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Effective synthesis of non-racemic prenalterol based on spontaneous resolution of 3-(4-hydroxyphenoxy)propane-1,2-diol

Zemfira A. Bredikhina, Alexey V. Kurenkov and Alexander A. Bredikhin

Contents

1. General remarks

NMR spectra were recorded on a Bruker Avance-400 (400.05 MHz for ^{1}H and 100.59 MHz for ^{13}C) or a Bruker Avance-600 (600.1 MHz for 1H and 150.9 MHz for ^{13}C) instruments with the signals of the solvent as the internal standard. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (concentration *c* is given as g per 100 ml). Melting points for general purposes were determined using a Boëtius apparatus and were uncorrected. Thin-layer chromatography was performed on Silufol UV-254 plates; TLC plates were visualized under UV light or by treatment with iodine vapor. HPLC analyses were performed on a Shimadzu LC-20AD system controller, UV monitor 275 nm were used as detectors. The columns used, from Daicel Inc., were Chiralcel OD (0.46 x 25 cm) and Chiralcel OD-RH (0.46 x 15 cm). For the determination of enantiomeric compositions, the columns were calibrated against the corresponding racemic compounds.

The NMR spectra were registered on the equipment of Assigned Spectral-Analytical Center of FRC Kazan Scientific Center of RAS.

2. Synthesis and characteristics of compounds 1-4

Racemic 3-chloropropane-1,2-diol (99%), 4-methoxyphenol (99%) and isopropylamine (99%) were purchased from Acros Organics. (*R*)-3-Chloropropane-1,2-diol (97%, 98% *ee*), (*S*)-3-chloropropane-1,2-diol (98%, 98% *ee*), diethyl azodicarboxylate (97%) and triphenylphosphine (99+%) were purchased from Alfa Aesar.

3-(4-Methoxyphenoxy)propane-1,2-diol 3. *Racemic 3-(4-methoxyphenoxy)propane-1,2-diol rac-**3**, (S)-**3** and (R)-**3*** were prepared from racemic or scalemic 3-chloropropane-1,2-diols and 4-methoxyphenol by analogy with published procedure [S1]; *rac*-**3**: mp 77-79 °C; (*R*)-**3**: mp 76-78 °C; $[\alpha]_D^{20}$ = -7.6 (*c* 1, MeOH); 97.0% *ee* [chiral HPLC analysis; Chiralcel OD column; 25 °C; eluent: hexane/2-propanol (7:3), 1.0 ml/min; t_R = 8.2 min]; (*S*)-**3**: mp 77.5-78.5ºC; $[\alpha]_D^{20}$ = +7.8 (*c* 1.0, MeOH), 97.2% *ee* [chiral HPLC analysis, t_R = 12.0 min].

rac-3-(4-Hydroxyphenoxy)propane-1,2-diol 2. *Racemic diol rac*-**2** was prepared by analogy with published procedure [S2]. After introducing of HBr (45% aq., 116 ml), drop by drop, to a vessel containing *rac*-3-(4-methoxyphenoxy)propane-1,2-diol *rac*-**3** (19.0 g, 96.0 mmol), the vessel was shaken for 54 hours at 50°C. The reaction mixture was gradually quenched with NH_4OH (20% aq., 93 ml) and then extracted with CH_2Cl_2 (4×75 ml). After evaporation of the CH_2Cl_2 extract, unreacted *rac*-3-(4-methoxyphenoxy)propane-1,2-diol *rac*-**3** (7.43 g, 39%) was recovered and can be reused without additional purification. The aqueous phase (pH ca. 2-3) was evaporated almost to dryness and taken up into hot ethyl acetate. After removal of the organic solvent and additional recrystallization of the crude precipitate, a crystalline solid corresponding to the pure expected product was obtained (6.61 g, 61%, counting on the reacted *rac*-**3**). Mp 127-129 °C (EtOAc) (lit. mp 132 °C (EtOAc) [S2]; lit. mp 128.5-130 °C (EtOH) [S3]); R_f = 0.32 (EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ: 3.63 (dd, *J* = 11.3, 5.3 Hz, 1H, C*H*$_2$OH), 3.69 (dd, *J* = 11.3, 4.7 Hz, 1H, C*H*$_2$OH), 3.87-3.99 (m, 3H, C*H*OH, OCH_2), 6.69-6.73 (m, *J* = 9.1 Hz; 2H, $C^{2,6}_{Ar}H$), 6.78-6.82 (m, *J* = 9.1 Hz, 2H, $C^{3,5}_{Ar}H$). ^{1}H NMR (400 MHz, $(CD_3)_2C{=}O$) δ: 3.60-3.71 (m, 2H, CH_2OH), 3.75 (t, *J* = 5.8, 5.8 Hz, 1H, CH_2O*H*), 3.88-4.00 (m, 3H, C*H*OH, OCH_2), 4.03 (d, *J* = 4.5 Hz, 1H, CHO*H*), 6.74-6.80 (m, 4H, $C^{2,3,5,6}_{Ar}H$), 7.89 (s, 1H, OH). ^{13}C NMR (100.5 MHz, CD_3OD) δ: 64.3 (CH_2), 71.2 (OCH_2), 71.9 (CH), 116.75 ($C^{2,6}_{Ar}$), 116.80 ($C^{3,5}_{Ar}$), 152.5 (C^4_{Ar}-ipso), 153.7 (C^1_{Ar}-ipso).

(S)-3-(4-Hydroxyphenoxy)propane-1,2-diol, (S)-2. Diol (*S*)-**2** used hereinafter as seed crystals was obtained from (*S*)-3-(4-methoxyphenoxy)propane-1,2-diol (*S*)-**3** (0.41 g, 2.1 mmol) as described for racemic diol *rac*-**2**. Yield 0.11 g, 69%; mp 150-151 °C (EtOAc); $[\alpha]_D^{20}$ = +8.0 (*c* 1, MeOH), {lit.

