A facile asymmetric synthesis of (*S*)-duloxetine

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Abstract
The asymmetric-transfer hydrogenation of 2-tosyloxy-1-(2-thiophenyl)ethanone and further elaboration of the cyclic carbamate derived from γ-aminoalcohol to provide a facile synthesis of (*S*)-duloxetine, a potent dual inhibitor of serotonin and norepinephrine reuptake, is described.

Keywords: (*S*)-Duloxetine, asymmetric-transfer hydrogenation, heteroaryl ketone, cyclic carbamate

Introduction

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 currently an important class of antidepressants, which includes fluoxetine, nisoxetine, tomoxetine, and duloxetine.[1] They have been approved already as racemates, but some of them are since being redeveloped as 'chiral switches' derived from the established racemates.[2] While fluoxetine and nisoxetine are currently available as racemates, (*S*)-duloxetine [(*S*)-*N*-methyl-3-(1-naphthyloxy)-3-(2-thienyl)-1-propanamine] has gained acceptance in the market because it inhibited serotonin reuptake in rat synaptosomes two times more potently than (*R*)-enantiomer.[3] The (*S*)-duloxetine, a dual inhibitor of both serotonin and norepinephrine reuptake, is effective for the treatment of major depressive disorder and is being considered for treatment of stress-related urinary incontinence. Several different approaches have been reviewed for the synthesis of duloxetine as a racemate or an enantiomerically enriched form;[4] however, there are only a few reports on the asymmetric and catalytic synthesis of duloxetine. One of the methods employs an asymmetric reduction of β-aminoketone or α-cyanoketone/ β-chloroketone with a chirally-modified LAH complex[5] or an oxazaborolidine-catalyzed borane,[3,6] respectively. The other involves the chemoenzymatic

synthesis, for the most part, lipase-mediated resolution of β-cyano-, γ-chloro-, and γ-azidoalcohols.[7]

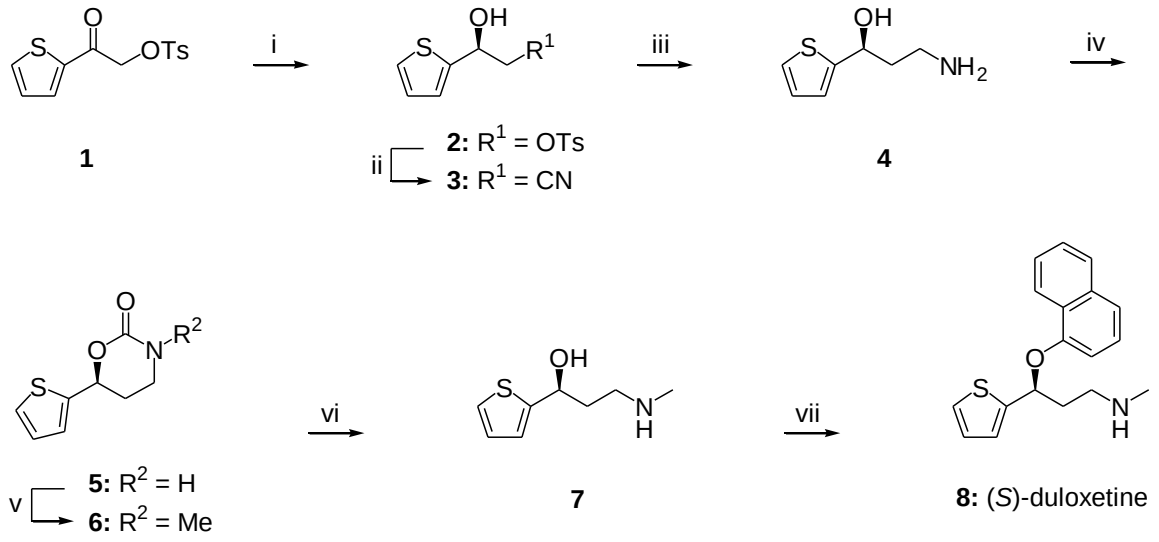
Recently, the application of asymmetric-transfer hydrogenation has been extended to enantioselective hydrogenation of unsaturated carbonyl and imine groups.[8] The asymmetric-transfer hydrogenation, rather, offers an operational simplicity, since the reaction does not involve molecular hydrogen and is insensitive to air oxidation, and thus is particularly valuable in scale-up syntheses of active pharmaceutical ingredients.[2b] In continuation of our earlier efforts towards the preparation of biologically important compounds, particularly possessing a chiral aminoalcohol unit,[9] we herein report an asymmetric-transfer hydrogenation of 2-tosyloxy-1-(2-thiophenyl)ethanone and further elaboration of a cyclic carbamate to access the facile synthesis of duloxetine.

