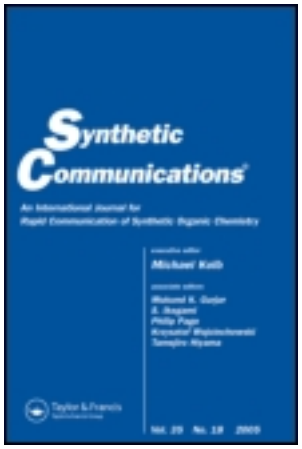

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Simple and Efficient Synthesis of (S)-Dapoxetine

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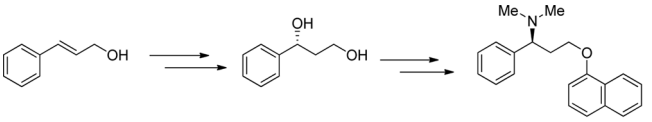
GRAPHICAL ABSTRACT



(*S*)-Dapoxetine 1

Abstract *A refinement in the synthetic strategy for (S)-dapoxetine **1** is described. The key features of synthetic strategy include (a) a Sharpless asymmetric epoxidation reaction and regioselective reductive ring opening of a 2,3-epoxy alcohol to elaborate the hydroxy-bearing stereogenic center at benzylic position; (b) regioselective functionalization of 1-naphthol and amine functionality through Mitsunobu procedures; and (c) Eschweiler–Clarke reductive methylation condition to access the target molecule.*

Keywords Intermolecular etherification; reductive methylation; Sharpless asymmetric epoxidation

INTRODUCTION

Premature ejaculation (PE) is one of the most common male sexual dysfunctions (MSDs). The prevalence of PE has been estimated to range from 21% to 32.5% in men aged 18–59.[1–3] Historically, the causes of PE were considered to be purely psychological, and therefore early approaches to treatment consisted primarily of behavioral therapy.[4] Conventional pharmacotherapy for PE involves off-label use of selective serotonergic reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, and other antidepressants, which are known to cause delayed ejaculation as a common side effect.[5–7] Dapoxetine is a serotonin transport inhibitor that has been developed specifically for PE as an on-demand oral treatment.[8]

The clinical studies have shown that (*S*)-enantiomer of **1** is 3.5 times more potent[9] than the (*R*)-**1** (Fig. 1). As a result, numerous reports describing the preparation of (*S*)-dapoxetine **1** have been reported.

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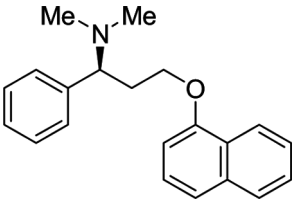
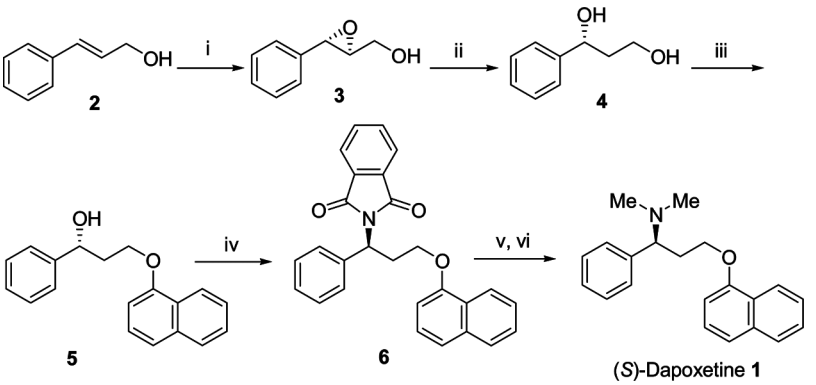


Figure 1. Structure of (*S*)-dapoxetine (**1**).

Generally, the methods include resolution of racemic intermediates,[10] chemoenzymatic routes,[11] or stereospecific procedures.[12–15] However, most of these methods have several drawbacks such as tedious and time-consuming experiments, radical deoxygenation of undesired hydroxyl group, expensive or not readily available chiral catalyst, and poor yield coupled with poor optical purity. Synthetic efforts now need to be directed at short, practical routes that are amenable to scale-up for drug preparation. Herein, we report a simple and efficient synthetic strategy for (*S*)-dapoxetine **1**.

