0 Hz , 2 H; ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4 (CH*C*H$_3$), 19.0 (*C*(CH$_3$)$_3$), 28.3 (C(*C*H$_3$)$_3$), 28.9 (C(*C*H$_3$)$_3$), 36.1 (*C*H$_2$), 48.0 (*C*HN), 52.4 (O*C*H$_3$), 54.1 (N*C*H(CH$_3$)), 80.3 (O*C*(CH$_3$)$_3$), 124.6 (ArCH=*C*H), 125.4 (*C*arom), 134.0 (Ar*C*H=CH), 134.9 (*C*arom), 136.0 (*C*arom), 137.3 (*C*arom), 155.5 (N*C*O$_2$), 170.9 (*C*ON), 173.0 ppm (*C*O$_2$CH$_3$); ^{29}Si NMR (99 MHz, $CDCl_3$): δ = +12.7 ppm (s); HRMS (ESI-Q-TOF) calcd. for $C_{28}H_{46}N_2O_5Si$ [M+Na]$^+$: 541.30682; found: 541.30724.

(*R,S+S,S*)-(*di-t-Butyl*)*hydrosilylated dipeptide* **18a.** The epimeric mixture of the silylated dipeptide **18a** was prepared from (±)-*trans*-**15a** and methyl L-alaninate **16** using the same procedure as described above. The epimeric mixure **18a** was obtained in 81% yield as colorless oil; R_f: 0.4, (petroleum ether/ AcOEt 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.03 (s, 18 H; C(CH_3)$_3$), 1.39 (d, ^3J(H,H) = 8.5 Hz, 3 H; CH_3), 1.42 (s, 9 H; OC(CH_3)$_3$), 2.65-2.69 (m, 2 H; CH_2), 3.70 (s, 1.33 H; OCH_3), 3.74 (s, 1.57 H; OCH_3), 3.84 (s, 1 H; SiH), 4.26 (brs, 1 H; CHN), 4.56-4.61 (m, 1 H; NCH(CH$_3$)), 5.03-5.06 (brs, 1 H; NH), 6.16-6.22 (m, 1 H; ArCH=CH), 6.47 (d, ^3J(H,H) = 16.0 Hz, 1 H; ArCH=CH), 6.66-6.69 (m, 1 H; NHCH(CH$_3$)), 7.31 (d, ^3J(H,H) = 7.5 Hz, 2 H; ArH), 7.52 (d, ^3J(H,H) = 7.5 Hz, 2 H; ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 18.2 (*C*H$_3$), 18.4 (*C*H$_3$), 19.0 (*C*(CH$_3$)$_3$), 28.2 (OC(*C*H$_3$)$_3$), 28.9 (C(*C*H$_3$)$_3$), 36.1 (*C*H$_2$), 48.0 (*C*HN), 48.1 (*C*HN), 52.4 (O*C*H$_3$), 54.2 (N*C*H(CH$_3$)), 80.5 (O*C*(CH$_3$)$_3$), 124.7 (ArCH=*C*H), 125.3 (*C*arom), 134.1 (Ar*C*H=CH), 134.9 (*C*arom), 136.0 (*C*arom), 137.3 (*C*arom), 155.5 (N*C*O$_2$), 170.9 (*C*ON), 173.0 (*C*O$_2$CH$_3$), 173.1 ppm (*C*O$_2$CH$_3$); ^{29}Si NMR (99 MHz, $CDCl_3$): δ = +12.7 ppm (s).

(*S*,*S*)-Hydro(di-*i*-propyl)silylated dipeptide 18b.

