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Radioiodinated Phenoxyacetic Acid Derivatives as Potential Brain Imaging Agents. I. Efficient Synthesis *via* Trimethylsilyl Intermediates

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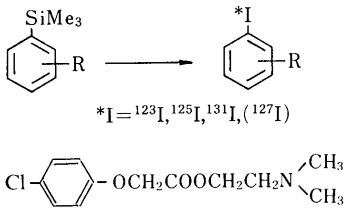
The usefulness of radioiodination *via* demetallation of aryltrimethylsilanes was demonstrated. The radioiodination reaction was found to be very rapid and the regiospecific incorporation of radioiodine could be carried out with high radiochemical yields and high radiospecific activity. ^{125}I-Labeled dimethylaminoethyl iodophenoxyacetate derivatives (5a—e), dimethylaminoethyl iodophenoxyacetamide derivatives (7a—c), iodophenoxyethyl ethylenediamine derivatives (9, 14) and an iodophenoxyethylpiperazine derivative (18) were efficiently synthesized from the corresponding aryltrimethylsilyl intermediates (4a—e, 6a—c, 8, 13, 17) by this method.

Keywords radioiodination; ^{125}I; ^{123}I; radioiodinated phenoxyacetic acid derivative; trimethylsilylphenoxyacetic acid derivative; brain imaging agent

The development of non-invasive brain diagnosis with single photon emission computed tomography (SPECT) with high sensitivity and good resolution has generated a need for new types of radiopharmaceuticals to measure brain functions, such as regional perfusion, metabolism and receptor function.[1] Because ^{123}I has superior physical properties, a short half-life ($T_{1/2}$ = 13.2 h) and a suitable gamma energy (159 keV) for imaging with SPECT devices, a number of radiopharmaceuticals labeled with ^{123}I have been synthesized and evaluated. Among these agents, ^{123}I-labeled *N*-isopropyl-*p*-iodoamphetamine (IMP),[2] *N*-(2-hydroxy-5-iodo-3-methylbenzyl)-*N*,*N*′,*N*′-trimethyl-1,3-propanediamine (HIPDM),[3] (*R*)-3-quinuclidinyl 4-iodobenzilate (QNB),[4] (*R*)-(+)-2,3,4,5-tetrahydro-8-iodo-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol (IBZP)[5] and (*S*)-(−)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-3-iodo-6-methoxybenzamide (IBZM)[6] are especially promising as brain functional imaging agents.

The most general synthetic methods of ^{123}I-labeled compounds have been halogen exchange reaction of aryl iodides with radioiodine and electrophilic radioiodination of aromatic compounds activated by electron-donating groups (such as phenols and anilines) in the presence of radioiodine and oxidizing agents. Recently, new approaches to the synthesis of radiohalogenated compounds *via* cleavage of the carbon–metal bond in organometallics, especially organosilicon and organotin compounds, have been reported.[7] The halodemetallation reaction is based on *ipso* electrophilic substitution in organometallics[8] and the rate is so rapid that it is promising as a general method for the fast, regiospecific incorporation of radiohalogens into a variety of aromatic compounds including non-activated aromatic systems.[9] It is also desirable to be able to introduce the radiolabel into compounds in the final step of the synthetic sequence with a good radiochemical yield and a high specific activity. Of the possible halodemetallation reactions for radiopharmaceutical synthesis, we selected radioiodination *via* demetallation of aryltrimethylsilanes for our purposes (Chart 1). Another notable advantage that silicon has over tin is that the silicon precursors are much more stable than their tin counterparts. So, it is possible to perform synthetic conversions of the molecule after the silicon group has been attached.

Thus, focussing on the chemical structure of meclofenoxate, *N*,*N*-dimethylaminoethyl *p*-chlorophenoxyacetate (Chart 1), used clinically as a brain metabolism stimulant,[10] we attempted to synthesize ^{123}I-labeled phenoxyacetic acid derivatives expected to be useful as potential brain imaging agents through trimethylsilyl precursors. We report here the synthesis of ^{125}I-labeled phenoxyacetic acid derivatives and related compounds. ^{125}I was used because it is a more convenient and suitable radionuclide than ^{123}I for basic research, and identical procedures are applicable for ^{123}I labeling.

