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Nonracemic Dimethylphenyl Glycerol Ethers in the Synthesis of Physiologically Active Aminopropanols

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Abstract—Six regioisomeric nonracemic dimethylphenyl glycerol ethers were synthesized by asymmetric dihydroxylation of the corresponding allyl dimethylphenyl ethers. The enantioselectivity of the reaction with *o*-methyl derivatives was lower (down to 34% *ee*) than with *m*-methylphenyl ethers (up to 86% *ee*). Enantiomeric 3-(3,4-dimethylphenoxy)propane-1,2-diols were used to obtain enantiomerically pure physiologically active amino alcohols and their derivatives.

Keywords: asymmetric dihydroxylation, glycerol ethers, enantiopure aminopropanols.

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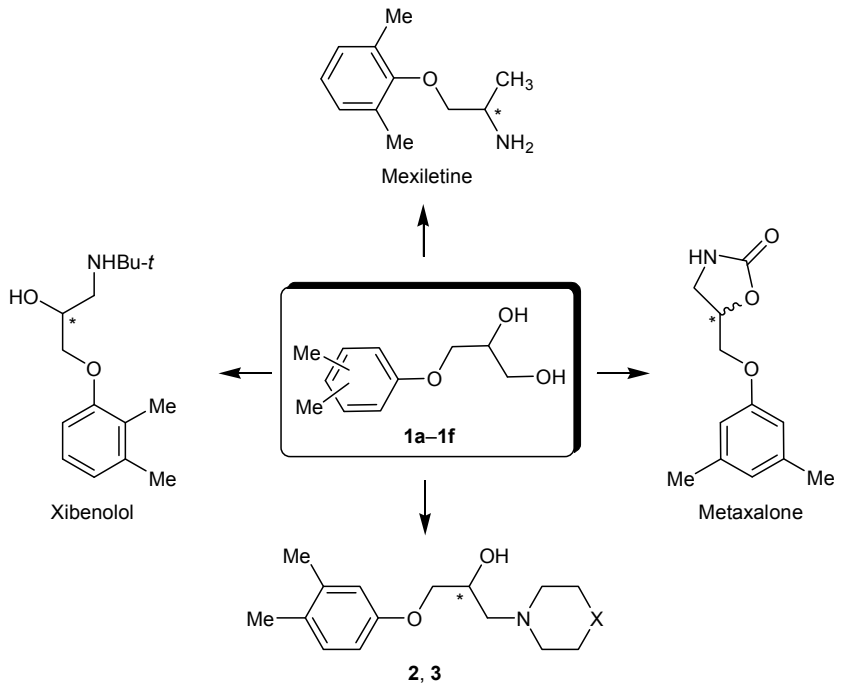
Since the beginning of the XXI century, newly designed drugs are represented mainly by enantiomerically pure chiral compounds [1], and this trend can be regarded as long-term. For example, 45 new drugs have been approved in the USA in 2015, 12 of which were complex biological products of the protein or other nature, and 33 were individual chiral compounds. The latter, with only one exception, were pure enantiomers [2]. The needs of pharmacology and medicinal chemistry stimulate extension of the range of accessible enantiomerically pure compounds and study of their properties which often remain unknown or relevant data are contradictory.

Chiral aromatic glycerol ethers of the general formula $ArOCH_2CH(OH)CH_2OH$ exhibit diverse biological activity [3–5] and are also used as synthetic precursors to medicines possessing various activities [6–9]. In this work we studied regioisomeric phenyl glycerol ethers **1** bearing two methyl groups in the aromatic ring (Scheme 1). Compounds of this series were used in the synthesis of enantiopure drugs such as mexiletine [10], xibenolol [11], and metaxalone [12]. Aminopropanol **2** hydrochloride coded as T0502-1048 was reported as a promising β_2-adrenoceptor antagonist [13]. Furthermore, there are patent data according to which stereoisomers of 1-(3,4-dimethylphenoxy)-3-(morpholin-4-yl)propan-2-ol (**3**) show useful activities (but different for the racemate and individual enantiomers) in the treatment of neurodegenerative and neuromuscular disorders, as well as of Friedreich's ataxia [14]. Nonracemic 3-(2,4-, 2,5-, and 3,4-dimethylphenoxy)propane-1,2-diols **1b**, **1c**, and **1e** were not reported. Both enantiomers of 3,5-dimethylphenyl derivative **1f** were isolated in the course of multistep syntheses from natural mannitol [15]. Pure enantiomers of **1a** and **1d** were isolated by us previously as a result of spontaneous optical resolution upon crystallization [10, 11, 16]. Therefore, the goal of the present work was to develop a general procedure for the synthesis of pure enantiomers of **1** by asymmetric dihydroxylation of the corresponding allyl phenyl ethers, estimate advantages and disadvantages of this approach, and obtain enantiomerically pure practically useful amino alcohols using diols **1** as precursors.

The Sharpless asymmetric dihydroxylation has found wide application in modern organic chemistry [17, 18], which is largely determined by the accessibility of the commercial chiral catalysts AD-mix-α and AD-mix-β. In most cases, dihydroxylation of allyl ethers derived from *para*-substituted phenols was characterized by a satisfactory enantioselectivity (89–95% *ee*). The presence of an *ortho* substituent in the initial ether reduced the enantioselectivity (28–63% *ee*; in particular 36% *ee* for (*S*)-**1d** [19]). It is also believed that AD-mix-β favors *S* configuration of the newly

Scheme 1.



