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A CHIRAL SYNTHESIS OF DAPOXETINE HYDROCHLORIDE, A SEROTONIN RE-UPTAKE INHIBITOR, AND ITS ^{14}C ISOTOPOMER[1]

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SUMMARY

The ^{14}C-isotopomer of dapoxetine-[^{14}C] HCl (*S* (+)-*N*,*N*-dimethyl-α-[2-(1-naphthalenyloxy)ethyl-2-^{14}C]benzenemethanamine hydrochloride, **1a**), a potent serotonin re-uptake inhibitor has been prepared by a chiral synthesis, starting with *tert.*-butyloxyphenylglycine (**3**). Borane reduction, followed by activation of the resulting alcohol **4** as its mesylate **5b**, provided the chiral starting material. The radiolabel was introduced by reaction of **5b** with sodium cyanide-[^{14}C]. The desired product (**1**) was then elaborated from nitrile **6a,b** via a five step synthesis in an overall 19.5% radiochemical yield.

Key words: serotonin re-uptake inhibitor, dapoxetine HCl, LY210448 HCl, carbon 14

INTRODUCTION

S-(+)-*N*,*N*-Dimethyl-α-[2-(1-naphthalenyloxy)ethyl]benzenemethanamine hydrochloride (**1**) (LY210448 HCl, dapoxetine hydrochloride), has recently been shown to be a potent serotonin re-uptake inhibitor.[2] Fluoxetine hydrochloride (**2**), also a serotonin re-uptake inhibitor has been found to be clinically useful in the treatment of depression[3] and has been suggested as having potentially useful activity in the treatment of a wide range of ancillary obsessive compulsive behavioral maladies (i.e. bulemia[4], alcoholism[5], and obesity[4]). Preliminary results have suggested that dapoxetine hydrochloride may be useful for the treatment of eating disorders.[2] As a prelude to potential clinical studies, radiolabeled material was needed to conduct pre-clinical drug metabolism and disposition studies in laboratory animals. We have reported herein, the first synthesis of dapoxetine hydrochloride and its ^{14}C-isotopomer, which proceeds without recourse to resolution of synthetic intermediates.

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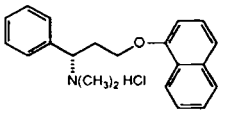
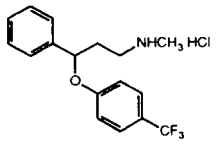


LY210448 HCl, **1a**

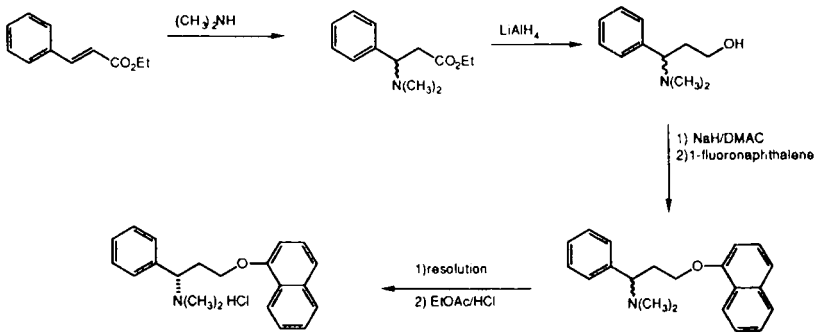


FLUOXETINE HYDROCHLORIDE, **2**

DISCUSSION

The original synthesis of **1a** (Scheme 1) involved Michael addition of dimethylamine to ethyl cinnamate, reduction of the resulting aminoester with lithium aluminum hydride, and finally aryl ether formation by reaction of the amino alcohol with 1-fluoronaphthalene in the presence of NaH/DMF. The resulting racemic product was then resolved to yield the desired *S*-enantiomer.[2] This synthetic sequence presented several problems for the

