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Regioselective synthesis of 6-fluorodopamine, 6-fluoro-*m*-tyramine and 4-fluoro-*m*-tyramine using elemental fluorine, oxygen difluoride and acetyl hypofluorite

Mohammad Namavari, N. Satyamurthy *, Jorge R. Barrio

Division of Nuclear Medicine, Department of Molecular and Medical Pharmacology, UCLA School of Medicine and Laboratory of Structural Biology and Molecular Medicine, Los Angeles, CA 90024, USA

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Abstract

6-Fluorodopamine was regioselectively synthesized in good yields from *N*-(trifluoroacetyl)-3,4-di-t-butoxycarbonyloxy-6-(trimethylstannyl)phenylethylamine (**6**) via a fluorodestannylation reaction using F_2, OF_2 or CH_3COOF followed by acid hydrolysis. Similarly, 6-fluoro-*m*-tyramine (**14**) and 4-fluoro-*m*-tyramine (**20**) were prepared from their corresponding trimethylstannyl derivatives. All precursors and products were fully characterized by multinuclear NMR spectroscopy and high resolution mass spectrometry.

Keywords: Dopamine neurotransmission; Norepinephrine synthesis; Dopamine agonist; 6-[^{18}F]fluorodopamine; Fluorodestannylation

1. Introduction

The investigation of the dopamine neurotransmission in human peripheral tissues has important significance [1]. For instance, a biochemical understanding of several neurocardiological diseases is made possible by following the dopamine neuro-process in the myocardial tissue [2]. In this regard, a number of derivatives of dopamine have been prepared to mimic endogenous dopamine function in the sympathetic nerve terminals, and among them 6-fluorodopamine (**8**) has emerged as a suitable candidate [3]. Both dopamine and 6-fluorodopamine are substrates for the enzyme dopamine β-hydroxylase, which converts them into their corresponding hydroxyalkyl derivatives, namely, norepinephrine and 6-fluoronorepinephrine, respectively [4]. As a result, 6-fluorodopamine has been proposed as a potential probe for in vivo endogenous norepinephrine synthesis [4]. This observation has led to the utilization of 6-fluorodopamine labeled with the positron emitting radiofluorine (^{18}F, half-life = 110 min) in the investigation of dopamine function and imaging of cardiac sympathetic innervation [5,6] using positron emission tomography (PET) [7].

The potential usefulness of 6-[^{18}F]fluorodopamine in PET investigations has generated considerable interest in its synthesis. The preparation of the ^{18}F-labeled counterpart of **8** based on an enzymatic decarboxylation reaction [8] and the direct radiofluorination of dopamine [9] involves either tedious reaction steps and low overall yields or provides a mixture of regioisomers. These shortcomings were rectified to a large extent in a more recently reported synthesis based on an [^{18}F]fluorodemercuration reaction [10,11]. However, this procedure is restricted in the selection of the fluorinating agents. It has been shown that fluorodemercuration of aromatic compounds occurs only with acetyl hypofluorite [12].

On the other hand, the fluorodestannylation reaction is versatile [13] and arylstannyl derivatives react efficiently with a variety of fluorinating agents such as F_2, OF_2, CH_3COOF [14–16], CF_3OF [17] and $CsSO_4F$ [18]. Thus, we now report the synthesis of the arylstannyl derivative **6** as a precursor for 6-fluorodopamine. This tin precursor regioselectively reacts with fluorine, oxygen difluoride and acetyl hypofluorite leading to the formation of **8** in good yields. The versatility of this synthetic technique is further demonstrated by its applicability to the preparation of 6-fluoro-*m*-tyramine (**14**) and 4-fluoro-*m*-tyramine (**20**). Interestingly, these *m*-tyramine derivatives maintain the structural requirements for dopamine agonistic activity (ethylamine side chain *meta* to a hydroxyl group), but are not substrates for the enzyme catechol-*O*-methyltransferase [19]. These characteristics have important biochemical implications and their significance is now beginning to emerge [19].

* Corresponding author.

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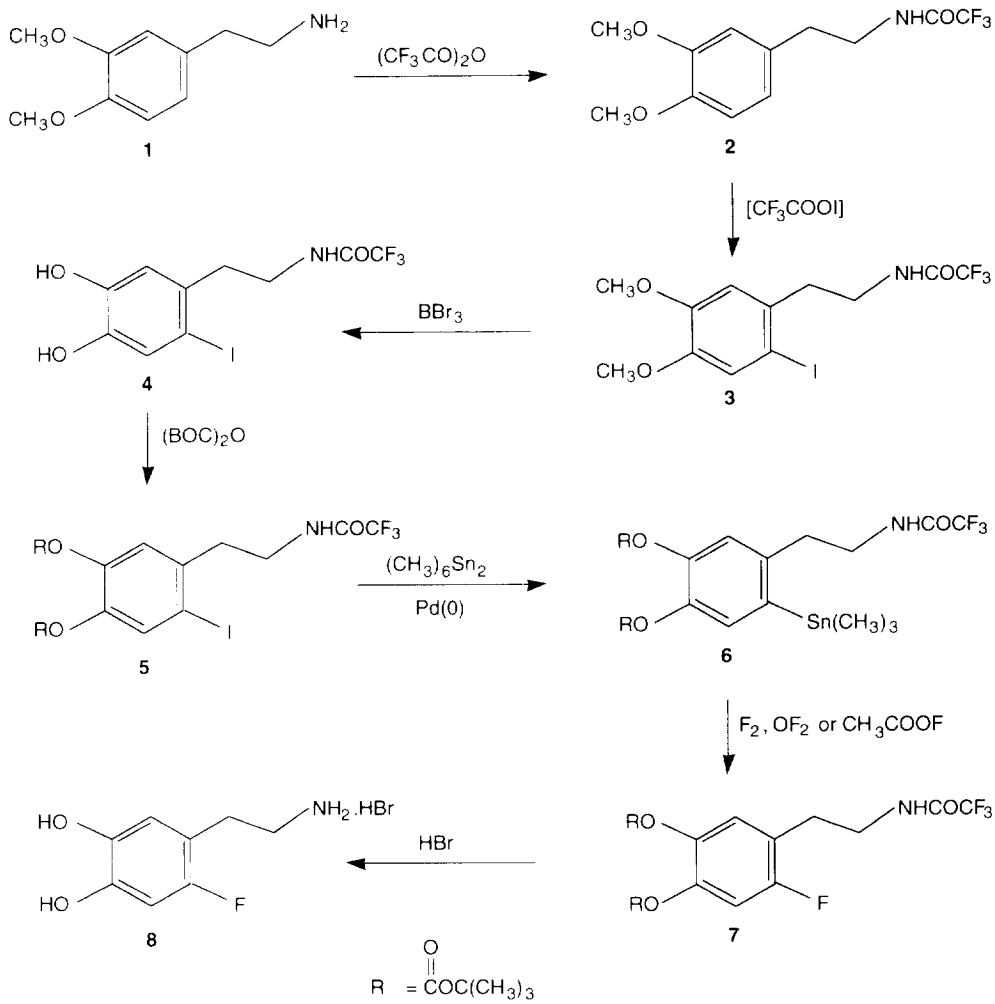


Scheme 1.

