A Convenient Synthesis of (−)-Paroxetine

László Czibula,[a] András Nemes,*[a] Ferenc Sebök,[a] Csaba Szántay, Jr.,[b] and Marianna Mák[b]

Keywords: Antidepressants / Hydrogenation / Neighboring-group effects / Azabicycloheptane intermediates

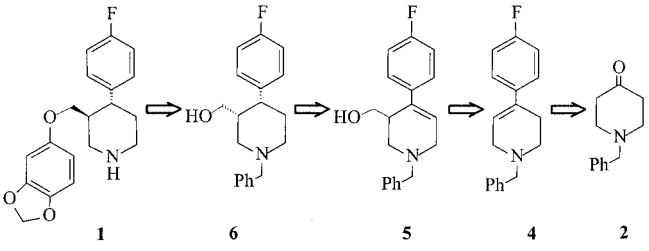
A convenient synthesis of the antidepressant paroxetine starting from 1-benzyl-4-piperidone (**2**) is reported. A stereoselective reduction resulted in *cis*-piperidine-3-methanol [(**+**)-**6**]. The reaction between *cis*-piperidine-3-methanol mesylate (**7**) and sesamol led to benzyl-protected *trans*-paroxetine (**9**) through an inversion reaction of the stereogenic center at position 3. The latter compound was deprotected by hydrogenolysis.

Introduction

(−)-Paroxetine hydrochloride (**1**), a selective serotonin reuptake inhibitor, is used for the treatment of depression, anxiety, and panic disorder. The therapeutic success of **1** has inspired continual synthetic efforts that have led to the development of several strategies for its stereo- and enantioselective synthesis.[1−14] In this paper we describe an alternative synthesis of (−)-paroxetine.[15] The common feature of the earlier stereocontrolled syntheses was to establish first a single enantiomer of an *N*-protected *trans*-4-(4-fluorophenyl)-3-piperidinemethanol **10**, including stereoselective LAH reduction, followed by selective recrystallization of diastereomeric salts,[1−3] enzymatic resolutions in earlier steps,[4−6] chiral auxiliary-assisted synthesis,[7−11] desymmetrization of prochiral diester intermediates,[12,13] or the catalytic enantioselective formation of the β- stereocenter of a 2-piperidone.[14] Etherification with sesamol, followed by a two-step dealkylation completed the synthesis that consisted of 12−14 steps.

Results and Discussion

Our own strategy for the stereoselective synthesis of (−)-paroxetine (**1**) is outlined in the retrosynthetic pathway depicted in Scheme 1. The compound *cis*-piperidine-3-methanol (**6**) can be prepared from the corresponding tetrahydropyridine **5**, which in turn is accessible from the benzyl-protected tetrahydropyridine **4**. Compound **4** can be derived from the readily available 1-benzyl-4-piperidone (**2**).[16,17]

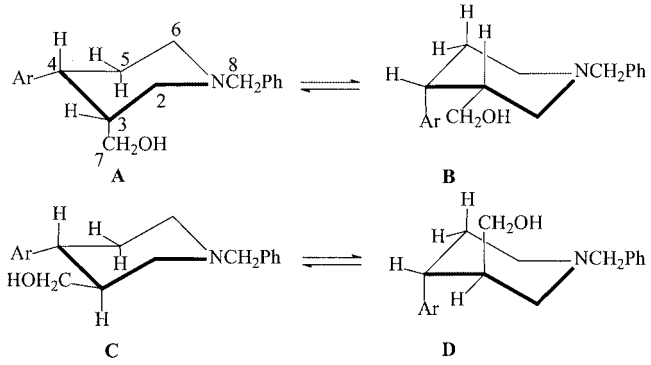


Scheme 1

The *N*-benzyl-tetrahydropyridine derivative **4** was isolated as *p*-toluenesulfonate in 73% yield, after dehydration of **3**[16,17] with *p*-toluenesulfonic acid. The Prins reaction of **4** afforded racemic tetrahydropyridine-3-methanol (*rac*-**5**) in 59% yield; the resolution of *rac*-**5** provided (−)-**5** in 41% yield. The stereoselective reduction of (−)-**5** on Pd/C catalyst, with the retention of the *N*-benzyl protective group, led to *cis*-piperidine-3-methanol (3*R*,4*R*)-**6**, which was contaminated with *trans*-piperidine-3-methanol [(3*R*,4*S*)-**10**, R = benzyl]. The final enantiomeric purity was ensured by repeated crystallization as the L-dibenzoyltartrate salt in 78% yield. The 3,4-*cis* stereochemistry of compound **6** is readily evident from the ^{1}H NMR coupling constants when the relevant ring conformations for the 3,4-*cis* (**A** and **B**) and 3,4-*trans* (**C** and **D**) geometries are considered, as shown schematically in Scheme 2. Clearly, the combination of having a small (4.5 Hz) vicinal coupling between 4-H and 3-H, and a large (12.0 Hz) coupling between 4-H and 5-H is only compatible with structure **A** as the predominant conformation.

