Bioorganic & Medicinal Chemistry 17 (2009) 7441–7448

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

New approach for the synthesis of [^{18}F]fluoroethyltyrosine for cancer imaging: Simple, fast, and high yielding automated synthesis

M. Zuhayra [a,*], A. Alfteimi [a], C. Von Forstner [a], U. Lützen [a], B. Meller [b], E. Henze [a]

[a] Klinik für Nuklearmedizin, Universitätsklinikum Schleswig-Holstein Campus Kiel, Arnold-Heller-Strasse 9, 24105 Kiel, Germany
[b] Abteilung Nuklearmedizin, KFO179, Georg-August-Universität Goettingen, Robert-Koch-Str. 40, 37075 Goettingen, Germany

ARTICLE INFO

Article history:
Received 7 May 2009
Revised 7 September 2009
Accepted 17 September 2009
Available online 20 September 2009

Keywords:
F-18
Fluoroethyltyrosine
PET
Fluoroethylation

ABSTRACT

O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) is one of the first ^{18}F-labeled amino acids for imaging amino acid metabolism in tumors. This tracer overcomes the disadvantages of [^{18}F]fluorodeoxyglucose, [^{18}F]FDG, and [^{11}C]methionine, [^{11}C]MET. Nevertheless, the various synthetic methods providing ^{18}F[FET] exhibit a big disadvantage concerning the necessity of two purification steps during the synthesis including HPLC purification, which causes difficulties in the automation, moderate yields, and long synthesis times >60 min.

A new approach for the synthesis of [^{18}F]FET is developed starting from 2-bromoethyl triflate as precursor. After optimization of the synthesis parameters including the distillation step of [^{18}F]-FCH_2CH_2Br combined with the final purification of [^{18}F]FET using a simple solid phase extraction instead of an HPLC run the synthesis [^{18}F]FET could be significantly simplified, shortened, and improved. The radiochemical yield (RCY) was about 45% (not decay corrected and calculated relative to [^{18}F]F^- activity that was delivered from the cyclotron). Synthesis time was only 35 min from the end of bombardment (EOB) and the radiochemical purity was >99% at the end of synthesis (EOS). Thus, this simplified synthesis for [^{18}F]FET offers a very good option for routine clinical use.

1. Introduction

Radiolabeled amino acids and their analogues are established tracers in diagnostic oncology.[1] Their use in the single-photon emission tomography (SPECT) and positron emission tomography (PET) is based on their enhanced accumulation into malignant transformed cells by increased expression of amino acid transporters. This is assumed to reflect an enhanced amino acid metabolism and protein synthesis in growing tumors.[2]

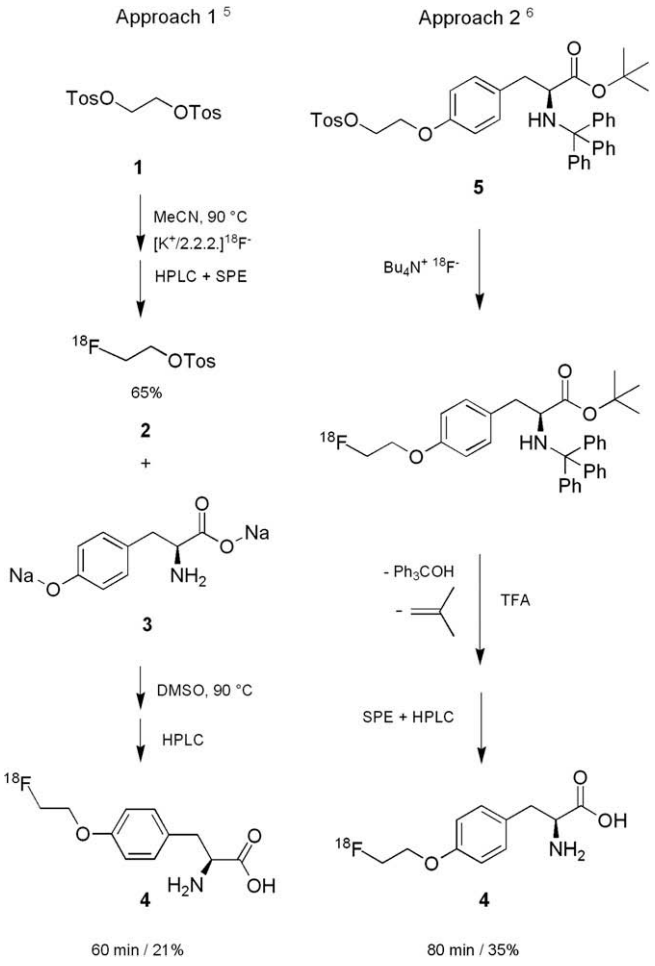
Currently the most used radiolabeled amino acids in nuclear medicine are 3-[^{123}I]iodo-α-methyl-L-tyrosine ([^{123}I]IMT) for SPECT and [^{11}C-methyl]-L-methionine ([^{11}C]MET) for PET.[3] Although [^{11}C]MET is the preferably tracer (due to the better imaging properties of PET technology and its incorporation into proteins) the short half-life of ^{11}C limited its widespread use to few PET centers with own cyclotron. For this reason ^{18}F-labeled amino acids were developed particularly for clinical routine (half-life time of ^{18}F is 110 min). Compared with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) radiolabeled amino acids are more specific tracers for the differentiation between tumor and inflammation since the expression of transporters for amino acids is not stimulated by cytokines.[4]

One of the first and most successful ^{18}F-labeled amino acids is *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET **4**).[5–10] For synthesizing [^{18}F]FET there are two approaches by nucleophilic substitution reaction (Scheme 1). The first one is a two-step reaction starting with the fluorination of 1,2-bis(tosyloxy)ethane (DITOS **1**) to form 1-tosyloxy-2-[^{8}F]fluoroethane (**2**) followed by fluoroethylation of unprotected L-tyrosine di-sodium salt (Ty-Di-Salt **3**) and finally using HPLC for purification to get 21% [^{18}F]FET **4** in 60 min.[5] The second possibility is the synthesis of [^{18}F]FET via direct nucleophilic radiofluorination of the protected precursor *O*-(2-tosyloxyethyl)-*N*-trityl-tyrosine *tert*-butylester (**5**) yielding about 36% [^{18}F]FET in 80 min.[6] In both approaches considerable efforts concerning the purification using HPLC are required and consume a lot of precious time causing long synthesis times and low yields. Later the introduction of a simple solid phase extraction instead of HPLC to separate the final product after direct nucleophilic radiofluorination of the protected precursor *N*-Boc-(*O*-2-tosyloxyethyl)-L-tyrosine methyl ester led to [^{18}F]FET **4** in only 35% yield after 60 min.[7]

