Pergamon

Tetrahedron 57 (2001) 9925–9929

TETRAHEDRON

Enantioselective synthesis of (*S*)- and (*R*)-fluoxetine hydrochloride

William H. Miles,* Elizabeth J. Fialcowitz and E. Scott Halstead

Department of Chemistry, Lafayette College, Easton, PA 18042, USA

Received 21 August 2001; revised 18 October 2001

Abstract—The enantioselective synthesis of fluoxetine hydrochloride, a potent serotonin-uptake inhibitor, is described. The synthesis of (*S*)-fluoxetine hydrochloride begins with the asymmetric carbonyl-ene reaction of benzaldehyde with 3-methylene-2,3-dihydrofuran (**1**) catalyzed by $Ti[OCH(CH_3)_2]_4$/(*S*)-BINOL to give (*S*)-2-(3-furyl)-1-phenyl-1-ethanol (**2**) in 90% yield and 95% ee. In five steps, alcohol **2** was converted into (*S*)-fluoxetine hydrochloride (97% ee and 56% overall yield from benzaldehyde). (*R*)-fluoxetine hydrochloride was prepared by the same sequence except that $Ti[OCH(CH_3)_2]_4$/(*R*)-BINOL was used in the first reaction to give the enantiomer of **2**.

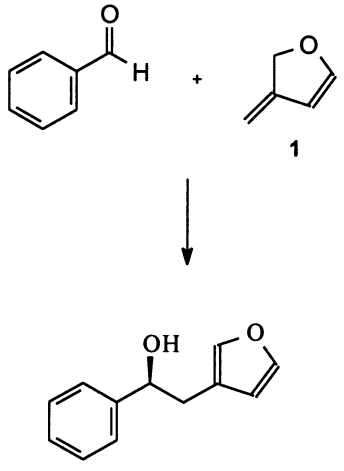
1. Introduction

The development of chiral Lewis acids for the ene,[1] Diels–Alder,[2] aldol,[3] allylation,[4,5] and many other reactions[6,7] is one of the most important advances in asymmetric synthesis. In the case of the carbonyl-ene reaction, the chiral Lewis acid catalysts typically are effective only for the reaction of alkenes with reactive enophiles such as glyoxylates.[8] In our recent studies of 3-methylene-2,3-dihydrofuran (**1**),[9–11] the alicyclic isomer of 3-methylfuran, we have demonstrated that **1** is an exceptionally reactive ene in the ene reaction. In addition to the thermal ene reaction of **1** with alkenyl enophiles,[9] including C_{60},[10] we have developed conditions for the Lewis acid-catalyzed reaction of **1** with aldehydes.[11] At that time, we also reported encouraging results for the asymmetric carbonyl-ene reaction of **1** with benzaldehyde using a Ti(IV)/BINOL system (Scheme 1).

Although the applicability of **1** to the synthesis of naturally occurring 3-substituted furans[12] has obvious potential, the chemical manipulation of the furanyl moiety also presented us with a wide array of potential synthetic targets.[13] For example, the furan ring has been exploited as a carboxylic acid equivalent in many syntheses.[14] When the asymmetric ene reaction of **1** with aldehydes is coupled with the oxidation of the furan to a carboxylic acid, **1** becomes a chiral acetate enolate equivalent. We have incorporated this synthetic manipulation in our synthesis of the enantiomers of fluoxetine hydrochloride,[15–19] a potent and commercially important serotonin-uptake inhibitor. Although fluoxetine hydrochloride is sold as a racemic mixture, the two enantiomers have different pharmacological profiles.[20] This paper describes the six-step synthesis of (*S*)- and (*R*)-fluoxetine hydrochloride using **1** and benzaldehyde as starting materials, with the asymmetric carbonyl-ene reaction of **1** establishing the critical stereogenic center.

