AN ASYMMETRIC SYNTHESIS OF DULOXETINE HYDROCHLORIDE, A MIXED UPTAKE INHIBITOR OF SEROTONIN AND NOREPINEPHRINE, AND ITS C-14 LABELED ISOTOPOMERS[1]

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SUMMARY

Two ^{14}C-isotopomers of duloxetine HCl (*S* -(+)-*N*-methyl-3(1-naphthalenyloxy)-3(2-thiophene)propanamine hydrochloride), a potent mixed serotonin/norepinephrine uptake inhibitor have been prepared by an asymmetric synthesis. The palladium catalyzed cross-coupling of 2-thienoyl chloride (**3c**) (or its [carbonyl-^{14}C] isotopomer **3d**) with vinyl tri-*n*-butylstannane, followed by addition of HCl afforded the key pro-chiral intermediate chloroketone (**5a,b**). Chiral reduction with borane in the presence of the appropriate oxazaborolidine catalyst (**14a or b**) provided the *S*-chloroalcohol (**7a**) and its ^{14}C-labeled counterpart **7b** or the analogous *R*-chloroalcohol (**6**). Activation of **7a,b** by reaction with NaI/acetone, followed by reaction of the corresponding iodoalcohol with methylamine yielded the penultimate aminoalcohols (**8a,b**). Formation of the alkoxide with NaH, followed by reaction with 1-fluoronaphthalene yielded duloxetine or its ^{14}C-labeled isotopomer **9**. Alternatively, reaction of **6** with 1-naphthol-[1-^{14}C] under Mitsunobu conditions afforded arylether **10a,b** , which was in turn activated by reaction with NaI/acetone. Subsequent reaction of **10c,d** with methylamine followed by salt formation yielded duloxetine or its naphthalene-labeled isotopomer (**13**) as their HCl salts .

Key words: mixed serotonin/norepinephrine uptake inhibitor, duloxetine HCl, carbon 14, LY248686

INTRODUCTION

Fluoxetine and tomoxetine are both neuronal uptake inhibitors, which have distinctly different mechanisms of action.[2] While fluoxetine selectively inhibits the neuronal uptake of serotonin (5-HT), tomoxetine selectively blocks the uptake of norepinephrine (NE). (±)-*N*-Methyl-3(1-naphthalenyloxy)-3(2-thiophene)propanamine maleate (LY227-942, the racemate of duloxetine) was shown by Wong *et al.* to be a competetive inhibitior of the uptake of 5-HT and NE both *in vitro* and *in vivo*.[3] In radioligand binding studies, LY227942 possessed only weak affinity for a variety of other neuronal receptors. Krushinski *et al.* later reported that the (+)-enantiomer (duloxetine, LY248686) was slightly more potent than the (-)-enantiomer (LY248685) as a 5-HT uptake inhibitor, while equipotent as an inhibitor of NE uptake.[4] Duloxetine·HCl was chosen for clinical

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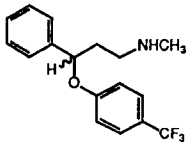
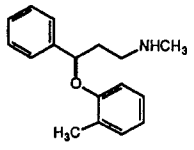
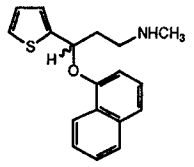
evaluation. In order to support the evaluation of duloxetine·HCl, radiolabeled material was needed for drug metabolism and disposition studies in both humans and laboratory animals. Deeter *et al.* recently reported on an asymmetric synthesis of duloxetine and the determination of its absolute stereochemistry.[5] Radiolabeled material has been prepared



FLUOXETINE



TOMOXETINE



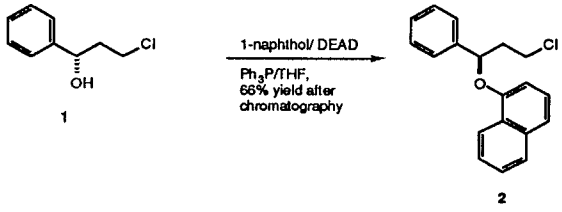
LY227942

by this route ([1- and 3-^{14}C])[6] although the route was somewhat cumbersome and the yields were variable. Preliminary studies concerning the stability of duloxetine indicated that under acidic conditions, duloxetine decomposed to form 1-naphthol as well as a number of other compounds[7]. In order to follow the metabolism and disposition of 1-naphthol which might be potentially formed *in vivo*, material radiolabeled in the naphthalene moiety was needed. Additional material labeled in the 3-position was also required. Our plan was to devise a synthetic sequence which would allow the synthesis of both of these isotopomers of duloxetine from a common intermediate and at the same time avoid the preparation of 1-fluoronaphthalene-[1-^{14}C]. The results reported herein, detail the synthetic route that enabled us to accomplish this task. This reaction path, would also allow for the synthesis of LY248685-[3-^{14}C] if needed as well.

