THE SYNTHESIS OF THE ^{14}C AND ^{2}H-ISOTOPOMERS OF (*R*)-N-[2-(2'-ETHOXYPHENOXY)-ETHYL]-N-2-[3-(4'-METHOXY-3'-SULFONAMIDO)-PHENYL]-PROPYLAMINE HYDROCHLORIDE, AN α_1–ADRENORECEPTOR ANTAGONIST[1]

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SUMMARY

The synthesis of [^{14}C]- and [^{2}H]-labeled LY253351 (YM12617-1), a potent α_1-receptor antagonist, which is potentially useful in the treatment of benign prostatic hypertrophy (BPH) is described. The [^{14}C]-isotopomer was synthesized from [^{14}C]-potassium cyanide in nine steps in 1.5% radiochemical yield. One of the key intermediates, [^{14}C]-4-methoxyphenylacetone, was synthesized from [^{14}C]-4-methoxyphenylacetyl chloride by a Pd(0)-catalyzed reaction with tetramethylstannane. The [^{2}H]-labeled material was synthesized by a Pd/C catalyzed reductive amination with deuterium gas.

KEYWORDS: LY253351, benign prostatic hypertrophy, carbon-14, deuterium, 4-methoxyphenylacetone, Pd(0)-catalyzed, tetramethylstannane, YM12617-1

INTRODUCTION

Takenaka *et al* ,in the search for compounds which might offer some advantage in terms of potency and selectivity, synthesized a group of desoxy derivatives of amosulalol (a mixed α/β-adrenergic antagonist). These analogs were found to possess potent α_1-adrenoreceptor blocking activity and were practically devoid of β_1-blocking activity. Among these analogs, YM12617 (LY253352) was found to be more potent than prazosin as an α_1-antagonist in anesthetized rats and in reducing blood pressure in anesthetized dogs.[2] Subsequent *in vitro* experiments have shown that although YM12617 (LY253352) was a competitive antagonist towards clonidine at prejunctional α_2-adrenoreceptors in isolated rat vas deferens, its affinity for these receptors was 5000 times less than for those in the rat aorta (a tissue known to contain primarily α_1-adrenoreceptors at postjunctional sites). Similar experiments conducted with rat brain membrane established the α_1/α_2-antagonist ratio to be 3800. YM12617 (LY253352) was shown to be considerably more potent than prazosin (an α_1-selective antagonist), phentolamine (a mixed α_1/α_2–antagonist), and yohimbine (an α_2-selective antagonist) in antagonizing α_1-adrenoreceptors.[3] *In vivo* experiments in pithed rats also demonstrated a strong selectivity for the α_1-receptors over the α_2-adrenoreceptors.

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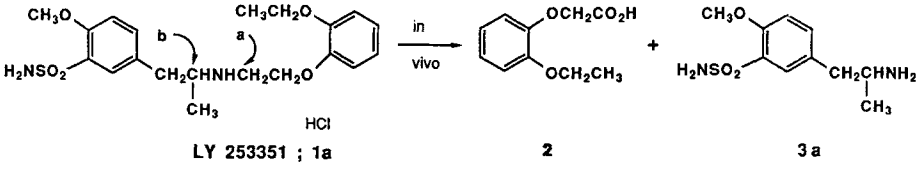
Subsequent experiments have demonstrated that the *R*-isomer (LY253351, YM12617-1, **1a**) is substantially more active than the corresponding *S*-isomer.[4,5,6]

Honda *et al* have recently conducted experiments identifying the α-adrenoreceptor subtypes which mediate smooth muscle contractions in the rat trigone, urethra, and prostate as α_1-receptors.[7] Kunisawa *et al* have reported similar results in human prostatic urethra and isolated bladder base.[8] These results indicate that LY253351 has the potential to be useful in the treatment of benign prostatic hypertrophy (BPH) and related disorders of the lower urinary tract.[7]

Radiolabeled LY253351 was needed for drug disposition and pharmacokinetic studies in animals and man. Preliminary metabolism studies have shown that 2-ethoxyphenoxyacetic acid (**2**) is the major metabolite in mice, rats, and dogs (**Equation 1**).[9]

Although the most convenient position to place the radiolabel would be in that portion of the molecule (a in **eq.1**), it seemed most prudent to place the label in the α-methylphenethylamine moiety (b in **eq.1**)(presumably the major portion of the pharmacophore). This required a chiral synthesis of **3b** which would allow introduction of the label as late as possible in the synthetic sequence (**Scheme 1**).

