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Asymmetric Synthesis of Both Enantiomers of Fluoxetine via Microbiological Reduction of Ethyl Benzoylacetate

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Key Words: Fluoxetine; asymmetric synthesis; bioreduction; bakers' yeast; *Beauveria sulfurescens; Geotrichum candidum.*

Abstract: Microbiological reduction of ethyl benzoylacetate by bakers' yeast (*Saccharomyces cerevisiae*), *Beauveria sulfurescens* or *Geotrichum candidum* afforded ethyl (S)-3-hydroxy-3-phenylpropionate in high optical yield. This enantiomerically pure alcohol was converted into both enantiomers of fluoxetine (7). The product resulting from the bakers' yeast reduction had ee values (87-93%) lower than the 100% value erroneously attributed in earlier studies.

Fluoxetine (7) or N-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine hydrochloride is one of the first serotonin uptake inhibitors with little effect on noradrenergic or dopaminergic systems.[1,2] Although fluoxetine is used therapeutically as a racemate, there is some stereospecificity associated with its biological action.[3,4] Consequently a number of methods have been developed for the asymmetric synthesis of fluoxetine. The key step of these syntheses is the production of a stereogenic center at the benzylic position (Ph-CHOH-). Sharpless *et al.*[5] reported a synthesis of fluoxetine from cinnamyl alcohol by asymmetric catalytic epoxidation and regioselective reduction of the epoxide. Robertson *et al.*[3] used a borane-mediated asymmetric reduction developed by Brown *et al.*[6] whereas Corey *et al.*[7] and Achiwa *et al.*[8] used different catalytic asymmetric reductions. Chemoenzymatic approaches to the synthesis of fluoxetine[9-11] or analogs[12] have also been reported.

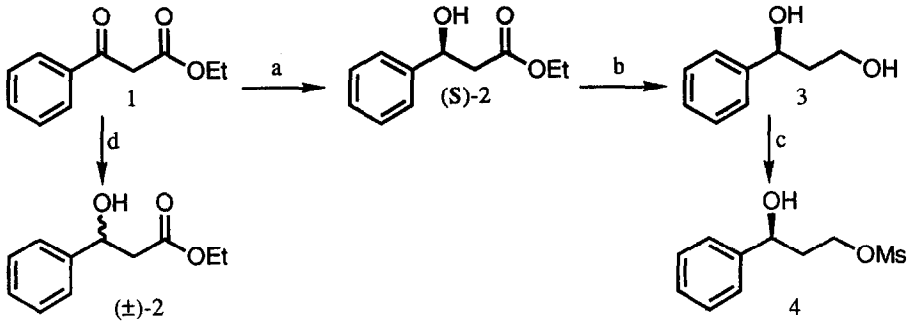
RESULTS AND DISCUSSION

The key step of our synthesis is the microbiological reduction of ethyl benzoylacetate. We have investigated in detail three whole cell systems: bakers' yeast (*Saccharomyces cerevisiae*), *Geotrichum candidum*, and *Beauveria sulfurescens*.

Active fermenting bakers' yeast reduced ethyl benzoylacetate **1** to give ethyl (S)-3-hydroxy-3-phenyl propionate **2** in moderate yield (Scheme 1). This bioreduction has been reported without mention of the enantiomeric purity of the product and an enantiomeric excess of 100% has been erroneously attributed to the product.[13-16] We established the enantiomeric purity of **2** by ^{1}H and ^{19}F NMR analysis (200 MHz) of the MTPA derivative (ester of α-methoxy-α-trifluoromethylphenylacetic acid, Mosher's reagent). Racemic **2** obtained by reduction of **1** with $NaBH_4$ was employed as a reference in these NMR experiments. Bioreductions performed with different brands of commercial yeast or with minor variations in experimental conditions resulted in a narrow range of chemical yields (50-63%) and ee values (87-93%)(Table 1).

We then looked for alternative microorganisms which might present opposite or better enantiospecificity.

Scheme 1



Reagents and conditions: (a) Bioreduction (see table 1), (b) $LiAlH_4$, ether, (c) MsCl, Et_3N, ether, -10°C to 0°C, (d) $NaBH_4$.