RESULTS AND DISCUSSION

As depicted in Scheme 1, synthesis of the target molecule (*S*)-dapoxetine **1** was initiated from commercially available *trans*-cinnamyl alcohol **2**, which was subjected to Sharpless asymmetric epoxidation[16] to give (2*S*,3*S*)-epoxy alcohol **3** in 89% yield and >98% *ee*; $[\alpha]_D^{25} = -49.3$ (*c* 2.4, $CHCl_3$) [lit.[16] $[\alpha]_D^{25} = -49.6$ (*c* 2.4, $CHCl_3$)]. (Enantiomeric excess was determined by ^1H NMR spectroscopic analysis of the Mosher's ester derived from (+)-MTPA chloride.) Regioselective reductive ring opening of (2*S*,3*S*)-epoxy alcohol **3** with Red-Al[17a] gave the expected 1,3-diol **4** in 93% yield. Then, the napthyloxy moiety was introduced regioselectively on the primary hydroxyl group of compound **4** through intermolecular etherification using Mitsunobu condition,[18] affording hydroxy ether **5** in 71% yield.



Scheme 1. Reagents and conditions: (i) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, 4-Å MS, DCM, −20 °C, 3 h, 89%; (ii) Red-Al, DME, 0 to 25 °C, 3 h, 93%; (iii) 1-naphthol, Ph_3P, DIAD, THF, 20 h, rt, 71%; (iv) phthalimide, Ph_3P, DIAD, THF, 4 h, 82%; (v) $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 h; (vi) HCHO, HCO_2H, reflux, 6 h, 73%, two steps.

The (*S*)-secondary alcohol **5** was readily transformed into (*R*)-phthalimido ether **6** by stereospecific substitution of hydroxy group with phthalimide, employing a typical Mitsunobu procedure.[19] Finally, a facile hydrazinolysis[19] of phthalimido ether **6** with hydrazine hydrate in ethanol afforded the crude amine, which was subjected directly to a reductive methylation using the Eschweiler–Clarke condition[20] to give (*S*)-dapoxetine **1** in 73% yield; $[\alpha]_D^{25} = +65.4$ (*c* 0.31, $CHCl_3$) [lit.[15] $[\alpha]_D^{28} = +63$ (*c* 0.3, $CHCl_3$)]. The structure of (*S*)-dapoxetine **1** was confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectroscopic analysis.

In conclusion, we synthesized (*S*)-dapoxetine in six steps from commercially available *trans*-cinnamyl alcohol with an overall yield of 35%. Sharpless asymmetric epoxidation and Mitsunobu reaction have been successfully employed to get the required amine functionality in a stereoselective manner. The present synthetic strategy is the refinement in the existing synthetic route for (*S*)-dapoxetine.

EXPERIMENTAL

All the reagents were purchased from Aldrich Chemical and were used without further purification. Solvents were purified and dried by standard procedures prior to use. Melting points were recorded in a Buchi capillary melting-point (R-535) apparatus and are uncorrected. Infrared (IR) spectra were recorded on Shimadzu Fourier transform (FT)–IR 8400 instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 and Varian Mercury spectrometers at 300 MHz using $CDCl_3$ as a solvent. Chemical shifts are given in parts per million (ppm) with respect to internal tetramethylsilane (TMS), and *J* values are quoted in hertz. Monitoring of reactions was carried out using thin-layer chromatographic (TLC) plates (Merck silica gel 60 F_{254}) and visualization with ultraviolet light (254 and 365 nm), I_2, and anisaldehyde in ethanol as development reagents. Optical rotations were measured with a Jasco P 1020 digital polarimeter. Mass spectra were recorded on Shimadzu GCMS-QP5050A spectrometer. Elemental analyses were carried out with a Carlo Erba CHNS–O EA 1108 elemental analyzer. Enantiomeric excess was determined by ^{1}H NMR analysis of Mosher's ester.

(2*S*,3*S*)-(3-Phenyl-oxiranyl)-methanol 3

$Ti(O^iPr)_4$ (0.59 mL, 2 mmol), and 5–6 M solution of TBHP in undecane (8 mL, 40 mmol) were added sequentially to a stirred solution of L-(+)-diisopropyl tartrate (0.53 mL, 2.5 mmol) in CH_2Cl_2 (180 mL) at −20°C, 1 g of activated powdered 4-Å molecular sieves. The mixture was allowed to stir at −20°C for 1 h and then a solution of freshly distilled (*E*)-3-phenyl-2-propenol **2** (2.57 mL, 20 mmol) in 5 mL CH_2Cl_2 was added dropwise over 30 min. After 3 h at −20°C, the reaction was quenched at −20°C with 10% aqueous solution of NaOH saturated with NaCl (2 mL). After diethyl ether (30 mL) was added, the cold bath was allowed to warm to 10°C, stirring was maintained at 10°C, while $MgSO_4$ (2 g) and celite (500 mg) were added. After another 15 min of stirring, the mixture was allowed to settle, and the clean solution was filtered through a pad of celite and washed with diethyl ether. Azeotropic removal of TBHP with toluene at a reduced pressure and high vacuum gave **3** as yellow oil. Recrystallization from petroleum ether–diethyl ether gave **3** as a white crystals (2.68 g, 89%); mp: 52–54°C [lit.[16] mp: 51.5–53°C]; $[\alpha]_D^{25} = -49.3$ (*c* 2.4, $CHCl_3$)