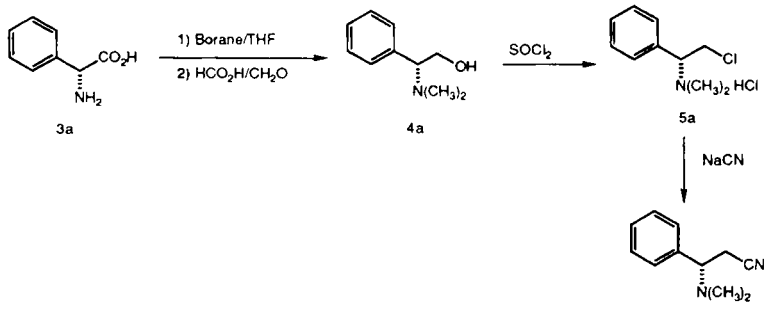
SCHEME I



radiosynthesis: i) the label would be introduced in the first step, ii) the Michael addition resulted in a poor yield, and iii) half of the labeled material was lost as the *R*-isomer (this was especially problematic since the resolution occurs after the last synthetic step). We decided to devise an alternative synthesis, using the readily available chiral precursor *R*-phenylglycine (**3a**). Initially, **3a** was converted to aminoalcohol **4a** by the two step sequence (**Scheme II**) of reduction and Eschweiler-Clarke methylation. Subsequent reaction of **4a** with thionyl chloride, provided the hydrochloride salt of **5a**. Reaction of **5a** under a variety of conditions, with sodium cyanide was unsatisfactory (yields <17%, the major product was acetophenone) . Hayashi *et al.* reported similiar difficulties in the reaction of **5a** with diphenylphosphine[6] (only a 12% yield of the corresponding

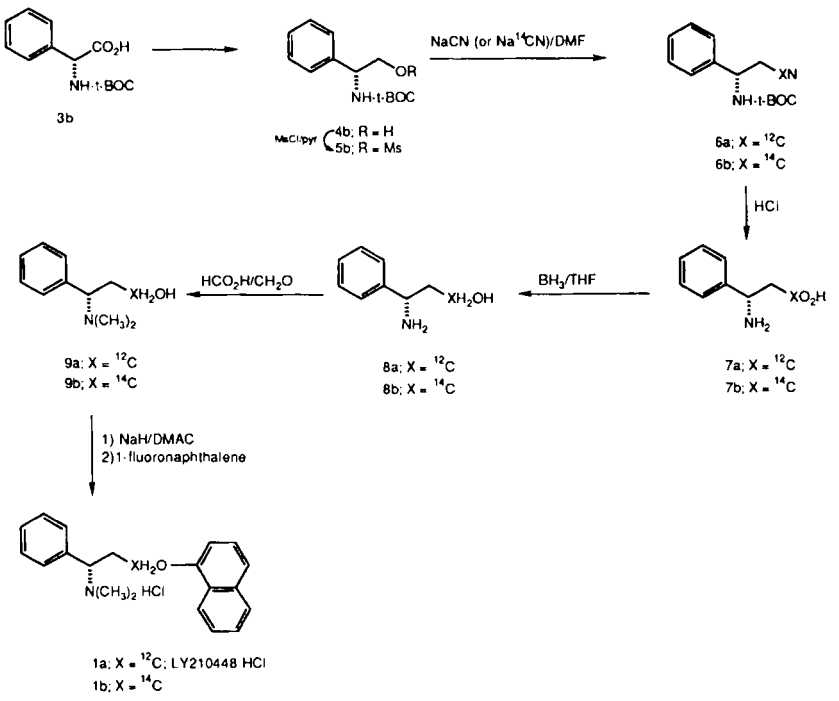
trisubstituted phosphine was obtained); the major product was acetophenone, presumably arising formally from the elimination of HCl and hydrolysis of the resulting enamine upon work-up.

SCHEME II



Alternatively, a similiar sequence starting with *R*-(-)-*tert.*-butyloxycarbonylphenylglycine (**3b**) was used (**Scheme III**). Borane reduction of **3b** provided the *t*-BOC-protected aminoalcohol **4b**. Activation of the *primary* alcohol **4b** by reaction with methanesulfonyl chloride/pyridine, followed by reaction with sodium cyanide (or sodium cyanide-^{14}C) in dimethylformamide provided the pivotal intermediate **6a** (or the corresponding ^{14}C isotopomer **6b**). Kaseda et al. recently reported the synthesis of **7a** from **4b** under similiar

