Tetrahedron: *Asymmetry* 23 (2012) 650–654

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

The synthesis of (*R*,*S*)-reboxetine employing a tandem cyclic sulfate rearrangement—opening process

Jin Yu, Soo Y. Ko *

Department of Chemistry, Ewha Womans University, Seoul 120-750, Republic of Korea

ARTICLE INFO

Article history:
Received 14 March 2012
Accepted 26 April 2012
Available online 8 June 2012

ABSTRACT

(*R*,*S*)-Reboxetine was synthesized in nine steps and with 43% overall yield starting from *trans*-cinnamyl alcohol. Following silylation and AD steps, the two hydroxyl groups at C-1 and C-2 were simultaneously activated to the cyclic sulfate. A series of tandem reactions initiated by desilylation transposed the activation to C-3, then to C-1, where nucleophilic displacements took place in succession. During this process, the configuration at C-2 was inverted while that at C-1 was retained through a double inversion.

1. Introduction

The phenylpropylamino group, with aryloxy substituents at the benzylic carbon, is a common structural motif in many compounds acting on the central nervous system. Examples include fluoxetine, tomoxetine, nisoxetine, and reboxetine (Fig. 1).[1] Reboxetine is a potent selective norepinephrine reuptake inhibitor and displays an efficacy for the treatment of depression and attention deficit/hyperactivity disorder (ADHD). It is currently marketed as a racemic mixture of (*S*,*S*)- and (*R*,*R*)-stereoisomers, of which the (*S*,*S*)-enantiomer is more potent than the (*R*,*R*)-isomer.[2]

Recently, the diastereomeric (*R*,*S*)- and (*S*,*R*)-reboxetine isomers have attracted interest. Some iodine-substituted (*R*,*S*)-reboxetine analogues show an affinity for the norepinephrine transporter which is very comparable to that of the (*S*,*S*)-isomers and much higher than that displayed by the (*S*,*R*)-antipodes. These observations have led to speculations that the diastereomeric (*R*,*S*)-reboxetine might become a useful therapeutic agent.[3]

Synthetic efforts toward the reboxetines have produced several approaches.[3–8] The strategies for stereochemical control include asymmetric reactions, the use of enantio-pure starting materials, and the use of chiral auxiliaries. Of the asymmetric reactions employed in the enantioselective synthesis of reboxetines, Sharpless's asymmetric oxidations, that is, epoxidation (AE) and dihydroxylation (AD), are popular protocols. It should be noted that both AE and AD processes have been employed for the synthesis of *syn*-(*S*,*S*)- or *syn*-(*R*,*R*)-reboxetine and derivatives, while for the synthesis of *anti*-(*R*,*S*)- or *anti*-(*S*,*R*)-stereoisomers, only AE-based strategies have been reported so far. It is presumed that the synthesis of the *anti*-isomers requires a configurational inversion at one of the stereocenters following the asymmetric oxidation step; the AE protocol may seem advantageous in this regard as the AE product has already one stereocenter activated toward nucleophilic displacement. Note that a chiral auxiliary-based approach has also been reported for the synthesis of (*R*,*S*)- and (*S*,*R*)-reboxetines (Scheme 1).[3]

We envisaged an efficient AD-based strategy for the synthesis of reboxetine, wherein the required activation at C-1 and C-3 (for the introduction of N-functionality at C-3, and the aryloxy functionality at C-1) would be realized in a single activation step using cyclic sulfate formation and a subsequent rearrangement—opening process. Herein we report the synthesis of diastereomeric (*R*,*S*)-reboxetine.

