A PRACTICAL PREPARATIVE SCALE SYNTHESIS OF D/L-6-FLUORODOPA

J.R. Grierson and M.J. Adam*, TRIUMF, 4004 Wesbrook Mall, University of British Columbia, Vancouver, B.C., Canada V6T 2A3

ABSTRACT

A practical preparative scale synthesis of D/L-6-fluorodopa (6-FD) is presented. From veratric acid the procedure affords D/L-6-FD in 12% overall yield in 11 steps. Useful batch quantities (>300 mg) of this material were readily obtained and used as an analytical standard for ^{19}F NMR and HPLC analyses in the preparation of L-[^{18}F]6-fluorodopa.

Key Words: D/L-6-fluorodopa, fluorinated aromatic amino acid, Schiemann reaction

INTRODUCTION

The recent interest in L-[^{18}F]6-fluorodopa ([1,2]) as a new radiopharmaceutical for the in vivo visualization of dopaminergic neuronal distributions in man has required the development of microscale syntheses of this compound ([3-6]). In order to develop our own procedure for the synthesis of L-[^{18}F]6-fluorodopa ([6]) we required a ^{19}F labelled "authentic" sample of 6-fluorodopa. The preparation and characterization (^{19}F NMR, reverse phase and ligand exchange HPLC) of ^{19}F labelled 6-fluorodopa has enabled us to conduct quality control testing in the radiosynthesis of ^{18}F labelled 6-fluorodopa from ^{18}F-acetyl hypofluorite; it is not practical to produce large amounts of non-radioactive material via the hypofluorite method. Furthermore, sizeable quantities of 6-FD labelled with the stable isotope were readily available for basic animal studies involving toxicology and histology.

Syntheses of ^{19}F labelled 6-FD have been reported by Firnau ([7]) and Creveling ([8]). The former method is not easily adapted to large scale while for the latter detailed procedures are not given. We now report a preparative scale synthesis of ^{19}F labelled 6-FD based on the classical Schiemann reaction. This procedure involves 11 steps and affords an overall 12% chemical yield. The synthetic route for the synthesis appears in scheme 1 while selected chromatographic, spectroscopic and analytical data for the intermediate compounds prepared appear in Tables 1 and 2.

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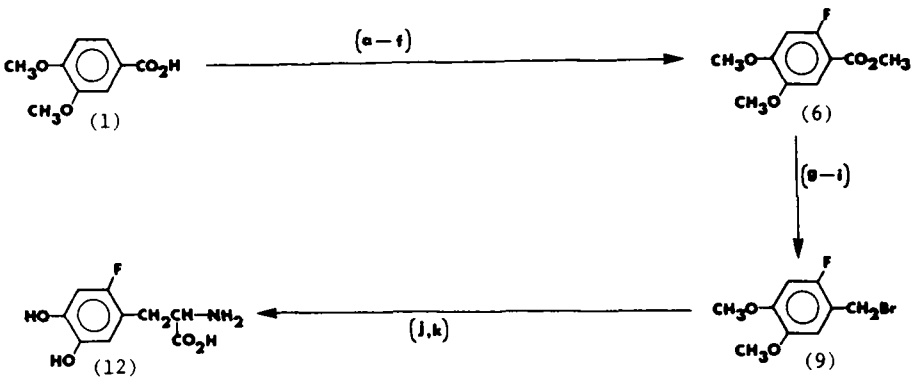
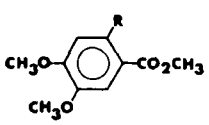
Scheme 1: Synthetic scheme and structures for the synthesis of D/L-6-Fluorodopa.



Reaction Conditions: (a) $CH_3OH/HCl_{(g)}$, r.t., 20 h; (b) HNO_3/HOAc, r.t., 1.5 h; (c) H_2/Pd-C, 1 atm, r.t., 6 h, H_2SO_4; (d) $NaNO_2$/THF/H_2O/H_2SO_4, -10 to 0°C; (e) $NaPF_6$, <5°C; (f) 165°C, vacuum; (g) $LiAlH_4$/THF, Δ; (h) TMSCl/TEA/$CHCl_3$, r.t.; (i) TMSBr(excess)/$CHCl_3$, r.t. to 40°C; (j) $Ph_2C{=}N{-}CH_2{-}CO_2Et$(10)/LDA /THF, -78°C to r.t., 18h; (k) HI/P(red)/H_2,Δ, 20 min.