SCHEME III



conditions.[7] Treatment of **6a,b** with concentrated HCl/methanol removed the protecting group and the resulting nitrile was hydrolysed to *S*-β-phenyl-β-alanine **7a,b** in refluxing 6N HCl. Borane reduction of **7a,b**, followed by Eschweiler-Clarke methylation of the intermediate amino alcohol **8a,b**, yielded the penultimate *tertiary* amino alcohol **9a,b**. Reaction of **9a,b** first with sodium hydride in dimethylacetamide, followed by reaction of the intermediate alkoxide with 1-fluoronaphthalene and subsequent reaction with HCl/EtOAc yielded **1a,b**. Thus, **1a** has been prepared enantioselectively from *R-tert.*-BOC-phenylglycine in seven chemical steps in an overall yield of 16.7%. While *R*-phenylglycine is comercially available, it is also conveniently prepared from benzaldehyde by a Strecker synthesis[8], followed by hydrolysis, esterification, and a very efficient second order asymmetric transformation.[9] This would enable one to conveniently radiolabel **1** in alternative positions, using this procedure (3-[^{14}C] starting with benzaldehyde-[^{14}C] or 2-[^{14}C] using Na^{14}CN in the Strecker synthesis). Starting from the mesylate **5b, 1b** has been prepared in five steps in a 19.5% radiochemical yield. The material thus prepared was shown to be identical in all respects with material synthesized using **Scheme I** and the RCP was ≥98.8% (*vide infra*); the specific activity was 35.98 μCi/mg (12.26 mCi/mmol).

EXPERIMENTAL

The sodium cyanide-[^{14}C] was purchased from DuPont NEN. The NMR spectra were obtained on a General Electric QE-300 spectrometer at 300 (^{1}H) and 75 (^{13}C) MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Direct chemical ionization mass spectra (DCI-MS) were recorded on a Nermag R30-10 triple stage quadrapole mass spectrometer; field desorption mass spectra were recorded on a Varian Associates MAT 731 mass spectrometer. High resolution fast atom bombardment mass spectra were obtained from a VG Analytical VG-ZAB-3F mass spectrometer.[10] The optical rotations were determined on a Perkin Elmer 241 polarimeter. Microanalytical data were provided by the Physical Chemistry Research Department of the Lilly Research Laboratories.

Flash chromatography was performed as described by Still *et al.*, using E.M. Science silica gel 60 (230-400 mesh).[11] Unless otherwise noted, the organic extracts were dried over anhydrous sodium sulfate.

Radiochemical purity (RCP) was assessed by autoradiography employing E. Merck silica gel F-254 TLC plates and Kodak BB-5 x-ray film. The radioactive lane was divided, suspended in methanol, and after sonication, the mixture was diluted with Amersham Corp. PCS scintillation cocktail and counted.

R-β-*N-tert.*-Butyloxycarbonylaminobenzeneethanol, 4b:

To a THF solution (80 mL) of *R-tert.*-butyloxycarbonylphenylglycine (10 g, 37.8 mmol) under argon at 0°C was added borane·THF (130 mL x 1M, 130 mmol) at such a rate that

the evolution of gas was not too vigorous. After the addition was complete, the mixture was allowed to warm to room temperature over 5 hr. The reaction was quenched by its portionwise addition to MeOH (100 mL). The solvent was removed *in vacuo* and the resulting white solid was redissolved in MeOH and again concentrated. This procedure was repeated three times to assure complete decomposition of the intermediate borate esters. The resulting white solid was dried *in vacuo*, to yield 9.14 g (97%) of **4b**: ^{1}H-NMR (DMSO/d_6) δ 1.39 (s, 9H, t-Bu), 3.45 (t, J = 6.19 Hz, 2H, CH_2), 4.52 (bq, 1H, CH), 4.76 (t, J = 5.73 Hz, 1H, OH), 7.18-7.30 ppm (m, 5H, aromatic); ^{13}C-NMR (DMSO/d_6) δ 28.17 (CH_3), 64.80 (CH_2OH), 77.64 (CMe_3), 126.58 (aromatic C-4), 126.74 (aromatic C-2 and C-6), 127.90 (aromatic C-3 and C-5), 141.82 (aromatic C-1), 155.15 ppm (C=O); FD-MS, $(M+H)^+$ 238; FT-IR, 3442 cm^{-1}(OH), 1706 cm^{-1} (CONH); $[\alpha]_D$ (MeOH) = -57.75° (c = 8.45). Anal. calc'd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; and N, 5.90. Found: C, 65.73; H, 8.18; and N, 6.15. TLC ($CHCl_3$/MeOH 7:3) showed that the product contained a small amount of unreacted starting material as well as the desired **4b** (R_f = 0.77), stains yellow-brown with ninhydrin.

