Chemoenzymatic synthesis of the non-tricyclic antidepressants Fluoxetine, Tomoxetine and Nisoxetine

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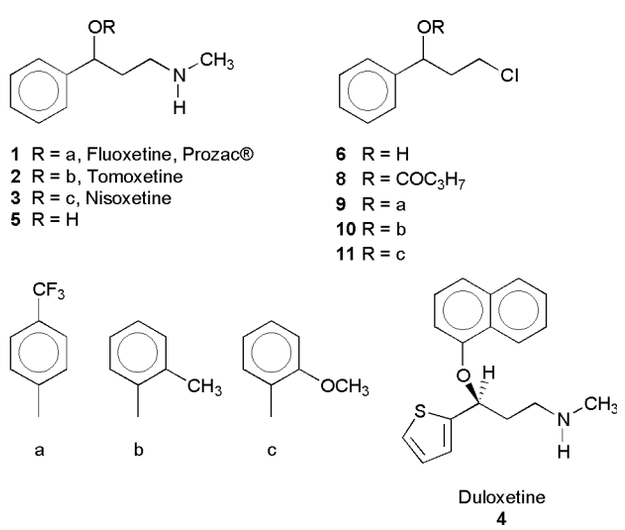
3-Chloro-1-phenylpropan-1-ol and the corresponding butanoate, 3-chloro-1-phenyl-1-propyl butanoate, were kinetically resolved using lipase B from *Candida antarctica* catalysis by transesterification and hydrolysis respectively. The resulting chiral building blocks (*S*)- and (*R*)-3-chloro-1-phenylpropanol were converted into both enantiomers of the antidepressant drugs, Fluoxetine, Tomoxetine and Nisoxetine.

Introduction

Fluoxetine (**1**), Tomoxetine (**2**), Nisoxetine (**3**) and Duloxetine (**4**) belong to the group of non-tricyclic antidepressants which



act by inhibiting the uptake of norepinephrine and serotonin.[1] A chemoenzymatic synthesis of Duloxetine has been reported.[2] Fluoxetine hydrochloride is sold as the racemate (Prozac, Eli Lilly Co.), but recently interest has been shown for marketing the more active (*R*)-enantiomer as a so-called "Improved Chemical Entity" version of the drug.[3] Tomoxetine (**2**) was the first norepinephrine reuptake inhibiting antidepressant to be reported, and the (*R*)-enantiomer is nine times more potent than the (*S*)-enantiomer.[4] Nisoxetine (**3**) is also a potent inhibitor. The drugs are derivatives of 3-methylamino-1-phenylpropan-1-ol (**5**) which contains a stereocenter, and retrosynthetic analysis reveals that enantiopure (*R*)-3-chloro-1-phenylpropan-1-ol (**6**) should be a suitable chiral building block.

Chirality has previously been introduced by applying Sharpless-asymmetric epoxidation,[5] by asymmetric reduction of 3-chloro-1-phenylpropan-1-one (**7**) catalyzed by diisopinocampheylchloroborane,[6] by borane in the presence of oxazaborolidine catalyst (chemzyme)[7] or by bakers' yeast.[8]

Results and discussion

We have developed an alternative strategy for introduction of chirality by kinetic resolution using lipase catalysis. Although resolutions only give a maximum yield of 50%, lipase catalysis has several advantages. Enzymes are mild catalysts, they are easily recovered after termination of the process, and can be reused several times. Moreover, high enantiomeric excess (ee) may be obtained even in cases when the important kinetic parameter, the enantiomeric ratio *E*, is moderate provided lower yield is acceptable. It is also possible to obtain 100% of one single enantiomer by combination of lipase-catalyzed resolution and Mitsunobu esterification-inversion in one pot.[9] Moreover, dynamic resolution, in which the unreacted substrate is continuously racemized also gives only one enantiomer starting from a racemic mixture. However, for biological testing single enantiomers of both forms may be needed.