[a] Chemical Works of Gedeon Richter Ltd., Technological Research Laboratory No. I.,
P. O. Box 27, 1475 Budapest 10, Hungary
[b] Chemical Works of Gedeon Richter Ltd., Spectroscopic Research Division,
P. O. Box 27, 1475 Budapest 10, Hungary

  DOI: 10.1002/ejoc.200400067

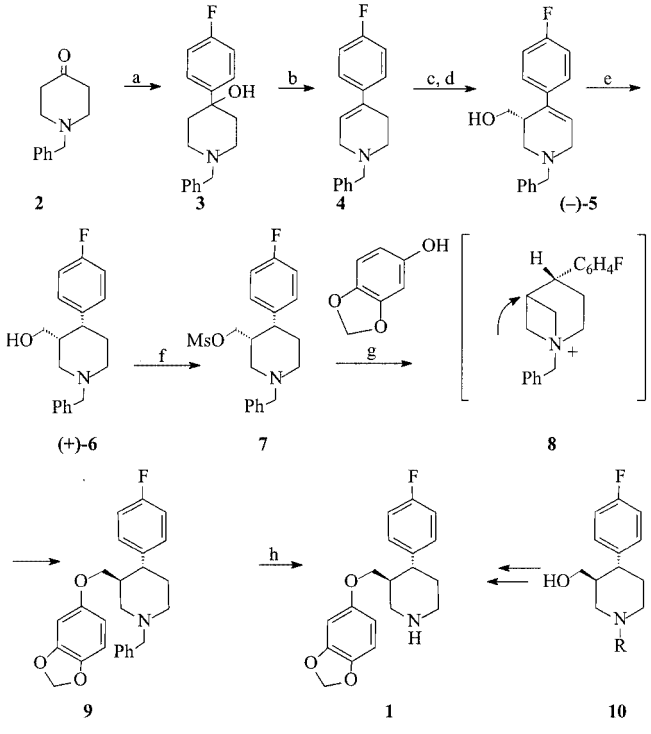


Scheme 2

The *cis*-amino alcohol methanesulfonate derivative **7** was then obtained in 97% yield with methanesulfonyl chloride. The reaction of **7** with sesamol in xylene in the presence of sodium hydroxide resulted in the formation of *trans*-*N*-benzylparoxetine (**9**).

Neighboring-group participation, i.e. the initial formation of an azabicyclo[3.1.1]heptane intermediate **8** followed by nucleophilic attack from the less crowded side opposite to the 4-aryl group, is the proposed mechanistic pathway for such reactions.[18,19] A considerable increase (78% vs. 38%) in the conversion of the *N*-benzyl sulfonate was observed relative to the *N*-methyl derivative.[19] Presumably, an elimination reaction is preferred by the quaternary *N*-methyl intermediate; the better results for the substitution reaction can be attributed to the withdrawal of electron density from the nitrogen atom through the $-I$ inductive effect of the phenyl group, as well as to the steric effect of the protective group. Deprotection by hydrogenolysis (90%) completed the synthesis of paroxetine.

The $[\alpha]_D$ value of the synthetic paroxetine prepared this way is similar to reported values,[8,13] and thus allows for the assignment of the absolute stereochemistry of the intermediates as shown in Scheme 3. In conclusion, an efficient eight-step synthesis of the antidepressant (−)-paroxetine has been described.