This dipeptide was prepared using the same procedure described above for **18a**, starting from the L-amino acid **15b** (40 mg, 0.100 mmol). DIPEA (90 µL, 0.55 mmol), HATU (46 mg, 0.12 mmol) and methyl L-alaninate.HCl **16** (22 mg, 0.15 mmol) were added to **15b** in DMF (1.5 mL) to afford the dipeptide **18b** (46 mg, 0.093 mmol, 93% yield) as a colorless solid. R_f: 0.31 (petroleum ether/ Et_2O 1:1); $[\alpha]_D^{20}$ = +7.9 (c = 0.9 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.98 (d, ^3J(H,H) = 7.3 Hz, 6 H; CH(CH_3)$_2$), 1.05 (d, ^3J(H,H) = 7.3 Hz, 6 H; CH(CH_3)$_2$), 1.20 (hept d, ^3J(H,H) = 7.3 Hz, ^3J(H,H) = 3.2 Hz, 2 H; CH(CH$_3$)$_2$), 1.40 (d, ^3J(H,H) = 7.5 Hz, 3 H; CHCH_3), 1.41 (s, 9 H; OC(CH_3)$_3$), 2.67 (m, 2 H; CH_2), 3.70 (s, 3 H; OCH_3), 3.92 (t, ^3J(H,H) = 3.2 Hz, 1 H; SiH), 4.24 (brs, 1 H; CHN), 4.57 (m, 1 H; NCH(CH$_3$)), 5.13 (brs, 1 H; NH), 6.15-6.19 (m, 1 H; ArCH=CH), 6.48 (d, ^3J(H,H) = 15.6 Hz, 1 H; ArCH=CH), 6.70 (brs, 1 H; NHCHCH$_3$), 7.32 (d, ^3J(H,H) = 7.6 Hz, 2 H; ArH), 7.44 ppm (d, ^3J(H,H) = 7.6 Hz, 2 H; ArH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.9 (*C*H(CH$_3$)$_2$), 18.4 (CH*C*H$_3$), 18.8 (CH(*C*H$_3$)$_2$), 28.4 (OC(*C*H$_3$)$_3$), 36.3 (*C*H$_2$), 48.2 (*C*HN), 52.5 (OCH$_3$), 53.5 (N*C*HCH$_3$), 80.4 (O*C*(CH$_3$)$_3$), 124.9 (ArCH=*C*H), 125.6 (*C*arom), 133.6 (Ar*C*H=CH), 134.1 (*C*arom), 135.8 (*C*arom), 137.7 (*C*arom), 155.6 (N*C*O$_2$), 171.1 (*C*ON), 173.1 ppm (*C*O$_2$CH$_3$); HRMS (ESI-Q-TOF) calcd. for $C_{26}H_{43}N_2O_5Si$ [M+H]$^+$: 491.29358; found: 491.29469.

(*E*,*Z*)-(*S*,*S*)-Hydroxy(di-*i*-propyl)silylated dipeptide 18c.

This dipeptide was prepared using the same procedure as described above for **18a**, from the (*E*,*Z*)-L-amino acid **15c** (270 mg, 0.64 mmol). The reaction of **15c** with DIPEA (0.56 mL, 3.2 mmol), HBTU (291 mg, 0.77 mmol) and methyl L-alaninate.HCl **16** (135 mg, 0.96 mmol) in DMF (10 mL) led to the dipeptide **18c** as an isomeric mixture (55:45) (122 mg, 0.24 mmol, 38% yield) and as a colorless solid. R_f: 0.31 (petroleum ether/ AcOEt 1:1); $[\alpha]_D^{20}$ = +4.8 (c = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, ^3J(H,H) = 4.2 Hz, 2.6 H; CH(CH_3)$_2$), 0.82 (d, ^3J(H,H) = 4.2 Hz, 3.2 H; CH(CH_3)$_2$), 0.88 (d, ^3J(H,H) = 3.6 Hz, 2.7 H; CH(CH_3)$_2$), 0.90 (d, ^3J(H,H) = 3.6 Hz, 3.2 H; CH(CH_3)$_2$), 1.05 (m, 2 H; CH(CH$_3$)$_2$), 1.27 (m, 12 H; OC(CH_3)$_3$, CHCH_3), 2.65 (m, 2 H; CH_2), 3.56 (m, 3 H; OCH_3), 4.08 (brs, 1 H; CHN), 4.41 (m, 1 H; NCHCH$_3$), 4.88 (brs, 1 H; SiOH), 5.49 (m, 0.5 H; ArCH=CH), 6.04 (m, 0.5 H; ArCH=CH), 6.30-6.54 (m, 1 H; ArCH=CH), 7.10 (m, 1 H; ArH), 7.18 (m, 1 H; ArH) , 7.35 ppm (m, 2 H; ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 12.4 (*C*H(CH$_3$)$_2$), 14.2 (*C*H(CH$_3$)$_2$), 16.9 (CH(*C*H$_3$)$_2$), 17.2 (CH(*C*H$_3$)$_2$), 18.4 (CHCH_3), 21.3 (CHCH_3), 28.2 (OC(*C*H$_3$)$_3$), 31.4 (*C*H$_2$), 48.1 (*C*HN), 52.5 (O*C*H$_3$), 60.4 (N*C*HCH$_3$), 125.5 (ArCH=*C*H), 127.9 (*C*arom), 134.1 (Ar*C*H=CH), 134.4 (*C*arom), 171.0 (*C*ON), 173.1 ppm (*C*O$_2$CH$_3$); 4C not observed; HRMS (ESI-Q-TOF) calcd. for $C_{26}H_{43}N_2O_6Si$ [M+H]$^+$: 507.28849; found: 507.28969.