2. Results and discussion

Guided by the studies of Keck[5] and others,[1,4] we optimized the asymmetric carbonyl-ene reaction of **1** with benzaldehyde to give alcohol **2** (Table 1). In our initial studies, we typically obtained excellent yields of **2** but had difficulty in reproducing good enantioselectivity. The cause of these inconsistent results was the paradoxical role played by the molecular sieves. Like most reactions employing titanium alkoxide/chiral alcohol catalysts, the absence of molecular sieves (entry 11) gives only moderate enantioselectivity, presumably due to importance of the molecular sieves in



Scheme 1. *Reaction conditions*: $Ti(OCH(CH_3)_2)_4$, (*S*)-BINOL.

Keywords: ene reactions; furans; asymmetric synthesis.

* Corresponding author. Tel.: +1-610-330-5221; fax: +1-610-330-5714; e-mail: milesw@lafayette.edu

0040–4020/01/$ - see front matter
PII: S0040-4020(01)01012-2

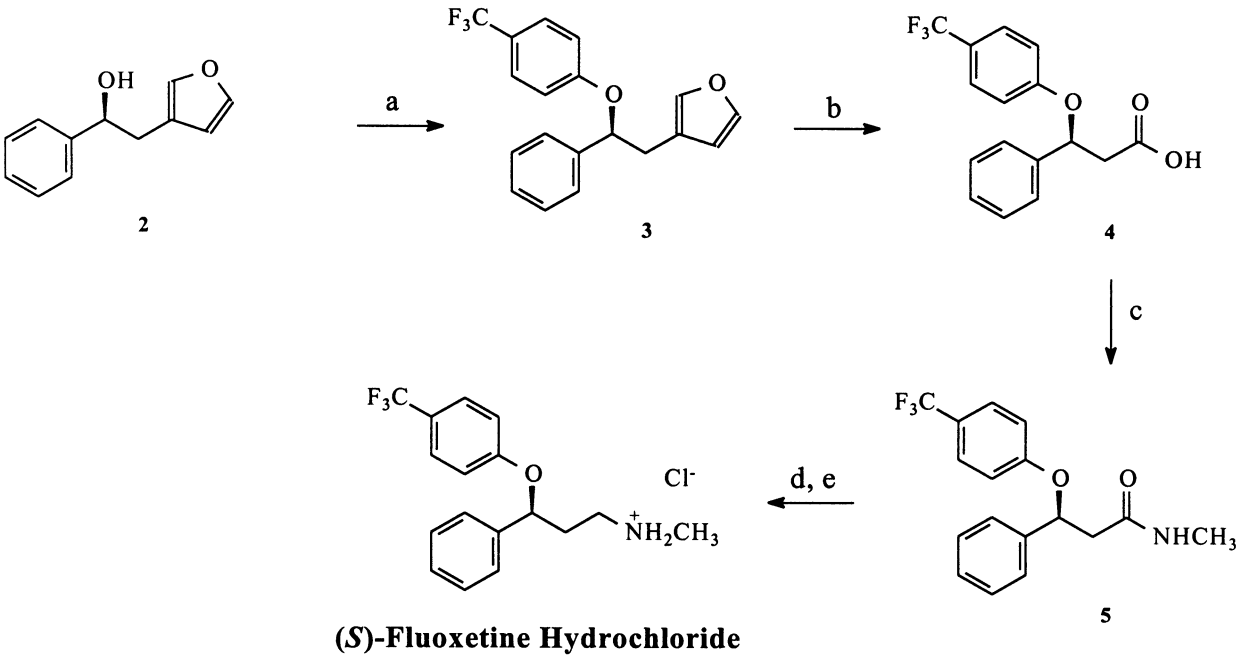
Table 1. Reaction of 3-methylene-2,3-dihydrofuran (**1**) with benzaldehyde