[lit.[16] $[\alpha]_D^{25} = -49.6$ (*c* 2.4, $CHCl_3$)]; IR ($CHCl_3$, cm^{-1}): 3446, 3032, 2922, 1606, 1462, 1400, 1199, 1074, 927, 854, 759; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.79–1.84 (dd, $J = 7.95$, 5.1 Hz, 1H, OH), 3.22–3.25 (m, 1H, CH), 3.76–3.85 (m, 1H, CH_2O), 3.92–3.93 (d, $J = 2.1$ Hz, 1H, benzylic CH), 4.02–4.09 (m, 1H, CH_2O), 7.26–7.39 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.5, 61.2, 62.5, 125.7, 128.3, 128.5, 136.5.

(*R*)-3-Phenyl-1,3-dihydroxypropane 4

To a solution of (2*S*,3*S*)-2,3-epoxycinnamyl alcohol **3** (1.5 g, 10 mmol) in dimethoxyethane (50 mL) was added a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene (3.1 mL, 10.5 mmol) dropwise under nitrogen at 0°C. After stirring at room temperature for 3 h, the solution was diluted with ether and quenched with 15% HCl solution. After further stirring at room temperature for 30 min, a white precipitate formed and was removed by filtration, boiled with ethyl acetate, and filtered again. The combined organic extracts were dried with magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography [silica gel, petroleum ether–ethyl acetate (70:30)] to afford **4** as a white crystal (1.42 g, 93%); mp: 62–64°C (lit.[17b] mp: 62–66°C); $[\alpha]_D^{25} = +66$ (*c* 1, $CHCl_3$) [lit.[17b] $[\alpha]_D^{25} = +65$ (*c* 1, $CHCl_3$)]; IR (KBr, cm^{-1}): 3392, 3313, 2955, 1595, 1489, 1444, 1209, 1082, 1037, 972, 879, 742; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.91–2.07 (m, 2H, CH_2), 2.34 (br s, 2H, OH), 3.86–3.89 (t, $J = 5.4$ Hz, 2H, CH_2O), 4.95–4.99 (dd, $J = 8.7$, 3.6 Hz, 1H, benzylic CH), 7.26–7.37 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.3, 61.1, 73.8, 125.6, 127.4, 128.4, 144.2; MS (*m*/*z*): 152 (23) [M^+], 134 (17), 117 (35), 107 (100).

(*R*)-3-(Naphthalen-1-yloxy)-1-pheny-propae-1-ol 5

A solution of DIAD (0.63 mL, 3.2 mmol) in anhydrous THF (5 mL) was added to a mixture of (*R*)-3-phenyl-1,3-dihydroxypropane **4** (456 mg, 3 mmol), 1-naphthol (576 mg, 4 mmol), and triphenylphosphine (840 mg, 3.2 mmol) in 15 mL of anhydrous THF under N_2 at room temperature. The resulting mixture was stirred until TLC indicated that the diol was consumed (20 h, TLC). The solvent was evaporated and residue was purified by flash column chromatography [silica gel 230–400 mesh, petroleum ether–ethyl acetate (80:20)] to afford **5** as colorless oil (592 mg, 71%); $[\alpha]_D^{25} = +122$ (*c* 1.3, $CHCl_3$); IR (neat, cm^{-1}): 3375, 3053, 2935, 1590, 1388, 1253, 1078, 765; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.66 (br s, 1H, OH), 2.15–2.26 (m, 1H, CH_2), 2.35–2.47 (m, 1H, CH_2), 3.83–3.91 (m, 1H, CH_2O), 3.95–4.03 (m, 1H, CH_2O), 5.57–5.62 (dd, $J = 8.8$, 3.9 Hz, 1H, benzylic CH), 6.64–6.66 (d, $J = 7.2$ Hz, 1H, Ar), 7.16–7.54 (m, 9H, Ar), 7.76–7.79 (m, 1H, Ar), 8.38–8.41 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 41.4, 59.7, 77.5, 106.9, 120.3, 121.8, 125.3, 125.6, 125.7, 126.3, 127.5, 127.6, 128.7, 134.5, 141.4, 153.2; MS (*m*/*z*): 278 (5) [M^+], 260 (5), 144 (100). Anal. calcd. for $C_{18}H_{19}O_2$: C, 81.91; H, 6.52%. Found: C, 81.89; H, 6.54%.

