Organic & Biomolecular Chemistry

Accepted Manuscript

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ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C7OB01283G

Journal Name

ARTICLE

Stereodivergent Synthesis of All the Four Stereoisomers of Antidepressant Reboxetine

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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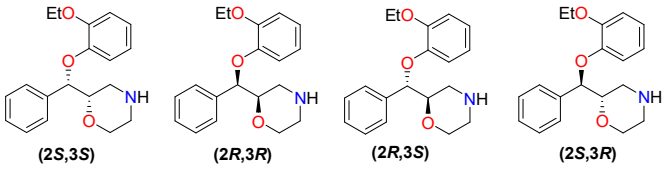
Chiral amino alcohol-copper(II) catalysts Cu-$\mathbf{L_{1c}}$ and Cu-*ent*-$\mathbf{L_{1c}}$ were utilized to promote the diastereoselective nitroaldol reactions of chiral aldehydes (*S*)-**3** or (*R*)-**3** with nitromethane, which respectively lead to the preferential formations of certain stereoisomer for nitro diol derivatives **4** . Using this catalytic protocol, all the four stereoisomers of antidepressant reboxetine are divergently prepared. The highest overall yield of this synthetic route reached up to 30.5% from aldehyde (S)-**3**.

Introduction

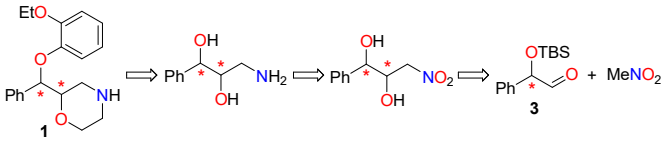
Reboxetine (**1**, Scheme 1) is a potent and selective norepinephrine reuptake inhibitor (NRI) and currently sold as an antidepressant in its racemic mixture of (*S*,*S*)- and (*R*,*R*)-enantiomers, under the trade names of Edronax, Prolift, Vestra, Norebox, and Integrex in over 60 countries.[1] In addition, Reboxetine is also found useful for the treatment of panic disorder, attention deficit/hyperactivity disorder (ADHD), narcolepsy, as well as cocaine dependence disorder.[2] Although its popularity as an antidepressant has continuously grown, reboxetine may cause several adverse effects, and even its efficacy was also challenged recently.[3]



Scheme 1. Structures of the four stereoisomers of reboxetine **1**

Several studies have shown that (*S*,*S*)-reboxetine is significantly more active and selective for the norepinephrine transporter (NET) than its (*R*,*R*)-enantiomer.[4] Therefore great efforts has been made over the past decade and several methods based on chemical resolution,[5] hydrolytic kinetic resolution,[6] optically active starting materials,[7] asymmetric epoxidation[5] and dihydroxylation,[8] as well as asymmetric transfer hydrogenation,[9] have been developed to the syntheses of (*S*,*S*)-reboxetine. Comparatively, less attention is given to the preparations of (*S*,*R*)- and (*R*,*S*)-reboxetine.[7a,9a,10] Actually, some iodinated (*R*,*S*)-reboxetines were also found to possess an affinity for NET which is very comparable to that of (*S*,*S*)-reboxetine.[11] These results mean that (*S*,*R*)- and (*R*,*S*)-reboxetine analogues should be considered as good candidates for new NRI. Therefore, a convenient and reliable approach for stereospecific syntheses of all stereoisomers of reboxetine and their analogues may greatly facilitate the research and development (R&D) of more efficacious and safer antidepressants.

Our interests in biologically active amino alcohols[12] as well as the intriguing pharmacological properties of reboxetine prompt us to develop a divergent approach to synthesize all its stereoisomers. A retrosynthetic analysis is performed and outlined in Scheme 2, which indicates that the diastereoselective nitroaldol reactions of optically active aldehydes (*S*)- or (*R*)-**3** with nitromethane are the key steps. Notably, aldehydes (*S*)- and (*R*)-**3** can be easily prepared in high yields from commercially available (*S*)- or (*R*)-mandelic acid respectively (see ESI).



Scheme 2. Retrosynthetic analysis of reboxetine

Results and discussion

Catalytic asymmetric nitroaldol (Henry) reaction is an economic and powerful tool in organic syntheses because their resulting β-nitro alcohols can be conveniently converted into β-amino alcohols and other valuable intermediates,[13] which are useful for the preparations of complex bioactive molecules. Although great progress has been made over the past two decades, the diastereoselective nitroaldol reactions of optically active α-

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Electronic Supplementary Information (ESI) available: Preparations of (*S*)- and (*R*)-**3**, Copies of HPLC and NMR data. See DOI: 10.1039/x0xx00000x

hydroxy-protected aldehydes are rarely investigated,[14] which lead to the formation of nitro diol derivatives.

