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Enantioselective synthesis of (*R*)- and (*S*)-*N*-Boc-morpholine-2-carboxylic acids by enzyme-catalyzed kinetic resolution: application to the synthesis of reboxetine analogs

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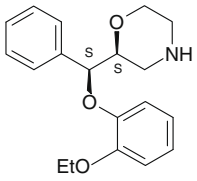
ABSTRACT

The (*R*)- and (*S*)-*N*-Boc-morpholine-2-carboxylic acids **9** and **10** were prepared using an enantioselective synthesis employing a highly selective enzyme-catalyzed kinetic resolution of racemic *n*-butyl 4-benzylmorpholine-2-carboxylate (**11**) as the key step. Acids **9** and **10** were then converted efficiently and stereoselectively to reboxetine analogs **3** and **4**.

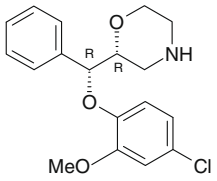
(±)-Reboxetine is an orally active, selective noradrenaline reuptake inhibitor (NRI) developed and launched for the treatment of depression.[1,2] The (+)-(*S*,*S*)-enantiomer of reboxetine (**1**) is currently undergoing advanced clinical evaluation as a potential treatment of fibromyalgia and neuropathic pain.[3] Esreboxetine (**1**) is more potent than the reboxetine racemate with respect to inhibiting the uptake of noradrenaline and much weaker at inhibiting uptake of serotonin; the combination of these two pharmacologies makes esreboxetine highly selective.[2]

Further investigation of the reboxetine template identified (±)-**2** as a lead with potential biological activity for dual noradrenaline and serotonin reuptake inhibition.[4,5] Evaluation of the single enantiomers **3** and **4** in pre-clinical disease models required the synthesis of multigram quantities of suitably functionalized, homochiral morpholine synthons. In this Letter, we disclose a new and highly efficient synthesis of homochiral (*R*)- and (*S*)-*N*-Boc-morpholine-2-carboxylic acids **9** and **10,** and describe their conversion to reboxetine analogs **3** and **4**.

The challenge of creating the molecular architecture of esreboxetine (**1**) has led to a number of noteworthy syntheses in recent years (Fig. 1). Henegar and Cebula reported a process development for the synthesis of esreboxetine succinate employing a Sharpless asymmetric epoxidation of cinnamyl alcohol to epoxy alcohol **5**.[6] Esreboxetine has also been prepared enantioselectively from cinnamyl bromide using a Sharpless asymmetric dihydroxylation as the key step to furnish diol **6**.[7] In a conceptually different approach, esreboxetine has been prepared from commercially available chiral



1: (+)-(*S*,*S*)-esreboxetine



2: (±)-(*RR*,*SS*)
3: (-)-(*R*,*R*)
4: (+)-(*S*,*S*)

pool reagents, (1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol (**7**)[8] and (*S*)-3-amino-1,2-propanediol (**8**).[9]

Our approach to the reboxetine template, as exemplified by compounds **3** and **4**, employed a new enantioselective synthesis

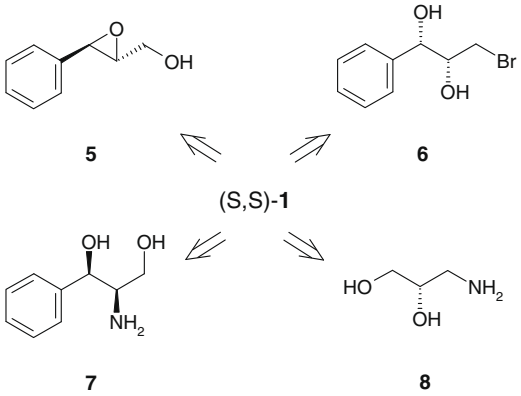


Figure 1. Chiral synthons employed for the synthesis of esreboxetine **1**.