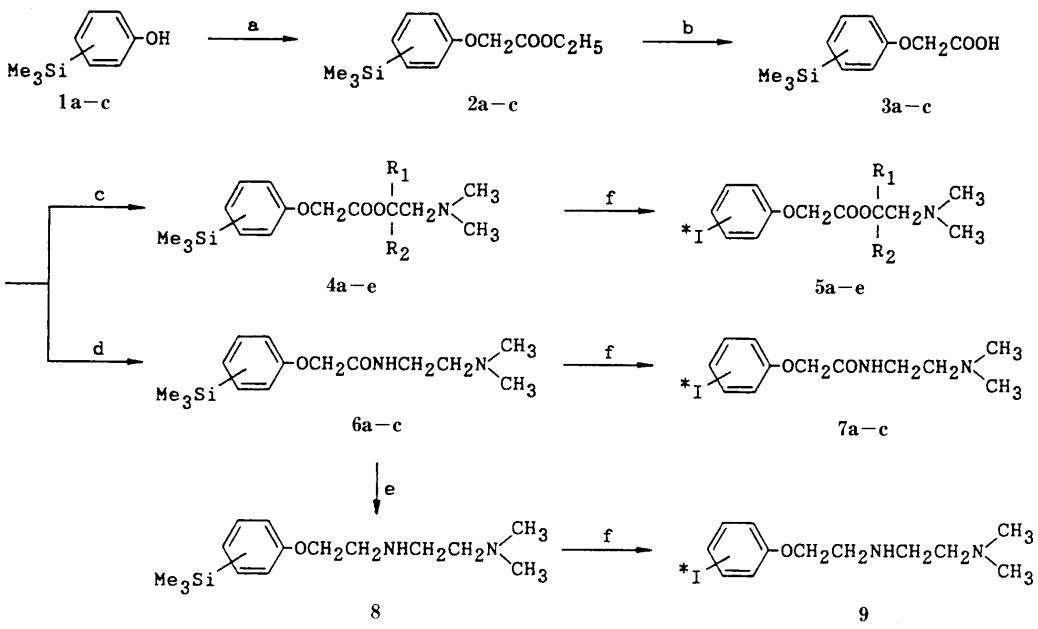


meclofenoxate

Chart 1

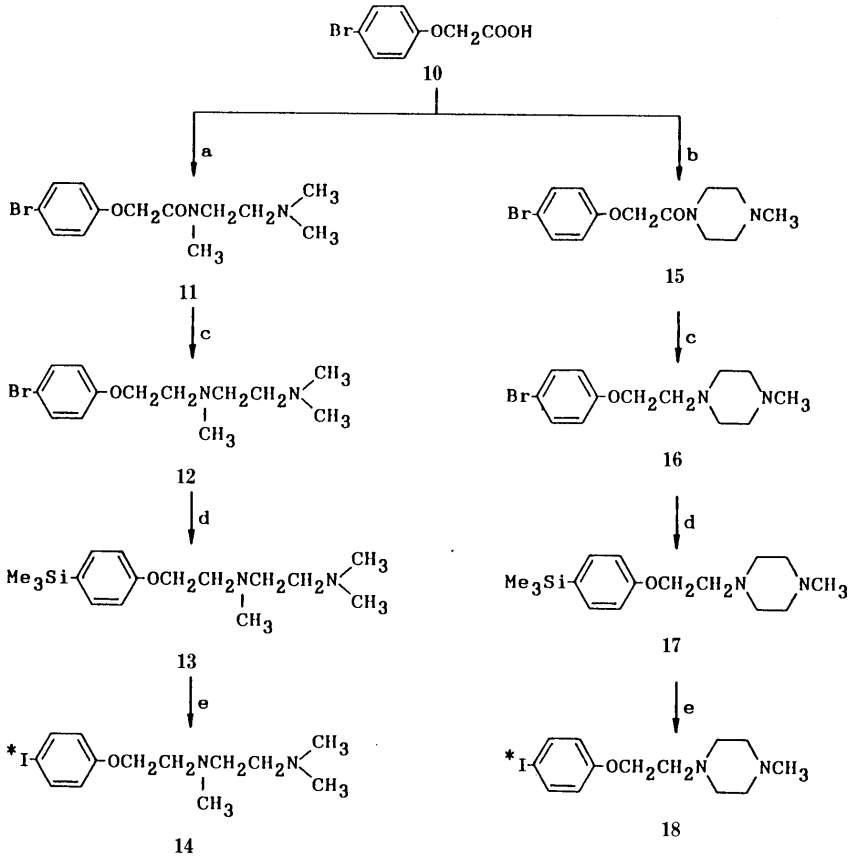
Refluxing of trimethylsilylphenols (**1a—c**)[11] with ethyl bromoacetate in ethanol in the presence of sodium ethylate gave ethyl trimethylsilylphenoxyacetates (**2a—c**). Hydrolysis of **2a—c** with 2N NaOH afforded trimethylsilylphenoxyacetic acids (**3a—c**). Among **3**, the *para* and *ortho* isomers (**3a**, **c**) underwent cleavage of the trimethylsilyl group in the reaction with thionyl chloride. So, *N*,*N*-dimethylaminoethyl trimethylsilylphenoxyacetates (**4a—e**) were obtained from **3a—c** and dimethylamino alcohols using phenyl dichlorophosphate–*N*,*N*-dimethyl formamide (DMF) complex[12] under virtually neutral conditions in good yields. *N*-(*N*,*N*-Dimethylaminoethyl)trimethylsilylphenoxyacetamides (**6a—c**) were also obtained from **3a—c** and *N*,*N*-dimethylethylenediamine using phenyl *N*-phenylphosphoramidochloridate[13] (Chart 2).

N,*N*-Dimethyl-*N*′-(4-trimethylsilylphenoxyethyl)ethylenediamine (**8**) was obtained by the reduction of **6a** with $LiAlH_4$ (Chart 2). Treatment of 4-bromophenoxyacetic acid (**10**) with thionyl chloride gave the acid chloride, which was reacted with either *N*,*N*,*N*′-trimethylethylenediamine or *N*-methylpiperazine to give the corresponding amides (**11**, **15**). The reduction of **11** or **15** with BH_3–tetrahydrofuran (THF) complex afforded diamines (**12**,



reagents: a=NaOEt, $BrCH_2COOEt$; b=NaOH; c=$HOC(R_1)(R_2)CH_2NMe_2$, $C_6H_5OPOCl_2$; d=$H_2NCH_2CH_2NMe_2$, $C_6H_5NHP(O)(Cl)OC_6H_5$; e=$LiAlH_4$; f=Na^*I($^*I$=^{127}I, ^{125}I), NCS

