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SiFA-Modified Phenylalanine: A Key Compound for the Efficient Synthesis of ^{18}F-Labelled Peptides[‡]

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Dedicated to Prof. Dr. Peter Klüfers on the occasion of his 60th birthday

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Both the racemic and the stereoselective synthesis of the silicon-modified amino acid *p*-(tBu$_2$FSi)C$_6$H$_4$CH$_2$(NH$_2$)COOH (SiFA-phenylalanine, **6**) and its derivatives *p*-(tBu$_2$FSi)C$_6$H$_4$CH$_2$(NHBoc)COOH (**10**) and *p*-(tBu$_2$FSi)C$_6$H$_4$CH$_2$(NHFmoc)COOH (**11**) are reported. The latter two compounds are valuable building blocks for the convenient introduction of silicon-based fluoride acceptors (SiFAs) into peptides by solid-phase peptide syntheses (SPPS). As prove of principle, the Tyr^3-octreotate derivatives **12**, **13** and **14** were prepared by using standard protocols of the solid-phase peptide synthesis (SPPS). They were labelled with ^{18}F-fluorine by isotopic exchange in radiochemical yields of up to 70 % (with radiochemical purity ranging between 92 and 99 %). The incorporation of ^{18}F-fluorine into the SiFA-modified amino acid **6** was studied as the latter may also serve as a tracer in PET. After purification, [^{18}F]-**6** showed a remarkable stability in an isotonic solution. Also reported is the molecular structure, as determined by single-crystal X-ray diffraction analysis, of *p*-(tBu$_2$FSi)C$_6$H$_4$CHCH[C(O)OMe]NHC(O)OCH$_2$Ph (**8**), which serves as a precursor for the stereoselective synthesis of compound **6**.

Introduction

^{18}F-fluorine is the most commonly used radionuclide for positron emission tomography (PET).[1] This noninvasive imaging modality is an important diagnostic tool in medicine because of its ability to locate and assess abnormalities in neurology, oncology and cardiology.[2a–2c] It enables the visualization and quantification of complex biochemical processes and allows the investigation of the in vivo distribution of radiolabelled biomarkers. The application of radiolabelled amino acids and peptides for the detection of cancer of various origin has gained widespread interest in nuclear medicine.[3a–3c] At the same time, there is a great interest in the synthesis and application of non-proteinogenic, organosilicon-modified amino acids that hold potential in the diagnostic and therapeutic medicine.[3d–3g] The large number of methods developed for the ^{18}F-labelling of peptides and proteins still suffer from drawbacks. Multistep synthetic pathways, the need to use HPLC or distillation for purification of the ^{18}F-synthon for final peptide coupling, or time-consuming workup often reduce the final preparative yields. Recently, a direct labelling protocol was reported for the introduction of ^{18}F into selected biomolecules. However, this approach lacks general applicability to more temperature-sensitive biomolecules.[2d]

Therefore, new ^{18}F-acceptors bearing functionalities that allow the facile conjugation to biomolecules under various conditions are highly sought after. Because of the short half life of ^{18}F (110 min), the ideal acceptor should allow the fast introduction of the radiolabel under mild labelling conditions. Recently, Perrin and co-workers published the carrier-added ^{18}F-labelling of trialkoxysilanes as potential labelling precursors for PET.[4a] In previous publications,[5,6] we have demonstrated (i) di-*tert*-butylphenylfluorosilane (tBu$_2$PhSiF) to exhibit ideal ^{19}F–^{18}F exchange with the ^{18}F-source and (ii) the resulting ^{18}F-labelled tBu$_2$PhSiF to be inert against hydrolysis under physiological conditions.[6] Consequently, the functionalized triorganofluorosilanes

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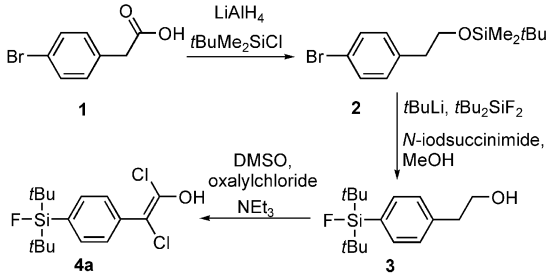
tBu$_2$[p-XC_6H_4]SiF were prepared as a silicon-based fluorine acceptor (SiFA) and linked, through the functionality X, to biomolecules; these were then successfully applied for evaluation in preclinical studies.[7] More recently, we and others described the in vivo application of tumour-affine peptides radiolabelled by the SiFA-approach in tumour-bearing mice.[2d,4d] In continuation of these studies, we report here the syntheses of SiFA-phenylalanine, the first SiFA-modified amino acid. Its applicability in solid-phase peptide syntheses is demonstrated by incorporation into the peptide sequence of Tyr^3-octreotate, which is a lead compound for radiotracers in cancer diagnostics.[8a,8b] Furthermore, we demonstrate the isotopic exchange of ^{19}F for ^{18}F for the free amino acid and – as a paradigm for its use in in vivo imaging – for the synthesized octreotate derivatives.

Results and Discussion

Strecker Amino Acid Synthesis of SiFA-Phenylalanine

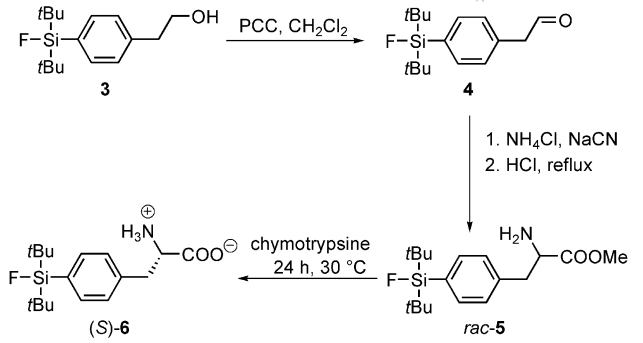
The Strecker amino acid synthesis is a well-established method for the preparation of natural and synthetic amino acids starting from an aldehyde or a ketone.[9,10] The aldehyde reacts in a one-pot reaction with ammonia (ammonium chloride) and cyanide (potassium or sodium cyanide) to form an α-imino nitrile, which is subsequently hydrolyzed with hydrochloric acid to give the free amino acid. A major drawback is the use of aqueous reaction medium and the very poor solubility of many organic aldehydes in water. In order to evade this problem, alcohols are often added to the reaction mixture.

The bromo-substituted phenyl acetic acid **1** was converted into compound **2** in two steps. Treatment of the protected *p*-bromobenzene derivative **2** with *tert*-butyllithium and di-*tert*-butyldifluorosilane at –78 °C provided the corresponding triorganofluorosilane. Deprotection under acidic conditions gave the SiFA-modified alcohol **3** in 90% yield (Scheme 1).



Scheme 1. Synthesis of the SiFA-2-phenylethanol derivative **3** and its reaction with Swern reagent.

Oxidation of alcohol **3** with Swern reagent to give the corresponding aldehyde *p*-(tBu$_2$FSi)$C_6H_4CH_2$CHO (**4**) failed. Instead, the alkene derivative **4a** was produced (Scheme 1). Therefore, PCC was used to effect the necessary oxidation of alcohol **3** to aldehyde **4**, in good yield (Scheme 2).

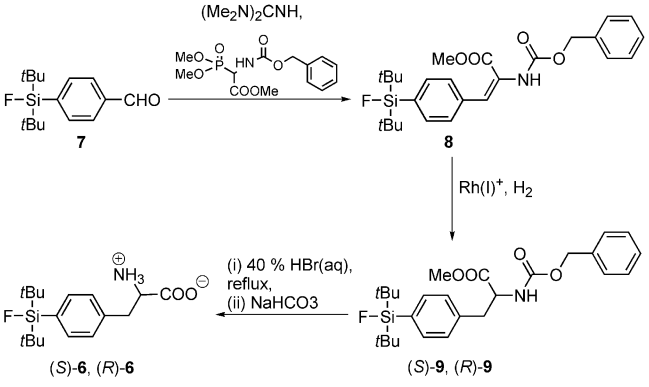


Scheme 2. Preparation of the SiFA-phenylalanine. PCC: pyridiniumchlorochromate.

The SiFA-aldehyde **4** was dissolved in methanol and treated with an aqueous solution of ammonium chloride and sodium cyanide to give the amino acid **6** (Scheme 2). After hydrolysis of the in situ formed cyanohydrine, we unfortunately isolated only the methyl ester of the amino acid. This ester **5** was cleaved by using chymotrypsine,[11] and the free (*S*)-SiFA-modified amino acid (*S*)-**6** was obtained in 16% yield with respect to *rac*-**5** (Scheme 2).

