Efficient Procedure for the Reduction of α-Amino Acids to Enantiomerically Pure α-Methylamines

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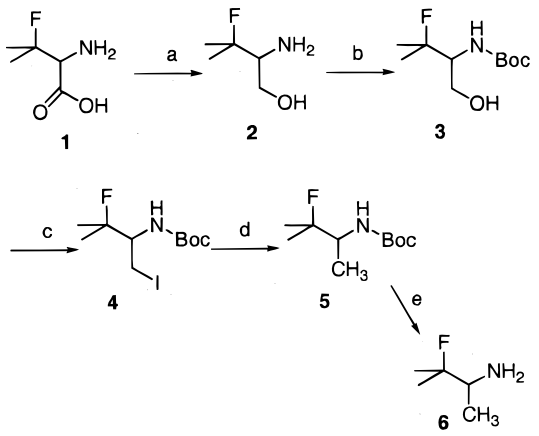
Recently, we required a variety of chiral α-methylamines for SAR studies in the course of drug discovery. It has been known that an alkyl substituent adjacent to a heteroatom can alter the biological activity and metabolic pathway in a related compound series.[1] Our SAR studies required a range of chiral intermediates possessing this single structural trait. We therefore undertook a program to identify an efficient synthesis of these branched amines.

We envisioned the use of α-amino acids as starting materials for the preparation of α-methylamines. The wide availability of optically pure α-amino acids renders them an excellent starting material for this transformation. Indeed, there are a few procedures in the literature that describe this conversion.[2−4] For our purposes we needed a procedure that was compatible with a wide range of functionality and adaptable to larger scale. We also required that the α-methylamines be prepared in enantiopure form. Bloom[2] and Yamada[4] have reported low-yielding routes for a single amino acid. Neither route was adaptable to a wide range of functional groups. We were unable to reproduce the procedure reported by Donner.[3] This Note describes an efficient and general method for the preparation of enantiomerically pure α-methylamines from corresponding chiral amino acids.

To investigate the effect of fluorine atom substitution on alkylamine groups for a discovery program in potassium channel modulation, we required 2-fluoro-1,2-dimethylpropylamine, **6**.[5] Since DL-3-fluorovaline, **1**, is commercially available, our synthetic studies were initiated using this racemic amino acid. As shown in Scheme 1, DL-3-fluorovaline, **1**, was reduced to amino alcohol **2** cleanly using lithium borohydride/trimethylsilyl chloride.[6] The amino group was protected as a *tert*-butyl carbamate to give **3** using di-*tert*-butyl dicarbonate.[7] The transformation of the carbinol into a methyl group was

Scheme 1[a]



[a] Reagents: (a) $LiBH_4$/TMSCl; (b) di-*tert*-butyl dicarbonate; (c) triphenylphosphine, iodine, imidazole; (d) Pearlman's catalyst, H_2; (e) trifluoroacetic acid, then neutralize.

carried out in two steps. It was found that the primary alcohol group was easily replaced by an iodide atom using the method of Caputo to afford **4**.[8] Reduction of the carbon−iodine bond to give **5** was accomplished by catalytic hydrogenation over Pearlman's catalyst.[9] Removal of the BOC protecting group was straightforward using trifluoroacetic acid.[10]

The above procedure, while efficient, required further refinement for the following reasons: (a) the need to determine whether there was racemization of the α-carbon of chiral amino acids during this transformation; (b) the catalytic hydrogenation step was not general and did not work well for several other amino acids; (c) flash chromatography was required to purify two steps of the original sequence. We wanted to design a route that avoided tedious chromatography and improved the yields for individual steps to greater than 85%, so refinement was necessary.

Optimization studies of our original sequence were carried out using both D- and L-phenylalanine. The reduction of amino acid **7** to amino alcohol **8**, using $LiBH_4$/TMSCl, proceeded cleanly and in high yield (Scheme 2). Importantly, chiral HPLC demonstrated that there was no racemization of the α carbon atom in this step.[11] As before, the amino group was protected as a *tert*-butyl carbamate to give **9**, using di-*tert*-butyl dicarbonate. To improve the alcohol to iodo transformation, we employed the polystyrene-supported triphenylphosphine reagent. This change improved the yield of **10** and avoided the need for chromatography. The catalytic hydrogenation step that worked well for 3-fluorovaline failed completely for this substrate. After trying several other reducing agents, we found that N-Selectride facilitated the reduc-

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(11) HPLC conditions: Chiralpak AD column (25 × 0.46 cm), 95/5 methanol/water + 0.095% DEA; 0.5 mL/min, detected 254 and 230 nm.

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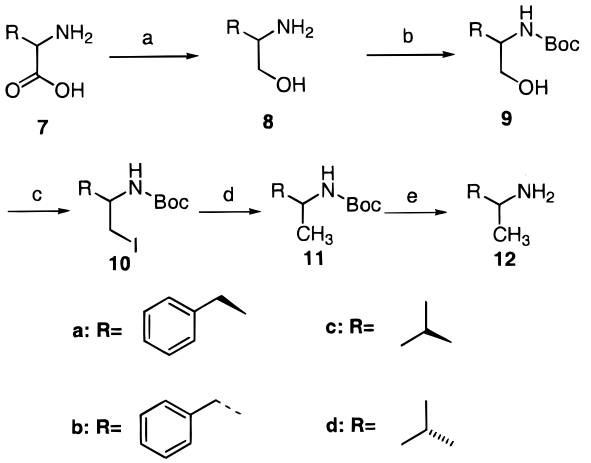
Scheme 2[a]

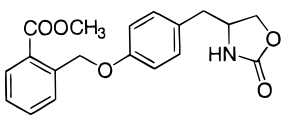


[a] Reagents: (a) $LiBH_4$/TMSCl; (b) di-*tert*-butyl dicarbonate; (c) triphenylphosphine polymer-supported, iodine, imidazole; (d) N-Selectride; (e) trifluoroacetic acid, then neutralize.

tion of the carbon−iodine bond cleanly in 1.5 h and afforded **11** in 94% yield. Purification was achieved simply by filtration through a pad of silica gel. Removal of the BOC protecting group was carried out using trifluoroacetic acid, and amine **12** was finally treated with dry HCl in diethyl ether to afford the crystalline hydrochloride salt of the desired α-methylamines. Last, we evaluated the enantiomeric excess of each derivative and found no loss of chiral purity at any step. This sequence proved to be quite general and was used to reduce D- and L-valine in high yield and enantiomeric purity.