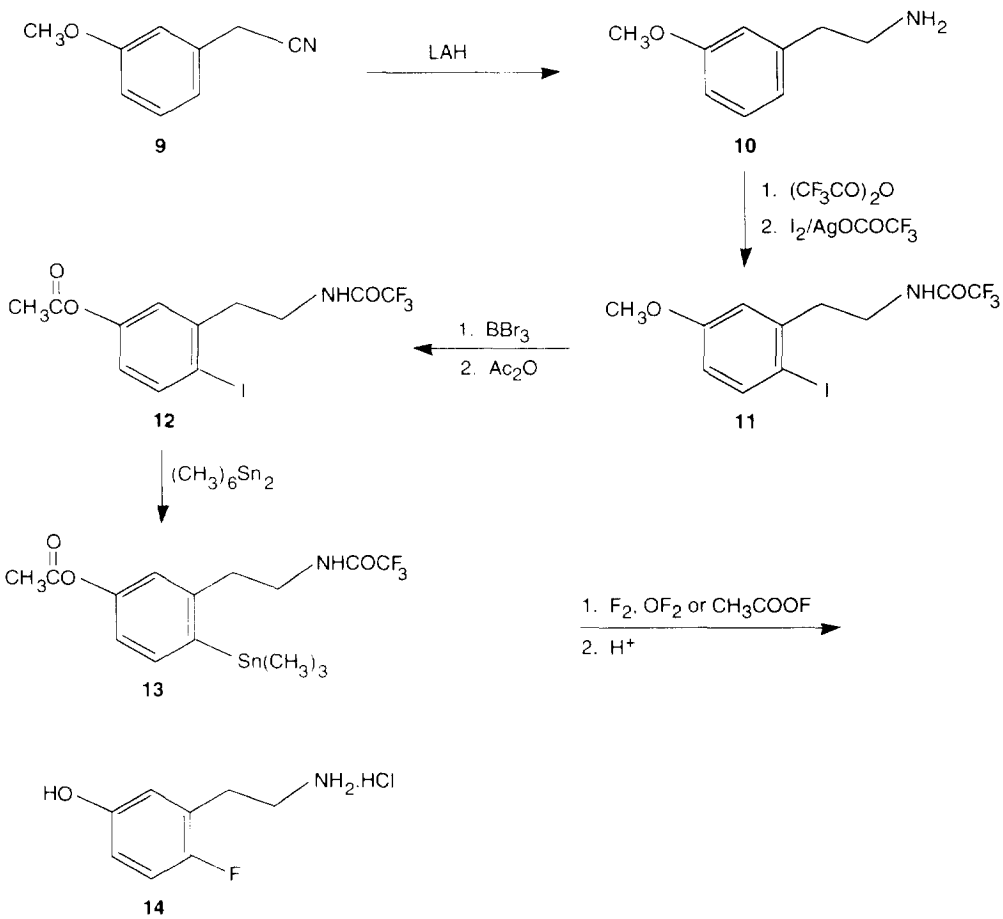
The synthetic methodology described herein has a clear advantage over other possible routes to fluorophenylethylamines starting from fluoroaryl precursors (e.g., fluorobenzaldehydes) in that the present fluorodestannylation method not only has preparative value but is also readily applicable to the synthesis of ^{18}F-labeled analogs with minimum number of reaction steps.

2. Results and discussion

The synthetic sequence used in the preparation of 6-fluorodopamine is shown in Scheme 1. Iodination of the trifluoroacetyl derivative **2** gave a single iodo product in excellent yields. The position of the iodo group in **3** was established by NMR spectroscopy. The ^{1}H NMR spectrum of **3** showed two singlets at δ 6.69 and 7.23 ppm for the two aromatic protons. The lack of coupling between these signals indicates that they are *para* to each other [20]. Such an arrangement in **3** is possible only when the iodo group is on C-6 in the aromatic ring. This rationale is further supported by a similar iodination of a protected dopamine derivative that yielded only the corresponding 6-iodo product [21]. To enhance the regioselectivity of the fluorination reaction later, as well as the ease of acid hydrolysis, the methoxyl groups in **3** were hydrolyzed with BBr_3, and the resulting phenolic functions were reprotected with tertiary butoxycarbonyl groups [16].

The palladium (0) catalyzed oxidative coupling of the iodo derivative **5** with hexamethylditin [22] yielded the stannyl product **6** as a stable white crystalline solid. Multinuclear (^{1}H, ^{13}C, ^{119}Sn) NMR spectroscopic analyses confirmed the structure of **6**. The introduction of the trimethylstannyl group on the aromatic ring, in general, caused a higher shielding of the neighboring ring protons and carbons. For example, the ^{1}H NMR signal due to H-5 in **5** at 7.74 ppm was shifted upfield to 7.28 ppm in the tin derivative **6**. Similarly, in the ^{13}C NMR there was a 3.5 ppm upfield shift for C-5 in **6** compared with the corresponding carbon in **5**. In general, both ^{1}H and ^{13}C NMR spectra exhibited couplings due to ^{119}Sn (see Experimental).

The fluorodestannylation of **6** with F_2, OF_2 or CH_3COOF proceeded smoothly at room temperature in freon to give the corresponding 6-fluoro derivative **7** in 60, 53 and 31% yields, respectively. The structure of **7** was confirmed by NMR anal-



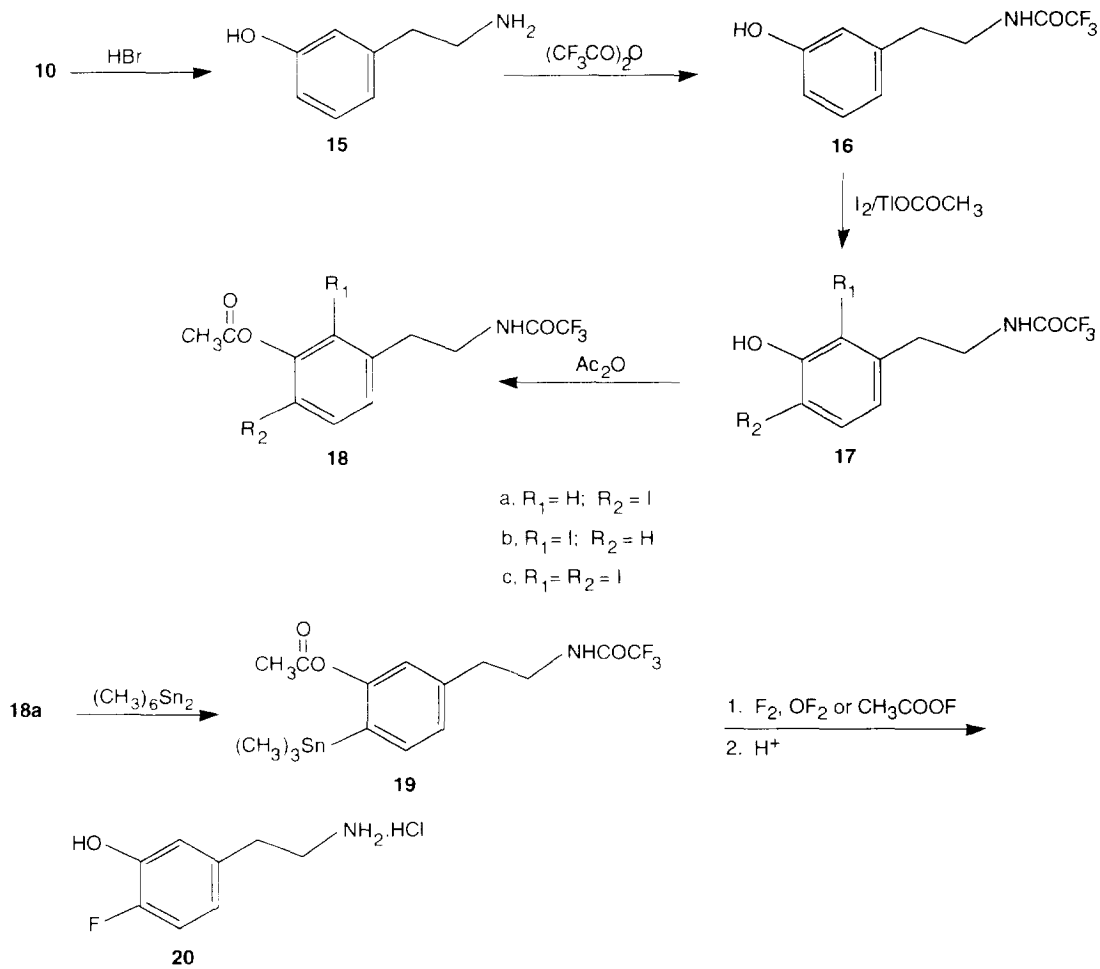
Scheme 2.