Results and Discussion

The starting material, 2-tosyloxy-1-(2-thiophenyl)ethanone **1** was prepared by α-sulfonyloxylation of the commercially available 2-acetylthiophene via trimethylsilyl enol ether with [hydroxy(tosyloxy)iodo]benzene, according to the literature procedure.[10] The catalytic reaction of **1** (substrate/catalyst molar ratio 500) with Cp*RhCl[(*S*,*S*)-TsDPEN],[11] where Cp* = pentamethylcyclopentadienyl, effectively performed with an azeotropic mixture of formic acid/triethylamine (molar ratio 5/2) in ethyl acetate to produce (*S*)-2-tosyloxy-1-(2-thiophenyl)ethanol **2**, $[\alpha]_D^{27}$ = -31.3 (*c* 1.08, $CHCl_3$), in 95% yield with 95% *ee*. It should be noted the observed enantioselectivity was similar to this reported in the corresponding α-chloroketone,[12] and thus represented a first successful application of α-tosyloxy heteroaryl ketone in transfer hydrogenation with high enantioselectivity. The *ee* value was measured by chiral HPLC analysis using Daicel Chiralcel OD-H column. The racemic alcohol (±)-**2** was prepared by sodium borohydride reduction of **1** in THF, and used as standard for *ee* determination.

In turn, most approaches to synthesis of the *N*-methylamine **7** routinely adopted lithium aluminum hydride reduction in refluxing THF of the ethyl carbamate derived from the aminoalcohol **4** with ethyl chloroformate, or mono-demethylation of the reduced Mannich product with 2,2,2-trichloroethyl formate with Zn in toluene. In order to circumvent these harsh conditions, we supposed that the formation of a cyclic carbamate[13] would offer a facile route to an introduction of *N*-methyl group into the γ-aminoalcohol, as shown in Scheme 1. It was ambitioned that the required aminoalcohol **4** can be easily prepared from the tosylate **2**, a versatile chiral building block. Thus, the tosylate (*S*)-**2** was readily converted into the nitrile **3** without loss of chirality, $[\alpha]_D^{20}$ = -39.7 (*c* 0.45 , $CHCl_3$); lit.[7b] $[\alpha]_D^{30}$ = -33.5 (*c* 1 , $CHCl_3$), by the treatment of sodium cyanide in DMSO. Subsequently, the nitrile **3** was reduced with borane-dimethyl sulfide in refluxing THF to give the γ-aminoalcohol which was directly cyclized using *N*,*N*-carbonyldiimidazole (CDI) in the presence of catalytic amount of DMAP to obtain the

corresponding cyclic carbamate **5** in 71% yield for the two steps. Indeed, this allowed a facile introduction of the *N*-methyl group, by the treatment of methyl iodide with sodium hydride in THF to give the *N*-methyl oxazinanone **6**. Hydrolysis of the oxazinanone **6** by refluxing with lithium hydroxide in aqueous methanol afforded the aminoalcohol **7**. The final installation was then carried out by nucleophilic aromatic substitution with 1-fluoronaphthalene by means of sodium hydride in DMSO to afford (*S*)-duloxetine **8** in 78% yield with 95% *ee*.



