(d, $J = 3.5$ Hz, H_α, 5*S* isomer), 3.99 (d, $J = 6$ Hz, H_α, 5*R* isomer), 3.34-3.13 (m, H_4).

Method B: **Using Boron Tribromide in Dichloromethane.** This was carried out by using the procedure of Felix.[30] To a stirred solution of the protected amino acid (0.5 mmol) in dry CH_2Cl_2 (15 mL) cooled to −10 °C was added dropwise BBr_3–CH_2Cl_2 (3 mL of a 1 M solution). Stirring was continued at −10 °C for 1 h and at room temperature for 2–5 h, after which the reaction mixture was cautiously treated with H_2O (5 mL). The aqueous phase was collected and the organic phase was extracted with H_2O (5 × 5 mL). The combined aqueous extracts were evaporated to dryness under reduced pressure. The resulting solid was dissolved in H_2O (2 mL) and then loaded onto an ion-exchange column that had earlier been equilibrated with 0.4 M pyridine acetate buffer (pH 4). The column was eluted with 0.4 M pyridine acetate buffer (pH 4). The ninhydrin fraction positive fractions were pooled and then lyophilized to give the free amino acid. Recrystallization from aqueous methanol gave the pure product.

(α*S*,5*S*)-α-Amino-4,5-dihydro-5-isoxazoleacetic Acid (6b). The deprotection of **6c** gave **6b** (88% yield; mp 171–173 °C dec) identical by ^1H NMR with that obtained previously.

Method C: **Using Boron Trichloride in Dichloromethane. (α*S*,5*S*)-α-Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic Acid (Acivicin) (1).** To s stirred ice-cold solution of the 3-chloro-4,5-dihydroisoxazole (**6d**) (88 mg, 0.35 mmol) in dry CH_2Cl_2 (5 mL) under a nitrogen atmosphere was added dropwise a solution of BCl_3 in CH_2Cl_2 (2 mL of a 1 M solution). The resulting reaction mixture was stirred at room temperature for 20 h and then cautiously treated with water (5 mL). The aqueous layer was separated and then the organic layer was extracted with water (5 × 5 mL). The combined aqueous extracts were evaporated to dryness under reduced pressure and then the resulting solid was dissolved in 2 N HCl (2 mL) and loaded onto an ion-exchange column. The column was eluted with 0.5 N NH_4OH. The ninhydrin positive fractions were pooled and then lyophilized to afford acivicin as a white solid (35 mg, 59.5%). Recrystallization from aqueous methanol gave a white powder: mp 180–192 °C dec; R_f 0.56 ($MeOH$–H_2O–pyridine, 20:5:1); $[\alpha]^{20}{}_D$ +139° (*c* 0.14, H_2O), [lit.[6] $[\alpha]^{20}{}_D$ +148° (*c* 0.845, H_2O)]; $[\alpha]^{20}{}_{578}$ +146° (*c* 0.14, H_2O), [lit.[7] $[\alpha]^{20}{}_{578}$ +135° (*c* 0.159, H_2O)]; IR (KBr) 3500–2500, 1590, 1480, 1390, 1300 cm^{-1}; ^1H NMR (D_2O) 5.36 (ddd, $J = 11, 8, 3$ Hz, 1 H, H_5), 4.12 (d, $J = 3$ Hz, 1 H, H_α), 3.60 (dd, $J = 18, 11$ Hz, 1 H, H_4), 3.52 (dd, $J = 18, 8$ Hz, 1 H, H_4).

(α*S*,5*S*)- and (α*R*,5*R*)-α-[(Methoxycarbonyl)amino]-3-methyl-4,5-dihydroisoxazole-5-acetic Acid Methylidene Ester (8a). To a stirred ice-cold solution of (2*S*)-*N*-(methoxycarbonyl)vinylglycine methylidene ester (**3b**) (1.54 g, 9.0 mmol) and phenyl isocyanate (2.5 mL, 2.737 g, 23 mmol) in dry benzene (20 mL) under nitrogen was added dropwise a solution of dry nitroethane (3 mL, 3.135 g, 42 mmol) and dry triethylamine (0.4 mL, 0.29 g, 2.8 mmol) in dry benzene (10 mL). The resulting mixture was stirred at room temperature overnight. Purification by column chromatography (hexanes–ethyl acetate, 1:1) gave the cycloadduct **8a** (1.51 g, 74%) as a mixture of two isomers: ^1H NMR 5.65 and 5.52 (br, 1 H, methylidene CH), 5.38 and 5.26 (d, $J = 4$ Hz, 1 H, methylidene CH), 5.10 (m, 1 H, H_5), 4.43 and 4.27 (br s, 1 H, H_α), 3.82 (s, 3 H, OCH_3), 3.42 (dd, $J = 18, 6$ Hz, 1 H, H_4), 3.16 (dd, $J = 18, 11$ Hz, 1 H, H_4), 2.01 and 1.99 (s, 3 H, CH_3).

