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Enantioselective synthesis of (*S*)-dapoxetine

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Abstract—An efficient enantioselective synthesis leading directly to (+)-(*S*)-dapoxetine has been described for the first time using a Sharpless asymmetric dihydroxylation, Barton–McCombie deoxygention, and Mitsunobu reaction as the key steps.

1. Introduction

Depression is a common psychiatric disorder and one of the most frequent illnesses in the world-affecting people of all gender, ages, and backgrounds. Stimulant abuse is a serious problem, with 37% of state and local law enforcement agencies identifying cocaine as their greatest drug threat.[1,2] The asymmetric synthesis of an individual enantiomer is extremely important because the (*S*)- and (*R*)-isomers usually display very different pharmacological or physiological properties.[3] For example, the enantiomer (*S*)-(+)-*N*,*N*-dimethyl-α-[2-(1-naphthalenyloxy)ethyl]benzene methanamine [(*S*)-dapoxetine] originally known as LY 210448 credited to Wong of Eli Lilly and Company is a potent selective serotonin re-uptake inhibitor (SSRIs), but is slightly different from the SSRIs (such as Zoloft, Paxil, and Prozac) (Fig. 1) widely prescribed for depression and other psychiatric disorders such as bulimia or anxiety.

Dapoxetine is structurally related to fluoxetine (Prozac) with antidepressant activity. Dapoxetine is the D-enantiomer of LY 243917 and is 3.5 times more potent as a serotonin reuptake inhibitor than the L-enantiomer.[4]

Moreover, (*S*)-dapoxetine (Fig. 2) is currently being tested as a treatment for premature ejaculation in men, 23–30% of men are suffering worldwide due to this problem.[5] Recent phase 3 clinical trials in patients with premature ejaculation have shown dapoxetine to be effective in improving the time of ejaculation, without any major adverse events, except nausea. Dapoxetine would make it join the ranks of sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levittra®), the erectile dysfunction drugs and cabergoline (Dostinex®) as a drug invented to improve male sexual health.[6]

Very few methods are currently available for the synthesis of this important and potent pharmacologically active

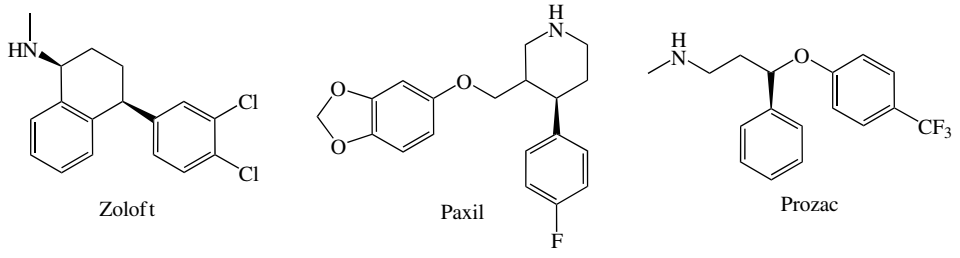

Figure 1. Structures of Zoloft, Paxil, and Prozac.

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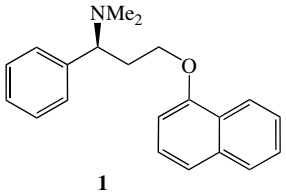

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(*S*)-Dapoxetine

Figure 2. (*S*)-Dapoxetine.

(*S*)-dapoxetine. Gotor et al. recently reported the asymmetric synthesis of (*S*)-dapoxetine in good overall yield and high enantiomeric excess by enzymatic resolution of 3-amino-3-phenylpropan-1-ol derivatives using *Candida antarctica* lipase A (CAL-A).[7] Toru Koizumi et al.[8] reported the synthesis of intermediate **2** (see Scheme 2) by employing asymmetric induction in the 1,3-dipolar cycloaddition of (*R*)-(+)-*p*-tolyl vinyl sulfoxide with acyclic nitrones in excellent isolated yield with high enantiomeric excess. Employing a chiral starting material, they did not elaborate the synthesis further to (*S*)-dapoxetine. Another method described in the literature to synthesize (*S*)-dapoxetine is a radiochemical synthesis from (*S*)-(+)-*N*-methyl-α-[2-(1-naphthalenyloxy)ethyl]benzene methanamine hydrochloride using $^{11}CH_3I$.[9]