Scheme 3. Reagents and conditions: (a) FC_6H_4MgBr, THF/toluene; (b) *p*-TsOH/ClC_6H_5, reflux; (c) CH_2O, $HCl/H_2SO_4/H_2O$, 80 °C; (d) (−)-dibenzoyltartaric acid/acetone; (e) (i) H_2, Pd/C, AcOH/HCl/H_2O, 40 °C, (ii) $NaOH/H_2O$, (iii) (−)-dibenzoyltartaric acid/acetone; (f) $MeSO_2Cl$, Et_3N/CH_2Cl_2; (g) $NaOH/H_2O$/xylene/*s*BuOH,140 °C; (h) H_2, Pd/C/*i*PrOH, 40 °C, 5×10^5 Pa

Experimental Section

General: Melting points are uncorrected. IR spectra were recorded with a Nicolet-205-FT-IR spectrometer with KBr pellets. ^1H NMR spectra were recorded with a Varian INOVA 300 spectrometer. Mass spectrometric (low- and high-resolution/LRMS and HRMS) measurements were performed with a Finnigan MAT 95XP mass spectrometer, with the electron-ionization method at 70 eV, with direct sample introduction at a source temperature of 200 °C.

1-Benzyl-4-(4-fluorophenyl)-1,2,5,6-tetrahydropyridine (4): A mixture of 1-benzyl-4-(4-fluorophenyl)-4-hydroxypiperidine[17] (80 g, 0.28 mol) and *p*-toluenesulfonic acid monohydrate (69.0 g,0.364 mol) was refluxed in chlorobenzene (400 mL) while distilling off water for 3 h. After cooling the mixture to 0 °C, the precipitated product was filtered and washed with acetone (2 × 10 mL) to give **4** (as *p*-toluenesulfonic acid salt) (90.5 g, 73%) as colorless crystals. M.p. 180−182 °C. IR (KBr): $\tilde{\nu}$ = 3000−2300, 1601, 1229, 1163, 815, 702, 683 cm^{-1}. ^1H NMR ([D$_6$]DMSO, δ_{TMS} = 0.00 ppm): δ = 2.27 (s, 3 H, Me), 2.76 (m, 2 H, 5-H_2), 3.18−3.92 (m, 4 H, 2,6-H_2), 4.45 (s, 2 H, benzyl-H_2), 6.12 (br. s, 1 H, 3-H), 7.08−7.60 (m, 13 H, Ar-H) ppm. HRMS for $C_{18}H_{18}FN$: calcd. 267.1418; found 267.1418. LRMS: *m*/*z* (%) = 267 (66), 91 (100).

(±)-1-Benzyl-4-(4-fluorophenyl)-3-(hydroxymethyl)-1,2,3,6-tetrahydropyridine (5): Sulfuric acid (98%; 140 mL) was slowly added to water (460 mL) whilst stirring and cooling. Hydrochloric acid (37%; 40 mL), **4** (as *p*-toluenesulfonic acid salt; 88 g, 0.2 mol), and paraformaldehyde (8 g, 0.267 mol) were then added at room temperature. After stirring at 80 °C for 1 h, toluene (300 mL) and water (300 mL) were added. Finally, the mixture was made basic by adding sodium hydroxide (240 g) in water (500 mL) below 40 °C. After separating the mixture at 30 °C, the aqueous layer was extracted with toluene (50 mL). The combined toluene solutions were extracted successively with hydrochloric acid (37%; 3.2 mL) in water (200 mL) and then with hydrochloric acid (37%; 1 mL) in water (100 mL). After drying ($MgSO_4$), the filtrate was concentrated to dryness under reduced pressure. The residual light yellow oil was dissolved in acetone (100 mL) and *p*-toluenesulfonic acid monohydrate (30 g) was added. The crystalline precipitate was stirred at 10 °C for 1 h, then filtered, washed with acetone (2 × 10 mL), and dried to yield **5** (as *p*-toluenesulfonic acid salt; 56 g, 59.7%). M.p. 170−172 °C. IR (KBr): $\tilde{\nu}$ = 3483, 2800−2200, 1660, 1214, 1065, 1606, 811, 756, 681 cm^{-1}. ^1H NMR ([D$_6$]DMSO, δ_{TMS} = 0.00 ppm): δ = 2.29 (s, 3 H, Me), 3.20−4.00 (br. m, 7 H, 2,6,7-H_2, 3-H), 4.38−4.58 (m, 2 H, 8-H_2), 5.99 (1 H, br, 5-H), 7.09−7.64 (m, 13 H, Ar-H) ppm. The *p*-toluenesulfonate salt of **5** (56 g) was suspended in dichloromethane (170 mL), and a solution

of sodium hydroxide (5.5 g) in water (66 mL) was added whilst stirring. After 30 min, the organic layer was separated, and the aqueous layer was washed with dichloromethane (40 mL). The organic layers were washed with brine (20 mL) and concentrated to give solvent-free **5** (34.5 g, 97%) as a pale-yellow viscous oil. HRMS for $C_{19}H_{20}FNO$: calcd. 297.1523; found 297.1525. LRMS: *m*/*z* (%) = 297 (11), 266 (37), 206 (24), 120 (33), 91 (100).

