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AN EFFICIENT SYNTHESIS OF *S*-γ-[(4-TRIFLUOROMETHYL)-PHENOXY]BENZENEPROPANAMINE-[1-^{14}C] MALEATE, AN IMPORTANT METABOLITE OF FLUOXETINE HYDROCHLORIDE

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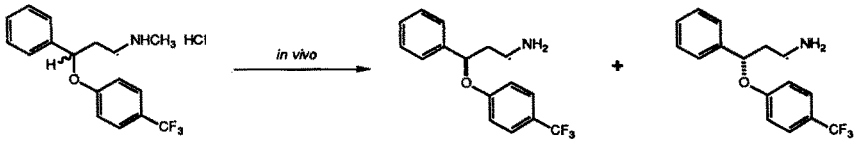
S-γ-[(4-Trifluoromethyl)phenoxy]benzenepropanamine-[1-^{14}C] maleate has been prepared in six steps from *R*-(-)1-phenyl-1,2-ethanediol. The isotope was incorporated by the reaction of NaCN-[^{14}C] with the *tert.*-butyldimethylsilyl ether of *R*-(-)1-phenyl-1,2-ethane-diol 2-tosylate. Borane reduction and arylation, followed by salt formation yielded *S*-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine-[1-^{14}C] maleate.

Key words: C14, *S*-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine-[1-^{14}C] maleate.

INTRODUCTION

N-Methyl-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine hydrochloride (fluoxetine hydrochloride, **1**), a specific serotonin re-uptake inhibitor which is clinically useful as an antidepressant[1], is a mixture of enantiomers.[2] Robertson *et al* have previously reported on the preparation of the individual enantiomers of fluoxetine from optically active precursors, as well as from the classical resolution of fluoxetine.[3] Only minor differences in their pharmacological activities were observed. Parli has shown that one of the principle routes of metabolism of fluoxetine is the cytochrome P_{450}-mediated oxidative N-demethylation to form the primary amines **2a,b** (*R,S-nor*-fluoxetine).[4] The *R*- and *S*-enantiomers of *nor*-fluoxetine have recently been synthesized and studied as pure enantiomers.[5] The *S*-enantiomer of *nor*-fluoxetine (**2b**, seproxetine) was equipotent with fluoxetine in the inhibition of serotonin uptake, but sixteen times more potent than the corresponding *R*-enantiomer (**2a**). Seproxetine was also found to be substantially more potent than *R-nor*-fluoxetine in a number of *in vivo* studies. In order for us to learn more about the disposition and metabolism of seproxetine, we have undertaken the preparation of its ^{14}C-isotopomer. Since the resolution of *nor*-fluoxetine has been unsuccessful, the synthesis of



1, FLUOXETINE HCl **2a** **2b**

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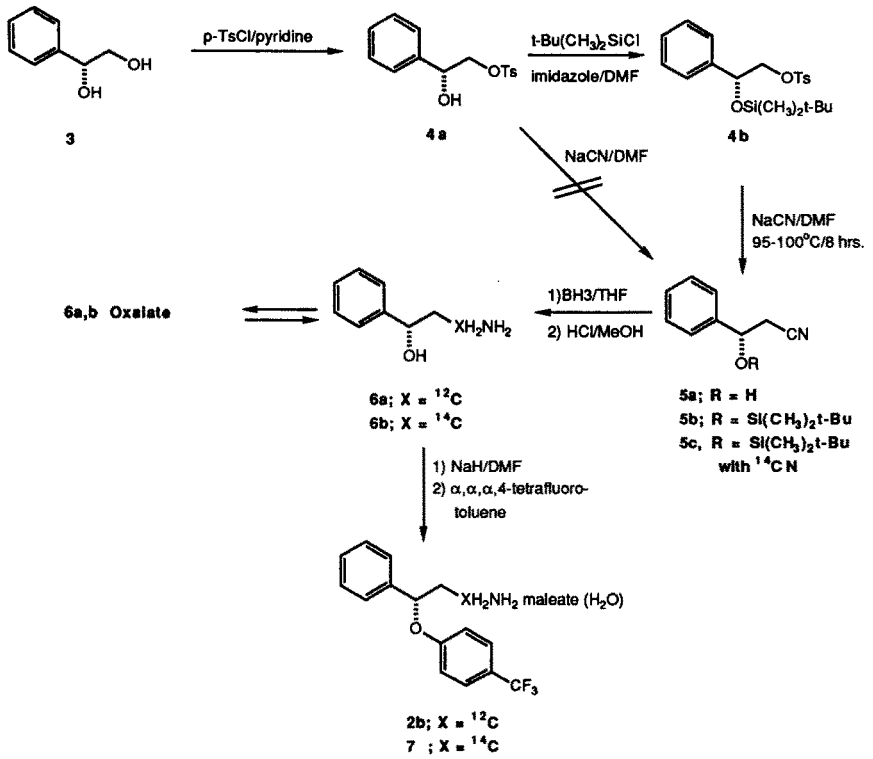
the *S*-isomer of radiolabeled *nor*-fluoxetine from the commercially available *R*-(-)1-phenyl-1,2-ethanediol has been completed and is the subject of this paper. This methodology is also applicable for the synthesis of *R*-γ-[(4-trifluoromethyl)phenoxy]benzenepropanamine-[1-^{14}C] maleate; however, this synthesis will not be reported herein.[6]