Aldehyde (*S*)-**3** was used as the model substrate to screen the catalysts and to optimize the reaction conditions. In the initial experiments, organic base NEt_3 (Table 1, entry 1) and inorganic base K_2CO_3 (Table 1, entry 2) were used as catalysts to check whether certain configured nitroaldol product can be preferentially formed. However, it is found that the reactions proceeded slowly and only low diastereoselectivities (*syn/anti*) are observed, which suggests that chiral catalysts are needed to activate the substrate and concomitantly direct the asymmetric nitroaldol orientation. Thus we turn to the chiral amino alcohol-copper(II) catalysts,[12,15] which are *in situ* generated from the coordination of amino alcohol ligands $\mathbf{L_1}$ or *ent*-$\mathbf{L_1}$ (Figure 1) with $Cu(OAc)_2{\cdot}H_2O$ in 1:1 ratio respectively. Based on the known structures of copper complexes with chelated amino alcohols, the composition of the catalyst is temporarily assigned as $CuL_1(OAc)_2{\cdot}H_2O$ or its mixture with different ratios of amino alcohol.[16]

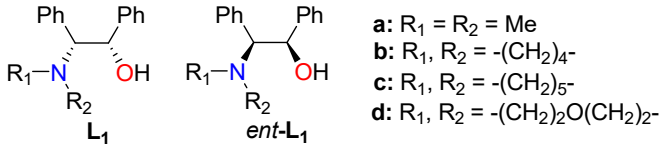
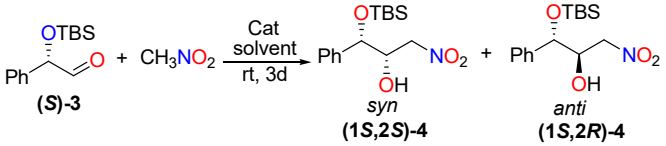


Figure 1. Chiral amino alcohol ligands $\mathbf{L_1}$ and *ent*-$\mathbf{L_1}$

The Cu-catalyzed nitroaldol reactions were summarized in Table 1 (entries 3-10), which clearly showed that catalysts Cu-$\mathbf{L_{1c}}$ (entry 7, *syn/anti* 5.9:1) and Cu-*ent*-$\mathbf{L_{1c}}$ (entry 8, *syn/anti* 1:5.0) were superior to the other catalysts. Further studies showed that solvent and catalyst loading were also crucial for the reaction. When pure $MeNO_2$ was used as solvent, both reactivity and diastereoselectivity were improved largely (entries 11-12). Catalyst Cu-$\mathbf{L_{1c}}$ gave a *syn/anti* ratio up to 10.5:1 (entry 11), while Cu-*ent*-$\mathbf{L_{1c}}$ gave a *syn/anti* ratio of 1:8.1 (entry 12); when the catalyst loading was reduced to 2.5 mmol%, both the reactivity and diastereoselectivity were simultaneously decreased (entries 13-14). Detail analysis of these data revealed that the yield as well as diastereoselectivity (*syn/anti*) from Cu-$\mathbf{L_{1c}}$ are higher than that from Cu-*ent*-$\mathbf{L_{1c}}$. This experimental observation can be explained by matched/mismatched pair between chiral substrate and the chiral catalyst (double diastereoselection).[17] In the matched case, the substrate (*S*)-**3** and the catalyst Cu-$\mathbf{L_{1c}}$ are cooperatively formed in transition state of the reaction with less steric hindrance;[15] by contrary, the mismatched pair between the substrate (*S*)-**3** and the catalyst Cu-*ent*-$\mathbf{L_{1c}}$ diminished the diastereoselectivity, producing not only the catalyst controlled product, but also minor product due to the inherent stereogenic carbon center of (*S*)-**3**. Nevertheless, the product is still formed in good diastereoselectivity (entry 12).

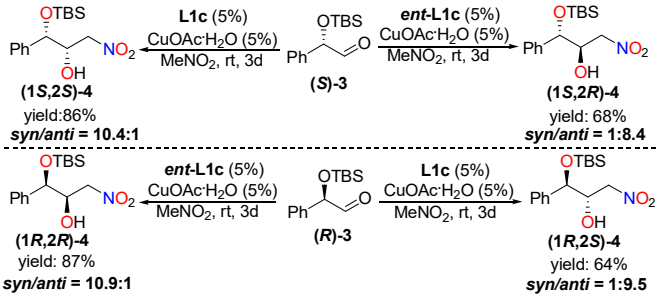
Table 1. Optimizations of the diastereoselective Henry reactions [a]



Entry	Cat (mmol)	solvent	Yield (%) [b]	*dr* (*syn/anti*) [c]
1	NEt_3 (5%)	Et_2O	8	1.7:1
2	K_2CO_3 (5%)	Et_2O	54	2.4:1
3	Cu*-$\mathbf{L_{1a}}$ (5%)	Et_2O	60	2.0:1
4	Cu*-*ent*-$\mathbf{L_{1a}}$ (5%)	Et_2O	53	1:4.3
5	Cu*-$\mathbf{L_{1b}}$ (5%)	Et_2O	54	1.7:1
6	Cu*-*ent*-$\mathbf{L_{1b}}$ (5%)	Et_2O	35	1:3.7
7	Cu*-$\mathbf{L_{1c}}$ (5%)	Et_2O	56	5.9:1
8	Cu*-*ent*-$\mathbf{L_{1c}}$ (5%)	Et_2O	45	1:5.0
9	Cu*-$\mathbf{L_{1d}}$ (5%)	Et_2O	9	2.5:1
10	Cu*-***ent***-$\mathbf{L_{1d}}$ (5%)	Et_2O	9	1:3.9
11	Cu*-$\mathbf{L_{1c}}$ (5%)	$MeNO_2$	85	10.5:1
12	Cu*-*ent*-$\mathbf{L_{1c}}$ (5%)	$MeNO_2$	69	1:8.1
13	Cu*-$\mathbf{L_{1c}}$ (2.5%)	$MeNO_2$	68	9.0:1
14	Cu*-*ent*-$\mathbf{L_{1c}}$ (2.5%)	$MeNO_2$	42	1:6.9

[a] All reactions were performed at 1-mmol scale; [b] isolated yield; [c] determined by chiral HPLC. Cu* = $Cu(OAc)_2{\cdot}H_2O$.

