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Tetrahedron: *Asymmetry* 16 (2005) 1873–1879

Polymer-supported chiral sulfonamide catalyzed one-pot reduction of β-keto nitriles: a practical synthesis of (*R*)-fluoxetine and (*R*)-duloxetine

Guangyin Wang, Xingshun Liu and Gang Zhao*

Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 FengLin Lu, Shanghai 200032, China

Received 9 March 2005; accepted 7 April 2005

Abstract—Enantioselective reduction of β-keto nitriles to optically active 1,3-amino alcohols has been carried out in one step using an excess of borane–dimethyl sulfide complex as a reductant and a polymer-supported chiral sulfonamide as a catalyst with moderate to high enantioselectivity. The facile and enantioselective method to prepare optically active 1,3-amino alcohols to be converted into 3-aryloxy-3-arylpropylamine-type antidepressant drugs (*R*)-fluoxetine, and (*R*)-duloxetine is also reported.
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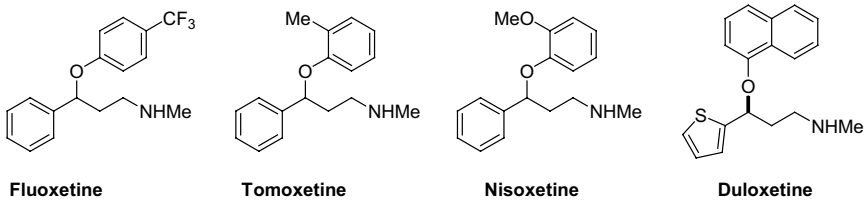
1. Introduction

The structure of 3-aryloxy-3-aryl propyl-amine exits in many antidepressants, such as fluoxetine,[1] tomoxetine,[2] nisoxetine, and duloxetine[3] (Fig. 1). Fluoxetine, tomoxetine, and nisoxetine are amongst the most important pharmaceuticals for the treatment of psychiatric disorders and metabolic problems,[4] while duloxetine is a dual inhibitor of serotonin and norepinephrine re-uptake and has a better pharmacological profile as an antidepressant drug.[3] The enantioselective synthesis of the individual enantiomers is necessary because their (*S*)- or (*R*)-isomers probably display different pharmacological potencies. This has led to many groups developing different methods of preparing enantiomerically pure building blocks for these compounds, in which enantioselective epoxidation followed by stereoselective opening,[5] asymmetric reduction,[6] microbial reductions and enzymatic or chemical resolutions[7] had been reported.

Over the past decade, several groups have reported the preparation and application of polymer-supported catalysts derived from chiral amino alcohols for enantioselective reduction.[8] Several years ago, we developed a new class of polymer-supported sulfonamides and applied them to the enantioselective reduction of functional ketones, such as β-keto sulfones and α-keto esters via $BH_3{\cdot}Me_2S$ or $NaBH_4/Me_3SiCl$.[9] In these studies, we found that the reducing systems could provide an efficient methodology for the synthesis of optically active secondary alcohols. In continuation of our recent studies, we found that β-keto nitriles could be reduced to optically active 1,3-amino alcohols in one step using an excess of borane–dimethyl sulfide complex as a reductant



Fluoxetine Tomoxetine Nisoxetine Duloxetine

Figure 1.

* Corresponding author. Fax: +86 21 641 66128; e-mail: zhaog@mail.sioc.ac.cn

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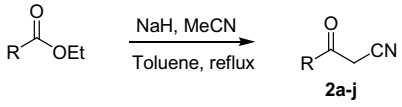
doi:10.1016/j.tetasy.2005.04.002

and a polymer-supported chiral sulfonamide as a catalyst. The use of β-keto nitriles and the high enantioselectivity of the reaction, a direct and enantioselective method to prepare 3-aryloxy-3-arylpropylamine-type antidepressant drugs, have been explored. Herein, we report this reaction and its application in the synthesis of (*R*)-fluoxetine and (*R*)-duloxetine.

2. Results and discussion

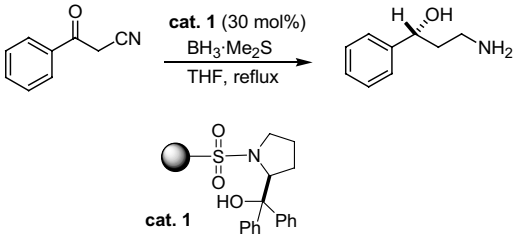
All the β-keto nitriles were prepared according to the literature[10] (Scheme 1).

To achieve the best enantioselectivity, the effect of the amount of catalyst was examined first, using the reduction of **2a** as a model reaction (Table 1). From these results, the fact that the ee increased when increasing the amount of catalyst **1** was obvious. When the catalyst was increased to 30 mol %, the ee of the product was up to 96%, which is as high as the results of the reduction of other types of functional ketones we had previously reported. Although the C/S ratio was increased to 40 mol %, the ee did not increase simultaneously but in fact decreased slightly. Although the optimal C/S ratio is relatively high when compared with our previous report, the catalyst could be recovered almost quantitatively by simple filtration when the reaction was complete, after washing with hot water and methanol, and could be reused without any decline of catalysis efficiency. In our previous work,[9] $NaBH_4/Me_3SiCl$ could replace $BH_3{\cdot}Me_2S$ as the reducing agent to give the same corresponding product with 89% ee under the same conditions, which $BH_3{\cdot}Me_2S$ gave 96% ee.