Recently we described a new protocol for fast and high yielding fully automated synthesis of [^{18}F]fluoroethylcholine via ^{18}F-fluoroethylation using 2-bromoethyl triflate (BETfO **6**).[11] Now we used also BETfO **6** as starting material for synthesizing [^{18}F]FET too and could provide after optimization of the synthesis parameters a novel and very simple synthesis approach to synthesis [^{18}F]FET ready

* Corresponding author. Tel.: +49 4315973101; fax: + 49 4315973065.
E-mail address: mzuhayra@nuc-med.uni-kiel.de (M. Zuhayra).

0968-0896/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.09.029



Scheme 1. Common syntheses of [^{18}F]FET **4**.

for human use within 35 min in high radiochemical yield (RCY) of 45% and without the need of any HPLC run.

2. Results and discussion

BETfO **6** was subjected to nucleophilic substitution with [^{18}F]KF–Kryptofix®-complex ([^{18}F]KF–K_{222}) as well as with [^{18}F]tetrabutylammonium fluoride ([^{18}F]Bu_4NF) to form the volatile 1-bromo-2-[^{18}F]fluoroethane ([^{18}F]BFE **7**) in 1,2-dichlorobenzene (*o*-DCB) (first reaction in Scheme 2). Because of the significantly lower boiling point of [^{18}F]BFE **7** (bp 71.5 °C)[12] compared with the precursor BETfO **6** (bp 230 °C) and the solvent, *o*-DCB: (bp 179 °C), the intermediate [^{18}F]BFE **7** could be elegantly distilled in a simple way into a second reactor within 8 min at 100 °C leaving all impurities of the first reaction behind in the first reactor. In this way, the second reaction of [^{18}F]BFE **7** with Ty-Di-Salt **3** can be easily performed under pure conditions in dimethylsulfoxide (DMSO) resulting in higher specific activity for [^{18}F]FET **4**.

The individual reaction steps shown in Scheme 2, the first reaction (formation of [^{18}F]BFE **7**), the distillation of [^{18}F]BFE **7** and the second reaction (formation of [^{18}F]FET **4**), were subsequently and systematically studied and optimized.

2.1. First reaction: formation of [^{18}F]BFE 7

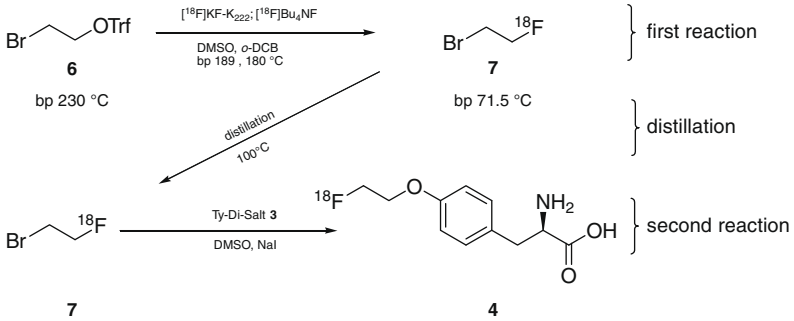
The adequate formation of the activated [^{18}F]fluoride either as [^{18}F]KF–K_{222}-complex or as [^{18}F]Bu_4NF by using K_2CO_3/Kryptofix® or tetrabutylammonium hydrogencarbonate (TBA) is essential for the subsequent fluorination reaction of BETfO **6** leading to the volatile intermediate [^{18}F]BFE **7**.

As described in our previous work it was found for the case of using of KF–K_{222}-complex that the maximum yield of [^{18}F]BFE **7** was achieved by using 80 μmol K_2CO_3/K_{222} and 95 μmol BETfO **6** as well as helium flow rate and drying temperature of 100 mL/min and 90 °C, respectively (Fig. 1).[11] TBA exhibits lower basic properties compared with Kryptofix®. Therefore higher radiochemical yield of [^{18}F]BFE **7** would be expected due to less elimination by-products. But the results in Figure 1 show no significant differences concerning formation of [^{18}F]BFE **7** by using [^{18}F]Bu_4NF instead of [^{18}F]KF–K_{222}-complex. The data indicate an optimum for the formation of [^{18}F]BFE **7** by using [^{18}F]Bu_4NF at 100 mL/min for the helium flow rate and 110 °C for the drying temperature. These results are summarized in Figure 1. In both cases no transfer of TBA or Kryptofix® from rector one into reactor two during the distillation step was detected, due to their high vapor pressures.

2.2. Distillation of [^{18}F]BFE 7

The distillation of [^{18}F]BFE **7** (bp 71.5 °C) into the second reactor was started directly after the drying step by adding 95 μmol BETfO **6** that was dissolved in 0.5 mL *o*-DCB to the activated [^{18}F]fluoride. This simple distillation at 100 °C under helium flow transfers the intermediate [^{18}F]BFE **7** in almost pure form into the second reactor containing Ty-Di-Salt **3** and sodium iodide (NaI) in DMSO. As shown in the distillation profile presented in Figure 2 the most radioactivity (83%) is already transported after 6 min from reactor one into reactor two. About 10% of the start activity remains in reactor one while about 7% of the start activity is lost by the distillation.

The dependence of the portion of the intermediate [^{18}F]BFE **7** transferred through the distillation on the temperature and the helium flow rate by using both [^{18}F]KF–K_{222}, and [^{18}F]Bu_4NF is shown in Figure 3. It turned out that the maximum yield of transferred radioactivity was obtained when a flow rate of 100 mL/min and a temperature of 100 °C were applied. Higher temperatures led to less transferred material due to decomposition of reactants. Gas chromatographic analysis of the distilled material showed no pres-



Scheme 2. Two-pot synthesis of [^{18}F]FET **4**.