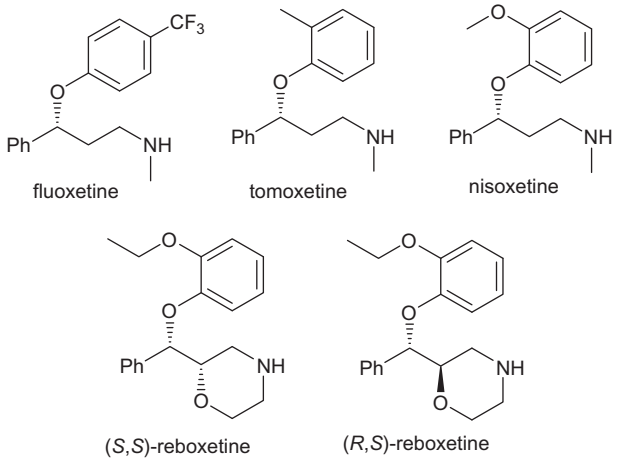
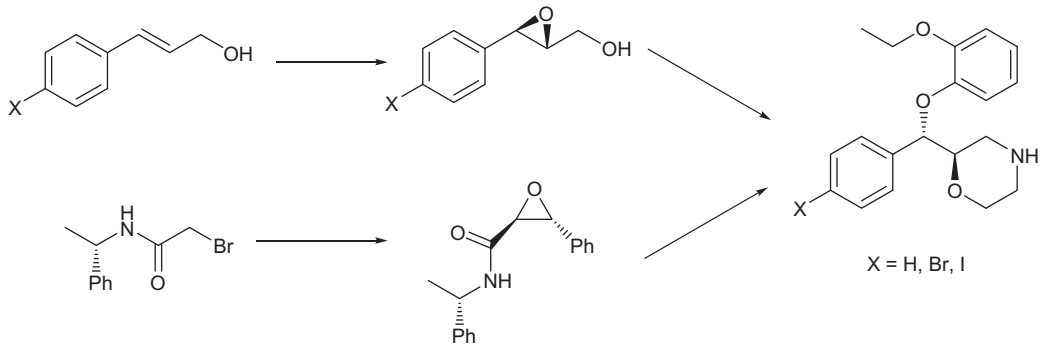


Figure 1. Aryloxy-substituted phenylpropylamino compounds acting on CNS.

* Corresponding author. Tel.: +82 2 3277 3283; fax: +82 2 3277 2384.
E-mail address: sooyko@ewha.ac.kr (S.Y. Ko).

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2012.04.018

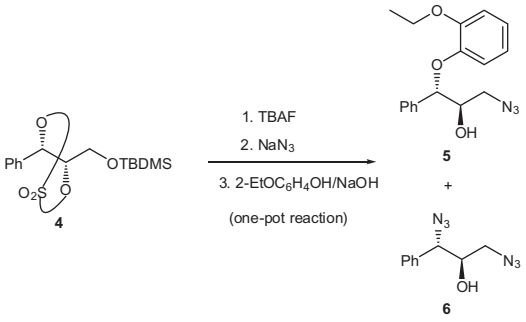


Scheme 1. Synthetic strategies for (*R*,*S*)-reboxetine (derivatives) in the literature.

2. Results and discussion

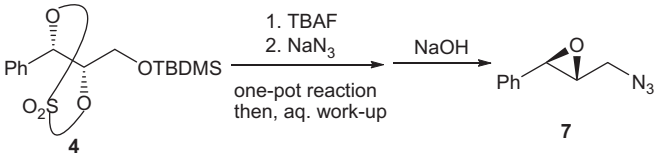
The cyclic sulfate rearrangement—opening process is a series of tandem reactions that produces *anti*-diols following AD reactions (Scheme 2).[9] It was originally developed to address the limitation of the AD protocol, that is, its inability to produce *anti*-diols directly since (*Z*)-alkenes are not good substrates for the AD. The inversion at C-2 and the introduction of various nucleophiles at C-3 are reminiscent of the Payne rearrangement—opening process of epoxy alcohols.[10] In the original protocol for a cyclic sulfate rearrangement—opening process, the reaction mixture was subjected to acidic hydrolysis conditions, to give *anti*-diol products **F**. Before the hydrolysis, intermediate **E** has a sulfate anion at C-1. We decided to explore a possible use for this potential leaving group in our synthetic efforts toward the reboxetines.

The *trans*-cinnamyl alcohol was TBDMS-protected (100%). The AD (AD-mix-α, 95%, >98% ee), cyclic sulfate formation ($SOCl_2$; $NaIO_4/RuCl_3$, 100%) sequence proceeded uneventfully (Scheme 3). Desilylation (TBAF) prompted a rearrangement to the terminal epoxide, which was then opened by N_3^-. The reaction mixture was then treated with 2-ethoxyphenol/NaOH. Two products were isolated after acidic work-up and were the 1-ethoxyphenoxy-3-azido-2-ol compound **5** (36%) and the 1,3-diazido-2-ol compound **6** (62%) (Eq. 1).