Chart 2



reagents: a=$SOCl_2$, $HN(Me)CH_2CH_2NMe_2$; b=$SOCl_2$, HN⟨⟩NCH_3; c=BH_3-THF; d=*n*-BuLi, Me_3SiCl; e=Na^*I($^*I$=^{127}I, ^{125}I), NCS

Chart 3

16). Then, the treatment of **12** or **16** with *n*-BuLi and trimethylsilyl chloride afforded *N,N,N′*-trimethyl-*N′*-[2-(4-trimethylsilylphenoxy)ethyl]ethylenediamine (**13**) and *N*-methyl-*N′*-[2-(4-trimethylsilylphenoxy)ethyl]piperazine (**17**), respectively (Chart 3).

Iodination of the aryltrimethylsilyl intermediates was

carried out using sodium iodide and *N*-chlorosuccinimide (NCS) as an oxidant in acetic acid at 65 °C[14] (Charts 2 and 3). The progress of the reaction was followed by high-performance liquid chromatography (HPLC) (Fig. 1). All reactions of the *para* and *ortho* aryltrimethylsilyl compounds (**4a**, **c**, **d**, **e**, **6a**, **c**, **8**, **13**, **17**) were completed within 5 min to give the corresponding iodinated compounds (**5a**, **c**, **d**, **e**, **7a**, **c**, **9**, **14**, **18**) in high yields (85—93%). In the reactions of the *meta* aryltrimethylsilyl compounds (**4b**, **6b**) 30 min was needed to obtain **5b** and **7b** in high yields (both 83%). These iodinated compounds were converted to the hydrochloride salts, which were purified by recrystallization. Physical and analytical data of the above-mentioned compounds are summarized in Tables I, II and III.

In a radiolabeling reaction with a short-life nuclide, it is especially desirable to achieve a high radiochemical yield within a short reaction time in a no-carrier-added reaction (a tracer-scale reaction). In such a reaction, the specific radioactivity can be expected to be over 100 Ci/mmol with ^{125}I and there ought to be no change in radiochemical purity. So, carrier-added and no-carrier-added radioiodinations with ^{125}I were carried out under the same reaction conditions as used for the iodination with the stable iodide. The progress of the reaction was followed by thin layer chromatography (TLC) and the radiochemical yield was calculated from the radioactivity of each fraction on a TLC chromatogram (Fig. 2). These results are summarized in Table IV. The carrier-added radioiodination was very efficient, as in the case of stable iodide. The no-carrier-added radioiodination resulted in lower radiochemical yields than the carrier-added reactions, especially in the case of *meta* aryltrimethylsilyl derivatives (**4b**, **6b**). However, the labeling efficiency of the *para* and *ortho* aryltrimethylsilyl intermediates seems to be sufficient to prepare ^{123}I-labeled radiopharmaceuticals, because the desired products could be easily purified by HPLC within a short time. Moreover, the halogen exchange reactions of the iodinated esters (**5a**—**c**) with $Na^{125}I$ in acetic acid at 125 °C

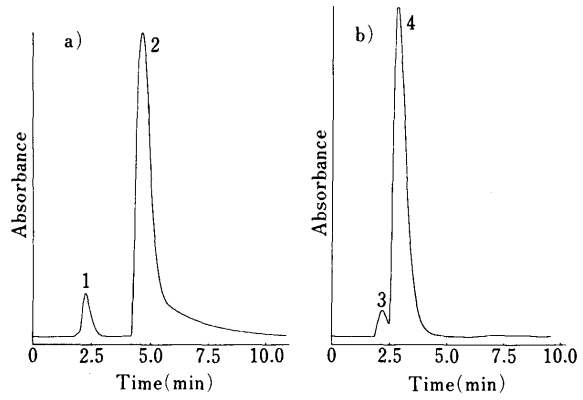


Fig. 1. HPLC Analysis of the Reaction Mixture of **4a** with NaI–NCS
a) $t=0$ min; b) $t=5$ min. 1, NCS; 2, **4a**; 3, succinimide; 4, **5a**.

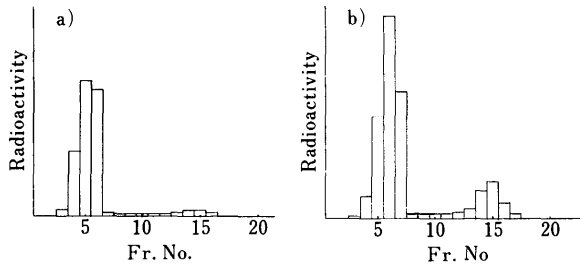
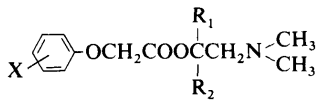


Fig. 2. TLC Analysis of the Reaction Mixture of **4a** with $Na^{125}I$–NCS
a) Carrier-added reaction, $t=5$ min. b) No-carrier-added reaction, $t=30$ min.