(*S*,*S*,*S*)-(di-*t*-Butyl)hydrosilylated tripeptide 19.

A solution of (*S*,*S*)-di-*t*-butylhydrosilylated dipeptide **18a** (70 mg, 0.135 mmol) in HCl (1M in AcOEt, 3 mL) was stirred at room temperature under argon for 12h. After removal of solvent under vacuum, the residue was dissolved in dry DMF (1mL) under argon and DIPEA (60 µL, 0.340 mmol) was added. The mixture was stirred for 1h. Meanwhile, a solution of (*S*)-Boc-Phe-OH **17** (36.1 mg, 0.136 mmol) in dry DMF (2 mL) was reacted with HATU (62.1 mg, 0.163 mmol) and DIPEA (60 µL, 0.340 mmol). The mixture was stirred at 0°C for 10 min and was then added to the activated dipeptide solution. The reaction mixture was stirred for 2h and subsequently treated with $KHSO_4$ (1M) and extracted with CH_2Cl_2. The organic phases were gathered, dried over $MgSO_4$ and then filtrated and the solvent removed under vacuum. The residue was purified by chromatography on silica gel using a mixture AcOEt/petroleum ether (1:1) as eluent to afford the silylated

tripeptide **19** (65 mg, 97.6 µmol, 72% yield) as an uncrystallized compound. *R*f: 0.30 (AcOEt/petroleum ether 1:1); $[\alpha]_D^{20}$ = -3.4 (c = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 18 H; C(C*H*$_3$)$_3$), 1.30 (s, 9 H; OC(C*H*$_3$)$_3$), 1.38 (d, ^3J(H,H) = 7.2 Hz, 3 H; CHC*H*$_3$), 2.53-2.72 (m, 2 H; C*H*$_2$), 3.06 (m, 2 H; PhC*H*$_2$), 3.69 (s, 3 H; OC*H*$_3$), 3.83 (s, 1 H; Si*H*), 4.30-4.42 (m, 1 H; C*H*N), 4.44-4.63 (m, 2 H, C*H*N overlapping signals), 4.95 (brs, 1 H; N*H*), 5.99-6.20 (m, 1 H; ArCH=C*H*), 6.32 (d, ^3J(H,H) = 15.9 Hz, 1 H; ArC*H*=CH), 6.58 (brs, 1 H; N*H*), 6.84 (brs, 1 H; N*H*), 7.13-7.31 (m, 7 H; Ar*H*), 7.49 ppm (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1 (CH*C*H$_3$), 19.1 (*C*(CH$_3$)$_3$), 28.3 (C(*C*H$_3$)$_3$), 29.0 (C(*C*H$_3$)$_3$), 35.7 (*C*H$_2$), 38.1 (Ph*C*H$_2$), 48.4 (*C*HN), 52.5 (C*H*N), 52.6 (OC*H*$_3$), 55.9 (C*H*N), 80.6 (O*C*(CH$_3$)$_3$), 124.3 (ArCH=*C*H), 125.5 (*C*arom), 127.3 (*C*arom), 128.9 (*C*arom), 129.4 (*C*arom), 134.3 (Ar*C*H=CH), 135.1 (*C*arom), 136.2 (*C*arom), 136.4 (*C*arom), 137.3 (*C*arom), 155.8 (N*C*O$_2$), 170.2 (*C*ON), 171.3 (*C*ON), 173.0 ppm (*C*O$_2$CH$_3$), 2 C are not observed; ^{29}Si NMR (59 MHz, $CDCl_3$): δ = +12.7 ppm; HRMS (ESI-Q-TOF) calcd. for $C_{37}H_{56}N_3O_6Si$ [M+H]$^+$: 666.39329; found: 666.39188.

(*S*,*S*)-di-*t*-Butylmethoxysilylated saturated dipeptide 20a.