Racemic 3-chloro-1-phenylpropan-1-ol (**6**) was obtained by reduction of 3-chloro-1-phenylpropan-1-one (**7**) with sodium borohydride. It was kinetically resolved by transesterification in *n*-hexane using vinyl butanoate as acyl donor, and lipase B from *Candida antarctica* (CALB) as catalyst. The resolution proceeded with an exceptionally high *E*-value of 1000, which implies that the enantiomers will be perfectly separable by this method. Gram-scale resolution was performed and optical rotation values[7] confirmed that the (*R*)-enantiomer was the faster reacting enantiomer, as expected based on the stereopreference of CALB.[10]

Racemic 3-chloro-1-phenylpropyl butanoate (**8**) was kinetically resolved by CALB-catalysed hydrolysis in phosphate buffer. The resolution proceeded excellently with an *E*-value of 923 and the (*R*)-butanoate was the faster reacting enantiomer. The isolated (*S*)-(**6**) after transesterification and (*R*)-(**6**) after hydrolysis, were reacted with three differently substituted phenols in the presence of triphenylphosphine and diethyl azodicarboxylate and inversion of configuration took place at the secondary center (Mitsunobu conditions[9]). Treatment of the obtained chloro ethers, **9**, **10** and **11**, with excess aqueous methylamine in ethanol afforded both enantiomers of the target products Fluoxetine (**1**), Tomoxetine (**2**) and Nisoxetine (**3**).

Experimental

General

Immobilized CALB (Novozyme 435, Novo-Nordisk A/S) had an activity of 7000 PLU (palm oil lipase units) g^{-1}, and a water content of 1–2% w/w. Solvents were dried over molecular sieves, column chromatography was performed using silica gel 60 from

Fluka and enzymatic reactions were performed in a shaker incubator (New Brunswick, Edison, NJ, USA).

Analyses

Optical rotations were determined using an Optical Activity Ltd. AA-10 automatic polarimeter, and are given in 10^{-1} deg cm^2 g^{-1}; concentrations are given in g 100 mL^{-1}. Chiral analyses were performed using Varian 3300 and 3400 gas chromatographs equipped with CP-Chirasil-dex CB columns from Chrompack (25 m, 0.25 mm, 0.25 or 0.32 μm film thickness) at 7.5 psi, split ratio 60 mL min^{-1}, with an outlet pressure of 3 bar. The alcohol and ester were analyzed using temperature programmes: 100–120, 2 °C min^{-1}; 120–140, 0.5 °C min^{-1}; 140–180, 15 °C min^{-1}, **1**, t_1 (*R*): 48.35, t_2 (*S*): 49.22, R_s (resolution): 3.8, **2**, t_1 (*S*): 44.664, t_2 (*R*): 45.786, R_s: 1.9. TLC: Al sheets, 20 × 20 cm, silica gel 60 F 254, Merck. NMR spectra were recorded in $CDCl_3$ solutions, using Bruker DPX 300 and 400 instruments, operating at 300 and 400 MHz for ^{1}H and 75 and 100 MHz for ^{13}C, respectively. Chemical shifts are in ppm relative to TMS and coupling constants in Hz. Enantiomeric ratios, *E* were calculated using the computer program *E & K calculator version 2.03*.[11]

Small scale transesterifications

Substrate alcohol (37.5 mg, 2.2×10^{-4} mol) was dissolved in *n*-hexane (3 mL), vinyl butanoate (5 equivalents) was added and the reaction was started by adding immobilized CALB (39 mg) to the reaction mixture at 30 °C. Chiral GLC analysis gave the enantiomeric excess of substrate (ee_s) and product (ee_p) from which conversion, *c*, was calculated [$c = ee_s/(ee_s + ee_p)$]. In control experiments without enzyme, no acylation was observed using vinyl butanoate as acyl donor.

Small scale hydrolyses

Substrate ester (26.6 mg, 1.11×10^{-4} mol) was dispersed in phosphate buffer (30 mL, 0.1 M, pH = 7). The reaction was started when immobilized CALB (34 mg) was added to the reaction mixture.

3-Chloro-1-phenylpropan-1-ol (6)

3-Chloro-1-phenylpropan-1-one (**7**) (4.22 g, 0.025 mol) was dissolved in EtOH (50 mL) at room temp. $NaBH_4$ (0.5 equiv.) was added, and the reaction mixture was stirred for 2 h. The reaction was stopped by slow addition of 0.1 M HCl (100 mL) and stirred for an additional 30 min. The mixture was extracted with Et_2O (3 × 40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, CH_2Cl_2–EtOAc, 10 : 1) to give racemic **6**, yield 3.75 g, 0.02 mol (88%). ^{1}H NMR: 2.00 and 2.12 (2 H, m, -CH_2-), 2.75 (1 H, s, OH), 3.48 and 3.66 (1 H each, m, CH_2Cl), 4.86 (1 H, t, CH, $J = 5.5$), 7.23–7.35 (5 H, m, aromatic). ^{13}C NMR: 41.4 and 41.7 (-CH_2CH_2-), 71.1 (-CHOH), 125.8 and 128.6 (both 2 Ph-C), 127.8 (Ph C-4), 143.7 (Ph C-1). TLC: (CH_2Cl_2–EtOAc, 10 : 1), $R_f = 0.53$.