(*S*)-2-[3-(Naphthalen-1-yloxy)-1-phenyl-propyl]-isoindole-1,3-dione 6

To a mixture of alcohol **5** (556 mg 2 mmol), phthalimide (367 mg, 2.5 mmol), and triphenylphosphine (577 mg, 2.2 mmol) in 10 mL of anhydrous THF under N_2

at room temperature was added a solution of DIAD (0.46 mL, 2.2 mmol) in anhydrous THF (2 mL). The resulting mixture was stirred until TLC indicated that the alcohol was consumed. The solvent was evaporated; the residue was subjected to chromatography on silica gel (100–200 mesh) with (95:5) petroleum ether–ethyl acetate to afford desired product **6** as a white crystal (0.67 g, 82%); mp: 156–158°C; $[\alpha]_D^{25} = +195.6$ (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3036, 2937, 1768, 1707, 1591, 1383, 1244,1084, 949; ^1H NMR (200 MHz, $CDCl_3$): δ_H 2.20–2.40 (m, 1H, CH_2), 2.50–2.69 (m, 1H, CH_2), 3.86–3.97 (m, 1H, CH_2O), 4.05–4.19 (m, 1H, CH_2O), 5.46–5.52 (dd, $J = 8$, 4 Hz, 1H, benzylic CH), 6.57–6.60 (d, $J = 6$ Hz, 1H, Ar), 7.12–7.44 (m, 9 H, Ar), 7.61–7.75 (m, 5H, Ar), 8.34–8.39 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 35.3, 37.2, 78.0, 106.6, 120.1, 121.9, 122.9, 125.0, 125.6, 126.1, 127.3, 127.6, 128.6, 131.9, 133.6, 134.3, 140.8, 152.9, 168.2; MS (*m/z*): 407 (3) [M^+], 266 (12), 264 (55), 160 (100), 144 (18). Anal. calcd. for $C_{27}H_{21}NO_3$: C, 79.59; H, 5.19; N, 3.44%. Found: C, 79.61; H, 5.13; N, 3.41%.

(*S*)-Dapoxetine 1

Hydrazine hydrate (80%) solution (0.5 mL, 8 mmol) was added to a stirred solution of **6** (407 mg, 1 mmol) in ethanol (10 mL), and the resulting mixture was refluxed for 3 h. The precipitated solid was filtered off, and the solvent was removed under reduced pressure. The residue was dissolved in ether and extracted with 2 N HCl, and the aqueous phase was treated with 2 N NaOH until pH > 12. The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was used in the next step.

To a solution of crude amine in 85% formic acid (227 μL, 5 mmol) was added 37% aqueous formaldehyde (220 μL, 3 mmol), and the mixture was heated at 95–100 °C for 6 h. After the solution was cooled, it was acidified with 4 *N* HCl until pH = 1 and basified with 4 *N* NaOH. The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 97:3) to afford (*S*)-**1** as pale yellow oil (223 mg, 73%); $[\alpha]_D^{25} = +65.4$ (*c* 0.31, $CHCl_3$) [lit.[15] $[\alpha]_D^{28} = +63$ (*c* 0.3, $CHCl_3$)]; IR (Neat, cm^{-1}): 3057, 2953, 2775, 1583, 1456, 1394, 1269, 1238, 1099, 1068, 1022, 912, 850, 769; ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.25 [s, 6H, N $(CH_3)_2$], 2.26–2.29 (m, 1H, CH_2), 2.58–2.69 (m, 1H, CH_2), 3.58–3.63 (dd, $J = 9.3$, 5.1 Hz, 1H, benzylic CH), 3.84–3.92 (m, 1H, CH_2O), 4.02–4.09 (m, 1H, CH_2O), 6.62–6.65 (dd, $J = 7.3$, 1.8 Hz, 1H, Ar), 7.23–7.79 (m, 7H, Ar), 7.43–7.50 (m, 2H, Ar), 7.76–7.79 (m, 1H, Ar), 8.21–8.25 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 32.9, 42.7, 65.5, 67.5, 104.4, 119.9, 121.9, 124.9, 125.5, 125.7, 126.2, 127.2, 127.3, 128.1, 128.5, 134.3, 139.4, 154.5; MS (*m/z*): 305 (4) [M^+], 134 (100), 115 (12). Anal. calcd. for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59%. Found: C, 82.54; H, 7.60; N, 4.50%.

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