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Research Article

Radiosynthesis of *O*-[^{11}C]methyl-L-tyrosine and *O*-[^{18}F]Fluoromethyl-L-tyrosine as potential PET tracers for imaging amino acid transport

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Summary

Two positron-emitting analogues of tyrosine, *O*-[^{11}C]methyl-L-tyrosine and *O*-[^{18}F]fluoromethyl-L-tyrosine were prepared as new tumor imaging agents. The alkylating agent, [^{11}C]methyl triflate or [^{18}F]fluoromethyl triflate, was simply bubbled through a dimethylsulfoxide solution of L-tyrosine disodium salt at room temperature. After subsequent HPLC purification the labeled L-tyrosine analogues were obtained in decay-corrected radiochemical yields of over 50%, based on their corresponding labeling agent, with radiochemical purities always higher than 98%. The quite straightforward preparation, together with the high radiochemical yields achieved, make both these syntheses suitable for routine production. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: PET, C-11; F-18; *O*-methyl-L-tyrosine; amino acid transport; tumor imaging

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Introduction

Imaging of amino acid transport and following protein synthesis are expected to be one of the most promising methods for the detection of tumors by positron emission tomography (PET).[1,2] Especially for brain tumors positron-emitting amino acids are reported to be superior to [^{18}F]FDG, which is currently the most successful and widely used PET radiopharmaceutical for cancer imaging. Among the relatively large number of ^{11}C- and ^{18}F-labeled natural and synthetic amino acids synthesized so far, L-[^{11}C]methionine is currently the most frequently used for routine PET studies, owing to its convenient and efficient synthesis from [^{11}C]methyl iodide. Unfortunately, the metabolism of this radiopharmaceutical involves also some trans-methylation so that its use for quantitative imaging makes interpretation of results complex.[3]

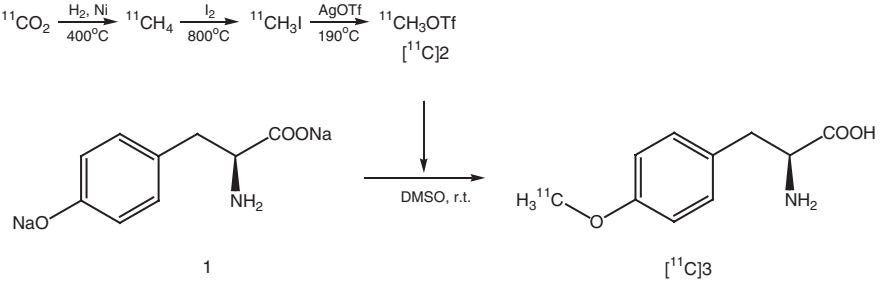
Using the same simple synthetic strategy several ^{18}F-labeled amino acids such as 2-[^{18}F]fluoro-L-phenylalanine[4,5] and 2-[^{18}F]fluoro-L-tyrosine[6] have been synthesized by electrophilic [^{18}F]fluorination from [^{18}F]fluorine or [^{18}F]acetyl hypofluorite. However, the well-known constraints related to these labeling agents (low starting activity; low specific activity; low production yield) contributes to make these approaches inconvenient. On the other hand, starting from [^{18}F]fluoride, which can be produced on a large scale by proton irradiation of enriched ^{18}O-water, the high yield radiosyntheses of 4-[^{18}F]fluoro-L-phenylalanine,[7] 4-[^{18}F]fluoro-L-proline,[8,9] 1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid[10,11] and *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET)[12] have recently been developed. Especially, the latter, prepared in a simple way and in high radiochemical yield via 2-[^{18}F]fluoroethyl tosylate or by direct ^{18}F-fluorination of *O*-(2-tosyloxyethyl)-*N*-trityl-L-tyrosine tert-butylester,[13] is expected to be a promising tracer for imaging amino acid transport.[12,14]

[^{11}C]Methyl triflate ([^{11}C]CH_3OTf, [^{11}C]**2**) is a powerful [^{11}C]methylating agent prepared on-line from [^{11}C]methyl iodide.[15] In general, its superior reactivity allows the [^{11}C]methylation to proceed faster and with no need for heating, thus greatly simplifying synthetic methods.[16–18] This main feature has induced us to recently develop the analogue [^{18}F]fluoromethyl triflate ([^{18}F]CH_2FOTf, [^{18}F]**4**).[19] Aim of the present study is to apply [^{11}C]CH_3OTf and [^{18}F]CH_2FOTf to the preparation of *O*-[^{11}C]methyl-L-tyrosine ([^{11}C]**3**) and *O*-[^{18}F]fluoromethyl-L-tyrosine ([^{18}F]**5**), respectively.

