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STEREOSELECTIVE SYNTHESIS OF 3-O-METHYL-6-[^{18}F]FLUORODOPA VIA FLUORODESTANNYLATION

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Abstract

3-O-Methyl-6-[^{18}F]fluorodopa was synthesized in 20% radiochemical yield in 60 min, with a specific activity of 500 mCi/mmol, by the fluorination of a stannylated dopa precursor with [^{18}F]-acetyl hypofluorite.

Key Words: Fluorodopa, dopamine metabolism, acetyl hypofluorite

Introduction

One of the major metabolites of 6-[^{18}F]fluorodopa (6FD), in the blood and brain, is 3-O-Methyl-6-[^{18}F]fluorodopa (Me6FD) (1). Isolation of 6FD uptake kinetics in the striatum thus require time course data measured in other brain regions and assumptions about the relationship between Me6FD kinetics in these regions (2). It has recently been reported (3) that the rate of transport of Me6FD across the blood brain barrier into the cerebellum was different than that for the striatum. Since this rate difference might affect analysis of 6FD scans we decided to confirm the results of this study using Me6FD $\geq$99% steriochemical purity. Our previously reported method of synthesizing Me6FD produced a 1:1 mixture of 2- and 6-fluoro isomers which required HPLC separation (4). Since a small contamination with the 2-fluoro isomer could confuse the interpetation of the data from the Me6FD study we now report a stereoselective synthesis of Me6FD based on the fluorodestannylation reaction similar to that recently reported for the synthesis of 6-fluorodopa (5).

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Experimental

General

3-Methoxy-L-tyrosine monohydrate was purchased from Sigma Ltd. and di-tert-butyldicarbonate were purchased from Aldrich. All other reagents were purchased commercially and used with no further purification. Thin layer chromatographic analysis (TLC) was performed on silica gel TLC plates (Merck No. 5534). The TLC plates were visualized by ultra violet light. ^{1}H and ^{19}F spectra were recorded at 200 MHz. Microanalyses were performed by Canadian Microanalytical Service, Ltd., Delta, B.C. All melting points were determined on a capillary oil bath instrument and are uncorrected. High Performance Liquid Chromatography (HPLC) was carried out on a Waters system equipped with a Nucleosil C-18 preparative column (250 mm X 22.5 mm) (Phenomenex, Inc.) using a 5% acetonitrile/0.07 M KH_2PO_4 eluant at a flow rate of 6 mL/min.

Synthesis of 3-Methoxy-4-hydroxy-L-phenylalanine methyl ester hydrochloride (2)

To 3-methoxy-L-tyrosine monohydrate (1) (2.44 g, 10.6 mmol) was added methanol (50 mL), and HCl gas was passed through the suspension (6). The resultant solution was heated at reflux for 4 hours, and the solvent subsequently evaporated to dryness to yield 2.7 g of white powder, m.p. 173-4°C.

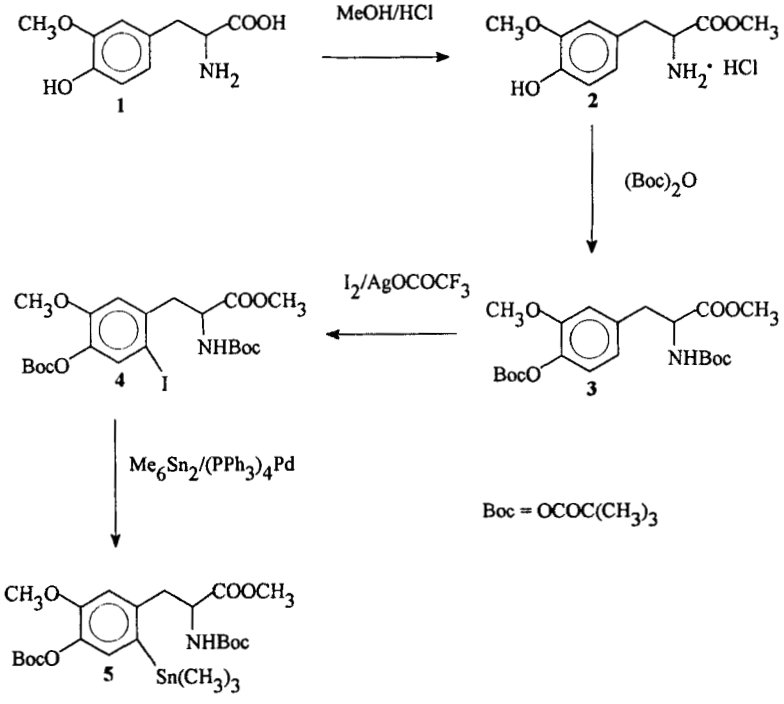
N-(tert-Butoxycarbonyl)-3-methoxy-4-*t*-butoxycarbonyloxy-L-phenylalanine methyl ester (3)

