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Research Article

Synthesis of the carbon-14 labeled isotopomers of (*R*)-*N*-methyl-3-[2-methylphenoxyl]-benzenepropanamine hydrochloride (atomoxetine hydrochloride, LY139603), and two of its metabolites†

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Summary

Carbon-14 labeled Straterra™ (Atomoxetine HCl, LY139603, (-)-*N*-methyl-3-(2-methylphenoxy)-benzenepropanamine hydrochloride), a potent inhibitor of the presynaptic norepinephrine transporter, and two of its major metabolites were synthesized. The key component, *S*-(+)-3-chloro-l-phenyl-l-propanol-[1-^{14}C] was synthesized by Stille coupling of benzoyl chloride-[carbonyl-^{14}C] with vinyl *tri-n*-butylstannane, followed by HCl addition to the vinyl ketone, and asymmetric reduction of the ketone by Corey's CBS reagent. Mitsunobu reaction of this *S*-(+)-3-chloro-l-phenyl-l-propanol-[1-^{14}C] with various phenol derivatives, followed by converting the chloride to amines, gave desired products. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: *S*-(+)-3-chloro-1-phenyl-1-propanol-[1-^{14}C]; LY139603-[^{14}C]; Straterra

Introduction

Straterra™ (Atomoxetine HCl, LY139603, (-)-*N*-methyl-3-(2-methylphenoxy)-benzenepropanamine hydrochloride) is a potent inhibitor of the presynaptic norepinephrine transporter. Atomoxetine has been approved for use as a therapeutic agent for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. The metabolism and disposition of atomoxetine has been extensively examined in a number of

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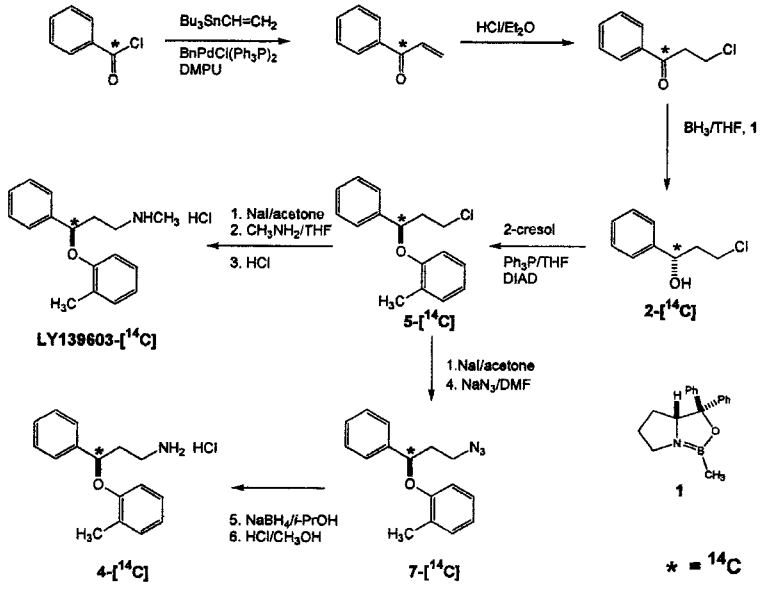
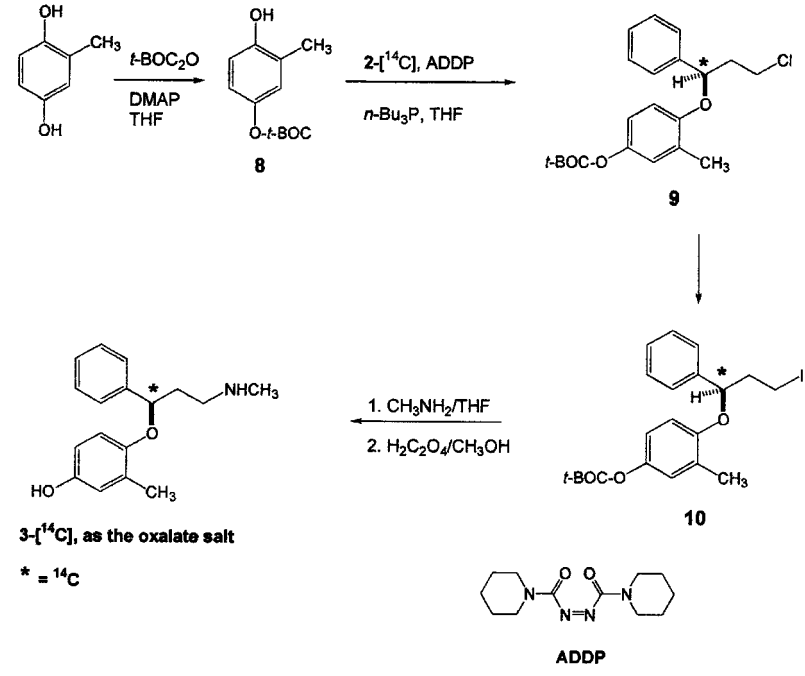
animal species as well as man using its ^{14}C-labeled isotopomer.[1,2] The biotransformation of atomoxetine was similar in the rat and dog, undergoing aromatic ring-hydroxylation, benzylic oxidation (rat only), and *N*-demethylation. The primary oxidative metabolite of atomoxetine was 4′-hydroxyatomoxetine **(3)**, which was subsequently conjugated forming *O*-glucuronide and *O*-sulfate (dog only) metabolites. Smaller amounts of *N-des*-methylatomoxetine **(4)** were also detected. The ^{14}C-isotopomers of **3** and **4** were also prepared for use in the determination of their protein binding. In this paper, we discuss the preparation of these compounds.

