DOI: 10.1002/cplu.201200022

[^{18}F]Si-RiboRGD: From Design and Synthesis to the Imaging of $\alpha_v\beta_3$ Integrins in Melanoma Tumors

Eric Amigues,[a] Jürgen Schulz,[b] Magali Szlosek-Pinaud,*[a] Philippe Fernandez,[b] Sandrine Silvente-Poirot,[c] Séverine Brillouet,[c] Frédéric Courbon,[c] and Eric Fouquet*[a]

Angiogenesis is involved in a variety of pathological processes, for example rheumatoid arthritis,[1] psoriasis,[2] as well as tumor growth.[3] Thus, the field of angiogenesis research has evolved to become one of the most rapidly growing biomedical disciplines. The fundamental angiogenesis research is sparked by the translational therapeutic potential aimed at developing antiangiogenesis drugs as novel therapeutics for tumors and a number of nononcological diseases. Thus noninvasive monitoring of molecular processes in the angiogenic cascade is of major interest for basic science, as well as clinical settings where it could help in planning and controlling corresponding antiangiogenic therapies. One major class of receptors involved in the angiogenic process are the integrins which are hetero dimeric glycoproteins consisting of α and β subunits. One of the most prominent members of this receptor class is the $\alpha_v\beta_3$ integrin and great efforts are made to develop $\alpha_v\beta_3$ antagonists for several therapeutic approaches based on cyclic pentapeptides containing the tripeptide sequence arginine–glycine–aspartic acid (RGD). Indeed, this is a recognition pattern used by several extracellular matrix proteins to bind a variety of integrins including $\alpha_v\beta_3$. Among the diagnostic tools in modern medicine, positron emission tomography (PET) allows high-resolution quantitative imaging of biochemical processes in vivo by detecting the distribution of labeled biomarkers over time.[4] Therefore, a variety of different radiolabeled RGD peptides has been introduced,[5] most efforts being carried out using [^{18}F]galacto-RGD,[6] a glycosylated cyclic pentapeptide with the sequence cyclo(-Arg-Gly-Asp-DPhe-Lys-(SAA)-; SAA = sugar amino acid). It has been demonstrated in murine tumor models,[7] as well as in patients,[8] that this compound allows noninvasive determination of $\alpha_v\beta_3$ expression. Indeed, $\alpha_v\beta_3$ expression has been imaged in variety of malignant tumors including melanomas, sarcomas, and head and neck cancer using this peptide.[9,10] Other ^{18}F-labeled RGD peptides in clinical trials such as [^{18}F]AH111585 and [^{18}F]RGD-K5,[11,12] have shown that PET with radiolabeled RGD peptides can be used to detect $\alpha_v\beta_3$-expressing tumors in patients and to quantitatively evaluate the expression levels of $\alpha_v\beta_3$ integrins. However, the synthesis of these ^{18}F-labeled peptides remained highly complex and time consuming, thus making the development of a remote-controlled synthesis hazardous. Particularly the radiolabeling step in the case of [^{18}F]galacto-RGD, remains problematic as it involves a multistep reaction sequence, thus making large-scale clinical studies challenging. As a consequence, the development of the clinical use of RGD peptides clearly needs new probes that are less complex to radiolabel. Such an alternative has been recently reported, involving the replacement of ^{18}F with ^{68}Ga or ^{64}Cu, thus leading to the corresponding derivatives of the [^{18}F]galacto-RGD.[13,14] However [^{18}F]galacto-RGD remains, in most cases, superior for imaging $\alpha_v\beta_3$ expression. The other way to circumvent this short coming is to keep ^{18}F-labeling and the major advantages of the original galacto-RGD, but rethinking the initial synthesis by using a particularly efficient, one-step method for a site specific ^{18}F-labeling under mild conditions. Recently, new strategies for direct one-step ^{18}F-labeling of peptides have been reported through a C–^{18}F bond formation.[15] Besides this, few research groups have reported the interest of phosphorous-,[16] boron-,[17] ^{18}F-aluminum-chelate,[18] and ^{18}F-silicon radiochemistry by using either ^{18}F–^{19}F isotope exchange (SiFA strategy),[19] or silicon-based building blocks.[20] This last procedure is based on the high Si–F bond energy (135 Kcal mol^{-1} vs. 116 kcal mol^{-1} for C–F) and enabling of fluoride substitution at silicon,[21] for the ^{18}F-labeling of biomolecules, in a last single step. Having already successfully applied this methodology to the fluorination of sensitive molecules such as fully deprotected oligonucleotides,[22] we decided to apply it for the fluorination of our target RGD derivative.

