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Synthesis of (*R*)-, (*S*)-, and (*RS*)-hydroxymethylmexiletine, one of the major metabolites of mexiletine

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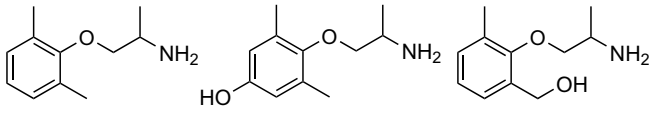
Abstract—Hydroxymethylmexiletine (HMM), one of the main metabolites of mexiletine, has been synthesized in both racemic and optically active forms following two alternative routes. The ee values for both HMM enantiomers were 98%, as assessed by ^{1}H NMR analysis in the presence of (−)-(*R*)-(2-naphthyloxy)phenylacetic acid as a chiral solvating agent and electrophoretic analysis using β-cyclodextrine sulfated sodium salt as a chiral auxiliary.

1. Introduction

Mexiletine, 1-(2,6-dimethylphenoxy)-2-propanamine (Mex, Fig. 1), is a chiral therapeutically relevant compound, clinically used as an antiarrhythmic,[1] antimyotonic,[2] and analgesic agent.[3] Recently, mexiletine has also been proposed for the treatment of tinnitus.[4] All these clinical applications require doses falling within a narrow therapeutic window (400–1200 mg/die); when doses near the higher limit are used, severe side-effects may occur.[1,5] In therapy, mexiletine is administered as a racemate, generally in the form of its hydrochloride salt. However, it has been reported that mexiletine enantiomers differ in both pharmacodynamic and pharmacokinetic properties. (−)-(*R*)-Mex is more potent than its enantiomer on experimental arrhythmias,[6] in binding studies on cardiac sodium channels,[7] and in blocking skeletal muscle sodium channels.[8–10] With regards to the analgesic action of Mex enantiomers, only controversal data may be found in the literature, in turn presenting (−)-(*R*)-,[11] (+)-(*S*)-Mex,[12] or neither[13,14] as the eutomer. Whenever pharmacodynamic prevalence of (−)-(*R*)-Mex was observed in vivo,[6,11] stereospecific indexes (SSI) were low (⩽2). Whether enantioselective disposition, which favors the elimination of the eutomer,[15–18] may cause partial compensation of the clinical outcome remains unanswered. However, the switch from the clinical use of racemic Mex to that of its (*R*)-enantiomer (chiral switching)[19] might be pursued given the higher toxicity of (+)-(*S*)-Mex.[13,14,20] Another possible way to overcome the Mex toxicity may be metabolite switching,[19] that is, the replacement of the parent compound with one of its metabolites. Mexiletine is extensively metabolized in humans[21,22] and the major metabolites formed by aliphatic and aromatic hydroxylation are referred to as hydroxymethylmexiletine (HMM, Fig. 1) and *p*-hydroxymexiletine (PHM, Fig. 1), respectively. Levy-Prades et al.,[23] following a personal communication of Danneberg and Haselbarth, reported that Mex metabolites are inactive as antiarrhythmic agents. Kamei studied the antinociceptive effects of (*RS*)-HMM in steptozocine-induced diabetic mice using the tail-pinch test and did not find any significant effect.[13] However, when sodium channel blocking activity on skeletal muscles was studied, both PHM and HMM were still able to reduce $I_{Na\ max}$ on single fibers of frog skeletal muscle, under both tonic and phasic (use-dependent) conditions.[24] IC_{50} values for the use-dependent blocking



Mex PHM HMM

Figure 1.

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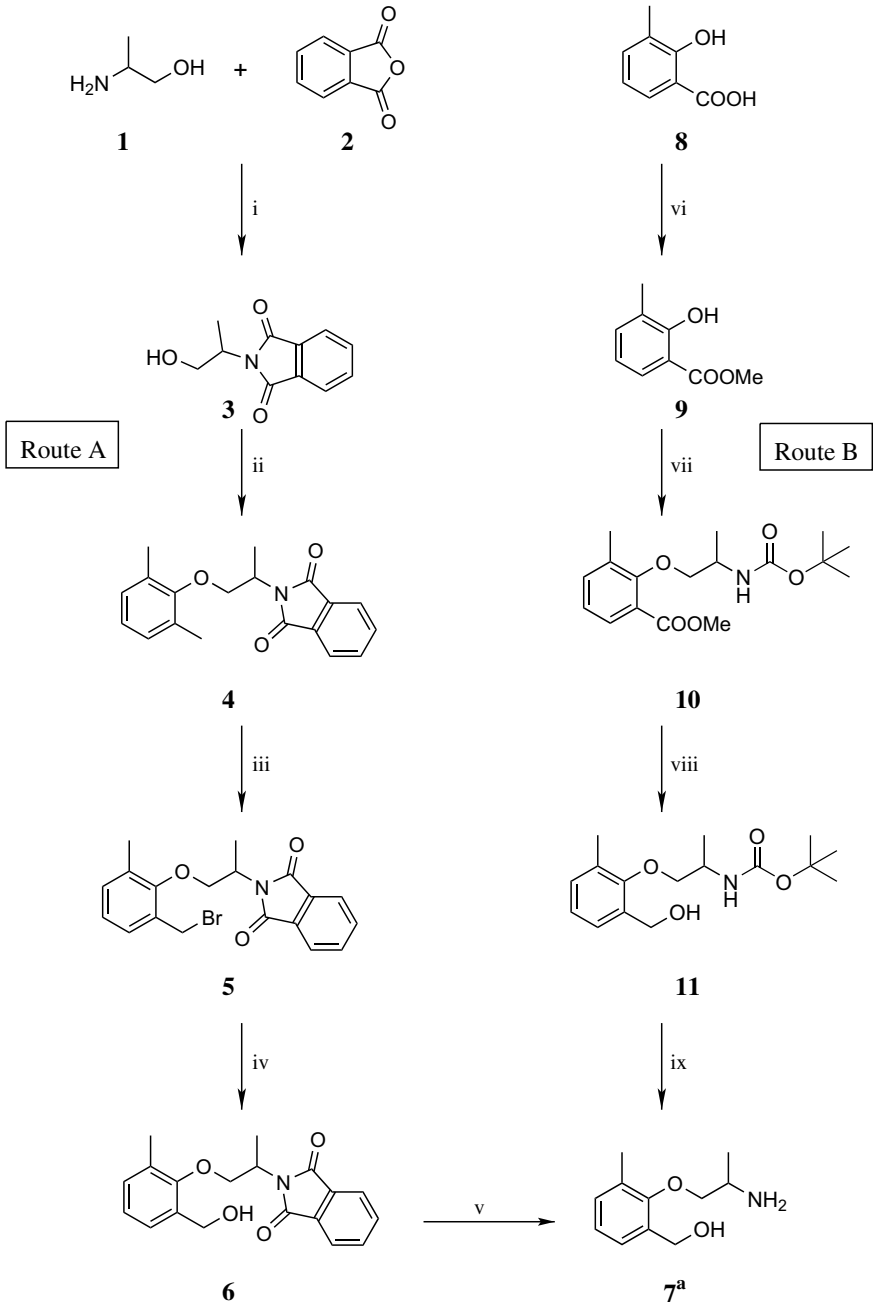
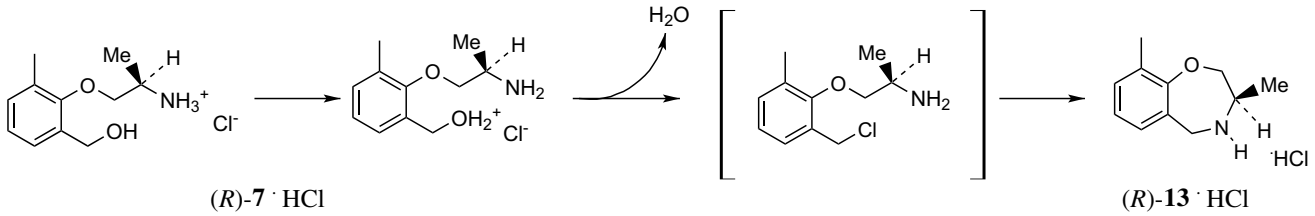
action of the metabolite were only 3–4 times higher than that of the parent compound and denoted only low SSI. In view of a possible dissociation of pharmacological activities, these preliminary in vitro results deserve further studies, which might be aided by easy access to homochiral PHM and HMM. Both resolution methods[6,25–28] and 'chiral pool' approach based syntheses[25,29–31] have been reported for Mex enantiomers. The synthesis of (+)-(*R*)- and (−)-(*S*)-PHM has already been reported.[32] Herein we report two alternative routes to homochiral HMM, which allow unambiguous attribution of the (*R*)- and (*S*)-absolute configurations to (−)- and (+)-HMM, respectively.