Entry	Solvent	Ti (mol%)	Ti/(*S*)-BINOL	Molecular sieves (g)[a]	Temperature (°C)	[C_6H_5CHO]	Yield (%)	ee (%)
1	Ether	5	1:1	0.5	0	0.5	82	85
2	Ether	10	1:1	0.5	0	0.5	90	87
3	Ether	20	1:1	0.5	0	0.5	92	87
4	Ether	10	1:1	0.5	35	0.5	87	83
5	Ether	10	1:1	0.5	−78 to 0	0.5	68	72
6	Ether	10	1:1	0.5	0	Inverse addition[b]	0	–
7	Ether	10	1:1	0.5	0	Coaddition[c]	79	89
8	Ether	10	1:2	0.5	0	0.5	87	92
9	*Ether*	*10*	*1:2*	*0.5*	*0*	*0.1*	*83*	*95*
10	Ether	10	1:2	0.5	−23	0.5	70	92
11	Ether	10	1:1	0	0	0.5	94	59
12	Ether	10	1:1	0.5[d]	0	0.5	94	4
13	Ether	10	1:1	0.5[e]	0	0.5	30	41
14	CH_2Cl_2	10	1:1	0.5	0	0.5	61	85
15	CH_2Cl_2	10	1:2	0.5	0	0.5	68	91
16	Toluene	10	1:2	0.5	0	0.5	40	93

[a] The molecular sieves were stored in an oven at 110°C at atmospheric pressure.
[b] Benzaldehyde was added as a 1 M solution in ether.
[c] Benzaldehyde and **1** were added as an ether solution.
[d] The molecular sieves were dried at 180°C at 0.1 T for 16 h.
[e] The molecular sieves were dried at 120°C at 0.05 T for 24 h and then placed in an open container for 24 h.

facilitating the ligand exchange reaction for the formation of the active chiral catalysts.[1] The level of hydration of the molecular sieves, however, was critical for high enantioselectivity. Unlike some studies,[4] molecular sieves that were rigorously dried gave very poor enantioselectivity (entry 12), but fully hydrated molecular sieves also gave low enantioselectivity (entry 13). The optimal level of hydration was achieved by storing the molecular sieves in an oven at 110°C. These results are similar to Posner's optimization of the Diels–Alder reaction of dihydropyrones[21] and Mikami's study of the ene reaction of glyoxylate esters using Ti(IV)/BINOL.[22]

The optimal Ti(IV)/BINOL ratio was found to be 1:2 (entries 8–10, 15, 16), with 10 mol% Ti(IV) being a practical catalyst load. Our survey of the solvents commonly employed with the titanium alkoxide catalysts revealed that both ether (entry 9) and methylene chloride (entry 15) were good solvents for this reaction, with higher yields observed in ether. The reactions in toluene (entry 16) were sluggish but also gave good enantioselectivity. An incremental increase in enantioselectivity was obtained with a lower starting concentration of benzaldehyde (entry 8 vs. 9), although a larger excess of furan **1** must be used to drive the complete conversion of benzaldehyde. The decomposition of **1** competes with the carbonyl-ene reaction of **1**, leading to incomplete conversions at lower temperatures (entries 5 and 10) and no product with inverse addition



Scheme 2. *Reaction conditions*: (a) NaH, DME, 4-fluorobenzotrifluoride; (b) $RuCl_3{\cdot}xH_2O$, $NaIO_4$, EtOAc, H_2O; (c) hydroxybenzotriazole hydrate, *N*-methylmorpholine, CH_3NH_2, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; (d) BH_3, THF; MeOH, 6 M HCl;(e) HCl in Et_2O.

(entry 6). Large-scale preparations based on our optimized procedure (entry 9) gave **2** in 90% yield in 95% ee. The enantioselectivity observed for the reaction of **1** with benzaldehyde is comparable to other studies employing the Ti(IV)/(*S*)-BINOL catalyst,[1,4,5] in which the *si*-face of the aldehyde is attacked (Scheme 2).