Discussion

In 1995, Wheeler and Kuo reported on the synthesis of ^{14}C-labeled duloxetine.[3] In that report, the Stille protocol[4] was used to prepare 1-(2-thienyl)-2-propen-l-one by the reaction of the acyl chloride of thiophene-2-carboxylic acid with vinyl-*tri*-*n*-butylstannane/DMPU in the presence of catalytic benzylchloro-*bis*-triphenyl-phosphine-palladium(II). Addition of HCl/Et_2O, followed by reduction with BH_3 THF/*S*-2-methyl-CBS-oxazaborolidine yielded *R*-(+)-3-chloro-1(2-thienyl)-l-propanol. This chloroalcohol represented a reasonable substrate for the Mitsunobu reaction with 1-naphthol. The model chemistry using the commercially available *R*-(+)-3-chloro-1-phenyl-1-propanol and 1-naphthol in the presence of diethyl azodicarboxylate/Ph_3P worked even better and provided the basis for much of the chemistry presented in this paper.



In the synthesis of atomoxetine, benzoyl-[carbonyl-^{14}C] chloride was reacted as described above with vinyl-*tri*-*n*-butylstannane/DMPU in the presence of catalytic benzylchloro-*bis*-triphenylphosphinepalladium-(II)[4] to yield 1-phenyl-2-propen-l-one-[1-^{14}C]. Addition of HCl/Et_2O, followed by reduction with BH_3THF/*R*-2-methyl-CBS-oxazaborolidine[5] (1), yielded *S*-(+)-3-chloro-l-phenyl-l-propanol-[1-^{14}C] **2** in 46% yield (from benzoic-[carbonyl-^{14}C] acid). Reaction of **2** with 2-cresol/THF in the presence of *di-iso*-propyl azodicarboxylate/Ph_3P yielded *R*-3-chloro-1-phenyl-1-(2-methylphenoxy)-propane-[1-^{14}C] (5) in 52% yield after chromatography. Activation of **5** (by reaction with NaI/acetone) followed by reaction of the iodide **(6)** with methylamine/THF and salt formation yielded atomoxetine-[^{14}C] HCl (LY139693-[^{14}C], 82% yield from **5**). Treatment of **5** with NaN_3/DMF (94%), followed by reduction of the corresponding azide **(7)** with $NaBH_4$/*i*-PrOH and salt formation by reaction with HCl/CH_3OH yielded **4-[^{14}C]** (24% yield for the last two steps).