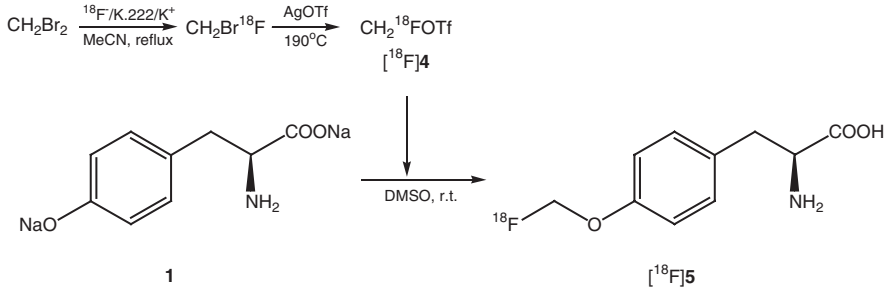
Results and Discussion

The two positron-emitting tyrosine analogues, [^{11}C]**3** and [^{18}F]**5**, were prepared by bubbling the corresponding triflates, [^{11}C]**2** and [^{18}F]**4**, into the precursor solution (Schemes 1 and 2). The capacity of the reaction solvent (0.5 ml) to efficiently retain the flowing alkylating agent was one of the crucial factors affecting the radiochemical yield. This was even more relevant for [^{18}F]**4** because of the relatively high flow rate (100 ml/min) coming from the Sep-Pak silica cartridges during its purification.[19] Thus, the solvents listed in Table 1 were compared in terms of trapping efficiency of [^{18}F]**4** and radiochemical yield of the subsequent [^{18}F]fluoromethylation reaction. DMSO was the first choice as it was used for the preparation of *O*-[^{18}F]fluoroethyl-L-tyrosine from [^{18}F]fluoroethyltosylate.[12] As expected it showed comparatively high trapping and [^{18}F]fluoromethylation yield. Conversely, in spite of its good trapping efficiency, no formation of [^{18}F]**5** was observed with DMF probably due to the low solubility of the precursor in this solvent. Ethanol afforded a reasonable trapping efficiency and radiochemical yield, although the latter was remarkably improved by heating at 110°C. On the other hand, methanol showed a low trapping efficiency and even lower [^{18}F]fluoromethylation yield, even when heated. Thus, these results reconfirmed DMSO as the best solvent also for the preparation of *O*-[^{18}F]fluoromethyl-L-tyrosine.

The main advantage in using triflates as labeling agents in nucleophilic substitution reactions is that they are, as a rule, more reactive than the corresponding halides, a feature which allows the reaction to proceed rapidly even at room temperature. Our results followed this line. As shown in Table 2, both [^{11}C]**2** and [^{18}F]**4** afforded



Scheme 1. Radiosynthesis of *O*-[^{11}C]methyl-L-tyrosine



Scheme 2. Radiosynthesis of *O*-[^{18}F]fluoromethyl-L-tyrosine

Table 1. Comparison of trapping yields of [^{18}F]fluoromethyl triflate ([^{18}F]4) and radiochemical yields of *O*-[^{18}F]fluoromethyl-L-tyrosine ([^{18}F]5) in various solvent

		[^{18}F]Fluoromethylation		
Solvent[a]	Trapping efficiency[b]	Temperature	Time[c]	Yield[d]
DMSO	75–87%	r. t.	5 min	>99%
		110°C	3 min	>99%
EtOH	~60%	r. t.	10 min	35% (64%)[e]
		110°C	10 min	90%
MeOH	40–60%	r. t.	10 min	8%
		60°C	10 min	26%
DMF	~80%	r. t./110°C	10 min	0%

[a] A volume of 0.5 ml was used for dissolving 1 mg precursor. No effort was made to optimize the volume.
[b] Flowing [^{18}F]**4** was trapped at room temperature.
[c] Reaction time after bubbling of [^{18}F]**4**.
[d] Reaction yield based on the trapped [^{18}F]**4**.
[e] 2 mg of precursor were used.

reasonable conversion rates at room temperature even after just 1 min, the main difference being that the yield of [^{18}F]**4** had a higher dependence on the amount of precursor used. It is interesting to note that radiochemical yields of [^{11}C]**3** could not be improved over 60% and were always, all things being equal, lower than those of [^{18}F]**5**.