***R*-β-*N*-*tert*.-Butyloxycarbonylaminobenzeneethanol, Methanesulfonate, 5b:** A pyridine solution (80 mL) of **4b** (5.0 g, 21.1 mmol) under argon was cooled to 0°C and treated dropwise with methanesulfonyl chloride (7.35 g, 6.40 mL, 63.89 mmol). After the addition was complete, stirring was continued at 0°C for 1 hr; then at room temperature for an additional 2 hr. The mixture was poured into ice water (250 mL) and the resulting precipitate was collected by filtration and dried *in vacuo* at room temperature over P_2O_5 to yield 5.48 g (82%) of **5b**: ^{1}H-NMR (DMSO/d_6) δ 1.35 (s, 9H, t-Bu), 3.13 (s, 3H, CH_3S), 4.20-4.25 (m, 2H, CH_2), 4.84-4.86 (m, 1H, CH), 7.18-7.30 ppm (m, 5H, aromatic); ^{13}C-NMR (DMSO/d_6) δ 28.10 (CH_3), 36.78 (CH_3SO_2), 71.25 (CH_2), 78.25 ($\underline{C}Me_3$), 126.93 (aromatic C-2 and C-6), 127.57 (aromatic C-4), 128.35 (aromatic C-3 and C-5), 138.93 (aromatic C-1), 154.99 ppm (C=O); FD-MS, $(M+H)^+$ 316; $[\alpha]_D$ (MeOH) = -28.78° (c = 4.17); FT-IR, 1713 cm^{-1} (CONH). Anal. calc'd for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; and N, 4.44. Found: C, 53.05; H, 6.46; and N, 4.45. The TLC ($CHCl_3$/MeOH 7:3) showed the mesylate **5b** as a single spot (R_f = 0.79, stains pink-orange with ninhydrin), which runs slightly ahead of **4b**.

***R*-3-*N*-*tert*.-Butyloxycarbonylamino-3-phenylpropionitrile, 6a:**

The mesylate **5b** (1.10 g, 3.48 mmol) was dissolved in DMF (15 mL) and treated with sodium cyanide (0.418 g, 8.53 mmol, 2.5 eq) and heated at 80°C. After heating for 1 hr, (the reaction was complete by TLC hexanes/EtOAc 7:3) and allowing to cool to room temperature, the solvent was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water. The aqueous layer was re-extracted with CH_2Cl_2 (5 x 20 mL); the combined organic extracts were washed with saturated aqueous brine (2 x 50 mL), dried, and concentrated *in vacuo* to yield **6a**.

The crude product was purified by flash chromatography (6 in x 40 mm, eluted with 20 mL fractions of 70:30 hexanes/EtOAc) to yield 0.721 g (84%) of **6a:** ^{1}H-NMR ($CDCl_3$) δ 1.44 (s, 9H, t-Bu), 2.83-3.01 (m, 2H, CH_2), 4.96-5.14 (m, 2H, NH and CH, collapses to a bs at 4.91 ppm upon treatment with CD_3OD), 7.25-7.38 ppm (m. 5H, aromatic); ^{13}C-NMR ($CDCl_3$) δ 25.42 (CH_2CN), 28.33 (CH_3), 51.47 (CH), 80.62 ($\underline{C}Me_3$), 117.0 (CN), 126.28 (aromatic C-2 and C-6), 128.73 (aromatic C-4), 129.22 (aromatic C-3 and C-5), 138.70 (aromatic C-1), 154.88 ppm (C=O); FD-MS $(M+H)^+$ 247; UV(EtOH) λ_M (ε_M) 206 nm (10337); FT-IR 2253 cm^{-1}(CN). Anal. calc'd for $C_{14}H_{18}N_2O_2$: C, 68.26; H, 7.36, and N, 11.37. Found: C, 68.56; H, 7.59; and N, 11.30. The TLC (hexanes/EtOAc 7:3) showed the nitrile **6a** as a single spot (R_f = 0.28).