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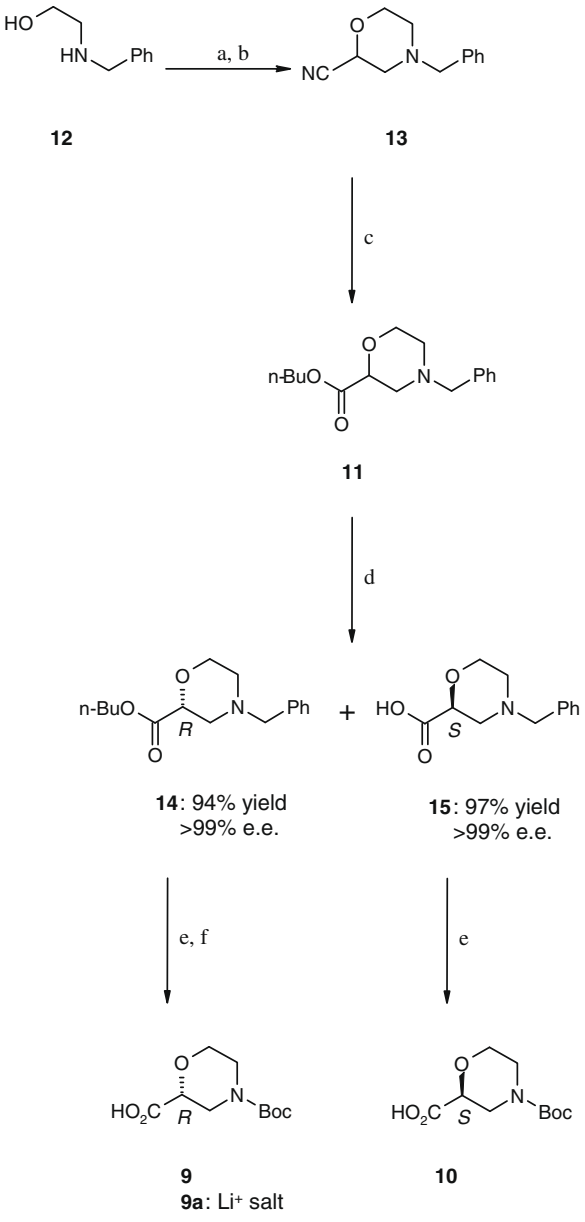
where the key (*R*)- and (*S*)-morpholine acids **9** and **10** were prepared by an enzyme-catalyzed kinetic resolution of racemic ester **11** (Scheme 1).[10,11] This route was attractive to us as it allowed for the late-stage installation of both the aryl and aryloxy rings providing flexibility in the synthesis of additional analogs. Furthermore, the resolution proved to be highly selective and operationally simple to perform on large scale.

Racemic ester **11** was prepared in two steps and in high yield from readily available starting materials. Condensation of *N*-benzylethanolamine (**12**) with 2-chloroacrylonitrile followed by *t*-BuOK-promoted cyclization gave morpholine nitrile **13**,[12] which then underwent alcoholysis with *n*-BuOH (or other alcohols, e.g., EtOH) in the presence of concd H_2SO_4 to give **11**.

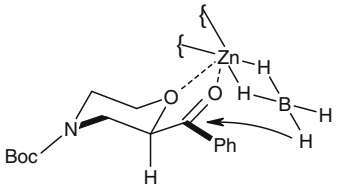
Racemic ester **11**, along with other esters (e.g., Et), were screened against a panel of 19 broadly specific lipases. The combination of the *n*-Bu ester with lipase *Candida rugosa*[13] was completely stereoselective, with the enzyme catalyzing the hydrolysis of the (*S*)-ester to give (*S*)-acid **15** whilst leaving the (*R*)-ester **14** untouched.[14,15] On scale-up, resolution of **11** (10 g) gave ester **14** (4.7 g, 94%; >99% ee) and acid **15** (3.9 g, 97%; >99% ee). The isolation of the ester **14** was straightforward as the organic layer was simply separated, dried, and concentrated in vacuo. In these early experiments, the reaction was buffered to pH 7.2, and so isolation of acid **15** from the aqueous phase required the use of ion exchange chromatography (Dowex 50W8X200 eluting with aqueous ammonia). The resolution was subsequently performed in water to give **14** and **15** in identical yields as before and with no loss in selectivity. The isolation of both ester **14** and acid **15** could now be achieved simply by separating the two layers and evaporating the solvent. This resolution has been performed on >100 g scale.[16]