(1)

The formation of these two products meant that the nucleophilic substitutions did take place at C-1, since the sulfate anion (in the intermediate corresponding to **E**) was displaced. The formation of the diazido compound **6** was due to the presence of excess N_3^- carried over from the epoxide-opening step; the entire sequence of the reactions was performed in a single reaction vessel. Close inspection of the products revealed that they were both the (1*S*,2*R*)-isomers. The inversion of configuration at C-2 from the AD-α product was a consequence of the cyclic sulfate rearrangement. On the other hand, the apparent retention of configuration at C-1, where the nucleophilic substitutions had also taken place, seemed surprising at first. Subsequent studies indicated that epoxide **7** was probably the precursor for the two products. When the cyclic sulfate rearrangement—opening product was subjected to a blank reaction (the excess N_3^- having been removed through extractive work-up and the 2-ethoxyphenol was omitted), epoxide **7** was isolated in >80% yield (Eq. 2). Clearly, the initial product following the cyclic sulfate rearrangement—opening process (**E** in Scheme 2) underwent an epoxide ring-closure to give **7**, the alkoxide at C-2 intramolecularly displacing the sulfate anion at C-1. The resulting epoxide was then ring-opened by nucleophiles at the benzylic C-1 site, with an overall double inversion (retention) of configuration at C-1 taking place. Similar intramolecular nucleophilic displacements of a sulfate anion have been reported for β-amino sulfate and β-malonyl sulfate compounds.[11,12]



(2)

Optimization of the reaction conditions led to a procedure that involved an extractive work-up after the cyclic sulfate rearrangement—opening step and subsequent treatment of the crude N_3^--opened product **E** with 2-ethoxyphenol/NaOH. The (1*S*,2*R*)-1-ethoxyphenoxy-3-azido-2-ol compound **5** was obtained in 84% yield from the cyclic sulfate **4**.

Reduction of the 3-azido functionality (H_2, Pd/C, 88%), amidation of **8** to **9** (chloroacetyl chloride, 84%), cyclization of **9** to **10** (KOtBu, 99%), and reduction of the lactam function of **10** to **11** ($BH_3{\cdot}Me_2S$, 73%) all proceeded smoothly to yield (*R*,*S*)-reboxetine **11** (Scheme 3).

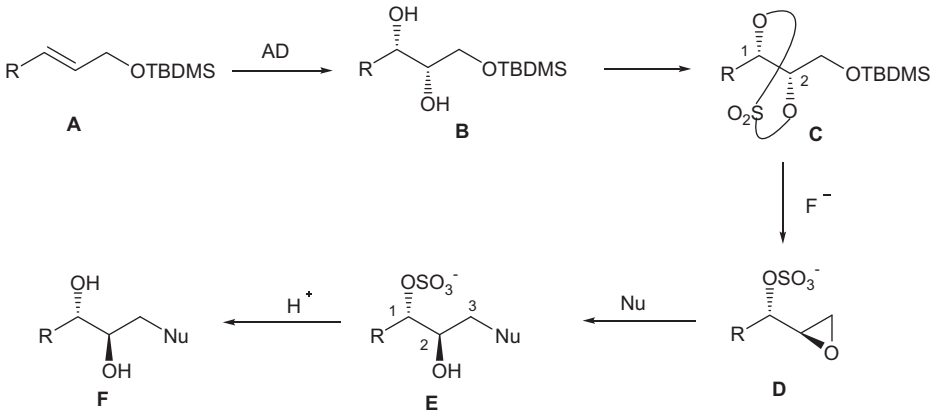
3. Conclusion

In conclusion, (*R*,*S*)-reboxetine was synthesized in nine steps and with 43% overall yield by starting from *trans*-cinnamyl alcohol. Following silylation and AD steps, the two hydroxyl groups at C-1 and C-2 were simultaneously activated in a single operation as the cyclic sulfate. A series of tandem reactions initiated by desilylation transposed the activation to C-3, then to C-1, where N_3^- and 2-ethoxyphenoxy nucleophiles were introduced, respectively. During this process, the configuration at C-2 was inverted while that at C-1 was retained through a double inversion.

