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Asymmetric dihydroxylation route to (*R*)-isoprenaline, (*R*)-norfluoxetine and (*R*)-fluoxetine

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Abstract—An efficient asymmetric synthesis of enantiomerically pure (*R*)-isoprenaline, (*R*)-norfluoxetine and (*R*)-fluoxetine is described using Sharpless asymmetric dihydroxylation as the key step.

1. Introduction

Due to the high demand and preference for the use of enantiomerically pure drugs, there has been an upsurge of interest in the asymmetric synthesis of pharmaceutical products. (*R*)-Isoprenaline **1** (Fig. 1) is a clinically potent β-adrenoreceptor agonist and sympathomimetic drug that dilates the bronchioles (small air passages in the lungs) and improves the transmission of electrical signals in the heart.[1] It is used as a bronchodilator to relieve the bronchopasm associated with asthma, bronchitis and emphysema. The (*R*)-form of isoprenaline is approximately 90 times more potent than the (*S*)-form.[2] Presently (*R*)-isoprenaline is produced by a resolution process.[3] To our knowledge there has been only one report of its asymmetric synthesis using the CBS catalyst.[4]

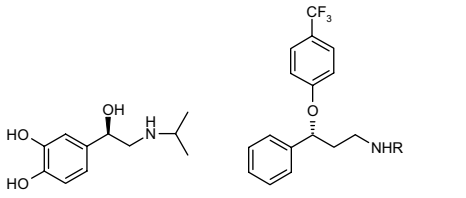

Figure 1.

Norfluoxetine **2** and fluoxetine **3** are among the most important pharmaceuticals for the treatment of psychiatric disorders (depression, anxiety, alcoholism) and also metabolic problems (obesity and bulimia).[5] In view of different pharmacological activities displayed by the individual enantiomers and differences in metabolic behaviour, the asymmetric synthesis of both enantiomers of fluoxetine and related compounds has received growing interest in recent years. Most of these approaches start with a three-carbon-chain segment and establish the configuration by enzymatic resolution,[6] asymmetric reduction,[7] asymmetric epoxidation,[8] chemical resolution[9] and an asymmetric carbonyl-ene reaction.[10] Recently a four-carbon-chain segment has been employed to make fluoxetine and its analogues by incorporating asymmetric reduction and Hofmann rearrangement.[11] As part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones and amino alcohols,[12] the Sharpless asymmetric dihydroxylation[13] was envisaged as a powerful tool to chiral dihydroxy compounds offering considerable opportunities for synthetic manipulation. Herein we report a new and highly enantioselective synthesis of (*R*)-isoprenaline, (*R*)-norfluoxetine and (*R*)-fluoxetine by employing Sharpless asymmetric dihydroxylation as the key step.

2. Results and discussion

The synthesis of (*R*)-isoprenaline started from commercially available 3,4-dimethoxybenzaldehyde **4** as depicted in Scheme 1. Compound **4** was subjected to Wittig olefination with methylenetriphenylphosphorane generated by the reaction of triphenylmethylphosphonium iodide and *n*-BuLi to give styrene **5** in 90% yield.[14]

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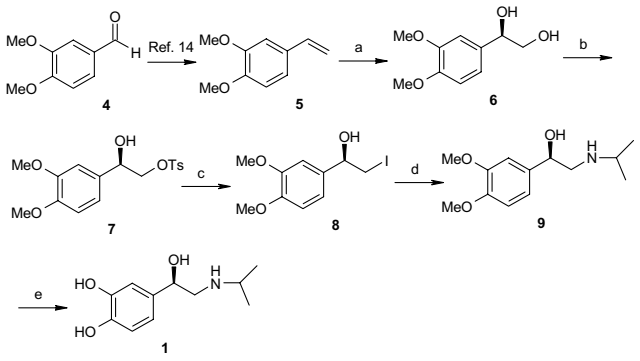
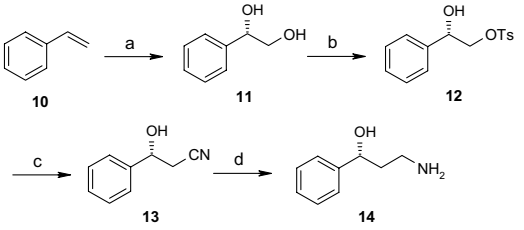