Stereoselective Synthesis of SiFA-Phenylalanine

Because of the low solubility of the alcohol **3** in water and the low yield of enantiomerically pure amino acid, we investigated an enantioselective synthesis.[12] The known SiFA-aldehyde was prepared in good yield as described in our previous works[5,7] and treated with tetramethylguanidine and methyl-2-(benzyloxycarbonylamino)-2-(dimethoxy-phosphoryl)acetate in a Horner–Wadsworth–Emmons reaction to give compound **8** as a colourless solid (Scheme 3).



Scheme 3. Synthesis of the amino acid pecursor **8** and enantioselective synthesis of the SiFA-phenylalanine.

Single crystals of **8** suitable for X-ray diffraction analysis were obtained by recrystallization from *n*-hexane. The molecular structure of compound **8** is shown in Figure 1. Selected geometric parameters are given in the figure caption.

In the solid state, the silicon atom is tetra-coordinated and shows distorted tetrahedral configuration with angles ranging between 116.0(3) and 103.8(3)°. The Si(1)–F(1) dis-

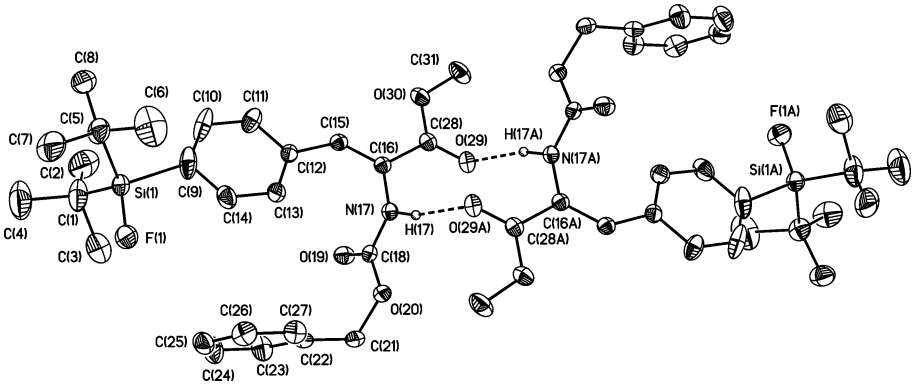
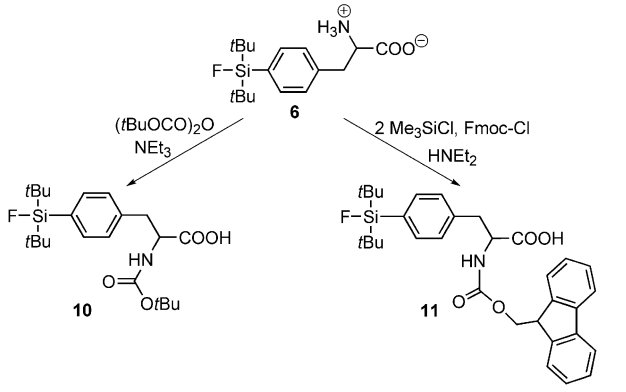


Figure 1. Molecular structure of compound **8**. Atomic displacement parameters are drawn at the 30% probability level. Selected bond lengths [Å] and angles [°]: Si(1)–F(1) 1.614(4), Si(1)–C(1) 1.886(4), Si(1)–C(5) 1.884(7), Si(1)–C(9) 1.974(4); F(1)–Si(1)–C(1) 113.4(2), F(1)–Si(1)–C(5) 103.8(3), F(1)–Si(1)–C(9) 111.6(2), C(1)–Si(1)–C(5) 116.0(3), C(1)–Si(1)–C(9) 105.9(2), C(5)–Si(1)–C(9) 106.0(2).

tance [1.614(4) Å] is rather similar to those in other SiFA-modified compounds.[7] A noteworthy feature is the asymmetric intramolecular N(17)-H···O (29) hydrogen bond that links two molecules of **8** into a dimer. Such hydrogen bonds are common for solid-state structures of *p*-silylarylcarboxylic acids and their derivatives.[7]

Hydrogenation of compound **8** in the presence of a chiral Rh^{I} catalyst gave the protected amino acid **9** with an *ee* of 98% for the *S*- and 99% for the *R* isomer, respectively. Deprotection took place in concentrated hydrobromic acid solution over a period of 15 min (Scheme 3).

The SiFA-modified amino acid was treated with Boc_2O and Fmoc-Cl under mild conditions in order to introduce protecting groups that are suitable for the solid-phase peptide synthesis (SPPS) (Scheme 4).



Scheme 4. Introduction of protecting groups for the solid-phase peptide synthesis.

Solid-Phase Peptide Synthesis (SPPS) with SiFA-Modified Phenylalanine

The 9-*mer* precursor peptide was synthesized by automated solid-phase peptide synthesis by standard 9-fluorenylmethoxycarbonyl (Fmoc) group chemistry protocols. The resin-bound 9-*mer* peptide was manually Fmoc-deprotected, and the final amino acid (*S*-SiFA-Phe) was coupled manually to save material (4–5 equiv. are routinely applied in an automated synthesis). Cleavage, final deprotection and HPLC-purification of the 10-*mer* peptide gave the labelling precursor **12**.

Likewise, the Tyr^3-octreotate derivatives **13** and **14** (Figure 2) were synthesized on solid supports by using standard 9-fluorenylmethoxycarbonyl (Fmoc) group chemistry protocols.[13] The amino acid D-phenylalanine[1] was replaced by the SiFA-modified *R*-configured amino acid. A polyethylene glycol linker and aspartic acid were added on the N terminus of the peptides, in order to improve the solubility of the labelling precursors **13** and **14** in water. By using

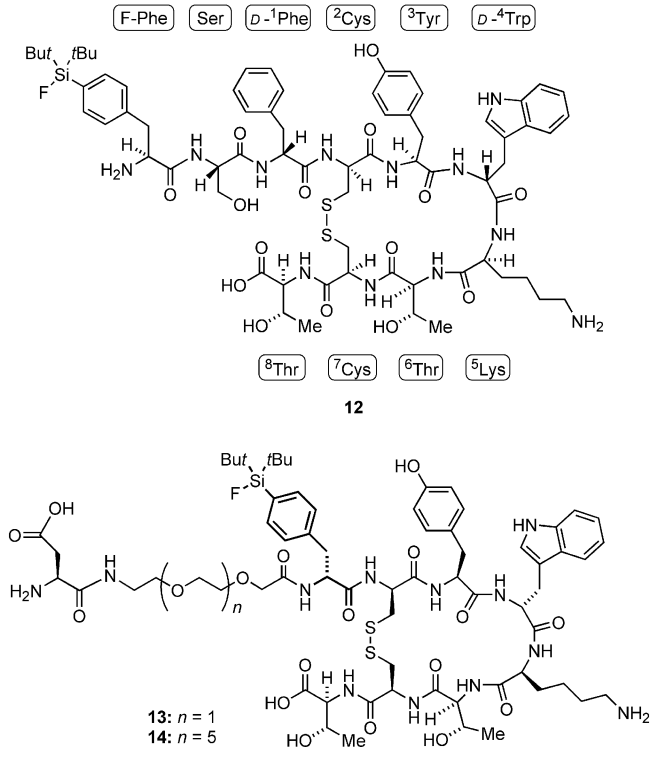


Figure 2. The SiFA-modified Tyr^3-octreotate derivatives **12**–**14**.

PEG linkers with different lengths, the hydrophilic properties of the peptides should be tailored.

Radiolabelling

Previous SiFA-labelling procedures with ^{18}F were mainly based on the synthesis of a small ^{18}F-label-containing reagent, which is then used to derivatize a peptide or protein of interest. In order to simplify such a modification, we have directly introduced a SiFA-modified amino acid **10** into the peptide chain. Thereby, we intended to apply a more simple and convenient method as described in ref.[4d] for ^{18}F-radiolabelling of the target peptides, which are functionalized with a fluoride-acceptor already during SPPS. Such an approach should be flexible and applicable to a wide range of potential targets, which can easily be purified before radiolabelling is conducted by a clean ^{18}F/^{19}F exchange reaction on the SiFA group, by using easily available K^{18}F as ^{18}F source. In this fashion, elaborate processing and purification of the hot ^{18}F-labelled target peptide by HPLC or other means could be avoided.

To demonstrate the feasibility of this approach, the labelling procedure was carried out with 3–5 GBq azeotropically dried $^{18}F^-$ in 500 μL dimethylsulfoxide (DMSO) or acetonitrile at room temperature for 5 min.