Nucleophilic aromatic substitution of 4-fluorobenzotrifluoride by the sodium alkoxide of **2** gave the desired aryloxyfuran **3** (92% yield). Several attempts were made to use the less expensive 4-chlorobenzotrifluoride as the electrophile but these reactions were fraught with incomplete conversions and/or contamination by elimination products. The oxidation of furan **3** using the standard Sharpless procedure[23] cleanly gave moderate yields of carboxylic acid **4** (45–50% yield), but the use of HIO_4 as the stoichiometric oxidant[24] gave higher yields (65–75% yield). The highest yields of **4** were obtained with the Yoshifuji procedure,[25] in which an 85% yield of analytically pure **4** was obtained using a simple extractive purification. Various carbodiimide procedures were effective for the conversion of carboxylic acid **4** to the secondary amide **5**, with the EDC/HOB method (91% yield) giving the best yields. The reduction of amide **5** with hydride reagents ($LiAlH_4$ or DIBAL) gave fluoxetine contaminated with elimination products. Borane in THF was very effective in reducing amide **5**,[26] although the boron–amine adduct must be carefully hydrolyzed (6 M HCl/CH_3OH, 30 min) due to the acid sensitivity of fluoxetine. Various attempts to employ I_2 for the oxidative cleavage of the boron–amine adduct,[27] which is very effective in the cleavage boron–amine adducts, gave good yields of (*S*)-fluoxetine contaminated with an unknown side product. The addition of ethereal HCl to crude (*S*)-fluoxetine gave (*S*)-fluoxetine hydrochloride in 87% yield (from **5**) in greater than 97% ee.

3. Conclusion

The six-step synthesis of (*S*)- and (*R*)-fluoxetine hydrochloride (>97% ee) in 56% overall yield from benzaldehyde demonstrates the synthetic potential for the asymmetric ene reaction of alicyclic isomers of aromatic compounds. We are continuing to examine the synthetic applications of **1** (and related compounds) and will report these studies in due course.

4. Experimental

4.1. General methods

All reactions were carried out under argon or nitrogen in oven-dried glassware. For reactions involving acid-sensitive 3-methylene-2,3-dihydrofuran (**1**), the glassware was washed first with aqueous NaOH. THF, EtO_2, and toluene were distilled from sodium and benzophenone. Methylene chloride was distilled from CaH_2. Anhydrous dimethylacetamide was purchased from Aldrich and used without further purification. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Powdered 4 Å molecular sieves (Aldrich) were stored in an oven at 110°C. (*S*)-BINOL and (*R*)-BINOL was purchased from TCI America or prepared by the method of the Merck chemists.[28]

The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Brucker AC-300 NMR spectrometer or at 400 and 100 MHz, respectively, on a JEOL Eclipse+400 spectrometer, using tetramethylsilane as an internal standard. IR spectra were obtained on a Perkin–Elmer 1600 Series FT-IR or a Mattson Satellite FT-IR spectrophotometer. Rotations were performed on a Jasco P-1010 polarimeter. Elemental analyses were performed by Atlantic Microlab or Galbraith Laboratories.

4.1.1. 3-Methylene-2,3-dihydrofuran (1).[9] 3-Furaldehyde (17.3 mL, 19.2 g, 0.20 mmol) and anhydrous hydrazine (6.6 mL, 6.7 g, 0.21 mmol) were added to ethylene glycol (400 mL; 1% H_2O) in a 500 mL three-neck round bottom flask fitted with a gas inlet, stopper, and short-path distillation apparatus connected to a condenser and round bottom flask open to the atmosphere. After stirring for 10 min, potassium hydroxide (33.7 g, 0.60 mol) was added. The reaction mixture was heated to 160–175°C with an oil bath as a gentle stream of argon (2–3 mL/sec) flowed through the reaction apparatus. The products and water were collected by distillation (bp 70–125°C) in an ice-cooled round bottom flask. After the distillation and gas evolution had ceased, the water in the distillate was removed by a Pasteur pipette and the organic phase was dried with $MgSO_4$. The clear liquid (13.24 g, a 3.5:1 mixture of **1**/3-methylfuran, 63% yield of **1**) was used without further purification. Although **1** can be stored in a freezer for one or two days without appreciable decomposition (as determined by ^1H NMR), we always use it on the same day. Smaller scale preparations of **1** gave the desired product in slightly lower yields of **1** and 3-methylfuran but with a higher ratio of **1**/3-methylfuran.

