Synthesis of metabolites of 6-fluoro-DOPA

Jun-ying Nie and Kenneth L. Kirk*

Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892 (USA)

(Received May 17, 1991; accepted August 7, 1991)

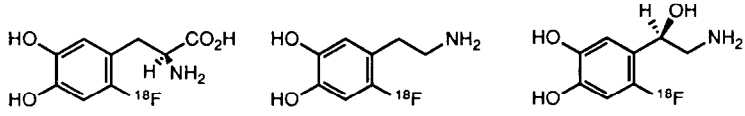
Abstract

Key metabolites of 6-fluoro-DOPA have been prepared by side-chain elaboration of 6-fluorovanillin and 6-fluoroveratraldehyde.

Introduction

The development of [^{11}C]- and [^{18}F]-labeled compounds for use in positron emission tomography (PET) is an area of active research. Because of its role as the biological precursor of dopamine, 3-(3,4-dihydroxyphenyl)alanine (DOPA) labeled with positron-emitting radionuclides has been studied as a potential scanning agent for the *in vivo* study of dopaminergic neural function. Thus, injected 6-[^{18}F]DOPA (**1**) crosses the blood–brain barrier, is decarboxylated, and the resulting [^{18}F]-6-fluorodopamine (6-[^{18}F]FDA) (**2**) is taken up and stored in central dopaminergic neurons [1]. Quantitation of stored 6-[^{18}F]FDA by PET has been used to study central dopaminergic function, both in normal and abnormal subjects [2].

In a related application, 6-[^{18}F]FDA is being developed as a PET-scanning agent for the study of peripheral adrenergic neural function. FDA does not cross the blood–brain barrier, but is efficiently taken up into peripheral adrenergically innervated organs, such as the heart [3]. The action of dopamine β-hydroxylase converts 6-[^{18}F]FDA to 6-[^{18}F]fluoronorepinephrine (6-[^{18}F]FNE) (**3**) which, serving as a false neurotransmitter, is taken up and stored in adrenergic neurons. PET quantitation of 6-[^{18}F]FNE then is used to measure the functioning of adrenergic neurons *in vivo*. 6-[^{18}F]FNE has



1 2 3

Scheme 1.

*To whom all correspondence should be addressed.

0022-1139/91/$3.50

recently been synthesized and shown by PET to be taken up rapidly and stored in the baboon heart [4].

Successful application of 6-[^{18}F]FDOPA and 6-[^{18}F]FDA (or any positron-emitting agent) as PET-scanning agents requires a firm knowledge of the identity of positron-emitting species present in the experimental subject as a function of time following injection. This presumes a knowledge of the metabolism and biodistribution of the administered agent. For several years, we have been studying the biochemistry and pharmacology of several ring-fluorinated catecholamines and amino acids, including fluorinated analogs of DOPA, DA, NE and epinephrine (EPI) [5], and the results of these studies have helped validate the use of 6-[^{18}F]fluoro analogs in this series for PET studies. However, we have also shown that the presence of fluorine in the 6-position of compounds downstream metabolically from DOPA can alter significantly such pharmacological behavior as receptor affinity [6] and metabolic rates [7]. Therefore, whilst a knowledge of the metabolism of the parent DOPA and dopamine is essential for PET, metabolic studies on the fluorinated analogs themselves also are required, and have been carried out, to place PET-scanning studies on solid footing. During the course of our research, and as a part of our involvement with the development of 6-[^{18}F]FDOPA and 6-[^{18}F]FDA we have synthesized several products of metabolism of these amines and have published brief descriptions of the syntheses of a limited number of these. In recognition of the importance of these fluorinated metabolites to many research groups that are working with 6-[^{18}F]FDOPA and 6-[^{18}F]FDA, and, in part, due to the large number of requests we have received for authentic samples of these fluorinated metabolites, we report here the details of the syntheses of several FDOPA metabolites.

Monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) are enzymes that play key roles in the metabolism of catecholamines. The former enzyme converts catecholamines to the corresponding aldehydes, which are subsequently oxidized to the acid, or are reduced to the alcohol. COMT is a relatively non-specific enzyme that can catalyze the transfer of a methyl group from *S*-adenosyl methionine to one of the hydroxy groups of a catechol. For catecholamines and for DOPA, methylation occurs predominantly at the 3-OH group. For example, methylation of DOPA, to produce 3-methoxytyrosine, is the principal mechanism by which DOPA is cleared from the circulation, and methylation of NE provides a mechanism for rapid deactivation of this neurotransmitter. MAO-catalyzed oxidation of catecholamines and subsequent processing, in combination with COMT-catalyzed methylation, produces a series of metabolites, including 4-hydroxy-3-methoxyphenethanolamine (normetanephrine), homovanillic acid (HVA), 4-hydroxy-3-methoxyhydroxymandelic acid (misnamed 'vanillyl mandelic acid', 'VMA'), 4-hydroxy-3-methoxyphenyl glycol (MHPG) and 3,4-dihydroxyphenylacetic acid (DOPAC) (a simplified summary of metabolic pathways is given in Fig. 1, with key intermediates related to this study emphasized) [8]. We describe here the details of the synthesis of the corresponding products that would be produced by the action of these enzymes on 6-fluoro-DOPA, including

