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Chemoenzymatic asymmetric synthesis of fluoxetine, atomoxetine, nisoxetine, and duloxetine

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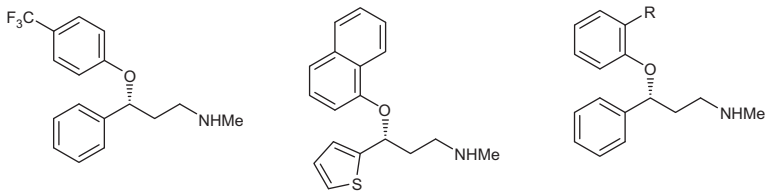
ABSTRACT

The asymmetric synthesis of two well-known anti-depressant drugs, fluoxetine and duloxetine has been accomplished in a chemoenzymatic manner. The main highlight of the synthesis is the enantioselective cyanohydrin formation by a plant (*R*)-HNL (hydroxynitrile lyase). The enantiopure cyanohydrins are then synthetically manipulated into the above two drug molecules and two of their structural analogues, atomoxetine and nisoxetine.

1. Introduction

Selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitor (SSRIs) are a class of organic molecules generally used as antidepressants for the treatment of several depression related disorders. They are believed to enhance the extracellular level of serotonin (the well-known neurotransmitter) by inhibiting its reuptake in the presynaptic cell.[1] Serotonin–norepinephrine reuptake inhibitors (SNRIs) are another class of organic molecules used mainly in the treatment of major depression. In principle, SNRIs are able to increase the level of two neurotransmitters (serotonin and norepinephrine) in the brain which are known to play an important role in mood related phenomenon.[2] Fluoxetine (known as Prozac, Saraferm, Fomtex as brand names) belongs to the SSRI class and is a very well-known antidepressant developed by Eli-Lilly in 1987. Fluoxetine was a blockbuster drug during the early 1990s and its estimated annual sales reached US$350 million within a year, as the drug was off patented in 2001 several generic versions came into the market. Duloxetine (sold under the brand name Cymbalta, Ariclaim, Duzela, Yentreve, and a few others) belongs to the SNRI class and was manufactured and marketed by Eli-Lilly and used mainly in the treatment of major depression and general anxiety disorder (GAD). Atomoxetine is another drug that belongs to the norepinephrine reuptake inhibitor (NRI or NERI) class and acts as a reuptake inhibitor of norepinephrine.[3] It blocks the action of norepinephrine transporter receptor and hence leads to enhanced concentration of that neurotransmitter in adrenergic neurotransmission. Atomoxetine was manufactured by Eli-Lilly and sold under the brand name Strattera worldwide and is approved for the treatment of ADHD (attention deficit hyperactivity disorder).[4] Nisoxetine, which is structurally similar to fluoxetine and atomoxetine was first synthesized by Eli-Lilly in 1970; it also belongs to the NRI class, and while it was not marketed, it was used widely in biochemical experiments as a selective NRI agent.

All of the aforementioned molecules have a common structural unit, *N*-methyl-3-aryloxy-3-aryl-proylamine (Fig. 1) hence a common intermediate would be effective for accessing all of these molecules in an efficient way. Numerous synthetic reports exist in the



(*R*)-fluoxetine **1** (*R*)-duloxetine **2** R = Me, (*R*)-atomoxetine **3**
R = OMe, (*R*)-nisoxetine **4**

Figure 1. Structure of the (*R*)-enantiomer of fluoxetine, duloxetine, atomoxetine, and nisoxetine.

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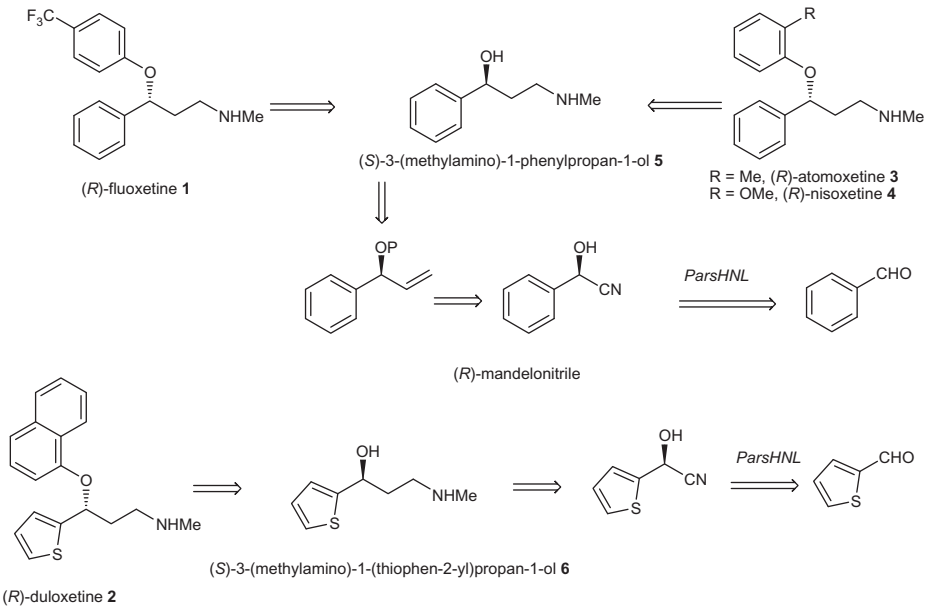
literature describing the asymmetric synthesis of all of the four molecules.[5]