(α*S*,5*S*)- and (α*S*,5*R*)-α-Amino-3-methyl-4,5-dihydroisoxazole-5-acetic Acid (8b). Deprotection of 4,5-dihydroisoxazole-5-acetic acid methylidene ester (**8a**) (555 mg, 2.4 mmol) by method B (BBr_3/CH_2Cl_2) gave (α*S*)-α-amino-3-methyl-4,5-dihydroisoxazole-5-acetic acid (**8b**) as a solid (298 mg, 74%): ^1H NMR (D_2O) 4.98 (m, H_5, 5*S* isomer), 4.80 (m, H_5, 5*R* isomer), 3.90 (d, $J = 3.5$ Hz, H_α, 5*S* isomer), 3.66 (d, $J = 8$ Hz, H_α, 5*R* isomer), 3.31–3.01 (m, H_4), 1.92 (s, CH_3, 5*R* isomer), 1.87 (s, CH_3, 5*S* isomer). Recrystallization from aqueous methanol gave a white powder consisting largely of the α*S*,5*R* diastereomer: ^1H NMR (D_2O) 4.83 (m, 1 H, H_5), 3.69 (d, $J = 8$ Hz, 1 H, H_α), 3.30 (dd, $J = 18, 11$ Hz, 1 H, H_4), 3.15 (dd, $J = 18, 6$ Hz, 1 H, H_4), 1.95 (s, 3 H, CH_3). Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.67; H, 6.29; N, 18.14. The mother liquor was freeze-dried to give a solid consisting largely of the α*S*,5*S* diastereomer: ^1H NMR (D_2O) 5.00 (m, 1 H, H_5), 3.93 (d, $J = 3.5$ Hz, 1 H, H_α), 3.22 (dd, $J = 18, 11$ Hz, 1 H, H_4), 3.07 (dd, $J = 18, 7$ Hz, 1 H, H_4), 1.89 (s, 3 H, CH_3).

Acknowledgment. We are grateful to Dr. D. G. Martin of The UpJohn Company, Kalamazoo, MI, for kindly providing an authentic sample of acivicin. Financial support of the Natural Sciences and Engineering Research Council of Canada, the Clare Nelson Bequest, and Mr. and Mrs. J. A. Whitney is gratefully acknowledged. The experimental assistance of Chang-Mo Yang, Pacific Chemical Industrial Co. Ltd., Seoul, Korea, in preliminary aspects of this work is also gratefully acknowledged. Professor Saul Wolfe is sincerely thanked for many fruitful discussions, particularly those concerning computational methods.

---

[30] Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427–1429.

Asymmetric Synthesis of Both Enantiomers of Tomoxetine and Fluoxetine. Selective Reduction of 2,3-Epoxycinnamyl Alcohol with Red-Al

Y. Gao and K. B. Sharpless*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received February 16, 1988

Both enantiomers of tomoxetine **7a**,**7b** and fluoxetine **8a**,**8b** (as their hydrochloride salts) have been synthesized from cinnamyl alcohol by asymmetric epoxidation, and their absolute configurations have been established. Optimal conditions for regioselective Red-Al reduction at C-2 of 2,3-epoxycinnamyl alcohol are discussed.