TABLE I. Physical and Analytical Data for Dimethylaminoethyl Phenoxyacetate Derivatives



Compd. No.	R_1	R_2	X	mp or bp/mmHg (°C)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N
4a	H	H	4-$SiMe_3$	134—136/1	80	$C_{15}H_{25}NO_3Si$	60.98 (60.64)	8.53 8.70	4.74 4.68)
4b	H	H	3-$SiMe_3$	148—150/2	74	$C_{15}H_{25}NO_3Si$	60.98 (60.91)	8.53 8.56	4.74 4.59)
4c	H	H	2-$SiMe_3$	154—156/3	72	$C_{15}H_{25}NO_3Si$	60.98 (60.73)	8.53 8.59	4.74 4.81)
4d	H	CH_3	4-$SiMe_3$	143—145/3	51	$C_{16}H_{27}NO_3Si$	62.10 (62.05)	8.79 8.82	4.53 4.59)
4e	CH_3	CH_3	4-$SiMe_3$	145—147/2	58	$C_{17}H_{29}NO_3Si$	63.12 (63.16)	9.04 8.90	4.33 4.35)
5a·HCl	H	H	4-I	144—145	69 (95)	$C_{12}H_{16}INO_3 \cdot HCl$	37.38 (37.29)	4.44 4.46	3.63 3.60)
5b·HCl	H	H	3-I	145—146	61 (82)	$C_{12}H_{16}INO_3 \cdot HCl$	37.38 (37.58)	4.44 4.45	3.63 3.85)
5c·HCl	H	H	2-I	148—149	59 (88)	$C_{12}H_{16}INO_3 \cdot HCl$	37.38 (37.47)	4.44 4.37	3.63 3.57)
5d·HCl	H	CH_3	4-I	224—226	57 (93)	$C_{13}H_{18}INO_3 \cdot HCl$	39.07 (39.12)	4.79 4.77	3.50 3.49)
5e·HCl	CH_3	CH_3	4-I	165—167	71 (96)	$C_{14}H_{20}INO_3 \cdot HCl$	40.65 (40.60)	5.12 5.07	3.39 3.32)

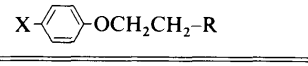
a) Yields reported are isolated yields. Yields in parentheses were obtained by HPLC analysis.

TABLE II. Physical and Analytical Data for Dimethylaminoethyl Phenoxyacetamide Derivatives

Compd. No.	X	mp or bp/mmHg (°C)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N
6a	4-$SiMe_3$	168—170/2	67	$C_{15}H_{26}N_2O_2Si$	61.18 (60.94)	8.90 8.76	9.51 9.38)
6b	3-$SiMe_3$	156—158/1	71	$C_{15}H_{26}N_2O_2Si$	61.18 (61.32)	8.90 8.99	9.51 9.37)
6c	2-$SiMe_3$	164—166/2	57	$C_{15}H_{26}N_2O_2Si$	61.18 (61.28)	8.90 8.68	9.51 9.32)
7a·HCl	4-I	193—194	73 (91)	$C_{12}H_{17}IN_2O_2 \cdot HCl$	37.47 (37.30)	4.72 4.73	7.28 7.19)
7b·HCl	3-I	156—157	64 (83)	$C_{12}H_{17}IN_2O_2 \cdot HCl$	37.47 (37.33)	4.72 4.71	7.28 7.27)
7c·HCl	2-I	155—156	60 (86)	$C_{12}H_{17}IN_2O_2 \cdot HCl$	37.47 (37.71)	4.72 4.61	7.28 7.06)

a) Yields reported are isolated yields. Yields in parentheses were obtained by HPLC analysis.

TABLE III. Physical and Analytical Data for Phenoxyethylethylenediamine Derivatives



Compd. No.	R	X	mp or bp/mmHg (°C)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N
8	$NHCH_2CH_2N(CH_3)_2$	$SiMe_3$	133—134/1	72	$C_{15}H_{28}N_2OSi$	64.23 (64.34)	10.06 10.06	9.99 9.77)
9·2HCl		I	218—220	75 (89)	$C_{12}H_{19}IN_2O \cdot 2HCl$	35.40 (35.45)	5.20 5.09	6.88 6.78)
12·2HCl		Br	240—241	84	$C_{13}H_{21}BrN_2O \cdot 2HCl$	41.73 (41.57)	6.20 6.08	7.49 7.37)
13	$NCH_2CH_2N(CH_3)_2$ with CH_3	$SiMe_3$	125—127/1	66	$C_{16}H_{30}N_2OSi$	65.25 (65.04)	10.27 10.24	9.51 9.46)
14·2HCl		I	243—245	80 (95)	$C_{13}H_{21}IN_2O \cdot 2HCl$	37.08 (37.02)	5.50 5.39	6.65 6.57)
16·2HCl		Br	219—220	77	$C_{13}H_{19}BrN_2O \cdot 2HCl$	41.96 (42.14)	5.69 5.61	7.53 7.57)
17		$SiMe_3$	129—131/1	74	$C_{16}H_{28}N_2OSi$	65.70 (65.83)	9.65 9.61	9.58 9.42)
18·2HCl		I	215—217	76 (90)	$C_{13}H_{19}IN_2O \cdot 2HCl$	37.25 (37.18)	5.05 5.11	6.68 6.58)

a) Yields reported are isolated yields. Yields in parentheses were obtained by HPLC analysis.