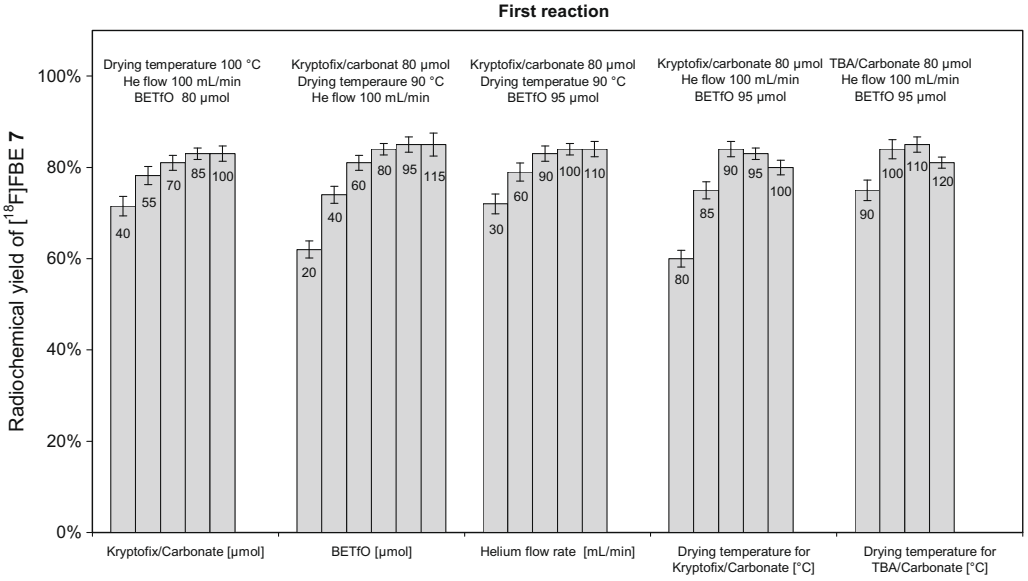


Figure 1. Dependence of the radiochemical yield of [^{18}F]BFE **7** on the amount of reactants, helium flow and drying temperature by using [^{18}F]KF–K_{222}, and [^{18}F]Bu_4NF (n = 3).

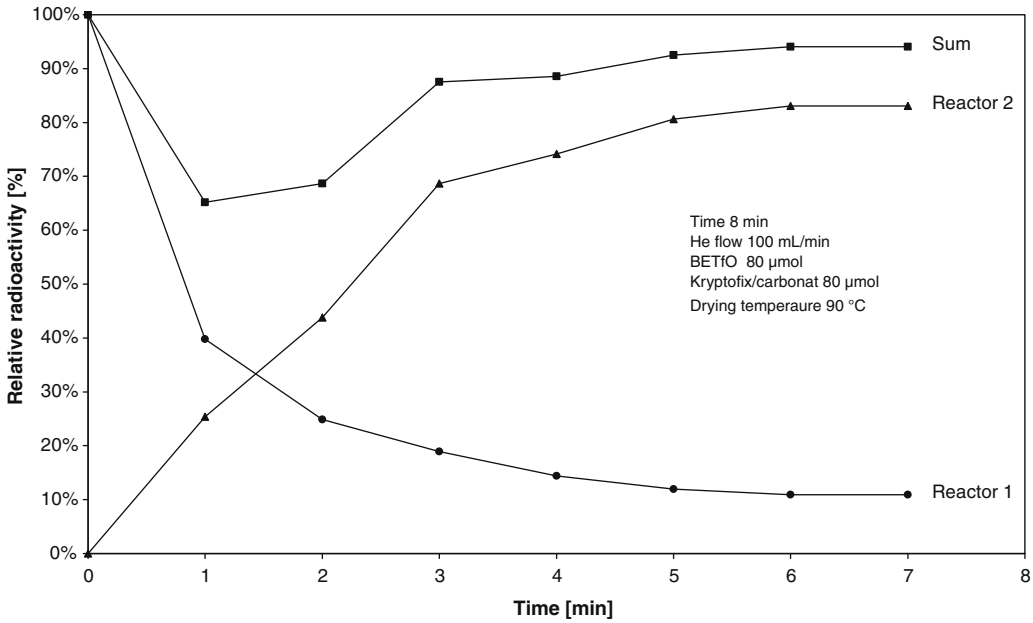


Figure 2. Distillation profile of [^{18}F]BFE **7** at 100 °C.

ence of BETfO **6** (bp 230 °C) in the second reactor when the temperature was kept ≤130 °C (detection limit 0.0014 mg/mL).

Applying the optimized conditions for the first reaction and for the distillation step has enabled to obtain the intermediate [^{18}F]BFE **7** in a pure form with a RCY of 73% in only 15 min without using HPLC or solid phase extraction (SPE). This is a significant improvement against the direct labeling approach using DITOS **1**,[5] which provides the corresponding intermediate [^{18}F]-fluoroethyltosylate ([^{18}F]FETos) in a RCY of only 65% by using both HPLC-run and SPE for purification (see Scheme 1).

2.3. Second reaction: formation of [^{18}F]FET 4

The second reaction between [^{18}F]BFE **7** and freshly prepared Ty-Di-Salt **3** was carried out after distilling [^{18}F]BFE **7** in a second reactor containing Ty-Di-Salt **3**, NaI and 800 µL DMSO. In order to optimize the radiochemical yield of [^{18}F]FET **4** the effect of reaction time and reaction temperature as well as the effect of the amount of Ty-Di-Salt **3** were subsequently studied. As it was known that NaI increases the yield of fluoroethylation[13,14] we studied also the effect of NaI on the second reaction. As shown in Figure 4 the optimization of the reaction time and reaction temperature both for the reaction with NaI as well as for the reaction without NaI resulted in a maximum yield obtained at 110 °C and 15 min, respectively. By adding of 33 µmol (5.5 mg) NaI the radiochemical yield of [^{18}F]FET **4** could be increased by 30% compared to the reaction without NaI.