To prepare specific α-methylamines required for a β 3-adrenergic receptor agonist program, we turned our attention to optical isomers of tyrosine. We began with commercially available L-tyrosinol hydrochloride as well as D-tyrosine methyl ester (Scheme 3).

The amino group of L-tyrosinol, **8f**, was protected as a *tert*-butyl carbamate as previously described and the phenolic oxygen was alkylated with methyl 2-bromomethylbenzoate[12] to give **14f**. The polystyrene-supported triphenylphosphine reagent and iodine afforded a clean transformation of the carbinol group into an iodomethylene to afford **15f**. Several reducing agents were examined as part of this investigation, including heating the iodo product with tri-*n*-butyltin hydride and AIBN.[13] This procedure gave the thermally induced cyclization product **18**. A similar result was reported recently by



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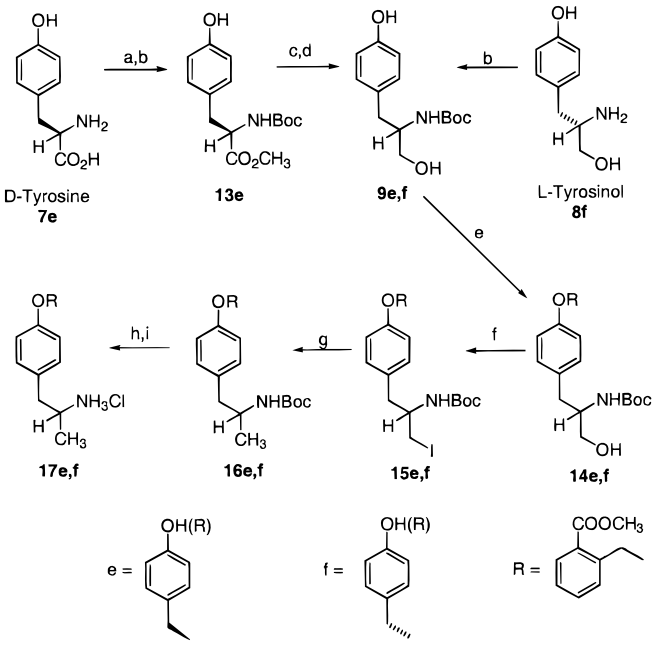
Zhao, who was using DAST at or below room temperature.[14] We found that N-Selectride cleanly reduced the iodomethylene group to the methyl, giving **16f**. Trifluoroacetic acid removed the carbamate protecting group

Scheme 3[a]



[a] Reagents: (a) MeOH, HCl*(g)*; (b) di-*tert*-butyl dicarbonate; $CHCl_3$ (c) LiOH, water, MeOH; (d) $LiBH_4$/TMSCl, THF; (e) potassium carbonate, 2-butanone, methyl 2-bromomethylbenzoate (f) triphenylphosphine polymer-supported, iodine, imidazole; (g) N-Selectride; (h) trifluoroacetic acid, then neutralize; (i) HCl(g).

and afforded the required α-methylamine, which after treatment with HCl afforded **17f**.

The amino group of D-tyrosine methyl ester was protected as a *tert*-butyl carbamate group as previously described to give **13e**. The carboxylic acid, obtained by hydrolysis of the methyl ester using lithium hydroxide, was reduced cleanly to alcohol **9e**. We found that the reduction of tyrosine could not be carried out using the $LiBH_4$/TMSCl conditions that were already developed. This was because of the insolubility of tyrosine in THF. The phenolic oxygen was alkylated with methyl 2-bromomethylbenzoate in the same manner as *N*-*t*-Boc-L-tyrosinol (vide supra) to give **14e.** Alternatively, *N*-Boc-tyrosine was alkylated with methyl 2-bromomethylbenzoate using sodium hydride to preform the phenolic sodium salt. The selective reduction of the acid group was successful, using more carefully controlled $LiBH_4$/TMSCl conditions in order to avoid reduction of the ester group to afford **14e**. Iodination to afford **15e** was straightforward using the polymer-supported triphenylphosphine, and the reduction of the carbon−iodine bond was clean and high yielding using N-Selectride. Removal of the amino protecting group and salt formation, carried out as described earlier, gave **17e**. Evaluation of epimerization was made at each step, and not unexpectedly, the ee values (shown in Table 1) were all determined to be 100% within the limits of detection.

We have demonstrated an efficient new method for the reduction of amino acids into α-methylamines that does not racemize the α carbon. This procedure should be applicable for suitably protected amino acids and for the reduction of carboxylic acids in a variety of systems.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 300 or 400 MHz. ^{13}C

(12) The preparation of this material is described in detail in the Experimental Section.

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Table 1. Yield, Enantiomeric Excess, and Rotation Data for Prepared Compounds

entry	compd	yield (%)	% ee	$[\alpha]^{25}_D$ (deg)
1	**7a**	sm[a]	>99	+32.39
2	**8a**	99	>99	+37.18
3	**9a**	95	>99	+26.78
4	**10a**	88	>99	−6.23
5	**11a**	94	>99	+10.91
6	**12a**	91	>99	+9.21
7	**7b**	sm[a]	>99	−32.34
8	**8b**	97	>99	−30.97
9	**9b**	88	>99	−27.14
10	**10b**	86	>99	+6.87
11	**11b**	94	>99	−10.05
12	**12b**	95	>99	−11.00
13	**7c**	sm[a]	>99	+27.50
14	**8c**	97	>99	+14.90
15	**9c**	99	>99	−14.00
16	**10c**	88	>99	−4.00
17	**11c**	92	>99	−8.00
18	**12c**	89	>99	−2.01
19	**7d**	sm[a]	>99	−27.35
20	**8d**	92	>99	−14.90
21	**9d**	99	>99	+14.99
22	**10d**	84	>99	+5.00
23	**11d**	91	>99	+6.61
24	**12d**	92	>99	+2.00
25	**7e**	sm[a]	>99	+10.3
26	**13e**	90	>99	−5.50
27	**9e**	82	>99	+24.60
28	**14e**	78	>99	+17.00
29	**15e**	89	>99	−5.50
30	**16e**	92	>99	+4.40
31	**17e**	96	>99	+17.50
32	**8f**	sm[a]	>99	−19.00
33	**9f**	87	>99	−25.00
34	**14f**	76	>99	−15.52
35	**15f**	85	>99	+7.37
36	**16f**	90	>99	−4.00
37	**17f**	91	>99	−17.00

[a] Starting material.

NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 100 MHz. Chemical shifts are reported in ppm relative to TMS but using residual non- or partially deuterated solvent as reference. Infrared spectra were recorded using a KBr pellet. Analytical HPLC was run using Chiralpak AD columns (25 × 0.46 cm) and a water/methanol (95/5) solvent system as the mobile phase. Flash chromatography was carried out using Kieselgel 60 (E Merck) with the mobile phase indicated. All reactions were carried out in flame-dried flasks under a dry N_2 atmosphere using magnetic stirring unless otherwise noted. The transfer of all liquids was performed via syringe. All solvents were anhydrous grade and used as is from freshly opened bottles unless otherwise noted.

3-Fluorovalinol (2). To a solution of lithium borohydride (74 mmol) in THF (40 mL) under a nitrogen atmosphere was added trimethylsilyl chloride (148 mmol) via pipet; a precipitate quickly formed. Three minutes later, 3-fluorovaline, **1** (37 mmol), was added in three portions. This mixture was stirred for 24 h.

The reaction was quenched by the dropwise addition of methanol. The methanol and THF were removed on a rotary evaporator (30 °C water bath), and 25 mL of water was added. The aqueous mixture was made basic with 2.5 N aqueous NaOH and was then extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to leave 3.83 g of very pure product: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.71 (dd, 1H, J = 3.8, 10.7 Hz), 3.36 (m, 1H), 2.90 (m,1H), 2.10 (br, 2H), 1.38 (d, 3H, J = 22.1 Hz), and 1.33 (d, 3H, J = 22.1 Hz).

***tert*-Butyl 2-Fluoro-1-(hydroxymethyl)-2-methylpropyl Carbamate (3).** To a solution of 3-fluorovalinol (31.36 mmol) in chloroform (35 mL) under a nitrogen atmosphere was added a solution of di-*tert*-butyl dicarbonate (31.36 mmol) in chloroform (15 mL). The mixture was stirred at room temperature for 4 h, and then the solvent was removed on a rotary evaporator. The residue was dissolved in diethyl ether (100 mL), washed with 20% phosphoric acid (1 × 50 mL), brine, saturated aqueous sodium bicarbonate, and finally brine, dried ($MgSO_4$), filtered, and evaporated. A total of 6.34 g of a pure white solid was obtained: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.08 (br, 1H), 3.82 (m, 1H), 3.68 (m, 1H), 1.46 (s, 9H), 1.46 (d, 3H, J = 7.5 Hz), and 1.39 (d, 3H, J = 7.5 Hz).

***tert*-Butyl 2-Fluoro-1-(iodomethyl)-2-methylpropyl Carbamate (4).** To a well-stirred mixture of polystyryl-supported triphenylphosphine (29.33 mmol) in dry dichloromethane (40 mL) under a nitrogen atmosphere was added iodine (29.33 mmol). After 10 min, imidazole (29.33 mmol) was added followed in 10 min by a solution of *tert*-butyl 2-fluoro-1-(hydroxymethyl)-2-methylpropyl carbamate (13.33 mmol) in dichloromethane (200 mL). The mixture was heated to reflux for 2 h. The cooled mixture was filtered through Celite, and the filtrate was evaporated. The residue was dissolved in diethyl ether (150 mL), and this solution was washed with dilute aqueous sodium thiosulfate and water. The organic layer was dried (Na_2SO_4), filtered through a pad of silica gel, and evaporated to afford 3.46 g of pure product: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.72 (br d, 1H), 3.86 (br m, 1H), 3.56 (dd, 1H, J = 3.4, 10.7 Hz), 1.47 (s, 9H), and 1.43 (m, 6H).

***tert*-Butyl 2-Fluoro-1,2-dimethylpropyl Ccarbamate (5).** A Parr bottle was charged with palladium(II) hydroxide (800 mg), a solution of *tert*-butyl 2-fluoro-1-(iodomethyl)-2-methylpropyl carbamate (9.8 mmol) in ethanol (80 mL), and triethylamine (9.8 mmol). The reaction mixture was placed under 50 psig of hydrogen gas and shaken for 20 h. The mixture was filtered through Celite and evaporated. The residue was dissolved in diethyl ether (100 mL), washed with 1 N aqueous HCl and then with water, dried ($MgSO_4$), filtered, and evaporated. The residue was flash chromatographed with silica gel using diethyl ether/hexane (3/1) as eluant to afford 1.80 g of the desired product: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65 (br, 1H), 3.70 (br m, 1H), 1.45 (s, 9H), 1.39 (d, 3H, J = 1.8 Hz), 1.32 (d, 3H, J = 1.3 Hz), and 1.18 (d, 3H, J = 6.9 Hz).

3-Fluoro-3-methyl-*n*-butyl-2-amine (6). A mixture of *tert*-butyl 2-fluoro-1,2-dimethylpropyl carbamate (1.74 g., 8.5 mmol), dichloromethane (5 mL), trifluoroacetic acid (4 mL), and methanol (0.75 mL) was warmed to 45 °C for 5 h. TLC showed that no starting material remained. The volatile components were removed on a rotary evaporator, and the syrupy residue was taken up into water and treated with saturated sodium carbonate until the pH of the solution was 12. The aqueous mixture was extracted with chloroform (3×). The organic extracts were dried (K_2CO_3), filtered, and evaporated to leave 0.89 g of a clear oil: MS (+FAB) m/z $[m + H]^+$ 106, $[m + Na]^+$ 129; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.92 (br, 2H), 2.90 (br m, 1H), 1.35 (d, 3H, J = 1.7 Hz), 1.30 (d, 3H, J = 1.4 Hz), and 1.13 (d, 3H, J = 6.2 Hz).

D-**Phenylalaninol (8a).** To a cold solution of lithium borohydride (1.32 g, 60.54 mmol) in THF (30 mL, freshly distilled from $LiAlH_4$) was added trimethylsilyl chloride (15.36 mL, 121.07 mmol). The ice/water bath was removed and the mixture allowed to stir at room temperature for 15 min. The mixture was recooled to 0 °C, and D-phenylalanine **7a** (5.00 g, 30.27 mmol) was added. The ice/water bath was removed, and the reaction mixture was stirred overnight. The mixture was again cooled to 0 °C, and methanol (45 mL) was added dropwise, followed by 2.5 M aqueous sodium hydroxide (25 mL) This mixture was evaporated in vacuo, and the residue extracted with chloroform (5×). The combined extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to leave 4.55 g (99%) of **2a** as a white crystalline solid: mp 88−90 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.28−7.15 (m, 5H), 3.29−3.25 (m, 1H), 3.18−3.14 (m, 1H), 2.85 (m, 1H), 2.68−2.64 (m, 1H), 2.43−2.38 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 40.1, 54.5, 65.8, 125.7, 128.1, 129.2, 139.8; IR (KBr) 3360, 3295, and 1580 cm^{-1}; MS, APCI(+) m/z 152 $[M + H]^+$; $[\alpha]^{25}_D$ +37.18 (*c* 10.30, water). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.10; H, 8.83; N, 9.17.