Scheme 1. Reagents and conditions: (a) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O, OsO_4, 0 °C, 24 h, 97%; (b) dibutyltin oxide (0.2 mol%), TsCl, NEt_3, CH_2Cl_2, rt, 45 min, 95%; (c) NaI, acetone, reflux, 6 h, 95%; (d) isopropylamine, sealed tube, 80 °C, 7 h, 90%; (e) $AlCl_3$, EtSH, CH_2Cl_2, rt, 3 h, 80%.

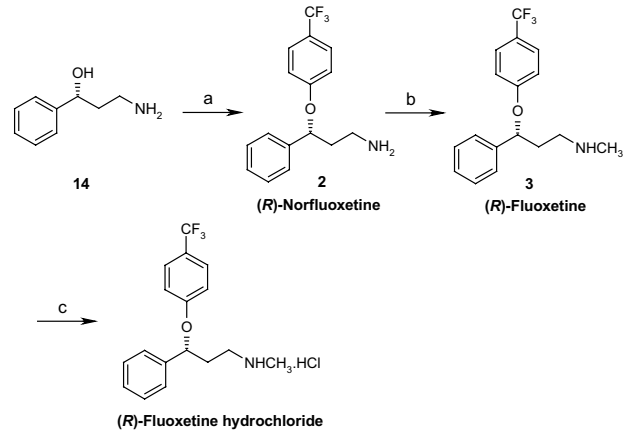
The dihydroxylation of **5** with osmium tetroxide and potassium ferricyanide as co-oxidant under Sharpless asymmetric dihydroxylation conditions[13] gave the diol **6** in 97% yield with 97% ee. Selective conversion of the primary hydroxyl group of **6** into a tosylate was carried out using tosyl chloride in the presence of a catalytic amount (0.2 mol%) of dibutyltin oxide[15] to afford **7** in 95% yield.

Our initial attempt to synthesize **1** either by the direct nucleophilic displacement of tosylate **7** with isopropylamine or by the conversion to epoxide and subsequent opening with isopropylamine was not very satisfactory. Hence, we attempted the following sequence of reactions. The nucleophilic displacement of tosylate **7** with sodium iodide in acetone under reflux furnished the iodo compound **8** in essentially quantitative yield. Compound **8** was reacted with isopropylamine at 80 °C in a sealed tube to afford **9** in 90% yield. Subsequent cleavage of the methoxy groups using aluminium chloride and ethanethiol[16] furnished the target compound **1** in 80% yield as a white solid.

The synthesis of (*R*)-norfluoxetine and (*R*)-fluoxetine is illustrated in Scheme 3. The 1,3-amino alcohol **14** is envisaged as a common building block from which (*R*)-fluoxetine and norfluoxetine can be synthesized (Scheme 2). The synthesis of intermediate **14** starts from



Scheme 2. Reagents and conditions: (a) $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O, OsO_4, 0 °C, 24 h, 97%; (b) dibutyltin oxide (0.2 mol%), *p*-TsCl, NEt_3, CH_2Cl_2, rt, 45 min, 99% (c) NaCN, EtOH–H_2O (4:1), rt, 24 h, 90%; (d) $BH_3{\cdot}SMe_2$, THF, reflux, 2 h, 96%.



Scheme 3. Reagents and conditions: (a) NaH, DMSO, 55 °C, 30 min, then 4-chlorobenzotrifluoride, 90 °C, 1 h, 90%; (b) (i) $ClCO_2Me$, CH_2Cl_2, aq K_2CO_3, 30 min, (ii) $LiAlH_4$, THF, 65 °C, 2 h, 90%; (c) HCl gas, ether, 95%.

styrene **10**. We planned to incorporate the amine functionality early in the synthesis via cyanide addition. Towards this end, the asymmetric dihydroxylation of styrene **10** gave the diol **11** essentially in quantitative yield with 97% ee. The diol **11** was first treated with dibutyltin oxide (0.2 mol%) followed by addition of tosyl chloride and triethylamine in dichloromethane to give the monotosyl compound **12** in quantitative yield.