The preparation of the 'cold' standard *O*-fluoromethyl-L-tyrosine **5** required a different approach. In fact, the straightforward transfer of the method used for the hot run failed to afford the fluoroalkylating agent **4**. A carrier-added reaction of [^{18}F]fluoride with CH_2Br_2 showed that the presence of large amount of fluoride, as in the cold preparation, led to the synthesis of [^{18}F]CH_2F_2 instead of [^{18}F]CH_2BrF. Thus, fluoromethyl tosylate, prepared from CH_2I_2 via $CH_2(OTs)_2$, was selected as an alternative to fluoromethyl triflate. [20] However, this

Table 2. Radiochemical yields of *O*-[^{11}C]methyl-L-tyrosine ([^{11}C]3) and *O*-[^{18}F]fluoromethyl-L-tyrosine ([^{18}F]5)

Compound	Precursor amount[a] (mg)	Reaction time[b] (min)	RCY[c]
[^{11}C]**3**	0.5	1.5	34%
	0.5	5	47%
	0.5	10	57%
	1	1	55%
	1.6	1	57%
	2.5	1	51%
[^{18}F]**5**	0.5	1	51%
	0.5	5	66%
	0.5	10	71%
	1	1	78%
	1	5	87%
	2.3	1	84%

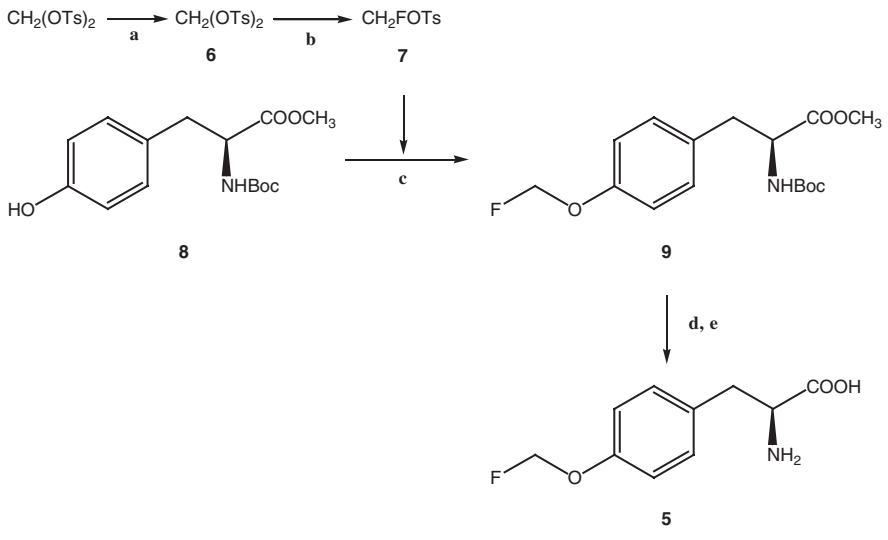
[a] Dissolved in 0.5 ml DMSO.
[b] Additional reaction time after bubbling at room temperature.
[c] Decay-corrected radiochemical yield, based on the labeling agent ($n = 1$).

agent was not highly reactive and hence the reaction with precursor **1** did not afford the desired product **5**. Consequently, CH_2FOTs was applied to a protected tyrosine following a method similar to that used for the synthesis of 'cold' FET[12] (Scheme 3).

Figure 1 shows the HPLC separation of the desired product, [^{11}C]**3** or [^{18}F]**5**, from the reaction mixture. It can be seen that the separation was easily carried out because no other chemical or radiochemical impurity peaks eluted near the product. Thus, radiochemical purities of both products after HPLC purification were usually greater than 98%.

Although the number of [^{18}F]fluoromethylated compounds synthesized so far is not large enough to establish a clear pattern of behavior, it has been reported that some [^{18}F]fluoromethylated compounds are not stable.[21,22] However, an HPLC investigation carried out over a 2-h period on [^{18}F]**5** in saline showed total absence of decomposition, thus enabling the use of this tracer in PET studies.