Table 1: Microbiological Reduction of Ethyl Benzoylacetate **1**

Microorganism	Yield[1] %	ee[1] %	Absolute configuration
Bakers' yeast	50-63	87-93	S
(Saccharomyces cerevesiae)			
Beauveria sulfurescens	72	96	S
Geotrichum candidum			
conditions A[2]	65	97	S
conditions B[3]	64	≥98	S

[1] Range using different brands and experimental conditions.
[2] Conditions A: substrate was added immediately after filtration and washing of the mycelium.
[3] Conditions B: substrate was added after a 24 h preincubation period.

Reduction of **1** with the fungus *Beauveria sulfurescens* gave the same enantiomer (S)-**2** in 72% chemical yield and 96% ee. The reduction with *Geotrichum candidum* was performed under two different sets of experimental conditions recently suggested by Buisson *et al.*[17] In the first set (conditions A), the substrate was directly added after filtration, washing and resuspension of the mycelium in water. In the second set (conditions B), the mycelium was separated and then preincubated during 24 h before the substrate was added. This microorganism gave also the same enantiomer (S)-**2** in good yield (~65%) and very high optical purity. The preincubation of the mycelium increased the selectivity of reduction and the R enantiomer is not detected by ^{19}F NMR analysis of the Mosher derivative (Fig. 1). The specific rotation ($[\alpha]_D^{25}$ -51.0 (c 1.5.$CHCl_3$)) of

alcohol **2** is much higher than the value reported by Ridley *et al.*[13] ($[\alpha]_D$ −25.8°) or Santaniello *et al.*[14] ($[\alpha]_D$ −39.8°).

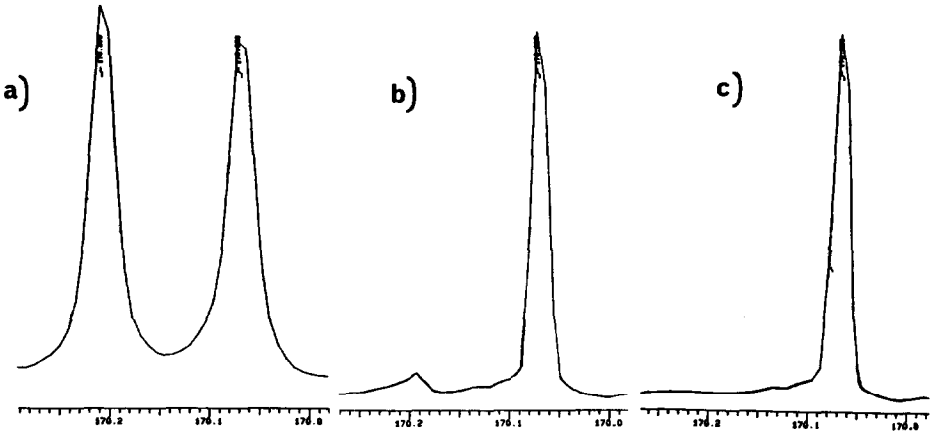


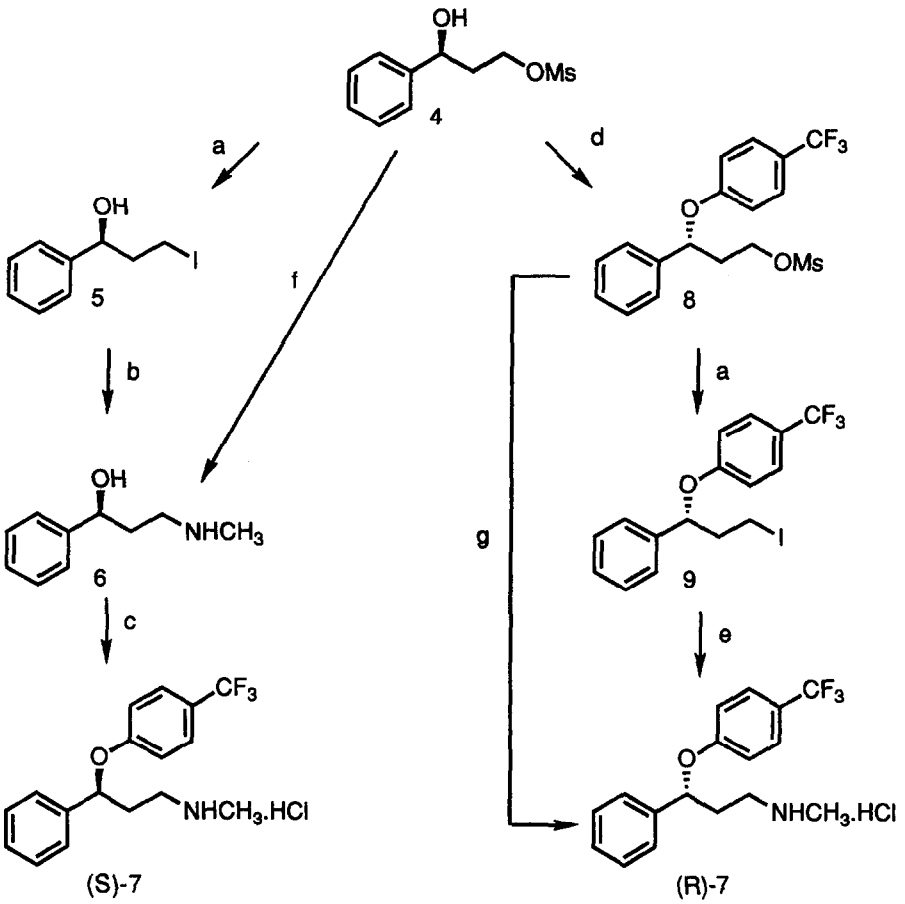
Fig. 1: ^{19}F NMR (188 MHz) spectra of (R)-MTPA derivative of ethyl (S)-3-hydroxy-3-phenyl propionate. a) racemic b) from bakers' yeast reduction c) from *Geotrichum candidum* reduction (conditions B).