The nucleophilic displacement of tosylate **12** with sodium cyanide furnished the cyano compound **13** in 90% yield. While the reduction of nitrile **13** with lithium aluminium hydride was not very satisfactory, the reaction proceeded smoothly with the use of borane dimethylsulfide as reducing agent to give the 1,3-amino alcohol **14** in 96% yield.

The key intermediate 1,3-amino alcohol **14** was then used to prepare the optically active (*R*)-norfluoxetine **2** and fluoxetine **3**. Thus, the arylation of **14** was carried out by nucleophilic aromatic substitution employing NaH as a base and 4-chlorobenzotrifluoride as an electrophile in DMSO to afford (*R*)-norfluoxetine in 90% yield as a viscous liquid. Conversion of (*R*)-norfluoxetine **2** to (*R*)-fluoxetine **3** was achieved via carbamate formation. Thus, the treatment of **2** with methyl chloroformate in aq K_2CO_3 afforded the carbamate, which on subsequent reduction with lithium aluminium hydride furnished (*R*)-fluoxetine **3**. This was treated with hydrogen chloride to form the colourless, crystalline hydrochloride of **3** in 95% yield.

3. Conclusion

In summary, a practical and highly enantioselective synthesis of (*R*)-isoprenaline **1**, (*R*)-norfluoxetine **2** and (*R*)-fluoxetine **3** has been achieved using the Sharpless asymmetric dihydroxylation as the key step and source of chirality. The synthetic strategy described can be further extended to other enantiomers and related analogues.

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 rotation was measured using sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on Perkin Elmer FT-IR spectrometer. Mass spectra were recorded either by GC–MS or with a Finnigan LCMS mass spectrometer. Enantiomeric excess was measured using either the chiral HPLC or by comparison with optical rotation. The enantiomeric excess determined for the diols was 97%. HPLC model: Merck-Hitachi Lachrom Photo Diode Array detector (PDA); column: Astec Cyclobond I (4.6 mm ID × 250 mm L); mobile phase: methanol–water: (40:60); flow: 1 mL/min.

4.2. Synthesis of isoprenaline

4.2.1. 3,4-Dimethoxystyrene 5. Prepared from 3,4-dimethoxy benzaldehyde in 90% yield following a literature procedure.[14]

4.2.2. (*R*)-1-(3,4-Dimethoxyphenyl)ethane-1,2-diol 6. To a mixture of $K_3Fe(CN)_6$ (30.07 g, 91.33 mmol) and K_2CO_3 (12.62 g, 91.33 mmol) and $(DHQD)_2PHAL$ (238 mg, 0.304 mmol) in *t*-BuOH–H_2O (1:1, 152 mL) cooled to 0 °C was added osmium tetroxide (1.3 mL, 0.1 M solution in toluene). After stirring for 5 min at 0 °C, olefin **5** (5.0 g, 30.45 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfide (7 g). The stirring was continued for an additional 45 min and then solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phase were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (3:7) as eluent gave **6** (5.85 g, 97%) as a white solid, mp 89–90 °C; $[\alpha]_D^{25} = -32.2$ (*c* 1.4, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05 (br s, 2H, OH), 3.61 (dd, J = 10.0, 8.0 Hz, 2H), 3.79 (s, 6H), 4.00–4.03 (m, 1H), 6.73–7.32 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.17, 68.30, 74.66, 109.83, 111.65, 118.67, 133.49, 149.10, 149.47; IR ($CHCl_3$): 3410, 2938, 2839, 1608, 1595 cm^{-1}; mass (ESI): 198 (M^+). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.49; H, 7.09. The ee obtained was 97% as determined by chiral HPLC.

