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Synthesis and hydrolytic stability of novel 3-[^{18}F]fluoroethoxybis (1-methylethyl)silyl]propanamine-based prosthetic groups

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ABSTRACT

Two new silicon-based prosthetic groups, derived from 3-[ethoxybis(1-methylethyl)silyl]propanamine, have been prepared in good yields. These silicon groups bearing an acid or an azide group were coupled to a model tripeptide (Leu-Gly-Gly) either through a classical amide bond formation or through "click chemistry" via the Huisgen cycloaddition. The radiolabelling with fluorine-18 by substitution of the ethoxy group at silicon has been carried out with success in 51–54% decay corrected radiochemical yields. Radiolabelled peptides were easily prepared by direct ^{18}F-fluorination of the silicon-bearing tripeptide or by coupling the peptide with a radiolabelled silicon-based prosthetic group. Their stabilities in physiological medium were studied and proved poor.

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1. Introduction

The use of bioactive radiolabelled biomolecules for diagnostic imaging has emerged for several decades as a useful tool in nuclear medicine [1]. In particular, ^{18}F-labelled proteins or peptides are useful for research and clinical investigation for positron emission tomography (PET) [2]. As the incorporation of fluorine-18 into organic compounds is usually carried out by nucleophilic substitution at carbon atom, under rather harsh conditions like high temperature and basic conditions [3], the labelling of complex biomolecules is not possible due to their limited stability in this process. Thus, labelling is usually performed on a so-called prosthetic group followed by ligation of this group to a reactive function of the macromolecule. Several fluorine-18 labelled reagents have already been described in the literature [4]. A variety of ^{18}F-labelled synthons have been developed and successfully used for ^{18}F-labelling of peptides and proteins with different coupling strategies such as amide bond formation [5], thiol alkylation [6], oxime or hydrazone formation [7], Staudinger ligation [8] and more recently Huisgen triazole formation using a "click-chemistry" approach [9]. This last coupling method is highly regio- and chemoselective, gives excellent yields and is carried out under mild conditions and last but not least can be performed in very short time.

The high affinity of silicon for fluorine allows facile introduction of ^{18}F under mild conditions through nucleophilic substitution at silicon atom. The introduction of ^{18}F into biomolecules using silicon chemistry was performed only recently by two methods. Indirect methods of ^{18}F-fluorination made use of an aromatic silicon prosthetic group labelled by an isotopic ^{19}F–^{18}F exchange or by ^{18}F-substitution of an hydroxyl function [10]. Other recent articles deal with a direct method, i.e. a suitable silicon group was coupled to the biomolecule then fluorine-18 was introduced by an isotopic ^{19}F–^{18}F exchange or by substitution of an alkoxy, hydroxy or hydride group at the silicon atom [11]. The silicon prosthetic group is usually coupled to the biomolecule by oxime formation [10a,11a], thiol reaction [10b] or amidation [11b–e].

In connection with our peptide labelling program, we have explored the use of readily available ω-silylated amine derivatives to prepare a prosthetic group. Two strategies for final labelling of model peptides were devised. The first strategy consisted of a direct ^{18}F-fluorination of our model peptide derivatized with our silicon building block 4-(3-[ethoxybis(1-methylethyl)silyl]propylamino)-4-oxo-butanoic acid **3** by means of amide coupling. The second one involved a click Huisgen coupling reaction between the previously fluorinated prosthetic group bearing an azide functionality and the suitable alkynylated tripeptide.

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2. Results and discussion

2.1. Synthesis

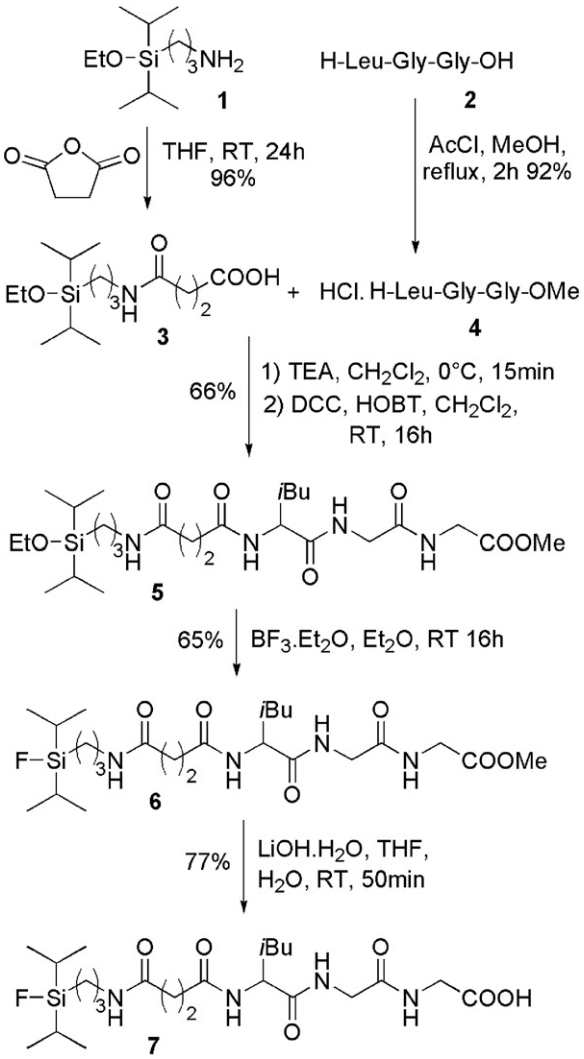
A silicon prosthetic group bearing a carboxylic moiety suitable for coupling with the *N*-terminus of a modified tripeptide Leu-Gly-Gly was first designed. A number of readily available 3-aminopropylalkoxysilanes were tested for their ability to be fluorinated. Coupling experiments of 3-phenylpropanoic acid with 3-[triethoxysilyl]propanamine or 3-[diethoxy(1-methylethyl)silyl]1-propanamine led to the expected amide but their fluorination gave very unstable and untractable mixtures [12]. We then turned to 3-[ethoxybis(1-methylethyl)silyl]propanamine **1** which gave more stable and easily purified products. Thus, **1** was reacted with succinic anhydride in THF to provide the carboxylic acid **3**. The tripeptide Leu-Gly-Gly **2** was converted to its C-terminal methyl ester **4** isolated as the hydrochloride (Scheme 1).

