A new precursor for the preparation of 6-[^{18}F]-Fluoro-*L*-m-tyrosine (FMT): Efficient synthesis and comparison of radiolabeling

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Abstract

For the electrophilic preparation of 6-[^{18}F]-Fluoro-*L*-m-tyrosine (FMT), a PET tracer for measuring changes in dopaminergic function in movement disorders, a novel precursor, N-(tert-butoxycarbonyl)-3-(tert-butoxycarbonyloxy)-6-trimethylstannnyl-L-phenylalanine ethyl ester, was synthesized in four steps and 26% yield starting from L-m-tyrosine. FMT produced by two methods at two institutions was comparable in decay corrected yield, 25-26%, and quality (chemical, enantiomeric, and radiochemical purity and specific activity) as that obtained with the original *N*-trifluoroacetyl-3-acetyl-6-trimethylstannyl-*L*-m-tyrosine ethyl ester FMT precursor.

1.0 Introduction

A widely used PET tracer for imaging dopaminergic metabolism is 6-[^{18}F]-Fluoro-3,4-dihydroxyphenylalanine (F-DOPA, **1**) (Garnett et al., 1983). The main application of this tracer is the visualisation of the dopaminergic function in the brain by measuring the activity of the enzyme aromatic *L*-amino acid decarboxylase (AAAD). One shortcoming that complicates the use of this agent is that F-DOPA is methylated in the periphery by the enzyme catecholamine-*O*-methyltransferase (COMT) producing 6-[^{18}F]-Fluoro-3-*O*-methyl-DOPA (OMFD) (Pauwels et al., 1994, DeJesus et al., 2000). OMFD crosses the blood-brain barrier bidirectionally, and distributes widely throughout the brain, compromising image contrast. Intricate kinetic models have been developed to address this metabolic interference (Shoghi-Jadid et al., 2000). FMT (6-[^{18}F]-Fluoro-*L*-m tyrosine **2**, Figure 1) represents an alternative tracer that is a substrate for AAAD but not COMT thus providing better visual contrast on the brain images while reducing the need for complex multi-compartment kinetic modeling (Barrio et al., 1996, Melega et al., 1989, Jordan et al., 1997).

FMT has been synthesized in two steps by electrophilic fluorodestannylation of *N*-trifluoroacetyl-3-acetyl-6-trimethylstannyl-*L*-m-tyrosine ethyl ester **3** (Figure 1) followed by exhaustive deprotection of the acid, amine and phenol (Namavari et al., 1993). Preparation of the FMT precursor **3** requires seven steps from L-m-tyrosine (3-hydroxy-l-phenylalanine). A short and simple synthesis of the precursor for F-DOPA, four steps from 3,4-dihydroxy-L-phenylalanine, has been described by Dolle et al. (1998) and, more recently, improved upon by Füchtner et al. (2002). This methodology was applied to prepare a new FMT precursor, N-(tert-butoxycarbonyl)-3-(tert-butoxycarbonyloxy)-6-trimethylstannnyl-L-phenylalanine ethyl ester **4**. A comparison of the reactivity of the two stannylated FMT precursors, **3** and **4** (Figure 1), towards electrophilic fluorination and the ultimate preparation of FMT was conducted.

2.0 Experimental

2.1 General- Organic Synthesis

NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 MHz for proton and 75.46 MHz for carbon-13 spectra. $CDCl_3$ was used as solvent. Chemical shifts are reported in ppm relative to the solvent peak of $CDCl_3$. Coupling constants are given in hertz (Hz). Analytical thin-layer chromatography was performed using Merck silica gel 60F-254 plates; flash chromatography was performed using Merck silica gel (60-200 mesh). All chemicals were obtained from VWR Darmstadt, Aldrich or Fluka and were used without further purification unless otherwise noted. *L-m*-Tyrosine (3-hydroxy-phenylalanine) was prepared from *D,L*-m-Tyrosine (Across) by literature methods (Tong et al., 1971).

*2.2 Synthesis of N(-tert-Butoxycarbonyl)-3-tert-butoxycarbonyloxy-L-phenylalanine ethyl ester (**6**)*

L-m-Tyrosine **5** (10g, 55.2 mmol) was dissolved in 250 mL of dry ethanol and cooled to 0 °C . A gentle stream of hydrogen chloride was then bubbled into the solution for about 30 min. At this point all of the *L*-m-tyrosine was dissolved. The cooling bath was removed and the solution was refluxed overnight. The solvent was removed and the remaining syrup was dried for 24 h in vacuo to yield 13.5 g (100 %) of a pale yellow foam. The product was used in the next step without further purification .

