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Research Paper

Short enantioselective routes to (S)-Dapoxetine

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Abstract: Two enantioselective approaches involving stereoselective conjugate addition of a homochiral lithium amide based on (R)-N-(1-phenylethyl)-benzylamine, and a stereo selective ketone reduction of a prochiral ketone, have been employed for the chiral synthesis of (S)-Dapoxetine. Both routes employ readily and commercially viable starting materials and reagents, and suitable for process synthesis of (S)-Dapoxetine.

Introduction

Application of SSRI (selective serotonin reuptake inhibitor) agents to treat premature ejaculation (PE) has been attributed to the perturbations in serotonergic 5-hydroxytryptamine (5-HT) neurotransmission.[1] While SSRIs are traditionally used to treat depression, some of the SSRIs drugs such as fluoxetine, sertraline, and paroxetine have been used for PE indication. However, these drugs do not reach peak plasma concentrations and their long half-lives may lead to side effects.

(S)-Dapoxetine **1** [(S)-(+)-N, N-dimethyl-[3-(naphthalene-1-yloxy)-1-phenylpropyl]amine; Priligy] (**Figure 1**), is a novel short-acting SSRI, unlike the long-acting SSRIs which are typically administered daily

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and may take several days to reach steady-state plasma concentrations. Dapoxetine exhibits unique characteristics of being a selective serotonin reuptake inhibitor (SSRI) marketed for the treatment of premature ejaculation in men.[2] Similar to other SSRIs, dapoxetine exerts its effects primarily through the inhibition of the serotonin reuptake transporter, with minimal inhibitory activity at the norepinephrine and dopamine reuptake transporters.[3] The S-isomer is 3.5 times more potent than the (R)-isomer.

(S)-Dapoxetine **1** is a 1-naphthol derivative possessing phenylpropane-1-amine substituent on oxygen and dimethyl group on amine respectively. Amongst the various routes described for the synthesis of (S)-Dapoxetine **1**, some of the key approaches involve resolution of racemic dapoxetine with L-(+)-tartaric acid to obtain **1**[4] and an enzymatic resolution of the key chiral intermediate 3-amino-3-phenylpropane-1-ol using Candida Antarctica lipase A (CAL-A).[5] Synthesis of ^{14}C-labeled **1** starting from unnatural amino acid (R)-N-Boc-phenylglycine as the chiral starting material, was reported by O'Bannon and co-workers.[6] An interesting synthesis of (S)-dapoxetine using an asymmetric C-H amination reaction with a chiral dirhodium (II) complex was reported by Lee and co-workers.[7] Also, a stereoselective synthesis of **1** from trans-cinnamyl alcohol and methyl cinnamate, employing Sharpless asymmetric epoxidation and dihydroxylation, respectively, as the key steps was reported.[8]

Despite several reports available for the synthesis of **1**, the need for the development of an efficient and scalable route which can be employed on a multi-ton process still exists. In order to avoid the use of multiple steps, lengthy procedures and expensive reagents, we decided to focus on two enantioselective strategies involving a chiral intermediate that could be easily accessed from commercially available starting materials.

Results and Discussion

Retrosynthetic strategies for the two approaches for **1** are shown in **Figure 2**. In the approach 1, we envisioned chiral alcohol **3** as a key precursor to **1**. Interestingly, **3** itself can be derived from a prochiral 3-chloro propiophenone **2**, and can be elaborated to **1** in a short sequence.[9] Approach 2 involves installation of the chiral N,N-dimethyl amino group using an diastereoselective conjugate addition of a secondary homochiral lithium amide derived from chiral N-(α-methyl benzyl)benzylamine on methyl cinnamate.[10]

As a part of our ongoing program on the identification of scalable and cost-effective processes for chiral APIs, we were interested in identifying inexpensive prochiral precursors which would serve as the starting point for the synthesis. Asymmetric reductions of prochiral ketones are important transformations in the syntheses of natural products, pharmaceuticals, and fine chemicals. In this regard, we identified prochiral 3-chloro propiophenone **2** as a readily available and inexpensive starting material, which could be converted to **1** in four steps as depicted in **Scheme 1**.