Scheme 1. Asymmetric synthesis of (*S*)-duloxetine. Reagents and conditions: i) 10 mmol of **1** (S/C = 500), Cp*RhCl[(*S*,*S*)-TsDPEN], HCO_2H/Et_3N (molar ratio 5/2, 2 ml), EtOAc, 3h, 95%, 95% *ee*; ii) NaCN, DMSO, 20h, 88%; iii) $BH_3 \cdot SMe_2$, THF, reflux, 2h; iv) CDI, cat. DMAP, CH_2Cl_2, 8h, 71% (for 2 steps); v) MeI, NaH, THF, ice-bath, 6h, 89%; vi) LiOH, MeOH-H_2O, reflux, 8h, 84%; vii) 1-fluoronaphthalene, NaH, DMSO, 8h, 78% .

Conclusions

(*S*)-Duloxetine, a potent dual inhibitor of serotonin and norepinephrine reuptake, has been successfully synthesized from 2-tosyloxy-1-(2-thiophenyl)ethanone via catalytic transfer hydrogenation and further elaboration through the cyclic carbamate derived from the γ-aminoalcohol.

Experimental Section

General. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (230-400 mesh). Melting points were

measured on an electrothermal apparatus and were uncorrected. NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Mass spectra were recorded on a GC/MS operating system at an ionization potential of 70eV. Optical rotations were measured on a high resolution digital polarimeter. The *ee* values of the samples were determined by HPLC analysis using Daicel Chiralcel OD-H chiral column.

Preparation of 1-(2-thienyl)-2-tosyloxyethanone (1). The starting material **1** was prepared by α-sulfonyloxylation of the commercially available 2-acetylthiophene via trimethylsilyl enol ether with [hydroxy(tosyloxy)iodo]benzene, according to the literature procedure.[10] **1:** ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.85 (d, 2H, *J* 8.1 Hz), 7.79 (d, 1H, *J* 3.9 Hz), 7.73 (d, 1H, *J* 4.8 Hz), 7.36 (d, 2H, *J* 8.4 Hz), 7.15 (t, 1H, *J* 4.5 Hz), 5.08 (s, 2H), 2.45 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 184.2, 139.4, 135.2, 132.5, 128.6, 69.6, 39.1; EIMS (70eV) *m/z* (rel intensity) 296 (M^+, 8), 111 (100).

General for catalytic transfer hydrogenation

The catalyst**,** Cp*RhCl[(*S,S*)-TsDPEN] was prepared from the reaction of dichloro(pentamethylcyclopentadienyl)rhodium (III) dimer and (*1S,2S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine in dichloromethane in the presence of triethylamine, according to the literature procedure.[11] It should be noted that the catalyst was used without any purification, so the catalyst includes an equal molar of hydrochloride/triethylamine salt.[9b] This catalyst mixture is very stable and insensitive to atmospheric manipulations, and does not show any deterioration in the catalytic activity comparing to that prepared from recrystalization. The formic acid/triethylamine (molar ratio 5/2) azeotrope was prepared by the double distillation of the mixtures, according to the literature procedure.[14] The catalytic reaction was carried out under an argon atmosphere with oven-dried glassware.