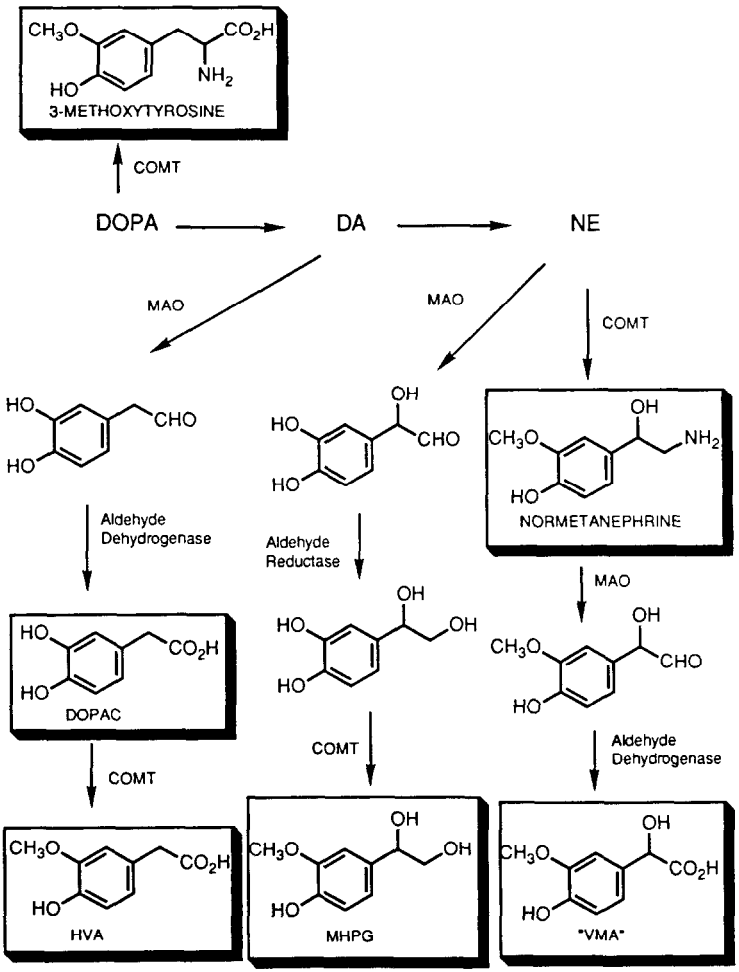


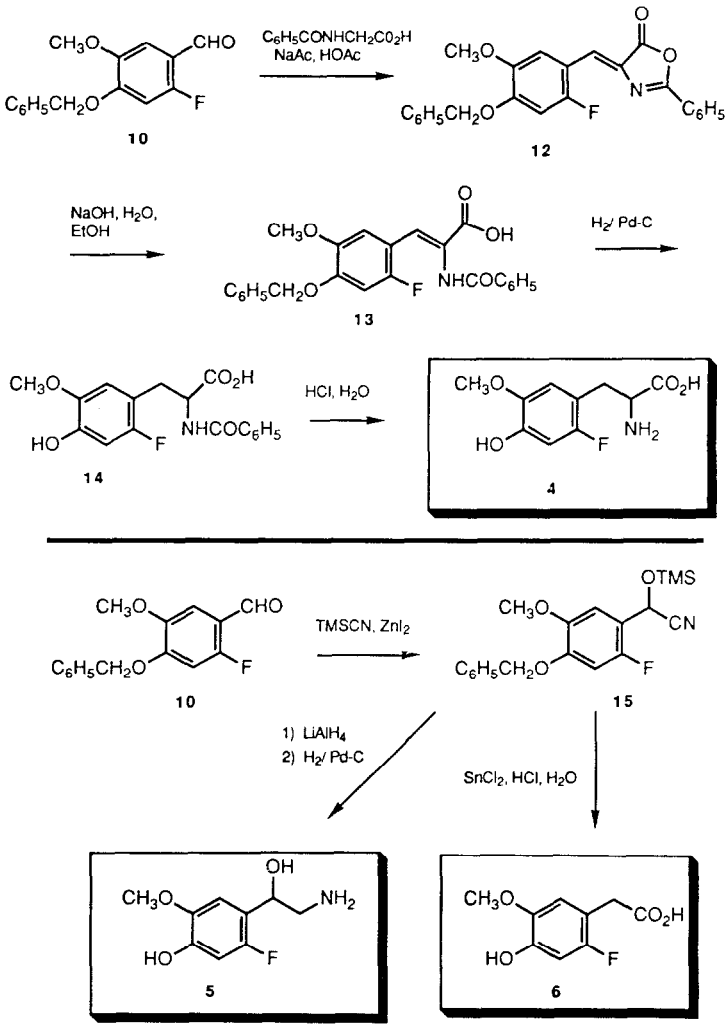
Fig. 1. Metabolism of 3,4-dihydroxyphenylalanine (DOPA).