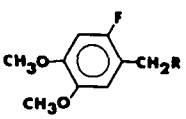


(2) R = -H

(3) R = $-NO_2$

(4) R = $-NH_2 \cdot H_2SO_4$

(5) = $-N_2^+PF_6^-$



(7) R = -OH

(8) R = $-OSi(CH_3)_3$

(11) R = $-CH(CO_2Et)-N=CPh_2$

Table 1: Analytical and/or Spectroscopic Data for Compounds (3),(5), (6),(7),(8),(9) and (12).

Compound (3) Anal. Calcd. for $C_{10}H_{11}NO_6$: C 49.80, H 4.60, N 5.81. Found C 49.79, H 4.58, N 5.81; ^1H nmr (60 MHz, $CDCl_3$)δ 3.90 (s, 3H), 3.95 (s, 6H), 7.05 (s, 1H), 7.45 (s, 1H).

Compound (5) Anal. Calcd. for $C_{10}H_{11}F_6N_2O_4P$: C 32.62, H 3.01, N 7.61. Found C 32.63, H 3.03, N 7.56; ^1H nmr (80 MHz, acetone - d^6)δ 4.05 (s, 6H), 4.25 (s, 3H), 8.00 (s, 1H), 8.43 (s, 1H).

Compound (6) Anal. Calcd. for $C_{10}H_{11}FO_4$: C 56.08, H 5.18. Found C 56.10, H 5.13; ^{1}H nmr (80 MHz, $CDCl_3$)δ 3.90 (S, 9H), 6.65 (d, J_{H-F} = 12 Hz, H-5), 7.40 (d,J_{H-F} = 6 Hz, H-2); ^{19}F nmr (254 MHz, $CFCl_3$ internal standard) δ -114.5 (d,d,$J_{F-H(5)}$ = 11.5 Hz, $J'_{F-H(2)}$ = 5.4 Hz).

Compound (7) ^{1}H nmr (80 MHz, $CDCl_3$) δ 2.33 (br s, 1H), 3.88 (s, 6H), 4.60-4.70 (m,2H), 6.60 (d,J_{H-F} = 11 Hz, H-5), 6.90 (d,J_{H-F}= 7 Hz, H-2); ^{19}F nmr (254 MHz, $CFCl_3$ internal standard) δ -127.6 (d,d,$J_{F-H(5)}$ = 11.5 Hz, $J_{F-H(2)}$ = 7.5Hz).

Compound (8) ^{1}H nmr (80 MHz, $CDCl_3$) δ 0.20 (s, 9H), 3.87 (s, 3H), 3.90 (s, 3H), 4.71 (d, J_{H-F} = 1.5 Hz, 2H), 6.63 (d,J_{H-F} = 12 Hz, H-5), 6.82 (d,J_{H-F} = 7 Hz, H-2); ^{19}F nmr (254 MHz, $CFCl_3$ internal standard) δ -127.5 (d,d,t,$J_{F-H(5)}$ = 12 Hz, $J'_{F-H(2)}$ = 7 Hz, J''_{F-H} = 1.5 Hz).

Compound (9) Anal. Calcd. for $C_9H_{10}BrFO_2$: C 43.40, H 4.05, Br 32.08. Found C 43.53, H 4.05, Br 31.84; ^{1}H nmr (80 MHz, $CDCl_3$) δ 3.85 (s, 6H), 4.50 (d,J_{H-F} = 1.5 Hz, 2H), 6.61 (d,J_{H-F} = 12 Hz, H-5), 6.82 (d,J_{H-F} = 7 Hz, H-2); ^{19}F nmr (254 MHz, $CFCl_3$ internal standard) δ -124.2 (d,d,t,$J_{F-H(5)}$ = 12 Hz, $J'_{F-H(2)}$ = 7 Hz, J''_{F-H} ≅ 1.5 Hz).