Chiral reduction of **2** using (+) DIP Chloride [(+)-B-Chlorodiisopinocampheyl borane,

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(+)-Ipc2BCl][11] furnished the (R)-isomer **3** with >98% ee.[12] Chiral reduction of 3-chloropropiophenone **2** was previously reported using CBS catalyst,[13] rhodium cyclopentadienyl complex[14] and a borane reduction using a catalytic system derived from (−)-α,α-diphenylpyrrolidinemethanol and 9-BBN.[15] However, the reported methods would increase the cost of the synthesis, and we found commercially available DIP-Chloride as a convenient reagent[16] to perform the asymmetric reduction of **2** with high selectivity.

The chiral alcohol **3**, obtained from the (+)-DIP chloride reduction of **2**, was reacted with 1-naphthol **4** in the presence of potassium carbonate in DMF to obtain **5**. We did not observe any racemization during the base-mediated alkylation and this set the stage for two-step one pot synthesis of **1**. Alcohol **5** was cleanly converted to its corresponding mesylate **6** and further transformed to (S)-dapoxetine **1** quantitatively in stereoselective manner by passing dimethyl amine gas into a solution of the mesylate **6** in THF. The free base **1** was then transformed to the hydrochloride using EtOAc-HCl to furnish (S)-dapoxetine hydrochloride with high enantiomeric purity. Last three steps viz., mesylation, displacement with dimethyl amine and formation of the hydrochloride salt were carried out sequentially without purification giving an overall 92% yield. MTBE-HCl could also be used for the preparation of the hydrochloride salt conveniently.

In an alternate approach, installation of the dimethyl amine group directly using an asymmetric Michael addition of homochiral lithium amide onto methyl cinnamate (**Scheme 2**) was explored. Michael addition of the lithium amide derived from (R)-N-(α-methylbenzyl)benzylamine **9** to methyl cinnamate **8** in THF gave **10** in 72% yield with >99% ee. Debenzylation of **10** was effected by hydrogenolysis in the presence of 10% palladium-charcoal in acetic acid under pressure (H_2, 60 psi), to obtain **11**. Alternatively, hydrogenolysis was carried out using palladium hydroxide at ambient pressure of hydrogen (1 atm) in a mixture of MeOH-water-acetic acid to furnish the debenzylated product **11**. However, the conversion rates were lower, and we did not observe complete conversion when the reaction was performed under 80 psi hydrogen pressure. Reduction of methyl ester **11** to the corresponding alcohol **12** using $LiAlH_4$ was performed on multi-gram scale and product was isolated in good purity without employing column purification. Eschweiler-Clarke methylation of aminoalcohol **12** using a mixture of aqueous formaldehyde and formic acid afforded **7** in 70% yield.

Our initial goal was to synthesize (S)-dapoxetine **1** by etherification of mesylate **14** with 1-napthol **4** (**Scheme 3**), once the chiral dimethyl amino group had been installed. Alcohol **7** was converted to its corresponding mesylate **14** using methane sulfonyl chloride/triethyl amine/DMAP in quantitative yield. Surprisingly, mesylate **14** on reaction with 1-naphtol exclusively afforded **16**, a rearranged substitution product which was obtained by the reaction of an azetidinium ion intermediate **15** at the activated benzylic position instead of **1**. Similar results were obtained when alcohol **7** was activated

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as its tosylate, or when performed on a racemic chloride as a model substrate.

In order to circumvent the formation of undesired **16**, alcohol **7** was treated with sodium hydride and the alkoxide intermediate was reacted with 1-fluoronaphthalene to afford (S)-Dapoxetine **1** in 65% yield. Hydrochloride salt of **1** was prepared by using MTBE-HCl, which was further purified by recrystallization using isopropyl alcohol to give (S)-Dapoxetine hydrochloride salt with >99% ee.

Conclusion

In summary, two enantioselective routes were developed for the synthesis of (S)-Dapoxetine **1**. Both routes involve commercially viable starting materials and reagents and are suitable for adaptation to process manufacturing & commercial synthesis of (S)-Dapoxetine **1**.

Experimental Section

General: Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light (254 nm) or iodine spray. Column chromatography was performed on silica gel (60-120 mesh) using a proper eluent. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ and DMSO solutions using Varian MR 400 (400 and 100 MHz) spectrometers respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.0) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FTIR spectrometer. Melting points were determined by using a Buchi melting point B-540 apparatus. MS spectra were recorded using an Agilent 6430 triple quadrapole mass spectrometer. Reverse phase HPLC analysis was recorded on a Waters Alliance HPLC (e2695) using xBridge C18 (150 x 4.6 mm, 5μ) column, UV (230 nm), Mobile phase: A) 5mM NH_4OAc in H_2O B) acetonitrile (Gradient system). Chiral HPLC analysis were performed on a Waters Alliance HPLC (e2695) using Chiralcel OD-H column (250 x 4.6 mm, 5μ).