Tomoxetine is the first norepinephrine (NE) reuptake-inhibiting antidepressant without strong affinity for α- or β-adrenergic receptors.[1] Fluoxetine is also a potent antidepressant with potential applications in treatment of other symptoms.[1b,2] The enantiomers of both compounds have been synthesized relying upon resolution of appropriate racemic precursors, and recently (*S*)-fluoxetine has

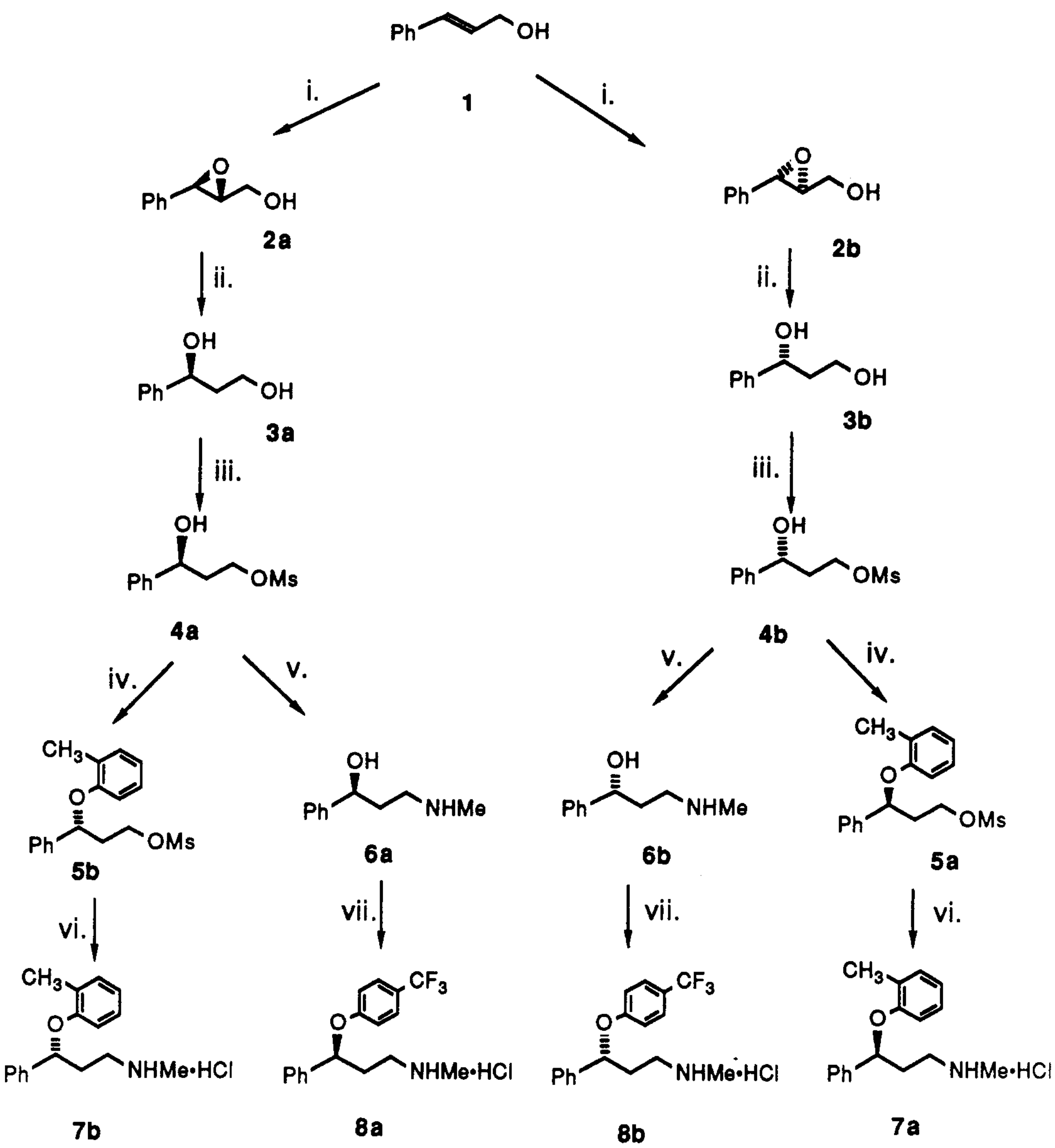
---

[1] (a) *Drugs Future* **1986**, *11*, 134. (b) Ankier, S. I. *Prog. Med. Chem.* **1986**, *23*, 121.

[2] Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.*, in press. The authors have developed a method for determination of enantiomeric excess of fluoxetine.

