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Lipase resolution of new (±)-3-aryloxy-1-halogenopropan-2-ols: Versatile building blocks for β-adrenergic receptor antagonists

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ABSTRACT

Using two commercial immobilized lipases Lipozyme® TL and Novozym® 435 effective kinetic resolution of several novel 3-aryloxy-1-halogenopropan-2-ols was achieved by acyl transfer reaction in organic solvents, yielding both enantiomers with 89–99% ee. In preparative resolutions carried out in *tert*-butyl methyl ether at 25 °C with vinyl acetate as acyl donor enantioselectivity ratio *E* was from 64 to 99. The resolved enantiomers were successfully used as chiral building blocks in the synthesis of new 1-alkylamino-3-aryloxypropan-2-ols, by nucleophilic halogen substitution with isopropylamine and *tert*-butylamine. The obtained products will be evaluated in vitro as potential new β-adrenergic receptors antagonists.

1. Introduction

Numerous β-adrenergic receptors antagonists [1,2] used in the treatment of hypertension, angina pectoris, other cardiac diseases and glaucoma are derivatives of 1-amino-3-aryloxypropan-2-ol. It is well known that for β-blockers of this structural class enantiomer (*S*) exhibits higher affinity for β-adrenergic receptors than enantiomer (*R*) [3] e.g. (*S*)-propranolol which is 130 times more active than its (*R*)-enantiomer. This can be understood in terms of substituents arrangement at stereogenic carbon, because in the (*S*) configuration, the alignment of aryloxymethyl, hydroxyl and amino functions corresponds to the spatial arrangement of respective groups in adrenaline or noradrenaline which are β-adrenergic receptors agonists. In spite of that knowledge, many β-blockers are still manufactured and used in therapy as racemates, even if there is evidence that distomers of β-blockers may exhibit side-effects. For instance (*R*)-propranolol may cause thyroid dysfunction [4]. Distomers are also unnecessary ballast which may cause the same side-effects as eutomers without contributing to desirable therapeutic activity. Due to increased demand for more effective, safe medicines, and the recommendations of institutions responsible for registration of new drugs, the synthesis of single enantiomers of chiral intermediates has become important for pharmaceutical industry [5,6]. These compounds may be produced by employing chiral synthetic catalysts or biocatalysts. The number of enzyme-catalyzed industrial processes is rapidly growing over past decade [7]. The advantages of biocatalysis include energy saving (ambient reaction temperature), easy catalyst separation and reusing, or its biodegradability.

Kinetic resolution of racemic 3-aryloxy-1-halogenopropan-2-ols, precursors of known β-blockers, by using isolated enzymes or whole-cell catalysts was studied by Bevinakatti et al. [8–10], Schneider et al. [11–13] and others [14–19]. Depending on the enzyme used, reaction type and conditions or substrate structure, enantioselectivities from rather low to excellent (far above 100) have been reported. Resolutions were mostly based on lipase-catalyzed ester hydrolysis, alcoholysis and O-acylation of halogenoalcohol. Alternative approach to enantiomers of 3-aryloxy-1-halogenopropan-2-ols was based on enantioselective reduction of corresponding chloroketones by reductases. These and other biocatalytic methods reported to date for known β-blockers preparation were recently reviewed [20,21].

During last decade a significant decrease in prices of commercial enzyme preparations made their industrial application economically attractive. However still prediction of enzyme enantioselectivity for a new substrate is doubtful and requires experimental checking. We decided to investigate how substitution pattern of aromatic system and kind of halogen in aryloxyhalogenopropanols affects enzyme enantioselectivity. Therefore several racemic 3-aryloxy-1-halogenopropan-2-ols were synthesised and their resolution by enzyme-catalyzed acetylation was investigated with the aim of using enantiomers as chiral precursors for new aryloxypropanolamines with potential β-blocking activity. It is known

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that their cardioselectivity is partially conditioned by the structure of aromatic system [20].