Equation 1

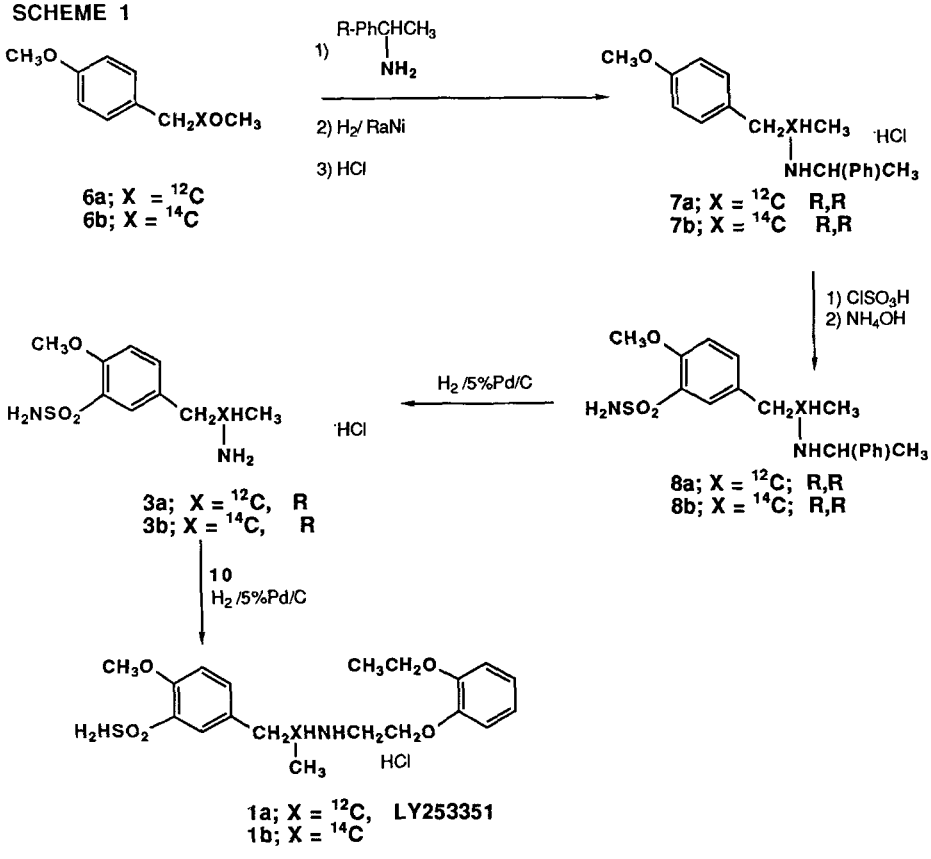


LY 253351 ; 1a 2 3a

RESULTS AND DISCUSSION

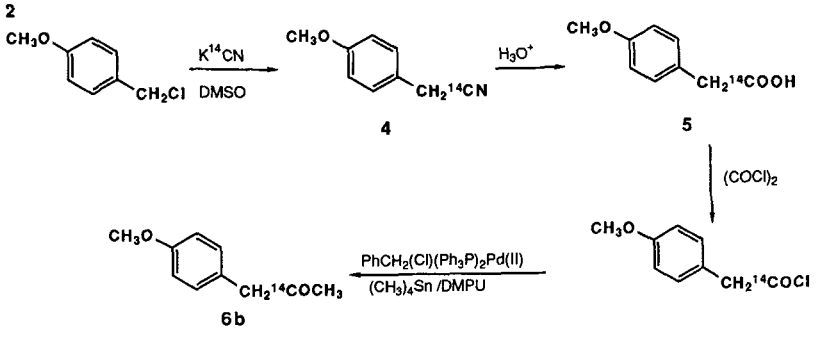
One of the pivotal intermediates in the synthesis of **3b** (and ultimately LY253351-^{14}C) was 3-(4-methoxyphenyl)-2-propanone (**6a,b**). Although substituted phenylacetones have been conveniently prepared by the Fe/HCl reduction of the requisite nitrostyrenes, the yields are frequently less than 50% for the two step synthesis.[10] Moreover, synthesis of the radiolabeled aromatic aldehydes needed as starting materials has been less than satisfactory.[11] Utilizing dithiane chemistry described by Seebach and Corey [12], ^{14}C-phenylacetone was synthesized from ^{14}C-benzoic acid, but only in 38% yield.[13] Reaction of 4-methoxybenzyl chloride with ^{14}C-potassium cyanide was an attractive alternative method for introducing the ^{14}C-label; however, reaction of phenylacetonitrile with CH_3MgBr yielded phenylacetone in only 5% yield, reportedly because of competition of the alpha-hydrogens for Grignard reagent.[14] Presumably the 4-methoxyl group would have little effect on the course of the reaction. Milstein and Stille recently reported a new and convenient synthesis of ketones involving the Pd(0)-catalyzed reaction of acyl chlorides with tetraalkyl tin reagents.[15] The reaction is reported to be complete in a matter of a few minutes when conducted in hexamethylphosphoric triamide (HMPA). Although equally successful, reaction in THF required overnight reflux. We found that reaction in 1,3-dimethyl-3,4,5,6-tetrahydro-

SCHEME 1



2(1H)-pyrimidone (DMPU) was also very fast (completed after heating at 60° for 15-20 min.), yielding 4-methoxyphenylacetone **6a** (or its ^{14}C-isotopomer **6b**) in 60% yield after purification by flash chromatography (**Scheme 2**).[16]

Scheme 2