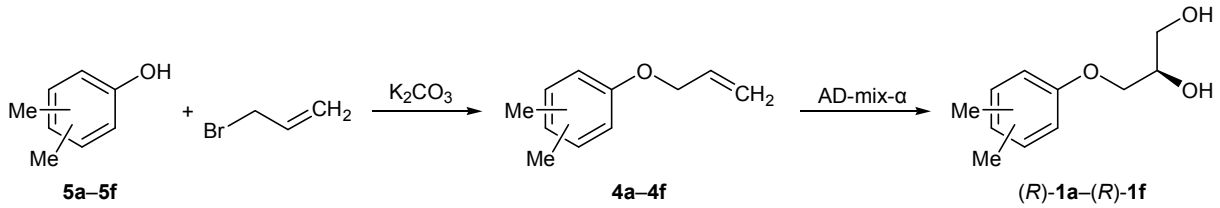
1, 2,3-Me_2 (**a**), 2,4-Me_2 (**b**), 2,5-Me_2 (**c**), 2,6-Me_2 (**d**), 3,4-Me_2 (**e**), 3,5-Me_2 (**f**); **2**, X = CH_2; **3**, X = O.

formed chiral center and that AD-mix-α gives rise to the corresponding *R* isomers; the only known exception is dihydroxylation of allyl *o*-nitrophenyl ether [20].

Precursors to the target compounds, ethers **4a**–**4f** were synthesized in moderate yields (~50–70%) from the corresponding phenols **5a**–**5f** and allyl bromide in the presence of potassium carbonate (Scheme 2). In fact, *o*-methyl derivatives **1b**–**1d** were obtained with reduced *ee* values (35–53%), whereas the dihydroxylation of **4a**, **4e**, and **4f** gave diols **1a**, **1e**, and **1f** with *ee* values exceeding 80%. In the latter cases, the substrate molecules contained a methyl group in the *meta* position; however, this factor may not be related to the obtained result. It should be noted that all diols **1a**–**1e** can be brought to a high degree of enantiomeric purity by recrystallization.

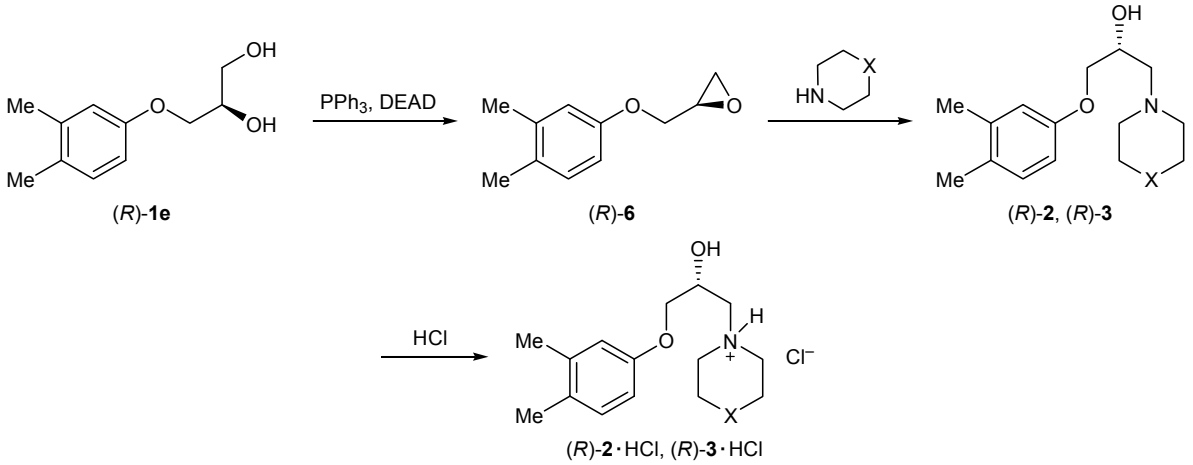
Enantiomeric diols **1a** and **1f** were converted by us previously to xibenolol and metaxalone, respectively [11, 12]. In this work, amino alcohols **2** and **3** were synthesized from enantiomeric diols **1e** according to Scheme 3. Aryloxypropanediols themselves can be precursors to amino alcohols of the general formula $ArOCH_2CH(OH)CH_2NR^1R^2$, though their preliminary activation via conversion to cyclic sulfites [21, 22] or oxiranes [19] is necessary for this purpose. The latter transformation offers a number of advantages. A reliable procedure for the synthesis of oxiranes from vicinal diols is based on the Mitsunobu reaction [23]. The reaction of **1e** with triphenylphosphine and diethyl azodicarboxylate was accompanied by a small loss of enantiomeric purity [from 99% *ee* for (*R*)-**1e** to 96% *ee* for (*R*)-**6**]. By analogy with the cyclizations performed by us previously [10, 11], we presumed that the initial

Scheme 2.



1, **4**, **5**, 2,3-Me_2 (**a**), 2,4-Me_2 (**b**), 2,5-Me_2 (**c**), 2,6-Me_2 (**d**), 3,4-Me_2 (**e**), 3,5-Me_2 (**f**); **2**, X = CH_2; **2** · HCl = T0502-1048; **3**, X = O.
1, *ee* = 86 (**a**), 50 (**b**), 53 (**c**), 35 (**d**), 83 (**e**), 82% (**f**).

Scheme 3.



2, X = CH_2; **3**, X = O.

configuration of the chiral center is retained. Pure enantiomers (*R*)-**2** and (*R*)-**3** were synthesized by heating epoxide (*R*)-**6** with an equimolar amount of piperidine or morpholine in boiling ethanol in the presence of a catalytic amount of pyridine. Taking into account that enantiomer (*S*)-**3** was reported [14] to possess the highest physiological activity, from diol (*S*)-**1e** we synthesized enantiomerically pure amino alcohols (*S*)-**3** and (*S*)-**2** according to a similar scheme. Amino alcohols **2** and **3** were converted to hydrochlorides by passing gaseous hydrogen chloride through a solution of the free base in acetone. All isolated compounds were fully characterized.

It should be noted that there are no published data on enantiomeric amines **2** and **3** hydrochlorides, whereas the optical rotation of free base **3** given in [14] is erroneous since the value $[\alpha]_D^{20} = -13.10°$ (c = 0.6, $CHCl_3$) was reported for both enantiomers [14]. We obtained the following data: (*R*)-**3**: $[\alpha]_D^{20} = +19.5°$ (c = 1.0, $CHCl_3$), 96% *ee*; (*S*)-**3**: $[\alpha]_D^{20} = -19.7°$ (c = 1.05, $CHCl_3$), 96% *ee*.