2. Experimental

2.1. Materials

Chemicals and solvents of reagent grade purchased from Fluka or Sigma–Aldrich were used without additional purification. Preparation of (±)-2-aryloxymethyloxiranes **3** and (±)-3-aryloxy-1-halogenopropan-2-ols **1** has been already described [22]. (S)-Epichlorohydrin purchased from Aldrich was 97% ee. Immobilized lipases Novozym® 435 (*Candida antarctica B*), Lipozyme® RM (*Rhizomucor miehei*), Lipozyme® TL (*Thermomyces lanuginosus*) produced by Novozymes, lipase A (*Aspergillus niger*), AY (*Candida rugosa*) and acylase produced by Amano, lipase *Candida cylindracea*, *C. rugosa* and porcine pancreas from Sigma have been used in this study. Whole-cell preparations of *Mucor racemosus* and *Mucor circinelloides* were kindly donated by Prof. Tadeusz Antczak from Institute of Technical Biochemistry, Łódź University of Technology.

2.2. Analytical methods

TLC was performed on Kieselgel 60 plates (Merck) with phosphomolybdic acid or potassium permanganate solution used for spots visualization. GC analyses were recorded on Chrom 5 using packed OV-17 column (2.5 m); temp. 60–300 °C at 6 °C/min.

MS spectra were taken on Thermo Electron apparatus model DSQ II Single Quadrupole GC/MS.

HPLC analyses were performed on ASI 100 Dionex chromatograph using analytical Chiralcel OD column (250 mm × 4.60 mm) at oven temperature 25 °C, UV detection at 225 nm, and hexane/isopropanol mobile phase (0.1% ethanolamine additive for 1-alkylamino-3-aryloxypropan-2-ols).

Column chromatography was performed on silica gel 70–230 mesh (Merck) with hexane–ethyl acetate mixtures as eluent.

^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 200 (250 MHz for proton, 62.5 MHz for carbon) in $CDCl_3$ with TMS as internal standard.

IR spectra were taken as films or $CHCl_3$ solutions on Shimadzu IR 408 or Thermo Scientific Nicolet™ iS™10 FT–IR apparatus.

Optical rotations were measured at 20 °C in a 1 dm cell using Rudolph Research polarimeter Autopol IV at 589 nm wavelength.

2.3. General procedure for preparation of (±)-3-aryloxy-1-halogenoprop-2-yl acetates (±)-(2a–i)

To 3 mmol (±)-3-aryloxy-1-halogenpropan-2-ol (**1a**–**i**) in 5 mL methylene chloride, 4 mmol pyridine and 4 mmol acetic anhydride were added. The solution was left at room temperature until disappearance of the starting halogenoalcohol was indicated by TLC. The mixture was diluted with CH_2Cl_2 (30 mL) and successively washed with saturated $NaHSO_4$ (1 × 10 mL), saturated $NaHCO_3$ (1 × 10 mL), and water (1 × 10 mL). Organic layer was dried over anhydrous $MgSO_4$ and solvent was evaporated. The purity of crude product was checked by GC and HPLC and when found insufficient (**2h**, **2i**), analytical sample was purified by column chromatography.

2.3.1. (±)-1-Bromo-3-(2-methoxyphenoxy)prop-2-yl acetate (±)-2a

Yellow liquid; yield 85%; purity 94% (GC); ^{1}H NMR: δ 2.11 (s, 3H, OAc), 3.66 (dd, 1H, J = 10.9 Hz, J = 5.4 Hz, CH_2Br), 3.76 (dd, 1H, J = 10.9 Hz, J = 5.1 Hz, CH_2Br), 3.84 (s, 3H, CH_3OAr), 4.21 (d, 2H, J = 5.2 Hz, CH_2OAr), 5.32 (qui, J = 5.2 Hz, C*H*OAc), 6.85–7.01 (m, 4H, Ar*H*); IR ($CHCl_3$), cm^{-1}: 3050, 1750, 1515, 1210, 750.