Beside the radiosynthesis, we also thought to improve the synthesis of the precursor (R–SiH), especially by using Huisgen 1,3-dipolar cycloaddition as the coupling reaction between the different building blocks of **12**. Indeed, this reaction proceeds under mild conditions in aqueous media and requires virtually no protection of other functional groups allowing its use for the preparation of ^{18}F-fluoropeptides.[23] Herein, we describe a convergent and efficient synthesis of a ^{18}F-labeled RGD derivative using advantages of both "click chemistry" and the one-step labeling protocol applying the silicon-based building blocks strategy. Thus, our target molecule could be divided in three different building blocks: a cyclo-RGD (recognition part) for the selectivity toward $\alpha_v\beta_3$ integrin, a silicon moiety (detection part) for the selective fluorination at the last step of the synthesis, and finally, between the two first parts, a sugar

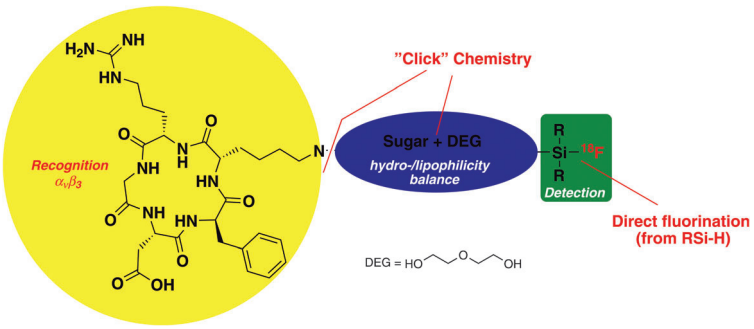
[a] *Dr. E. Amigues,[+] Dr. M. Szlosek-Pinaud,[+] Prof. E. Fouquet[+]*
ISM, UMR5255, Synthesis–Bioactive Molecules Group
Université de Bordeaux
351, Cours de la Liberation, 33405 Talence (France)
Fax: (+33) 0540006386
E-mail: m.szlosek@ism.u-bordeaux1.fr
e.fouquet@ism.u-bordeaux1.fr

[b] *Dr. J. Schulz,[+] Prof. P. Fernandez[+]*
INCIA, UMR5287, Université de Bordeaux
146, Rue Leo Saignat, 33076 Bordeaux (France)

[c] *Dr. S. Silvente-Poirot, Dr. S. Brillouet, Prof. F. Courbon*
CRCT, UMR1037, Insitut Claudius Regaud
20/24 Rue du Pont Saint-Pierre, 31052 Toulouse (France)

[+] *Core members of the TRAIL Labex.*

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cplu.201200022.



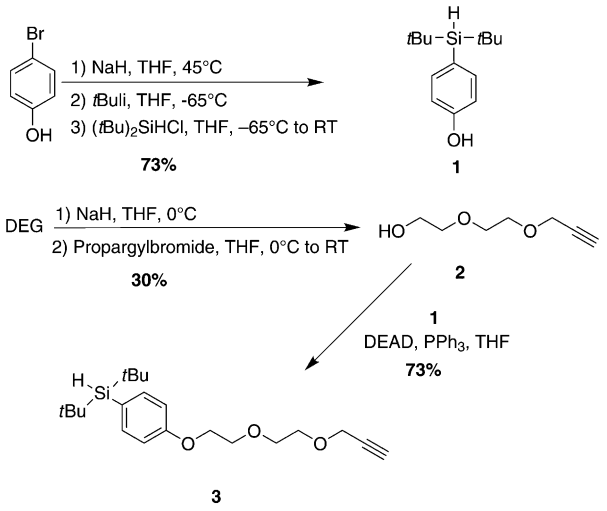
Scheme 1. General structure of the target $\alpha_v\beta_3$ PET radiotracer.