4.1.2. General procedure for optimization reactions of 1 with benzaldehyde. The following example (entry 4, Table 1) illustrates the protocol for the small-scale reactions designed to optimize the yield and enantioselectivity for the ene reaction of **1** with benzaldehyde. (*S*)-1-1′-Bi-2-naphthol (0.143 g, 0.499 mmol) and titanium (IV) isopropoxide (0.143 mL, 0.138 g, 0.484 mmol) were added to 4 Å molecular sieves (0.5 g) in ether (10 mL). The mixture was refluxed for 1 h and then benzaldehyde (0.510 mL, 0.532 g, 5.02 mmol) was added. After stirring at reflux for 5 min, 3-methylene-2,3-dihydrofuran (**1**) (0.75 g of a 3.5:1 mixture of **1**/3-methylfuran, approximately 7 mmol) was added over 5 min at reflux. The reaction mixture was stirred at reflux for an additional 0.25 h. Saturated sodium bicarbonate solution (1 mL) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was filtered through a Celite bed, which was washed with additional ether (40 mL). The ether solution was washed with 5% NaOH (50 mL), dried over Na_2SO_4, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (75 g of silica gel; 9:1 hexanes/ethyl acetate) to give **2** (0.78 g, 87% yield) as a clear oil: IR (neat) 3395, 3028, 2917, 1498, 1454, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.34 (m, 6H), 7.18 (s, 1H), 6.17 (s, 1H), 4.74 (t, J=6.6 Hz, 1H), 2.89 (d, J=6.6 Hz, 2H), 2.37 (br s, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 143.8, 142.8, 140.4, 128.4, 127.6, 125.9, 120.8, 111.4, 74.1, 34.9. The enantiomeric excess was determined by the use of the chiral shift reagent Eu(hfc)$_3$. The *ortho*-protons of the phenyl ring for the two enantiomers resonate as doublets (J=7.3 Hz) at δ 8.30 for (*S*)-**2** and δ 8.15 for (*R*)-**2** (0.11 M of **2** with 15 mol% Eu(hfc)$_3$ in $CDCl_3$).

4.1.3. (*S*)-2-(3-Furyl)-1-phenyl-1-ethanol (2). Preparative scale synthesis of 2. (*S*)-1-1′-Bi-2-naphthol (3.44 g, 12.0 mmol) and titanium (IV) isopropoxide (1.77 mL, 1.70 g, 6.00 mmol) were added to 4 Å molecular sieves (5.0 g) in dry ether (100 mL). The reaction mixture was refluxed for 1 h, cooled to room temperature, and then additional ether (500 mL) was added. After stirring for 15 min at room temperature, benzaldehyde (6.10 mL, 6.37 g, 60.0 mmol) was added and the reaction mixture was stirred for an additional 5 min at room temperature. After cooling the reaction mixture to 0°C, 3-methylene-2,3-dihydrofuran (**1**) (10.0 g of a 3.5:1 mixture of **1**/3-methylfuran, approximately 95 mmol) was added over 7 min. The reaction mixture was stirred for an additional 15 min at 0°C. Saturated sodium bicarbonate solution (12 mL) was added and the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was filtered through a Celite bed, which was washed with additional ether (200 mL). The ether solution was washed with 5% NaOH (200 mL), dried over $MgSO_4$, and the volatiles were removed on the rotary evaporator. The crude product was slurried with ether (50 mL) and filtered through a small plug of silica gel (50 g), washing the silica gel with additional ether (100 mL). The ether was removed on the rotary evaporator and the crude product was distilled under vacuum (bp 138–140°C, 2.0 mm) to give 10.21 g (90% yield, 95% ee) of **2**: $[\alpha]^{22}_D$=−25.7° (c=1.1, CH_2Cl_2). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.31; H, 6.37.