Scheme 1.

Table 1. The effect of the dosage of catalyst on the asymmetric reaction[a]



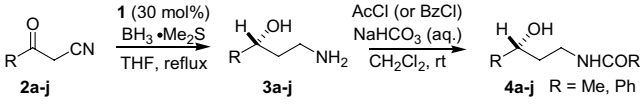
Entry	C/S (mol%)	Yield (%)[b]	Ee (%)[c]
1	15	74	68
2	20	78	84
3	25	77	90
4	30	76	96
5	40	76	93

[a] Experiments were performed at a 1 mmol scale; molar ratio: $BH_3{\cdot}Me_2S$/**cat.1**/β-keto nitrile = 3:0.3:1.
[b] Isolated yield after column purification.
[c] Determined by chiral HPLC with a Chiralcel OB column after the product was converted to its acetamide.

To extend this synthetic procedure to the preparation of 1,3-amino alcohols, we investigated the reaction of a variety of β-keto nitriles (Table 2). The reductions afforded the corresponding 1,3-amino alcohols in moderate to good yields. It is noteworthy that aromatic β-keto nitriles **2a**–**g** were reduced in good enantioselectivities (85–96% ee). To gain further insight into the effect of the electron density of the aromatic ring, a series of β-keto nitriles **2a**–**g** bearing different substituents at the *para* position on the phenyl group were studied. The results show that the electron density of the aromatic ring has little effect on the enantioselectivity (Table 2, entries 1–7). When the substituent was at the *meta* position, the asymmetric reduction of the β-keto nitrile **2d** afforded a slightly lower enantioselectivity when compared with its *para* substituted analogues (Table 2, entry 4). For aliphatic β-keto nitriles **2i** and **2j**, both chemical yield and enantiomeric excess were lowered compared with those obtained from aromatic analogues (Table 2, entries 9 and 10). A higher enantioselectivity was obtained when the reaction occurred at the most hindered carbonyl group (Table 2, entry 10).

The absolute configuration of **3a** was confirmed by the comparison of the specific rotation with the literature value[6e] and is consistent with results we had obtained in the reduction of other functional ketones, such as β-keto sulfones.[9c] Although the absolute configurations of the corresponding 1,3-amino alcohols **3b**–**g** and **3i**–**j** could not be assigned, in view of the same reaction mechanism, we assume the absolute configurations to be the same with **3a**.

Table 2. Asymmetric reduction of β-keto nitriles[a]

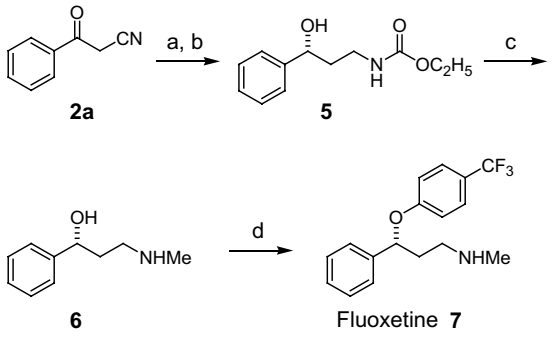


Entry	R	β-Keto nitriles	1,2-Amino alcohols	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	Ph	**2a**	**3a**	76	96	*R*
2	*p*-F-C_6H_4	**2b**	**3b**	74	93	—[e]
3	*p*-Cl-C_6H_4	**2c**	**3c**	79	94	—[e]
4	*m*-Cl-C_6H_4	**2d**	**3d**	74	88	—[e]
5	*p*-Br-C_6H_4	**2e**	**3e**	74	94	—[e]
6	*p*-Me-C_6H_4	**2f**	**3f**	67	90	—[e]
7	*p*-MeO-C_6H_4	**2g**	**3g**	56	95	—[e]
8	Thiophen-2-yl	**2h**	**3h**	77	85	*R*
9	*n*-Bu	**2i**	**3i**	43	64	—[e]
10	*t*-Bu	**2j**	**3j**	49	77	—[e]

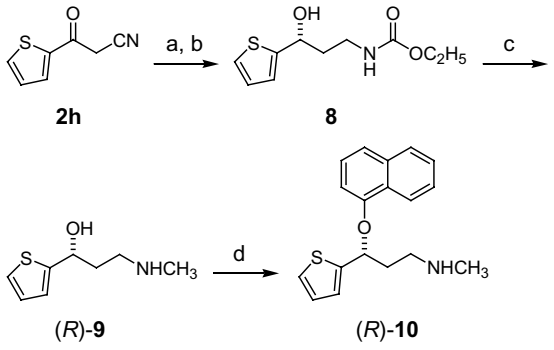
[a] Experiments were performed at a 1 mmol scale.
[b] Isolated yield after column purification.
[c] Analytical samples were converted to their amide **4a**–**j**; Determined by chiral HPLC.
[d] The absolute configurations were determined by the comparison of the reported specific rotations or predicted by the mechanism of the reaction.

