A stereoselective synthesis of (*S*)-dapoxetine starting from *trans*-cinnamyl alcohol

K. Venkatesan[a, b] and K. V. Srinivasan*[a]

[a]*Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411 008, India*
[b]*Department of Chemistry, McMaster University, Hamilton L8S4M1, Canada*
E-mail: kumarv.srinivasan@gmail.com

Abstract
A novel stereoselective synthesis of (*S*)-dapoxetine starting from commercially available *trans*-cinnamyl alcohol is described. Sharpless Asymmetric Epoxidation (SAE) is utilized as the key step in this synthetic strategy.

Keywords: Sharpless asymmetric epoxidation, (*S*)-dapoxetine, antidepressant, stereoselective synthesis

Introduction

Recently, it has been suggested that premature ejaculation (PE) might be associated with perturbations in serotonergic 5-hydroxytryptamine (5-HT) neurotransmission.[1,2] It has been proposed that PE may be caused by decreased central serotonergic signaling, hyposensitivity of the 5-HT_{2C} receptor, or hypersensitivity of the 5-HT_{1A} receptor, all of which have been shown to decrease ejaculatory latency time in animal model systems.[3,4] PE is a common problem, which may be associated with considerable anxiety, frustration, and negative impact on affected men and their sexual partners. No pharmaceutical agents have been approved for this indication. However, therapies that target 5-HT neurotransmission, such as selective serotonin reuptake inhibitor (SSRI) *anti*-depressants, have been used in this setting with varying efficacy and tolerability.

Dapoxetine is the first agent to be developed specifically to treat PE. This agent significantly prolongs IELT and increases the sense of control and sexual satisfaction for men with PE and their partners. Dapoxetine is well tolerated, with a favorable pharmacokinetic profile that allows for on-demand use. Dapoxetine hydrochloride is an SSRI with a short half-life developed specifically for the treatment of men with PE,[5-8] but is slightly different from the SSRIs (such as

zoloft, paxil, and prozac) (Figure 1) widely prescribed for depression and other psychiatric disorders such as bulimia or anxiety. The American Urological Association as well as the International Consultation on Sexual Dysfunctions now recommends the off-label use of SSRIs, which increase 5-HT neurotransmission, for the management of PE.[1,9,10] Although the off-label use of antidepressant SSRIs such as fluoxetine, sertraline, and paroxetine may increase ejaculatory latency time[11-13] these SSRIs do not reach peak plasma concentrations for several hours after administration; many require a long lead-in dosing period for efficacy[1] and the typically long half-lives of these drugs can result in significant drug accumulation in the body, increased exposure to medication and, consequently, an increased likelihood of adverse events.[6,14] In addition, men taking antidepressant SSRIs daily have reported sexual side effects such as decreased libido and erectile dysfunction after prolonged treatment with these drugs.[6] If approved by the Food and Drug Administration (FDA), this would make dapoxetine join the ranks of erectile dysfunction drugs such as sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra) and some dopamine agonists such as cabergoline (Dostinex) and pramipexole, as drugs which can be used to improve male sexual health.[15]

