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A Practical Synthesis of the Antidepressant (*S*)-Duloxetine

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Serotonin and norepinephrine neurotransmitters are intimately involved in a number of neurochemical and physiological processes, such as depression and pain disorders. Selective serotonin or norepinephrine reuptake inhibitors are the important class of antidepressants, such as fluoxetine, nisoxetine, tomoxetine, and duloxetine featuring the structural similarity of 1-ary-3-aminopropanol.[1] Among them, duloxetine belongs to a class of antidepressant drugs that simultaneously inhibit the reuptake of serotonin as well as norepinephrine. Even though duloxetine was originally marketed as a racemic mixture, (*S*)-enantiomeric form is now available since it has substantially beneficial biological effects compared with its antipode.[2] This also could draw much attention for the preparation of enantiomerically pure duloxetine. Currently, (*S*)-duloxetine is prescribed for the treatment of major depressive disorder and stress-related urinary incontinence under the name of Cymbalta.

Recently, numerous avenues to provide an enantiomerically pure duloxetine have been elaborated using various precursors, in which Friedel-Crafts reaction of thiophene with glyoxylate, aldol reaction of thiophene-2-carboxaldehyde with thioamide or malonic acid half thioester, and dynamic kinetic resolution of 2-hydroxy-2-(2-thienyl)acetonitrile have been reported.[3] Nonetheless, asymmetric reduction of β-substituted ketones is perhaps among the most attractive and straightforward strategies to meet practical demands, in fact enantiomerically enriched γ-chloro or -dimethylamino alcohols are most frequently employed for the preparation of (*S*)-duloxetine. The initial synthesis of (*S*)-duloxetine has been reported based on a chirally-modified LAH reduction of 3-(dimethylamino)-1-(2-thienyl)-1-propanone.[4] Further utilization of the tertiary amino ketone has been made through Ru-catalyzed asymmetric hydrogenation.[5] It is interesting to note the enantioselective synthesis of γ-methylamino alcohol has been successfully accomplished *via* catalytic hydrogenation of β-methylamino ketone with Rh-duanphos complex[6a] and Rh-catalyzed transfer hydrogention after its *N*-Boc protection, respectively.[6b] However, the most common approach involves borane reduction of 3-chloro-1-(2-thienyl)-1-propanone catalyzed by chiral oxazaborolidine to exhibit good to excellent enanatioselectivities.[2,7] Recently, hydrosilylation of the β-chloro ketone catalyzed by Cu-dipyridylphosphine system with phenylsilane has been developed.[8]

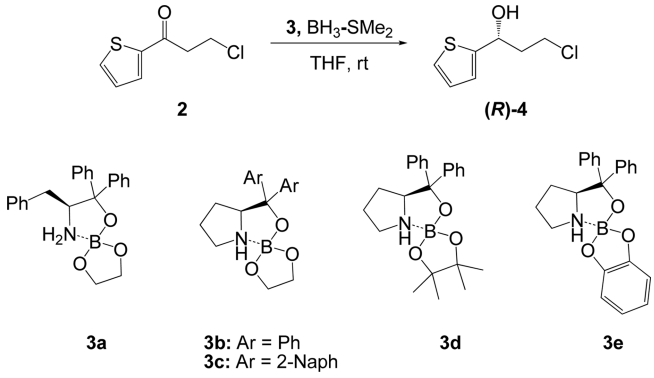
In continuation of our earlier efforts towards the preparation of biologically important compounds particularly possessing a chiral aminoalcohol unit,[9] siproborate ester-catalyzed ketone reduction caught our attention. Recently, the chiral spiroborate esters derived from amino alcohols showed high catalytic activity toward reductions of simple aromatic ketones and oxime ethers.[10] The reaction bypassed the need for highly air/moisture-sensitive and precious metal catalysts or expensive reducing agents. We envisaged, thus, that a strategy to improve application development is particularly valuable in scale-up synthesis of active pharmaceutical ingredients. Herein we report an asymmetric borane reduction of 3-chloro-1-(2-thienyl)-1-propanone mediated by tetra-coordinated spiroborate ester to highlight the enantioselective synthesis of the antidepressant drug (*S*)-duloxetine (**1**).

The β-chloro ketone **2** was available through Friedel-Crafts acylation of thiophene with 3-chloropropionyl chloride in the presence of aluminum chloride as the Lewis acid catalyst.[11] Spiroborate esters **3a-3e** were readily prepared by heating equimolar amount of chiral 1,1-diaryl-2-aminoethanols derived from amino acids, 1,2-diols, and triisopropyl borate in toluene, according to the literature procedures.[12] They are white, crystalline solids and stable for long term storage.

