Synthesis of Homochiral 5- and 8-Substituted 2-[((2-(2,6-Dimethoxyphenoxy)-ethyl)amino)methyl]-1,4-benzodioxanes and Electrophoretic Determination of Their Enantiomeric Excess

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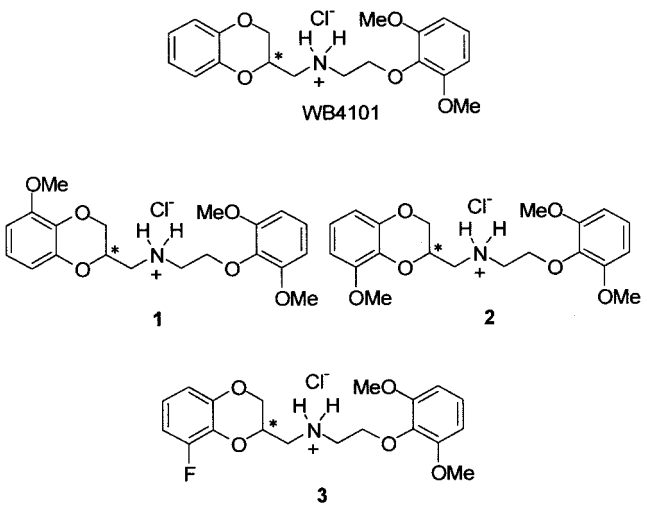
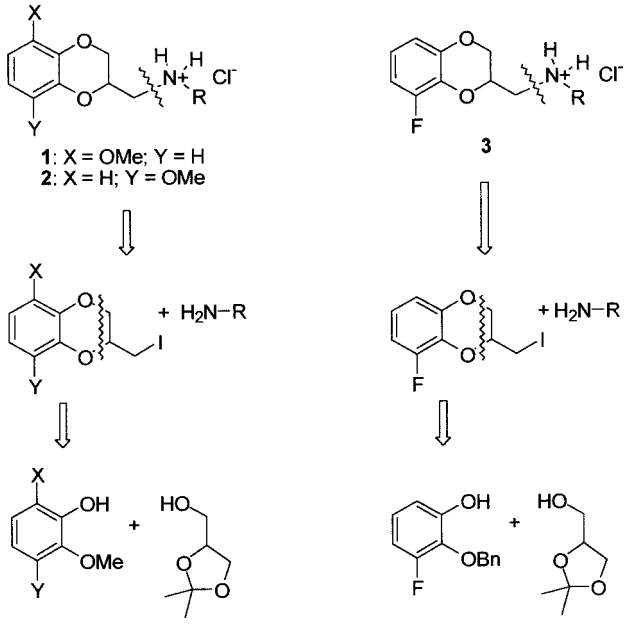
Among the structures which have the capacity to interact with α_1-adrenoceptors, benzodioxanes are one of the main classes. In particular, WB4101, which can be considered the lead compound of such a class, exhibits a nanomolar affinity toward α_1-adrenoceptor, the *S* enantiomer possessing remarkably higher affinity than the *R* enantiomer.[1] As part of our ongoing program aimed at the study of chiral benzodioxane derivatives as type-selective α-adrenoceptor ligands, we wish to report herein the synthesis of the enantiomers of the 5-methoxy, 8-methoxy, and 8-fluoro analogues (**1**−**3**; see Chart 1) of WB4101 and, in addition, a practical method to determine their enantiomeric excess. In fact, an accurate assessment of the stereoisomeric purity of the optical isomers of WB4101 and of its analogues is strictly required for the binding experiments on account of the known high enantioselectivity displayed by the α_1 adrenoceptor toward WB4101 and, in general, toward its derivatives with considerable affinity.

To the best of our knowledge, no report on the synthesis of racemic or homochiral 2-(aminomethyl)-benzodioxanes substituted at position 5 or 8 has appeared up to now in the literature. In this regard, the main challenges are the regioselective introduction of the substituent into the desired position of the phenyl ring of benzodioxane and the development of efficient methods for the synthesis of *S* and *R* derivatives with high enantiomeric excess. In this paper, we report a united solution to both problems. In fact, our approach for the construction of the disubstituted benzodioxane skeleton of the *S* and *R* forms of **1**−**3** was based on the use of the appropriate 2,6- or 2,3-disubstituted phenol and respectively of (*S*)- and (*R*)-glycerol acetonide as building blocks. The availability of both enantiomers of such a glycerol derivative is ensured by an easy and efficient resolution we had previously developed.[2] As retrosynthetically illustrated in Scheme 1, the employment of 2,6- and 2,3-disubstituted phenols circumvented the problem of the regioselective substitution at the phenyl of benzodioxane allowing to perform the 2-substituted 1,4-dioxane ring closure with resultant unambiguous position of the second benzodioxane substituent in 5 and 8, respectively. On the other hand, the use of (*S*)- and (*R*)-glycerol acetonide, both with higher than 99.6% enantiomeric excess, and the consequent possibility of following parallel synthetic routes led to the *S* and *R* forms of **1**−**3** in analogous optical yields (ee > 99.6%).

Chart 1



Scheme 1



As outlined in Scheme 2, the reaction sequence for preparing the *S* isomers of **1**−**3** consisted in the following steps: (a) displacement of tosylate from the tosyl ester of (*S*)-glycerol acetonide [(*R*)-**4**] by 2,6-dimethoxy-, 2,3-dimethoxy- and 2-(benzyloxy)-3-fluorophenoxide, respectively; (b) hydrolysis of the cyclic ketals (*S*)-**5**, (*S*)-**12,** and (*S*)-**19**; (c) tosylation of the resultant *vic*-diols (*R*)-**6**, (*R*)-**13,** and (*R*)-**20;** (d) removal of the two methyl or of the benzyl from the phenoxy residue of (*S*)-**7**, (*S*)-**14,** and (*S*)-**21,** respectively; (e) intramolecular nucleophilic substitution of the tosylate at C_2 of the glycerol skeleton by the *ortho*-phenoxy moiety to give 1,4-dioxane ring closure [(*R*)-**9**, (*R*)-**16**, and (*R*)-**23**]; (f) conversion into iodomethyl

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(1) Villa, L.; Valoti, E.; Villa, A. M.; Pallavicini, M.; Ferri, V.; Iuliano, E.; Brunello, N. *Farmaco* **1994**, *49*, 587.
(2) Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1994**, *5*, 5.

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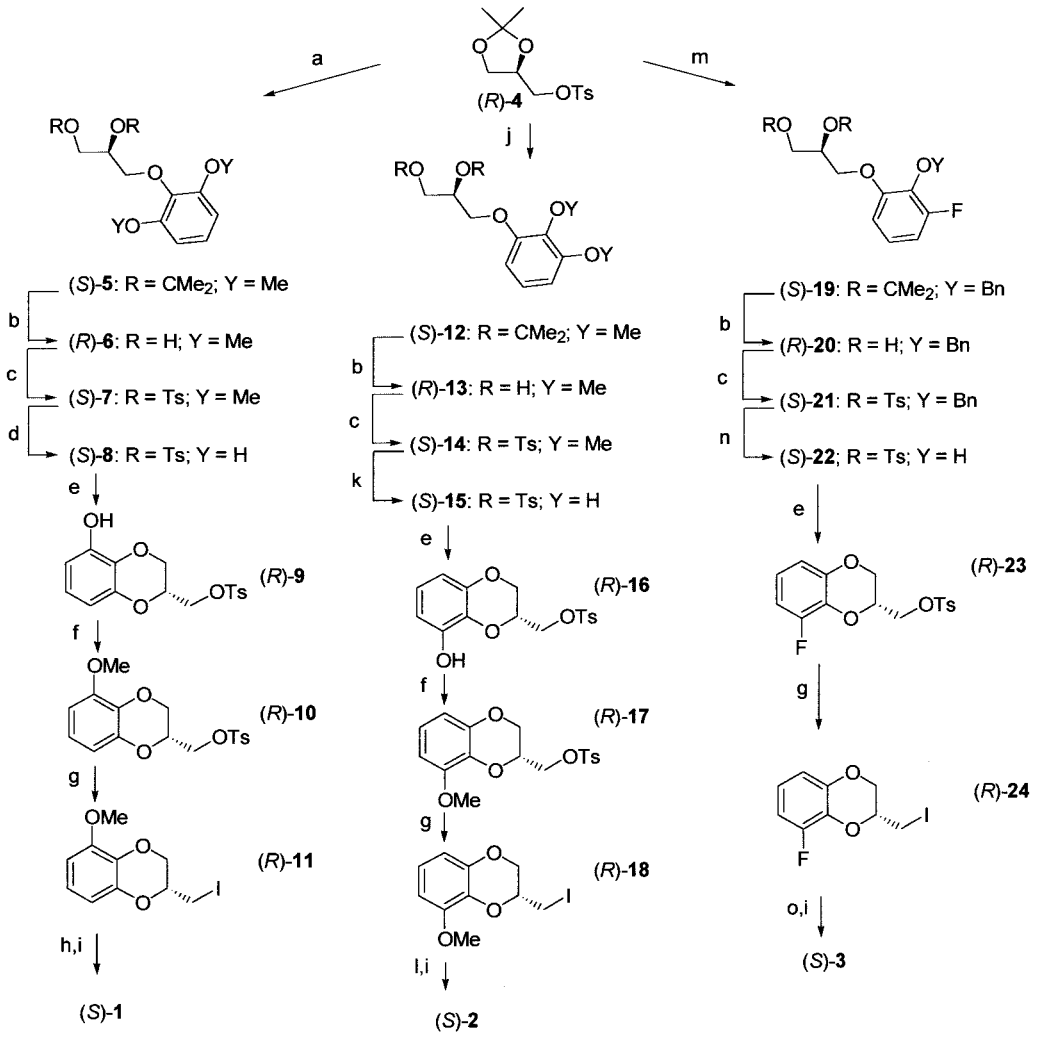
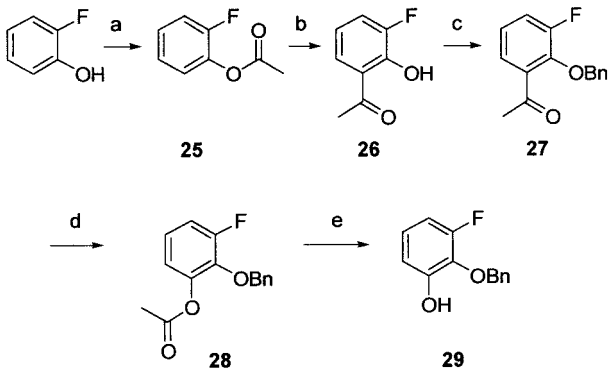
Scheme 2