(*S*)-1-(2-Thienyl)-2-tosyloxyethanol (2). To a mixture of (*S,S*)-Rh catalyst (15.6 mg, equivalent to 0.02 mmol) and **1** (2.96 g, 10 mmol) was charged with ethyl acetate (40 ml), and then an azeotropic mixture of formic acid/triethylamine (2 ml). The reaction mixture was stirred at room temperature for 3h. After dilution with ethyl acetate (50 ml), the mixture was washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The product was purified by flash chromatography (hexane/ethyl acetate/dichloromethane, 5/1/1) to yield 2.83 g (95%) of **2** as a slight yellow solid**:** mp 79 °C; lit.[15a] mp 78-79.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* 8.4 Hz), 7.35 (d, 2H, *J* 8.1 Hz), 7.28-7.26 (m, 1H), 6.98-6.95 (m, 2H), 5.25-5.20 (m, 1H), 4.23 (dd, 1H, *J* 10.2 and 3.6 Hz), 4.17-4.08 (m, 1H), 2.67 (d, 1H, *J* 3.9 Hz), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 127.0, 125.7, 125.1, 73.2, 68.3, 37.6; EIMS (70eV) *m/z* (rel intensity) 113 (M^+-CH_2OTs, 5), 172 (100), 91 (100); $[\alpha]_D^{27}$ = -31.3 (*c* 1.08, $CHCl_3$); HPLC analysis: 95% *ee* (Chiralcel OD-H, hexane/Pr^{i}OH, 94/6, 0.5 ml/min; t_R (*S*) 66 min, t_R (*R*) 76 min.

(*S*)-3-Hydroxy-3-(2-thienyl)propionitrile (3). To a solution of the tosylate **2** (1.20 g, 4.0 mmol) in DMSO (25 ml), was added sodium cyanide (591 mg, 12.1 mmol) slowly. After stirring for 20h, the reaction mixture was partitioned with ethyl acetate and water. After an extractive

workup, the combined organic layers were dried and concentrated in vacuo. The crude material was purified by flash chromatography (hexane/ethyl acetate, 5/1) to yield 540 mg (88%) of **3** as a colorless oil**:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, 1H, *J* 5.1 and 1 Hz), 7.13 (d, 1H, *J* 3.5 Hz), 7.05-7.03 (m, 1H), 5.34 (q, 1H, *J* 4.3 Hz), 2.93-2.90 (m, 2H), 2.56 (d, 1H, *J* 4.2 Hz); ^{13}C NMR(75 MHz, $CDCl_3$) δ 144.3, 127.1, 125.8, 124.7, 116.8, 66.3, 28.2; EIMS (70eV) *m/z* (rel intensity) 153 (M^+, 13), 112 (100), 85 (61); $[\alpha]_D^{20}$ = -39.7 (*c* 0.45, $CHCl_3$); lit.[7b] $[\alpha]_D^{30}$ = -33.5 (*c* 1, $CHCl_3$).

(*S*)-6-(2-Thienyl)-1,3-oxazinan-2-one (5). To a solution of the nitrile **3** (153 mg, 1 mmol) in THF (5 ml), was added borane-dimethyl sulfide (0.14 ml, 1.5 mmol) dropwise over a period of 5 min and the mixture was brought to reflux. After 2h, the reaction mixture was cooled to room temperature and methanol (6 ml) was carefully added over 5 min. The mixture was concentrated in vacuo to give the crude aminoalcohol **4:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, 1H, *J* 4.9 and 1.3 Hz), 6.98-6.92 (m, 2H), 5.22 (ddd, 1H, *J* 8.8 and 3.3 and 0.4 Hz), 3.19-3.12 (m, 1H), 3.02-2.94 (m, 1H), 2.71 (brs, 3H), 2.04-1.81 (m, 2H); EIMS (70eV) *m/z* (rel intensity) 157 (M^+, 24), 140 (100), 111 (16). The crude **4** was dissolved in dichloromethane. To this solution, was added a catalytic amount of DMAP and then CDI (243 mg, 1.5 mmol). The reaction mixture was left to stir for 8h, then the solvent was evaporated and the residue was purified by flash chromatography (hexane/ethyl acetate/dichloromethane, 1/9/1) to yield 130 mg (71%) of **5** as a white solid**:** mp 151 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.32 (dd, 1H, *J* 5.0 and 1.2 Hz), 7.10-7.08 (m, 1H), 7.02-6.99 (m, 1H), 5.77 (brs, 1H), 5.59 (ddd, 1H, *J* 9.2, 3.1, and 0.6 Hz), 3.50-3.43 (m, 2H), 2.37-2.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 141.5, 126.8, 125.7, 125.1, 74.7, 38.8, 28.4; EIMS (70eV) *m/z* (rel intensity) 183 (M^+, 26), 138 (21), 110 (100); HRMS (EI) calcd for $C_8H_9NO_2S$: 183.0354, found: 183.0352; $[\alpha]_D^{20}$ = +23.2 (*c* 0.46, $CHCl_3$).