We first examined an asymmetric reduction of **2** with borane dimethyl sulfide (0.7 equiv) in the presence of **(*S*)-3a** (10 mol %) in THF at room temperature. Indeed, the reduction was completed within 1 h to give **(*R*)-4** in 91% yield with 77% *ee* (entry 1). Enantiomeric excess (*ee*) was determined by GC using a chiral column (CP-Chirasil-Dex CB). The effectiveness of several spiroborate ester catalysts was investigated under the same conditions and the results are summarized in Table 1. Among them, diphenylprolinol-derived **(*S*)-3b** revealed good yield with high enantioselectivity (entry 2). Furthermore, even the catalyst loading was reduced to 5 mol %, a complete conversion was sustained with no loss of enantioselectivity (entry 3). However, there is a significant deterioration in enantioselectivity upon changes associated with the 1,2-diol partners from ethylene glycol to highly hindered diols such as pinacol or catechol, presumably, due to the steric congestion to the incoming ketone substrate (entries 6 and 7).

Synthesis of (*S*)-duloxetine is quite straightforward and the results are illustrated in Scheme 1. Again, asymmetric

Table 1. Asymmetric catalytic borane reduction of **2** with spiroborate ester catalysts

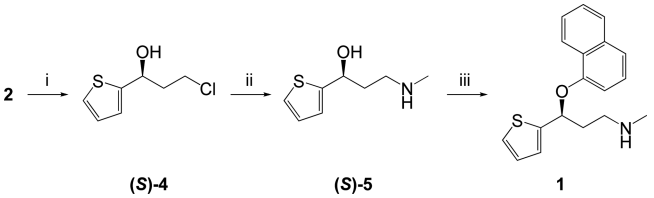


Entry[a]	Catalyst	Time (h)	Yield (%)	*ee* (%)[b]
1	**(*S*)-3a**	1	91	77
2	**(*S*)-3b**	1	88	96
3[c]	**(*S*)-3b**	1	89	95
4[d]	**(*S*)-3b**	12	84	59
5	**(*S*)-3c**	3	89	93
6	**(*S*)-3d**	3	86	34
7	**(*S*)-3e**	3	89	48

[a]Unless specified otherwise, the reaction was carried out employing **2** (1.2 mmol) and BH_3-SMe_2 (0.7 equiv) in the presence of 10 mol % of catalyst **3**. [b]Determined by GC on chiral column (CP-Chirasil-Dex CB). [c]Used 5 mol % of the catalyst. [d]Used 2 mol % of the catalyst.

borane reduction of **2** using **(*R*)-3b** in THF gave the chloro-alcohol **(*S*)-4** in 92% yield with 95% *ee*. Treatment of **(*S*)-4** with saturated sodium iodide in acetone at reflux for 12 h provided iodo-alcohol, which was used for the next reaction without any purification. Thus, reaction of the iodide with 40% aqueous methylamine at room temperature for 6 h provided amino-alcohol **(*S*)-5** in 71% yield. The final installation was then carried out by nucleophilic aromatic substitution of **(*S*)-5** with 1-fluoronaphthalene employing sodium hydride in DMSO to afford (*S*)-duloxetine (**1**) in 78% yield with 96% *ee*.

In summary, we have prepared (*S*)-duloxetine from 3-chloro-1-(2-thienyl)-1-propanone in good yield with an excellent enantioselectivity *via* asymmetric borane reduction catalyzed by the spiroborate ester. The mild reaction conditions and operational simplicity make this method attractive for a practical synthesis of (*S*)-duloxetine, a potent dual inhibitor of serotonin and norepinephrine reuptake.



Scheme 1. Reagents and conditions: i) **2** (12 mmol), **(*R*)-3b** (5.5 mol %), BH_3-SMe_2 (0.7 equiv), THF, 1 h; **(*S*)-4** (92%, 95% *ee*), ii) NaI, acetone, reflux, 12 h; 40% aq. $MeNH_2$, THF, 6 h; **(*S*)-5** (71% for two steps), iii) 1-fluoronaphthalene, NaH, DMSO, 8 h; **1** (78%, 96% *ee*).

Experimental

Preparation of 3-Chloro-1-(2-thienyl)-1-propanone (2). The β-chloro ketone **2** was prepared through Friedel-Crafts acylation of thiophene with 3-chloropropionyl chloride in the presence of $AlCl_3$.[11] Yield: 19.2 g (95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, 1H, J = 3.8, 1.1 Hz), 7.67 (dd, 1H, J = 4.9, 1.1 Hz), 7.14 (dd, 1H, J = 5.0, 3.8 Hz), 3.90 (t, 2H, J = 6.8 Hz), 3.40 (t, 2H, J = 6.8 Hz); MS (EI) *m/z* (%) 174 (M^+, 58), 139 (50), 111 (100), 83 (30).

Preparation of (*R*)-2-[(1,3,2-Dioxaborolan-2-yloxy)diphenylmethyl]pyrrolidine, (*R*)-3b. The **(*R*)-3b** was prepared as a white crystalline precipitate by heating equimolar amount of (*R*)-α,α-diphenyl-2-pyrrolidinemethanol, ethylene glycol, and triisopropyl borate in toluene.[10b] Yield: 1.13 g (90%); mp 270 °C; $[\alpha]_D^{25}$ = 158.4 (*c* 0.12, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.72 (d, J = 7.2 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.06-7.28 (m, 6H), 6.69 (t, 1H, NH), 4.54 (m, 1H), 3.67-3.79 (m, 2H), 3.55-3.63 (m, 2H), 3.02-3.11 (m, 1H), 2.86-2.97 (m, 1H) 1.56-1.83 (m, 3H), 1.31 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.5, 147.1, 128.2, 128.2, 126.7, 125.8, 78.0, 64.3, 63.2, 47.4, 27.1, 26.2; HRMS (EI): *m/z* calcd for $C_{19}H_{22}BNO_3$ 323.1693; found: 323.1691.

