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Stereoselective synthesis of (*S*)-dapoxetine: A chiral auxiliary mediated approach

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Abstract— An imidazolidin-2-one chiral auxiliary mediated acetate aldol reaction was explored in the enantioselective synthesis of (*S*)-dapoxetine (SSRI). The diastereoselective aldol adduct was transformed to highly enantiopure (*S*)-dapoxetine with overall good yield.

Several drugs possess one or more chiral centres and are found to interact stereoselectively with their receptors. Hence asymmetric synthesis of drugs always outweighs the nonstereoselective methods. Selective Serotonin Reuptake Inhibitors (SSRIs) are most widely prescribed for treating depression and have been proven to be safer as well as effective than other classes of antidepressants by virtue of their high specificity.[1] SSRIs increase the concentration of serotonin selectively by inhibiting its reuptake at the neuronal junction.[2] Some of the commercially well known SSRI medications are illustrated in Figure 1. Based on our interests in chiral auxiliary mediated synthesis of natural products and drug scaffolds,[3] we had recently reported the stereoselective synthesis of (*R*)- and (*S*)-fluoxetine.[3h] Herein, we further extend our inquisitions on another SSRI by exploring a stereoselective synthesis of (*S*)-dapoxetine. Dapoxetine, initially marketed as an antidepressant, has been recently used for the treatment of premature ejaculation.[4] It is reported to have a rapid absorption and elimination from the body and was evaluated safe when used in combination with other existing drugs for erectile dysfunction such as sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levittra).[5]

The (*S*) enantiomer of dapoxetine is 3.5 times more potent than its counterpart.[6] However, there are only a few reports available on its stereoselective synthesis. The earlier methods include chiral/enzymatic resolution,[7] and radiochemical synthesis[8] whereas the newer approaches encompass asymmetric dihydroxylation of *trans* methyl cinnamate or cinnamyl alcohol,[9] chiral azetidin-2,3-dione,[10] asymmetric C-H amination reactions of a prochiral sulfamate,[11] oxazaborolidine reduction[12] of 3-chloropropiophenone or ketone and recently reported *Carica papaya* lipase (CPL) catalyzed enantioselective alcoholysis.[13]

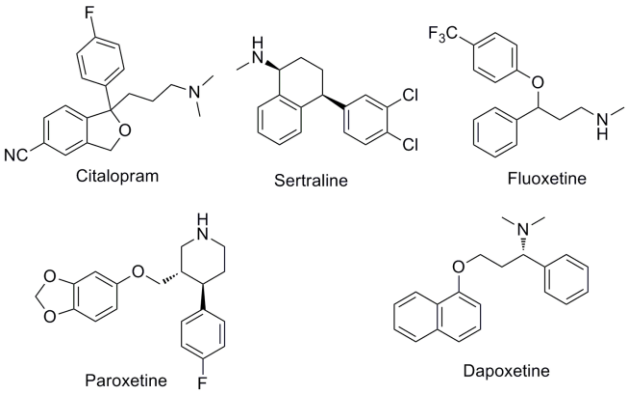

Figure 1. Selective Serotonin Reuptake Inhibitors (SSRIs).

The above mentioned methods are undermined by poor yields/low enantio selectivities/complex synthetic procedures. We therefore envisioned a simple asymmetric induction strategy through a chiral auxiliary mediated acetate aldol reaction. The resulting aldol adduct could be subjected to undergo functional group transformations to yield (*S*)-dapoxetine.

The retrosynthetic analysis is illustrated in Scheme 1. The preferential selection of *N*-acetyl-(*S*)-4-isopropyl-1-