4.1.4. (*S*)-2-(3-Furyl)-1-phenylethyl[1-(trifluoromethyl)-phenyl] ether (3). Sodium hydride (2.06 g, 60% w/w in oil, 51.5 mmol) was added in small portions to a stirring solution of **2** (9.41 g, 50.0 mmol; 95% ee) in dimethylacetamide (100 mL) at room temperature. After the addition was complete, the reaction mixture was warmed to 50–55°C and stirred for 45 min. 4-Fluorobenzotrifluoride (10.8 mL, 14.0 g, 85.3 mmol) was added in one portion and the reaction mixture was heated to 95°C for 2.5 h. The reaction mixture was allowed to cool to room temperature and was quenched with water (10 mL). The contents of the reaction flask were transferred to a separator funnel with water (300 mL) and toluene (300 mL). The organic phase was separated and the aqueous phase was further extracted with toluene (2×300 mL). The combined organic phases were washed with water (300 mL), dried over $MgSO_4$, and concentrated on the rotary evaporator. The crude product was purified by flash chromatography (100 g of silica gel; hexanes→2% ethyl acetate in hexanes) to give **3** (15.33 g, 92% yield) as a clear oil: $[\alpha]^{23}_D$=−0.5° (c=1.0, CH_2Cl_2); IR (neat) 3062, 3029, 2921, 1613, 1589, 1515, 1326, 1250, 1111, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J=8.8 Hz, 2H), 7.20–7.35 (m, 7H), 6.88 (d, J=8.7 Hz, 2H), 6.23 (s, 1H), 5.25 (dd, J=7.8, 5.0 Hz, 1H), 3.12 (dd, J=14.8, 7.9 Hz, 1H), 2.95 (dd, J=14.8, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4 (q, J_{C-F}=1.3 Hz), 142.7, 140.4, 140.3, 128.7, 128.0, 126.8 (q, J_{C-F}=3.8 Hz), 126.0, 124.4 (q, J_{C-F}=280.2 Hz), 122.9 (q, J_{C-F}=32.7 Hz), 120.5, 115.8, 111.6, 80.7, 34.3. Anal. Calcd for $C_{19}H_{15}F_3O_2$: C, 68.67; H, 4.55. Found: C, 68.89; H, 4.62.

4.1.5. (*S*)-3-Phenyl-3-(4-(trifluoromethyl)phenoxy)propionic acid (4). Ruthenium chloride hydrate (0.048 g, 0.23 mmol) was added to a solution of sodium periodate (18.00 g, 84.2 mmol) in water (200 mL) and stirred for 10 min. Furan **3** (3.86 g, 11.6 mmol) in ethyl acetate (200 mL) was added with vigorous stirring. The reaction was slightly exothermic (32°C) with gas evolution. The reaction mixture was stirred for 1.75 h while a slow stream of argon continuously flushed the reaction flask. The reaction mixture was transferred to a separatory funnel, the organic phase was separated, and the aqueous phase was extracted once with ethyl acetate (200 mL). The combined organic phases were washed with 2 M sodium bisulfite/brine (200 mL) and brine (400 mL), dried over $MgSO_4$, and concentrated on the rotary evaporator. The crude product was dissolved in diethyl ether (200 mL) and extracted with 2% Na_2CO_3 (3×200 mL). The combined aqueous phases were washed with ether (200 mL) and then neutralized with 2 M $KHSO_4$ (approximately 130 mL). The aqueous phase was extracted with diethyl ether (3×150 mL), the combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, and concentrated on the rotary evaporator. The product was redissolved in ethyl acetate (50 mL), and activated charcoal (1 g) was added. The solution was passed through a short plug of silica gel. After removal of the solvent on the rotary evaporator, carboxylic acid **4** (3.049 g, 85% yield) was isolated as an oil that solidified to a white solid on standing: mp 79–83°C. $[\alpha]^{23}_D$=+25.9° (c=1.0, CH_2Cl_2); IR (CH_2Cl_2) 2500–3300, 1752, 1715, 1614, 1516, 1327, 1248, 1164, 1121, 1066, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J=8.8 Hz, 2H), 7.25–7.39 (m, 5H), 6.91 (d, J=8.7 Hz, 2H), 5.66 (dd, J=9.3, 4.1 Hz, 1H), 3.09 (dd, J=16.3, 9.4 Hz, 1H), 2.84 (dd, J=16.3, 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 160.0 (q, J_{C-F}=1.2 Hz), 139.2, 129.1, 128.5, 126.8 (q, J_{C-F}=3.8 Hz), 125.9, 124.3 (q, J_{C-F}=271.2 Hz), 123.4 (q, J_{C-F}=32.7 Hz), 116.0, 76.5, 43.4. Anal. Calcd for $C_{16}H_{13}F_3O_3$: C, 61.94; H, 4.22. Found: C, 61.79; H, 4.31.