(*S*)-3-Methyl-6-(2-thienyl)-1,3-oxazinan-2-one (6). To a solution of the cyclic carbamate **5** (183 mg, 1 mmol) in THF under ice-bath, were added sodium hydride (36 mg, 1.5 mmol) and then methyl iodide (0.21 ml, 3.4 mmol). After stirring for 6h, the solvent was removed and the residue was taken up with ethyl acetate three times. The combined organic layers were dried and concentrated in vacuo. The crude material was purified by flash chromatography (hexane/ethyl acetate/dichloromethane, 1/5/1) to yield 175 mg (89%) of **6** as a white solid**:** mp 125 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.30 (m, 1H), 7.08-7.06 (m, 1H), 7.01-6.98 (m, 1H), 5.54 (ddd, 1H, *J* 9.0, 3.5, and 0.7 Hz), 3.52-3.43 (m, 1H), 3.36-3.28 (m, 1H), 3.01 (s, 3H), 2.41-2.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 141.6, 126.7, 125.7, 125.1, 74.3, 46.0, 36.6, 29.4; EIMS (70eV) *m/z* (rel intensity) 197 (M^+, 100), 153 (59), 110 (41); HRMS (EI) calcd for $C_9H_{11}NO_2S$: 197.0510, found: 197.0513; $[\alpha]_D^{20}$ = +31.8 (*c* 0.5, $CHCl_3$).

(*S*)-1-(2-Thienyl)-3-methylaminopropanol (7). The *N*-methyl carbamate **6** (197 mg, 1 mmol) was dissolved in MeOH and H_2O (10 ml, 4/1). To this solution, was added lithium hydroxide (168 mg, 7 mmol) and the resulting mixture was allowed to reflux for 8h. The solvent was evaporated and the residue was taken up with ethyl ether three times. The combined organic layers were dried and concentrated in vacuo. The crude material was purified by flash chromatography (ammonium hydroxide/methanol/dichloromethane, 0.1/1/4) to yield 144 mg

(84%) of **7:** ^{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, and 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; EIMS (70eV) *m/z* (rel intensity) 171 (M^+, 35), 139 (22), 128 (100), 111(31); $[\alpha]_D^{20}$ = -10.8 (*c* 0.52, MeOH); lits. for its enantiomer $[\alpha]_D^{22}$ = +9.74 (*c* 3.8, MeOH),[7a] $[\alpha]_D^{34}$ = +13.9 (*c* 2.4, MeOH).[7b]

(*S*)-Duloxetine (8). To a solution of **7** (171 mg, 1 mmol) in DMSO (5 ml), were added sodium hydride (36 mg 1.5 mmol) and then 1-fluoronaphthalene (190 mg, 1.3mmol). After stirring for 8h, 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 (ammonium hydroxide/methanol/ dichloromethane, 0.1/1/4) to yield 232 mg (78%) of **8**: ^{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 and 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; EIMS (70eV) *m/z* (rel intensity) 297 (M^+, 4), 187 (80), 153 (69), 144 (100); $[\alpha]_D^{20}$ = +110.5 (*c* 1.1, MeOH); lit.[7b] $[\alpha]_D^{30}$ = +114 (*c* 1, MeOH); lit.[15b] $[\alpha]_D^{20}$ = +112 (*c* 1, MeOH); HPLC analysis: 95% *ee* (Chiralcel OD-H, hexane/Pr^{i}OH, 85/15, 0.5 ml/min; t_R (*S*) 18 min, t_R (*R*) 25 min.

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