yses and high resolution mass spectroscopy. The ^{1}H NMR of **7** showed two sets of doublets due to fluorine–proton couplings in the aromatic region for H-2 and H-5, in agreement with its structure. The fluoro derivative **7** upon hydrolysis with 48% HBr gave 6-fluorodopamine (**8**).

The synthetic approach to 6-fluoro-*m*-tyramine (**14**) and its isomeric 4-fluoro derivative **20** is outlined in Schemes 2 and 3. The iodo derivatives **11** and **17a** were the key intermediates for the synthesis of the precursor tin derivatives **13** and **19**, respectively. Iodination of the *N*-trifluoroacetyl derivative of **10** by trifluoroacetyl hypoiodite, generated in situ, gave the iodo product **11** as the sole regioisomer in good yields. A similar regioselectivity could not be attained for the preparation of the product **17a**. Nevertheless, iodination of **16** in the presence of thallium (I) acetate [23] afforded a mixture of iodo derivatives from which the 4-iodo analog was isolated in acceptable yields by flash chromatography. The positions of the halogen in **11** and **17** were established by NMR spectral data. The identical ^{1}H NMR patterns of the aromatic regions in the demethylated derivative of **11** and a structurally related 6-iodo-*m*-tyrosine derivative [24] provide supplementary evidence for the position of the iodine in **11**. A similar relationship between **17a** and a 4-iodo-*m*-tyrosine derivative [25] was also observed.

It has been observed that the regiospecificity of the fluorodestannylation reaction depends upon the nature of the phenolic protecting groups [16]. Mildly electron withdrawing groups such as acetoxy and t-Boc generally enhanced the regioselectivity over the electron donating methoxyl group. Thus, the phenolic function in **12** and **18** was protected as the acetoxy group for optimal regioselectivity during the fluorodestannylation reaction. The aryltin precursors **13** and **19** were fluorodemetallated with F_2, OF_2 or CH_3COOF to the corresponding protected fluoro derivatives, which were characterized by NMR and mass spectroscopy. Elemental fluorine invariably gave higher yields, as previously noted for simpler substrates [15]. The amines **14** and **20** were then obtained as their hydrochlorides from the acid hydrolysis of the corresponding protected fluoro derivatives. In this context, the direct fluorination of *m*-tyramine has been shown to yield a mixture of monofluorinated isomers along with unidentified derivatives from which pure products have not been isolated [26].

All attempts to convert the iodo compounds **18b** and **18c** into their corresponding trimethylstannyl derivatives by the Pd(0) catalyzed oxidative coupling reactions were unsuccessful. Further, the reaction of the lithium salt of **18b** (generated with nBuLi) and $(CH_3)_3SnCl$ also failed to yield the



Scheme 3.

tin derivative. The failure of these reactions may presumably be due to the steric hindrance involved in these cases.

In summary, the fluorodestannylation procedure provides a new synthetic approach to the preparation of fluorophenylethylamines. The simple synthesis of aryltin precursors and the ease of the fluorination process are the highlights of this methodology.

3. Experimental

All melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. ^{1}H, ^{13}C, ^{19}F and ^{119}Sn NMR spectra were recorded at 360.14, 90.57, 338.87 and 134.30 MHz, respectively, on a Bruker AM-360 WB spectrometer. The ^{13}C, ^{19}F and ^{119}Sn NMR data were collected with proton decoupling. Selected off-resonance spectra were also obtained to support various signal assignments. The ^{1}H NMR chemical shifts were referenced to an internal TMS or external DSS standards while the ^{13}C chemical shifts were referenced to an internal TMS standard unless stated otherwise. The ^{19}F and ^{119}Sn NMR spectra were referenced to external $CFCl_3$ and $(CH_3)_4Sn$, respectively. Direct chemical ionization (DCI; ammonia) and electron impact high resolution mass spectral data were recorded on a ZAB 7070 mass spectrometer. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, TN.

3.1. N-(Trifluoroacetyl)-3,4-dimethoxyphenylethylamine (2)

A solution of 3,4-dimethoxyphenylethylamine (**1**) (2.53 g, 14.0 mmol) in anhydrous 1,4-dioxane (15 ml) was added slowly to trifluoroacetic anhydride (6.3 g, 30.0 mmol) and the resulting solution was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the residue was flash chromatographed (silica gel, ether–petroleum ether, 1:1) to give the trifluoroacetyl derivative **2** as a white solid (2.94 g, 76%), m.p. 83–84 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.83 (t, 2H, $J = 6.9$ Hz, benzylic H); 3.60 (q, 2H, $J = 6.6$ Hz, CH_2N); 6.28 (broad s, 1H, NH); 6.69 (s, 1H, H-2); 6.73 (d, 1H, $J_{6,5} = 8.6$ Hz, H-6); 6.83 (d, 1H, $J_{5,6} = 8.6$Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 34.54 (benzylic carbon); 41.17 (CH_2N); 55.84 (CH_3O); 55.94 (CH_3O); 111.56 (C-2); 111.78 (C-5); 115.84 (q, $^{1}J_{C,F} = 288.0$ Hz, CF_3); 120.67 (C-6); 130.06 (C-1); 148.08 (C-4); 149.26 (C-3); 157.19 (q, $^{2}J_{C,F} = 37.0$ Hz, $COCF_3$)

ppm. HRMS calcd for $C_{12}H_{14}NO_3F_3$: 277.0926. Found: 277.0931.