DISCUSSION

Corey and Reichard have described an enantioselective synthesis of the *R*-enantiomer of fluoxetine; the pivotal step in that synthesis was the oxazaborolidine catalyzed borane reduction of γ-chloropropiophenone to afford the corresponding *R*-chloroalcohol.[8] Gao and Sharpless previously had described the syntheses of the pure enantiomers of fluoxetine and tomoxetine, from the common intermediate *S*-3-phenyl-1,3-dihydroxypropane.[9] One of the key steps in these syntheses was the Mitsunobu reaction between 2-methylphenol (or 4-trifluoromethylphenol) and *S*-3-phenyl-3-hydroxypropyl methanesulfonate. To test the suitability of this protocol for the synthesis of naphthyl ethers, *S*-3-chloro-1-phenyl-1-propanol (**1**) was treated with 1-naphthol in the presence of diethyl azodicarboxylate (DEAD). The corresponding naphthyl ether **2** was obtained in 66% yield, after chromatography (Scheme I).

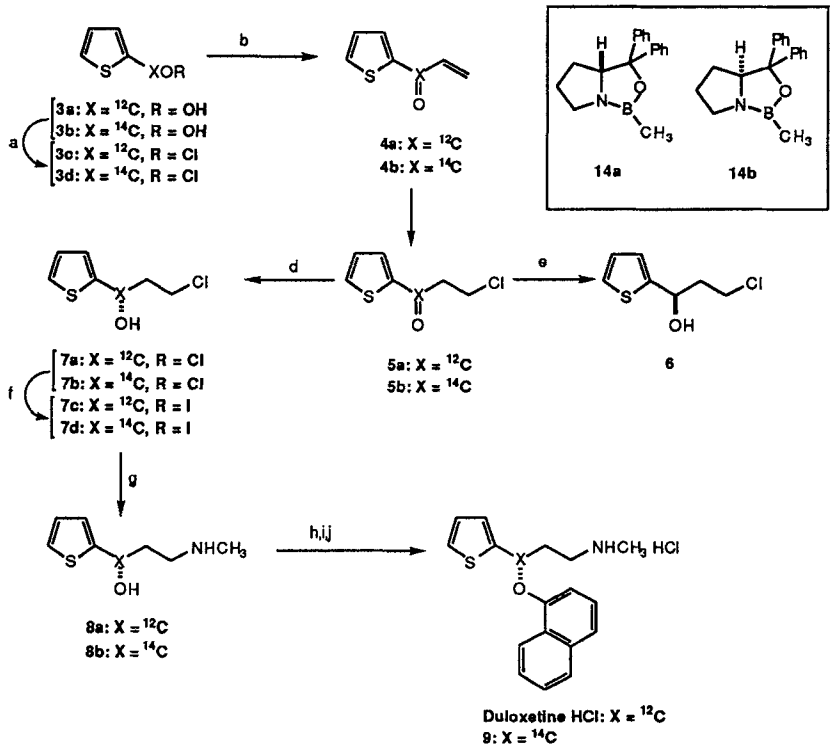
SCHEME I



Although the synthesis of 3-chloro-1-(2-thienyl)-propanone (**5a**) has been reported,[10] the preparation was not amenable to radiosynthesis. It was envisioned that **5a,b** could readily be prepared from the vinyl ketone **4a,b**, which in turn could be synthesized from the palladium catalyzed cross-coupling of vinyl tri-n-butylstannane and thienoyl chloride (**3c,d**) using the Stille protocol.[11] This would enable the use of thiophene-2-carboxylic-[carbonyl-^{14}C] acid (**3b**) as one of the radioactive starting materials.

Indeed, reaction of thienoyl chloride (**3c**) (or its carbonyl-labeled ^{14}C isotopomer **3d**, prepared *in situ* by reaction of thiophene-2-carboxylic acid (**3a,b**) with oxalyl chloride) with vinyl tri-*n*-butylstannane/catalytic benzylchloro-*bis*-(triphenylphosphine)palladium^{II} in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (alternatively named dimethyl-propyleneurea or DMPU), provided vinyl ketone **4a** (or its [carbonyl-^{14}C] analog **4b**) in reasonable yield after chromatography (Scheme II). Reaction of **4a,b** with anhydrous hydrogen chloride in ether yielded the chloroketone **5a,b** which slowly decomposed in the presence of silica gel and was therefore used without any further purification. Borane