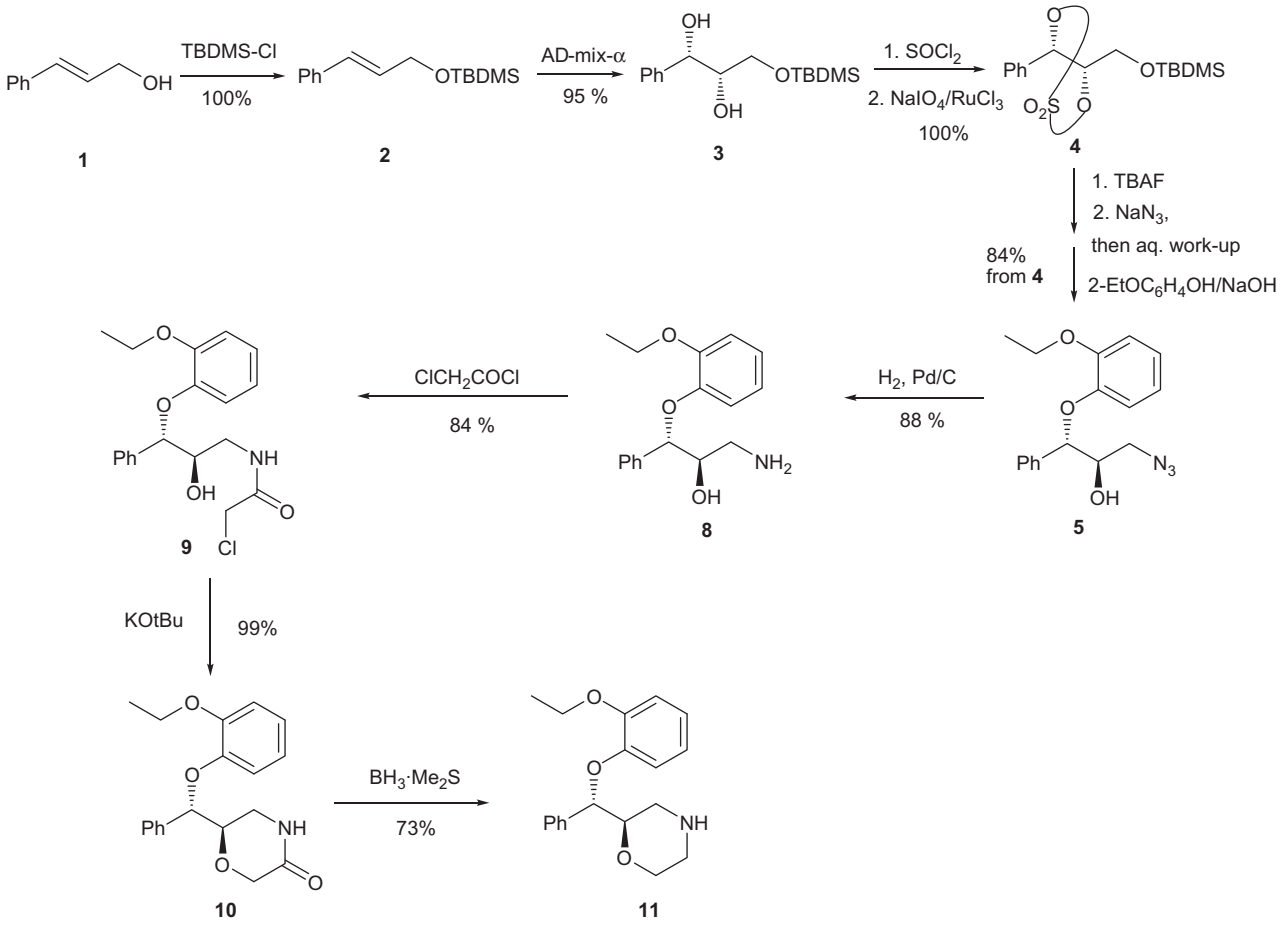
4. Experimental

4.1. General

Reactions were monitored by TLC on silica gel glass-backed plates. Proton NMR spectra were recorded in ppm relative to TMS



Scheme 2. Cyclic sulfate rearrangement-opening process.



Scheme 3. Synthetic pathway for (*R,S*)-reboxetine.

as an internal standard. The following abbreviations designate splitting patterns: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet), br (broad). IR spectra were recorded as thin films on KRS-5 or KBr plates. HRMS were recorded by electronspray ionization. Melting points are uncorrected.

4.1.1. Cinnamyloxy-*tert*-butyldimethylsilane 2[13]

A solution of *trans*-cinnamyl alcohol (4.794 g, 35.73 mmol) in DMF (120 mL) was treated with *tert*-butyldimethylchlorosilane (8.076 g, 53.38 mmol) and imidazole (3.649 g, 53.6 mmol). The mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure, and the residue was extractively worked-up ($CHCl_3$–brine). The combined organic phases were dried (anhydrous Na_2SO_4) and concentrated. Flash column chromatography (hexane–EtOAc 10:1) yielded the desired product **2** as a colorless liquid (8.875 g, 35.74 mmol, 100%). ^{1}H NMR($CDCl_3$): δ 7.40–7.21 (5H, m, *Ar*), 6.59 (1H, d, J = 15.9 Hz, Ph-C*H*), 6.29 (1H, dt, J = 15.8, 5.0 Hz, Ph-CH=C*H*), 4.35 (2H, dd, J = 1.7, 5.0 Hz, CH_2–O), 0.94 (9H, s, *t-Bu*), 0.11 (6H, s, SiMe_2) ppm. IR: 3027(s), 2956(s), 2929(s), 2857(s), 2101(s), 1472(s), 1257(s), 835(s), 681(s) cm^{-1}.