The study of the effect of the amount of tyrosine on the radiochemical yield of [^{18}F]FET **4** was started by the use of various quantities of tyrosine which were always dissolved in 28 µL of 25% sodium methanolate solution (CH_3ONa) in methanol. Figure 4 shows that the radiochemical yield of [^{18}F]FET **4** increases by

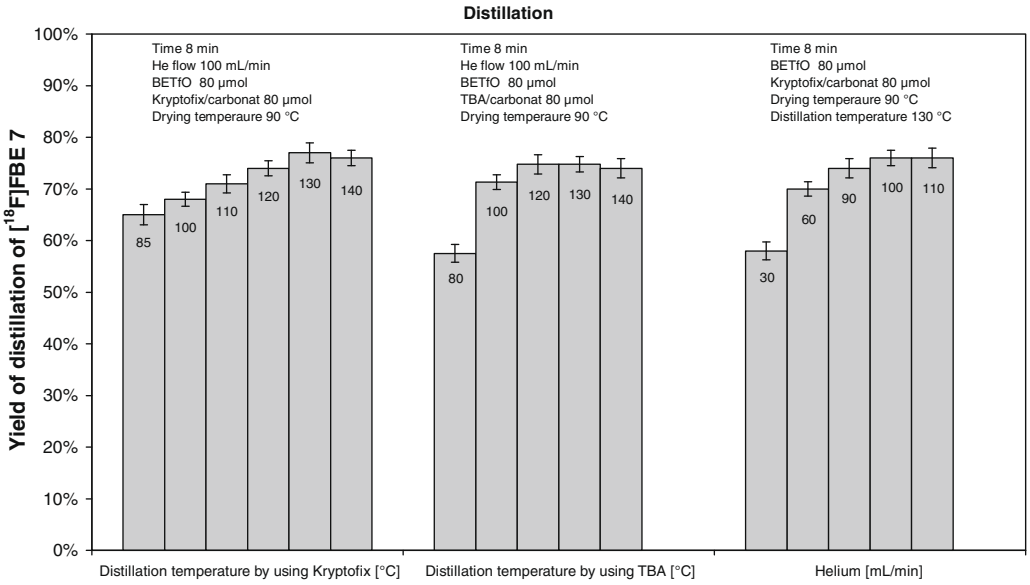


Figure 3. Dependence of the yield of distillation of [^{18}F]BFE **7** on temperature and helium flow (n = 3).

increasing the amount of tyrosine, but starts to fall after reaching a maximum by 63.4 µmol. For further investigations, we then varied the amount of the added sodium methanolate but kept the quantity of tyrosine constant by 63.4 µmol. We found out that when a molar ratio of CH_3ONa over tyrosine of less than two was used the radiochemical yield of [^{18}F]FET **4** decreased and the HPLC radio chromatogram of the reaction solution exhibited in addition to [^{18}F]FET **4** a second radioactive substance, compound **8**, by 13.5 min, which is assumed to be the 2-fluoroethyl ester of tyrosine (Fig. 5b and c). This assumption corresponds to the fact that a double molar excess of CH_3ONa over tyrosine is necessary for the deprotonation of the phenolic group and building of Ty-Di-Salt **3**. For the unambiguous identification of compound **8** we performed the cold reaction with [^{19}F]KF with 126.9 µmol tyrosine and 28 µL of 25% sodium methanolate solution in 800 µL DMSO (CH_3ONa molar ratio = 1.0). The HPLC fraction by 13.5 min was isolated and investigated with ESI mass spectrometry. The resulting mass spectra of compound **8** and [^{19}F]fluoroethyltyrosine ([^{19}F]FET **9**) taken with both cone voltages at 20 and 40 V are demonstrated in Figure 6. Both compound **8** and [^{19}F]FET **9** have the same highest peak at M+1 = 228.1 $(C_{11}H_{15}FNO_3)^+$ (spectra A and C) but they differ in their fragmentation musters at higher cone voltage of 40 V (spectra B and D). With the help of the fragment mass at m/z = 136.0 which belongs to the fragment $(C_8H_{10}NO)^+$ (**10**) that only appears in the spectrum of compound **8** at 40 V (spectrum D) we could identify compound **8** to be 2-fluoroethyl ester of tyrosine because the fragment **10** is built by breaking the C–C bond between the α and β carbon atoms from the tyrosine ester. It is unlikely that the same fragment is derived from [^{19}F]FET **9**, since it has to be built by double fragmentation. On the other hand breaking the same C–C bond between the α and β carbon atoms in [^{19}F]FET **9** leads to the fragment $(C_{10}H_{13}FNO)^+$ (**11**) with m/z = 182.1 which is only present in the spectrum of [^{19}F]FET **9** (spectrum B).

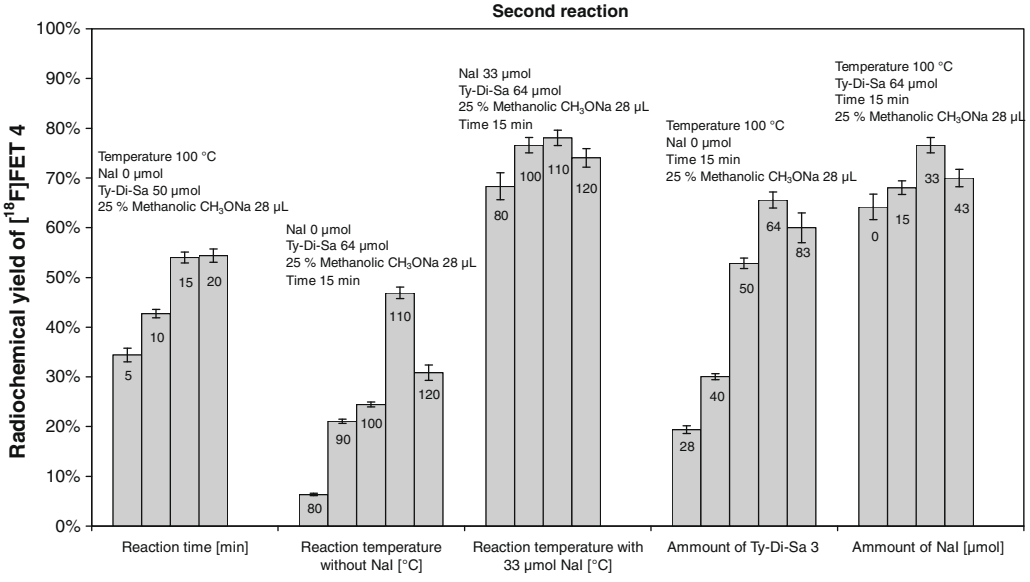


Figure 4. Dependence of the radiochemical yield of [^{18}F]FET **4** on reaction time, reaction temperature as well as on the amount of tyrosine and NaI (n = 3).