In accordance with the amount of labelling precursor used, the incorporation of ^{18}F-fluorine into SiFA-Phe reached levels of 40–60%, as determined by radio-HLPC. The calculated specific activity for [^{18}F]SiFA-Phe was between 11–31 GBq/μmol (298–919 Ci/mmol). After quick solid-phase extraction (Waters SepPak C18) for purification, the radiolabelled target [^{18}F]SiFA-Phe was released into isotonic NaCl solution and filtered sterile for direct injection. According to HPLC analysis, the chemical- and radiochemical purity was between 92 and 99% in all cases. The injection solution obtained in such a manner was stable over a period of 45 min in physiological buffer. Hence, our procedure should be suitable for application in vivo. In a similar fashion, isotopic exchange experiments with labelling precursors **12**, **13** and **14** provided the ^{18}F-labelled peptides in radiochemical yields ranging from 34 (**12**) to 70% (**13**).

In order to further simplify the labelling procedure, we also investigated the labelling step with ^{18}F-fluoride ions in aqueous medium. No reaction was detected at room temperature even after a reaction time of 15 min. After heating the reaction mixture to 90 °C, a radiochemical yield of 10% was observed after 5 min, and after 15 min, 27% was achieved. Further heating did not improve the radiochemical yields, but several radioactive and nonradioactive decay products began to form. While certainly more experimentation must be carried out along these lines, these data show that the ^{18}F-SiFA radiolabel can be expected to be stable for diagnostic applications at moderate temperatures in vivo. Furthermore, they demonstrate that labelling of a SiFA-carrying biomolecule target with ^{18}F fluoride ion by thermodynamically driven ^{18}F/^{19}F exchange up to diagnostically useful levels is feasible in the absence of any catalyst, if the target molecule is stable enough to withstand fluoride ion treatment at elevated temperatures for a short period of time.

Conclusions

In this manuscript we have demonstrated that the di-*tert*-butylfluoridosilyl-substituted phenylalanine, *p*-(*t*Bu$_2$FSi)-C$_6$H$_4$CH$_2$(NH$_2$)COOH (**6**), can easily be synthesized both as a racemic mixture and enantioselectively. Notably, the SiFA-moiety in compound **6** tolerates the harsh conditions of standard solid-phase peptide synthesis and simplifies the preparation of the SiFA-modified octreotate derivatives **12**–**14**. This strategy for the synthesis of such peptides is an alternative to the previously reported route according to which the SiFA-moiety was introduced into amino-oxy prefunctionalized peptides by using SiFA-aldehyde in a click-chemistry-type reaction.[5]

The fact that both the amino acid derivative **6** and the peptides **12**–**14** can easily be labelled with ^{18}F, that the labelled compounds are stable under physiological conditions and that, very likely, other SiFA-substituted amino acids can also be prepared opens new opportunities for the development of SiFA-based ^{18}F-labelled radiopharmaceutical peptides, and potentially proteins too.

Experimental Section

General Methods: All solvents used for the synthesis of **6** were purified by distillation under argon from appropriate drying agents. Solvents and chemicals used in the labelling experiments were purchased in the highest available grade and used without further purification. The NMR experiments were carried out with Bruker DRX 400, Bruker DRX 300 and Varian Mercury 200 spectrometers. The chemical shifts δ are referenced to the solvent peaks with the usual values calibrated against tetramethylsilane (^{1}H, ^{13}C, ^{29}Si) and $CFCl_3$ (^{19}F). The high resolution mass spectra were obtained with a LTQ Orbitrap mass spectrometer (Thermo Electron) with acetonitrile as the mobile phase. The acetonitrile solutions were injected by a TriPlus Autosampler onto a DFS-system (Perfluorokerosene as reference), connected with a Trace GC Ultra 2000 system [column: DB-5MS (25 m, 0.25 mm ID, film 0.1 μm)]. FT infrared spectra were recorded with a Bruker IFS28 spectrometer. Elemental analyses were performed on a LECO-CHNS-932 analyzer.

Crystallography: Crystals of compound **8** suitable for single-crystal X-ray diffraction analysis were grown by recrystallization from *n*-hexane. Crystallographic data are summarized in Table 1. Intensity data were collected with a Bruker AKS single-crystal Smart apex CCD diffractometer with graphite-monochromated Mo-K_α radiation. The data collections covered almost the whole sphere of the reciprocal space with 5 sets at different κ angles and 1125 frames by ω-rotation (Δ/ω = 0.5°) at per frame. Crystal decay was monitored by repeating the initial frames at the end of the data collection. After analysis of the duplicate reflections, there was no indication of any decay. The structure was solved by direct methods (SHELXS97[14]). Refinement applied full-matrix least-squares methods (SHELXL97[15]). All H atoms were located in the difference Fourier map, and their positions were isotropically refined with U_{iso} constrained at 1.2 times U_{eq} of the carrier C atom for

non-methyl and 1.5 times U_{eq} of the carrier C atom for methyl groups. Atomic scattering factors for neutral atoms and real and imaginary dispersion terms were taken from International Tables for X-ray Crystallography.[16] The figure was created by SHELXTL.[17] CCDC-793484 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Crystallographic data for **8**.

	8
Empirical formula	$C_{26}H_{34}FNO_4Si$
Formula mass [g/mol]	471.63
Crystal system	triclinic
Crystal size [mm]	$0.38 \times 0.35 \times 0.15$
Space group	$P\bar{1}$
a [Å]	7.8992(8)
b [Å]	9.2159(10)
c [Å]	19.301(2)
α [°]	83.149(3)
β [°]	79.017(3)
γ [°]	72.545(3)
V [Å^3]	1312.9(2)
Z	2
$\rho_{calcd.}$[mg/m^3]	1.193
μ [mm^{-1}]	0.127
$F(000)$	504
θ range [°]	2.15–27.79
Index ranges	$-10 \le h \le 10$ $-12 \le k \le 12$ $-25 \le l \le 25$
No. of reflections collected	15474
Completeness of θ_{max} [%]	99.6
No. of independent reflections/$R_{int.}$	6199/0.038
No. of reflections observed with $[I > 2\sigma(I)]$	3845
No. of refined parameters	333
GoF(F^2)	1.028
$R_1(F)$ $[I > 2\sigma(I)]$	0.0646
$wR_2(F^2)$ (all data)	0.2040
$(\Delta/\sigma)_{max}$	0.000
Largest difference peak/hole [e Å^{-3}]	0.449/–0.275

Synthetic Route I

[2-(4-Bromophenyl)ethoxy]-*tert*-butyldimethylsilane (2): In a 500-mL three-necked round-bottomed flask $LiAlH_4$ (2.21 g, 5.8 mmol) was suspended in diethyl ether (70 mL).[18] 2-(4-Bromophenyl)-acetic acid (10 g, 4.7 mmol) was dissolved in diethyl ether (80 mL) and slowly dropped into the suspension. After the suspension was stirred for 15 min at room temperature, the excess $LiAlH_4$ was hydrolyzed with water. Sulfuric acid (10% aq., 70 mL) was added to dissolve the precipitate, and a clear solution resulted. The organic phase was washed with water (80 mL) and brine (80 mL), and the combined water phases were extracted with diethyl ether (3×50 mL). The organic phases were combined, dried with $MgSO_4$ and filtered, and the solvent was evaporated in vacuo to yield 2-(4-bromophenyl)ethanol (8.71 g, 43 mmol, 92%) as a colourless liquid. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.39 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_m), 7.05 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_o), 3.75 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, CH_2-OH), 2.75 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, Ph-CH_2), 2.35 (s, 1 H, OH) ppm. ^{13}C{^{1}H} (100.63 MHz, $CDCl_3$): δ 137.5 (s, C$_i$) 131.4 (s, C$_m$) 130.6 (s, C$_p$) 120.1 (s, C$_m$), 63.1 (s, Ph-CH_2), 38.3 (s, CH_2OH) ppm. In a 250-mL two-necked round-bottomed flask 2-(4-bromophenyl)ethanol (4.26 g, 22 mmol) and imidazole (1.73 g, 25 mmol) were dissolved in CH_2Cl_2 (40 mL) and stirred for 15 min at room temperature.[19,20] *tert*-Butylchlorodimethylsilane (3.83 g, 25 mmol) was dissolved in CH_2Cl_2 and dropped into the reaction mixture. After stirring the mixture for 22 h at ambient temperature, it was washed with water (120 mL) and brine (120 mL). The water phases were extracted with CH_2Cl_2 (30 mL), the combined organic phases were dried with $MgSO_4$, and the solvent was evaporated in vacuo to yield **2** (6.19 g, 20 mmol, 93%) as a colorless liquid. ^{1}H NMR (400.63 MHz, $CDCl_3$): δ = 7.36 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_m), 7.05 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_o), 3.75 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, CH_2), 2.73 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, CH_2), 0.83 [s, 9 H, SiC(CH_3)$_3$], –0.05 [s, 6 H, Si(CH_3)$_2$] ppm.