2. Results and discussion

The first route (Route A) to (*RS*)-HMM (*RS*)-**7** and highly enantiomerically enriched (*R*)- and (*S*)-HMM (*R*)- and (*S*)-**7** is shown in Scheme 1. It starts from the efficient protection of the racemic and optically active 2-aminopropanols **1** with phthalic anhydride **2**.[33] Alcohols **3** undergo conversion to ethers **4** under Mitsunobu conditions,[34] as previously reported.[31,32] Ethers **4** were converted into their bromo derivatives **5** following the procedure described by Mallory et al.[35] The time-dependent formation of a dibromo derivative of **4** was also observed. Thus, the times

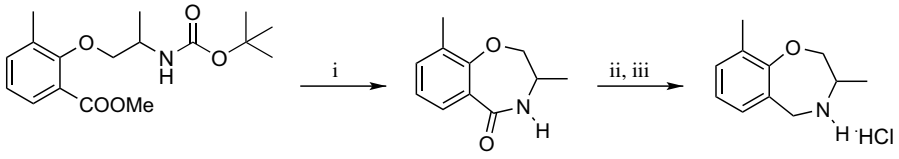


Scheme 1. Reagents and conditions: (i) Et_3N, toluene, reflux; (ii) 2,6-dimethylphenol, PPh_3, DIAD, anhyd THF; (iii) *N*-bromosuccinimide, benzoyl peroxide, CCl_4; (iv) H_2O/dioxane; (v) $N_2H_4{\cdot}H_2O$, glacial AcOH, abs EtOH; (vi) concd H_2SO_4, MeOH, 65 °C; (vii) *t*-BOCNHCH(CH_3)CH_2OH, PPh_3, DIAD, anhyd THF; (viii) $LiAlH_4$, anhyd THF, 0 °C; (ix) 98% HCOOH, 0 °C. [a] The free amine was purified in the form of several salts (see text for details).



(*R*)-**7** · HCl (*R*)-**13** · HCl

Scheme 2. Possible mechanism for the intramolecular condensation of (*R*)-**7** hydrochloride to give (*R*)-3,9-dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride, (*R*)-**13**·HCl.



(*RS*)-**10** (*RS*)-**14** (*RS*)-**13**·HCl

Scheme 3. Reagents and conditions: (i) 98% HCOOH, 0 °C; (ii) $LiAlH_4$, anhyd THF, rt, then 85 °C, then rt; (iii) aq HCl.

of reaction should not be longer than 16 h in order to avoid lowering the yield. The hydroxy derivatives **6** were obtained by modifying a procedure reported in the patent literature for the conversion of benzyl chloride into benzyl alcohol[36] and were deprotected from the phthalimido groups by hydrazinolysis.[37] The free amines were converted into their oxalate salts, which were fully characterized. Given that the oxalate anion may precipitate calcium ions contained in the buffer used for pharmacological trials, the free amines, recovered from their oxalate salts, were converted into their corresponding hydrochloride salts with gaseous HCl. (*RS*)-HMM·HCl was recrystallized from abs EtOH/Et_2O. When passing to (*R*)-HMM·HCl we were unable to recrystallize the salts and the solutions became yellow. Thus, we tried to convert (*R*)-HMM into the corresponding hydrochloride salt by treating the homochiral free amine with a few drops of 2 M HCl and azeotropically removing water, as we had done in the past for other analogues of Mex[31] and for PHM.[32] Even this time, we didn't manage in crystallizing the hydrochloride salt from abs EtOH/Et_2O. Furthermore, in the following days, we noticed that the solution was becoming more and more yellow. Removal of the solvents gave a crude solid. Spectrometry analyses showed that there had been an intramolecular condensation between the hydroxy and the amino groups, resulting in the formation of 3,9-dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (*R*)-**13**. A plausible mechanism for the formation of (*R*)-**13**, passing through the benzyl chloride reactive intermediate **12**, is given in Scheme 2. (*S*)-HMM behaved similarly, when we tried to convert it into its hydrochloride form by treatment with gaseous HCl. The free amine (*S*)-**13**, extracted from the corresponding salt, was converted into its hydrobromide salt. The same procedure carried out on (*R*)-**13** gave (*R*)-**13**·HBr. Compound (*RS*)-**13** was obtained following another synthetic route shown in Scheme 3. Compound (*RS*)-**10** was treated with 98% HCOOH at 0 °C to give (*RS*)-**14**, which was reacted with $LiAlH_4$ to give (*RS*)-**13**. The free amine was treated with a few drops of 2 M HCl and water was removed azeotropically to give (*RS*)-**13**·HCl. Spectrometry analyses of the racemate were identical to those of the (*R*)-isomer, confirming our hypothesis. The ee values of (*R*)- and (*S*)-**13** were evaluated by capillary electrophoresis. Finally, the HMM hydrobromides were obtained following another route (Route B, Scheme 1). The commercially available 3-methylsalicylic acid **8** was easily converted into methyl 2-hydroxy-3-methylbenzoate **9**,[38] which is now commercially available. Ester **9** was reacted with the appropriate *N*-Boc protected alaninol (which is commercially available for the enantiomers and easily preparable as the racemate, following the procedure routinely used for β-aminoalchohols)[39] under Mitsunobu conditions[34] to give compound **10**, which was easily reduced to the corresponding alcohol **11**. Removal of the Boc protecting group gave the desired product (HMM), which was purified as the hydrobromide salt. This time, we succeded in the recrystallization of (*RS*)-**7**·HBr and (*R*)-**7**·HBr, while (*S*)-**7**·HBr was only obtained in a mixture containing 20% of (*S*)-**13**·HBr as assessed by ^1H NMR and elemental analyses. Ee values of HMM enantiomers were evaluated by both chiral ^1H NMR analysis and capillary electrophoresis. The former was performed on free amine samples, recovered by extraction of a sample from the corresponding hydrobromide salts, using (−)-(*R*)-(2-naphthyloxy)phenylacetic acid as a CSA.[40,41] Capillary electrophoretic analyses were performed directly on the oxalate salts, using β-cyclodextrin sulfated sodium salt as a chiral selector. In both cases, ee values were 98% for both enantiomers.