moiety to enhance the hydrophilicity of the final compound, because it has been shown that it improved several pharmacological properties of the resulting tracer.[24]

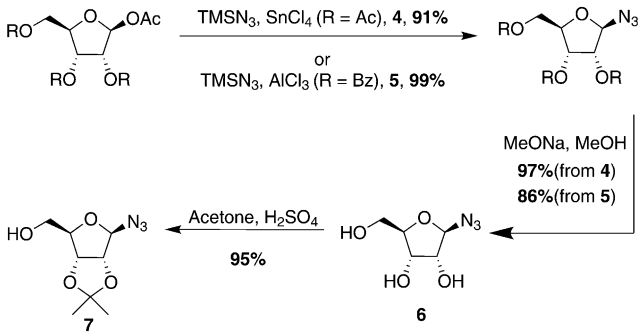
Anticipating that the introduction of the silicon part could dramatically enhance the lipophilicity of the target molecule,[25] we have envisaged to add, to the sugar, a diethylene glycol moiety to adjust the hydrophilicity/lipophilicity balance (Scheme 1). Furthermore, in preliminary experiments, we tested both galactose and ribose units, and found that the ribose approach is far more superior in the last steps of the synthesis.

The first task of the synthesis was the preparation of building block **3**. The introduction of the silyl group on the 4-bromophenol unit was realized by using the procedure already described with the 4-bromobenzyl alcohol as starting material, and we followed a variation developed by Schreiber and coworkers.[26,27] Thus, the lithiated derivative of the 4-bromophenol, generated in situ, was treated with di-*tert*-butylchlorosilane, leading to **1** with 73% yield. On the other hand, the monopropargylation of diethylene glycol was achieved using the propargylbromide, after deprotonation using sodium hydride leading to **2** with 30% yield. Finally **1** and **2** were coupled under Mitsunobu conditions leading to **3** with 73% yield, thus constituting the suitable alkyne partner of the first "click" reaction involving 1-azido-ribose as the coupling partner (Scheme 2). The sugar moiety was obtained starting from the commercially available 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranoside or the 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (Scheme 3). The first step was the transformation of the anomeric acetate into the corresponding azido derivative. In both case, azidotrimethylsilane was used in the presence of $SnCl_4$, a Lewis acid, (R = OAc) or $AlCl_3$ (R = Bz), leading, respectively with 91% and 99% yields to the desired compounds **4** and **5**. Then, the protecting group was removed using sodium methoxide in methanol to give compound **6** respectively with 97% yield starting from **4** and 86% yield starting from **5**. Finally, for the following steps, the *cis*-diol has to be re-protected, and this was done selectively using acetone under acidic conditions leading to the corresponding acetonide **7** with 95% yield.

Thus, building block **3** and 1-azido-ribose **7** were subjected to classic conditions of Huisgen cycloaddition, using the $CuSO_4$/sodium ascorbate couple in a mixture of *tert*-butanol and water, at 80 °C overnight. This reaction led to the desired triazolyl derivative **8**, with 85% yield (Scheme 4). The last section to be added is the cyclo-RGD to act as the azido partner for the second cycloaddition, and this involved the introduction of an alkyne group at the 5-position of the ribose moiety of **8**. In the event, treatment of **8** with propargylbromide in the presence of sodium hydride led to **9** with 78% yield. Finally, according to preliminary experiments,[28] we realized removal of the protecting group of **9** prior to coupling using TFA in CH_2Cl_2, thus leading to **10** with 87% yield. With regard to the preparation of the