2.3.2. (±)-1-Bromo-3-(4-ethyl-2-methoxyphenoxy)prop-2-yl acetate (±)-2b

Yellow liquid; yield 69%; purity 97% (GC); ^{1}H NMR: δ 1.22 (t, 3H, J = 7.6 Hz, CH_3CH$_2$), 2.11 (s, 3H, OAc), 2.60 (q, 2H, J = 7.6 Hz, CH$_3$CH_2), 3.66 (dd, 1H, J = 10.9 Hz, J = 5.4 Hz, CH_2Br), 3.76 (dd, 1H, J = 10.9 Hz, J = 5.0 Hz, CH_2Br), 3.84 (s, 3H, CH_3OAr), 4.18 (d, 2H, J = 5.2 Hz, **CH_2OAr), 5.31 (qui, 1H, J = 5.2 Hz, C*H*OAc), 6.71 (d, 1H, J = 8.5 Hz, Ar*H*), 6.73 (s, 1H, Ar*H*), 6.86 (d, 1H, J = 8.5 Hz, Ar*H*); IR ($CHCl_3$), cm^{-1}: 3050, 1750, 1515, 1210, 750.

2.3.3. (±)-1-Chloro-3-(4-ethyl-2-methoxyphenoxy)prop-2-yl acetate (±)-2c

Yellow liquid; yield 80%; purity 93% (GC); ^{1}H NMR: δ 1.22 (t, 3H, J = 7.6 Hz, CH_3CH$_2$), 2.11 (s, 3H, OAc), 2.60 (q, 2H, J = 7.6 Hz, CH$_3$CH_2), 3.81 (dd, 1H, J = 12.0 Hz, J = 5.6 Hz, CH_2Cl), 3.84 (s, 3H, CH_3OAr) 3.90 (dd, 1H, J = 11.7 Hz, J = 4.8 Hz, CH_2Cl), 4.18 (d, 2H, J = 5.3 Hz, CH_2OAr), 5.33 (qui, 1H, J = 5.2 Hz, C*H*OAc), 6.72 (d, 1H, J = 8.5 Hz, Ar*H*), 6.73 (s, 1H, Ar*H*), 6.86 (d, 1H, J = 8.5 Hz, Ar*H*); IR ($CHCl_3$), cm^{-1}: 3040, 1750, 1515, 1210, 1140, 750.

2.3.4. (±)-1-Bromo-3-(2-nitrophenoxy)prop-2-yl acetate (±)-2d

Yellow solid; yield 96%; purity 93% (GC); ^{1}H NMR: δ 2.14 (s, 3H, OAc), 3.68 (dd, 1H, J = 11.8 Hz, J = 5.1 Hz, CH_2Br), 3.77 (dd, 1H, J = 11.8 Hz, J = 5.8 Hz, CH_2Br), 4.13 (dd, 1H, J = 9.3 Hz, J = 4.3 Hz, CH_2OAr), 4.37 (dd, 1H, J = 9.3 Hz, J = 4.1 Hz, CH_2OAr), 5.33 (qui, 1H, J = 5.1 Hz, C*H*OAc), 7.06–7.12 (m, 2H, Ar*H*), 7.56 (ddd, 2H, J = 8.5 Hz, J = 7.5 Hz, J = 1.7 Hz, Ar*H*), 7.88 (dd, 1H, J = 8.3 Hz, J = 1.7 Hz, Ar*H*); IR ($CHCl_3$), cm^{-1}: 3050, 1750, 1610, 1360, 1230, 1040.

2.3.5. (±)-1-Chloro-3-(2-nitrophenoxy)prop-2-yl acetate (±)-2e

Yellow solid; yield 79%; purity 83% (GC); ^{1}H NMR: δ 2.14 (s, 3H, OAc), 3.84 (dd, 1H, J = 11.7 Hz, J = 5.1 Hz, CH_2Cl), 3.92 (dd, 1H, J = 11.7 Hz, J = 5.6 Hz, CH_2Cl), 4.33 (d, 2H, J = 4.9 Hz, CH_2OAr), 5.35 (qui, 1H, J = 5.0 Hz, C*H*OAc), 7.08 (ddd, 1H, J = 8.2 Hz, J = 5.5 Hz, J = 1.1 Hz, Ar*H*), 7.55 (ddd, 2H, J = 8.5 Hz, J = 5.4 Hz, J = 1.1 Hz, Ar*H*), 7.88 (dd, 1H, J = 8.3 Hz, J = 1.7 Hz, Ar*H*); IR ($CHCl_3$), cm^{-1}: 3050, 1750, 1615, 1530, 1360, 1230, 1050.