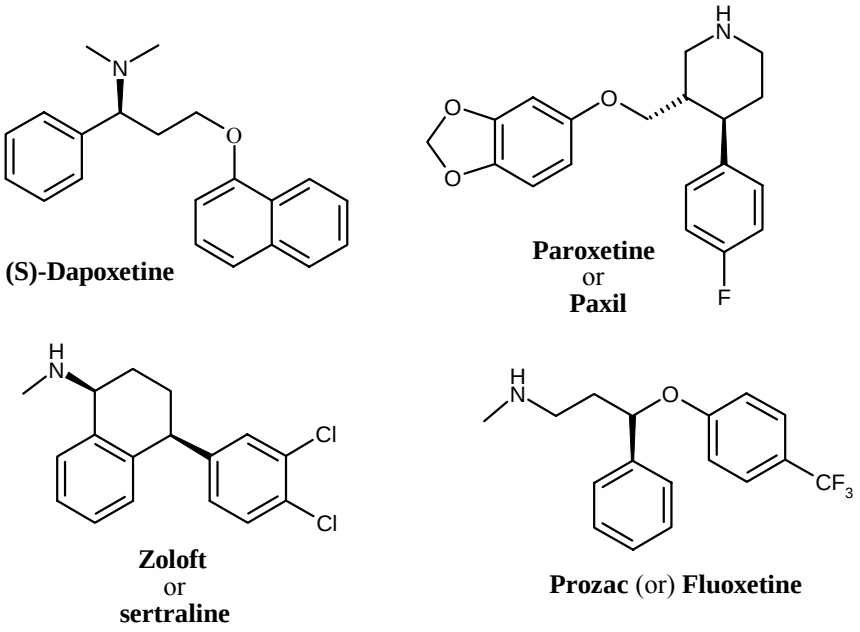
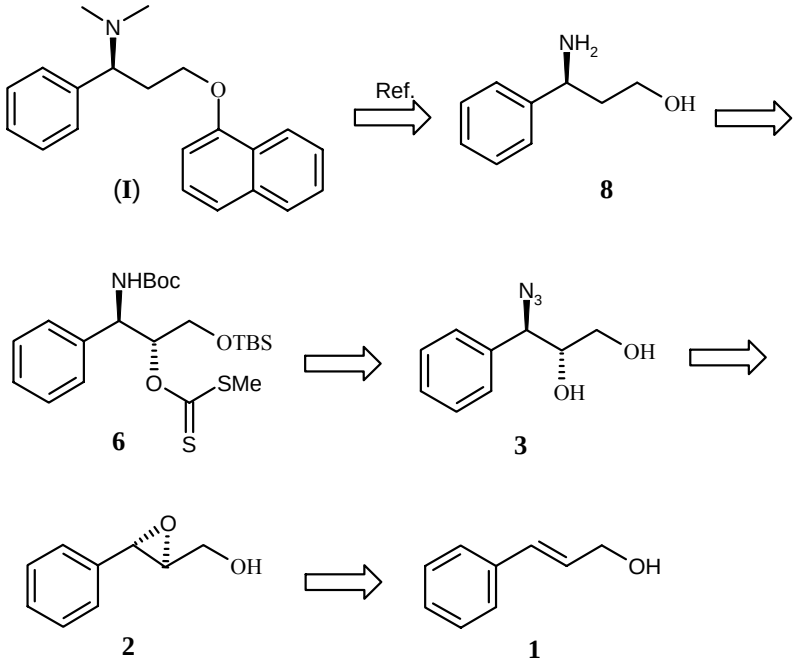


Figure 1. Structure of (*S*)-dapoxetine and various SSRI *anti*-depressants.

Very few methods are currently available for the synthesis of pharmaceutically important and potent (*S*)-dapoxetine. Toru Koizumi *et al.* reported only synthesis of intermediate **8** (Scheme **1**) by employing asymmetric induction in the 1,3-dipolar cyclo-addition of (R)-(+)-*p*-tolylvinyl sulfoxide with acyclic nitrones in high enantiomeric excess.[16a] Another method described in the literature to synthesize (*S*)-dapoxetine is a radiochemical synthesis from (*S*)-(+)-*N*-methyl-α-[2-(1-naph-thalenyloxy)ethyl]benzene methanamine hydrochloride using $^{11}CH_3I$.[16b] Recently, two

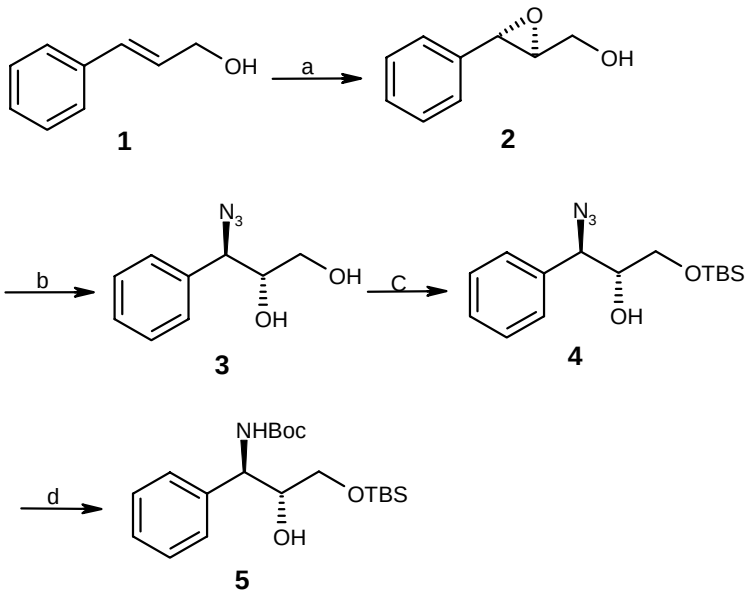
asymmetric synthetic approaches have been reported for the synthesis of (*S*)-dapoxetine starting from achiral starting materials.[17] As a part of our ongoing project for the asymmetric synthesis of biologically active compounds,[18] herein we wish to report a novel synthetic route for the synthesis of (*S*)-dapoxetine (**I**), starting from the commercially available and inexpensive achiral starting material *trans*-cinnamyl alcohol **1**.