3.2. N-(Trifluoroacetyl)-3,4-dimethoxy-6-iodophenylethylamine (3)

To a solution of **2** (1.99 g, 7.2 mmol) and silver trifluoroacetate (2.0 g, 9.1 mmol) in CH_2Cl_2 (150 ml) iodine (1.88 g, 7.4 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was filtered and the residue was washed with CH_2Cl_2. The CH_2Cl_2 filtrate was washed with 0.1 M $Na_2S_2O_3$ solution (2×50 ml), water (2×100 ml) and dried (Na_2SO_4). Removal of the solvent in a rotary evaporator left a solid residue which was purified by flash chromatography (silica gel, hexane–ether, 5:4) to give **3** as a white solid (2.14 g, 74%), m.p. 130–131 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.98 (t, 2H, J=7.2 Hz, benzylic H); 3.61 (q, 2H, J=6.7 Hz, CH_2N); 6.28 (broad s, 1H, NH); 6.69 (s, 1H, H-2); 7.23 (s, 1H, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 39.00 (benzylic carbon); 40.04 (CH_2N); 55.91 (OCH_3); 56.21 (OCH_3); 87.96 (C-6); 112.71 (C-2); 115.83 (q, $^1J_{C,F}$=287.0 Hz, CF_3); 121.97 (C-5); 132.76 (C-1); 148.61 (C-4); 149.64 (C-3); 157.38 (q, $^2J_{C,F}$=37.0 Hz, $COCF_3$) ppm. HRMS calcd. for $C_{12}H_{13}NO_3F_3I$: 402.9892. Found: 402.9886. Anal. Calcd for $C_{12}H_{13}NO_3F_3I$: C, 35.75; H, 3.25; N, 3.47; F, 14.14; I, 31.48. Found: C, 35.75; H, 3.27; N, 3.43; F, 14.09; I, 31.49%.

3.3. N-(Trifluoroacetyl)-3,4-dihydroxy-6-iodophenylethylamine (4)

Boron tribromide (17.7 ml of 1 M solution in CH_2Cl_2) was added dropwise to a solution of the iodo derivative **3** (2.0 g, 4.96 mmol) in CH_2Cl_2 (35 ml) at −78 °C and the mixture was stirred at that temperature for 15 min. The reaction mixture was gradually allowed to warm to room temperature and stirred for another 30 min and poured onto ice (100 g). The methylene chloride layer was separated and the aqueous phase was extracted with ethyl acetate (2×75 ml). The organic layers were combined, dried (Na_2SO_4) and the solvents were removed under reduced pressure to give the dihydroxy derivative **4** as a brown solid (1.60 g, 86%), m.p. 182–183 °C, which was used in the next step without further purification. ^{1}H NMR (acetone-d_6/TMS) δ: 2.86 (t, 2H, J=7.3 Hz, benzylic H); 3.51 (q, 2H, J=6.7 Hz, CH_2N); 6.81 (s, 1H, H-2); 7.25 (s, 1H, H-5); 8.56 (broad s, 1H, NH) ppm. HRMS calcd for $C_{10}H_9NO_3F_3I$: 374.9579. Found: 374.9586.

3.4. N-(Trifluoroacetyl)-3,4-di-t-butoxycarbonyloxy-6-iodophenylethylamine (5)

To a solution of the iodo derivative **4** (1.50 g, 4.0 mmol) and triethylamine (0.53 g, 5.24 mmol) in anhydrous DMF (18 ml) was added a solution of di-t-butyl dicarbonate (2.62 g, 12.0 mmol) in anhydrous DMF (18 ml). After stirring the mixture at room temperature for 16 h, ethyl acetate (150 ml) was added and the reaction mixture was washed successively with saturated NaCl solution (3×50 ml) and water (3×50 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to a syrup which was chromatographed on silica gel (hexane–diethyl ether, 1:1) to afford **5** as a white solid (1.68 g, 73%); m.p. 102–103 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.54 [s, 9H, $C(CH_3)_3$]; 1.55 [s, 9H, $C(CH_3)_3$]; 3.01 (t, 2H, J=6.8 Hz, benzylic H); 3.60 (q, 2H, J=6.5 Hz, CH_2N); 6.57 (broad t, 1H, J=4.9 Hz, NH); 7.1 (s, 1H, H-2); 7.74 (s, 1H, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 27.63 (CH_3 of t-butyl groups); 39.03 (benzylic carbon); 39.76 (CH_2N); 84.44 (quaternary carbon of t-butyl groups); 94.70 (C-6); 115.79 (q, $^1J_{C,F}$=287.0 Hz, CF_3); 124.18 (C-2); 133.92 (C-5); 139.08 (C-1); 141.71 (C-4); 142.96 (C-3); 150.44 (OCO-t-butyl); 157.51 (q, $^2J_{C,F}$=37.0 Hz, $COCF_3$) ppm. DCI high resolution mass spectrum calcd for $C_{20}H_{29}N_2O_7F_3I$ ($M^+ + NH_4$): 593.0972. Found: 593.0986. Anal. Calcd for $C_{20}H_{25}NO_7F_3I$: C, 41.75; H, 4.38; N, 2.43; F, 9.91. Found: C, 41.54; H, 4.33; N, 2.27; F, 9.85%.

3.5. N-(Trifluoroacetyl)-3,4-di-t-butoxycarbonyloxy-6-(trimethylstannyl)phenylethylamine (6)

To a mixture of the iodo derivative **5** (0.90 g, 1.56 mmol) and tetrakis-triphenylphosphine palladium (0) catalyst (0.06 g) in 1,4-dioxane (12 ml), hexamethylditin (0.66 g, 2.01 mmol) was added and stirred under reflux for 7 h in an atmosphere of argon. The mixture was cooled to room temperature and filtered. The black residue in the filter was washed with ethyl acetate. The filtrate and the washings were combined and the solvents were removed in a rotary evaporator. The residual yellow oily material was flash chromatographed on silica gel (hexane–diethyl ether, 5:4) to give the stannyl derivative **6** as a white solid (0.58 g, 61%), m.p. 149–150 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 0.36 [s, 9H, Sn satellites $^2J_{Sn,H}$=54.0 Hz, $Sn(CH_3)_3$]; 1.54 [s, 9H, $C(CH_3)_3$]; 1.56 [s, 9H, $C(CH_3)_3$]; 2.89 (t, 2H, J=7.0 Hz, benzylic H); 3.57 (q, 2H, J=6.7 Hz, CH_2N); 6.45 (broad t, 1H, NH); 7.11 (s, 1H, Sn satellites $^4J_{Sn,H}$=16.0 Hz, H-2); 7.28 (s, 1H, Sn satellites $^3J_{Sn,H}$=48.0 Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: −8.08 (s, Sn satellites $^1J_{Sn,C}$=354 Hz, $Sn(CH_3)_3$]; 27.65 (CH_3 of t-butyl groups); 37.19 (s, Sn satellites $^3J_{Sn,C}$=22.0 Hz, benzylic carbon); 41.30 (CH_2N); 83.86 (quaternary carbon of t-butyl group); 83.96 (quaternary carbon of t-butyl group); 115.80 (q, $^1J_{C,F}$=287.0 Hz, CF_3); 123.23 (s, Sn satellites $^3J_{Sn,C}$=40.7 Hz, C-2); 130.58 (s, Sn satellites $^2J_{Sn,C}$=40.7 Hz, C-5); 140.85 (C-6); 141.07 (C-1 and C-4); 142.89 (s, Sn satellites $^4J_{Sn,C}$=30.4 Hz, C-3); 150.95 (OCO-t-butyl); 151.03 (OCO-t-butyl); 157.36 (q, $^2J_{C,F}$=37.0 Hz, $COCF_3$) ppm. ^{119}Sn NMR ($CDCl_3$) δ: −26.36 ppm. Anal. Calcd for $C_{23}H_{34}NO_7F_3Sn$: C, 45.12; H, 5.60; N, 2.29; F, 9.31. Found: C, 45.20; H, 5.47; N, 2.24; F, 9.17%.