2.3.6. (±)-1-Bromo-3-(2-isopropyl-5-methylphenoxy)prop-2-yl acetate (±)-2f

Yellow liquid; yield 76%; purity 94% (GC); ^{1}H NMR: δ 1.20 (d, 6H, J = 7.0 Hz, (CH_3)$_2$CH), 2.12 (s, 3H, OAc), 2.32 (s, 3H, CH_3Ar), 3.22 (sp, 1H, J = 6.9 Hz, (CH$_3$)$_2$C*H*), 3.80 (dd, 1H, J = 11.6 Hz, J = 5.4 Hz, CH_2Br), 3.87 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz, CH_2Br), 4.14 (dd, 1H, J = 10.1 Hz, J = 5.1 Hz, CH_2OAr), 4.19 (dd, 1H, J = 9.8 Hz, J = 4.4 Hz, CH_2OAr), 5.38 (qui, 1H, J = 5.1 Hz, C*H*OAc), 6.65 (s, 1H, Ar*H*), 6.78 (d, 1H, J = 7.7 Hz, Ar*H*), 7.10 (d, 1H, J = 7.7 Hz, Ar*H*): IR ($CHCl_3$), cm^{-1}: 3040, 1750, 1220, 750.

2.3.7. (±)-1-Chloro-3-(2-isopropyl-5-methylphenoxy)prop-2-yl acetate (±)-2g

Yellow liquid; yield 75%; purity 94% (GC); ^{1}H NMR: δ 1.20 (d, 6H, J = 7.0 Hz, (CH_3)$_2$CH), 2.12 (s, 3H, OAc), 2.32 (s, 3H, CH_3Ar), 3.22 (sp, 1H, J = 6.9 Hz, (CH$_3$)$_2$C*H*), 3.65 (dd, 1H, J = 10.8 Hz, J = 5.4 Hz, CH_2Cl), 3.73 (dd, 1H, J = 10.8 Hz, J = 5.5 Hz, CH_2Cl), 4.14 (dd, 1H, J = 9.8 Hz, J = 4.8 Hz, CH_2OAr), 4.20 (dd, 1H, J = 9.9 Hz, J = 4.7 Hz, CH_2OAr), 5.36 (qui, 1H, J = 5.3 Hz, C*H*OAc), 6.64 (s, 1H, Ar*H*), 6.77 (d, 1H, J = 7.7 Hz, Ar*H*), 7.10 (d, 1H, J = 7.7 Hz, Ar*H*): IR ($CHCl_3$), cm^{-1}: 3040, 1750, 1220, 750.

2.3.8. (±)-1-Bromo-3-(4-(3-oxobutyl)phenoxy)prop-2-yl acetate ***(±)-2h***

Brown liquid; yield 79%; purity 99% (HPLC); ^{1}H NMR: δ 2.12 (s, 3H, OAc), 2.13 (s, 3H, COCH_3), 2.67–2.88 (m, 4H, CH_2CH_2Ar), 3.62 (dd, 1H, J = 10.9 Hz, J = 5.4 Hz, CH_2Br), 3.71 (dd, 1H, J = 10.9 Hz, J = 5.4 Hz, CH_2Br), 4.12 (dd, 1H, J = 10.1 Hz, J = 5.2 Hz CH_2OAr), 4.18 (dd, 1H, J = 10.2 Hz, J = 4.9 Hz, CH_2OAr), 5.29 (qui, 1H, J = 5.2 Hz, C*H*OAc), 6.83 (ddd, 2H, J = 8.7 Hz, J = 2.5 Hz, J = 0.5 Hz, Ar*H*), 7.10 (ddd, 2H, J = 8.7 Hz, J = 2.5 Hz, J = 0.5 Hz, Ar*H*); IR ($CHCl_3$), cm^{-1}: 3040, 1750, 1720, 1515, 1215, 750.