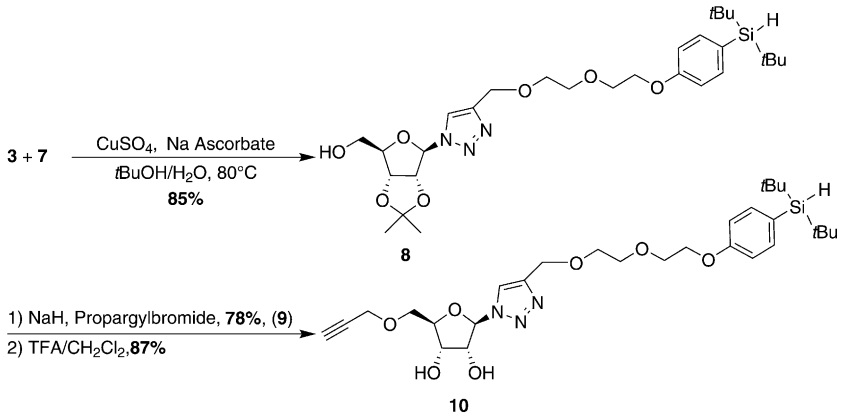
Scheme 2. Synthesis of **3**. DEAD = diethyl azodicarboxylate, THF = tetrahydrofuran.



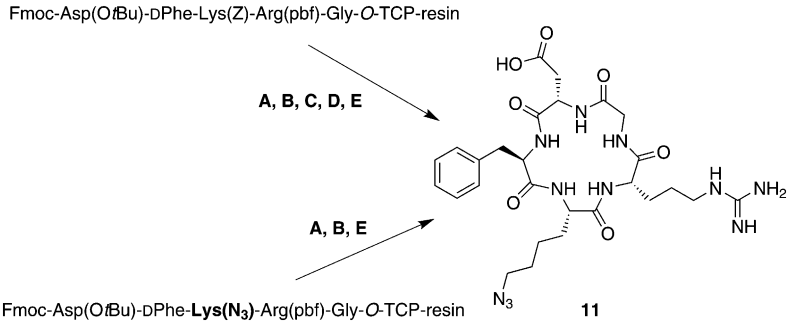
Scheme 3. Synthesis of **7**. Bz = benzoyl, TMS = trimethylsilyl.

cyclo-RGDN$_3$, two approaches were followed: 1) the conversion of the ε-lysine amino function was carried out on the cyclized peptide with 48% yield (Scheme 5, step D), or 2) this conversion was carried out directly and quantitatively from a Fmoc-Lys-OH, before assembly of the peptide, using, in both cases, the imidazole-1-sulfonyl azide hydrochloride as the reactant in the presence of $CuSO_4$.[29]

The linear peptides were synthesized by solid-phase synthesis using the trityl chloride resin, applying the Fmoc strategy. The final Fmoc protection group was removed with a 20% solution of piperidine in DMF.[30] The next steps (step A: removal



Scheme 4. Synthesis of **10**. TFA = trifluoroacetic acid.