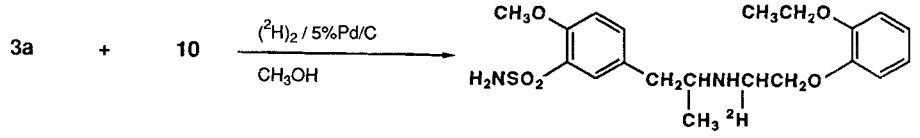
Using a modification of the procedure reported by Nichols *et al*, *R*-α-methylbenzylamine was utilized as a chiral auxiliary which would later be removed by hydrogenolysis.[17] Reaction of **6a** (or **6b**) with *R*-α-methylbenzylamine in refluxing toluene, followed by hydrogenation of the intermediate Schiff's base over 5% Pd/C, yielded *R,R*-amine **7a**(or **7b**), which was contaminated with the *S,R*-isomer. Crystallization of **7a** (or **7b**) as its hydrochloride salt from ethanol/acetone

yielded the *R,R*-isomer which was found to be free of the *S,R*-isomer by TLC (autoradiography on the ^{14}C-isotopomer) on silica gel.

Reaction of *R,R*-amine **7a** (or **7b**) with $ClSO_3H/CHCl_3$, followed by aminolysis of the intermediate chlorosulfonyl derivative with concentrated ammonium hydroxide, yielded sulfonamide **8a**(or **8b**) in 66% yield. Removal of the α-methylbenzylamine moiety by hydrogenolysis over RaNi yielded primary amine **3a**(or its ^{14}C isotopomer **3b**), which was purified as its HCl salt by crystallization from methanol/2-propanol. Reductive amination of 2-[(2'-ethoxy)-phenoxy]- acetaldehyde (**10**) with **3b** (or the corresponding non-labeled isotopomer **3a**) yielded LY253351-^{14}C (**1b**) (or its unlabeled counterpart **1a**) after conversion to the HCl salt and recrystallization from water. Thus, LY253351-^{14}C(**1a**) was synthesized in nine steps from ^{14}C-potassium cyanide in 1.85% overall yield. The material was shown to be >98% radiochemical purity by TLC on silica gel ($CHCl_3/CH_3OH/NH_4OH$ 100:10:1) and HPLC (Supelco C-18 [1:1 CH_3CN/CH_3OH]/[0.05 M NH_4OAc with 0.1% morpholine], 1:4 and 1:1) and contained less than 0.1% of the *S*-isomer as determined by HPLC.[18] The specific activity was 122.8 μCi/mg or 54.5 mCi/mmol.