149.5-151 ºC (MeOH/$CHCl_3$); $[\alpha]_D^{20}$ = +8.01 (*c* 1.0, MeOH) [S4]}; 99% *ee* [chiral HPLC analysis, Chiralcel OD column at 25 °C; flow rate 1.0 ml min^{-1}; eluent: hexane/2-propanol/TFA (7:3:0.005); t_R = 9.0 min (minor), t_R = 11.6 min (major)]. NMR spectra were identical to those for *rac*-**2**.

(R)-3-(4-Hydroxyphenoxy)propane-1,2-diol, (R)-2. Diol (*R*)-**2** used as seed was obtained from diol (*R*)-**3** as described for diol (*S*)-**2**. Mp 149.5-151 °C (EtOAc); $[\alpha]_D^{20}$ = –8.2 (*c* 1.0, MeOH); $[\alpha]_{365}^{20}$ = –27.0 (*c* 1.0, MeOH); 99% *ee* [chiral HPLC analysis, Chiralcel OD column; column temperature 25 °C; flow rate 1.0 ml min^{-1}; eluent: hexane/2-propanol/TFA (7:3:0.005); t_R = 9.3 min (major), t_R = 12.8 min (minor)]. NMR spectra were identical to those for *rac*-**2**.

Resolution of racemic 3-(4-hydroxyphenoxy)propane-1,2-diol, rac-2 by preferential crystallization (resolution by entrainment). Racemic diol *rac*-**2** (3.00 g) was dissolved in water (50 ml) at 45 °C. The solution was cooled to 24 °C and then seeded with finely pulverized (*R*)-**2** (8 mg). The progress of the resolution was monitored by chiral HPLC (Figure S1).

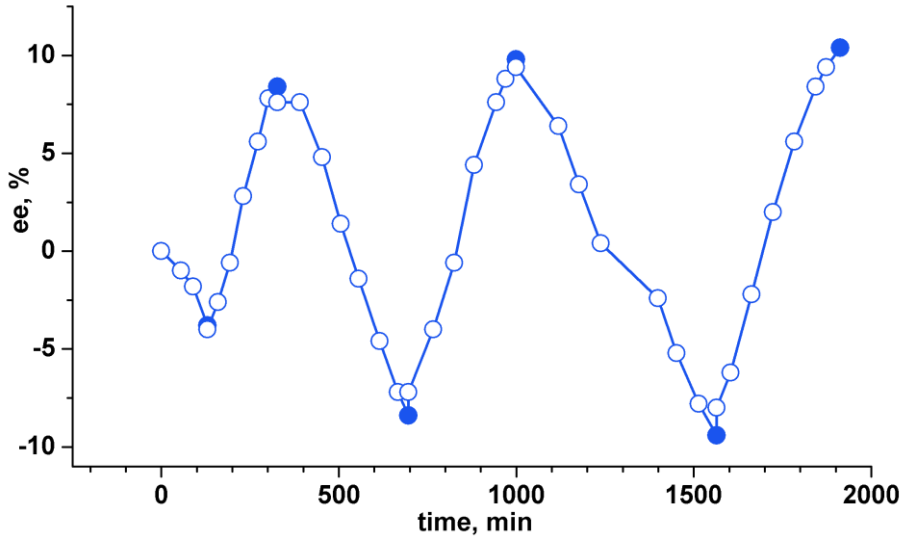

Figure S1. Mother liquor enantiomeric excess vs. time of preferential crystallization of diol **2** (3 cycles, 6 runs). Shaded circles stand for the *ee* values on reaching which the process was interrupted; time spent on technical operations associated with the interruption and resumption of stereoselective crystallization process is not reflected.

After stirring the mixture for 150 min at 24-23 °C, precipitated (*R*)-**2** was collected by filtration (0.310 g after drying; 39% *ee*) (see main text, Table 1, run 1). The next portion of *rac*-**2** (0.302 g) was then dissolved in the mother liquor at 45 °C; the resulting solution was cooled to 27 °C. After the addition of (*S*)-**2** (8 mg) as seed crystals and stirring the mixture for 215 min at 27 °C, (*S*)-**2** (0.519 g after drying; 57% *ee*) was collected by filtration (run 2). The next portion of *rac*-**2** (0.512 g) was then dissolved in the mother liquor at 45 °C; the resulting solution was cooled to 28 °C. After the addition of (*R*)-**2** as seed crystals and stirring the mixture for 390 min at 28-27 °C, (*R*)-**2** (0.516 g after drying; 74% *ee*) was collected by filtration (run 3). Further resolution was carried

out at 27-26 °C by adding specified amounts of *rac*-**2** to the filtrate in a manner similar to that described above (see the main text, Table 1). Further improvement in enantiomeric purity of collected diols can be achieved by recrystallization from water and ethyl acetate. For example: a portion of (*R*)-**2** (1.345 g, 67% *ee*) was crystallized from water (50 ml) and then from EtOAc (50 ml); to afford pure (*R*)-**2** {0.612 g (45%); $[\alpha]_D^{20}$ = –8.1 (*c* 1; MeOH), 98% *ee*}. Similarly, after recrystallization of combined portions of (*S*)-enantiomer (1.415 g, 74 % *ee*), pure (*S*)-**2** {0.684 g (51%); $[\alpha]_D^{20}$ = +8.0 (*c* 1; MeOH), 99% *ee*} was obtained.