0022-3263/88/1953-4081$01.50/0

Scheme I[a]



[a] (i) See ref 3; (ii) Red-Al, DME, 0–25 °C; (iii) MsCl, Et_3N, ether, −10 to 0 °C; (iv) *o*-cresol, Ph_3P, DEAD, ether, −10 °C; (v) 40% aqueous $MeNH_2$, THF, 65 °C; (vi) (1) 40% aqueous $MeNH_2$, THF, 65 °C; (2) HCl (gas), ether; (vii) (1) NaH, DMAC, 90 °C; *p*-chlorobenzotrifluoride, 100–105 °C; (2) HCl (gas), ether.

Table I. Reaction of Epoxycinnamyl Alcohol with Red-Al[a]

entry	epoxy alcohol	Red-Al, equiv	alcohol (equiv)[b]	solvent	concn,[c] M	ratio 1,3-:1,2-diol[d]
1	**2b**	2.0		THF	0.12	4.5:1
2	**2b**	2.0	MeOH (1.0)	THF	0.4	9.5:1
3	**2b**	2.0	ME (2.0)	THF	0.2	15:1
4	**2b**	1.0		DME	0.5	16:1
5	**2b**	1.0		DME	0.2	22:1
6	**2b**	1.0		DME	0.1	17:1
7	**2a**	1.0		THF	0.2	14:1
8	**2a**	1.0		Et_2O	0.2	6.3:1
9	**2a**	1.0		benzene	0.2	6.7:1
10	**2a**	1.0		toluene	0.2	5.5:1

[a] All reactions were performed as described in the Experimental Section. [b] ME is for 2-methoxyethanol. [c] Concentration of 2,3-epoxycinnamyl alcohol. [d] Ratios were determined by ^1H NMR analyses of the derived diacetates focused on the methine proton of the diacetate of the diol; for 1,3-diacetate, this proton appears at 5.88 ppm as a doublet of doublets; for 1,2-diacetate, it appears at 5.26 ppm as a multiplet.

been synthesized from (*S*)-(−)-3-chloro-1-phenylpropanol.[2] They have been found to have a different spectrum of clinical efficacy.[1,2] Herein we report a versatile enantioselective synthesis of both enantiomers of tomoxetine and fluoxetine from cinnamyl alcohol by the catalytic asymmetric epoxidation and regioselective reduction of the corresponding epoxycinnamyl alcohol with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, Aldrich Chemical Co.) (Scheme I).

In the following discussion, only one enantiomer series is described. The other enantiomers were obtained similarly.

Catalytic asymmetric epoxidation of cinnamyl alcohol (1) using L-(+)-diisopropyl tartrate (DIPT) gave (–)-(2*S*,3*S*)-2,3-epoxycinnamyl alcohol **2b**.[3] Reductions of **2b** and **2a** with Red-Al to (*R*)- and (*S*)-3-phenyl-1,3-dihydroxypropane (**3b** and **3a**) were studied in detail, and the results are shown in Table I.

Red-Al is a highly regioselective reducing agent in the case of aliphatic 2,3-epoxy alcohols.[4] However, when epoxycinnamyl alcohol **2b** was treated with Red-Al under the standard conditions (2.0 equiv, Red-Al, THF, 25 °C), selectivity was only 4.5:1 in favor of the 1,3-diol (entry 1). Reduction of epoxy alcohol in the presence of an alcohol has been shown to increase the selectivity of the reaction.[5] Thus, the presence of 1.0 equiv of methanol resulted in better selectivity in THF (9.5:1, entry 2). When 2-methoxyethanol (2.0 equiv) was used in dimethoxyethane (DME), the ratio of 1,3-diol to 1,2-diol increased to 15:1 (entry 3). The regioselective reduction is thought to involve initial attachment of Red-Al to the hydroxy group followed by intramolecular hydride reduction. Attack at the C-2 position of the epoxy alcohol is favored due to the intramolecular delivery of the hydride through a five-membered cyclic transition state. In reduction of epoxycinnamyl alcohol, the phenyl group reduces the selectivity for C-2 opening by enhancing the competitive C-3 (benzylic) opening process. The observed low selectivity when 2.0 equiv of Red-Al is used is most likely due to the competing intermolecular reduction by excess Red-Al. Therefore, the selectivity for C-2 opening could be increased by reducing either the amount or the reactivity of the Red-Al (e.g. addition of an alcohol); the former method is more convenient and economical.