4.1.6. (*S*)-*N*-Methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propanamide (5). To a solution of carboxylic acid **4** (2.482 g, 8.00 mmol), hydroxybenzotriazole hydrate (1.30 g, 8.49 mmol), *N*-methylmorpholine (1.22 mL, 1.12 g, 11.1 mmol), and 2 M methylamine in THF (6 mL, 12 mmol) in DMF (50 mL) cooled in a water–ice bath was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.84 g, 9.60 mmol). The reaction mixture was stirred for an additional 1 h at 0°C and then at 22°C for 21 h. After concentrating by vacuum distillation, the crude product was dissolved in methylene chloride (400 mL), and washed with 2% sodium carbonate (200 mL) and brine (200 mL). After concentrating on the rotary evaporator, the crude product was purified by flash chromatography (100 g of silica gel; 33→50% ethyl acetate in hexanes) to give amide **5** (2.345 g, 91% yield) as a white solid: mp 74–76°C. $[\alpha]^{23}_D$=+20.2° (c=1.0, CH_2Cl_2); IR (CH_2CL_2) 3455, 3058, 2945, 1675, 1614, 1517, 1328,

1247, 1164, 1119, 1068, 1009, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J=8.7 Hz, 2H), 7.25–7.38 (m, 5H), 6.91 (d, J=8.7 Hz, 2H), 5.84 (br s, 1H), 5.72 (dd, J=8.8, 4.3 Hz, 1H), 2.85 (dd, J=14.6, 8.8 Hz, 1H), 2.78 (d, J=4.7 Hz, 3H), 2.64 (dd, J=14.5, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 159.9, 139.9, 128.9, 128.2, 126.8 (q, J_{C-F}=3.8 Hz), 125.7, 124.3 (q, J_{C-F}=271.4 Hz), 123.2 (q, J_{C-F}=32.5 Hz), 116.0, 77.3, 45.9, 26.4. Anal. Calcd for $C_{17}H_{16}F_3NO_2$: C, 63.15; H, 4.99. Found: C, 63.23; H, 5.06.