4-(2,3-Epoxypropoxy)phenol 4 (general procedure). To a stirred solution of the corresponding diol **2** (0.5 g, 2.72 mmol) and triphenylphosphine (0.86 g, 3.26 mmol) in dry THF (15 ml), a solution of diethyl azodicarboxylate (0.57 g, 3.26 mmol) in THF (6 ml) was added dropwise for 5 min at 4°C. The resulting mixture was refluxed for 25 h under argon. The solvent was removed in vacuum, and the residue was purified by column chromatography (silica gel 0.125-0.25 mm, eluent: light petroleum/CH_2Cl_2/EtOAc = 7:2:1-6:2:1) to afford epoxide **4** as a colorless gradually solidifying oil.

rac-4-(2,3-Epoxypropoxy)phenol, rac-4 was obtained from diol *rac*-**2**. Yield 0.33 g, 73%; mp 72-75 °C (lit. mp 69 °C[S5]); R_f = 0.50 (light petroleum/EtOAc = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.76 (dd, *J* = 4.9, 2.8 Hz, 1H, C*H*$_2$O), 2.90 (apparent t, *J* = 4.9, 4.3 Hz, 1H, C*H*$_2$O), 3.33-3.37 (m, 1H, C*H*OH), 3.89 (dd, *J* = 11.1, 5.6 Hz; 1H, OC*H*$_2$), 4.16 (dd, *J* = 11.1, 3.0 Hz, 1H, OC*H*$_2$), 5.46 (s, 1H, OH), 6.72-6.80 (m, 4H, $C^{2,3,5,6}{}_{Ar}H$). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ:44.8 (CH_2), 50.5 (CH), 69.5 (OCH_2), 116.0 ($C^{2,6}{}_{Ar}$), 116.1 ($C^{3,5}{}_{Ar}$), 150.2 ($C^{1}{}_{Ar}$-ipso), 152.5 ($C^{4}{}_{Ar}$-ipso).

(S)-4-(2,3-Epoxypropoxy)phenol, (S)-4 was obtained from diol (*S*)-**2**. Yield 0.44 g, 97%; mp 81-83.5 °C (hexane/EtOAc); $[\alpha]_D^{20}$ = +12.8 (*c* 1.0, MeOH), $[\alpha]_{365}^{20}$ = +32.6 (*c* 1.0, MeOH), 93% *ee* [chiral HPLC analysis, Chiralcel OD column; column temperature 25 °C; flow rate 1.0 ml min^{-1}; eluent: hexane/2-propanol (7:3); t_R = 10.2 min (minor), t_R = 13.8 min (major)]. NMR spectra were identical to those for *rac*-**4**.

(R)-4-(2,3-Epoxypropoxy)phenol, (R)-4 was obtained from diol (*R*)-**2**. Yield 0.43 g, 95 %; mp 81-84 °C (hexane/EtOAc); $[\alpha]_D^{20}$ = –13.5 (*c* 1.0, MeOH), $[\alpha]_{365}^{20}$ = –33.9 (*c* 1.0, MeOH) 92% *ee* [chiral HPLC analysis, Chiralcel OD column; column temperature 25 ºC; flow rate 1.0 ml min^{-1}; eluent: hexane/2-propanol (7:3); t_R = 8.8 min (major), t_R = 11.9 min (minor)]. NMR spectra were identical to those for *rac*-**4**.

1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol (Prenalterol) 1 (general procedure). To a stirred solution of the corresponding 4-(2,3-epoxypropoxy)phenol **4** (0.15 g, 0.90 mmol) in EtOH (1 ml), isopropylamine (1.0 ml, 24.6 mmol) and water (0.13 ml) were added in argon atmosphere. The resulting solution was heated at 45 °C for 17 h. The solvent was removed in vacuum, and the

residue was purified by column chromatography (silica gel, eluent: EtOAc/MeOH = 1:0–1:1-0:1) to afford prenalterol **1** as a solid.

rac-1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol, rac-Prenalterol, rac-1. Yield 0.18 g, 89%; mp 158-162 °C (EtOAc) (lit. mp 155-156 °C (MeCN) [S6]); R_f = 0.10 (MeOH); R_f = 0 (EtOAc). ^{1}H NMR (600 MHz, CD_3OD) δ: 1.10 (d, J = 6.3 Hz, 3H, CH_3), 1.11 (d, J = 6.3 Hz, 3H, CH_3), 2.66 (dd, J = 12.1, 8.6 Hz, 1H, CH_2NH), 2.83-2.88 (m, 2H, CH_2NH, CH(CH_3)$_2$), 3.87-3.88 (m, 2H, OCH_2), 4.00-4.05 (m, 1H, CHCH$_2$), 6.71-6.74 (m, 2H, $C^{2,6}{}_{Ar}$H), 6.78-6.80 (m, 2H, $C^{3,5}{}_{Ar}$H). ^{13}C NMR (150.9 MHz, CD_3OD) δ:21.1 (CH_3), 21.2 (CH_3), 48.6 (CH(CH_3)$_2$), 49.5 (CH_2NH), 68.5 (CHOH), 71.5 (OCH_2), 115.5 ($C^{2,6}{}_{Ar}$), 115.6 ($C^{3,5}{}_{Ar}$), 151.3 ($C^1{}_{Ar}$-ipso), 152.2 ($C^4{}_{Ar}$-ipso).