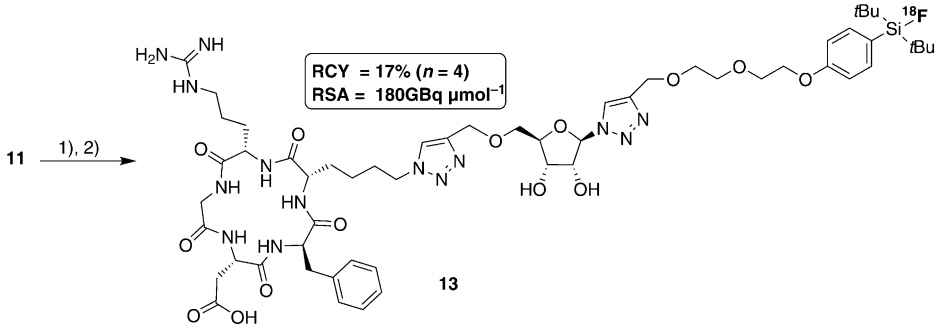


Scheme 5. Synthesis of Cyclo-RGDN$_3$ **11**. The protected linear peptide was assembled on trityl chloride resin by applying the Fmoc strategy. A) Removal from the resin. B) Cyclization of the side chain. C) Protecting group removal from the lysine ε-amino function. D) Conversion of the lysine ε-amino function into an azide group (48% yield). E) Complete protecting group removal from the peptide.

from the resin; step B: cyclization; step C: removal of the Z protecting group; step E: complete removal of protecting groups on the peptide) were successfully realized according to the procedure described by Haubner et al. (Scheme 5).[6]

The use of Fmoc-LysN_3 appears to be a real improvement to the cyclo-RGDN$_3$ synthesis. Indeed, the introduction of the azide function is much more efficient when starting from the amino acid rather than from the cyclic peptide (quantitative versus 48% yield), thus shortening the post peptide synthesis (3 steps versus 5 steps) as well as to simplifying the purification steps. Only the final compound needs to be purified by HPLC, the resin-free peptide was simply precipitated in diethyl ether (step **A**), and the protected cyclo-RGDN$_3$ (step **B**) was easily purified by chromatography on silica gel ($CHCl_3$/MeOH 3:1) allowing us to prepare larger amounts of the desired peptide **11**. This sequence gave us several hundred milligrams of the cyclo-RGDN$_3$, thus overcoming one of the drawbacks often met in the synthesis of tracers based on biomolecules such as peptides. Once the two coupling partners were obtained, the last step involved the Huisgen cycloaddition between **10** and **11**. This time, better results were obtained by using microwaves activation, allowing a total conversion, without any degradation, in only 20 minutes (Scheme 6).

Finally the ^{18}F-fluorination of **12** was realized according to our procedure, already described for oligonucleotides,[22] using potassium fluoride in the presence of kryptofix[2.2.2] in DMSO at 100 °C for 15 minutes. These conditions allowed us to obtain, after purification by semipreparative HPLC, in only one step, the desired fluorinated derivate **13**, in 17% ($n = 4$) not decay corrected radiochemical yield (RCY) and with 180 GBq μmol^{-1} radioactive specific activity (RSA; Scheme 6). Synthetically, this straightforward method of labeling appears to be a real improvement because it avoided multiple time-consuming steps (synthesis and purification) needed by adopting a prosthetic-group strategy. Thus, it allows the convenient production of, on a commercially available automate (TRACERLab Fx_{F-N}, GE Healthcare) and under production conditions of clinically useful radiopharmaceuticals (starting from around 100 GBq), the target compound with higher RCY and RSA than any currently available compounds—even higher than those already in clinical trials for imaging $\alpha_v\beta_3$ integrin expression. Furthermore, preliminary preclinical results using **13** are very



Scheme 6. Synthesis of **13** (RCY not decay corrected). 1) **11**, $CuSO_4$, Na ascorbate, *tert*-butanol/water (3:1), MW (50 W), 100 °C, 20 min, leading to **12** in quantitative yield; 2) K[^{18}F]F-K_{222}, DMSO, CH_3COOH, 100 °C, 15 min. DMSO = dimethyl sulfoxide.

promising. Indeed, the radiolabeled ligand **13** was injected intravenously into C57black/6 mice ($n=12$) bearing subcutaneous $B_{16}F_{10}$ melanoma xenografts and PET-CT imaging was realized on a clinical imager (Discovery ST, General Electric, Milwaukee, US) and the first fused images obtained after 75 minutes with 4.60 MBq of **13** showed a significant uptake in tumor cells along with a tumor-to-background ratio of 6.1 ± 1.5, thus allowing a clear identification (Figure 1) and the confirmation of the in vivo stability of the Si–F bond, only reported once up to date.[31]