The carboxylic acid **3** was activated by DCC-HOBt and was reacted with the free amine obtained from compound **4** by treatment with triethylamine in dichloromethane. The amide **5** was obtained in 66% yield after purification. Fluorine introduction was first attempted on ester **5**. The usual reaction with tetrabutylammonium fluoride in THF failed to give acceptable yields of fluorination. As seen from silicon NMR, a hydroxylated silicon species was formed instead of the expected silicon–fluoride. Finally boron trifluoride–ethyl ether complex gave good results and the expected fluorinated compound **6** was isolated in 65% yield. Saponification of the ester function of **6** was then achieved using LiOH in THF/H_2O giving the cold reference **7** in 77% yield. Alternatively, saponification of **5** was carried out under the same conditions giving the precursor of radiolabelling **8** (Scheme 2).

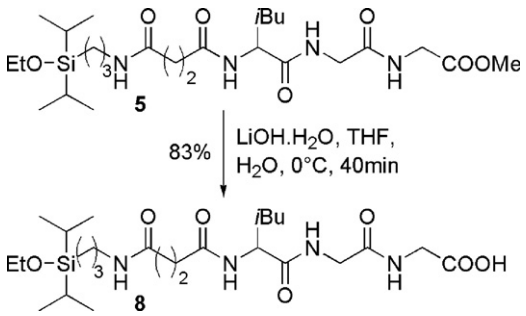
In the second strategy we explored the coupling of the prosthetic group with the tripeptide by a click reaction. To do so, the prosthetic group was modified with an azide functionality and the tripeptide with an alkyne moiety.

Compound **1** was reacted with the activated azide **9**, prepared from 3-bromopropionic acid using sodium azide [13]; giving the labelling precursor **10** in 60% yield. The cold reference **11** was easily obtained by treatment of **10** with $BF_3{\cdot}Et_2O$ complex in diethylether (Scheme 3).

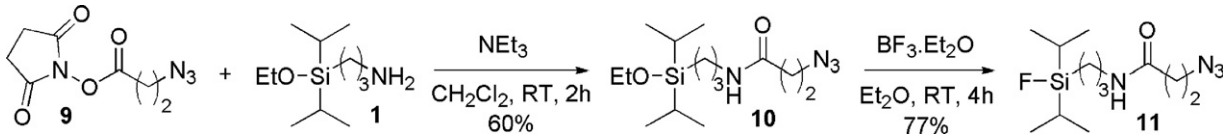
The alkynylated tripeptide **13** was prepared by coupling propiolic acid with tripeptide **12** in the presence of the DCC-HOBt activating system (Scheme 4). Copper(I)-catalyzed triazole formation proceeded uneventfully providing the cold reference **14** in 40% yield as the only isomer.



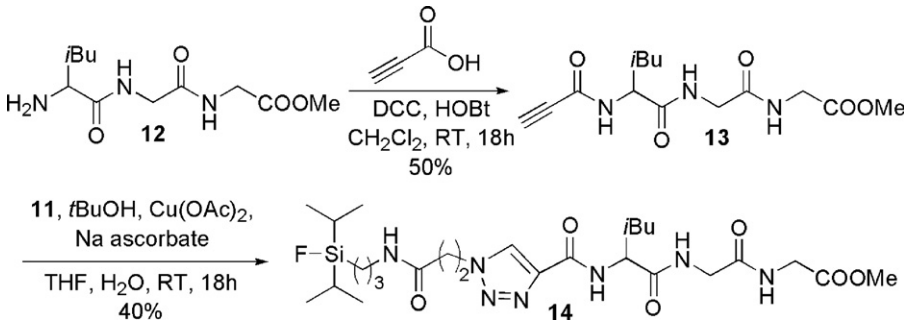
Scheme 1. Synthesis of the fluorinated peptide **7**.



Scheme 2. Synthesis of the radiolabelled peptide precursor **8**.



Scheme 3. Preparation of the labelling precursor **10** and the prosthetic group **11**.



Scheme 4. Synthesis of the cold peptide reference **14** by a Huisgen click reaction.

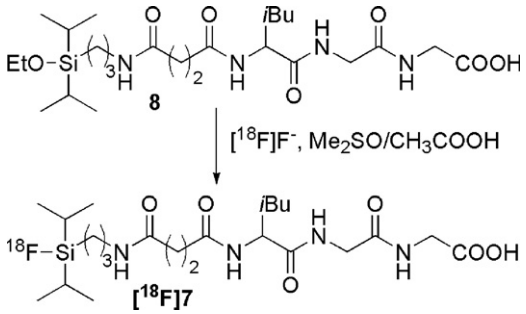
2.2. Radiolabelling

Rapid and efficient recovery of cyclotron produced [^{18}F]F$^-$ from [^{18}O]water has been achieved thanks to a polymeric solid support loaded with a long alkyl chain quaternary ammonium. A low water content organic solution compatible with fast nucleophilic labelling of most precursors PET radiopharmaceuticals is eluted from this cartridge [14]. Direct radiolabelling of the precursor **8** was performed in Me_2SO with glacial acetic acid for 20 min at 90 °C (Scheme 5). [^{18}**F**]**7** was purified on an Oasis HLB extraction cartridge eluted with water to eliminate unreacted [^{18}F]F$^-$, DMSO, acetic acid and carbonate salts. The labelled compound was obtained with good radiochemical purity (>95%). The decay corrected radiochemical yield was about 51%.