2-[4-(Di-*tert*-butylfluorosilanyl)phenyl]ethanol (3): To a solution of **2** (2.9 g, 9.2 mmol) in diethyl ether (15 mL) *tert*-butyllithium (1.5 M in pentane, 12.9 mL, 19.3 mmol, 2.1 equiv.) was slowly added at –78 °C, and the solution was stirred for another 15 min at this temperature.[21] Di-*tert*-butyldifluorosilane (1.99 g, 10.1 mmol, 1.2 equiv.) was added, and the solution was stirred for an additional 22 h, during which it was warmed to room temperature. The reaction mixture was hydrolyzed with brine (100 mL). The organic phase was washed with water (50 mL) and brine (100 mL), and the combined aqueous phases were extracted with diethyl ether (3×50 mL). The organic phases were combined, dried with $MgSO_4$ and filtered. The solvent was evaporated to yield 1-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-4-(di-*tert*-butylfluorosilanyl)benzene (3.26 g, 8.2 mmol, 90%), which was used in the next step without further purification. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 7.50 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_m), 7.20 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_o), 3.81 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, CH_2-O), 2.81 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, Ph-CH_2), 1.04 [d, $^4J_{H\text{-}F}$ = 1 Hz, 18 H, SiC(CH_3)$_3$], 0.82 [s, 9 H, C(CH_3)$_3$], –0.07 [s, 6 H, Si(CH_3)$_2$] ppm. ^{19}F{^{1}H} (188.28 MHz, $CDCl_3$): δ = –189.53 ppm. In a 25-mL one-necked round-bottom flask 1-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-4-(di-*tert*-butylfluorosilanyl)-benzene (1 g, 2.5 mmol, 1.0 equiv.) was dissolved in methanol (8 mL).[22] To this magnetically stirred solution, *N*-iodosuccinimide (NIS, 30 mg, 0.1 mmol, 0.2 equiv.) was added, and the reaction mixture was stirred for another 24 h at room temperature. The solvent was evaporated, and the solid material thus obtained was washed several times with hexane in order to remove residues of iodine. The resulting residue was dissolved in diethyl ether/hexane (3:1) and purified by flash chromatography (SiO_2, diethyl ether/hexanes = 3:1) to yield **3** (0.440 mg, 1.6 mmol, 64%) as a white solid (m.p. 53 °C). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 7.53 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_m), 7.22 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_o), 3.88 (dt, $^3J_{H\text{-}H}$ = 6 Hz, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, CH_2-OH), 2.88 (t, $^3J_{H\text{-}H}$ = 7 Hz, 2 H, Ph-CH_2), 1.38 (t, $^3J_{H\text{-}H}$ = 6 Hz, 1 H, OH), 1.05 [d, $^4J_{H\text{-}F}$ = 1 Hz, 18 H, SiC(CH_3)$_3$] ppm. ^{13}C{^{1}H} (100.13 MHz, $CDCl_3$): δ = 142.3 (s, C_i), 134.2 [d, $^3J(^{13}C–^{19}F)$ = 4 Hz, C$_m$], 129.6 [d,$^2J(^{13}C–^{19}F)$ = 14 Hz, C$_p$], 128.2 (s, C$_o$), 63.4 (s, Ph-CH_2), 39.2 (s, CH$_2$-OH), 27.3 (s, CH$_3$), 20.1 [d, $^2J(^{13}C–^{19}F)$ = 12 Hz, CCH$_3$] ppm. ^{19}F (188.28 MHz, $CDCl_3$): δ = –189.4 (s) ppm. $C_{16}H_{27}FOSi$ (282.47 g/mol): calcd. C 68.0, H 9.6; found C 68.1, H 9.5. HR-GC–MS: calcd. for $C_{16}H_{27}OF^{28}Si$ 282.1810; found 282.1810.

Transformation of Alcohol 3 with Swern Reagent: A solution of the alcohol **3** (0.28 g, 1 mmol) in CH_2Cl_2 (10 mL) was added slowly at –60 °C to a freshly prepared solution of the oxidizing reagent [1 mL, 11 mmol oxalylchloride $(COCl)_2$; 1.7 mL, 22 mmol DMSO, 25 mL CH_2Cl_2]. The reaction mixture was stirred for 15 min at this temperature during which the solution became cloudy. The reaction was terminated by the addition of NEt_3. By doing so, the solution became clear. After the reaction mixture had been warmed to room temperature, water (100 mL) was added. The phases were separated, and the water phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were subsequently washed with a solution of HCl (2 M, 50 mL) and a saturated $NaHCO_3$ solution

(50 mL), dried with $MgSO_4$ and filtered. The solvent of the filtrate was removed in vacuo to give an oily residue. The latter was purified by chromatography (SiO_2, hexane/diethyl ether, 1:1) to give compound **4a** as yellow oil (0.29 g, 82%). ^{1}H NMR (599.83 MHz, C_6D_6): δ = 8.71 (s, 1 H, COH), 7.54 [d, $^3J(^1H\text{-}^1H)$ = 7 Hz, 2 H, H_m], 7.43 [d, $^3J(^1H\text{-}^1H)$ = 7 Hz, 2 H, H_o], 0.98 {s, 18 H, Si[C-$(CH_3)_3]_2$} ppm. ^{13}C{^{1}H} (125.77 MHz, C_6D_6): δ = 182.7 [s, C(Cl)-OH], 136.2 (s, C_i), 134.4 [d, $^3J(^{13}C\text{-}^{19}F)$ = 4 Hz, C_m], 127.8 [d, $^2J(^{13}C\text{-}^{19}F)$ = 14 Hz, C_p], 126.4 (s, C_o), 125.4 (s, PhCCl), 27.3 {s, Si[C($CH_3)_3]_2$}, 20.3 {d, $^2J(^{13}C\text{-}^{19}F)$ = 12 Hz, Si[$C(CH_3)_3]_2$} ppm. ^{19}F (188.28 MHz, [D$_6$]DMSO): δ = –190.2 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 298 Hz]. LR-GC-EI-MS: calcd. for ($[C_{16}H_{23}NFSiCl_2]^+$ 349.3; found 349.3.

[4-(Di-*tert*-butylfluorosilanyl)phenyl]acetaldehyde (4): To a magnetically stirred suspension of pyridinium chlorochromate (PCC, 8.05 g, 37 mmol, 3.7 equiv.) in CH_2Cl_2 (300 mL)[12b] was added dropwise a solution of **5** (2.93 g, 10 mmol) in CH_2Cl_2 (250 mL) at 0 °C. The reaction mixture was stirred for an additional 3 h and warmed to room temperature. The upper solution was decanted from the gumlike residue, the residue was washed with diethyl ether (3 × 100 mL), and the solvent of the combined organic phases was evaporated to yield **4** (1.75 g, 6 mmol, 60%) as a yellowish oil, which solidified on standing. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 9.75 (t, $^3J_{H\text{-}H}$ = 2 Hz, 1 H, C*H*O), 7.60 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_m), 7.23 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, H_o), 3.68 (d, $^3J_{H\text{-}H}$ = 2 Hz, 2 H, CH_2-CHO), 1.05 [d, $^4J_{H\text{-}F}$ = 1 Hz, 18 H, SiC($CH_3)_3$] ppm. ^{13}C{^{1}H} (100.13 MHz, $CDCl_3$): δ = 189.3 (s, *C*HO), 138.7 (s, C_i), 135.2 [d, $^3J(^{13}C\text{-}^{19}F)$ = 4 Hz, C_m], 130.9 [d, $^2J(^{13}C\text{-}^{19}F)$ = 14 Hz, C_p], 128.8 (s, C_o), 27.2 (s, CH_3), 20.2 [d, $^2J(^{13}C\text{-}^{19}F)$ = 12 Hz, *C*CH_3] ppm. ^{19}F (188.28 MHz, $CDCl_3$): δ = –189.9 (s) ppm. HR-GC–MS: calcd. for $C_{16}H_{25}OF^{28}Si$ 280.1659; found 280.1651. $C_{16}H_{25}FOSi$ (280.47 g/mol): calcd. C 68.5, H 9.0; found C 68.7, H 9.2.