Scheme 1. Retrosynthetic approach to (*S*)-dapoxetine (**I**).

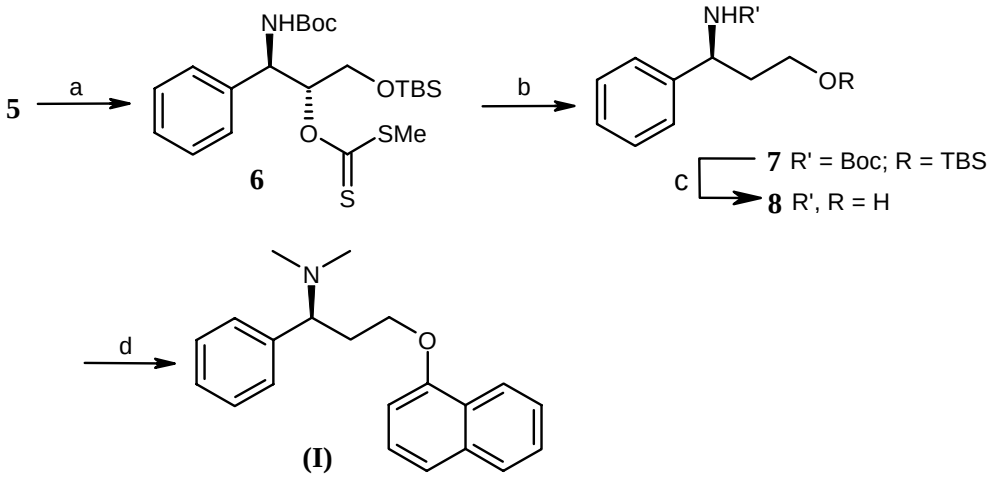
Results and Discussion

The Sharpless asymmetric epoxidation (SAE) can be envisioned as a powerful tool offering considerable opportunities for synthetic manipulations,[19] which has been employed as a key step in our synthetic strategy as shown in Scheme **1**. We envisioned that the amino alcohol **8** could be prepared from the xanthate ester **6,** which in turn could be prepared from the azido diol **3**. The azido diol **3** itself could be prepared from the epoxide **2** which in turn could be synthesized by Sharpless asymmetric epoxidation of the commercially available *trans*-cinnamyl alcohol **1**.
trans-cinnamyl alcohol **1** was subjected to SAE conditions[20] to give the epoxide **2** in 88% yield with 98% ee.[21] Regioselective opening of the epoxide **2** with NaN_3 gave the azido diol **3** as the single product in 97% yield. The azido diol **3** was converted into the mono-TBS protected azido alcohol **4** in 96% yield, which on reduction with 5%Pd(C) in EtOAc followed by treatment of the amine with $(Boc)_2O$ afforded the *N*-Boc protected alcohol **5** in 88% yield (Scheme **2**).



Scheme 2. Synthesis of intermediate **5** (SAE as the key step): (a) (*R*,*R*)-(+)-DET, $Ti(O^iPr)_4$, ^{t}-BuOOH, MS 4 Å, –20 °C, 3 h, 88%; (b) NaN_3, MeOH:H_2O (8:1), 65 °C, 4 h, 97%; (c) TBSCl, dry DCM, imidazole, 0 °C-RT, 6 h, 96%; (d) H_2-Pd(C), $(Boc)_2O$, EtOAc, RT, 12 h, 88%.

The secondary alcohol **5** was converted into its xanthate ester **6** under standard reaction conditions in 84% yield, followed by a deoxygenation under the Barton-McCombie[22] protocol using *n*-Bu_3SnH and a catalytic amount of AIBN in toluene under reflux conditions affording the protected amino alcohol **7**, which was further treated with TFA in DCM to give the amino alcohol **8** in 81% isolated yield in two steps. The amino alcohol **8** was converted in to (*S*)-dapoxetine (I) by employing the literature procedure[17a] (85% yield from **8**, Scheme **3**).