(S)-1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol, (S)-Prenalterol, (S)-1. Yield 0.18 g, 89%; mp 125-127 °C (ethyl acetate); $[\alpha]_D^{20}$ = –1.9 (*c* 1.0, MeOH); $[\alpha]_D^{20}$ = –21.0 (*c* 1.0, 0.1 *N* HCl), $[\alpha]_{365}^{20}$ = –55.8 (*c* 1.0, 0.1 *N* HCl); (lit. mp 127-128 ºC (ethyl acetate); $[\alpha]_D^{20}$ = –1 ± 1 (*c* 0.94, MeOH) [S7]; lit. $[\alpha]_D^{25}$ = –20.67 (*c* 1.0, 0.1N HCl) [S8]; lit. $[\alpha]_D^{25}$ = –22.1 (*c* 1.0%, 0.1 *N* HCl) [S4]); 98% *ee* [chiral HPLC analysis, Chiralcel OD-RH column; column temperature 25 °C; flow rate 0.5 ml min^{-1}; eluent: 0.05 *M* NH_4PF_6 aq./MeCN (9:1); t_R = 18.8 min (minor), t_R = 24.6 min (major)]. NMR spectra were identical to those for *rac*-**1**.

(R)-1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol, (R)-Prenalterol, (R)-1. Yield 0.19 g, 94%; mp 124-126 °C (EtOAc); $[\alpha]_D^{20}$ = +2.4 (*c* 1.0, MeOH), $[\alpha]_D^{20}$ = +18.4 (*c* 1.0, 0.1 *N* HCl), $[\alpha]_{365}^{20}$ = +52.2 (*c* 1.0, 0.1 *N* HCl); (lit. mp 126-127 ºC (acetone); $[\alpha]_D^{25}$ = +20.85 (*c* 1.0, 0.1N HCl) [S8]; lit. $[\alpha]_D^{20}$ = +0.9±0.5 (*c* 1.0, MeOH) [S9]); 95% *ee* [chiral HPLC analysis, Chiralcel OD-RH column; column temperature 22 °C; flow rate 0.5 ml min^{-1}; eluent: 0.05M NH_4PF_6 aq./MeCN (9:1); t_R = 22.2 min (major), t_R = 30.5 min (minor)]. NMR spectra were identical to those for *rac*-**1**.

References

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3. Copies of NMR spectra for compounds 2, 4, 1

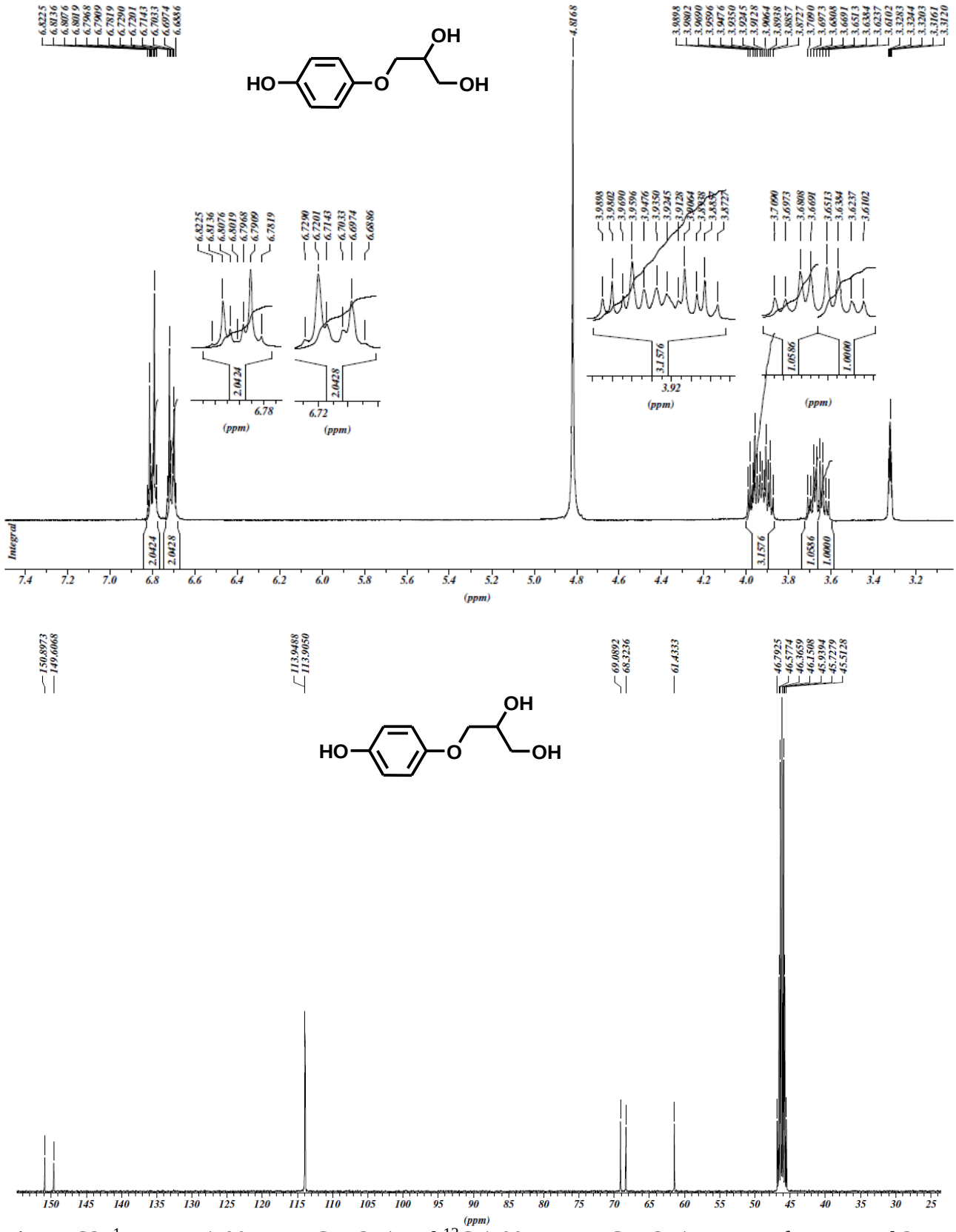


Figure S2. ^{1}H NMR (400 MHz, CD_3OD) and ^{13}C (100.5 MHz, CD_3OD) spectra of compound **2**.