2. Results and discussion

To the best of our knowledge enantiopure cyanohydrins have not been used as chiral intermediates for the synthesis of the above molecules. Although fluoxetine was sold as a racemic compound, it was later shown that the (*R*)-enantiomer is the so-called 'Improved Chemical Entity' version of the drug.[6] Herein we report the asymmetric synthesis of the (*R*)-enantiomer of all of these four molecules from enantiopure cyanohydrins. The retrosynthetic analysis is presented below (Scheme 1). One of the most promising and interesting way to synthesize enantiomerically pure cyanohydrins is the HNL catalyzed addition of a cyanide source to the respective carbonyl compounds.[7] HNLs are now widely used as efficient biocatalysts for the asymmetric synthesis of various cyanohydrins. The resulting cyanohydrins are versatile intermediates for a broad variety of chiral synthons. The reaction is extremely important, since it allows the synthesis of enantiomerically pure compounds from prochiral substrates in a quantitative yield.

from the corresponding γ,δ-unsaturated aldehydes with excellent enantioselection.[8b] We have also synthesized some novel enantiopure aromatic cyanohydrins from the respective aromatic aldehydes.[8c] At this point we thought that it would be appropriate to use the new enzyme *ParsHNL* for the asymmetric biocatalytic synthesis of a few enantiopure cyanohydrins which can be synthetically manipulated to drug molecules such as fluoxetine, atomoxetine, nisoxetine, and duloxetine.

We have started our synthesis from commercially available benzaldehyde. An asymmetric hydrocyanation reaction with *Prunus armeniaca* hydroxynitrile lyase (*ParsHNL*) and HCN in DIPE (diisopropyl ether) solvent afforded the corresponding (*R*)-cyanohydrin [(*R*)-mandelonitrile] in 92% yield (er = 98%). The enzymatic hydrocyanation with hydroxynitrile lyase is a well documented strategy for the asymmetric synthesis of cyanohydrins, and we have explored the methodology extensively by using an (*R*)-HNL (*hydroxynitrile lyase* from *Prunus armeniaca*) from Himalayan apricot (Shakarpara cultivar). The reaction is very efficient in terms of chemical yield and excellent enantioselection is obtained in the product cyanohydrin. (*R*)-Mandelonitrile serves as a chiral intermediate for the synthesis of fluoxetine, atomoxetine, and nisoxetine.



Scheme 1. Retrosynthetic analysis of fluoxetine, atomoxetine, nisoxetine, and duloxetine by enzymatic hydrocyanation.

We envisioned that (*S*)-3-(methylamino)-1-phenylpropan-1-ol **5** could act as a common intermediate for the synthesis of the (*R*)-enantiomer of fluoxetine **1**, atomoxetine **3**, and nisoxetine **4** by Mitsunobu inversion with the required phenols. In the case of duloxetine **2**, the Mitsunobu reaction of 1-naphthol with (*S*)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol **6** would lead to the target molecule. The intermediates **5** and **6** were planned to be synthesized from the respective cyanohydrins by straightforward synthetic manipulation. The enantiopure cyanohydrins were accessed from their respective aldehydes by an HNL route developed earlier in our group. Recently we have found a new (*R*)-HNL from white apricot (shakarpara cultivar, found in the Himalayan region of Nepal and India; *Prunus armeniaca*). The new enzyme (*ParsHNL*) exhibits excellent enantioselectivity during the preparation of several cyanohydrins from aliphatic and aromatic carbonyl compounds.[8] By employing this newly found HNL we have synthesized several enantiopure δ,ε-unsaturated cyanohydrins

2-Thiophene-carboxaldehyde was subjected to an asymmetric hydrocyanation reaction by employing similar reaction conditions as stated above. The respective enantiopure cyanohydrin was obtained in 88% yield with excellent enantioselection (er = 97%). In general, we followed the modified method developed by Griengl et al.[9] for the HNL catalyzed hydrocynation reaction (see Section 4 for details).

With the enantiopure cyanohydrins in hand, we then proceeded further for the total synthesis of the target molecules. (*R*)-Mandelonitrile was protected as its TBS (*tert*-butyldimethyl silyl) ether by treatment with imidazole and TBS–Cl at 25 °C to afford the protected cyanohydrin **7** in 88% yield. Compound **7** was not purified further, and so the crude mixture of **7** was subjected to DIBAL-H treatment at −78 °C for 2 h, which yielded the corresponding aldehyde **8** in almost quantitative yield. The aldehyde after usual work-up (no chromatographic separation is needed) was subjected to one carbon Wittig olefination with $Ph_3P{=}CH_2$ to afford olefin **9** in