The synthesis of LY253351-^2H (**12**) was completed by the reductive amination of 2-[(2'-ethoxy)-phenoxy]-acetaldehyde (**10**) with **3a** over 5% Pd/C using deuterium (**Equation 2**). FAB mass spectrometry showed that the product contained incorporation by a single deuterium in 64% of the molecules, while 14% contained two deuteria.[19] Another 22% contained no deuterium, presumably as a result of deuterium-hydrogen exchange (from the CH_3OH on the catalyst surface).[20]

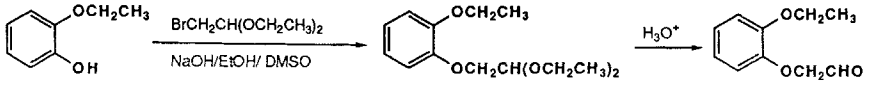
Equation 2



12

Aldehyde **10** was prepared (via the corresponding acetal **9**) in two steps from 2-ethoxyphenol (**Scheme 3**).

Scheme 3



9 **10**

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on a General Electric QE-300 NMR spectrometer at 300 MHz. Chemical shifts are reported in parts per million (ppm) downfield from

tetramethylsilane. Mass spectra were recorded on a Varian Associates MAT 731 mass spectrometer (field desorption) or a VG Analytical VG-ZAB3F mass spectrometer (fast atom bombardment). Microanalytical data were provided by the Physical Chemistry Research Department of the Lilly Research Laboratories.

Radiochemical purity (RCP) was assessed by autoradiography employing E. Merck silica gel F-254 TLC plates and Kodak X-ray film BB-5. In addition, RCP was determined using HPLC utilizing a Radiomatic Flo-One radiochemical detector.

Flash chromatography was performed using the method described by Still *et al* using E.M. Scientific silica gel 60 (230-400 mesh).[16] Thin layer chromatography was conducted using E.M. Scientific silica gel F 254 plates.

2-(4'-Methoxyphenyl)-acetonitrile-1-[^{14}C], 4:

4-Methoxybenzyl chloride (prepared just prior to use by the reaction of 4-methoxybenzyl alcohol with thionyl chloride in methylene chloride followed by vacuum distillation[20]) (1.42 g, 9.1 mmol) was added to a dimethylsulfoxide solution (15 mL) of potassium [^{14}C]-cyanide (DuPont NEN, 0.6 g, 9.1 mmol, sp. act. 54.9 mCi/mmol, 500 mCi). The resulting mixture was stirred at room temperature for 18 hrs, then poured into ice (50 mL) and water (50 mL) and extracted 3 times with 1:1 pentane/ether. The combined extracts were dried (anhyd. $MgSO_4$) and concentrated to yield 1.26 g (93.8%) of **4** as a light yellow oil. This material co-migrated with an authentic sample of 2-(4'-methoxyphenyl)-acetonitrile on TLC (4:1 toluene/ethyl acetate, r_f= 0.71).

2-(4'-Methoxyphenyl)-acetic Acid 1-[^{14}C], 5:

A 75% aqueous ethanolic solution (24 mL) of **4** (1.26 g, 8.55.mmol) was treated with an excess of potassium hydroxide (6.74 g, 120 mmol) and was stirred under gentle reflux for 24 hrs, then allowed to cool to room temperature. The reaction mixture was diluted with 50 mL of water and washed two times with ether (250 mL). The aqueous layer was then acidified with 11 mL of ice cold 12 N HCl and re-extracted three times with 50 mL of ether. The combined ether extracts were dried (anhyd. $MgSO_4$) and concentrated to a pale yellow oil which crystallized upon standing (1.23 g, 86.6%). This material was identical to authentic 2-(4'-methoxyphenyl)-acetic acid by TLC (ethyl ether/hexane/acetic acid 3:1:1, r_f= 0.67).

