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Application of amide-stabilized sulfur ylide reactivity to the stereodivergent synthesis of (*R*,*S*)- and (*S*,*R*)-reboxetine

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ABSTRACT

A simple access to (*R*,*S*)- and (*S*,*R*)-reboxetine from a single chiral sulfonium salt **4** is reported. This approach, based on a stabilized sulfur ylide-mediated epoxidation, followed by a regioselective opening reaction, enables the preparation of these two potentially biologically active compounds in 35.6% and 13.7% overall yield.

1. Introduction

Reboxetine is an important noradrenaline reuptake inhibitor used in the treatment of depressive disorder and marketed as a racemic mixture of the (*R*,*R*) and (*S*,*S*) enantiomers. Recently, several research groups have discovered that esreboxetine **1** is more potent than its enantiomer with a better affinity and selectivity for the noradrenaline transporter (NAT).[1] Numerous methods have been reported to isolate the (*S*,*S*)-enantiomer, including resolution,[2] capillary electrophoresis,[3] and chiral HPLC.[4] Asymmetric syntheses based on chiral starting materials,[5] Sharpless epoxidations,[6] or dihydroxylations[7] have also been reported.

While much research has been carried out for the preparation of reboxetine, its (*S*,*S*) enantiomer, and their pharmacological properties, very little is known about the biological properties of the corresponding diastereomers (*R*,*S*)-**2a** and (*S*,*R*)-**2b** (Fig. 1). Only recently, Sutherland et al. have reported that iodinated (*R*,*S*)-reboxetine **3a** has a high affinity for the NAT (K_i = 58.2 nM), very close to the affinity of iodinated (*S*,*S*)-reboxetine (K_i = 53.8 nM). Its enantiomer **3b** was much less potent in the same binding assay (K_i = 320 nM).[8] These results strongly suggest that isomers **2a** and **2b** could also possess interesting inhibitory properties.

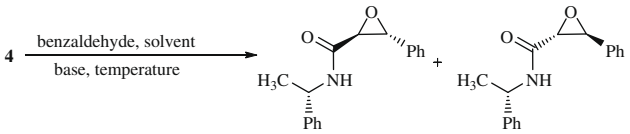
Herein we report a stereodivergent and straightforward access to (*R*,*S*) and (*S*,*R*)-reboxetine diastereoisomers using sulfur ylide **4** derived from (*S*)-phenylethylamine (Scheme 1).

2. Results and discussion

Amide-stabilized sulfur ylides are known to be excellent tools for the construction of epoxides.[9] These kinds of semi-stabilized ylides, which usually react in high yield with non-enolizable aldehydes to give the corresponding *trans* epoxides, have been extensively investigated by Aggarwal et al.[10] Thus, *trans* epoxide **5** should enable the rapid construction of the reboxetine skeleton.

Chiral sulfonium salt **4** was prepared in two steps from (*S*)-(−)-phenylethylamine in quantitative yield (Scheme 2).

Condensation with benzaldehyde was then investigated (Table 1). The ylide was first generated under our previously established conditions (entry 1),[11] but the reaction proved to be sluggish. The best results were obtained in THF, using potassium *tert*-butoxide as a base, leading to the quantitative formation of a 73/27 diastereomeric mixture of *trans* epoxides **5a** and **5b** (entry 12). The exclusive formation of the *trans* adducts was confirmed by the magnitude of the coupling constants of the epoxides (J = 2.1 and 1.6 Hz).[12]



5a + 5b

As the separation of the diastereomers proved to be difficult at this stage, the nucleophilic opening of epoxides was conducted on the diastereomeric mixture. Our first attempts using NaH or *t*-BuOK were unsuccessful, leading to only trace amounts of the desired amido-alcohols. Finally, the diastereomeric mixture of compounds **6a**+**6b**[13] was obtained in 95% yield by a slight modification of the original reaction conditions reported by Kim et al.,[14] which consisted of the addition of 20 mol % of ether 18-crown-6 (Scheme 3).