Reduction of hydroxy-ester **2** with lithium aluminum hydride gave diol **3**. Treatment of diol **3** with one equivalent of methanesulfonyl chloride in the presence of triethylamine led to the monomesylate **4** (scheme 1). Both enantiomers of fluoxetine have been synthesized from mesylate **4** (scheme 2). Treatment of **4** with an excess of 40% aqueous methylamine in THF under reflux according to the method reported by Sharpless *et al.*[5] failed to give hydroxy-amine **6** in good yield. However, this reaction gave high yields when performed in a pressure tube. In an alternative two-step procedure, **4** was treated with sodium iodide in acetone under reflux to give **5** and then with aqueous methylamine in THF at room temperature to give **6**. Generation of the sodium alkoxide of **6** in the presence of sodium hydride in dimethylacetamide and reaction with p-chlorobenzotrifluoride, followed by acidification with gaseous hydrogen chloride led to the hydrochloride salt of (S)-fluoxetine **7**.

The monomesylate **4** was also converted to (R)-fluoxetine in the following way: reaction with trifluoro-p-cresol under Mitsunobu conditions (triphenylphosphine, diethyl azodicarboxylate) produced **8** with inversion of the chiral center. This compound was then treated with an excess of 40% aqueous methylamine in THF in a pressure tube at 70°C followed by acidification with gaseous hydrochloric acid to give the hydrochloride salt of (R)-fluoxetine **7** . The two-step procedure mentioned above has also been used: transformation of mesylate **8** to the iodo intermediate **9** followed by substitution with methylamine and acidification to give (R)-fluoxetine **7** .

To summarize our results, we have shown that bioreduction of ethyl benzoylacetate provides ethyl (S)-3-hydroxy-3-phenylpropionate in good chemical and very high optical yield. This alcohol was converted into both enantiomers of fluoxetine.[18] Advantages of the method are the low cost of reagents and operational

Scheme 2



Reagents and conditions: a) NaI, acetone; b) 40% aqueous CH_3NH_2, THF, rt; c) (1) NaH, dimethylacetamide, 90°C; p-chlorobenzotrifluoride, 100-105 °C; (2) HCl(gas), ether; d) trifluoro-p-cresol, Ph_3P, DEAD, ether, -23 °C; e) (1) 40% aqueous CH_3NH_2, THF, rt, ; (2) HCl(gas), ether; f) 40% aqueous CH_3NH_2, THF, 70°C, pressure tube; g) (1) same as f); (2) HCl(gas), ether.

simplicity compared to nonbiological procedures.[5-7] The method provides higher enantiomeric purity (ee ≥ 98%) than the process based on catalytic asymmetric hydrogenation (ee 67-90%) reported by Achiwa.[8] Also, previous chemoenzymatic syntheses suffered from low yields. For instance, the bakers' yeast reduction of 3-chloropropiophenone provided 30% of propiophenone as a useless by-product.[11]

EXPERIMENTAL

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. The IR spectra were recorded on a Beckman 4250 or a Bomem FT-IR MB 102 spectrometer. NMR spectra were obtained on a Varian XL-200 instrument. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Mass spectra were recorded from a Hewlett-Packard 5890 spectrometer at 70 e.v. ionization voltage. Elemental analyses were done on a Carlo Erba Strumentazione-1106. GC analyses were carried out on a Hewlett-Packard 5890 chromatograph with a 25 m × 0.32 mm, carbowax chrompack column at 150°C and with a flame ionization detector.