It was envisioned that 4′-hydroxyatomoxetine **(3)** could be prepared by using the same strategy as was used for the preparation of atomoxetine (reaction of *S*-3-chloro-l-phenyl-1-propanol **(2)** with an appropriately protected 2-methylhydroquinone). The key was to regioselectively protect the 4-hydroxyl in 2-methylhydro-quinone. McGill found that when 2-methylhydroquinone was reacted with *t*-BOC_2O and DMAP in THF, the desired carbonate **8** was obtained in 76% yield.[6] Reaction of **8** with

S-3-chloro-1-phenyl-1-propanol-[1-^{14}C] **(2-[^{14}C])** in the presence of ADDP/*n*-Bu_3P/THF yield **9**. Reaction of **9** with NaI/acetone yielded 10(64%). Reaction of **10** with CH_3NH_2/THF followed by salt formation with oxalic acid/CH_3OH yielded **3-[^{14}C]** oxalate (72% for the last two steps). The analytical results for LY136903-[^{14}C] and its metabolites **(4-[^{14}C]** HCl and **3-[^{14}C]** oxalate are shown in Table 1.

Conclusions

A general and simple method has been developed for the synthesis of a carbon-14 labeled LY139603, a potent inhibitor of the presynaptic norepinephrine transporter, and its metabolites. The key component, *S*-(+)-3-chloro-l-phenyl-1-propanol-[1-^{14}C] **2-[^{14}C]** was synthesized by Stille coupling of benzoyl chloride-[carbonyl-^{14}C], followed by HCl addition to the olefin and asymmetric ketone reduction by Corey's CBS reagent. Mitsunobu reaction of *S*-(+)-alcohol-[^{14}C] with various phenols derivatives, followed by amination of the halides gave the desired products.

Experimental

Benzoic acid-[^{14}C] acid was purchased from ChemSyn Laboratories. NMR spectra were obtained on a General Electric QE-300 nuclear magnetic resonance spectrometer at 300 MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Direct chemical ionization mass spectra (DCI-MS) and electron impact mass spectra (EI-MS) were recorded on a Nermag R30-10 triple stage quadrapole mass spectrometer. Flash chromatography was performed as described by Still *et al.*[7] using E.M. Science silica gel 60 (230–400 mesh). 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,

Table 1. Analytical results

	LY136903-[^{14}C]	**4-[^{14}C]** HCl	**3-[^{14}C]** Ox.
Specific activity in μCi/mg	66.3	66.7	55.8
Radiochemical purity (%)	99.9[a], 100[b]	99.0[b]	99.0[b]
Optical purity (%S)[c]	0.2		
Identity	Co-elutes with standard	Co-elutes with standard	Co-elutes with standard
ES-MS: $[M+H]^+$, m/z	256		

[a] TLC (silica gel): $CH_2Cl_2/CH_3OH/NH_4OH$ (100:10:1), $r_f = 0.37$.
[b] HPLC: Altima Phenyl (4.6 × 250 mm), gradient elution at 1 ml/min. (30% B for 20 min. increasing to 70% B over 10 min. and holding at 70% B for 5 min.) with radiochemical detection (Solvent A = pH 2.0 DEA, Solvent B = CH_3CN).
[c] Chiral HPLC: Chiralcel OD-H eluting with IPA/hexanes (85:15) with 0.2% DEA at 1 ml/min, UV detection at 271 nm.

suspended in methanol, and after sonication, the mixture was diluted with Aquassure™ scintillation cocktail (DuPont NEN) and counted. As a further check of the radiochemical purity, the sample was subjected to radio-HPLC; 30 s samples of the eluent were collected, diluted with Aquassure™ and counted.

