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

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Abstract: An efficient hemisynthesis of silvlated L-amino acids is described by reaction of silvlated benzaldehydes with a phosphonium L-amino acid used as Wittig reagent. The efficiency of the silvlated 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 ¹⁸F-labeling of the di-t-butylsilylated saturated and unsaturated dipeptides was achieved in hot DMSO with a mixture of K[18F]/cryptand (K2.2.2) and acetic acid. The radiolabeled 18F-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 ¹⁸F-labeling of Si-based amino acids and peptide derivatives, applicable in PET imaging

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 ⁶⁴Cu, ⁶⁸Ga. ¹⁷⁷Lu, ^{99m}Tc or ¹⁸⁶Re complexed to polydentate chelators.^[4] Due to the increasing use of 2-[18F]fluoro-2-deoxy-D-glucose (FDG) for cancer diagnosis via positron emission tomography (PET) during the last decades, the ¹⁸F-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 the ¹⁸F-radionuclide,^[7] the formation of Si-¹⁸F bond is one of the rare hydrosilane, fluorosilane (via an isotopic exchange), silanol or butyl)fluorosilyl]phenylalanine derivative 7 by asymmetric Rh-

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 ¹⁸F-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 ¹⁸F-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 size comparable to proton which gives good hydrophilic-lipophilic peptides and to enhance their resistance toward enzyme balance and modestly alters the amino acid or peptide frameworks.^{[4-} degradation,^[12] but very few examples concerning their use in ¹⁸F-^{6]} Among the methods used for labeling amino acid and peptides by labeling have been reported. This is explained by *in vivo* hydrolysis of ¹⁸F-fluorosilane moiety unless bulky groups such as *i*-propyl or *t*-butyl ¹⁸F-labeling strategies not employing the carbon-¹⁸F bond formation. Substitute the silicon center (Figure 1).^[9a,10c] In this context, This method is based on the insertion of prosthetic groups bearing Wängler/Jurkschat et al have described the synthesis of (S)-4-[(di-t-

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catalyzed hydrogenation of dehydroamino acid substrate **6**. The Siamino acid was then incorporated in Tyr³-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 ¹⁸F-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 ¹⁸F-labeling of peptides

In connection with our ongoing investigations in phosphorus- and boron-derivatives useful in ¹⁸F-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 ¹⁸F-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. ¹H- and ²⁹Si-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 silvlated 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 ¹⁸F (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 silvlated 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 ²⁹Si and ¹⁹F NMR signals at +13.9 ppm (d, ${}^{1}J_{Si-F} = 298$ Hz) and -188 ppm, respectively (Table 1, entry 1).

Table 1. Preparation of fluorosilylated amino acid and dipeptide derivatives21												
R Si H F	15,18	≈~~ Nł	CO ₂ R ¹ HBoc KF/K2.2.2 or TBAF	F R 21	СО; NHBoo (79–97%)	2 ^{R1} c						
Entry	R	₂Si-sub R	strate R ¹	Conditions	R₂SiF-P Yie	roduct eld [%] ^{[a}}						
1	15a	<i>t</i> Bu	Н	KF/ K2.2.2 AcOH/ THF reflux 48h	21a	97 %						
2	15b	<i>i</i> Pr	н	TBAF/ THF rt/ 20 min	21b	79 %						
3	18a	<i>t</i> Bu	(L)-Ala- OMe	KF/ K2.2.2 AcOH/ THF reflux 24h	21c	96 %						
4	18b	<i>i</i> -Pr	(<i>L</i>)-Ala- OMe	"	21d	92 %						
[a] Isolate	d vields.											

On the other hand, the fluorination of the di-i-propylsilyl amino acid analogue (15b) was achieved reaction with by 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 ¹⁸F-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 ¹⁹F-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 $^{19}\mathrm{F}$ 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 $^{19}\mathrm{F}$ NMR

¹⁸F-Labeling of dipeptides derivatives 18a and 20a

The ¹⁸F-labeling of organosilylated compounds is currently achieved using K[¹⁸F] 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 ¹⁸F-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[¹⁸F], cryptand K2.2.2 and AcOH in DMSO. The initial activity of the ¹⁸F 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 ¹⁸F (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												
<i>t</i> Bu Y Si <i>t</i> Bu	δ γ δ 8a Cl 20a Cl	O NHBoc H=CH H ₂ CH ₂	LCO ₂ Me K	¹⁸ F/K2.2.2 /Bu :OH, DMSO 15 min ¹⁸ F	βί /Bu	О С. NH NHBoc [¹⁸ F]-216 [¹⁸ F]-216	CO ₂ Me					
Entry	Dipe	eptide Y	Initial activity [GBq]	Conditions T[°C]	¹⁸ F-Labe	eled dipe RCY ^[a,b] [%] [f	eptide A _m [c] GBq/μmol]					
1	18a	Н	120	100	[¹⁸ F]-21c	18	410					
2	18a	Н	103	80	[¹⁸ F]-21c	27	260					
3	18a	Н	122	80 ^[d]	[¹⁸ F]-21c	13	117					
4	18a	Н	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 μ L AcOH instead of 3 μ L												