3.6. N-(Trifluoroacetyl)-3,4-di-t-butoxycarbonyloxy-6-fluorophenylethylamine (7)

Into a solution of the stannyl precursor **6** (0.061 g, 0.1 mmol) in freon-11 (15 ml) taken in a 25 ml dry glass test tube F_2 (1% in helium, 0.2 mmol), OF_2 (1% in helium, 0.2 mmol) or CH_3COOF [27] (prepared from 0.2 mmol of 1% F_2 in helium) was bubbled in over a period of 45 min. The freon solution was decanted off the white precipitate and the reaction vessel was rinsed with CH_2Cl_2 (3×8 ml). The rinsings and the Freon solution were combined, washed with 0.1 M $Na_2S_2O_3$ solution (2×20 ml), water (2×20 ml) and dried (Na_2SO_4). Evaporation of the solvents gave an oily residue which was flash chromatographed on silica gel (petroleum ether–diethyl ether, 5:4) to yield the fluoro derivative **7** as a colorless viscous oil; yield: 60%, 53% and 31% for F_2, OF_2 and CH_3COOF, respectively. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.55 (s, 18H, t-butyl groups); 2.91 (t, 2H, J=6.7 Hz, benzylic H); 3.59 (q, 2H, J=6.5 Hz, CH_2N); 6.51 (broad t, 1H, NH); 7.05 (d, 1H, J=10.2 Hz, H-5); 7.08 (d, 1H, J=8.1 Hz, H-2) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 27.59 (CH_3 of t-butyl groups); 28.25 (benzylic carbon); 39.86 (CH_2N); 84.20 (quaternary carbon of t-butyl groups); 84.43 (quaternary carbon of t-butyl group); 111.11 (d, $^2J_{C,F}$=27.1 Hz, C-5); 115.74 (q, $^1J_{C,F}$=287.0 Hz, CF_3); 122.85 (d, $^2J_{C,F}$=18.0 Hz, C-1); 124.81 (d, $^3J_{C,F}$=5.3 Hz, C-2); 138.83 (C-3); 142.03 (d, $^3J_{C,F}$=11.3 Hz, C-4); 150.35 (OCO-t-butyl); 150.80 (OCO-t-butyl); 157.4 (q, $^2J_{C,F}$=37.0 Hz, $COCF_3$); 157.89 (d, $J_{C,F}$=245.0 Hz, C-6) ppm. ^{19}F NMR ($CDCl_3$) δ: −119.09 (s, fluorine at C-6); −76.38 (s, CF_3) ppm. DCI high resolution mass spectrum calcd for $C_{20}H_{29}N_2O_7F_4$ ($M^+ + NH_4$): 485.1911. Found 485.1906.

3.7. 6-Fluoro-3,4-dihydroxyphenylethylamine (6-fluorodopamine) (8)

Hydrobromic acid (48% solution, 4.2 ml) was added to the fluoro derivative **7** (0.10 g, 0.21 mmol) and stirred at 140–145 °C (oil bath) for 20 min. Evaporation of the acidic mixture under vacuum gave 6-fluorodopamine (**8**) as the hydrobromide salt in 94% yield; m.p. 206–209 °C. ^{1}H NMR (D_2O/DSS) δ: 2.90 (t, 2H, J=7.0 Hz, benzylic H); 3.20 (t, 2H, J=7.0 Hz, CH_2N); 6.77 (d, 1H, $J_{H,F}$=10.9 Hz, H-5); 6.84 (d, 1H, $J_{H,F}$=7.5 Hz, H-2) ppm. ^{13}C NMR (D_2O/external TMS) δ: 28.4 (benzylic carbon); 42.1 (CH_2N); 106.5 (d, $^2J_{C,F}$=26.3 Hz, C-5); 116.8 (d, $^2J_{C,F}$=18.1 Hz, C-1); 119.9 (d, $^3J_{C,F}$=5.8 Hz, C-2); 142.8 (C-3); 146.7 (C-4); 157.4 (d, $^1J_{C,F}$=236.0 Hz, C-6) ppm. ^{19}F NMR ($CDCl_3$) δ: −125.2 (s) ppm. The ^{1}H and ^{19}F NMR spectral data are in agreement with the literature values [28].

3.8. 3-Methoxyphenylethylamine (10)

(3-Methoxyphenyl)acetonitrile **9** (2.5 g, 17 mmol) in anhydrous diethyl ether (35 ml) was added dropwise to a slurry of lithium aluminum hydride (1.9 g, 50 mmol) in anhydrous ether (70 ml) at 0 °C under argon. The reaction mixture was stirred under reflux for 10 h, cooled to room temperature and the excess hydride was carefully destroyed with ice water. The resultant emulsion was filtered, the organic layer separated and the aqueous layer extracted with ether (3×100 ml). The combined organic layer was extracted with 1 N HCl (4×50 ml). The aqueous layer was adjusted to pH ~9.0 with 1 N NaOH and extracted with ether (4×100 ml). The combined ether layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford **10** as a colorless oil (1.75 g, 68%) which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.73 (t, 2H, J=6.9 Hz, benzylic H); 2.97 (t, 2H, J=6.9 Hz, CH_2N); 3.80 (s, 3H, OCH_3); 6.75 (s, 1H, H-2); 6.78–6.80 (m, 2H, H-4 and H-6); 7.22 (t, 1H, J=7.8 Hz, H-5) ppm. HRMS calcd for $C_9H_{13}NO$: 151.0997. Found: 151.0995.

3.9. N-(Trifluoroacetyl)-3-methoxyphenylethylamine

Trifluoroacetylation of the phenylethylamine **10** (1.51 g, 10.0 mmol) as described for **2** gave the title product as a colorless oil (1.70 g, 69%). ^{1}H NMR ($CDCl_3$/TMS) δ: 2.87 (t, 2H, J=6.8 Hz, benzylic H); 3.62 (q, 2H, J=6.5 Hz, CH_2N); 3.81 (s, 3H, OCH_3); 6.35 (broad s, 1H, NH); 6.73 (d, 1H, J=1.9 Hz, H-2); 6.78 (d, 1H, J=7.7 Hz, H-6); 6.81 (dd, 1H, J=7.7 Hz and 1.9 Hz, H-4); 7.26 (t, 1H, J=7.7 Hz, H-5) ppm. HRMS calcd for $C_{12}H_{12}NO_2F_3$: 247.0820. Found: 247.0831.

3.10. N-(Trifluoroacetyl)-6-iodo-3-methoxyphenylethylamine (11)

Iodination of the above trifluoroacetyl derivative (1.78 g, 7.2 mmol) as described for the synthesis of **3** afforded the 6-iodomethoxyphenylethyamine derivative **11** as a white solid (2.18 g, 81%), m.p. 71–72 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 3.00 (t, 2H, J=7.0 Hz, benzylic H); 3.62 (q, 2H, J=6.7 Hz, CH_2N); 3.78 (s, 3H, OCH_3); 6.34 (broad s, 1H, NH); 6.57 (dd, 1H, J=8.7 and 3.0 Hz, H-4); 6.76 (d, 1H, J=3.0 Hz, H-2); 7.70 (d, 1H, J=8.7 Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 39.46 (benzylic carbon); 39.74 (CH_2N); 55.30 (OCH_3); 88.57 (C-6); 115.74 (q, $^1J_{C,F}$=287.0 Hz, CF_3); 115.09 (C-2); 115.83 (C-4); 140.23 (C-5); 141.31 (C-3); 148.25 (C-1); 157.28 (q, $^2J_{C,F}$=38.0 Hz, $COCF_3$) ppm. HRMS calcd for $C_{11}H_{11}NO_2F_3I$: 372.9787. Found: 372.9802.