With the optimized reaction conditions in hand, larger scale of Cu-catalyzed nitroaldol reactions were performed (30.0 mmol). The results are listed in Scheme 3, which clearly showed that four stereoisomers of the nitroaldol adducts **4** were respectively formed with satisfied isolated yields as well as *syn/anti* ratios.



Scheme 3. Henry reactions performed at 30.0 mmol scale

Next (1*S*,2*S*)-**4** was selected as a model reactant for the synthesis of (2*S*,3*S*)-reboxetine, and only the optimized reaction sequences were illustrated in Scheme 4. Removal of TBS group in aqueous HCl-methanol[18] afforded almost quantitative yield of nitro diol (1*S*,2*S*)-**5**, which was then recrystallized from diethyl ether-petroleum ether in 84% yield. Subsequent catalytic hydrogenation of the nitro group of (1*S*,2*S*)-**5** into amino group and followed reaction with chloroacetyl chloride in the presence of two equivalents of potassium carbonate afforded chloroacetamide (2*S*,3*S*)-**6** in a yield of 71%. This compound was transformed into morpholinone by treatment with ^{t}BuOK (2.5 equiv) in ^{t}BuOH.[7b] The reaction proceeded well and the resulting morpholinone was not separated and directly reduced by $LiAlH_4$ into morpholine, which was protected into Boc-amide (2*S*,3*S*)-**7** in 70%

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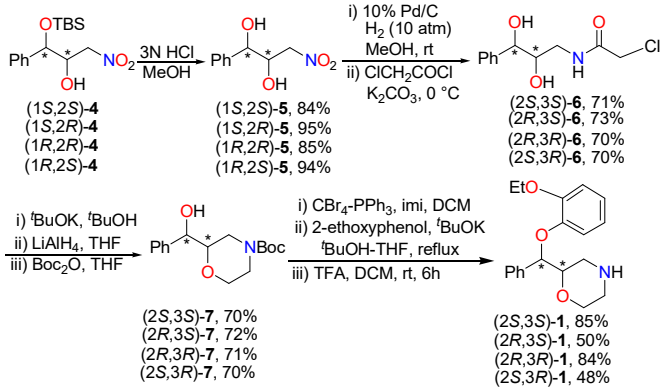
yield over three steps. Finally, following the literature methods[6,9a] with small modifications, (2*S*,3*S*)-**7** was transformed into (2*S*,3*S*)-reboxetine **1** in 85% yield. Notably, the overall ratio of this synthetic route reached up to 30.5% from aldehyde (*S*)-**3**.

Using the same procedure described above, (2*R*,3*S*)-, (2*R*,3*R*)-, and (2*S*,3*R*)-reboxetines were also prepared from their corresponding nitroaldol adducts **4** (Scheme 4).



Scheme 4. Syntheses of all four stereoisomers of reboxetine **1**

Conclusions

In summary, we have successfully utilized copper catalysts Cu-**L$_{1c}$** and Cu-*ent*-**L$_{1c}$** to promote the diastereoselective nitroaldol reactions of chiral aldehydes (*S*)- or (*R*)-**3** with nitromethane, which lead to the preferential formation of certain stereoisomer for nitro diol derivatives **4** respectively. Using this catalytic protocol, all four stereoisomers of antidepressant reboxetine were divergently prepared. Furthermore by using the synthetic approach developed herein, structurally diverse reboxetine analogues can be conveniently prepared because phenols are plentiful and commercially available. We wish this work may help the research and development of novel NRIs.

Experimental sections

General: Unless otherwise noted, reagents and solvents were commercially available and used as received without any further purification. Tetrahydrofuran (THF) was distilled from sodium wire prior to use. Dichloromethane (DCM) was distilled from calcium hydride prior to use. ^{1}H and ^{13}C NMR spectra were determined in deuterated solvents on a Bruker av500 NMR spectrometer. Chemical shifts were reported in delta (δ) units, parts per million (ppm) downfield from TMS. High resolution mass spectra were recorded on a Bruker Apex ultra 7.0T FT-MS. Optical rotations were measured in a MCP500 automatic polarimeter, sodium lamp, 1 dm cuvette lengths, *c* in g/100 mL. Analytical HPLC was performed on a Shimadzu liquid chromatography equipped with a SPD-M20A diode array detector, using a Chiralcel™ OD-H column (4.6 mm × 250 mm, 5 μm).

General procedure for diastereoselective Henry reaction

A solution of **L$_{1c}$** or *ent*-**L$_{1c}$** (420 mg, 1.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (300 mg, 1.5 mmol) and aldehyde (*S*)-**3** or (*R*)-**3** (7.50 g, 30.0 mmol) in $MeNO_2$ (45 mL) was stirred at room temperature for 3 days. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (20:1, v/v) to give the nitroaldol product **4** as a pale yellow oil.