The 1,3-amino alcohol **3a** was envisaged as a key building block from which (*R*)-fluoxetine or related analogues could be synthesized (Scheme 2). The synthesis of intermediate **3a** starts from β-keto nitrile **2a**, a readily available starting material as illustrated in Scheme 1. The reaction proceeded smoothly with the use of borane–dimethyl sulfide as the reducing agent, catalyzed by polymer-supported chiral sulfonamide **1**, providing the 1,3-amino alcohol **3a** in 76% yield having $[\alpha]_D^{20} = +40.5$ (*c* 1.4, $CHCl_3$) {lit.[6e] $[\alpha]_D^{25} = +40.5$ (*c* 1.0, $CHCl_3$)}. This key intermediate could then be used without purification in the next reaction with ethylchloroformate in aq $NaHCO_3$ to give carbamate **5**, which on subsequent reduction with lithium aluminum hydride furnished methyl amine **6** having $[\alpha]_D^{20} = +35.1$ (*c* 0.75, $CHCl_3$) {lit.[7j] $[\alpha]_D^{30} = +37.1$ (*c* 1.0, $CHCl_3$)}. The arylation of **6** was then carried out by nucleophilic aromatic substitution employing NaH as a base and 4-chlorobenzotrifluoxetine as an electrophile in DMSO to afford (*R*)-fluoxetine **7** in 92% yield. $[\alpha]_D^{20} = +3.8$ (*c* 0.9, $CHCl_3$) {lit.[7j] $[\alpha]_D^{20} = +4.1$ (*c* 1.0, CH_3Cl)}. The physical and spectroscopic data of **7** are in agreement with the literature data.[7j]

Similarly, with the procedure described above in the synthesis of (*R*)-fluoxetine, (*R*)-duloxetine (*R*)-**10** was synthesized (Scheme 3). $[\alpha]_D^{20} = +113$ (*c* 0.9, MeOH) {lit.[7k] $[\alpha]_D^{20} = +117$ (*c* 1.0, MeOH)}. The physical and spectroscopic data of **10** are also in full agreement with the literature data.[7k]



Scheme 2. Reagents and conditions: (a) $BH_3{\cdot}Me_2S$, **1** (30 mol %), THF, reflux; (b) $ClCO_2Et$, $NaHCO_3$ (aq), CH_2Cl_2, rt, 2 h, 63% (two steps); (c) $LiAlH_4$, THF, reflux, 2 h, 93%; (d) NaH, DMSO, 55 °C, 30 min, then 4-chlorobenzotrifluoride, 80–90 °C, 1 h, 92%.



Scheme 3. Reagents and conditions: (a) $BH_3{\cdot}Me_2S$, **1** (30 mol%), THF, reflux; (b) $ClCO_2Et$, $NaHCO_3$ (aq), CH_2Cl_2, rt, 2 h, 67% (two steps); (c) $LiAlH_4$, THF, reflux, 2 h, 93%; (d) NaH, DMSO, rt, 30 min, then 1-fluoro-naphthalene, 45–50 °C, 1 h, 88%.

3. Conclusion

In summary, the results reported herein offer a practical and highly enantioselective methodology for the synthesis of optically active 1,3-amino alcohol. Due to the efficiency and high enantioselectivity observed, this method represents a very useful alternative to previously reported procedures. Finally, we applied this method to the enantioselective synthesis of antidepressant drugs (*R*)-fluoxetine and (*R*)-duloxetine.

4. Experimental

General: All reactions were carried out under a dry Ar atmosphere. THF was freshly distilled over sodium/benzophenone before use. α-Keto nitriles were prepared according to the reported procedures and further purified by silica gel column. All NMR spectra were recorded in $CDCl_3$ as the solvent unless otherwise stated.

4.1. General procedure for the asymmetric reduction of α-keto nitriles

Cat. **1** (0.3 mmol) was added to a 50 mL three-necked flask, at which point was added 10 mL of THF and 1.6 mL of $BH_3{\cdot}Me_2S$ (2 M in THF). The suspension was heated under reflux and stirred for 0.5 h. Then, a THF (8 mL) solution of β-keto nitrile (1 mmol) was added at a rate of 3 mL/h by a syringe pump. After the addition was completed, the mixture was treated with 10 mL of methanol and filtered. The polymeric catalyst was washed several times with hot water, EtOAc, and methanol. The resulting solution was evaporated and purified by silica gel chromatography employing NH_4OH–CH_3OH–EtOAc (1:10:90) to give corresponding 1,3-amino alcohol.

4.1.1. (*R*)-3-Amino-1-phenyl-propan-1-ol 3a. Colorless oil, 74% yield, $[\alpha]_D^{20} = 40.5$ (*c* 1.40, $CHCl_3$) {lit.[6e] $[\alpha]_D^{20} = 40.5$ (*c* 1.0, $CHCl_3$)}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.23 (m, 5H), 4.93 (dd, $J = 3.3$ Hz, 8.5Hz, 1H), 3.05 (br, 3H), 2.97–2.89 (m, 2H), 1.90–1.69 (m, 2H); IR (film): 3355, 3029, 2940, 1878, 1574, 1492, 1452, 1323, 1062 cm^{-1}.