[a] Key: (a) 2,6-dimethoxyphenol, Na, EtOH. (b) HCl. (c) TsCl, Py. (d) BBr_3, CH_2Cl_2. (e) K_2CO_3, acetone. (f) CH_3I, NaOH, EtOH. (g) NaI, acetone. (h) 2-(2,6-dimethoxyphenoxy)ethylamine, 2-propanol. (i) HCl, EtOH. (j) 2,3-dimethoxyphenol, NaOMe, EtOH. (k) BCl_3, CH_2Cl_2. (l) 2-(2,6-dimethoxyphenoxy)ethylamine. (m) 2-benzyloxy-3-fluorophenol; K_2CO_3, DMF. (n) H_2-Pd/C, EtOAc. (o) 2-(2,6-dimethoxyphenoxy)ethylamine, isobutyl alcohol.

derivatives (*R*)-**11**, (*R*)-**18,** and (*R*)-**24** after methylating, in the case of the synthesis of (*S*)-**1** and (*S*)-**2**, the residual phenolic function of (*R*)-**9** and (*R*)-**16**; (g) amination with 2-(2,6-dimethoxyphenoxy)ethylamine. The *R* enantiomers of **1**−**3** were synthesized by the same strategy as illustrated in Scheme 1 but starting from the tosyl ester of (*R*)-glycerol acetonide [(*S*)-**4**]. 2-(Benzyloxy)-3-fluorophenol used in the first step of the syntesis of (*S*)-**3** and (*R*)-**3** was prepared from 2-fluorophenol as outlined in Scheme 3. Esterification with acetyl chloride, followed by Fries rearrangement and benzylation of the resulting hydroxyketone **26**, afforded 2-(benzyloxy)-3-fluoroacetophenone (**27**), which was converted into the corresponding phenyl acetate **28** by the Baeyer−Villiger reaction and finally submitted to methanolysis.

Scheme 3



[a] Key: (a) Acetyl chloride, Py, CH_2Cl_2. (b) $AlCl_3$, dichlorobenzene. (c) Benzyl bromide, tetrabutylammonium bromide, 10% NaOH, CH_2Cl_2. (d) *m*-CPBA, CH_2Cl_2. (e) MeOH, TsOH.

The enantiomeric purity of the optical isomers of WB4101 and of its three novel analogues was initially investigated by applying chromatographic methods. However, their previous conversion into diastereomeric amides by reaction with optically pure α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was required to obtain analytical HPLC separation, while attempts at direct resolution of the enantiomers by HPLC on chiral station-

ary phases were ineffective. The alternative use of a more practical method was therefore planned. Prompted by the reports on the application of capillary electrophoresis (CE) to the separation of enantiomeric pairs,[3] we considered the possibility of evaluating the stereoisomeric purity of the title compounds by cyclodextrin (CD)-modified CE.

The use of CDs as mobile-phase additives has been shown to impart enantioselectivity to CE separations.[3] Chiral resolution occurs on the basis of differences in the stability or rate of formation of the analyte−CD inclusion complex for each enantiomer. With neutral CDs, the mobility of cationic analytes decreases since the combined charge/mass ratio of their inclusion complexes with CDs is lower than that of the same analytes in the free form. Under such conditions, the enantiomer forming the more stable complex elutes last. In the present study, the analyses were performed under acidic conditions employing phosphate buffer adjusted to pH 2.5 as a running electrolyte. At this pH value the electroosmotic flow was minimized and all the analytes were positively charged.

In the absence of chiral discriminators, as shown in Figure 1, a rapid separation, with baseline or near baseline resolution, of 2-(aminomethyl)-1,4-benzodioxane hydrochloride, WB4101, **1**, and **2** was achieved, while WB4101 and its 8-fluoro analogue **3** were coeluted. Initial attempts of enantioseparation were made adding the most commonly used β-CD to the running electrolyte. As expected, the addition of β-CD slightly increased migration times. However, this chiral discriminator gave only poor resolution of the enantiomers of WB4101 and of compounds **1** and **3** and failed to resolve those of 2-(aminomethyl)-1,4-benzodioxane hydrochloride. The inability to achieve complete resolution under the above conditions led to the subsequent use of derivatized CDs, in particular of the hydroxyalkyl β- and γ-CD, whose inclusion properties significantly differ from those of the native counterparts. In fact, they have larger and less rigid cavities and addtional interactive potentialities with the analytes due to the hydroxyalkyl moiety. Moreover, their increased water solubility permits the use of higher mobile-phase concentrations. Indeed, addition of hydroxyethyl β-CD fully resolved the enantiomers of all investigated compounds except those of **2**, causing only moderate enhancements of the migration times in comparison with native β-CD (Figure 2). The high efficiency of these resolutions is well demonstrated by the electropherogram presented in Figure 3, which shows the complete separation of the eight stereoisomers of 2-(aminomethyl)-1,4-benzodioxane hydrochloride, WB4101 and its 5-methoxy and 8-fluoro analogues under a single set of operating conditions. Finally, the enantiomers of **2** could be resolved only using hydroxypropyl γ-CD (Figure 4). In this case, however, migration times were dramatically increased indicating strong analyte−CD interactions.

The electophoretic analysis of the optical antipodes of **1**−**3**, under the above specified conditions, allowed one to determine invariably higher than 99.6% enantiomeric

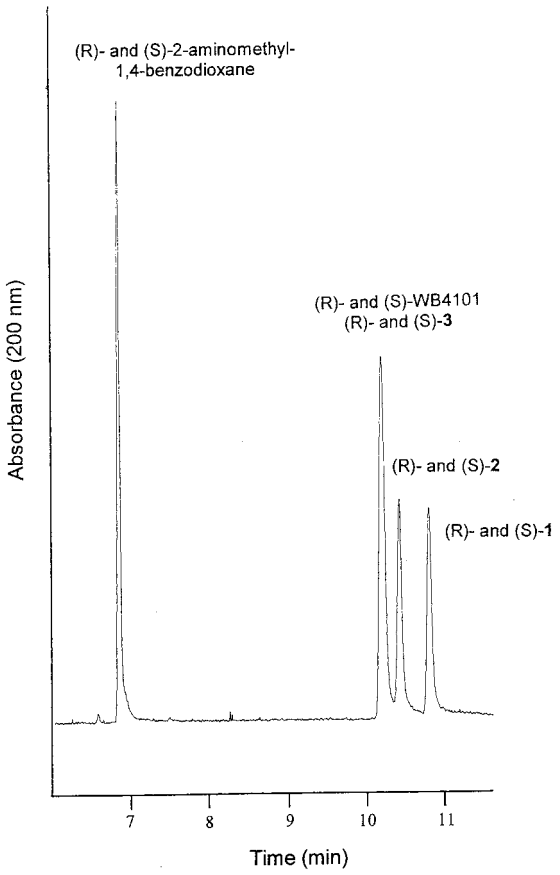


Figure 1. Electropherogram of a solution containing the enantiomeric pairs of 2-(aminomethyl)-1,4-benzodioxane hydrochloride, WB4101, and **1**−**3**. The running electrolyte consisted of 5 mM phosphate buffer (pH 2.5) without chiral selector.