Synthesis of (S)-(-)-3-chloro-1-phenyl-1-propanol-[1-^{14}C], ***2-[^{14}C]***

Benzoic acid-[carboxyl-^{14}C] (70 mCi, 55.3 mCi/mmol) and benzoic acid (310 mg, 2.54 mmol) were suspended in 15 ml of toluene and treated with 1 ml of oxalyl chloride and three drops of dimethylformamide. The solution was stirred at room temperature over the weekend (about 70 h). The solution was concentrated; to the residue was added 10 ml of toluene, and the solution was concentrated again. The concentrating step was repeated three times to remove oxalyl chloride completely. The final residue was dissolved in 4 ml of toluene and treated with 1.14 ml of tributyl(vinyl)tin and 50 mg of *tetra-kis*-(triphenylphosphine)palladium(0) and heated for 4 h at 40°C in an oil bath. TLC (SiO_2,10:1 hexanes/ether) indicated the complete consumption of starting material.

The solution was concentrated and the residue was dissolved in 6 ml of ether, added to an ether/HCl solution (20 ml, bubbled with anhydrous HCl for 2 min), stirred at 0°C for 30 min and then at room temperature for 1 h. After storing in the refrigerator overnight, the solution was concentrated and the residue was dried *in vacuo* for 30 min to give crude chloroketone. A mixture of crude ketone (in 10 ml of THF) and (*R*)-2-methyl-CBS-oxazaborolidine (2.5 ml × 1 M in toluene) was concentrated *in vacuo* and redissolved in 10 ml of THF. The solution was cooled in an ice bath under argon, treated dropwise with borane-THF complex (3.8 ml × 1 M in THF) over a period of 50 min, and stirred for another hour thereafter. The excess of borane was destroyed by the dropwise addition of methanol (10 ml) and the resulting solution was concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 4:1 hexanes/ether, twice) to give the desired product **2-[^{14}C]** as a white solid (297 mg, 1.75 mmol, 46% from benzoic acid). It was co-eluted with a non-labeled reference on TLC (SiO_2, 4:1 = hexanes/Et_2O). Proton NMR of non-labeled product: (in $CDCl_3$, ppm) 7.40 (m, 5 H), 5.0 (m, 1 H), 3.8 (m, 1 H), 3.6 (m, 1 H), 2.3 (m, 1 H), 2.1 (m, 1 H), 2.0 (br. S, 1 H).

Synthesis of (R)-3-chloro-1-phenyl-1-[2-methylphenoxy]-propane-[1-^{14}C], ***5-[^{14}C]***

To a THF solution (18 ml) of **2-[^{14}C]** (279 mg, 1.75 mmol) was added 2-methylphenol (*o*-cresol) (239 mg, 2.21 mmol), triphenylphosphine (599 mg, 2.29 mmol) and chilled in an ice bath under argon, Di-*iso*-propyl azodicarboxylate (DIAD, 0.4 ml, 2.0 mmol) was added dropwise over 45 min. The solution

was stirred in the ice bath for another hour then at room temperature overnight. The solution was concentrated *in vacuo* and the residue was stirred in 100 ml of 5% EtOAc in hexanes for 90 min. The white precipitate was filtered and rinsed with 5% EtOAc in hexanes. The combined filtrates were concentrated and the residue was purified by chromatography (SiO_2, hexanes). The desired fractions were pooled and concentrated, and the residue was further dried *in vacuo* to give the product **5-[^{14}C]** (236 mg, 0.91 mmol, 51.9%) as a colorless viscous oil. It was co-eluted with a non-labeled reference on TLC (SiO_2, hexanes). Proton-NMR of non-labeled product: ($CDCl_3$, ppm) 7.4 (m, 5 H), 7.15 (d, 1 H), 7.0 (t, 1 H), 6.85 (t, 1 H), 6.65 (d, 1 H), 5.42 (m, 1 H), 3.85 (m, 1 H), 3.65 (m, 1 H), 2.55 (m, 1 H), 2.3 (M, 1 H), 2.35 (s, 3 H).