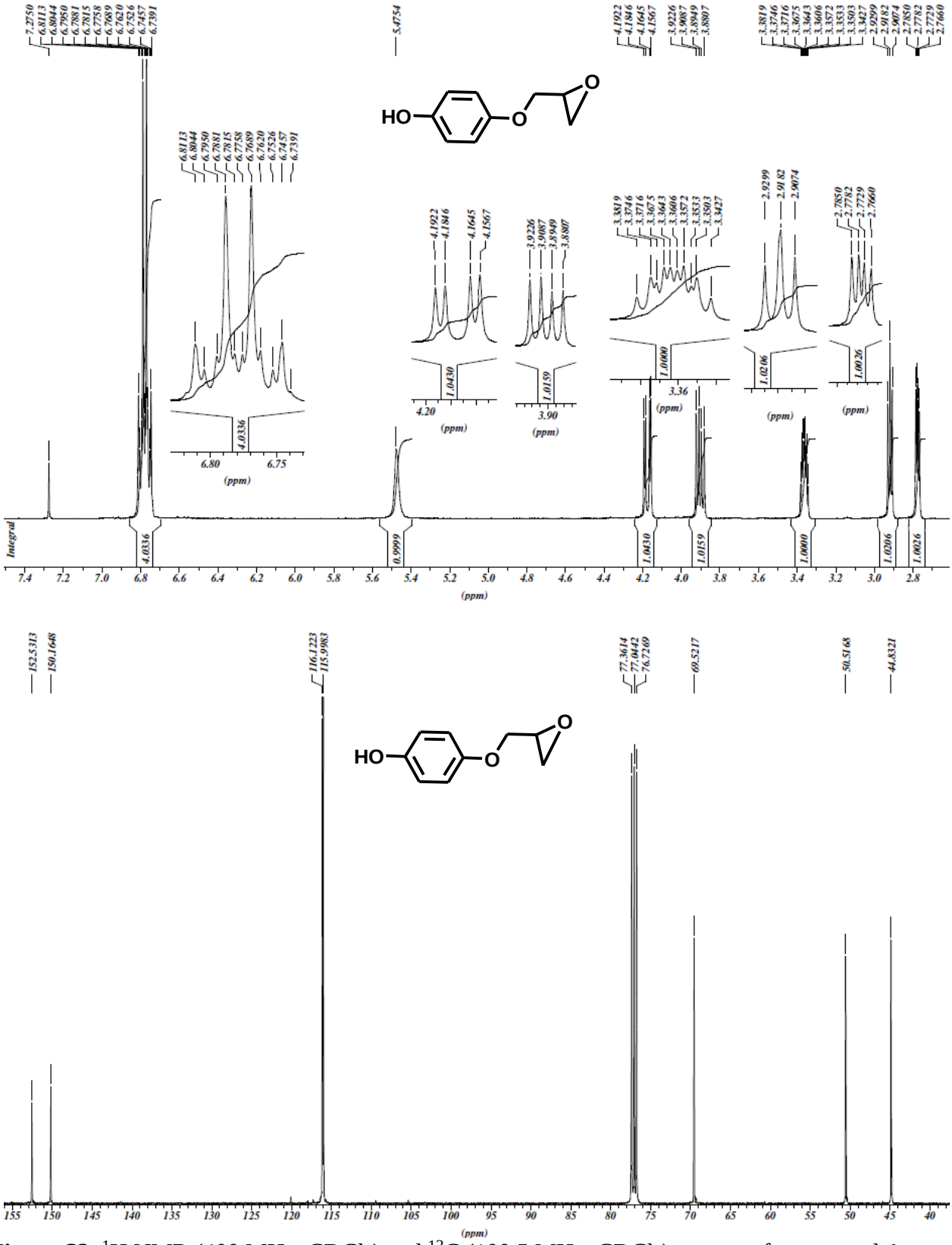


Figure S3. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C (100.5 MHz, $CDCl_3$) spectra of compound **4**.