Amino acid transport is a relatively rapid process and tumor imaging based on amino acid transport can be performed within a relatively short time.[2] From this point of view *O*-[^{11}C]methyl-L-tyrosine, due to its easy preparation, is expected to serve as a useful imaging agent. On the other hand, *O*-[^{18}F]fluoromethyl-L-tyrosine, thanks to its longer-half-life and high production yield, has the further advantage of possible distribution to satellite PET centers.



Scheme 3. Synthesis of *O*-fluoromethyl-L-tyrosine (a) AgOTs, MeCN, reflux; (b) TBAF, MeCN, reflux; (c) K_2CO_3, acetone, reflux; (d) aqueous NaOH, MeOH, 70°C; (e) HCl/Et_2O, CH_2Cl_2

Experimental

All reagents and solvents were commercially available and used without further purification. Anhydrous acetonitrile (MeCN), anhydrous dimethysulfoxide (DMSO), dibromomethane and 1 M hydrogen chloride in ether were purchased from Aldrich, disodium salt of L-tyrosine **1** from Sigma, Kryptofix 222 (K. 222) from Merck, and *O*-methyl-L-tyrosine from Bachem. Solid-phase extraction columns (Sep-Pak Plus silica and AC-2) were obtained from Waters.

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} TLC plates (aluminum) or RP-18 F_{254} TLC plates (glass). Column chromatography was performed using Silica Gel 60 (spherical, 40–50 μm) purchased from Kanto Chemical Co., Inc. ^{1}H NMR spectra were recorded on a Bruker AM-600 (600 MHz). Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a JEOL JMS-DX303 and -DX500, respectively.

A silver triflate-Graphpac (AgOTf, Aldrich; Graphpac GC, Alltech) column (4×60 mm) was prepared as previously described.[17] The column was heated at 190°C under He flow (30 ml/min) for at least 20 min before starting the synthesis.

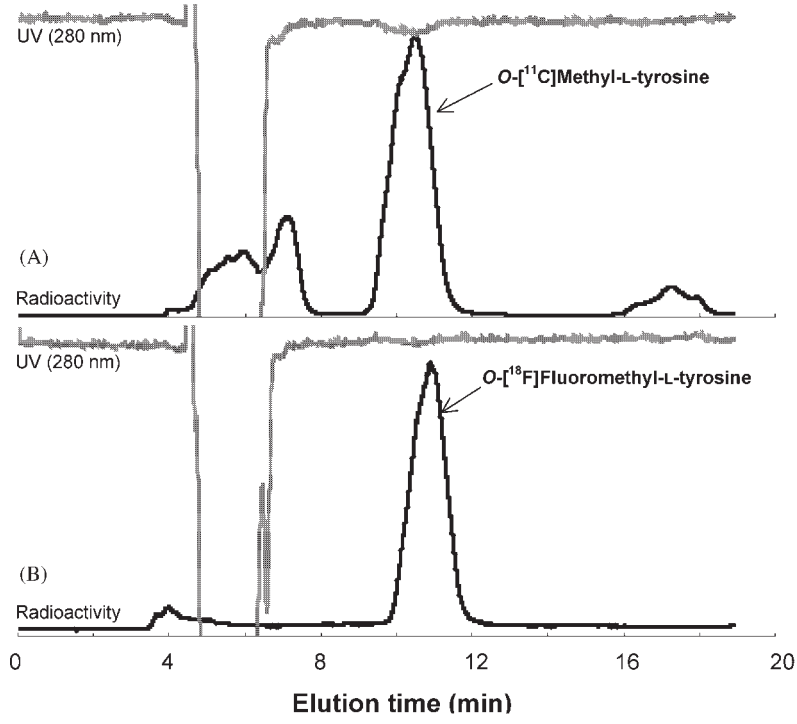


Figure 1. HPLC purification of *O*-[^{11}C]methyl-L-tyrosine (A) and *O*-[^{18}F]fluoromethyl-L-tyrosine (B)

HPLC analysis was performed on a Puresil C18 column (4.6 × 150 mm, Waters) with a solvent system of MeOH/AcOH/1 mM sodium octylsulfate-1 mM EDTA (250:6:744) at a flow rate of 2.0 ml/min. Retention times of *O*-methyl-L-tyrosine and *O*-fluoromethyl-L-tyrosine were 4.1 min and 4.3 min, respectively.