3-(2-fluoro-4-hydroxy-5-methoxyphenyl)alanine (**4**), 2-fluoro-4-hydroxy-5-methoxyphenethanolamine (6-fluoronormetanephrine) (**5**) [9], 6-fluorohomovanillic acid (6-FHVA) (**6**), 2-fluoro-4-hydroxy-5-methoxyphenylglycol (6-FMHPG) (**7**), 2-fluoro-4-hydroxy-5-methoxymandelic acid (**8**) and 2-fluoro-4,5-dihydroxyphenylacetic acid (6-FDOPAC) (**9**).

Experimental

4-Benzyloxy-2-fluoro-5-hydroxybenzaldehyde (11)

A mixture consisting of 1.872 g (12.0 mmol) 4,5-dihydroxy-2-fluorobenzaldehyde, 2.155 g (12.6 mmol) benzyl bromide and 1.65 g (12.0 mmol) potassium carbonate in 50 ml acetone was stirred for 24 h at room temperature.

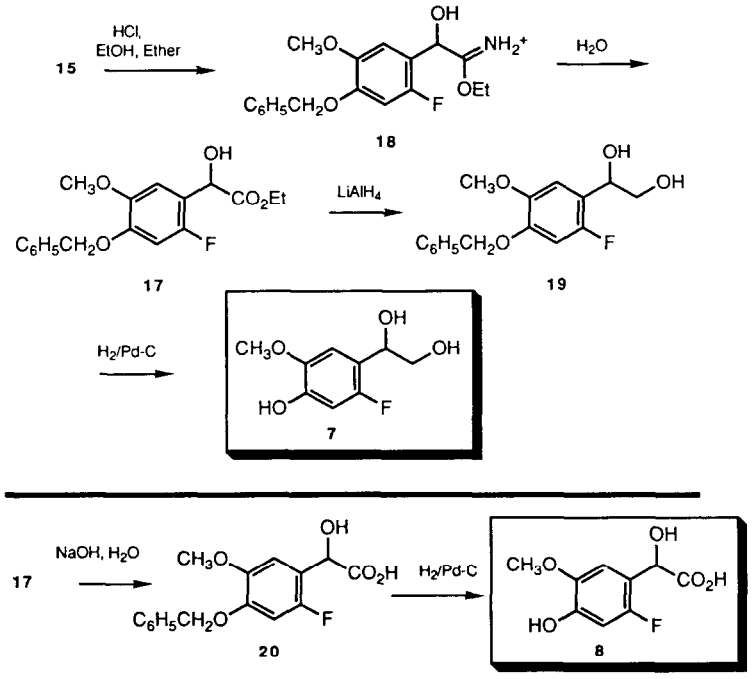


Scheme 2.

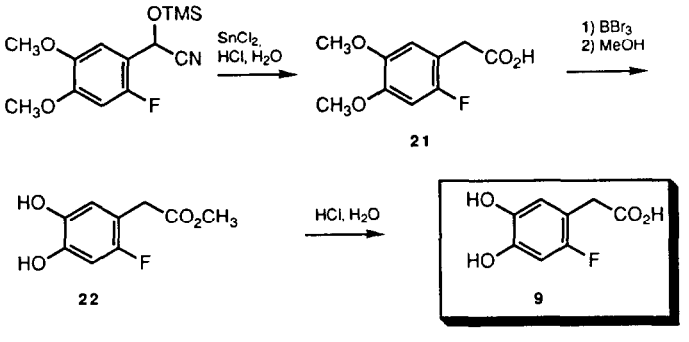
After the removal of solvent by rotary evaporation, water (15 ml) was added and the products were isolated by extraction with ethyl acetate. Drying (Na_2SO_4) and rotary evaporation of the solvent gave a mixture of **11** and 4,5-dibenzyloxy-2-fluorobenzaldehyde. Flash chromatography gave 1.25 g (5.08 mmol, 42%) of **11** (m.p., 94–95 °C) and 1.30 g of dibenzylated product.