***R*-3-*N*-*tert*.-Butyloxycarbonylamino-3-phenylpropionitrile-[1-^{14}C], 6b:**

The mesylate **5b** (1.62 g, 5.13 mmol) was dissolved in DMF (15 mL). To this solution was added sodium cyanide-[^{14}C] (0.0464 g, 100 mCi, 52.8 mCi/mmol, 1.89 mmol) in DMF (20 mL), followed by 0.205 g (4.18 mmol) of carrier sodium cyanide. The mixture was then stirred at 65°C for 3 hr. After allowing to cool to room temperature, the solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was re-extracted with CH_2Cl_2 (5 x 20 mL); the combined organic extracts were washed with saturated aqueous brine (2 x 50 mL), dried, and concentrated *in vacuo* to yield 1.41 g of crude **6b**.

The crude product was purified by flash chromatography (6 in x 40 mm, eluted with 20 mL fractions of 70:30 hexanes/EtOAc) to yield 0.733 g (58%) of **6b,** which was one spot co-eluting with **6a** by TLC (70:30 hexanes/EtOAc).

R-3-Amino-3-phenylpropionic Acid, Hydrochloride Salt, 7a:

A methanolic solution (2.5 mL) of nitrile **6a** (0.220 g, 0.89 mmol) was treated with 12N HCl (2.5 mL). After the gas evolution (isobutylene and carbon dioxide from the *tert.*-BOC removal) had subsided, the mixture was refluxed for five hr. The solvent was removed *in vacuo*; TLC ($CHCl_3$/MeOH 7:3) of the residue showed a mixture of products, one running slightly behind (R_f = 0.55) the starting nitrile **6a** (R_f = 0.86), and the other at a considerably lower R_f. FD-MS showed major peaks at m/z 165 and 166, suggesting a mixture of the desired acid **7a** and the corresponding carboxamide.

The white crystalline residue was redissolved in 6N HCl (5 mL), heated at reflux for five hours, and then allowed to cool to room temperature. The mixture was concentrated *in vacuo* to yield **7a** (0.160g, 88%): TLC (EtOAc/MeCN/H_2O/HOAc, 21:7:7:9, R_f = 0.55); $[\alpha]_D$ (1N HCl, c = 3.28) = 4.86; ^{1}H-NMR (D_2O/DCl) δ 2.87–3.07 (m, 2H, CH_2CO_2H), 4.61 (bt, 1H, J = 7.11 Hz, $CHNH_2$), 7.30 ppm (s, 5H, aromatic); ^{13}C-NMR (D_2O/DCl) δ 37.63 (CH_2), 51.49 ($CHNH_2$), 127.06 (aromatic C-2 and C-6), 129.42 (aromatic C-3 and C-5), 129.69 (aromatic C-4), 135.07 (aromatic C-1), 173.32 ppm (C=O); UV(EtOH) $\lambda_M(\varepsilon_M)$ 206 nm (8169); FD-MS $(M+H)^+$ 166. Anal. calc'd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.73; H, 6.58; N, 8.24.

R-3-Amino-3-phenylpropionic Acid-[1-^{14}C], Hydrochloride Salt, 7b:

The nitrile **6b** (0.733 g, 2.98 mmol) was dissolved in a minimum amount of MeOH and 14 mL of concentrated HCl was added (a vigorous evolution of gas ensued). After the gas evolution was complete and the mixture was concentrated *in vacuo*; the white crystalline residue was redissolved in 6N HCl (15 mL) and heated at reflux for 6 hr. No significant hydrolysis had taken place (TLC, 7:3 $CHCl_3$/MeOH showed mainly starting material with a small amount of slower moving material, which was presumeably the intermediate amide), so an additional 5 mL of 6N HCl was added and heating was continued for an additional 8 hr (TLC, 7:3 $CHCl_3$/MeOH , showed complete loss of starting material). The aqueous solution was concentrated *in vacuo*. The residue was redissolved in methanol and reconcentrated to yield 0.764 g of the crude product (contaminated with NH_4Cl). TLC (EtOAc/MeCN/H_2O/HOAc 21:7:7:9) showed a major component corresponding to the desired acid **7b** (R_f = 0.55, stains brown with ninhydrin) along with a minor component

moving slightly ahead (R_f = 0.66, stains yellow with ninhydrin) which corresponds to the intermediate amide.