82% yield. Compound **9** upon hydroboration with BH_3 SMe_2 afforded the corresponding alcohol **10** in 86% yield (no chromatographic separation was needed). Alcohol **10** was then treated with methanesulfonyl chloride (Ms-Cl) and Et_3N to furnish the respective mesylate **11** in 90% yield (no chromatographic separation is needed). Mesylate **11** upon treatment with an aq. solution of 40% $MeNH_2$ in refluxing THF afforded the corresponding amine **12** in 78% yield. Desilylation (TBS deprotection) of compound **12** was achieved by treatment with TBAF/THF to afford aminoalcohol **5** in 88% yield (no chromatographic separation was needed). Mitsunobu reaction[10] of **5** with 4-trifluromethyl phenol, 2-methyl phenol, and 2-methoxy phenol afforded fluoxetine **1** (overall yield = 23%), atomoxetine **3** (overall yield = 24.7%), and nisoxetine **4** (overall yield = 23.5%), respectively, (Scheme 2). For the synthesis of (*R*)-duloxetine, a similar reaction sequence was applied starting from (*S*)-2-hydroxy-2-(thiophen-2-yl)acetonitrile. By following a similar strategy, we obtained compound **6** in good yield. The Mitsunobu reaction of compound **6** with 1-naphthol afforded the target molecule (*R*)-duloxetine (overall yield = 21% from compound **13**).

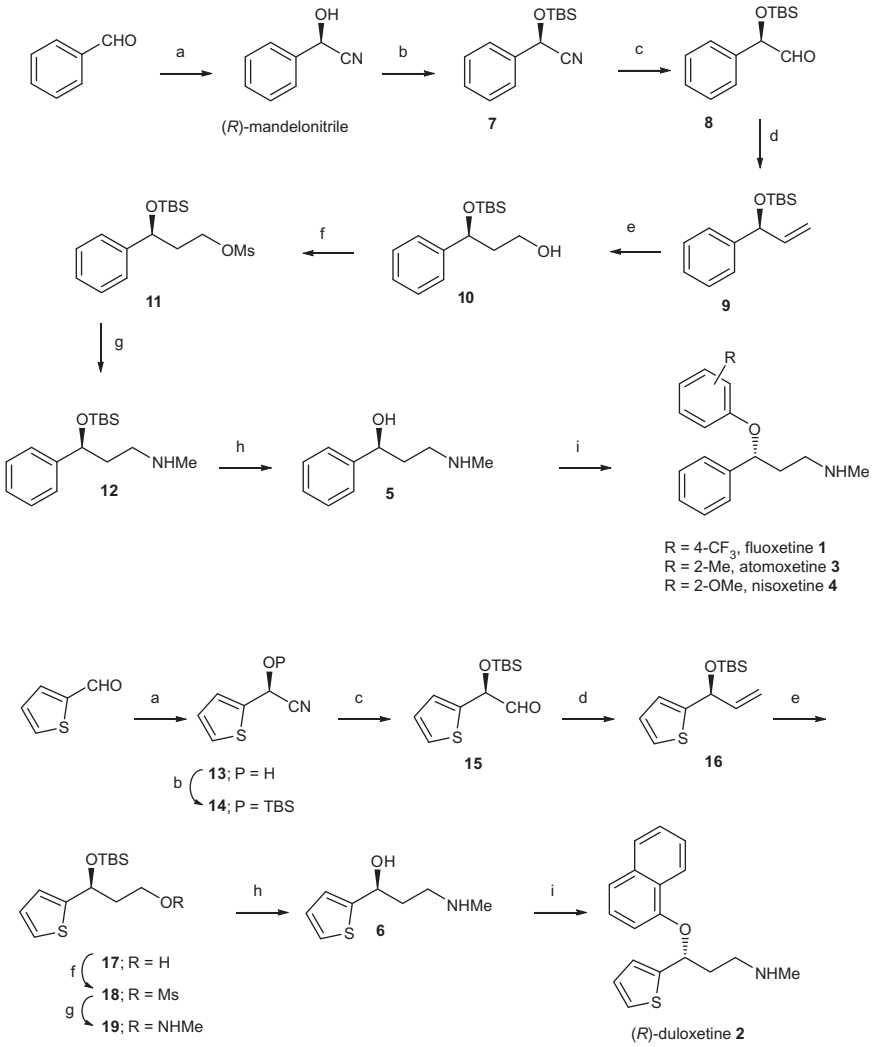
3. Conclusion

In conclusion, we have reported an efficient and general synthetic strategy for the enantiopure synthesis of a few important antidepressant drug molecules. The main highlight of our synthesis is the enzymatic formation of enantiopure cyanohydrins from their respective aldehydes by a plant HNL (*ParsHNL*). The enantiopure cyanohydrins were then synthetically manipulated to the target molecules. It is also noteworthy that out of the nine synthetic steps employed, we have used chromatographic purification methods in only three steps. As a result, the synthesis is cost effective and green also, as chromatographic separation in some steps is avoided.