TABLE IV. ^{125}I-Radioiodination of Trimethylsilyl Intermediates[a]

Reaction	Carrier-added reaction (min) 5	10	30	60	No-carrier-added reaction (min) 5	10	30	60
4a→5a	93	94	94	—[b]	80	81	82	84
4b→5b	43	54	78	82	38	38	39	39
4c→5c	87	87	88	—	58	61	66	66
6a→7a	90	90	90	—	31	40	50	52
6b→7b	70	72	83	83	18	19	20	22
6c→7c	85	86	86	—	32	41	54	56
8→ 9	88	89	89	—	50	50	51	51
13→14	93	95	95	—	60	61	65	68
17→18	89	89	90	—	33	40	60	66

a) The values are radiochemical yields (%) obtained by TLC analysis. *b*) Not determined.

failed to cause cleavage of the trimethylsilyl moiety.

In conclusion, the usefulness of radioiodination *via* demetallation of aryltrimethylsilanes was demonstrated. The *ipso* electrophilic substitution reactions were found to be rapid and regiospecific, so that radioiodination could be carried out with high radiochemical yields. ^{125}I-Labeled phenoxyacetic acid esters, amides and related ethylenediamines were efficiently synthesized by this method and the identical procedure is applicable for the labeling reaction with ^{123}I. The results of preliminary *in vivo* studies of the obtained radioiodinated compounds will be reported in the succeeding paper.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear

magnetic resonance (^{1}H-NMR) spectra were measured with a Varian Gemini-200 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard.

General Procedure for Preparation of Trimethylsilylphenoxyacetic Acids (3a—c) A solution of a trimethylsilylphenol (**1a—c**)[11] (16.6 g, 100 mmol) in anhydrous EtOH (50 ml) was added to a stirred 1 M solution of $NaOC_2H_5$ in anhydrous EtOH (100 ml), followed by the slow addition of ethyl bromoacetate (16.7 g, 100 mmol). The reaction mixture was refluxed for 3 h. The resulting mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was refluxed with 2 N NaOH (100 ml) for 30 min, and then acidified with concentrated HCl. The resulting precipitate was collected by suction, washed with H_2O, and recrystallized from *n*-hexane to give the corresponding acid (**3a—c**).

Compound **3a**: Yield 78%, mp 87—88 °C. *Anal.* Calcd for $C_{11}H_{16}O_3Si$: C, 58.89; H, 7.19. Found: C, 58.59; H, 7.11. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.24 (9H, s), 4.69 (2H, s), 6.92 (2H, d, J=8.8 Hz), 7.46 (2H, d, J=8.8 Hz), 9.74 (1H, br).

Compound **3b**: Yield 87%, mp 128—129 °C. *Anal.* Calcd for $C_{11}H_{16}O_3Si$: C, 58.89; H, 7.19. Found: C, 58.77; H, 7.18. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1570. ^{1}H-NMR ($CDCl_3$) δ: 0.26 (9H, s), 4.70 (2H, s), 6.88—7.31 (4H, m), 8.80 (1H, br).

Compound **3c**: Yield 61%, mp 111—112 °C. *Anal.* Calcd for $C_{11}H_{16}O_3Si$: C, 58.89; H, 7.19. Found: C, 58.93; H, 7.22. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.30 (9H, s), 4.68 (2H, s), 6.71—7.44 (4H, m), 9.06 (1H, br).

General Procedure for Preparation of *N,N*-Dimethylaminoethyl Trimethylsilylphenoxyacetate Derivatives (4a—e) Phenyl dichlorophosphate (1.88 ml, 12.5 mmol) was added to DMF (1.5 ml) at 0—5 °C with stirring and the mixture was allowed to stand for 5 min at the same temperature. To this stirred mixture was added sequentially at about 10 min intervals a solution of an acid (**3a—c**) (10 mmol) in CH_2Cl_2 (50 ml), a dimethylamino alcohol (20 mmol), and pyridine (3.0 ml). The mixture was allowed to stand for 3 h at room temperature. The solution was washed with 10% $NaHCO_3$ (3 × 30 ml) and H_2O (2 × 30 ml), then dried (Na_2SO_4) and evaporated. The resulting oil was distilled under reduced pressure to give the corresponding ester (**4a—e**). Yield, boiling point and elemental analysis data are summarized in Table I.

Compound **4a**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 1760, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.24 (9H, s), 2.29 (6H, s), 2.61 (2H, t, J=5.7 Hz), 4.32 (2H, t, J=5.7 Hz), 4.66 (2H, s), 6.90 (2H, d, J=8.5 Hz), 7.44 (2H, d, J=8.5 Hz).

Compound **4b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2960, 1760, 1570. ^{1}H-NMR ($CDCl_3$) δ: 0.25 (9H, s), 2.28 (6H, s), 2.60 (2H, t, J=5.7 Hz), 4.32 (2H, t, J=5.7 Hz), 4.67 (2H, s), 6.87—7.29 (4H, m).

Compound **4c**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 1760, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.31 (9H, s), 2.27 (6H, s), 2.59 (2H, t, J=5.8 Hz), 4.30 (2H, t, J=5.8 Hz), 4.65 (2H, s), 6.68—7.42 (4H, m).

Compound **4d**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 1750, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.24 (9H, s), 1.26 (3H, d, J=6.2 Hz), 2.24 (6H, s), 2.23—2.29 (1H, m), 2.49—2.56 (1H, m), 4.62 (2H, s), 5.14—5.23 (1H, m), 6.91 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz).