(R)-3-Chloro-1-phenylpropan-1-ol (3): 3-Chloropropiophenone **2** (6 g, 0.0355 moles) in dichloromethane (80 mL) was added drop wise to a solution of (+) DIP Chloride (18 g, 0.0561 moles) in dichloromethane (100 mL) at 0 $^{\circ}C$ under nitrogen atmosphere and stirred for 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After the completion of the reaction, the reaction mixture was slowly poured on to 10% aq. acetic acid (20 mL) while maintaining the temperature below 10 $^{\circ}C$, and then diluted with water (100 mL), till the layers were separated. The organic layer was washed with water (2 x150 mL), brine solution (150 mL) and dried over anhydrous sodium sulfate. The combined organic layers were concentrated under reduced pressure to give **3** (5.5 g, 90%) as light yellow liquid with 98 % ee as determined by HPLC [Chiralcel OD-H column, hexane/ethanol=95/5, 0.8 mL min^{-1}, λ=210 nm, t_r = 11.3 min]; ^{1}H NMR (400 MHz,

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$CDCl_3$): δ (ppm) 7.37 – 7.29 (m, 5H), 4.95 (m, 1H), 3.74 (m,1H), 3.56 (m, 1H), 2.23 (m, 1H), 2.12 (m, 1H), 1.95 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)143.4, 128.4, 127.6, 125.6, 70.9, 41.5 41.1.

(R)-3-(Naphthalen-1-yloxy)-1-phenylpropan-1-ol (5): To a solution of **3** (6 g, 0.0352 moles), 1-naphthol **4** (5.10 g, 0.0352 moles), potassium carbonate (5.33 g, 0.0386 moles) in DMF (30 mL) were added under nitrogen atmosphere at RT. The resulting reaction mixture was heated to 80-85 °C and stirred for 8 h. The reaction was quenched with ice cold water and extracted with ethyl acetate (2 x 80 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **5** (7.35 g, 75 %) as light brownish syrup with 98% ee as determined by HPLC [Chiralcel OD-H column, hexane/ethanol=90/10, 0.8 mL min^{-1}, λ=210 nm, t_r= 9.1 min]; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.23 (dd, 1H, *J* = 2.4 Hz, 5.6 Hz), 7.80(dd, 1H, *J* = 5.6 Hz, 2.4 Hz), 7.51-7.27 (m, 9H), 6.80 (m. 1H, *J* = 7.2 Hz), 5.14 (dd, 1H, *J* = 7.8 Hz, 5.2 Hz), 4.35 (m,1H), 4.20 (m, 1H), 2.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.5, 144.2, 134.5, 128.6, 127.7, 127.6, 126.4, 125.9, 125.9, 125.6, 125.3, 121.9, 120.4, 104.8, 72.2, 65.4, 38.6.