In an autoclave, to a solution of silylated dipeptide **18a** (250 mg, 0.48 mmol) in dry MeOH (2 mL), was added under argon Pd/C 10% (29 mg, 27 µmol). After stirring overnight under H_2 (10 bar), the reaction mixture was filtrated over celite and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel using a mixture petroleum ether/acetone (8:2) as eluent, to afford quantitatively the saturated methoxysilylated dipeptide **20a** (265 mg, 0.48 mmol, quantitative) as a colorless uncrystallyzed compound. *R*f: 0.32 (petroleum ether/acetone 8:2); $[\alpha]_D^{20}$ = -4.8 (c = 0.5 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (s, 18 H; C(C*H*$_3$)$_3$), 1.32 (d, ^3J(H,H) = 7.3 Hz, 3 H; CHC*H*$_3$), 1.37 (s, 9 H; OC(C*H*$_3$)$_3$), 1.62-1.83 (m, 4 H; (C*H*$_2$)$_2$), 2.55-2.58 (m, 2 H; ArC*H*$_2$), 3.65-3.66 (m, 6 H, OC*H*$_3$ overlapping signals), 4.03 (brs, 1 H; C*H*N), 4.51 (p, ^3J(H,H) = 7.5 Hz, 1 H; C*H*CH$_3$), 4.88 (brs, 1 H; NH), 6.41 (d, ^3J(H,H) = 7.5 Hz, 1 H; N*H*), 7.09 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 7.44 ppm (d, ^3J(H,H) = 8 Hz, 2 H; Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5 (CH*C*H$_3$), 21.0 (*C*(CH$_3$)$_3$), 27.2 (*C*H$_2$CHN), 28.5 (C(*C*H$_3$)$_3$), 28.6 (C(*C*H$_3$)$_3$), 32.3 (PhCH$_2$*C*H$_2$), 35.7 (Ph*C*H$_2$), 48.2 (*C*HN), 52.6 (O*C*H$_3$), 53.2 (*C*HN), 54.5 (SiO*C*H$_3$), 80.3 (OC(CH$_3$)$_3$), 127.6 (*C*arom), 135.3 (*C*arom), 142.7 (*C*arom), 159.5 (N*C*O$_2$), 171.7 (N*C*O), 173.2 ppm (*C*O$_2$CH$_3$), 1C not observed; HRMS (ESI-Q-TOF) calcd. for $C_{29}H_{51}N_2O_6Si$ [M+H]$^+$: 551.35109; found: 551.35067.

(*S*,*S*)-Hydroxy- and methoxy(di-*i*-propyl)silylated saturated dipeptide 20b and 20c.

These dipeptides were obtained using the same procedure described above for **20a**. Pd/C 10% (15 mg, 13 µmol) was added to the enantiopure (*E*/*Z*)-isomeric mixture peptide **18c** (92 mg, 0.18 mmol) in dry MeOH (1.8 mL) and the mixture was stirred under H_2 (10 bar) overnight. After filtration over celite and removing the solvent under vacuum, a mixture of saturated dipeptide **20b** and **20c** was obtained in 2:3 ratio (79 mg, 0.15 mmol, 85%) as a colorless foam. R*f*: 0.50 (petroleum ether/AcOEt 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (m, 12 H; CH(C*H*$_3$)$_2$), 1.26 (m, 2 H; C*H*CH$_3$), 1.39 (d, ^3J(H,H) = 7.3 Hz, 3 H; CHC*H*$_3$), 1.44 (s, 9 H; OC(C*H*$_3$)$_3$), 1.70-1.90 (m, 4 H; (C*H*$_2$)$_2$), 2.64 (m, 2 H; PhCH$_2$), 3.6 (s, 2 H; OC*H*$_3$), 3.72 (s, 3 H; OC*H*$_3$), 4.15 (brs, 1 H; C*H*N), 4.57 (m, 1 H; NC*H*CH$_3$), 5.13 (brs, 1 H; N*H*), 6.77 (brs, 1 H; N*H*), 7.17 (m, 2 H; Ar*H*), 7.46 ppm (m, 2 H; Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 12.0 (*C*H(CH$_3$)$_2$), 12.5 (*C*H(CH$_3$)$_2$), 17.0 (CH(*C*H$_3$)$_2$), 17.2, CH(*C*H$_3$)$_2$), 17.3 (CH(*C*H$_3$)$_2$), 17.5 (CH(*C*H$_3$)$_2$), 18.2 (CH*C*H$_3$), 27.1 (*C*H$_2$CHN), 32.1 (PhCH$_2$*C*H$_2$), 32.3 (PhCH$_2$*C*H$_2$), 35.5 (Ph*C*H$_2$), 35.6 (Ph*C*H$_2$), 48.0 (*C*HN), 52.0 (O*C*H$_3$), 52.4 (SiO*C*H$_3$), 52.5 (*C*HN), 54.3 (*C*HN), 80.1 (O*C*(CH$_3$)$_3$), 127.8 (*C*arom), 131.1 (*C*arom), 134.3 (*C*arom), 134.8 (*C*arom), 142.9 (*C*arom), 155.7 (N*C*O$_2$), 171.7 (N*C*O), 173.1 (*C*O$_2$CH$_3$), 173.2 ppm (*C*O$_2$CH$_3$); HRMS (ESI-Q-TOF) calcd. for $C_{26}H_{44}N_2O_6SiNa$ (silanol **20b**) [M+Na]$^+$: 531.28608; found: 531.28686; and calcd. for $C_{27}H_{46}N_2O_6SiNa$ (siloxane **20c**) [M+Na]$^+$: 545.30229; found: 545.302680.