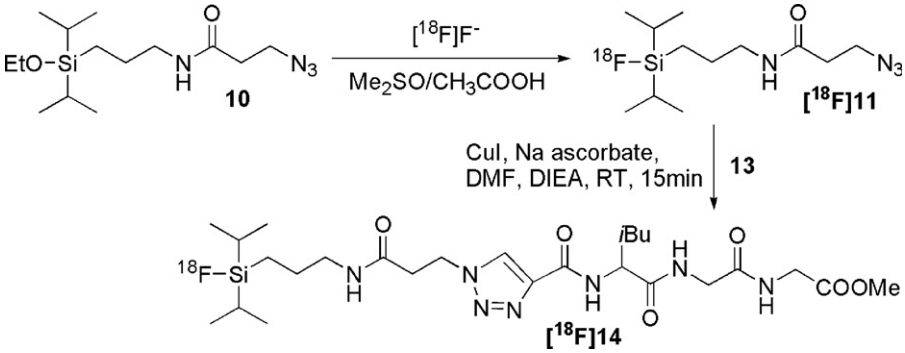
Labelling of the precursor **10** was performed under the same conditions (Me_2SO with glacial acetic acid) (Scheme 6). [^{18}**F**]**11** was purified on a Oasis HLB extraction cartridge and isolated with a radiochemical purity > 95% (DMF or acetonitrile solution). Identification of the labelled compounds was achieved by HPLC comparison with reference compounds (Fig. 1). The decay corrected radiochemical yield was about 54%.

The azide [^{18}**F**]**11** obtained in DMF (1 mL) was engaged in the coupling reaction with the model tripeptide **13** (Scheme 6). The click coupling reaction was catalyzed by copper iodide in the presence of sodium ascorbate and diisopropylethylamine. The reaction was carried out at room temperature under gentle agitation. After 15 min, azide [^{18}**F**]**11** was totally consumed and a new radiochemical compound was detected (radio-TLC, radio-HPLC). This compound was identified as [^{18}**F**]**14**, as it retention time matches the cold reference **14** (Fig. 1). After purification on an Oasis HLB extraction cartridge, [^{18}**F**]**14** was obtained with a radiochemical purity superior to 97% and a corrected radiochemical yield of 75%.

As precursor and potential related impurities were not eliminated by the cartridge purification, semi-preparative HPLC



Scheme 5. Synthesis of radiolabelled peptide [^{18}**F**]**7** by direct radiolabelling of precursor **8**.



Scheme 6. Radiolabelling of **10** and coupling with peptide **13**.

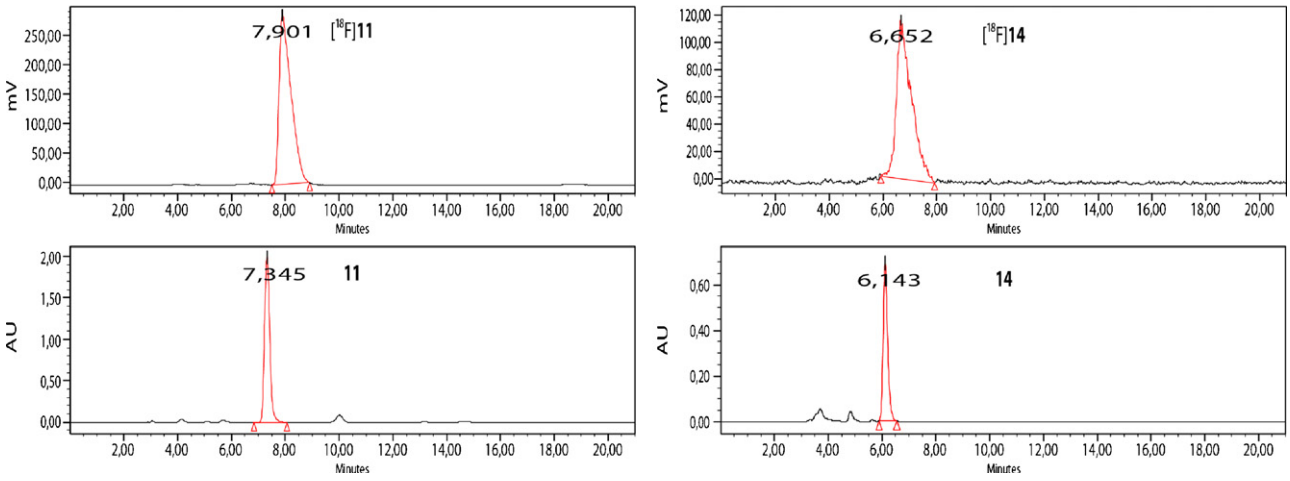


Fig. 1. Radio-HPLC chromatograms of [^{18}**F**]**11** and [^{18}**F**]**14** after Oasis HLB cartridge purification and UV chromatograms of corresponding reference compounds.

purifications were applied to perform the hydrolytic stability test. This purification is imperative as that stability studies of fluorine-18 labelled compounds present in very low concentrations can be influence by the presence of non-radioactive compounds.

2.3. Stability of the radiolabelled compounds

Despite the good thermodynamic stability of the Si–F bond, fluorosilanes are relatively unstable in water [15]. For in vivo imaging applications, it is crucial to keep the radionucleide fixed on the organic backbone at least until the end of the image acquisition. If not, the radioactivity is trapped by the bones instead of the targeted biological process. Ametamey and Schirrmacher groups [10a,11] show that this shortcoming can be overcome by the use of bulky substituents on the fluorosilane moiety. More particularly, di-*tert*-butylphenylfluorosilanes have demonstrated sufficient stability in physiological conditions. In this work, we investigated the stability of the less sterically hindered diisopropylalkylfluorosilane. As demonstrated by Mu et al. [11d] this moiety is labelled in milder conditions than di-*tert*-butylphenylfluorosilanes. Moreover diisopropylalkylfluorosilane groups may induce less modification to the pharmacokinetics and biodistribution of the labelled biological vector than di-*tert*-butylphenylfluorosilanes. In 2009 Ametaney group [11b] have reported hydrolytic half-lives of 12 h for similar diisopropylalkylfluorosilanes. In view of these results we were expecting a sufficient stability of our ^{18}F-radiolabelled molecules.