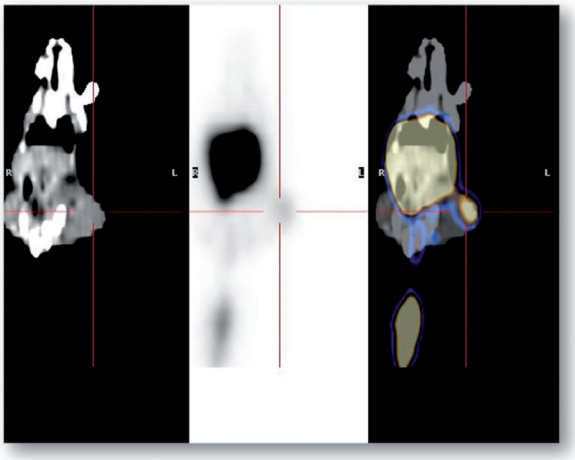


Figure 1. Computed tomography (CT), positron emission tomography (PET), and overlaid images taken 75 min after intravenous injection of **13**.

The complete small-animal PET biological studies (pharmacokinetics, biodistribution, blocking studies) are still under investigation and will be shortly reported elsewhere.

In conclusion, the proposed strategy offers a unique and very efficient way to prepare the first ^{18}F-labeled RGD PET probe showing the best combination between structural advantages of [^{18}F]galacto-RGD (hydrophilicity, ^{18}F-labeling, high RSA) and the ease of radiolabeling similarly to ^{68}Ga- or ^{64}Cu-labeled RGD conjugates. Furthermore, whenever in vivo characteristics of **13** have to be further evaluated by complete small-animal PET studies, the versatility of the described synthetic method allows us to envisage **13** as a "lead compound", and thus a starting point for a family of optimized analogues dedicated to the improvement of PET imaging for $\alpha_v\beta_3$ integrin expression.

Acknowledgements

We gratefully acknowledge the Regional Councils of Aquitaine, Midi-Pyrénées, and FEDER funds for the financial support of this project.

Keywords: click chemistry · ^{18}F-labeling · RGD peptides · PET imaging · silicon