To the best of our knowledge, there have been no chemical methods reported so far, which directly lead to the asymmetric synthesis of (+)-(*S*)-dapoxetine. In the chemical methodology presented for the first time herein, the Sharpless asymmetric dihydroxylation[10] and subsequent transformation of the diols formed via a cyclic sulfite[11] were envisioned as powerful tools offering considerable opportunities for synthetic manipulation.

As part of our ongoing project for the synthesis of biologically active compounds from easily available starting materials, we herein report the enantioselective synthesis of (*S*)-dapoxetine from the easily available cinnamyl ester using Sharpless asymmetric dihydroxylation as a source of chiral induction.

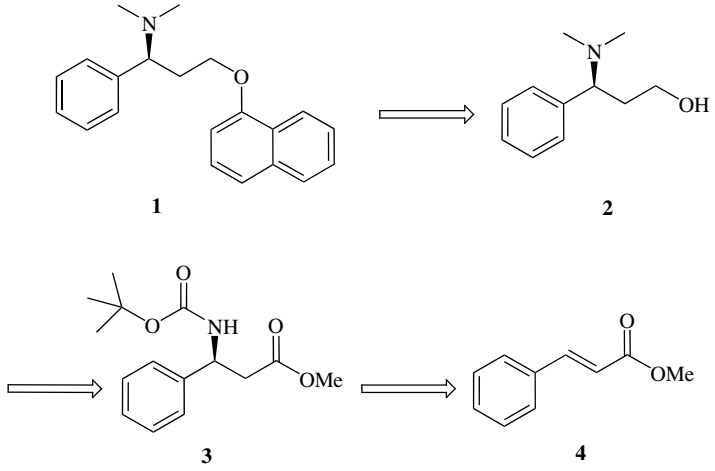
2. Results and discussion

Our retro synthetic strategy for the synthesis of (+)-(*S*)-dapoxetine is outlined in Scheme 1. We envisioned that (+)-(*S*)-dapoxetine **1** could be prepared from amino alcohol **2**, which in turn would be obtained from intermediate **3**, which can be obtained from easily available *trans*-cinnamyl ester **4** by Sharpless asymmetric dihydroxylation as the source of chirality induction.

The synthesis of (+)-(*S*)-dapoxetine was carried out via the synthetic route as shown in Scheme 2. The enantioselective synthesis of (+)-(*S*)-dapoxetine started with the *trans*-cinnamyl ester **4** on subjecting it to asymmetric dihydroxylation under Sharpless conditions using osmium tetroxide and NMO as cooxidant in the presence of the chiral ligand $(DHQ)_2PHAL$ to afford (2*R*,3*S*)-methyl-2,3-dihydroxy-3-phenylpropanoate **5** in 80% yield with 99% ee and $[\alpha]_D^{25} = +3.2$ (*c* 1.19, EtOH).[10b]