(1*S*,2*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-nitro-1-phenylpropan-2-ol [(1*S*,2*S*)-4]

Reaction using **L$_{1c}$** and (*S*)-**3**, 8.03 g, 25.8 mmol, 86%. $[\alpha]_D^{20}$ +44.7 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.38-7.31 (m, 5H), 4.67 (d, *J* = 5.96 Hz, 1H), 4.39-4.33 (m, 2H), 4.27 (dd, *J* = 8.78, 12.76 Hz, 1H), 2.83 (br s, 1H), 0.90 (s, 9H), 0.06 (s, 3H), -0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.3, 128.6(5), 128.6(3), 126.8, 77.3, 75.6, 73.4, 25.7, 18.1, -4.6, -5.2; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}NO_4Si$ [M+Na]$^+$ 334.1445, found 334.1447; HPLC (Chiralpak OD-H, 95:5 Hex:^{i}PrOH, 1.0 mL/min, 20 °C, 208 nm): *syn* (major) = 9.8 min, *anti* (minor) = 6.9 min, *dr* (*syn/anti*) = 10.4:1.

(1*S*,2*R*)-1-(*tert*-Butyldimethylsilyloxy)-3-nitro-1-phenylpropan-2-ol [(1*S*,2*R*)-4]

Reaction using *ent*-**L$_{1c}$** and (*S*)-**3**, 6.35 g, 20.4 mmol, 68%. $[\alpha]_D^{20}$ +62.3 (*c* 1.0 in $CHCl_3$), [lit[19]: $[\alpha]_D^{20}$ +48.2 (*c* 0.5 in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.39-7.35 (m, 2H), 7.34-7.29 (m, 3H), 4.76 (d, *J* = 5.33 Hz, 1H), 4.47 (dd, *J* = 4.25, 13.00 Hz, 1H), 4.44 (dd, *J* = 7.55, 13.00 Hz, 1H), 2.50 (br s, 1H), 0.91 (s, 9H), 0.07 (s, 3H), -0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ139.9, 128.7, 128.4, 126.5, 77.1, 76.3, 73.6, 25.8, 18.1, -4.7, -5.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}NO_4Si$ [M+Na]$^+$ 334.1445, found 334.1451; HPLC (Chiralpak OD-H, 95:5 Hex:^{i}PrOH, 1.0 mL/min, 20 °C, 208 nm): *syn* (minor) = 10.2 min, *anti* (major) = 7.0 min, *dr* (*syn/anti*) = 1:8.4.

(1*R*,2*R*)-1-(tert-Butyldimethylsilyloxy)-3-nitro-1-phenylpropan-2-ol [(1*R*,2*R*)-4]

Reaction using *ent*-**L$_{1c}$** and (*R*)-**3**, 8.12 g, 26.1 mmol, 87%. $[\alpha]_D^{20}$ -45.2 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.38-7.35 (m, 2H), 7.34-7.31 (m, 3H), 4.67 (d, *J* = 5.96 Hz, 1H), 4.40-4.33 (m, 2H), 4.27 (dd, *J* = 8.82, 12.80 Hz, 1H), 2.83 (br s, 1H), 0.90 (s, 9H), 0.06 (s, 3H), -0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.3, 128.6(6), 128.6(3), 126.8, 77.3, 75.6, 73.4, 25.7, 18.1, -4.6, -5.2; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}NO_4Si$ [M+Na]$^+$ 334.1445, found 334.1448; HPLC (Chiralpak OD-H, 95:5 Hex:^{i}PrOH, 1.0 mL/min, 20 °C, 208 nm): *syn* (major) = 8.2 min, *anti* (minor) = 6.2 min, *dr* (*syn/anti*) = 10.9:1.

(1*R*,2*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-nitro-1-phenylpropan-2-ol [(1*R*,2*S*)-4]

Reaction using **L$_{1c}$** and (*R*)-**3**, 5.98 g, 19.2 mmol, 64%. $[\alpha]_D^{20}$ -67.0 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.39-7.35 (m, 2H), 7.34-7.30 (m, 3H), 4.77 (d, *J* = 5.27 Hz, 2H), 4.48-4.43 (m, 2H), 4.40-4.36 (m, 1H), 2.45 (br s, 1H), 0.91 (s, 9H), 0.07 (s, 3H), -0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ139.8, 128.7, 128.4, 126.5, 77.1, 76.3, 73.6, 25.8, 18.1, -4.7, -5.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}NO_4Si$ [M+Na]$^+$ 334.1445, found 334.1447; HPLC (Chiralpak OD-H, 95:5 Hex:^{i}PrOH, 1.0 mL/min, 20 °C, 208 nm): *syn* (minor) = 8.0 min, *anti* (major) = 6.1 min, *dr* (*syn/anti*) = 1:9.5.

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DOI: 10.1039/C7OB01887C

General procedure for transformation of compound 4 into 5

A solution of **4** (6.22 g, 20.0 mmol) in a mixture of methanol (50 mL) and diluted HCl (3N, 50 mL) was stirred at room temperature until the starting material consumed (as monitored by TLC). Methanol was removed under reduced pressure, and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (2:1, v/v) [and followed recrystallization from diethyl ether-petroleum ether (1:10, v/v) for *syn*-isomer] to give the nitro diol **5**.