***N*-*t*-Boc-D-phenylalaninol (9a).** To a stirred, chilled (0 °C) solution of D-phenylalaninol **8a** (5.00 g, 33.1 mmol) in 85 mL of chloroform was added solid di-*tert*-butyl dicarbonate (7.22 g, 33.1 mmol). The solution was stirred at 0 °C for 0.5 h and then stirred at room temperature overnight. The solution was washed with

20% phosphoric acid, a saturated $NaHCO_3$ solution, and a saturated NaCl solution, then dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The resulting solid was recrystallized from a hot hexane/ethyl acetate mixture to afford 7.48 g (95%) of **9a** as white fibrous crystals: mp 96 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22−1.46 (m, 9H), 2.52−2.57 (m, 1H), 2.78−2.82 (m, 1H), 3.22−3.36 (m, 2H), 3.52−3.59 (m, 1H), 4.67 (t, J = 5.5, 1H), 6.55−6.57 (d, J = 8, 1H), 7.13−7.26 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.1, 139.4, 129.1, 128.0, 125.7, 77.4, 62.9, 53.9, 36.8, 28.2; IR (KBr) 3360, 1685, and 1525 cm^{-1}; $[\alpha]^{25}_D$ +26.78 (*c* 10.828, MeOH). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.78; H, 8.49; N, 5.51.

***tert*-Butyl (1*R*)-1-Benzyl-2-iodoethyl Carbamate (10a).** To a stirred, chilled (0 °C) suspension of 2.92 g of polymer-supported triphenylphosphine (~8.75 mmol) in dry dichloromethane (35 mL) was added 2.22 g of iodine (8.75 mmol), followed by 0.65 g of imidazole (9.55 mmol). The mixture was allowed to warm to ambient temperature, and after 0.5 h a solution of 1.26 g (3.98 mmol) of alcohol **9a** in dichloromethane (15 mL) was added dropwise. The mixture was then heated at reflux for 2 h. The cooled mixture was then filtered and the solution was washed with dilute aqueous $Na_2S_2O_3$ and water, dried (Na_2SO_4), and evaporated to a white crystalline solid. Passing the residue through a short silica gel column (3:2, EtOAc:hexane) yielded the pure product which was recrystallized from hot hexane to obtain 1.09 g of **10a** (88%) as white crystals: mp 121−22 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.25−7.29 (m, 1H), 7.19−7.21 (m, 3H), 7.00, 7.22 (d, J = 8, 1H), 3.60−3.62 (m, 1H), 3.32−3.36 (m, 1H), 3.16−3.20 (m, 1H), 2.79−2.83 (m, 1H), 1.22−1.47 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.9, 138.3, 129.0, 128.2, 126.2, 77.8, 53.1, 28.2, 12.7; IR (KBr) 3350, 1690, and 1525 cm^{-1}; $[\alpha]^{25}_D$ −6.23 (*c* 10.115, MeOH); MS (ESI$^+$) m/z 362 [M + H]$^+$, m/z 379 [M + NH$_4$]$^+$. Anal. Calcd for $C_{14}H_{20}INO_2$: C, 46.55; H, 5.58; N, 3.88. Found: C, 46.57; H, 5.54; N, 3.84.

***tert*-Butyl (1*S*)-1-Methyl-2-phenylethyl Carbamate (11a).** A solution of 1.00 g (2.77 mmol) of iodo compound **10a** in anhydrous THF (20 mL) was stirred at −15 °C as 3.04 mL (3.04 mmol) of a 1.0 M solution of N-Selectride (in THF) was added dropwise via syringe. The mixture was allowed to warm to 5 °C over 1.5 h. Reaction progress was monitored by TLC (4:1 hexane:EtOAc). The solution was cooled to 0 °C, and the reaction was quenched by the slow addition of 1.3 mL of water. This was followed by the dropwise addition of a solution made by combining 15 mL of H_2O, 1.0 g of K_2CO_3, and 2.6 mL of 30% H_2O_2. The reaction mixture was stirred at ambient temperature for 1 h. The THF was evaporated under reduced pressure, and the product was extracted from the residue with dichloromethane (3×). The organic extracts were dried (Na_2SO_4) and the solvent evaporated to yield a white solid. Passing this material through a short silica gel column (4:1, hexane:EtOAc) yields **11a** (0.61 g; 94%) as a white crystalline solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.24−7.27 (m, 2H), 7.15−7.18 (m, 3H), 6.74, 6.76 (d, J = 8, 1H), 3.62−3.65 (m, 1H), 2.69−2.74 (m, 1H), 2.49−2.56 (m, 1H), 1.29−1.35 (m, 9H), 0.97, 0.99 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.8, 139.3, 129.1, 128.0, 125.9, 77.3, 47.5, 42.1, 28.2, 20.2; IR (KBr) 3360, 1687, 1680 s, and 1520 cm^{-1}; $[\alpha]^{25}_D$ +10.91 (*c* 10.086, MeOH); MS (+)ESI, m/z 236 [M + H]$^+$, m/z 471 [2 M + H]$^+$. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.66; H, 9.33; N, 5.90.

(1*S*)-1-Methyl-2-phenylethylamine Hydrochloride Salt (12a). To a stirred, cooled (0 °C) solution of **11a** (2.59 g; 11.0 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (5 mL). The solution was stirred at ambient temperature for 18 h. The volatile components were removed under reduced pressure, and the residue was treated with water (10 mL), chloroform (15 mL), and an NaOH solution (2 mL, 50%). The mixture was shaken, and the layers were separated. The aqueous layer was extracted with chloroform (5×), and the combined organic extracts were dried over Na_2SO_4 and filtered. To this was added 6 mL of a 1.0 M HCl solution (in diethyl ether), and the solvents were removed to yield a yellow solid. This was recrystallized in hot hexane/acetone to yield **12a** as white, needle-shaped crystals, 1.34 g (91%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 3H), 7.30−7.34 (m, 2H), 7.22−7.26 (m, 3H), 3.35 (s, broad, 1H), 3.07 (dd, J = 5, 13 Hz, 1H), 2.64 (dd, J = 13, 9 Hz, 1H), 1.09 (d, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.8, 129.2, 128.5, 126.7, 48.0, 40.0, 17.4; IR (KBr) 2925 and 2900 s cm^{-1}; $[\alpha]^{25}_D$ +9.21 (*c* 9.56, MeOH); MS, (+)APCl, m/z 136 [M + H]$^+$. Anal. Calcd for C_9H_{14}-NCl: C, 62.97; H, 8.22; N, 8.16. Found: C, 62.94; H, 8.33; N, 8.05.