Methyl *rac*-2-Amino-3-[4-(di-*tert*-butyl-fluoro-silanyl)-phenyl]-propionate (5): In a 10-mL glass vessel with a Teflon tap, a saturated aqueous solution of ammonium chloride (0.25 mL), a concentrated solution of ammonia (0.27 mL) and sodium cyanide (72 mg in 0.14 mL water) were added.[10] The solution was cooled to 0 °C, and a methanol solution of **4** (370 mg, 1.3 mmol, 0.27 mL) was added dropwise. The reaction mixture was stirred for an additional 2 h at room temperature. A concentrated aqueous solution of HCl (4 mL) was added, and the reaction mixture was heated at reflux for an additional 12 h. The solvent was evaporated, and the residue was purified by flash chromatography (SiO_2, diethyl ether/hexane = 1:1, then Et_2O, elution of the product with MeOH) to yield racemic **5** (0.21 g, 62 μmol, 44%) as a white solid (m.p. 78 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, $H_{arom.}$), 7.33 (d, $^3J_{H\text{-}H}$ = 8 Hz, 2 H, $H_{arom.}$), 7.05 (br., 2 H, NH_2), 4.61 [dd, $^3J_{H\text{-}H(erythro)}$ = 6 Hz, $^3J_{H\text{-}H(threo)}$ = 7 Hz, 1 H, CH_2-C*H*(NH_2)], 3.70 (s, 3 H, OCH_3), 3.56 [dd, $^3J_{H\text{-}H}$ = 6 Hz, $^2J_{H\text{-}H(threo)}$ = 14 Hz, 1 H, CH_2-CH(NH_2), $H_{erythro}$], 3.44 [dd, $^3J_{H\text{-}H}$ = 7 Hz, $^2J_{H\text{-}H(erythro)}$ = 14 Hz, 1 H, CH_2-CH(NH_2), H_{threo}], 1.02 [s, 18 H, C(C$H_3)_3$] ppm. ^{13}C{^{1}H} (100.13 MHz, $CDCl_3$): δ = 168.9 (s, COOMe), 138.7 (s, C_i), 135.2 [d, $^3J(^{13}C\text{-}^{19}F)$ = 4 Hz, C_m], 130.9 [d, $^2J(^{13}C\text{-}^{19}F)$ = 14 Hz, C_p], 128.8 (s, C_o), 27.2 {s, Si[C($CH_3)_3]_2$}, 20.2 {d, $^2J(^{13}C\text{-}^{19}F)$ = 12 Hz, Si[$C(CH_3)_3]_2$} ppm. ^{19}F (188.28 MHz, $CDCl_3$): δ = –188.9 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 298 Hz] ppm. HR-LC-ESI-MS: calcd. for $[C_{18}H_{30}O_2NF^{28}Si+H]^+$ 340.2103; found 340.2103.

***S*-2-Amino-3-[4-(di-*tert*-butylfluorosilanyl)phenyl]propionic Acid (6):** A solution of the methyl ester **5** (0.21 g, 62 μmol) in acetonitrile (2 mL) was added to an aqueous solution of α-chymotrypsine[11] (5 mg) in phosphate buffer (1 mL, 1 M Na_2HPO_4, pH = 7.8). The reaction mixture was kept for 24 h at 30 °C. Acetonitrile was added, and the enzyme was removed by centrifugation. The remaining solution was concentrated and purified on RP-silica gel [CH_3CN/H_2O (4:1)]. After evaporation of the solvents, compound **6** (6.5 mg, 19 μmol, 32%) was obtained as a white amorphous solid (m.p. 196–198 °C). ^{1}H NMR (500.13 MHz, [D$_4$]MeOH): δ = 7.58 [d, $^3J(^1H\text{-}^1H)$ = 8 Hz, 2 H, H_m], 7.37 [d, $^3J(^1H\text{-}^1H)$ = 8 Hz, 2 H, H_o], 3.70 [dd, $^3J(H_\alpha\text{-}H_{erythro})$ = 5 Hz, $^3J(H_\alpha\text{-}H_{threo})$ = 9 Hz, 1 H, CH_2-C*H*(NH_2)], 3.27 [dd, $^3J(H_{erythro}\text{–}H_\alpha)$ = 5 Hz, $^2J(H_{erythro}\text{–}H_{threo})$ = 14 Hz, 1 H, CH_2-CH(NH_2), $H_{erythro}$], 2.94 [dd, $^3J(H_{threo}\text{–}H_\alpha)$ = 9 Hz, $^2J(H_{threo}\text{–}H_{erythro})$ = 14 Hz, 1 H, CH_2-CH(NH_2), H_{threo}], 1.05 {s, 18 H, Si[C($CH_3)_3]_2$} ppm. ^{13}C{^{1}H} (125.77 MHz, [D$_4$]MeOH): δ = 176.7 (s, COOH), 140.3 (s, C_i), 135.5 [d, $^3J(^{13}C\text{-}^{19}F)$ = 4 Hz, C_m], 133.1 [d, $^2J(^{13}C\text{-}^{19}F)$ = 14 Hz, C_p], 129.9 (s, C_o), 57.9 (s, CHN), 40.1 (s, CH_2), 27.9 {s, Si[C($CH_3)_3]_2$}, 21.1 {d, $^2J(^{13}C\text{-}^{19}F)$ = 12 Hz, Si[$C(CH_3)_3]_2$} ppm. ^{19}F (188.28 MHz, [D$_4$]MeOH): δ = –192.4 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 296 Hz] ppm. HR-LC-ESI-MS: calcd. for $[C_{17}H_{28}O_2NF^{28}Si+H]^+$ 326.1945; found 326.1946. $[\alpha]_D^{20}$ (ethanol): –21.82°.

Synthetic Route II

Methyl *Z*-2-Benzyloxycarbonylamino-3-[4-(di-*tert*-butyl-fluoro-silanyl)-phenyl]-acrylate (8): To a –78 °C cooled solution of 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (3.63 g, 10.9 mmol) in THF (50 mL) was added tetramethylguanidine (1.79 mL, 14.1 mmol), and the reaction mixture was stirred for 30 min. A solution of the SiFA-aldehyde **7** (2.89 g, 10.9 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was stirred for 1 h at –78 °C and for an additional 4 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 1 M HCl, 1 M $CuSO_4$ and saturated $NaHCO_3$ solution. After drying the organic layer over $MgSO_4$, it was filtered, and the solvent of the filtrate was evaporated in vacuo. The crude product thus obtained was purified by column chromatography on silica gel (hexane/diethyl ether, 3:1) to give **8** (3.29 g, 7.0 mmol, 64%) as a colorless oil, which solidified (mp. 34 °C). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.60 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, H_o), 7.41 (s, 1 H, CH), 7.45 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, H_m), 7.16 (m, 5 H, H_{phenyl}), 6.24 (s, 1 H, NH), 5.06 (s, 2 H, O-CH_2), 3.44 (s, 3 H, $COOCH_3$), 1.10 [s, 18 H, 2 × SiC($CH_3)_3$] ppm. ^{13}C{^{1}H} (100.63 MHz, C_6D_6): δ = 165.4 (s, COOMe), 154.0 (s, NCOO), 136.5 (s, C_i), 135.2 (s, C_i), 134.2 [d, $^3J(^{13}C\text{-}^{19}F)$ = 4 Hz, C_m], 131.4 [d, $^2J(^{13}C\text{-}^{19}F)$ = 14 Hz, C_p], 129.1 (s, C_m), 128.4 (s, C_p), 128.3 (s, C_o), 128.0 (s, C_o), 127.6 (s, HC=*C*NH), 125.7 (s, H*C*=CNH), 67.2 (s, $PhCH_2O$), 51.9 (s, OCH_3), 27.2 {s, Si[C($CH_3)_3]_2$}, 20.1 {d, $^2J(^{13}C\text{-}^{19}F)$ = 12 Hz, Si[$C(CH_3)_3]_2$} ppm. ^{19}F (282.38 MHz, C_6D_6): δ = –189.3 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 297 Hz] ppm. ^{29}Si {^{1}H} (59.63 MHz, C_6D_6): δ = 14.5 [d, $^1J(^{29}Si\text{-}^{19}F)$ = 297 Hz] ppm. $C_{26}H_{34}FNO_4Si$ (471.64 g/mol): calcd. C 66.2, H 7.3, N 3.0; found C 66.1, H 7.3, N 2.9. HR-LC-ESI-MS: calcd. for $[C_{26}H_{34}FNO_4{}^{28}Si+H]^+$ 472.2314; found 472.2310.