The ethyl ester hydrochloride salt (13.5 g, 54.9 mmol) was dissolved in 40 mL of dry DMF. Triethylamine (30.5 mL, 220 mmol) was added slowly. The reaction mixture was cooled to 0 °C and di-tert-butyldicarbonate (30 g, 137 mmol) in 40 mL of DMF was added dropwise . The reaction mixture was stirred at room temperature for 48 h. Then the reaction mixture was diluted with ethyl acetate (200 mL) and washed with brine (3 x 100 mL). The combined aqueous phases were reextracted with ethyl acetate (3 x 50 mL). The pooled organic phases

were dried over sodium sulfate and the solvent was evaporated. The product was purified by flash chromatography over silica gel (petrol ether/ethyl acetate = 4/1). The fractions with an R_f-value of 0.41 were collected and the solvent was evaporated to give the product as colourless oil (14.2 g, 63 %). ^{1}H-NMR: 1.19 (t, *J* = 7.14, 3H, CH_3); 1.40 (s, 9H), 1.53 (s, 9H), 3.07 (m, 1H); 4.13 (q, *J* = 7.14, 2H, CH_2); 4.53 (dd, J = 13.7 and 6.2, 1H); 4.98 (d, *J* = 8.1, 1H, NH); 6.90 –7.05 (m, 3H); 7.26 (t, partially obscured by $CDCl_3$ peak, *J* = 7.9, 1H).

*2.3 Synthesis of N(-tert-Butoxycarbonyl)-3-tert-butoxycarbonyloxy-6-iodo-L-phenylalanine ethyl ester (***7***)*

O,N-DiBoc-*L*-m-tyrosine ethyl ester **6** (10 g, 24.4 mmol) was dissolved in dichloromethane (200 mL) under an argon atmosphere. Silver trifluoroacetate (6.63 g, 30 mmol) and iodine (6.8 g, 26.8 mmol) were subsequently added. The flask was protected from light and the mixture was stirred for 48 h at room temperature. The solid was filtered off and the solvent was evaporated. Flash chromatography (petrol ether/ethyl acetate = 4/1) afforded the product as yellow viscous oil (8.9 g, 68 %). ^{1}H-NMR: 1.21 (t, *J* = 7.2, 3H, CH_3), 1.39 (s, 9H, Boc), 1.55 (s, 9H, Boc), 3.10 (dd, *J* = 13.3 and 7.9, 1H), 3.25 (dd, *J* = 13.3 and 6.2, 1H), 4.17 (m, 2H), 4.61 (dd, *J* = 14.2 and 7.6, 1H), 5.06 (d, *J* = 9.6, 1H), 6.81 (dd, *J* = 8.4 and 2.6, 1H), 7.05 (d, *J* = 2.8, 1H), 7.8 (d, *J* = 8.5, 1H).

*2.4 Synthesis of N(-tert-Butoxycarbonyl)-3-tert-butoxycarbonyloxy-6-(trimethylstannyl)-L-phenylalanine ethyl ester (***4***)*

The Diboc-iodo-*L*-m-tyrosine ethyl ester **7** (5.25 g, 11.1 mmol) was dissolved in 110 mL of dioxane. Tetrakistriphenylphosphine palladium (0) (1.28 g, 10 mol%) and hexamethyldistannane (9.7 mL, 22.2 mmol) were added. The mixture was degassed, flushed with argon and heated to reflux until the solution turned black. The solution was filtered over

celite, the filter cake was washed with ether and the combined organic solution was evaporated. The residue was purified by flash chromatography over silica gel (hexane/ethyl acetate = 10/1). The product was a clear viscous oil (3.9 g, 62 %). ^{1}H-NMR: □ 0.32 (s, with Sn satellites, $^{2}J_{Sn,H}$ = 54, 9H, $Sn(CH_3)_3$), 1.18 (t, *J* = 6.9, 3H, CH_3), 1.36 (s, 9H), 1.53 (s, 9H), 2.99 (m, 1 H), 3.09 (m, 1H), 4.14 (q, *J* = 7.1, 2H, CH_2), 4.47 (dd, *J* = 14.1 and 7.9, 1 H), 4.87 (d, *J* = 8.6, 1H), 7.0 (m, 2 H), 7.41 (d, *J* = 7.8, with Sn satellites, $^{2}J_{Sn,H}$ = 46.1, 1H).