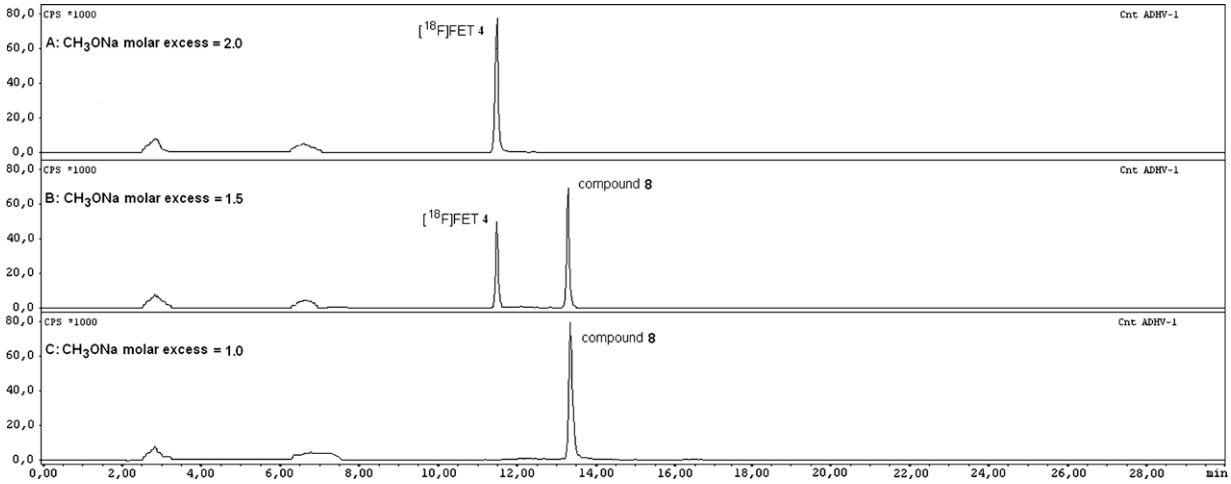


Figure 5. Radio HPLC chromatograms of reaction solutions of reaction two by different molar excess of NaOH over tyrosine.

The effect of the amount of CH_3ONa on the radiochemical yield of [^{18}F]FET **4** is dramatic, because of the necessity to deprotonate the phenolic hydroxyl group of tyrosine before it can act as a nucleophilic agent toward [^{18}F]BFE **7**. Due to the lower p*K*s value of the carboxyl group of tyrosine compared with the p*K*s value of the phenolic hydroxyl group (pKs_{COOH} = 2.2; pKs_{OH} = 10.07)[15] a molar ratio of CH_3ONa/tyrosine $\geq$2 is necessary to completely deprotonate the phenolic hydroxyl group and avoid the formation of the 2-fluoroethyl ester of tyrosine.

The RCY of the second reaction after optimization of all reaction parameters amounts to 65%. Compared with the second reaction of the indirect labeling approach using 1-tosyloxy-2-[^{18}F]fluoroethane **2** with RCY about 30%,[5] this is an improvement of more than 35%. Also, the total RCY of the here described approach with 45% is about 23% higher than the total RCY of the indirect labeling approach and about 10% more than the total RCY provided by direct labeling methods using protected precursors.[6,7] In addition the presented approach allows the synthesis of [^{18}F]FET **4** in significantly higher specific activity without need of purification with the HPLC and reduces the synthesis time by half.

Due to the distillation step, which allows to obtain very pure [^{18}F]BFE **7**, we could achieve high specific activity of more than 80 GBq/μmol for [^{18}F]FET **4**. In comparison, the direct labeling approach leads to 18.5 GBq/μmol.[6]