L-Phenylalaninol (8b). Lithium borohydride (1.32 g, 60.5 mmol), trimethylsilyl chloride (13.2 g, 121 mmol), and L-phenylalanine (5.0 g, 30 mmol) were combined under experimental conditions identical to that for the synthesis of **8a** (above) to yield 4.40 g (97%) of **8b** as a white crystalline solid: mp 89−90 °C. The NMR, IR, and MS data are identical to those shown for **8a** (above). $[\alpha]^{25}_D$ −30.99 (*c* 10.39, water). Anal. Calcd for C_9H_{13}-NO: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.00; H, 8.78; N, 9.11.

***N*-*t*-Boc-L-phenylalaninol (9b).** L-Phenylalaninol (3.00 g, 19.8 mmol), and di-*tert*-butyl dicarbonate (4.33 g, 19.8 mmol), were combined and worked up in a manner identical to the materials in **9a** (above). The procedure yields 4.38 g (88%) of white fibrous crystals: mp 96 °C. The NMR, IR, and MS data are identical to those shown for **9a** (above). $[\alpha]^{25}_D$ −27.14 (*c* 9.763, MeOH). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.87; H,8.63; N, 5.50.

***tert*-Butyl (1*S*)-1-Benzyl-2-iodoethyl Carbamate (10b).** Polymer-supported triphenylphosphine (2.92 g, ~8.75 mmol), iodine (2.22 g; 8.75 mmol), imidazole (0.65 g, 9.55 mmol), and *N*-(*t*-Boc)-L-phenylalaninol **9b** (1.00 g; 3.98 mmol) were combined and worked up in an identical manner tothat for the materials in **10a** (above). The procedure yielded 1.23 g (86%) of **10b** as a white crystalline solid: mp 121−122 °C. The NMR, IR and MS data are identical to those shown for **10a** (above). $[\alpha]^{25}_D$ +6.87 (*c* 9.990, MeOH). Anal. Calcd for $C_{14}H_{20}INO_2$: C, 46.55; H, 5.58; N, 3.88. Found: C, 46.66; H, 5.61; N, 3.83.

***tert*-Butyl (1*R*)-1-Methyl-2-phenylethyl Carbamate (11b).** *tert*-Butyl (1*S*)-1-benzyl-2-iodoethyl carbamate **10b** (1.00 g, 2.77 mmol) and N-Selectride (3.04 mL, 3.04 mmol) were combined and worked up in a manner identical to that outlined for **11a** (above). The procedure yielded 0.61 g (94%) of **11b** as white crystals: mp 59−60 °C. The NMR, IR, and MS data are identical to those shown for **11a** (above). $[\alpha]^{25}_D$ −10.05 (*c* 9.951, MeOH). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.73; H, 9.27; N, 5.91.

(1*R*)-1-Methyl-2-phenylethylamine (12b). The procedure outlined for **12a** (above) was carried out using *tert*-butyl (1*R*)-1-methyl-2-phenylethylcarbamate **11b** (1.17 g, 4.97 mmol). The experiment yielded 0.81 g (95%) of the title compound as a white crystalline solid: mp 155−6 °C. The NMR, IR, and MS data are identical to those shown for **12a** (above). $[\alpha]^{25}_D$ −11.00 (*c* 9.998, MeOH). Anal. Calcd for $C_9H_{14}NCl$: C, 62.97; H, 8.22; N, 8.16;. Found: C, 62.86; H, 8.43; N, 8.05.

L-Valinol (8d). The procedure outlined for **8a** (above) is carried out using L-valine (5.0 g, 42.7 mmol) to yield 4.30 g of a colorless oil (97%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.34 (dd, J = 4.6, 10.3 Hz, 1H), 3.13 (dd, J = 7.5, 10.3, 1H), 2.37−2.41 (m, 1H), 2.59 (s, broad, 3H), 1.50−1.57 (m, 1H), 0.82 (dd, J = 6.8, 9.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 64.5, 57.9, 30.0, 19.6, 17.7; IR (KBr) 3340, 3280, 2905, 1607, cm^{-1}; $[\alpha]^{25}_D$ +14.90 (*c* 10.067, MeOH); MS, (+)ESI, m/z 104, [M + H]$^+$. Anal. Calcd for $C_5H_{13}NO$: C, 58.21; H, 12.70; N, 13.58. Found: C, 58.48; H, 12.88; N, 13.77.

***N*-*t*-Boc-L-valinol (9d).** The representative procedure found for **9a** (above) was followed using d-valinol **8d** (5.0 g, 48.5 mmol). The procedure yielded the title compound as 9.80 g (99%) of a clear, colorless oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.33 (d, J = 9, 1H), 4.42 (s, 1H), 3.20−3.27 (m, 1H), 3.31−3.34 (m, 2H), 1.70−1.79 (m, 1H), 1.36 (s, 9H), 0.80 (dd, J = 6.8, 5.4; 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.7, 77.1, 61.5, 57.2, 28.5, 28.2, 19.5, 17.9; IR (KBr) 2962, 1684, and 1506 cm^{-1}; $[\alpha]^{25}$ −14.00 (*c* 9.997, MeOH); MS, (+)ESI, m/z 204, [M + H]$^+$. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.09; H, 10.41; N, 6.89. Found: C, 59.17; H, 10.68; N, 6.85.