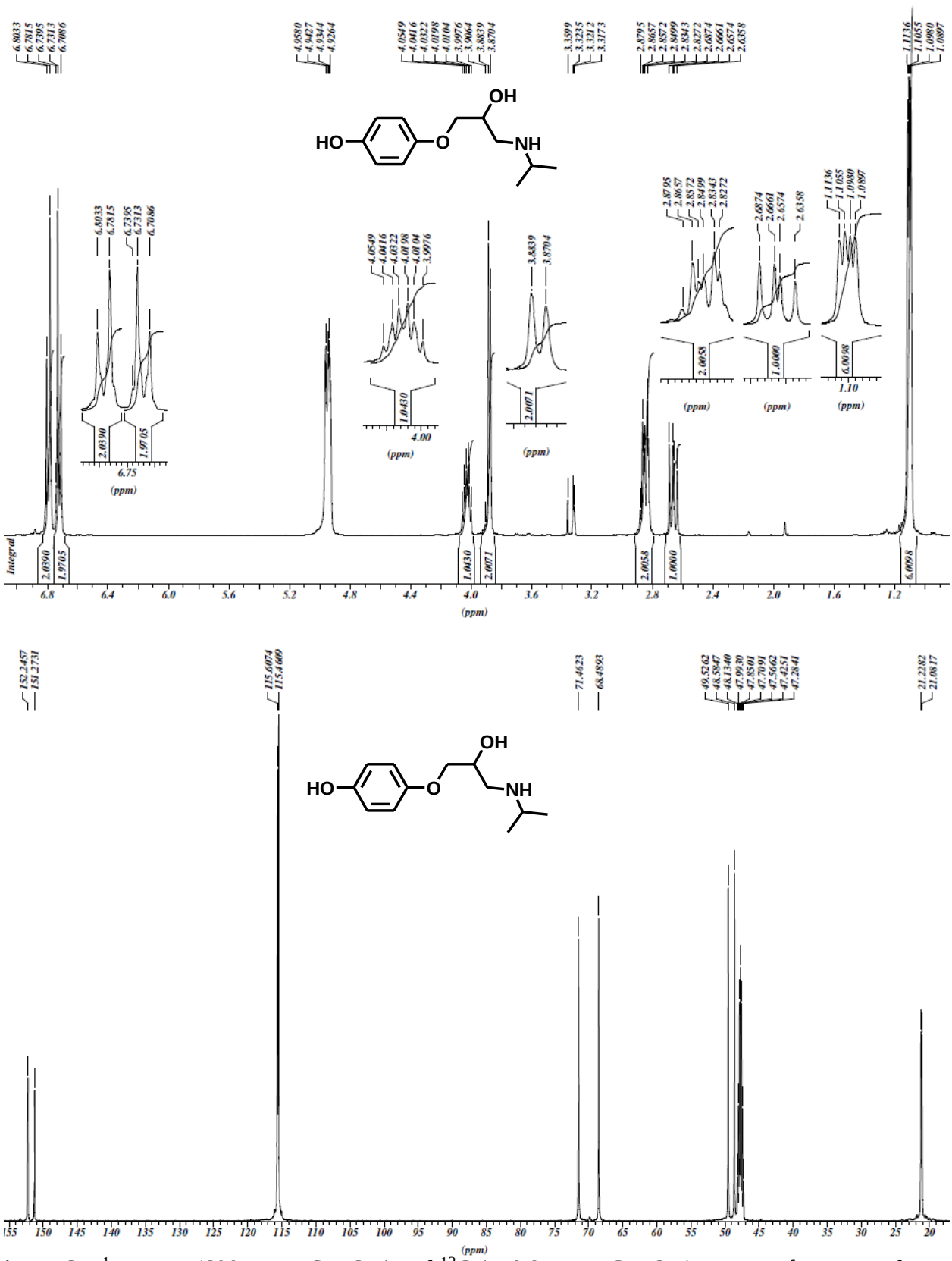
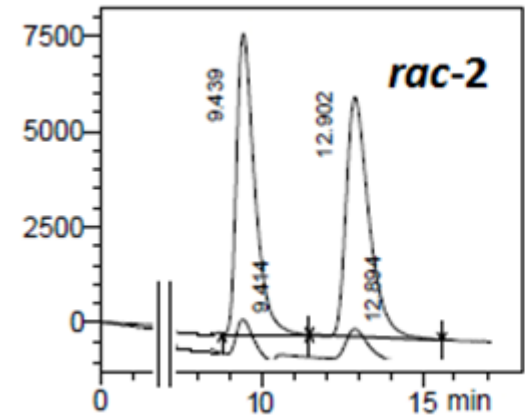


Figure S4. ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C (150.9 MHz, CD_3OD) spectra of compound **1**.

4. Copies of HPLC tracks for compounds 2, 4, 1



Detector A Ch2 275nm

Peak#	Ret. Time	Area	Area %
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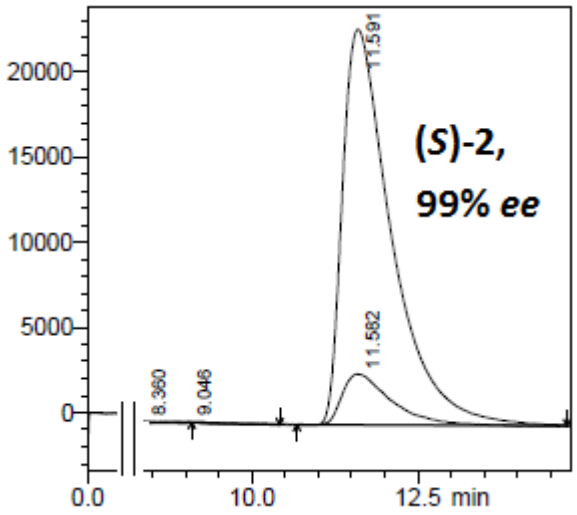
2	12.902	308227	49.879
Total		617946	100.000



Detector A Ch2 275nm

Peak#	Ret. Time	Area	Area %
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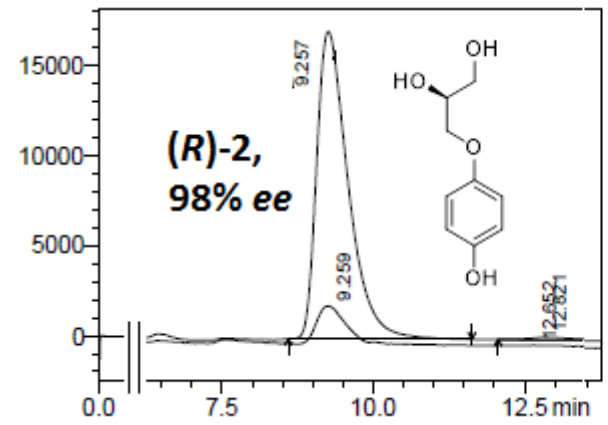
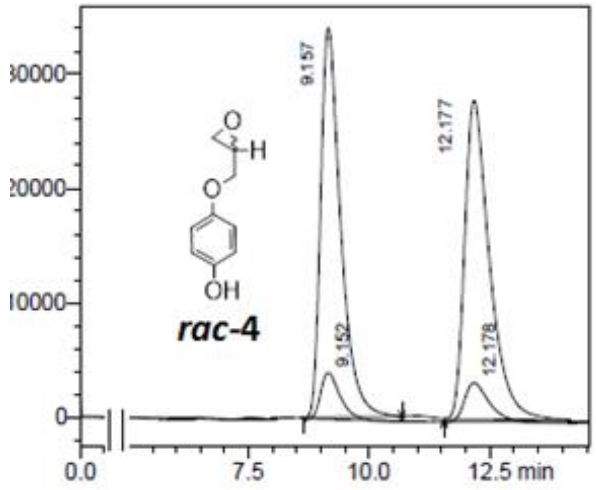
Total		1205083	100.000