The diastereomers were easily separated by chromatographic purification. Fortunately, the major diastereomer **6a** crystallized,

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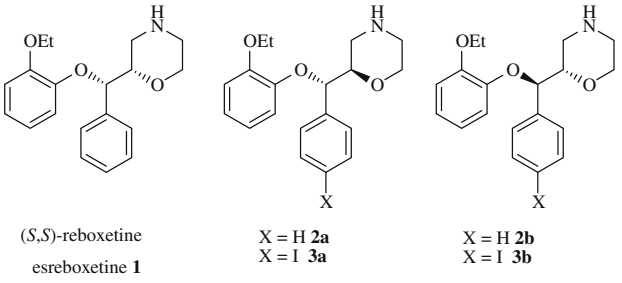
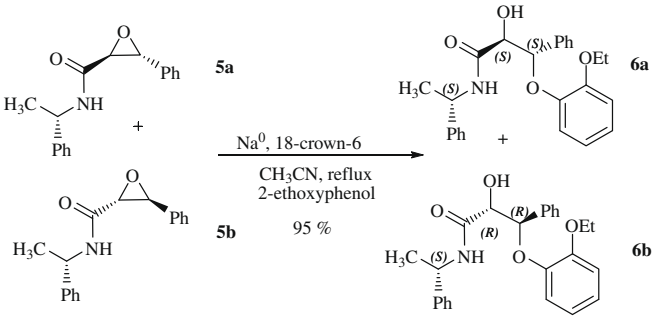
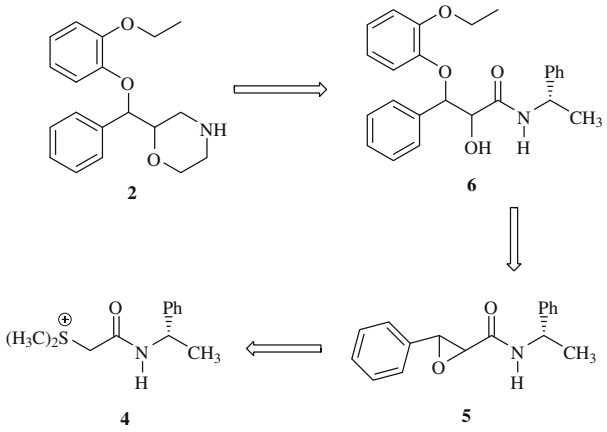


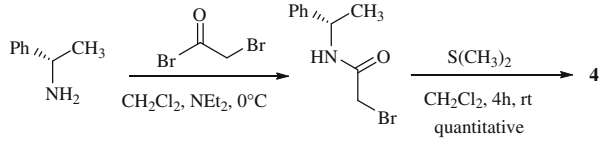
Figure 1.



Scheme 3. Nucleophilic opening of epoxides.



Scheme 1. Retrosynthetic analysis.



Scheme 2. Preparation of chiral sulfonium salt **4**.

Table 1
Effect of base, temperature, and time on conversion and diastereoselectivity

Entry	Solvent	Base	Temp	Time (h)	Yield[a] (%)	dr[b] (*trans*)
1	CH_3CN/H_2O	KOH	0 °C to rt	15	50	55:45
2	CH_2Cl_2/H_2O	KOH	0 °C to rt	15	51	50:50
3	MeOH	KOH	−50 °C	30	92	55:45
4	CH_2Cl_2/H_2O	NaOH	0 °C to rt	15	53	50:50
5	Et_2O/H_2O	KOH	0 °C to rt	15	50	54:46
6	DMM/H_2O	KOH	0 °C to rt	15	50	62:38
7	THF/H_2O	KOH	0 °C to rt	15	64	63:37
8	THF/H_2O	LiOH	0 °C to rt	15	50	62:38
9	THF	NaH	0 °C to rt	5	50	55:45
10	THF	DBU	0 °C to rt	15	50	50:50
11	THF	*t*-BuOK	0 °C	3	55	73:27
12	THF	*t*-BuOK	−30 °C	15	100	73:27
13	THF	*t*-BuOK	−50 °C to rt	15	80	73:27
14	THF	*t*-BuOK	−80 °C to rt	15	45	73:27

[a] Isolated yield of diastereomeric mixture.
[b] Determined by ^1H NMR of the crude.

enabling the determination of its absolute configuration by X-ray diffraction analysis (Fig. 2).[15]

The reduction of **6a** by Red-Al[5c,e,6a] or $LiAlH_4$[16] only resulted in the total degradation of the amide, while the use of BH_3·THF afforded compound **7a** in a 10% yield. We found that the use of BH_3·Me_2S led to **7a**, in 75% yield after column chromatography (Scheme 4).