3-Chloro-1-phenylpropyl butanoate (8)

Racemic **6** (2.24 g, 13 mmol), butanoic anhydride (2.28 g, 14 mmol) and pyridine (1.11 g, 14 mmol) were dissolved in CH_2Cl_2 (50 mL), cooled to 0 °C and DMAP (25 mg) was added. The mixture was stirred for 20 min at 0 °C and then at room temp. overnight. The reaction mixture was washed with 0.1 M HCl (10 × 25 mL), then with saturated $NaHCO_3$ (3 × 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane–acetone, 4 : 1) to give racemic **8**, yield 3.0 g, 12.5 mmol (93%). ^{1}H NMR: 0.92 (3 H, t, $J = 7.4$, -CH_3), 1.65 (2 H, sextet, -CH_2-), 2.16 (2 H, t, -CH_2-), 2.20 and 2.33 (1 H each, m, -CH_2-), 3.43 and 3.54 (1 H each, m, -CH_2Cl), 5.94 (1 H, dd, $J = 5.5$ and 8.2, CH), 7.25–7.35 (5 H, m, phenyl). ^{13}C NMR: 39.2 and 40.7 (-CH_2CH_2-), 72.9 (-CHOR), 126.3 and 128.6 (both 2 Ph-C), 128.2 (Ph C-4), 139.7 (Ph C-1), 172.6, 36.3, 18.4 and 13.6 (butanoyl). TLC (*n*-hexane–acetone, 4 : 1), $R_f = 0.52$.

(*S*)-3-Chloro-1-phenylpropan-1-ol [(*S*)-6] and (*R*)-3-chloro-1-phenylpropyl butanoate [(*R*)-8]

Racemic **6** (1.0 g, 5.9 mmol) and vinyl butanoate (3.4 g, 29.4 mmol) were dissolved in *n*-hexane (80 mL). Immobilized CALB (130 mg) was added, and the reaction mixture was shaken at 30 °C for 8 days until 50% conversion was reached. The enzyme was filtered off, and the reaction mixture concentrated *in vacuo*. The unreacted alcohol and the produced ester were separated by column chromatography (*n*-hexane–acetone, 4 : 1), to give (*S*)-**6**, yield 0.33 g, 1.93 mmol (33%), ee = 96%, $[\alpha]_D^{22} = -23$ ($c = 1$, $CHCl_3$), and (*R*)-**8**, yield 0.44 g, 1.83 mmol (31%), ee = 97%, $[\alpha]_D^{22} = +33$ ($c = 1$, $CHCl_3$). ^{1}H NMR corresponded with racemic **6** and **8** respectively.

(*R*)-3-Chloro-1-phenylpropan-1-ol [(*R*)-6]

Racemic **8** (1.21 g, 5.0 mmol) was suspended in buffer (180 mL, 0.1 M, pH = 7). Immobilized CALB (303 mg) was added, and the reaction mixture was shaken at 30 °C for 12 days until 50% conversion was reached. The enzyme was filtered off, the reaction mixture was extracted with Et_2O (3 × 80 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The produced alcohol and the remaining ester were separated by column chromatography (*n*-hexane–acetone, 4 : 1) to afford (*R*)-**6**, yield 0.35 g, 2.1 mmol (42%), ee = 95%, $[\alpha]_D^{22} = +24$ ($c = 1$, $CHCl_3$), lit.[7] +24. ^{1}H NMR corresponded with racemic **6**.