Synthesis of (R)-N-methyl-3-[2-methylphenoxy]-benzenepropanamine-[3-^{14}C]-hydrochloride, LY139603-[^{14}C]

A solution of chloride **5** (236 mg, 0.91 mmol) in 50 ml of acetone was refluxed with 5 g of NaI over the weekend (about 68 h). The solution was concentrated and the residue, as a light yellow solid, was dissolved in 20 ml of water and 20 ml of hexanes. The organic layer was separated, washed with water (25 ml × 3), and concentrated to give a colorless oil. HPLC (Zorbax ODS, 3 × 250 mm, 30:70 H_2O/CH_3CN, 0.8 ml/min, UV at 220 nm) indicated less than 0.5% of chloride **5** remained. The colorless oil was dissolved in 15 ml of THF and stirred with 5 ml of 40% aqueous CH_3NH_2 at room temperature overnight (about 20 h). TLC indicated that iodide was consumed. The solution was concentrated, the aqueous residue was added to 25 ml of EtOAc, and the solution was washed with water. Removal of solvent and chromatography (SiO_2, 100:10:1 CH_2Cl_2/MeOH/NH_4OH) gave the product (free base of **LY139603-[^{14}C]**, co-eluted with non-labeled reference) as a colorless viscous oil (222 mg, 0.87 mmol). Proton-NMR of non-labeled product ($CDCl_3$, ppm) 7.35 (m, 5 H), 7.15 (d, 1 H), 7.0 (t, 1 H), 6.82 (t, 1 H), 6.65 (d, 1 H), 5.35 (m, 1 H), 2.6–3.2 (m, 2 H), 2.45 (s, 3 H), 2.37 (s, 3 H), 2.3–2.5 (m, 2 H). This free base was dissolved in 30 ml of CH_2Cl_2, to which a solution of 0.5 ml of 12 N HCl in 2 ml of MeOH was added with stirring, and the solution was then concentrated. The residue was added to 20 ml of anhydrous EtOH and concentrated again to remove the residual water. The residue was dissolved in 2 ml of anhydrous EtOH, diluted with 20 ml of ether, and stirred at room temperature for 30 min. The white precipitate was filtered off, washed with ether, and dried *in vacuo* to give the final product **LY139603-[^{14}C]** as a white hydrochloride salt (217 mg, 0.74 mmol, 82% from chloride **5**). Radiochemical purity: 99% by radio-HPLC and TLC. Specific activity = 60.94 μCi/mg, The white salt was mixed with 400 mg of LY139603, dissolved in CH_2Cl_2, and concentrated to give a white salt. Recrystalization from EtOH and ether gave the product **LY139603-[^{14}C]** as a white crystalline solid (502 mg, 1.72 mmol). MS: M + H = 256/258.

Radiochemical purity: 99% by radio-HPLC. Chirality: 99% e.e. by chiral HPLC. Specific activity: 22.43 μCi/mg. Proton NMR of a non-labeled product ($CDCl_3$, ppm) 7.35 (m, 5 H), 7.15 (d, 1 H), 7.0 (t, 1 H), 6.83(t, 1 H), 6.62 (d, 1 H), 5.0 (dd, 1 H), 3.2 (m, 2 H), 2.2–2.6 (m, 5 H), 2.14 (s, 3 H).

Radio-HPLC conditions: Alltech, Alltima phenyl column, 4.6 × 250 mm. Mobile phase: 30:70 CH_3CN/buffer (1% Et_2NH in water, adjusted to pH 2.03 with conc. H_2SO_4).

Flow rate: 1 ml/min at 40°C. UV: at 220 nm.