4.1.2. 3-Amino-1-(4-flurophenyl)-propan-1-ol 3b. White solid, 76% yield, $[\alpha]_D^{20} = +27.6$ (*c* 1.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (dd, $J = 5.4$ Hz, 8.3 Hz, 2H), 7.00 (t, $J = 8.8$ Hz, 2H), 4.88 (dd, $J = 3.2$ Hz, 7.7 Hz, 1H), 3.13 (br, 3H), 3.07–3.00 (m, 1H), 2.94–2.85 (m, 1H), 1.84–1.63 (m, 2H); ^{19}F NMR (300 MHz, $CDCl_3$): δ −116.6; IR (KBr): 3291, 2937, 2873, 1604, 1509, 1326, 1221, 1516, 1069 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.75(d, $J_{C-F} = 242.7$Hz), 140.85 (d, $J_{C-F} = 2.8$ Hz), 127.11, (d, $J_{C-F} = 7.8$ Hz), 114.86 (d, $J_{C-F} = 21.2$ Hz), 74.42, 40.25, 39.84. EIMS (*m*/*z*, relative intensity): 169 (M^+, 5.27), 152 ($M^+ - NH_3$, 100), 151

(M^+-H_2O, 90.37), 125 (37.10), 123 (76.81), 122 (90.69), 97 (69.23), 96 (30.72), 95 (43.31), 71 (33.31), 75 (26.64), 45 (76.12), 44 (58.80); HRMS Calcd for $C_9H_{13}FNO$: 170.0981. Found: 170.0976.

4.1.3. 3-Amino-1-(4-chlorophenyl)-propan-1-ol 3c. Colorless oil, 79% yield, $[\alpha]_D^{20} = +31.7$ (*c* 0.92, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 4H), 4.91 (dd, *J* = 3.2 Hz, 7.8 Hz, 1H), 3.30 (br, 3H), 3.09–3.05 (m, 1H), 2.9–2.89 (m, 1H), 1.86–1.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.03, 132.89, 128.70, 127.39, 74.98, 40.69, 39.89; IR (film): 3359, 3289, 2934, 2871, 1594, 1490, 1406, 1333, 1089, 1014 cm^{-1}.

4.1.4. 3-Amino-1-(3-chlorophenyl)-propan-1-ol 3d. Colorless oil, 79% yield, $[\alpha]_D^{20} = +32.2$ (*c* 1.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.28–7.21 (m, 3H), 4.90 (dd, *J* = 3.2 Hz, 7.5 Hz, 1H), 3.24 (br, 3H), 3.11–3.04 (m, 1H), 2.97–2.88 (m, 1H), 1.88–1.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.99, 133.78, 129.16, 126.66, 125.50, 123.44, 74.44, 40.06, 39.08; IR (film): 3358, 3171, 2937, 2871, 1596, 1573, 1475, 1430, 1321, 1200, 1073 cm^{-1}; EIMS (*m*/*z*, relative intensity): 187 (2.49), 185 (M^+, 7.57), 168 (M^+-NH_3, 22.67), 167 (M^+-H_2O, 10.54), 138 (52.66), 133 (70.45), 113 (21.87), 103 (28.75), 77 (100), 75 (25.00), 45 (52.70), 44 (52.58); HRMS Calcd for $C_9H_{13}ClNO$: 186.0686. Found: 186.0680.

4.1.5. 3-Amino-1-(4-bromophenyl)-propan-1-ol 3e. Colorless oil, 74% yield, $[\alpha]_D^{20} = +23.8$ (*c* 1.81, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.90 (dd, *J* = 2.9 Hz, 8.7Hz, 1H), 3.24 (br, 3H), 3.12–3.04 (m, 1H), 2.98–2.90 (m, 1H), 1.86–1.62 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 144.18, 131.29, 127.40, 120.64, 74.83, 40.42, 39.44. IR (film): 3356, 3172, 2937, 2936, 2869, 1590, 1475, 1486, 1400, 1071, 1010 cm^{-1}; EIMS (*m*/*z*, relative intensity): 231 (3.73), 229 (M^+, 3.79), 212 (M^+-NH_3, 14.15), 211 (M^+-H_2O, 5.79), 185 (28.06), 133 (100), 85 (40.64), 83 (61.29), 77 (77.90), 51 (27.38), 47 (25.26), 45 (56.39); HRMS Calcd for $C_9H_{13}NOCl$: 252.0000. Found: 251.9994.

4.1.6. 3-Amino-1-*p*-tolyl-propan-1-ol 3f. Colorless oil, 62% yield, $[\alpha]_D^{20} = +24.4$ (*c* 1.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.90 (dd, *J* = 3.6 Hz, 8.6 Hz, 1H), 3.09–3.01 (m, 4H), 2.96–2.87 (m, 1H), 2.33 (s, 3H), 1.88–1.68 (m, 2H); IR (film): 3356, 3289, 2922, 2866, 1584, 1513, 1456, 1332, 1068 cm^{-1}.