Thus, the Sharpless asymmetric dihydroxylation is appropriate for the synthesis of chiral 3-(3,4-, 3,5-, and 2,3-dimethylphenoxy)propane-1,2-diols which can be used to obtain physiologically active compounds. The reactions with 2,4-, 2,5-, and 2,6-dimethyl analogs are characterized by a low enantioselectivity, so that alternative approaches should be sought for in these cases.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker Avance-400 spectrometer at 399.9 MHz for ^1H and 100.6 MHz for ^{13}C using $CDCl_3$ as solvent and reference. The IR spectra were recorded in KBr on a Bruker Tensor 27 spectrometer. The optical rotations were measured on a Perkin Elmer 341 polarimeter. The melting points were determined with a Boetius hot stage and are uncorrected. The elemental analyses were obtained on a Euro Vector EA3000 CHN analyzer. Silufol UV-254 plates were used for analytical TLC; spots were visualized under UV light or by treatment with iodine vapor. HPLC analyses were performed on a Shimadzu LC-20AD chromatograph equipped with an SPD-20A UV detector (λ 275 nm); Chiralpak AD-RH (0.46×25 cm), Chiralpak AS-H (0.46×25 cm), or Chiralcel OD (0.46×25 cm) column (Daicel), eluent flow rate 1 mL/min. The corresponding racemic compounds were used as calibration standards. Racemic diols *rac*-**1a**–*rac*-**1f** were synthesized from racemic 3-chloropropane-1,2-diol and the corresponding phenols by analogy with the procedure reported in [10]; their melting points were as follows: *rac*-**1a**: mp 80–89°C (81.5–90°C [16]); *rac*-**1b**: 91–93°C (92–93°C [24]); *rac*-**1c**: 67–69°C (69–70°C [25]); *rac*-**1d**: 50–52°C (49–50°C [10]); *rac*-**1e**: 75–77°C (75–76°C [25]); *rac*-**1f**: 65–66°C (66–67°C [25]).

Racemic 3-chloropropane-1,2-diol and substituted phenols (Acros Organics), allyl bromide (Alfa Aesar), and AD-mix-α and AD-mix-β (Aldrich) were commercial products.

General procedure for the synthesis of allyl aryl ethers 4a–4f. A suspension of 1.00 g (8.3 mmol) of phenol **5a**–**5f**, 1.06 g (8.8 mmol) of allyl bromide, and 1.21 g (8.8 mmol) of ground fused potassium carbonate in 13 mL of anhydrous acetone was refluxed for about 12 h (TLC, $R_f \sim 0.7$, hexane–ethyl acetate, 9:1). The mixture was diluted with 40 mL of water and

extracted with diethyl ether (3×50 mL). The extract was washed with 20 mL of a 1 M aqueous solution of sodium hydroxide and dried over $MgSO_4$, the solvent was distilled off under reduced pressure, and the oily residue was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1 to 8:2) as eluent.

2,3-Dimethyl-1-(prop-2-en-1-yl)benzene (4a). Yield 69%, n_D^{20} = 1.5161. ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, CH_3), 2.31 s (3H, CH_3), 4.56 d.t (2H, OCH_2, *J* = 5.0, 1.6, 1.6 Hz), 5.30 d.d.d (1H, =CH_2, *J* = 10.6, 3.0, 1.5 Hz), 5.47 d.d.d (1H, =CH_2, *J* = 17.3, 3.4, 1.7 Hz), 6.07–6.16 m (1H, =CH), 6.74 d (1H, 6′-H, *J* = 8.2 Hz), 6.82 d (1H, 4′-H, *J* = 7.5 Hz), 7.07 d (1H, 5′-H, *J* = 7.9 Hz) (cf. [26]).

2,4-Dimethyl-1-(prop-2-en-1-yl)benzene (4b). Yield 52%, n_D^{20} = 1.5125. ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, CH_3), 2.26 s (3H, CH_3), 4.52 d.t (2H, OCH_2, *J* = 5.0, 1.6, 1.6 Hz), 5.26 d.d.d (1H, =CH_2, *J* = 10.6, 3.0, 1.5 Hz), 5.42 d.d.d (1H, =CH_2, *J* = 17.3, 3.4, 1.7 Hz), 6.02–6.12 m (1H, =CH), 6.72 d (1H, 3′-H, *J* = 8.2 Hz), 6.92–6.96 m (2H, 5′-H, 6′-H) (cf. [27]).

2,5-Dimethyl-1-(prop-2-en-1-yl)benzene (4c). Yield 56%, n_D^{20} = 1.5120. ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, CH_3), 2.33 s (3H, CH_3), 4.54 d.t (2H, OCH_2, *J* = 5.0, 1.6, 1.6 Hz), 5.28 d.d.d (1H, =CH_2, *J* = 10.6, 3.1, 1.5 Hz), 5.45 d.d.d (1H, =CH_2, *J* = 17.3, 3.3, 1.7 Hz), 6.05–6.14 m (1H, =CH), 6.67 d.d (2H, 4′-H, 6′-H, *J* = 18.3, 7.4 Hz), 7.03 d (1H, 3′-H, *J* = 7.5 Hz) (cf. [28]).

2,6-Dimethyl-1-(prop-2-en-1-yl)benzene (4d). Yield 61%, n_D^{20} = 1.5005. ^{1}H NMR spectrum, δ, ppm: 2.37 s (6H, CH_3), 4.38 d.t (2H, OCH_2, *J* = 5.6, 1.5, 1.5 Hz), 5.33 d.d.d (1H, =CH_2, *J* = 10.4, 2.9, 1.4 Hz), 5.51 d.d.d (1H, =CH_2, *J* = 17.2, 3.3, 1.7 Hz), 6.24–6.14 m (1H, =CH), 6.99 d.d (1H, 4′-H, *J* = 8.2, 6.2 Hz), 7.08 d (2H, 3′-H, 5′-H, *J* = 7.7 Hz).