3-(4'-Methoxyphenyl)-2-propanone-2-[^{14}C], 6b:

A mixture of **5** (1.23 g, 7.4 mmol) and oxalyl chloride (1.49 g, 17.1 mmol) in 25 mL of toluene was stirred at room temperature for 48 hr. The toluene was removed *in vacuo*. The residue was re-dissolved and evaporated three times with 30 mL of toluene. The crude acid chloride was dissolved in DMPU (5 mL) and treated with 1.04 mL (7.47 mmol) of tetramethylstannane and 0.031 g of benzylchloro-*bis*-triphenylphosphinepalladium (II)[22] and heated at 65°C with stirring for 45 min. (Initial results under a cover of argon gas were unsuccessful; Milstein and Stille have reported that this reaction is catalysed by oxygen.[15] There is a visual color change when the reaction is complete as the black Pd(0) precipitates). The reaction mixture was poured into water and extracted with 100 mL of ether/pentane (1:1) and two additional times with 50 mL of ether:

pentane (1:1). The combined organic extracts were washed with water, dried (anhyd. $MgSO_4$), and concentrated *in vacuo* to yield the crude ketone as a yellow oil (1.123 g), which was purified by flash chromatography. The product was eluted with 4:1 toluene/ethyl acetate, collecting 25 mL fractions. Fractions 11-14 were combined and concentrated to yield **6b**: 0.861 g (71%) which was identical to authentic 3-(4'-methoxyphenyl)-2-propanone by TLC (toluene/ethyl acetate 4:1, r_f= 0.57).

R,R-N-(α-Phenethyl)-3-(4'-methoxyphenyl)-2-propylamine-2-[^{14}C] Hydrochloride Salt, 7b:

A mixture of **6b** (0.861 g, 5.25.mmol) and *R*-α-methylbenzylamine (0.75 g, 5.25 mmol) in 10 mL of toluene was stirred at reflux for 6 hr. (removing the water produced in a Dean-Stark trap). The toluene was removed *in vacuo* and the residual Schiff's base was re-dissolved in 25 mL of 2-propanol (IPA). RaNi was added and the mixture was hydrogenated at 60 psi for 24 hr. The catalyst was removed by filtration and washed with 50 mL of fresh IPA. The IPA was evaporated *in vacuo*; the residue was re-dissolved in 5 mL of acetone and treated with 1.8 mL of IPA/HCl (*ca.* 3.28M). The mixture was stirred and the product slowly crystallized. After storing at -5°C overnight, the mixture was diluted with 5 mL of additional acetone and filtered. The crystalline product was washed with 5 mL of acetone and dried (0.525 g, 33%). TLC-autoradiography (CH_3OH) showed that **7b** (r_f= 0.46) was contaminated with the corresponding *S,R*-isomer (r_f=0.54). Recrystallization from absolute ethanol/acetone yielded **7b** as a pure diastereomer in two crops: 0.377 g, 23.5%). This material was shown to be pure and identical to the unlabeled product[17] by TLC (CH_3OH) followed by autoradiography (r_f= 0.46).

R,R-N-(2-Phenethyl)-3-(3'-sulfonamido-4'-methoxyphenyl)-2-propylamine, 8a:

Chlorosulfonic acid (34.8 g, 19.8 mL, 0.17 mol) was chilled to 15-20°C and a solution of **7** (15.3 g, 0.05 mol) in 80 mL of methylene chloride was added dropwise to the stirred solution under nitrogen. The addition rate was controlled such that the temperature of the reaction mixture did not exceed 20°C. Following the addition, the resulting mixture was stirred at 15-20°C for two hr. The resulting solution was then added dropwise to a rapidly stirred mixture of conc. ammonium hydroxide (100 mL), THF (300 mL), and 150 g of chipped ice (chilled to -10°C), maintaining the temperature at 0° to -5°C. The reaction was followed by TLC ($CHCl_3$/CH_3OH/conc. NH_4OH 50:5:1). After 3 hr., there was no remaining sulfonyl chloride (r_f=0.95) and showed only **8a** (r_f= 0.50). The reaction mixture was saturated with sodium chloride and extracted with four 1000 mL portions of ether. The combined organic phases were washed with saturated sodium chloride, dried (anhydr. Na_2CO_3), and concentrated to an oil which solidified to yield 12.2g (77%) of **8a** as a white solid: mp 103-105°C; NMR ($CDCl_3$) δ 0.88 (d,J = 6 Hz,3H, CH_3); 1.32 (d,J = 6 Hz,3H, α-CH_3); 2.44-2.54 (m,1H,CHN); 2.66-2.88 (m,2H,CH_2); 3.93 (q,J = 6 Hz,1H, CHMe); 3.99 (s,3H, OCH_3); 5.16 (bs,3H, NH_2 and NH); 6.90-7.70 (m,8H,aromatic); MS(FD) M^+ 348; $[\alpha]_D$(CH_3OH) = +41.8°.