4.1.2. (1*S*,2*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-phenylpropane-1,2-diol 3[13]

At first, AD-mix-α (11.82 g) was dissolved in ^{t}BuOH and H_2O (1:1 v/v, 50 mL). Methanesulfonamide (0.804 g, 8.46 mmol) was then added and the mixture was cooled at 0 °C. Next, (cinnamyloxy)-*tert*-butyldimethylsilane **2** (2.163 g, 8.706 mmol) was added as a ^{t}BuOH–H_2O (1:1 v/v, 40 mL) solution. The mixture was cooled at 0 °C and stirred for 9.5 h. The reaction was quenched by adding Na_2SO_3 (13.1 g). The mixture was stirred for 1 h at rt, then extracted with ethyl acetate. The organic phases were combined, washed with brine, and dried (Na_2SO_4). Flash silica column chromatography (hexane–EtOAc 4:1) yielded the product **3** (2.326 g, 8.324 mmol, 95%). Chiral HPLC analysis (Chiralpak AD-H) indicated the product to be >98% ee. ^{1}H NMR ($CDCl_3$): δ 7.41–7.32 (5H, m, *Ar*), 4.72 (1H, dd, *J* = 2.8, 5.8 Hz, Ph-C*H*), 3.75–3.53 (3H, m, C*H*(OH)–CH_2O), 3.14 (1H, d, *J* = 2.8 Hz, O*H*), 2.67 (1H, d, *J* = 6.3 Hz, O*H*), 0.92 (9H, s, *t-Bu*), 0.07 (6H, s, Si*Me*$_2$) ppm. IR: 3429(br), 2955(s), 2929(s), 2857(s), 1472(s), 1120(s) cm^{-1}. HRMS(EI) calcd for $C_{15}H_{26}O_3Si$ [M]$^+$ 282.1651, found 282.1668. $[\alpha]_D^{28} = +11.9(c1.03, \text{EtOH})$.

4.1.3. Formation of the cyclic sulfate 4[13]

Compound **3** (1.809 g, 6.406 mmol) was dissolved in dichloromethane (65 mL). Next, Et_3N (2.105 mL, 15.12 mmol) was added followed by $SOCl_2$ (0.5909 mL, 8.136 mmol). The mixture was stirred at 0 °C for 10 min. Extractive work-up ($CHCl_3$–brine) was followed by concentration. The crude cyclic sulfite thus obtained was dissolved in CCl_4 (18 mL). Next, $NaIO_4$ (2.609 g, 12.2 mmol) and $RuCl_3{\cdot}3H_2O$ (0.0728 g, 0.351 mmol) were added, and the mixture was diluted by adding H_2O (27 mL) and CH_3CN (18 mL). The mixture was stirred at 0 °C for 1 h. The mixture was concentrated and the residue was isolated by extractive work-up ($CHCl_3$–brine). Drying (Na_2SO_4) and concentration yielded the desired cyclic sulfate **4** (2.199 g, 6.383 mmol, 100%). ^{1}H NMR($CDCl_3$) δ 7.46 (5H, s, *Ar*), 6.20 (1H, d, *J* = 8.8 Hz, Ph-C*H*), 4.81 (1H, dt, *J* = 8.9, 3.2 Hz, Ph–CH–CH–CH_2) 4.03 (1H, dd, *J* = 12.7, 3.1 Hz, CH_AH$_B$O) 3.81 (1H, dd, *J* = 12.7, 3.3 Hz, CH$_A$$H_B$O) 0.91 (9H, s, *t-Bu*) 0.11 (6H, d, *J* = 7.1 Hz, Si*Me*$_2$) ppm.

4.1.4. (1*S*,2*R*)-3-Azido-1-(2-ethoxyphenoxy)-1-phenylpropan-2-ol 5

Cyclic sulfate **4** (1.028 g, 2.984 mmol) was dissolved in THF (20 mL). Tetrabutylammonium fluoride (1 M in THF, 3.58 mL, 3.58 mmol) was added and the mixture was stirred at rt for 30 min. Next, NaN_3 (0.388 g, 5.973 mmol), THF (34 mL), and H_2O (5.4 mL) were added and the mixture was stirred at 70 °C for 21 h. The mixture was concentrated and the residue was partitioned between H_2O and $CHCl_3$. Extractive work-up ($CHCl_3$–brine), drying (Na_2SO_4), and concentration yielded the crude epoxide ring-opened product (2.35 g, 2.95 mmol as quantified by NMR with an external standard, 99%).