(–)-(S)-Ethyl 3-hydroxy-3-phenylpropanoate (2): a) Bioreduction with bakers' yeast. Bakers' yeast (10 g, Springer brand) was suspended in 250 mL of distilled water containing 12.5 g of saccharose. Ethyl benzoylacetate **1** (200 mg) was added and the mixture was shaken on an orbit shaker at 27°C for 48 h. The reaction was monitored by gas chromatography. The mixture was filtered and the filtrate was extracted (continuous extraction) with ether. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography (8% ethyl acetate in CH_2Cl_2) to give **2** as an oil.

b) Bioreduction with *G. candidum* (CBS 233-76) and *B. sulfurescens* (ATCC 7159). The mycelium was filtered from the culture medium and washed with an aqueous sodium chloride solution (8 g/L). The mycelium (5 g) was suspended in 50 mL of distilled water and 50 mg of compound **1** was added immediately (conditions A) or after 24 h (conditions B). The mixture was shaken on an orbit shaker at 27°C for 48 h. The product was extracted as above. Yields and ee values are in Table 1. $[\alpha]_D^{25}$ –51.0° (c 1.5, $CHCl_3$); lit.[14] $[\alpha]_D$ –39.8° (c 1.5, $CHCl_3$). IR (film) 3450, 3040, 2960, 1715, 1490, 1440, 1360, 1260, 1190, 1020, 755, 695 cm^{-1}. MS, m/z (Rel. int.): 194 (M^+, 35), 107 (100), 105 (68), 79 (44), 77 (32). ^1H NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7 Hz), 2.68 (2H, 2d, J_1 = 4.5 Hz, J_2 = 8 Hz), 3.56 (1H, s), 4.11 (2H, q, J = 7 Hz), 5.08 (1H, dd, J_1 = 4.5 Hz, J_2 = 8 Hz), 7.25 (5H, m). ^{13}C NMR ($CDCl_3$) δ 13.99, 43.37, 60.59, 70.09, 125.42, 127.39, 128.17, 142.49, 171.86.

(S)-3-Phenyl-1,3-dihydroxypropane (3): Ester **2** (1.09 g, 5.6 mmol) was dissolved in 10 mL of dry ether and the solution was added dropwise to a stirred suspension of $LiAlH_4$ (0.319 g, 8.4 mmol) in 10 mL of dry ether under nitrogen at 0°C. The mixture was stirred overnight at room temperature. The mixture was cooled and quenched by addition of 10% HCl. The product was extracted with ether and the organic phase washed with brine, dried and evaporated. Chromatography on silica (ethyl acetate/CH_2Cl_2, 2:3) gave diol **3** (0.69 g). Yield: 80%; $[\alpha]_D^{25}$ –63.8° (c 1, $CHCl_3$). IR (film) 3315, 3020, 2935, 1595, 1490, 1450, 1200, 1050, 750, 695 cm^{-1}.

MS, m/z (Rel. int.) 152 (M^+, 26), 107 (100), 105 (28), 79 (45), 77 (31), 51 (15). ^{1}H NMR ($CDCl_3$) δ 1.94 (2H, m), 2.91 (2H, s), 3.81 (2H, t, J = 5.5 Hz), 4.91 (1H, dd, J_1 = 4.5 Hz, J_2 = 8 Hz), 7.29 (5H, m). ^{13}C NMR ($CDCl_3$) δ 40.35, 60.10, 72.63, 125.39, 127.00, 128.02, 144.03.