Chiral-HPLC conditions: Chiralcel OD-H, 4.6 × 250 mm. Mobile phase: 15:85 isopropanol/hexanes with 0.2% diethylamine. Flow rate: 1 ml/min at room temperature UV at 271 nm.

Synthesis of (R)-3-chloro-1-phenyl-1[2-methyl-4-(tert.-butyloxycarbonyl)-oxy] propane-[1-^{14}C] ***(9)***

A stirred toluene (3 ml) solution of (*S*)-(-)-3-chloro-1-phenyl-1-propanol-[1-^{14}C] (**2**, 0.083 g, 0.488 mmol), 2-methyl-4-[(*tert*.-butyloxycarbonyl)oxy]phenol (**8**, 0.164 g, 0.732 mmol), and tri-*n*-butylphosphine (0.188 ml, 0.732 mmol) was chilled in an ice bath (under argon) and treated with 1,1-(azodicarbonyl)-dipiperidine (ADDP, 0.185 g, 0.732 mmol). Stirring in the cold was continued for 1 h; the ice bath was removed and stirring was continued overnight. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30 × 150 mm) eluting with 10 ml fractions of toluene. Fractions 6–10 (co-eluted with authentic material) were combined and concentrated *in vacuo* to yield (*R*)-3-chloro-1-phenyl-1-[2-methyl-4-(*tert*.-butyloxycarbonyl)-oxy]propane-[1-^{14}C] (**9**, 0.139 g, 76% yield).

Synthesis of (R)-3-iodo-1-phenyl-1[2-methyl-4-(tert.-butyloxycarbonyl)-oxy]-propane-[1-^{14}C] ***(10)***

A mixture of (*R*)-3-chloro-1-phenyl-1[2-methyl-4-(*tert*.-butyloxycarbonyl)-oxy]propane-[1-^{14}C] (**9**, 0.139 g, 0.370 mmol) and sodium iodide (0.555 g, 3.70 mmol) was dissolved in 2-propanone (MEK, 25 ml) and stirred at reflux (under argon) overnight. The reaction mixture was allowed to cool to room temperature and poured into ether. A white precipitate was formed which was removed by filtration. The filtrate was concentrated *in vacuo*. The residue was re-dissolved in ether and filtered. The filtrate was purified by flash chromatography on silica gel (40 × 150 mm) eluting with 10 ml fractions of pentane/EtOAc (98:2). Fractions 6–7 were combined and concentrated *in vacuo* to yield (*R*)-3-iodo-1-phenyl-1[2-methyl-4-(*tert*.-butyloxycarbonyl)-oxy] propane-[1-^{14}C] (**10**, 0.111 g, 64% yield): ES-MS; $[M + NH_4^+]^+$ $m/z =$ 486/488.

Synthesis of γ-(R)-N-methyl(2-methyl-4-hydroxyphenoxy)benzene-propanamine-[3-^{14}C] oxalate salt, (3-[^{14}C]) oxalate salt

A mixture of (*R*)-3-iodo-l-phenyl-1[2-methyl-4-(*tert*.-butyloxycarbonyl)-oxy]-propane-[1-^{14}C] (**10**, 0.111 g, 0.237 mmol) and methylamine (2 N in THF, 1.66 ml, 3.32 mmol) in THF (10 ml) was stirred at room temperature (under argon) overnight. After *ca*. 18 h, TLC (silica gel, pentane/EtOAc, 80:20) showed that 73% of the material remained at the origin while 24% co-eluted with starting material. Another 15 eq. of methylamine was added and stirring was continued. After an additional 24 h, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30×150 mm) eluting with 10-ml fractions of $CH_2Cl_2/CH_3OH/NH_4OH$ (100:10:1). Fractions 12–20 were combined and concentrated *in vacuo* to yield γ-(*R*)-*N*-methyl(2-methyl-4-hydroxyphenoxy)benzenepropanamine-[3-^{14}C] **(3-[^{14}C]**, 0.046 g, 72%).