2.5. General- Radiosynthesis

All chemicals, unless otherwise stated, were purchased from Aldrich or Fluka and used without further purification. Authentic 6-fluoro-*L*-m-tyrosine was obtained from ABX or purified from decayed ^{18}F-FMT preparations. *N*-trifluoroacetyl-3-acetyl-6-trimethylstannyl-*L-m*-tyrosine ethyl ester **3** was prepared according to published methods. (Namavari, 1993). Neon gas and 1% F_2 in neon gas were purchased from CarbaGas. Oxygen-18 gas (^{18}O-O_2, >99%) was purchased from Isotec (Miamisburg, OH). HPLC separation and analysis were performed with the equipment and columns described below for each institution.

2.6 Radiosynthesis of FMT *Method 1- LBNL:*

Fluorine-18 labeled F_2 gas was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction using a modification of the 'two shoot' method (Nickles, 1994). Proton (10-11 MeV) irradiation of ^{18}O-O_2- using the CTI RDS-111 cyclotron followed by cryogenic trapping of the ^{18}O-O_2 and a second irradiation of fluorine gas (^{19}F-F_2) in argon produces the ^{18}F-F_2.

In a remotely controlled synthetic apparatus the ^{18}F-F_2 / argon gas mixture (110-120 □mol, 300 mL volume) was bubbled through a solution of the stannylated precursor **3** or **4** (~50 mg, ~100 □mol) in Freon 11 (15 mL) into a pyrex reaction vessel at room temperature. The reaction mixture was then passed through 1500g of silica gel in two cartridges (Alltech Maxi-clean 600 mg/ 900 mg cartridges or PJ Cobert Xpertec Snap Cap SPE Cartridge 600

mg/ 900 mg silica). The protected ^{18}F-FMT was eluted from the silica column using a 25% diethyl ether/hexane solution. The column eluent was monitored for the desired major radioactive peak by an inline radiation detector (Carroll Ramsey Associates, CRA) and the labeled intermediate was collected in a test tube containing aqueous 48% HBr heated to 130°C. A gentle stream of nitrogen was used to evaporate the ether/ hexane to dryness and hydrolysis was continued for an additional 5 min. The reaction mixture was cooled by turning off the heater for 1 minute and the warm solution was partially neutralized with aqueous NaOH. This mixture was then injected onto a reversed-phase HPLC column (Whatman M9/50 ODS-3, 9.4 x 500 mm, 0.01% ascorbic acid /0.1% acetic acid in water, Eldex CC-100-S pump, flow = 5 mL/min, inline CRA radiation detector) and eluted to provide the labeled FMT (T_r = 12-13 min.). The FMT was collected through a 0.22 μm filter into a dose vial.

An aliquot of the ^{18}F-FMT solution was injected on an analytical reversed-phase HPLC column (Phenomenex Bondclone 10 C18, 3.9 x 300 mm, 3% methanol/ 0.1% acetic acid/ water, Waters Model 590 pump with a Linear UV detector, 282 nm, and an inline CRA radiation detector, flow = 1 mL/min, T_r = 7-8 min) to determine the radiochemical purity. Specific activity was calculated using the integrated peak from the analytical HPLC chromatogram and a standard curve developed from known quantities of non-radioactive FMT. An additional aliquot of the FMT solution was injected onto a chiral HPLC column (Phenomenex Chirex D-penicillamine column, 4.6 x 150 mm, 2mM Cu_2SO_4 in 15% methanol/ water, Waters Model 590 pump with a Linear UV detector, 282 nm, and an inline CRA radiation detector, flow = 1 mL/min, T_r (L) = 16.7 min, T_r (D) = 21.0 min) to determine the enantiomeric purity of the FMT . Enantiomeric excess was calculated from the integrated area under the peaks on the HPLC chromatogram.

A total tin analysis (Total Tin by EPA Method 200.8) was performed on decayed samples of the final product by Toxscan, Inc. (Watsonville, CA).

2.7 Radiosynthesis of FMT *Method 2 - PSI*

^{18}F-F_2 gas was produced by the $^{20}Ne(d, \_)^{18}F$ nuclear reaction (Cyclotron system: PETtrace, GE Medical Systems).