SCHEME II

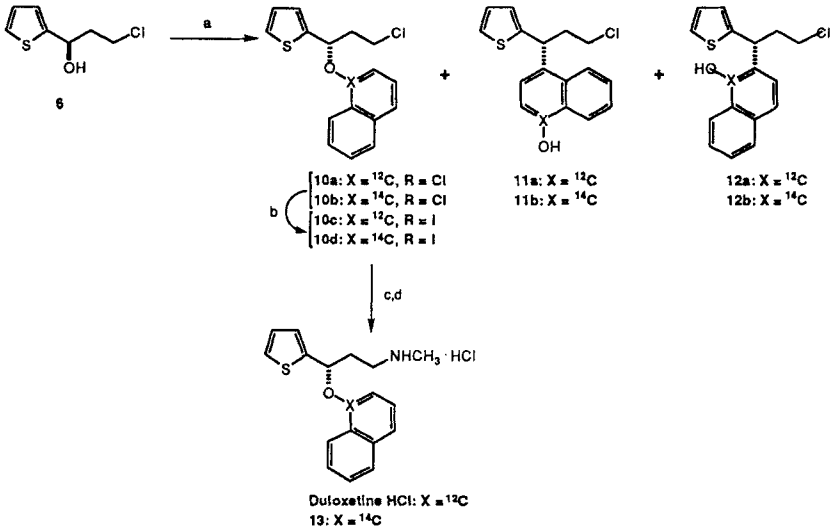


Reagents and conditions: (a) $(COCl)_2$/$PhCH_3$/trace DMF; (b) vinyl tri-n-butylstannane/$Bn(Ph_3P)_2ClPd(II)$/DMPU/60°C; (c) HCl/Et_2O/0°C; (d) BH_3 (THF)/**14a**/0°C; (e) BH_3 (THF)/**14b**/0°C; (f) NaI/acetone/reflux (g) CH_3NH_2/THF/60°C; (h) NaH/DMAC; (i) 1-fluoronaphthalene; (j) HCl/EtOAc

reduction of **5a,b** in the presence of catalytic oxazaborolidine **14a**, yielded the *S*-chloroalcohol **7a,b**. Reaction of **7a,b** with NaI/acetone, followed by reaction of the resulting iodoalcohol **7c,d** with methylamine/THF at room temperature yielded aminoalcohol **8a,b**. The alkoxide of **8a,b**, formed by reaction with NaH/DMAC, was in turn reacted with 1-fluoronaphthalene. Subsequent reaction with HCl/EtOAc yielded duloxetine HCl (or its 3-^{14}C isotopomer **9**). Thus **9** was prepared in six steps in an overall radiochemical yield of 31%. The specific activity was 16.33 μCi/mg (5.43 mCi/mmol) and the radiochemical purity was ≥99.5% (*vide infra*). None of the undesired enantiomer (LY248685) was detected in the final product as assessed by chiral HPLC.

Alternatively, borane reduction of **5a**, in the presence of catalytic oxazaborolidine **14b** yielded the *R*-chloroalcohol **6**. Subsequent reaction of **6** with 1-naphthol (or 1-naphthol-[1-^{14}C]) in the presence of triphenylphosphine and DEAD yielded a complex mixture of products (Scheme III). Even when a large excess of **6** was used, unreacted 1-naphthol was recovered in addition to the desired naphthyl ether **10a,b** and the products of carbon alkylation of 1-naphthol (**11a,b and 12a,b**). Following separation of the components by flash chromatography, **10a,b** was converted to the corresponding iodoether **10c,d** by reaction with NaI/acetone. The iodoether (**10c,d**) was reacted in a closed vessel with a large excess of methylamine in THF at 60°C and then reacted with HCl/EtOAc to afford duloxetine HCl or its [1-naphthyl-^{14}C] isotopomer **13**. Although **13** was prepared in only *ca.* 1% overall radiochemical yield, alternative routes would have necessitated a laborious synthesis of 1-fluoronaphthalene-[1-^{14}C]. The specific activity of **13** was 13.3 μCi/mg (4.03 mCi/mmol). The radiochemical purity was ≥ 99.1% (*vide infra*). No LY248685 was observed in the final product.

SCHEME III



Reagents and conditions: (a) 1-naphthol or 1-naphthol-[1-^{14}C]/Ph_3P/DEAD/THF/0°C; (b) NaI/acetone/reflux (c) CH_3NH_2/THF/55-60°C; (d) HCl/EtOAc

EXPERIMENTAL

Thiophene-2-carboxylic-[carbonyl-^{14}C] and 1-naphthol-[1-^{14}C] were purchased from American Radiolabeled Chemicals, Inc. The NMR spectra were obtained on a General Electric QE-300 spectrometer at 300 (^{1}H) or a Bruker AMX500 spectrometer at 500 MHz[12]. 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.[13] The optical rotations were determined on a Perkin Elmer 241 polarimeter. Microanalytical data were provided by the Chemistry and Biotechnology 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).[14] Unless otherwise noted, the organic extracts were dried over anhydrous magnesium sulfate. Thin-layer chromatography was performed on E. Merck silica gel F-254 plates.