An EtOAc (3 ml) solution of γ-(*R*)-*N*-methyl(2-methyl-4-hydroxyphenoxy) benzene-propanamine-[3-^{14}C] (0.046 g, 0.169 mmol) was stirred and treated with oxalic acid (0.015 g, 0.167 mmol) in CH_3OH (0.5 ml). A white crystalline solid formed which was collected by filtration, washed with EtOAc (2×15 ml), Et_2O (15 ml) and dried *in vacuo* to yield γ-(*R*)-*N*-methyl(2-methyl-4-hydroxyphenoxy)benzenepropanamine-[3-^{14}C] oxalate **(3-[^{14}C]** oxalate, 0.02 g, 47.5% yield).

Physical data for the non-labeled product: ^{1}H-NMR: (DMSO/d_6 + D_2O) δ 1.98 (1H, m, CH_2CH), 2.08 (3H, s, aromatic CH_3), 2.09 (1H, m, CH_2CH), 2.46 (1H, s, NCH_3), 2.91 (2H, m, CH_2N), 5.19 (1H, m, CH), 6.27 (1H, dd, 6′-H), 6.43 (1H, m, 5′-H), 7.19 (1H, m, 3′-H), 7.28 (5H, s, aromatic); **Anal. Calc'd for $C_{19}H_{23}NO_6$:** C, 63.15; H, 6.41; N, 3.88. Found: C, 63.32; H, 6.59; N, 3.99; HPLC on a Zorbax Eclipse XDB-C18 column (4.6×150 mm) eluting with 0.05 M NH_4OAc/acetonitrile (80:20) at 10 ml/min (column temperature 30°C) showed a single peak at R_T 8.57 min (20 µl of a 1 mg/ml sample dissolved in 0.05 M NH_4OAc was injected). UV detection at 210 nm was used.

Synthesis of (R)-3-azido-1-phenyl-1(2-methylphenoxy)propane-[1-^{14}C](7-[^{14}C])

An aqueous (1 ml) solution of sodium azide (0.094 g, 1.45 mmol) was added at room temperature to a DMF (4 ml) solution of (*R*)-3-chloro-1-phenyl-1(2-methylphenoxy)-propane-[1-^{14}C] **(5-[^{14}C]**, 7.2 mCi, 20 mCi/mmol, 0.36 mmol) under argon. The mixture was stirred at 85–90°C overnight. The DMF was removed *in vacuo* and the residue was partitioned between water and EtOAc. The aqueous layer was washed with EtOAc; the combined EtOAc extracts were washed with saturated aqueous NaCl solution, dried (anhydrous $MgSO_4$), and concentrated *in vacuo* to yield (*R*)-3-azido-l-

phenyl-1(2-methylphenoxy)-propane-[1-^{14}C] **(7-[^{14}C]**, 0.090 g, 94% yield). TLC (silica gel, pentane/EtOAc 98:2) showed a new spot running slightly ahead of **5-[^{14}C]**.

A subsequent preparation of **7-[^{14}C]** from **5-[^{14}C]** (0.028 g, 0.107 mmol) yielded an additional 0.023 g of material.

*Synthesis of γ-(R)-(2-methylphenoxy)benzenepropanamine-[3-^{14}C] **(4-[^{14}C])** method A*