(S)-3-Phenyl-3-hydroxypropyl methanesulfonate (4): Methanesulfonyl chloride (0.80 mL, 10.3 mmol) was added dropwise to a solution of diol **3** (1.50 g, 9.9 mmol) and triethylamine (2 mL, 14.3 mmol) in ether (50 mL) under nitrogen at −10°C. After stirring at 0°C for 2 h, the mixture was poured into ice water. The organic phase was washed with 20% H_2SO_4, saturated aqueous $NaHCO_3$ and dried. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel eluting with CH_2Cl_2-ethyl acetate 9/1 to give **4** as an oil (1.78 g). Yield: 85%; $[\alpha]_D^{25}$ −24.0° (c 1.6, $CHCl_3$). IR (film) 3450, 3040, 2930, 1605, 1495, 1450, 1345, 1170, 760, 695 cm^{-1}; MS, m/z (Rel. int.) 230 (M^+, 6), 134 (59), 133 (77), 107 (100), 106 (38), 105 (95), 77 (38), 79 (66). ^{1}H NMR ($CDCl_3$) δ 2.11 (2H, m), 2.43 (1H, s), 2.96 (3H, s), 4.28 (1H, m), 4.45 (1H, m), 4.83 (1H, dd, J_1 = 6.5 Hz, J_2 = 7 Hz), 7.32 (5H, m). ^{13}C NMR ($CDCl_3$) δ 37.13, 38.11, 67.18, 70.07, 125.52, 127.77, 128.52, 143.34.

(S)-3-(Methylamino)-1-phenyl-1-propanol (6) (from 4): A solution of mesylate **4** (0.40 g, 1.8 mmol) and methylamine (6 mL, 40% solution in water) in THF (6 mL) was heated at 70°C in a pressure tube for 4 h. After cooling, THF was evaporated and replaced by ether. The organic phase was washed with 2N NaOH, brine, dried and evaporated. The crude product was purified by flash chromatography on silica gel eluting with 40% ethyl acetate in methanol to give **6** as an oil (0.28 g). Yield: 90%; $[\alpha]_D^{25}$ −33.5° (c 0.5, $CHCl_3$). IR (film) 3300, 3060, 2930, 1600, 1540, 1470, 1200, 1060, 750, 700 cm^{-1}; Ms, m/z (Rel. int.) 165 (M^+, 100), 105 (37), 104 (56), 79 (31), 77 (59). ^{1}H NMR ($CDCl_3$) δ 1.80 (2H, m), 2.41 (3H, s), 2.82 (2H, m), 3.91 (2H, s), 4.90 (1H, dd, J_1 = 4 Hz, J_2 = 8 Hz), 7.29 (5H, m). ^{13}C NMR ($CDCl_3$) δ 35.80, 37.02, 49.86, 74.60, 125.30, 126.53, 127.82, 144.96.

(S)-3-Iodo-1-phenyl-1-propanol (5): A solution of **4** (0.20 g, 0.9 mmol) in 30 mL of acetone previously saturated with NaI by refluxing overnight. The acetone was evaporated and the residue dissolved in ether. The latter was washed with brine, dried and evaporated. Chromatography on silica (ether/petroleum ether, 1:9) and recrystallization from petroleum ether gave **5** as a white solid (0.22 g). Yield: 90%; mp 53-54°C; $[\alpha]_D^{22}$ +3.3° (c 1, $CHCl_3$); lit.: mp 54-55°C; $[\alpha]_D^{22}$ +3.14° (c 1 $CHCl_3$). IR (film) 3360, 3045, 2900, 1490, 1460, 1225, 1020, 760, 695 cm^{-1}. SM, m/z (Rel. int.) 262 (M^+, 8), 107 (100), 79 (33), 77 (25). ^{1}H NMR ($CDCl_3$) δ 2.18 (2H, m, J_1 = 5 Hz, J_2 = 6 Hz, J_3 = 7 Hz), 2.45 (1H, s), 3.29 and 3.15 (2H, 2m, J = 6 Hz), 4.76 (1H, dd, J_1 = 5 Hz, J_2 = 7 Hz), 7.32 (5H, m). ^{13}C NMR ($CDCl_3$) 2.79, 42.20, 73.98, 125.66, 127.73, 128.46, 143.20.

(S)-3-(Methylamino)-1-phenyl-1-propanol (6) (from 5): A solution of **5** (0.98 g, 3.7 mmol) and methylamine (2.9 mL, 40% solution in water) in 10 mL of THF was stirred at room temperature overnight. Workup as

above gave **6** (0,53g, 86%). Physical data were identical to those reported above.