Anal. Calcd for $C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.94; N, 8.04. Found: C, 61.75; H, 6.85; N, 7.77.

R,R-N-(2-Phenethyl)-3-(3'-sulfonamido-4'-methoxyphenyl)-2-propylamine-2-[^{14}C], Hydrochloride Salt, 8b:

The radiolabeled **8b** was prepared according to the method previously described for **8a** (*vide supra*). Thus, 0.377 g (1.24 mmol) of **7b** was converted to the free base of **8b**, which was obtained as a white foam. TLC ($CHCl_3/CH_3OH/NH_4OH$ 50:5:1 showed that the material was identical to **8a** (r_f= 0.50). HPLC (4.5 mm x 15 cm Supelco C-18 column eluted with a mixture consisting of 188 mL of 1:1 CH_3OH/CH_3CN and 500 mL of 0.05 M NH_4OAc (containing 0.1% morpholine) at 1.5 mL/min) indicated that the material was free of the *S,R*-isomer (r_t= 13.2 min for *R,R*-isomer and 15.4 min for the *S,R*-isomer).

The white foam was redissolved in 3.2 mL of IPA and treated with 1.1 mL of *ca.*.3.28 M HCl/ IPA, then concentrated to a foam *in vacuo*. The amorphous solid was dissolved in acetone (6.5 mL) and stirred until crystallization occured. After 0.5 hr., the mixture was filtered; the solid was washed with acetone and dried to afford **8b** as a white solid: 0.315 g (66.4% yield).

R-3-(3'-Sulfonamido-4'-methoxyphenyl)-2-propylamine, Hydrochloride Salt, 3a:

A methanolic (100 mL) solution of **8a** (7.40 g, 17.8 mmol) was added to 2.0 g of 5% Pd/C covered with absolute EtOH. The mixture was diluted to 200 mL with absolute EtOH and hydrogenated at 60 psi for 5.5 hrs. The mixture was filtered and the filtrate concentrated to a white solid which was recrystallized from CH_3OH/IPA to yield 4.16 g of **3a** as a white crystalline solid: mp 269-270°C; NMR (CH_3OD) δ 1.26 (d,J = 9 Hz,3H,CH_3CH), 2.81 and 2.99 (dd,J = 9,15 Hz,1H,CH_2Ar), 3.50 (m,1H,CHMe), 4.00 (s,3H,OCH_3), 7.20 (d,J = 9 Hz,1H,2'-aromatic), 7.50 (dd,J = 3,9 Hz,1H,3'-aromatic), 7.76 (d,J = 3 Hz,1H,6'-aromatic); MS(FD) M^+ 244. Anal. Calcd for $C_{10}H_{17}N_2O_3Cl$: C, 42.78; H, 6.10; N, 9.98. Found: C, 43.07; H, 5.84; N, 9.78.

R-3-(3'-Sulfonamido-4'-methoxyphenyl)-2-propylamine-2-[^{14}C], Hydrochloride Salt, 3b:

An anhydrous methanolic solution (10 mL) of **8b** (0.316 g, 0.823 mmol) was added to 5% Pd/C (0.092 g, previously wetted with absolute EtOH). The resulting mixture was diluted to 30 mL with absolute EtOH and hydrogenated at 60 psi for 18 hr. The catalyst was removed by filtration and washed twice with 10 mL of additional EtOH. The combined filtrates were evaporated to yield a white solid, which was re-dissolved in 15 mL of methanol and diluted with 9 mL of IPA. The resulting mixture was concentrated to 12 mL whereupon white crystals were formed. These were collected by filtration to yield **3b** (0.171 g, 74%). TLC ($CHCl_3/CH_3OH/NH_4OH$ 50:25:5, r_f= 0.75; and $CHCl_3/CH_3OH/NH_4OH$ 50:5:1, r_f= 0.20) showed a single component which co-migrated with **3a.**