(2*S*,4*E*)-2-(*t*-Butoxycarbonylamino)-5-[4-(di-*t*-butylfluorosilyl)phenyl]-4-pentenoic acid 21a.

KF (11mg, 0.18 mmol), K2.2.2 (16 mg, 0.04 mmol) and acetic acid (20 µL, 0.35 mmol) were successively added to a solution of **15a** (26 mg, 0.058 mmol) in dry THF (3 mL). The reaction was heated at reflux of THF under stirring for 48h. After cooling, the solvent was removed under vacuum. The crude residue was purified by chromatography on silica gel using a mixture CH_2Cl_2/MeOH (2% to 10%) as eluent to afford the compound **21a** (25 mg, 97% yield) as a colorless solid. *R*f: 0.30 (petroleum ether/AcOEt 8:2 + 1% AcOH); $[\alpha]_D^{20}$ = +7.6 (c = 1 in MeOH); FTIR (neat): 3322 (NH, OH), 2970-2850 (CH), 1727 (C=O), 1659 (C=O), 1599 (C=C), 1397-1367 (CC), 1162 (CO), 1110, 1048 (CO), 835, 823, 811, 686, 646, 585, 492, 442; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05 (s, 18 H; C(C*H*$_3$)$_3$), 1.42 (s, 9 H; OC(C*H*$_3$)$_3$), 2.68-2.80 (2 brs, 2 H; C*H*$_2$), 4.48 (m, 1 H; NC*H*CH$_3$), 5.07 (d, ^3J(H,H) = 7.0 Hz, 1 H; N*H*), 6.16-6.22 (m, 1 H; ArCH=C*H*), 6.50 (d, ^3J(H,H) = 15.5 Hz, 1 H; ArC*H*=CH), 7.35 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 7.54 ppm (d, ^3J(H,H) = 8.0 Hz, 2 H; ArH), H acid not observed; ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ = 20.4 (*C*(CH$_3$)$_3$), 27.5 (C(*C*H$_3$)$_3$), 28.3 (C(*C*H$_3$)$_3$), 36.0 (*C*H$_2$), 53.1 (*C*HN), 80.6 (O*C*(CH$_3$)$_3$), 124.4 (ArCH=*C*H), 125.5 (*C*arom), 133.3 (Ar*C*H=CH), 134.2 (*C*arom), 137.9 (*C*arom), 155.4 (N*C*O$_2$), 180.5 ppm (*C*O$_2$H), 1C not observed; ^{19}F NMR (470 MHz, $CDCl_3$): δ = -188.9 (s, 0.95F, $^{28/30}$Si-F), -188.9 ppm (d, 0.05F, ^{1}J(Si,F) = 298 Hz, ^{29}Si/F); ^{29}Si NMR (99 MHz, $CDCl_3$): δ = +13.9 ppm (d, ^{1}J(Si,F) = 298 Hz); HRMS (ESI-Q-TOF) calcd. for $C_{24}H_{38}FNO_4SiNa$ [M+Na]$^+$: 474.24463; found: 474.24364.

(2*S*,4*E*)-2-(*t*-Butoxycarbonylamino)-5-[4-fluoro-(di-*i*-propyl)fluorosilyl) phenyl]-4-pentenoic acid 21b.