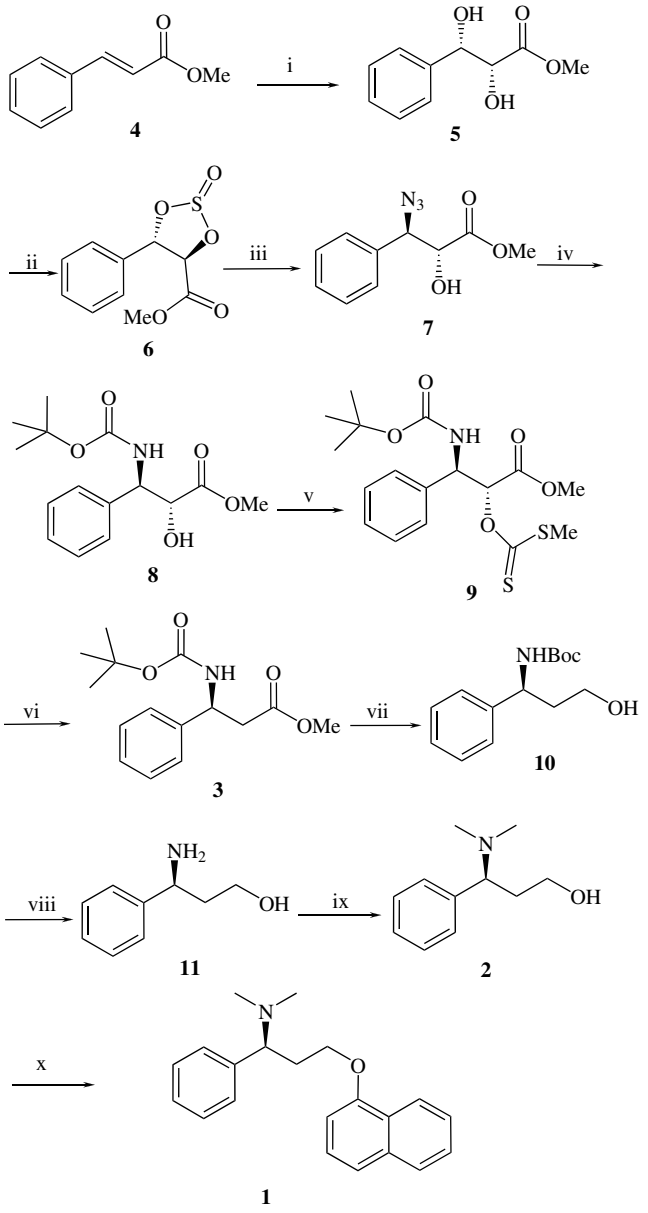
The vicinal diol on treatment with thionyl chloride in the presence of Et_3N in CH_2Cl_2 at 0 °C gave the corresponding cyclic sulfite **6** as a diastereomeric mixture in a 1:1 ratio.[11] Several attempts to oxidize cyclic sulfite **6** to cyclic sulfate were unsuccessful, possibly due to the formation of several by-products, which were difficult to isolate.[12]

The synthetic strategy shown in Scheme 1 was based on the presumption that the nucleophilic opening of cyclic sulfite **6** would occur in a regiospecific manner at the α-carbon atom. Indeed, the cyclic sulfite reacted with NaN_3 with apparent complete selectivity for attack at C-2 to furnish azido alcohol **7** in 85% yield. The aromatic ring must be responsible for the increased reactivity of the α-position. Thus, we turned our attention to reduce the azide and protect it as its Boc derivative. Accordingly, the azide on reaction with Pd/C in EtOAc in the presence of $(Boc)_2O$ and



1 2 3 4

Scheme 1. Retrosynthetic analysis for (*S*)-dapoxetine.



Scheme 2. Reagents and conditions: (i) $(DHQ)_2PHAL$ (5 mol %), OsO_4, NMO, *t*-BuOH, rt, 16 h; (ii) CH_2Cl_2, Et_3N, $SOCl_2$, 0 °C to rt, 1 h; (iii) NaN_3 (5 equiv), DMF, rt, 48 h; (iv) H_2/Pd–C, EtOAc, rt, 24 h, $(Boc)_2O$, Et_3N; (v) MeI, CS_2, MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h; (vi) *n*-Bu_3SnH, AIBN, toluene, reflux, 75% after two steps; (vii) $LiAlH_4$, THF, rt, 12 h; (viii) TFA, DCM, rt; (ix) HCHO, HCOOH; (x) Ph_3P, DEAD, 1-naphthol, THF, rt.

Et_3N delivered the Boc protected **8**.[13] In the IR spectrum disappearance of strong absorption at 2106 cm^{-1} was observed. The ^1H NMR and ^{13}C NMR data were in good agreement with the structure.