3. Conclusions

In conclusion, we have reported the synthesis of HMM in its racemic and enantiomeric forms. (+)- and (−)-HMM were fully characterized and were unambiguously given (*S*)- and (*R*)-configurations, respectively. Overall yields were moderate, but all steps were easily performed and gave (*R*)- and (*S*)-**7** oxalate salts in highly enriched optically active forms. The ee values were 98% for both enantiomers, as stated by both ^1H NMR and capillary

electrophoresis. The practical synthetic routes presented herein may be useful to meet the needs of reliable analytical standards in order to feed further studies on Mex disposition.[42,43] It is noteworthy that the halohydrates of HMM are not easy to crystallize because of competing intramolecular condensation to give benzoxazepine **13**. The formation of this degradation product, which may be considered as a rigid analogue of Mex, should be taken into account when considering the pharmacological activities of HMM. HMM as long as PHM, although less active than Mex, is still able to reduce $I_{Na\ max}$ under both tonic and phasic conditions.[24] Thus, we suggest to use PHM and HMM as the key starting synthons for the preparation of dimeric compounds, potentially active on the Na^+ channels.[32,44]

4. Experimental

All chemicals were purchased from Sigma–Aldrich or Lancaster. (−)-(*R*)-(2-Naphthyloxy)phenylacetic acid, used as chiral solvating agent (CSA), was prepared in house.[40] Solvents were RP grade unless otherwise indicated. Compounds **3** and **4** were prepared as previously described.[31] Yields refer to purified products and are not optimized. The structures of the compounds were confirmed by routine spectrometric analyses. Only spectra for compounds not previously described are given. Melting points were determined on a Gallenkamp melting point apparatus in open glass capillary tubes and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer (Norwalk, CT) Spectrum One FT spectrophotometer and band positions are given in reciprocal centimeters (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-VX spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C, respectively, using $CDCl_3$ or CD_3OD (where indicated) as solvents. Chemical shifts are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^1H NMR) and δ 77.3 (^{13}C NMR); CD_3OD, δ 3.31, unless otherwise indicated (^1H NMR) and variable (^{13}C NMR) as indicated below for each compound. *J* values are given in Hz. Electrophoretic runs were performed on a BioFocus 3000 CE system (Bio-Rad, USA). A fused silica capillary of 69.7 cm (effective length 65.2 cm) and 0.05 mm i.d. (Quadrex Corporation) thermostated at 20 °C was used as a separation tube. The samples (0.1 mg/mL) were pressure injected and detected at 214 nm. When determining ee values by ^1H NMR, (*RS*)-, (*R*)-, and (*S*)-**7** were recovered by extraction of a sample of the corresponding hydrobromide salts and dissolved with 1.5 equiv. of CSA in $CDCl_3$. Spectra were registered at 25 °C and the splitting of the α-methyl groups doublet was observed ($\Delta\delta = 0.093$ ca). EIMS spectra were recorded on a Hewlett-Packard 6890-5973 MSD gas chromatograph/mass spectrometer at low resolution. ESI^+/MS/MS analyses were performed with an Agilent 1100 Series LC-MSD trap system VL workstation. Elemental analyses were performed on a Eurovector Euro EA 3000 analyzer. Optical rotations were measured on a Perkin Elmer (Norwalk, CT) Mod 341 spectropolarimeter; concentrations are expressed in g/100 mL, and the cell length was 1 dm, thus $[\alpha]_D^{20}$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040–0.063 mm, Merck, Darmstadt, Germany) using the technique described by Still et al.[45] TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel $60F_{254}$, Merck).

4.1. (*RS*)-2-[2-(2,6-Dimethylphenoxy)-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (*RS*)-4

Prepared as reported in the literature.[31] Yield: 84%; IR (neat): 1775, 1713 (C=O) cm^{-1}; ^1H NMR: δ 1.55 (d, $J = 6.9$ Hz, 3H, C*H*$_3$CH), 2.19 (s, 6H, C*H*$_3$Ar), 3.91 (dd, $J = 9.4$, 5.5 Hz, 1H, C*H*H), 4.37 (apparent t, $J = 9.2$ Hz, 1H, CH*H*), 4.80–4.94 (m, 1H, C*H*), 6.82–6.91 (m, 1H, ArO *H*C-4), 6.91–7.01 (m, 2H, ArO *H*C-3,5), 7.68–7.76 (m, 2H, Ar *H*C-5,6), 7.8–7.9 (m, 2H, Ar *H*C-4,7); ^{13}C NMR: δ 14.7 (1C), 15.8 (2C), 46.9 (1C), 71.4 (1C), 122.9 (2C), 123.7 (1C), 128.6 (2C), 130.4 (2C), 132.0 (2C), 133.7 (2C), 155.1 (1C), 168.1 (2C); MS (70 eV) *m*/*z* (%) 309 (M^+, 7), 188 (100).

4.2. (*RS*)-2-{2-[2-(Bromomethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (*RS*)-5

To a stirred solution of (*RS*)-2-[2-(2,6-dimethylphenoxy)-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (*RS*)-**4** (4.53 g, 14.6 mmol) in CCl_4 (210 mL), *N*-bromosuccinimide (2.60 g, 14.6 mmol) and benzoyl peroxide (250 mg, 1.02 mmol) were added. The reaction mixture was refluxed for 4 h. The solid residue was filtered off. After evaporation of the solvent under vacuum, the residue (7.50 g) was purified by flash chromatography (EtOAc/petroleum ether 0.5:9.5) and a slightly yellowish oil (3.30 g, 58%) was obtained: IR (neat): 1774, 1708 (C=O) cm^{-1}; ^1H NMR: δ 1.56 (d, $J = 6.9$ Hz, 3H, C*H*$_3$CH), 2.21 (s, 3H, C*H*$_3$Ar), 4.06 (dd, $J = 9.2$, 5.4 Hz, 1H, C*H*HO), 4.39 (d, $J = 9.6$ Hz, 1H, C*H*HBr), 4.58 (apparent t overlapping d at 4.61, $J = 9.3$ Hz, 1H, CH*H*O), 4.61 (d overlapping apparent t at 4.58, $J = 9.9$ Hz, 1H, CH*H*Br), 4.90–5.0 (m, 1H, C*H*), 6.96 (apparent t, $J = 7.6$ Hz, 1H, Ar *H*C-4), 7.08 (d, $J = 7.4$ Hz, 1H, Ar *H*C-5), 7.16 (d, $J = 7.7$ Hz, 1H, Ar *H*C-3), 7.68–7.74 (m, 2H, Ar *H*C-5,6), 7.82–7.88 (m, 2H, Ar *H*C-4,7); ^{13}C NMR: δ 15.3 (1C), 16.6 (1C), 28.9 (1C), 47.4 (1C), 72.5 (1C), 123.5 (2C), 124.7 (1C), 129.2 (1C), 131.4 (1C), 131.8 (1C), 132.3 (3C), 134.2 (2C), 155.3 (1C), 168.8 (2C); MS (70 eV) *m*/*z* (%) 387 (M^+, <1), 188 (100).

4.3. (−)-(*R*)-2-{2-[2-(Bromomethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (−)-(*R*)-5

Prepared as above using (−)-(*R*)-2-[2-(2,6-dimethylphenoxy)-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (−)-(*R*)-**4**. Yield: 67%; $[\alpha]_D^{20} = -90.0$ (*c* 2.7, $CHCl_3$). Spectrometry data were in agreement with those found for the racemate.