Compound **4e**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 1750, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.23 (9H, s), 1.51 (6H, s), 2.31 (6H, s), 2.55 (2H, s), 4.53 (2H, s), 6.89 (2H, d, J=8.7 Hz), 7.44 (2H, d, J=8.7 Hz).

General Procedure for Preparation of *N*-(*N,N*-Dimethylaminoethyl)-trimethylsilylphenoxyacetamide Derivatives (6a—c) Phenyl *N*-phenylphosphoramidochloridate (1.34 g, 5 mmol) was added with stirring to a solution of an acid (**3a—c**) (5 mmol), triethylamine (1.01 g, 10 mmol) and *N,N*-dimethylethylenediamine (0.44 g, 5 mmol) in CH_2Cl_2 (15 ml), and the mixture was allowed to stand overnight at room temperature. The solution was washed with H_2O (3 × 10 ml), dried (Na_2SO_4) and evaporated. The resulting oil was distilled under reduced pressure to give the corresponding amide (**6a—c**). Yield, boiling point and elemental analysis data are summarized in Table II.

Compound **6a**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2970, 1670, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.25 (9H, s), 2.21 (6H, s), 2.43 (2H, t, J=5.9 Hz), 3.41 (2H, q, J=5.9 Hz), 4.51 (2H, s), 6.93 (2H, d, J=8.5 Hz), 7.05 (1H, br), 7.46 (2H, d, J=8.5 Hz).

Compound **6b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2970, 1670, 1570. ^{1}H-NMR ($CDCl_3$) δ: 0.27 (9H, s), 2.22 (6H, s), 2.43 (2H, t, J=5. 9 Hz), 3.42 (2H, q, J=5.9 Hz), 4.52 (2H, s), 6.88—7.34 (5H, m).

Compound **6c**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2970, 1670, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.32 (9H, s), 2.20 (6H, s), 2.45 (2H, t, J=5.8 Hz), 3.43 (2H, q, J=5.8 Hz), 4.52 (2H, s), 6.78—7.43 (5H, m).

***N,N*-Dimethyl-*N'*-(4-trimethylsilylphenoxyethyl)ethylenediamine (8)** A solution of **6a** (2.94 g, 10 mmol) in dry THF (5 ml) was added dropwise to a stirred mixture of $LiAlH_4$ (0.76 g, 20 mmol) in dry THF (25 ml). The mixture was refluxed for 3 h. Then H_2O (5 ml) was added dropwise with vigorous stirring and cooling. The mixture was filtered, and the filtrate was evaporated. The residue was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated. The resulting oil was distilled under reduced pressure to give **8** (2.02 g, 72%). Boiling point and elemental analysis data are summarized in Table III. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 1590, 1500. ^{1}H-NMR ($CDCl_3$) δ: 0.24 (9H, s), 1.81 (1H, br), 2.23 (6H, s), 2.43 (2H, t, J=6.1 Hz), 2.77 (2H, t, J=6.1 Hz), 3.03 (2H, t, J=5.4 Hz), 4.09 (2H, t, J=5.4 Hz), 6.91 (2H, d, J=8.4 Hz), 7.43 (2H, d, J=8.4 Hz).

***N*-[2-(4-Bromophenoxy)ethyl]-*N,N',N'*-trimethylethylenediamine (12)** A mixture of 4-bromophenoxyacetic acid (**10**) (11.6 g, 50 mmol) and $SOCl_2$ (50 ml) was refluxed for 3 h. The excess $SOCl_2$ was removed *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (10 ml) and the solution was added dropwise with stirring and cooling to a solution of *N,N,N'*-trimethylethylenediamine (10.2 g, 100 mmol) in dry CH_2Cl_2 (50 ml). The mixture was allowed to stand for 1 h at 0—5 °C, then overnight at room temperature. The solution was washed with 10% $NaHCO_3$ (3 × 50 ml) and H_2O (2 × 50 ml), and dried (Na_2SO_4). Evaporation of the solvent gave the crude amide (**11**).

The crude **11** dissolved in anhydrous THF (10 ml) was added slowly to a 1 M solution of BH_3–THF complex in anhydrous THF (75 ml) and the mixture was refluxed for 5 h. After cooling, the reaction was quenched by the careful addition of H_2O (100 ml). The mixture was acidified with 10% HCl (100 ml), then heated at 80—90 °C for 2 h. The solution was washed with ether (2 × 50 ml), basified with 40% NaOH and extracted with ether (3 × 100 ml). The ethereal extract was dried (Na_2SO_4), and bubbled through with dry HCl gas. The resulting precipitate was recrystallized from EtOH–ether to give **12**·2HCl (15.7 g, 84%). Melting point and elemental analysis data are summarized in Table III. IR ν_{max}^{KBr} cm^{-1}: 2920, 1590, 1470. ^{1}H-NMR (free amine, $CDCl_3$) δ: 2.24 (6H, s), 2.36 (3H, s), 2.42 (2H, t, J=7.4 Hz), 2.60 (2H, t, J=7.4 Hz), 2.82 (2H, t, J=5.9 Hz), 4.04 (2H, t, J=5.9 Hz), 6.79 (2H, d, J=9.2 Hz), 7.36 (2H, d, J=9.2 Hz).