Entry 5 shows that reduction of epoxycinnamyl alcohol with just 1.0 equiv of Red-Al led to 1,3-diol in very high selectivity (>20:1). This reaction was also slightly affected by the concentration of the reagents, and 0.2 M in epoxycinnamyl alcohol appeared to be the optimum concentration (entries 4–6). DME was the best solvent; other solvents (THF, ethyl ether, benzene, toluene) resulted in much lower selectivity (entries 7–10). The reduction was usually complete within 3 h at room temperature, and the yield of (*S*)- or (*R*)-3-phenyl-1,3-dihydroxypropane (**3a** or **3b**) was very high (≥90%). The crude 1,3-diols were used directly in subsequent transformations without further purification.

Treatment of the crude diol **3a** with 1.0 equiv of methanesulfonyl chloride (MsCl) led to (*S*)-monomethanesulfonate **4a** in 80–85% yield after chromatographic purification.[6] With *p*-toluenesulfonyl chloride in pyridine, the corresponding tosylate could be obtained in similar yield, although the rate of its formation was slower. Reaction of **4a** with *o*-cresol under Mitsunobu conditions[7] produced (*R*)-3-phenyl-3-(2-methylphenoxy)propyl methanesulfonate (**5b**) in only 30–53% yield in THF at room temperature or at lower temperatures. However, when the reaction was performed in ethyl ether at –10 °C, the desired product **5b** could be obtained in 71–83% yield. Compound **5b** was then treated with an excess of methylamine in aqueous THF followed by acidification with hydrogen chloride to give the hydrochloride of (*R*)-(–)-tomoxetine (**7b**) ($[\alpha]^{23}_{D}$ –41.37° (*c* 1.02, MeOH)) in ca. 85%. Similarly, (*S*)-(+)-tomoxetine hydrochloride (**7a**) ($[\alpha]^{23}_{D}$ +43.2° (*c* 0.81, MeOH)) was obtained from **5a**. (*R*)-Tomoxetine was thereby obtained from (2*S*,3*S*)-epoxycinnamyl alcohol, while (*S*)-tomoxetine derived from (2*R*,3*R*)-epoxycinnamyl alcohol.

The synthesis of (*S*)-fluoxetine was straightforward with monomethanesulfonate **4a** as the starting material. Thus, treatment of **4a** with an excess of methylamine in aqueous THF afforded hydroxy amine **6a** in greater than 90% yield. Reaction of the sodium alkoxide of **6a** with *p*-chlorobenzotrifluoride, followed by acidification with hydrogen chloride, led to the hydrochloride of (*S*)-fluoxetine **8a** ($[\alpha]^{23}_{D}$ –7.12° (*c* 1.53, H_2O)) in 70% yield. In the same manner, (*R*)-fluoxetine hydrochloride (**8b**) ($[\alpha]^{23}_{D}$ +7.08° (*c* 1.30, H_2O)) was prepared from **6b** in 75% yield. Interestingly, (*S*)-fluoxetine is dextrorotatory in methanol and levorotatory in water (of course (*R*)-fluoxetine exhibits the opposite rotatory behavior in these two solvents); these results are in agreement with the observations by Dr. D. W. Robertson and co-workers.[2]

In conclusion, both enantiomers of tomoxetine and fluoxetine have been synthesized in five steps from cinnamyl alcohol with overall yields of 39% and 40%. Their absolute configurations are also established by these syntheses, since the configurations of the starting epoxycinnamyl alcohols are on firm ground.[8]

Experimental Section

Materials. All melting points are uncorrected. The ^{1}H NMR spectra were obtained at 250 MHz. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter using a 1-cm^3 capacity (10-cm path length) quartz cell.

All reagents were used as received from Aldrich Chemical Co. (+)-(2*R*,3*R*)- and (–)-(2*S*,3*S*)-2,3-epoxycinnamyl alcohols were prepared according to the procedure in ref 3. The preparative details are given for only one of the enantiomeric series.