We studied the hydrolytic stability of purified [^{18}**F**]**7**, [^{18}**F**]**11** and [^{18}**F**]**14** by radio-TLC. Unfortunately, in water (pH 7.5) and in acidic medium, all showed a reduced stability ($t_{1/2} < 10$ min). Stability of [^{18}**F**]**11** has also been studied under several other conditions (Table 1).

These results clearly demonstrate that diisopropylalkylfluorosilane are rather unstable in presence of water. The presence of **11** as a carrier increases by a factor 3 the hydrolytic half-live. In organic solvent as DMF, compounds [^{18}**F**]**7**, [^{18}**F**]**11** and [^{18}**F**]**14** are chemically stable. Undoubtedly, bulkier substituents are required on fluorosilane for *in vivo* applications. The longer stability of diisopropylalkylfluorosilanes obtained by Ametaney has been obtained on concentrated non-radioactive fluorosilane solution in acetonitrile/H_2O mixture. In 2009, Bohn et al. reported hydrolytic half-lives for other diisopropylalkylfluorosilanes of about 15 min [15]. These hydrolytic half-lives values are closer of those reported in this work. Although determined on the fluorine-19 compound, Bohn's data have been acquired in more physiological conditions, as diluted solutions (10^{-6} M) were used and no organic solvent was added. Thus, we advocate for the use of conditions as close as possible to the *in vivo* environment to determine hydrolytic half-lives.

Table 1
Hydrolytic half-lives $t_{1/2}$ of [^{18}**F**]**11** at room temperature.

Conditions	$t_{1/2}$ determined by radio-TLC
Phosphate buffer pH 7.5	<5 min
Ascorbic acid pH 2.5	10 min
Phosphate buffer pH 7.5 + 5 mg of **11**	13 min
Acetonitrile/H_2O 2/1	34 min
MeOH/H_2O 85/15	40 min
DMF	No hydrolysis within 5 h

3. Conclusion

We developed two novel silicon based prosthetic groups for peptide or protein radiolabelling. Thanks to the presence of two isopropyl groups on silicon, good chemical stability of all intermediates was observed and mild fluorination conditions at silicon were found. This allows a facile direct fluorination of peptides. We also developed an indirect fluorination method which gave good radiochemical yields allowing the coupling of the radioactive prosthetic group with a peptide by a Huisgen reaction. However, in both cases, the unstability of the Si–F bond under physiological conditions precludes their use as radiotracer in vivo. As it has been shown recently, the hydrolytic stability of these silicon prosthetic groups is poor and depends on the nature of the substituents on the silicon. Different prosthetic groups have already been tested and it is known that the presence of bulky substituents is a primary requirement to sustain stability of the silicon labelling building blocks [11,15]. Our results show that the presence of the two isopropyl groups on our new prosthetic groups do not enough stabilize the silicon fluoride bond, they are not stable enough to be used in nuclear medicine. We are currently trying to overcome this difficulty by examining bulkier substituents like benzyl, *tert*-butyl or isobutyl groups.

4. Experimental

4.1. General

Solvents and liquid reagents were purified and dried according to recommended procedures. TLC analyses were performed using standard procedures on Kieselgel 60 F_{254} plates or RP-18 F_{254} plates (Merck). Compounds were visualized using UV light (254 nm) and a solution of cerium sulfate tetrahydrate and phosphomolybdic acid in 10% aqueous sulfuric acid. Column chromatographies were performed on silica gel SI 60 (63–200 μm) (Merck). HPLC analyses were run on a Waters system (616 pump, a manual Rheodyne injector, 996 PDA detector and NaI(Tl) scintillation detector from Eberline) controlled by the Empower software. Analyses were performed on an XBridge C18 column from Waters (250 mm × 4.6 mm, 3.5 μM) with MeOH and H_2O containing 0.1% TFA mixture (proportions given in parentheses) at 1 mL/min. Preparative HPLC were performed on a Xbridge C18 column from Waters (250 mm × 10 mm, 5 μM) at 4 mL/min. Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^{1}H and ^{13}C NMR, ^{19}F spectra were recorded on a Bruker spectrometer DPX250 (250 MHz, 62.9 MHz and 235 MHz, respectively) or DRX400 (400 MHz and 100.6 MHz, respectively). For complete assignment of ^{1}H and ^{13}C signals, two-dimensional ^{1}H,^{1}H COSY and ^{1}H,^{13}C correlation spectra were recorded. Chemical shifts (δ) are given in ppm relative to the solvent residual peak. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad signal and app = apparent signal. The given *J* values refer to apparent multiplicities and do not represent the true coupling constants. Mass spectra were obtained with a VG-Platform Micromass-Waters (ESI$^+$/quad). HRMS spectra were recorded on a Bruker MicroTOFQ apparatus. The ratio of the solvent systems is v/v everywhere.

4.2. Chemistry

4.2.1. Preparation of 4-(3-[ethoxybis(1-methylethyl)silyl]propylamino)-4-oxo-butanoic acid (3)

To a solution of succinic anhydride (400 mg, 1 equiv., 4 mmol) in 40 mL of dry THF, under argon atmosphere, was added dropwise at room temperature a solution of 3-aminopropyldiisopropylethoxysilane **1** (870 mg, 1 equiv., 4 mmol) in 10 mL of THF. The reaction mixture was stirred at room temperature for 24 h, and then evaporated to dryness. The residue was dissolved in CH_2Cl_2, washed with a 5% citric acid aqueous solution and with brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to obtain **3** (1.22 g, 96%). The crude product was used without further purification.

White solid: mp 54–56 °C; IR (film) ν 3303, 2941, 2892, 1715, 1648, 1557 cm^{-1}; ^{1}H NMR (250 MHz, CD_3OD): δ 0.63–0.70 (2H, m), 1.01–1.07 (14H, m), 1.18 (3H, t, *J* = 7.0 Hz), 1.52–1.65 (2H, m), 2.42–2.62 (4H, m), 3.15 (2H, t, *J* = 7.0 Hz), 3.75 (2H, q, *J* = 7.0 Hz), 4.90 (2H, brs); ^{13}C NMR (62.9 MHz, CD_3OD): δ 7.3, 12.3 (2C), 16.6 (4C), 17.6, 23.2, 29.0, 30.2, 42.4, 58.6, 173.0, 174.8; MS (*m*/*z*, ESI) 318 [M+H]$^+$.