2-[(2'Ethoxy)-phenoxyl-acetaldehyde Diethylacetal, 9:

2-Ethoxyphenol (100 g, 0.68 mol) dissolved in 200 mL of ethanol was added dropwise to a stirred

mixture of sodium hydroxide (26.9 g, 0.675 mol) and 600 mL of ethanol. After stirring for two hours, the mixture was concentrated *in vacuo*. The residue was re-dissolved in dimethyl sulfoxide (300 mL) and added dropwise to a dimethyl sulfoxide solution (250 mL) of bromoacetaldehyde diethylacetal (131.2 g, 0.70 mol) at 15°C. After 15 hr at 25°C, the reaction mixture was heated at 105-110°C for 5 hr. The reaction mixture was allowed to cool to room temperature, diluted with water, and extracted twice with ether. The combined ether extracts were washed successively with 0.5 N sodium hydroxide, water, and saturated aqueous sodium chloride. After drying (anhyd. Na_2SO_4), the solvent was removed *in vacuo* and the residue was vacuum distilled yielding 154 g (91%) of **9**: bp 90-95°C (0.08-0.10 mm), NMR(DMSO/d_6): δ 1.25 (t,J = 7 Hz,6H, acetal CH_3), 1.42 (t,J = 8 Hz,3H, ethoxy CH_3), 3.6-3.8 (m,4H), 4.0-4.1(m,4H), 4.89 (t,J = 5 Hz,1H,CH), and 6.80-6.94 (m,4H,aromatic); MS (FD) M^+ 254.
Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.25; H, 8.61.

2-[(2'-Ethoxy)-phenoxyl-acetaldehyde, 10:

A solution of the acetal **9** (30.0 g, 118 mmol) in 90 mL of acetonitrile was treated with 60 mL of diluted perchloric acid (prepared from 60 mL of 70% perchloric acid and 160 mL of water) at 25°C. After 3 hrs at 25°C, the mixture was stirred at 0°C for 18 hrs and then poured carefully into an aqueous solution of sodium bicarbonate. The mixture was extracted with ether several times and the combined extracts were washed with saturated sodium chloride and dried (anhyd. Na_2SO_4). After removing the solvent, the oily residue was distilled at 80-82°C (0.1 mm) to yield 15.81 g (74%) **10** as an oil which solidified upon standing. It was necessary to re-distill this material just prior to use for best results. NMR ($CDCl_3$) δ 1.45 (t,J = 8 Hz,3H,CH_3), 4.10 (q,J = 8 Hz,2H,CH_2O), 4.59 (s,2H,CH_2CHO), 6.80-7.05 (m,4H,aromatic), 9.95 (s,1H,CHO); MS(FD), M^+180; IR, 1737 cm^{-1}.
Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.42; H, 6.45.

N-[2-(2'-Ethoxyphenoxy)-ethyl]-*R*-(3"-sulfonamido-4"-methoxyphenyl)-2-propylamine, Hydrochloride Salt, LY253351, 1a:

A methanolic solution (100 mL) of **3a** (2.81 g, 10mmol), **10** (2.07 g, 11.5 mmol), and sodium cyanoborohydride (0.601 g, 9.7 mmol) was stirred at room temperature overnight. Aqueous 3N HCl (25 mL) was added and stirring was continued for 0.5 hr. The mixture was concentrated and re-partitioned between EtOAc and water. The pH was adjusted to ca. 9 with $KHCO_3/Na_2CO_3$. The EtOAc layer was dried (anhydr. Na_2SO_4) and concentrated *in vacuo*. The residue was re-dissolved in methanol/IPA and treated with 20 mL of ether/HCl. The white precipitate was collected by filtration and washed with IPA and ether (3.02 g). This material was recrystallized from CH_3OH to yield **1a** (2.54 g, 57.2%): mp 231-3°; NMR (DMSO/d_6) δ 1.19 (d,J = 9 Hz,3H, CH_3CH), 1.25 (t,J = 6 Hz,3H,CH_3CH_2), 2.72 and 3.38 (dd,J = 9,15 Hz,2H,CH_2Ar), 3.41 (m,2H,CH_2N), 3.55 (m,1H, CHMe), 3.89 (s,3H,OCH_3), 4.02 (q,J = 6 Hz,2H,OCH_2CH_3), 4.36 (dd,J = 5,9 Hz,2H,CH_2O), 6.91-7.08 (m,6H,3'-6' aromatic and H_2NSO_2), 7.19 (d,J = 7 Hz,1H,5' aromatic), 7.47 (dd,J = 2,7 Hz,1H,6' aromatic), 7.64 (d,J = 2 Hz,1H,2' aromatic), 9.59 (bs,2H,NH_2^+); MS (FAB) $(M+1)^+$ 409.