4.4. (+)-(*S*)-2-{2-[2-(Bromomethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-5

Prepared via the above reaction starting from (+)-(*S*)-2-[2-(2,6-dimethylphenoxy)-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-**4**. Yield: 70%; $[\alpha]_D^{20} = +84.2$ (*c* 2.05, $CHCl_3$).

Spectrometry data were in agreement with those found for the racemate.

4.5. (*RS*)-2-{2-[2-(Hydroxymethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (*RS*)-6

(*RS*)-2-{2-[2-(bromomethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (*RS*)-**5** (3.33 g, 8.6 mmol) was dissolved in a mixture of H_2O (20 mL) and dioxane (20 mL). The reaction mixture was kept at reflux for 19 h. Dioxane was removed by evaporation under vacuum and the aqueous phase was extracted several times with EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated under vacuum to give 4.27 g of a yellow oil. Purification of the crude residue by silica gel column chromatography (EtOAc/petroleum ether 1:1) gave 1.56 g of a yellow oil. Yield: 56%; IR (neat): 3470 (OH), 1773, 1708 (C=O) cm^{-1}; ^1H NMR: δ 1.51 (d, $J = 7.1$ Hz, 3H, CH_3CH), 2.18 (s, 3H, CH_3Ar), 2.64 (br s, 1H, O*H*), 3.92 (dd, $J = 9.4$, 5.5 Hz, 1H, C*H*HCH), 4.46 (apparent t, $J = 9.4$ Hz, 1H, CH*H*CH), 4.55 (d overlapping d at 4.61, $J = 12.7$ Hz, 1H, AB system, C*H*HOH), 4.61 (d overlapping d at 4.55, $J = 12.7$ Hz, 1H, AB system, CH*H*OH), 4.78–4.92 (m, 1H, C*H*), 6.94 (apparent t, $J = 7.6$ Hz, 1H, ArO *H*C-4), 7.03 (d, $J = 6.9$ Hz, 1H, ArO *H*C-5), 7.13 (d, $J = 7.4$ Hz, 1H, ArO *H*C-3), 7.64–7.74 (m, 2H, Ar), 7.77–7.86 (m, 2H, Ar); ^{13}C NMR: δ 15.2 (1C), 16.4 (1C), 47.4 (1C), 61.2 (1C), 72.9 (1C), 123.5 (2C), 124.5 (1C), 127.3 (1C), 131.1 (1C), 131.2 (1C), 132.1 (2C), 134.0 (1C), 134.3 (2C), 155.1 (1C), 168.9 (2C); MS (70 eV) *m*/*z* (%) 325 (M^+, 6), 188 (100).

4.6. (−)-(*R*)-2-{2-[2-(Hydroxymethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (−)-(*R*)-6

Prepared via the above reaction starting from (−)-(*R*)-2-{2-[2-(bromomethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (−)-(*R*)-**5**. Yield: 67%; $[\alpha]_D^{20} = -53.4$ (*c* 2.15, $CHCl_3$); IR ($CHCl_3$): 3565 (OH), 1774, 1709 (C=O) cm^{-1}; ^1H NMR: δ 1.53 (d, $J = 7.1$ Hz, 3H, CH_3CH), 2.20 (s, 3H, CH_3Ar), 2.33 (br t, $J = 6.0$ Hz, 1H, exch D_2O, O*H*), 3.94 (dd, $J = 9.4$, 5.4 Hz, 1H, C*H*HCH), 4.50 (apparent t, $J = 9.5$ Hz, 1H, CH*H*CH), 4.57 (dd overlapping apparent t at 4.50, $J = 11.9$, 5.5 Hz, 1H, AB system coupled to br t at 2.33, C*H*HOH), 4.61 (dd, $J = 11.9$, 5.5 Hz, 1H, AB system coupled to br t at 2.33, CH*H*OH), 4.80–4.95 (m, 1H, C*H*), 6.96 (apparent t, $J = 7.4$ Hz, 1H, ArO *H*C-4), 7.06 (d, $J = 6.3$ Hz, 1H, ArO *H*C-5), 7.13 (d, $J = 7.3$ Hz, 1H, ArO *H*C-3), 7.67–7.76 (m, 2H, Ar), 7.80–7.88 (m, 2H, Ar); MS (70 eV) *m*/*z* (%) 325 (M^+, 12), 188 (100).

4.7. (+)-(*S*)-2-{2-[2-(Hydroxymethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-6

Prepared via the above reaction starting from (+)-(*S*)-2-{2-[2-(bromomethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-**5**. Yield: 56%; $[\alpha]_D^{20} = +59.6$ (*c* 2.4, $CHCl_3$); Spectrometry data were in agreement with those reported for (−)-(*R*)-**6**.

4.8. (*RS*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol (*RS*)-7

Method A: To a stirred solution of (*RS*)-2-{2-[2-(hydroxymethyl)-6-methylphenoxy]-1-methylethyl}-1*H*-isoindole-1,3(2*H*)-dione (*RS*)-**6** (0.63 g, 1.90 mmol) in absolute EtOH (7.4 mL), glacial AcOH (5.80 mmol) and $N_2H_4{\cdot}H_2O$ (5.80 mmol) were added and the mixture was kept at reflux for 2 h. The solid residue was then filtered off. After evaporation of the filtrate, the residue was taken up with EtOAc and extracted with 2 M HCl, after which the aqueous phase was made alkaline with 2 M NaOH and extracted several times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The final product was a sligthly yellowish oil (0.37 g, 99%). *Method B*: (*RS*)-*tert*-Butyl{2-[2-(hydroxymethyl)-6-methylphenoxy]-1-methylethyl}carbamate (*RS*)-**11** (0.92 g, 3.1 mmol) was dissolved in 98% HCOOH (30 mL) and the reaction mixture was stirred at 0 °C for 5 h. After evaporation of the solvent under reduced pressure, the residue was taken up with EtOAc and extracted with 2 M HCl; then the aqueous phase was made alkaline and extracted several times with EtOAc. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and concentrated under vacuum to give 0.47 g of a yellow oil (77%): IR (neat): 3357 (NH_2), 3292 (OH) cm^{-1}; ^1H NMR: δ 1.19 (d, $J = 6.6$ Hz, 3H, CH_3CH), 2.29 (s, 3H, CH_3Ar), 3.10 (br s, 3H, NH_2 + O*H*), 3.35–3.50 (br m, 1H, C*H*), 3.64 (apparent t, $J = 8.5$ Hz, 1H, C*H*HCH), 3.94 (dd, $J = 9.2$, 2.9 Hz, 1H, CH*H*CH), 4.55 (d, $J = 12.1$ Hz, 1H, C*H*HOH), 4.71 (d, $J = 12.4$ Hz, 1H, CH*H*OH), 6.97 (apparent t, $J = 7.4$ Hz, 1H, Ar *H*C-4), 7.05–7.15 (m, 2H, Ar *H*C-3,5); ^{13}C NMR: δ 16.9 (1C), 19.9 (1C), 47.5 (1C), 61.6 (1C), 78.4 (1C), 124.3 (1C), 128.3 (1C), 131.0 (1C), 131.6 (1C), 134.6 (1C), 156.6 (1C); MS (70 eV) *m*/*z* (%) 195 (M^+, 2), 44 (100).