2-Ethoxyphenol (0.68 mL, 5.415 mmol) was treated with NaOH (5.41 mmol) in H_2O (4.5 mL). The mixture was stirred at rt for 1 h. The crude intermediate obtained above (2.16 g, 2.70 mmol) and H_2O (7 mL) were then added. The mixture was heated at reflux for 5 h. Extractive work-up ($CHCl_3$–brine) was followed by drying (Na_2SO_4) and concentration. Flash silica column chromatography (hexane–EtOAc 4:1) yielded the desired product **5** as a yellow liquid (0.719 g, 2.294 mmol, 84% from **4**). ^{1}H NMR ($CDCl_3$) δ 7.46–7.26 (5H, m, *Ar*), 6.98–6.71 (4H, m, O*Ar*), 5.05 (1H, d, *J* = 5.1 Hz, Ph-C*H*), 4.19–4.04 (3H, m, C*H*(OH)–CH_2, O–CH_2–CH_3), 3.56 (1H, dd, *J* = 12.6, 7.8 Hz, CH_AH$_B$N$_3$), 3.33 (1H, dd, *J* = 12.9, 3.3 Hz, CH$_A$$H_BN_3$), 3.25 (1H, d, *J* = 6.9 Hz, O*H*), 1.51 (3H, t, *J* = 6.9 Hz, O–CH$_2$–CH_3) ppm. IR: 3442(br), 2102(s), 1501(s), 1254(s), 1124(s) cm^{-1}. $[\alpha]_D^{29} = +33.8(c1.04, \text{EtOH})$. HRMS(EI) calcd for $C_{17}H_{19}N_3O_3$ [M]$^+$ 313.1426, found 313.1425.

4.1.5. (1*S*,2*R*)-3-Amino-1-(2-ethoxyphenoxy)-1-phenylpropane-2-ol 8

Azide compound **5** (0.159 g, 0.508 mmol) was dissolved in EtOAc (20 mL) and Pd/C 10% (0.049 g) was added. The mixture was subjected to an H_2 atmosphere for 30 min. The mixture was filtered through Celite, which was washed with MeOH. The filtrate and washings were combined and concentrated. Flash silica column chromatography (MeOH–EtOAc 9:1) yielded the product **8** (0.128 g, 0.446 mmol, 88%). ^{1}H NMR ($CDCl_3$): δ 7.39–7.26 (5H, m, *Ar*), 6.88–6.49 (4H, m, O*Ar*), 5.15 (1H, d, *J* = 4.2 Hz, Ph-C*H*), 4.09 (2H, q, *J* = 6.9 Hz, O–CH_2–CH_3), 3.85 (1H, dd, *J* = 9.6, 4.2 Hz, C*H*(OH)), 2.98 (1H, dd, *J* = 12.9, 5.7 Hz, CH_AH$_B$N), 2.82 (1H, dd, *J* = 12.9, 4.2 Hz, CH$_A$$H_B$N), 2.55 (3H, br s, O*H*, NH_2), 1.48 (3H, t, *J* = 6.9 Hz, O–CH$_2$–CH_3) ppm. IR: 3373(br), 1593(s), 1507(s), 1251(s), 1221(s), 1124(s), 742(s), 697(s) cm^{-1}. Mp: 102–103 °C. HRMS(EI) calcd for $C_{17}H_{21}NO_3$ [M]$^+$ 287.1521, found 287.1524. $[\alpha]_D^{29} = +20.3(c0.74, \text{EtOH})$.

4.1.6. *N*-[(2*R*,3*S*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenylpropyl]-2-chloroacetamide 9