4.1.7. 3-Amino-1-(4-methoxyphenyl)-1-ol 3g. White solid, 57% yield, $[\alpha]_D^{20} = +25.2$ (*c* 1.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.90 (dd, *J* = 3.5 Hz, 8.3 Hz, 1H), 3.80 (s, 3H), 3.13–3.06 (m, 1H), 2.90–2.70 (m, 1H), 2.77 (br, 3H), 1.88–1.68 (m, 2H); IR (film): 3356, 2935, 2836, 1611, 1585, 1513, 1302, 1246, 1175, 1033 cm^{-1}.

4.1.8. (*R*)-3-Amino-1-thiophen-2-yl-propan-1-ol 3h. Colorless oil, 77% yield, $[\alpha]_D^{26} = +8.7$ (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–7.27 (m, 1H), 6.94–6.98 (m, 2H), 5.21 (dd, *J* = 3.2 Hz, 8.6 Hz, 1H), 3.10–2.93 (m, 5H), 2.03–1.81 (m, 2H); IR (film): 3281, 2936, 2871, 1578, 1482, 1361, 1037, 853 cm^{-1}.

4.1.9. 1-Amino-heptan-3-ol 3i. Colorless oil, 54% yield, $[\alpha]_D^{20} = -15.2$ (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.87–3.77 (m, 1H), 3.19–3.12 (m, 1H), 2.89–2.81 (m, 1H), 2.58 (br, 3H), 1.66–1.30 (m, 8H), 0.91 (t, *J* = 7.7 Hz, 3H). IR (film): 3360, 2956, 2931, 2860, 1594, 1467, 1378, 1338, 1129, 1047 cm^{-1}.

4.1.10. 1-Amino-4,4-dimethyl-petan-3-ol 3j. Colorless oil, 49% yield, $[\alpha]_D^{20} = -10.8$ (*c* 1.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.45 (dd, *J* = 1.5 Hz, 10.7 Hz, 1H), 3.16 (br, 1H), 2.80 (m, 4H), 1.66–1.59 (m, 1H), 1.44–1.31 (m, 1H), 0.9 (s, 9H); IR (film): 3362, 3292, 2954, 2869, 1596, 1479, 1391, 1363, 1077, 1011 cm^{-1}.

4.2. Acylation of the reduction products 3a–j to form 4a–j

To determine the ee of the reduction products on HPLC, all the 1,3-amino alcohols were converted to their acetamides **4a**–**h** or benzamides **4i**–**j** under Schotten Baumann conditions with saturated sodium bicarbonate and methylene chloride. The products were purified through silica gel column chromatography (NH_4OH/CH_3OH/EtOAc 1:10:90).

4.2.1. *N*-(3-Hydroxy-3-phenylpropyl)-acetamide 4a. White solid, 90% yield, $[\alpha]_D^{20} = +22.2$ (*c* 1.67, $CHCl_3$), 96% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.27 (m, 5H), 6.10 (br, 1H), 4.72 (m, 1H), 3.74–3.62 (m, 1H), 3.57 (br, 1H), 3.27–3.17 (m, 1H), 1.98 (s, 3H), 1.90–1.84 (m, 2H). IR (KBr): 3296, 3086, 3031, 2930, 2875, 1651, 1557, 1453, 1369, 1298, 1106, 1064, 998 cm^{-1}.

4.2.2. *N*-[3-(4-Fluorophenyl)-3-hydroxy-propyl]-acetamide 4b. Colorless oil, 64% yield, $[\alpha]_D^{20} = +16.0$ ($CHCl_3$, *c* 0.93), 93% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.28 (m, 2H), 7.05–6.98 (m, 2H), 6.23 (br, 1H), 4.70 (m, 1H), 4.00 (br, 1H), 3.70–3.61 (m, 1H) 3.23–3.12 (m, 1H), 2.00 (s, 3H), 1.84–1.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.19, 125.10, 124.99, 113.12, 112.84, 68.74, 36.93, 34.54, 20.97. ^{19}F NMR (300 MHz, $CDCl_3$): δ −115.8. IR (film): 3305, 3095, 2938, 2878, 1894, 1651, 1597, 1557, 1510, 1435, 1370, 1295, 1222, 1157, 1083, 1014, 837 cm^{-1}. EIMS (*m*/*z*, abundance): 211 (M^+, 1.36), 86 (64.28), 84 (100), 73 (11.98), 49 (17.96), 47 (19.35). HRMS Calcd for $C_{11}H_{14}NO_2FNa^+$: 234.0906. Found: 234.0901.

4.2.3. *N*-[3-(4-Chlorophenyl)-3-hydroxy-propyl]-acetamide 4c. White solid, 61% yield, $[\alpha]_D^{20} = +9.1$ (*c* 0.425, $CHCl_3$), 94% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.29 (m, 4H), 6.53 (br, 1H), 4.65 (dd, *J* = 4.2 Hz, 8.8 Hz, 1H), 3.66–3.55 (m, 1H) 3.24–3.15 (m, 1H), 1.98 (s, 3H), 1.84–1.73 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.22, 142.36, 132.53, 128.13, 126.68, 70.47, 38.60, 36.34, 22.75. IR (film): 3300, 3097, 2934, 2877, 1904, 1651, 1556, 1491, 1435, 1369, 1294, 1090, 1014, 826 cm^{-1}. ESIMS for $C_{11}H_{15}NO_2^+$: 227.95. Anal. Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.03; H, 6.20; N, 6.15. Found: C, 57.86; H, 6.15; N, 6.08.