4.9. (−)-(*R*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol (−)-(*R*)-7

Prepared via the above reaction starting from either (−)-(*R*)-**6** (method A, yield: 97%) or (+)-(*R*)-**11** (method B, yield: 81%): $[\alpha]_D^{20} = -9.6$ (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3373 (NH_2), 3197 (OH) cm^{-1}; ^1H NMR: δ 1.18 (d, $J = 6.6$ Hz, 3H, CH_3CH), 2.30 (s, 3H, CH_3Ar), 3.06 (br s, 3H, NH_2 + O*H*), 3.34–3.48 (m, 1H, C*H*), 3.62 (dd, $J = 9.2$, 7.8 Hz, 1H, C*H*HCH), 3.93 (dd, $J = 9.2$, 3.2 Hz, 1H, CH*H*CH), 4.57 (d, $J = 12.4$ Hz, 1H, AB system, C*H*HOH), 4.73 (d, $J = 12.4$ Hz, 1H, AB system, CH*H*OH), 6.98 (apparent t, $J = 7.4$ Hz, 1H, Ar *H*C-4), 7.11 (d overlapping d at 7.12, $J = 7.2$ Hz, 1H, Ar *H*C-5), 7.12 (d overlapping d at 7.11, $J = 7.2$ Hz, 1H, Ar *H*C-3); ^{13}C NMR: δ 16.7 (1C), 20.1 (1C), 47.3 (1C), 61.4 (1C), 78.6 (1C), 124.2 (1C), 128.1 (1C), 130.9 (1C), 131.4 (1C), 134.6 (1C), 156.5 (1C); MS (70 eV) *m*/*z* (%) 195 (M^+, 5), 44 (100).

4.10. (+)-(*S*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol (+)-(*S*)-7

Prepared as reported above for (*RS*)-**7**, starting from either (+)-(*S*)-**6** (method A, yield: 88%) or (−)-(*S*)-**11** (method B, yield: 96%): $[\alpha]_D^{20} = +8.4$ (*c* 2, $CHCl_3$); MS (70 eV) *m*/*z* (%) 195 (M^+, 3), 44 (100).

4.11. (*RS*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol hydrochloride (*RS*)-7·HCl

(*RS*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol (*RS*)-**7** (0.80 g, 4.1 mmol) was treated with a few drops of hydrochloric aqueous solution. Removal of water by azeotropic distillation (abs EtOH/toluene) afforded a white solid, which was recrystallized from EtOH/Et_2O to give 0.26 g of white crystals (40%): mp 143–144 °C; ^{1}H NMR (CD_3OD): δ 1.43 (d, $J = 6.9$ Hz, 3H, CH_3CH), 2.33 (s, 3H, CH_3Ar), 3.69–3.81 (m, dd upon irradiation at 1.43, $J = 6.9$, 3.6 Hz, 1H, C*H*), 3.94 (dd, $J = 10.3$, 7.0 Hz, 1H, C*H*HCH), 4.04 (dd, $J = 10.2$, 3.6 Hz, 1H, CH*H*CH), 4.64 (s, 2H, CH_2OH), 7.06 (apparent t, $J = 7.5$ Hz, 1H, Ar *H*C-4), 7.18 (d, $J = 7.4$ Hz, 1H, Ar *H*C-5), 7.23 (d, $J = 7.4$ Hz, 1H, Ar *H*C-3); Anal. Calcd for ($C_{11}H_{17}NO_2$·HCl): C, 57.02; H, 7.83; N, 6.04. Found: C, 56.64; H, 7.59; N, 5.93.

4.12. (*RS*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol oxalate (*RS*)-7·$H_2C_2O_4$

To an ether solution of (*RS*)-[2-(2-aminopropoxy)-3-methylphenyl]methanol (*RS*)-**7** (0.30 g, 1.54 mmol), a 3% $H_2C_2O_4$ ether solution (4.6 mL, 1.54 mmol) was added. Ethyl ether was removed by evaporation under vacuum to give (*RS*)-**7**·$H_2C_2O_4$ as a white solid, which was recrystallized from MeOH/Et_2O to give 0.25 g (57%) of white crystals: mp 189–190 °C; ^{1}H NMR (CD_3OD): δ 1.40 (d, $J = 6.6$ Hz, 3H, CH_3CH), 2.31 (s, 3H, CH_3Ar), 3.60–3.75 (m, 1H, C*H*), 3.90 (dd, $J = 9.9$, 6.9 Hz, 1H, C*H*HCH), 3.99 (dd, $J = 10.0$, 4.0 Hz, 1H, CH*H*CH), 4.64 (s, 2H, CH_2OH), 7.03 (apparent t, $J = 7.6$ Hz, 1H, Ar *H*C-4), 7.14 (d, $J = 7.4$ Hz, 1H, Ar *H*C-5), 7.22 (d, $J = 7.4$ Hz, 1H, Ar *H*C-3); ^{13}C NMR (CD_3OD, δ 46.2): δ 12.9 (1C), 13.6 (1C), 46.2 (1C), 57.9 (1C), 71.9 (1C), 122.9 (1C), 125.9 (1C), 129.3 (2C), 132.4 (1C), 153.2 (1C), 171.0 (2C); Anal. Calcd for ($C_{11}H_{17}NO_2$·0.5$H_2C_2O_4$): C, 59.99; H, 7.55; N, 5.83. Found: C, 60.14; H, 7.56; N, 6.05.

4.13. (−)-(*R*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol oxalate (−)-(*R*)-7·$H_2C_2O_4$

Prepared as reported above for (*RS*)-**7**·$H_2C_2O_4$, starting from (−)-(*R*)-**7**. Yield: 33%; mp 203–204 °C (MeOH/Et_2O); >98% ee (capillary electrophoresis, injection: 10 psi/s; BGE: phosphate buffer 0.035 M at pH 3.0; chiral selector: β-cyclodextrin sulfated sodium salt 5.5 mg/mL; voltage: 20 kV); $[\alpha]_D^{20} = -5.7$ (*c* 2, MeOH); Anal. Calcd for ($C_{11}H_{17}NO_2$·0.5$H_2C_2O_4$): C, 59.98; H, 7.55; N, 5.83. Found: C, 59.78; H, 7.50; N, 6.00. Spectroscopic data were in agreement with (+)-(*S*)-**7**·$H_2C_2O_4$.

4.14. (+)-(*S*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol oxalate (+)-(*S*)-7·$H_2C_2O_4$

Prepared as reported above for (*RS*)-**7**·$H_2C_2O_4$, starting from (+)-(*S*)-**7**. Yield: 34%; mp 197–199 °C (MeOH/Et_2O); >98% ee (capillary electrophoresis using the conditions described for the *R*-enantiomer); $[\alpha]_D^{20} = +6.7$ (*c* 2, MeOH); ^{1}H NMR (D_2O/CD_3OD 3:2, δ 3.11): δ 1.24 (d, $J = 6.6$ Hz, 3H, CH_3CH), 2.10 (s, 3H, CH_3Ar), 3.55–3.67 (m, 1H, C*H*), 3.68–3.84 (m, 2H, CH_2CH), 4.46 (s, 2H, CH_2OH), 6.91 (apparent t, $J = 7.6$ Hz, 1H, Ar *H*C-4), 7.02 (d overlapping d at 7.05, $J = 9.2$ Hz, 1H, Ar *H*C-5), 7.05 (d overlapping d at 7.02, $J = 7.7$ Hz, 1H, Ar *H*C-3); Anal. Calcd for ($C_{11}H_{17}NO_2$·0.5$H_2C_2O_4$): C, 59.98; H, 7.55; N, 5.83. Found: C, 59.67; H, 7.47; N, 6.06. Other spectroscopic data were in agreement with those of the racemate.