Scheme 3. Synthesis of (*S*)-dapoxetine (**I**): (a) CS_2, NaH, MeI, THF, 0 °C-RT, over night, 84%; (b) *n*-Bu_3SnH, AIBN, toluene, reflux, 6 h; (c) TFA, DCM, 0 °C-RT, 5 h, 81% (for two steps); (d) Ref. 17a.

Conclusions

In conclusion, a novel total synthesis of (*S*)-dapoxetine with high enantio-selectivity starting from a commercially available achiral starting material has been developed in which the chiral center was established by Sharpless asymmetric epoxidation to afford (*S*)-dapoxetine (**I**).

Experimental Section

General Procedures. Solvents were purified and dried by standard procedures prior to use. All the fine chemicals used were reagent grade procured commercially and used without further purification. Optical rotation was measured using sodium D line (589 nm) on a JASCO-P-1020-polarimeter under standard conditions. Infrared spectra were recorded on Perkin Elmer FT-IR spectrometer. Enantiomeric excess was measured using either the chiral HPLC (Lichrocart 250-4 [4 mmID × 25 cm] HPLC-Cartridge (R.R.-Whelk-01)) or by comparison with optical rotation. Elemental analyses were carried out with a Carlo Erba CHNS–O EA 1108 Elemental analyzer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DPX 200/400 spectrometer by using TMS as internal standard. MS analyses were performed on a Peseiex API QSTAR Pulsar with an electrospray ionization mass spectrometer (LC-MS), using MeOH as a solvent (m/z, fragentor 70 V).

((2*S*,3*S*)-3-Phenyloxiran-2-yl)-methanol (2). To a stirred solution of (*R*,*R*)-(+)-diisopropyl tartrate (0.83 mL, 0.92 g, 3.91 mmol) in CH_2C1_2 (450 mL) at −20 °C, 2.8 g activated powdered 4 Å molecular sieves, $Ti(OPr^i)_4$ (0.78 mL, 0.74 g, 2.61 mmol) and 3.0 M solution of TBHP in toluene (34.78 mL, 104.34 mmol) were added sequentially. The mixture was allowed to stir at −20 °C for 1 h and then a solution of freshly distilled (*E*)-3-phenyl-2-propenol (*trans*-cinnamyl alcohol) (7.0 g, 52.17 mmol) in 10 mL of CH_2C1_2 was added drop wise 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 (4.2 mL). After diethyl ether (60 mL) was added the cold bath was allowed to warm to 10 °C, stirring was maintained at 10 °C while $MgSO_4$ (5 g) and Celite (500 mg) were added. After another 15 min of stirring, the mixture was allowed to settle and 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 subjecting the residue to high vacuum gave **2** as pale yellow oil. Recrystallization from petroleum ether/diethylether gave yellow crystals of **2** (6.89 g, 88%, 98% 'ee' determined by spectroscopic analysis of the ester derived from (+)-MTPA chloride). mp = 53.6-54.2 °C. $[\alpha]_D^{25}$ = –48.9 (*c* 2.40, $CHCl_3$) {lit.[20] $[\alpha]_D^{25}$ = –49.6 (*c* 2.40, $CHCl_3$)}. IR ($CHCl_3$, γ_{max}): 3435, 3019, 2927, 1384, 1216, 1069, 1025, 929, 757, 669 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.74 (br s, 1H), 3.21-3.25 (m, 1H), 3.74 (dd, *J* = 4.4, 12.8 Hz, 1H), 3.92 (d, *J* = 2.2 Hz, 1H), 4.02 (dd, *J* = 2.4, 12.7 Hz, 1H), 7.22–7.41 (m, 5H). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ

55.6, 61.2, 62.5, 125.7, 128.3, 128.4, 136.6. Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71%. Found: C, 71.89; H, 6.79%.