Compound (12) Anal. Calcd. for $C_9H_{10}FNO_4 \cdot H_2O$: C 46.36, H 5.19, N 6.01, F 8.15. Found C 46.55, H 5.20, N 5.97, F 7.87. ^{1}H nmr (80 MHz, D_2O containing a trace of HCl, DDS external standard) δ 3.00-3.20 (m, 2H, $-\underline{CH_2}-$), 4.20 (d,d,J = 7 Hz, J' = 6 Hz, 1 H, $-\underline{CH}-(NH_2)CO_2H$), 6.62 (d,$J_{H-F}$ = 11 Hz, H-5), 6.68 (d,J_{H-F} = 7 Hz, H-2); ^{19}F nmr (254 MHz, CF_3CO_2H external standard) δ -50.2 (d,d,$J_{F-H(5)}$ = 10.9 Hz, $J_{F-H(2)}$ = 7.5 Hz).

[a]Solvent: A(99:1 $CHCl_3$/MeOH), B(95:5 $CHCl_3$/MeOH), C(20:80 EtOAc/Hex), D(4:1:1, n-BuOH/HOAc/H_2O, ninhydrin visualization), [b]Column E: 6' × 1/8" OD stainless steel packed column, 5% OV-101 on 100-120 mesh Chrom (W)HP, 180°C isothermal, 30 mℓ/min; Column F: 30 M × 0.75 mm ID Supelco SPB-1 wide bore capillary column, 180°C isothermal, 1.9 mℓ/min N_2 carrier.

EXPERIMENTAL

General. Sodium hexafluorophosphate ([9]) was prepared by the neutralization of the corresponding commercially available ammonium salt (Merck). Ethyl glycinate benzophenone imine ([10]) was prepared from ethyl glycinate ([11]) and benzophenone.

Table 2: Chromatographic Characteristics for Compounds (3),(6),(7), (8),(9),(11) and (12).

Compound	Tlc (silica)		Glc	
	R_f	solvent[a]	R_t(min): Column E[b]	Column F[b]
(3)	0.65	A	---	---
(6)	0.70(0.86)	A(B)	1.6	6.4
(7)	0.34	B	1.2	5.0
(8)	0.45	C	1.7	6.1
(9)	0.35	C	---	---
(11)	0.20	C	---	---
(12)	0.35	D	---	---

Bromotrimethylsilane (TMSBr), n-BuLi, and Hydriodic acid (57%, d 1.71) were obtained from Aldrich. The acid was distilled from red phosphorus under hydrogen prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under argon. Chloroform was distilled from P_2O_5. Triethylamine (TEA) was distilled from CaH_2 under argon. Dry chlorotrimethylsilane (TMSCl) was obtained by distilling commercial grade TMSCl (Aldrich), containing 5% (v/v) N,N-dimethylaniline. n-Butylithium (1.8 M in hexane) was standardized using Gilman's procedure ([12]). Thin layer chromatographic analysis (tlc) was performed on silica gel plates (Merck Art. 5534). Tlc plates were visualized by either exposure to ultraviolet light or spraying with an acidic solution (10% H_2SO_4) of ammonium molybdate (5% solution) followed by heating. HPLC analyses were performed with a Waters Radial-Pak® C-18 reverse phase column (10 μm, 10.0 cm × 8 mm I.D.). Melting points are uncorrected. NMR chemical shifts are in ppm and relative to TMS unless otherwise stated. The structures of the compounds referred to in the reactions (a-k) are located in Scheme 1.

Reaction (a). To a cooled (0°C) suspension of veratic acid (1) (40.0 g) in dry methanol (300 mL) was introduced anhydrous HCl gas for 10 min. The mixture was allowed to warm to room temperature followed by stirring for 20 h. The mixture was concentrated to a dark brown oil which was taken up into and concentrated from 2 × 300 mL portions of methanol. The residue was taken up into EtOAc (300 mL) and the solution was washed with water, saturated $NaHCO_3$ and

brine. The solution was concentrated to afford a brown oil which solidified upon standing. This procedure afforded 42.3 g of the crude ester (2) which exhibited mp 58-60°C.