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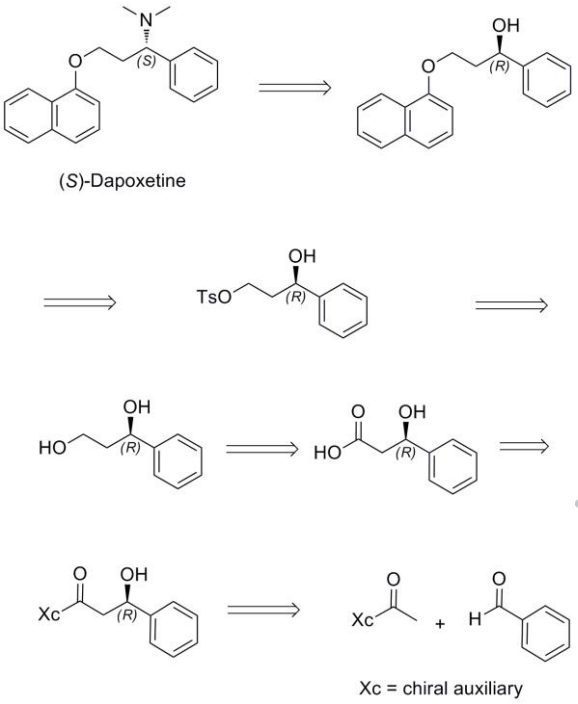
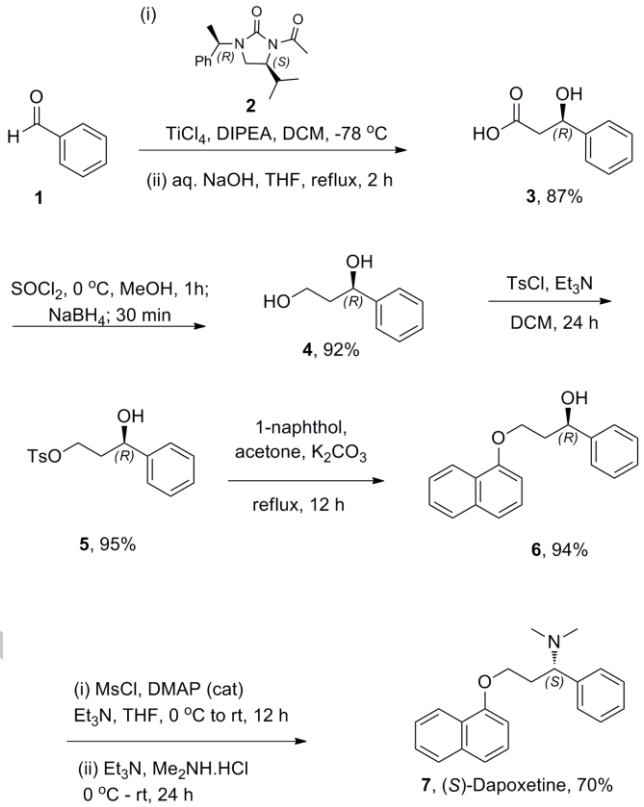
[(*R*)-1-phenylethyl]imidazolidin-2-one (**1**) as a chiral auxiliary was based on our previous investigations.[3h] The chiral auxiliary was subjected to reaction with *N,N*-diisopropylethylamine (DIPEA) and titanium tetrachloride at -78 °C under anhydrous conditions for enolate generation. Subsequent reaction with benzaldehyde afforded the s*yn:anti* acetate aldol product with a diasteroselectivity of 99:01 respectively (determined by ^{1}H NMR of the crude product).[3h]



Scheme 1. Retrosynthetic analysis.

Cleavage of the auxiliary from the *syn* aldol adduct with aq. NaOH afforded (*R*)-3-hydroxy-3-phenylpropanoic acid (**3**) with high enantiopurity without any racemization. The absolute configuration of the acid was confirmed by comparing the optical rotation {$[\alpha]_D^{20}$ +55.9 (*c* 1.00, $CHCl_3$)} with the reported value.[4h,14] (*R*)-3-Hydroxy-3-phenylpropanoic acid (**3**) was then subjected to esterification using thionyl chloride in methanol and subsequently reduction with $NaBH_4$ afforded (*R*)-1-phenylpropan-1,3-diol (**4**)**.** A selective primary hydroxyl tosylation[15] using TsCl succeeded by a nucleophilic substitution with 1-naphthol in the presence of K_2CO_3 afforded (*R*)-3-(naphthalen-1-yloxy)-1-phenylpropan-1-ol (**6**) in excellent yield.

Attempts to isolate the *O*-mesylated derivative of **6** failed due to the product instability. However, *in situ* generation of the mesylated product at 0 °C under anhydrous atmosphere followed by reaction with dimethyl amine solution in THF afforded (*S*)-dapoxetine (**7**) in 42% yield. Volatility of dimethylamine was reasoned for the low yield. We assumed that this problem could be resolved by using a dimethyl amine salt that would release the free amine *in situ* upon treatment with triethylamine, and further react with the mesylated adduct.



Scheme 2. Stereoselective synthesis of (*S*)-dapoxetine.

Accordingly an aq. solution of dimethylamine was reacted with conc. HCl in equimolar amounts and dried under vacuum to yield the dimethylamine hydrochloride salt ($Me_2NH.HCl$) as a white solid. Further its reaction, in the presence of triethylamine, with the *in situ* generated mesylate product had improved the yield to 70% (Scheme 2).[16] The product was confirmed by the spectral data and specific rotation $[\alpha]_D^{20}$ +65.9 (c 1.00, $CHCl_3$), which were in complete agreement with the reported values.[9a]

In conclusion, the stereoselective synthesis of (*S*)-dapoxetine was successfully achieved in 50% overall good yield by utilizing a chiral auxiliary mediated approach through an asymmetric acetate aldol reaction as the key steps.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at www.elsevier.com/locate/tetlett.