TBAF 1M in THF (0.2 mL, 200 µmol) was added under argon to a solution of **15b** (35 mg, 86 µmol) in dry THF (2 mL). After 20 min under stirring the solvent was removed under vacuum and the residue was purified by chromatography on silica gel using petroleum ether/AcOEt 9:1 + 1% AcOH as eluent to afford the compound **21b** (28.7 mg, 68 µmol, 79% yield) as a colorless solid. *R*f: 0.20 (petroleum ether/AcOEt 9:1 + 1% AcOH); $[\alpha]_D^{20}$ = +11.4 (c = 0.5 in CH_2Cl_2);^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (dd, ^3J(H,H) = 7.4 Hz, ^3J(H,H) = 1.5 Hz, 6 H; CH(C*H*$_3$)$_2$), 1.00 (dd, ^3J(H,H) = 7.4 Hz, ^3J(H,H) = 1.5 Hz, 6 H; CH(C*H*$_3$)$_2$), 1.15-1.21 (m, 2 H; C*H*(CH$_3$)$_2$), 1.42 (s, 9 H; OC(C*H*$_3$)$_3$), 2.63-2.68 (m, 2 H; C*H*$_2$), 4.41 (brs, 1 H; C*H*N), 5.20 (brs, 1 H; N*H*), 6.09-6.14 (m, 1 H; ArCH=C*H*), 6.43 (d, ^3J(H,H) = 15.9 Hz, 1 H; ArC*H*=CH), 7.29 (d, ^3J(H,H) = 7.8 Hz, 2 H; Ar*H*), 7.41 ppm (d, ^3J(H,H) = 7.8 Hz, 2 H; Ar*H*), H acid not observed; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 12.4 (d, ^2J(C,F) = 12.8 Hz; *C*H(CH$_3$)$_2$), 16.8 (d, ^3J(C,F) = 10.0 Hz; CH(*C*H$_3$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 36.0 (*C*H$_2$), 80.6 (O*C*(CH$_3$)$_3$), 124.7 (ArCH=*C*H), 125.9 (*C*arom), 132.3 (*C*arom), 134.2 (Ar*C*H=CH), 134.3 (*C*arom), 138.4 (*C*arom), 155.7 (N*C*O$_2$), 176.3 ppm (*C*O$_2$H), 1C not observed; ^{19}F NMR (282 MHz, $CDCl_3$): δ = -187.2 ppm; HRMS (ESI-Q-TOF) calcd. for $C_{22}H_{34}FNO_4SiNa$ [M+Na]$^+$: 446.21333; found: 446.214333.

di-*t*-Butylfluorosilylated dipeptide 21c.

KF (36.8 mg, 0.63 mmol), K2.2.2 (94 mg, 0.251 mmol) and acetic acid (80 µL, 1.4 mmol) were added successively under argon to a solution of (*S*,*S*)-di-*t*-butylhydrosilylated dipeptide **18a** (130 mg, 0.251 mmol) in dry THF (6.5 mL). The reaction mixture was heated to reflux of THF for 24h. After cooling, the solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel using a mixture petroleum ether/Et$_2$O (1:1) as eluent, to afford the fluorinated dipeptide **21c** (130 mg, 0.242 mmol, 96% yield) as a colorless foam. *R*f: 0.25 (petroleum ether/Et$_2$O 1:1); $[\alpha]_D^{20}$ = +8.46 (c = 1.9 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 18 H; SiC(C*H*$_3$)$_3$), 1.39 (d, ^3J(H,H) = 7.0 Hz, 3 H; CHC*H*$_3$), 1.41 (s, 9 H; OC(C*H*$_3$)$_3$), 2.62-2.71 (m, 2 H; C*H*$_2$), 3.70 (s, 3 H; OC*H*$_3$), 4.26 (m, 1 H; C*H*N), 4.55-4.61 (m, 1 H; NC*H*CH$_3$), 5.11 (d, ^3J(H,H) = 7.0 Hz, 1 H; N*H*), 6.18-6.24 (m, 1 H; ArCH=C*H*), 6.48 (d, ^3J(H,H) = 15.5 Hz, 1 H; ArC*H*=CH), 6.71 (br d, ^3J(H,H) = 7.0 Hz, 1 H; N*H*), 7.34 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 7.53 ppm (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3 (CH*C*H$_3$), 20.2 (d, ^2J(C,F) = 12.5 Hz; *C*(CH$_3$)$_3$), 27.3 (C(*C*H$_3$)$_3$), 28.2 (OC(*C*H$_3$)$_3$), 36.2 (*C*H$_2$), 48.1 (*C*HN), 52.4 (O*C*H$_3$), 53.7 (*C*HN), 80.3 (O*C*(CH$_3$)$_3$), 125.2 (ArCH=*C*H), 125.5 (*C*arom), 132.9 (*C*arom), 133.8 (Ar*C*H=CH), 134.2 (*C*arom), 138.0 (*C*arom), 155.6 (N*C*O$_2$), 170.9 (*C*ON), 173.0 (*C*O$_2$CH$_3$); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -188.9 (s, 0.95F, $^{28/30}$Si-F), -188.9 ppm (d, 0.05F, ^1J(Si,F) = 298 Hz, ^{29}Si-F); ^{29}Si NMR (99 MHz, $CDCl_3$): δ = +13.9 (d, ^1J(Si,F) = 297 Hz); HRMS (ESI-Q-TOF) calcd. for $C_{28}H_{45}FN_2O_5SiNa$ [M+Na]$^+$: 559.29740; found: 559.29540.