(1*S*,2*S*)-3-Nitro-1-phenylpropane-1,2-diol [(1*S*,2*S*)-5]

Colourless solid, 3.31 g, 84%. $[\alpha]_D^{20}$ +41.2 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.42-7.39 (m, 2H), 7.38-7.34 (m, 3H), 4.66 (d, *J* = 5.70 Hz, 1H), 4.49-4.39 (m, 2H), 4.34 (dd, *J* = 12.37, 2.16 Hz, 1H), 3.07 (br s, 1H), 2.80 (br s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ138.9, 129.0(3), 128.9(8), 126.5, 77.5, 74.6, 72.7; HRMS (ESI): *m/z* calcd for $C_9H_{11}NO_4$ $[M+Na]^+$ 220.0580, found 220.0584.

(1*S*,2*R*)-3-nitro-1-phenylpropane-1,2-diol [(1*S*,2*R*)-5]

Pale yellow oil, 3.75 g, 95%. $[\alpha]_D^{20}$ +42.6 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.47-7.32 (m, 5H), 4.87 (s, 1H), 4.55-4.48 (m, 2H), 4.45-4.39 (m, 1H), 2.90 (d, *J* = 3.17 Hz, 1H), 2.62 (d, *J* = 2.26 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 138.8, 128.9, 128.5, 126.1, 76.7, 74.7, 72.7; HRMS (ESI): *m/z* calcd for $C_9H_{11}NO_4$ $[M+Na]^+$ 220.0580, found 220.0582.

(1*R*,2*R*)-3-Nitro-1-phenylpropane-1,2-diol [(1*R*,2*R*)-5]

Colourless solid, 3.35 g, 85%. $[\alpha]_D^{20}$ -41.5 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.43-7.34 (m, 5H), 4.67 (d, *J* = 5.72 Hz, 1H), 4.49-4.40 (m, 2H), 4.35 (dd, *J* = 2.32, 12.45 Hz, 1H), 3.04 (br s, 1H), 2.74 (br s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ138.9, 129.0(3), 128.9(8), 126.5, 77.5, 74.6, 72.8; HRMS (ESI): *m/z* calcd for $C_9H_{11}NO_4$ $[M+Na]^+$ 220.0580, found 220.0584.

(1*R*,2*S*)-3-Nitro-1-phenylpropane-1,2-diol [(1*R*,2*S*)-5]

Pale yellow oil, 3.71 g, 94%. $[\alpha]_D^{20}$ -41.6 (*c* 1.0 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.43-7.33 (m, 5H), 4.88 (d, *J* = 1.73 Hz, 1H), 4.55-4.49 (m, 2H),4.46-4.40 (m, 1H), 2.86 (d, *J* = 4.28 Hz, 1H), 2.57 (d, *J* = 2.39 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ138.8, 128.9, 128.6, 126.1, 76.7, 74.7, 72.7; HRMS (ESI): *m/z* calcd for $C_9H_{11}NO_4$ $[M+Na]^+$ 220.0580, found 220.0584.

General procedure for transformation of 5 to chloroacetamide 6

A solution of **5** (1.97 g, 10.0 mmol) in methanol (20 mL) was catalytically hydrogenated (10 atm) over 10% Pd/C (0.2 g) overnight, filtered and the filtrate was transferred into a round-bottomed flask. Powdered potassium carbonate (2.76 g, 20.0 mmol) and chloroacetyl chloride (1.20 mL, 15.0 mmol) were sequentially added at 0 °C. The mixture was stirred at the same temperature for additional 1 hour, filtered and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (1:2, v/v), which afforded the product **6** as a pale yellow oil.

2-Chloro-*N*-((2*S*,3*S*)-2,3-dihydroxy-3-phenylpropyl)acetamide [(2*S*,3*S*)-6]

1.73 g, 7.1 mmol, 71%. $[\alpha]_D^{20}$ +18.0 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.38-7.29 (m, 5H), 6.97 (br s, 1H), 4.52 (d, *J* = 6.21 Hz, 1H), 3.98 (s, 2H), 3.82 (td, *J* = 4.25, 6.97 Hz, 1H), 3.38 (ddd, *J* = 4.23, 6.26, 14.00 Hz, 1H), 3.24 (ddd, *J* = 5.49, 7.24, 12.75 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.3, 140.3, 128.7, 128.3, 126.7, 75.4, 74.1, 42.4(9), 42.4(5); HRMS (ESI): *m/z* calcd for $C_{11}H_{14}ClNO_3$ $[M+Na]^+$ 266.0560, found 266.0558.