(3*R*)-1-Benzyl-4-(4-fluorophenyl)-3-(hydroxymethyl)-1,2,3,6-tetrahydropyridine [(−)-5]: (−)-L-Dibenzoyltartaric acid monohydrate (56.4 g, 0.15 mol) in acetone (180 mL) was added to a solution of **5** (44.7 g, 0.15 mol) in acetone (70 mL) at room temperature, and the mixture was then stirred at room temperature for 5 h. The precipitated crystals were filtered at 10 °C, washed with acetone (2 × 20 mL), and dried in air to give (−)-**5** (as L-dibenzoyltartaric acid salt; 42 g, 85.6%). M.p. 126−128 °C. $[\alpha]_D^{20} = -93.5$ (*c* = 2, methanol). IR (KBr): $\tilde{\nu}$ = 1727, 1680, 1270, 1103, 1225, 1069, 1602, 812, 730, 714, 701 cm^{-1}. ^1H NMR ([D$_6$]DMSO, δ_{TMS} = 0.00 ppm): δ = 2.80−3.48 (m, 7 H, 2,6,8-H$_2$ and 3-H), 3.90 (d, $J_{8x,8y}$ = 12.9 Hz, 1 H, 7-H$_x$), 3.96 (d, $J_{7x,7y}$ = 12.9 Hz, 1 H, 7-H$_y$), 5.82 (s, 2 H, −C*H*−C*H*−), 5.92 (t, 1 H, 5-H), 7.12−8.03 (m, 19 H, ArH) ppm. $C_{37}H_{34}FNO_9$ (655.68): calcd. C 67.82, H 5.23, N 2.14; found C 67.45, H 5.23, N 2.12. The obtained salt was suspended in a mixture of water (200 mL) and dichloromethane (200 mL), and the solution was made basic by a solution of sodium hydroxide (4.5 g) in water (20 mL) whilst stirring. After separation, the aqueous layer was extracted with dichloromethane (50 mL). The combined organic phases were dried ($MgSO_4$), and the filtrate was concentrated under reduced pressure to yield the (−)-**5** (18.5 g, 97%). M.p. 67−68.5 °C (diisopropyl ether). $[\alpha]_D^{20} = -73.1$ (*c* = 1, chloroform). IR (KBr): $\tilde{\nu}$ = 3270, 1651, 1602, 1509, 1234, 1162, 1043, 817, 739, 699, 513 cm^{-1}. ^1H NMR ($CDCl_3$, δ_{TMS} = 0.00 ppm): δ = 2.67 (dddd, $J_{2x,2y}$ = 10.8, $J_{2x,3}$ = 3.9, $J_{2x,6x}$ = 2.1, $J_{2x,8x}$ = 2.1 Hz, 1 H, 2-H$_x$), 2.75 (m, 1 H, 3-H), 2.83 (dt, $J_{6x,6y}$ = 17.1, $J_{6x,5}$ = 2.1, $J_{6x,2x}$ = 2.1 Hz, 1 H, 6-H$_x$), 3.18 (dt, $J_{2x,2y}$ = 10.8, $J_{2y,3}$ = 1.5 Hz, 1 H, 2-H$_y$), 3.38 (dd, $J_{6x,6y}$ = 17.1, $J_{6y,5}$ = 4.8 Hz, 1 H, 6-H$_y$), 3.59 (ddd, 1 H, $J_{8x,8y}$ = 10.7, $J_{8x,3}$ = 3.0, $J_{2x,8x}$ = 2.1 Hz, 8-H$_x$), 3.60 (d, $J_{7x,7y}$ = 12.6 Hz, 1 H, 7-H$_x$), 3.66 (d, $J_{7x,7y}$ = 12.6 Hz, 1 H, 7-H$_y$), 3.77 (dd, $J_{8x,8y}$ = 10.7, $J_{7y,3}$ = 3.0 Hz, 1 H, 8-H$_y$), 6.02 (dd, $J_{6x,5}$ = 2.1, $J_{6y,5}$ = 4.8 Hz, 1 H, 5-H), 7.00 (m, 2 H, 3′′-H + 5′′-H), 7.25−7.40 (m, 7 H, ArH) ppm.