About 50 µmol of the corresponding precursor were dissolved in approx. 5 ml Freon 11 and the solution cooled to -30°C. During the first labeling step, ^{18}F-F_2 / Neon gas mixture was bubbled through for a period of 7 min. Thereafter the solvent was evaporated at 50°C using vacuum and a gentle stream of He. Then the protecting groups were removed in one additional step upon heating the mixture for 10 min at 130°C with 0.8 ml HBr (48% solution).

After cooling the reaction mixture to room temperature the solution was partially neutralized (0.7 ml 5M NaOH) and 0.3 ml of HPLC eluent were added. The reaction mixture was injected without further treatment onto the semi-preparative HPLC column (Alltech Adsorboshere C18 5µ, L 300 mm, ID 10 mm; eluent: 5 mM sodium acetate, 0.1% acetic acid, 0.01% ascorbic acid, flow 7 ml/min) equipped with an appropriate guard column. The radioactive peak corresponding to authentic FMT was collected through a sterile filter and analyzed (Alltech Alltima C18 5µ, L 250 mm, ID 4.6 mm; eluent: 3% MeOH, 0.1% acetic acid, flow 1 ml/min).

3.0 Results and Discussion

The original synthesis of *N*-trifluoroacetyl-3-acetyl-6-trimethylstannyl-*L-m*-tyrosine ethyl ester **3** FMT precursor requires seven synthetic manipulations, with multiple protecting groups, from L-m-tyrosine (Namavari 1993). Given that a large amount of the precursor is needed for each FMT preparation, a precursor that is more convenient to obtain and efficient to produce, especially in higher yield, and provides equivalent or better radiochemical yield of FMT is warranted. Following the shorter and simpler synthetic template for the FDOPA precursor synthesis from Dolle et al. (1998), we were able to reduce the number of protecting groups and, more importantly, the number of synthetic steps that are necessary to afford a suitable FMT precursor. The synthetic route to the di-Boc protected precursor is depicted in Figure 2. Briefly, *L*-m-Tyrosine **5** was converted into the corresponding ethyl ester in ethanol under acid catalysis using gaseous hydrochloric acid. The ester hydrochloride was then reacted with excess Boc-anhydride under basic conditions to afford the di-Boc-protected ester **6**. Iodination with elemental iodine in the presence of silver trifluoroacetate proceeded cleanly to give the desired 6-iodo compound. Finally, the iodo-derivative **7** was stannylated to afford the tin precursor **4**. The overall yield for this four-step process was 26-27%. The reported yield for the seven-step synthesis of **3** is 15-16% (Namavari et al., 1993). Thus, the new synthetic pathway is more efficient and yields nearly 75% more FMT precursor based on the starting L-m-tyrosine **5.**

The reactivity of both FMT precursors **3** and **4** was compared under identical radiosynthetic conditions in two institutions, Lawrence Berkeley National Laboratory (LBNL) and Paul Scherrer Institute (PSI). The reaction sequence leading to FMT **2,** shown in Figure 3, is identical for both precursors. Fluorine-18 labeled F_2 gas produced either by irradiation of [^{18}O]-O_2 or neon-20 gas is bubbled into a Freon solution containing ~50 mg (~100 μmol) of the trialkyltin precursor. At LBNL the reaction solution was passed through

silica SPE cartridges and eluted with 25% ether/ hexane. The ether/ hexane solution containing the labeled intermediate was collected into a test tube containing the 48% HBr and evaporated. At PSI the initial reaction solution was evaporated to dryness under vacuum and 48% HBr was added to the same pot. Following exhaustive deprotection of the acid, amine, and phenol protecting groups, the HBr solution was partially neutralized and the FMT was purified by reversed phase HPLC. A series of preparations with each precursor ($n > 6$) were undertaken and the radiosyntheses were accomplished in less than 60 min after end of bombardment. The decay corrected yields of FMT by precursor and institution/ method are shown in Table 1.

The preparation of FMT from either precursor, at two institutions using slightly different methods produced identical yields. There is no distinct advantage to using one particular precursor or synthetic method. Interestingly, the yield of FDOPA from the new triBoc precursor was also reported to be 26% (Dolle et al., 1998). In all of these syntheses this yield represents about half of the maximum obtainable yield of 50% (half of the activity is incorporated into trimethyltin fluoride) based on the $[^{18}F]F_2$ extracted from the cyclotron target. These yields agree with those originally obtained for FMT from the N-trifluoroacetoxy precursor **3** by Namavari et al. (1993).