2-chloro-N-((2*R*,3*S*)-2,3-dihydroxy-3-phenylpropyl)acetamide [(2*R*,3*S*)-6]

1.78 g, 73%. $[\alpha]_D^{20}$ +12.0 (*c* 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.35 (m, 4H), 7.34-7.30 (m, 1H), 7.05 (br s, 1H), 4.61 (d, *J* = 6.18 Hz, 1H), 4.05 (d, *J* = 1.23 Hz, 2H), 3.87 (td, *J* = 3.51, 5.90 Hz, 1H), 3.57 (dt, *J* = 5.86, 14.22 Hz, 1H),3. 47 (ddd, *J* = 3.50, 6.15, 14.31 Hz, 1H), 2.57 (br s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ167.8, 140.1, 128.6, 128.1, 126.6, 75.1, 74.0, 42.5, 41.6; HRMS (ESI): *m/z* calcd for $C_{11}H_{14}ClNO_3$ $[M+Na]^+$ 266.0560, found 266.0560.

2-Chloro-*N*-((2*R*,3*R*)-2,3-dihydroxy-3-phenylpropyl)acetamide [(2*R*,3*R*)-6]

1.70 g, 70%. $[\alpha]_D^{20}$ -19.5 (*c* 1.0 in $CHCl_3$), [lit[11a]: $[\alpha]_D^{21}$ -22.6 (*c* 1.0 in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.39-7.29 (m, 5H), 6.99 (br s, 1H), 4.52 (d, *J* = 6.21 Hz, 1H), 3.99 (s, 2H), 3.83 (td, *J* = 4.25, 6.78 Hz, 1H), 3.39 (ddd, *J* = 4.23, 6.24, 14.00 Hz, 1H), 3.25 (ddd, *J* = 5.52, 7.20, 12.75 Hz, 1H), 2.98 (br s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.3, 140.3, 128.7, 128.3, 126.7, 75.4, 74.1, 42.4(9), 42.4(5); HRMS (ESI): *m/z* calcd for $C_{11}H_{14}ClNO_3$ $[M+Na]^+$ 266.0560, found 266.0561.

2-Chloro-*N*-((2*S*,3*R*)-2,3-dihydroxy-3-phenylpropyl)acetamide [(2*S*,3*R*)-6]

1.71 g, 70%. $[\alpha]_D^{20}$ -14.5 (*c* 1.0 in $CHCl_3$), [lit[7b]: $[\alpha]_D^{20}$ -13.6 (*c* 2.5 in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.39-7.35 (m, 4H), 7.34-7.29 (m, 1H), 7.07 (br s, 1H), 4.61 (d, J = 6.06 Hz, 1H), 4.02 (s, 2H), 3.88-3.82 (m, 1H), 3.56-5.50 (m, 1H), 3.46 (ddd, *J* = 3.53, 6.00, 14.28 Hz, 1H), 2.75 (br s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ167.8, 140.1, 128.6, 128.1, 126.6, 75.1, 74.0, 42.5, 41.6; HRMS (ESI): *m/z* calcd for $C_{11}H_{14}ClNO_3$ $[M+Na]^+$ 266.0560, found 266.0558.

General procedure for transformation of 6 into Boc-amide 7

To a solution of **6** (2.43 g, 10.0 mmol) in ^{t}BuOH (20 mL) was added ^{t}BuOK (2.24 g, 20.0 mmol) in one portion. The mixture was stirred at room temperature for additional 2 hours, quenched with saturated aqueous ammonium chloride, and then concentrated under reduced pressure. The resulting solution was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced

pressure. The residue was dissolved in dry THF (10 mL), and was then dropwise added into a suspension of $LiAlH_4$ (0.95 g, 25.0 mmol) in THF (10 mL) at 0 °C. After completion of the addition, the reaction mixture was refluxed for additional 6 hours, cooled with an ice bath, carefully quenched with saturated aqueous potassium carbonate, and Boc_2O (2.18 g, 10.0 mmol) was then added. The resulting mixture was vigorously stirred at room temperature overnight, filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized from petroleum ether-ethyl acetate (10:1, v/v), which afforded the Boc-amide **7** as colourless solid.

(2*S*,3*S*)-2-(α-Hydroxyphenylmethyl)morpholine-4-carboxylic acid *t*-butyl ester [(2*S*,3*S*)-7]

2.06 g, 70%. $[\alpha]_D^{20}$ +35.5 (*c* 1.0 in $CHCl_3$), [lit[7c]: $[\alpha]_D^{20}$ +34.0 (*c* 1.24 in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.28 (m, 5H), 4.53 (dd, *J* = 2.34, 7.39 Hz, 1H), 3.97 (d, *J* = 11.44 Hz, 1H), 3.81 (d, *J* = 11.23 Hz, 1H), 3.67-3.42 (m, 3H), 3.05-2.89 (m, 2H), 2.70 (br s, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ154.7, 139.3, 128.5, 128.4, 126.9, 80.1, 79.3, 75.0, 66.4, 44.5, 43.7, 28.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{23}NO_4$ $[M+Na]^+$ 316.1525, found 316.1526.

(2*R*,3*S*)-2-(α-Hydroxyphenylmethyl)morpholine-4-carboxylic acid *t*-butyl ester [(2*R*,3*S*)-7]

2.11 g, 72%. $[\alpha]_D^{20}$ -0.7 (*c* 5.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.26 (m, 5H), 4.84 (s, 1H), 3.94-3.71 (m, 3H), 3.62-3.50 (m, 2H), 2.96-2.78 (m, 2H), 2.45 (br s, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ154.9, 139.6, 128.4, 127.9, 126.4, 80.0, 78.6, 74.4, 66.7, 43.8, 43.0, 28.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{23}NO_4$ $[M+Na]^+$ 316.1525, found 316.1523.