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 DuPont Aquassurescintillation cocktail and counted. Radiochemical Purity was further assessed by HPLC by collecting the eluant at 30 sec intervals; the samples were diluted with DuPont Aquassure and counted.

S-(-)-3-Chloro-1-phenyl-1-(1-naphthalenyloxy)propane (2): Chloroalcohol **1** (1.0 g, 5.88 mmol), 1-naphthol (0.848 g, 5.88 mmol), and triphenylphosphine (1.54 g, 5.88 mmol) were dissolved in THF (25 mL). The mixture was stirred under argon at room temperature and treated with diethyl azodicarboxylate (DEAD, 0.926 mL, 5.88 mmol). After stirring overnight, the mixture was concentrated *in vacuo*. The residue was dissolved in ether and the triphenylphosphine oxide was allowed to crystallize. The crystals were collected by filtration and the residue was concentrated. The residue was purified by flash chromatography; the product was eluted with pentane/ether (50:1) in 10 mL fractions. Fractions 23-28 were combined and concentrated to yield **2** (0.881 g, 50.6%) as a clear viscous oil: ^{1}H-NMR ($CDCl_3$) δ 2.15 and 2.62 (2H, m, 2-CH_2), 3.63 and 3.90 (2H, m, CH_2Cl), 5.60 (1H, m, CH), and 6.61-8.41 (12H, m, aromatic); DCI-MS $[M+H]^+$ 297.

1(2-Thienyl)-2-propen-1-one (4a): Thiophene-2-carboxylic acid (**3a**, 12.8 g, 100 mmol) was suspended in toluene (260 mL) and treated dropwise with oxalyl chloride (25.2 g, 17.3 mL, 200 mmol) The mixture gradually darkened and **3a** dissolved. The mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The dark purple residual oil was redissolved in DMPU (50 mL) and vinyl-*tri-n*-butylstannane (31.9 g, 29.3 mL, 100 mmol) was added along with benzylchloro-*bis*-(triphenylphosphine)-palladium^{II} (20 mg). The mixture was stirred at 60-65°C for 3.5 hr whereupon a finely divided black precipitate of Pd^o was deposited. The mixture was poured into water (300 mL) and extracted with ether/pentane (1:1, 50 mL x 6). The combined organic extracts were washed with water (100 mL x 3), dried, and concentrated *in vacuo*.. The residue

was purified by flash chromatography eluting first with pentane to remove the chloro-*tri*-*n*-butylstannane and then with pentane/ether (9:1) to yield **4a** as a yellow oil (8.8 g, 63.7%): ^{1}H-NMR ($CDCl_3$) δ 5.87 (1H, dd, J = 1.35, 10.4 Hz, vinyl proton *cis* to thienyl), 6.50 (1H, dd, J = 1.35, 15.6 Hz, vinyl proton *trans* to thienyl), 7.06 (1H, dd, J = 10.4, 15.6 Hz, vinyl proton geminal to thienyl), 7.15 (1H, dd, J = 4, 5.3 Hz, C4-thienyl), 7.67 (1H, d, J = 5.3 Hz, C5-thienyl), and 7.73 (1H, d, J = 4 Hz, C3-thienyl); DCI-MS: M^+ 138, 111 (M - $CH{=}CH_2$); TLC 9:1 pentane/ether, R_f = 0.33.

1(2-Thienyl)-2-propen-1-one-[1-^{14}C] (4b): Thiophene-2-carboxylic-[carbonyl-^{14}C] acid (0.616 g, 4.82 mmol, sp. act. 20.7 mCi/mmol, 100 mCi) in toluene (15 mL) was treated with oxalyl chloride (0.9 mL). The resulting acyl chloride was reacted with vinyl-*tri*-*n*-butylstannane (1.4 mL) in the presence of benzylchloro-*bis*-(tri-phenylphosphine)palladium^{II} (10 mg) as described above to yield **4b** (0.460 g, 69%) as a pale yellow oil. This material co-eluted with **4a** on TLC 9:1 pentane/ether.