*4-Benzyloxy-2-fluoro-5-methoxybenzaldehyde (**10**)*

A mixture consisting of 1.26 g (5.12 mmol) **11**, 1.29 g dimethyl sulfate (10.25 mmol) and 903 mg K_2CO_3 (6.54 mmol) in 135 ml acetone was refluxed for 16 h. After removal of the solvent, water was added to the residue and the solution was extracted three times with ether. The combined ether extracts



Scheme 3.



Scheme 4.

were washed with water and then stirred for 1.5 h with a dilute solution of NH_4OH. The ether was then washed three additional times with water, dried over Na_2SO_4 and then removed by rotary evaporation. Flash chromatography (10% ethyl acetate in petroleum ether) gave 1.195 g (89%) of **10** as a white solid, recrystallized from cyclohexane/ethyl acetate, m.p., 95–96 °C; lit. value [10] m.p., 65–76 °C.

2-Benzoylamino-3-(4-benzyloxy-2-fluoro-5-methoxyphenyl)acrylic acid azlactone (12)

A solution of 1.04 g (4 mmol) **10**, 810 mg (4.52 mmol) hippuric acid and 371 mg (4.52 mmol) anhydrous sodium acetate in 2 ml of acetic acid was heated at 95 °C for 2 h. A yellow solid separated. After cooling the reaction mixture, the solid was triturated with 5 ml cold ethanol, filtered and washed with water. Drying gave 1.27 g (3.15 mmol, 78.8%) of **12**, used in the next step without further purification. A sample was recrystallized from toluene for analysis, m.p., 172–175 °C.

Analysis: Calcd. for $C_{24}H_{18}FNO_4$: C, 71.46; H, 4.50; N, 3.47%. Found: C, 71.51; H, 4.51; N, 3.43%.

2-Benzoylamino-3-(4-benzyloxy-2-fluoro-5-methoxyphenyl)acrylic acid (13)

The azlactone **12** was refluxed with 30 ml of 40% sodium hydroxide solution in 50% aqueous ethanol for 10 min. Cooling and acidification with 2 N HCl gave a white precipitate, m.p., 234–236 °C, used in the next step without purification. A sample was recrystallized from methanol/ethyl acetate for analysis.

Analysis: Calcd. for $C_{24}H_{20}FNO_5$: C, 68.40; H, 4.78; N, 3.32%. Found: C, 68.30; H, 4.79; N 3.31%.

N-*Benzoyl*-3-(2-*fluoro*-3-*hydroxy*-4-*methoxyphenyl*)*alanine* (*14*)

A solution of 842 mg (2.0 mmol) **13** in 190 ml methanol was hydrogenated over 350 mg of 10% Pd–C at 40–45 p.s.i. for 6 h. Removal of catalyst and solvent gave 418 mg (1.25 mmol, 62.8%) of **14** as an off-white solid (m.p. 166–168 °C).

Analysis: Calcd. for $C_{17}H_{16}FNO_5$ (H_2O): C, 59.65; H, 5.01; N, 4.09%. Found: C, 59.71; H, 5.28; N 3.69%.

3-(2-Fluoro-4-hydroxy-5-methoxyphenyl)alanine (4)

A 167 mg (0.5 mmol) sample of **14** was refluxed for 24 h in 10 ml of 3 N HCl. After rotary evaporation of the solvent, water was added to the residue and the aqueous solution was washed with ether. The solution was neutralized (pH 6) with 15% NaOH. The precipitate that formed was filtered and dried, m.p., 243–245 °C. ^{1}H NMR (DMSO): δ 3.71 (3H, s, OCH_3), 3.57–3.65 (2H, m, $ArCH_2CH$), 3.13–3.19 (1H, m CH_2CH), 6.55 (1H, d, J=11.0 Hz, 3-ArH), 6.86 (1H, d, J=7.4 Hz, 6-ArH) ppm.

Analysis: Calcd. for $C_{10}H_{12}FNO_4$ (H_2O): C, 48.58; H, 5.71; N, 5.67%. Found: C, 48.50; H, 5.71; N, 5.67%.