4.2.4. *N*-[3-(3-Chloro-phenyl)-3-hydroxy-propyl]-acetamide 4d. Colorless oil, 71% yield, $[\alpha]_D^{20} = +11.1$ (*c* 2.48, $CHCl_3$), 88% ee, ^1H NMR (300 MHz, 300 MHz,): δ 7.33 (s, 1H), 7.24–7.17 (m, 3H), 6.64 (br, 1H), 4.63 (m, 2H), 3.63–3.49 (m, 1H) 3.22–3.12 (m, 1H), 1.94 (s, 3H), 1.83–1.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.55, 146.33, 134.11, 129.61, 127.27, 125.75, 123.74, 70.78, 38.76, 36.57, 22.96. IR (film):3300, 3094, 2940, 2877, 1894, 1651, 1598, 1556, 1433, 1369, 1297, 1196, 1076, 999 cm^{-1}. EIMS (*m*/*z*, abundance): 229 (4.61), 227 (M^+, 12.77), 87 (70.27), 77 (48.96), 73 (100), 72 (50.89), 44 (36.41), 43 (74.81). HRMS Calcd for $C_{11}H_{14}NO_2ClNa^+$: 250.0611. Found: 250.0605.

4.2.5. *N*-[3-(3-Bromo-phenyl)-3-hydroxyl-propyl]-acetamide 4e. White solid, 50% yield, $[\alpha]_D^{20} = +12.1$ (*c* 1.88, $CHCl_3$), 94% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.46–7.44 (m, 2H), 7.27 (m, 2H), 3.71–3.59 (m, 1H) 3.22–3.11 (m, 1H), 1.99 (s, 3H), 1.84–1.71 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.94, 142.66, 130.90, 126.84, 120.48, 70.28, 38.51, 36.13, 22.61. IR (KBr): 3304, 3094, 2940, 2873, 1651, 1552, 1487, 1437, 1401, 1369, 1293, 1071, 1010, 821 cm^{-1}. EIMS (*m*/*z*, abundance): 273 (64.31), 271 (78.87), 185 (100), 183 (59.28), 87 (48.44), 77 (23.20), 73 (50.74), 43 (27.91). HRMS Calcd for $C_{11}H_{14}NO_2\ Br^+$: 272.0286. Found: 272.0281.

4.2.6. *N*-(3-Hydroxyl-3-*p*-tolyl-propyl)-acetamide 4f. Colorless oil, 35% yield, $[\alpha]_D^{20} = 12.4$ (*c* 1.71, $CHCl_3$), 90% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, $J = 7.9$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 6.33 (br, 1H), 4.62 (m, 1H), 4.16 (br, 1H), 357–3.46 (m, 1H), 3.19–3.09 (m, 1H), 2.30 (s, 3H), 1.83–1.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.02, 141.23, 137.10, 129.12, 125.59, 72.01, 38.75, 36.96, 23.16, 21.06. IR (film): 3302, 3095, 3022, 2925, 2872, 1654, 1555, 1515, 1438, 1369, 1297, 1075, 818 cm^{-1}. EIMS (*m*/*z*, abundance): 207 (1091), 189 (0.89), 135 (20.47), 133 (22.25), 119 (20.24), 93 (25.11), 91 (47.33), 87 (100), 77 (26.54), 73 (58.03), 72 (48.87), 43 (60.98). HRMS Calcd for $C_{11}H_{17}NO_2Na^+$: 230.1157. Found: 230.1152.

4.2.7. *N*-[3-Hydroxyl-2-(4-methoxy-phenyl-propyl)-acetamide 4g. Colorless oil, 82% yield, $[\alpha]_D^{20} = +16.4$ (*c* 0.995, $CHCl_3$), 94% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.2$ Hz, 2H), 6.42 (br, 1H), 4.65 (t, $J = 6.3$ Hz, 1H), 3.85 (br, 1H), 3.79 (s, 3H), 3.62–3.52 (m, 1H), 3.22–3.15 (m, 1H), 1.95 (s, 3H), 1.85–1.79 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.53, 158.38, 135.74, 126.34, 113.27, 71.14, 54.73, 38.19, 36.42, 22.67. IR (film): 3303, 3094, 2936, 2837, 1652, 1553, 1513, 1442, 1369, 1301, 1248, 1176, 1074, 1034, 832 cm^{-1}. ESIMS(*m*/*z*, abundance): 223. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.2. Found: C, 64.17; H, 7.60; N, 6.04.