A solution of di-*t*-butyl dicarbonate (8.4g, 38.3 mmol) in anhydrous DMF (10 mL) was added slowly to a solution of 3-methoxy-4-hydroxy-L-phenylalanine methyl ester hydrochloride (2) (2.7g, 10.6 mmol) in anhydrous DMF (10 mL) and triethylamine (4.6 mL, 33 mmol) (5). After stirring the reaction mixture at room temperature for 24 h ethyl acetate (250 mL) was added and the reaction mixture was washed with saturated NaCl solution (3 × 50 mL) and water (3 × 50 mL). Evaporation of the organic layer and crystallization from ethyl acetate/hexane afforded 2.8 g (71% of 3); m.p. 93-4°C. ^{1}H-nmr ($CDCl_3$/TMS): δ 1.30 (s, 9H, C-CH_3), δ 1.48 (s, 9H, C-CH_3), δ 3.02(m, 2H, CH_2), δ 3.68

(s, 3H, $COOCH_3$), δ 3.80 (s, 3H, OCH_3), δ 4.58 (m, 1H, CH), δ 4.99 (d, 1H, NH), δ 6.70 (m, 2H, ArH), δ 7.03 (m, 1H, ArH). Anal. Calcd for $C_{21}H_{31}NO_8$; C 59.28, H 7.34, N 3.29. Found: C 58.93, H 7.22, N 3.27.

N-(tert-Butoxycarbonyl)-3-methoxy-4-*t*-butoxycarbonyloxy-6-iodo-L-phenylalanine methyl ester (4)

Iodine (1.9 g, 7.6 mmol) was added to a solution of N-(tert-butoxycarbonyl)-3-methoxy-4-*t*-butoxycarbonyloxy-L-phenylalanine methyl ester (3) (2.8 g, 6.6 mmol) and silver trifluoroacetate (1.9 g, 8.6 mmol) in methylene chloride (100 mL) and the reaction mixture was stirred at room temperature for 24 h (5). The precipitate was filtered and washed with methylene chloride. The combined filtrates were washed with 1M sodium thiosulfate (3 × 50 mL), water (3 × 50 mL), dried and concentrated under reduced pressure to give a solid residue. Recrystallization from ethyl acetate/hexane gave a white powder (3.0 g, 83% yield), m.p. 150-2°C. ^{1}H-nmr ($CDCl_3$/TMS): δ 1.32 (s, 9H, C-CH_3), δ 1.50 (s, 9H, C-CH_3), δ 3.22 (m, 2H, CH_2), δ 3.68 (s, 3H, $COOCH_3$), δ 3.82 (s, 3H,



OCH_3), δ 4.58 (m, 1H, CH), δ 5.00 (m, 1H, NH), δ 6.8 (s, 1H, ArH), δ 7.48 (s, 1H, ArH). Anal. Calcd. for $C_{21}H_{30}INO_8$; C 45.75; H 5.48; N 2.54. Found: C 45.85, H 5.46, N 2.54.

N-(tert-Butoxycarbonyl)-3-methoxy-4-*t*-butoxycarbonyloxy-6-(trimethylstannyl)-L-phenylalanine methyl ester (5)

Hexamethylditin (0.86 g, 2.63 mmol) was added to a mixture of N-(tert-butoxycarbonyl)-3-methoxy-4-*t*-butoxycarbonyloxy-6-iodo-L-phenylalanine methyl ester (4) (1 g, 1.8 mmol) and tetrakis-triphenylphosphine palladium (0) (0.1 g) in anhydrous 1,4-dioxane (24 mL) and the reaction mixture was stirred under reflux in a nitrogen atmosphere for 3 h.