Amino compound **8** (0.127 g, 0.443 mmol) was dissolved in ethyl ether (2 mL). Saturated aq $NaHCO_3$ solution (2 mL) was added and the mixture was cooled to −10 °C. Chloroacetyl chloride (0.0388 mL, 0.487 mmol) was added as an ethyl ether solution (2 mL) over 5 min. The mixture was stirred at −10 °C for 10 min and then warmed to rt where it was stirred for further 10 min. Extractive work-up ($CHCl_3$–brine), drying (Na_2SO_4), concentration, and flash silica column chromatography (hexane–EtOAc 2:3) yielded the product **9** as a white solid (0.135 g, 0.369 mmol, 84%). ^{1}H NMR ($CDCl_3$): δ 7.47–7.31 (5H, m, *Ar*), 7.16 (1H, s, N*H*), 7.01–6.72 (4H, m, O*Ar*), 5.06 (1H, d, *J* = 4.5 Hz, Ph-C*H*), 4.21–4.11 (2H, m, O-CH_2-CH_3), 4.06–3.98 (3H, m, CH_2-Cl, C*H*(OH)), 3.73 (1H, ddd, *J* = 14.4, 7.2, 3.6 Hz, CH_AH$_B$N), 3.67 (1H, d, *J* = 7.2 Hz, O*H*), 3.35 (1H, ddd, *J* = 13.8, 7.5, 4.2 Hz, CH$_A$$H_B$N), 1.53 (3H, t, *J* = 7.2 Hz, O–CH$_2$–CH_3) ppm. IR: 3537(s), 3398(s), 1679(s) 1503(s), 1251(s), 1125(s), 743(s) cm^{-1}. Mp: 59–63 °C. $[\alpha]_D^{28} = +36.5(c0.69, \text{EtOH})$. HRMS(EI) calcd for $C_{19}H_{22}ClNO_4$ [M]$^+$ 363.1237, found 363.1238.

4.1.7. (*R*)-6-[(*S*)-(2-Ethoxyphenoxy)(phenyl)methyl]morpholin-3-one 10

To a solution of KO^{t}Bu (0.144 g, 1.281 mmol) in ^{t}BuOH (2 mL) was added compound **9** (0.233 g, 0.641 mmol) in ^{t}BuOH (5 mL). The mixture was stirred at rt for 1 h. The reaction was quenched by adding 0.5 M HCl (10 mL). Extractive work-up ($CHCl_3$–brine), drying (Na_2SO_4), concentration, and flash silica column chromatography (EtOAc–EtOH 15:1) yielded the desired product **10** as a liquid (0.207 g, 0.633 mmol, 99%). ^{1}H NMR ($CDCl_3$): δ 7.44–7.33 (5H, m, *Ar*), 6.91–6.65 (4H, m, O*Ar*), 5.95 (1H, s, N*H*), 5.13 (1H, d, *J* = 6.9 Hz, Ph-C*H*), 4.30 (1H, d, *J* = 16.8 Hz, C(=O)-CH_AH$_B$), 4.12–4.03 (4H, m, C(=O)-CH$_A$$H_B$, O–C$H_2$–$CH_3$, Ph–CH–CH–C$H_2$), 3.75–3.72 (2H, m, C$H_2$–NH), 1.47 (3H, t, *J* = 7.2 Hz, O-CH$_2$-CH_3) ppm. IR: 3227(br), 1680(s), 1594(s), 1501(s), 1455(s), 1253(s), 1216(s), 744(s) cm^{-1}. $[\alpha]_D^{28} = +67.8(c0.53, \text{EtOH})$. HRMS(EI) calcd for $C_{19}H_{21}NO_4$ [M]$^+$ 327.1471, found 327.1470.

4.1.8. (*R*)-2-[(*S*)-(2-Ethoxyphenoxy)(phenyl)methyl]morpholine 11 [(*R*,*S*)-reboxetine]

A solution of compound **10** (0.168 g, 0.513 mmol) in THF (5 mL) was cooled to 0 °C. Next, $BH_3{\cdot}SMe_2$ (2 M THF, 0.9 mL, 1.8 mmol) was added over 30 min. The mixture was slowly warmed to rt, then heated to 70 °C, where it was stirred for 20 h. The mixture was cooled to rt and H_2O (6 mL) was added. The mixture was then concentrated. Ethyl acetate (1 mL) and 5 M HCl (18 mL) were added and the mixture was stirred at rt for 2 h. Aqueous NaOH solution (10 M, 14 mL) was then added and the mixture extracted with $CHCl_3$ (20 mL × 9). The combined organic phases were washed with