4.2.3. (*R*)-Toluene-4-sulfonic acid 2-(3,4-dimethoxyphenyl)-2-hydroxyethyl ester 7. To a mixture of diol **6** (2.9 g, 14.63 mmol), in dry dichloromethane (30 mL) was added dibutyltin oxide (8.0 mg, 0.2 mol% of diol) followed by the addition of *p*-toluensulfonyl chloride (3.03 g, 15.93 mmol) and triethylamine (2.2 mL, 15.70 mmol) and the reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC. After completion of reaction (45 min), the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 × 25 mL) and then combined organic phase were washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether–EtOAc (6:4) as eluent afforded monotosyl compound **7** (4.88 g, 95%) as a viscous liquid: $[\alpha]_D^{25} = -21.0$ (*c* 2.64, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.89 (s, 3H), 3.77 (s, 1H, OH), 4.28 (s, 3H), 4.31 (s, 3H), 4.54 (d, J = 3 Hz, 2H), 5.30 (t, J = 3Hz, 1H), 7.27–7.30 (m, 3H), 7.77 (d, J = 9 Hz, 2H) 8.20 (d, J = 9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 21.12. 55.48, 71.26, 73.80, 109.05, 110.94, 118.23, 127.48, 129.40, 130.71, 132.48, 144.57, 148.87; IR ($CHCl_3$): 3509, 2939, 1733, 1517 cm^{-1}; mass (ESI): 370 ($M^+ + H_2O$). Anal. Calcd for $C_{17}H_{20}O_6S$: C, 57.94; H, 5.72; S, 9.10. Found: C, 57.98; H, 5.80, S, 9.20.

4.2.4. (*R*)-1-(3,4-Dimethoxyphenyl)-2-iodo-ethanol 8. To a solution of tosyl compound **7** (0.25 g, 0.71 mmol) in acetone (3 mL) was added sodium iodide (1.06 g, 7.0 mmol) and reaction mixture was refluxed for 6 h. The reaction mixture was cooled to room temperature and solvent was evaporated and water (2.0 mL) was added and extracted with ethyl acetate (3 × 20 mL); the combined organic layer were washed with water and dried over sodium sulfate (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether–EtOAc (4:1) as eluent gave the iodo compound **8** (0.207 g, 95%); $[\alpha]_D^{25} = -27.9$ (*c* 1.74, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.38–3.48 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 4.77–4.81 (m, 1H), 6.82–6.91 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.98, 55.60, 73.53, 108.42, 110.77, 117.90, 133.56, 148.59; IR ($CHCl_3$): 3401, 3020, 2936, 1720, 1595, 1516 cm^{-1}; GC–MS (ESI): 308 (M^+), $C_{10}H_{13}IO_3$: C, 38.98; H, 4.25; I, 41.19. Found: C, 39.02; H, 4.20; I, 41.11.

4.2.5. (*R*)-1-(3,4-Dimethoxyphenyl)-2-isopropyl amino-ethanol 9. A solution of iodo compound **8** (0.2 g, 0.65 mmol) and freshly distilled isopropylamine (0.383 g, 6.5 mmol) was kept under sealed tube at 80 °C for 7 h. Removal of the excess isopropylamine afforded crude compound **9**, which on purification by silica gel column chromatography using ethyl acetate–methanol (9:1) as eluent afforded a yellow coloured product, mp 127 °C (lit.[17] mp 126–128 °C). The spectroscopic data were in full agreement with the literature values.[17]

4.2.6. (*R*)-(−)-Isoprenaline 1. To a mixture of dry ethanethiol (1 mL) in dichloromethane was added aluminium chloride (0.8 g, 6.0 mmol) at 0 °C. The resulting solution was warmed to room temperature, and compound **9** (0.079 g, 0.313 mmol) was added with stirring. After stirring overnight, the reaction mixture was poured into water, acidified with dilute HCl and extracted with dichloromethane. The organic layer was evaporated to give a crude product. Chromatography over a silica gel column using chloroform–methanol (9.5:0.5) as eluent gave **1** (0.055 g, 80%) as a white solid. Mp 160 °C (lit.[4] 163–164 °C), $[\alpha]_D^{25} = -42.3$ (*c* 1, 2 M HCl) [lit.[4] $[\alpha]_D^{23} = -43.5$ (*c* 1, 2 M HCl)]. The spectroscopic data of **1** were in full agreement with the literature values.[4]