*Fluoromethyl tosylate (***7***, Scheme 3)*[20]

Bis(tosyloxy)methane **6** was prepared from diiodomethane and silver tosylate in dry acetonitrile by heating at reflux according to the literature.[23] To a solution of bis(tosyloxy)methane **6** (7.40 g, 20.7 mmol) in dry MeCN (50 ml) was added a solution of tetra-*n*-butylammonium fluoride (5.42 g, 21.0 mmol) in dry MeCN (10 ml) and the solution was stirred under reflux. After 2 h, the solvent was removed under reduced pressure and the residue dissolved in AcOEt and washed with H_2O. The organic solution was dried over $MgSO_4$, filtrated, and removed under reduced pressure. The residue was purified by chromatography on silica gel eluted with hexane/AcOEt (5:2) to afford 1.30 g (6.37 mmol, 31%) of

7 as a colorless oil. ^{1}H NMR ($CDCl_3$/TMS): δ 2.46 (3 H, s), 5.74 (2 H, d, $J = 50.7$ Hz), 7.36 (2 H, d, $J = 7.8$ Hz), 7.83 (2 H, d, $J = 8.1$ Hz). EI-MS (m/z, %): 204 (M^+, 57), 155 ($[M\text{-}OCH_2F]^+$, 86), 91 ($[M\text{-}SO_3CH_2F]^+$, 100). EI-HRMS (M^+): calculated for $C_8H_9FO_3S$ 204.0254, found 204.0245.

*2-tert-Butoxycarbonylamino-3-(4-fluoromethoxyphenyl)-propionic acid methyl ester (**9**, Scheme 3)*

To a solution of 2-*tert*-butoxycarbonylamino-3-(4-hydroxyphenyl)-propionic acid methyl ester **8** (610 mg, 2.06 mmol) and K_2CO_3 (552 mg, 3.99 mmol) in acetone (8.0 ml) a solution of **7** (520 mg, 2.54 mmol) in acetone (2.0 ml) was added and thereafter refluxed for 2 days. After being cooled to room temperature, the reaction solution was diluted with saturated aqueous NH_4Cl solution and extracted with AcOEt. The organic layer was dried over $MgSO_4$, filtrated, and removed under reduced pressure. The residue was purified by chromatography on silica gel eluted with hexane/AcOEt (2:1) to give 273 mg (0.83 mmol, 40%) of **9** as a white solid. ^{1}H NMR ($CDCl_3$/TMS): δ 1.49 (9 H, s), 3.02 (1 H, dd, $J = 13.9$, 5.9 Hz), 3.09 (1 H, dd, $J = 13.8$, 5.8 Hz), 3.72 (3 H, s), 4.54–4.58 (1 H, m), 4.97 (1 H, d, $J = 7.7$ Hz), 5.69 (2 H, d, $J = 54.7$ Hz) 7.01 (2 H, d, $J = 8.5$ Hz), 7.08 (2 H, d, $J = 8.4$ Hz). EI-MS (*m*/*z*, %): 327 (M^+, 1.6), 139 ($[CH_2C_4H_4OCH_2F]^+$, 100), EI-HRMS (M^+): calculated for $C_{16}H_{22}FNO_5$ 327.1476, found 327.1459.

*2-Amino-3-(4-fluoromethoxyphenyl)-propionic acid (O-fluoromethyl-*L*-tyrosine, **5**, Scheme 3)*

To a solution of **9** (264 mg, 0.806 mmol) in MeOH (3.0 ml) 2N NaOH (600 µl) was added and the reaction mixture heated for 2.5 h at 70°C. After cooling down to room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with H_2O, acidified with 2N HCl (650 µl), and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$, filtered, and removed under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (2.0 ml) and then treated with a 1 M solution of HCl in ether (1.0 ml, 1.0 mmol). After stirring the reaction solution for 18 h, a white precipitate was formed which was filtered, washed with Et_2O and dried to afford a white powder (85 mg). A portion of this powder (11 mg) was purified with reversed-phase HPLC (YMC-Pack ODS-A column, 300 × 10 mm) eluted with EtOH/H_2O/

AcOH (10:87.5:2.5) to afford, after evaporation, pure **5** as a white powder (7 mg). ^{1}H NMR (D_2O/TSP): δ 3.12 (1 H, dd, $J = 14.7$, 7.7 Hz), 3.26 (1 H, dd, $J = 14.8$, 5.3 Hz), 3.97 (1 H, dd, $J = 7.7$, 5.3 Hz), 5.82 (2 H, d, $J = 54.5$ Hz), 7.17 (2 H, d, $J = 8.5$ Hz), 7.32 (2 H, d, $J = 8.6$ Hz). EI-MS (m/z, %): 213 (M^+, 3.7), 168 ($[M\text{-}CO_2H]^+$, 5.5), 139 ($[CH_2C_4H_4OCH_2F]^+$, 100), EI-HRMS (M^+): calculated for $C_{10}H_{12}FNO_3$ 213.0798, found 213.0775.