Synthesis of (*S*)-3-Chloro-1-(2-thienyl)-1-propanol, (*S*)-4. To a stirred solution of **(*R*)-3b** (215 mg, 0.66 mmol) in anhydrous THF (20 mL), BH_3·SMe_2 (634 mg, 8.34 mmol) was added in one portion under nitrogen atmosphere. The resulting mixture was stirred for 15 min until a transparent solution was observed. To this solution, a solution of **1** (2.09 g, 11.9 mmol) in THF (5 mL) was added dropwise for 5 min. The resulting mixture was stirred at room temperature for 1 h, and quenched with MeOH (5 mL). The solvents were removed under reduced pressure and the residue was partitioned with EtOAc and water. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The crude was purified by silica gel column chromatography on silica gel (hexane/EtOAc = 3/1) to afford **(*S*)-4** (1.93 g, 92%) as an oil. $[\alpha]_D^{25}$ = −5.60 (*c* 1.2, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, 1H, J = 4.9, 1.3 Hz), 7.00 (m, 2H), 5.18 (m, 1H), 3.75 (m, 1H), 3.58 (m, 1H), 2.39-2.14 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 126.8, 124.9, 124.1, 67.2, 41.5, 41.4; HRMS (EI) *m/z* calcd for C_7H_9ClOS 176.0063; found: 176.0041; GC analysis: CP-Chirasil-Dex CB (25 m, 0.25 mm, 0.25 mm), Injector: 280 °C; Oven: 70 °C for 3 min to 210 °C at 10 °C/min hold 3 min, FID: 280 °C; t_1 = 69.9 min (*R*), t_2 = 70.3 min (*S*); *ee* = 95%.

Synthesis of (*S*)-3-Iodo-1-(2-thienyl)-1-propanol. A mixture of **(*S*)-4** (390 mg, 2.20 mmol) and a NaI-saturated acetone solution (20 mL) was stirred at reflux overnight in a dark place away from light. The mixture was filtered to remove the precipitated NaCl and the filtrate was concentrated *in vacuo*. The residue was dissolved in water (20 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to yield the corresponding iodide (560 mg) as a

yellow oil. This material was used without any further purification.

Synthesis of (*S*)-3-Methylamino-1-(2-thienyl)-1-propanol, (*S*)-5. To a solution of the previously prepared iodide (560 mg, 2.08 mmol) in THF (5 mL), was added 40% aqueous $MeNH_2$ (2.2 mL, 25.4 mmol). The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was treated with 5 N NaOH (1 mL), and then concentrated *in vacuo*. The residue was dissolved in water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH = 40:10:1) to afford **(*S*)-5** (267 mg, 71% for two steps) as a clear oil. $[\alpha]_D^{25}$ = −12.5 (*c* 1.2, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.20 (m, 1H), 6.98-6.91 (m, 2H), 5.21 (ddd, 1H, *J* = 8.2, 3.2, 0.7 Hz), 3.56 (brs, 2H), 3.01-2.83 (m, 2H), 2.45(s, 3H), 2.04-1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 126.5, 123.7, 122.3, 72.1, 50.2, 36.8, 35.9; MS (EI) *m/z* (%) 171 (M^+, 35), 139 (22), 128 (100), 111(31).

Synthesis of (*S*)-Duloxetine (1). To a solution of **(*S*)-5** (171 mg, 1 mmol) in DMSO (5 mL), were added NaH (36 mg 1.5 mmol) and 1-fluoronaphthalene (190 mg, 1.3 mmol). After stirring for 8 h, the reaction mixture was partitioned with ethyl acetate and water. After an extractive workup, the combined organic layers were dried over sodium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH = 40:10:1) to yield **1** (232 mg, 78%) as a colorless oil. $[\alpha]_D^{25}$ = +110.5 (*c* 1.1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37-8.33 (m, 1H), 7.79-7.74 (m, 1H), 7.50-7.44 (m, 2H), 7.39-7.37 (m, 1H), 7.28-7.18 (m, 2H), 7.05-7.04 (m, 1H), 6.93-6.90 (m, 1H), 6.86-6.84 (m, 1H), 5.78 (dd, 1H, *J* = 7.6, 5.3 Hz), 2.86-2.78 (m, 2H), 2.50-2.39 (m, 4H), 2.27-2.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 145.2, 134.5, 127.4, 126.5, 126.2, 126.1, 125.7, 125.2, 124.6, 124.5, 122.1, 120.5, 106.9, 74.7, 48.3, 39.0, 36.5; MS (EI) *m/z* (%) 297 (M^+, 4), 187 (80), 153 (69), 144 (100); HPLC analysis: (Chiralcel OD-H, hexane/IPA = 85/15, 0.5 mL/min; t_1 = 18 min (*S*), t_2 = 25 min (*R*); *ee* = 96%.

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