(*S*)-Methyl 2-(Bezyloxycarbonylamino)-3-[4-(di-*tert*-butylfluorosilyl)phenyl]propanoate (*S*-9): A solution of **8** (3.29 g, 7.0 mmol) and a catalytic amount of (+)-1,2-bis[(2*S*,5*S*)-diethylphospholanolbenzenecyclooctadiene]rhodium(I) triflate in dry dichloromethane (50 mL) was stirred under H_2 atmosphere (1 bar) for 24 h. The catalyst was separated by filtration through a short silica gel pad. After evaporation of the solvent, compound **9** was obtained as a colourless oil in quantitative yield (3.32 g, 7.0 mmol). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.63 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, H_o), 7.10–7.25 (m, 5 H, H_{phenyl}), 7.07 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, H_m), 5.26 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, NH), 5.07 (q, 2 H, O-CH_2-Ph), 4.77 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, H_c), 3.24 (s, 3 H, $COOCH_3$), 3.04 (dd, $^3J_{H,H}$ = 6.0 Hz, $^2J_{Ha\text{-}Hb}$ = 13.6 Hz, 1 H, H_b), 2.87 (dd, $^3J_{H,H}$ = 6.8 Hz, $^2J_{Ha\text{-}Hb}$ = 13.6 Hz, 1 H, H_a), 1.10 [s, 18 H, 2 × SiC($CH_3)_3$] ppm. ^{13}C NMR

(400 MHz, C_6D_6): δ = 171.6 (s, COO), 155.5 (s, NCOO), 138.0 (s, $C_{i(aromat.)}$), 136.7 (s, $C_{i(aromat.)}$), 134.1 (d, $^3J_{C,F}$ = 3.8 Hz, $C_{m(aromat.)}$), 131.9 (d, $^2J_{C,F}$ = 13.4 Hz, $C_{p(aromat.)}$), 128.7 (s, $C_{m(aromat.)}$), 128.3 (s, $C_{p(aromat.)}$), 128.1 (s, $C_{o(aromat.)}$), 127.9 (s, $C_{o(aromat.)}$), 66.6 (s, Ph-*C*H_2-O), 54.9 (s, CH-N), 51.3 (s, O-CH_3), 38.1 (s, CH_2), 27.2 [s, C(*C*H_3)$_3$], 20.1 [d, $^2J_{C,F}$ = 12.5 Hz, *C*$(CH_3)_3$] ppm. ^{19}F (188.28 MHz, $CDCl_3$): δ = –189.9 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 298 Hz] ppm. ^{29}Si{^{1}H } NMR (59.63 MHz, $CDCl_3$): δ = 14.4 [d, $^1J(^{29}Si\text{-}^{19}F)$ = 298 Hz] ppm. HR-LC-ESI-MS: calcd. for $C_{26}H_{36}FNO_4{}^{28}Si$ 473.2398; found 474.2466 $[M + H]^+$. $C_{26}H_{36}FNO_4Si$ (473.64 g/mol): calcd. C 65.9, H 7.7, N 3.0; found C 65.7, H 7.7, N 2.8.

(*R*)-Methyl 2-(Bezyloxycarbonylamino)-3-[4-(di-*tert*-butylfluorosilyl)phenyl]propanoat (*R*-9): The preparation of this compound was performed in analogy to the synthesis of the (*S*)-isomer. (+)-1,2-Bis[(2*R*, 5*R*)-diethylphospholano]benzolcyclooctadienerhodium(I) triflate was used as catalyst.

(*S*)-2-Amino-3-[4-(di-*tert*-butylfluorosilanyl)phenyl]propionic Acid (6): Compound *S*-**9** (1.86 g, 3.9 mmol) and an aqueous solution of HBr (2 mL, 15.7 mmol) were heated for 15 min at 110 °C. The volatiles were removed in vacuo, and the residue was dissolved in diethyl ether. The solution was washed with saturated $NaHCO_3$ solution. A white solid (insoluble in water and diethyl ether) is formed at the interface and isolated by filtration. The analytical data for this compound are identical to the data for the (*S*)-amino acid obtained by the enzymatic cleavage of the methyl ester. $[\alpha]_D^{20}$ (ethanol): –21.89°.

(*R*)-2-Amino-3-[4-(di-*tert*-butylfluorosilanyl)phenyl]propionic Acid (6): The synthesis of this compound was performed in analogy to the preparation of the (*S*)-isomer. $[\alpha]_D^{20}$ (ethanol): 21.96°.

(*S*)-2-*tert*-Butoxycarbonylamino-3-[4-(di-*tert*-butylfluorosilanyl)phenyl]propionic Acid (10): To a solution of *S*-**6** (1 g, 3.2 mmol) in CH_3CN/CH_2Cl_2 (1:4, 10 mL) was added a solution of *tert*-butyloxycarbonylanhydride $[(t\text{BuOCO})_2O]$ (0.64 g, 3.2 mmol) in CH_2Cl_2 (10 mL). Triethylamine (NEt_3) (0.65 mL) was added to the reaction mixture, and the latter was stirred for 24 h at room temperature. The mixture was diluted with HCl solution (10 mL, 0.5 M). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2× 30 mL). The combined organic phases were dried with $MgSO_4$ and filtered, and the volatiles were removed in vacuo to give a crude product that was recrystallized from benzene to provide compound *S*-**10** as an amorphous, white solid (0.98 g, 2.30 mmol, 75%, m.p. 144–147 °C). ^{1}H NMR (400.13 MHz, C_6D_6): δ = 7.65 [d, $^3J(^1H\text{-}^1H)$ = 7 Hz, 2 H, H_m], 7.11 [d, $^3J(^1H\text{-}^1H)$ = 7 Hz, 2 H, H_o], 4.86 (br., 1 H, NH), 4.72 [dd, $^3J(H_\alpha\text{-}H_{erythro})$ = 6 Hz, $^3J(H_\alpha\text{-}H_{threo})$ = 8 Hz, 1 H, CH_2-C*H*(NH_2)], 3.10 [dd, $^3J(H_{erythro}\text{–}H_\alpha)$ = 6 Hz, $^2J(H_{erythro}\text{–}H_{threo})$ = 14 Hz, 1 H, CH_2-CH(NH_2), $H_{erythro}$], 2.78 [dd, $^3J(H_{threo}\text{–}H_\alpha)$ = 8 Hz, $^2J(H_{threo}\text{–}H_{erythro})$ = 14 Hz, 1 H, CH_2-CH(NH_2), H_{threo}], 1.40 [s, 9 H, OC(O)-C$(CH_3)_3$], 1.11 {s, 18 H, Si[C$(CH_3)_3]_2$} ppm. ^{13}C{^{1}H} (100.63 MHz, C_6D_6): δ = 178.7 (s, COOH), 162.4 (s, COO*t*Bu), 141.3 (s, C_i), 135.7 [d, $^3J(^{13}C\text{-}^{19}F)$ = 4 Hz, C_m], 130.2 [d, $^2J(^{13}C\text{-}^{19}F)$ = 14 Hz, C_p], 127.4 (s, C_o), 73.1 [s, O*C*$(CH_3)_3$], 58.4 (s, CNH), 41.3 (s, CH_2), 29.8 [s, OC(*C*$H_3)_3$], 27.9 {s, Si[C(*C*$H_3)_3]_2$}, 21.1 {d, $^2J(^{13}C\text{-}^{19}F)$ = 12 Hz, Si[*C*$(CH_3)_3]_2$} ppm. ^{19}F (188.28 MHz, $CDCl_3$): δ = –188.3 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 298 Hz] ppm. ^{29}Si{^{1}H} (59.63 MHz, $CDCl_3$): δ = 14.5 [d, $^1J(^{29}Si\text{-}^{19}F)$ = 298 Hz] ppm. $C_{22}H_{36}FNO_4Si$ (425.69 g/mol): calcd. C 62.1, H 8.5, N 3.3; found C 62.1, H 8.2, N 3.5. HR-LC-ESI-MS: calcd. for $[2(C_{26}H_{36}NFO_4{}^{28}Si)+H]^+$ 851.4868; found 851.4870.