4.2.8. *N*-(3-Hydroxy-3-thiophen-2-yl-propyl)-acetamide 4h. Colorless oil, 50% yield, $[\alpha]_D^{23} = -4.8$ (*c* 1.30, $CHCl_3$), 85% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–7.19 (m, 1H), 6.95–6.92 (m, 2H), 6.64 (br, 1H), 4.92 (dd, $J = 4.6$ Hz, 8.6 Hz, 1H), 4.68 (br, 1H), 3.64–3.52 (m, 1H), 3.26–3.16 (m, 1H), 1.98–1.89 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.98, 148.48, 127.02, 124.70, 123.65, 67.96, 39.30, 36.94, 23.46. IR (film): 3304, 3102, 2931, 2874, 1651, 1557, 1435, 1370, 1295, 1078 cm^{-1}. EIMS (*m*/*z*, abundance): 199 (M^+, 9.8), 140 (22.3), 87 (26.2), 73 (30.8), 43 (100.0). HRMS Calcd for $C_9H_{13}NO_2SNa^+$: 222.05647. Found: 222.05592.

4.2.9. *N*-(3-Hydroxy-heptyl)benzamide 4i. White solid, 87% yield, $[\alpha]_D^{20} = +1.6$ (*c* 1.825, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.79–7.76 (m, 2H), 3.72–3.69 (m, 1H), 3.19 (br, 1H), 1.75–1.31 (m, 8H), 0.89 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.77, 133.82, 131.00, 128.05, 126.48, 69.48, 37.02, 36.70, 36.12, 27.50, 22.24, 13.58. IR (KBr): 3332, 3065, 3031, 2931, 2860, 1641, 1578, 1544, 1489, 1450, 1377, 1311, 1199, 1132, 1100, 1075, 1027, 969 cm^{-1}. EIMS (*m*/*z*, abundance): 235 (M^+, 0.23), 217 (3.63), 178 (10.82), 148 (12.98), 134 (20.81), 122 (21.50), 105 (100), 77 (35.6). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.11; H, 8.96; N, 5.80.

4.2.10. *N*-(3-Hydroxy-4,4-dimethyl-pentyl)-benzamide 4j. White solid, 87% yield, $[\alpha]_D^{23} = +1.3$ (*c* 1.07, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.80–7.76 (m, 2H), 7.50–7.43 (m, 3H), 4.0–3.88 (m, 1H), 3.39–3.28 (m, 2H), 2.78 (br, 1H), 1.84–1.78 (m, 1H), 1.58–1.49 (m, 1H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.96, 136.33, 133.32, 130.43, 128.86, 40.37, 36.72, 32.67, 27.65. IR (KBr): 3261, 2947, 1636, 1577, 1546, 1078, 948 cm^{-1}. EIMS (*m*/*z*, abundance): 235 (M^+, 0.20), 178 (32.17), 105 (100), 77 (35.8). Anal. Calcd for $C_{14}H_{21}NO_2$: C,71.46; H, 8.99; N, 5.95. Found: C, 71.18; H, 8.99; N, 5.80.

When **4i** and **4j** were not separated on HPLC, they were converted to their acetate **4i**–**a** and **4j**–**a** with acetyl chloride and DMAP. The products were purified through silica gel column chromatography (*n*-Hexane/EtOAc 10:1).

4.2.11. 1-Benzamidoheptan-3-yl acetate 4i–a. Colorless oil, 90% yield, $[\alpha]_D^{18} = +64.4$ (*c* 0.8075, $CHCl_3$), 64% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.84–7.80 (m, 2H), 7.46–7.43 (m, 3H), 6.98 (br, 1H), 4.96 (m, 1H), 3.89–3.78 (m, 1H), 3.09–2.98 (m, 1H), 2.11 (s, 3H), 1.98–1.28 (m, 8H), 0.89 (t, $J = 4.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.28, 167.59, 134.84, 131.68, 128.85, 127.25, 72.59, 36.29, 34.57, 30.01, 27.93, 22.77, 21.51, 14.25. IR (film): 3331, 2957, 2933, 1736, 1642, 1541, 1242, 1022 cm^{-1}. ESIMS (*m*/*z*, abundance): 278.2 ($M+1^+$, 100), 279.2 (20). HRMS Calcd for $C_{16}H_{23}NO_3Na^+$: 300.1576. Found: 300.1570.

4.2.12. 1-Benzamido-4,4-dimethylpentan-3-yl acetate 4j–a. Colorless oil, 92% yield, $[\alpha]_D^{18} = +96.9$ (*c* 1.00, $CHCl_3$), 64% ee, ^1H NMR (300 MHz, $CDCl_3$): δ 7.87–7.83 (m, 2H), 7.50–7.41 (m, 3H), 7.10 (br, 1H), 4.75 (dd, $J = 2.1$ Hz, 11.0 Hz, 1H), 4.00–3.89 (m, 1H), 2.94–282 (m, 1H), 2.12 (s, 3H), 2.02–1.92 (m, 1H), 1.69–1.58 (m, 1H), 0.8 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.82, 167.46, 134.88, 131.69, 128.91, 127.30, 79.17, 36.48, 34.61, 29.53, 26.24, 21.37. IR (film): 3331, 2957, 2933, 1736, 1642, 1541, 1242, 1022 cm^{-1}. EIMS (*m*/*z*, abundance): 277 (M^+, 5.58), 217 (18.54), 178 (19.34),

160 (18.01), 105 (100), 77 (24.16). HRMS Calcd for $C_{16}H_{24}NO_3^+$: 278.1757. Found: 278.1751.