***tert*-Butyl (1*S*)-1-(Iodomethyl)-2-methylpropyl Carbamate (10d).** The procedure for **10a** (above) was carried out using 4.76 g (23.4 mmol) of **9d**, to yield 6.43 g (88%) of the title compound as a clear crystalline solid: mp 69−72 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.83 (d, J = 8.79, 1H), 3.39 (dd, J = 3.7, 9.8; 1H), 3.32−3.34 (m, 1H), 3.17 (dd, J = 8.8, 9.8; 1H), 2.86−3.37 (m, 1H), 1.38 (s, 9H), 0.81 (d, J = 3.3, 6H); ^{13}C NMR (100

MHz, DMSO-d_6) δ 155.4, 77.6, 57.0, 31.8, 28.2, 19.2, 17.8, 11.8; IR (KBr) 3330, 2962, 1670, and 1520 cm^{-1}; $[\alpha]^{25}_D$ −4.00 (*c* 9.997, MeOH); MS, (+)ESI, *m*/*z* 314, $[M + H]^+$. Anal. Calcd for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44; N, 4.47. Found: C, 38.52; H, 6.52; N, 4.42.

***tert*-Butyl (1*R*)-1,2-Dimethylpropyl Carbamate (11d).** The procedure used here was identical to that for **11a**. The starting material **10d** (2.39 g, 7.63 mmol) yielded 1.32 g (92%) of the title compound as a clear crystalline solid: mp 35−36 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.57 (d, J = 8.5, 1H), 3.23−3.28 (m, 1H), 1.52−1.60 (m, 1H), 1.36 (s, 9H), 0.93 (d, J = 6.6, 3H), 0.79 (dd, J = 3.4, 6.8; 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.1, 77.1, 50.9, 32.7,28.3, 18.8, 18.5, 17.3; $[\alpha]^{25}_D$ −8.00; IR (KBr) 3300, 2970, 1669, and 1532 cm^{-1}; MS, (+)APCI, $[M + H]^+$ *m*/*z* 188. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.14; H, 11.50; N, 7.45.

(1*R*)-1,2-Dimethylpropylamine (12d). The procedure used for **12a** (above) was carried out using 0.46 g (2.46 mmol) of **11d** to yield 0.27 g (89%) of the title compound as white needle-shaped crystals: mp 218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (s broad, 3H), 2.93−2.99 (m, 1H), 1.79−1.87 (m, 1H), 2.21 (d, J = 6.6, 3H), 0.88 (dd, J = 6.8, 10.5; 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.6, 30.7, 18.8, 16.9, 14.5; IR (KBr) 2885, 1604, 1515 cm^{-1}; $[\alpha]^{25}_D$ +2.00 (*c* 10.004, MeOH); MS, (+)APCI, *m*/*z* 88, $[M + H]^+$. Anal. Calcd for $C_5H_{14}ClN$: C, 48.58; H, 11.41; N, 11.33. Found: C, 48.70; H, 11.57; N, 11.32.

D-Valinol (8c). The representative procedure found for **8a** (above) was followed using L-valine (5.0 g, 42.7 mmol) to yield 4.04 g of a colorless oil (92%). The NMR, IR, and MS data are identical to those shown for **8d** (above). $[\alpha]^{25}_D$ −14.03 (*c* 9.980, MeOH). Anal. Calcd for $C_5H_{13}NO$: C, 58.21; H, 12.70; N, 13.58. Found: C,58.11; H,12.55; N,13.49.

***N*-*t*-Boc-D-valinol (9c).** The representative procedure found for **9a** (above) was followed using d-valinol (5.0 g; 48.5 mmol). The procedure yielded 9.84 g (99%) of the title compound as a clear, colorless oil. The NMR, IR, and MS data are identical to those shown for **9d** (above). $[\alpha]^{25}_D$ +14.99 (*c* 10.004, MeOH). Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.09; H, 10.41; N, 6.89. Found: C, 59.06; H, 10.39; N, 6.71.

***tert*-Butyl (1*R*)-1-(Iodomethyl)-2-methylpropyl Carbamate (10c).** The representative procedure for **10a** (above) was employed with **9c** (4.06 g, 20.0 mmol) and yielded 5.26 g (84%) of the title compound as a light-yellow crystalline solid: mp 68−70 °C. The NMR, IR, and MS data are identical to those shown for **10d** (above). $[\alpha]^{25}_D$ +5.00 (*c* 10.001, MeOH). Anal. Calcd for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44; N, 4.47. Found: C, 38.58; H, 6.66; N, 4.39.

***tert*-Butyl (1*S*)-1,2-Dimethylpropyl Carbamate (11c).** The representative procedure for **11a** (above) was carried out on **10c** (3.78 g; 12.1 mmol) and yielded 2.07 g (91%) of the title compound as clear, colorless crystals: mp 35−37 °C. The NMR, IR, and MS data are identical to those shown for **11d** (above). $[\alpha]^{25}_D$ +6.61 (*c* 7.41, MeOH). Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.21; H, 11.40; N, 7.49.

(1*S*)-1,2-Dimethylpropylamine Hydrochloride (12c). The representative procedure for **12a** (above) was carried out on **11c** (0.13 g; 0.69 mmol) and yielded 0.083 (92%) of the title compound as clear, colorless crystals: mp 35−37 °C. The NMR, IR, and MS data are identical to those shown for **12d** (above): mp 217−218 °C; $[\alpha]^{25}_D$ −2.01 (*c* 9.946, MeOH). Anal. Calcd for $C_5H_{14}NCl$: C, 48.58; H, 11.41; N, 11.33. Found: C, 48.63; H, 11.76; N, 11.28.

Bromomethyl 2-Methylbenzoate. A solution of 9.4 g (62.9 mmol) of methyl 2-methylbenzoate, 11.2 g (62.9 mmol) of *N*-bromosuccinimide, and AIBN (2−3 mg) in carbon tetrachloride (90 mL) was heated at 90 °C for 18 h. The solution was cooled to 0 °C, and the solid was filtered from the solution. The organic solution was washed twice with dilute aqueous $Na_2S_2O_3$. The CCl_4 was evaporated at reduced pressure. The residue was taken up in diethyl ether, dried over Na_2SO_4, and filtered through a 5 cm pad of silica gel rinsed with additional ether. Evaporation gave 11.96 g (83%) of a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.6 and 1.16 Hz, 1H), 7.48 (m, 2H), 7.39 (m, 1H), 4.96 (s, 2H), and 3.95 (s, 3H).