3,4-Dimethyl-1-(prop-2-en-1-yl)benzene (4e). Yield 73%, n_D^{20} = 1.5095. ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 2.24 s (3H, CH_3), 4.51 d.t (2H, OCH_2, *J* = 5.3, 1.5, 1.5 Hz), 5.27 d.d.d (1H, =CH_2, *J* = 10.5, 2.9, 1.4 Hz), 5.40 d.d.d (1H, =CH_2, *J* = 17.3, 3.3, 1.6 Hz), 6.01–6.11 m (1H, =CH), 6.66 d.d (1H, 6′-H, *J* = 8.3, 2.7 Hz), 6.74 d (1H, 2′-H, *J* = 2.6 Hz), 7.02 d (1H, 5′-H, *J* = 8.3 Hz).

3,5-Dimethyl-1-(prop-2-en-1-yl)benzene (4f). Yield 71%, n_D^{20} = 1.5110. ^{1}H NMR spectrum, δ, ppm: 2.30 s (6H, CH_3), 4.52 d.t (2H, OCH_2, *J* = 5.3, 1.5, 1.5 Hz), 5.28 d.d.d (1H, =CH_2, *J* = 10.5, 2.9, 1.4 Hz), 5.42 d.d.d (1H, =CH_2, *J* = 17.3, 3.3, 1.7 Hz), 6.02–6.12 m (1H, =CH), 6.57 s (2H, 2′-H, 6′-H), 6.62 t (1H, 4′-H, *J* = 0.6 Hz) (cf. [28]).

Sharpless asymmetric dihydroxylation (*general procedure***)** [19]**.** A suspension of 1.4 g of AD-mix-α in a mixture of 5 mL of *tert*-butyl alcohol and 5 mL of water was cooled to 0°C, 1 mmol of allyl phenyl ether **4a**–**4f** was added, and the mixture was stirred for 20 h at 0°C. The mixture was then treated with 1.5 g of sodium sulfite and stirred for 30 min at room temperature. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×30 mL). The extracts were combined with the organic phase, washed with 20 mL of brine, and dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using hexane–ethyl acetate (8:2 to 4:6) as eluent. The enantiomeric composition of the product was determined by HPLC. The enantiomeric purity was increased by recrystallization from hexane–ethyl acetate (3:1).

(*R*)-3-(2,3-Dimethylphenoxy)propane-1,2-diol (*R*-1a). Yield 0.15 g (77%), mp 95–102°C, $[\alpha]_D^{20}$ = +9.6° (*c* = 1.0, MeOBu-*t*), 86.1% *ee* [Chiralcel OD, 20°C; hexane–propan-2-ol, 4:1; t_R, min: 8.9 (major), 10.7 (minor)]; mp 102–103°C (after recrystallization); published data: mp 101–102.5°C [11, 16], $[\alpha]_D^{20}$ = +13.4° (*c* = 1.0, MeOBu-*t*), $[\alpha]_D^{20}$ = +1.4° (*c* = 1.0, EtOH), 99.3% *ee*. IR spectrum: ν 3267 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 1.99 br.s (2H, OH), 2.16 s (3H, CH_3), 2.28 s (3H, CH_3), 3.78 d.d (1H, C**H**$_2$OH, *J* = 11.4, 5.5 Hz), 3.87 d.d (1H, C**H**$_2$OH, *J* = 11.4, 3.9 Hz), 4.04 d (2H, OCH_2, *J* = 5.3 Hz), 4.11–4.16 m (1H, C**H**OH), 6.72 d (1H, 6′-H, *J* = 7.6 Hz), 6.81 d (1H, 4′-H, *J* = 7.6 Hz), 7.05 t (1H, 5′-H, *J* = 7.9 Hz).

(*R*)-3-(2,4-Dimethylphenoxy)propane-1,2-diol (*R*-1b). Yield 0.16 g (82%; after column chromatography), mp 90–93°C, $[\alpha]_D^{20}$ = +5.0° (*c* = 1.0, MeOBu-*t*), 50.5% *ee* [Chiralpak AD-RH, 26°C, acetonitrile–water, 22.5:77.5, 0.4 mL/min; t_R, min: 25.0 (major), 28.5 (minor)]. After recrystallization: mp 103–104°C, $[\alpha]_D^{20}$ = +0.9° (*c* = 1.0, EtOH), $[\alpha]_D^{20}$ = +11.7° (*c* = 1.0, MeOBu-*t*), 99.4% *ee*. IR spectrum: ν 3224 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 2.22 s (3H, CH_3), 2.65 s (2H, OH), 3.72 d.d (1H, CH_2, *J* = 11.5, 5.7 Hz), 3.80 d.d (1H, CH_2, *J* = 11.5, 3.7 Hz), 3.96 d (2H, OCH_2, *J* = 5.2 Hz), 4.04–4.09 m (1H, C**H**OH), 6.67 d (1H, 6′-H, *J* = 8.1 Hz), 6.88–6.91 m (2H, 3′-H, 5′-H). ^{13}C NMR spectrum, δ_C, ppm: 16.1 (2′-CH_3), 20.4 (4′-CH_3), 63.9 (CH_2), 69.5 (OCH_2), 70.6

(CH), 111.4 ($C^{6'}$), 126.5 ($C^{2'}$), 127.1 ($C^{5'}$), 130.3 ($C^{4'}$), 131.7 ($C^{3'}$), 154.4 ($C^{1'}$). Found, %: C 67.52; H 8.14. $C_{11}H_{16}O_3$. Calculated, %: C 67.32; H 8.22.