(3*R*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine [(+)-6]: Compound (−)-**5** (65.6 g,0.1 mol) was dissolved in a mixture of water (120 mL), acetic acid (12 mL), and hydrochloric acid (37%, 6 mL), and was hydrogenated at 45 °C in the presence of Pd/C catalyst (10%,1.5 g). After completion of the reaction, the catalyst was filtered off at room temperature. Dichloromethane (80 mL) was added to the filtrate and the solution was adjusted to pH = 9 with sodium hydroxide (40%) solution. The organic phase was separated, and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were concentrated, the residue was dissolved in acetone (100 mL), and (−)-L-dibenzoyltartaric acid monohydrate (36.9 g, 0.098 mol) in acetone (150 mL) was added. The precipitated crystals were filtered at 5 °C to obtain (−)-**6**-(−) (as L-dibenzoyltartaric acid salt; 51.2 g, 78%). M.p. 118−119 °C. $[\alpha]_D^{20} = -29.5$ (*c* = 1, methanol). IR (KBr): $\tilde{\nu}$ = 1728, 1714, 1267, 1104, 1224, 1070, 1601, 842, 730, 712, 702 cm^{-1}. ^1H NMR ([D$_6$]DMSO, δ_{TMS} = 0.00 ppm): δ = 1.64 (m, 1 H, 5-H$_e$), 1.94−2.10 (m, 2 H, 3-H and 5-H$_a$), 2.60−2.76 (m, 2 H, 2-H$_a$, 6-H$_a$), 2.86 (dd, $J_{8x,8y}$ = 10.5 Hz, $J_{8x,3}$ = 3.9 Hz, 1 H, 8-H$_x$), 2.97 (dt, $J_{4a,5a}$ = 12.6, $J_{4a,5e}$ = 3.6, $J_{4a,3e}$ = 3.6 Hz, 1 H, 4-H), 3.27−3.35 (m, 2 H, 2-H$_e$, 6-H$_e$), 3.50 (t, $J_{8x,8y}$ = 10.5 Hz, $J_{8x,3}$ = 10.5 Hz, 1 H, 8-H$_y$), 3.94 d (d, $J_{7x,7y}$ = 13.2 Hz, 1 H, 7-H$_x$), 4.10 (d, $J_{7x,7y}$ = 12.9 Hz, 1 H, 7-H$_y$), 5.81 (s, 2 H, −C*H*−C*H*−), 7.07−8.04 (m, 19 H, ArH) ppm. After suspending the salt in a mixture of water (100 mL) and dichloromethane (100 mL), the pH of the mixture was adjusted to 9 with aqueous ammonia (25%) solution. After separation, the aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were concentrated to give (+)-**6** (22.6 g, 76%). M.p. 65−66 °C. $[\alpha]_D^{20} = +54.1$ (*c* = 1, chloroform). IR (KBr): $\tilde{\nu}$ = 3280, 2790, 1597, 1510, 1232, 1130, 1090, 831, 760, 733, 697, 549 cm^{-1}. ^1H NMR ($CDCl_3$, δ_{TMS} = 0.00 ppm): δ = 1.63 (m, 1 H, 5-H$_e$), 1.66 (m, 1 H, 3-H), 2.05 (td, $J_{6a,6e}$ = 12.0, $J_{6a,5a}$ = 12.0, $J_{6a,5e}$ = 3.0 Hz, 1 H, 6-H$_a$), 2.42 (m, 1 H, 2-H$_a$), 2.45 (qd, $J_{5a,6e}$ = 12.0, $J_{5a,4a}$ = 12.0, $J_{5a,5e}$ = 12.0, $J_{5a,6e}$ = 4.5 Hz, 1 H, 5-H$_a$), 2.80 (dt, $J_{4a,5a}$ = 12.0, $J_{4a,5e}$ = 4.5, $J_{4a,3e}$ = 4.5 Hz, 1 H, 4-H), 3.01 (dm, $J_{6e,6a}$ = 12.0 Hz, 1 H, 6-H$_e$), 3.14 (dt, $J_{2e,2a}$ = 12.0, $J_{2e,3e}$ = 2.1, $J_{2e,6e}$ = 2.1 Hz, 1 H, 2-H$_e$), 3.42 (d, $J_{7x,7y}$ = 12.9 Hz, 1 H, 7-H$_x$), 3.47 (d, $J_{7x,7y}$ = 12.9 Hz, 1 H, 7-H$_y$), 3.48 (dt, $J_{8x,8y}$ = 11.1 Hz, $J_{8x,3}$ = 2.4, $J_{8x,2a}$ = 2.4 Hz, 1 H, 8-H$_x$), 3.55 (dd, $J_{8x,8y}$ = 11.1 Hz, $J_{8y,3}$ = 3.0 Hz, 1 H, 8-H$_y$), 6.91 (m, 2 H, 3′′-H + 5′′-H), 7.13−7.28 (m, 7 H, ArH) ppm. HRMS for $C_{19}H_{22}FNO$: calcd. 299.1680; found 299.1686. LRMS: *m*/*z* (%) = 299 (24), 268 (24), 208 (16), 176 (19), 120 (47), 91 (100). $C_{19}H_{22}FNO$ (299.39): calcd. C 76.28, H 7.41, N 4.68; found C 75.91, H 7.38, N 4.66.