*O-[^{11}C]Methyl-L-tyrosine ([^{11}C]**3**, Scheme 1)*

[^{11}C]Carbon dioxide was produced by the $^{14}N(p,\alpha)^{11}C$ reaction on a N_2 target containing 0.5% O_2 with 12 MeV protons from a Cypris HM12 cyclotron (SHI) at CYRIC. It was then converted into [^{11}C]methyl iodide by gas phase iodination via [^{11}C]CH_4 with a MeI MicroLab system (GE). The [^{11}C]methyl iodide produced was then passed through the heated AgOTf column (190°C) with a He flow (35 ml/min) and converted to [^{11}C]methyl triflate ([^{11}C]**2**).

[^{11}C]**2** was bubbled over about 1 min through a DMSO solution of precursor **1** (1 mg/0.5 ml) in a small vented vial (Wheaton V vial, 5 ml) at room temperature. A disposable charcoal column (Sep-Pak AC-2) placed on the vent adsorbed the unretained [^{11}C]**2** and was used to determine the trapping efficiency. The reaction was immediately quenched by adding water (0.5 ml). The resulting mixture was transferred to an HPLC sample loop and then injected onto a semi-preparative C18 column (YMC ODS A-324, 10×300 mm) and eluted with a solvent system of ethanol/acetic acid/water (10:2.5:87.5) at a flow rate of 4 ml/min. As seen in Figure 1 (A), the desired product eluted between 9 and 11 min. This fraction was collected, evaporated to dryness under reduced pressure and the residue dissolved in saline. The total synthesis time from the end of bombardment (EOB) was about 40 min. The final product was identified as *O*-[^{11}C]methyl-L-tyrosine by analytical HPLC. Its radiochemical purity was also determined at the same time.

*[^{18}F]Fluoromethyl triflate ([^{18}F]**4**, Scheme 2)*

[^{18}F]Fluoride was produced by 12 MeV proton irradiation of ^{18}O-enriched water (0.7 ml) and recovered onto an anion exchange resin. The [^{18}F]fluoride retained by the resin was eluted with an aqueous K_2CO_3 solution (33 mM, 1 ml).

The detailed procedure for the preparation of [^{18}F]fluoromethyl triflate ([^{18}F]**4**) from [^{18}F]fluoride is described elsewhere.[19] Briefly, the [^{18}F]fluoride was added to a MeCN solution of K.222 (15 mg, 40 μmol) in a septum-sealed round bottom flask, which was then dipped in an oil bath (110°C) to evaporate off the solvent under a stream of He (200 ml/min). A solution of CH_2Br_2 (50 μl) in dry MeCN (1 ml) was added to the residue and the solution was stirred and heated for 4 min. After reaction the flask was allowed to cool to room temperature and [^{18}F]CH_2BrF formed was then passed through four Sep-Pak silica cartridges connected in series by a He flow (100 ml/min) to separate the product from CH_2Br_2. When [^{18}F]CH_2BrF began to elute from the Sep-Paks, it was allowed to flow through the heated (190°C) AgOTf column to convert it to [^{18}F]**4**. The decay-corrected radiochemical yield of [^{18}F]**4** from [^{18}F]fluoride was usually 50%.

*O-[^{18}F]Fluoromethyl-*L*-tyrosine ([^{18}F]**5**, Scheme 2)*

The preparation and purification of *O*-[^{18}F]fluoromethyl-L-tyrosine from [^{18}F]**4** was performed with the same procedure used for *O*-[^{11}C]methyl-L-tyrosine. The [^{18}F]**4** was passed at a flow rate of 100 ml/min through a DMSO solution of precursor (0.5 ml) in a small vial (Wheaton V vial, 5 ml) vented to a Sep-Pak AC-2 cartridge. The concentration of precursor was varied from 1 to 4 mg/ml to optimize the reaction. After trapping [^{18}F]**4** the reaction was continued by either standing at room temperature for another several minutes or heating in the oil bath for up to 10 min at 110°C and then quenched by adding water (0.5 ml). The whole solution was injected onto a semi-preparative C18 column (YMC ODS A-324, 10 × 300 mm) and eluted with a solvent system of ethanol/acetic acid/water (10:2.5:87.5) at a flow rate of 4 ml/min. As seen in Figure 1 (B), the desired product eluted between 10 and 12 min. This fraction was collected, evaporated to dryness under reduced pressure, and the residue dissolved in saline (2 ml). The overall synthesis time from the EOB was about 50 min.The final product was identified as *O*-[^{18}F]fluormethyl-L-tyrosine by analytical HPLC. Its radiochemical purity was also determined at the same time and chemical stability in saline was checked by HPLC over a 2-h range.