5-Benzyloxy-2-fluoro-4-methoxyphenethanolamine (16)

Addition of a few mg of anhydrous ZnI_2 to a suspension of 184 mg of **10** in 0.20 ml trimethylsilyl cyanide led to an immediate exothermic reaction. The resulting homogeneous mixture was allowed to stir overnight. After removal of excess trimethylsilyl cyanide *in vacuo*, the crude trimethylsilyl-

cyanohydrin (**15**) was reduced by refluxing in ether for 2 h with 100 mg of lithium aluminum hydride. Decomposition of the excess hydride according to the method of Fieser and Fieser [11] and removal of solvent gave 142 mg of **16**. Recrystallization from cyclohexane/ethyl acetate gave 88 mg, m.p., 103–105 °C. ^{1}H NMR (CD_3OD): δ 2.75–2.79 (2H, m, $CHCH_2NH_2$), 3.29–3.31 (D*H*O), 3.83 (3H, s, OCH_3), 4.85–4.89 (m, $ArCH(OH)CH_2$; partially obscured by CD_2HOD), 5.08 (s, 2H, $PhOCH_2Ar$), 6.77 (1H, d, $J=11.5$ Hz, 3-Ar*H*), 7.06 (1H, d, $J=7.0$ Hz, 6-Ar*H*) ppm.

Analysis: Calcd. for $C_{16}H_{18}FNO_3$: C, 65.96; H, 6.23; N, 4.81%. Found: C, 65.74; H, 6.26; N, 4.63%.

2-Fluoro-4-hydroxy-5-methoxyphenethanolamine·$\frac{1}{2}$ oxalate [6-fluoronormethanephrine (5)]

A 50 mg sample of **16** was converted to the oxalate salt by addition of 10 mg of oxalic acid hydrate. This was hydrogenated overnight in 25 ml methanol in the presence of 25 mg of 10% Pd–C. Removal of catalyst and solvent, and recrystallization of the solid residue from methanol/H_2O gave 17 mg of **5**·$\frac{1}{2}$oxalate, m.p., 187–190 °C. ^{1}H NMR (D_2O): δ 3.27–3.34 (2H, m, $CHCH_2NH_2$), 3.86 (3H, s, OCH_3), 5.16–5.20 (1H, m, $ArCH(OH)CH_2$), 6.75 (1H, d, $J=11.3$ Hz, 3-Ar*H*), 7.07 (1H, d, $J=7.0$ Hz, 6-Ar*H*) ppm.

Analysis: Calcd. for $C_{10}H_{13}FNO_5$: C, 48.78; H, 5.32; N, 5.68%. Found: C, 48.48; H, 5.32; N, 6.30%.

2-Fluoro-4-hydroxy-5-methoxyphenylacetic acid [6-fluorohomovanillic acid (6)]

Trimethylsilylcyanohydrin (**15**) prepared from 260 mg of **10** was treated with 0.52 ml acetic acid, 0.87 ml concentrated HCl and 780 mg of $SnCl_2$ dihydrate. The mixture was heated at reflux for 3 h and then evaporated to dryness. Trituration of the residue with chloroform gave 95 mg of **6** as yellow crystals. Recrystallization from water gave an analytically pure sample, m.p., 152–154 °C. ^{1}H NMR (DMSO): δ 3.47 (2H, s, $ArCH_2$), 3.72 (3H, s, OCH_3), 6.57 (1H, d, $J=10.8$ Hz, 3-Ar*H*), 6.85 (1H, d, $J=7.3$ Hz, 6-Ar*H*) ppm.

Analysis: Calcd. for $C_9H_9FO_4$: C, 54.00; H, 4.53%. Found: C, 53.79; H, 4.63%.

Ethyl 2-(4-benzyloxy-2-fluoro-5-methoxyphenyl)-2-hydroxyacetate (17)

A solution of anhydrous ethanolic HCl was prepared by slow addition of 7.86 ml (10.91 g, 0.14 mol) acetyl chloride to 28 ml cold anhydrous ethanol. This was diluted with 35 ml of ether to give an approximately 2 N HCl solution. To this was added trimethylsilylcyanohydrin (**15**) prepared from 2.6 g (10 mmol) of **10**. The mixture was protected from moisture and stirred at room temperature for 4 d, during which time a yellow precipitate formed. To the reaction mixture was added 25 ml of water and the mixture was stirred for two additional days. After removal of the ether and ethanol

in vacuo, the aqueous solution was extracted with ether, the organic layer dried (Na_2SO_4) and the ether evaporated. Flash chromatography of the residue gave 1.254 g (3.75 mmol, 37.5%) of (**17**) as light yellow crystals, m.p., 69–71 °C. ^{1}H NMR ($CDCl_3$): δ 1.23 (3H, t, J=7.2 Hz, CH_3CH_2O), 3.42 (1H, d, J=5.1 Hz, O*H*), 3.86 (3H, s, OCH_3), 4.25 (2H, q, J=7.1 Hz, CH_3CH_2O), 5.13 (2H, s, $C_6H_5CH_2O$), 5.32 (d, J=5.1 Hz, C*H*(OH)), 6.66 (1H, d, J=11.2 Hz, 3-Ar*H*), 6.83 (1H, d, J=6.8 Hz), 7.30–7.41 (5H, m, $C_6H_5CH_2$) ppm.