The completion of the synthesis was performed by the amidification of **7a** with bromoacetyl bromide to give the corresponding haloamide **8a** which was treated with *t*-BuOK to afford the morpholinone **9a**.

Reduction of the resulting morpholinone **9a** with BH_3·Me_2S gave morpholine **10a** in 83% overall yield after three steps.

As expected, typical hydrogenolysis conditions (H_2, 10% Pd-C) for **10a** led to a mixture of O- and O,N-debenzylation products.

A fully chemoselective hydrogenolysis was obtained when **10a** was treated under transfer hydrogenation conditions,[17] to give the desired (*R*,*S*)-reboxetine in 80% yield (Scheme 4).

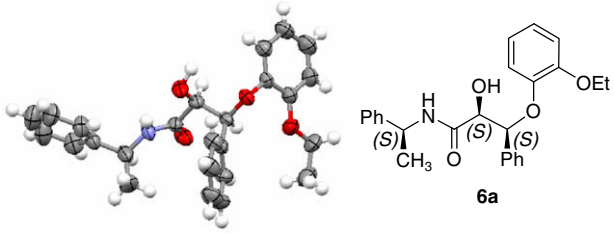
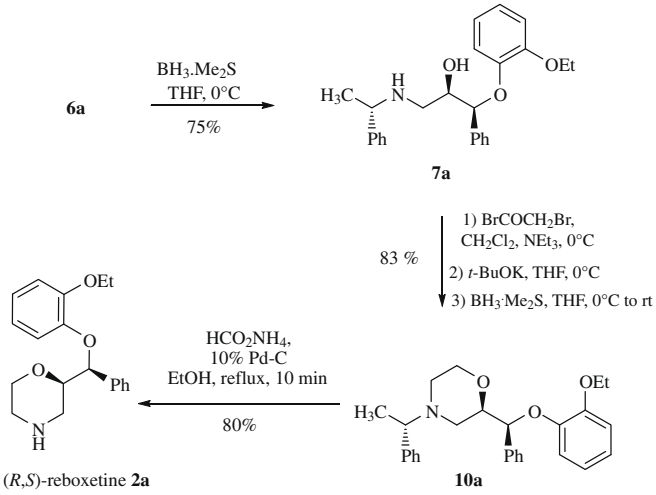


Figure 2.



Scheme 4. Synthesis of (*R*,*S*)-reboxetine **2a**.

The (*S*,*R*)-reboxetine enantiomer was also obtained using the same procedure of diastereomer **6b** in 51.7% yield.

3. Conclusion

We have shown that chiral non-racemic amide-stabilized sulfur ylide **4** is a valuable starting material for the preparation of the reboxetine skeleton. Using only six steps, (*R*,*S*)-reboxetine was obtained in 35.6% overall yield whereas its enantiomer (*S*,*R*)-reboxetine was prepared in 13.7% yield from the same precursor. This new, versatile, and scalable access to both enantiomers opens the route to the pharmacological investigation of these promising compounds as well as the design of analogs.

4. Experimental

4.1. General methods

Melting points are uncorrected. ^{1}H NMR and ^{13}NMR spectra were acquired on Varian VX400 (400 MHz), chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on Nicolet FT-IR Magna 750. Mass spectra were recorded on JEOL JEM-AX505HA at a voltage of 70 eV. Optical rotations were measured on Perkin–Elmer 341 polarimeter at room temperature. Column chromatography was performed on silica gel (60, 0.063–0.2 mm/70–230 mesh ASTM). All reagents and solvents were analytically pure.

4.1.1. Synthesis of a diastereomeric mixture of (1*S*,2*R*/*S*,3*S*/*R*,)-3-phenyloxirane-2-carboxylic acid (1-phenyl-ethyl)amides 5a and 5b