Reaction (b). To a cooled solution of the crude ester (2) (42.3 g) in glacial acetic acid (200 mL) was added, over a 20 min period, 90% fuming nitric acid (40 mL) at a temperature below 15°C. After the addition was complete the mixture was stirred at room temperature for 1.5 h. A beige coloured material precipitated during this time resulting in the production of a thick paste. The mixture was poured into 3 L of rapidly stirred water and then filtered. The yellow filtrate was discarded. The filtered solids were re-suspended in and filtered from 3 × 1 L portions of water. The collected solid was dried under vacuum for 18 h to afford 50.0 g of the slightly moist nitro-ester (3) which exhibited mp 144-145.5°C (lit. [13,14] mp 144-145°C, 143-144°C). This material may be recrystallized from HOAc (7 mL/g).

Reaction (c). A suspension of the crude nitro-ester (3) (50.0 g) and 5% Pd-C (2 g) in methanol (2 L) was stirred at room temperature for 6 h under an atmosphere of hydrogen. The nitro-ester was slowly taken into solution and approximately 14 L of hydrogen was absorbed. When the uptake was essentially complete a solution of concentrated H_2SO_4 (21.1 g) in methanol (200 mL) was added followed by Celite (5 g). The mixture was filtered and the collected solids were washed liberally with methanol. The clear brown solution of the combined filtrates was concentrated to a moist grey solid residue. This material was triturated with portions of Et_2O (2 × 500 mL) and EtOAc (2 × 500 mL) and then dried under vacuum for 24 h to afford 64.1 g of the crude amino-ester·H_2SO_4 (4).

Reactions (d) and (e). To a mechanically stirred mixture of the crude amino-ester·H_2SO_4 (4) (64.1 g) in a mixture of crushed ice (600 mL), concentrated H_2SO_4 (85 mL) and THF (150 mL), at an initial temperature of -10°C, was added a solution of $NaNO_2$ (20.0 g) in water (100 mL) over 20 min. During the addition the reaction temperature was not allowed to rise above -5°C. After the addition was complete the mixture was allowed to warm to 0°C with stirring for 15 min after which a clear red-brown solution was obtained. A spot test with starch-

iodine paper revealed the presence of excess oxidant.

To the cold (below 5°C) rapidly stirred solution of the diazonium salt was added $NaPF_6$ (41.2 g) in water (100 mL) over 10 min which resulted in the precipitation of a yellow solid material. The mixture was stirred for a further 10 min then filtered. The filtered solids were washed liberally with water (3 × 1 L) followed by drying under vacuum to a constant weight [67.0 g, 83% overall yield from veratric acid (1)]. The crude diazonium PF_6·salt (5) exhibited mp 160-162°C (decomp). This material may be stored at -5°C indefinitely. The crude product may be recrystallized from anhydrous acetone to afford material which exhibits mp 162-164°C (decomp). However, the diazo-decomposition (reaction f) of the purified material does not result in an improved yield of the fluoro-ester (6).

Reaction (f). Within a sublimitation apparatus a sample of the crude diazonium·PF_6 salt (5) (5.00 g, 13.6 mmol) was heated to 165°C under vacuum (mechanical pump). This led to the gradual formation of a black residual tar (CH_2Cl_2 soluble) and the deposition of a sublimate onto the inner wall of the apparatus and the water cooled probe. The sublimate was collected and dissolved in EtOAc (100 mL). The solution was washed successively with 1N NaOH, water and brine and then dried. The solution was concentrated to dryness to afford an off-white solid residue (1.43 g), mp 99-105°C. The residue was distilled (air bath, bp 120-125°/ 0.3 mm) to afford 1.26 g of the fluoro-ester (6), mp 99-105°C.

By this procedure the decomposition of identical lots of the crude diazonium·PF_6 salt (5) (10 × 5.00 g) consistently provided modest yields (43-47%) of the fluoro-ester (6) of practical purity (mp 99-105°C). Combined samples of the distilled fluoro-ester could be obtained pure by recrystallization from either 10% EtOAc/Hex (23 mL/g of distillate) or 1:1 methanol water (16 mL/g) to afford material which exhibited mp 108-110°C in an overall yield of 36-39% from the crude diazo·PF_6 salt (5).