(*R*)-3-[4-(Di-*tert*-butylfluorosilyl)phenyl]-2-*N*-[(9*H*-fluoren-9-yl)methylformyl]propionic Acid (11): To a suspension of the *R*-amino acid **6** (1 g, 3.2 mmol) in CH_2Cl_2 (10 mL) were added diethylamine (0.94 g, 1.3 mL, 12 mmol) and chlorotrimethylsilane (0.35 g, 0.26 mL, 6.4 mmol, 2 equiv.). The reaction mixture was stirred for 30 min at room temperature followed by addition of 9-fluorenylmethylchloroformiate (Fmoc-Cl, 0.91 g, 1.1 equiv.); the clear solution was stirred for an additional 24 h at room temperature. Water (10 mL) was added to the reaction mixture, the organic phase was separated and the aqueous phase was washed with CH_2Cl_2 (3× 20 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the volatiles of the filtrate were removed in vacuo. The product was purified by column chromatography (SiO_2 acetone/*n*-hexane, 3:1). Compound *R*-**11** (1.41 g, 3.1 mmol, 80%) was obtained as a slightly yellow amorphous solid (m.p. 132 °C). ^{1}H NMR (400.13 MHz, [D_6]DMSO): δ = 7.98–7.14 (m, 11 H, $H_{arom.}$), 4.09 (m, 1 H, $H_{9\text{-}Fluorenyl}$), 4.06 (m, 2 H, $H_{Fluorenyl}$), 3.97 [dd, $^3J(H_\alpha\text{-}H_{erythro})$ = 5 Hz, $^3J(H_\alpha\text{-}H_{threo})$ = 9 Hz 1 H, CH_2-C*H*(NHFmoc)], 3.08 [dd, $^3J(H_{erythro}\text{–}H_\alpha)$ = 5 Hz, $^2J(H_{erythro}\text{–}H_{threo})$ = 14 Hz, 1 H, CH_2-CH(NH_2), $H_{erythro}$], 2.85 [dd, $^3J(H_{threo}\text{–}H_\alpha)$ = 9 Hz, $^2J(H_{threo}\text{–}H_{erythro})$ = 14 Hz, 1 H, CH_2-CH(NH_2), H_{threo}], 1.02 {s, 18 H, Si[C$(CH_3)_3]_2$} ppm. ^{13}C{^{1}H} (100.63 MHz, [D_6]DMSO): δ = 174.2 (s, COOH), 153.1 (s, NCOO), 142.2 (s, $C_{arom.}$), 141.9 (s, C_i), 137.4 (s, $C_{arom.}$), 136.2 [d, $^3J(^{13}C\text{-}^{19}F)$ = 4 Hz, C_m], 131.0 [d, $^2J(^{13}C\text{-}^{19}F)$ = 14 Hz, C_p], 129.3 (s, $C_{arom.}$), 128.1 (s, $C_{arom.}$), 127.9 (s, $C_{arom.}$), 127.4 (s, C_o), 71.8 (s, OCH_2), 62.2 (s, CNH), 37.2 (OCH_2*C*H), 36.6 (s, PhCH_2), 27.1 {s, Si[C(*C*$H_3)_3]_2$}, 21.1 {d, $^2J(^{13}C\text{-}^{19}F)$ = 12 Hz, Si[*C*$(CH_3)_3]_2$} ppm. ^{19}F (188.28 MHz, [D_6]DMSO): δ = –188.0 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 296 Hz] ppm. ^{29}Si{^{1}H } (59.63 MHz, [D_6]DMSO): δ = 14.1 [d, $^1J(^{29}Si\text{-}^{19}F)$ = 296 Hz] ppm. LR-LC-ESI-MS: calcd. for $[(C_{32}H_{38}NFO_4{}^{28}Si)+Na]^+$ 570.2; found 570.2.

Thr-Cys-Thr-Lys-*D*-Trp-Tyr-Cys-*D*-Phe-Ser-*L*-SiFA-Phe (12): The 9-*mer* precursor peptide (Thr-Cys-Thr-Lys-D-Trp-Tyr-Cys-D-Phe-Ser) was synthesized by automated solid-phase peptide synthesis (CEM peptide synthesizer, Matthews, NC, USA) by using standard 9-fluorenylmethoxycarbonyl (Fmoc) group chemistry protocols.[13] STr, *N*-Boc and *Ot*Bu were used for side chain protection. 2-Chloro-trityl resin (0.5 mmol, 0.769 mg) was used as solid support. The corresponding amino acid (5 equiv.), *O*-benzotriazolyl-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexafluorophosphate (HBTU) (5 equiv.) and *N*,*N*-di-isopropylethylamine (DIPEA) (5 equiv.) in dimethylformamide (DMF) was used for the couplings. Piperidine in DMF (20%) was used for deprotection. The N-terminus of the resin-bound 9-*mer* peptide was manually Fmoc-deprotected (20% piperidine in DMF), and the N-terminal amino acid [Boc-protected *S*-SiFA-Phe (*S*-**10**), 283 mg, 0.664 mmol,1.8 equiv.] was coupled to the resin-bound peptide by using HBTU (336 mg, 0.886 mmol, 2.4 equiv., 0.5 M in DMF) and DIPEA (183 μL, 1.11 mmol, 3.0 equiv.) for 20 h. The 10-*mer* peptide was released from the solid support and deprotected by incubating the resin with excess cleavage cocktail [95% trifluoroacetic acid (TFA), 2.5% H_2O, 2.5% Et_3-SiH] for 1 h. The resulting solution was concentrated to volume of 2 mL, and the crude peptide was precipitated by adding ice-cold methyl *tert*-butyl ether (MTBE, 10 vol.) and isolated by centrifugation. To ensure complete removal of Boc-derived carbamic acid residues from tryptophan, the precipitate was resuspended in H_2O/MeOH (1:1, 10 mL). TFA was added (250 μL), and the mixture was warmed to 40 °C and stirred for 1.5 h. Removal of all volatiles and lyophilization yielded the crude linear peptide as a colourless powder (445 mg). Installation of the intramolecular disulfide bridge was achieved by dissolving the material in MeOH (0.3 M), adding DIPEA (610 μL, 3.69 mmol, 10 equiv.), and incubating the solution under O_2 atmosphere for 72 h. The crude product was recovered by freeze-drying, dissolved in H_2O/acetonitrile (3:1), and purified by reversed-phase HPLC on a Nucleodur C4 column (250×20 mm, Macherey–Nagel, Düren, Germany) at a flow rate