[1] C. M. Storgard, D. G. Stupack, A. Jonczyk, S. L. Goodman, R. I. Fox, D. A. Cresh, *Clin. Invest.* **1999**, *103*, 47–54.
[2] D. Creamer, D. Sullivan, R. Bicknell, J. Barker, *Angiogenesis* **2002**, *5*, 231–236.
[3] J. Folkman, *Semin. Oncol.* **2002**, *29*, 15–18.
[4] R. Haubner, A. J. Beer, H. Wang, X. Chen, *Eur. J. Nucl. Med. Mol. Imaging* **2010**, *37*, 86–103.
[5] Radiolabeled RGD peptides are of interest to document the $\alpha_v\beta_3$ expression of tumors prior to administration of $\alpha_v\beta_3$ antagonists. Thus allowing an appropriate selection of patients entering clinical trials as well as the determination of the optimal dose of $\alpha_v\beta_3$ antagonists. For leading reference, see: R. Haubner, *Eur. J. Nucl. Med. Mol. Imaging* **2006**, *33*, 54–63.
[6] R. Haubner, B. Kuhnast, C. Mang, W. A. Weber, H. Kessler, H. J. Wester, M. Schwaiger, *Bioconjugate Chem.* **2004**, *15*, 61–69.
[7] R. Haubner, H. J. Wester, W. A. Weber, C. Mang, S. I. Ziegler, S. L. Goodman, R. Senekowitsch-Schmidtke, H. Kessler, M. Schwaiger, *Cancer Res.* **2001**, *61*, 1781–1785.
[8] A. J. Beer, R. Haubner, M. Sarbia, C. Mang, M. Goebel, S. Luderschmidt, A. L. Grosu, O. Schnell, M. Niemeyer, H. Kessler, H. J. Wester, W. A. Weber, M. Schwaiger, *Clin. Cancer. Res.* **2006**, *12*, 3942–3949.
[9] R. Haubner, W. A. Weber, A. J. Beer, E. Vabuliene, D. Reim, M. Sarbia, K. F. Becker, M. Goebel, R. Hein, H. J. Wester, H. Kessler, M. Schwaiger, *Plos. Med.* **2005**, *2*, e70.
[10] A. J. Beer, M. Schwaiger, *Cancer Metastasis Rev.* **2008**, *27*, 631–644.
[11] L. Kenny, R. C. Coombes, I. Oulie, K. B. Contractor, M. Miller, T. J. Spinks, B. McParland, P. S. Cohen, A.-M. Hui, C. Palmieri, S. Osman, M. Glaser, D. Turton, A. Al-Nahhas, E. O. Aboagye, *J. Nucl. Med.* **2008**, *49*, 879–886.
[12] H. J. L. J. Cho, J. Y. Park, M. Yun, *J. Nucl. Med.* **2009**, *50*, S2, 1910.
[13] C. Decristoforo, I. Hernandes-Gonzalez, J. Carlsen, M. Rupprich, M. Huisman, I. Virgolini, H. J. Wester, R. Haubner, *Eur. J. Nucl. Med. Mol. Imaging* **2008**, *35*, 1507–1515.
[14] R. A. Dumont, F. Deininger, R. Haubner, H. R. Maecke, W. A. Weber, M. Fani, *J. Nucl. Med.* **2011**, *52*, 1276–1284.
[15] a) J. Becaud, L. Mu, M. Karramkam, P. A. Schubiger, S. M. Ametamey, K. Graham, T. Stellfeld, L. Lehmann, S. Borkowski, D. Berndorff, L. Dinkelborg, A. Srinivasan, R. Smits, B. Koksch, *Bioconjugate Chem.* **2009**, *20*, 2254–2261; b) U. Roehn, J. Becaud, L. Mu, A. Srinivasan, T. Stellfeld, A. Fitzner, K. Graham, L. Dinkelborg, A. P. Schubiger, S. M. Ametamey, *J. Fluorine Chem.* **2009**, *130*, 902–912.
[16] A. R. Studenov, M. J. Adam, J. S. Wilson, T. J. Ruth, *J. Labelled Compd. Radiopharm.* **2005**, *48*, 497–500.
[17] a) R. Ting, M. J. Adam, T. J. Ruth, D. M. Perrin, *J. Am. Chem. Soc.* **2005**, *127*, 13094–13095; b) R. Ting, C. W. Harwig, J. Lo, Y. Li, M. J. Adam, T. J. Ruth, D. M. Perrin, *J. Org. Chem.* **2008**, *73*, 4662–4670; c) R. Ting, T. A. Aguilera, J. L. Crisp, D. J. Hall, W. C. Eckelman, D. R. Vera, R. Y. Tsien, *Bioconjugate Chem.* **2010**, *21*, 1811–1819.
[18] a) C. W. McBride, C. A. D'Souza, R. M. Sharkey, H. Karacay, E. A. Rossi, C.-H. Chang, D. M. Goldenberg, *Bioconjugate Chem.* **2010**, *21*, 1331–1340; b) P. Laverman, W. J. McBride, R. M. Sharkey, A. Eek, L. Joosten, W. J. G. Oyen, D. M. Goldenberg, O. C. Boerman, *J. Nucl. Med.* **2010**, *51*, 454–461.
[19] a) R. Schirrmacher, G. Brandtmöller, E. Schirrmacher, O. Thews, J. Fillmanns, T. Siessmeier, H. G. Buchholz, P. Bartenstein, B. Wängler, C. M. Niemeyer, K. Jurkschat, *Angew. Chem.* **2006**, *118*, 6193–6197; *Angew. Chem. Int. Ed.* **2006**, *45*, 6047–6050; b) E. Schirrmacher, B. Wängler, M. Cypryk, G. Brandtmöller, M. Schäfer, M. Eisenhut, K. Jurkschat, R. Schirrmacher, *Bioconjugate Chem.* **2007**, *18*, 2085–2089; c) B. Wängler, G. Quandt, L. Iovkova, E. Schirrmacher, C. Wängler, G. Boening, M. Hacker, M. Schmoeckel, K. Jurkschat, P. Bartenstein, R. Schirrmacher, *Bioconjugate Chem.* **2009**, *20*, 317–321; d) L. Iovkova, B. Wängler, E. Schirrmacher, R. Schirrmacher, G. Quandt, G. Boening, M. Schürmann, K. Jurkschat, *Chem. Eur. J.* **2009**, *15*, 2140–2147.
[20] 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.* **2008**, *120*, 5000–5003; *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. Borowski, D. Berndorff, U. Klar, U. Voigtmann, J. E. Cyr, M. Friebe, L. Dinkelborg, A. Srinivasan, *Bioconjugate Chem.* **2008**, *19*, 1871–1879.