Another task was the deoxygenation of the secondary alcohol **8**, which we achieved by converting the corresponding alcohol to its xanthate derivative followed by deoxygenation under the Barton–McCombie[14] protocol using *n*-Bu_3SnH and a catalytic amount of AIBN in toluene under reflux conditions to give product **3** in 75% isolated yield after two steps. The ^1H NMR and ^{13}C NMR-DEPT data were in good agreement with the structure.

The ester group was reduced by LAH in THF to give intermediate **10** in 75% yield. In the IR spectrum, the disappearance of the strong absorption at 1735 cm^{-1} indicative of the reduction of the ester was observed. The Boc group was subsequently deprotected by TFA in chloroform at room temperature to give **11** in good yield. Spectral data of **11** were in good agreement with the known literature values. Then, amine **11** was alkylated using the Clarke–Eschweiler[15] method using formaldehyde and formic acid as the hydrogen source, which gave **2** in 83% isolated yield. The final reaction in the sequence is the coupling between the alcohol hydroxyl of **2** and 1-naphthol for which we attempted the Ullmann protocol, which did not work despite the use of a variety of bases for the study. We ultimately opted for Mitsunobu reaction[16] conditions, which gave (+)-(*S*)-dapoxetine **1** in 72% yield.

3. Conclusion

In conclusion, we have developed an enantioselective total chemical synthesis of (+)-(*S*)-dapoxetine for the first time, comprising of 10 steps in an overall yield of 17% and stereoselectivity of 96% ee.

4. Experimental

4.1. General experimental

The solvents were purified and dried by the standard procedures prior to use; petroleum ether of boiling range 60–80 °C was used. Optical rotations were measured using sodium D line on a JASCO-P-1020-polarimeter. Enantiomeric excess was measured using either the chiral HPLC or by comparison with specific rotation. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer.

4.2. Synthesis of (2*R*,3*S*)-methyl 2,3-dihydroxy-3-phenylpropanoate 5

A 100 mL round-bottomed flask was charged with $(DHQ)_2PHAL$ (0.120 g, 0.5 mol %), *trans*-cinnamyl methyl ester (5 g, 3 mmol), NMO (7.71 mL, 60% w/v in water), and *t*-BuOH (15.42 mL). Under stirring, OsO_4 (0.156 mL, 0.2 mol %) was added. The reaction mixture was stirred at room temperature until completion of the reaction (progress of reaction was monitored by TLC, 24 h) and then poured into a solution of sodium sulfite (6.66 g) in water (22.2 mL). The mixture was stirred at room temperature for 2 h. The organic phase was separated and solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (2×25 mL). The organic phases were combined and washed with 5% aqueous HC1 (2×5 mL) and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the crude diol was pure enough for processing in further steps (single spot on TLC) and was recrystallized from toluene to give **5** (5 g, 83%,) as colorless needles. Mp = 86–87 °C; $[\alpha]_D^{25} = +3.5$ (*c* 1.19, EtOH); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.69$ (br s, 2H), 3.74 (s, 3H), 4.3–4.31 (d, $J = 2.94$ Hz,

1H), 4.94–4.96 (d, $J = 3$ Hz, 1H), 7.19–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 52.5$, 74.3, 74.8, 126.1, 127.8, 128.2, 139.7, 173. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.18; H, 6.02.