(*R*)-3-Phenyl-1,3-dihydroxypropane (3b). To a solution of (–)-(2*S*,3*S*)-2,3-epoxycinnamyl alcohol (**2b**) (1.5 g, 10.0 mmol) in dimethoxyethane (50 mL) was added a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene (3.1 mL, 10.5 mmol) dropwise under nitrogen at 0 °C. After stirring at room temperature for 3 h, the solution was diluted with ether and quenched with 5% HCl solution. After further stirring at room temperature for 30 min, the white precipitate formed was removed by filtration and boiled with ethyl acetate and filtered again. The combined organic extracts were dried with magnesium sulfate. Concentration gave (*R*)-3-phenyl-1,3-dihydroxypropane (**3b**) as a slightly yellow oil, which was used without further purification (1.5 g, 98%): ^{1}H NMR ($CDCl_3$) δ 7.2–7.3 (m, 5 H), 4.88–4.98 (m, 1 H), 3.78–3.86 (t, J = 7.5 Hz, 2 H), 3.3–3.4 (br s, 1 H), 2.85–2.95 (br s, 1 H), 1.84–2.08 (m, 2 H); the ratio of 1,3-diol to 1,2-diol was 20:1 by ^{1}H NMR analysis of the derived diacetate.

(*S*)-3-Phenyl-1,3-dihydroxypropane (**3a**) was prepared according to the above procedure with 300 mg of (+)-epoxycinnamyl alcohol (**2a**) as the starting material to provide 300 mg of (*S*)-3-phenyl-1,3-dihydroxypropane. (1,3-diol:1,2-diol = 21:1)

(*S*)-3-Phenyl-3-hydroxypropyl Methanesulfonate (4a). To a solution of (*S*)-3-phenyl-1,3-dihydroxypropane (**3a**) (2.71 g, 17.8 mmol) and triethylamine (2.60 g, 25.6 mmol) in ether (90 mL) was added dropwise MsCl (1.45 mL, 18.7 mmol) under nitrogen at –10 °C. After stirring at –10 to 0 °C for 3 h, the mixture was poured into ice water (30 mL), washed with 20% H_2SO_4, saturated aqueous $NaHCO_3$, and brine, and dried over magnesium sulfate. The crude product was purified by chromatography on silica gel eluting with 45% ethyl acetate in hexane to give the title compound **4a** as an oil (3.50 g, 85%): ^{1}H NMR ($CDCl_3$) δ 7.3–7.4 (m, 5 H), 4.85–4.91 (t, J = 7.7 Hz, 1 H), 4.42–4.52 (m, 1 H), 4.22–4.32 (m, 1 H), 3.0 (s, 3 H), 2.3 (s, 1 H), 2.1–2.2 (q, J = 7.7 Hz, 2 H).

---

(3) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(4) (a) Finn, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, 2719. (b) Viti, S. M. *Tetrahedron Lett.* **1982**, 4541.

(5) Bulman Page, P. C.; Sutherland, I. O. *Tetrahedron Lett.* **1986**, 3535.

(6) Crossland, R. K.; Servis, K. K. *J. Org. Chem.* **1970**, *35*, 3195.

(7) Mitsunobu, O. *Synthesis* **1981**, 1.

(8) Melloni, P.; Torre, A. D.; Lazzari, E.; Mazzini, G.; Meroni, M. *Tetrahedron* **1985**, *41*, 1393.

(*R*)-3-Phenyl-3-hydroxypropyl methanesulfonate (**4b**) was prepared from (*R*)-3-phenyl-1,3-dihydroxypropane (**3b**) by the above procedure in 74% yield.

These two compounds were either stored at 0 °C or used soon after preparation.