(2*R*,3*R*)-3-Azido-3-phenylpropane-1,2-diol (3). The epoxy alcohol **2** (2.0 g, 13.32 mmol), NaN_3 (1.73 g, 26.63 mmol) and NH_4Cl (1.42 g, 26.63 mmol) in a solvent mixture of methanol (12 mL) and water (1.5 mL) were warmed at 65 °C for 6 h. The reaction mixture was cooled to rt and the solid was filtered. The filtrate was concentrated to a residue, which was taken into ethyl acetate, washed with brine and water, dried and concentrated to give a syrup, which was purified by column chromatography (petroleum ether/EtOAc 7:3) to afford the azido diol **3** as a yellow oily liquid (2.49 g, 97%). $[\alpha]_D^{25} = -166.8$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, γ_{max}): 3402, 3055, 2926, 2855, 2106, 1602, 1493, 1454, 1384, 1265, 1093, 1041, 741 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.90 (br s, 2H), 3.47-3.67 (m, 2H), 3.69-3.82 (m, 1H), 4.43-4.59 (d, *J* = 7.1 Hz, 1H), 7.2-7.47 (m, 5H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 62.8, 67.0, 73.9, 127.7, 128.8, 128.9, 136.0. Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75%. Found: C, 55.99; H, 5.78; N, 21.81%.

(1*R*,2*R*)-1-Azido-3-(*tert*-butyldimethylsilyloxy)-1-phenylpropan-2-ol (4). To a stirred solution of azido diol **3** (0.421 g, 2.18 mmol) in CH_2Cl_2 (15 mL) was added imidazole (0.180 g, 2.62 mmol). To this solution was added *t*-butylchlorodimethylsilane (0.329 g, 2.18 mmol) at 0 °C and the reaction mixture was stirred at rt for 5 h. Then, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Silica gel column chromatography of the crude product using Pet ether/EtOAc (10:0.3) as eluent afforded mono-TBS protected azido alcohol **4** as a colorless liquid (0.643 g, 96%). $[\alpha]_D^{27} = -33^o$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, γ_{max}): 3339, 3015, 2955, 2930, 2105, 1463, 1389, 1255, 1117, 837, 759 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ –0.02 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 2.10 (br s, 1H), 3.55-3.80 (m, 3H), 4.48 (d, *J* = 7.0 Hz, 1H), 7.25-7.32 (m, 5H). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ –5.5, –3.6, 18.1, 25.8, 63.2, 66.7, 73.7, 127.8, 128.7, 128.9, 136.3. Anal. Calcd for $C_{15}H_{25}N_3O_2Si$: C, 58.60; H, 8.20; N, 13.67%. Found: C, 58.68; H, 8.12; N, 13.76%.

***tert*-Butyl (1*R*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-1-phenylpropyl- carbamate (5).** To a solution of **4** (0.310 g, 1.008 mmol) in EtOAc (12 mL) was added $(Boc)_2O$ (0.242 g, 1.10 mmol), a catalytic amount of 5% Pd/C and the reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm. balloon pressure) for 12 h. The reaction mixture was then filtered through a pad of Celite and the solvent was removed under reduced pressure to give the crude product, which was then purified by column chromatography over silica-gel using petroleum ether/EtOAc (60:40) as eluent to afford **5** as a pale yellow oil (0.338 g, 88%). $[\alpha]_D^{26} = -12.6^o$ (*c* 0.55, $CHCl_3$). IR ($CHCl_3$, γ_{max}): 2955, 2930, 2451, 2210, 1678, 1479, 1447, 1372, 1165, 837, 759 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ –0.02 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 1.40 (s, 9H), 2.10 (br s, 1H), 3.55-3.80 (m, 3H), 4.48 (d, *J* = 7.0 Hz, 1H), 5.54 (br s, 1H), 7.25-7.32 (m, 5H). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ –5.6, –4.5, 18.1, 25.8, 28.3, 58.1, 63.9, 72.9, 79.4, 126.8, 127.4, 128.4, 139.5, 155.6. Anal. Calcd for $C_{20}H_{35}NO_4Si$: C, 62.95; H, 9.25; N, 3.67%. Found: C, 62.88; H, 9.29; N, 3.75%. LC-MS (ESI-TOF) *m*/*z*: [M+23] = 404.30.