excesses. On the contrary, in the case of WB4101 and 2-(aminomethyl)-1,4-benzodioxane hydrochloride, the *S* and the *R* forms, both previously prepared from (*S*)-glycerol acetonide by two different synthetic pathways according to literature methods,[1,4,5] showed disparity in stereoisomeric purity. In fact, only the *S* isomers proved to be more than 99.6% enantiomerically pure, while the enantiomeric excesses of the *R* forms were 95.95% and 96.97%, respectively. These results indicate the higher enantioselectivity of the present syntheses, based on the initial efficient resolution of glycerol acetonide and on the successive transformations illustrated in Scheme 2, in comparison with the previously described syntheses of the *R* isomers of WB4101 and 2-(aminomethyl)-1,4-benzodioxane hydrochloride,[1,4,5] consisting in using the same antipod of glycerol acetonide as for the preparation of the *S* isomers of the above compounds and in formally exchanging the attachment site of the functional groups at the glycerol moiety.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 60 or 200 MHz. The *S* and *R* enantiomers of WB4101 and of 2-(aminomethyl)-1,4-benzodioxane hydrochloride were synthesized as previously reported.[1,4,5] (*S*)- and (*R*)-glycerol acetonide were prepared by chemical resolution of the racemate as described in the literature [2] and successively transformed into

(3) For example, see: (a) Wren, S. A. C.; Rowe, R. *J. Chromatogr.* **1993**, *635*, 113. (b) Lurie, I. S.; Klein, R. F. X.; Dal Cason, T. A.; LeBelle, M. J.; Brenneisen, R.; Weinberger, R. E. *Anal. Chem.* **1994**, *66*, 4019. (c) Tait, R. J.; Thompson, D. O.; Stella, V. J.; Stobaugh, J. F. *Anal. Chem.* **1994**, *66*, 4013. (d) Szeman, J.; Ganzler, K.; Salgo, A.; Szejtli, J. *J. Chromatogr., A* **1996**, *728*, 423. (e) Williams, R. L.; Vigh, G. *J. Chromatogr., A* **1996**, *730*, 273. (f) Wan, H.; Engström, A.; Blomberg, L. G. *J. Chromatogr., A* **1996**, *731*, 283.

(4) Nelson, W. L.; Wennerstrom, J. E. *J. Med. Chem.* **1977**, *20*, 880.
(5) Nelson, W. L.; Powell, M. L. *J. Med. Chem.* **1979**, *22*, 1125.

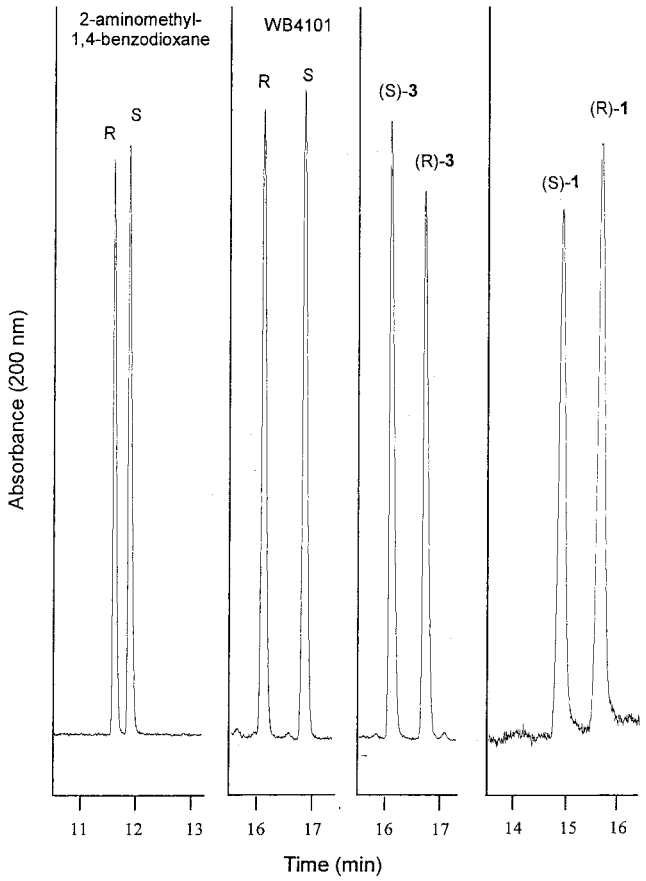


Figure 2. Electropherograms of the solutions of the single enantiomeric pairs of 2-(aminomethyl)-1,4-benzodioxane hydrochloride, WB4101, **3**, and **1**. The running electrolyte consisted of 40 mM hydroxyethyl β-CD in 5 mM phosphate buffer (pH 2.5).

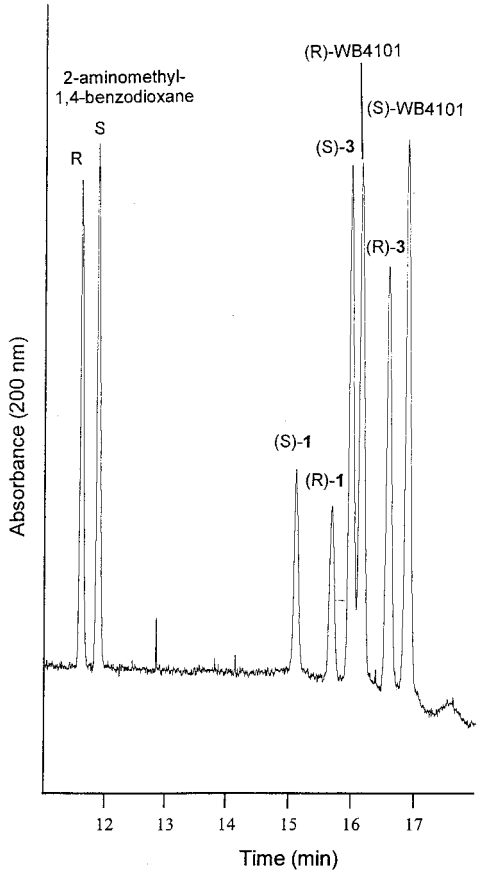


Figure 3. Electropherogram of a solution containing the enantiomeric pairs of 2-(aminomethyl)-1,4-benzodioxane hydrochloride, WB4101, **1**, and **3**. The running electrolyte consisted of 40 mM hydroxyethyl β-CD in 5 mM phosphate buffer (pH 2.5).

the corresponding tosyl esters (*R*)-**4** and (*S*)-**4** by treatment with tosyl chloride in pyridine according to standard procedures.

(2*S*)-3-(2,6-Dimethoxyphenoxy)-1,2-propanediol Acetonide [(*S*)-5]. A mixture of 2,6-dimethoxyphenol (18.96 g, 0.123 mol) and sodium (2.8 g, 0.123 mol) in ethanol (300 mL) was refluxed for 30 min and, after adding (*2R*)-3-tosyloxy-1,2-propanediol acetonide [(*R*)-**4**] (31.64 g, 0.110 mol), for 72 h. The solvent was evaporated and the residue treated with diethyl ether (400 mL). The resulting suspension was filtered and the filtrate washed with water, 10% sodium hydroxide, and water again. The organic layer was dried and concentrated to give a residue which was chromatographed on silica gel. Elution with cyclohexane/ethyl acetate (90/10) afforded 19.5 g (57%) of (*S*)-**5** as a white solid: mp 32−35 °C; $[\alpha]_D^{25} = +16.4$ (*c* 1, ethanol); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.38 (s, 3 H), 1.43 (s, 3 H), 3.79−3.88 (m, 1 H), 3.84 (s, 6 H), 3.99−4.20 (m, 3 H), 4.39−4.50 (m, 1 H), 6.56 (d, 2 H), 6.99 (t, 1 H). Anal. Calcd for $C_{14}H_{20}O_5$ (268.31): C, 62.67; H, 7.51. Found: C, 62.44; H, 7.47.