Analysis: Calcd. for $C_{18}H_{19}FO_5$: C, 64.66; H, 5.73%. Found: C, 64.73; H, 5.73%.

*4-Benzyloxy-2-fluoro-5-methoxyphenyl glycol (**19**)*

To a stirred suspension of 235 mg (0.62 mmol) of $LiAlH_4$ in 30 ml ether, cooled in an ice bath under an argon atmosphere, was added dropwise a solution of 208 mg (0.62 mmol) of **17** in 6 ml ether. The reaction mixture was then heated to reflux and stirred for 5 h. After cooling, the excess hydride was decomposed according to the method of Fieser and Fieser. Removal of the solvent gave 114 mg of **19**, m.p., 84–88 °C. ^{1}H NMR ($CDCl_3$): δ 3.60–3.67 (2H, m, CH_2OH), 3.88 (3H, s, CH_3O), 5.05–5.09 (1H, m, ArC*H*(OH)), 5.27 (2H, s, $C_6H_5CH_2O$), 6.62 (1H, d, J=11.4 Hz, 3-Ar*H*), 7.01 (1H, d, J=6.8 Hz), 7.31–7.44 (5H, m, $C_5H_6CH_2$) ppm. This material was used in the next step without further purification. A sample for analysis was recrystallized from ethyl acetate/petroleum ether.

Analysis: Calcd. for $C_{16}H_{17}FO_4$: C, 65.74; H, 5.86%. Found: C, 65.66; H, 5.94%.

*2-Fluoro-4-hydroxy-5-methoxyphenyl glycol (6-fluoro-MHPG) (**7**)*

A solution of 114 mg (0.39 mmol) of **19** in 35 ml ethanol was hydrogenated over 43 mg of 10% Pd–C at 45–50 psi for 16 h. Removal of catalyst and solvent gave 80 mg of crude **7**. Recrystallization from ether–petroleum ether gave 43 mg of the pure sample (0.21 mmol, 54%) m.p., 115–116 °C. ^{1}H NMR (DMSO-d_6): δ 3.33–3.41 (2H, m, CH_2OH; partially obscured by CH_3), 3.73 (3H, s, CH_3O), 4.68–4.74 (1H, m, J=5.70 Hz, ArC*H*(OH)), 6.54 (1H, d, J=11.4 Hz, 3-Ar*H*), 6.94 (1H, d, J=6.9 Hz) ppm.

Analysis: Calcd. for $C_9H_{11}FO_4$: C, 53.47; H, 5.48%. Found: C, 53.38; H, 5.53%.

*4-Benzyloxy-2-fluoro-5-methoxymandelic acid (**20**)*

A solution of **17** in 15 ml of 40% aqueous NaOH was refluxed for 2 h. The reaction mixture was cooled, washed twice with ether and acidified with aqueous HCl. The yellow precipitate formed was collected by filtration and washed with water. The filtrate was extracted with ethyl acetate, and the organic layer dried and evaporated. The combined solids were dried to give 304 mg (97%) of crude product. Recrystallization from ether–petroleum ether gave white crystals, m.p., 103–106 °C. ^{1}H NMR (acetone-d_6): δ 3.79 (3H, s, OCH_3), 5.15 (2H, s, $C_6H_5CH_2O$), 5.36 (s, 1H, C*H*(OH)), 6.87 (1H, d, J=11.5 Hz, 3-Ar*H*), 7.06 (1H, d, J=7.1 Hz, 6-Ar*H*), 7.34–7.50 (5H, m, C_6H_5) ppm.

Analysis: Calcd. for $C_{16}H_{15}FO_5$: C, 62.74; H, 4.94%. Found: C, 62.64; H, 5.02%.

2-Fluoro-4-hydroxy-5-methoxymandelic acid (8)

A solution of 153 mg of **20** in 300 ml ethanol was hydrogenated over 55 mg of 10% Pd–C at 45 p.s.i. for 18 h. The catalyst was removed by filtration and the solvent evaporated to give 100 mg of a semi-crystalline solid. ^{1}H NMR (DMSO-d_6): δ 3.71 (3H, s, OC*H*$_3$), 5.08 (s, 1H, C*H*(OH)), 6.57 (1H, d, J=11.2 Hz, 3-Ar*H*), 6.91 (1H, d, J=7.1 Hz, 6-Ar*H*) ppm.