2.3.9. (±)-1-Chloro-3-(4-(3-oxobutyl)phenoxy)prop-2-yl acetate ***(±)-2i***

Colourless liquid; yield 53%; purity 90% (GC); ^{1}H NMR: δ 2.12 (s, 3H, OAc), 2.13 (s, 3H, COCH_3), 2.69–2.88 (m, 4H, CH_2CH_2Ar), 3.77 (dd, 1H, J = 11.7 Hz, J = 5.3 Hz, CH_2Cl), 3.86 (dd, 1H, J = 11.7 Hz, J = 5.1 Hz, CH_2Cl), 4.12 (dd, 1H, J = 10.4 Hz, J = 5.2 Hz, CH_2OAr), 4.17 (dd, 1H, J = 10.3 Hz, J = 4.9 Hz, CH_2OAr), 5.32 (qui, 1H, J = 5.1 Hz, C*H*OAc), 6.83 (ddd, 2H, J = 8.7 Hz, J = 2.5 Hz, J = 0.5 Hz, Ar*H*), 7.11 (ddd, 2H, J = 8.7 Hz, J = 2.5 Hz, J = 0.5 Hz, Ar*H*); IR ($CHCl_3$), cm^{-1}: 3040, 1750, 1720, 1515, 1215, 750.

*2.4. General procedure for resolution of (±)-3-aryloxy-1-halogenopropan-2-ols (**1a**–**i**) by Lipozyme® TL*

To 10 mmol halogenopropanol **1a**–**i** dissolved in 20 mL *tert*-butyl methyl ether, 20 mmol vinyl acetate and 400 mg Lipozyme® TL were added. The mixture was shaken at 25 °C, and the reaction progress was monitored by HPLC. For **1a**, **1d**, **1e** resolution was stopped at 50% conversion, by enzyme filtration. Solvent and excess of vinyl acetate were evaporated and residue separated by column chromatography yielding alcohol (*R*)-**1**, and acetate (*S*)-**2**. Halogenopropanols (±)-**1b**, **1c**, **1f**, **1g**, **1h**, **1i** were resolved by two-step procedure. When conversion reached ~45%, enzyme was filtered off, solvent evaporated and halogenopropanol (*R*)-**1** separated from acetate (*S*)-**2** by column chromatography. Enriched halogenopropanol **1** (~90% ee) was dissolved in 20 mL *tert*-butyl methyl ether, 20 mmol of vinyl acetate, 400 mg of fresh enzyme were added and reaction continued until ca. 10% of acetate was formed. Then enzyme was filtered and the residue after solvent evaporation separated again by column chromatography.

2.4.1. (R)-1-Bromo-3-(2-methoxyphenoxy)propan-2-ol ***(R)-1a***

Colourless liquid; yield 45%; purity 95% (GC); 91% ee (R_T = 24.93 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = −4.1 (*c* 5.8, CH_3OH).

2.4.2. (S)-1-Bromo-3-(2-methoxyphenoxy)prop-2-yl acetate ***(S)-2a***

Colourless liquid; yield 45%; purity 97% (GC); 92% ee (R_T = 10.99 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +14.8 (*c* 7.1, CH_3OH).

2.4.3. (R)-1-Bromo-3-(4-ethyl-2-methoxyphenoxy)propan-2-ol ***(R)-1b***

Yellow liquid; yield 42%; purity 97% (GC); 99% ee (R_T = 11.38 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +6.1 (*c* 2.5, $CHCl_3$).

2.4.4. (S)-1-Bromo-3-(4-ethyl-2-methoxyphenoxy)prop-2-yl acetate ***(S)-2b***

Yellow liquid; yield 38%; purity 97% (GC); 97% ee (R_T = 8.63 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +15.9 (*c* 30.5, $CHCl_3$).