(S)-Fluoxetine hydrochloride (7): To a solution of **6** (0.35 g, 2.1 mmol) in dry dimethylacetamide (5 mL) at 0°C was added 97% NaH (100 mg, 4.2 mmol). The mixture was heated to 70°C for 30 min. Trifluoromethyl-p-chlorobenzene (0.31 mL, 2.3 mmol) was added and the reaction was heated at 90-95°C for 4 h. After cooling and dilution with ether, the mixture was washed with brine, dried and concentrated under vacuum. Chromatography on silica (methanol/CH_2Cl_2/ammonium hydroxide, 10/100/1) provided (S)-fluoxetine free base (0.49 g). Yield: 75%; IR (film) 3300, 3040, 2900, 1610, 1585, 1515, 1325, 1245, 1175, 1155, 1110, 1065, 830, 750, 695 cm^{-1}; MS, m/z (Rel. int.) 309 (M^+, 36), 162 (100), 161 (25), 143 (48), 133 (50), 115 (28), 104 (78), 103 (47), 78 (41), 77 (34). ^1H NMR ($CDCl_3$) δ 1.34 (1H, s), 2.19 and 2.06 (2H, m), 2.43 (3H, s), 2.74 (2H, t, J = 7 Hz), 5.32 (2H, dd, J_1 = 5 Hz, J_2 = 8 Hz), 6.91 (2H, d, J = 9 Hz), 7.33 (5H, m), 7.43 (2H, d, J = 9 Hz). ^{13}C NMR δ 36.42, 38.69, 48.17, 78.56, 115.64, 121,60, 123.53, 125.62, 126.59, 127.64, 128.59, 140.90, 160.40.

The oil was dissolved in ether and acidified with HCl gas. The solution was concentrated to give a solid which was recrystallized from ether/hexane to provide pure (S)-fluoxetine hydrochloride **7**. Yield: 80%; mp 139-140°C; $[\alpha]_D^{25}$ +14.0° (c 1, $CHCl_3$), $[\alpha]_D^{25}$ −10.2° (c 1, H_2O); lit.[3]: mp 140-141°C, $[\alpha]_D$ +13.8° (c 1, $CHCl_3$), $[\alpha]_D$ −10.85° (c 1, H_2O). IR (film) 2960, 2800, 2730, 2470, 1620, 1595, 1520, 1340, 1250, 1185, 1165, 1130, 1115, 1070, 840 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.48 (2H, m), 2.63 (3H, m), 3.13 (2H, m), 5.47 (2H, dd, J_1 = 5 Hz, J_2 = 8 Hz), 6.90 (2H, d, J = 8 Hz), 7.26 (5H, m), 7.42 (2H, d, J = 8 Hz), 9.70 (2H, s). ^{13}C NMR ($CDCl_3$) 32.99, 34.56, 46.10, 77.00, 115.84, 125.76, 126.77, 128.41, 129.04, 139.09, 159.69.

(S)-3-Phenyl-3-(4-trifluoromethylphenoxy)propyl methanesulfonate (8): To a stirred solution of **4** (1.03 g, 4.5 mmol), triphenylphosphine (1.77 g, 6.8 mmol), and trifluoro-p-cresol (1.44 g, 8.9 mmol) in dry ether (50 mL) was added dropwise diethyl azodicarboxylate (1.05 mL, 6.7 mmol) at −23°C under nitrogen. The solution was stirred at −10°C for 4 h, concentrated under vacuum and diluted with 30% ethyl acetate in hexane. The precipitate was removed by filtration, the filtrate was evaporated and the product was purified by chromatography on silica (ethyl acetate/hexane 3:7) to give **8** (1.18 g). Yield: 65%; $[\alpha]_D^{25}$ +3.5° (c 1.2, $CHCl_3$); IR (film) 3045, 2945, 1615, 1590, 1520, 1455, 1355, 1325, 1245, 1170, 1120, 1070, 840 cm^{-1}; SM, m/z (Rel. int.) 374 (M^+, 0,2), 118 (18), 117 (100), 79 (17); ^1H NMR ($CDCl_3$) δ 2.35 (2H, m), 2.94 (3H, s), 4.48 and 4.35 (2H, 2m), 5.36 (1H, dd, J_1 = 5 Hz, J_2 = 8.5 Hz), 6.90 (2H, d, J = 9 Hz), 7.34 (5H, m), 7.43 (2H, d, J = 9 Hz). ^{13}C NMR ($CDCl_3$) 36.98, 37.95, 66.29, 75.93, 115.56, (121.58, 122.24, 122.89, 123.55, J = 33 Hz), (115.20, 120.93, 126.67, 132.40, J = 288 Hz), 125.48, 126.45, 127.93, 128.62, 139.41, 159.80.