(*R*)-3-Phenyl-3-(2-methylphenoxy)propyl Methanesulfonate (5b). To a stirred solution of (*S*)-3-phenyl-3-hydroxypropyl methanesulfonate (**4a**) (460 mg, 2.0 mmol), *o*-cresol (433 mg, 4.0 mmol), and triphenylphosphine (787 mg, 3.0 mmol) in ether (20 mL) was added dropwise diethyl azodicarboxylate (0.47 mL, 3.0 mmol) at -10 to -15 °C under nitrogen. After stirring at -10 °C for 4 h, the mixture was concentrated and diluted with 30% ethyl acetate in hexane. Suspended solid was removed by filtration, the filtrate was concentrated, and the crude product was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexane to give the title compound **5b** as a pale yellow oil (460 mg, 71%): IR (neat) 3040, 2950, 1600, 1490, 1360, 1240, 1120, 970, 760, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25–7.35 (m, 5 H), 7.10–7.13 (d, *J* = 7.4 Hz, 1 H), 6.93–6.99 (t, *J* = 7.3 Hz, 1 H), 6.76–6.82 (t, *J* = 7.3 Hz, 1 H), 6.58–6.62 (d, *J* = 7.4 Hz, 1 H), 5.34 (dd, *J* = 4.5, 8.5 Hz, 1 H), 4.33–4.42 (m, 1 H), 4.46–4.55 (m, 1 H), 2.91 (s, 3 H), 2.30–2.42 (m, 5 H).

(*S*)-3-Phenyl-3-(2-methylphenoxy)propyl methanesulfonate (**5a**) was prepared in 83% yield from (*R*)-3-phenyl-3-hydroxypropyl methanesulfonate (**4b**) by the above method.

(*R*)-Tomoxetine Hydrochloride (7b). A solution of (*R*)-3-phenyl-3-(2-methylphenoxy)-propyl methanesulfonate (**5b**) (450 mg, 1.45 mmol) and methylamine (10 mL, 40% in water) in THF (10 mL) was heated at 65 °C for 3 h. After cooling, the solution was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, and dried with anhydrous potassium carbonate. After concentration, a pale yellow oil was obtained. The oil was dissolved in ether and hydrogen chloride gas was bubbled through the solution until a white precipitate was formed (pH 2–3). The precipitate was collected and recrystallized from acetonitrile to provide the title compound **7b** as a white solid (400 mg, 94%): mp 162–164 °C (lit.[1] mp 166–168 °C); $[\alpha]^{23}{}_D$ -41.37° (*c* 1.02, MeOH); $[\alpha]^{25}{}_D$ -40.3° (*c* 0.94, EtOH) (lit.[1] $[\alpha]^{20}{}_D$ -37.6°); IR (KBr, $CHCl_3$) 2945, 2625, 1592, 1495, 1220, 1280, 1120, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.6–9.8 (br s, 2 H), 7.2–7.4 (m, 5 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 6.94 (t, *J* = 7.5 Hz, 1 H), 6.77 (t, *J* = 7.5 Hz, 1 H), 6.59 (d, *J* = 7.2 Hz, 1 H), 5.36 (dd, *J* = 4.7, 7.7 Hz, 1 H), 3.1–3.2 (br s, 2 H), 2.55–2.65 (br s, 3 H), 2.42–2.55 (m, 2 H), 2.30 (s, 3 H). Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; N, 4.80; Cl, 12.15. Found: C, 69.62; H, 7.47; N, 4.73; Cl, 12.34.

(*S*)-Tomoxetine hydrochloride (**7a**) was prepared in 87% yield from (*S*)-3-phenyl-3-(2-methylphenoxy)propyl methanesulfonate (**5a**) by the above procedure: mp 162–164 °C; $[\alpha]^{23}{}_D$ +43.2° (*c* 0.81, MeOH); $[\alpha]^{25}{}_D$ +40.5° (*c* 1.06, EtOH). Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; N, 4.80; Cl, 12.15. Found: C, 69.71; H, 7.51; N, 4.89; Cl, 12.39.

(*S*)-*N*-Methyl-3-phenyl-3-hydroxypropylamine (6a). A solution of (*S*)-3-phenyl-3-hydroxypropyl methanesulfonate (**4a**) (690 mg, 3.0 mmol) and methylamine (10 mL, 40% in water) in THF (10 mL) was heated at 65 °C for 3 h. After cooling, the solution was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, and dried with anhydrous potassium carbonate. Concentration to dryness provided the title compound (476 mg, 96%): ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5 H), 4.94 (dd, *J* = 3.8, 7.2 Hz, 1 H), 3.4–3.9 (br s, 1 H), 2.84–2.92 (m, 2 H), 2.45 (s, 3 H), 1.68–1.92 (m, 3 H).