***N*-*t*-Boc-L-tyrosinol (9f).** To a room temperature mixture of L-tyrosinol hydrochloride (15.278 g, 75.0 mmol) and triethylamine (10.45 mL, 75.0 mmol) in chloroform (100 mL) was added di-*tert*-butyl dicarbonate (16.37 g, 75.0 mmol) in chloroform (35 mL). After 16 h the reaction mixture was extracted with 15% (v/v) aqueous phosphoric acid (2×), brine (1×), dilute aqueous sodium bicarbonate (1×), and water (1×). The organic phase was dried (Na_2SO_4), filtered through a 1 in. pad of silica gel, and evaporated to give 17.24 g of a white solid (86%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.09 (s,1H), 6.95 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 8.5 Hz, 2H), 6.48 (d, J = 8.3 Hz, 1H), 4.61 (t, J = 5.6 Hz, 1H), 3.47 (m, 1H), 3.28 (m, 2H), 2.65 (ABX m, 1H), 2.47 (ABX m, 1H), and 1.32 (s, 9H); MS(ESI(−)), $[M - H]^-$ at *m*/*z* 266; $[\alpha]^{25}_D$ −25.00 (*c* 10.0, MeOH).

Methyl 2-[(4-{(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxypropyl}phenoxy)methyl]benzoate (14f). A mixture of *N*-*t*-Boc-L-tyrosinol **(9f)** (15.50 g, 58.0 mmol), bromomethyl 2-methylbenzoate (13.30 g, 58.0 mmol), potassium carbonate (8.02 g, 58.0 mmol), and potassium iodide (250 mg) in acetonitrile/acetone (75 mL/25 mL) was heated to reflux for 14 h. The cooled reaction mixture was cooled and filtered. The organic phase was washed with aqueous sodium thiosulfate, H_2O, and brine (1× each), dried (Na_2SO_4), filtered, and evaporated to leave a yellow solid. The product was purified by crystallization from hexane/ethyl acetate to afford 20.00 g (83%) as a white solid with mp 102−4 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.9 and 1.5 Hz, 1H), 7.74 (dd, J = 7.9 and 0.6 Hz, 1H), 7.55 (dt, J = 7.5 and 1.5 Hz), 7.37 (dt, J = 8.6 and 0.6 Hz), 7.12 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.48 (s, 2H), 4.70 (br, 1H), 3.90 (s, 3H), 3.82 (br, 1H), 3.66 (ABX m, 1H), 3.56 (ABX m, 1H), 2.77 (d, J = 7.0 Hz, 2H), and 1.42 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 156.5, 155.1, 138.4, 132.3, 131.6, 130.10, 130.07, 128.5, 128.0, 127.7, 114.3, 77.3, 67.5, 62.8, 54.0, 52.1, 35.9, 28.2; IR (KBr) 1723, 1684, and 1529 cm^{-1}; MS(EI), $[M^+]$ at *m*/*z* 415; $[\alpha]^{25}_D$ −15.52 (*c* 6.70, MeOH). Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.18; H, 7.18; N, 3.42.

Methyl 2-[(4-{(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-iodopropyl}phenoxy)methyl]benzoate (15f). The representative procedure for **10a** (above) was employed with **14f (**1.16 g, 2.79 mmol) of the alcohol yielded 1.00 g (68%) of the title compound as white crystals: mp 63−71 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88−7.90 (m, 1H), 7.58−7.65 (m, 2), 7.43−7.47 (m, 1H), 7.12 (d, 2H), 6.98 (d, 1H), 6.88 (d, 2H), 5.36 (s, 2H), 3.79 (s, 3H), 3.54 (m, 1H) 3.31−3.33 (m, 1H), 3.14−3.18 (m, 1H), 2.71−2.76 (m, 1H), 2.61−2.63 (m, 1H), 1.24−1.47 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 158.6, 157.0, 156.8, 154.9, 138.3, 138.2, 130.6, 130.5, 130.1, 130.0, 128.8, 128.6, 128.5, 128.1, 128.0, 127.8, 127.6, 114.6, 114.5, 110.8, 77.8, 68.0, 67.5, 53.2, 52.6, 52.1, 28.2, 27.9, 27.8, 23.9, 12.8; IR (KBr) 1718, 1688, and 1512 cm^{-1}; $[\alpha]^{25}_D$ +7.37 (*c* 6.38, MeOH); MS, ESI(+), *m*/*z* 543, $[M + NH_4]^+$. Anal. Calcd for $C_{23}H_{28}INO_5$: C, 52.58; H, 5.37; N, 2.67. Found: C, 52.41; H, 5.36; N, 2.57.

Methyl2-[(4-{(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]propyl}-phenoxy)methyl]benzoate (16f). The representative procedure for **11a** (above) was employed with **15f** (0.32 g, 0.61 mmol) for the iodo compound to yield 0.185 g (76%) of the title compound as white crystals: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88−7.90 (m, 1H), 7.58−7.65 (m, 2H), 7.43−7.47 (m, 1H), 7.06−7.09 (m, 2H), 6.85−6.88 (m, 2H), 6.71 (d, J = 8.5 Hz, 1H), 5.36 (s, 2H), 3.79 (m, 1H), 3.79 (s, 3H), 3.56−3.60 (m, 1H), 2.61−2.66 (m, 1H), 2.44−2.46 (m, 1H), 1.33−1.35 (m, 9H), and 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 156.4, 154.8, 138.4, 132.3, 131.6, 130.1, 128.5, 128.0 (2C), 127.7 (2C), 114.3, 77.2, 67.5, 52.1, 47.6, 41.2, 28.2, 27.6, and 20.2; IR (KBr) 1722, 1683, and 1512 cm^{-1}; $[\alpha]^{25}_D$ −4.00 (*c* 9.993, MeOH); MS, (+)ESI, *m*/*z* 400, $[M + H]^+$. Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 68.88; H, 7.45; N, 3.46.

Methyl 2-({4-[(2*R*)-2-Aminopropyl]phenoxy}methyl)-benzoate Hydrochloride (17f). The representative procedure for **12a** (above) was carried out on **16f** (0.13 g, 0.69 mmol) and yielded 0.083 g (92%) of the title compound as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (dd, J = 7.8 and 1.0 Hz, 1H), 7.63 (m, 2H), 7.43 (dt, J = 7.3 and 1.5 Hz, 1H), 7.07 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.36 (s, 2H), 3.79 (s, 3H), 2.93 (m, 1H), 2.43 (d, J = 6.6 Hz, 2H), and 0.92 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 156.5, 138.4, 132.3, 130.1, 128.4, 128.0 (2C), 127.7 (2C), 114.3, 67.5, 52.1, 48.3, 45.3, and 23.2; $[\alpha]^{25}_D$ −17.00 (*c* 10.00, MeOH); MS, (+)ESI, *m*/*z* 300 $[M + H]^+$.