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[18F], the labeled product [18F]-21e was obtained in 10% RCY and with a SA of 82 GBq/µmol (entry 5). By heating at 80°C, the radiolabelled dipeptide [18F]-21e was obtained in only 9% RCY and with a SA of 104 GBq/µmol (entry 6). HPLC analyses of dipeptide [18F]-21c and [18F]-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 [18F]-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*Bu₂SiH compounds are more difficult to fluorinate than the corresponding *i*Pr derivatives, the resulting fluorinated *t*Bu₂SiF dipeptides are more resistant in aqueous conditions. Dipeptides carrying silane and methoxysilane moieties were easily labeled with ¹⁸F, 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-ipropylsilane, dichloro-di-t-butylsilane, cryptand K2.2.2 (Kryptofix®), diphenvldisufide. ethyl-di-*i*-propylamine (DIPEA), O-(7-Aza-1Hbenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), N,N,N',N'-Tetramethyl-O-(1H-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 $\mu m;$ SDS). The 1H, $^{13}C,$ ^{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 ¹H, ¹³C and ²⁹Si NMR, and CCl₃F for ¹⁹F 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 C₁₈ column (250 \times 4.6 mm, 5 μ m, 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 , Na₂HPO₄·7H₂O (5.3 g) and NaH₂PO₄·H₂O (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 HCI 1M until pH = 3 and stirring at room temperature for 1 h, the reaction mixture was extracted with 3 x 50 mL of CH₂Cl₂. The organic phases were gathered, dried over MgSO4, 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 almondlike smell (2.2 g, 8.83 mmol, 88% yield) which crystallizes as a white solid; m.p. 60-61°C; Rf: 0.58 (petroleum ether/Et2O 9:1); FTIR (neat): 2959-2856 (CH,CHO), 2105 (SiH), 1701 (C=O), 1592 (C=C), 1466, 1207, 793, 686; ¹H NMR (500 MHz, CDCl₃): δ = 1.05 (s, 18 H; C(CH₃)₃), 3.92 (s, 1 H; SiH), 7.76 $(d, {}^{3}J(H,H) = 8.0 Hz, 2 H; ArH), 7.83 (d, {}^{3}J(H,H) = 8.0 Hz, 2H; ArH), 10.03$ ppm (s, 1 H; CHO); ¹³C NMR (75 MHz, CDCl₃): δ = 19.2 (C(CH₃)₃), 29.0 (C(CH3)3), 128.5 (Carom), 136.4 (Carom), 136.7 (Carom), 144.6 (Carom), 192.7 ppm (CHO); ²⁹Si NMR (99 MHz, CDCl₃): δ = +12.9 ppm; HRMS (ESI-Q-TOF) calcd. for C15H24OSiNa [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] tBuLi in hexane (2.23M, 1.8 mL, 4 mmol) was added dropwise at -78°C under argon to a solution of 4-bromobenzaldehvde 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 CH₂Cl₂, the organic phases were gathered, dried over MgSO₄, 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: 0.40 (petroleum ether/Et₂O 19:1); FTIR (neat): 2944-2864 (CH, CHO), 2107 (SiH), 1702 (C=O), 783; ¹H NMR (500 MHz, CDCl₃): δ = 1.00 (d, ³*J*(H,H) = 7.4 Hz, 6 H; CH(CH₃)₂), 1.08 (d, ³*J*(H,H) = 7.4 Hz, 6 H; CH(CH₃)₂), 1.24 (hept d, ³J(H,H) = 7.4 Hz, ³J(H,H) = 3.3 Hz, 2 H; 2 CH(CH₃)₂), 4.00 (t, ³J(H,H) = 3.3 Hz, 1 H; SiH), 7.70 (d, ³J(H,H) = 8.0 Hz, 2 H; ArH), 7.84 (d, ³J(H,H) = 8.0 Hz, 2 H; ArH), 10.03 ppm (s, 1 H; CHO); ¹³C NMR (125 MHz, CDCl₃): δ = 10.8 (CH(CH₃)₂), 18.6 (CH(CH₃)₂), 18.7 (CH(CH₃)₂), 128.6 (Carom), 136.1 (Carom), 136.9 (Carom), 143.4 (Carom), 192.7 ppm (CHO); HRMS (ESI-Q-TOF) calcd. for C13H21OSi [M+H]+: 221.13562; found: 221.13478.

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

tBuLi 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 CH₂Cl₂, the organic phases were then gathered, dried over MgSO₄, 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-tbutyl)silyl]benzaldehyde 13c as a pale yellow liquid (1.07 g, 4.52 mmol, 91% yield); Rf: 0.60 (petroleum ether/AcOEt 6:4); FTIR (neat): 3442 (OH), 2946-2864 (CH, CHO), 1683 (C=O), 810; ¹H NMR (300 MHz, CDCl₃): δ= 090 (d, ³*J*(H,H) = 7.2 Hz, 6 H; CH(CH₃)₂), 0.99(d, ³*J*(H,H) = 7.2 Hz, 6 H; CH(CH₃)₂), 1.17 (hept, ³J(H,H) = 7.4 Hz, 2 H; CH(CH₃)₂), 2.16 (brs, 1 H; SiOH), 7.67 (d, ³*J*(H,H)= 7.8 Hz, 2 H; Ar*H*), 7.88 (d, ³*J*(H,H) = 7.8 Hz, 2 H; Ar*H*), 9.95 ppm (s, 1 H; CHO); ¹³C NMR (125 MHz, CDCl₃): $\delta = 12.4$ (CH(CH₃)₂), 16.8 (CH(CH₃)₂), 17.1 (CH(CH₃)₂), 128.6 (Carom), 134.6 (Carom), 136.8 (Carom), 144.2 (Carom), 192.8 ppm (CHO); HRMS (ESI-Q-TOF) calcd. for C13H21O2Si [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 KHSO₄ (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; $R_{\rm f}$: 0.39 (petroleum ether/AcOEt 8:2 + 1% AcOH); [α] $_{\rm D}^{20}$ = +17.1 (c = 0.2 in CHCl₃); FTIR (neat): 3346 (OH), 2981-2881 (CH), 2105 (SiH), 1714 (C=O), 1400, 1356, 1160; ¹H NMR (500 MHz, CDCl₃): δ = 1.05 (s, 18 H; C(CH₃)₃), 1.43 (s, 9 H; OC(CH₃)₃), 2.61-2.99 (m, 2 H; CH₂), 3.86 (s, 0.6 H; SiH), 3.87 (s, 0.4 H; SiH), 4.26 (brs, 0.4 H; CHN), 4.49 (brs, 0.6 H; CHN), 5.09-5.13 (m, 1 H; NH), 5.65 (m, 0.3 H; ArCH=CH), 6.15-6.19 (m, 0.7 H; ArCH=CH), 6.49 (d, ³J(H,H) = 16 Hz, 0.7 H; ArCH=CH), 6.58 (d, ³J(H,H) = 11.5 Hz, 0.3 H; ArCH=CH), 7.22-7.55 (m, 4 H; ArH), 11.03 ppm (s, 1 H; CO₂H); ¹³C NMR (125 MHz, CDCl₃): δ = 19.1 (*C*(CH₃)₃, *trans*), 19.2 (C(CH₃)₃, cis), 28.4 (C(CH₃)₃), 29.0 (C(CH₃)₃), trans), 29.1 (C(CH₃)₃), cis), 36.0 (CH2, trans), 36.2 (CH2, cis), 53.2 (CHN, trans), 53.4 (CHN, cis), 80.5 (OC(CH3)3), 124.0 (CH=), 125.6 (Carom, trans), 125.9 (CH=), 128.0 (Carom, cis), 134.4 (CH=), 135.1 (Carom), 135.9 (Carom, cis), 136.2 (Carom, trans), 137.4 (Carom), 155.7 (NCO₂), 176.7 (CO₂H, cis), 176.9 ppm (CO₂H, trans); ²⁹Si NMR (99 MHz, CDCl₃): δ = +12.7 (s, *trans*), +12.8 ppm (s, *cis*). HRMS (ESI-Q-TOF) calcd. for C₂₄H₃₈NO₄Si [M-H]: 432.25646; found: 432.25790.