Scheme 1. Reagents and conditions: (a) CH_2=C(Cl)CN, Et_2O, 40 °C, quant.; (b) *t*-BuOK, DME, reflux 65%; (c) *n*-BuOH, concd H_2SO_4, reflux, 85%; (d) lipase *Candida rugosa*, *t*-BuOMe–H_2O, rt, 24–30 h; (e) 2,5-dihydrotoluene, 10%-Pd/C, Boc_2O, EtOH, reflux, quant.; (f) LiOH (0.95 equiv), THF–H_2O, 0 °C, 90%.

The *N*-benzyl-protecting group of **14** and **15** was then exchanged to the corresponding *N*-Boc amines,[17] and base hydrolysis of the *n*-butyl ester gave the acid **9** which was isolated as the lithium salt **9a** for convenience. Hence, (*R*)- and (*S*)-morpholine acids **9** and **10** were prepared efficiently in just five and four steps with overall yields of 46% and 53%, respectively; both acids were obtained with very high chiral purity (>99% ee).

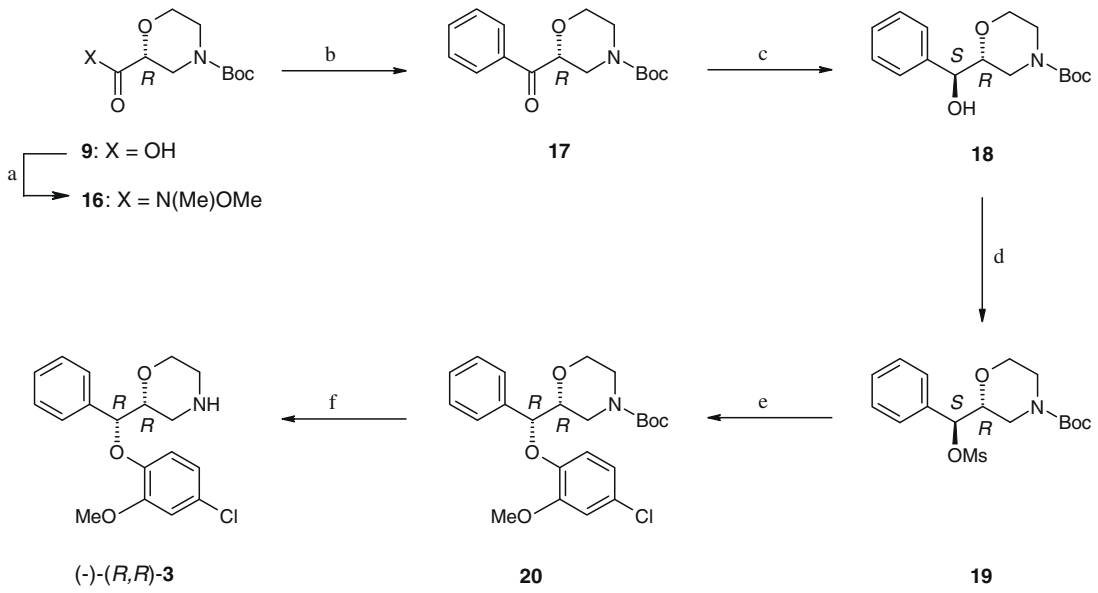
The conversion of acid **9** to **3** is outlined in Scheme 2, where the second stereocenter was introduced by a diastereoselective reduction of ketone **17**. Activation of **9** with 1-propanephosphonic anhydride (T3P) followed by reaction with HN(Me)OMe gave Weinreb amide **16** in good yield (>97% ee), and then treatment of **16** with the Grignard reagent PhMgBr gave the phenyl ketone **17** with no detectable loss in ee. Reduction of **17** was achieved most selectively with zinc borohydride[18] to give (*S*,*R*)-alcohol **18** with creation of the second stereocenter with good diastereoselectivity (*S*,*R*:*R*,*R* 16:1). The high diastereoselectivity was attributed to a Zn-chelated transition state (**I**); this outcome is entirely consistent with the model of Frein and Rovis.[19]