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16. *Experimental:*

Synthesis of (R)-3-hydroxy-3-phenylpropanoic acid (**3**).

To a solution of (*S*)-3-acetyl-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one (**1,** 3 g, 11 mmol, 1.0 equiv) in anhydrous DCM (50 mL, dried over calcium hydride) and under N_2 environment, was added $TiCl_4$ solution (22 mL, 22 mmol, 2.0 equiv, 1 M in DCM) at –78 °C. The reaction mixture was warmed to 0 °C, stirred for 10 min and again cooled to –78 °C. To this reaction mixture, DIPEA (2 mL, 11 mmol, 1.0 equiv) was added and stirred for 1 h. Further benzaldehyde (1.25 mL, 12 mmol, 1.1 equiv) was introduced into it and stirred for 30 min. The reaction mixture was quenched with water and extracted with DCM, further product was purified (yield 3.8 g) and dissolved in THF (50 mL) was added aq NaOH (0.8 g, 20 mmol, 2.0 equiv, 20 mL H_2O) and refluxed for 2 h. The reaction mixture was extracted with DCM to remove auxiliary, and then aqueous layer was acidified upto pH ~3 with dil. HCl. The resulting solution was extracted with ethyl acetate, dried and concentrated to afford **3** (yield 2 g, 87%).

White solid; Mp 115–119 °C; $[\alpha]_D^{20}$ +55.9 (c 1.00, $CHCl_3$. ^1H NMR (400 MHz, $CDCl_3$) δ 2.72–2.85 (m, 2H), 5.15 (dd, J = 9.29, 3.76 Hz, 1H), 7.28–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.04, 70.24, 125.69, 128.00, 128.66, 142.18, 176.55; HRMS (ESI-TOF) calcd for $C_9H_{10}O_3$ $[M]^+$:166.0630; found: 166.1227; and $C_9H_{10}O_3Na$ $[M+Na]^+$: 189.0528; found: 189.1081.

Synthesis of (R)-1-phenylpropane-1,3-diol (**4**).

A solution of **3** (1.2 g, 7.23 mmol, 1.0 equiv.) in methanol (20 mL) was cooled to 0 °C and $SOCl_2$ (0.53 mL, 7.23 mmol, 1.0 equiv) was added to it. The reaction mixture was stirred for 1h and then $NaBH_4$ (0.21 g, 5.54 mmol, 1.0 equiv) was added to it and then stirred for another 30 min. The reaction was quenched with water, and methanol was evaporated under reduced pressure. The crude product was extracted into ethyl acetate, dried over anhydrous sodium sulfate and concentrated to afford **4** (yield 0.78 g, 92%).

White solid; Mp 60–64 °C; $[\alpha]_D^{20}$ +59.1 (c 1.00, $CHCl_3$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83–1.93 (m, 2H), 3.65–3.88 (m, 2H), 4.92 (dd, J = 8.78, 3.76 Hz, 1H), 5.32 (brs, 2H), 7.19–7.29 (m, 1H) 7.29–7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.35, 61.01, 73.79, 125.67, 127.49, 128.46, 144.23; HRMS (ESI-TOF) calcd for $C_9H_{12}O_2$ ($[M+Na]^+$): 175.0735; found: 175.0733.

Synthesis of (R)-3-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate (**5**).

To a solution of **4** (0.7 g, 4.59 mmol, 1.0 equiv.) in DCM (20 mL) at 0 °C was added triethylamine (1.27 mL, 9.18 mmol, 2.0 equiv) and a solution of tosyl chloride (0.96 g, 5.04 mmol, 1.1 equiv) in DCM (10 mL). The reaction mixture was allowed to stir at rt for 24 h. It was then extracted with ethyl acetate, washed with aq $NaHCO_3$, dried over anhydrous sodium sulfate and concentrated under vacuum to afford **5** (yield 1.44 g, 95%).

Gummy; $[\alpha]_D^{20}$ – 16.4 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.00–2.04 (m, 3H), 2.45 (s, 3H), 4.03–4.08 (m, 1H), 4.25– 4.31 (m, 1H), 4.80 (t, J = 6.6 Hz, 1H), 7.26– 7.31 (m, 5H), 7.34 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.67, 38.07, 67.63, 70.18, 125.55, 127.95, 128.50, 128.61, 129.90, 132.92, 143.54, 144.86; HRMS (ESI-TOF) calcd for $C_{16}H_{18}O_4SNa$ $[M+Na]^+$: 329.0823; found: 329.0826.