DISCUSSION

R-(-)1-phenyl-1,2-ethanediol (**3**) was reacted with *p*-toluenesulfonyl chloride, according to the procedure of Berti *et al* to provide the primary tosylate **4a**.[7] Subsequent reaction of **4a** with NaCN, yielded R-phenyloxirane, rather than the desired nitrile **5a**. Protection of the secondary alcohol as its *tert.*-butyldimethylsilyl ether (**4b**) (*tert.*-butyldimethylsilyl chloride/imidazole/DMF), followed by reaction with NaCN (or Na^{14}CN) in DMF provided the desired silyl-protected nitrile **5b** (or **5c**) in reasonable yield. After heating **4b** in the presence of DMF at 50-55°C/24 hr, **5b/4b** was only 59:41 (by NMR); an additional 24 hr at 50-55°C raised the ratio to 86:13. Subsequently, we found that heating at 95-100°C provided for the smooth conversion of **4b** to **5b** in 5 hr (62%, >95% **5b**). Borane reduction yielded the pivotal intermediate **6a,b** (the *tert.*-butyldimethylsilyl protecting group was lost in the acidic work-up) which was purified by conversion to its crystalline oxalate salt. Neutralization of the oxalate salt with aqueous KOH, followed by reaction of the dried free base with NaH/DMF, and subsequent reaction of the alkoxide with α,α,α,4-tetrafluorotoluene, provided S-γ-[(4-trifluoro-methyl)phenoxy]benzenepropanamine (**2b**



or its 1-^{14}C-isotopomer **7**). Purification by flash chromatography, followed by salt formation with maleic acid, and recrystallization from water, resulted in material of excellent enantiomeric and radiochemical purity; the specific activity was 14.8 μCi/mg (6.35 mCi/mmol). The overall radiochemical yield was 4.4%.

EXPERIMENTAL

The sodium cyanide-[^{14}C] was purchased from DuPont NEN. The 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. High resolution FAB mass spectra were recorded on a VG Analytical VG-ZAB 3F mass spectrometer.[8] Microanalytical,IR, and UV 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).[9] 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 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. Enantiomeric purity was determined by HPLC after derivatization with (*R*)-(-)-1-(1-naphthyl)ethylisocyanate (Aldrich Chemicals).[10]

The dimethylformamide (DMF) was stired over 4A-molecular sieves; the tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone.

R-(-)-1-Phenyl-1,2-ethanediol-2-tosylate, 4a:

A mixture of *R*-(-)-1-phenyl-1,2-ethanediol (**3**) (10 g, 72.46 mmol) and pyridine (40 mL) was stirred and chilled to 0-5°C, and treated dropwise with a pyridine (40 mL) solution of p-toluenesulfonyl chloride (13.3g, 70 mmol). After the addition was complete, the solution was stirred at 0-5°C for two hr, the concentrated *in vacuo*. The residue was thoroughly triturated with ether (2 x 100 mL) and decanted. The ether solution was washed with water (3 x 50 mL) and saturated brine, then dried and concentrated *in vacuo*. The residue was triturated with hexane to crystallize and was subsequently recrystallized from benzene/ hexane to yield **4a** (10.68 g, 52.2%); mp 66-69°C (lit. 73-4°C): TLC (4:1 ether/ hexanes) showed one component co-eluting with the *S*-isomer (Aldrich Chemicals), r_f = 0.72; NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 2.73 (bs, 1H, OH), 4.09 (m, 2H, CH_2), 4.95 (dd, J = 3.25, 8.5 Hz, 1H, CH), 7.29 (s, 5H, phenyl), 7.32 and 7.75 ppm (q_{AB}, J = 8.3 Hz, 4H, tosyl); DCI-MS, $(M + H)^+$ 293.