4,5-Dimethoxy-2-fluorophenylacetic acid (21)

A suspension of 1.28 g (6.9 mmol) of 6-fluoroveratraldehyde was stirred under an argon atmosphere in 1.5 ml trimethylsilyl cyanide and treated with a few mg of ZnI_2. An immediate exothermic reaction ensued and the mixture became homogeneous. This mixture was stirred overnight at ambient temperature, after which the excess trimethyl silylcyanide was removed *in vacuo*. The crude trimethylsilylcyanohydrin was stirred under reflux for 4 h with 1.84 ml acetic acid, 2.1 ml concentrated hydrochloric acid and 2.35 g of stannous chloride dihydrate. The reaction mixture was cooled, diluted with water and extracted with chloroform. After drying, the solvent was removed and the residue was triturated with carbon tetrachloride to give 620 mg (42%) of **21**, m.p., 104–105 °C (recrystallized from water). ^{1}H NMR ($CDCl_3$): δ 3.56 (2H, s, ArC*H*$_2$), 3.77 (6H, s, OC*H*$_3$), 6.57 (1H, d, J=10.8 Hz, 3-Ar*H*), 6.64 (1H, d, J=7.0 Hz, 6-Ar*H*) ppm.

Analysis: Calcd. for $C_8H_7FO_4$: C, 56.08; H, 5.18%. Found: C, 55.93; H, 5.33%.

Methyl 4,5-dihydroxy-2-fluorophenyl acetate (22)

A 212 mg (1 mmol) sample of **21** was dissolved in 5 ml methylene chloride under an argon atmosphere, cooled in a dry ice/acetone bath and treated with 3 ml of a 1 M solution of boron tribromide in hexane. The reaction mixture was allowed to warm to room temperature and was stirred overnight. After cooling the reaction in an ice bath, sufficient anhydrous methanol was added dropwise to decompose the excess boron tribromide. The solvent and trimethyl borate were removed by rotary evaporation. Methanol was added to the residue and was again evaporated. This process was repeated four times to remove traces of HBr and trimethyl borate. There was obtained 160 mg of **22**, m.p., 128–129 °C (recrystallized from ethyl acetate/cyclohexane). ^{1}H NMR (CD_3COCD_3): δ 3.50 (2H, s, ArC*H*$_2$), 3.62 (3H, s, OC*H*$_3$), 6.57 (1H, d, J=10.7 Hz, 3-Ar*H*), 6.75 (1H, d, J=7.5 Hz, 6-Ar*H*) ppm.

3,4-Dihydroxy-2-fluorophenylacetic acid (6-FDOPAC) (9)

A 60 mg sample of **22** was refluxed in 10 ml of 3 N HCl for 6 h. After thorough evaporation of the reaction mixture, the crystalline residue was recrystallized from toluene to give 36 mg of **9**, m.p. 162–164 °C. ^{1}H NMR

(CH_3OH): δ 3.46 (2H, s, ArCH_2), 6.49 (1H, d, J=10.7 Hz, 3-ArH), 6.66 (1H, d, J=7.4 Hz, 6-ArH) ppm.

Analysis: Calcd. for $C_8H_7FO_4$: C, 51.62; H, 3.79%. Found: C, 51.30; H, 3.99%.

Results and discussion

2-Fluoro-4-benzyloxy-5-methoxybenzaldehyde (**10**), previously synthesized by a different route [10], was the key intermediate used to prepare the COMT-derived metabolites. Selective benzylation of the more acidic 4-hydroxy group of 2-fluoro-4,5-dihydroxybenzaldehyde gave 2-fluoro-4-benzyloxy-5-hydroxybenzaldehyde (**11**), methylation of which produced **10**. Condensation of **10** with hippuric acid and hydrolysis of the intermediate azlactone (**12**) gave the *N*-benzoylaminoacrylate (**13**). Catalytic reduction of **13** with concommitant debenzylation to give **14**, followed by amide hydrolysis produced 3-(2-fluoro-4-hydroxy-5-methoxyphenylalanine (**4**). Reaction of **10** with trimethylsilyl cyanide, catalyzed by zinc iodide, gave the intermediate protected cyanohydrin (**15**). Lithium aluminum hydride reduction of **15**, followed by Pd/C-catalyzed hydrogenolysis of the benzyloxy groups of the resulting substituted phenethanolamine (**16**), produced 6-fluoronormetanephrine (**5**), isolated as the oxalate salt [9]. Treatment of **15** with stannous chloride in a refluxing mixture of HCl and acetic acid gave 6-FHVA (**6**) in one step.