(*R*)-4-(3-Chloro-1-phenylpropoxy)-1-trifluoromethylbenzene [(*R*)-9]

Triphenylphosphine (0.51 g, 1.93 mmol), and diethyl azodicarboxylate (0.3 mL, 0.34 g, 1.93 mmol) were added to a solution of (*S*)-**6** (0.33 g, 1.93 mmol) and trifluoromethyl-*p*-cresol (0.31 g, 1.93 mmol) in THF (5 mL). The mixture was stirred at room temp. overnight until the reaction was completed (TLC). THF was removed *in vacuo* and the residue was triturated with pentane (3 × 5 mL). The combined pentane fractions were concentrated, and the residue was purified by flash chromatography (pentane–Et_2O, 4 : 1) to give (*R*)-**9** as a thick liquid, yield 0.28 g, 0.89 mmol (46%). ^{1}H NMR: 2.25 and 2.48 (1 H each, m, -CH_2-), 3.59 and 3.78 (1 H each, m, -CH_2Cl), 5.43 (1 H, dd, $J = 4.6$ and 8.5, CH), 6.91 and 7.43 (2 H each, AA′XX′-system of *p*-disubstituted benzene), 7.24–7.36 (5 H, m, phenyl). ^{13}C NMR: 41.1 and 41.2, (-CH_2CH_2-), 77.0 (-CHOR), 125.9 and 129.0 (both 2 Ph-C), 128.2 (Ph C-4), 134.0 (Ph C-1), *p*-trifluoromethyl phenoxy part: 160.3 (C-1), 115.9 (2 C-2), 126.8 (q, $^3J_{CF} = 3.7$ Hz, 2 C-3), 123.2 (q ($^2J_{CF} = 32.7$ Hz, C-4), 124.3 (q, $^1J_{CF} = 271.6$ Hz, -CF_3). $[\alpha]_D^{22} = -1.3$ ($c = 5.2$, $CHCl_3$). TLC: (*n*-pentane–Et_2O, 4 : 1), $R_f = 0.60$.

(*S*)-4-(3-Chloro-1-phenylpropoxy)-1-trifluoromethylbenzene [(*S*)-9]

Using the same procedure as for (*R*)-**9**, (*S*)-**9** was synthesized starting with (*R*)-**6**. Workup gave (*S*)-**9** (0.23 g, 0.73 mmol), yield 54%, $[\alpha]_D^{22} = +1.0$ ($c = 5.1$, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical with those of (*R*)-**9**.

(*R*)-Fluoxetine [(*R*)-1] [(*R*)-4-(3-methylamino-1-phenylpropoxy)-1-trifluoromethylbenzene]

The chloro ether (*R*)-**9** (0.28 g, 0.89 mmol) and aqueous $MeNH_2$ (40%, 3 mL) were dissolved in EtOH (5 mL). The solution was refluxed at 130 °C for 6 h, cooled to room temp. and poured into water (40 mL). The mixture was extracted by Et_2O

(3 × 20 mL). The Et_2O extract was washed with water and aqueous NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2–MeOH–NH_4OH, 40 : 10 : 1) to afford (*R*)-**1**, yield 0.17 g, 0.55 mmol (62%), $[\alpha]_D^{22} = +2.0$ ($c = 1$, $CHCl_3$). ^{1}H NMR: 2.11 and 2.27 (1 H each, m, -CH_2-), 2.46 (3 H, s, -CH_3), 2.82 (2 H, br t, -CH_2N), 5.33 (1 H, dd, $J = 4.7$ and 8.3, CH), 6.90 and 7.42 (2 H each, AA′XX′-system of *p*-disubstituted benzene), 7.25–7.38 (5 H, m, phenyl). ^{13}C NMR: 37.8 and 51.51, (-CH_2CH_2-), 78.3 (-CHOR), 35.7 (-NCH_3), 125.8 and 128.9 (both 2 Ph-C), 128.0 (Ph C-4), 140.6 (Ph C-1), *p*-trifluoromethylphenoxy part: 160.4 (C-1), 115.8 (2 C-2), 126.8 (q, $^3J_{CF} = 3.7$ Hz, 2 C-3), 123.2 (q, $^2J_{CF} = 32.7$ Hz, C-4), 124.8 (q, $^1J_{CF} = 271.2$ Hz, -CF_3). TLC (CH_2Cl_2–MeOH–NH_4OH, 40 : 10 : 1), $R_f = 0.60$.

(*S*)-Fluoxetine [(*S*)-1)] [(*S*)-4-(3-methylamino-1-phenylpropoxy)-1-trifluoromethylbenzene]

(*S*)-Fluoxetine [(*S*)-**1**] was prepared in the same way as (*R*)-**1** using (*S*)-**9**. Workup gave (*S*)-**1** (0.14 g, 0.46 mmol), yield 63%, $[\alpha]_D^{22} = -3.0$ ($c = 1$, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical with those of (*R*)-**1**.