4.3. Synthesis of sulfite 6

To a stirred solution of diol **5** (1 g, 0.5 mmol) in dry CH_2Cl_2 (10 mL) cooled at 0 °C was added Et_3N (2.34 g, 1.2 mmol) and a solution of $SOCl_2$ (2.34 g, 1.45 mL, 2.3 mmol) in CH_2Cl_2 (5 mL) was added over a period of 20 min. After the addition was over, the reaction mixture was continued for a further 45 min at 0 °C. After the reaction was over (monitored by TLC), the reaction mixture was quenched by chilled water (10 mL) followed by the addition of CH_2Cl_2 (10 mL). The organic layer was washed with water (3×5 mL), brine (5 mL), dried over $MgSO_4$, and the mixture was filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a yellow oily liquid **6** (1.1g, 90%) (its mixture of diastereomers 1:1), which was separated by flash column chromatography. $[\alpha]_D^{25} = -92.3$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.85$ (s, 3H), 4.82–4.86 (d, $J = 7.51$ Hz, 0.5H), 5.19–5.23 (d, $J = 8.38$ Hz, 0.5H), 5.58–5.62 (d, $J = 8.45$ Hz, 0.5H), 6.15–6.18 (d, $J = 7.44$ Hz, 0.5H), 7.26–7.51 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 53.2$, 81.2, 87.8, 127.8, 129.0, 129.5, 133.9, 166.5.

4.4. Synthesis of (2*R*,3*R*)-methyl-3-azido-2-hydroxy-3-phenylpropanoate 7

To a solution of **6** (1 g, 0.4 mmol) in DMF (10 mL), sodium azide (1.3 g, 2 mmol) was added and the reaction mixture stirred at 80 °C for 48 h (progress of reaction was monitored by TLC) under an argon atmosphere. After the completion of the reaction, the solvent was evaporated under a reduced pressure. The resulting solid mass was dissolved in methanol (20 mL) and filtered through a pad of silica gel–Celite mixture. Methanol was evaporated and the thick solid mass diluted by water (10 mL). The resulting suspension was stirred for 30 min. The suspension was extracted with ethyl acetate (3×5 mL) and the organic layer was separated and washed with water (2×5 mL), dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified further by flash column chromatography to afford **7** as a yellow liquid (0.73 g, 80%). $[\alpha]_D^{25} = -60.0$ (*c* 4.44, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.91$ (br s, 1H), 3.74 (s, 3H), 4.55–4.57 (d, $J = 4.3$ Hz, 1H), 4.90–4.92 (d, $J = 4.3$ Hz, 1H), 7.30–7.41 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 52.5$, 67.1, 73.6, 126.5, 127.6, 128.5, 128.8, 134.2. 171.7. Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.10; H, 4.81; N, 18.78.

4.5. Synthesis of *tert*-butyl (1*R*,2*R*)-2-(methoxy carbonyl)-2-hydroxy-1-phenylethylcarbamate 8

To a solution of **7** (1.5 g, 5.74 mmol) in EtOAc were added Et_3N (0.88 mL, 6.32 mmol), $(Boc)_2O$ (1.45 mL, 6.32 mmol), and 10 % Pd/C (0.05 g). The mixture was stirred at room temperature under a hydrogen atmosphere (1 atm balloon pressure) for 12 h. After the completion of reaction (monitored by TLC), the reaction mixture was filtered off and concentrated under reduced pressure and the residue was further purified by flash column chromatography using light petroleum ether/EtOAc (3:1) as an eluent to afford pure **8** as a white solid (1.761 g, 88%). Mp = 123–124 °C; $[\alpha]_D^{25} = -78.4$ (*c* 1.91, acetone); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.31$ (s, 9H), 3.33 (s, 3H), 5.25–5.29 (d, $J = 9.21$ Hz, 1H), 5.49–5.53 (d, $J = 8.91$ Hz, 1H), 7.27–7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 27.5$, 52.1, 60.6, 74.6, 84.3, 126.5, 128.5, 129.1, 134.9, 148.1, 151.1, 165.8. Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.69; H, 7.02; N, 4.56.

4.6. Synthesis of *tert*-butyl (1*R*,2*R*)-2-(methoxy carbonyl)-2-*O*-(*S*-methyl dithiocarbonate)-1-phenyl ethyl carbamate 9