(2S,4E)-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; Rf: 0.46 (petroleum ether/AcOEt 7:3 + 1% AcOH); $[\alpha]_D^{20} = +19$ (c = 0.2 in CHCl₃); FTIR (neat): 3368 (OH), 2929-2855 (CH), 2096 (SiH), 1715 (C=O), 1501 (CC), 1248 (C-O), 1104, 796, 669; ¹H NMR (500 MHz, CDCl₃): δ = 1.04 (s, 18 H; C(CH₃)₃), 1.43 (s, 9 H; OC(CH₃)₃), 2.67-2.77 (m, 2 H; CH₂), 3.86 (s, 1 H; SiH), 4.50 (m, 1 H; CHN), 5.15 (brs, 1 H; NH), 6.15-6.18 (m, 1 H; ArCH=CH), 6.49 (d, ³J(H,H) = 16.0 Hz, 1 H; ArCH=CH), 7.32 (d, ³J(H,H) = 8.0 Hz, 2 H; ArH), 7.52 (d, ³J(H,H) = 8.0 Hz, 2 H; ArH), 10.76 ppm (brs, 1 H; CO₂H); ¹³C NMR (125 MHz, CDCI₃): δ = 19.0 (*C*(CH₃)₃), 28.3 (C(*C*H₃)₃), 28.9 (C(CH₃)₃), 35.9 (CH₂), 53.1 (CHN), 80.4 (OC(CH₃)₃, 123.9 (CH=), 125.5 (Carom), 134.3 (CH=), 134.9 (Carom), 136.0 (Carom), 137.3 (Carom), 155.5 (*C*O₂*t*Bu), 176.8 ppm (*C*O₂H); ²⁹Si NMR (99 MHz, CDCl₃): *δ*=+12.7 ppm (s).

 (\pm) -(4*E*)-*lsomer* **15a.** The racemic silylated amino acid *trans*-**15a** was synthesized from (\pm) -amino acid Wittig reagent **14**, previously prepared from (\pm) -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 K₃PO₄ (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 CH₂Cl₂ (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; Rf: 0.23 (petroleum ether/AcOEt 9:1 + 1% AcOH); ¹H NMR (500 MHz, CDCl₃): δ = 0.98 (d, ³J(H,H) = 7.2 Hz, 4.2 H; CH(CH₃)₂ trans), 1.00 (d, ³J(H,H) = 7.1 Hz, 1.8 H; CH(CH₃)₂ cis), 1.06 (d, ³J(H,H) = 7.2 Hz, 4.2 H; CH(CH₃)₂ trans), 1.07 (d, ³J(H,H) = 7.1 Hz, 1.8 H; CH(CH₃)₂ cis), 1.21 (m, 2 H; CH(CH₃)₂ Z, E overlapping), 1.42 (s, 9 H; OC(CH₃)₃), 2.50-3.03 (m, 2 H; CH₂), 3.92 (t, ³J(H,H) = 3.1 Hz, 0.7 H; SiH trans), 3.93 (t, ³J(H,H) = 3.1 Hz, 0.3 H; S*iH cis*), 4.17-4.57 (brs, 1 H; C*H*N), 4.92-5.09 (brs, 1 H; NH), 5.64 (m, 0.3 H; ArCH=CH), 6.17 (m, 0.7 H; ArCH=CH), 6.49 (d, ³J(H,H) = 15.8 Hz, 0.7 H; ArCH=CH trans), 6.58 (d, ³J(H,H) = 11.7 Hz, 0.3 H; ArCH=CH cis), 7.23 (d, 0.7 H, ³J(H,H) = 8.1 Hz; ArH cis), 7.32 (d, 1.3 H, ³*J*(H,H) = 8.1 Hz, 1.3 H; Ar*H trans*), 7.45 (d, ³*J*(H,H) = 8 Hz, 1.3 H; Ar*H trans*), 7.58 (d, 0.7 H, ³*J*(H,H) = 8.1 Hz, Ar*H cis*), 9.50 ppm (brs, 1 H; CO₂*H*).

(2S,4E)-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; Rf: 0.23 (petroleum ether/AcOEt (9:1) + 1% AcOH); $[\alpha]_D^{20} = +9.6$ (c = 4.1 in CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ = 0.99 (d, ³J(H,H) = 7.4 Hz, 6 H; CH(CH₃)₂), 1.06 (d, ³*J*(H,H) = 7.4 Hz, 6 H; CH(CH₃)₂), 1.24 (d, ³*J*(H,H) = 7.3 Hz, ³*J*(H,H) = 3.2 Hz, 2 H; CH(CH₃)₂), 1.43 (s, 9 H; OC(CH₃)₃), 2.70-2.78 (m, 2 H; CH₂), 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; Ar*H*), 9.26 ppm (brs, 1 H; CO₂*H*); ¹³C NMR (CDCl₃, 125 MHz): δ= 10.7 (CH(CH₃)₂), 18.5 (CH(CH₃)₂), 18.6 (CH(CH₃)₂), 28.3 (C(CH₃)₃), 35.8 (CH₂), 53.1 (CHN), 80.4 (OC(CH3)3), 123.9 (CH=), 125.6 (Carom), 133.7 (CH=), 134.3 (Carom), 135.7 (Carom), 137.5 (Carom), 155.6 (NCO₂), 176.5 ppm (CO2H); HRMS (ESI-Q-TOF) calcd. for C22H35NO4SiNa [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 ¹H 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: 0.4 (petroleum ether/AcOEt 1:1 + 1% AcOH); ¹H NMR (300 MHz, CD₃CN): δ = 0.92 (d, ³*J*(H,H) = 7.1 Hz, 6 H; CH(CH₃)₂)), 1.00 (d, ³*J*(H,H) = 7.1 Hz, 6 H; CH(CH₃)₂), 1.15 (m, 2 H; CH(CH₃)₂), 1.38 (s, 9 H; C(CH₃)₃), 2.77 (m, 2 H; CH₂), 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); ¹³C NMR (75 MHz, CD₃CN): δ = 12.9 (CH(CH₃)₂), 16.9 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), 28.1 (C(CH₃)₃), 127.8 (CH=), 128.3 (Carom), 132.0 (CH=), 134.8(Carom), 135.6 (Carom), 138.2 ppm (Carom), 5C not observed; HRMS (ESI-Q-TOF) calcd. for C22H35NO5SiNa [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 Lalaninate.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/Et₂O (1:1) as eluent to afford the silvlated dipeptide 18a (850 mg, 1.64 mmol, 74.5% yield); Colorless foam; Rf: 0.30 (petroleum ether/Et₂O 1:1); $[\alpha]_{D^{20}} = +13.3$ (c = 0.6 in CHCl₃); 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; ¹H NMR (500 MHz, CDCl₃): δ = 1.03 (s, 18 H; C(CH₃)₃), 1.41 (d, ³J(H,H) = 8.5 Hz, 3 H; CH₃), 1.42 (s, 9 H; C(CH₃)₃), 2.67 (m, 2 H; CH₂), 3.70 (s, 3 H; OCH₃), 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, ${}^{3}J$ (H,H) = 16.0 Hz, 1 H; ArCH=CH), 6.68 (d, ³J(H,H) = 7.0 Hz, 1 H; NCH(CH₃)), 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); ¹³C NMR (125 MHz, CDCl₃): δ = 18.4 (CHCH₃), 19.0 (C(CH₃)₃), 28.3 (C(CH₃)₃), 28.9 (C(CH₃)₃), 36.1 (CH₂), 48.0 (CHN), 52.4 (OCH₃), 54.1 (NCH(CH₃)), 80.3 (OC(CH₃)₃), 124.6 (ArCH=CH), 125.4 (Carom), 134.0 (ArCH=CH), 134.9 (Carom), 136.0 (Carom), 137.3 (Carom), 155.5 (NCO₂), 170.9 (CON), 173.0 ppm (CO_2CH_3); ²⁹Si NMR (99 MHz, CDCl₃): δ = +12.7 ppm (s); HRMS (ESI-Q-TOF) calcd. for C₂₈H₄₆N₂O₅Si [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_i : 0.4, (petroleum ether/ AcOEt 7:3); ¹H NMR (500 MHz, CDCl₃): δ = 1.03 (s, 18 H; C(CH₃)₃),