(R)-3-Iodo-3-(4-trifluoromethylphenoxy)propane (9): Compound **9** was prepared by using the same procedure as for the preparation of **5**. Chromatography on silica (petroleum ether) gave **9**. Yield: 90%; $[\alpha]_D^{25}$

$-10.0°$ (c 1.1, $CHCl_3$). IR (film) 3060, 2930, 1615, 1590, 1515, 1490, 1330, 1250, 1170, 1115, 1065, 1010, 830 cm^{-1}. MS, m/z (Rel. int.) 406 (M^+, 1), 245 (46), 133 (23), 118 (21), 117 (100), 115 (29), 91 (38). ^1H NMR ($CDCl_3$) δ 2.49 and 2.32 (2H, 2m), 3.35 and 3.25 (2H, 2m), 5.31 (1H, dd, J_1 = 4.5 Hz, J_2 = 8 Hz), 6.92 (2H, d, J = 8.5 Hz), 7.35 (5H, m), 7.45 (2H, d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 1.68, 41.94, 79.89, 115.79, (122.00, 122.64, 123.28, 123.91, J = 32 Hz), (116.28, 121.71, 127.14, 132.57, J = 273 Hz), 125.83, 126.82, 128.20, 128.92, 139.71, 160.26.

(R)-Fluoxetine hydrochloride (7): (R)-Fluoxetine was prepared from **9** (yield 85%) by the same procedures as for the preparation of **6** from **5**. (R)-Fluoxetine was also prepared from **8** (yield 80%) by the procedure described for the preparation of **6** from **4**. The hydrochloride salt of (R)-fluoxetine was prepared as described above for the S isomer (yield 80%). Mp 141-142°C; lit.[3] 142-143°C. $[\alpha]_D^{25}$ $-14.8°$ (c 1.1, $CHCl_3$); lit.[3] $[\alpha]_D^{25}$ $-13.8°$ (c 1, $CHCl_3$).

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REFERENCES AND NOTES

1. Robertson, D.W.; Jones, N.D.; Swartzendruber, J.K.; Yang, K.S.; Wong, D.T. *J. Med. Chem.* **1988**, *31*, 185.
2. Ives, J.L.; Heym, J. *Ann. Rep. Med. Chem.* **1989**, *24*, 21.
3. Robertson, D.W.; Krushinski, J.H.; Fuller, R.W.; Leander, J.D. *J. Med. Chem.* **1988**, *31*, 1412.
4. Wong, D.T.; Fuler, R.W.; Robertson, D.W. *Acta Pharm. Nord.* **1990**, *2*, 171.
5. Gao, Y.; Sharpless, K.B. *J. Org. Chem.* **1988**, *53*, 4081.
6. Srebnik, M.; Ramachandran, P.V.; Brown, H.C. *J. Org. Chem.* **1988**, *53*, 2916.
7. Corey, E.J.; Reichard, G.A. *Tetrahedron Lett.* **1989**, *30*, 5207.
8. Sakuraba, S.; Achiwa, K. *Synlett.* **1991**, 689.
9. For a preliminary report see: Chênevert, R.; Fortier, G. *Chem. Lett.* **1991**, 1603.
10. Kumar, A.; Ner, D.H.; Dike, S.Y. *Tetrahedron Lett.* **1991**, *32*, 1901.
11. Fronza, G.; Fuganti, C.; Grasselli, P.; Mele, A. *J. Org. Chem.* **1991**, *56*, 6019.
12. Cregge, R.J.; Wagner, E.R.; Freedman, J.; Margolin, A.L. *J. Org. Chem.* **1990**, *55*, 4238.
13. Deol, D.S.; Ridley, D.D.; Simpson, G.W. *Aust. J. Chem.* **1976**, *29*, 2459.
14. Manzocchi, A.; Casati, R.; Fiecchi, A.; Santaniello, E. *J. Chem. Soc. Perkin Trans I.* **1987**, 2753.
15. Servi, S. *Synthesis.* **1990**, 1.
16. Csuk, R.; Glänzer, B.I. *Chem. Rev.* **1991**, *91*, 49.
17. Buisson, D.; Azerad, R.; Sanner, C.; Larchevêque, M. *Tetrahedron Asymmetry.* **1991**, *2*, 987.
18. Presented, in part, at the NATO Workshop on "Microbial Reagents in Organic Synthesis". Sestri Levante, Italy, March 23-27, 1992.