(*R*)-3-(2,5-Dimethylphenoxy)propane-1,2-diol (*R*-1c). Yield 0.15 g (77%), mp 71–76°C, $[\alpha]_D^{20}$ = +5.2° (*c* = 1.0, MeOBu-*t*), 53.0% *ee* [Chiralpak AS-H, 28°C, hexane–propan-2-ol, 9:1; t_R, min: 10.7 (major), 12.2 (minor)]. After recrystallization: mp 80–82°C, $[\alpha]_D^{20}$ = +0.9° (*c* = 1.1, EtOH), $[\alpha]_D^{20}$ = +9.5° (*c* = 1.1, MeOBu-*t*), 99.9% *ee*. IR spectrum: ν 3313 cm^{-1} (OH). ^1H NMR spectrum, δ, ppm: 2.19 s (3H, CH_3), 2.31 s (3H, CH_3), 3.41 s (2H, OH), 3.77 d.d (1H, C**H**$_2$OH, *J* = 11.5, 5.9 Hz), 3.86 d.d (1H, C**H**$_2$OH, *J* = 11.5, 3.6 Hz), 4.01 d (2H, OCH_2, *J* = 5.3 Hz), 4.10–4.15 m (1H, C**H**OH), 6.65 s (1H, 6′-H), 6.70 d (1H, 4′-H, *J* = 7.5 Hz), 7.01 d (1H, 3′-H, *J* = 7.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.8 (2′-CH_3), 21.3 (5′-CH_3), 63.9 (CH_2), 69.1 (OCH_2), 70.7 (CH), 112.3 ($C^{6'}$), 121.6 ($C^{4'}$), 123.5 ($C^{2'}$), 130.5 ($C^{3'}$), 136.8 ($C^{5'}$), 156.4 ($C^{1'}$). Found, %: C 67.20; H 8.34. $C_{11}H_{16}O_3$. Calculated, %: C 67.32; H 8.22.

(*R*)-3-(2,6-Dimethylphenoxy)propane-1,2-diol (*R*-1d). Yield 0.14 g (71%), mp 53–66°C, $[\alpha]_D^{20}$ = +1.4° (*c* = 1.0, MeOBu-*t*), 35% *ee* [Chiralcel OD, 20°C, hexane–propan-2-ol, 4:1; t_R, min: 8.6 (minor), 11.1 (major)]. After recrystallization: mp 75–76°C (75–75.5°C [10]), $[\alpha]_D^{20}$ = +5.6° (*c* = 1.0, MeOBu-*t*), $[\alpha]_D^{20}$ = –2.5° (*c* = 1.0, EtOH), 99.3% *ee*. IR spectrum: ν 3265 cm^{-1} (OH). ^1H NMR spectrum, δ, ppm: 2.23 br.s (2H, OH), 2.29 s (6H, CH_3), 3.79–3.91 m (4H, CH_2O, C**H**$_2$OH), 4.08–4.12 m (1H, CH), 6.94 d.d (1H, 4′-H, *J* = 8.3, 6.5 Hz), 7.02 d (2H, 3′-H, 5′-H, *J* = 7.3 Hz).

(*R*)-3-(3,4-Dimethylphenoxy)propane-1,2-diol (*R*-1e). Yield 0.17 g (87%), mp 90–95°C, $[\alpha]_D^{20}$ = –6.2° (*c* = 1.0, EtOH), 83% *ee* [Chiralcel OD, 22°C, hexane–propan-2-ol, 4:1; t_R, min: 9.4 (major), 14.5 (minor)]. After recrystallization: mp 96–98°C, $[\alpha]_D^{20}$ = –7.7° (*c* = 1.0, EtOH), $[\alpha]_D^{20}$ = +2.3° (*c* = 1.0, MeOBu-*t*), $[\alpha]_D^{20}$ = –2.9° (*c* = 1.1, $CHCl_3$), 99.7% *ee*. IR spectrum: ν 3227 cm^{-1} (OH). ^1H NMR spectrum, δ, ppm: 2.19 s (3H, 4′-CH_3), 2.22 s (3H, 3′-CH_3), 2.72 s (2H, OH), 3.73 d.d (1H, C**H**$_2$OH, *J* = 11.5, 5.6 Hz), 3.83 d.d (1H, C**H**$_2$OH, *J* = 11.5, 3.8 Hz), 3.97–4.03 m (2H, OCH_2), 4.07–4.11 m (1H, C**H**OH), 6.65 d.d (1H, 6′-H, *J* = 8.2, 2.7 Hz), 6.73 d (1H, 2′-H, *J* = 2.7 Hz), 7.02 d (1H, 5′-H, *J* = 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.8 (4′-CH_3), 20.0 (3′-CH_3), 63.8 (CH_2), 69.2 (OCH_2), 70.6 (CH), 111.5 ($C^{6'}$), 116.2 ($C^{2'}$), 129.2 ($C^{4'}$), 130.4 ($C^{5'}$), 137.8 ($C^{3'}$), 156.6 ($C^{1'}$). Found, %: C 67.18; H 8.45. $C_{11}H_{16}O_3$. Calculated, %: C 67.32; H 8.22.

(*S*)-3-(3,4-Dimethylphenoxy)propane-1,2-diol (*S*-1e) was synthesized according to the general procedure using AD-mix-β. Yield 0.16 g (84%), mp 90–95°C, $[\alpha]_D^{20}$ = +5.6° (*c* = 1.2, EtOH), 89% *ee* [t_R, min: 9.0 (minor), 13.4 (major)]. After recrystallization: mp 96–97.5°C, $[\alpha]_D^{20}$ = +6.7° (*c* = 1.0, EtOH), 99.5% *ee*. Found, %: C 67.20; H 8.05. $C_{11}H_{16}O_3$. Calculated, %: C 67.32; H 8.22. The NMR spectra of (*S*)-**1e** were similar to those of (*R*)-**1e**.