3.11. N-(Trifluoroacetyl)-3-hydroxy-6-iodophenylethylamine

Demethylation of the iodo derivative **11** with BBr_3 as described earlier for the preparation of **4** gave the title product after chromatographic purification (silica gel, ether–hexane, 4:5) as a colorless viscous oil in 91% yield. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.97 (t, 2H, J=6.9 Hz, benzylic H); 3.62 (q, 2H, J=6.8 Hz, CH_2N); 6.38 (broad s, 1H, NH); 6.52 (dd, 1H, J=8.5 Hz and 2.7 Hz, H-4); 6.73 (d, 1H, J=2.7

Hz, H-2); 7.66 (d, $J=8.5$ Hz, 1H, H-5) ppm. HRMS calcd for $C_{10}H_9NO_2F_3I$: 358.9630. Found: 358.9633.

3.12. N-(Trifluoroacetyl)-3-acetoxy-6-iodophenylethylamine (12)

Acetic anhydride (1.53 g, 15.0 mmol) was added to a solution of *N*-(trifluoroacetyl)-3-hydroxy-6-iodophenylethylamine (1.79 g, 5.0 mmol) in anhydrous pyridine (5 ml) at 0 °C. The reaction mixture was brought to room temperature and stirred for 1 h. The mixture was concentrated under vacuum and the residual product was purified by flash chromatography (silica gel, hexane–ether, 5:4) to give pure **12** (1.74 g, 87%), m.p. 73–74 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.30 (s, 3H, CH_3); 3.03 (t, 2H, $J=6.8$ Hz, benzylic H); 3.62 (q, 2H, $J=6.6$ Hz, CH_2N); 6.45 (broad s, 1H, NH); 6.76 (dd, 1H, $J=8.5$ Hz, and 3.2 Hz, H-4); 6.96 (d, 1H, $J=3.2$ Hz, H-2); 7.84 (d, 1H, $J=8.5$ Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 21.09 (CH_3); 39.53 (benzylic carbon); 39.74 (CH_2N); 95.98 (C-6); 115.84 (q, $^1J_{C,F}=287.0$ Hz, CF_3); 122.43 (C-4); 124.18 (C-2); 140.60 (C-5); 142.01 (C-1); 151.24 (C-3); 157.51 (q, $^2J_{C,F}=37.0$ Hz, $COCF_3$); 169.00 ($OCOCH_3$) ppm. Anal. Calcd for $C_{12}H_{11}NO_3F_3I$: C, 35.93; H, 2.76; N, 3.49. Found: C, 35.71; H, 2.62; N, 3.29%.

3.13. N-(Trifluoroacetyl)-3-acetoxy-6-(trimethylstannyl)phenylethylamine (13)

Stannylation of the iodo derivative **12** as described above for the synthesis of **6** gave the trimethylstannylphenylethylamine derivative **13** as a white solid (0.38 g, 55%), m.p. 72–73 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 0.33 [s, 9H, Sn satellites $^2J_{Sn,H}=53.0$ Hz, $Sn(CH_3)_3$]; 2.30 (s, 3H, CH_3CO); 2.90 (t, 2H, $J=7.2$ Hz, benzylic H); 3.56 (q, 2H, $J=6.8$ Hz, CH_2N); 6.55 (broad s, 1H, NH); 6.93 (d, 1H, $J=2.3$ Hz, H-2); 6.97 (dd, 1H, $J=7.9$ and 2.3 Hz, H-4); 7.46 (d, 1H, $J=7.9$ Hz, Sn side bands, $^3J_{Sn,H}=47.0$ Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: −8.11 [s, Sn satellites, $^1J_{Sn,C}=346.0$ Hz, $Sn(CH_3)_3$]; 21.11 (CH_3 of acetyl group); 37.48 (s, Sn satellites, $^3J_{Sn,C}=20.0$ Hz, benzylic carbon); 41.17 (CH_2N); 115.8 (q, $^1J_{C,F}=287.0$ Hz, CF_3); 119.67 (s, Sn satellites, $^3J_{Sn,C}=47.0$ Hz, C-4); 121.60 (s, Sn satellites, $^3J_{Sn,C}=39.0$ Hz, C-2); 137.79 (s, Sn satellites, $^2J_{Sn,C}=38.0$ Hz, C-5); 139.80 (C-6); 145.75 (C-1); 151.57 (C-3); 157.28 (q, $^2J_{C,F}=37.0$ Hz, $COCF_3$); 169.57 ($OCOCH_3$) ppm. ^{119}Sn NMR ($CDCl_3$) δ: −29.15 ppm. Anal. Calcd for $C_{15}H_{20}NO_3F_3Sn$: C, 41.13; H, 4.60; N, 3.20; F, 13.01. Found: C, 40.93; H, 4.79; N, 3.16; F, 12.87%.

3.14. N-(Trifluoroacetyl)-3-acetoxy-6-fluorophenylethylamine

Fluorine (1% in He, 0.4 mmol), OF_2 (1% in He, 0.4 mmol) or CH_3COOF [27] (prepared from 0.4 mmol of 1%F_2 in He), was bubbled into a solution of the trimethylstannylphenylethylamine derivative **13** (0.088 g, 0.2 mmol) in freon-11 (15 ml) at room temperature over a period of 1.5 h. The reaction mixture was diluted with methylene chloride (25 ml) and washed with 0.1 M $Na_2S_2O_3$ solution (2×25 ml), water (2×25 ml) and dried ($MgSO_4$). The solvent was evaporated and the syrupy residue was chromatographed on silica gel (ether–hexane, 1:1) to give the title compound as a white solid, m.p. 78–79 °C; yield (based on the tin derivative) 65, 63, and 28% for OF_2, F_2 and CH_3COOF, respectively. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.29 (s, 3H, CH_3CO); 2.93 (t, 2H, $J=6.7$ Hz, benzylic H); 3.50 (q, 2H, $J=6.5$ Hz, CH_2N); 6.42 (broad s, 1H, NH); 6.91–6.99 (m, 2H, H-2 and H-4); 7.07 (t, 1H, $J=9.0$ Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 21.00 (CH_3); 28.69 (benzylic carbon); 39.81 (CH_2N); 115.74 (q, $^1J_{C,F}=289.0$ Hz, CF_3); 116.34 (d, $^2J_{C,F}=24.4$ Hz, C-5); 121.87 (d, $^3J_{C,F}=8.9$ Hz, C-2); 124.02 (d, $^3J_{C,F}=4.4$ Hz, C-4); 125.76 (d, $^2J_{C,F}=18.1$ Hz, C-1); 146.63 (C-3); 157.35 (q, $^2J_{C,F}=37.0$ Hz, $COCF_3$); 158.64 (d, $^1J_{C,F}=244.0$ Hz, C-6); 169.48 ($OCOCH_3$) ppm. ^{19}F NMR ($CDCl_3$) δ: −76.4 (s, CF_3); −122.5 (s, fluorine at C-6) ppm. DCI HRMS calcd for $C_{12}H_{15}N_2O_3F_4$ ($M^+ + NH_4$): 311.1019. Found: 311.1019. Anal. Calcd for $C_{12}H_{11}NO_3F_4$: C, 49.16; H, 3.78; N, 4.78. Found: C, 48.79; H, 3.67; N, 4.72%.