1(2-Thienyl)-3-chloropropan-1-one (5a): An ether solution (25 mL) of **4a** (3.0 g, 21.7 mmol) was rapidly added to a HCl/ether (prepared by bubbling anhydrous HCl through ether for 2 min) solution (25 mL). After stirring the mixture for 15 min, TLC (toluene) showed the disappearance of starting material (R_f = 0.26) and the formation of a new product (R_f = 0.36). The mixture was concentrated *in vacuo* to yield **5a** (3.78 g, 100%): ^{1}H-NMR ($CDCl_3$) δ 3.38 (2H, t, J = 6.7 Hz, CH_2Cl), 3.90 (2H, t, J = 6.7 Hz, $COCH_2$, 7.14 (1H, q, J = 3.75 4.89 Hz, C4-thienyl), 7.67 (1H, d, J = 4.89 Hz, C5-thienyl), and 7.73 (1H, d, J = 3.75 Hz, C3-thienyl); DCI-MS $[M+H]^+$ 175, 139 (M - HCl), 111 (M - CH_2CH_2Cl).

1(2-Thienyl)-3-chloropropan-1-one-[1-^{14}C] (5b): Utilizing the procedure described above for the preparation of **5a**, **5b** was prepared in quantitative yield from **4b** (0.460 g, 3.33 mmol). The ^{14}C-labeled material co-eluted with **5a** on TLC (toluene).

***R*-(+)-3-Chloro-1(2-thienyl)-1-propanol (6)**: Oxazaborolidine **14b** (0.139 g, 0.5 mmol), prepared according to Corey et al. , was dissolved in anhydrous THF (5 mL) and chilled to 0°C. The stirred solution was treated with BH_3·THF (1*M* in THF, 3 mL, 3 mmol) whereupon a THF solution (40 mL) of **5a** (0.870 g, 5 mmol) was added dropwise over 0.5 hr. The resulting mixture was stirred for an additional 1 hr at 0°C and then quenched by the dropwise addition of MeOH (3 mL). The reaction mixture was concentrated *in vacuo* and the residue was redissolved in MeOH (3 mL) and reconcentrated. The residue was dissolved in ether (5 mL) and filtered. The filtrate was purified by flash chromatography, eluting with 20 mL fractions of pentane/ether (4:1) to yield **6** (0.534 g, 61%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 2.26 (3H, m, OH and 2-CH_2), 3.60 and 3.78 (2H, m, CH_2Cl), 5.18 (1H, m, CH), 6.95 (2H, m, C2 and C4-thienyl) and 7.30 (1H, dd, C5-thienyl); DCI-MS $[M+H]^+$ 177, (M-H_2O) 159; $[\alpha]_D(25°)$ = +17.12° (MeOH, c = 4.44); TLC (4:1 pentane/ether) R_f = 0.285; Anal. calc'd for C_7H_9OSCl: C, 47.59; H, 5.14. Found: C, 47.57; H, 5.05.

***S*(-)-3-Chloro-1(2-thienyl)-1-propanol (7a)**: Utilizing oxaborolidine **14a** (0.0973, 0.35 mmol), **5a** (0.520 g, 2.99 mmol), and 1.8 mL of 1*M* BH_3·THF under the conditions described above yielded **7a** (0.455, 86%): ^{1}H-NMR δ 2.28 (3H, m, OH and 2-CH2), 3.58 and 3.75 (2H, m, CH2Cl), 5.21 (1H, m, CH), 6.99 (2H, C2 and C4-thienyl), and 7.27 (1H, dd, C5-thienyl); DCI-MS, M^+ 176, ($M-H_2O$) 159, $M-H_2O$-Cl) 123; $[\alpha]_D(25^o)$ = -11.65° (PrOH, c = 2.06); TLC (4:1 pentane/ether) R_f = 0.285; Anal. calc'd for C_7H_9OSCl: C, 47.59; H, 5.14. Found: C, 47.65; H, 5.14.

***S*(-)-3-Chloro-1(2-thienyl)-1-propanol-[1-^{14}C] (7b)**: Utilizing oxaborolidine **14a** (0.0973, 0.35 mmol), **5b** (0.579 g, 3.33 mmol), and 2.0 mL of 1*M* BH_3·THF under the conditions described above yielded **7b** (0.530, 90%). This material co-eluted with **7a** upon TLC (4:1 pentane/ether).

***S*(-)-3-Iodo-1(2-thienyl)-1-propanol (7c)**: A NaI saturated acetone solution (18 mL) of **7a** (0.352 g, 2.0 mmol) was stirred at reflux (protected from the light) overnight. The mixture was filtered to remove the precipitated NaCl and the filtrate was concentrated *in vacuo*. The residue was dissolved in water (20 mL) and extracted with ether (3 x 10 mL). The combined ether extracts were washed with brine, dried, and concentrated to yield **7c** as a yellow oil (0.534 g, 100%). TLC (7:3 pentane/ether) showed **7c** as a slightly higher R_f spot as compared to **7a**. This material was used without any further purification.