(S)-Dapoxetine hydrochloride (1*HCl): To a solution of **5** (160 g, 0.577 mol) in THF (1300 mL) was under nitrogen atmosphere were added triethyl amine (1164 g, 1.15 mol) and DMAP (7 g, 0.057 mol). The reaction mixture was cooled to 0 °C. Methanesulfonyl chloride (98.9 g, 0.863 moles) was added drop wise to the reaction mixture and stirred at 0 °C for 3 h. After completion of reaction, dimethyl amine gas [generated by using dimethyl amine hydrochloride (480 g, 5.9 mol) in water (900 mL) followed by addition of sodium hydroxide (360 g) in water (620 mL) at 85 °C] was purged into the reaction mixture at 0 °C. The reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched with water (4.8 L), and pH was adjusted to ~11-12 with 5N sodium hydroxide, and extracted with ethyl acetate (3 L). The combined organic layer was washed with water (2 x 2.6 L), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was dissolved in ethyl acetate (800 mL), and stirred in the presence of activated carbon (8 g) for 20 min. After filtration through hyflow bed, the filtrate was cooled to 5-10 °C, and EtOAc-HCl (240 mL) was added drop wise. The resulting mixture was stirred at 20 °C for 30 min, and the solid obtained was filtered, washed with ethyl acetate (400 mL) and dried under vacuum to afford (S)-**Dapoxetine hydrochloride (1*HCl)** (180 g, 92%) as a white solid with 99.9 % Purity as determined by reverse phase HPLC analysis (λ=210 nm) and 99.7% ee as determined by HPLC (Chiralcel OD-H, hexane/ethanol/DEA=98/02/0.2, 0.8 mL min-1, λ=230 nm, t_r (S-isomer) = 8.1 min); $[\alpha]_D^{25}$ = +132.2° (c 1, CH_3OH); ^1H NMR (400 MHz, *DMSO-d_6*): δ (ppm) 11.38 (br s,1H), 8.06 (d, 1H, J = 8.4 Hz), 7.84 (d,1H, J = 8.4 Hz), 7.65 (m, 2H), 7.54-7.44 (m, 6H), 7.31 (t,1H, J = 8.0 Hz), 6.74 (d, 1H, J = 8.0 Hz), 4.72 (m, 1H), 4.12 (m, 1H), 3.70 (m, 1H), 2.90 (m, 1H), 2.84 (d, 3H, *J* = 4.0 Hz), 2.75 (m, 1H), 2.58 (d, 3H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) : δ (ppm) 153.5, 133.9, 132.6, 129.8, 129.5, 128.9, 127.3, 126.4, 126.0, 125.2, 124.7, 121.7, 120.1, 104.9, 67.1,

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64.4, 41.3, 29.5; MS (ESI+, m/z): 306 $(M+H)^+$,261 [(M-NMe2]

Methyl (3S, αR)-3-(*N*-benzyl-*N*-α-methyl benzyl amino)-3-phenylpropanoate (10): To a solution of (R)-*N*-benzyl-*N*-α-methyl benzyl amine **9** (73 g, 0.345 mol) in THF (875 mL) under nitrogen atmosphere was added n-BuLi [1.4M in Hexane] (215.6 mL, 0.323 mol) at -78 °C and stirred for 45 min. A solution of methyl cinnamate **8** (35 g, 0.216 mol) in THF (175 mL) was added drop wise at -78 °C to the reaction mixture and stirred for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution (200 mL) at -78 °C and allowed to gradually warm to RT. The aqueous layer was extracted with ethyl acetate (2 x 200 mL); the combined organic layers were washed with brine, dried over anhydrous Sodium sulfate and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography using silica gel eluting with 2-4 % EtOAc/Hexane to give **10** (58 g, 72 %) as yellow liquid with 99.4% ee as determined by HPLC (Chiralcel OD-H, hexane/ethanol/DEA=98/02/0.2, 1 mL min^{-1}, λ=210 nm, t_r = 6.0 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52-7.17 (m, 15H), 4.43 (dd,1H, *J* = 6.0 Hz, 9.0 Hz), 4.00 (q, 1H), 3.70 (AB q, 2H, *J* = 14.4 Hz, 33.8 Hz), 3.46 (s, 3H), 2.68 (dd, 1H, J = 5.2 Hz, 14.8 Hz), 2.56 (dd, 1H, *J* = 9.6 Hz, 14.8 Hz), 1.21(d, 3H, *J*= 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 144.1, 141.8, 141.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.3, 126.9, 126.7, 59.3, 56.7, 51.5, 50.8, 37.5, 15.8; MS (ESI+, m/z): 374 $(M+H)^+$.

(S)-Methyl 3-amino-3-phenylpropanoate (11): To a solution of **10** (57 g, 0.153 moles) in acetic acid (470 mL) was added 10% Pd/C (14.25 g, 25% w/w) and the reaction mixture was subjected to hydrogen pressure (60 psi) for 14 h. The reaction mixture was filtered through celite pad and washed thoroughly with methanol (200 mL); the filtrate was concentrated under reduced pressure to get crude product. The crude product was diluted with water (400 mL) and washed with ethyl acetate (2 x 160 mL). Aqueous layer was neutralized with saturated sodium bicarbonate solution and extracted with EtOAc (2 x 250 mL). The combined organic layer were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **11** (21 g, 77 %); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37-7.26 (m, 5H), 4.42 (t,1H, J= 6.4 Hz), 3.68 (s, 3H), 2.66 (d, 2H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.1, 144.3, 128.3, 127.1, 125.9, 52.3, 51.3, 43.6; MS (ESI+, m/z): 179.9 $(M+H)^+$.