(2*R*,3*R*)-2-(α-Hydroxyphenylmethyl)morpholine-4-carboxylic acid *t*-butyl ester [(2*R*,3*R*)-7]

2.09 g, 71%. $[\alpha]_D^{20}$ -35.8 (*c* 1.0, $CHCl_3$), [lit[11a]: $[\alpha]_D^{28}$ -42.5 (*c* 1.0 in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.27 (m, 5H), 4.53 (dd, *J* = 2.33, 7.38 Hz, 1H), 3.97 (dd, *J* = 1.15, 11.37 Hz, 1H), 3.81 (d, *J* = 11.74 Hz, 1H), 3.67-3.42 (m, 3H), 3.05-2.88 (m, 2H), 2.70 (br s, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.7, 139.3, 128.5, 128.4, 126.9, 80.1, 79.3, 75.0, 66.4, 44.4, 43.7, 28.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{23}NO_4$ $[M+Na]^+$ 316.1525, found 316.1525.

(2*S*,3*R*)-2-(α-Hydroxyphenylmethyl)morpholine-4-carboxylic acid *t*-butyl ester [(2*S*,3*R*)-7]

2.07 g, 70%. $[\alpha]_D^{20}$ +0.8 (*c* 5.0 in $CHCl_3$), [lit[7b]: $[\alpha]_D^{20}$ +3.45 (*c* 2.35 in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.39-7.32 (4H), 7.32-7.27 (m, 1H), 4.84 (s, 1H), 3.94-3.70 (m, 3H), 3.63-3.50 (m, 2H), 2.98-2.77 (m, 2H), 2.48 (br s, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ154.9, 139.8, 128.4, 127.8, 126.4, 80.0, 78.7, 74.3, 66.7, 43.8, 43.0, 28.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{23}NO_4$ $[M+Na]^+$ 316.1525, found 316.1526.

General procedure for transformation of 7 into reboxetine 1

To a stirred solution of (2*S*,3*S*)-**7** (586 mg, 2.0 mmol), PPh_3 (630 mg, 2.4 mmol) and imidazole (164 mg, 2.4 mmol) in DCM (10 mL) was added CBr_4 (795 mg, 2.4 mmol) at 0 °C. The mixture was stirred at room temperature for 2 hours, quenched with 10% sodium thiosulfate and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The oily residue was dissolved in THF (3 mL), and dropwise added into a solution of potassium 2-ethoxyphenoxide in ^{t}BuOH (6 mL) that was pre-prepared from 2-ethoxyphenol (552 mg, 4.0 mmol) and potassium *tert*-butoxide (448 mg, 4.0 mmol). This mixture was refluxed overnight, cooled to room temperature, and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in DCM (10 mL) and TFA (1.0 mL, 13 mmol) was added. The mixture was stirred at room temperature for additional 6 hours and then evaporated under reduced pressure. The residue was dissolved in DCM (10 mL) and then an aqueous solution of NaOH (4N, 3 mL) was added. After being stirred for 10 min, the organic layer was separated and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. Flash column chromatography on silica gel eluting with ethyl acetate-methanol (95:5, v/v) afforded reboxetine as a pale yellow oil.

(2*S*,3*S*)-Reboxetine [(2*S*,3*S*)-1]

532 mg, 85%. $[\alpha]_D^{20}$ +27.6 (*c* 1.0 in $CHCl_3$), [lit[7b]: $[\alpha]_D^{20}$ +11.5 (*c* 0.6 in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.41-7.36 (m, 2H), 7.32-7.28 (m, 2H), 7.27-7.23 (m, 1H), 6.90-6.87 (m, 1H), 6.83-6.78 (m, 2H), 6.72-6.67 (m, 1H), 5.17 (d, *J* = 6.06 Hz, 1H), 4.09-4.01 (m, 2H), 3.93-3.87 (m, 2H), 3.62 (ddd, *J* = 5.02, 9.10, 11.58 Hz, 1H), 2.78-2.71 (m, 2H), 2.61 (dd, *J* = 9.84, 12.57 Hz, 1H), 2.56 (dd, *J* = 2.98, 12.61 Hz, 1H), 1.41 (t, *J* = 7.00 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ149.7, 147.8, 137.7, 127.9, 127.8, 127.3, 121.9, 120.7, 117.4, 114.3, 82.5, 78.7, 67.1, 64.5, 46.5, 44.7, 14.0; HRMS (ESI): *m/z* calcd for $C_{19}H_{23}NO_3$ $[M+H]^+$ 314.1756, found 314.1757.