4.15. (*RS*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol hydrobromide (*RS*)-7·HBr

(*RS*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol [(*RS*)-**7**] (0.25 g, 1.28 mmol) was dissolved in anhydrous Et_2O and treated with gaseous HBr for a few seconds to give a white solid, which was recrystallized by abs EtOH/Et_2O/iPr_2O to give 0.090 g of white crystals (25%): mp 148–149 °C; ^{1}H NMR (CD_3OD): δ 1.23 (d, $J = 6.6$ Hz, 3H, CH_3CH), 2.29 (s, 3H, CH_3Ar), 3.30–3.42 (m, 1H, C*H*), 3.68 (dd, $J = 9.2$, 7.3 Hz, 1H, C*H*HCH), 3.78 (dd, $J = 9.2$, 4.1 Hz, 1H, CH*H*CH), 4.65 (s, 2H, CH_2OH), 7.02 (apparent t, $J = 7.6$ Hz, 1H, Ar *H*C-4), 7.12 (d, $J = 6.9$ Hz, 1H, Ar *H*C-5), 7.23 (d, $J = 6.9$ Hz, 1H, Ar *H*C-3); ^{13}C NMR (CD_3OD, δ 47.8): δ 15.2 (1C), 17.5 (1C), 47.0 (1C), 59.3 (1C), 77.7 (1C), 124.1 (1C), 127.1 (1C), 130.6 (1C), 130.8 (1C), 134.1 (1C), 155.1 (1C). Anal. Calcd for ($C_{11}H_{17}NO_2$·0.12HBr): C, 64.33; H, 8.40; N, 6.82. Found: C, 64.43; H, 8.30; N, 6.65.

4.16. (*R*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol hydrobromide (*R*)-7·HBr

Prepared as reported above for (*S*)-**7**·HBr, starting from (−)-(*R*)-**7**. Yield: 26%; mp 114–116 °C (abs EtOH/iPr_2O); 98% ee (^{1}H NMR); ^{1}H NMR (CD_3OD): δ 1.46 (d, $J = 6.6$ Hz, 3H, CH_3CH), 2.33 (s, 3H, CH_3Ar), 3.82 (apparent sextet, $J = 6.0$ Hz, 1H, C*H*), 4.07 (d, $J = 9.9$ Hz, 2H, CH_2CH), 4.63 (d, $J = 9.9$ Hz, 1H, AB system, C*H*HOH), 4.67 (d, $J = 9.9$ Hz, 1H, AB system, CH*H*OH), 7.06 (apparent t, $J = 7.6$ Hz, 1H, Ar *H*C-4), 7.21 (d, $J = 6.6$ Hz, 1H, Ar *H*C-5), 7.27 (d $J = 7.2$ Hz, 1H, Ar *H*C-3); ESI$^+$/MS *m*/*z* 218.1 (MNa^+); ESI$^+$/MS/MS *m*/*z* 161 (100); Anal. Calcd for ($C_{11}H_{17}NO_2$·0.25HBr): C, 61.31; H, 8.07; N, 6.50. Found: C, 61.45; H, 7.72; N, 6.35. Spectroscopic data were in agreement with (+)-(*S*)-**7**·HBr.

4.17. (*S*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol hydrobromide (*S*)-7·HBr

(+)-(*S*)-[2-(2-Aminopropoxy)-3-methylphenyl]methanol [(+)-(*S*)-**7**] (0.80 g, 4.1 mmol) was dissolved in anhydrous Et_2O and treated with gaseous HBr for a few seconds to give a white solid, which was recrystallized from abs EtOH/Et_2O/iPr_2O to give 0.11 g of white crystals (10%): mp 121–122 °C; 98% ee (^{1}H NMR); ^{1}H NMR (CD_3OD) was in agreement with that of the (*R*)-enantiomer but denoted the presence of about 20% of (*S*)-**13**·HBr; ESI$^+$/MS *m*/*z* 218.1 (MNa^+); ESI$^+$/MS/MS *m*/*z* 161 (100). Anal. Calcd for ($C_{11}H_{17}NO_2$·HBr + 0.2$C_{11}H_{15}NO$·HBr): C, 48.37; H, 6.52; N, 5.13. Found: C, 48.26; H, 6.49; N, 5.12.

4.18. Methyl 3-methylsalicylate 9

3-Methylsalicylic acid (4.0 g, 26.3 mmol) was dissolved in MeOH (32 mL) and treated with concd H_2SO_4 (12 mL). The reaction mixture was kept at 65 °C for 30 h. Excess MeOH was removed by evaporation under vacuum and the aqueous phase was extracted several times with Et_2O. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, then dried over Na_2SO_4 and concentrated under vacuum to give 3.43 g of a yellow oil (78%): IR (neat): 3423 (OH), 1676 (C=O) cm^{-1}; ^1H NMR: δ 2.26 (s, 3H, CH_3CH), 3.94 (s, 3H, CH_3O), 6.78 (apparent t, $J = 7.7$ Hz, 1H, Ar *H*C-4), 7.31 (d, $J = 7.1$ Hz, 1H, Ar *H*C-5), 7.67–7.70 (m, 1H, Ar *H*C-3), 11.0 (s, 1H, O*H*); MS (70 eV) *m*/*z* (%) 166 (M^+, 62), 134 (100).

4.19. (*RS*)-Methyl 2-{2-[(*tert*-butoxycarbonyl)amino]-propoxy}-3-methylbenzoate (*RS*)-10

To a stirred solution of *N*-*t*-Boc-DL-alaninol (2.40 g, 13.7 mmol), methyl 3-methylsalicylate **9** (3.41 g, 20.6 mmol), and triphenylphosphine (5.40 g, 20.6 mmol) in dry THF (120 mL), under an N_2 atmosphere, a solution of DIAD (4.16 g, 20.6 mmol) in dry THF (60 mL) was added dropwise. The mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure, Et_2O was added and the precipitate formed was filtered off. The filtrate was evaporated in vacuo and the residue was purified by flash chromatography using silica gel (eluent EtOAc/petroleum ether 1:9) to give 3.32 g of a yellow oil (75%): IR (neat): 3382 (NH), 1713 (C=O) cm^{-1}; ^1H NMR: δ 1.35 (d, $J = 6.7$ Hz, 3H, CH_3CH), 1.46 (s, 9H, *t*-Bu), 2.30 (s, 3H, CH_3Ar), 3.84–3.92 (m overlapping s at 3.90, 3H, CH_2 + C*H*), 3.90 (s overlapping m at 3.84–3.92, 3H, CH_3O), 5.44 (br s, 1H, N*H*), 7.06 (apparent t, $J = 7.7$ Hz, 1H, Ar *H*C-4), 7.34 (dd, $J = 7.5$, 1.1 Hz, 1H, Ar *H*C-5), 7.65 (dd, $J = 7.6$, 1.6 Hz, 1H, Ar *H*C-3); ^{13}C NMR: δ 16.4 (1C), 18.0 (1C), 28.6 (3C), 47.0 (1C), 52.4 (1C), 76.4 (1C), 79.3 (1C), 124.0 (1C), 124.6 (1C), 129.6 (1C), 133.0 (1C), 135.6 (1C), 155.8 (1C), 156.8 (1C), 167.0 (1C); MS (70 eV) *m*/*z* (%) 323 (M^+, <1), 134 (100).