of 20 mL/min by employing a linear 30–45% acetonitrile/water (0.1% TFA) gradient over 45 min. The pure title compound **12** was retrieved after lyophylization of suitable fractions as a colourless powder (102 mg, 0.071 mmol, 19%). M.p. >240 °C (decomp.). R_f = 0.03 (SiO_2, $CHCl_3$/MeOH/HCOOH, 90:10:2). ^{19}F NMR (188.28 MHz, [D$_6$]DMSO): δ = –186.6 [d, $^1J(^{19}F\text{-}^{29}Si)$ = 297.9 Hz] ppm. ^{29}Si{^{1}H } NMR (59.63 MHz, [D$_6$]DMSO): δ = 14.5 [d, $^1J(^{29}Si\text{-}^{19}F)$ = 297.6Hz] ppm. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 10.80 (s, 1 H, $NH_{Trp4\text{-}indole}$), 8.98 (d, J = 7.8 Hz, 1 H, NH_{Cys2}), 8.77 (d, J = 4.8 Hz, 1 H, NH_{Trp4}), 8.69 (d, J = 6.3 Hz, 1 H, NH_{Ser}), 8.58–8.52 (m, 2 H, NH_{Tyr3} + NH_{Cys7}), 8.35–8.28 (m, 2 H, NH_{Lys5}, NH_{Thr8}), 8.17–8.00 (m, 3 H, NH_{Phe1}, NH_2, SiFA-Phe), 7.78–7.63 (m, 2 H, NH_2, Lys5-ε), 7.59 (d, J = 9.1 Hz, 1 H, NH_{Thr6}), 7.47 (d, J = 7.8 Hz, 2 H, C$H_{Ar\text{-}o}$, SiFA-Phe), 7.42 (d, J = 7.9 Hz, 1 H, CH_{Ar}, Trp4), 7.33 (d, J = 7.7 Hz, 3 H, $CH_{Ar\text{-}m}$, SiFA-Phe and C$H_{Ar\text{-}Trp4}$), 7.29 (d, J = 7.4 Hz, 2 H, C$H_{Ar\text{-}o}$, Phe1), 7.20–7.15 (m, 2 H, C$H_{Ar\text{-}m}$, Phe1), 7.07 (d, J = 7.5 Hz, 1 H, CH_{Ar}, Trp4), 7.05 (s, 1 H, C$H_{Ar\text{-}o}$, Trp4), 7.00 (t, J = 7.4 Hz, 1 H, CH_{Ar}, Trp4), 6.91 (d, J = 8.4 Hz, 2 H, C$H_{Ar\text{-}o}$, Tyr3), 6.64 (d, J = 8.2 Hz, 2 H, C$H_{Ar\text{-}m}$, Tyr3), 5.34 (d, J = 10.5 Hz, 1 H, C$H\alpha$, Cys7), 5.29 (d, J = 9.7 Hz, 1 H, C$H\alpha$, Cys2), 4.87 (dd, J = 10.7, 3.8 Hz, 1 H, C$H\alpha$, Phe1), 4.59–4.51 (m, 2 H, C$H\alpha$, Tyr3, Thr6), 4.39–4.34 (m, 1 H, C$H\alpha$, Ser), 4.34–4.30 (m, 1 H, C$H\beta$, Thr8), 4.22 (d, J = 2.8 Hz, 1 H, C$H\alpha$, Thr8), 4.19 (dd, J = 9.5, 6.0 Hz, 1 H, C$H\alpha$, Trp4), 4.13–4.07 (m, 1 H, C$H\alpha$, SiFA-Phe), 4.00–3.92 (m, 2 H, C$H\alpha$, Lys5, and C$H\beta$, Thr6), 3.34 (d, J = 7.2 Hz, 1 H, C$H_2\beta'$, Ser), 3.19 (d, J = 10.2 Hz, 2 H, C$H_2\beta''$, Ser, and C$H_2\beta'$, Phe1), 3.15 (dd, J = 14.4, 3.0 Hz, 2 H, C$H_2\beta'$, SiFA-Phe, and C$H_2\beta'$, Tyr3), 3.01 (dd, J = 13.9, 9.9 Hz, 1 H, C$H_2\beta'$, Trp4), 2.94–2.72 (m, 8 H, C$H_2\beta$, Cys2, and C$H_2\beta$, Cys7, and C$H_2\beta''$, SiFA-Phe, and C$H_2\beta''$, Tyr3, and C$H_2\beta''$, Phe1), 2.68 (dd, J = 14.0, 5.4 Hz, 1 H, C$H_2\beta''$, Trp4), 2.58–2.52 (m, 2 H, CH_2, Lys5-ε), 1.73–1.65 (m, 1 H, C$H_2\beta'$, Lys5), 1.28 (d, J = 8.0 Hz, 2 H, CH_2, Lys5-δ), 1.24 (d, J = 6.4 Hz, 3 H, C$H_3\gamma$, Thr8), 1.21–1.17 (m, 1 H, C$H_2\beta''$, Lys5), 1.07 (d, J = 6.3 Hz, 3 H, C$H_3\gamma$, Thr6), 1.00 (d, J = 8.7 Hz, 18 H, CH3, *t*Bu), 0.72–0.56 (m, 2 H, C$H_2\gamma$, Lys5) ppm. ^{13}C{^{1}H} NMR (150.8 MHz, [D$_6$]DMSO): δ = 172.6 (*C*O, Trp4), 172.0 (*C*O, Lys5), 171.3 (*C*O, Thr6), 169.0 (*C*O, Ser), 156.5 (*C*q, Ar-OH, Tyr3), 136.6 (*C*q, Ar, Trp4), 134.5 (*C*H, Ar_{ortho}, SiFA-Phe), 130.5 (*C*H, Ar_{ortho}, Tyr3), 130.2 (*C*H, Ar_{ortho}, Phe1), 130.1 (*C*q, Ar, Phe1), 129.5 (*C*H, Ar_{meta}, SiFA-Phe), 127.6 (*C*q, Ar, Trp4), 126.9 (*C*H, Ar_{meta}, Phe1), 124.3 (*C*H, Ar_{ortho}, Phe1), 121.6 (*C*H, Ar, Trp4), 119.1 (*C*H, Ar, Trp4), 118.8 (*C*H, Ar, Trp4), 115.6 (*C*H, Ar_{meta}, Tyr3), 111.9 (*C*H, Ar, Trp4), 109.6 (*C*H, Ar, Trp4), 67.9 (β-*C*H, Thr6), 66.8 (β-*C*H, Thr8), 62.4 (β-*C*H_2, Ser), 58.9 (α-*C*H, Thr8), 58.8 (α-*C*H, Thr6), 56.3 (α-*C*H, Ser), 56.0 (α-*C*H, Trp), 54.8 (α-*C*H, Tyr3), 54.0 (α-*C*H, Phe1), 53.7 (α-*C*H, SiFA-Phe), 53.1 (α-*C*H, Cys2), 53.0 (α-*C*H, Lys5), 52.4 (α-*C*H, Cys7), 45.7 (β-*C*H_2, Cys7), 45.6 (β-*C*H_2, Cys2), 40.0 (β-*C*H_2, Phe1), 39.1 (ε-*C*H_2, Lys5), 37.6 (β-*C*H_2, SiFA-Phe), 37.6 (β-*C*H_2, Tyr3), 31.0 (β-*C*H_2, Lys5), 27.8 (*C*H_3, *t*Bu), 27.1 (δ-*C*H_2, Lys5), 26.5 (β-*C*H_2, Trp4), 22.4 (γ-*C*H_2, Lys5), 20.9 (γ-*C*H_3, Thr8), 20.3 (*C*q, *t*Bu), 20.1 (γ-*C*H_3, Thr6) ppm. HRMS (ESI): calcd. for $[C_{69}H_{96}N_{12}O_{15}FS_2Si]^+$ 1443.631; found 1443.632.

Thr-Cys-Thr-Lys-*D*-Trp-Tyr-Cys-*D*-SiFA-Phe-(PEG)$_1$-Asp (13): The Tyr^3-octreotate derivatives **13** and **14** were synthesized according to standard Fmoc-solid-phase peptide synthesis procedures[13] by using the corresponding amino acid (4 equiv.), HBTU (4 equiv.), and DIPEA (8 equiv.) in DMF for the couplings and piperidine (20%) in DMF for Fmoc-deprotection. The deprotection of the thiol groups (PG = acetamido methyl) and the cyclization were performed by adding $Tl(OCOCF_3)_3$ (4 equiv.). Global deprotection and cleavage from the resin were performed by using a cleavage cocktail of trifluoroacetic acid, water and triisopropylsilane (95:2.5:2.5). The crude peptides were precipitated with ice-cold diethyl ether, and the solid residue was redissolved in acetonitrile/water (9:1) and purified in analogy to **12** by reversed-phase HPLC. ^{19}F (188.28 MHz, [D$_6$]DMSO): δ = –187.1 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 298 Hz] ppm. ^{29}Si{^{1}H } (59.63 MHz, [D$_6$]DMSO): δ = 14.2 [d, $^1J(^{29}Si\text{-}^{19}F)$ = 298 Hz] ppm. LR-LC-ESI-MS: calcd. for $[C_{67}H_{98}N_{12}O_{18}FS_2Si]^+$ 1469.6; found 1469.8.

Thr-Cys-Thr-Lys-*D*-Trp-Tyr-Cys-*D*-SiFA-Phe-(PEG)$_5$-Asp (14): **^{19}F** (188.28 MHz, [D$_6$]DMSO): δ –186.8 [s, $^1J(^{19}F\text{-}^{29}Si)$ = 298 Hz]. ^{29}Si{^{1}H} (59.63 MHz, [D$_6$]DMSO): δ 14.1 [d, $^1J(^{29}Si\text{-}^{19}F)$ = 298 Hz]. LR-LC-ESI-MS: calcd. for $[C_{67}H_{98}N_{12}O_{18}FS_2Si]^+$ 1659.8; found 1660.0.

Radiolabelling: Aqueous ^{18}F-fluoride ion (4000–7500 MBq) that had been produced by the $^{18}O(p,n)^{18}F$ nuclear reaction on an enriched [^{18}O]water (95%) target was loaded onto a Chromabond PS-HCO_3 cartridge (Macherey–Nagel, Düren, Germany) and eluted with a mixture of acetonitrile (800 μL), water (200 μL), potassium oxalate solution (1 M, 10 μL) and Kryptofix 2.2.2.® (12.5 mg) (method 1), or acetonitrile (800 μL), water (200 μL), potassium carbonate solution (1 M, 10 μL) and Kryptofix 2.2.2.® (12.5 mg), (method 2) or acetonitrile (800 μL), 75 mM tetrabutyl ammonium hydrogen carbonate solution (300 μL), (method 3), respectively. The solvents were removed under reduced pressure (650 mbar) by co-evaporation by using a stream of helium at 87 °C for 4 min. The drying step was repeated twice with CH_3CN (800 μL, 3 min), and full vacuum (ca. 10 mbar) was applied in the final drying step (4 min). The dried ^{18}F complex K (Kryptofix 2.2.2[^{18}F]) was dissolved in dry acetonitrile or DMSO (500 μL), respectively, and used for labelling.

Radiosynthesis of [^{18}F]-6, 12, 13 and 14: The SiFA-phenylalanine-containing peptides **12**, **13** and **14** (10–25 nmol, 10–25 μL of a 1 mmol/L stock solution in dry DMSO or acetonitrile) were added to the solution containing the ^{18}F complex (3–5 GBq) and reacted at ambient temperature for 5–15 min without stirring. Subsequently, the reaction mixture was added to water (800 μL) and loaded on a Waters SepPak C-18 light cartridge. The latter had been preconditioned by subsequent rinsing with ethanol (5 mL) and water (10 mL). The trapped [^{18}F]SiFA-phenylalanine or [^{18}F] SiFA-peptides were washed with water for injection (5 mL), eluted from the cartridge with ethanol (1000 μL) and diluted with isotonic saline (10 mL). The solution was filtered sterile for further use. Reverse-phase HPLC revealed radiochemical purities ranging from 92 (**13**) to 99% (**6**). The syntheses yielded 0.31 (**6**) to 1.2 GBq (**14**) of [^{18}F]-**6**, -**12**, -**13** and -**14** starting from 3–5 GBq of the [^{18}F]F-/Kryptofix 2.2.2.®/K^+ complex of the used solution. The products were obtained in maximum specific activities between 31 (**6**) and 48 GBq/μmol (**14**).

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