1.39 (d, ${}^{3}J(H,H) = 8.5 Hz, 3 H; CH_{3}), 1.42 (s, 9 H; OC(CH_{3})_{3}), 2.65-2.69 (m, 2 H; CH_{2}), 3.70 (s, 1.33 H; OCH_{3}), 3.74 (s, 1.57 H; OCH_{3}), 3.84 (s, 1 H; SiH), 4.26 (brs, 1 H; CHN), 4.56-4.61 (m, 1 H; NCH(CH_{3})), 5.03-5.06 (brs, 1 H; NH), 6.16-6.22 (m, 1 H; ArCH=CH), 6.47 (d, <math>{}^{3}J(H,H) = 16.0 Hz, 1 H; ArCH=CH), 6.66-6.69 (m, 1 H; NHCH(CH_{3})), 7.31 (d, <math>{}^{3}J(H,H) = 7.5 Hz, 2 H; ArH), 7.52 (d, {}^{3}J(H,H) = 7.5 Hz, 2 H; ArH); {}^{13}C NMR (125 MHz, CDCI_{3}): \delta = 18.2 (CH_{3}), 18.4 (CH_{3}), 19.0 (C(CH_{3})_{3}), 28.2 (OC(CH_{3})_{3}), 28.9 (C(CH_{3})_{3}), 36.1 (CH_{2}), 48.0 (CHN), 48.1 (CHN), 52.4 (OCH_{3}), 54.2 (NCH(CH_{3})), 80.5 (OC(CH_{3})_{3}), 124.7 (ArCH=CH), 125.3 (Carom), 134.1 (ArCH=CH), 134.9 (Carom), 136.0 (Carom), 137.3 (Carom), 155.5 (NCO_{2}), 170.9 (CON), 173.0 (CO_{2}CH_{3}), 173.1 ppm (CO_{2}CH_{3}); {}^{29}Si NMR (99 MHz, CDCI_{3}): \delta = +12.7 ppm (s).$