Fluoro-di-*i*-propylsilylated dipeptide 21d.

KF (16.6 mg, 0.285 mmol), K2.2.2 (53.7 mg, 0.143 mmol) and acetic acid (70 µL) were successively added to a solution of (*S*,*S*)-**18b** (70 mg, 0.143 mmol) in dry THF (2.4 mL) under argon. The reaction mixture was heated at reflux of THF for 24h. After cooling the solvent was removed under vacuum and the residue was purified by chromatography on silica gel using a mixture petroleum ether/Et$_2$O (1:1) as eluent, to afford the fluorosilylated

dipeptide **21d** (67 mg, 0.132 mmol, 92% yield) as a colorless foam. R_f: 0.25 (petroleum ether/Et_2O 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, ^3J(H,H) = 7.5 Hz, 6 H; CH(CH_3)$_2$), 1.00 (d, ^3J(H,H) = 7.5 Hz, 6 H; CH(CH_3)$_2$), 1.18 (m, 2 H; C*H*(CH$_3$)$_2$), 1.33 (d, ^3J(H,H) = 7.25 Hz, 3 H, CH(CH_3)), 1.34 (s, 9 H; OC(CH_3)$_3$), 2.60 (m, 2 H; CH_2), 3.63 (s, 3 H, OCH_3), 4.20 (brs, 1 H; C*H*N), 4.51 (m, 1 H; NC*H*(CH$_3$), 5.08 (brs, 1 H; N*H*), 6.17 (m, 1 H; ArCH=C*H*), 6.42 (d, ^3J(H,H) = 16.0 Hz, 1 H; ArC*H*=CH), 6.70 (brs, 1 H; N*H*), 7.29 (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*), 7.41 ppm (d, ^3J(H,H) = 8.0 Hz, 2 H; Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.2 (d, ^2J(C,F) = 13.7 Hz; *C*H(CH$_3$)$_2$), 15.6 (d, ^3J(C,F) = 19 Hz; CH(*C*H$_3$)$_2$), 17.3 (CH*C*H$_3$), 27.3 (OC(*C*H$_3$)$_3$), 35.2 (*C*H$_2$), 47.1 (*C*HN), 51.4 (O*C*H$_3$), 53.1 (*C*HN), 79.3 (OC(*C*H$_3$)$_3$), 124.4 (ArCH=*C*H), 124.7 (*C*arom), 130.9 (*C*arom), 132.7 (Ar*C*H=CH), 133.1 (*C*arom), 137.4 (*C*arom), 155.6 (N*C*O$_2$), 170.0 (*C*ON), 172.0 ppm (CO_2CH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -187.2 (s, 0.95F, $^{28/30}$Si-F), -187.2 ppm (d, 0.05F, ^1J(Si,F) = 294 Hz, ^{29}Si-F); HRMS (ESI-Q-TOF) calcd. for $C_{26}H_{41}FN_2O_5SiNa$ $[M+Na]^+$: 531.26610; found: 531.26647.

Hydrogenation of the di-*t*-butylfluorosilyl dipeptide 21c into saturated derivative 21e (see Supporting Information)**.**