***N,N,N'*-Trimethyl-*N'*-[2-(4-trimethylsilylphenoxy)ethyl]ethylenediamine (13)** A 1.6 M solution of *n*-BuLi in hexane (4 ml, 6.4 mmol) and then trimethylsilyl chloride (1.5 ml, 12 mmol) were added sequentially dropwise to a stirred solution of **12** (1.81 g, 6 mmol) in anhydrous THF (20 ml) at −78 °C under an argon atmosphere. The mixture was allowed to stand and −78 °C under an argon atmosphere. The mixture was allowed to stand at −78 °C for 30 min, then overnight at room temperature. The solvent was evaporated *in vacuo*, and the residue was dissolved in ether (30 ml). The ethereal solution was washed with H_2O (3 × 15 ml), dried (Na_2SO_4) and evaporated. The resulting oil was distilled under reduced pressure to give **13** (1.16 g, 66%). Boiling point and elemental analysis data are summarized in Table III. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 1590, 1500. ^{1}H-NMR ($CDCl_3$) δ: 0.24 (9H, s), 2.25 (6H, s), 2.37 (3H, s), 2.42 (2H, t, J=7.3 Hz), 2.61 (2H, t, J=7.3 Hz), 2.84 (2H, t, J=6.0 Hz), 4.09 (2H, t, J=6.0 Hz), 6.91 (2H, d, J=8.6 Hz), 7.43 (2H, d, J=8.6 Hz).

***N*-[2-(4-Bromophenoxy)ethyl]-*N'*-methylpiperazine (16)** **10** (11.6 g, 50 mmol) and *N*-methylpiperazine (10.5 g, 100 mmol) were treated as described for the preparation of **12** to give **16**·2HCl. Yield, melting point and elemental analysis data are summarized in Table III. IR ν_{max}^{KBr} cm^{-1}: 2910, 1590, 1490. ^{1}H-NMR (free amine, $CDCl_3$) δ: 2.29 (3H, s), 2.49 (4H, br), 2.62 (4H, br), 2.80 (2H, t, J=5.8 Hz), 4.07 (2H, t, J=5.8 Hz), 6.79 (2H, d, J=8.8 Hz), 7.37 (2H, d, J=8.8 Hz).

***N*-Methyl-*N'*-[2-(4-trimethylsilylphenoxy)ethyl]piperazine (17)** **16** (1.8 g, 6 mmol) and timethylsilyl chloride (1.5 ml, 12 mmol) were treated as described for the preparation of **13** to give **17**. Yield, boiling point and elemental analysis data are summarized in Table III. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2940, 1590, 1500. ^{1}H-NMR ($CDCl_3$) δ: 0.24 (9H, s), 2.29 (3H, s), 2.48 (4H, br), 2.62 (4H, br), 2.82 (2H, t, J=5.8 Hz), 4.12 (2H, t, J=5.8 Hz), 6.91 (2H, d, J=8.6 Hz), 7.44 (2H, d, J=8.6 Hz).

General Procedure for Iodination A solution of NCS (134 mg, 1 mmol) in AcOH (1.5 ml) was added to a stirred mixture of a trimethylsilyl compound (1 mmol) and NaI (150 mg, 1 mmol) in AcOH (4.5 ml). The mixture was heated at 65 °C. Progress of the reaction was followed by HPLC (Waters HPLC system) using a C-18 reversed-phase column (4.6 × 150 mm: Nacalai Tesque) and a ultraviolet (UV) detector (model 490, Waters) set at 254 nm. The solvent system of MeOH–1% AcOH (55 : 45) and the flow rate of 1 ml/min were used. All of the reactions were completed within 60 min. After the reaction had ended, the solvent was evaporated off *in vacuo*. The residue was taken up in 0.1 N NaOH (10 ml) and extracted with ether (3 × 10 ml). The ethereal extract was washed with H_2O (2 × 10 ml), dried (Na_2SO_4), and bubbled through with dry HCl gas. The resulting precipitate was recrystallized from EtOH–ether to give the HCl salt of the corresponding iodinated compound. Yield, melting point

and elemental analysis data are summarized in Tables I, II and III.

Compound **5a**·HCl: HPLC t_R: 2.38 min. IR ν_{max}^{KBr} cm^{-1}: 1760, 1590. ^{1}H-NMR (DMSO-d_6) δ: 2.76 (6H, s), 3.38 (2H, t, J=5.1 Hz), 4.48 (2H, t, J=5.1 Hz), 4.90 (2H, s), 6.86 (2H, d, J=9.0 Hz), 7.60 (2H, d, J=9.0 Hz), 10.96 (1H, br).

Compound **5b**·HCl: HPLC t_R: 2.36 min. IR ν_{max}^{KBr} cm^{-1}: 1760, 1580. ^{1}H-NMR (DMSO-d_6) δ: 2.77 (6H, s), 3.39 (2H, t, J=5.0 Hz), 4.48 (2H, t, J=5.0 Hz), 4.92 (2H, s), 7.02—7.36 (4H, m), 10.78 (1H, br).

Compound **5c**·HCl: HPLC t_R: 2.35 min. IR ν_{max}^{KBr} cm^{-1}: 1760, 1580. ^{1}H-NMR (DMSO-d_6) δ: 2.77 (6H, s), 3.39 (2H, t, J=5.0 Hz), 4.49 (2H, t, J=5.0 Hz), 4.99 (2H, s), 6.78—7.79 (4H, m), 10.88 (1H, br).