***S*(-)-3-Iodo-1(2-thienyl)-1-propanol -[1-^{14}C] (7d)**: Chloroalcohol **7b** (0.515 g, 2.96 mmol) was treated in refluxing NaI saturated acetone (20 mL) as described above to yield **7d** (0.790 g, 100 %).

***S*(-)-3-N-Methylamino-1(2-thienyl)-1-propanol (8a)**: Methylamine (40% aqueous, 2.2 mL, 20 mmol) was mixed with **7c** (0.534 g, 2.0 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 6 hr. The reaction mixture was concentrated and the residue was partitioned between water and ether. The aqueous layer was treated with 5*N* NaOH (1 mL) and the layers were separated. The aqueous layer was re-extracted with ether (3 x 20 mL); the combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (25 x 170 mm) eluting with 10 mL fractions of CH_2Cl_2/MeOH/NH_4OH (40:10:1) to yield **8a** (0.244 g, 71.5%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 1.92 (2H, m, 2-CH_2), 2.43 (3H, s, NCH_3), 2.89 (2H, m, CH_2N), 5.19 (1H, m, CH), 6.94 (2H, m, thienyl H-3 and H-4), 7.19 (1H, dd, thienyl H-5); $[\alpha]_D$ (35°C) = -12.14 (MeOH, c = 4.12); FAB-MS $[M+H]^+$ 172. The material was a single spot on TLC (CH_2Cl_2/MeOH/ NH_4OH, 40:10:1), R_f = 0.35. HR-FABMS, calc'd for $C_8H_{13}NOS$ + H:172.079611. Found: 172.079700.

***S*-(-)-3-N-Methylamino-1(2-thienyl)-1-propanol-[1-^{14}C] (8b)**: A THF (4 mL) solution of **7d** (0.790 g, 2.96 mmol) was added dropwise to 40% aqueous methylamine with vigorous stirring in the dark. After stirring overnight, the reaction was worked up and

purified as described above to yield **8b** (0.403 g, 81%) as a white solid. This material co-eluted with **8a** on TLC (CH_2Cl_2/MeOH/NH_4OH (40:10:1).

***S*-(+)-*N*-Methyl-3(1-naphthalenyloxy)-3-(2-thiophene)propanamine Hydrochloride (Duloxetine HCl), Method A (Scheme II):** A mineral dispersion of NaH (66%, 0.050g, 1.375 mmol) was washed with pentane (3 mL) and suspended in dimethylacetamide (DMAC). Aminoalcohol **8a** (0.171 g, 1 mmol) was added and the mixture was heated at 60-70°C. After stirring for 40 min, the solution became clear (light yellow-brown) and 1-fluoronaphthalene (0.266 g, 0.2 mL, 1.1 mmol) was added. The temperature was raised to 90°C and stirring was continued for 2 hr. The mixture was poured into water (50 mL) and extracted with ether (3 x 20 mL). The ether extracts were washed with brine (2 x 20 mL), dried, and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with CH_2Cl_2/MeOH/NH_4OH (100:10:1) in 10 mL fractions to yield duloxetine (0.173 g, 58%). The duloxetine was dissolved in EtOAc (1.3 mL) and treated dropwise with 0.44*M* HCl/EtOAc. A white precipitate formed within 5 min. Stirring was continued for 1 hr at room temperature. After chilling to -20°C for an additional hr, the mixture was diluted with ether (10 mL) and filtered. The white solid was washed with fresh ether and dried to yield duloxetine HCl (0.150 g, 45%). This material was combined with duloxetine HCl[5] (0.300 g) and recrystallized from EtOH/ether to yield duloxetine HCl (0.310 g) which was identical to reference material in all respects.[5]

***S*-(+)-*N*-Methyl-3(1-naphthalenyloxy)-3-(2-thiophene)propanamine-[3-^{14}C] Hydrochloride (Duloxetine-[3-^{14}C] HCl, 9), Method A (Scheme II):** A mixture of **8b** (0.400 g, 2.34 mmol) and NaH (0.150 g, 66% mineral oil dispersion washed with 3 mL of hexanes) were heated in DMAC (8 mL) at 63°C for 30 min under nitrogen with stirring, whereupon 1-fluoronaphthalene (0.45 mL, 2.56 mmol) was added. The mixture was heated at 90°C for an additional 3 hr and then worked up and purified as described above to yield duloxetine-[1-^{14}C] (**9**, 0.481 g, 67.2%) as a thick oil. This material co-eluted with reference material on TLC (CH_2Cl_2/MeOH/NH_4OH, 90:10:1). The oil was dissolved in EtOAc (4 mL) and treated dropwise with 3.7 mL of 0.44*M* HCl/EtOAc. After 15 min, a white precipitate was deposited. After stirring for another 30 min, the mixture was cooled to -20°C for 3 hr and filtered. The white solid was washed with ether and dried to yield duloxetine-[1-^{14}C] HCl (0.501 g). This material was mixed with carrier duloxetine HCl (1.5 g) and recrystallized from ethanol/ether to yield diluted duloxetine-[1-^{14}C] HCl (**9**, 1.925 g): DCI-MS $[M+H]^+$ 298, $[(M-HCl)+H]^+$ 262 (base); specific activity 16.33 μCi/mg (5.43 mCi/mmol). The radiochemical purity was ≥ 99.5% as determined in the following TLC systems:

CH_3OH/EtOAc/NH_4OH	95:5:0.5	RCP = 99.7%
CH_2Cl_2/CH_3OH/NH_4OH	90:10:1	RCP = 99.6%
$CHCl_3$/CH_3OH/HOAc	4:86:10	RCP = 99.7%

Radiochemical purity as determined by radio-HPLC on Zorbax CN (250 x 4.6 mm), eluting with 2% aqueous Et_3N (pH adjusted to 7.5 with HOAc)/MeCN (55:45) at a flow rate of 1.5 mL.min was 99.5%. A chiral assay on a Diacel Chiralcel column (4.6 x 250

mm) eluting with 0.2% diethylamine in hexanes/17% *i*-PrOH at a flow rate of 1.0 mL/min and UV detection at 230 nm showed no detectable LY248685 (R_T = 14.6 min). The R_T for duloxetine was 11 min. The method is capable of detecting 0.2% of LY248685.

***S*-3-Chloro-1(2-thienyl)-1(1-naphthalenyloxy)propane (10a):** A stirred solution of **6** (0.407 g, 2.31 mmol), 1-naphthol (0.333 g, 2.31 mmol), and triphenylphosphine (0.788 g, 3.0 mmol) in anhydrous THF (20 mL) was chilled to 0°C and treated dropwise with DEAD (1.40 mL, 3.0 mmol) in THF (5 mL). The mixture was allowed to warm to room temperature and stirring was continued overnight. The solvent was removed *in vacuo* and the residue was redissolved in ether whereupon a precipitate of triphenylphosphine oxide formed. The mixture was filtered; the filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography. The mixture was loaded using 1:1 toluene/pentane; the product was eluted with pentane/ether (30:1) in 20 mL fractions. Fractions 5-12 were combined and rechromatographed to yield **10a** (fractions 11-13, 0.126 g, 18%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 2.43 and 2.80 (2H, m, 2-CH_2), 3.70 and 3.89 (2H, m, CH_2Cl), 5.97 (1H, m, CH), 6.98-8.40 (10H, m, aromatic); DCI-MS $[M+H]^+$ 303; HR-FABMS, calc'd for $C_{17}H_{15}OSCl$: 302.053215. Found: 302.052400; TLC (30:1 pentane/ether) R_f = 0.46.

Fractions 13-18 from the first chromatography and 15-18 from the second were combined to yield 0.158 g (22.6%) of the two products of C-alkylation (**11a** and **12a**) as an inseparable mixture: DCI-MS $[M+H]^+$ 303; HR-FABMS, calc'd for $C_{17}H_{15}OSCl$: 302.053215. Found: 302.054700; TLC (30:1 pentane/ether) R_f = 0.28.

***S*-3-Chloro-1(2-thienyl)1-(1-naphthalenyloxy)propane-[1-naphthalene-^{14}C] (10b):** A mixture of **6** (1.320 g, 7.5 mmol), 1-naphthol-[1-^{14}C] (150 mCi, 20 mCi/mmol, 7.5 mmol), triphenylphosphine (2.56 g, 9.75 mmol) were dissolved in THF (60 mL) and chilled to 0-5°C under argon. The stirred solution was treated dropwise with DEAD (1.54 mL, 9.75 mmol) in THF (15 mL) as described above. After work-up, the crude residue was purified by flash chromatography. The product was eluted with 10 mL fractions of 30:1 pentane/ether. Fractions 10-25 were combined and rechromatographed. Fractions 16-20 were combined to yield **10b** (0.17107 g). Fractions 15 and 21-23 were purified again to yield an additional quantity of **10b** (0.02867 g, total yield 8.8%): ^{1}H-NMR ($CDCl_3$) δ 2.46 and 2.76 (2H, m, 2-CH_2), 3.69 and 3.87 (2H, m, CH_2Cl), 5.94 (1H, t, CH), and 6.91-7.50 (8H, m, aromatic), 7.80 (1H, d, thienyl-H-2), and 8.33 (1H, d, thienyl-H-4); DCI-MS M^+ 302 (304), (M-HCl) (base) 266, (M-C_2H_4Cl) 239; TLC (silica gel) 30:1 pentane/ether, co-eluted with **10a**.