4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. Benzaldehyde and thiophene-2-carbaldehyde were freshly distilled or



Scheme 2. Reagents and conditions: (a) HCN in iPr_2O, *ParsHNL*, citrate buffer (pH 4.0), 92% (90% for **13**); (b) imidazole, TBS–Cl, rt, 88% (92% for **14**); (c) DIBAL-H, −78 °C; (d) LHMDS, $Ph_3P^+MeI^-$, 0 °C, 82% (75% for **16**); (e) BH_3 SMe_2, 0 °C, H_2O_2, NaOH, 86% (84% for **17**); (f) $MeSO_2Cl$, Et_3N, DMAP, 90% (88% for **18**); (g) $MeNH_2$ (40% aq), THF, 78% (72% for **19**); (h) TBAF, THF, 88% (90% for **6**); (i) Ph_3P, DIAD, THF, Ar-OH.

washed with an aq $NaHCO_3$ solution in order to minimize the amount of free acid, which is supposed to inhibit HNL activity. The enzymatic hydrocyanation reactions were performed in well ventilated fume hoods with proper glassware, handware (gloves), and using a mask if necessary. Any excess HCN remaining after the reaction was destroyed cautiously by treatment with an excess of bleach solution and disposed of in a proper way. Reactions were monitored by TLC, carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 200 MHz spectrometer at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Chiral HPLC was performed using chiral OJ-H column (0.46 × 25 cm, Daicel industries) with Shimadzu Prominence 20AT and UV–vis detector (254 nm). Eluting solvent used was different ratios of hexane and 2-propanol.

4.2. (*R*)-2-Hydroxy-2-phenylacetonitrile

To a solution of benzaldehyde (1.06 g, 1.0 mol) in DIPE (60 ml), a solution of *ParsHNL* (300 IU/10 mmol of aldehyde, approximately 10 ml of crude enzyme solution) was added and the resulting mixture was stirred vigorously until an emulsion was formed. The pH of the enzyme solution was previously adjusted to 4.0 with 10% citric acid solution. Freshly prepared HCN in DIPE (2 equiv) was added to it, and the temperature of the solution was kept at 10 °C. After completion of the reaction, it was extracted thoroughly with ether several times and the organic layer was dried over $MgSO_4$. Evaporation of the solvent yielded the crude cyanohydrin in 92% yield. The (*R*)-mandelonitrile obtained provides comparable spectroscopic and optical data with those reported in the literature.[11]

4.3. Preparation of HCN in DIPE

At first, NaCN (10 g) and citric acid (0.1 g) were dissolved in water (100 ml). The solution was cooled in an ice/water bath and extracted with DIPE (50 ml), while acidifying with 33% HCl until pH 5.5. The water layer, which contained a suspension of NaCl, was extracted twice with DIPE (25 ml). The combined DIPE layers were stored in a dark bottle. The above procedure must be performed in a well ventilated fume hood with proper glassware and handware (gloves).

4.4. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylacetonitrile 7

(*R*)-Mandelonitrile (500 mg, 3.75 mmol) was taken in anhydrous DCM (15 ml) and cooled to 0 °C. Imidazole (281 mg, 4.13 mmol) and DMAP (catalytic) were then added to the reaction mixture followed by the addition of TBS–Cl (620 mg, 4.13 mmol). The reaction mixture was then allowed to warm at room temperature for 6 h, after which water was added to it and the organic layer was diluted with DCM, washed with brine and dried over $MgSO_4$. Evaporation afforded the TBS-protected compound in 88% yield. The TBS protected cyanohydrin is used in the next step without further purification.

4.5. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylacetaldehyde 8

The crude TBS protected cyanohydrin (815 mg, 3.3 mmol) was taken in 10 ml of dry DCM under an argon atmosphere. To this solution was added DIBAL-H (1 M in DCM, 3.3 ml), dropwise at −45 °C, and the mixture was warmed up to 0 °C. After stirring for 1 h at this temperature, the reaction mixture was poured into a mixture of ether and saturated aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. It was then concentrated in a rotary evaporator which yielded the corresponding aldehyde **8** in almost quantitative yield, which was used in the next step without any further purification. $[\alpha]_D^{28} = -19.5$ (*c* 0.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 9.54 (d, *J* = 2 Hz, 1H), 7.42–7.30 (m, 5H), 5.04 (d, *J* = 2.2 Hz, 1H), 0.97 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 199.6, 136.7, 128.8, 128.5, 126.5, 80.1, 25.9, 18.4, −4.6.

4.6. ((*S*)-1-Phenylallyloxy)(*tert*-butyl)dimethylsilane 9

To a suspension of methyltriphenylphosphonium iodide (1.5 g, 3.74 mmol) in dry THF was added LiHMDS (3.4 ml) at 0 °C. The yellow mixture was stirred at 0 °C for 15 min. A solution of the aldehyde **8** (800 mg, 3.23 mmol) in 10 ml of THF was added to the reaction mixture. The yellow suspension was then stirred at room temperature for a further 1 h. After completion of the reaction, as indicated by TLC analysis, the reaction was quenched with water and the layers were separated. The organic layer was extracted with 50 ml of ether, washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the crude residue was purified by flash column chromatography to afford compound **9** (EtOAc/hexane = 1:20) in 82% yield. $[\alpha]_D^{28} = -31.4$ (*c* 0.9, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.47–7.29 (m, 5H), 6.13–5.96 (m, 1H), 5.44–5.14 (m, 3H), 1.04 (s, 9H), 0.21 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 143.9, 141.9, 128.4, 127.2, 126.2, 113.5, 76.1, 26.1, 18.5, −4.4, −4.5. HRMS (ESI) for $C_{15}H_{24}NaOSi$ $[M+Na]^+$, calcd 271.1494, found: 271.1490.