4.2.2. Preparation of N-(N-L-leucylglycyl)glycinemethyl ester, monohydrochloride (4)

To a solution of 30 mL of dry MeOH in a dry round-bottomed flask equipped with a condenser flushed with argon and cooled in an ice bath was added dropwise acetyl chloride (0.7 mL, 2.4 equiv., 9.8 mmol). The solution was stirred for 5 min, then the tripeptide Leu-Gly-Gly **2** (1.0 g, 1 equiv., 4.1 mmol) in 30 mL of MeOH was added. The reaction was slowly heated to reflux for 2 h then the solvent was evaporated. The residue was washed with Et_2O and dried to obtain **4** (1.1 g, 92%). The crude product was used in the next step without further purification.

White solid: mp 93–95 °C; $[\alpha]_D^{20} + 23°$ (*c* 1; MeOH); IR (film) ν 3217, 2959, 1748, 1670, 1542, 1218 cm^{-1}; ^{1}H NMR (250 MHz, CD_3OD): δ 1.00–1.02 (6H, m), 1.65–1.80 (3H, m), 3.73 (3H, s), 3.83–4.10 (5H, m); ^{13}C NMR (62.9 MHz, CD_3OD): δ 20.7, 21.6, 24.0, 40.1, 40.4, 41.6, 51.2, 51.7, 169.8, 170.1, 170.2; MS (*m*/*z*, ESI) 260 [M−HCl+H]$^+$.

4.2.3. Preparation of N-[N-(N-(4-(3-[ethoxybis(1-methylethyl)silyl)]propylamino)-1,4-dioxo-butyl)L-leucyl)glycyl]glycinemethylester (5)

To a solution of **4** (400 mg, 1 equiv., 1.36 mmol) in 20 mL of dry dichloromethane, under argon atmosphere, was added dropwise Et_3N (3.8 mL, 2 equiv., 2.71 mmol) at 0 °C. The mixture was stirred for 15 min and **3** (430 mg, 1 equiv., 1.36 mmol) in 10 mL of CH_2Cl_2 was added. DCC (336 mg, 1.2 equiv., 1.63 mmol) and HOBt (200 mg, 1.2 equiv., 1.63 mmol) were then introduced. The reaction mixture was stirred for 16 h at room temperature, the solvent was evaporated and the residue dissolved in ethylacetate. The organic layer was washed with $NaHCO_3$ aqueous solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, Hex/EtOAc 1/7, then CH_2Cl_2/MeOH 15/1) to obtain **5** (500 mg, 66%).

Colorless oil: $[\alpha]_D^{20} + 6.5°$ (*c* 1; $CHCl_3$); IR (film) ν 3290, 3085, 2956, 1748, 1652, 1538, 1210, 1110, 733 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.56–0.63 (2H, m), 0.91 (3H, d, *J* = 6.1 Hz), 0.95 (3H, d, *J* = 6.0 Hz), 0.98–1.03 (14H, m), 1.19 (3H, t, *J* = 7.0 Hz), 1.50–1.80 (5H, m), 2.40–2.70 (3H, m), 2.70–2.78 (1H, m), 2.99–3.07 (1H, m), 3.22–3.33 (1H, m), 3.70 (3H, s), 3.71 (2H, q, *J* = 7.0 Hz), 3.78 (1H, dd, *J* = 17.5 Hz, *J* = 5.5 Hz), 3.87 (1H, dd, *J* = 17.5 Hz, *J* = 5.5 Hz), 4.03–4.17 (2H, m), 4.25–4.35 (1H, m), 6.40 (1H, brt, *J* = 5.5 Hz), 6.78 (1H, brd), 7.35 (1H, brt, *J* = 5.5 Hz), 7.65 (1H, brt, *J* = 6.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.8, 12.4 (2C), 17.5 (2C), 17.6 (2C), 18.7, 21.5, 23.0, 23.3, 24.9, 31.4, 31.6, 40.1, 41.0, 42.8, 43.0, 52.1, 53.2, 58.9, 169.8, 170.5, 172.5, 172.7, 174.0; MS (*m*/*z*, ESI) 581 [M+Na]$^+$.

*4.2.4. Preparation of N-[N-(N-(4-(3-[fluorobis(1-methylethyl)silyl]propylamino)-1,4-dioxo-butyl)L-leucyl)glycyl]glycinemethylester (**6**)*

To a solution of **5** (260 mg, 1 equiv., 0.466 mmol) in 10 mL of dry Et_2O, under argon atmosphere, was added $BF_3{\cdot}Et_2O$ (0.6 mL, 1 equiv., 0.466 mmol) and the reaction mixture was stirred at room temperature during 16 h. $NaHCO_3$ aqueous solution was added and the solution was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography (silica gel, CH_2Cl_2/MeOH 15/1) to obtain **6** (161 mg, 65%).