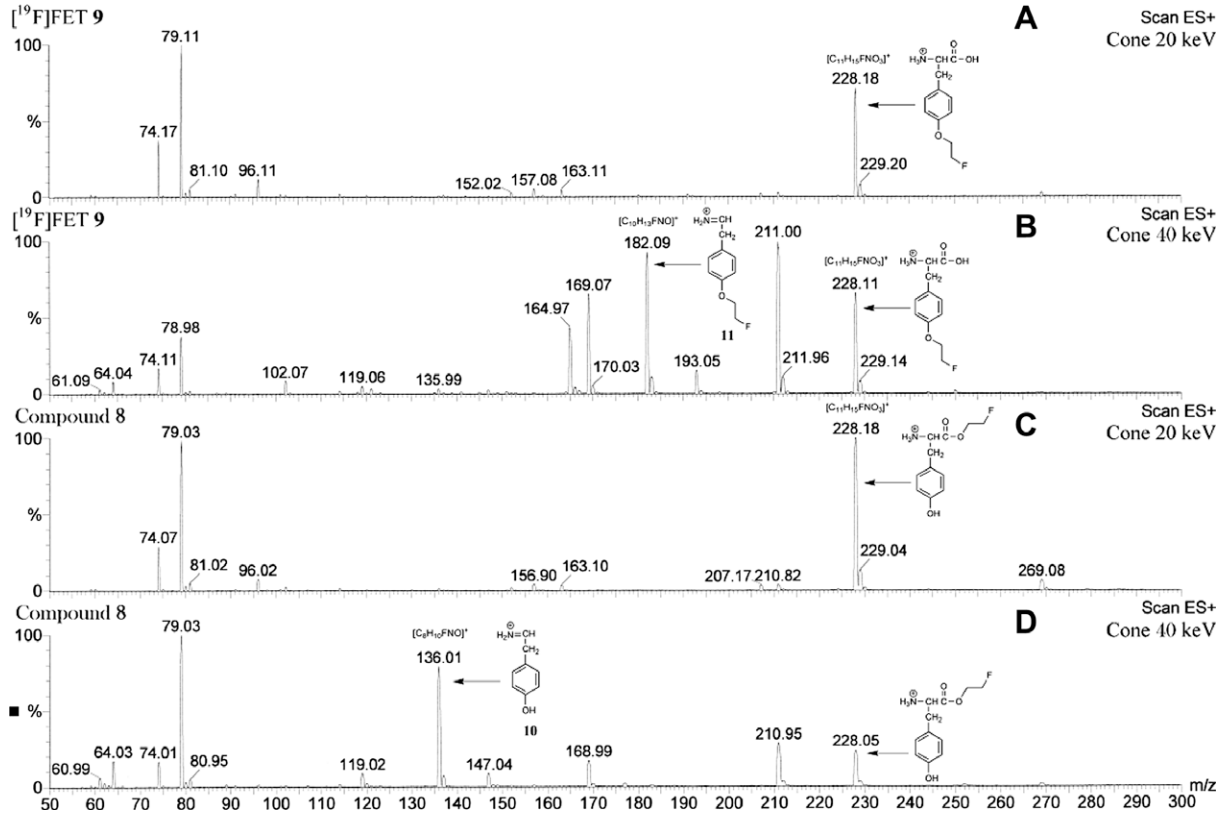


Figure 6. ESI mass spectra of compounds **8** and **9** at cone voltages 20 and 40 V.

2.4. Chemical and radiochemical purity

All non-volatile reactants and products of the first reaction, K_{222}, K_2CO_3, [^{18}F]KF–K_{222} as well as TBA and [^{18}F]Bu_4NF stay behind in reactor one and only [^{18}F]BFE **7** is transferred into reactor two upon distillation at 100 °C . Thus, they do not interfere with the second reaction. The only compounds that might possibly be also transferred into reactor two would be *o*-DCB (bp 180 °C) and BETfO **6** (bp 230 °C) due to their considerable vapor pressure. GC measurements of the distillate, however, clearly revealed that only a trace amount of *o*-DCB (5 μL/mL) is actually present in the distillate whereas BETfO **6** was not detected at all (detection limit 0.0014 mg/mL). This is an important finding because BETfO **6** could also react with Ty-Di-Salt **3** to give by-products which would cause problems in the following separation of [^{18}F]FET **4** by solid phase extraction (SPE). The contamination with *o*-DCB, however, could easily be removed together with DMSO by diluting the reaction mixture with 0.1 M ammonium acetate buffer (NH_4Ac), loading

Table 1
Chemical purity of the final ready for humane use solution of [^{18}F]FECh **4** in saline detected with the gas chromatography

Solvent	Acetone	Ethanol	*o*-DCB	DMSO	Acetonitrile
(μL/mL)	1.19	100	—	—	—
Det. limit (μL/mL)	0.005	0.006	0.002	0.007	0.020

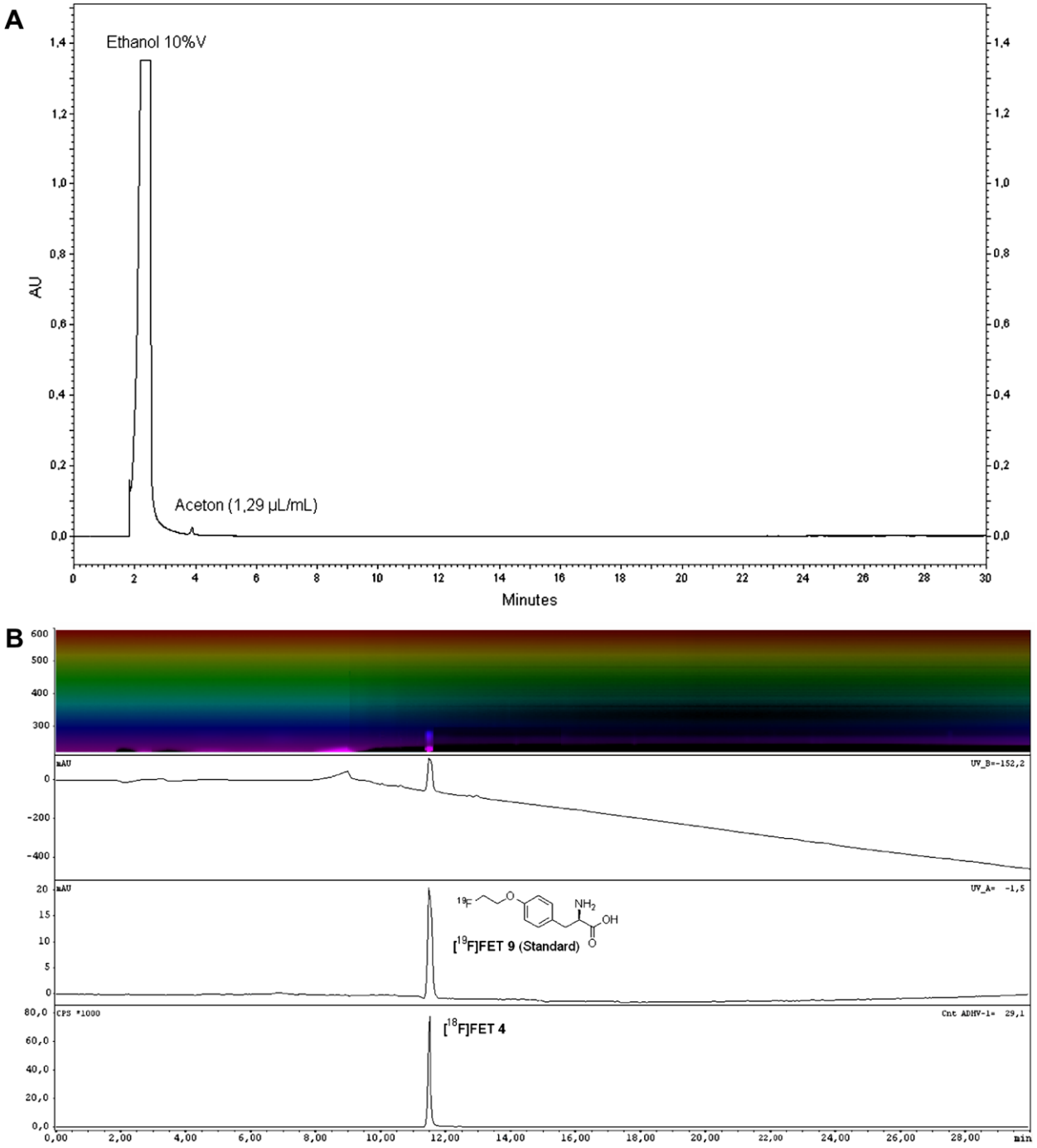


Figure 7. Chemical and radiochemical purity detection with (A) gas chromatography, (B) radio HPLC with diode array detection.