Reactions (g), (h) and (i). To a room-temperature suspension of $LiAlH_4$ (1.40 g, 37 mmol) in dry THF (150 mL) under an inert atmosphere was added, over 10 min, a solution of the recrystallized fluoro-ester (6) (7.94 g, 37 mmol) in THF (40 mL). After the addition was complete the mixture was refluxed for 5 min. The

reaction mixture was quenched by the cautious addition of brine to a point where a freely stirred suspension was obtained. The mixture was diluted with EtOAc (150 mL) followed by filtration. The filtered solids were washed liberally with EtOAc (100 mL) and the combined filtrates were concentrated. The residue was taken up into EtOAc (100 mL) and the solution was dried and concentrated to afford a colourless mobile oil. This material was dried further at room temperature under vacuum for 2h during which the oil had partially crystallized. Tlc and glc analyses of the crude fluoro-alcohol (7) revealed it to be homogeneous.

To a room temperature solution of the fluoro-alcohol (7) in dry $CHCl_3$ (100 mL) were added successively triethylamine (10.3 mL, 74 mmol) and chlorotrimethylsilane (7.0 mL, 56 mmol). A mild exothermic reaction took place and the mixture was stirred for 10 min after which the reaction had subsided. The volatile materials were removed and the residue, a moist solid mass, was extracted with hexanes (200 mL) followed by filtration of the suspended solids. The filtrate was concentrated to afford a faint brown oil which contained a small amount of precipitate. This material was dried further under vacuum for 17 h. The material was taken up into hexanes and the precipitate was filtered off. The filtrate was concentrated to afford the crude fluoro-OTMS ether (8) as a near colourless oil. This material was homogeneous by tlc and glc.

To a room temperature (water bath) solution of the crude fluoro-OTMS ether (8) in dry $CHCl_3$ (5 mL) under an inert atmosphere was added bromotrimethylsilane (TMSBr, 19.5 mL, 148 mmol). The mixture was stirred for 5 min then the volatile materials were removed <u>in vacuo</u> (-78°C trap) to afford a light brown mobile oil. Tlc analysis (20% EtOAc/Hex) revealed the presence of a large portion of the fluoro-OTMS ether (8) within the residue. Thus, the residue was treated as before with 10 mL of TMSBr with stirring for 20 min. After removal of the volatile materials a partially crystalline residue was obtained. Tlc analysis again revealed the presence of the fluoro-OTMS ether (8). The material was again treated with a 10 mL portion of TMSBr but the solution was gently heated (~40°C) for 2-3 min. The volatile materials were removed and the residue rapidly crystallized. This material was dried further for 1 h under

vacuum. The crude fluoro-benzyl bromide (9) was taken up into EtOAc and the solution washed successively with 0.5 N K_2CO_3 and brine and then dried. The solution was concentrated and the residue was taken up into a minimum of 20% EtOAc/Hex. The solution was rapidly filtered through a short column of silica (230-400 mesh, 3 × 5 cm) followed by elution with 20% EtOAc/Hex (150-200 mL). At the head of the column there was retained an orange-yellow band while a colourless eluate was obtained. The eluate was concentrated to a colourless mobile oil which crystallized under vacuum to afford 8.356 g of practically pure fluoro-benzyl-bromide (9), mp 59-61°C. This material was obtained pure by recrystallization from 16 mL of 5% EtOAc/Hex which afforded 6.62 g [71% overall yield from the fluoro-ester (6)], mp 62-63.5°C.