S-γ-Aminobenzenepropanol, 8a:

The crude amino acid **7a** (0.081 g, 0.40 mmol) was suspended in THF (2 mL) at 0°C under argon and treated by the dropwise addition of borane·THF (1M x 3 mL, 3 mmol). After stirring for 30 min in the cold, stirring was continued at room temperature for 5 hr. The reaction was quenched by adding the reaction mixture portionwise to MeOH (50 mL). After the gas evolution had ceased, the solvents were removed *in vacuo*. The residue was redissolved in MeOH (50 mL) and reconcentrated (this exchange was repeated three times); the resulting residue was dissolved in CH_2Cl_2 (5 mL) and washed with 1N NaOH (5 mL). The aqueous layer was re-extracted with CH_2Cl_2 (5 x 10 mL); the combined organic extracts were washed with saturated brine (2 x 20 mL), dried, and concentrated to yield **8a** (0.050 g, 83%). TLC (CH_2Cl_2/MeOH/conc. NH_4OH 90:10: 1, R_f = 0.25) showed a single spot and the material was used without any further purification; ^{1}H-NMR ($CDCl_3$) δ 1.82-1.92 (m, 2H, CH_2), 2.60 (bs, 2H, NH_2), 3.75-3.87 (m, 2H, CH_2OH), 4.11 (dd, 1H, J = 5.25 and 5.41 Hz, CH), 5.28 (s, 1H, OH), 7.30 ppm (m, 5H, aromatic); ^{13}C-NMR ($CDCl_3$) δ 39.92 (CH_2), 55.92 (CH), 61.61 (CH_2OH), 125.80 (aromatic C-2 and C-6), 127.12 (aromatic C-4), 128.67 (aromatic C-3 and C-5), 146.10 ppm (aromatic C-1); UV(EtOH) λ_M (ε_M) 257.8 (172), 205.6 nm (7339); $[\alpha]_D$ (MeOH, c = 18) = 4.66; DCI-MS $(M + H)^+$ 152. HR FAB-MS calcd for $C_9H_{13}NO$ + H: 152.1075. Found: 152.1062.

S-γ-Aminobenzenepropanol-[1-^{14}C], 8b:

The crude amino acid **7b** (0.764 g) was suspended in THF (15 mL) at 0°C and treated by the dropwise addition of borane·THF (1M x 25 mL, 25 mmol). After stirring for thirty minutes in the cold, stirring was continued at room temperature overnight whereupon, most of the suspended material dissolved. The reaction was quenched by the portionwise addition to MeOH (50 mL). After the gas evolution had ceased, the solvents were removed *in vacuo*. The residue was redissolved in MeOH (50 mL) and reconcentrated (this procedure was repeated three times); the resulting residue was dissolved in CH_2Cl_2 (10 mL) and washed with 1N NaOH (10 mL). The aqueous layer was re-extracted with CH_2Cl_2 (4 x 10 mL); the combined organic extracts were washed with saturated brine (2 x

20 mL), dried, and concentrated to yield **8b** (0.395 g, 88%). TLC (CH_2Cl_2/MeOH/conc. NH_4OH 90:10:1) showed a single spot co-migrating with **8a**.

S-(+)-γ-N,N-(Dimethylamino)benzenepropanol, 9a:

The *primary* aminoalcohol **8a** (0.099 g, 0.656 mmol) was converted to its HCl salt by dissolving in ethanolic HCl and concentration *in vacuo*. The crude residue was dissolved in formic acid (2.88 mL), treated with aqueous formaldehyde solution (37%, 4.6 mL), and heated to reflux. After 5 hr, the NMR of an aliquot, showed that the reaction mixture was mostly the mono-methyl derivative (δ 2.0 ppm versus δ 2.2 ppm for the dimethyl). After an additional 24 hr reflux, NMR showed that the reaction still was not complete, so heating was continued overnight (16 hr). The mixture was chilled to 0°C and sodium hydroxide (0.450 mL x 5N) was added. The mixture was extracted with methylene chloride (5 x 40 mL). The combined organic extracts were washed with saturated brine (2 x 25 mL), dried, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (eluted in 20 mL fractions with CH_2Cl_2/MeOH/conc. NH_4OH 90:10:1) to yield **9a** as a yellow oil (0.050g, 49%):TLC (single spot on CH_2Cl_2/MeOH/conc. NH_4OH 90:10:1, $R_f = 0.36$) ; ^1H-NMR ($CDCl_3$) δ 1.65-1.72 (m, 1H, CH_2), 2.37-2.45 (m, 1H, CH_2), 2.19 (s, 6H, $N(CH_3)_2$), 3.74-3.85 (m, 3H, CH and CH_2OH), 7.12-7.37 ppm (m, 5H, aromatic); ^{13}C-NMR ($CDCl_3$) δ 32.18 (CH_2), 41.06 (CH_3), 63.28 (CH_2OH), 70.06 (CH), 127.6 (aromatic C-4), 127.98 (aromatic C-2 and C-6), 128.88 (aromatic C-3 and C-5), 135.89 ppm (aromatic C-1); UV(EtOH) λ_M (ε_M) 205 (8505); $[\alpha]_D$ (MeOH, c = 3.8) = 17.89; DCI-MS $(M + H)^+$ 180. HR FAB-MS calcd for $C_{11}H_{17}NO$ + H: 180.1388. Found: 180.1376.