4.3. Synthesis of norfluoxetine and fluoxetine

4.3.1. (*S*)-1-Phenylethane-1,2-diol 11. To a mixture of $K_3Fe(CN)_6$ (47 g, 144 mmol), K_2CO_3 (19.88 g, 144 mmol) and $(DHQ)_2PHAL$ (0.378 g, 0.48 mmol) in *t*-BuOH–H_2O (1:1, 240 mL:240 mL) cooled to 0 °C was added OsO_4 (1.94 mL, 0.4 mol%, 0.1 M solution in toluene). After stirring for 5 min at 0 °C, styrene **10** (5.0 g, 48.0 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite. The stirring was continued for 1 h and the solution was extracted with ethyl acetate. The combined organic phase were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether–EtOAc (3.5:1.5) as eluent gave (*S*)-phenylethylene glycol **11** as a white solid. (6.6 g, 99%). Mp 65 °C $[\alpha]_D^{25} = +54.9$ (*c* 1, $CHCl_3$). The spectroscopic data were in full agreement with the literature values.[18]

4.3.2. (*S*)-Toluene-4-sulfonic acid 2-hydroxy-2-phenylethyl ester 12. To a mixture of (*S*)-phenylethane-1,2-diol **11** (4.42 g, 32.02 mmol), in dry dichloromethane (65 mL) was added dibutyltin oxide (15 mg, 0.2 mol% of diol) followed by the addition of *p*-toluenesulfonyl chloride (6.17 g, 32.02 mmol) and triethylamine (4.4 mL, 32.02 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC. After completion of reaction (45 min), the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 × 25 mL) and then combined organic phase were washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether–EtOAc (4:1) as eluent gave the monotosyl compound **12** (9.27 g, 99%) as a white solid. Mp 63–64 °C $[\alpha]_D^{25} = +49.9$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.75 (br s, 1H), 4.00–4.25 (m, 2H), 5.00 (dd, $J = 3.5$, 8.0 Hz, 1H), 7.30 (s, 5H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.75 (d, $J = 8.2$ Hz, 2H). IR ($CHCl_3$): 3529, 1598, 1360 cm^{-1}; MS (*m*/*z*, rel int.%): M^+ 292 (0.2), 262 (4), 155 (3), 107 (100), 91 (38), 79 (45), 77 (31).

4.3.3. (*R*)-3-Hydroxy-3-phenylpropanenitrile 13. To a stirring mixture of monotosyl compound **12** (3.0 g, 10.26 mmol) in ethanol–H_2O (35 mL:25 mL) at 0 °C was added NaCN (1.76 g, 35.92 mmol) in one portion. The reaction mixture was stirred at room temperature for 24 h, then concentrated at 50 °C on rotatory evaporator and extracted with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether–EtOAc (3:1) as eluent gave (*R*)-3-phenyl-3-hydroxypropanenitrile **13** (1.351 g, 90%) as a pale yellow oil. $[\alpha]_D^{25} = +60.2$ (*c* 1, $CHCl_3$) [lit.[19] $[\alpha]_D^{20} = +58.0$ (*c* 1, EtOH)]. The spectroscopic data were in full agreement with the literature values.[6j]

4.3.4. (*R*)-3-Amino-1-phenylpropane-1-ol 14. To a THF (10.0 mL) solution of (*R*)-3-phenyl-3-hydroxypropanenitrile **13** (1.25 g, 8.5 mmol) was slowly added borane dimethyl sulfide complex (0.84 g, 11.0 mmol) at room temperature. Methyl sulfide was then distilled from the reaction vessel and the resulting THF solution refluxed for 2.5 h. After cooling to room temperature, methanolic HCl (6.25 mL, 1.0 M) was added to the reaction mixture. Methanol and methyl borate were removed by distillation and the reaction mixture neutralized with sodium hydroxide (6.0 mL, 5 N). Extraction of the mixture with dichloromethane followed by concentration provided the crystalline (*R*)-3-phenyl-3-hydroxypropylamine **14** (1.23 g, 96%). $[\alpha]_D^{25} = +40.5$ (*c* 1, $CHCl_3$). The spectroscopic data were in full agreement with the literature values.[6j]