(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 $\mu L,\, 0.55$ mmol), HATU (46 mg, 0.12 mmol) and methyl L-alaninate.HCl $\mathbf{16}$ (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. Rf: 0.31 (petroleum ether/ Et₂O 1:1); $[\alpha]_D^{20} = +7.9$ (c = 0.9 in CHCl₃); ¹H NMR (CDCl₃, 500 MHz): $\delta = 0.98$ (d, ${}^{3}J(H,H) = 7.3$ Hz, 6 H; CH(CH₃)₂), 1.05 (d, ${}^{3}J(H,H) =$ 7.3 Hz, 6 H; CH(CH₃)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, ${}^{3}J(H,H) = 7.5$ Hz, 3 H; $CHCH_3$), 1.41 (s, 9 H; OC(CH₃)₃), 2.67 (m, 2 H; CH₂), 3.70 (s, 3 H; OCH₃), 3.92 (t, ³J(H,H) = 3.2 Hz, 1 H; SiH), 4.24 (brs, 1 H; CHN), 4.57 (m, 1 H; NCH(CH₃)), 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; NHCHCH₃), 7.32 (d, ³J(H,H) = 7.6 Hz, 2 H; ArH), 7.44 ppm (d, ${}^{3}J(H,H) = 7.6$ Hz, 2 H; ArH); ${}^{13}C$ NMR (CDCl₃, 125 MHz): $\delta =$ 10.9 (CH(CH₃)₂), 18.4 (CHCH₃), 18.8 (CH(CH₃)₂), 28.4 (OC(CH₃)₃), 36.3 (CH2), 48.2 (CHN), 52.5 (OCH3), 53.5 (NCHCH3), 80.4 (OC(CH3)3), 124.9 (ArCH=CH), 125.6 (Carom), 133.6 (ArCH=CH), 134.1 (Carom), 135.8 (Carom), 137.7 (Carom), 155.6 (NCO₂), 171.1 (CON), 173.1 ppm (CO₂CH₃); HRMS (ESI-Q-TOF) calcd. for C₂₆H₄₃N₂O₅Si [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); [α]_D²⁰ = +4.8 (c = 0.8 in CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ = 0.80 (d, ³J(H,H) = 4.2 Hz, 2.6 H; CH(CH₃)₂), 0.82 (d, ³J(H,H) = 4.2 Hz, 3.2 H; CH(CH₃)₂), 0.88 $(d, {}^{3}J(H,H) = 3.6 Hz, 2.7 H; CH(CH_{3})_{2}), 0.90 (d, {}^{3}J(H,H) = 3.6 Hz, 3.2 H;$ CH(CH₃)₂), 1.05 (m, 2 H; CH(CH₃)₂), 1.27 (m, 12 H; OC(CH₃)₃, CHCH₃), 2.65 (m, 2 H; CH₂), 3.56 (m, 3 H; OCH₃), 4.08 (brs, 1 H; CHN), 4.41 (m, 1 H; NCHCH₃), 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; Ar*H*), 7.35 ppm (m, 2 H; Ar*H*); 13 C NMR (CDCl₃, 75 MHz): $\delta_{=}$ 12.4 (CH(CH₃)₂), 14.2 (CH(CH₃)₂), 16.9 (CH(CH₃)₂), 17.2 (CH(CH₃)₂), 18.4 (CHCH₃), 21.3 (CHCH₃), 28.2 (OC(CH₃)₃), 31.4 (CH₂), 48.1 (CHN), 52.5 (OCH3), 60.4 (NCHCH3), 125.5 (ArCH=CH), 127.9 (Carom), 134.1 (ArCH=CH), 134.4 (Carom), 171.0 (CON), 173.1 ppm (CO2CH3); 4C not observed; HRMS (ESI-Q-TOF) calcd. for C₂₆H₄₃N₂O₆Si [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 KHSO₄ (1M) and extracted with CH₂Cl₂. The organic phases were gathered, dried over MgSO₄ 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 CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ = 1.02 (s, 18 H; C(CH₃)₃), 1.30 (s, 9 H; OC(CH₃)₃), 1.38 (d, ³*J*(H,H) = 7.2 Hz, 3 H; CHCH₃), 2.53-2.72 (m, 2 H; CH₂), 3.06 (m, 2 H; PhCH₂), 3.69 (s, 3 H; OCH₃), 3.83 (s, 1 H; SiH), 4.30-4.42 (m, 1 H; CHN), 4.44-4.63 (m, 2 H, CHN overlapping signals), 4.95 (brs, 1 H; NH), 5.99-6.20 (m, 1 H; ArCH=CH), 6.32 (d, ³J(H,H) = 15.9 Hz, 1 H; ArCH=CH), 6.58 (brs, 1 H; NH), 6.84 (brs, 1 H; NH), 7.13-7.31 (m, 7 H; ArH), 7.49 ppm (d, ³J(H,H) = 8.0 Hz, 2 H; ArH); ¹³C NMR (75 MHz, CDCl₃): δ = 18.1 (CHCH₃), 19.1 (C(CH3)3), 28.3 (C(CH3)3), 29.0 (C(CH3)3), 35.7 (CH2), 38.1 (PhCH2), 48.4 (CHN), 52.5 (CHN), 52.6 (OCH3), 55.9 (CHN), 80.6 (OC(CH3)3), 124.3 (ArCH=CH), 125.5 (Carom), 127.3 (Carom), 128.9 (Carom), 129.4 (Carom), 134.3 (ArCH=CH), 135.1 (Carom), 136.2 (Carom), 136.4 (Carom), 137.3 (Carom), 155.8 (NCO₂), 170.2 (CON), 171.3 (CON), 173.0 ppm (CO₂CH₃), 2 C are not observed; ²⁹Si NMR (59 MHz, CDCl₃): 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 H₂ (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. Rf: 0.32 (petroleum ether/acetone 8:2); $[\alpha]_D^{20} = -4.8 \text{ (c} = 0.5 \text{ in CH}_2\text{Cl}_2); ^1\text{H NMR} (500 \text{ MHz}, \text{CDCl}_3): \delta = 0.97 \text{ (s}, 18$ H; C(CH₃)₃), 1.32 (d, ³J(H,H) = 7.3 Hz, 3 H; CHCH₃), 1.37 (s, 9 H; OC(CH₃)₃), 1.62-1.83 (m, 4 H; (CH2)2), 2.55-2.58 (m, 2 H; ArCH2), 3.65-3.66 (m, 6 H, OCH₃ overlapping signals), 4.03 (brs, 1 H; CHN), 4.51 (p, ${}^{3}J(H,H) = 7.5$ Hz, 1 H; CHCH₃), 4.88 (brs, 1 H; NH), 6.41 (d, ³J(H,H) = 7.5 Hz, 1 H; NH), 7.09 (d, ³J(H,H) = 8.0 Hz, 2 H; ArH), 7.44 ppm (d, ³J(H,H) = 8 Hz, 2 H; ArH); ¹³C NMR (125 MHz, CDCl₃): δ = 18.5 (CHCH₃), 21.0 (C(CH₃)₃), 27.2 (CH₂CHN), 28.5 (C(CH_3)₃), 28.6 (C(CH_3)₃), 32.3 (PhCH₂ CH_2), 35.7 (Ph CH_2), 48.2 (CHN), 52.6 (OCH3), 53.2 (CHN), 54.5 (SiOCH3), 80.3 (OC(CH3)3), 127.6 (Carom), 135.3 (Carom), 142.7 (Carom), 159.5 (NCO₂), 171.7 (NCO), 173.2 ppm (CO₂CH₃), 1C not observed; HRMS (ESI-Q-TOF) calcd. for C₂₉H₅₁N₂O₆Si [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 $H_2\left(10\,\text{bar}\right)$ 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. Rf: 0.50 (petroleum ether/AcOEt 1:1); ¹H NMR (CDCl₃, 300 MHz): δ= 1.04 (m, 12 H; CH(CH₃)₂), 1.26 (m, 2 H; CHCH₃), 1.39 (d, ³J(H,H) = 7.3 Hz, 3 H; CHCH₃), 1.44 (s, 9 H; OC(CH₃)₃), 1.70-1.90 (m, 4 H; (CH₂)₂), 2.64 (m, 2 H; PhCH₂), 3.6 (s, 2 H; OCH₃), 3.72 (s, 3 H; OCH₃), 4.15 (brs, 1 H: CHN), 4.57 (m, 1 H; NCHCH₃), 5.13 (brs, 1 H; NH), 6.77 (brs, 1 H; NH), 7.17 (m, 2 H; Ar*H*), 7.46 ppm (m, 2 H; Ar*H*); ¹³C NMR (CDCl₃, 75 MHz): δ₌ 12.0 (CH(CH₃)₂), 12.5 (CH(CH₃)₂), 17.0 (CH(CH₃)₂), 17.2, CH(CH₃)₂), 17.3 (CH(CH3)2), 17.5 (CH(CH3)2), 18.2 (CHCH3), 27.1 (CH2CHN), 32.1 (PhCH₂CH₂), 32.3 (PhCH₂CH₂), 35.5 (PhCH₂), 35.6 (PhCH₂), 48.0 (CHN), 52.0 (OCH₃), 52.4 (SiOCH₃), 52.5 (CHN), 54.3 (CHN), 80.1 (OC(CH₃)₃), 127.8 (Carom), 131.1 (Carom), 134.3 (Carom), 134.8 (Carom), 142.9 (Carom), 155.7 (NCO₂), 171.7 (NCO), 173.1 (CO₂CH₃), 173.2 ppm (CO₂CH₃); HRMS (ESI-Q-TOF) calcd. for C₂₆H₄₄N₂O₆SiNa (silanol 20b) [M+Na]+: 531.28608; found: 531.28686; and calcd. for C27H46N2O6SiNa (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 μ L, 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 CH₂Cl₂/MeOH (2% to 10%) as eluent to afford the compound **21a** (25 mg,