(2*R*)-3-(2,6-Dimethoxyphenoxy)-1,2-propanediol [(*R*)-6]. A suspension of (*S*)-**5** (19.26 g, 71.7 mmol) in 10% HCl (150 mL) was heated at 75 °C for 14 h. After cooling, acetone was removed by vacuum distillation and the residual aqueous phase submitted to continuous extraction with dichloromethane. The organic extract was dried and concentrated to give a solid residue (16.62 g), which was chromatographed on silica gel. Elution with dichloromethane/methanol (95/5) yielded 8.2 g (50%) of (*R*)-**6** as a white solid: mp 73−74 °C; $[\alpha]_D^{25} = -13.3$ (*c* 1, ethanol); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.1 (s, 2 H), 3.61−3.80 (m, 2 H), 3.86 (s, 6 H), 3.83−4.09 (m, 2 H), 4.16−4.31 (m, 1 H), 6.60 (d, 2 H), 7.15 (t, 1 H). Anal. Calcd for $C_{11}H_{16}O_5$ (228.25): C, 57.88; H, 7.06. Found: C, 57.86; H, 7.01.

(2*S*)-3-(2,6-Dimethoxyphenoxy)-1,2-bis(tosyloxy)propane [(*S*)-7]. Tosyl chloride (25.24 g, 0.132 mol) was added in small portions to a stirred solution of (*R*)-**6** (15.12 g, 0.066 mol) in pyridine (35 mL) at 0 °C. The resulting mixture was stirred for 18 h at room temperature, diluted with ethyl acetate (300 mL), and washed with 10% HCl and then with water. The organic phase was dried and concentrated to give the crude product (38.42 g), which was crystallized from diethyl ether yielding 34.54 g (97%) of (*S*)-**7** as a white solid: mp 91−92 °C; $[\alpha]_D^{25} = +25.0$ (*c* 1, chloroform); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.40 (s, 6 H), 3.78 (s, 6 H), 3.95−4.15 (m, 2 H), 4.24−4.38 (dd, 1 H), 4.42−4.65 (dd, 1 H), 4.80−4.90 (m, 1 H), 6.52 (d, 2 H), 6.98 (t, 1 H), 7.25−7.38 (2d, 4 H), 7.60−7.75 (2d, 4 H). Anal. Calcd for $C_{25}H_{28}O_9S_2$ (536.62): C, 55.96; H, 5.26; S, 11.95. Found: C, 55.67; H, 5.18; S, 11.81.

(2*S*)-3-(2,6-Dihydroxyphenoxy)-1,2-bis(tosyloxy)propane [(*S*)-8]. Boron tribromide (6.42 mL, 68 mmol) was added dropwise to a solution of (*S*)-**7** (36.5 g, 68 mmol) in dichloromethane (200 mL) at 0 °C. The mixture was stirred for 2 h at room temperature and then poured into water (500 mL) cooled at 10 °C. The organic phase was separated and water reextracted with dichloromethane. The organic extracts were combined, washed with brine, dried, and concentrated. The resulting residue was chromatographed on silica gel. Elution with hexane/ethyl acetate (75/25) afforded 14.7 g (42%) of (*S*)-**8** as a colorless oil: $[\alpha]_D^{25} = +22.5$ (*c* 1, ethanol); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.43 (s, 6 H), 4.10−4.25 (m, 3 H), 4.30−4.42 (dd, 1 H), 4.95−5.10 (m, 1 H), 6.05 (s, 2 H), 6.45 (d, 2 H), 6.83 (t, 1 H), 7.30−7.40 (2d, 4 H), 7.70−7.85 (2d, 4 H).

(2*R*)-2-((Tosyloxy)methyl)-5-hydroxy-1,4-benzodioxane [(*R*)-9]. A mixture of (*S*)-**8** (14.62 g, 28.7 mmol) and K_2CO_3 (3.97 g, 28.7 mmol) in acetone (100 mL) was refluxed for 24 h. After evaporation of the solvent, the residue was treated with diethyl ether (200 mL) and 10% HCl (150 mL). The aqueous phase was separated and extracted with diethyl ether. The combined organic extracts were washed with water, dried, and concentrated. The residue was purified by chromatography on

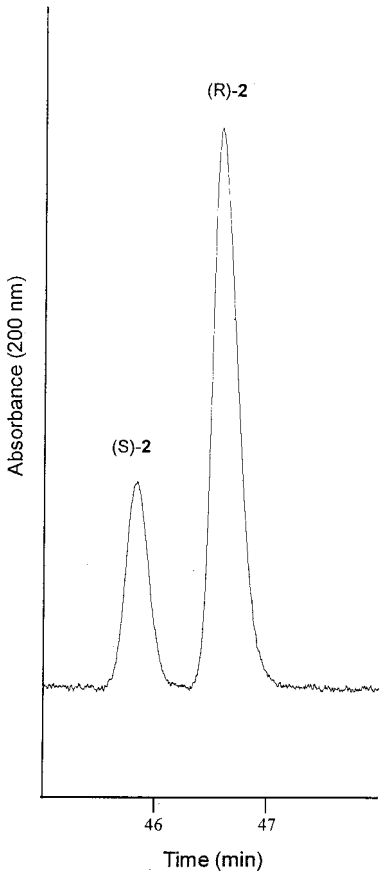


Figure 4. Electropherogram of a solution containing the enantiomeric pair of **2**. The running electrolyte consisted of 60 mM hydroxypropyl γ-CD in 5 mM phosphate buffer (pH 2.5).

silica gel eluting with cyclohexane/ethyl acetate (70/30). The pure fractions gave 4.5 g (47%) of (*R*)-**9** as a colorless oil: $[\alpha]_D^{25} = -27.8$ (*c* 1, chloroform); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 4.20−4.50 (m, 5 H), 5.30 (s, 1 H), 6.35 (d, 1 H), 6.55 (d, 1 H), 6.75 (t, 1 H), 7.35 (d, 2 H), 7.80 (d, 2 H).

(*2R*)-2-(Tosyloxy)-5-methoxy-1,4-benzodioxane [(*R*)-10]. A solution of (*R*)-**9** (3.6 g, 10.7 mmol) in ethanol (30 mL) and then iodomethane (2.0 mL, 32.1 mmol) were added dropwise to a solution of sodium hydroxide (428 mg, 10.7 mmol) in ethanol (50 mL) at 10 °C. After the solution was stirred for 24 h at room temperature, the solvent was evaporated and the residue treated with 10% HCl (80 mL) and ethyl acetate (80 mL). The aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined and washed with an acidic aqueous solution of sodium bisulfite and then with water. After drying, ethyl acetate was removed under vacuum and the residue purified by chromatography on silica gel. Elution with cyclohexane/acetone (80/20) yielded 2.4 g (64%) of (*R*)-**10** as a yellow oil: $[\alpha]_D^{25} = -24.4$ (*c* 1, chloroform); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.83 (s, 3 H), 4.00−4.45 (m, 5 H), 6.45 (dd, 2 H), 6.78 (t, 1 H), 7.38 (d, 2 H), 7.80 (d, 2 H).

(*2R*)-2-(Iodomethyl)-5-methoxy-1,4-benzodioxane [(*R*)-11]. A mixture of (*R*)-**10** (2.4 g, 7.84 mmol) and sodium iodide (22.47 g, 0.15 mol) in acetone (80 mL) was refluxed for 3 h. After evaporation of the solvent, the residue was treated with 10% HCl (30 mL) and diethyl ether (60 mL). The aqueous layer was separated and extracted with diethyl ether again. The combined organic extracts were dried and concentrated to give a residue which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (95/5) afforded 1.6 g (80%) of (*R*)-**11** as an oil: $[\alpha]_D^{25} = -16.1$ (*c* 1, chloroform); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.36 (d, 2 H), 3.91 (s, 3 H), 4.15−4.38 (m, 2 H), 4.81 (dd, 1 H), 6.10 (d, 1 H), 6.57 (d, 1 H), 6.80 (t, 1 H).

(*2S*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)methyl]-5-methoxy-1,4-benzodioxane Hydrochloride [(*S*)-1]. A mixture of (*R*)-**11** (1.5 g, 4.90 mmol) and 2-(2,6-dimethoxyphenoxy)-ethylamine (1.74 g, 8.82 mmol) in 2-propanol (10 mL) was refluxed for 48 h. The solvent was evaporated and the residue treated with ethyl acetate and 10% NaOH. The aqueous phase was separated and extracted with ethyl acetate twice. The combined extracts were dried and concentrated to give a residue which was chromatographed on silica gel. Elution with dichloromethane/methanol (98/2) yielded 780 mg of (*2S*)-2-[((2-(2,6-dimethoxyphenoxy)ethyl)amino)methyl]-5-methoxy-1,4-benzodioxane: $[\alpha]_D^{25} = -29.2$ (*c* 1, chloroform). The secondary amine was dissolved in ethanol (2 mL), and 3.57 N HCl/EtOH (2 mL) was added. The solvent was evaporated, and the semisolid residue was crystallized from diisopropyl ether/acetone (90/10) yielding 380 mg (45%) of (*S*)-**1** as a white solid: mp 128−129 °C; $[\alpha]_D^{25} = -48.5$ (*c* 1, methanol); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.30−3.50 (m, 4 H), 3.80 (s, 3 H), 3.82 (s, 6), 4.05−4.20 (m, 3 H), 4.44 (dd, 1 H), 4.78 (m, 1 H), 6.55−6.90 (m, 5 H), 7.14 (t, 1 H), 9.54 (br s, 2 H). Anal. Calcd for $C_{20}H_{26}ClNO_6 \cdot 1/2\ H_2O$ (420.89): C, 57.07; H, 6.47; N, 3.33; Cl, 8.42. Found: C, 56.90; H, 6.10; N, 3.22; Cl, 8.59.