(3*R*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-3-{[(methylsulfonyl)oxy]-methyl}piperidine (7): Triethylamine (5.8 g, 0.0574 mol) and methanesulfonyl chloride (6.6 g, 0.0576 mol) were added to a solution of (+)-**6** (14.9 g, 0.05 mol) in dichloromethane (75 mL). The mixture was stirred at room temperature for 3 h, water (40 mL) was added, and the pH of the solution was then adjusted to 8 by addition of sodium hydrogencarbonate (10%) solution. After separating the phases, the aqueous layer was extracted with dichloromethane (20 mL). The combined organic phases were washed with water (20 mL), dried ($MgSO_4$) and concentrated to afford solvent-free **7** (18.3 g, 97%) as a pale-yellow viscous oil. IR (KBr): $\tilde{\nu}$ = 2930, 1510, 1336, 1225, 1178, 1160, 945, 833, 743, 700 cm^{-1}. ^1H NMR ([D$_6$]DMSO, δ_{TMS} = 0.00 ppm): δ = 1.63 (m, 1 H, 5-H$_e$), 1.91−2.13 (m, 2 H, 5-H$_a$ and 6-H$_a$), 2.20 (m, 1 H, 2-H$_e$), 2.26 (m, 1 H, 3-H), 2.91−3.04 (m, 3 H, 2-H$_a$, 6-H$_e$, 4-H), 2.95 (s, 3 H, SO_2Me), 3.50 (d, $J_{7x,7y}$ = 13.5 Hz, 1 H, 7-H$_x$), 3.54 (d, $J_{7x,7y}$ = 13.5 Hz, 1 H, 7-H$_y$), 3.62 (dd, 1 H, $J_{8x,8y}$ = 9.6 Hz; $J_{8x,3}$ = 3.3 Hz, 8-H$_x$), 4.55 (t, $J_{8x,8y}$ = 9.6 Hz, $J_{8y,3}$ = 9.6 Hz, 1 H, 8-H$_y$), 7.15 (m, 2 H, 3′′-H + 5′′-H), 7.22−7.36 (m, 7 H, ArH) ppm. HRMS for $C_{20}H_{24}FNO_3S$: calcd. 377.1455; found 377.1460. LRMS: *m*/*z* (%) = 377 (31), 298 (15), 282 (23), 268 (29), 134 (25), 91 (100).

(3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-3-{[3,4-(methylenedioxy)-phenoxy]methyl}piperidine Hydrochloride (9·HCl): Sesamol (3 g, 0.022 mol) and sodium hydroxide (3.6 g, 0.09 mol) in water (5.5 mL) were added to a solution of **7** (7.54 g, 0.02 mol) in xylene (30 mL) and *sec*-butanol (15 mL), and the mixture was heated to reflux for 10 h. The reaction mixture was chilled, and water (30 mL) was added. After separation, the organic phase was washed with water until neutral and concentrated to afford solvent-free product under reduced pressure. The residue was dissolved in 2-propanol (35 mL) and acidified to pH = 2 by concentrated aqueous hydrochloric acid (37%). The precipitated product was filtered at 0 °C and washed with acetone (2 × 20 mL) to give **9**·HCl (7.13 g, 78.5%). M.p. 236−238 °C. $[\alpha]_D^{20} = -38$ (*c* = 1, methanol). IR (KBr): $\tilde{\nu}$ = 2850−2200, 1184, 1036, 1218, 1630, 1602, 825 cm^{-1}. ^1H NMR ($CDCl_3$, δ_{TMS} = 0.00 ppm): δ = 1.97 (m, 1 H, 5-H$_x$), 2.72−3.36 (m, 5 H, 5-H$_y$, 2-H$_x$, 6-H$_x$, 3-H, 4-H), 3.45 (dd, $J_{8x,8y}$ = 9.6 Hz, $J_{8x,3}$ = 3.9 Hz, 1 H, 8-H$_x$), 3.53−3.64 (m, 3 H, 2-H$_y$, 6-H$_y$, 8-H$_y$), 4.21 (d, $J_{7x,7y}$ = 12.9 Hz, 1 H, 7-H$_x$), 4.28 (d, $J_{7x,7y}$ = 12.9 Hz, 1 H, 7-H$_y$), 5.89 (s, 2 H, OCH_2O), 6.10 (dd, $J_{6',5'}$ = 8.4 Hz,