(S)-3-Amino-3-phenylpropan-1-ol (12): To a suspension of $LiAlH_4$ (4.77 g, 0.012 moles) in dry THF (225 mL) under inert atmosphere was added **11** (15 g, 0.084 moles) in THF (150 mL) drop wise at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The reaction mixture was quenched with saturated sodium sulphate solution (60 mL). The reaction mixture was filtered through celite pad and washed thoroughly with EtOAc (2 x 50 mL) and layer was separated. The combined organic layer were washed with brine, dried over anhydrous Sodium sulfate and concentrated under reduced pressure to give a **(S)-3-amino-3-phenylpropan-1-ol (12)** (12 g, 95 %) as a brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37-7.19 (m, 5H), 4.13 (dd,1H, J= 6.0 Hz, 7.8 Hz), 3.83 (m, 2H), 1.90

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(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 136.9, 128.1, 127.3, 126.7, 67.9, 60.7, 41.0, 33.3; MS (ESI+, m/z): 151.9 $(M+H)^+$.

(S)-3-(Dimethylamino)-3-phenylpropan-1-ol (7): (S)-3-amino-3-phenylpropan-1-ol **(12)** (11.6 g, 0.0767 moles) and 37 % Formalin (20.3 mL, 0.25 moles) were stirred at RT for 10 min. 85% formic acid (13.2 mL, 0.244 moles) was added to the reaction mixture slowly at 10 °C. The reaction mixture was heated at 90 °C for 10 h. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, and then acidified with 6N HCl (pH-2). The reaction mixture was washed with dichloromethane (2 x 100 mL). Aqueous layer was basified with saturated sodium bicarbonate solution (pH: 7.0-8.0) and extracted with EtOAc (2 x 90 mL). The combined organic layer were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **7** (9.6 g, 70 %) as yellow liquid with 98.17 % purity as determined by reverse phase HPLC analysis (λ=210 nm) and 99% ee as determined by HPLC (Chiralcel OD-H, hexane/ethanol=90/10, 0.8 mL min^{-1}, λ=210 nm, t_r (major) = 12.3 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36-7.17 (m, 5H), 3.85 (m,2H), 3.75 (dd, 1H, J = 3.6 Hz, 10.6 Hz), 2.41 (m, 1H) 2.18 (s, 6H) 1.67 (qq, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 136.5, 128.8, 127.9, 127.5, 69.6, 69.6, 62.7, 41.2, 32.7; MS (ESI+, m/z): 180 $(M+H)^+$

(S)-Dapoxetine hydrochloride (1*HCl): A suspension of Sodium hydride {60% in mineral oil (7.83 g, 0.196 moles)} and *n*-hexane (30 mL) under inert atmosphere were stirred at RT for 10 min, and n-hexane was removed by quick decantation under nitrogen atmosphere. **7** (9 g, 0.05 moles) in *N*,*N*-dimethylacetamide (180 mL) was added drop wise to the reaction mixture at RT. After the completion of addition, the reaction mixture was heated to 60 °C for 30 min. 1-Fluoronaphthalene (8.79 g, 0.060 moles) was added to the reaction mixture at 60 °C, and the resulting reaction mixture was stirred at 90 °C for 3 h. The reaction mixture was quenched with ice cold water (300 mL), aqueous layer was acidified with 6N HCl (pH-2) and washed with EtOAc (2 x150 mL). The aqueous layer was cooled to 0 °C, and the pH was adjusted to ~8.0 with saturated sodium bicarbonate solution, and extracted with EtOAc (3 x140 mL). The combined organic layers were washed with water (3 x 240 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a **1 (free base)** (10 g, 65 %) as brownish yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.23 (dd, 1H, J = 2.4 Hz, 6.2 Hz), 7.78 (dd, 1H, J = 6.2 Hz, 2.4 Hz), 7.47 (m, 2H), 7.38 (d, 1H, J = 7.2 Hz), 7.36-7.24 (m, 6H), 6.64 (d, 1H, J = 7.2 Hz), 4.06 (m, 1H), 3.92 (m, 1H), 3.60 (dd, 1H, J = 9.0 Hz, 5.2 Hz), 2.62 (m, 1H), 2.28 (m, 1H), 2.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.7, 136.6, 134.5, 128.6, 128.2, 127.5, 127.4, 126.3, 125.9, 125.7, 125.1, 122.1, 120.0, 104.6, 67.7, 65.7, 42.8, 33.0; MS (ESI+, m/z): 306 $(M+H)^+$.