brine, dried (Na_2SO_4), and concentrated. Flash silica column chromatography (EtOAc–MeOH 1:2) yielded (*R*,*S*)-reboxetine **11** (0.117 g, 0.374 mmol, 73%). Chiral HPLC analysis (Chiralcel OD-H) indicated the product to be >98% ee. ^{1}H NMR ($CDCl_3$): δ 7.41–7.33 (5H, m, *Ar*), 6.85–6.67 (4H, m, O*Ar*), 5.06 (1H, d, J = 6.3 Hz, Ph-C*H*), 4.07 (2H, td, J = 6.9, 1.2 Hz, O–CH_2–CH_3), 3.88 (1H, dt, J = 11.1, 2.7 Hz, Ph–CH–C*H*–CH_2), 3.83–3.78 (1H, m, OCH_AH$_B$), 3.54 (1H, td, J = 11.1, 2.7 Hz, OCH$_A$$H_B$), 3.33 (1H, dd, J = 12.3, 2.1 Hz, CH_AH$_B$-NH), 2.99–2.88 (2H, m, CH_2-NH), 2.82 (1H, t, J = 12.3 Hz, CH$_A$$H_B$-NH), 1.74 (2H, s, N*H*), 1.45 (3H, t, J = 7.2 Hz, O-CH_2-CH_3) ppm. IR: 3334(br), 2976(br), 1592(s), 1501(s), 1455(s), 1254(s), 1217(s), 1124(s), 1045(s), 746(s) cm^{-1}. $[\alpha]_D^{28} = +16.0 (c 0.68, CH_2Cl_2)$. HRMS(EI) calcd for $C_{19}H_{23}NO_3$ [M]$^+$ 313.1678, found 313.1679.

References

1. (a) Kent, J. M. *Lancet* **2000**, *355*, 911; (b) Dostert, P.; Benedetti, M. S.; Poggesi, I. *Eur. Neuropsychophamacol.* **1997**, S23.
2. (a) Melloni, P.; Carniel, G.; Della Torre, A.; Bensignon, A. .; Buonamici, A.; Pozzi, O.; Ricciardi, S.; Rossi, A. C. *Eur. J. Med. Chem.* **1984**, *19*, 235; (b) Hajós, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev.* **2004**, *10*, 23.
3. (a) Jobson, N. K.; Spike, R.; Crawford, A. R.; Dewar, D.; Pimlott, S. L.; Sutherland, A. *Org. Biolol. Chem.* **2008**, *6*, 2369; (b) Jobson, N. K.; Crawford, A. R.; Dewar, D.; Pimlott, S. L.; Sutherland, A. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 4940; (c) Bischoff, R.; Hamilton, D. J.; Jobson, N. K.; Sutherland, A. J. *Label. Compd. Radiopharm.* **2007**, *50*, 523; (d) Aparicio, D. M.; Terán, J. L.; Gneco, D.; Galindo, A.; Juárez, J. R.; Orea, M. L.; Mendoza, A. *Tetrahedron: Asymmetry.* **2009**, *20*, 2764.
4. (a) Melloni, P.; Della Torre, A.; Lazzari, E.; Mazzini, G.; Meroni, M. *Tetrahedron* **1985**, *41*, 1393; (b) Harding, W. W.; Hodge, M.; Wang, Z.; Woolverton, W. L.; Parrish, D.; Deschamps, J. R.; Prisinzano, T. E. *Tetrahedron: Asymmetry*. **2005**, *16*, 2249; (c) Henegar, K. L.; Cebula, M. *Org. Process Res. Dev*. **2007**, *11*, 354.
5. Siddiqui, S. A.; Narkhede, U. C.; Lahoti, R. J.; Srinivasan, K. V. *Synlett* **2006**, 1771.
6. Métro, T.-X.; Padro, D. G.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 707.
7. Brenner, E.; Baldwin, R. M.; Tamagnan, G. *Org. Lett.* **2005**, *7*, 937.
8. (a) Fish, P. V.; Mackenny, M.; Bish, G.; Buxton, T.; Cave, R.; Drouard, D.; Hoople, D.; Jessiman, A.; Miller, D.; Pasquinet, C.; Patel, B.; Reeves, K.; Ryckmans, T.; Skerten, M.; Wakenhut, F. *Tetrahedron Lett.* **2009**, *50*, 389; (b) Akashi, M.; Arai, N.; Inoue, T.; Ohkuma, T. *Adv. Synth. Catal.* **1955**, *2011*, 353.
9. Ko, S. Y.; Malik, M.; Dickinson, A. F. *J. Org. Chem.* **1994**, *59*, 2570.
10. (a) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819; (b) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687; (c) Hanson, R. M. Organic Reactions Vol. 60, Chapter 1 (2002).
11. (a) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623; (b) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999; (c) Lohray, B. B. *Synthesis* **1992**, 1035.
12. A report of β-hydroxyalkyl sulfate anions being converted into epoxides has appeared in the literature. See (a) Jang, D. O.; Joo, Y. H.; Cho, D. H. *Synth. Commun.* **2000**, *30*, 4489; (b) It may be possible that the epoxide precursors herein were actually β-hydroxyalkyl methyl sulfate diesters and the leaving group was a methyl sulfate anion, and not a sulfate dianion.
13. Ko, S. Y.; Lerpiniere, J. *Tetrahedron Lett.* **1995**, *36*, 2101.