[21] N. S. Marans, L. H. Sommer, F. C. Whitmore, *J. Am. Chem. Soc.* **1951**, *73*, 5127 – 5130.
[22] J. Schulz, D. Vimont, T. Bordenave, D. James, J.-M. Escudier, M. Allard, M. Szlosek-Pinaud, E. Fouquet, *Chem. Eur. J.* **2011**, *17*, 3096 – 3100.
[23] a) J. Marik, J. L. Sutcliffe, *Tetrahedron Lett.* **2006**, *47*, 6681 – 6684; b) M. Glaser, E. Årstad, *Bioconjugate Chem.* **2007**, *18*, 989 – 993; c) L. S. Campbell-Verduyn, L. Mirfeizi, A. K. Shoonen, R. A. Dierckx, P. H. Elsinga, B. L. Feringa, *Angew. Chem.* **2011**, *123*, 11313 – 11316; *Angew. Chem. Int. Ed.* **2011**, *50*, 11117 – 11120.
[24] a) R. Albert, P. Marbach, W. Bauer, U. Briner, G. Fricker, C. Bruns, J. Pless, *Life Sci.* **1993**, *53*, 517 – 525; b) M. Marastoni, S. Spinasi, R. Tomatis, *Arzneim.-Forsch.* **1994**, *44*, 984 – 987.
[25] a) C. Wängler, B. Waser, A. Alke, L. Iovkova, H.-G; Bucholtz, S. Niedermoser, K. Jurkschat, C. Fottner, P. Bartenstein, R. Schirrmacher, J.-C. Reubi, H.-J. Wester, B. Wängler, *Bioconjugate Chem.* **2010**, *21*, 2289 – 2296; b) A. P. Kostikov, L. Iovkova, J. Chin, E. Schirrmacher, B. Wängler, C. Wängler, K. Jurkschat, G. Cosa, R. Schirmacher, *J. Fluorine Chem.* **2011**, *132*, 27 – 34.
[26] M. Sternson, J. C. Wong, M. Grozinger, S. L. Schreiber, *Org. Lett.* **2001**, *3*, 4239 – 4242.
[27] D. James, J.-M. Escudier, E. Amigues, J. Schulz, C. Vitry, T. Bordenave, M. Szlosek-Pinaud, E. Fouquet, *Tetrahedron Lett.* **2010**, *51*, 1230 – 1232.
[28] When the deprotection step is carried out after the coupling, by using conditions to also remove protecting groups on the side chain of the peptide, this led to some desilylation side product.
[29] E. D. Goddard-Borger, R. V. Stick, *Org. Lett.* **2007**, *9*, 3797 – 3800.
[30] C. G. Fields, D. H. Lloyd, R. L. MacDonald, K. M. Otteson, R. L. Noble, *Pept. Res.* **1991**, *4*, 95 – 101.
[31] 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.

Received: January 30, 2012
Published online on March 1, 2012