(*2R*)-3-(2,6-Dimethoxyphenoxy)-1,2-propanediol Acetonide [(*R*)-5]. Prepared from (*2S*)-3-(tosyloxy)-1,2-propanediol acetonide [(*S*)-**4**] as described for (*S*)-**5**: mp 32−34 °C; $[\alpha]_D^{25} = -15.3$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*S*)-**5**.

(*2S*)-3-(2,6-Dimethoxyphenoxy)-1,2-propanediol [(*S*)-6]. Prepared from (*R*)-**5** as described for (*R*)-**6**: mp 73−74 °C; $[\alpha]_D^{25} = +11.9$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*R*)-**6**.

(*2R*)-3-(2,6-Dimethoxyphenoxy)-1,2-bis(tosyloxy)propane [(*R*)-7]. Prepared from (*S*)-**6** as described for (*S*)-**7**: mp 91−92 °C; $[\alpha]_D^{25} = -24.7$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*S*)-**7**.

(*2R*)-3-(2,6-Dihydroxyphenoxy)-1,2-bis(tosyloxy)propane [(*R*)-8]. Prepared from (*R*)-**7** as described for (*S*)-**8**: $[\alpha]_D^{25} = -23.9$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*S*)-**8**.

(*2S*)-2-((Tosyloxy)methyl)-5-hydroxy-1,4-benzodioxane [(*S*)-9]. Prepared from (*R*)-**8** as described for (*R*)-**9**: $[\alpha]_D^{25} = +28.5$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*R*)-**9**.

(*2S*)-2-(Tosyloxy)methyl)-5-methoxy-1,4-benzodioxane [(*S*)-10]. Prepared from (*S*)-**9** as described for (*R*)-**10**: $[\alpha]_D^{25} = +22.6$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*R*)-**10**.

(*2S*)-2-(Iodomethyl)-5-methoxy-1,4-benzodioxane [(*S*)-11]. Prepared from (*S*)-**10** as described for (*R*)-**11**: $[\alpha]_D^{25} = +15.3$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*R*)-**11**.

(*2R*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)methyl]-5-methoxy-1,4-benzodioxane Hydrochloride [(*R*)-1]. Prepared from (*S*)-**11** as described for (*S*)-**1**: mp 128−129 °C; $[\alpha]_D^{25} = +47.4$ (*c* 1, methanol) ($[\alpha]_D^{25} = +27.0$ (*c* 1, chloroform) for the free amine); ^{1}H NMR identical to that of (*S*)-**1**. Anal. Calcd for $C_{20}H_{26}ClNO_6 \cdot 1/4\ H_2O$ (416.38): C, 57.69; H, 6.41; N, 3.36; Cl, 8.51. Found: C, 57.73; H, 6.14; N, 3.25; Cl, 8.68.

(*2S*)-3-(2,3-Dimethoxyphenoxy)-1,2-propanediol Acetonide [(*S*)-12]. A mixture of 2,3-dimethoxyphenol (75 g, 0.486 mol) and sodium methoxide (26.25 g, 0.486 mol) in ethanol (600 mL) was refluxed for 30 min and, after adding (*2R*)-3-(tosyloxy)-1,2-propanediol acetonide [(*R*)-**4**] (125.56 g, 0.438 mol), for 24 h. The solvent was evaporated and the residue treated with diethyl ether (500 mL). The resulting suspension was filtered and the filtrate washed with water, 5% potassium hydroxide, and water again. The organic phase was dried and concentrated to give a residue which was crystallized from methanol yielding 56.4 g (48%) of (*S*)-**12** as a white solid: mp 95−96 °C; $[\alpha]_D^{25} = +18.6$ (*c* 1, ethanol); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.42 (s, 3 H), 1.48 (s, 3 H), 3.88 (s, 6 H), 3.6−4.8 (m, 5 H), 6.4−7.4 (m, 3 H). Anal. Calcd for $C_{14}H_{20}O_5$ (268.31): C, 62.67; H, 7.51. Found: C, 62.97; H, 7.56.

(*2R*)-3-(2,3-Dimethoxyphenoxy)-1,2-propanediol [(*R*)-13]. Prepared from (*S*)-**12** in quantitative yield as described for (*R*)-**6**: mp 93−96 °C; $[\alpha]_D^{25} = -9.3$ (*c* 1, ethanol); ^{1}H NMR (60 MHz, acetone-d_6) δ 3.6−4.25 (m, 5 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 4.05 (s, 2 H), 6.5−7.27 (m, 3 H). Anal. Calcd for $C_{11}H_{16}O_5$ (228.25): C, 57.88; H, 7.06. Found: C, 57.99; H, 7.09.

(*2S*)-3-(2,3-Dimethoxyphenoxy)-1,2-bis(tosyloxy)propane [(*S*)-14]. Tosyl chloride (56 g, 0.293 mol) was added in small portions to a stirred solution of (*R*)-**13** (30 g, 0.131 mol) in pyridine (100 mL) at 0 °C. The resulting mixture was stirred for 18 h at room temperature, diluted with dichloromethane (1500 mL), and washed with 10% HCl and then with water. The

organic phase was dried and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with dichloromethane/methanol (98/2) and successive crystallization from methanol yielded 37 g (52%) of (*S*)-**14** as a white solid: mp 79−80 °C; $[\alpha]_D^{25} = +13.9$ (*c* 1, ethanol); ^{1}H NMR (60 MHz, acetone-d_6) δ 2.48 (s, 6 H), 3.66 (s, 3 H), 3.84 (s, 3 H), 4.2 (d, 2 H), 4.4 (d, 2 H), 4.8−5.2 (m, 1 H), 6.4−7.1 (m, 3 H), 7.4 (d, 2 H), 7.53 (d, 2 H), 7.75 (d, 2 H), 7.88 (d, 2 H). Anal. Calcd for $C_{25}H_{28}O_9S_2$ (536.62): C, 55.96; H, 5.26; S, 11.95. Found: C, 56.11; H, 5.25; S, 12.07.

(2*S*)-3-(2,3-Dihydroxyphenoxy)-1,2-bis(tosyloxy)propane [(*S*)-15]. A solution of (*S*)-**14** (35 g, 65.22 mmol) in dichloromethane (100 mL) was added dropwise to a 1 M solution of boron trichloride in dichloromethane (1755 mL) maintained at 0 °C under N_2. The reaction mixture was stirred at the same temperature for 1 h and at room temperature for 48 h and then added dropwise to water (800 mL) at 10 °C. After addition of 10% NaOH (100 mL), the organic layer was separated and the aqueous one extracted with dichloromethane. The organic phases were combined, washed with water, dried, and concentrated to give 24.5 g (74%) of (*S*)-**15** as a solid: mp 108−109 °C; $[\alpha]_D^{25} = +13.0$ (*c* 1, ethanol); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.45 (s, 6 H), 3.9−4.4 (m, 5 H), 4.9−5.2 (m, 1 H), 5.4−5.9 (m, 1 H), 6.2−6.8 (m, 3 H), 7.35 (2d, 4 H), 7.7−7.85 (2d, 4 H). Anal. Calcd for $C_{23}H_{24}O_9S_2$ (508.56): C, 54.32; H, 4.76; S, 12.61. Found: C, 53.95; H, 4.71; S, 12.52.

(2*R*)-2-((Tosyloxy)methyl)-8-hydroxy-1,4-benzodioxane [(*R*)-16]. A mixture of (*S*)-**15** (24 g, 47.2 mmol) and potassium carbonate (6.52 g, 47.2 mmol) in acetone (150 mL) was refluxed for 12 h. After cooling, the reaction mixture was filtered and the filtrate concentrated to yield 7.6 g (48%) of (*R*)-**16** as an oil: $[\alpha]_D^{25} = -6.5$ (*c* 1, chloroform); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.4 (s, 3 H), 3.95−4.55 (m, 5 H), 5.0−5.45 (m, 1 H), 6.2−6.8 (m, 3 H), 7.3 (d, 2 H), 7.78 (d, 2 H).