A solution of **1** (free base) (7.8 g, 0.0255 moles) in MTBE (78 mL) under inert atmosphere were stirred at RT for 10 min and cooled to 10 °C. MTBE-HCl (16 mL) [pH-2.0] was added drop wise to the reaction mixture at 10 °C and stirred for 20 min. filtered the solid, washed with MTBE (2 x 20 mL) and dried under vacuum. The obtained solid was re-

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crystallized with isopropyl alcohol (24 mL) to give a (S)-Dapoxetine hydrochloride (**1*HCl**) (7.5 g, 85 %) as white solid with 99.9 % ee as determined by HPLC (Chiralcel OD-H, hexane/ethanol/DEA=98/02/0.2, 0.8 mL min-1, λ=230 nm, t_r (S-isomer) = 8.1 min)

***N,N*-dimethyl-3-(naphthalen-1-yloxy)-3-phenylpropan-1-amine (16):** To a solution of **7** (1.6 g, 0.009 mol) in dichloromethane (32 mL) under nitrogen atmosphere was added triethyl amine (1.8 g, 0.02 mol). The reaction mixture was stirred for 10 min at RT, and then cooled to 0 °C. Methanesulfonyl chloride (1.5 g, 0.013 moles) was added drop wise to the reaction mixture; the reaction mixture was allowed to warm to RT and stirred for 2 h. After completion of reaction, the reaction mixture was quenched with water (20 mL), extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Resulting crude product was dissolved in DMF (10 mL).

In another flask, K_2CO_3 (2.89 g, 0.02 moles), NaI (0.42 g, 0.003moles), 1-naphthol **4** (1 g, 0.007 moles) and DMF (15 mL) were charged. The reaction mixture was stirred for 10 min at RT. Above obtained product in DMF was added drop wise to the reaction mixture at RT. The resulting reaction mixture was heated to 65 °C and stirred for 14 h. The reaction mixture was quenched with ice cold water (50 mL), and extracted with EtOAc (3 x 75 mL). The combined organic layer were washed with water (2 x120 mL), dried over anhydrous Sodium sulfate and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography using silica gel eluting with 2-5 % MeOH /EtOAc to give **16** (0.52 g, 25 %) as pale brown syrupy liquid with 97% purity as determined by reverse phase HPLC analysis (λ= 210 nm); ^{1}H NMR (400 MHz, $CDCl_3$: δ (ppm) 8.43 (dd, 1H, *J* = 6.2 Hz, 2.4 Hz), 7.76 (dd, 1H, *J* = 6.2 Hz, 2.4 Hz), 7.50 (m, 2H), 7.46 (d, 2H, *J* = 8.4 Hz), 7.34 (m, 3H), 7.22 (m, 1H), 7.18 (t, 1H, J = 8.0 Hz), 6.62 (d, 1H, = 7.2 Hz), 5.44 (dd, 1H, *J* = 4.8 Hz, 8.4 Hz), 2.53 (t, 2H), 2.34 (m, 1H), 2.25 (s, 6H), 2.11 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.4, 141.5, 134.6, 128.7, 127.7, 127.6, 126.3, 125.9, 125.8, 125.8, 125.2, 122.0, 120.2, 106.9, 78.1, 55.9, 45.2, 36.5; MS (ESI+, m/z): 306 $(M+H)^+$.

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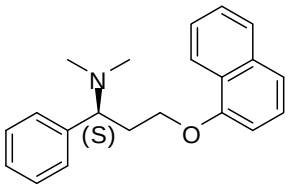