97% yield) as a colorless solid. Rf: 0.30 (petroleum ether/AcOEt 8:2 + 1% AcOH); [α]_D²⁰ = +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; ¹H NMR (500 MHz, CDCl₃): δ = 1.05 (s, 18 H; C(CH₃)₃), 1.42 (s, 9 H; OC(CH₃)₃), 2.68-2.80 (2 brs, 2 H; CH₂), 4.48 (m, 1 H; NCHCH₃), 5.07 (d, ³J(H,H) = 7.0 Hz, 1 H; NH), 6.16-6.22 (m, 1 H; ArCH=CH), 6.50 (d, ³J(H,H) = 15.5 Hz, 1 H; ArCH=CH), 7.35 (d, ³J(H,H) = 8.0 Hz, 2 H; ArH), 7.54 ppm (d, ³J(H,H) = 8.0 Hz, 2 H; ArH), H acid not observed; ¹³C NMR (125 MHz, CDCl₃, 300 K): $\delta = 20.4 (C(CH_3)_3), 27.5 (C(CH_3)_3), 28.3 (C(CH_3)_3), 36.0 (CH_2), 53.1 (CHN),$ 80.6 (OC(CH₃)₃), 124.4 (ArCH=CH), 125.5 (Carom), 133.3 (ArCH=CH), 134.2 (Carom), 137.9 (Carom), 155.4 (NCO₂), 180.5 ppm (CO₂H), 1C not observed; ¹⁹F NMR (470 MHz, CDCl₃): 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, CDCl₃): δ = +13.9 ppm (d, ¹J(Si,F) = 298 Hz); HRMS (ESI-Q-TOF) calcd. for C24H38FNO4SiNa [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 $\mu mol)$ 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. $R_{\rm f}$: 0.20 (petroleum ether/AcOEt 9:1 + 1% AcOH); $[\alpha]_{\rm D}^{20}$ = +11.4 (c = 0.5 in CH₂Cl₂);¹H NMR (300 MHz, CDCl₃): δ = 0.93 (dd, ³J(H,H) = 7.4 Hz, ${}^{3}J(H,H)$ = 1.5 Hz, 6 H; CH(CH₃)₂), 1.00 (dd, ${}^{3}J(H,H)$ = 7.4 Hz, ³J(H,H) = 1.5 Hz, 6 H; CH(CH₃)₂), 1.15-1.21 (m, 2 H; CH(CH₃)₂), 1.42 (s, 9 H; OC(CH₃)₃), 2.63-2.68 (m, 2 H; CH₂), 4.41 (brs, 1 H; CHN), 5.20 (brs, 1 H; NH), 6.09-6.14 (m, 1 H; ArCH=CH), 6.43 (d, ³J(H,H) = 15.9 Hz, 1 H; ArCH=CH), 7.29 (d, ³J(H,H) = 7.8 Hz, 2 H; ArH), 7.41 ppm (d, ³J(H,H) = 7.8 Hz, 2 H; ArH), H acid not observed; ¹³C NMR (CDCl₃, 75 MHz): δ = 12.4 (d, ²J(C,F) = 12.8 Hz; CH(CH₃)₂), 16.8 (d, ³J(C,F) = 10.0 Hz; CH(CH₃)₂), 28.4 $(C(CH_3)_3)$, 36.0 (CH_2), 80.6 ($OC(CH_3)_3$), 124.7 (ArCH=CH), 125.9 (Carom), 132.3 (Carom), 134.2 (ArCH=CH), 134.3 (Carom), 138.4 (Carom), 155.7 (NCO₂), 176.3 ppm (CO₂H), 1C not observed; ¹⁹F NMR (282 MHz, CDCl₃): δ = -187.2 ppm; HRMS (ESI-Q-TOF) calcd. for C₂₂H₃₄FNO₄SiNa [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 μ L, 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/Et₂O (1:1) as eluent, to afford the fluorinated dipeptide 21c (130 mg, 0.242 mmol, 96% yield) as a colorless foam. $R_{\rm f}$: 0.25 (petroleum ether/Et₂O 1:1); [α]_D²⁰ = +8.46 $(c = 1.9 \text{ in CHCl}_3); {}^{1}H \text{ NMR} (500 \text{ MHz}, CDCl}_3): \delta = 1.04 (s, 18 \text{ H}; SiC(CH_3)_3),$ 1.39 (d, ³*J*(H,H) = 7.0 Hz, 3 H; CHCH₃), 1.41 (s, 9 H; OC(CH₃)₃), 2.62-2.71 (m, 2 H; CH₂), 3.70 (s, 3 H; OCH₃), 4.26 (m, 1 H; CHN), 4.55-4.61 (m, 1 H; NCHCH₃), 5.11 (d, ³J(H,H) = 7.0 Hz, 1 H; NH), 6.18-6.24 (m, 1 H; ArCH=CH), 6.48 (d, ³J(H,H) = 15.5 Hz, 1 H; ArCH=CH), 6.71 (br d, ³J(H,H) = 7.0 Hz, 1 H; N*H*), 7.34 (d, ³*J*(H,H) = 8.0 Hz, 2 H; Ar*H*), 7.53 ppm (d, ³*J*(H,H) = 8.0 Hz, 2 H; ArH); ¹³C NMR (125 MHz, CDCl₃): δ = 18.3 (CHCH₃), 20.2 (d, ²J(C,F) = 12.5 Hz; $C(CH_3)_3$), 27.3 ($C(CH_3)_3$), 28.2 ($OC(CH_3)_3$), 36.2 (CH_2), 48.1 (CHN), 52.4 (OCH₃), 53.7 (CHN), 80.3 (OC(CH₃)₃), 125.2 (ArCH=CH), 125.5 (Carom), 132.9 (Carom), 133.8 (ArCH=CH), 134.2 (Carom), 138.0 (Carom), 155.6 (NCO₂), 170.9 (CON), 173.0 (CO₂CH₃); ¹⁹F NMR (470 MHz, CDCl₃): δ = -188.9 (s, 0.95F, ^{28/30}Si-F), -188.9 ppm (d, 0.05F, ¹J(Si,F) = 298 Hz, ²⁹Si-F); ²⁹Si NMR (99 MHz, CDCl₃): $\delta = +13.9$ (d, ¹J(Si,F) = 297 Hz); HRMS (ESI-Q-TOF) calcd. for C₂₈H₄₅FN₂O₅SiNa [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 μ L) 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/Et₂O (1:1) as eluent, to afford the fluorosilylated