4.7. (*S*)-3-(*tert*-Butyldimethylsilylyloxy)-3-phenylpropan-1-ol 10

To a cooled (0 °C), stirred solution of **9** (635 mg, 2.56 mmol) in THF (8 ml) was added BH_3 SMe_2 (1.4 ml, 2.8 mmol). The mixture was stirred for an additional 2 h and then quenched with EtOAC (30 ml) followed by the addition of 1 M aqueous NaOH (4.6 ml) and 30% H_2O_2 (4.6 ml) at 0 °C dropwise. The mixture was stirred vigorously for 3.5 h. It was then extracted with EtOAc and washed with brine. The organic solvent was dried ($MgSO_4$), and concentrated to provide the crude alcohol **10** in 86% yield, which was used in the next step without further purification. $[\alpha]_D^{28} = -16.8$ (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.27–7.25 (m, 5H), 4.93–4.87 (m, 1H), 3.75–3.65 (m, 2H), 1.93–1.84 (m, 2H), 0.85 (s, 9H), 0.01 (s, 3H), −0.19 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 144.6, 128.3, 127.3, 125.9, 74.5, 60.3, 42.3, 25.9, 18.2, −4.5, −5.0. HRMS (ESI) for $C_{15}H_{26}NaO_2Si$ $[M+Na]^+$, calcd 289.1600, found: 289.1606.

4.8. (*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-phenylpropyl methanesulfonate 11

To a cooled (0 °C), stirred solution of **10** (681 mg, 2.56 mmol) in DCM (8 ml) were added Et_3N (391 μl, 2.81 mmol) and methanesulfonyl chloride (218 μl, 2.81 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction was then stopped by adding 5 ml of saturated NH_4Cl. The water phase was extracted with DCM twice. The combined extracts were dried and evaporated to furnish the respective mesylate **11** in 90% yield. $[\alpha]_D^{28} = -22.5$ (*c* 1.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.22–7.20 (m, 5H), 4.74 (t, *J* = 6.4 Hz, 1H), 4.31–4.26 (m, 1H), 4.15–4.08 (m, 1H), 2.86 (s, 3H), 2.00–1.93 (m, 2H), 0.80 (s, 9H), −0.03 (s, 3H), −0.26 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 144.1, 128.3, 127.5,

125.8, 71.0, 66.9, 40.1, 37.3, 25.8, 22.6, 18.1, 14.4, −4.6, −5.1. HRMS (ESI) for $C_{16}H_{28}NaO_4SSi$ $[M+Na]^+$, calcd 367.1375, found: 367.1381.

4.9. (*S*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methyl-3-phenylpropan-1-amine 12

A solution of (*S*)-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropyl methanesulfonate **11** (450 mg, 1.30 mmol) and methylamine (9 ml, 40% in water) in THF (9 ml) was heated at 65 °C for 3 h. After cooling, the solution was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, and dried over anhydrous potassium carbonate. After concentration, a pale yellow oil was obtained. The residue was then purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH, 90:5:1) to afford the desired product in 78% yield. $[\alpha]_D^{28} = -19.2$ (*c* 0.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) 7.27–7.26 (m, 5H), 4.77 (t, *J* = 5.8 Hz, 1H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 2.00–1.96 (m, 2H), 0.87 (s, 9H), 0.01 (s, 3H), −0.16 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 144.9, 128.1, 127.1, 125.7, 73.4, 47.7, 39.5, 35.3, 25.8, 18.1, −4.6, −5.0. HRMS (ESI) for $C_{16}H_{29}NNaOSi$ $[M+Na]^+$, calcd 302.1916, found: 302.1921.

4.10. (*S*)-3-(Methylamino)-1-phenylpropan-1-ol 5

Compound **12** (279 mg, 1.0 mmol) was taken in dry THF (3 ml) after which TBAF (1 M in THF, 1.2 ml) was added to it, and the reaction mixture was stirred for 3 h at room temperature, after which THF was evaporated, and water (1 ml) was added to it. The reaction mixture was extracted with EtOAc (10 ml), washed with $NaHCO_3$ and brine, then dried by using $CaCO_3$ and concentrated to afford the desired product **5** in 88% yield, which was subsequently used in the next step without further purification. $[\alpha]_D^{28} = -36.5$ (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.36–7.20 (m, 5H), 4.84 (dd, J_1 = 4.0 Hz, J_2 = 7.8 Hz, 1H), 4.02 (br s, 2H, –NH and –OH), 2.80–2.73 (m, 2H), 2.36 (s, 3H), 1.84–1.72 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 145.2, 128.2, 126.9, 125.6, 74.8, 50.0, 37.0, 35.9. HRMS (ESI) for $C_{10}H_{15}NNaO$ $[M+Na]^+$, calcd 188.1051, found: 188.1056.

4.11. Mitsunobu procedure

Triphenylphosphine (100 mg, 0.4 mmol), and diethyl azodicarboxylate (63 μl, 0.4 mmol) were added to a solution of **5** (66 mg, 0.4 mmol) and the properly substituted phenols (0.4 mmol) in THF (2 ml). The mixture was stirred at room temperature overnight until the reaction was completed (TLC). Next, the THF was removed in vacuo and the residue was extract with EtOAc (3 × 5 ml). The combined organic fractions were concentrated, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH, 97:2:1) to afford the desired product in 60–70% yield.