1

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

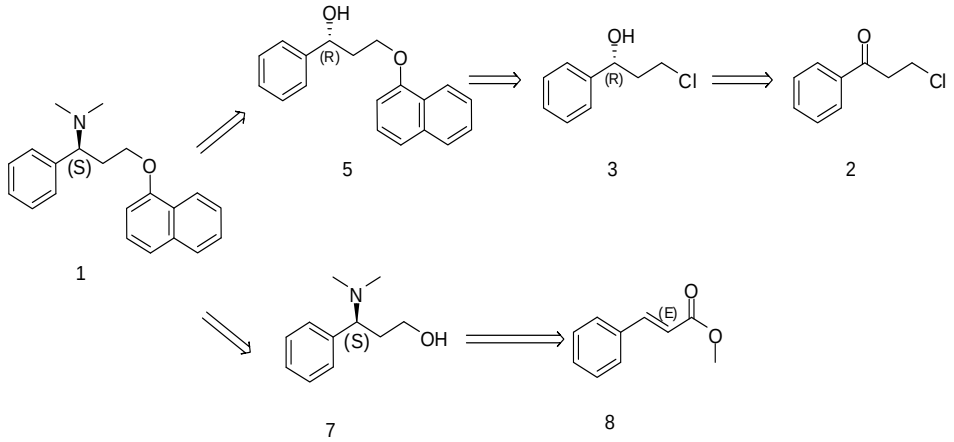
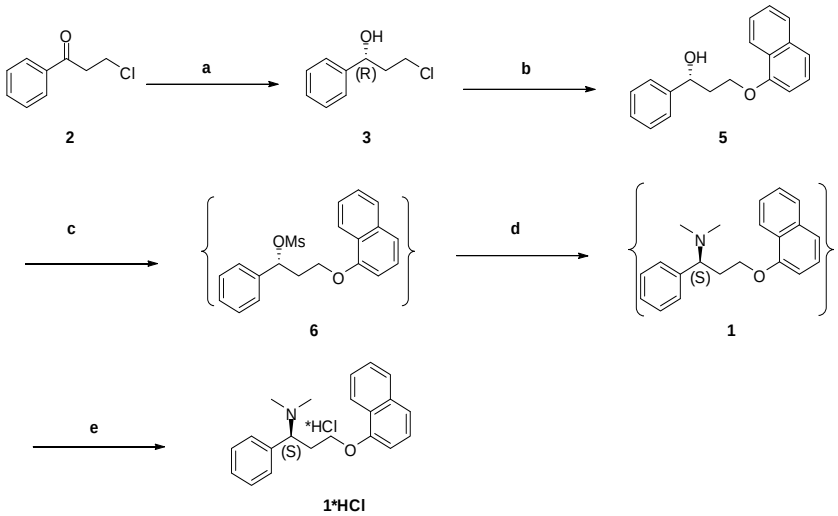


Figure 2 Retrosynthetic strategies for (S)-Dapoxetine **1**



Scheme 1: *Reagents and Conditions:* (a) (+)DIP Chloride, CH_2Cl_2, 0°C – rt, 12h, 90%; (b) 1-Naphthol **4**, K_2CO_3, DMF, 80 °C, 8h, 75%;(c) CH_3SO_2Cl, Et_3N, cat. DMAP, THF, 0 °C, 3h; (d) $(CH_3)_2NH.HCl$, NaOH, -10 °C – rt, 16h; (e) EtOAc-HCl, EtOAc, 10 °C – rt, 30 min, 92% for 3 steps.