(2*R*)-2-((Tosyloxy)methyl)-8-methoxy-1,4-benzodioxane [(*R*)-17]. A solution of (*R*)-**16** (7.5 g, 22.3 mmol) in ethanol (40 mL) and then iodomethane (3.08 mL, 49.48 mmol) were added dropwise to a solution of sodium hydroxide (892 mg, 22.3 mmol) in ethanol (40 mL) at 10 °C. After the solution was stirred for 24 h at room temperature, the solvent was evaporated and the residue treated with 10% HCl (200 mL) and ethyl acetate (100 mL). The aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined and washed with an acidic aqueous solution of sodium bisulfite and then with water. After drying, ethyl acetate was removed under vacuum and the residue purified by chromatography on silica gel. Elution with hexane/ethyl acetate (90/10) yielded 3.5 g (45%) of (*R*)-**17** as a white solid: mp 92−94 °C; $[\alpha]_D^{25} = -6.9$ (*c* 1, chloroform); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.85 (s, 3 H), 3.5−4.1 (m, 5 H), 6.3−7.0 (m, 3 H), 7.35 (d, 2 H), 7.82 (d, 2 H).

(2*R*)-2-(Iodomethyl)-8-methoxy-1,4-benzodioxane [(*R*)-18]. A mixture of (*R*)-**17** (2 g, 5.71 mmol) and sodium iodide (18.74 g, 125 mmol) in acetone (80 mL) was refluxed for 12 h, cooled to room temperature, filtered, and concentrated to give a residue which was treated with 10% HCl and diethyl ether. The organic phase was separated, dried, and concentrated. The resulting residue was purified by chromatography on silica gel. Elution with hexane/ethyl acetate (90/10) afforded 1.52 g (87%) of (*R*)-**18** as an oil: $[\alpha]_D^{25} = +39.8$ (*c* 1, chloroform); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.42 (d, 2 H), 3.9 (s, 3 H), 4.2−4.6 (m, 3 H), 6.4−7.06 (m, 3 H).

(2*S*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)methyl]-8-methoxy-1,4-benzodioxane Hydrochloride [(*S*)-2]. A mixture of (*R*)-**18** (1.52 g, 4.97 mmol) and 2-(2,6-dimethoxyphenoxy)-ethylamine (1.96 g, 9.93 mmol) was heated at 130 °C for 2 h and, after cooling, treated with ethyl acetate (50 mL) and 10% NaOH (75 mL). The aqueous phase was separated and extracted with ethyl acetate. The combined extracts were washed with water, dried, and concentrated to give a residue which was chromatographed on silica gel. Elution with dichloromethane/methanol (95/5) yielded 980 mg of (2*S*)-2-[((2-(2,6-dimethoxyphenoxy)ethyl)amino)methyl]-8-methoxy-1,4-benzodioxane. The secondary amine was dissolved in ethanol (2 mL), and 4 N HCl/EtOH (1.5 mL) was added. The resulting precipitate was isolated and twice crystallized from ethanol yielding 540 mg (26%) of (*S*)-**2** as a white solid: mp 169−171 °C; $[\alpha]_D^{25} = -67$ (*c* 1, chloroform); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.30−3.55 (m, 4 H), 3.79 (s, 3 H), 3.83 (s, 6 H), 4.10−4.25 (m, 3 H), 4.48 (dd, 1 H), 4.77 (m, 1 H), 6.55−6.90 (m, 5 H), 7.10 (t, 1 H), 9.60 (br s, 2 H). Anal. Calcd for $C_{20}H_{26}ClNO_6$ (411.88): C, 58.32; H, 6.36; N, 3.40; Cl, 8.61. Found: C, 58.25; H, 6.37; N, 3.43; Cl, 8.33.

(2*R*)-3-(2,3-Dimethoxyphenoxy)-1,2-propanediol Acetonide [(*R*)-12]. Prepared from (2*S*)-3-(tosyloxy)-1,2-propanediol acetonide [(*S*)-**4**] as described for (*S*)-**12**: mp 95−96 °C; $[\alpha]_D^{25} = -18.0$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*S*)-**12**.

(2*S*)-3-(2,3-Dimethoxyphenoxy)-1,2-propanediol [(*S*)-13]. Prepared from (*R*)-**12** as described for (*R*)-**13**: mp 93−96 °C; $[\alpha]_D^{25} = +8.9$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*R*)-**13**.

(2*R*)-3-(2,3-Dimethoxyphenoxy)-1,2-bis(tosyloxy)propane [(*R*)-14]. Prepared from (*S*)-**13** as described for (*S*)-**14**: mp 79−80 °C; $[\alpha]_D^{25} = -10.6$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*S*)-**14**.

(2*R*)-3-(2,3-Dihydroxyphenoxy)-1,2-bis(tosyloxy)propane [(*R*)-15]. Prepared from (*R*)-**14** as described for (*S*)-**15**: mp 108−109 °C; $[\alpha]_D^{25} = -12.3$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*S*)-**15**.

(2*S*)-2-((Tosyloxy)methyl)-8-hydroxy-1,4-benzodioxane [(*S*)-16]. Prepared from (*R*)-**15** as described for (*R*)-**16**: $[\alpha]_D^{25} = +6.0$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*R*)-**16**.

(2*S*)-2-((Tosyloxy)methyl)-8-methoxy-1,4-benzodioxane [(*S*)-17]. Prepared from (*S*)-**16** as described for (*R*)-**17**: mp 92−94 °C; $[\alpha]_D^{25} = +7.6$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*R*)-**17**.

(2*S*)-2-(Iodomethyl)-8-methoxy-1,4-benzodioxane [(*S*)-18]. Prepared from (*S*)-**17** as described for (*R*)-**18**: $[\alpha]_D^{25} = +39.2$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*R*)-**18**.

(2*R*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)methyl]-8-methoxy-1,4-benzodioxane Hydrochloride [(*R*)-2]. Prepared from (*S*)-**18** as described for (*S*)-**2**: mp 170−171 °C; $[\alpha]_D^{25} = +66.1$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*S*)-**2**. Anal. Calcd for $C_{20}H_{26}ClNO_6$ (411.88): C, 58.32; H, 6.36; N, 3.40; Cl, 8.61. Found: C, 58.19; H, 6.38; N, 3.42; Cl, 8.39.

(2*S*)-3-(2-(Benzyloxy)-3-fluorophenoxy)-1,2-propanediol Acetonide [(*S*)-19]. A mixture of 2-(benzyloxy)-3-fluorophenol (7 g, 0.032 mol) and potassium carbonate (4.5 g, 0.032 mol) in dimethylformamide (100 mL) was stirred for 30 min. After dropwise addition of (2*R*)-3-(tosyloxy)-1,2-propanediol acetonide [(*R*)-**4**] (9.5 g, 0.033 mol), the mixture was heated at 120 °C for 36 h. The solvent was evaporated under vacuum and the residue treated with dichloromethane. The resulting suspension was filtered and the filtrate washed with 10% HCl and then with water. The organic phase was separated, dried, and concentrated to give a residue, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (80/20) afforded 6.4 g (60%) of (*S*)-**19** as an oil:; $[\alpha]_D^{25} = +13.69$ (*c* 1, ethanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 3 H), 1.44 (s, 3 H), 3.80−4.20 (m, 4 H), 4.30−4.58 (m, 1 H), 5.1 (s, 2 H), 6.68−6.80 (m 2 H), 6.82−7.00 (m, 1 H), 7.20−7.60 (m, 5 H).

(2*R*)-3-(2-(Benzyloxy)-3-fluorophenoxy)-1,2-propanediol [(*R*)-20]. A suspension of (*S*)-**19** (6.4 g, 19.2 mmol) in 10% HCl (100 mL) was heated at 75 °C for 14 h. After cooling, acetone was removed by vacuum distillation and brine (50 mL) was added to the residual aqueous phase which was successively extracted with ethyl acetate. The organic extract was dried and concentrated, and the resulting residue was chromatographed on silica gel. Elution with dichloromethane/methanol (95/5) yielded 4.5 g (80%) of (*R*)-**20** as an oil: $[\alpha]_D^{25} = -4.58$ (*c* 0.5, ethanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 1 H), 3.00 (s, 1 H), 3.60−3.70 (m, 4 H), 3.96−4.13 (m, 3 H), 5.08 (s, 2 H), 6.66−6.80 (m, 2 H), 6.90−7.00 (m, 1 H), 7.33−7.40 (m, 5 H).