dipeptide 21d (67 mg, 0.132 mmol, 92% yield) as a colorless foam. Rf: 0.25 (petroleum ether/Et₂O 1:1); ¹H NMR (500 MHz, CDCl₃): δ = 0.93 (d, ³J(H,H) = 7.5 Hz, 6 H; CH(CH₃)₂), 1.00 (d, ${}^{3}J$ (H,H) = 7.5 Hz, 6 H; CH(CH₃)₂), 1.18 (m, 2 H; C*H*(CH₃)₂), 1.33 (d, ³*J*(H,H) = 7.25 Hz, 3 H, CH(CH₃)), 1.34 (s, 9 H; OC(CH₃)₃), 2.60 (m, 2 H; CH₂), 3.63 (s, 3 H, OCH₃), 4.20 (brs, 1 H; CHN), 4.51 (m, 1 H; NCH(CH₃), 5.08 (brs, 1 H; NH), 6.17 (m, 1 H; ArCH=CH), 6.42 (d, ³J(H,H) = 16.0 Hz, 1 H; ArCH=CH), 6.70 (brs, 1 H; NH), 7.29 (d, ³J(H,H) = 8.0 Hz, 2 H; ArH), 7.41 ppm (d, ³J(H,H) = 8.0 Hz, 2 H; ArH); ¹³C NMR (CDCl₃, 125 MHz): $\delta_{=}$ 11.2 (d, ²*J*(C,F) = 13.7 Hz; *C*H(CH₃)₂), 15.6 (d, ${}^{3}J(C,F) = 19$ Hz; CH(CH₃)₂), 17.3 (CHCH₃), 27.3 (OC(CH₃)₃), 35.2 (CH₂), 47.1 (CHN), 51.4 (OCH₃), 53.1 (CHN), 79.3 (OC(CH₃)₃), 124.4 (ArCH=CH), 124.7 (Carom), 130.9 (Carom), 132.7 (ArCH=CH), 133.1 (Carom), 137.4 (Carom), 155.6 (NCO₂), 170.0 (CON), 172.0 ppm (CO₂CH₃); ¹⁹F NMR (470 MHz, CDCl₃): δ = -187.2 (s, 0.95F, ^{28/30}Si-F), -187.2 ppm (d, 0.05F, ¹J(Si,F) = 294 Hz, ²⁹Si-F); HRMS (ESI-Q-TOF) calcd. for C₂₆H₄₁FN₂O₅SiNa [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 H₂ (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. $R_{\rm f}$: 0.30 (petroleum ether/acetone 8:2); $[\alpha]_{\rm D}^{20} = -5.8$ (c = 1 in CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ = 1.05 (s, 18 H; C(CH₃)₃), 1.40 (d, ³*J*(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, (CH₂)₂ overlapping signals), 2.63-2.65 (m, 2 H; ArCH₂), 3.73 (s, 3 H; OCH₃), 4.10 (brs, 1 H; C*H*N), 4.57 (q, ³*J*(H,H) = 7.5 Hz, 1H; NC*H*CH₃), 4.95 (brs, 1 H; NH), 6.48 (d, ³J(H,H) = 7.5 Hz, 1 H; NHCHCH₃), 7.17 (d, ³J(H,H) = 7.8 Hz, 2 H; ArH), 7.50 ppm (d, ³J(H,H) = 8.1 Hz, 2 H; ArH). ¹³C NMR (75 MHz, CDCl₃): δ = 18.4 (CH*C*H₃), 20.3 (d, ²*J*(C,F) = 12.8 Hz; *C*(CH₃)₃), 27.0 (ArCH₂CH₂CH₂), 27.4 (C(CH₃)₃), 28.3 (C(CH₃)₃), 32.1 (ArCH₂CH₂), 35.5 (ArCH2), 48.0 (CHN), 52.4 (OCH3), 57.1 (CHN), 80.3 (OC(CH3)3), 127.7 (ArCH=CH), 130.6 (Carom), 134.2 (ArCH=CH), 143.5 (Carom), 159.5 (NCO₂), 171.5 (CON), 173.2 ppm (CO₂CH₃); ¹⁹F NMR (CDCl₃, 282 MHz): δ = -189.0 (s, 0.95F, ^{28/30}Si-F), -189.0 ppm (d, ¹J(Si,F) = 296 Hz, 0.05F, ²⁹Si-F); ²⁹Si NMR (CDCl₃, 59 MHz); δ = +14.0 ppm (d, ¹J(Si,F) = 296 Hz); HRMS (ESI-Q-TOF) calcd. for C₂₈H₄₈FN₂O₅Si [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 D₃. 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 ¹⁹F NMR spectroscopy. ¹⁹F NMR spectra were acquired at different times and the integration was determined from spectra. The ratio of ¹⁹F-signal existing as the fluorosilylated compound to the total ¹⁹F 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 [18F]-fluoride was produced via the 18O(p,n)18F nuclear reaction by irradiation of enriched [18O]H2O. [18F]-Fluoride production: Bombarded 30-60 min; 60 µA; target volume 1.8-2.5 mL, 100-130 GBq are obtained. [18F]-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 H₂O (0.3 mL) and CH₃CN (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[18F]F/ K2.2.2 complex was prepared by azeotropic drying using CH₃CN (4 x 0.25 mL). Silylated compound 18a (or 20a) (4.8-5.4 mg) diluted in a mixture of DMSO (500 μ L) and acetic acid (3 μ L) was added to the dry K[¹⁸F]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 CH₃CN (3 mL) and H₂O (2 mL). This solution was injected into a semi preparative HPLC 85/15 (CH₃CN/ (H₂O/TFA, 0.1%, v/v)), 2.5 mL/min. Then [18F]-21c (or [18F]-21e) was formulated in an aqueous physiological solution (0.9% NaCl solution) and purity was checked by analytical HPLC 85/15 (CH₃CN/(H₂O/TFA, 0.1%, v/v)) with 1 mL/min flow, using non-radioactive molecule 21c (or 21e) as reference. Results showed that [18F]-21c and [18F]-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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- (a) J. K. Willmann, N. van Bruggen, L. M. Dinkelborg, S. S. Gambhir, *Nature Rev.* 2008, 7, 591-607. (b) F. C. Wong, E. E. Kim, *Eur. J. Radiol.* 2009, *70*, 205-211.
- [2] (a) S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* 2008, *108*, 1501-1516 and 2008, *108*, 4036. (b) D. M. Patterson, L. A. Nazarova, J. A. Prescher, *ACS Chem. Biol.* 2014, *9*, 592-605. (c) R. Liu, S. Zhang, C. Wei, Z. Xing, S. Zhang, X. Zhang, *Acc. Chem. Res.* 2016, *49*, 775-783. (d) C. Freidel, S. Kaloyanova, K. Peneva, *Amino Acids* 2016, *48*, 1357-1372.
- (a) S. Chattopadhaya, F. B. Abu Bakar, S. Q. Yao, *Curr. Med. Chem.* 2009, 16, 4527-4543. (b) I. R. Corrêa Jr., in *Site-Specific Protein Labeling: Method and Protocols, Methods in Molecular Biology*, A. Gautier, M. J. Hinner, (Eds); Springer Science + Business Media, New York, 2015, Vol. 1266, Chap. 4, pp 55-79.
- [4] S. Lee, J. Xie, X. Chen, Chem. Rev. 2010, 110, 3087-3111.
- [5] (a) R. Schirrmacher, C. Wängler, E. Schirrmacher, *Mini-Rev. Org. Chem.*2007, 4, 317-329. (b) Z. Li, P. S. Conti, *Adv. Drug Deliv. Rev.* 2010, *62*, 1031-1051. (c) G. E. Smith, H. L. Sladen, S. C. G. Biagini, P. J. Blower, *Dalton Trans.* 2011, *40*, 6196-6205. (d) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* 2016, *116*, 719-766. (e) C. L. Charron, A. L. Farnsworth, P. D. Roselt, R. J. Hicks, C. A. Hutton, *Tetrahedron Lett.* 2016, *57*, 4119-4127.
- [6] (a) P. Laverman, O. C. Boerman, F. H. M. Corstens, W. J. G. Oyen, *Eur. J. Nucl. Med.* 2002, *29*, 681-690. (b) J. McConathy, M. M. Goodman, *Cancer Met. Res.* 2008, *17*, 555-573. (c) A. van Waarde, P. H. Elsinga, *Curr. Pharm. Des.* 2008, *14*, 3326-3339. (d) J. Ermert, H. H. Coenen, *Label. Compd. Radiopharm.* 2013, *56*, 225-236. (e) C. Huang, J. McConathy, *J. Nucl. Med.* 2013, *54*, 1007-1010. (f) D. Schäfer, P. Wieβ, J. Ermert, J. C. Melean, F. Zarrad, B. Neumaier, *Eur. J. Org. Chem.* 2016, 4621-4628.
- [7] For a recent comparative study of ¹⁸F-labeling methods in peptide series, see: M. Glaser, P. Iveson, S. Hoppmann, B. Indrevoll, A. Wilson, J. Arukwe, A. Danikas, R. Bhalla, D. Hiscock, *J. Nucl. Med.*, **2013**, *54*, 1981-1988.
- [8] R. Ting, M. J. Adam, T. J. Ruth, D. M. Perrin, J. Am. Chem. Soc. 2005, 127, 13094-13095.
- [9] (a) R. Schirrmacher, G. Bradtmöller, E. Schirrmacher, O. Thews, J. Tillmanns, T. Siessmeier, H. G. Buchholz, P. Bartenstein, B. Wängler, C. M. Niemeyer, K. Jurkschat, *Angew. Chem. Int. Ed.*, 2006, *45*, 6047-6050.
 (b) C. Wängler, A. Kostikov, J. Zhu, J. Chin, B. Wängler, R. Schirrmacher, *Appl. Sci.* 2012, *2*, 277-302. (c) V. Bernard-Gauthier, C. Wängler, E. Schirrmacher, A. Kostikov, K. Jurkschat, B. Wängler, R. Schirrmacher, *BioMed Research Intern.* 2014, ID 454503, 1-20. (d) V. Bernard-Gauthier, J. J. Bailey, Z. Liu, B. Wängler, C. Wängler, K. Jurkschat, D. M. Perrin, R. Schirrmacher, *Bioconjugate Chem.* 2016, *27*, 267-279.