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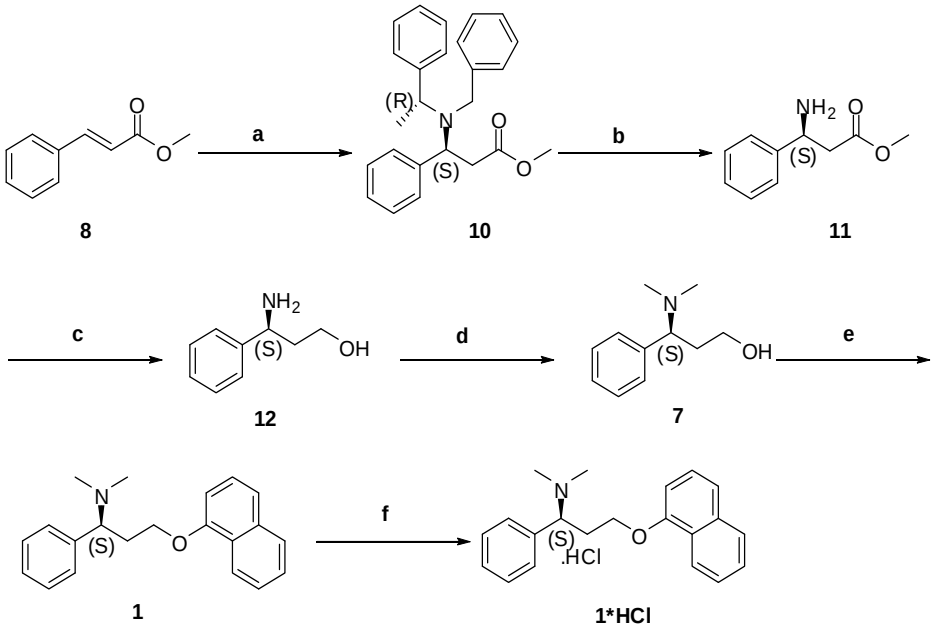
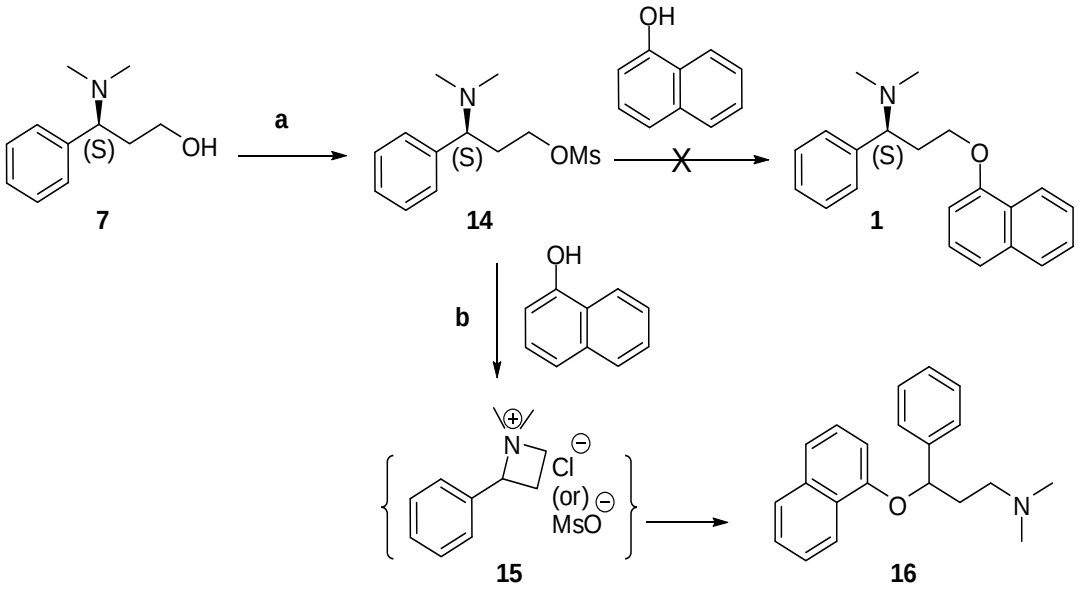


Scheme 2: *Reagents and Conditions:* (a) (R)-N-benzyl-N-α-methyl benzyl amine **9**, n-BuLi, THF, -78°C, 2h, 72%; (b) 10% Pd-C, H_2 (60 psi), Acetic acid, rt, 14h, 77%; (c) $LiAlH_4$, THF, 0°C - rt, 2h, 95%; (d) 37% Formalin, Formic acid, 90°C, 10h, 70%; (e) 1-Fluoronaphthalene, Sodium hydride (60% in mineral oil), N,N-Dimethylacetamide, 90°C, 3h, 65%; (f) (i) MTBE-HCl, MTBE, 10 °C, 20 min, (ii) Isopropanol, reflux, 85%.



Scheme 3: *Reagents and Conditions:* (a) CH_3SO_2Cl, Et_3N, DMAP, THF, 0 °C - rt, 2h; (b) 1-Naphthol **4**, K_2CO_3, cat. NaI, DMF, 65 ^oC, 14h.

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[9] During the course of our process development, we came across the articles: a) Mahale, R. D.; Chaskar, S. P.; Patil, K. E.; Maikap, G. C.; Gurjar, M. K. *Org. Process. Res. Dev.* **2012**, *16*, 710-713, which describes the asymmetric reduction of 3-chloropropiophenone using an oxazaborolidine catalyst for the large-scale synthesis of Dapoxetine; b) Kim, S. J.; Jeon, T. H.; Min, I. S.; Kim, I. S.; Jung, Y. H. *Tetrahedron Lett.* **2012**, *53*, 3680-3682.

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