R-(-)-1-Phenyl-1,2-ethanediol-2-tosylate, 1-*tert.*-Butyldimethylsilyl Ether, 4b:

A mixture of **4a** (3.0 g, 10.26 mmol), *tert.*- butyldimethylsilyl chloride (1.70 g, 11.26 mmol), and imidazole (0.767 g, 11.26 mmol) were stirred overnight at room temperature in

DMF (100 mL). The DMF was evaporated *in vacuo*, and the residue was triturated with ether and filtered. The filtrate was washed with water (3 x 25 mL) and brine (25 mL), then dried and concentrated. The residue was purified by flash chromatography, eluting with benzene in 25 mL fractions. Fractions 11-20 were combined and concentrated to yield 4b (2.35 g, 56%); TLC showed one component (toluene, $r_f = 0.43$; 4:1 pentane/ether, $r_f = 0.67$); NMR ($CDCl_3$) δ -0.08 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.85 (s, 9H, *t*-Bu), 2.45 (s, 3H, CH_3), 3.95 (m, 2H, CH_2), 4.91 (m, 1H, CH), 7.28 (s, 5H, phenyl), 7.32 and 7.75 (q_{AB}, J = 8.3 Hz, 4H, tosyl); DCI-MS, $(M + H)^+$ 407.

Anal. calc'd for $C_{21}H_{30}O_4SSi$: C, 62.03; H, 7.44. Found: C, 62.11; H, 7.52.

S-(-)-3-Phenyl-3-[(*tert.* Butyldimethylsilyl)oxy]propionitrile, 5b[11]:

A DMF (12 mL) solution of 4b (0.520 g, 1.28 mmol) was treated with sodium cyanide (0.094 g, 1.92 mmol) and stirred with heating at 97-100°C for six hr, then stirred at room temperature overnight. The DMF was removed *in vacuo* and the residue was triturated with ether (50 mL) and filtered. The filtrate was washed with water (3 x 25 mL), dried, and concentrated *in vacuo*. The NMR of the residue showed that the resulting solid was >95% **5b**. The residue was purified by flash chromatography (4:1 pentane/ether) to yield **5b** (0.2082 g, 62.3%); TLC (4:1 pentane/ether, $r_f = 0.68$; and 9:1 toluene/hexanes, $r_f = 0.43$, showed a single component, identical to the material prepared from the silylation of (±)-3-phenyl-3-hydroxypropionitrile); NMR ($CDCl_3$) δ -0.08 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.95 (s, 9H, *t*-Bu), 2.68 (m, 2H, CH_2), 4.98 (dd, J = Hz, CH), and 7.38 (s, 5H, aromatic); DCI-MS, $(M + H)^+$ 262.

HRMS (EI) $(M\text{-}t\text{-}Bu)^+$ calc'd for $C_{11}H_{14}NOSi$. Theory: 204.084468. Found: 204.084468.

S-(-)-3-Phenyl-3-[(*tert.* Butyldimethylsilyl)oxy]propionitrile-[1-^{14}C], 5c:

A mixture of **4b** (0.767 g, 1.89 mmol), sodium cyanide-[^{14}C] (100 mCi, sp. act. 52.8 mCi/mmol, 1.89 mmol), and sodium cyanide (0.0463 g, 0.945 mmol) was heated at 97-100°C in DMF (25 mL) as described above. After work-up, the crude residue was purified by flash chromatography (eluted with 10 mL fractions of 9:1 toluene/hexanes) to yield **5c** (0.3209 g, 65.1%); TLC (4:1 pentane/ether and 9:1 toluene/hexanes; co-elutes with **5b**).