S-(+)-γ-N,N-(Dimethylamino)benzenepropanol-[1-^{14}C], 9b:

The *primary* aminoalcohol **8b** (0.395 g, 2.98 mmol) was dissolved in EtOAc (20 mL) and treated with 0.4M HCl/EtOAc (20 mL). A white gummy solid formed; sufficient MeOH was added to redissolve the salt and the resulting solution was evaporated under reduced pressure. The residual white solid was dissolved in formic acid (13 mL) , treated with 37% aqueous formaldehyde solution (21 mL), and heated under reflux for 48 hr. After allowing to cool to room temperature, the mixture was made basic (pH 12) with 5N NaOH and extracted with CH_2Cl_2 (5 x 25 mL). The combined organic extracts were washed with

saturated brine (2 x 25 mL), dried, and concentrated *in vacuo* to yield 0.720 g of crude **9b** as an oil. Purification by flash chromatography (eluted in 20 mL fractions with CH_2Cl_2/MeOH/conc. NH_4OH 90:10:1) provided **9b** as a yellow oil (0.275 g, 52%). TLC (CH_2Cl_2/MeOH/conc. NH_4OH 90:10:1) showed **9b** was a single spot co-eluting with **9a**.

S(+)-*N*,*N*-Dimethyl-α-[2-(1-naphthalenyloxy)ethyl-[2-^{14}C]]benzene-methanamine, Hydrochloride Salt, 1b:

The amino alcohol **9b** (0.275 g, 1.54 mmol) was dissolved in DMAC (20 mL) under argon. To this mixture was added a 60% mineral oil dispersion of sodium hydride (0.239 g, 5.98 mmol) and the resulting mixture was heated at 65°C (the reaction mixture turned yellow-brown). After heating at 65°C for 1 hr, 1-fluoronaphthalene (0.20 mL, 1.82 mmol) was added all at once. The external temperature was raised to 100°C and heating was continued for 2 hr (the reaction mixture became a deep reddish-purple). Stirring was then continued at room temperature overnight. MeOH (*ca.* 2 mL) was added to destroy the excess sodium hydride and the mixture was poured into water (50 mL). The mixture was extracted with Et_2O (5 x 20 mL). The combined ethereal extracts were washed with water (50 mL) and brine (50 mL), dried, and concentrated *in vacuo*. The crude product (0.650 g) was purified by flash chromatography (6 in. x 40 mm, eluted in 20 mL fractions with hexanes/EtOAc 2:1) to yield 0.388 g (83%) of the desired free base. This material was mixed with 0.189 g of non-radiolabeled free base (LY210448) and dissolved in ethyl acetate (8 mL). The resulting solution was treated dropwise with 0.4M HCl/EtOAc (4.7 mL). After stirring for a short time, a white crystalline solid formed. The resulting suspension was stirred at room temperature overnight and the filtered to yield **1b** (0.542 g, 84%): $[\alpha]_D$ (MeOH, c = 2.18) = 135.78°.This material was shown to be identical in all respects with material synthesized using **Scheme I**; **1b** co-migrated with **1a** by TLC using MeOH/EtOAc/conc. NH_4OH (R_f = 0.67, RCP 99.8%) and $CHCl_3$/i-PA/conc. NH_4OH 95:5:0.5 (R_f = 0.46, RCP 98.8%). The specific activity was 35.98 μCi/mg (12.26 mCi/mmol).

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