I

The introduction of the aryl ether was most efficiently achieved from **18** with a two-step process of mesylation and displacement. Reaction of **18** with $MeSO_2Cl$ gave mesylate **19,** and displacement of the MsO group of **19** with 4-chloro-2-methoxyphenol furnished the corresponding (*R*,*R*)-aryloxy ether **20** in good yield, with complete inversion of the benzylic stereocenter and no detectable loss of ee. This two-step process proved to be superior to Mitsunobu reactions with alcohol **18** as reaction rates were faster, yields were higher, and product isolation was straightforward. Finally, deprotection of the *N*-Boc amine of **20** with HCl afforded the (*R*,*R*)-amine **3**. The (*S*,*S*)-enantiomer **4**[20] was prepared by an identical sequence, but starting with the (*S*)-acid **10**.

In summary, (*R*)- and (*S*)-*N*-Boc-morpholine-2-carboxylic acids **9** and **10** were prepared using an enantioselective synthesis employing a highly specific enzyme-catalyzed kinetic resolution of racemic *n*-butyl 4-benzylmorpholine-2-carboxylate (**11**) as the key step. Acids **9** and **10** were then converted efficiently and stereoselectively to reboxetine analogs **3** and **4**.



Scheme 2. Reagents and conditions: (a) T3P, HN(Me)OMe, NEt_3, CH_2Cl_2, then aq K_2CO_3, 85%; (b) PhMgBr, THF, rt, 98%; (c) $Zn(BH_4)_2$, Et_2O, rt, 87%, ratio (*S*,*R*):(*R*,*R*) 16:1; (d) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C, quant.; (e) 2-MeO–4-ClC_6H_3OH, Cs_2CO_3, microwave in THF or reflux in dioxane, 95%; (f) HCl in dioxane, CH_2Cl_2, 95%.