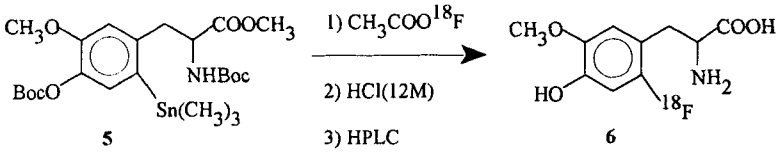
After cooling, the black reaction mixture was filtered and the insoluble material was washed with ethyl acetate. Evaporation of the combined filtrate gave a yellow oil which was chromatographed on silica gel (ethyl acetate-hexane) to give a white oil (0.6 g, 56%). Crystallization from ether/hexane afforded a white solid, m.p. 48-9°C. ^{1}H-nmr ($CDCl_3$/TMS): δ 0.18 (s, 9H, Sn-CH_3), δ 1.20 (s, 9H, C-CH_3), δ 1.38 (s, 9H, C-CH_3), δ 2.88 (m, 2H, CH_2), δ 3.48 (s, 3H, $COOCH_3$), δ 3.62 (s, 3H, OCH_3), δ 4.42 (m, 1H, CH), δ 4.62 (m, 1H, NH), δ 6.64 (s, 1H, ArH), δ 6.93 (s, 1H, ArH). Anal. Calcd. for $C_{24}H_{39}NO_8Sn$: C 49.00; H 6.68, N 2.38. Found: C 49.20; H 6.51; N 2.41.

Synthesis of 3-O-Methyl-6-[^{18}F]-Fluorodopa (6)

The fully protected carbamate (5) (80 mg, 0.136 mmol) was placed in a glass reaction vessel (2 x 10 cm) and dissolved in freon 11 ($CFCl_3$) (20 mL). ^{18}F-Acetyl hypofluorite (7) was bubbled into the mixture at a flow rate of 120 mL/min. The product was then pushed through a silica SEP-PAK into a rotary evaporator. The SEP-PAK was rinsed with 20 mL of ether and combined with the first fraction. The solvent was removed and to the residue was added 12N HCl (5 mL) and boiled for 15 minutes. The mixture was evaporated to dryness and water (3mL) was added and evaporated to remove any remaining acid. The crude product was dissolved in potassium dihydrogen phosphate buffer (0.06 M, 2 x 2.5 mL) and purified by HPLC using a Nucleosil C-18 column (5 μ, 250 mm x 22.5 mm) with an eluant of 5% acetonitrile/0.07 M KH_2PO_4 at a flow rate of 6 mL/min. The product (6) which eluted at 29 minutes was obtained in 20%

radiochemical yield with a specific activity of 500 Ci/mmol. ^{19}F-nmr was recorded (D_2O, referenced to CF_3COOH): δ -48.9 (dd, $J_{H5,F}$ = 10.4 Hz, $J_{H2,F}$ = 7.3 Hz.).

For patient use, the collected fraction is evaporated to dryness and the residue was reconstituted in USP water, filtered through a 0.22 μm membrane filter into a sterile multi-injection vial.



Results and Discussion

The synthesis of the stannylated precursor was achieved by the palladium catalyzed stannylation of the iodo-intermediate using hexamethylditin in a similar way to that recently reported for the synthesis of 6-^{18}F-fluorodopa (5). The synthesis of Me6FD was achieved in a 20% radiochemical yield by the ^{18}F-acetyl hypofluorite-fluorodestannylation reaction with deprotection using HCl. The fluorination was both high yielding and highly stereoselective with no detectable amount of the 2-isomer in the crude product before HPLC purification. The fluorination was carried out in the same apparatus as that used for our routine production of 6-fluorodopa. Fluorinations using ^{18}F-F_2 were tried with similar results obtained for the radiochemical yield but resulting in a small amount of the 2-fluoro isomer ($\leq$ 5%) in the crude product before HPLC purification. Although the 2-isomer was completely removed by HPLC the F_2 method was not used to ensure a pure product.

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