(2*R*,3*S*)-Reboxetine [(2*R*,3*S*)-1]

314 mg, 50%. $[\alpha]_D^{20}$ +11.6 (*c* 1.0 in $CHCl_3$), [lit[9a]: $[\alpha]_D^{29}$ +33.3 (*c* 0.3 in $CHCl_3$)]; ^{1}H NMR (MeOH-d4, 500 MHz) δ7.37 (d, *J* = 7.23 Hz, 2H), 7.29 (t, *J* = 7.43 Hz, 2H), 7.26-7.22 (m, 1H), 6.92-6.88 (m, 1H), 6.84-6.79 (m, 1H), 6.70-6.64 (m, 2H), 5.08 (d, *J* = 6.22 Hz, 1H), 4.12-4.03 (m, 2H), 3.83-3.78 (m, 2H), 3.52 (td, *J* =3.17, 11.24 Hz, 1H), 3.23 (dd, *J* = 1.88, 12.71 Hz, 1H), 2.86 (dd, *J* = 10.09, 12.72 Hz, 1H), 2.83-2.77 (m, 1H), 2.77-2.73 (m, 1H), 2.22 (br s, 1H), 1.43 (t, *J* = 6.99 Hz, 3H); ^{13}C NMR (MeOH-d4, 126 MHz) δ 149.6, 147.5, 138.7, 127.8, 127.6, 127.2, 121.9, 120.6, 117.2, 114.1, 82.3, 79.1, 67.1, 64.4, 46.5, 44.8, 14.1; HRMS (ESI): *m/z* calcd for $C_{19}H_{23}NO_3$ $[M+H]^+$ 314.1751, found 314.1752.

(2*R*,3*R*)-Reboxetine [(2*R*,3*R*)-1]

526 mg, 84%. $[\alpha]_D^{20}$ -27.7 (*c* 1.0 in $CHCl_3$), $[\alpha]_D^{20}$ -10.0 (*c* 1.0 in MeOH), [lit[9a]: $[\alpha]_D^{29}$ -13.9 (*c* 0.3 in MeOH)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.40-7.37 (m, 2H), 7.32-7.28 (m, 2H), 7.27-7.23 (m, 1H), 6.88 (dd, *J* = 1.25, 7.94 Hz, 1H), 6.83-6.78 (m, 2H), 6.72-6.67 (m, 1H), 5.16 (d, *J* = 6.06 Hz, 1H), 4.10-4.01 (m, 2H), 3.94-3.88 (m, 2H), 3.62 (ddd, *J* = 4.67, 9.47,

11.55 Hz, 1H), 2.78-2.72 (m, 2H), 2.61 (dd, *J* = 9.81, 12.57 Hz, 1H), 2.57 (dd, *J* = 3.00, 12.61 Hz, 1H), 1.41 (t, *J* = 6.99 Hz, 3H); ^{13}C NMR (MeOH-d_4, 126 MHz) δ149.7, 147.7, 137.7, 127.9, 127.8, 127.3, 121.9, 120.7, 117.4, 114.3, 82.5, 78.7, 67.1, 64.5, 46.5, 44.7, 14.0; HRMS (ESI): *m/z* calcd for $C_{19}H_{23}NO_3$ $[M+H]^+$ 314.1751, found 314.1753.

(2*S*,3*R*)-Reboxetine [(2*S*,3*R*)-1]

292 mg, 48%. $[\alpha]_D^{20}$ -11.7 (*c* 1.0 in $CHCl_3$), [lit[9a]: $[\alpha]_D^{29}$ -32.0 (*c* 0.4 in $CHCl_3$)]; ^{1}H NMR (MeOH-d4, 500 MHz) δ7.39-7.36 (m, 2H), 7.32-7.27 (m 2H), 7.26-7.22 (m, 1H), 6.892-6.88 (m, 1H), 6.84-6.79 (m, 1H), 6.70-6.64 (m, 2H), 5.08 (d, *J* = 6.22 Hz, 1H), 4.10-4.04 (m, 2H), 3.83-3.77 (m, 2H), 3.52 (td, *J* = 3.14, 11.24 Hz, 1H), 3.22 (dd, *J* = 1.84, 12.69 Hz, 1H), 2.86 (dd, *J* = 10.08, 12.72 Hz, 1H), 2.83-2.77 (m, 1H), 2.77-2.72 (m, 1H), 1.43 (t, *J* = 6.99 Hz, 3H); ^{13}C NMR (MeOH-d4, 126 MHz) δ149.6, 147.5, 138.6, 128.2, 127.9, 127.1, 122.0, 120.8, 117.2, 114.0, 82.8, 79.3, 67.7, 64.6, 46.8, 45.3, 14.9; HRMS (ESI): *m/z* calcd for $C_{19}H_{23}NO_3$ $[M+H]^+$ 314.1751, found 314.1760.

Acknowledgements

This work was financially supported by the fundamental research funds for the central universities (No. 20720160047 and 20720170022) and NSFC (No. 21502158).

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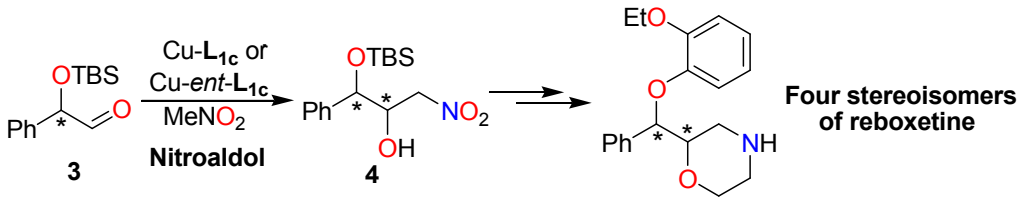
DOI: 10.1039/C7OB01283G



Four stereoisomers of antidepressant reboxetine were divergently prepared via Cu-catalyzed diastereoselective nitroaldol reactions