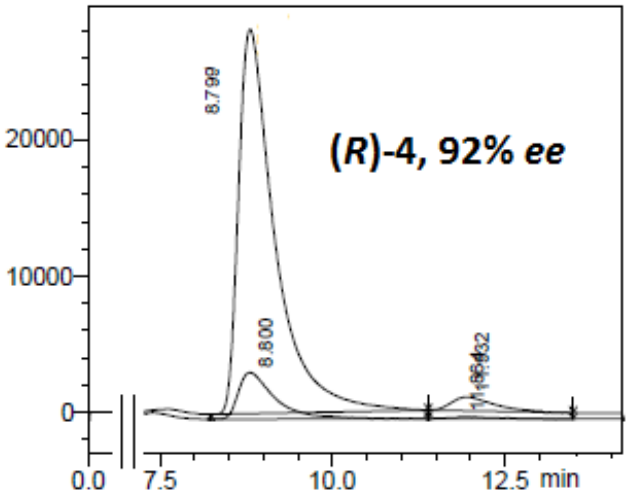
Detector A Ch2 275nm

Peak#	Ret. Time	Area	Area %
1	9.257	616755	98.860
2	12.821	7112	1.140
Total		623867	100.000

Figure S5. Fragments of experimental chromatograms for different samples of 3-(4-hydroxyphenoxy)propane-1,2-diol, compound **2**. The conditions of the chromatographic experiments are given in the text of part 2 of the ESM (see above).

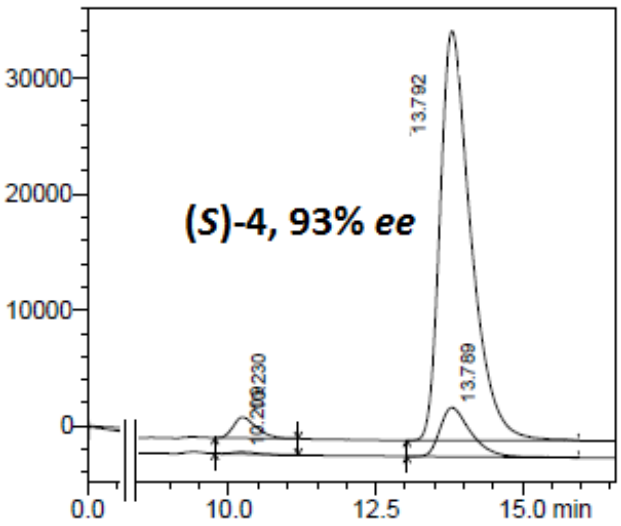


Peak#	Ret. Time	Area	Area %
1	9.157	981429	49.450
2	12.177	1003262	50.550
Total		1984690	100.000



Detector A Ch2 275nm

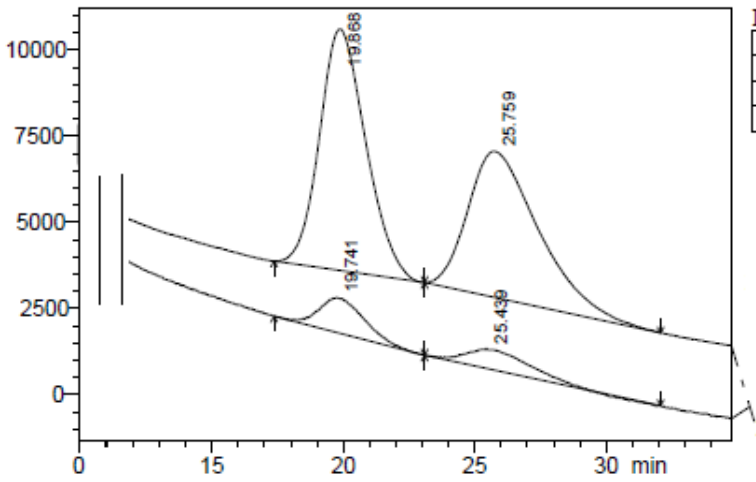
Peak#	Ret. Time	Area	Area %
1	8.799	1046376	96.086
2	11.932	42618	3.914
Total		1088993	100.000



Detector A Ch2 275nm

Peak#	Ret. Time	Area	Area %
1	10.230	49321	3.687
2	13.792	1288331	96.313
Total		1337652	100.000

Figure S6. Fragments of experimental chromatograms for different samples of 4-(2,3-epoxypropoxy)phenol, compound **4**. The conditions of the chromatographic experiments are given in the text of part 2 of the ESM (see above).