(*R*)-3-(3,5-Dimethylphenoxy)propane-1,2-diol (*R*-1f). Yield 0.13 g (66%), mp 66–69°C, $[\alpha]_D^{20}$ = –6.1° (*c* = 1.0, EtOH), 81.9% *ee* [Chiralcel OD, 22°C, hexane–propan-2-ol, 4:1; t_R, min: 6.7 (major), 9.3 (minor)]. After recrystallization: mp 73–74°C (74.5–75.5°C [15]), $[\alpha]_D^{20}$ = –7.8° (*c* = 1.0, EtOH), $[\alpha]_D^{20}$ = +2.3° (*c* = 1.0, MeOBu-*t*), $[\alpha]_D^{20}$ = –4.4° (*c* = 1.1, $CHCl_3$), 99.9% *ee*. IR spectrum: ν 3260 cm^{-1} (OH). ^1H NMR spectrum, δ, ppm: 2.28 s (6H, CH_3), 2.77 s (2H, OH), 3.73 d.d (1H, C**H**$_2$OH, *J* = 11.5, 5.6 Hz), 3.82 d.d (1H, C**H**$_2$OH, *J* = 11.5, 3.6 Hz), 3.97–4.03 m (2H, OCH_2), 4.06–4.11 m (1H, C**H**OH), 6.55 s (2H, 2′-H, 6′-H), 6.64 s (1H, 4′-H). ^{13}C NMR spectrum, δ_C, ppm: 21.4 (3′-CH_3, 5′-CH_3), 63.8 (CH_2), 69.2 (OCH_2), 70.4 (CH), 112.4 ($C^{2'}$, $C^{6'}$), 123.1 ($C^{4'}$), 139.4 ($C^{3'}$, $C^{5'}$), 158.5 ($C^{1'}$).

Mitsunobu intramolecular etherification of diols 1e (*general procedure*). A solution of 1.07 g (6.12 mmol) of diethyl azodicarboxylate in 10 mL of anhydrous THF was added dropwise over a period of 5 min to a solution of 1.00 g (5.10 mmol) of diol **1e** and 1.61 g (6.12 mmol) of triphenylphosphine in 10 mL of anhydrous THF with stirring at 4°C under argon. The mixture was then refluxed for 24 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (0.125–0.25 mm) using petroleum ether–methylene chloride–ethyl acetate (9:2:1 to 8:2:1) as eluent to isolate ~0.59 g (65%) of oily oxirane **6**; R_f 0.45 (petroleum ether–methylene chloride–ethyl acetate, 4:2:1).

(*R*)-2-[(3,4-Dimethylphenoxy)methyl]oxirane (*R*-6) was synthesized from diol (*R*)-**1e**. Yield 0.59 g (65%), $[\alpha]_D^{20}$ = –3.1° (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$ = +2.1° (*c* = 1.0, $CHCl_3$); $[\alpha]_D^{20}$ = –11.2° (*c* = 1.1, EtOH), $[\alpha]_{365}^{20}$ = –24.3° (*c* = 1.1, EtOH); 95.2% *ee* [Chiralcel OD, 25°C; hexane–propan-2-ol, 9:1; t_R, min: 7.8 (major), 10.0 (minor)]. ^1H NMR spectrum, δ, ppm: 2.25 s (3H, 4′-CH_3), 2.29 s (3H, 3′-CH_3), 2.77 d.d (1H, CH_2, *J* = 5.1, 2.7 Hz), 2.91 d.d (1H, CH_2, *J* = 5.1, 4.3 Hz), 3.35–3.39 m (1H, CH), 3.97 d.d (1H, OCH_2,

J = 11.1, 5.6 Hz), 4.21 d.d (1H, OCH_2, J = 11.1, 3.2 Hz), 6.72 d.d (1H, 6′-H, J = 8.3, 2.7 Hz), 6.80 d (1H, 2′-H, J = 2.6 Hz), 7.08 d (1H, 5′-H, J = 8.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.7 (4′-CH_3), 19.9 (3′-CH_3), 44.6 (CH_2), 50.2 (CH), 68.8 (OCH_2), 111.6 ($C^{6'}$), 116.3 ($C^{2'}$), 129.1 ($C^{4'}$), 130.3 ($C^{5'}$), 137.7 ($C^{3'}$), 156.7 ($C^{1'}$) (cf. [14]).

(*S*)-2-[(3,4-Dimethylphenoxy)methyl]oxirane (*S*-6) was synthesized from diol (*S*)-**1e**. Yield 0.50 g (55%); $[\alpha]_D^{20}$ = +2.1° (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$ = –2.7° (*c* = 1.0, $CHCl_3$); $[\alpha]_D^{20}$ = +10.4° (*c* = 1.0, EtOH), $[\alpha]_{365}^{20}$ = +23.1° (*c* = 1.0, EtOH); 95.9% *ee* [Chiralcel OD, 25°C; hexane–propan-2-ol, 9:1; t_R, min: 7.8 (minor), 10.0 (major)]. The NMR spectra of (*S*)-**6** were similar to those of (*R*)-**6**.

***rac*-2-[(3,4-Dimethylphenoxy)methyl]oxirane (*rac*-6)** was synthesized from diol *rac*-**1e**. Yield 0.54 g (60%).

Amino alcohols 2 and 3 (*general procedure*). A solution of 0.20 g (1.12 mmol) of oxirane **6**, 1.12 mmol of piperidine or morpholine, and a catalytic amount of pyridine in 10 mL of ethanol was refluxed for 4 h with stirring. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (0.125–0.25 mm) using methylene chloride–methanol (100:3) as eluent. Compounds **2** and **3** were isolated as oily materials in almost quantitative yield (≥97%). The free bases were converted to the corresponding hydrochlorides by passing gaseous hydrogen chloride through a solution of the base in acetone, followed by recrystallization of the precipitated salt from methanol–ethyl acetate.