4.3.5. (*R*)-Norfluoxetine 2. A solution of (*R*)-3-phenyl-3-hydroxypropylamine **14** (1.0 g, 6.6 mmol) in DMSO (2.0 mL) was stirred with sodium hydride (0.47 g, 9.9 mmol 50% in oil) at 55 °C for 30 min under nitrogen atmosphere. 4-Chlorobenzotrifluoride (1.8 g, 9.9 mmol) in 1.0 mL DMSO was then slowly added to the above reaction mixture and the resulting solution heated to 90 °C for 1 h. The resulting mixture was cooled to room temperature and diluted with NaOH (10.0 mL, 2N aq solution). Toluene (4 × 3 mL) was used to extract the product **2** from the hydroxide solution as viscous liquid (1.96 g, 90%). $[\alpha]_D^{25} = +10.2$ (*c* 0.62, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.90–2.20 (m, 2H), 2.1 (br s, 2H), 2.90 (t, $J = 7.35$ Hz, 2H), 5.35 (dd, $J = 3.45$, 8.55 Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 2H), 7.20–7.35 (m, 5H), 7.45 (d, $J = 8.6$ Hz, 2H); IR ($CHCl_3$): 3369, 3298, 1613, 1500 cm^{-1}; MS (*m*/*z*, rel int.%): (M^+-2) 295 (0.4), 278 (0.2), 251 (1), 197 (18), 162 (15), 134 (100), 104 (85), 91 (40), 77 (67).

4.3.6. (*R*)-Norfluoxetine hydrochloride. (*R*)-Norfluoxetine (1.9 g) was dissolved in toluene (4.0 mL) and heptane (10.0 mL) was added, HCl gas was passed to form (*R*)-norfluoxetine hydrochloride (1.92 g, 90%). Solid; mp 129–130 °C [lit.[8b] 131 °C] $[\alpha]_D^{25} = -36.0$ (*c* 1.5, MeOH) [lit.[8b] $[\alpha]_D^{25}$ +36.3 (*c* 2, MeOH) for (*S*)-enantiomer].

4.3.7. (*R*)-Fluoxetine 3. To a solution of norfluoxetine **2** (1.0 g, 3.38 mmol) and methyl chloroformate (0.29 mL, 3.72 mmol) in dichloromethane (15.0 mL) was added aqueous K_2CO_3 (2.33 g, 16.89 mol in 30 mL water). The reaction was rapidly stirred for 20 min and then diluted with H_2O. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phase were dried (Na_2SO_4) and concentrated to give carbamate as a pale yellow oil. To a stirring suspension of lithium aluminum hydride (0.25 g) in dry THF (15.0 mL) at 0 °C was added a solution of carbamate in dry THF (5.0 mL) under nitrogen. The ice bath was removed and then the reaction mixture was refluxed for 2 h. Excess lithium aluminium hydride was destroyed by adding H_2O and EtOAc. The white precipitate obtained was filtered and washed with MeOH. The combined filtrate was concentrated to give (*R*)-fluoxetine **3** (0.94 g, 90%) as an viscous oil $[\alpha]_D^{25} = +5.0$ (*c* 1, $CHCl_3$). The spectroscopic data were in full agreement with the literature values.[6j]

4.3.8. (*R*)-Fluoxetine hydrochloride. Fluoxetine (0.90 g) was dissolved in ether (15 mL). HCl gas was passed through until a pH of 3–4 was achieved and no precipitate was formed. The solution was concentrated at room temperature to give a yellow solid, which was washed with ether and recrystallized from CH_2Cl_2/EtOAc to give pure (*R*)-fluoxetine hydrochloride (0.91 g, 90%) as a solid; mp 139–140 °C [lit.[7a] 142–143 °C] $[\alpha]_D^{25} = -13.6$ (*c* 1, $CHCl_3$) [lit.[7a] $[\alpha]_D^{25} = -13.8$ (*c* 1, $CHCl_3$)]. The spectroscopic data were in full agreement with the literature.[8a]

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