***tert*-Butyl (1*R*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-(methylthio-carbonothioyloxy) -1-phenylpropylcarbamate (6).** To a solution of **5** (0.404 g, 1.06 mmol) in THF (10 mL) at 0 ^{o}C was added sodium hydride (50% assay, 0.056 g, 1.17 mmol). Vigorous gas evolution was observed. After the reaction mixture was stirred for 20 min, carbon disulfide (0.100 mL, 1.64 mmol) was added in one portion. Stirring was continued for the next 30 min after which methyl iodide (0.20 mL, 3.18 mmol) was added in a single portion. The reaction mixture was stirred for another 2 h (progress of reaction mixture was monitored by TLC) and the reaction was quenched by the addition of ice-cold water (2 mL). The solution was filtered, concentrated in *vacuo* and the residue was extracted with ethyl acetate (3 X 5 mL). The combined organic extracts were washed with saturated sodium bicarbonate (5 mL) solution. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography using 12% ethyl acetate in petroleum ether as eluent, to give **6** as a pale yellow solid (0.418 g, 84%); M.P. = 107-109 ^{o}C; $[\alpha]_D^{26}$ = –12.4^{o} (*c* 1.0, acetone); IR ($CHCl_3$, γ_{max}): 3398, 3064, 3031, 2976, 1693, 1513, 1435, 1310, 1215, 837, 759 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ –0.02 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 1.40 (s, 9H), 2.35 (s, 3H), 4.21 (m, 2H), 5.37 (d, *J*= 7.1 Hz, 1H), 6.13 (d, *J* = 7.0 Hz, 1H), 7.30-7.40 (m, 5H). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ –5.6, –4.5, 18.1, 19.4, 25.8, 28.3, 57.6, 63.9, 72.8, 79.5, 89.5, 126.8, 127.4, 128.3, 139.4, 155.6, 212.4. Anal. Calcd for $C_{22}H_{37}NO_4S_2Si$: C, 56.01; H, 7.91; N, 2.97; S, 13.59%. Found: C, 56.09; H, 7.99; N, 2.90; S, 13.44%.

(*S*)-3-Amino-3-phenylpropan-1-ol (8). To a solution of the xanthate ester **6** (0.250 g, 0.53 mmol) in toluene (15 mL) tri-*n*-butyltin hydride (0.462g, 1.59 mmol) and a catalytic amount of AIBN (0.1 mol% w/w based on 6) were added at room temperature under inert atmosphere. The reaction mixture was heated at reflux till completion of reaction (progress of reaction was monitored by TLC). After the completion of the reaction (as shown by TLC), toluene was removed under reduced pressure to give a thick viscous residue. This residue was dissolved in 15 mL of THF and 1.0 mL of TFA was added to the solution at 10 ^{o}C under a nitrogen atmosphere. The reaction mixture was stirred at RT for 5 h. Then, 20 mL of 1.0 M NaOH solution was slowly added at 0 ^{o}C and the mixture was extracted with EtOAc/MeOH (95:5) (2x15mL). The organic extracts were combined dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The separated crude product was purified by silica-gel column chromatography with $CHCl_3$/MeOH (9:1) to afford **8** as a colorless solid 0.065 g (81% for two steps). $[\alpha]_D^{25}$ = –11.6^{o} (*c* 0.52, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.10 (m, 2H), 3.55 (t, 2H), 3.96 (m, 1H), 7.09-7.24 (m, 5H). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 39.4, 57.4, 56.4, 126.1, 128.2, 128.9, 139.9. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26%. Found: C, 71.40; H, 8.60; N, 9.36%.

(*S*)-Dapoxetine (I). The synthesis was completed using the literature procedure.[17a] The spectral and analytical data of I are in good conformity with the reported values.[17a] $[\alpha]_D^{25}$ = +61.7 (*c* 0.30, $CHCl_3$) [lit.[17a] $[\alpha]_D^{25}$ = +62.5 (*c* 0.3, $CHCl_3$)]; colorless oily liquid; IR ($CHCl_3$): 2962, 2950, 2311, 2103, 1922, 1728, 1346, 1265, 1168, 1046, 914, 848, 733 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.22 (s, 6H), 2.34-2.45 (m, 1H), 2.59-2.71 (m, 1H), 3.55-3.63 (m, 1H), 3.93-4.12 (m, 2H), 7.19-7.52 (m, 9H), 7.70-7.74 (m, 1H), 7.95-8.21 (m, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ

32.0, 36.4, 63.1, 67.5, 104.5, 120.1, 121.9, 125.5, 126.2, 127.1, 127.4, 127.8, 128.3, 128.9, 132.1, 136.0, 138.1, 155.2. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59%. Found: C, 82.50; H, 7.50; N, 4.65%.

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