(*R*)-2-(3-Chloro-1-phenylpropoxy)-1-methylbenzene [(*R*)-10]

(*R*)-**10** was synthesized using the same procedure as for synthesis of (*R*)-**9** using (*S*)-**6** (0.31 g, 1.8 mmol), *o*-cresol (0.20 g, 1.8 mmol), triphenylphosphine (0.47 g, 1.8 mmol) and diethyl azodicarboxylate (0.31 g, 1.8 mmol, 0.28 mL) in dry THF (8 mL) at room temp. Workup and purification afforded (*R*)-**10** as a thick liquid, yield 0.27 g, 1.03 mmol (57%), $[\alpha]_D^{22} = -10.8$ ($c = 3.4$, $CHCl_3$). ^{1}H NMR: 2.23 and 2.48 (1 H each, m, -CH_2-), 3.61 and 3.79 (1 H each, m, -CH_2Cl), 5.38 (1 H, dd, $J = 4.4$ and 8.5, CH), 7.23–7.37 (5 H, m, phenyl), *o*-methylphenoxy part: 2.31 (3 H, s, -CH_3), 6.62 (1 H, d, $J = 8.2$, H-6), 6.78 (1 H, t, H-5), 6.96 (1 H, m, H-4), 7.12 (1 H, d, $J = 7.5$, H-3). ^{13}C NMR: 41.4 and 41.5, (-CH_2CH_2-), 77.2 (-CHOR), 125.8 and 128.7 (both 2 Ph-C), 127.8 (Ph C-4), 141.0 (Ph C-1), *o*-methylphenoxy part: 16.6 (-CH_3), 155.7 (C-1), 127.0 (C-2), 130.7 (C-3), 120.5 (C-4), 126.6 (C-5), 112.8 (C-6). TLC (*n*-pentane–Et_2O, 4 : 1), $R_f = 0.71$.

(*R*)-Tomoxetine [(*R*)-2] [(*R*)-2-(3-methylamino-1-phenylpropoxy)-1-methylbenzene]

(*R*)-Tomoxetine [(*R*)-**2**] was synthesized using a similar method as for (*R*)-**1**. The chloro ether (*R*)-**10** (0.20 g, 0.77 mmol) was refluxed with aqueous $MeNH_2$ (40%, 3 mL) in EtOH (5 mL) and (*R*)-**2** was isolated, yield 0.12 g, 0.46 mmol (60%), $[\alpha]_D^{22} = -44$ ($c = 1$, MeOH). ^{1}H NMR: 1.75 (1 H, br s, NH), 2.03 and 2.19 (1 H each, m, -CH_2-), 2.40 (3 H, s, -NCH_3), 2.75 (2 H, m, -CH_2N), 5.25 (1 H, dd, $J = 4.5$ and 8.2, CH), 7.19–7.35 (5 H, m, phenyl), *o*-methylphenoxy part: 2.32 (3 H, s, -CH_3), 6.60 (1 H, d, $J = 8.1$, H-6), 6.75 (1 H, t, H-5), 6.94 (1 H, t, H-5), 7.10 (1 H, d, 7.4, H-3). ^{13}C NMR: 38.7 and 48.5 (-CH_2CH_2-), 78.1 (-CHOR), 125.7 and 128.6 (both 2 Ph-C), 127.5 (Ph C-4), 142.0 (Ph C-1), *o*-methylphenoxy part: 16.6 (-CH_3), 156.0 (C-1), 127.0 (C-2), 130.6 (C-3), 120.2 (C-4), 126.6 (C-5), 112.8 (C-6). TLC (CH_2Cl_2–MeOH–NH_4OH, 40 : 10 : 1), $R_f = 0.58$.

(*S*)-2-(3-Chloro-1-phenylpropoxy)-1-methylbenzene [(*S*)-10] and (*S*)-Tomoxetine [(*S*)-2)] [(*S*)-2-(3-methylamino-1-phenylpropoxy)-1-methylbenzene]

(*S*)-**10** and (*S*)-Tomoxetine [(*S*)-**2**)] were synthesized by using the same procedures as for (*S*)-**9** and (*S*)-**1**, respectively, (*S*)-**10**, yield 0.21 g, 0.81 mmol (51%), $[\alpha]_D^{22} = +11.1$ ($c = 3.4$, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical with those of (*R*)-**10**. (*S*)-**2**, yield 0.11 g, 0.43 mmol (53%), $[\alpha]_D^{22} = +44$ ($c = 1$, MeOH), ^{1}H and ^{13}C NMR spectra were identical with those of (*R*)-**2**.