Anal. Calcd for $C_{20}H_{29}N_2O_5SCl$: C, 53.98; H, 6.57; N, 6.30. Found: C, 54.02; H, 6.36; H, 6.40.

N-[2-(2'-Ethoxyphenoxy)-ethyl]-*R*-(3"-Sulfonamido-4"-methoxyphenyl)-2-propylamine-2-[^{14}C], Hydrochloride Salt, LY253351-[^{14}C], 1b:

A mixture of **3b** (0.171 g, 0.610 mmol) and freshly distilled **10** (0.143 g, 0.792 mmol) in 15 mL of CH_3OH was added to 5% Pd/C (0.03 g) (previously wetted with THF), then diluted with CH_3OH to 30 mL. The resulting mixture was hydrogenated at 50 psi for 48 hr, then filtered through Super-Cel™. The filter pad was washed with CH_3OH and the filtrate was then concentrated *in vacuo*. The oily residue was triturated with 3 mL of absolute EtOH and stirred until crystalline, then stored overnight at 5°C. The crystals were collected by filtration and dried. TLC ($CHCl_3/CH_3OH/NH_4OH$ 100:10:1) followed by autoradiography showed slight contamination with **3b**; the filtrate was mostly **3b**. The crude product was recrystallized twice from water to yield 0.0753 g (27.8%) of **1b** (LY253351-[^{14}C] as a white solid: sp. act. 122.8 μCi/mg or 54.52 mCi/mmol.

TLC ($CHCl_3/CH_3OH/NH_4OH$ 100:10:1) and autoradiography showed that **1b** co-migrated with **1a** (r_f= 0.61) and was >98% RCP. The RCP was also shown to be >98% by HPLC (Supelco C-18 1:4 (1:1 CH_3OH/CH_3CN)/ 0.05 M NH_4OAc (with 0.1% morpholine) (r_t= 42.9 min) and 1:1 of the same solvent (r_t= 6.4 min) at 1.5 mL/min). Separate HPLC analysis showed less than 0.1% of the *S*-isomer.[18]

N-[2-(2'-Ethoxyphenoxy)-ethyl -2-[^{2}H]]-*R*-(3"-Sulfonamido-4"- methoxy - phenyl)-2-propylamine, Hydrochloride Salt, LY253351-[^{2}H], 12:

A mixture of **3a** (0.280 g, 1 mmol) and freshly distilled **10** (0.226 g, 1.25 mmol) was dissolved in CH_3OH (30 mL) and added to 5% Pd/C (0.050 g)(previously wetted with THF).
Deuterium gas was introduced and evacuated several times into the reaction vessel. The deuteration was conducted at atmospheric pressure for 24 hr with stirring. The reaction mixture was filtered through a pad of Super-Cel. The filter pad was washed with CH_3OH and the combined filtrates were concentrated *in vacuo*. The residue was triturated with 3 mL of absolute EtOH and stirred until crystalline. The solid was collected by filtration and recrystallized twice from water to yield 0.146 g (32.8 %) of **12:** mp 229-231°C; NMR (DMSO/d_6) δ 4.16 (d,J = 6 Hz,1H, CHDN); MS(FAB) shows 22% D_0, 64% D_1, 14% D_2, $(M+1)^+$ 410.
High Resolution MS(FAB) $C_{20}H_{28}DN_2O_5S$ +1: 410.18599. Found: 410.18596

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