Colorless oil: $[\alpha]_D^{20} + 1.7°$ (*c* 1; $CHCl_3$); IR (film) ν 3295, 3083, 2954, 1748, 1652, 1548, 1210, 702 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 0.61–0.71 (2H, m), 0.91 (3H, d, *J* = 6.0 Hz), 0.94 (3H, d, *J* = 6.0 Hz), 1.00–1.05 (14H, m), 1.52–1.73 (5H, m), 2.44–2.73 (4H, m), 3.00–3.14 (1H, m), 3.19–3.33 (1H, m), 3.70 (3H, s), 3.82 (1H, dd, *J* = 18.0 Hz, 5.7 Hz), 3.89 (1H, dd, *J* = 18.0 Hz, *J* = 5.5 Hz), 4.06 (1H, dd, *J* = 12.0 Hz, *J* = 5.5 Hz), 4.11 (1H, dd, *J* = 12.0 Hz, *J* = 5.5 Hz), 4.31–4.40 (1H, m), 6.46 (1H, brt, *J* = 5.5 Hz), 6.97 (1H, brd, *J* = 7.0 Hz), 7.42 (1H, brt, *J* = 5.5 Hz), 7.68 (1H, brt, *J* = 5.5 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.7 (d, *J* = 13.7 Hz), 12.2 (d, *J* = 13.0 Hz, 2C), 16.8 (4C), 21.7, 22.8, 22.9, 24.9, 31.5, 31.6, 40.3, 41.0, 42.5, 43.0, 52.1, 53.0, 169.8, 170.5, 172.6, 172.8, 173.8; ^{19}F NMR (235 MHz, $CDCl_3$) δ −181.3; HRMS (*m*/*z*, ESI) calcd. for $C_{24}H_{45}FN_4O_6SiNa$ $[M+Na]^+$: 555.2985. Found: 555.3001.

*4.2.5. Preparation of N-[N-(N-(4-(3-[fluorobis(1-methylethyl)silyl]propylamino)-1,4-dioxo-butyl)L-leucyl)glycyl]glycine (**7**)*

To a solution of **6** (80 mg, 1 equiv., 0.15 mmol) in 10 mL of dry THF, was added slowly at 0 °C $LiOH{\cdot}H_2O$ (6 mg, 1 equiv., 0.15 mmol) in 5 mL of H_2O. Reaction mixture was stirred for 50 min at room temperature, then Amberlite IR-120 was added until pH = 7 and stirred for 5 min. The resin was filtered off and solvents were evaporated. The crude product was purified by chromatography (silica gel, CH_2Cl_2/MeOH 9/1) to obtain **7** (60 mg, 77%).

White solid: mp 93–95 °C; IR (film) ν 3337, 2943, 2868, 1638, 1464 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.70–0.77 (2H, m), 0.94 (3H, d, *J* = 6.0 Hz), 0.99 (3H, d, *J* = 6.0 Hz), 1.03–1.10 (14H, m), 1.55–1.77 (5H, m), 2.50–2.60 (4H, m), 3.13–3.18 (2H, m), 3.82 (2H, brs), 3.87 (1H, d, *J* = 17.0 Hz), 3.93 (1H, d, *J* = 17.0 Hz), 4.32 (1H, dd, *J* = 9.5 Hz, *J* = 5.5 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 7.7 (d, *J* = 13.5 Hz), 12.5 (d, *J* = 13.0 Hz, 2C), 16.2 (4C), 20.8, 22.5, 22.9, 24.9, 30.9, 31.0, 40.2, 42.5, 42.6, 42.8, 52.9, 170.5, 173.5, 173.6, 174.6, 174.7; ^{19}F NMR (235 MHz, MeOH-d_4) δ −182.9; HRMS (*m*/*z*, ESI) calcd. for $C_{23}H_{44}FN_4O_6Si$ $[M+H]^+$: 519.3009. Found: 519.3002.

*4.2.6. Preparation of N-[N-(N-(4-(3-[ethoxybis(1-methylethyl)silyl]propylamino)-1,4-dioxo-butyl)L-leucyl)glycyl]glycine (**8**)*

To a solution of **5** (220 mg, 1 equiv., 0.394 mmol) in 8 mL of THF was added slowly at 0 °C $LiOH{\cdot}H_2O$ (16 mg, 1 equiv., 0.394 mmol) dissolved in 8 mL of H_2O. The reaction mixture was stirred for 40 min at 0 °C, then Amberlite IR-120 was added until pH = 7 and stirred for 5 min. The resin was filtered off and solvents were evaporated. The crude product was purified by chromatography (silica gel, CH_2Cl_2/MeOH 9/1) to obtain **8** (178 mg, 83%).

White solid: mp 84–86 °C; IR (film) ν 3316, 2940, 2867, 1638, 1465, 1111 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 0.65–0.70 (2H, m), 0.94 (3H, d, *J* = 6.0 Hz), 0.99 (3H, d, *J* = 6.0 Hz), 1.01–1.10 (14H, m), 1.20 (3H, t, *J* = 7.0 Hz), 1.50–1.80 (5H, m), 2.48–2.59 (4H, m), 3.15 (2H, t, *J* = 7.0 Hz), 3.76 (2H, q, *J* = 7.0 Hz), 3.80 (2H, bs), 3.86 (1H, d, *J* = 17.0 Hz), 3.92 (1H, d, *J* = 17.0 Hz), 4.31 (1H, dd, *J* = 9.0 Hz, 5.2 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 7.8, 12.7 (2C), 17.0 (4C), 18.0, 20.8, 22.5, 23.6, 24.9, 30.9, 31.0, 40.2, 42.6, 42.9 (2C), 52.9, 59.1, 170.4, 173.5, 174.6 (2C), 174.7; HRMS (*m*/*z*, ESI) calcd. for $C_{25}H_{48}N_4O_7SiNa$ $[M+Na]^+$: 567.3184. Found: 567.3149.

*4.2.7. Preparation of 3-Azido-N-[3-(ethoxybis(1-methylethyl)silyl)propyl]propanamide (**10**)*

To a solution of activated 3-azidopropanoate-*N*-hydroxysuccinimide ester **9** (400 mg, 1 equiv., 1.88 mmol) in 50 mL of dry CH_2Cl_2, under argon atmosphere, was added compound **1** (0.51 mL, 1.1 equiv., 2.07 mmol) and TEA (0.52 mL, 2 equiv., 3.7 mmol). The reaction mixture was stirred at room temperature for 2 h then 5% $NaHCO_3$ aqueous solution was added. The mixture was extracted with CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, CH_2Cl_2/EtOAc 6/1) to obtain **10** (350 mg, 60%).