Detector A Ch2 275nm

Peak#	Ret. Time	Area	Area %
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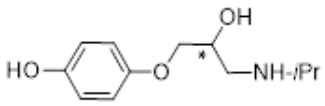
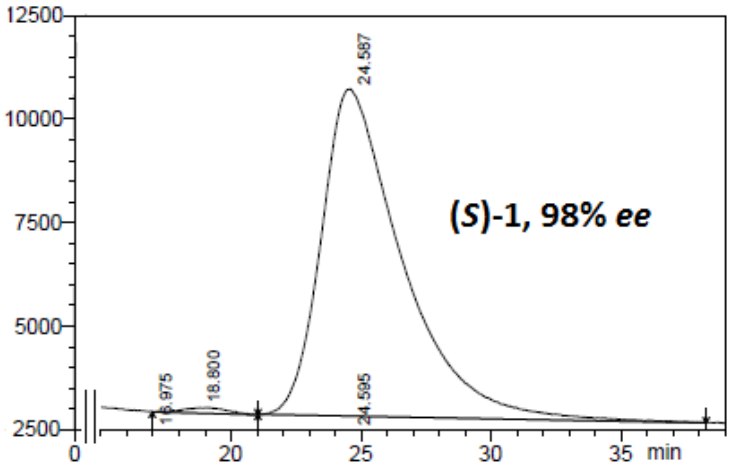
Total		1657747	100.000

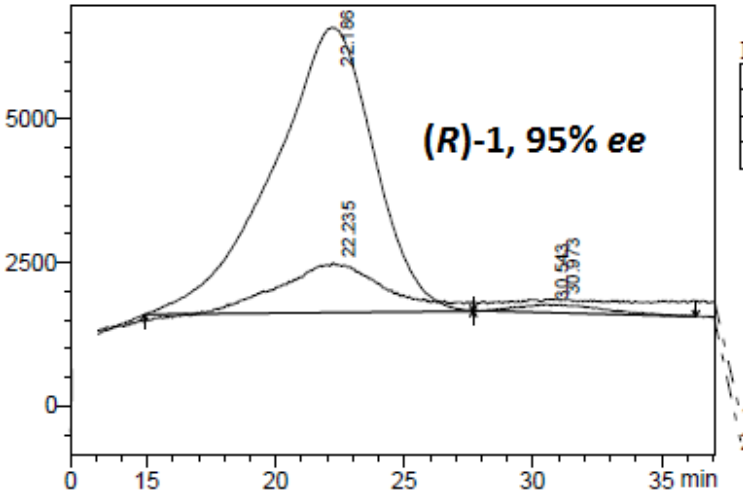


***rac*-1**



Detector A Ch2 275nm

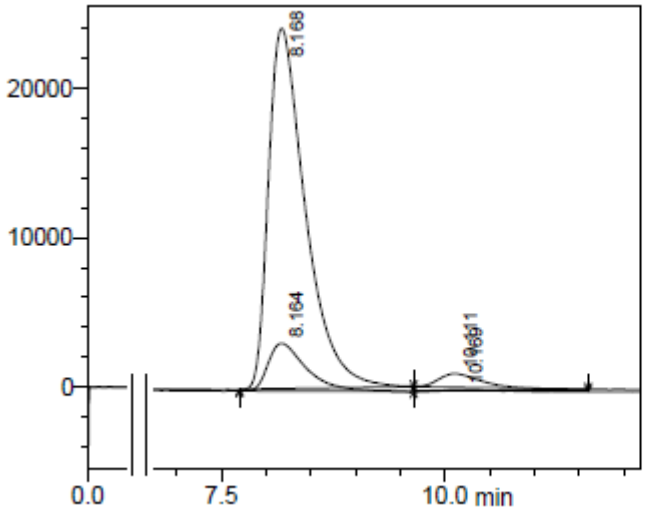
Peak#	Ret. Time	Area	Area %
1	18.800	16060	0.930
2	24.587	1710542	99.070
Total		1726602	100.000



Detector A Ch2 275nm

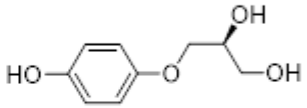
Peak#	Ret. Time	Area	Area %
1	22.186	1359022	97.566
2	30.543	33910	2.434
Total		1392931	100.000

Figure S7. Fragments of experimental chromatograms for different samples of 1-(4-hydroxyphenoxy)-3-isopropylaminopropan-2-ol (Prenalterol), compound **1**. The conditions of the chromatographic experiments are given in the text of part 2 of the ESM (see above).



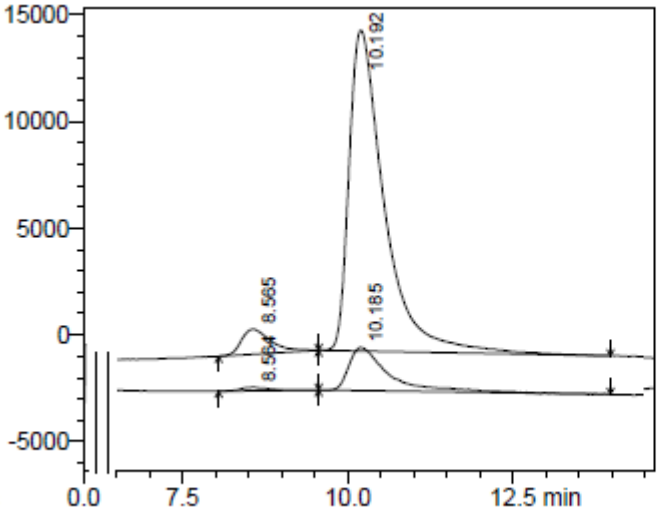
Detector A Ch2 275nm

Peak#	Ret. Time	Area	Area %
1	8.168	694081	96.028
2	10.111	28708	3.972
Total		722789	100.000



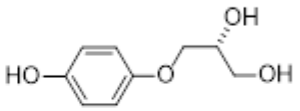
(*R*)-2, 92% *ee*

1 Det.A Ch1/254nm
2 Det.A Ch2/275nm



Detector A Ch2 275nm

Peak#	Ret. Time	Area	Area %
1	8.565	36642	6.127
2	10.192	561382	93.873
Total		598024	100.000



(*S*)-2, 88% *ee*

1 Det.A Ch1/254nm
2 Det.A Ch2/275nm

Figure S8. Fragments of experimental chromatograms for some samples of 3-(4-hydroxyphenoxy)propane-1,2-diol, obtained during resolution by entrainment process. The temperature of the chromatographic experiments is 40 °C.