Via a procedure identical with that above, 1.15 g of (*R*)-3-phenyl-3-hydroxypropyl methanesulfonate (**4b**) yielded 837 mg of (*R*)-*N*-methyl-3-phenyl-3-hydroxypropylamine (**6b**).

(*R*)-Fluoxetine Hydrochloride (8b). To a solution of (–)-*N*-methyl-3-phenyl-3-hydroxypropylamine (**6b**) (1.23 g, 7.45 mmol) in dimethylacetamide (7 mL) was added sodium hydride (215 mg, 8.95 mmol) with cooling. The mixture was heated at 90 °C for 1.5 h, and an orange solution resulted. To this solution was then added 4-chlorobenzotrifluoride (3.23 g, 2.40 mL, 17.9 mmol), and the mixture was heated at 100–105 °C for 2.5 h. After cooling and dilution with toluene, the mixture was washed with water, and the aqueous layer was separated and extracted with toluene. The combined toluene solutions were then washed with saturated aqueous sodium bicarbonate and brine and dried over magnesium sulfate. Concentration provided (*R*)-fluoxetine as an orange oil (1.97 g, 86%). The oil was dissolved in ether and acidified with hydrogen chloride gas (pH 3–4) to give an acidic ethereal solution (no precipitate formed). The solution was concentrated at room temperature to give a yellow solid, which was washed with ether to remove most of the orange color. The slightly yellow solid was then recrystallized from acetonitrile at –20 °C. The solid was collected and washed with ether to provide (*R*)-fluoxetine hydrochloride (**8b**) as a white powder (1.90 g, 75%): mp 140–142 °C (lit.[2] mp 140–141.5 °C); $[\alpha]^{23}{}_D$ -2.16° (*c* 1.62, MeOH) [lit.[2] $[\alpha]^{23}{}_D$ -1.97° (*c* 1.00, MeOH)]; $[\alpha]^{23}{}_D$ +7.08° (*c* 1.30, H_2O) [lit.[2] $[\alpha]^{23}{}_D$ +10.32° (c 1.00, H_2O)]; IR (KBr, $CDCl_3$) 2950, 2640, 2450, 1620, 1595, 1520, 1360, 1250, 1180, 1170, 1130, 1114, 1070, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.72 (br s, 2 H), 7.40–7.43 (d, *J* = 8.7 Hz, 2 H), 7.25–7.33 (m, 5 H), 6.88–6.92 (d, *J* = 8.7 Hz, 2 H), 5.45–5.50 (dd, *J* = 4.6, 7.9 Hz, 1 H), 3.12 (br s, 2 H), 2.55–2.62 (br s, 3 H), 2.42–2.52 (m, 2 H). Anal. Calcd for $C_{17}H_{19}ClF_3NO$: C, 59.05; H, 5.54; N, 4.05; F, 16.48; Cl, 10.25. Found: C, 58.84; H, 5.55; N, 3.94; F, 16.28; Cl, 10.50.

(*S*)-Fluoxetine hydrochloride (**8a**) was prepared in 70% yield by the above procedure from (*S*)-*N*-methyl-3-phenyl-3-hydroxypropylamine (**6a**): mp 140–142 °C (lit.[2] mp 135–137 °C); $[\alpha]^{23}{}_D$ -7.12° (*c* 1.53, H_2O) [lit.[2] $[\alpha]^{23}{}_D$ -10.85° (*c* 1.00, H_2O)]; Anal. Calcd for $C_{17}H_{19}ClF_3NO$: C, 59.05; H, 5.54; N, 4.05. Found: C, 59.19; H, 5.42; N, 3.89.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM 28384) for financial support, and we thank Dr. D. W. Robertson of Eli Lilly for providing a preprint of their publication and reviewers for their comments and corrections.

Registry No. **2a**, 98819-68-2; **2b**, 104196-23-8; **3a**, 96854-34-1; **3b**, 103548-16-9; **4a**, 115290-77-2; **4b**, 115290-78-3; **5a**, 115290-80-7; **5b**, 115290-79-4; **6a**, 114133-37-8; **6b**, 115290-81-8; **7a**, 82857-39-4; **7b**, 82248-59-7; **8a**, 114247-06-2; **8b**, 114247-09-5; **8b** (free base), 100568-03-4; *o*-cresol, 95-48-7; 4-chlorobenzotrifluoride, 98-56-6.