(2*S*)-3-(2-(Benzyloxy)-3-fluorophenoxy)-1,2-bis(tosyloxy)-propane [(*S*)-21]. Tosyl chloride (6 g, 31.5 mmol) was added in small portions to a stirred solution of (*R*)-**20** (4.5 g, 15.4 mmol) in pyridine (10 mL) at 0 °C. The resulting mixture was stirred for 18 h at room temperature, diluted with ethyl acetate, and washed with 10% HCl and then with water. The organic phase was dried and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (80/20) yielded 6 g (65%) of (*S*)-**21** as a viscous oil: $[\alpha]_D^{25} = -4.27$ (*c* 1, ethanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.42 (s, 3 H), 4.09−4.11 (m, 2 H), 4.14−4.21 (m, 2 H), 4.85 (m, 1 H), 4.94 (s, 2 H), 6.52−6.74 (m, 1 H), 6.79−6.86 (m, 1 H), 6.90−6.97 (m, 1 H), 7.26−7.55 (m, 9 H), 7.63−7.76 (2d, 4 H).

(2*S*)-3-(2-Hydroxy-3-fluorophenoxy)-1,2-bis(tosyloxy)-propane [(*S*)-22]. A solution of (*S*)-**21** (6 g, 9.99 mmol) in ethyl acetate (50 mL) was added with 10% Pd/C (50 mg) and vigorously shaken under hydrogen at room temperature for 6 h. The catalyst was removed by filtration and the filtrate concentrated to give a residue which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (70/30) afforded 4 g (78%) of (*S*)-**22** as a colorless oil: $[\alpha]_D^{25} = -8.54$ (*c* 1, chloroform); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.4 (s, 6 H), 4.08−4.22 (m, 4 H), 4.94−5.00 (m, 1 H), 5.8 (s, 1 H), 6.48−6.51 (m, 1 H), 6.68−6.76 (m, 2 H), 7.26−7.33 (2d, 4 H), 7.69−7.77 (2d, 4 H).

(2*R*)-2-((Tosyloxy)methyl)-8-fluoro-1,4-benzodioxane [(*R*)-23]. A mixture of (*S*)-**22** (4 g, 7.83 mmol) and potassium carbonate (1.08 g, 7.83 mmol) in acetone (25 mL) was refluxed for 5 h. After cooling, the reaction mixture was concentrated and the residue treated with ethyl acetate and 10% HCl. The organic phase was separated, washed with water, dried, and concentrated to yield a residue which was chromatographed on silica gel eluting with cyclohexane/ethyl acetate (70/30). The pure fractions gave 2.5 g (94%) of (*R*)-**23** as a yellow oil: $[\alpha]_D^{25} = -24.14$ (*c* 1, chloroform); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 4.04−4.13 (m, 1 H), 4.20−4.33 (m, 3 H), 4.39−4.45 (m, 1 H), 6.62−6.76 (m, 3 H), 7.35 (d, 2 H), 7.80 (d, 2 H).

(2*R*)-2-(Iodomethyl)-8-fluoro-1,4-benzodioxane [(*R*)-24]. A mixture of (*R*)-**23** (2.5 g, 7.39 mmol) and sodium iodide (13 g, 86.7 mmol) in acetone (20 mL) was refluxed for 6 h, cooled to room temperature, and concentrated to give a residue which was treated with 10% HCl and ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined, washed with an aqueous solution of sodium metabisulfite, dried, and concentrated. The resulting residue was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (70/30) afforded 1.53 g (70%) of (*R*)-**24** as a yellow oil: $[\alpha]_D^{25} = +7.96$ (*c* 1, chloroform); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.29−3.47 (m, 2 H), 4.16−4.45 (m, 3 H), 6.66−6.79 (m, 3 H).

(2*S*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)methyl]-8-fluoro-1,4-benzodioxane Hydrochloride [(*S*)-3]. A mixture of (*R*)-**24** (1.53 g, 5.20 mmol) and 2-(2,6-dimethoxyphenoxy)-ethylamine (2 g, 10.1 mmol) in isobutyl alcohol (7 mL) was refluxed for 24 h. The solvent was evaporated and the residue treated with ethyl acetate and 10% NaOH. The aqueous phase was separated and extracted with ethyl acetate. The combined extracts were washed with water, dried, and concentrated to give a residue which was chromatographed on silica gel. Elution with dichloromethane/methanol (98/2) yielded 860 mg of (2*S*)-2-[((2-(2,6-dimethoxyphenoxy)ethyl)amino)methyl]-8-fluoro-1,4-benzodioxane: $[\alpha]_D^{25} = -25.8$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.15 (br s, 1 H), 2.89−3.03 (m, 4 H), 3.84 (s, 6 H), 4.05−4.16 (m, 3 H), 4.20−4.39 (m, 2 H), 6.52−6.80 (m, 5 H), 7.00 (t, 1 H). The secondary amine was treated with 3.8 N HCl/EtOH (4 mL). The solvent was evaporated, and the semisolid residue was crystallized from ethyl acetate yielding 370 mg (18%) of (*S*)-**3** as a white solid: mp 137 °C; $[\alpha]_D^{25} = -53.2$ (*c* 1, methanol); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.30−3.55 (m, 4 H), 3.82 (s, 6 H), 4.10−4.30 (m, 3 H), 4.54 (dd, 1 H), 4.89 (m, 1 H), 6.70−7.00 (m, 5 H), 7.05−7.15 (t, 1 H), 9.64 (br s, 2 H). Anal. Calcd for $C_{19}H_{23}ClFNO_5$ (399.85): C, 57.07; H, 5.80; N, 3.50; F, 4.75; Cl, 8.87. Found: C, 56.99; H, 5.81; N, 3.47; F, 4.83; Cl, 8.84.

(2*R*)-3-(2-(Benzyloxy)-3-fluorophenoxy)-1,2-propanediol Acetonide [(*R*)-19]. Prepared from (2*S*)-3-(tosyloxy)-1,2-propanediol acetonide [(*S*)-**4**] as described for (*S*)-**19**: $[\alpha]_D^{25} = -13.63$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*S*)-**19**.

(2*S*)-3-(2-(Benzyloxy)-3-fluorophenoxy)-1,2-propanediol [(*S*)-20]. Prepared from (*R*)-**19** as described for (*R*)-**20**: $[\alpha]_D^{25} = +6.39$ (*c* 0.5, ethanol); ^{1}H NMR identical to that of (*R*)-**20**.

(2*R*)-3-(2-(Benzyloxy)-3-fluorophenoxy)-1,2-bis(tosyloxy)-propane [(*R*)-21]. Prepared from (*S*)-**20** as described for (*S*)-**21**: $[\alpha]_D^{25} = +5.93$ (*c* 1, ethanol); ^{1}H NMR identical to that of (*S*)-**21**.

(2*R*)-3-(2-Hydroxy-3-fluorophenoxy)-1,2-bis(tosyloxy)-propane [(*R*)-22]. Prepared from (*R*)-**21** as described for (*S*)-**22**: $[\alpha]_D^{25} = +9.26$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*S*)-**22**.

(2*S*)-2-((Tosyloxy)methyl)-8-fluoro-1,4-benzodioxane [(*S*)-23]. Prepared from (*R*)-**22** as described for (*R*)-**23**: $[\alpha]_D^{25} = +27.5$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*R*)-**23**.

(2*S*)-2-(Iodomethyl)-8-fluoro-1,4-benzodioxane [(*S*)-24]. Prepared from (*S*)-**23** as described for (*R*)-**24**: $[\alpha]_D^{25} = -7.66$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*R*)-**24**.

(2*R*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)methyl]-8-fluoro-1,4-benzodioxane Hydrochloride [(*R*)-3]. Prepared from (*S*)-**24** as described for (*S*)-**3**: mp 137 °C; $[\alpha]_D^{25} = +51.27$ (*c* 1, methanol) ($[\alpha]_D^{25} = +23.5$ (*c* 1, chloroform) for the free amine); ^{1}H NMR identical to that of (*S*)-**3**. Anal. Calcd for $C_{19}H_{23}ClFNO_5$ (399.85): C, 57.07; H, 5.80; N, 3.50; F, 4.75; Cl, 8.87. Found: C, 57.00; H, 5.80; N, 3.48; F, 4.76; Cl, 8.75.

2-Fluorophenyl Acetate (25). Acetyl chloride (35.3 g, 0.45 mol) was slowly added to a solution of 2-fluorophenol (50 g, 0.45 mol) and pyridine (40 mL) in dichloromethane (300 mL) at 25 °C. After 2 h, 10% HCl (200 mL) was added and the aqueous layer was separated and extracted with dichloromethane. The organic phases were combined, washed with water, dried, and concentrated to give 65 g (94%) of **25** as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 7.10−7.29 (m, 4 H).