To a stirred suspension of potassium *tert*-butoxide (0.15 g, 1.25 mmol, 1.1 equiv) and sulfonium salt **4** (0.37 g, 1.24 mmol, 1 equiv) in anhydrous THF (30 mL) at −30 °C was added benzaldehyde (0.26 g, 2.48 mmol, 2 equiv). The resulting mixture was stirred for 15 h at −30 °C. The reaction was then quenched by the successive addition of an aqueous brine solution (25 mL) and the organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by evaporation. The resulting diastereomeric mixture was purified via flash column chromatography. The diastereomeric mixture of **5a** and **5b** was obtained as a white solid in a quantitative yield and dr = 73:27. Spectroscopic details of the diastereomeric mixture **5a** and **5b**; IR (film) 3277, 1654, 1552, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, J = 7.2 Hz, 3H), 1.47 (d, J = 7.2 Hz, 3H), 3.45 (d, J = 2 Hz, 1H), 3.50 (d, J = 2 Hz, 1H), 3.77 (d, J = 2 Hz, 1H), 3.90 (d, J = 1.6 Hz, 1H), 5.14 (m, J = 7.2 Hz, 2H), 6.73 (br, NH, 2H), 7.20–7.37 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.66, 21.73, 48.24, 48.27, 58.78, 58.91, 125.73, 126.07, 126.12, 127.48, 128.52, 128.57, 128.65, 128.90, 128.61, 128.92, 134.88, 142.46, 142.68, 166.51.

4.1.2. Opening of epoxide function of diastereomeric mixture 5a and 5b

To a stirred suspension of Na° in anhydrous THF at room temperature was added 2-ethoxyphenol (0.34 g, 2.48 mmol). The mixture was then stirred until the total formation of the corresponding sodium alkoxy salt (20–30 min). Later, the excess Na° was eliminated by filtration, and the solvent was removed under reduced pressure to give the 2-ethoxyphenoxy sodium salt. The resulting salt and a catalytic amount of 18-crown-6-ether (0.13 g, 0.49 mmol, 20%) were placed in anhydrous CH_3CN. The mixture was stirred at room temperature for 30 min. A solution of diastereomeric mixture **5a** and **5b** (0.33 g, 1.23 mmol) in CH_3CN (5 mL) was then added. The resulting mixture was refluxed for 16 h. The reaction was quenched with an aqueous brine solution (15 mL) and the organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and the solvent removed in vacuo to give the desired diastereomeric mixture **6a**+**6b** (95% yield, dr = 73:27). The diastereomeric mixture was separated by column chromatography on silica gel with petroleum ether/ethyl acetate.

4.1.3. (1′*S*,2*S*,3*S*)-(−)-3-(2-Ethoxy-phenoxy)-2-hydroxy-3-phenyl-*N*-(1′-phenyl-ethyl)propionamide 6a

Major diastereoisomer. Mp = 116–118 °C; $[\alpha]_D^{20} = -46.0$ (c 1.0, CH_2Cl_2); IR (film) 3393, 1652, 1498, 1248 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J = 7.2 Hz, 3H), 1.42 (t, J = 7.2 Hz, 3H), 4.02 (m, 2H), 4.44 (b, OH), 4.53 (d, J = 4.4 Hz, 1H), 4.99 (m, J = 7.1, 7.2 Hz, 1H), 5.37 (d, J = 4.4 Hz, 1H), 6.65–7.62 (m, 14H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.81, 21.39, 48.11, 64.49, 72.91, 83.15, 113.37, 118.60, 121.47, 123.14, 125.95, 125.96, 127.12, 127.61, 128.01, 128.19, 128.43, 128.44, 136.39, 142.72, 146.20, 149.65, 169.30. HRMS (FAB): Calcd for $C_{25}H_{27}NO_4$: 405.1940. Found: 405.1931.

4.1.4. (1′*S*,2*R*,3*R*)-(−)-3-(2-Ethoxy-phenoxy)-2-hydroxy-3-phenyl-*N*-(1′-phenyl-ethyl)propionamide 6b

Minor diastereoisomer. Mp = 140–142 °C; $[\alpha]_D^{20} = -26.5$ (c 1.0, CH_2Cl_2); IR (film) 3382, 1654, 1498, 1249 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.8 Hz, 3H), 1.43 (t, J = 7.2 Hz, 3H), 4.08 (m, 2H), 4.31 (d, J = 3.2 Hz, OH), 4.60 (dd, J = 3.2, 4.4 Hz, 1H), 5.00 (dq, J = 7.1, 7.2 Hz, 1H), 5.41 (d, J = 4.8 Hz, 1H), 6.79–7.42 (m, 14H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.79, 21.47, 47.85, 64.60, 72.96, 83.50, 113.44, 119.19, 121.59, 123.38, 125.92, 126.93, 127.68, 128.13, 128.16, 128.36, 136.22, 142.49, 146.20, 149.90, 169.21. HRMS (FAB): Calcd for $C_{25}H_{27}NO_4$: 405.1940. Found: 405.1933.