A mixture of (*R*)-3-azido-l-phenyl-1(2-methylphenoxy)-propane-[1-^{14}C] **(7-[^{14}C]**, 0.090 g, 0.337 mmol) and triphenylphosphine (0.177 g, 0.674 mmol) in THF/water (15 ml/2 ml) was stirred at 50–55°C under argon for 16 h. An aliquot was worked up (see below); TLC (silica gel, pentane/EtOAc 98:2) showed loss of starting material (except for a small amount of 2 remaining from the previous reaction). TLC (silica gel, $CH_2Cl_2/CH_3OH/NH_4OH$ 100:10:1) showed the formation of the desired product **(7-[^{14}C])** as well as contamination by **5-[^{14}C]**, unreacted iminophosphorane, and what is presumably an adduct of **5-[^{14}C]** and Ph_3P). The entire reaction mixture was diluted with water (10 ml) and stirred for 0.5 h. The resulting mixture was extracted with EtOAc (50 ml). Solid NaCl was added to clear the emulsion and the aqueous layer was re-extracted with EtOAc (50 ml). The combined EtOAc extracts were washed with saturated brine, dried (anhydrous Na_2SO_4), and concentrated *in vacuo*. The residue was re-dissolved in EtOAc and extracted with HC1 (1 N). The aqueous layer was re-washed with EtOAc and then made basic with conc. NH_4OH. This solution was extracted with EtOAc (3 × 15 ml). This material was saved for later purification with the material from method B (see below).

The EtOAc extracts from the acidic solution were concentrated and re-dissolved in CH_3OH (2 ml) and treated with NH_4OH. This solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (40 × 140 mm) eluting with 10-ml fractions of $CH_2Cl_2/CH_3OH/NH_4OH$ (100:10:1). Fractions 9–10 were combined and concentrated *in vacuo* to yield γ-(*R*)-(2-methylphenoxy)benzene-propanamine-[3-^{14}C] **(4-[^{14}C]**, 0.009 g). Fraction **8** was contaminated and was retained for later purification with the material from method **B** (see below).

*Synthesis of γ-(R)-(2-methylphenoxy)benzenepropanamine-[3-^{14}C] **(4-[^{14}C])** method B*

An IPA (5 ml) solution of (*R*)-3-azido-1-phenyl-1(2-methylphenoxy)-propane-[1-^{14}C] **(7-[^{14}C]**, 0.023 g, 0.086 mmol) was treated with $NaBH_4$ (0.023 g) and stirred overnight at 80–90°C. TLC (silica gel, $CH_2Cl_2/CH_3OH/ NH_4OH$, 100: 10:1) showed a mixture of **4-[^{14}C]** and **7-[^{14}C]**. An additional 0.023 g of $NaBH_4$ was added and heating was continued for an additional 7 h. There was still

unreacted **7-[^{14}C]** remaining, so the mixture was diluted with THF (5 ml) and IPA (1 ml) and an additional 0.023 g of $NaBH_4$ was added and heating was continued overnight. TLC showed that the reaction was 75% complete. The reaction was quenched with HCl (1 N × 1 ml); conc. NH_4OH (3 ml) was added and the mixture was extracted with EtOAc (25 ml). The EtOAc layer was washed with saturated brine, dried (anhydrous $MgSO_4$), and concentrated *in vacuo*. The residue was mixed with the residual material as well as fraction 8 from method A and purified by flash chromatography on silica gel (30 × 150 mm) eluting with 10-ml fractions of $CH_2Cl_2/CH_3OH/NH_4OH$ (100:10:1). Fraction 6 was concentrated *in vacuo* to yield γ-(*R*)-(2-methylphenoxy)benzenepropanamine-[3-^{14}C] **(4-[^{14}C]**, 0.019 g).

Synthesis of γ-(R)-(2-methylphenoxy)benzenepropanamine-[3-^{14}C] (4-[^{14}C] HC1)

A methanol (2 ml) solution of γ-(*R*)-(2-methylphenoxy)benzenepropanamine-[3-^{14}C] **(4-[^{14}C]**, 0.009 g from method A and 0.019 g from method B) was treated with HCl (5 N × 0.025 ml) and concentrated *in vacuo* to a white foam. This material was triturated with EtOAc (3 ml) and stirred until the material crystallized. The white material was collected by filtration, washed with EtOAc (5 ml) and Et_2O (5 ml) and dried *in vacuo* to yield γ-(*R*)-(2-methylphenoxy) benzenepropanamine-[3-^{14}C] hydrochloride **(4-[^{14}C] HCl,** 0.025 g).

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