Synthesis of (R)-3-(naphthalen-1-yloxy)-1-phenylpropan-1-ol (**6**).

A mixture of **5** (1.0 g, 3.26 mmol, 1.0 equiv.), 1-naphthol (0.51 g, 3.59, 1.1 equiv) and K_2CO_3 (1.35 g, 7.78 mmol, 3.0 equiv) in acetone (50 mL) was refluxed for 12 h. The

reaction mixture was cooled and acetone was evaporated. It was extracted with ethyl acetate, dried over anhydrous sodium sulphate and concentrated to afford the crude product which was purified by column chromatography [silica gel (60-120 mesh), eluent hexanes:EtOAc = 9:1] to afford the **6** (yield 0.89 g, 94%).

White solid; Mp 71–74 °C; $[\alpha]_D^{20}$ –30.5 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.31–2.41 (m, 2H), 2.42 (d, J = 3.1 Hz, 1H), 4.16–4.23 (m, 1H), 4.31–4.36 (m , 1H), 5.12–5.14 (m, 1H), 6.79 (d, J = 7.5 Hz, 1H), 7.28–7.31 (m, 1H), 7.33–7.37 (m, 3H), 7.41–7.43 (m, 3H), 7.45–7.53 (m, 2H), 7.79–7.81 (m, 1H), 8.23–8.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.72, 38.50, 65.39, 104.79, 120.08, 121.97, 125.09, 125.60, 125.85, 126.32, 127.45, 127.64, 128.38, 128.67, 134.44, 138.76, 154.52; HRMS (ESI-TOF) calcd for $C_{19}H_{18}O_2Na$ $[M+Na]^+$: 301.1204; found: 301.1204.

Synthesis of (S)-dapoxetine **7**.

A solution of **6** (0.5 g, 1.8 mmol, 1.0 equiv.), triethylamine (0.75 mL, 5.4 mmol, 3.0 equiv) and DMAP (0.02 g, 0.18 mmol, 0.1 equiv) in THF (20 mL) was cooled to 0 °C. To this reaction mixture, mesyl chloride (0.41 mL, 3.6 mmol, 2.0 equiv) was added and stirred for 12 h at rt. The reaction mixture was cooled to 0 °C and to this excess triethyl amine (0.75 mL, 5.4 mL, 3.0 equiv) followed by $Me_2NH.HCl$ (0.44 g, 5.4 mmol, 3.0 equiv,) was added. The reaction mixture was then stirred at rt for another 24 h. It was extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated to afford crude which was purified by column chromatography [silica gel (60-120 mesh), eluent DCM:MeOH = 9:1] to afford an oily compound **7** (yield 0.38 g, 70%).

$Me_2NH.HCl$ was prepared from aq. dimethylamine solution (5.0 mL, 40%) by the addition of conc. HCl (5.0 mL, 35%) at 0°C. The reaction mixture was stirred for 0.5 h and then the water was evaporated.The solid fraction was azeotroped thrice with toluene to afford white solid compound (3.0 g), which was stored under inert atmosphere.

Liquid; $[\alpha]_D^{20}$ +65.9 (c 1.00, $CHCl_3$), lit[9a] $[\alpha]_D^{25}$ +64:2 (c 0.3,$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 6H), 2.33–2.35 (m, 1H), 2.65–2.70 (m, 1H), 3.68 (dd, J = 9.4, 5.1 Hz, 1H), 3.85–3.91 (m, 1H), 4.05–4.10 (m, 1H), 6.63 (d, J = 7.6 Hz, 1H), 7.28–7.35 (m, 6H), 7.38 (d, J = 8.2 Hz, 1H), 7.44–7.50 (m, 2H), 7.76–7.79 (m, 1H), 8.20–8.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.79, 42.69, 65.46, 67.87, 104.57, 120.08, 121.97, 125.09, 125.60, 125.85, 126.32, 127.45, 127.64, 128.38, 128.67, 134.44, 138.36, 154.52; HRMS (ESI-TOF) calcd for $C_{21}H_{24}NO$ $[M+H]^+$: 306.1858; found: 306.1860; and $C_{21}H_{23}NONa$ $[M+Na]^+$: 328.1677; found: 328.1677.

Graphical Abstract

Stereoselective synthesis of (*S*)-dapoxetine: A chiral auxiliary mediated approach

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