- [10] (a) L. Mu, A. Höhne, P. A. Schubiger, S. M. Ametamey, K. Graham, J. E. Cyr, L. Dinkelborg, T. Stellfeld, A. Srinivasan, U. Voigtmann, U. Klar, *Angew. Chem. Int. Ed.* 2008, *47*, 4922-4925. (b) A. Höhne, L. Mu, M. Honer, P. A. Schubiger, S. M. Ametamey, K. Graham, T. Stellfeld, S. Borkowski, D. Berndorff, U. Klar, U. Voigtmann, J. E. Cyr, M. Friebe, L. Dinkelborg, A. Srinivasan, *Bioconjugate Chem.* 2008, *19*, 1871-1879. (c) A. Höhne, L. Yu, L. Mu, M. Reiher, U. Voigtmann, U. Klar, K. Graham, P. A. Schubiger, S. M. Ametamey, *Chem. Eur. J.* 2009, *15*, 3736-3743. (d) L. Mu, P. A. Schubiger, S. M. Ametamey, *Curr. Radiopharm.* 2010, *3*, 224-242.
- [11] E. Amigues, J. Schulz, M. Szlosek-Pinaud, P. Fernandez, S. Silvente-Poirot, S. Brillouet, F. Courbon, E. Fouquet, *ChemPlusChem* 2012, 77, 345-349.
- [12] E. Rémond, C. Martin, J. Martinez, F. Cavelier, Chem. Rev. 2016, 116, 11654-11684.
- [13] L. Iovkova, D. Könning, B. Wängler, R. Schirrmacher, S. Schoof, H.-D. Arndt, K. Jurkschat, *Eur. J. Inorg. Chem.* 2011, 2238-2246.
- [14] L. O. Dialer, S. V. Selivanova, C. J. Müller, A. Müller, T. Stellfeld, K. Graham, L. M. Dinkelborg, S. D. Krämer, R. Schibli, M. Reiher, S. M. Ametamey, *J. Med. Chem.* **2013**, *56*, 7552-7563.
- [15] For the fluorolabeling of ethoxysilylamino acid derivative prepared according to Huisgen cyclisation, see: E. Balentova, C. Collet, S. Lamandé-Langle, F. Chrétien, D. Thonon, J. Aerts, C. Lemaire, A. Luxen, Y. Chapleur, *J. Fluor. Chem.* **2011**, *132*, 250-257.
- [16] (a) H. Audi, E. Rémond, M.-J. Eymin, A. Tessier, R. Malacea-Kabbara, S. Jugé *Eur. J. Org. Chem.* 2013, 7960-7972. (b) J. Bernard, R. Malacea-Kabbara, G. S. Clemente, B. P. Burke, M.-J. Eymin, S. J. Archibald, S. Jugé, *J. Org. Chem.* 2015, *80*, 4289-4298.
- [17] E. Rémond, J. Bayardon, M.-J. Ondel-Eymin, J. Jugé, J. Org. Chem. 2012, 77, 7579-7587.
- [18] For the preparation of methoxysilane from hydrosilane, see: K. Hirakue, M. Kusano, Jpn Kokai Tokkyo Koho 2007262025.

- [19] For example of silanol amino acids, see: (a) R. J. Smith, S. Bienz, *Helv. Chim. Acta* 2004, *87*, 1681-1696. (b) M. Mortensen, R. Husmann, E. Veri, C. Bolm, *Chem. Soc. Rev.* 2009, *38*, 1002-1010. (c) J. K. Kim, S. McN. Sieburth, *J. Org. Chem.* 2012, *77*, 2901-2906.
- [20] R. Schirrmacher, C. Wängler, E. Schirrmacher, in *Fluorine-18 Radiochemistry: Theory and Practice in Pharmaceutical Radiochemistry* (*I*), H. J. Wester, (Ed.), Vol.1. Munich Molecular Handbook series, Scintomics Print Media and Publishing, **2010**, pp 5-73.
- [21] For recent progresses in radiofluorination using crown ether with both chelating and leaving group properties, see: (a) M. H. Al-huniti, S. Lu, V. W. Pike, S. D. Lepore, *J. Fluor. Chem.* 2014, *158*, 48-52. (b) S. Jana, M. H. Al-huniti, B. Y. Yang, S. Lu, V. W. Pike, S. D. Lepore, *J. Org. Chem.* 2017, *82*, 2329-2335.
- [22] All attemps of radiofluorination of the fluorosilylated saturated dipeptide 21e into [18F]-21e according to the SiFA method described in reference (13), were underperforming.
- [23] The formation of the by-product from [18F]-21c may be explained by reaction of the double bond either by hydration or by formation of oxazoline derivative by internal cyclization involving the N-Boc function (see Supporting Information).
- [24] V. T. Lien, P. J. Riss, BioMed Research Intern. 2014, ID 380124, 1-10.
- [25] C.-H. Chen, W.-H. Chen, Y.-H. Liu, T.-S. Lim, T.-Y. Luh, Chem. Eur. J. 2012, 18, 347-354.