(*R*)-2-(3-Chloro-1-phenylpropoxy)-1-methoxybenzene [(*R*)-11]

(*R*)-**11** was synthesized using a similar procedure as for (*R*)-**9**, using (*S*)-**6** (0.53 g, 3.1 mmol), guaiacol (0.39 g, 3.1 mmol), Ph_3P (0.81 g, 3.1 mmol) and diethyl azodicarboxylate (0.54 g, 0.48 mL, 3.1 mmol) in dry THF (7 mL) at room temp. Workup and chromatography gave (*R*)-**11**, yield 0.35 g, 1.3 mmol (42%) as a thick liquid, $[\alpha]_D^{22} = +26$ ($c = 2$, $CHCl_3$). ^{1}H NMR: 2.21 and 2.55 (1 H each, m, -CH_2-), 3.64 and 3.88 (1 H each, m, -CH_2Cl), 5.33 (1 H, dd, $J = 4.3$ and 8.8, CH), 7.22–7.41 (5 H, m, phenyl), *o*-methoxyphenoxy part: 3.86 (3 H, s, -OCH_3), 6.71 (2 H, m, H-3,6), 6.86 (2 H, m, H-4,5). ^{13}C NMR: 41.4 and 41.6, (-CH_2-CH_2-), 78.5 (-CHOR), 125.8 and 128.6 (both 2 Ph-C), 127.8 (Ph C-4), 141.0 (Ph C-1), *o*-methoxyphenoxy part: 55.9 (-OCH_3), 150.2 (C-1), 147.4 (C-2), 116.6 (C-3), 120.7 (C-4), 121.8 (C-5), 112.0 (C-6). TLC (*n*-pentane–Et_2O, 4 : 1), $R_f = 0.51$.

(*R*)-Nisoxetine [(*R*)-3] [(*R*)-2-(3-methylamino-1-phenylpropoxy)-1-methoxybenzene]

(*R*)-Nisoxetine was synthesized like (*R*)-Fluoxetine [(*R*)-**1**], using the chloro ether (*R*)-**11** (0.22 g, 0.80 mmol) and excess aqueous $MeNH_2$ (40%, 3 mL) in EtOH (7 mL) at 130 for 6 h. Workup gave (*R*)-**3**, yield 0.12 g, 0.44 mmol (55%), $[\alpha]_D^{30} = +35$ ($c = 1$, $CHCl_3$). ^{1}H NMR: 1.88 (1 H, br s, NH), 2.03 and 2.26 (1 H each, m, -CH_2-), 2.43 (3 H, s, NCH_3), 2.77 (2 H, br m, -CH_2Cl), 5.20 (1 H, dd, $J = 4.7$ and 8.4, CH), 7.23–7.39 (5 H, m, phenyl), *o*-methoxyphenoxy part: 3.87 (3 H, s, -OCH_3), 6.68 (2 H, m, H-3,6), 6.85 (2 H, m, H-4,5). ^{13}C NMR: 36.5 (-NCH_3), 38.5 and 48.8, (-CH_2CH_2-), 80.6 (-CHOR), 126.0 and 128.5 (both 2 Ph-C), 127.5 (Ph C-4), 142.0 (Ph C-1), *o*-methoxyphenoxy part: 56.0 (-OCH_3), 150.1 (C-1), 147.7 (C-2), 116.4 (C-3), 120.7 (C-4), 121.4 (C-5), 112.1 (C-6). TLC (CH_2Cl_2–MeOH–NH_4OH, 40 : 10 : 1), $R_f = 0.35$.

(*S*)-2–(3-Chloro-1-phenylpropoxy)-1-methoxybenzene [(*S*)-11] and (*S*)-Nisoxetine [(*S*)-3] [(*S*)-2-(3-methylamino-1-phenylpropoxy)-1-methoxybenzene]

[(*S*)-**11**] and (*S*)-Nisoxetine [(*S*)-**3**] were synthesized in the same way as (*S*)-**9** and (*S*)-**1**, respectively. The yield of (*S*)-**11** was 0.22 g, 0.82 mmol (46.4%), $[\alpha]_D^{22} = -26$ ($c = 2$, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical with those of (*R*)-**11**. The yield of (*S*)-**3** was 80 mg, 0.29 mmol (50%), $[\alpha]_D^{22} = -30$ ($c = 1$, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical with those of (*R*)-**3**.

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