The remaining 3-*O*-methyl metabolites were derived from ethyl 4-benzyloxy-2-fluoro-5-methoxymandelate (**17**), synthesized by hydrolysis of the imino ester **18** which had been prepared by acid-catalyzed ethanolysis of **15**. Lithium aluminium hydride reduction of **17** gave **19**, which was debenzylated to give 6-FMHPG (**7**), while basic hydrolysis of **17** gave **20** which was debenzylated to produce 2-fluoro-4-hydroxy-5-methoxymandelic acid (**8**).

6-FDOPAC (**9**) was prepared from 6-fluoroveratraldehyde by the same strategy used to prepare 6-FHVA. Treatment of the trimethylsilyl cyanohydrin of 6-fluoroveratraldehyde with stannous chloride in refluxing acetic acid and hydrochloric acid gave the dimethyl ether of 6-FDOPAC (**21**). Demethylation of **21** with BBr_3 and methanolic workup produced 6-FDOPAC methyl ester (**22**), acid hydrolysis of which gave (**9**).

References

1 E. S. Garnett, G. Firnau and C. Nahmias, *Nature (London), 305* (1983) 137.
2 C. C. Chiueh, R. N. Cohen, K. L. Kirk, R. D. Finn, G. Firnau and H. F. Kung, in P. M. Beart, G. N. Woodruff and D. M. Jackson (eds.), *Pharmacology and Functional Regulation of Dopaminergic Neurons*, MacMillan, New York, 1988, p. 329.
3 G. Eisenhofer, D. Hovevey-Sion, I. J. Kopin, R. Miletich, K. L. Kirk, R. Finn and D. S. Goldstein, *J. Exp. Pharmacol. Therapeut., 248* (1989) 319; D. S. Goldstein, D. P. C. Chang, G. Eisenhofer, R. Miletich, R. Finn, J. Bacher, K. L. Kirk, S. Bacharach and I. J. Kopin, *Circulation, 81* (1990) 1606; Y.-S. Ding, J. S. Fowler, S. J. Gatley, S. L. Dewey, A. P. Wolf and D. J. Schlyer, *J. Med. Chem., 34* (1991) 863.

4 Y.-S. Ding, J. S. Fowler, S. J. Gatley and A. P. Wolf, *J. Med. Chem.*, *34* (1991) 767.
5 K. L. Kirk, D. Cantacuzene and C. R. Creveling, in R. Filler and Y. Kobayashi (eds.), *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha, Tokyo, 1982, p. 75; K. L. Kirk and C. R. Creveling, *Medicinal Res. Rev.*, *4* (1984) 189; K. L. Kirk, in J. D. Welch (ed.), *ACS Symp. Ser. No. 456*, Am. Chem. Soc., Washington, D. C., 1991, p. 136.
6 K. L. Kirk, A. Adejare, S. Calderon, G. Chen, D. C. Furlano and F. Gusovsky, in A. Dahlström, R. H. Belmeker and M. Sandler (eds.), *Progress in Catecholamine Research. Part A: Basic Aspects and Peripheral Mechanisms*, Alan R. Liss, New York, 1988, p. 393.
7 C. R. Creveling and K. L. Kirk, *Biochem. Biophys. Res. Commun.*, *136* (1985) 1123; D. R. Thakker, C. Boehlert, C. K. L. Kirk and C. R. Creveling, in A. Dahlström, R. H. Belmeker and M. Sandler (eds.), *Progress in Catecholamine Research. Part A: Basic Aspects and Peripheral Mechanisms*, Alan R. Liss, Inc., New York, 1988, p. 397; G. Firnau, S. Sood, R. Pantel and S. Garnett, *Mol. Pharmacol.*, *19* (1981) 130.
8 J. R. Cooper, F. E. Bloom and R. H. Roth, *The Biochemical Basis of Neuropharmacology*, 3rd Edn., Oxford University Press, New York, 1978, p. 46.
9 D. H. Thakker, C. Boehlert, K. L. Kirk, R. Antkowiak and C. R. Creveling, *J. Biol. Chem.*, *261* (1986) 178.
10 C. R. Creveling, E. T. McNeal, D. Cantacuzene and K. L. Kirk, *J. Med. Chem.*, *24* (1981) 1395.
11 L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Vol. 1, Wiley, New York, 1967, p. 584.