In an autoclave, Pd/C 10% (15 mg, 13 µmol) was added to a solution of fluorosilylated dipeptide **21c** (82 mg, 0.15 mmol) in dry MeOH (1.5 mL). The mixture was stirred under H_2 (10 bar) overnight. After filtration over celite and removing the solvent under vacuum, the fluorosilyl-saturated dipeptide **21e** was quantitatively obtained (82 mg, 0.15 mmol) as a colourless oily compound. R_f: 0.30 (petroleum ether/acetone 8:2); $[\alpha]_D^{20}$ = -5.8 (c = 1 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 18 H; C(C*H*$_3$)$_3$), 1.40 (d, ^3J(H,H) = 7.5 Hz, 3 H; CHC*H*$_3$), 1.44 (s, 9 H; OC(C*H*$_3$)$_3$), 1.69-1.71 (m, 4 H, (C*H*$_2$)$_2$ overlapping signals), 2.63-2.65 (m, 2 H; ArC*H*$_2$), 3.73 (s, 3 H; O*CH*$_3$), 4.10 (brs, 1 H; C*H*N), 4.57 (q, ^3J(H,H) = 7.5 Hz, 1H; NC*H*CH$_3$), 4.95 (brs, 1 H; N*H*), 6.48 (d, ^3J(H,H) = 7.5 Hz, 1 H; N*H*CHCH$_3$), 7.17 (d, ^3J(H,H) = 7.8 Hz, 2 H; Ar*H*), 7.50 ppm (d, ^3J(H,H) = 8.1 Hz, 2 H; Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4 (CH*C*H$_3$), 20.3 (d, ^2J(C,F) = 12.8 Hz; *C*(CH$_3$)$_3$), 27.0 (ArCH$_2$CH$_2$*C*H$_2$), 27.4 (C(*C*H$_3$)$_3$), 28.3 (C(*C*H$_3$)$_3$), 32.1 (ArCH$_2$*C*H$_2$), 35.5 (Ar*C*H$_2$), 48.0 (*C*HN), 52.4 (O*C*H$_3$), 57.1 (*C*HN), 80.3 (O*C*(CH$_3$)$_3$), 127.7 (ArCH=*C*H), 130.6 (*C*arom), 134.2 (Ar*C*H=CH), 143.5 (*C*arom), 159.5 (N*C*O$_2$), 171.5 (*C*ON), 173.2 ppm (CO_2CH_3); ^{19}F NMR ($CDCl_3$, 282 MHz): δ = -189.0 (s, 0.95F, $^{28/30}$Si-F), -189.0 ppm (d, ^1J(Si,F) = 296 Hz, 0.05F, ^{29}Si-F); ^{29}Si NMR ($CDCl_3$, 59 MHz); δ = +14.0 ppm (d, ^1J(Si,F) = 296 Hz); HRMS (ESI-Q-TOF) calcd. for $C_{28}H_{48}FN_2O_5Si$ $[M+H]^+$: calcd 539.33110; found: 539.33081.

^{19}F NMR spectroscopic kinetic analyses: A small quantity of the fluorosilylated compound (5 mg) was introduced into the NMR tube and dissolved in 0.1 mL acetonitrile D_3. At the beginning of the solvolysis (t = 0 min), 0.4 mL of phosphate buffer solution pH 7.2 (0.2M) was added and the hydrolysis was monitored by ^{19}F NMR spectroscopy. ^{19}F NMR spectra were acquired at different times and the integration was determined from spectra. The ratio of ^{19}F-signal existing as the fluorosilylated compound to the total ^{19}F signals was plotted against time to determine the kinetic of the hydrolysis.

Radiofluorination of compounds 18a and 20a into [^{18}F]-21c and [^{18}F]-21e:

No-carrier-added [^{18}F]-fluoride was produced *via* the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of enriched [^{18}O]H_2O. [^{18}F]-Fluoride production: Bombarded 30-60 min; 60 µA; target volume 1.8-2.5 mL, 100-130 GBq are obtained. [^{18}F]-Fluoride was trapped on an anion-exchange resin cartridge (Sep-Pak QMA light, Waters). The cartridge was eluted with a solution of Kryptofix (K2.2.2, 22 mg) and potassium carbonate (7 mg) in H_2O (0.3 mL) and CH_3CN (0.3 mL). Solvents were removed by heating at 100°C for 8 min applying a gentle stream of nitrogen. During this time, dry K[^{18}F]F/ K2.2.2 complex was prepared by azeotropic drying using CH_3CN (4 x 0.25 mL). Silylated compound **18a** (or **20a**) (4.8-5.4 mg) diluted in a mixture of DMSO (500 µL) and acetic acid (3 µL) was added to the dry K[^{18}F]F/K2.2.2 complex and then allowed to react for 15 min at 60-100°C under constant stirring before to be diluted with CH_3CN (3 mL) and H_2O (2 mL). This solution was injected into a semi preparative HPLC 85/15 (CH_3CN/ (H_2O/TFA, 0.1%, v/v)), 2.5 mL/min. Then **[^{18}F]-21c** (or **[^{18}F]-21e**) was formulated in an aqueous physiological solution (0.9% NaCl solution) and purity was checked by analytical HPLC 85/15 (CH_3CN/(H_2O/TFA, 0.1%, v/v)) with 1 mL/min flow, using non-radioactive molecule **21c** (or **21e**) as reference. Results showed that **[^{18}F]-21c** and **[^{18}F]-21e** were obtained with radiochemical purity > 97%, with RCY (Decay uncorrected) in the range 9-27% and with SA from 82 to 410 GBq.µmol^{-1} (Table 2).

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