(*R*)-1-(3,4-Dimethylphenoxy)-3-(piperidin-1-yl)-propan-2-ol (*R*-2) was synthesized from oxirane (*R*)-**6** and piperidine. Yield 0.27 g (92%), R_f 0.03 (CH_2Cl_2); $[\alpha]_D^{20}$ = +27.4° (*c* = 1.1, $CHCl_3$), $[\alpha]_{365}^{20}$ = +77.2° (*c* = 1.1, $CHCl_3$); $[\alpha]_D^{20}$ = –1.2° (*c* = 1.1, EtOH), $[\alpha]_{365}^{20}$ = –5.1° (*c* = 1.1, EtOH); 96% *ee* [Chiralcel OD, 22°C; hexane–propan-2-ol–diethylamine, 6:4:0.01; t_R, min: 5.5 (major), 7.0 (minor)]. ^{1}H NMR spectrum, δ, ppm: 1.47–1.51 m (2H, CH_2) and 1.59–1.66 m (4H, CH_2) (piperidine), 2.21 s (3H, 4′-CH_3), 2.25 s (3H, 3′-CH_3), 2.37–2.43 m (2H, NCH_2, piperidine), 2.48–2.55 m (2H, NCH_2), 2.60–2.65 m (2H, NCH_2, piperidine), 3.85 s (1H, OH), 3.93–4.00 m (2H, OCH_2), 4.07–4.13 m (1H, CH), 6.70 d.d (1H, 6′-H, J = 8.3, 2.6 Hz), 6.78 d (1H, 2′-H, J = 2.6 Hz), 7.04 d (1H, 5′-H, J = 8.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.7 (4′-CH_3), 19.9 (3′-CH_3), 24.2 and 26.0 (CH_2, piperidine), 54.7 (NCH_2, piperidine), 61.4 (NCH_2), 65.5 (CH), 70.6 (OCH_2), 111.4 ($C^{6'}$), 116.2 ($C^{2'}$), 128.6 ($C^{4'}$), 130.1 ($C^{5'}$), 137.4 ($C^{3'}$), 156.9 ($C^{1'}$).

(*R*)-1-(3,4-Dimethylphenoxy)-3-(piperidin-1-yl)-propan-2-ol hydrochloride [(*R*)-2·HCl]. mp 175–176°C; $[\alpha]_D^{20}$ = +40.8° (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$ = +129.3° (*c* = 1.0, $CHCl_3$), $[\alpha]_D^{20}$ = +26.0° (*c* = 1.0, EtOH), $[\alpha]_{365}^{20}$ = +78.2° (*c* = 1.0, EtOH); 99.7% *ee* [the HPLC conditions were the same as for (*R*)-**2**; t_R, min: 5.5 (major), 7.0 (minor)]. IR spectrum, ν, cm^{-1}: 3268 (OH), 2726, 2651, 2633, 2586, 2542 (NH^+). ^{1}H NMR spectrum, δ, ppm: 1.39–1.48 m (1H) and 1.84–1.87 m (3H) (CH_2, piperidine), 2.16 s (3H, 4′-CH_3), 2.19 s (3H, 3′-CH_3), 2.24–2.36 m (2H, CH_2, piperidine), 2.72–2.88 m and 3.14–3.27 m (2H each, N^+CH_2, piperidine), 3.67 d (2H, N^+CH_2, J = 9.6 Hz), 3.85 d.d (1H, OCH_2, J = 9.5, 7.9 Hz), 4.09 d.d (1H, OCH_2, J = 9.5, 4.6 Hz), 4.54–4.63 m (1H, CH), 5.44 br.s (1H, OH), 6.59 d.d (1H, 6′-H, J = 8.2, 2.5 Hz), 6.67 s (1H, 2′-H), 6.99 d.d (1H, 5′-H, J = 8.2, 5.0 Hz), 11.25 br.s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 18.9 (4′-CH_3), 20.1 (3′-CH_3); 22.0, 22.76, 22.83 (CH_2, piperidine); 54.2 (NCH_2); 56.0, 56.2, 62.6, 62.9 (NCH_2, piperidine); 64.4 (CH), 69.2 (OCH_2), 111.6 ($C^{6'}$), 116.1 ($C^{2'}$), 129.6 ($C^{4'}$), 130.5 ($C^{5'}$), 138.0 ($C^{3'}$), 156.2 ($C^{1'}$). Found, %: C 64.29; H 8.94; N 4.45. $C_{16}H_{26}ClNO_2$. Calculated, %: C 64.09; H 8.74; N 4.67.

(*S*)-1-(3,4-Dimethylphenoxy)-3-(piperidin-1-yl)-propan-2-ol (*S*-2) was synthesized from oxirane (*S*)-**6** and piperidine. Yield 0.29 g (98%), $[\alpha]_D^{20}$ = –26.9° (*c* = 1.0, $CHCl_3$), 95% *ee* [t_R, min: 5.5 (minor), 7.0 (major)].

(*S*)-1-(3,4-Dimethylphenoxy)-3-(piperidin-1-yl)-propan-2-ol hydrochloride [(*S*)-2·HCl]. mp 175.5–177.5°C; $[\alpha]_D^{20}$ = –40.6° (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$ = –128.2° (*c* = 1.0, $CHCl_3$), 99.4% *ee* [t_R, min: 5.5 (minor), 7.0 (major)]. The NMR spectra were similar to those of (*R*)-**2**·HCl.

***rac*-1-(3,4-Dimethylphenoxy)-3-(piperidin-1-yl)-propan-2-ol (*rac*-2)** was synthesized from oxirane *rac*-**6** and piperidine. Yield 0.29 g (98%), mp 75–77°C (from aqueous EtOH) [29]).

***rac*-1-(3,4-Dimethylphenoxy)-3-(piperidin-1-yl)-propan-2-ol hydrochloride (*rac*-2·HCl).** mp 171–174°C (171–173°C [29]). IR spectrum, ν, cm^{-1}: 3234 (OH), 2730, 2681, 2543 (NH^+).