Fractions 26-30 from the first chromatography and 24-35 from the second were combined to yield a mixture of the C-alkylated products **11b** and **12b** (0.07537 g). Although a mixture, the 500 MHz ^{1}H-NMR indicated a clear predominance for only one regioisomer, probably **11b**. 500 MHz ^{1}H-NMR ($CDCl_3$) d 2.21 and 2.42 (2H, m, 2-CH_2), 3.51 and 3.75 (2H, CH_2Cl), 4.99 (1H, m, CH), and 6.59-8.15 (9H, m, aromatic); DCI-MS $[M+H]^+$ 303 (305), (M-C_2H_4Cl) 239.

S-3-Iodo-1(2-thienyl)-1(1-naphthalenyloxy)propane (10c): An acetone (10 mL) solution of **10a** (0.042 g, 0.139 mmol) was saturated with NaI and the resulting solution was stirred at reflux under argon for 16 hr. The mixture was diluted with ether and filtered. The filtrate was concentrated *in vacuo*; the residue was triturated with ether, filtered,and the filtrate concentrated to yield **10c** (0.055 g, 100%) as a yellow oil: ^{1}H-NMR δ 2.51 and 2.82 (2H, m, 2-CH_2), 3.30 and 3.45 (2H, m, CH_2Cl), 5.82 (1H, m, CH), 6.97-7.50 (8H, m, aromatic), 7.82 (1H, m, aromatic), 8.35 (1H, m, aromatic); DCI-MS M^+ 393.

S-3-Iodo-1(2-thienyl)-1(1-naphthalenyloxy)propane-[1-naphthalene-^{14}C] (10d): A NaI saturated acetone solution of **10b** (0.1997 g, 0.661 mmol) was treated as described above to yield **10d** (0.260 g, 100%): DCI-MS $[M+H]^+$ 394/396, (M-C_4H_3S) 311/313, (M-C_2H_4I) 239.

S (+)-*N*-methyl-3(1-naphthalenyloxy)-3(2-thiophene)propanamine (Duloxetine) Method B (Scheme III): Methylamine (40% aqueous, 0.120 mL, 1.39 mmol) and **9b** (0.055 g, 0.139 mmol) were heated at 55-60°C in THF (10 mL) for 24 hr. The flask was tightly stoppered to prevent evaporation of the methylamine. The THF was removed and the residue was purified by flash chromatography (20 x 150 mm), eluting with 10 mL fractions of CH_2Cl_2/MeOH/NH_4OH (90:10:1) to yield duloxetine (0.0207 g, 50%) as a clear oil which was identical in all respects to duloxetine prepared by previously reported methods.

S (+)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thiophene)propanamine-[1-naphthalene-^{14}C] Hydrochloride Salt (Duloxetine-[1-Naphthalene-^{14}C] HCl, 13), Method B (Scheme III): The iodoether **10d** (0.260 g, 0.661 mmol) was dissolved in THF (35 mL) and treated with 40% aqueous methylamine (0.570 mL, 6.61 mmol). The flask was heated at 55-60°C in a tightly stoppered flask for 24 hr. The THF was evaporated and the residue was purified by flash chromatography (40 x 160 mm). The product was eluted with CH_2Cl_2/MeOH/NH_4OH (90:10:1) in 10 mL frac-tions. Fractions 13-17 were combined and concentrated *in vacuo*. The residue was redissolved in EtOAc (1.25 mL) and treated with 0.44 *M* HCl/EtOAc (0.57 mL). After about 15 min, crystals began to form; the mixture was stirred for an additional 1 hr at room temperature and 1 hr at -10°C. The white solid was collected by filtration, washed with fresh EtOAc, then ether and dried to yield **13** (0.0788 g, 36%).

A mixture of **13** (0.079 g) and duloxetine HCl (0.194 g) was recrystallized from absolute EtOH (7 mL) to yield diluted **13** (0.219, 80%): specific activity 14.04 μCi/mg (4.68 mCi/mmol). The radiochemical purity was ≥ 99.1% as determined in the following TLC systems:

$CH_3OH/EtOAc/NH_4OH$	95:5:0.5	RCP = 99.1%
$CH_2Cl_2/CH_3OH/NH_4OH$	90:10:1	RCP = 99.1%
$CHCl_3/CH_3OH/HOAc$	4:86:10	RCP = 99.3%

Radiochemical purity as determined by the HPLC method outlined above was 99.4%; no LY248685 was detected by the aforementioned chiral assay.

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