onto the C18 cartridges, and subsequent cleaning with ammonium acetate buffer and 5%V ethanol containing saline. All educts were hereby eluted into the waste. [^{18}F]FET **4** was finally extracted from the C18 cartridges with 10 mL 10%V ethanol containing saline. As shown in Figure 7, the investigation of final sterile solution of [^{18}F]FET **4** via gas chromatography showed only the present of minimal amounts of acetone from the cleaning procedure (1.19 μL/mL) and ethanol (10%V). No other solvents could be detected (Table 1). Figure 7 shows HPLC radio chromatogram, GC chromatogram and ultra-violet spectrum of the final product. According to the high vapor pressures of TBA and Kryptofix®, which prevent their transfer during the distillation step into reactor two, the investigation of the final sterile solution of [^{18}F]FET **4** via LC–MS showed no presence of both compounds.

The purity and identity were checked by RP C18 chromatography (Nucleosil 100-5 HD 4–250 mm, solvents: A: NH_4Ac (0.1 M); B: acetonitrile; gradient: 0–5 min 100% A, 5–30 min 0–100% B; flow rate: 1.5 mL/min). Typical chromatograms of the quality control are shown in Figure 7.

3. Experimental

3.1. Materials and methods

Chemicals were purchased from commercial sources and were used without further purification. The Chromafix C18 cartridges were purchased from Macherey Nagel, [^{18}F]fluoride was produced via the $^{18}O(p,n)^{18}F$ reaction with a CTI RDS 111 cyclotron (Berlin). HPLC was performed with HP 1100 pump with UV and gamma radiation detection (Gabi, Raytest), ESI spectra were performed with Platform LC (Waters). The radiochemical yield was not decay corrected and calculated relative to [^{18}F]F^- activity that was delivered from the cyclotron. Synthesis time was measured from the end of bombardment (EOB) and the specific activity at the end of synthesis EOS. Gas chromatography was performed with Varian 3350 spectrometer and FID detection.

3.2. 2-Bromoethyl triflate BETfO 6

BETfO **5** was synthesized as described in the literature.[16] 2-Bromoethanol (1 g, 8.0 mmol) was dissolved in 2.05 mL of 2,6-lutidine (17.6 mmol), diluted with 10 mL of CH_2Cl_2 and cooled to 0 °C. Trifluoromethanesulfonic acid anhydride (2.83 mL, 16.8 mmol) was added dropwise. After being stirred for 30 min, the solvent was removed in vacuum and the product was distilled (50 °C at 0.5 mm Hg) to give 1.1 g (54%) of BETfO **6** as a colorless liquid: GC chromatogram, single peak, t_R = 7.82 min (column Rtx® 200, 0.25 mm ID, 30 m, carrier gas N_2, 0.95 mL/min, injector 250 °C, program 50 °C (5 min hold, than 10 °C/min)).

3.3. Radiosynthesis

The synthesis of [^{18}F]FET **4** was carried out in the style of GMP. [^{18}F]FET **4** was produced in a hot cell equipped with a commercially available automated synthesis module using sterile filtered helium as gas carrier. A schematic diagram of the automated synthesis module is presented in Figure 8. All starting materials were tested using validated methods and qualified equipment. The quality control involved measurement of the chemical and the radiochemical purity via HPLC, gas chromatography and the pH and other parameters were tested.

[^{18}F]fluoride ion (2–10 GBq) obtained from the target was trapped in a small anion exchange column (30 mg, HCO_3 form). The radioactivity was eluted with an aqueous solution of K_2CO_3 (11 mg; 0.08 mmol) in 0.8 mL of H_2O into reactor one. A solution of K_{222} (30 mg; 0.08 mmol) in 1.5 mL of CH_3CN was added, and the mixture was evaporated at 90 °C under reduced pressure with a helium flow of 100 mL/min for 2 min and without helium flow for additional 2 min. 0.5 mL of *o*-DCB were then added to the