3.15. 6-Fluoro-3-hydroxyphenylethylamine hydrochloride (14)

Hydrochloric acid (6.0 N, 15 ml) was added to the above protected fluoro-*m*-tyramine derivative (0.15 g, 0.5 mmol) and the mixture was heated under reflux for 1.5 h. Evaporation of the reaction mixture under reduced pressure afforded **14** (0.075 g, 95%), m.p. 171–173 °C (d). ^{1}H NMR (D_2O/DSS) δ: 3.00 (t, 2H, $J=7.2$ Hz, benzylic H); 3.28 (t, 2H, $J=7.2$ Hz, CH_2N); 6.81–6.84 (m, 2H, H-2 and H-4); 7.06 (t, 1H, $^3J_{H,H}=^3J_{H,F}=9.7$ Hz, H-5) ppm. ^{13}C NMR (D_2O/external TMS) δ: 29.2 (benzylic carbon); 41.9 (CH_2N); 118.1 (d, $^3J_{C,F}=8.1$ Hz, C-4); 118.8 (d, $^3J_{C,F}=3.7$ Hz, C-2); 118.9 (d, $^2J_{C,F}=23.4$ Hz, C-5); 125.8 (d, $^2J_{C,F}=17.6$ Hz, C-1); 154.2 (C-3); 157.9 (d, $^1J_{C,F}=236.0$ Hz, C-6) ppm. ^{19}F NMR (D_2O) δ: −128.1 (s) ppm. DCI HRMS calcd for $C_8H_{11}NOF$ ($M^+ + H$) (free base): 156.0825. Found: 156.0832.

3.16. 3-Hydroxyphenylethylamine hydrobromide (15)

A mixture of 3-methoxyphenylethyl amine (**10**) (1.2 g, 7.94 mmol) and freshly distilled 48% HBr (6 ml) was heated in an oil bath at 135–140 °C under nitrogen for 45 min. The acid was evaporated under vacuum to afford **15** as a white solid (1.61 g, 92%) and was used for the preparation of **16** without further purification. ^{1}H NMR (D_2O/DCl/DSS) δ: 3.01 (t, 2H, $J=7.3$ Hz, benzylic H); 3.33 (t, $J=7.3$ Hz, 2H, CH_2N); 6.89 (s, 1H, H-2); 6.90 (d, 1H, $J=7.7$ Hz, H-4); 6.95 (d, 1H, $J=7.7$ Hz, H-6); 7.36 (t, 1H, $J=7.7$ Hz, H-5) ppm. ^{13}C NMR (D_2O/DCl/external TMS) δ: 35.2 (benzylic

carbon); 43.0 (CH_2N); 116.8 (C-4); 118.3 (C-2); 123.5 (C-6); 133.0 (C-5); 141.1 (C-1); 158.4 (C-3) ppm.

3.17. N-(Trifluoroacetyl)-3-hydroxyphenylethylamine (16)

Trifluoroacetylation of **15** using the procedure described earlier gave **16** in 64% yield, m.p. 53–54 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.84 (t, 2H, J = 6.9 Hz, benzylic H); 3.62 (q, 2H, J = 6.5 Hz, CH_2N); 6.29 (broad s, 1H, NH); 6.68 (s, 1H, H-2); 6.73–6.77 (m, 2H, H-4 and H-6); 7.21 (t, 1H, J = 7.8 Hz, H-5) ppm. ^{19}F NMR ($CDCl_3$) δ: −76.42 (s, CF_3) ppm. HRMS calcd for $C_{10}H_{10}NO_2F_3$: 233.0664. Found: 233.0671.

3.18. Iodination of the hydroxyphenylethylamine 16

A solution of iodine (1.31 g, 5.16 mmol) in CH_2Cl_2 (100 ml) was added dropwise to a solution of the hydroxyphenylethylamine **16** (1.20 g, 5.15 mmol) and thallium (I) acetate [23] (1.54 g, 5.85 mmol) in dichloromethane (15 ml) and the reaction mixture was stirred at room temperature for 3 h. The precipitated thallium (I) iodide was removed by filtration and the filtrate was washed with 0.1 M $Na_2S_2O_3$ solution (2×50 ml), water (2×50 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil which was chromatographed on silica gel (diethyl ether–benzene, 1:9) to give *N*-(trifluoroacetyl)-3-hydroxy-4-iodophenylethylamine (**17a**) (0.70 g, 38%; m.p. 79–80 °C), *N*-(trifluoroacetyl)-3-hydroxy-2-iodophenylethylamine (**17b**) (0.33 g, 18%; m.p. 86–87 °C) and *N*-(trifluoroacetyl)-2,4-diiodo-3-hydroxyphenylethylamine (**17c**) (0.55 g, 22%; m.p. 118–119 °C).

17a: ^{1}H NMR ($CDCl_3$/TMS) δ: 2.82 (t, 2H, J = 6.9 Hz, benzylic H); 3.60 (q, 2H, J = 6.6 Hz, CH_2N); 5.55 (s, 1H, OH); 6.43 (broad s, 1H, NH); 6.52 (dd, 1H, J = 7.9 and 1.6 Hz, H-6); 6.83 (d, 1H, J = 1.6 Hz, H-2); 7.60 (d, 1H, J = 7.9 Hz, H-5) ppm. HRMS calcd for $C_{10}H_9NO_2F_3I$: 358.9630. Found: 358.9631.

17b: ^{1}H NMR ($CDCl_3$/TMS) δ: 3.06 (t, 2H, J = 6.8 Hz, benzylic H); 3.63 (q, 2H, J = 6.6 Hz, CH_2N); 5.70 (s, 1H, OH); 6.48 (broad s, 1H, NH); 6.76 (d, 1H, J = 7.6 Hz, H-4); 6.90 (d, 1H, J = 7.6 Hz, H-6); 7.18 (t, 1H, J = 7.6 Hz, H-5) ppm. HRMS calcd for $C_{10}H_9NO_2F_3I$: 358.9630. Found: 358.9636.

17c: ^{1}H NMR ($CDCl_3$/TMS) δ: 3.04 (t, 2H, J = 7.2 Hz, benzylic H); 3.60 (q, 2H, J = 6.7 Hz, CH_2N); 5.94 (s, 1H, OH); 6.53 (d, 1H, J = 7.6 Hz, H-6); 6.63 (broad s, 1H, NH); 7.61 (d, 1H, J = 7.6 Hz, H-5) ppm. HRMS calcd for $C_{10}H_8NO_2F_3I_2$: 484.8597. Found: 484.8606.

3.19. Acetylation of the hydroxy derivatives 17a–c

Using the procedure described for the preparation of **12**, the hydroxy derivatives **17a–c** were acetylated.

18a: Yield 83%, m.p. 70–71 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.36 (s, 3H, CH_3CO); 2.85 (t, 2H, J = 7.2 Hz, benzylic H); 3.57 (q, 2H, J = 6.7 Hz, CH_2N); 6.80–6.90 (m, 2H, NH and H-6); 6.94 (s, 1H, H-2); 7.75 (d, 1H, J = 8.2 Hz, H-5) ppm. HRMS calcd for $C_{12}H_{11}NO_3F_3I$: 400.9736. Found: 400.9740. Anal. Calcd for $C_{12}H_{11}NO_3F_3I$; C, 35.93; H, 2.76; N, 3.49. Found: C, 35.74; H, 2.71; N, 3.31%.