The reaction vessel was flushed with nitrogen and the nitrogen atmosphere was maintained during the ensuing steps. To a solution of **8** (0.315 g, 1.06 mmol) in THF (10 mL) at 0 °C was added sodium hydride (50% oil dispersion, 0.053 g, 2.2 mmol). Vigorous gas evolution was observed. After the reaction mixture was stirred for 20 min carbon disulfide (0.255 g, 0.202 mL, 3.3 mmol) was added at once. Stirring was continued for the next 30 min after which iodomethane (0.272 g, 0.123 mL, 1.9 mmol) was added in a single portion. The reaction mixture was stirred for another 2 h (progress of reaction mixture was monitored by TLC). On completion, glacial acetic acid (5 mL) was added drop wise to destroy any excess sodium hydride. The solution was filtered and the filtrate was concentrated under reduced pressure. The semisolid residue was extracted with diethyl ether (3×5 mL) and the combined ether extracts were washed with saturated sodium bicarbonate (5 mL) solution and water (5 mL). The ether solution was dried over anhydrous $MgSO_4$, after which the drying agent was removed by filtration, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography, which gave **9** as a pale yellow solid (0.337 g, 82%). Mp = 118–119 °C; $[\alpha]_D^{25} = -47.3$ (*c* 1.13, acetone); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H), 2.56 (s, 3H), 3.62 (s, 3H), 5.37 (d, 1H), 6.12–6.14 (d, $J = 4.94$ Hz, 1H), 7.30–7.40 (m, 5H).

4.7. Synthesis of *tert*-butyl (*S*)-2-(methoxy carbonyl)-1-phenylethyl carbamate 3

To a solution of **9** (0.2 g, 0.519 mmol) in toluene (10 mL), tri-*n*-butyltin hydride (0.453 g, 1.558 mmol), and catalytic amount of AIBN (0.1 mol % w/w based on **9**) were added at room temperature under an inert atmosphere. The reaction mixture was heated at reflux till the completion of reaction (progress of reaction was monitored by TLC). During the course of the reaction, the solution of the reaction mixture changed from deep yellow to nearly colorless. After the reaction was over, toluene was removed under a reduced pressure to give a thick oily residue, which was partitioned between petroleum ether and acetonitrile. The acetonitrile layer was separated and washed with petroleum ether (3×5 mL). The acetonitrile was evaporated under reduced pressure. The crude product separating out was purified by flash column chromatography, which affor-

ded **3** as a solid (0.116 g, 80%). Mp = 95–96 °C; $[\alpha]_D^{25} = -31.5$ (*c* 1.31, acetone); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 2.85–2.87 (q, 2H), 3.61 (s, 3H), 5.08–5.48 (t, 1H), 7.25–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.2$, 40.7, 51.6, 79.6, 126.1, 127.4, 128.5, 155.0, 171.3. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.33;H, 7.19; N, 4.88.

4.8. Synthesis of *tert*-butyl (*S*)-3-hydroxy-1-phenylpropylcarbamate 10

A solution of *tert*-butyl (*S*)-2-(methoxycarbonyl)-1-phenylethylcarbamate **9** (0.1 g, 3.98 mmol) in dry THF (10 mL) was cooled to 0 °C and $LiAlH_4$ (0.06 g, 15.9 mmol) added in small portions. The reaction mixture was refluxed for 2 h following the complete disappearance of the starting material by TLC analysis. The reaction mixture was cooled to 0 °C, and the excess hydride was destroyed by chilled water (5 mL). The gray mixture was extracted by ethyl acetate (3 × 5 mL) and the organic phases were combined, dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The crude mixture separating out was purified by flash column chromatography using petroleum ether and ethyl acetate as eluents, which gave **10** as a white solid (0.073 g, 81%). Mp = 104–105 °C; $[\alpha]_D^{25} = -53.0$ (*c* 1.27, acetone); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.44$ (s, 9H); 1.77–2.17 (m, 2H), 3.66–3.72 (m, 2H), 4.89–5.09 (t, 1H) 7.27–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.2$, 39.3, 51.5, 58.9, 79.9, 126.3, 127.4, 128.7, 141.9, 156.3. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.75; H, 8.29; N, 5.28.