4.1.5. Representative procedure for the reduction of an amide function with borane dimethyl sulfide complex (BMS)

4.1.5.1. (1′*S*,2*R*,3*S*)-(−)-1-(2-Ethoxy-phenoxy)-1-phenyl-3-(1′-phenyl-ethylamino)-propan-2-ol 7a. To a stirred solution of **6a** (0.1 g, 0.246 mmol) in anhydrous THF (10 mL) at 0 °C was added a solution of BMS (0.07 mL, 0.055 g, 0.724 mmol, 3 equiv). Then, the reaction mixture was stirred at room temperature for 8 h. The reaction was quenched with methanol (2 mL) and stirred for 1 h at room temperature. Finally, the solvents were evaporated under reduced pressure. The product was purified via flash column chromatography and the corresponding aminoalcohol **7a** was obtained as a white oil (0.072 g, 75% yield). $[\alpha]_D^{20} = -23.4$ (c 1.0, CH_2Cl_2); IR (film) 3431, 1498, 1251, 1042 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 6.4 Hz, 3H), 1.42 (t, J = 7.6 Hz, 3H), 2.60 (dd, J = 4.2, 12.6 Hz, 1H), 2.71 (dd, J = 6.2, 10.2 Hz, 1H), 3.75 (q, J = 6.4 Hz, 2H), 3.91 (q, J = 6 Hz, 1H), 4.06 (q, J = 6.8 Hz, 2H), 5.10 (d, J = 4 Hz, 1H), 6.69–7.35 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.94, 24.29, 47.76, 58.22, 64.37, 72.76, 85.16, 113.38, 117.27, 120.89, 122.16, 126.65, 126.81, 126.85, 127.77, 128.36, 138.18, 145.18, 147.63, 149.46. HRMS (FAB): Calcd for $C_{25}H_{29}NO_3$: 391.2147. Found: 391.2123.

4.1.5.2. (1′*S*,2*S*,3*R*)-(−)-1-(2-Ethoxy-phenoxy)-1-phenyl-3-(1-phenyl-ethylamino)-propan-2-ol 7b. The corresponding aminoalcohol was obtained as a white oil (0.075 g, 78% yield). $[\alpha]_D^{20} = -18.2$ (c 1.0, CH_2Cl_2); IR (film) 3431, 1498, 1251, 1042 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 6H), 2.69 (dd, J = 4.1, 12.2 Hz, 3H), 2.70 (dd, J = 4.2, 12.0 Hz, 1H), 3.25 (s, NH, OH), 3.69 (q, J = 6.4 Hz, 1H), 3.96 (q, J = 6 Hz, 1H), 4.03 (q, J = 6.6 Hz, 2H), 5.14 (d, J = 4.1 Hz, 1H), 6.639–7.331 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.92, 24.27, 29.86, 47.56, 58.27, 62.38, 64.30, 72.86, 85.11, 113.30, 116.91, 120.85, 122.03, 126.37, 126.62, 126.84, 127.73, 128.39, 128.43, 138.25, 145.30, 147.73,

149.23. HRMS (FAB): Calcd for $C_{25}H_{29}NO_3$: 391.2147. Found: 391.2130.

4.1.6. Representative procedure for the condensation of the corresponding aminoalcohol 7a or 7b with bromo acetyl bromide to give bromo acetamide 8a or 8b

4.1.6.1. (1′*S*,2*R*,3*S*)-(−)-2-Bromo-*N*-[3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropyl]-*N*-(1′-phenyl-ethyl)acetamide (8a). To a stirred solution of aminoalcohol **7a** (0.07 g, 0.178 mmol) in 20 mL of CH_2Cl_2 at 0 °C was added dropwise and alternately a solution of triethylamine (0.017 g, 0.178 mmol) and bromo acetyl bromide (0.035 g, 0.178 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at 0 °C for 20 min. Finally, the reaction was quenched with an aqueous solution of HCl (0.5 M, 3 mL). The organic phase was washed with a brine solution (15 mL) and dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated to yield the desired chiral bromo acetamide **8a** (0.09 g, 95% yield) as a white oil. $[\alpha]_D^{20} = -17.6$ (*c* 1.0, CH_2Cl_2); IR (film) 3431, 1640, 1512, 1256 cm^{-1}. The spectroscopic details of ^1H NMR and ^{13}C NMR were omitted because their spectra show the presence of a complex rotameric mixture. HRMS (FAB): Calcd for $C_{27}H_{30}BrNO_4$: 511.1358. Found: 511.1312.