4.12. (*R*)-3-(4-(Trifluoromethyl)phenoxy)-*N*-methyl-3-phenylpropan-1-amine 1 (fluoxetine)

$[\alpha]_D^{28} = +3.2$ (*c* 1.0, $CHCl_3$). Lit. $[\alpha]_D^{28} = +3.8$ (*c* 0.9, $CHCl_3$).[5f] ^1H NMR (400 MHz, $CDCl_3$): 7.38–7.20 (m, 7H), 6.85–6.81 (m, 2H), 5.32 (dd, J_1 = 4.4 Hz, J_2 = 8.2 Hz, 1H), 2.84–2.81 (m, 2H), 2.47 (s, 3H), 2.29–2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 160.3, 140.5, 128.7, 128.3, 127.9, 126.7, 126.6, 125.7, 115.7, 78.2, 47.7, 35.7, 35.6. HRMS (ESI) for $C_{17}H_{18}F_3NNaO$ $[M+Na]^+$, calcd 332.1238, found: 332.1232.

4.13. (*R*)-3-(*o*-Tolyloxy)-*N*-methyl-3-phenylpropan-1-amine 3 (atomoxetine)

$[\alpha]_D^{28} = -35.0$ (*c* 1.0, $CHCl_3$). Lit. $[\alpha]_D^{28} = -44.0$ (*c* 1.0, MeOH).[5t] ^1H NMR (400 MHz, $CDCl_3$): 7.36–7.22 (m, 5H), 7.11 (d, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 5.25 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 2.78–2.74 (m, 2H), 2.42 (s, 3H), 2.31 (s, 3H), 2.20–2.17 (m, 1H), 2.05–2.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 142.2, 130.8, 129.0, 128.8, 128.5, 127.6, 126.7, 125.9, 125.8, 120.4, 112.9, 78.1, 48.7, 39.0, 36.7, 16.8. HRMS (ESI) for $C_{17}H_{21}NNaO$ $[M+Na]^+$, calcd 278.1521, found: 278.1526.

4.14. (*R*)-3-(2-Methoxyphenoxy)-*N*-methyl-3-phenylpropan-1-amine 2 (nisoxetine)

$[\alpha]_D^{28} = +36.2$ (*c* 1.0, $CHCl_3$). Lit. $[\alpha]_D^{28} = +35.0$ (*c* 1.0, $CHCl_3$).[5o] ^1H NMR (400 MHz, $CDCl_3$): 7.36–7.26 (m, 5H), 6.88–6.87 (m, 2H), 6.70–6.68 (m, 1H), 6.62–6.60 (m, 1H), 5.19 (dd, J_1 = 4 Hz, J_2 = 8.4 Hz), 3.97 (s, 3H), 2.96–2.89 (m, 2H), 2.53 (s, 3H), 2.36–2.29 (m, 1H), 2.10–2.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 149.7, 147.1, 141.2, 128.6, 127.7, 125.8, 121.7, 120.7, 116.1, 81.1, 55.9, 48.2, 36.9, 35.1, 11.7. HRMS (ESI) for $C_{17}H_{21}NNaO_2$ $[M+Na]^+$, calcd 294.1470, found: 294.1474.

4.15. (*S*)-2-Hydroxy-2-(thiophen-2-yl)acetonitrile 13

$[\alpha]_D^{28} = +42.2$ (*c* 1.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.33–7.30 (m, 1H), 7.20–7.15 (m, 1H), 6.94 (dd, J_1 = 3.8 Hz, J_2 = 5.0 Hz, 1H), 5.74 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 136.9, 127.3, 126.9, 126.8, 118.4, 58.8.

4.16. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(thiophen-2-yl)acetonitrile 14

$[\alpha]_D^{28} = +55.8$ (*c* 0.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.35 (dd, J_1 = 1.2 Hz, J_2 = 5.0 Hz, 1H), 7.18 (dd, J_1 = 1 Hz, J_2 = 2.4 Hz, 1H), 7.00 (dd, J_1 = 3.6 Hz, J_2 = 5.0 Hz, 1H), 5.77 (s, 1H), 0.96 (s, 9H), 0.24 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 140.0, 127.0, 126.9, 125.9, 118.4, 60.2, 25.5, 18.2, −5.0, −5.1. HRMS (ESI) for $C_{12}H_{19}NNaOSSi$ $[M+Na]^+$, calcd 276.0854, found: 276.0850.

4.17. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(thiophen-2-yl)acetaldehyde 15

$[\alpha]_D^{28} = +13.5$ (*c* 0.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 9.52 (d, *J* = 2.2 Hz, 1H), 7.34–7.31 (m, 1H), 7.04–7.02 (m, 2H), 5.22 (d, *J* = 2 Hz, 1H), 0.95 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 197.7, 140.4, 127.5, 126.3, 125.0, 76.6, 25.9, 18.5, −4.7. HRMS (ESI) for $C_{12}H_{20}NaO_2SSi$ $[M+Na]^+$, calcd 276.0854, found: 276.0850.