S-(-)-α-(2-Aminoethyl)benzenemethanol, 6a:

Borane-THF (2.65 mL, 1M, 2.65 mmol) was added via a gas-tight syringe to a THF solution (50 mL) of 5b (0.1731 g, 0.66 mmol) under argon. The resulting solution was then stirred at room temperature overnight. The excess borane was decomposed by the dropwise addition of methanol. The solution was concentrated; the residue was re-dissolved in methanol and re-concentrated. A methanolic solution (25 mL) of the borazine

complex was treated with aqueous HCl (1N, 3 mL) and allowed to stand at room temperature for 16 hr. The methanol was removed in vacuo, the residue was dissolved in water and extracted with ether. The aqueous layer was made basic with NaOH (4 x 1N), saturated with sodium chloride and extracted with ether (4 x 25 mL). The combined ether extracts were dried and concentrated *in vacuo*. The residue (0.050 g, 0.33 mmol) was dissolved in methanol (1.04 mL) and treated with oxalic acid (0.027 g, 0.3 mmol) in methanol (0.137 mL) to yield **6a** as its oxalate salt (0.04722 g, 47%); NMR (DMSO/d_6); TLC (methylene chloride/methanol/ammonium hydroxide 100:30:1) showed a single spot co-eluting with authentic material; $[\alpha]_D(CH_3OH) = -32.6^o$ (lit. $[\alpha]_D = -41.63^o$ [5]).

S-(-)-α-(2-Aminoethyl)benzenemethanol-[2-^{14}C], 6b:

A THF solution (25 mL) of **5c** (0.32087 g, 1.23 mmol) was treated by the dropwise addition of borane-THF (6.22 mL x 1N, 6.22 mmol) as described above for the preparation of **6a**. Conversion of the crude amino alcohol **6b** to its oxalate salt yielded 0.19195 g (72%); $[\alpha]_D(CH_3OH) = -34.67^o$; TLC (methylene chloride/ methanol/ ammonium hydroxide 100:30:1) showed a single spot co-eluting with authentic material.

S-(-)-γ-[4-(Trifluoromethyl)phenoxy]benzenepropanamine-[1-^{14}C], Maleate Salt, 7:

The oxalate salt of **6b** (0.17695 g, 0.734 mmol) was suspended in water (5 mL), made basic with 5N potassium hydroxide, and extracted with ether (5 x 25 mL). The combined extracts were dried and concentrated in vacuo. The residue was re-dissolved in dimethylacetamide (DMAC, 4 mL) and added dropwise to a suspension of sodium hydride (0.028 g of a 66% mineral oil dispersion, 0.693 mmol) in DMAC (1 mL). The mixture was slowly warmed to 65°C for one half hr; then treated dropwise with α,α,α,4-tetrafluorotoluene (0.0773 ml, 0.693 mmol) in DMAC (2 mL). The temperature was raised to 90-95°C and heating was continued for 3 hr whereupon the mixture was poured into ice and was extracten with ether (4 x 50 mL). The combined extracts were washed with water, dried, and concentrated in vacuo. TLC (methylene chloride/methanol/ammonium hydroxide 100:30:1) of the residue showed the desired product (**7**), with minor contamination by **6b** and a radioactive impurity moving with the solvent front.

The crude product was purified by flash chromatography (methylene chloride/ methanol/ ammonium hydroxide 100:30:1 in 10 mL fractions). Fractions 4-6 were combined to yield **7** (0.05165 g, 27%), which was re-dissolved in ether (0.6 mL) and was treated with maleic acid (0.020 g) in 1.43 mL of ether. The white crystalline salt was collected by filtration, washed with fresh ether, and dried (0.0594 g) (99.93% *S* by HPLC after derivatization).

A mixture of **7** (0.0594 g) and 2b (0.280 g) were recrystallized from water (3.5 mL) to yield **7** as its maleate (H_2O) (0.30054 g, 88.65%)(this material co-eluted with authentic 2b by HPLC and TLC-autoradiography (*vida supra*): sp. act. 14.8 μCi/mg (6.35 mCi/mmol);

99.98% S by HPLC after derivatization; radiochemical purity(RCP) by radio-HPLC (μ-bondapak C-18, 45% acetonitrile/55% 0.5 M ammonium phosphate at 2.0 mL/min, r_T = 5.44 min) 98.60%; RCP by TLC autoradiography: methylene chloride/methanol/ammonium hydroxide 100:30:1, 98.8%; chloroform/methanol/acetic acid 70:30:1, 99.16%; $[\alpha]_D$ (CH_3OH) = + 7.94°.

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