4.1.6.2. (1′*S*,2*S*,3*R*)-2-Bromo-*N*-[3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropyl]-*N*-(1′-phenyl-ethyl)acetamide 8b. Amino-alcohol **7b** (0.05 g, 0.127 mmol) was converted into **8b** (0.06 g, 95%). $[\alpha]_D^{20} = -56.5$ (*c* 1.0, CH_2Cl_2); IR 3411, 1634, 1501, 1250 cm^{-1}. The spectroscopic details of ^1H NMR and ^{13}C NMR were omitted because their spectra present the presence of a complex rotameric mixture. HRMS (FAB): Calcd for $C_{27}H_{30}BrNO_4$: 511.1358. Found: 511.1323.

4.1.7. Representative procedure for the cyclization of haloamide 8a or 8b to give chiral morpholin-3-one (9a or 9b)

4.1.7.1. (1′*S*,6*R*)-(+)-6-[(*S*)-(2-Ethoxy-phenoxy)-phenyl-methyl)-4-(1′-phenyl-ethyl)-morpholin-3-one 9a. To a stirred solution of haloamide **8a** (0.097 g, 0.189 mmol) in anhydrous THF (6 mL) at 0 °C was added a solution of *t*-BuOK (0.023 g, 0.207 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred for 30 min at 0 °C, and then the reaction was quenched with brine solution (10 mL), and the organic phase was dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to give the corresponding morpholinone-3-one **9a** (0.077 g) as a white oil in a 95% yield. $[\alpha]_D^{20} = +4.8$ (*c* 1.0, CH_2Cl_2); IR (film) 1644, 1495, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7 Hz, 3H), 1.55 (d, J = 7.1 Hz, 3H), 3.10 (dd, J = 10.1, 12.5 Hz, 1H), 3.61 (dd, J = 2.9, 12.6 Hz, 1H), 3.93 (m, 2H), 4.05 (m, 1H), 4.11 (d, J = 9.8 Hz, 1H), 4.34 (d, J = 16.6 Hz, 1H), 4.92 (d, J = 7.7 Hz, 1H), 6.12 (q, J = 7.0 Hz, 1H), 6.53–7.36 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.87, 15.26, 29.68, 42.61, 49.74, 64.09, 67.93, 76.72, 82.04, 113.44–149.80, 166.34. HRMS (FAB): Calcd for $C_{27}H_{29}NO_4$: 431.2097. Found: 431.2074.

4.1.7.2. (1′*S*,6*S*)-(−)-[(*R*)-(2-Ethoxy-phenoxy)-phenyl-methyl]-4-(1′-phenyl-ethyl)-morpholin-3-one 9b. $[\alpha]_D^{20} = -102.6$ (*c* 1.0, CH_2Cl_2); IR (film) 1644, 1495, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.0 Hz, 3H), 1.55 (d, J = 7.2 Hz, 3H), 3.35 (dd, J = 12.3, 2.8 Hz, 1H), 3.51 (dd, J = 10.0, 12.2 Hz, 1H), 3.97 (q, J = 7.0 Hz, 2H), 4.11 (d, J = 16.6 Hz, 1H), 4.33 (d, J = 16.6 Hz, 1H), 4.99 (d, J = 7.2 Hz, 1H), 6.11 (q, J = 7.1 Hz, 1H), 6.56–7.36 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.99, 15.41, 42.45, 49.68, 64.22, 67.79, 76.47, 81.88, 113.60–149.64, 166.37. HRMS (FAB): Calcd for $C_{27}H_{29}NO_4$: 431.2097. Found: 431.2077.