4.18. 2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)allyl)thiophene 16

$[\alpha]_D^{28} = +40.6$ (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.26–7.22 (m, 1H), 7.00–6.91 (m, 2H), 6.14–5.97 (m, 1H), 5.47–5.40 (m, 1H), 5.34–5.30 (m, 1H), 5.22–5.15 (m, 1H), 0.99 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 148.7, 140.9, 126.5, 124.5, 123.1, 114.3, 72.4, 25.9, 18.4, −4.5, −4.8. HRMS (ESI) for $C_{13}H_{22}NaOSSi$ $[M+Na]^+$, calcd 277.1058, found: 277.1052.

4.19. (*S*)-3-(*tert*-Butyldimethylsilylyloxy)-3-(thiophen-2-yl)propan-1-ol 17

$[\alpha]_D^{28} = +22.4$ (*c* 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.21–7.18 (m, 1H), 6.97–6.89 (m, 2H), 5.23 (t, *J* = 5.8 Hz, 1H), 3.86–3.64 (m, 2H), 2.30 (br, s), 2.08–1.99 (m, 2H), 0.91 (s, 9H), 0.09 (s, 3H), −0.05 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 149.1, 126.5, 124.1, 123.1, 115.1, 70.3, 60.1, 43.0, 25.9, 18.2, −4.7, −4.9. HRMS (ESI) for $C_{13}H_{24}NaO_2SSi$ $[M+Na]^+$, calcd 295.1164, found: 295.1157.

4.20. (*S*)-3-(4-Methoxybenzyloxy)-3-(thiophen-2-yl)propylmethanesulfonate 18

$[\alpha]_D^{28} = +16.75$ (*c* 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.23–7.19 (m, 1H), 6.94–6.92 (m, 2H), 5.13 (dd, $J_1 = 5.4$ Hz, $J_2 = 7.2$ Hz, 1H), 4.43–4.07 (m, 2H), 2.98 (s, 3H), 2.25–2.16 (m, 2H), 0.89 (s, 9H), 0.09 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 148.5, 126.5, 124.5, 123.5, 67.4, 66.8, 40.5, 37.4, 25.8, 18.2. HRMS (ESI) for $C_{14}H_{26}NaO_4S_2Si$ $[M+Na]^+$, calcd 373.0939, found: 373.0944.

4.21. (*S*)-3-(4-*tert*-Butyldimethtylsilyloxy)-*N*-methyl-3-(thiophen-2-yl)propan-1-amine 19

$[\alpha]_D^{28} = +28.2$ (*c* 0.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.17–7.15 (m, 1H), 6.92–6.87 (m, 2H), 5.10–4.98 (m, 1H), 2.72–2.65 (m, 2H), 2.42 (s, 3H), 2.06–1.90 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H), −0.06 (s, 3H). ^{13}C NMR (50 MHz $CDCl_3$): 149.7, 126.4, 124.0, 122.9, 69.7, 48.0, 40.4, 36.0, 25.9, 18.3, −4.7, −4.8. HRMS (ESI) for $C_{14}H_{27}NNaOSSi$ $[M+Na]^+$, calcd 308.1480, found: 308.1474.

4.22. (*S*)-3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol 6

$[\alpha]_D^{28} = +13.2$ (*c* 1.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 7.20–7.18 (m, 1H), 6.97–6.93 (m, 2H), 5.17 (dd, $J_1 = 4$ Hz, $J_2 = 7.6$ Hz, 1H), 2.95–2.86 (m, 2H), 2.43 (s, 3H), 2.00–1.90 (m, 2H). ^{13}C NMR (50 MHz $CDCl_3$): 149.6, 126.8, 123.9, 122.7, 71.4, 49.9, 36.8, 35.8. HRMS (ESI) for $C_8H_{13}NNaOS$ $[M+Na]^+$, calcd 194.0616, found: 194.0610.

4.23. (*R*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl) propan-1-amine 2 (duloxetine)

$[\alpha]_D^{28} = -109.5$ (*c* 1.2, $CHCl_3$). Lit. $[\alpha]_D^{21} = -114.3$ (*c* 1.0, MeOH).[5b] ^1H NMR (400 MHz, $CDCl_3$): 8.34–8.32 (m, 1H), 7.80–7.77 (m, 1H), 7.52–7.49 (m, 2H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.29–7.27 (m, 1H), 7.25–7.21 (m, 1H), 7.20–7.09 (m, 1H), 6.92 (dd, $J_1 = 3.6$ Hz, $J_2 = 5.2$ Hz, 1H), 6.90 (d, $J = 7.6$ Hz, 1H), 5.86 (dd, $J_1 = 5.2$ Hz, $J_2 = 7.6$ Hz, 1H), 3.27–3.20 (m, 2H), 2.64–2.61 (m, 1H), 2.54 (s, 3H), 2.47–2.41 (m, 1H). ^{13}C NMR (100 MHz $CDCl_3$): 153.1, 144.9, 134.3, 127.2, 126.3, 126.1, 125.8, 125.5, 125.0, 124.5, 121.9, 120.3, 106.7, 74.5, 48.0, 38.7, 36.3. HRMS (ESI) for $C_{18}H_{19}NNaOS$ $[M+Na]^+$, calcd 320.1085, found: 320.1081.