Colorless oil: IR (film) ν 3298, 2941, 2867, 2101, 1646, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 0.57–0.64 (2H, m), 0.93–1.02 (14H, m), 1.17 (3H, t, *J* = 7.0 Hz), 1.52–1.65 (2H, m), 2.39 (2H, t, *J* = 6.5 Hz), 3.23 (2H, app q, *J* = 7.0 Hz), 3.59 (2H, t, *J* = 6.5 Hz), 3.70 (2H, q, *J* = 7.0 Hz), 6.10 (1H, brs); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.7, 12.4 (2C), 17.5 (2C), 17.6 (2C), 18.7, 23.4, 36.0, 42.9, 47.3, 58.9, 169.7; HRMS (*m*/*z*, ESI) calcd. for $C_{14}H_{30}N_4NaO_2$ $[M+Na]^+$: 337.2030. Found: 337.2024.

*4.2.8. Preparation of 3-Azido-N-[3-(fluorobis(1-methylethyl)silyl)propyl]propanamide (**11**)*

To a solution of **10** (130 mg, 1 equiv., 0.414 mmol) in 8 mL of dry Et_2O, under argon atmosphere, was added $BF_3{\cdot}Et_2O$ (0.058 mL, 1.1 equiv., 0.454 mmol) at room temperature. The solution was stirred for 4 h, then the solvent was evaporated and the crude product was purified by chromatography (silica gel, CH_2Cl_2/EtOAc 6/1) to obtain **11** (90 mg, 77%).

Colorless oil: IR (film) ν 3298, 2945, 2869, 2102, 1646, 826 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 0.64–0.74 (2H, m), 1.00–1.08 (14H, brs), 1.56–1.69 (2H, m), 2.40 (2H, t, *J* = 6.5 Hz), 3.26 (2H, app q, *J* = 7.0 Hz), 3.61 (2H, t, *J* = 6.5 Hz), 5.84 (1H, brs); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.7 (d, *J* = 13.5 Hz), 12.2 (d, *J* = 13.0 Hz, 2C), 16.7 (4C), 23.0, 35.9, 42.5, 47.5, 169.8; ^{19}F NMR (235 MHz, $CDCl_3$) δ −181.3; HRMS (*m*/*z*, ESI) calcd. for $C_{12}H_{25}FN_4NaO$ $[M+Na]^+$: 311.1674. Found: 311.1685.

*4.2.9. Preparation of N-[N-(N-(1-oxo-prop-2-yne)L-leucyl)glycyl]glycinemethylester (**13**)*

To a stirred solution of **4** (800 mg, 1 equiv., 2.7 mmol) in 50 mL of CH_3CN, under argon, was added K_2CO_3 (3.73 g, 10 equiv., 27 mmol). The mixture was stirred at room temperature for 2 h, then filtered and concentrated to give the free amine (500 mg, 1.9 mmol, 70%). To a solution of free amine (500 mg, 1 equiv., 1.9 mmol) in CH_2Cl_2 (10 mL) was added propiolic acid (1.3 mL, 1.1 equiv., 2.1 mmol) in 5 mL of CH_2Cl_2, then HOBt (313 mg, 1.2 equiv., 2.3 mmol) and DCC (480 mg, 1.2 equiv., 2.3 mmol) were added. The reaction mixture was stirred for 18 h then hydrolyzed with brine and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography (silica gel, CH_2Cl_2/MeOH 20/1) to obtain **13** (295 mg, 50%).

Yellowish solid: mp 49–51 °C; $[\alpha]_D^{20} + 3.9°$ (*c* 0.5; CH_2Cl_2); IR (film) ν 3281, 2958, 2109, 1748, 1645, 1539, 1215 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 0.92 (3H, d, *J* = 6.0 Hz), 0.94 (3H, d, *J* = 6.0 Hz), 1.57–1.74 (3H, m), 2.92 (1H, s), 3.73 (3H, s), 3.90–4.14 (4H, m), 4.48–4.58 (1H, m), 7.35 (1H, brt, *J* = 5.5 Hz), 7.49 (1H, brd, *J* = 7.5 Hz), 7.68 (1H, brt, *J* = 5.5 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.8, 22.8, 24.8, 40.8, 41.1, 43.0, 52.4, 52.6, 74.8, 76.8, 152.6, 169.5, 170.4, 172.4; HRMS (*m*/*z*, ESI) calcd. for $C_{14}H_{21}N_3NaO_5$ $[M+Na]^+$: 334.1373. Found: 334.1384.

*4.2.10. Preparation of N-[N-(N-(2-(1-(3-(fluorobis(1-methylethyl)silyl)propylamino)-1H-1,2,3-triazol-4-yl)-1-oxo-ethyl)L-leucyl)glycyl]glycinemethylester (**14**)*

To a solution of **11** (51 mg, 1 equiv., 0.176 mmol) and **13** (55 mg, 1 equiv., 0.176 mmol) in 2 mL of THF was added 2 mL of *t*BuOH, $Cu(OAc)_2$ (3.5 mg, 0.1 equiv., 0.018 mmol) diluted in 1 mL of H_2O and sodium ascorbate (7 mg, 0.2 equiv., 0.035 mmol) diluted in 1 mL of H_2O. The reaction mixture was stirred for 18 h, then organic solvents were evaporated and the mixture was extracted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography (silica gel, CH_2Cl_2/MeOH 15/1) to obtain **14** (36 mg, 40%).

White solid: mp 80–82 °C; $[\alpha]_D^{20} - 7.8°$ (*c* 1; CH_2Cl_2); IR (film) ν 3307, 2955, 2869, 1749, 1652, 1558, 1215 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 0.60–0.70 (2H, m), 0.91 (3H, d, *J* = 6.0 Hz), 0.94 (3H, d, *J* = 6.0 Hz), 0.97–1.05 (14H, m), 1.51–1.79 (5H, m), 2.85 (2H, t, *J* = 6.5 Hz), 3.14–3.24 (2H, m), 3.68 (3H, s), 3.88-4.09 (4H, m), 4.57–4.72 (3H, m), 6.53 (1H, brs), 7.43 (1H, brt, *J* = 5.0 Hz), 7.68 (1H, brs), 7.79 (1H, brd, *J* = 7.5 Hz), 8.25 (1H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.7 (d, *J* = 14.0 Hz), 12.2 (d, *J* = 13.0 Hz, 2C), 16.8 (4C), 21.7, 22.9, 22.9, 24.8, 29.7, 35.9, 40.6, 42.6, 43.1, 46.6, 52.2, 52.3, 126.9, 142.1, 160.6, 168.9, 169.7, 170.3, 172.8; ^{19}F NMR (235 MHz, $CDCl_3$) δ −181.0; HRMS (*m*/*z*, ESI) calcd. for $C_{26}H_{46}FN_7NaO_6Si_1$ $[M+Na]^+$: 622.3155. Found: 622.3138.