The final FMT was analyzed by analytical HPLC to detemine the purity and specific activity from each precursor and method. A typical set of chromatograms of the HPLC analysis of ^{18}F-FMT is shown in Figure **4**. The chemical and radiochemical purities determined by HPLC were greater than 96% regardless of the precursor or the method of synthesis. Likewise, the specific radioactivity of the labeled FMT ranged between 28 and 74 MBq / μmol (0.75-2 Ci/mmol). This is the expected specific activity range given the fluorine-19 present in the $[^{18}F]F_2$ gas production. The enatiomeric excess for precursor **3** and **4,** as measured by chiral HPLC, was greater than 95% (~97.5% L vs 2.5% D). This does not represent a racemization

during the synthesis but rather how well the L-m-tyrosine is initially separated from the D enantiomer. By all measures the FMT produced from either precursor by either method at either institution is identical.

In summary, we have synthesized a new precursor for the preparation of FMT. The synthetic route to this compound is more efficient resulting in a 75% increase in material from L-m-tyrosine compared the original precursor. FMT produced, by two methods at two institutions, from this new precursor was found to be equivalent to that formed from the original compound in both yield and quality. This new precursor represents a significant improvement for the measurement of dopamine function in the brain by providing a more accessible and economical means to produce FMT.

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Figure Captions

Figure 1. F-DOPA **1**, FMT **2**, the original electrophilic fluorination precursor **3**, and the new diboc precursor **4**.

Figure 2. Synthesis of FMT di-Boc precursor **4**.

Figure 3. Radiosynthesis of FMT from two precursors.

Figure 4. A typical analytical HPLC chromatogram of ^{18}F-FMT.

Figure 1.

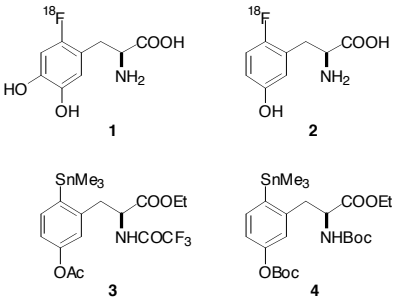
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Figure 2.

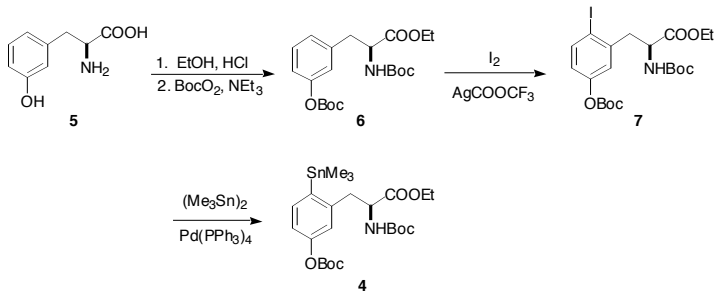
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Figure 3

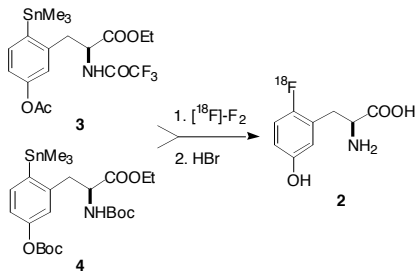
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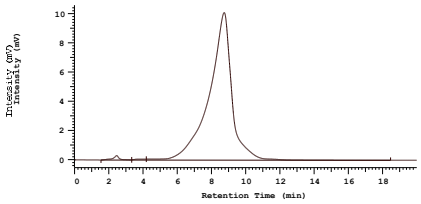
Figure 4.



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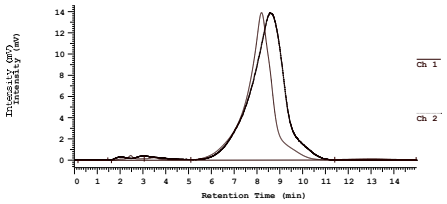

Product

Table 1. Decay corrected radiochemical yields of ^{18}F-FMT

Location/ Method	**Precursor**	
	$NCOCF_3$-OAc **3**	di-Boc **4**
LBNL / Method 1[a]	26 ± 2	26 ± 3.0
PSI / Method 2[b]	26 ± 3	25 ± 6

[a] 2 pot synthesis
[b] 1 pot synthesis