4.3. (*R*)-(3-Hydroxy-3-phenylpropyl)carbamic acid ethyl ester 5

To a solution of **3a** which was prepared from 0.7 g of **2a** and not purified in 10 mL dichloromethane, 15 mL of saturated aqueous $NaHCO_3$ was added. Ethyl chloroformate (0.4 mL) in 15 mL dichloromethane was added to the mixture dropwise. Colorless oil, 63% yield, $[\alpha]_D^{20} = 21.4$ (*c* 1.65, $CHCl_3$) {lit.[7j] $[\alpha]_D^{30} = 24.1$ (*c* 1.0, $CHCl_3$)}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.24 (m, 5H), 5.23 (br, 1H), 4.76–4.70 (m, 1H), 4.08 (q, $J = 7.0$ Hz, 2H), 3.45–3.17 (m, 3H), 1.89–1.82 (m, 2H), 1.23 (t, $J = 7.0$ Hz, 3H); IR (film): 3342, 2980, 2934, 1697, 1529, 1453, 1264, 1142, 1038 cm^{-1}.

4.4. (*R*)-3-Methylamino-1-phenylpropane-1-ol 6

Colorless oil, 93% yield, $[\alpha]_D^{20} = +35.1$ (*c* 0.75, $CHCl_3$). {lit.[7j] $[\alpha]_D^{30} = +37.1$ (*c* 1.0, $CHCl_3$)}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.24 (m, 5H), 4.94 (dd, $J = 3.3$ Hz, 8.7 Hz, 1H), 3.58 (br, 2H), 2.94–2.80 (m, 2H), 2.44 (s, 3H), 1.92–1.70 (m, 2H); IR (film): 3308, 3061, 3028, 2938, 2852, 2799, 1492, 1452, 1200, 1109, 1064, 1027, 751 cm^{-1}.

4.5. (*R*)-Fluoxetine (7)

Colorless oil, 92% yield, $[\alpha]_D^{20} = +3.8$ (*c* 0.90, $CHCl_3$) {lit.[7j] $[\alpha]_D^{20} = 4.1$ (*c* 1.0, $CHCl_3$)}, ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, $J = 9.0$ Hz, 2H), 7.35–7.26 (m, 5H), 6.90 (d, $J = 9.0$ Hz, 2H), 5.30 (m, 1H), 2.75 (t, $J = 7.0$ Hz, 2H), 2.44 (s, 3H), 2.24–2.15 (m, 2H), 2.02–1.97 (m, 1H), 1.64 (br, 1H); ^{19}F NMR (300 MHz, $CDCl_3$): δ −61.946; IR (film): 2946, 2848, 2796, 1615, 1517, 1329, 1251, 1178, 1162, 1111, 1068, 1009, 836 cm^{-1}.

4.6. (*R*)-(3-Hydroxy-3-thiophen-2-yl-propyl)carbamic acid ethyl ester 8

Colorless oil, 67% yield, $[\alpha]_D^{22} = -2.0$ (*c* 1.28, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$): δ 7.24–7.22 (m, 1H), 6.96–6.95 (m, 1H), 5.17(br, 1H), 5.02–4.97 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.68 (br, 1H), 3.54–3.45 (m, 1H), 3.29–3.19 (m, 1H), 2.04–1.95 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H); IR (film): 3407, 3338, 3104, 2980, 2937, 1701, 1535, 1268, 1038 cm^{-1}.

4.7. (*R*)-3-Methylamino-1-thiophen-2-yl-propan-1-ol 9

Colorless oil, 89% yield, $[\alpha]_D^{24} = +13.3$ (*c* 1.05, MeOH) {lit.[7k] $[\alpha]_D^{34} = +13.9$ (*c* 2.4, MeOH)}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 1H), 6.98–6.91 (m, 1H), 5.18 (m, 1H), 3.58 (br, 2H), 2.99–2.81 (m, 2H), 2.43 (s, 3H), 2.02–1.84 (m, 1H); IR (film): 3302, 3103, 2939, 2853, 2793, 1473, 1315, 1074, 1038 cm^{-1}.

4.8. (*R*)-Duloxetine 10

Colorless oil, $[\alpha]_D^{20} = +113$ (*c* 0.9, MeOH) {lit.[7k] $[\alpha]_D^{20} = +117$ (*c* 1.0, MeOH)}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.36–8.33 (m, 1H), 7.78–7.75 (m, 1H), 7.49–7.18 (m, 5H), 6.92–6.83 (m, 3H), 5.77 (dd, $J = 5.2$ Hz, 7.7 Hz, 1H), 2.82 (t, $J = 7.6$ Hz, 2H), 2.51–2.42 (m, 1H), 2.42 (s, 3H), 2.28–2.16 (m, 1H); IR (film): 3317, 3052, 2946, 2845, 2794, 1595, 1578, 1462, 1397, 1264, 1094 cm^{-1}.

Acknowledgements

Financial support by the Major State of Basic Research Development Program (No. G2000048007), the National Natural Science Foundation of China, QT Program, and Shanghai Natural Science Council is gratefully acknowledged.

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