2-Hydroxy-3-fluoroacetophenone (26). A solution of **25** (65 g, 0.42 mol) in dichlorobenzene (40 mL) was added dropwise to a solution of aluminum chloride (56.2 g, 0.42 mol) in dichlorobenzene (50 mL). After being warmed to 100 °C for 24 h, the reaction mixture was allowed to cool to room temperature, added with dichloromethane, and poured into 10% HCl cooled at 0 °C. The aqueous layer was separated and extracted with dichloromethane. The organic extracts were combined, rinsed with water, dried, and concentrated. Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 95/5) of the resulting residue allowed to isolate, in sequence, 25 g (38.6%) of **26** and 39 g (60.2%) of 3-fluoro-4-hydroxyacetophenone. **26**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.65 (s, 3 H), 6.79−6.89 (dd, 1 H), 7.24−7.34 (dd, 1 H), 7.51−7.55 (dd, 1 H), 12.28 (s, 1 H). 3-Fluoro-4-hydroxyacetophenone: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.55 (s, 3 H), 6.5 (br s, 1 H), 7.05−7.15 (m, 1 H), 7.62−7.80 (m, 2 H).

2-(Benzyloxy)-3-fluoroacetophenone (27). Tetrabutylammonium bromide (7.1 g, 22 mmol) and 10% NaOH (200 mL) were added to a solution of **26** (33.9 g, 0.22 mol) in dichloromethane (300 mL). Benzyl bromide (28.8 mL, 0.242 mol) was added dropwise to the mixture while vigorously stirring. After 3 h at room temperature, the reaction mixture was poured into 10% HCl (350 mL). The organic layer was separated and the aqueous phase extracted with dichloromethane. The organic extracts were combined, washed with water, dried, and concentrated. Column chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 95/5) of the resulting residue allowed the isolation of 47 g (87.5%) of **27** as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.51 (s, 3 H), 5.29 (s, 2 H), 7.06−7.12 (m, 1 H), 7.21−7.31 (m, 2 H), 7.34−7.40 (m, 5 H).

2-(Benzyloxy)-3-fluorophenyl Acetate (28). 3-Chloroperoxybenzoic acid (55%) (150 g, 0.478 mol) was added in small portions to a solution of **27** (47 g, 0.192 mol) in dichloromethane at 0 °C. The reaction mixture was stirred for 4 days at room temperature and then poured into 1 N NaOH (300 mL). The aqueous layer was separated and extracted with dichloromethane. The organic phases were combined, washed with water, dried, and concentrated to give 45 g (90%) of **28** as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.25 (s, 3 H), 5.18 (s, 2 H), 6.82−6.92 (m, 1 H), 6.95−7.15 (m, 2 H), 7.35−7.5 (m, 5 H).

2-(Benzyloxy)-3-fluorophenol (29). A solution of **28** (45 g, 0.173 mol) and *p*-toluenesulfonic acid monohydrate (2 g) in methanol (300 mL) was refluxed for 24 h. The solvent was evaporated and the resulting residue treated with ethyl acetate (200 mL) and 10% HCl (100 mL). The aqueous layer was separated and extracted with ethyl acetate. The organic phases were combined, washed with water, dried, and concentrated. The crude product was purified by chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 80/20) yielding 27 g (71.5%) of **29** as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.15 (s, 2 H), 5.80 (br s, 1 H), 6.65−6.80 (m, 2 H), 6.82−6.98 (m, 1 H), 7.35−7.45 (m, 5 H).

Capillary Electrophoresis Analyses. All runs were done with a CE Perkin-Elmer 270A-HT instrument. The electrophoretic separations were performed on a fused-silica capillary of 72 cm (50 cm effective length) × 50 μm i.d. Detection was

done by UV absorbance recording at 200 nm. Sample injection was performed hydrodynamically at 127 mmHg for 0.2 s. For CE analysis at the optimum conditions, the applied voltage was 25 kV. The capillary temperature was controlled at 30 °C. The running electrolyte was 5 mM phosphate buffer (pH 2.5). The following chiral selectors (Sigma) were used: β-CD (10 mM), hydroxyethyl β-CD (40 mM) and hydroxypropyl γ-CD (60 mM). The capillary was conditioned with 1 M NaOH for 20 min followed by 0.1 M NaOH for 5 min and then by water (18 MΩ) for 5 min, prior to use. After each run, the capillary was washed with 0.1 M NaOH and then with water for 1 min, respectively, and finally with running buffer for 4 min before the next run.

The following samples for injection were prepared: (i) aqueous solution containing (*S*)-WB4101, (*R*)-WB4101, (*S*)-2-(aminomethyl)-1,4-benzodioxane hydrochloride, (*R*)-2-(aminomethyl)-1,4-benzodioxane hydrochloride, (*S*)-**1**, (*R*)-**1**, (*S*)-**2**, (*R*)-**2**, (*S*)-**3,** and (*R*)-**3** at respective concentrations of 5 μg mL^{-1}; (ii) 0.02% w/v solutions of the enantiomeric pairs of WB4101, 2-(aminomethyl)-1,4-benzodioxane hydrochloride, and **1**−**3** obtained by preparation of aqueous solutions (10 mL) containing 10 mg of both the enantiomers of the above pairs and successive 10-fold dilution with the same CD-added running buffer as used for the electrophoretic run; (iii) 0.01% w/v solutions of (*S*)-WB4101, (*R*)-WB4101, (*S*)-2-(aminomethyl)-1,4-benzodioxane hydrochloride, (*R*)-2-(aminomethyl)-1,4-benzodioxane hydrochloride, (*S*)-**1**, (*R*)-**1**, (*S*)-**2**, (*R*)-**2**, (*S*)-**3,** and (*R*)-**3** obtained by diluting the respective 0.1% w/v aqueous solutions with the same CD-added running buffer as selected for the electrophoretic run.

In the absence of chiral selector, i.e., using the mere 5 mM phosphate as a running electrolyte, injection of sample i gave four peaks corresponding, in sequence, to (*S*)- and (*R*)-2-(aminomethyl)-1,4-benzodioxane (retention time (t_r) = 6.81 min), to the coeluted enantiomers of WB4101 and of **3** (t_r = 10.14 min), to (*S*)- and (*R*)-**2** (t_r = 10.31 min), and, finally, to (*S*)- and (*R*)-**1** (t_r = 10.72 min) (see Figure 1).

Injection of the solutions of the single enantiomeric pairs, prepared as described in sample ii, produced two completely separated peaks in the following cases: (a) (*R*)-2-(aminomethyl)-1,4-benzodioxane and (*S*)-2-(aminomethyl)-1,4-benzodioxane (t_r = 11.63 and 11.91 min, respectively; running electrolyte, 40 mM hydroxyethyl β-CD in 5 mM phosphate buffer); (b) (*R*)-WB4101 and (*S*)-WB4101 (t_r = 16.10 and 16.84 min, respectively; running electrolyte, 40 mM hydroxyethyl β-CD in 5 mM phosphate buffer); (c) (*S*)-**3** and (*R*)-**3** (t_r = 16.08 and 16.70 min, respectively; running electrolyte, 40 mM hydroxyethyl β-CD in 5 mM phosphate buffer); (d) (*S*)-**1** and (*R*)-**1** (t_r = 14.85 and 15.60 min, respectively; running electrolyte, 40 mM hydroxyethyl β-CD in 5 mM phosphate buffer); (e) (*S*)-**2** and (*R*)-**2** (t_r = 45.80 and 46.67 min, respectively; running electrolyte, 60 mM hydroxypropyl γ-CD in 5 mM phosphate buffer) (see Figures 2 and 4). Under the above conditions, which had produced complete enantioseparation, the analysis of the 10 single enantiomers, namely of the corresponding solution prepared as described in sample iii, allowed us to determine the following enantiomeric excesses: 99.99 ((*S*)-2-(aminomethyl)-1,4-benzodioxane); 96.97 ((*R*)-2-(aminomethyl)-1,4-benzodioxane); 99.95 ((*S*)-WB4101); 95.95 ((*R*)-WB4101); 99.74 ((*S*)-**1**); 99.62 ((*R*)-**1**); 99.81 ((*S*)-**2**); 99.72 ((*R*)-**2**); 99.83 ((*S*)-**3**); 99.66 ((*R*)-**3**).

Finally, an aqueous solution, prepared as in sample i but excluding (*S*)-**2** and (*R*)-**2**, was submitted to electrophoretic analysis using 40 mM hydroxyethyl β-CD in 5 mM phosphate buffer as a running electrolyte. The corresponding electropherogram, which shows the complete resolution of the four enantiomeric pairs contained in the sample, is presented in Figure 3.

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Supporting Information Available: ^{1}H NMR spectra for compounds (*S*)-**1**, (*R*)-**1**, (*S*)-**2**, (*R*)-**2**, (*S*)-**3**, (*R*)-**3**, (*S*)-**19**, (*R*)-**20**, (*S*)-**21**, (*S*)-**22**, (*R*)-**23**, (*R*)-**24**, and **25**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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