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References

1. (a) Barlow, D. H.; Durand, V. M. In *Mood Disorders and Suicide. Abnormal Psychology: An integrative approach*, 6th ed.; Belmont, CA, 2011; p 241. ISBN: 1-111-34362-4.; (b) Preskorn, S. H.; Ross, R.; Stanga, C. Y. *'Selective Serotonin Reuptake Inhibitors'. Antidepressants: Past, Present and Future*; Springer: Berlin, 2009; pp 241–262. ISBN: 978-3-540-43054-4; (c) Jay, C. F.; Robert, J. D.; Hollon, S. D.; Dimidjian, S.; Amsterdam, J. D.; Shelton, R. C.; Fawcett, J. *J. Am. Med. Assoc.* **2010**, *303*, 47–53; (d) Pies, R. *J. Clin. Psychopharmacol.* **2010**, *30*, 101–104.
2. (a) Deecher, D. C.; Beyer, C. E.; Johnston, G. *J. Pharmacol. Exp. Ther.* **2006**, *318*, 657–665; (b) Iyenger, S.; Webster, A. A.; Hemrick-Luecke, S. K.; Xu, J. Y.; Simmons, R. M. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 576–584; (c) Sindrup, S. H.; Otto, M.; Finnerup, N. B.; Jensen, T. S. *Basic Clin. Pharmacol. Toxicol.* **2005**, *96*, 399–409.
3. Wee, S.; Woolverton, W. L. *Drug Alcohol Depend.* **2004**, *75*, 271–276.
4. (a) Garnock-Jones, K. P.; Keating, G. M. *Paediatr. Drugs* **2009**, *11*, 203–226; (b) Simpson, D.; Polsker, G. L. *CNS Drugs* **2004**, *18*, 397–401.
5. (a) Buitrago, E.; Lundberg, H.; Andersson, H.; Rydberg, P.; Adolfsson, H. *ChemCatChem* **2012**, *4*, 2082–2089; (b) Tra, A.; Lihammar, R.; Backvall, J. *J. Org. Chem.* **2011**, *76*, 3917–3921; (c) Iwata, M.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1688–1694; (d) Chea, H.; Sim, H.-S.; Yun, H. *Adv. Synth. Catal.* **2009**, *351*, 855–858; (e) Mauro, P.; Emiliano, T.; Elisa, B.; Eileen, C.; Antonio, D.; Vicennati, P. *Tetrahedron* **2006**, *62*, 12270–12280; (f) Li, Y.; Li, Z.; Li, F.; Wang, Q.; Tao, F. *Org. Biomol. Chem.* **2005**, *3*, 2513–2518; (g) Wang, G.; Liu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1873–1879; (h) Liu, D.; Gao, W.; Wang, C.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 1687–1689; (i) Xu, C.; Yuan, C. *Tetrahedron* **2005**, *61*, 2169–2186; (j) Kumar, P.; Upadhyay, R. K.; Pandey, R. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3955–3959; (k) Panunzio, M.; Rossi, K.; Tamanini, E.; Campana, E.; Martelli, G. *Tetrahedron: Asymmetry* **2004**, *15*, 3489–3493; (l) Kamal, A.; Khanna, G. B.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039–2051; (m) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425–4426; (n) Miles, W. H.; Fialcowitz, E. J.; Scott, H. E. *Tetrahedron* **2001**, *57*, 9925–9929; (o) Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919–8921; (p) Liu, H.; Hoff, B. H.; Anthonsen, T. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 1767–1769; (q) Devine, P. N.; Heid, R.; Tschaen, D. M. *Tetrahedron* **1997**, *53*, 6739–6746; (r) Chenevert, R.; Fortier, G.; Bel Rhlid, R. *Tetrahedron* **1992**, *48*, 6769–6776; (s) Kumar, A.; Ner, D. H.; Dike, S. Y. *Tetrahedron Lett.* **1991**, *32*, 1901–1904; (t) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207–5210; (u) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081–4084.
6. Rogers, R. S. *Chem. Eng. News* **1998**, 11–15.
7. (a) Dadashipour, M.; Asano, Y. *ACS Catal.* **2011**, *1*, 1121–1149; (b) Holt, J.; Hanefeld, U. *Curr. Org. Synth.* **2009**, *6*, 14–37.
8. (a) Das, T.; Mahapatra, T.; Nanda, S. *Tetrahedron Lett.* **2012**, *53*, 1186–1189; (b) Bhunya, R.; Jana, N.; Das, T.; Nanda, S. *Synlett* **2009**, 1237–1240; (c) Bhunya, R.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1526–1530.
9. Griengl, H.; Klempier, N.; Pochlauer, P.; Schimdt, M.; Shi, N.; Zabelinskaja-Mackova, A. A. *Tetrahedron* **1998**, *54*, 14477–14486.
10. Mitsunobu, O. *Synthesis* **1981**, 1–28.
11. Okrob, D.; Paravidino, M.; Orru, R. V. A.; Wiechert, W.; Hanefeld, U.; Martina, P. *Adv. Synth. Catal.* **2011**, *353*, 2399–2408.