Acknowledgments

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References and notes

1. Wong, E. H. F.; Sonders, M. S.; Amara, S. G.; Tinbolt, P. M.; Piercey, M. F. P.; Hoffmann, W. P.; Hyslop, D. K.; Franklin, S.; Porsolt, R. D.; Bonsignori, A.; Carfagna, N.; McArthur, R. A. *Biol. Psychiatry* **2000**, *47*, 818.
2. Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev.* **2004**, *10*, 23.
3. Pfizer Pipeline as of 28 February, 2008; see: www.pfizer.com. [Search date: 19 September, 2008].
4. Fish, P. V.; Deur, C.; Gan, X.; Greene, K.; Hoople, D.; Mackenny, M.; Para, K. S.; Reeves, K.; Ryckmans, T.; Stiff, C.; Stobie, A.; Wakenhut, F.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2562.
5. Caution must be exercised, when evaluating biological activities of racemic compounds as the contribution to the observed effects may not be equal for each enantiomer; this is further complicated, when seeking dual activities at two biological targets.
6. Henegar, K. E.; Cebula, M. *Org. Process Res. Dev.* **2007**, *11*, 354.
7. Siddiqui, S. A.; Narkhede, U. C.; Lahoti, R. J.; Srinivasan, K. V. *Synlett* **2006**, 1771.
8. Metro, T.-X.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 707.
9. Brenner, E.; Baldwin, R. M.; Tamagnan, G. *Org. Lett.* **2005**, *7*, 937.
10. Henegar has recently reported a concise synthesis of (*S*)-morpholine-2-carboxylic acid from (*R*)-epichlorohydrin. This Note summarizes current methods for the synthesis of racemic and single enantiomers of morpholine-2-carboxylic acids, and includes a comprehensive summary of their use in the preparation of pharmaceutically active compounds; see: Henegar, K. E. *J. Org. Chem.* **2008**, *73*, 3662.
11. Racemic ethyl 4-benzylmorpholine-2-carboxylate has been resolved by chiral HPLC; see: Campbell, G. I.; Cases-Thomas, M. J.; Man, T.; Masters, J. J.; Rudyk, H. C. E.; Walter, M. W. WO Patent 047272, 2005; *Chem. Abstr.* **2005**, *142*, 482071.
12. King, F. D.; Hadley, M. S.; Joiner, K. T.; Martin, R. T.; Sanger, G. J.; Smith, D. M.; Smith, G. E.; Smith, P.; Turner, D. H.; Watts, E. A. *J. Med. Chem.* **1993**, *36*, 683.
13. Lipase *Candida rugosa* is commercially available from Sigma (Catalogue No. L-1754; 1140 units/mg).
14. The absolute stereochemistry was determined by conversion of **10** to an authentic sample of (*S*,*S*)-esreboxetine (**1**) and was confirmed by single crystal X-ray structure determinations of the (*R*,*R*)-**3** hemi-fumarate and (*S*,*S*)-**4** $PhSO_3H$ salts. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 680330 and 680331. Copies of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.
15. Enantioselectivities were determined by chiral HPLC (Chiralcel OJ-H, 250 × 4.6 mm; hexane/0.1% TFA in EtOH, 80:20 isocratic, 1 mL/min).
16. *Typical procedure*: A solution of **11** (50 g, 0.18 mol) in *t*-BuOMe (1 L) was added to a solution of *Candida rugosa* (1 g) in H_2O (1 L), and the mixture was stirred thoroughly at room temperature for 24–30 h (monitored by HLPC). The phases were separated, and the aqueous layer was washed with *t*-BuOMe (0.5 L). The combined organic layers were washed with H_2O (0.3 L), were dried ($MgSO_4$), and were evaporated in vacuo to give (*R*)-ester **14** (24.9 g) as a clear oil. The aqueous layer was evaporated in vacuo to give (*S*)-acid **15** (19.9 g) as a white solid. Data for **14**: $[\alpha]_D$ −31.5 (MeOH; *c* 1.2); >99% ee by chiral HPLC, t_R = 6.5 min; ^1H NMR (CD_3OD, 400 MHz) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.34 (m, 2H), 1.59 (m, 2H), 2.41–2.30 (m, 2H), 2.59 (m, 1H), 2.84 (m, 1H), 3.52 (dd, *J* = 15.5 Hz, *J* = 12.9 Hz, 2H), 3.67 (m, 1H), 3.98 (m, 1H), 4.14 (m, 2H), 4.20 (m, 1H), 7.25 (m, 1H), 7.30 (m, 4H); LRMS ES$^+$ *m/z* 278 (MH^+); Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.26; H, 8.49; N, 5.02. Found C, 69.31; H, 8.50; N, 5.03. Data for **15**: $[\alpha]_D$ +35.9 (MeOH; *c* 1.26); >99% ee by chiral HPLC, t_R = 10.2 min; ^1H NMR (CD_3OD, 400 MHz) δ 2.80–2.66 (m, 2H), 3.00 (m, 1H), 3.35 (m, 1H), 3.70 (m, 1H), 4.00 (s, 2H), 4.04 (m, 1H), 4.13 (m, 1H), 7.47–7.36 (m, 5H); LRMS ES$^+$ *m/z* 222 (MH^+).
17. In the context of the synthesis of **3** and **4**, swapping the *N*-protecting group from Bn to Boc had a beneficial effect on the yields of subsequent reactions and simplified deprotection at the final step.
18. (a) Ramu, B. C. *Synlett* **1993**, 885; (b) Oishi, T.; Nakata, T.. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 8, pp 5536–5539; (c) Narasimhan, S.; Balakumar, R. *Aldrichim. Acta* **1998**, *31*, 19.
19. Frein, J. D.; Rovis, T. *Tetrahedron* **2006**, *62*, 4573.
20. Data for **4** HCl salt: mp 148 °C; $[\alpha]_D$ +14.4 (MeOH; *c* 0.20); ^1H NMR (CD_3OD, 400 MHz) δ 3.05–3.20 (m, 3H), 3.25 (d, 1H), 3.78–3.87 (m, 4H), 4.08–4.20 (m, 2H), 5.31 (d, 1H), 6.70 (m, 2H), 6.95 (s, 1H), 7.28–7.44 (m, 5H); LRMS APCI *m/z* 334 (MH^+); >99% ee by chiral HPLC.