(*R*)-1-(3,4-Dimethylphenoxy)-3-(morpholin-4-yl)propan-2-ol [(*R*)-3] was synthesized from oxirane (*R*)-**6** and morpholine. Yield 0.28 g (95%), R_f 0.03 (CH_2Cl_2); $[\alpha]_D^{20}$ = +19.5° (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$ = +56.1° (*c* = 1.0, $CHCl_3$); published data [14]: $[\alpha]_D^{20}$ =

–13.10° (*c* = 0.6, $CHCl_3$); 96% *ee* [the HPLC conditions were the same as for (*R*)-**2**; t_R, min: 7.2 (major), 17.3 (minor)]. ^{1}H NMR spectrum, δ, ppm: 2.21 s (3H, 4′-CH_3), 2.25 s (3H, 3′-CH_3), 2.47–2.52 m (2H, NC**H**$_2$$CH_2O$), 2.54–2.61 m (2H, NCH_2), 2.65–2.70 m (2H, NC**H**$_2$$CH_2O$), 3.21 s (1H, OH), 3.73–3.76 m (4H, NCH_2C**H**$_2$O), 3.97 d (2H, OCH_2, *J* = 5.0 Hz), 4.08–4.14 m (1H, CH), 6.68 d.d (1H, 6′-H, *J* = 8.3, 2.7 Hz), 6.75 d (1H, 2′-H, *J* = 2.5 Hz), 7.04 d (1H, 5′-H, *J* = 8.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.9 (4′-CH_3), 20.1 (3′-CH_3), 54.0 (CH_2, N**C**H_2CH_2O), 61.3 (NCH_2), 65.7 (CH), 67.1 (NCH_2**C**H_2O), 70.4 (OCH_2), 111.6 (C$^{6'}$), 116.4 (C$^{2'}$), 129.1 (C$^{4'}$), 130.4 (C$^{5'}$), 137.8 (C$^{3'}$), 157.0 (C$^{1'}$) (cf. [14]).

(*R*)-1-(3,4-Dimethylphenoxy)-3-(morpholin-4-yl)propan-2-ol hydrochloride [(*R*)-3·HCl]. mp 169–171°C; $[\alpha]_D^{20}$ = +35.2°C (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$ = +112.2° (*c* = 1.0, $CHCl_3$); $[\alpha]_D^{20}$ = +22.9° (*c* = 1.0, EtOH), $[\alpha]_{365}^{20}$ = +68.1° (*c* = 1.0, EtOH); 99.9% *ee* [the HPLC conditions were the same as for (*R*)-**2**; t_R, min: 7.3 (major), 16.7 (minor)]. IR spectrum, ν, cm^{-1}: 3259 (OH), 2731, 2644, 2596, 2469 (NH^+). ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, 4′-CH_3), 2.21 s (3H, 3′-CH_3), 2.97–3.05 m (2H, N^+C**H**$_2$$CH_2O$, *J* = 14.1 Hz), 3.29 d (2H, N^+CH_2, *J* = 6.2 Hz), 3.71 d.d (2H, N^+C**H**$_2$$CH_2O$, *J* = 22.3, 12.0 Hz), 3.89 d.d (1H, OCH_2, *J* = 9.6, 7.3 Hz), 3.93–3.99 m (2H, NCH_2C**H**$_2$O), 4.09 d.d (1H, OCH_2, *J* = 9.6, 4.6 Hz), 4.28 t (2H, NCH_2C**H**$_2$O, *J* = 12.8 Hz), 4.65–4.71 m (1H, CH), 5.23 br.s (1H, OH), 6.60 d.d (1H, 6′-H, *J* = 8.3, 2.7 Hz), 6.68 d (1H, 2′-H, *J* = 2.5 Hz), 7.00 d (1H, 5′-H, *J* = 8.3 Hz), 12.02 br.s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 18.9 (4′-CH_3), 20.1 (3′-CH_3), 52.9 and 54.5 (N**C**H_2CH_2O), 62.6 (NCH_2), 63.8 and 63.9 (NCH_2**C**H_2O), 64.2 (CH), 69.3 (OCH_2), 111.6 (C$^{6'}$), 116.2 (C$^{2'}$), 129.7 (C$^{4'}$), 130.6 (C$^{5'}$), 138.1 (C$^{3'}$), 156.2 (C$^{1'}$). Found, %: C 60.08; H 8.23; N 4.58. $C_{15}H_{24}ClNO_3$. Calculated, %: C 59.69; H 8.02; N 4.64.

(*S*)-1-(3,4-Dimethylphenoxy)-3-(morpholin-4-yl)-propan-2-ol [(*S*)-3]. Yield 0.29 g (97%), $[\alpha]_D^{20}$ = –19.7° (*c* = 1.05, $CHCl_3$), $[\alpha]_{365}^{20}$ = –56.6° (*c* = 1.05, $CHCl_3$); published data [14]: $[\alpha]_D^{20}$ = –13.10° (*c* = 0.5, $CHCl_3$); 96% *ee* [the HPLC conditions were the same as for (*R*)-**2**; t_R, min: 7.2 (minor), 17.3 (major)].

(*S*)-1-(3,4-Dimethylphenoxy)-3-(morpholin-4-yl)-propan-2-ol hydrochloride [(*S*)-3·HCl]. mp 168–171°C; $[\alpha]_D^{20}$ = –35.0° (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$ = –111.5° (*c* = 1.0, $CHCl_3$); $[\alpha]_D^{20}$ = –23.3° (*c* = 1.0, EtOH), $[\alpha]_{365}^{20}$ = –70.4° (*c* = 1.0, EtOH); 99% *ee* [the HPLC conditions were the same as for (*R*)-**2**; t_R, min: 7.3 (minor), 16.7 (major)]. The spectral parameters were the same as those of (*R*)-**3**·HCl.

***rac*-1-(3,4-Dimethylphenoxy)-3-(morpholin-4-yl)propan-2-ol (*rac*-3)** was synthesized from oxirane *rac*-**6** and morpholine. Yield 0.29 g (97%).

***rac*-1-(3,4-Dimethylphenoxy)-3-(morpholin-4-yl)propan-2-ol hydrochloride (*rac*-3·HCl).** mp 148–151°C. IR spectrum, ν, cm^{-1}: 3229 (OH), 2735, 2695, 2596, 2465 (NH^+). The spectral parameters were similar to those of (*R*)-**3**·HCl.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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