4.1.8. General procedures for the reduction of an amide function with borane dimethyl sulfide complex (BMS)

4.1.8.1. (1′*S*,2*R*,2a*S*)-(−)-2-[(2-Ethoxy-phenoxy)-phenyl-methyl]-4-(1′-phenyl-ethyl)-morpholine 10a. To a stirred solution of morpholin-3-one **9a** (0.077 g, 0.178 mmol) in anhydrous THF at 0 °C, under a nitrogen atmosphere, was added BMS (0.05 mL, 0.040 g, 0.530 mmol). The reaction mixture was stirred for 8 h at room temperature. Later, the reaction was quenched with methanol (2 mL) and stirred for 1 h. Finally, the solvent was evaporated under reduced pressure, and the crude was purified via flash chromatography column giving the desired compound **10a** as a white oil (0.07 g, 95% yield). $[\alpha]_D^{20} = -5.5$ (*c* 1.0, CH_2Cl_2); IR (film) 1496, 1210, 1117 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.6 Hz, 3H), 1.34 (d, J = 6.8 Hz, 3H), 2.20 (m, 2H), 2.73 (dd, J = 1.9, 11.2 Hz, 1H), 3.14 (m, 1H), 3.47 (q, J = 6.72 Hz, 1H), 3.60 (m, 1H), 3.90 (m, 4H), 4.96 (d, J = 7 Hz, 1H), 6.63 (m, 2H), 6.79 (m, 2H), 7.30 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.03, 18.62, 49.76, 52.88, 64.62, 64.70, 67.15, 78.86, 82.32, 114.54–149.63. HRMS (FAB): Calcd for $C_{27}H_{31}NO_3$: 417.2304. Found: 417.2300.

4.1.8.2. (1′*S*,2*S*,2a*R*)-(−)-2-[(2-Ethoxy-phenoxy)-phenyl-methyl]-4-(1′-phenyl-ethyl)-morpholine 10b. $[\alpha]_D^{20} = -18.5$ (*c* 1.0, CH_2Cl_2); IR (film) 1501, 1250, 1116 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.4 Hz, 3H), 1.42 (d, J = 7 Hz, 3H), 2.04 (m, 1H), 2.21 (dd, J = 10.6, 10.6 Hz, 1H), 2.47 (dd, J = 11.2, 2 Hz, 1H), 3.33 (q, J = 6.8 Hz, 1H), 3.53 (m, 2H), 3.74 (m, 1H), 3.98 (m, 3H), 5.04 (d, J = 6.8 Hz, 1H), 6.68 (m, 2H), 6.83 (m, 2H), 7.29 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.10, 20.22, 51.22, 52.63, 64.56, 65.51, 67.21, 78.96, 82.48, 114.09–149.64. HRMS (FAB): Calcd for $C_{27}H_{31}NO_3$: 417.2304. Found: 417.2298.

4.1.9. Chemoselective N-debenzylation by a catalytic transfer hydrogenation process

To a stirred suspension of 10% Pd-C (0.08 g) in absolute ethanol (6 mL) at room temperature was added the corresponding *N*-benzylmorpholine (0.08 g, 1 equiv, 0.195 mmol). To the resulting mixture, ammonium formate (0.030 g, 2.5 equiv, 0.475 mmol) was added and the mixture was refluxed for 10 min. Finally, the mixture was filtered through a path of diatomite and the solvent was eliminated in vacuo. The corresponding reboxetine was purified by column chromatography (Silica gel, CH_2Cl_2/MeOH, 95:5) giving the desired compound.

4.1.9.1. (2*R*)-(+)-2-[(*S*)-(2-Ethoxy-phenoxy)-phenyl-methyl]-morpholine. (*R*,*S*)-Reboxetine (0.048 g, yield 80%) $[\alpha]_D^{20} = +16.1$ (*c* 1.0, CH_2Cl_2); IR (film) 2919, 1500, 1252, 1119, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.0 Hz, 3H), 2.64 (b, 2H), 2.91 (m, 3H), 3.31 (dd, J = 2.02, 12.54 Hz, 1H), 3.55 (td, J = 2.8, 11.06 Hz, 1H), 3.82 (m, 1H), 3.87 (m, 1H), 4.06 (qd, J = 2.8, 6.98 Hz, 2H), 5.06 (d, J = 6.16 Hz, 1H), 6.66 (m, 2H), 6.83 (m, 2H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.06, 29.69, 45.59, 47.12, 64.56, 67.92, 79.46, 82.78, 114.00, 117.27, 120.80, 121.98, 127.20, 127.42, 127.87, 128.24, 138.72, 147.60, 149.64. HRMS (FAB): Calcd for $C_{19}H_{23}NO_3$: 313.1678. Found: 313.1665.

4.1.9.2. (2*S*)-(+)-2-[(*R*)-(2-Ethoxy-phenoxy)-phenyl-methyl]-morpholine. (*S*,*R*)-Reboxetine (yield 80%) $[\alpha]_D^{20} = -15.9$ (*c* 1.0, CH_2Cl_2).

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