***N*-*t*-Boc-D-tyrosine Methyl Ester (13e).** To a mixture of D-tyrosine methyl ester hydrochloride (prepared from D-tyrosine, methanol, and HCl(g)) (4.636 g, 20.0 mmol), triethylamine (2.93 mL, 21.0 mmol), pyridine (1.70 mL, 21.0 mmol) in chloroform (15 mL), and THF (15 mL) at 10 °C was added solid di-*tert*-butyl dicarbonate (4.58 g, 21.0 mmol). The solution was stirred at 10 °C for 0.5 h and then stirred at room temperature overnight. The solution was washed with 15% phosphoric acid, dilute aqueous $NaHCO_3$ solution, and a saturated NaCl solution, then dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The resulting clear oil crystallized to a low-melting white solid upon standing. The yield was 5.61 g (95%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 7.20 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 8.3 Hz, 2H), 6.63 (d, J = 8.3 Hz, 2H), 4.05 (m, 1H) 3.58 (s, 3H), 2.83 (ABX m, 1 H), 2.72 (ABX m, 1H), and 1.32 (s, 9H); IR (KBr) 3390 br, 1710 m, 1690 s, 1515 s, and 1150 cm^{-1}; $[\alpha]^{25}_D$ −5.50 (*c* 10.00, MeOH); MS, (−)APCI, *m*/*z* 294, $[M-H]^-$. Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.83; H, 7.39; N, 4.49.

***N*-*t*-Boc-D-tyrosinol (9e).** To a solution of *N*-*t*-Boc-D-tyrosine methyl ester **(13e)** (4.05 g, 13.56 mmol) in methanol (30 mL) was added a solution of lithium hydroxide (1.0 g) in water (15 mL). This solution was stirred overnight at room temperature. The methanol was removed in vacuo, and the aqueous phase was acidified to pH 1.5. The aqueous phase was extracted with ethyl acetate (2×) and chloroform (2×). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to leave *N*-*t*-Boc-D-tyrosine which was used as is in the following.

To a cold solution of lithium borohydride (0.356 g, 16.35 mmol) in THF (25 mL, freshly distilled from $LiAlH_4$) was added trimethylsilyl chloride (4.15 mL, 32.70 mmol). The ice/water bath was removed, and the mixture was allowed to stir at room temperature for 25 min. The mixture was recooled to 0 °C, and *N*-*t*-Boc-D-tyrosine (1.84 g, 6.54 mmol) was added. The ice/water bath was removed, and the reaction mixture was stirred overnight. The mixture was again cooled to 0 °C, methanol (10 mL) was added dropwise, and then water (5.0 mL) was added. The pH was adjusted to 3.5 by the addition of 2.5 M aqueous sodium hydroxide. This mixture was evaporated in vacuo and the residue extracted with chloroform (5×). The combined extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to leave 0.890 g of a white foam. This proved to be the desired product in a form sufficiently pure for subsequent steps: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.09 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.4 Hz, 2H), 6.49 (d, J = 8.6 Hz, 1H), 4.61 (br t, 1H), 3.47 (m, 1H), 3.28 (m, 2H), 2.66 (ABX m, 1 H), 2.45 (ABX m, 1H), and 1.32 (s, 9H); $[\alpha]^{25}_D$ +24.60 (*c* 10.00, MeOH); MS, (−)APCI, *m*/*z* 266, $[M-H]^-$. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.72; N, 5.24. Found: C, 63.11; H, 8.10; N, 5.23.

Methyl 2-[(4-{(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-hydroxypropyl}phenoxy) methyl]benzoate (14e). The representative procedure for **14f** (above) was employed with **9e (**0.610 g, 2.28 mmol) to yield 0.738 g (78%) of the title compound as a white solid. The NMR, IR, and MS data are identical to those shown for **14f** (above). $[\alpha]^{25}_D$ +17.00 (*c* 10.002, MeOH).

Methyl 2-[(4-{(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-iodopropyl}phenoxy)methyl]benzoate (15e). The representative procedure for **15f** (above) was employed with **14e (**0.280 g, 0.674 mmol) to yield 0.315 g (89%) of the title compound as a white solid. The NMR, IR, and MS data are identical to those shown for **15f** (above). $[\alpha^{25}_D$ −5.50 (*c* 9.989, MeOH).

Methyl2-[(4-{(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]propyl}-phenoxy)methyl]benzoate (16e). The representative procedure for **16f** (above) was employed with **15e** (0.120 g, 0.228 mmol) to yield 0.084 g (92%) of the title compound as a white solid. The NMR, IR, and MS data are identical to those shown for **16f** (above). $[\alpha]^{25}_D$ +4.60 (*c* 10.008, MeOH).

Methyl 2-({4-[(2*R*)-2-Aminopropyl]phenoxy}methyl)-benzoate Hydrochloride (17e). The representative procedure for **17f** (above) was carried out on **16e** (0.075 g, 0.188 mmol) and yielded 0.054 (96%) of the title compound as a white solid. The NMR, IR, and MS data are identical to those shown for **16f** (above). $[\alpha]^{25}_D$ +17.50 (*c* 9.999, MeOH).

Methyl 2-({4-[(2-Oxo-1,3-oxazolidin-4-yl)methyl]phenoxy}-methyl)benzoate (18). A solution of methyl 2-[(4-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-iodopropyl}phenoxy)methyl]benzoate **(15f)** (4.50 g, 8.60 mmol), tri-*n*-butyltin hydride (2.42 mL, 9.00 mmol), and AIBN (200 mg) in toluene (55 mL) and dioxane (15 mL) was heated to 110 °C for 6 h. The cooled reaction mixture was quenched with methanol followed by water. The organic phase was separated, dried (Na_2SO_4), and evaporated in vacuo.

The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate: 3/1) to afford 2.12 g (72%) of a clear oil that crystallized on standing: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (dd, J = 7.7 and 0.9 Hz, 1H), 7.75 (s, 1H), 7.64 (m, 2H), 7.45 (dt, J = 7.7 and 1.5 Hz, 1H), 7.16 (d, J = 6.6 Hz, 2H), 6.90 (d, J = 6.6 Hz, 2H), 5.37 (s, 2H), 4.23 (m, 1H), 3.97 (m, 2H), 3.79 (s, 3H), 2.70 (ABXm, 1H) and 2.66 (ABXm, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 158.6, 157.0, 138.3, 132.4, 130.5, 130.2, 128.8, 128.6, 128.1, 127.8, 114.6, 68.0, 67.5, 52.6, 52.1 and 39.3; IR (KBr) 3300 (m), 1750 (s), and 1250 (s) cm^{-1}; MS(EI), $[M^+]$ at *m*/*z* 341.

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