4.9. Synthesis of (*S*)-3-(dimethyl amino)-3-phenylpropan-1-ol 2

To a solution of (*S*)-3-amino-3-phenylpropan-1-ol (0.05 g, 0.19 mmol) in formic acid (39 μL), was added a 30% aqueous solution of formaldehyde (78 μL, 1.05 mmol) and the mixture refluxed over 8 h when the reaction is complete as monitored by TLC. The solution was then acidified with concd HCl to pH 1 and basified with 4 M NaOH. The organic phases were combined, dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The crude was purified by flash column chromatography to give **2** (0.05 g, 85%). $[\alpha]_D^{25} = +39.2$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.66$–1.75 (m, 1H); 2.15 (s, 6H); 2.51–2.68 (m, 1H); 3.39–3.66; (m, 1H); 3.88–3.94 (m, 1H); 7.30–7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 32.1$, 36.4, 63.1, 67.5, 127.1, 127.8, 128.3, 128.8, 128.9, 136.1. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.44; H, 9.27; N, 7.65.

4.10. (*S*)-*N*,*N*-Dimethyl-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine 1

To a solution of **2** (20 mg, 0.11 mmol) in dry THF (2.4 mL) under a nitrogen atmosphere was added 1-naphthol (32 mg, 0.22 mmol). The mixture was cooled to 0 °C and PPh_3 (0.22 mmol) and DEAD (0.22 mmol) were successively added. The solution was allowed to warm till room temperature and then stirred further for 15 h. After the reaction was completed (progress of reaction monitored by TLC), the solution was evaporated and the crude product was purified by flash column chromatography using EtOAc/MeOH mixture, which afforded (*S*)-dapoxetine as a colorless oil (0.02 g, 74%). $[\alpha]_D^{25} = +64.2$ (*c* 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.22$ (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), 7.7–7.74 (m, 1H), 7.95–8.21 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 32.0$, 36.4, 63.1, 67.5, 104.5, 120.1, 127.1, 127.4, 127.8, 128.3, 128.9, 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, 82.19; H, 7.38; N, 4.31.

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References

1. Melloni, P.; Della Torre, A.; Lazzari, E.; Mazzini, G.; Alberto, B.; Matilde, B.; Ottorino, X.; Sante, R.; Alessandro, R. C. *Eur. J. Med. Chem.* **1984**, *19*, 235.
2. Federsel, H. J. *CHEMTECH* **1993**, *23*, 24.
3. Feret, B. *Formulary* **2005**, *40*, 227.
4. Anon, N. Z. *Drugs R&D* **2005**, *6*, 307.
5. Modi, N. B.; Dresser, M. J.; Simon, M.; Lin, D.; Desai, D.; Gupta, S. *J. Clin. Pharmacol.* **2006**, *46*, 301.
6. http://www.jnj.com.
7. Torre, O.; Gotor-Fernandez, V.; Gotor, V. *Tetrahedron: Asymmetry* **2006**, *17*, 860.
8. Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4005.
9. (a) Robertson, D. W.; Thompson, D. C.; Wong, D. T. Eur. Pat. Appl. EP 288188 A1 19881026, 1988; (b) Livni, E.; Satterlee, R. W.; Robey, R. L.; Alt, C. A.; Van Meter, E. E.; Babich, J. W.; Wheeler, W. J.; O'Bannon, D. D.; Thrall, J. H. *Nucl. Med. Biol.* **1994**, *21*, 669.
10. (a) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725; (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; (c) Wang, Z.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104; (d) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843; (e) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2005**, *70*, 4209; (f) Siddiqui, S. A.; Narkhede, U. C.; Lahoti, R. J.; Srinivasan, K. V. *Synlett* **2006**, 1771.
11. Byun, H. S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
12. Sayyed, I. A.; Sudalai, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3111.
13. Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3238.
14. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
15. (a) Eschweiler, W. *Chem. Ber.* **1905**, *38*, 880; (b) Clarke, H. T. *J. Am. Chem. Soc.* **1933**, *55*, 4571; (c) Moore, M. L. *Org. React.* **1949**, *5*, 301.
16. (a) Mistunobu, O. *Synthesis* **1981**, 1; (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.