4.20. (+)-(*R*)-Methyl 2-{2-[(*tert*-butoxycarbonyl)amino]-propoxy}-3-methylbenzoate (+)-(*R*)-10

Prepared via the above reaction starting from the commercial *N*-*t*-Boc-D-alaninol. Yield: 63%; $[\alpha]_D^{20} = +15.0$ (*c* 2, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those of the racemate.

4.21. (−)-(*S*)-Methyl 2-{2-[(*tert*-butoxycarbonyl)amino]-propoxy}-3-methylbenzoate (−)-(*S*)-10

Prepared via the above reaction starting from the commercial *N*-*t*-Boc-L-alaninol. Yield: 75%; $[\alpha]_D^{20} = -15.0$ (*c* 2, $CHCl_3$); ^1H NMR: δ 1.35 (d, $J = 6.7$ Hz, 3H, CH_3CH), 1.46 (s, 9H, *t*-Bu), 2.31 (s, 3H, CH_3Ar), 3.84–3.90 (m, 2H, CH_2), 3.90 (s overlapping m at 3.90–4.0, 3H, CH_3O), 3.90–4.0 (m overlapping s at 3.90, 1H, C*H*), 5.44 (br s, 1H, N*H*), 7.05 (apparent t, $J = 7.5$ Hz, 1H, Ar *H*C-4), 7.33 (dd, $J = 7.5$, 1.1 Hz, 1H, Ar *H*C-5), 7.65 (dd, $J = 7.8$, 1.2 Hz, 1H, Ar *H*C-3). Other spectroscopic and spectrometric data were in agreement with those of the racemate.

4.22. (*RS*)-*tert*-Butyl {2-[2-(hydroxymethyl)-6-methylphenoxy]-1-methylethyl}carbamate (*RS*)-11

To a suspension of $LiAlH_4$ (0.65 g, 17.0 mmol) in anhydrous THF (50 mL), (*RS*)-methyl 2-{2-[(*tert*-butoxycarbonyl)amino]propoxy}-3-methylbenzoate (*RS*)-**10** (2.75 g, 8.5 mmol) was added. The reaction mixture was stirred at 0 °C for 7 h, then it was quenched by the careful addition of cold water until the end of gas evolution. The residue was removed by filtration and the filtrate additioned with H_2O. The aqueous phase was extracted several times with Et_2O. The combined extracts were dried over Na_2SO_4 and the filtrate was concentrated under vacuum to give 2.13 g of a yellow oil (85%), which was recrystallized from EtOAc/petroleum ether: mp 79–80 °C; IR ($CHCl_3$): 3446 (NH, OH), 1705 (C=O) cm^{-1}; ^1H NMR: δ 1.34 (d, $J = 6.6$ Hz, 3H, CH_3CH), 1.46 (s, 9H, *t*-Bu), 1.67 (br s, 1H, O*H*), 2.28 (s, 3H, CH_3Ar), 3.77–3.90 (m, 2H, CH_2CH), 4.01 (br s, 1H, C*H*), 4.65 (d, $J = 12.4$ Hz, 1H, AB system, C*H*HOH), 4.71 (d, $J = 12.4$ Hz, 1H, AB system, CH*H*OH), 4.95 (br d, $J = 8.0$ Hz, 1H, N*H*), 7.02 (apparent t, $J = 7.4$ Hz, 1H, Ar *H*C-4), 7.12 (d, $J = 6.6$ Hz, 1H, Ar *H*C-5), 7.18 (d, $J = 7.4$ Hz, 1H, Ar *H*C-3); ^{13}C NMR: δ 16.3 (1 C), 18.0 (1C), 28.6 (3C), 47.0 (1C), 61.4 (1C), 75.8 (1C), 79.8 (1C), 124.5 (1C), 127.5 (1C), 131.3 (1C), 131.4 (1C), 134.0 (1C), 155.3 (1C), 155.8 (1C); MS (70 eV) *m*/*z* (%) 295 (M^+, <1), 120 (100). Anal. Calcd for ($C_{16}H_{25}NO_4$): C, 65.06; H, 8.53; N, 4.74. Found: C, 65.39; H, 8.51; N, 4.88.

4.23. (+)-(*R*)-*tert*-Butyl {2-[2-(hydroxymethyl)-6-methylphenoxy]-1-methylethyl}carbamate (+)-(*R*)-11

Prepared via the above reaction starting from (+)-(*R*)-methyl 2-{2-[(*tert*-butoxycarbonyl)amino]propoxy}-3-methylbenzoate [(+)-(*R*)-**10**]. Yield: 46%: mp 71–72 °C (EtOAc/petroleum ether); $[\alpha]_D^{20} = +25.6$ (*c* 2, $CHCl_3$). Anal. Calcd for ($C_{16}H_{25}NO_4$): C, 65.06; H, 8.53; N, 4.74. Found: C, 65.07; H, 8.49; N, 4.97. Spectroscopic and spectrometric data were in agreement with those of the racemate.

4.24. (−)-(*S*)-*tert*-Butyl {2-[2-(hydroxymethyl)-6-methylphenoxy]-1-methylethyl}carbamate (−)-(*S*)-11

Prepared via the above reaction starting from (−)-(*S*)-methyl 2-{2-[(*tert*-butoxycarbonyl)amino]propoxy}-3-methylbenzoate (−)-(*S*)-**10**. Yield: 65%: mp 67–68 °C (EtOAc/petroleum ether); $[\alpha]_D^{20} = -26.7$ (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3446 (NH, OH), 1705 (C=O) cm^{-1}; ^1H NMR: δ 1.34 (d, $J = 6.9$ Hz, 3H, CH_3CH), 1.46 (s, 9H, *t*-Bu), 2.28 (s, 3H, CH_3Ar), 2.52 (br s, 1H, O*H*), 3.76–3.87 (m, 2H, CH_2CH), 3.92–4.06 (br m, 1H, C*H*), 4.65 (d, $J = 12.4$ Hz, 1H, AB system, C*H*HOH), 4.70 (d, $J = 12.4$ Hz, 1H, AB system, CH*H*OH), 4.95 (br d, $J = 7.1$ Hz, 1H, N*H*), 7.01 (apparent t, $J = 7.4$ Hz, 1H, Ar *H*C-4), 7.12 (d, $J = 7.1$ Hz, 1H, Ar *H*C-5), 7.18 (d, $J = 7.4$ Hz, 1H, Ar *H*C-3). Anal. Calcd for ($C_{16}H_{25}NO_4$): C, 65.06; H, 8.53; N, 4.74. Found: C, 64.93; H, 8.50; N,

4.96. Other spectroscopic and spectrometric data were in agreement with those of the racemate.

4.25. (*RS*)-3,9-Dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (*RS*)-13·HCl