Conclusion

O-[^{11}C]Methyl-L-tyrosine and *O*-[^{18}F]fluoromethyl-L-tyrosine were prepared in satisfactorily high radiochemical yields from [^{11}C]methyl

triflate and [^{18}F]fluoromethyl triflate, respectively (> 50%, decay-corrected, based on the labeling agent). Owing to the high reactivity of the labeling agents the reactions proceeded rapidly without heating, resulting in a simplified synthesis procedure feasible for routine production. A biodistribution study of *O*-[^{18}F]fluoromethyl-L-tyrosine in comparison to *O*-[^{18}F]fluoroethyl-L-tyrosine is currently in progress.

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References

1. Jager PI, Vaalburg WV, Pruim J, de Vries EGE, Langen K-J, Piers DA. *J Nucl Med* 2001; **42**: 432–445.
2. Laverman P, Boerman OC, Cortens FHM, Oyen WJG. 2002; *Eur J Nucl Med* **29**: 681–690.
3. Pascali C, Bogni A, Iwata R, Decise D, Crippa F, Bombardieri E. *J Label Compds Radiopharm* 1999; **42**: 715–724.
4. Hoyte RM, Lin SS, Christman DR, Atokins HL, Hauser WL, Wolf AP. *J Nucl Med* 1971; **12**: 280–286.
5. Murakami M, Takahashi T, Kondo Y, *et al*. *J Label Compds Radiopharm* 1988; **25**: 573–578.
6. Coenen HH, Kling P, Stoecklin G. *J Nucl Med* 1989; **30**: 1367–1372.
7. Lemaire C, Guillaume M, Palmer AJ, Cantineau R. *Appl Radiat Isot* 1987; **38**: 1033–1038.
8. Hamacher K. *J Label Compds Radiopharm* 1999; **42**: 1135–1144.
9. Mazza SM. *J Label Compds Radiopharm* 2000; **43**: 1047–1058.
10. Shoup TM, Goodman MM. *J Label Compds Radiopharm* 1999; **42**: 215–225.
11. Shoup TM, Olson J, Hoffman JM, *et al*. *J. Nucl. Med*. 1999; **40**: 331–338.
12. Wester HJ, Herz M, Weber W, *et al*. *J Nucl Med* 1999: **40**: 205–212.
13. Hamacher K, Coenen HH. *Appl Radiat Isot* 2002; **57**: 853–856.
14. Weber WA, Wester HJ, Grosu AL, *et al*. *Eur J Nucl Med* 2000; **27**: 542–549.
15. Jewett DM. *Appl Radiat Isot* 1992; **43**: 1383–1385.

16. Nagren K, Muller L, Halldin C, Swahn C-G, Lehikoinen P. *Nucl Med Biol* 1995; **22**: 235–239.
17. Iwata R, Pascali C, Bogni A, Miyake Y, Yanai K, Ido T. *Appl Radiat Isot* 2001; **55**: 17–22.
18. Iwata R, Pascali C, Bogni A, *et al*. *J Label Compds Radiopharm* 2002; **45**: 271–280.
19. Iwata R., Pascali C, Bogni A, Furumoto S, Terasaki K, Yanai K. *Appl Radiat Isot* 2002; 57: 347–352.
20. Block D, Coenen HH, Stöcklin G. *J Label Compds Radiopharm* 1987, **24**: 1029–1042.
21. Petric A., Barrio JR, Namavari M, Huang SC, Satyamurthy N. *Nucl Med Biol* 1999; **26**: 529–535.
22. Zessin J, Eskola O, Brust P, *et al*. *Nucl Med Biol* 2001; 28: 857–863.
23. Emmons WD, Ferries AF. *J Am Chem Soc* 1953; **75**: 2257.