Reactions (j) and (k). To a cold (-78°C) solution of diisopropylamine (0.42 mL, 3.0 mmol) in THF (10 mL) under argon was added n-BuLi in hexane (1.5 mL, 2.6 mmol). The stirred mixture was warmed to 0°C for 5 min then cooled to -78°C. To the cold solution was added a solution of ethyl glycinate benzophenone imine (10) (0.61 g, 2.5 mmol) in THF (10 mL) over 2 min. After a further 5 min a solution of the fluoro-benzyl-bromide (9) (0.622 g, 2.5 mmol) in THF (10 mL) was added rapidly to the deep red-orange solution. The light yellow solution which resulted was allowed to slowly warm to room temperature over 18 h. The solution was poured into 10 mL of sat NH_4Cl and sufficient water was added to dissolve the precipitated salts. The mixture was extracted with 2 × 50 mL of EtOAc and the combined extracts were washed with brine and dried. Concentration of the extract afforded an orange oil which was taken up into a minimum of 20% EtOAc/Hex (~5 mL, some precipitate present) followed by flash chromatography ([15]) of the solution on silica (230-400 mesh, 15 × 5 cm column) using 20% EtOAc/Hex to elute the column. The desired product had eluted from the column just after the elution of the bulk of a migrating yellow material. Selected fractions of the eluate were combined and concentrated to afford (0.854 g, 85%) of a straw coloured oil which had partially crystallized during a 30 min period. Tlc analysis (20% EtOAc/Hex) of this material revealed it to be homogeneous.

The crude alkylated Schiff's base (11) was refluxed for 20 min in a mixture of 10 mL of concentrated HI (57%) and red phosphorus (200 mg) under the

purge of H_2. The mixture was diluted with 30 mL of water and transferred to a stillpot fitted with a steam inlet. The mixture was steam distilled until ~100-120 mL of distillate had been collected. The distillate containing benzophenone was discarded. The mixture within the stillpot was filtered and a fresh portion (100 mg) of red phosphorus was added to the filtrate. The mixture was concentrated at 60-80°C under reduced pressure and the residue was taken up into and concentrated from 2 × 20 mL portions of water. The final residue was taken up into 10 mL of water then filtered (0.45 μm membrane). Under a continual sweeping atmosphere of argon the mixture was neutralized to pH 4-5 with hot 6N NH_4OH while the solution gently boiled. The solution was concentrated until 2-3 mL remained. A few small crystals of Na_2SO_3 were added followed by 2-3 mL of hot ethanol. The crystallization flask containing the solution was sealed and cooled to -10°C. The crystallization was essentially complete after 1 h. The white crystalline mass was collected and washed successively with ice cold water (3 × 3 mL), EtOH and ether. The air dried material was dried further at room temperature under vacuum for 5 h to afford 0.323 g [55% overall yield from compound (**9**)] of pure 6-fluorodopa (**12**) mono-hydrate which exhibited loss of water at ~120°C and mp 243-245°C (decomp., 5°C/min from 220°C). Analysis of the reaction product (**12**) by HPLC (C-18 reverse phase, 0.1% HOAc, 4 mL/min, UV detection at 280 nm, R_t 6-FD ~2 min) revealed it to be homogeneous before and after crystallization.

DISCUSSION

The individual synthetic procedures described for the preparation of 6-FD have been optimized for the minimum number of purifications of intermediate products en route to 6-FD. The yield obtained for the Schiemann reaction [reaction (f)] is reproducible. However, this is the case only when the sublimation of the formed fluoro-ester (**6**) from the reaction mixture proceeds at an intermediate rate, resulting in the deposition of a heavy crust of the product onto the water cooled probe of the sublimation apparatus. If the reaction is too vigorous a much reduced yield of the sublimate is obtained and little can be done to isolate additional amounts of product from the reaction residue. Too slow of a reaction rate results in the growth of long needles of the product on the probe which readily dislodge and are lost within the reaction

mixture. Efficient trapping of the hazardous reaction by-product, PF_5, at liquid N_2 temperature is recommended.

Attempts to purify compounds (7),(8) and (9) by distillation may result in extensive decomposition. Compound (9) in crude form is particularly sensitive and must be purified as described. Material purified in this manner may be stored indefinitely at -5°C in the dark. The method used to prepare the fluoro ester (9) from the fluoro-OTMS ether (8) is novel and is a useful method for the preparation of other p-methoxy benzyl bromides. The acid hydrolysis of the Schiff's base (11) to afford 6-FD may also be accomplished with either boiling HBr (48%)-red phosphorus under H_2 (2h) or HCl (12N, 18h). However, a purer product is obtained if HI is used. The use of HI-red phosphorus does not lead to defluorination of 6-FD.

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