18b: Yield: 80%, m.p. 105–106 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.38 (s, 3H, CH_3CO); 3.11 (t, 2H, J = 6.7 Hz, benzylic H); 3.63 (q, 2H, J = 6.5 Hz, CH_2N); 6.41 (broad s, 1H, NH); 6.99 (d, 1H, J = 7.7 Hz, H-4); 7.07 (d, 1H, J = 7.7 Hz, H-6); 7.32 (t, 1H, J = 7.7 Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 21.30 (CH_3); 39.63 (benzylic carbon); 39.72 (CH_2N); 97.39 (C-2); 115.74 (q, $^1J_{C,F}$ = 288.0 Hz, CF_3); 121.62 (C-4); 127.45 (C-6); 129.41 (C-5); 142.75 (C-1); 151.82 (C-3); 157.34 (q, $^2J_{C,F}$ = 37.0 Hz, $COCF_3$); 168.73 ($OCOCH_3$) ppm. Anal. Calcd for $C_{12}H_{11}NO_3F_3I$: C, 35.93; H, 2.76; N, 3.49. Found: C, 35.75; H, 2.71; N, 3.33%.

18c: Yield 86%, m.p. 153–154 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.42 (s, 3H, CH_3CO); 3.08 (t, 2H, J = 6.8 Hz, benzylic H); 3.60 (q, 2H, J = 6.5 Hz, CH_2N); 6.52 (broad s, 1H, NH); 6.80 (d, 1H, J = 8.4 Hz, H-6); 7.74 (d, 1H, J = 8.4 Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 21.46 (CH_3); 39.47 (benzylic carbon); 39.63 (CH_2N), 88.50 (C-4); 97.62 (C-2); 115.71 (q, $^1J_{C,F}$ = 288.0 Hz, CF_3); 128.70 (C-6); 139.15 (C-5); 143.27 (C-1); 152.08 (C-3); 157.41 (q, $^2J_{C,F}$ = 37.0 Hz, $COCF_3$); 167.45 ($OCOCH_3$) ppm. Anal. Calcd for $C_{12}H_{10}NO_3F_3I_2$: C, 27.35; H, 1.91; N, 2.66; I, 48.16. Found: C, 27.04; H, 1.73; N, 2.47; I, 48.29%.

3.20. N-(Trifluoroacetyl)-3-acetoxy-4-(trimethylstannyl)-phenylethylamine (19)

The stannyl derivative **19** was prepared in 62% yield as a white solid using the procedure described for the preparation of **6**; m.p. 91–92 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 0.30 [s, 9H, Sn satellites $^2J_{Sn,H}$ = 55.0 Hz, Sn $(CH_3)_3$]; 2.29 (s, 3H, CH_3CO); 2.88 (t, 2H, J = 6.7 Hz, benzylic H); 3.62 (q, 2H, J = 6.4 Hz, CH_2N); 6.40 (broad s, 1H, NH); 6.94 (s, 1H, Sn side bands $^4J_{Sn,H}$ = 13.4 Hz, H-2); 7.05 (d, 1H, J = 7.3 Hz, H-6); 7.43 (d, 1H, J = 7.3 Hz, Sn side bands $^3J_{Sn,H}$ = 44.0 Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: −9.20[Sn $(CH_3)_3$]; 21.21 (CH_3 of acetyl group); 34.64 (benzylic carbon); 40.88 (CH_2N); 115.79 (q, $^1J_{C,F}$ = 287.0 Hz, CF_3); 121.72 (s, Sn satellites, $^3J_{Sn,C}$ = 23.8 Hz, C-2); 126.21 (s, Sn satellites, $^2J_{Sn,C}$ = 41.8 Hz, C-5); 132.20 (C-1); 137.12 (s, Sn satellites, $^3J_{Sn,C}$ = 21.2 Hz, C-6); 139.75 (C-4); 156.22 (C-3); 157.26 (q, $^2J_{C,F}$ = 38.0 Hz, $COCF_3$); 169.62 ($OCOCH_3$) ppm. ^{119}Sn NMR ($CDCl_3$) δ: −28.25 ppm. Anal. Calcd for $C_{15}H_{20}NO_3F_3Sn$: C, 41.13; H, 4.60; N, 3.20. Found: C, 40.86; H, 4.50; N, 3.17%.

3.21. Fluorination of the arylstannyl derivative 19

Fluorination of **19** with F_2, OF_2 and CH_3COOF was carried out as described above to give *N*-(trifluoroacetyl)-3-acetoxy-4-fluorophenylethylamine in 41, 10 and 18% yields, respectively, m.p. 79–80 °C. ^{1}H NMR ($CDCl_3$/TMS) δ: 2.34 (s, 3H, CH_3CO); 2.87 (t, 2H, J = 6.8 Hz, benzylic H); 3.59 (q,

2H, J=6.6 Hz, CH_2N); 6.39 (broad s, 1H, NH); 6.96 (d, 1H, J=6.5 Hz, H-2); 7.00–7.06 (m, 1H, H-6); 7.13 (t, 1H, $^3J_{F,H}$=9.4 Hz, H-5) ppm. ^{13}C NMR ($CDCl_3$/TMS) δ: 20.36 (CH_3); 34.20 (benzylic carbon); 40.92 (CH_2N); 115.75 (q, $^1J_{C,F}$=288.0 Hz, CF_3); 117.08 (d, $^2J_{C,F}$=18.7 Hz, C-5); 123.99 (C-2); 127.20 (d, $^3J_{C,F}$=6.8 Hz, C-6); 134.20 (C-1); 138.26 (d, $^2J_{C,F}$=12.9 Hz, C-3); 153.10 (d, $J_{C,F}$=249.0 Hz, C-4); 157.29 (q, $^2J_{C,F}$=37.0 Hz, $COCF_3$); 168.35 ($OCOCH_3$) ppm. ^{19}F NMR ($CDCl_3$) δ: −76.4 (s, CF_3); −131.1 (s, fluorine at C-4) ppm. Anal. Calcd for $C_{12}H_{11}NO_3F_4$: C, 49.16; H, 3.78; N, 4.78; F, 25.92. Found: C, 48.66; H, 3.75; N, 4.75; F, 25.53%.

3.22. 4-Fluoro-3-hydroxyphenylethylamine hydrochloride (20)

Acid hydrolysis of the above protected derivative as described for **14** yielded the title product **20** as a pale yellow solid in 93% yield, m.p. 160–162 °C (d). ^{1}H NMR (D_2O/DSS) δ: 2.95 (t, 2H, J=7.2 Hz, benzylic H); 3.26 (t, 2H, J=7.2 Hz, CH_2N); 6.85 (m, 1H, H-6); 6.97 (dd, 1H, $^4J_{H}$=8.4 Hz and J=2.2 Hz, H-2); 7.16 (dd, 1H, $^3J_{F,H}$=11.2 Hz, J=8.4 Hz, H-5) ppm. ^{13}C NMR (D_2O/external TMS) δ: 34.6 (benzylic carbon); 43.0 (CH_2N); 118.9 (d, $^2J_{C,F}$=18.4 Hz, C-5); 120.6 (d, $^3J_{C,F}$=13.5 Hz, C-2); 123.6 (d, $^3J_{C,F}$=5.9 Hz, C-6); 135.8 (C-1); 145.9 (C-3); 153.2 (d, $^1J_{C,F}$=239.0 Hz, C-4) ppm. ^{19}F NMR (D_2O) δ: −137.4 (s) ppm. DCI HRMS calcd for $C_8H_{11}NOF$ (M^++H) (free base): 156.0825. Found: 156.0830.

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