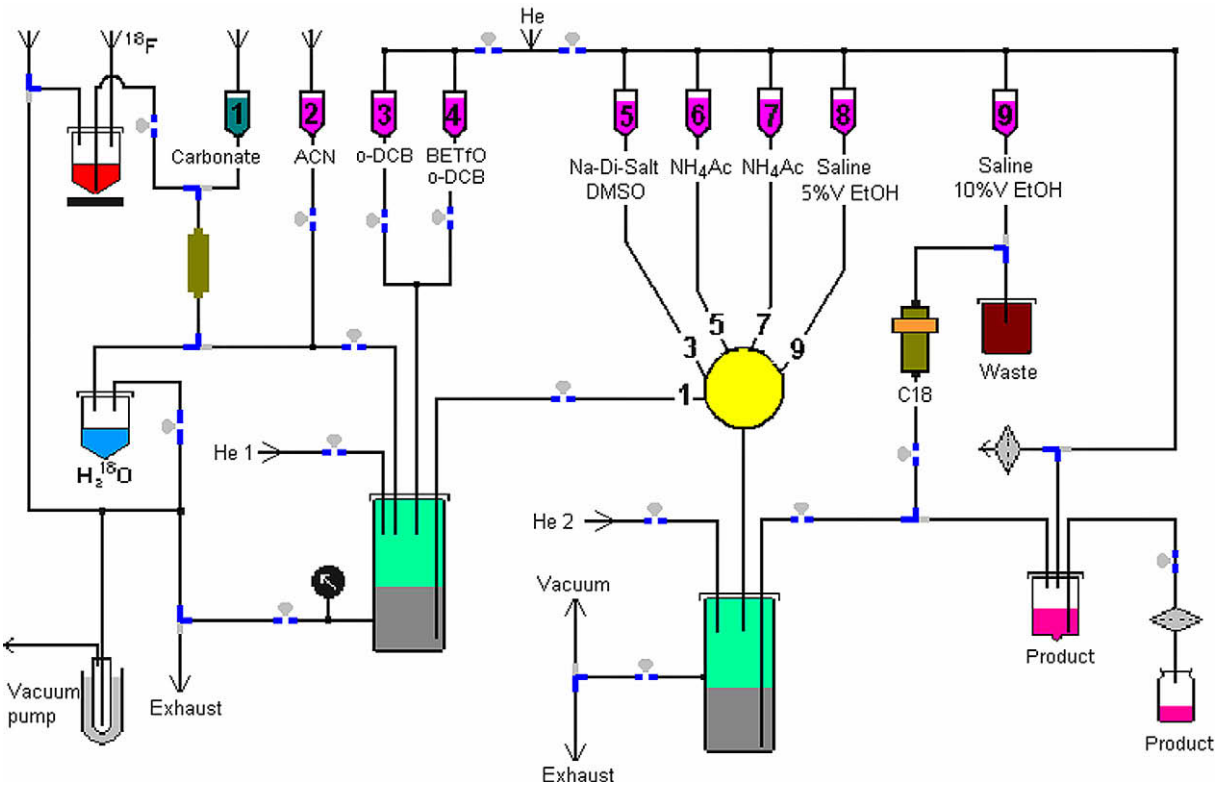


Figure 8. Schematic diagram of the automated synthesis module.

dried [^{18}F]KF–K_{222}. After 1 min of stirring at 100 °C BETfO **5** (15 μL) dissolved in 0.5 mL of *o*-DCB was added while [^{18}F]BFE **7** was transferred within 8 min into the second reactor containing 11.5 mg tyrosine (63.4 μmol), 28 μL of 25% sodium methanolate solution (CH_3ONa) in methanol, 5 mg NaI (33 μmol), and 800 μL of DMSO. The second reactor was then tempered for 15 min at 110 °C. Afterwards the temperature was decreased to 60 °C, 20 mL of NH_4Ac (0.1 mol/L) were added and the reaction mixture was passed through two C18 Chromafix cartridges (Macherey Nagel). The cartridges were then washed with 10 mL of NH_4Ac and 3 mL of 5%V ethanol containing saline, respectively. The [^{18}F]FET **4** was then eluted with 10 mL of 10%V ethanol containing saline. If necessary the [^{18}F]FET **4** solution can be diluted with saline to reduce the EtOH concentration to be, for example, 5%V. After sterile filtration 0.9–4.5 ± 5% GBq [^{18}F]FET **4** were obtained (45 ± 5%). The radiochemical purity was >99% and the specific activity >80 GBq/μmol at the end of synthesis (EOS). Synthesis time was 35 min from EOB.

4. Conclusion

The synthesis of *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine could be significantly simplified, shortened, and improved. The use of the non-volatile 2-bromoethyl triflate as the starting material and the introduction of a distillation step substitute the HPLC purification steps in common synthesis procedures making the synthesis simple and short. At the same time both the radiochemical yield and the chemical purity could be increased dramatically. Thus, the routine synthesis of *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine became more practicable and economically profitable.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.09.029.

References and notes

1. Vaalburg, W.; Coenen, H. H.; Crouzel, C.; Elsinga, P. H.; Långström, B.; Lemaire, C. *Nucl. Med. Biol.* **1992**, *19*, 227.
2. Langena, K. J.; Hamacher, K.; Weckesser, M.; Floeth, F.; Stoffelsa, G.; Bauer, D.; Coenen, H. H.; Pauleit, D. *Nucl. Med. Biol.* **2006**, *33*, 287.
3. Jager, P. L.; Vaalburg, W.; Pruim, J.; de Vries, E. G.; Langen, K. J.; Piers, D. A. *J. Nucl. Med.* **2001**, *42*, 432.
4. Del Sole, A.; Falini, A.; Ravasi, L.; Ottobrini, L.; De Marchis, D.; Bombardieri, E.; Lucignani *Eur. J. Nucl. Med.* **2001**, *28*, 1851.
5. Wester, H. J.; Herz, M.; Weber, W.; Heiss, P.; Senekowitsch-Schmidtke, R.; Schwaiger, M.; Stöcklin, G. *J. Nucl. Med.* **1999**, *40*, 205.
6. Hamacher, K.; Coenen, H. H. *Appl. Radiat. Isot.* **2002**, *57*, 853.
7. Wang, H.-E.; Wua, S.-Y.; Chang, C.-W.; Liu, R.-S.; Hwang, L.-C.; Lee, T.-W.; Chen, J.-C.; Hwan, J.-J. *Nucl. Med. Biol.* **2005**, *32*, 367.
8. Krasikova, R. N.; Kuznetsova, O. F.; Fedorova, O. S.; Maleev, V. I.; Saveleva, T. F.; Belokon, Y. N. *Bioorg. Med. Chem.* **2008**, *16*, 4994.
9. Tang, G.; Tang, X.; Wang, M.; Luo, L.; Gan, M.; Huang, Z. *J. Labelled Compd. Radiopharm.* **2003**, *46*, 661.
10. Wei, W. M.; Zhi, Y. D.; Qiang, L. S.; Xian, W. Y. *Sci. China, Ser. B* **2007**, *50*, 276.
11. Zuhayra, M.; Alfteimi, A.; Papp, L.; Lützen, U.; Lützen, A.; Von Forstner, C.; Meller, B.; Henze, E. *Bioorg. Med. Chem.* **2008**, *16*, 9121.
12. Pattison, F. L. M.; Peters, D. A. V.; Dean, F. H. *Can J. Chem.* **1965**, *43*, 1689.
13. Zhang, M.-R.; Furutsuka, K.; Yoshida, Y.; Suzuki, K. *J. Labelled Compd. Radiopharm.* **2003**, *46*, 587.
14. Bauman, A.; Piel, M.; Schirrmacher, R.; Rösch, F. *Tetrahedron Lett.* **2003**, *44*, 9165.
15. Jakubke, H.-D.; Jeschkeit, H. *Aminosäuren, Peptide, Proteine*, Verlag Chemie: Weinheim, 1982; ISBN 3-527-25892-2, p 40.
16. Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Welch, M. J. *J. Org. Chem.* **1987**, *52*, 658.