$J_{6',2'}$ = 2.4 Hz, 1 H, 6′-H), 6.32 (d, $J_{6',2'}$ = 2.4 Hz, 1 H, 2′-H), 6.62 (d, $J_{5',6'}$ = 8.4 Hz, 1 H, 5′-H), 6.95 (m, 2 H, 3′′,5′′-H), 7.23 (m, 2 H, 2′′,6′′-H), 7.43−7.50 (m, 3 H), 7.70 (m, 2 H, 7-OAr-H), 12.86 (br. s, 1 H, NH) ppm. HRMS for $C_{26}H_{26}FNO_3$: calcd. 419.1891; found 419.1896. LRMS: *m*/*z* (%) = 419 (1.3), 328 (2.0), 296 (1.8), 282 (20), 267 (28), 159 (15), 134 (34), 91 (100). $C_{26}H_{27}ClFNO_3$ (455.93): calcd. C 68.53, H 5.96, N 3.07; found C 68.79, H 5.96, N 3.05.

(3*S*,4*R*)-4-(4-Fluorophenyl)-3-{[3,4-(methylenedioxy)phenoxy]-methyl}piperidine Hydrochloride Hemihydrate (1·HCl·1/2H$_2$O): A suspension of **8**·HCl (9.1 g, 0.02 mol) in 2-propanol (150 mL) and distilled water (3 mL) was hydrogenated in an autoclave in the presence of Pd/C catalyst (10%; 0.3 g) at 40 °C under 5 × 10^4−10^5 Pa pressure for 3 h. After the reaction was complete, the catalyst was filtered off at 30 °C. The filtrate was concentrated to 35 mL, and the resulting solution was set aside for crystallization at 0 °C. The precipitated product was filtered, washed with 2-propanol (2 × 10 mL), and dried in air to obtain **1** HCl (as hemihydrate; 6.55 g, 89.5%). M.p. 136−138 °C (ref.[2]: 128−133 °C). $[\alpha]_D^{20}$ = −86.5 (*c* = 1, methanol) [ref.[8]: −80.8 (*c* = 1.25, methanol), ref.[13]: −84 (*c* = 0.77, methanol)]; water content for $C_{19}H_{21}ClFNO_3$·1/2H_2O: calcd. 2.40%, found 2.44% (Karl Fischer's method). IR (KBr): $\tilde{\nu}$ = 3401, 2817, 1606, 1512, 1223, 1185, 1042, 931, 857, 542 cm^{-1}. ^1H NMR ($CDCl_3$, δ_{TMS} = 0.00 ppm): δ = 2.02 (m, 1 H, 5-H_e), 2.41 (qd, $J_{5a,5e}$ = 13.2, $J_{5a,4a}$ = 13.2, $J_{5a,6a}$ = 13.2, $J_{5a,6e}$ = 3.6 Hz, 1 H, 5-H_a), 2.68 (m, 1 H, 3-H), 2.90 (td, $J_{4a,5a}$ = 13.2, $J_{4a,3a}$ = 13.2, $J_{4a,5e}$ = 3.9 Hz, 1 H, 4-H), 3.04 (td, $J_{6a,6e}$ = 12.9, $J_{6a,5a}$ = 13.2, $J_{6a,5e}$ = 3.0 Hz, 1 H, 6-H_a), 3.16 (t, $J_{2a,2e}$ = 12.3, $J_{2a,3a}$ = 12.3 Hz, 1 H, 2-H_a); 3.48 (dd, $J_{8x,8y}$ = 9.6 Hz, $J_{8x,3}$ = 4.8 Hz, 1 H, 8-H_x), 3.61 (dd, $J_{8x,8y}$ = 9.6 Hz; $J_{8y,3}$ = 2.7 Hz; 1 H, 8-H_y), 3.67 (dm, $J_{6e,6a}$ = 12.9 Hz, 1 H, 6-H_e), 3.75 (dd, $J_{2e,2a}$ = 12.3, $J_{2e,3a}$ = 3.6 Hz, 1 H, 2-H_e), 5.88 (s, 2 H, −OCH_2O−), 6.12 (dd, $J_{6',5'}$ = 8.4 Hz, $J_{6',2'}$ = 2.4 Hz, 1 H, 6′-H), 6.33 (d, $J_{6',2'}$ = 2.4 Hz, 1 H, 2′-H), 6.61 (d, $J_{5',6'}$ = 8.4 Hz, 1 H, 5′-H), 6.99 (m, 2 H, 3′′,5′′-H), 7.21 (m, 2 H, 2′′,6′′-H) ppm. HRMS for $C_{19}H_{20}FNO_3$: calcd. 329.1422; found 329.1428. LRMS: *m*/*z* (%) = 329 (54), 192 (100), 177 (20), 138 (45), 109 (20), 70 (21), 44 (37).