To a suspension of $LiAlH_4$ (0.24 g, 6.28 mmol) in anhydrous THF (20 mL), (*RS*)-3,9-dimethyl-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (*RS*)-**14** (0.60 g, 3.14 mmol) was added. The reaction mixture was stirred at room temperature for 6 h, then at 85 °C for 2 h, and then again at room temperature overnight. The reaction mixture was quenched by the careful addition of cold water until the end of gas evolution. The residue was removed by filtration and the filtrate additioned with H_2O. The aqueous phase was washed with Et_2O, then made alkaline with 2 M NaOH, and extracted several times with Et_2O. The combined extracts were dried over Na_2SO_4 and the filtrate was concentrated under vacuum to give 0.19 g of (*RS*)-**13** as a yellow oil (34%). The free amine was treated with a few drops of hydrochloric aqueous solution. Removal of water by azeotropic distillation (abs EtOH/toluene) afforded (*RS*)-**13**·HCl as a white solid, which was recrystallized from MeOH/Et_2O to give 0.11 g of white crystals (48%): mp 230–231 °C; IR (KBr): 2937–2881 NH_2^+; ^{1}H NMR (CD_3OD): δ 1.33 (d, $J = 6.6$ Hz, 3H, C*H*$_3$CH), 2.27 (s, 3H, C*H*$_3$Ar), 3.68 (dd, $J = 13.5$, 9.3 Hz, 1H, C*H*HCH), 3.77–3.91 (m, 1H, C*H*), 4.30 (d, $J = 14.3$ Hz, 1H, AB system, C*H*HNH), 4.38 (d overlapping dd at 4.45, $J = 14.3$ Hz, 1H, AB system, CH*H*NH), 4.45 (dd overlapping d at 4.38, $J = 13.5$, 2.7 Hz, 1H, CH*H*CH), 7.06 (apparent t, $J = 7.6$ Hz, 1H, Ar *H*C-7), 7.22 (d overlapping d at 7.28, $J = 7.1$ Hz, 1H, Ar *H*C-8), 7.28 (d overlapping d at 7.22, $J = 8.2$ Hz, 1H, Ar *H*C-6); Anal. Calcd for ($C_{11}H_{15}NO$·HCl·0.20H_2O): C, 60.80; H, 7.61; N, 6.45. Found: C, 61.17; H, 7.50; N, 6.65.

4.26. (+)-(*R*)-3,9-Dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (+)-(*R*)-13·HCl

(*R*)-**7** (0.61 g, 3.13 mmol) was treated with a few drops of 2 M HCl and water was removed azeotropically. After 48 h in EtOH/Et_2O solution at 0 °C, the solvent was removed to give a 0.30 g of a slightly yellowish solid (70%): mp >250 °C (EtOAc); $[\alpha]_D^{20} = +71.0$ (*c* 0.4, $CHCl_3$); 98% ee (capillary electrophoresis, injection: 15 psi/s; BGE: phosphate buffer 0.035 M at pH 2.9; chiral selector: hydroxypropyl-β-cyclodextrin 60 mg/mL; voltage: 10 kV); IR (KBr): 2918–2449 NH_2^+; ^{1}H NMR (CD_3OD, COSY): δ 1.33 (d, $J = 6.6$ Hz, 3H, C*H*$_3$CH), 2.27 (s, 3H, C*H*$_3$Ar), 3.68 (dd, $J = 13.5$, 9.3 Hz, 1H, C*H*HCH), 3.77–3.91 (m, 1H, C*H*), 4.31 (d, $J = 14.3$ Hz, 1H, AB system, C*H*HNH), 4.38 (d overlapping dd at 4.45, $J = 14.3$ Hz, 1H, AB system, CH*H*NH), 4.45 (dd overlapping d at 4.38, $J = 13.4$, 2.6 Hz, 1H, CH*H*CH),7.06 (apparent t, $J = 7.4$ Hz, 1H, Ar *H*C-7), 7.22 (d overlapping d at 7.28, $J = 7.4$ Hz, 1H, Ar *H*C-8), 7.28 (d overlapping d at 7.22, $J = 7.7$ Hz, 1H, Ar *H*C-6); ^{13}C NMR (CD_3OD, δ 47.8): δ 13.3 (1C), 14.7 (1C), 48.1 (1C), 57.1 (1C), 72.8 (1C), 124.3 (1C), 125.2 (1C), 128.6 (1C), 130.5 (1C), 132.4 (1C), 158.4 (1 C); ESI^+/MS *m*/*z* 178.2 (MH^+); ESI^+/MS/MS *m*/*z* 161 (100); Anal. Calcd for ($C_{11}H_{15}NO$·HCl·0.50H_2O): C, 59.32; H, 7.69; N, 6.29. Found: C, 59.09; H, 7.32; N, 5.93.

4.27. (+)-(*R*)-3,9-Dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrobromide (+)-(*R*)-13·HBr

(*R*)-**13** (0.20 g, 1.13 mmol), obtained by extraction from the corresponding hydrochloride salt, was dissolved in EtOAc (3 mL) and treated with 48% HBr (1 mL). Water was removed azeotropically to give 0.25 g of a slightly yellowish solid, which was recrystallized from EtOAc (52%): mp >250 °C; $[\alpha]_D^{20} = +91.0$ (*c* 0.15, $CHCl_3$); 98% ee (capillary electrophoresis, injection: 15 psi/s; BGE: phosphate buffer 0.035 M at pH 2.9; chiral selector: hydroxypropyl-β-cyclodextrin 60 mg/mL; voltage: 10 kV). Spectroscopic and spectrometric data were in agreement with those found for (*R*)-**13**·HCl. Anal. Calcd for ($C_{11}H_{15}NO$·HBr): C, 51.18; H, 6.25; N, 5.43. Found: C, 51.13; H, 6.25; N, 5.44.

4.28. (−)-(*S*)-3,9-Dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrobromide (−)-(*S*)-13·HBr

Prepared as above starting from (*S*)-**13**. Yield: 48%; White solid: mp >250 °C (EtOAc); $[\alpha]_D^{20} = -82.0$ (*c* 0.4, $CHCl_3$); 97% ee (capillary electrophoresis, injection: 15 psi/s; BGE: phosphate buffer 0.035 M at pH 2.9; chiral selector: hydroxypropyl-β-cyclodextrin 60 mg/mL; voltage: 10 kV). Spectroscopic and spectrometric data were in agreement with those found for (*R*)-**13**·HCl. Anal. Calcd for ($C_{11}H_{15}NO$·HBr): C, 51.18; H, 6.25; N, 5.43. Found: C, 51.34; H, 6.24; N, 5.40.

4.29. (*RS*)-3,9-Dimethyl-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (*RS*)-14

A solution of (*RS*)-**10** (0.27 g, 0.83 mmol) in 98% HCOOH (10 mL) was stirred at 0 °C for 2 h. The solvent was removed under vacuum; the residue was taken up with EtOAc and washed with a $NaHCO_3$ saturated solution. The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give 0.08 g (51%) of a slightly yellowish solid: mp 118–119 °C; IR ($CHCl_3$): 3408 (NH), 1644 (C=O) cm^{-1}; ^{1}H NMR: δ 1.25 (d, $J = 6.6$ Hz, 3H, C*H*$_3$CH), 2.27 (s, 3H, C*H*$_3$Ar), 3.63–3.79 (m, 1H, C*H*), 4.10 (apparent t, $J = 9.9$ Hz, 1H, C*H*H), 4.22 (dd, $J = 11.0$, 3.6 Hz, 1H, CH*H*), 6.54 (br s, 1H, N*H*), 7.04 (apparent t, $J = 7.5$ Hz, 1H, Ar *H*C-7), 7.30 (d, $J = 7.4$ Hz, 1H, Ar *H*C-8), 7.71 (d, $J = 7.4$ Hz, 1H, Ar *H*C-6); MS (70 eV) *m*/*z* (%) 191 (M^+, 65), 119 (100).

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