Compound **5d**·HCl: HPLC t_R: 2.64 min. IR ν_{max}^{KBr} cm^{-1}: 1760, 1590. ^{1}H-NMR (free amine, $CDCl_3$) δ: 1.25 (3H, d, J=6.3 Hz), 2.24 (6H, s), 2.20—2.29 (1H, m), 2.46—2.57 (1H, m), 4.60 (2H, s), 5.17—5.24 (1H, m), 6.71 (2H, d, J=9.0 Hz), 7.56 (2H, d, J=9.0 Hz).

Compound **5e**·HCl: HPLC t_R: 2.77 min. IR ν_{max}^{KBr} cm^{-1}: 1760, 1580. ^{1}H-NMR (DMSO-d_6) δ: 1.60 (6H, s), 2.83 (6H, s), 3.45 (2H, s), 4.80 (2H, s), 6.83 (2H, d, J=9.0 Hz), 7.60 (2H, d, J=9.0 Hz,), 10.49 (1H, br).

Compound **7a**·HCl: HPLC t_R: 2.31 min. IR ν_{max}^{KBr} cm^{-1}: 1680, 1560. ^{1}H-NMR (DMSO-d_6) δ: 2.76 (6H, s), 3.16 (2H, t, J=6.0 Hz), 3.50 (2H, q, J=6.0 Hz), 4.53 (2H, s), 6.85 (2H, d, J=8.9 Hz), 7.62 (2H, d, J=8.9 Hz), 8.50 (1H, t, J=6.0 Hz), 10.50 (1H, br).

Compound **7b**·HCl: HPLC t_R: 2.30 min. IR ν_{max}^{KBr} cm^{-1}: 1670, 1580. ^{1}H-NMR (DMSO-d_6) δ: 2.77 (6H, s), 3.17 (2H, t, J=6.0 Hz), 3.52 (2H, q, J=6.0 Hz), 4.56 (2H, s), 7.01—7.39 (4H, m), 8.52 (1H, t, J=6.0 Hz), 10.50 (1H, br).

Compound **7c**·HCl: HPLC t_R: 2.29 min. IR ν_{max}^{KBr} cm^{-1}: 1660, 1580. ^{1}H-NMR (DMSO-d_6) δ: 2.78 (6H, s), 3.18 (2H, t, J=6.0 Hz), 3.53 (2H, q, J=6.0 Hz), 4.66 (2H, s), 6.76—7.82 (4H, m), 8.35 (1H, t, J=6.0 Hz), 10.63 (1H, br).

Compound **9**·2HCl: HPLC t_R: 1.87 min. IR ν_{max}^{KBr} cm^{-1}: 1590, 1480. ^{1}H-NMR (free amine, $CDCl_3$) δ: 1.88 (1H, br), 2.23 (6H, s), 2.43 (2H, t, J=6.2 Hz), 2.76 (2H, t, J=6.2 Hz), 3.01 (2H, t, J=5.4 Hz), 4.04 (2H, t, J=5.4 Hz), 6.69 (2H, d, J=9.0 Hz), 7.55 (2H, d, J=9.0 Hz).

Compound **14**·2HCl: HPLC t_R: 2.43 min. IR ν_{max}^{KBr} cm^{-1}: 1590, 1480. ^{1}H-NMR (free amine, $CDCl_3$) δ: 2.24 (6H, s), 2.36 (3H, s), 2.41 (2H, t, J=7.2 Hz), 2.59 (2H, t, J=7.2 Hz), 2.82 (2H, t, J=5.8 Hz), 4.04 (2H, t, J=5.8 Hz), 6.68 (2H, d, J=8.6 Hz), 7.54 (2H, d, J=8.6 Hz).

Compound **18**·2HCl: HPLC t_R: 2.70 min. IR ν_{max}^{KBr} cm^{-1}: 2900, 1580, 1470. ^{1}H-NMR (free amine, $CDCl_3$) δ: 2.29 (3H, s), 2.47 (4H, br), 2.61 (4H, br), 2.80 (2H, t, J=5.8 Hz), 4.07 (2H, t, J=5.8 Hz), 6.69 (2H, d, J=9.0 Hz), 7.55 (2H, d, J=9.0 Hz).

General Procedure for Radioiodination A) Carrier-Added Reaction: A solution Na^{125}I (Amersham, specific activity 13.2 mCi/μg, radiochemical purity 99.8%) in 0.1 N NaOH (10 μl, 10—100 μCi) was added to a stirred mixture of a trimethylsilyl compound (0.1 mmol) and NaI (15.0 mg, 0.1 mmol) in AcOH (0.5 ml), followed by the addition of NCS (13.4 mg, 0.1 mmol) in AcOH (0.15 ml). The mixture was heated at 65 °C. Progress of the reaction was followed by silica gel TLC (Merck, DC-Alufolien Kieselgel 60), MeOH–AcOH (95 : 5), Rf 0.2—0.4 for labeled compounds and 0.8 for free iodide. Radioactivity of each fraction on the TLC chromatogram was determined with an Aloka automatic gamma counter (model ARC-300). The results of the radioiodination are summarized in Table IV.

B) No-Carrier-Added Reaction: A solution of Na^{125}I in 0.1 N NaOH (10 μl, 10—100 μCi) was added to a stirred solution of a trimethylsilyl compound (50 μmol) in AcOH (100 μl), followed by the addition of NCS (6.7 mg, 50 μmol) in AcOH (100 μl). The procedure described for the carrier-added reaction was then followed. The results of the radioiodination are summarized in Table IV.

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