[1] J. A. Christensen, R. F. Squires, US Pat. 4,007,196, **1977**; *Chem. Abstr.* **1974**, *81*, 152011.
[2] R. D. Barnes, M. W. Wood-Kaczmar, A. D. Curzons, I. R. Lynch, J. E. Richardson, P. C. Buxton, EP 223 403, **1988**; *Chem. Abstr.* **1987**, *107*, 141102.
[3] J. M. Lundbeck, P. Everland, S. Treppendahl, P. Jakobsen, EP 374 674, **1990**; *Chem. Abstr.* **1990**, *114*, 6300.
[4] C. M. Zepp, Y. Gao, D. L. Heefner, US Pat. 5,258,517, **1993**; *Chem. Abstr.* **1993**, *120*, 217289.
[5] G. Gonzalo, R. Brieva, V. M. Sánchez, M. Bayod, V. Gotor, *J. Org. Chem.* **2001**, *66*, 8947−8953.
[6] J. M. Palomo, G. Fernández-Lorente, C. Mateo, R. Fernández-Lafuente, J. M. Guisan, *Tetrahedron: Asymmetry* **2002**, *13*, 2375−2381.
[7] M. Amat, J. Hidalgo, J. Bosch, *Tetrahedron: Asymmetry* **1996**, *7*, 1591−1594.
[8] M. Amat, J. Hidalgo, J. Bosch, M. Cantó, M. Pérez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque, *J. Org. Chem.* **2000**, *65*, 3074−3084.
[9] T. A. Johnson, M. D. Curtis, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 1004−1005.
[10] L. T. Liu, P.-C. Hong, H.-L. Huang, S.-F. Chen, C.-I. J. Wang, Y.-S. Wen, *Tetrahedron: Asymmetry* **2001**, *12*, 419−426.
[11] J. Cossy, O. Mirguet, D. G. Pardo, J.-R. Desmurs, *Eur. J. Org. Chem.* **2002**, *42*, 3543−3551.
[12] M. S. Yu, I. Lantos, Z.-Q. Peng, J. Yu, T. Cacchio, *Tetrahedron Lett.* **2000**, *41*, 5647−5651.
[13] D. A. Greenhalgh, N. S. Simpkins, *Synlett* **2002**, 2074−2076.
[14] G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253−11258.
[15] J. Kreidl, L., Czibula, A. Nemes, I. Juhász, É. Papp, J. Bagdy, L. Dobay, I. Hegedüs, K. Harsányi, I. Borza, PCT Int. Appl., WO 9801424, **1998**; *Chem. Abstr.* **1998**, *128*, 127941.
[16] J. Perreggaard, E. K. Moltzen, E. Meier, C. Sánchez, *J. Med. Chem.* **1995**, *38*, 1998−2008.
[17] S. Sakamuri, I. J. Enyedi, A. P. Kozikowski, W. A. Zaman, K. M. Johnson, S. Wang, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 495−500.
[18] J. A. Christensen, M. Engelstoft, K. Schaumburg, H. Schou, F. Wätjen, *Tetrahedron Lett.* **1983**, *24*, 5151−5152.
[19] K. Wilcocks, R. D. Barnes, D. C. Rustidge, D. J. D. Tidy, *J. Labelled Compd. Radiopharm.* **1993**, *33*, 783−794.

Received February 2, 2004