4.3. Radiochemistry

4.3.1. Preparation of the [^{18}F]fluoride quaternary ammonium salt in Me_2SO

No-carrier-added [^{18}F]fluoride was obtained by proton bombardment of ^{18}O-enriched water via $^{18}O(p,n)^{18}F$ reaction. The activity was recovered following a previously published method allowing transferring directly [^{18}F]fluoride in dry aprotic solvent as a quaternary ammonium salt [14]. Briefly, 100 mg of N-vinyl lactame/divinylbenzene copolymer sorbent (Waters Oasis HLB), loaded with 20 mg of n-dodecyl-trimethylammonium bromide ([n-DDTMA$^+$][Br$^-$]), was conditioned in a cartridge (Isolute empty reservoir 1 mL, internal diameter 5–6 mm) with 500 μL of a solution of 1 g of potassium carbonate in 1 mL of water. The cartridge was rinsed with 3 mL of water. The water solution containing [^{18}F]F$^-$ was passed through the extraction cartridge at 1 mL/min using a motorized syringe pump. The cartridge was dried for 4 min with a nitrogen flow (10 L/min). The radioactivity was eluted from the cartridge with 2 mL of Me_2SO to obtain the solution [n-DDTMA$^+$][^{18}F]F$^-$/Me_2SO (about 85% of the trapped activity was eluted).

*4.3.2. Radiosynthesis of N-[N-(N-(4-(3-[[^{18}F]fluorobis(1-methylethyl)silyl]propylamino)-1,4-dioxo-butyl)L-leucyl)glycyl]glycine ([^{18}**F**]**7**)*

6 mg of starting precursor **8** (0.011 mmol) was dissolved in 300 μL of [n-DDTMA$^+$][^{18}F]F$^-$/Me_2SO (∼37 MBq) and 5 μL of glacial acetic acid. The reaction mixture was heated to 90 °C for 20 min and then cooled down (3 min). Labelling efficiency was checked by radio-TLC (silica gel, MeOH; Rf values: [^{18}F]fluoride: 0; [^{18}**F**]**7**: 0.75; radiochemical purity: 73%). The mixture was diluted with 20 mL of water and passed through a Water Oasis HLB 200 mg cartridge. The cartridge was washed with 5 mL of water and the activity was then recovered in 1 mL DMF. The radiochemical yield, corrected for decay and radiochemical purity was then 51%.

*4.3.3. Radiosynthesis of 3-Azido-N-[3-([^{18}F]fluorobis(1-methylethyl)silyl)propyl] propanamide ([^{18}**F**]**11**)*

To 5.4 mg of starting precursor **10** (0.017 mmol) dissolved in 100 μL Me_2SO and 5 μL of glacial acetic acid was added 200 μL of [n-DDTMA$^+$][^{18}F]F$^-$/Me_2SO (∼160 MBq). The reaction mixture was heated to 90 °C for 20 min. Labelling efficiency was checked by radio-TLC. The mixture was diluted with 20 mL of water and passed through a Waters Oasis HLB 200 mg cartridge. The cartridge was washed with 5 mL of water and the activity was then recovered in 1 mL DMF. The radiochemical yield, corrected for decay was 64%.

Analysis by radio-TLC (silica gel, DCM/MeOH 15/1; Rf values: [^{18}**F**]**11**: 0.88. HPLC analysis: t_R = 7.9 min (MeOH/H_2O 85/15 0.1% TFA). Radiochemical yield (decay corrected): 64%.

4.3.3.1. Hydrolytic stability test. To remove the precursor and potential related impurities, semi-preparative HPLC purifications were applied before the hydrolytic stability test (MeOH/H_2O 85/15 0.1% TFA). The collected peaks were diluted by 20 mL of water, fixed on a Waters Oasis HLB cartridge, washed with 5 mL of water to remove MeOH and TFA and finally eluted by 1 mL of DMF. Efficiency of the purification was checked by analytical HPLC.

Hydrolytic stability was monitored by radio-TLC in time intervals of 15 min by adding an aliquot of each labelled product (100 μL in DMF) into 900 μL of water. For [^{18}**F**]**11** it showed an almost full degradation in water after 40 min.

Stability of [^{18}**F**]**11** in DMF was followed during 5 h and no degradation was observed at room temperature.

*4.3.4. Radiosynthesis of N-[N-(N-(2-(1-(3-([^{18}**F**]fluorobis(1-methylethyl)silyl) propylamino)-1H-1,2,3-triazol-4-yl)-1-oxo-ethyl)L-leucyl)glycyl]glycinemethylester ([^{18}**F**]**14**)*

71 MBq of [^{18}**F**]**11** in 1 mL of DMF was added to 5 mg of **13** (0.016 mmol), 15 mg of CuI (0.08 mmol), and 34 mg of sodium ascorbate (0.18 mmol), 100 μL DIEA (0.56 mmol) was added to this medium. The crude reaction medium was diluted with 14 mL of water and promptly trapped on a OASIS HLB extraction cartridge. The cartridge was washed by 10 mL of water and eluted with 1.5 mL of DMF.

Analysis by radio-TLC (silica gel, MeOH, Rf values: 0.89. HPLC analysis: t_R: 6.7 min (MeOH/H_2O 85/15 0.1% TFA). Radiochemical yield from [^{18}**F**]**11** (decay corrected): 75%.

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