4.1.7. (*S*)-Fluoxetine hydrochloride. Borane (7.5 mL, 1 M in THF, 7.5 mmol) was added dropwise to the amide **5** (0.647 g, 2.00 mmol) dissolved in THF (5 mL) at 0°C. After stirring for 0.5 h at 0°C, the reaction mixture was heated to reflux for 6 h and then allowed to cool to room temperature. Methanol (5 mL) was added dropwise to the reaction mixture, stirred for 5 min, and then 6 M HCL (5 mL) was added. The reaction mixture was refluxed for 0.5 h. The volatile organics were removed under vacuum with gentle heating. Sodium hydroxide (50%, 3 mL) was added and the reaction mixture was transferred to a separatory funnel with water (25 mL) and ether (25 mL). The phases were separated and the aqueous phase was extracted with ether (3×25 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated on the rotary evaporatory to give of crude (*S*)-fluoxetine (0.60 g). The crude product was redissolved in ether (10 mL) and 1 M HCl in ether (2.0 mL, 2.0 mmol) was added. The resulting white crystalline solid was filtered and washed with ether (2×5 mL) to give (*S*)-fluoxetine hydrochloride (0.602 g, 87% yield): mp 138–140°C (lit.[15] 142–143°C). $[\alpha]^{23}_D$=+15.5° (c=6.0, $CHCl_3$) [lit.[15] $[\alpha]^{22}_D$=+15.83° (c=6, $CHCl_3$)]; IR (CH_2Cl_2) 2965, 2717, 2456, 1614, 1592, 1517, 1328, 1246, 1165, 1120, 1068, 838; ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, 2H), 7.41 (d, J=8.8 Hz, 2H), 7.22–7.37 (m, 5H), 6.90 (d, J=8.4 Hz, 2H), 5.47 (dd, J=4.2, 8.7 Hz, 1H), 3.12 (br s, 2H), 2.62 (t, J=4.7 Hz, 3H), 2.38–2.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 139.1, 129.0, 128.4, 126.8 (q, J_{C-F}= 3.8 Hz), 125.7, 124.7 (q, J_{C-F}=270.6 Hz), 123.3 (q, J= 32.3 Hz), 115.8, 76.9, 46.1, 34.5, 33.0. The enantiomeric excess of fluoxetine was determined by the reaction of the free base using the method of Robertson.[29] Analysis of the ^1H NMR of the chiral amide revealed greater than 97% ee.

4.1.8. (*R*)-Fluoxetine hydrochloride. Using (*R*)-BINOL/ $Ti(O(CH(CH_3)_2)_4$ as a catalyst for the reaction of **1** with benzaldehyde, *ent*-**2** was synthesized and converted into (*R*)-fluoxetine hydrochloride in yields and enantiomeric purity comparable to the sequence used to prepare (*S*)-fluoxetine hydrochloride.

Acknowledgements

We would like to thank the Petroleum Research Fund, administered by the American Chemical Society, for financial support and the Lafayette Committee on Academic Research for support of E. J. F. in the form of a summer stipend. We gratefully acknowledge a grant from the Kresge Foundation for the purchase of the 400 MHz NMR.

References

1. Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954.
2. Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335.
3. Machajewski, T. D.; Wong, C. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1352–1374.
4. Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001–7002.
5. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468.
6. Gathergood, N.; Zhuang, W.; Jørgenson, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517–12522.
7. Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089–3103.
8. Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305–342.
9. Miles, W. H.; Berreth, C. L.; Smiley, P. M. *Tetrahedron Lett.* **1993**, *34*, 5221–5222.
10. Miles, W. H.; Smiley, P. M. *J. Org. Chem.* **1996**, *61*, 2559–2561.
11. Miles, W. H.; Berreth, C. L.; Anderton, C. A. *Tetrahedron Lett.* **1996**, *37*, 7893–7896.
12. Cimino, G.; DeRosa, S.; DeStevano, S.; Morrone, R.; Sodano, G. *Tetrahedron* **1985**, *41*, 1093–1100.
13. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819.
14. Danishefsky, S.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929–3940.
15. Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2916–2920.
16. Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081–4084.
17. Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207–5210.
18. Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339–1342.
19. Devine, P. N.; Heid Jr., J. M.; Tshaen, D. M. *Tetrahedron* **1997**, *53*, 6739–6746.
20. Wong, D. T.; Threlkeld, P. C.; Robertson, D. W. *Neuropsychopharmacology* **1991**, *5*, 43–47.
21. Posner, G. H.; Dai, H.; Bull, D. S.; Jee, J.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Petr Jr., S. *J. Org. Chem* **1996**, *61*, 671–676.
22. Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1997**, 281–282.
23. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem* **1981**, *46*, 3936–3938.
24. Nuñez, M. T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 1928–1932.
25. Jones, D. M.; Nilsson, B.; Szelke, M. *J. Org. Chem.* **1993**, *58*, 2286–2290.
26. Brown, H. C.; Heim, P. *J. Am. Chem. Soc.* **1964**, *84*, 3566–3567.
27. Hall, D. G.; Laplante, C.; Manku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698–699.
28. Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991–7994.
29. Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412–1417.