2.4.5. (R)-1-Chloro-3-(4-ethyl-2-methoxyphenoxy)propan-2-ol ***(R)-1c***

Yellow liquid; yield 34%; purity 98% (GC); 99% ee (R_T = 11.37 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +6.9 (c 30.0, $CHCl_3$).

2.4.6. (S)-1-Chloro-3-(4-ethyl-2-methoxyphenoxy)prop-2-yl acetate ***(S)-2c***

Yellow liquid; yield 49%; purity 97% (GC); 95% ee (R_T = 8.47 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +20.0 (*c* 27.0, $CHCl_3$).

2.4.7. (R)-1-Bromo-3-(2-nitrophenoxy)propan-2-ol ***(R)-1d***

Dark yellow liquid; yield 48%; purity 96% (GC); 86% ee (R_T = 18.19 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +16.9 (*c* 6.0, $CHCl_3$).

2.4.8. (S)-1-Bromo-3-(2-nitrophenoxy)prop-2-yl acetate ***(S)-2d***

Dark yellow liquid; yield 48%; purity 96% (GC); 91% ee (R_T = 12.64 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +43.3 (*c* 6.8, $CHCl_3$).

2.4.9. (R)-1-Chloro-3-(2-nitrophenoxy)propan-2-ol ***(R)-1e***

Dark yellow liquid; yield 48%; purity 96% (GC); 89% ee (R_T = 17.01 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +31.3 (*c* 2.3, $CHCl_3$).

2.4.10. (S)-1-Chloro-3-(2-nitrophenoxy)prop-2-yl acetate ***(S)-2e***

Dark yellow liquid; yield 48%; purity 96% (GC); 92% ee (R_T = 12.23 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +54.2 (*c* 20.0, $CHCl_3$).

2.4.11. (R)-1-Bromo-3-(2-isopropyl-5-methylphenoxy) propan-2-ol ***(R)-1f***

Colourless liquid; yield 40%; purity 99% (HPLC); 98% ee (R_T = 11.53 min; hexane/i-PrOH 95:5, 0.6 mL/min); $[\alpha]_D$ = −5.7 (*c* 10.0, $CHCl_3$).

2.4.12. (S)-1-Bromo-3-(2-isopropyl-5-methylphenoxy)prop-2-yl acetate ***(S)-2f***

Colourless liquid; yield 48%; purity 99% (HPLC); (enantiomers not resolved, R_T = 6.88 min; hexane/i-PrOH 95:5, 0.6 mL/min); $[\alpha]_D$ = +20.9 (*c* 10.0, $CHCl_3$).

2.4.13. (R)-1-Chloro-3-(2-isopropyl-5-methylphenoxy) propan-2-ol ***(R)-1g***

Colourless liquid; yield 36%; purity 99% (GC); 99% ee (R_T = 11.66 min; hexane/i-PrOH 95:5, 0.6 mL/min); $[\alpha]_D$ = −6.8 (*c* 10.0, $CHCl_3$).

2.4.14. (S)-1-Chloro-3-(2-isopropyl-5-methylphenoxy)prop-2-yl acetate ***(S)-2g***

Colourless liquid; yield 44%; purity 99% (HPLC); (enantiomers not resolved, R_T = 5.99 min; hexane/i-PrOH 95:5, 0.6 mL/min); $[\alpha]_D$ = +28.6 (*c* 10.0, $CHCl_3$).

2.4.15. (R)-1-Bromo-3-(4-(3-oxobutyl)phenoxy)propan-2-ol ***(R)-1h***

Colourless liquid; yield 48%; purity 97% (GC); 99% ee (R_T = 25.42 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = −0.5 (*c* 1.0, $CHCl_3$).

2.4.16. (S)-1-Bromo-3-(4-(3-oxobutyl)phenoxy)prop-2-yl acetate ***(S)-2h***

Colourless liquid; yield 36%; purity 98% (GC); 99% ee (R_T = 13.75 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +20.5 (*c* 1.0, $CHCl_3$).

2.4.17. (R)-1-Chloro-3-(4-(3-oxobutyl)phenoxy)propan-2-ol ***(R)-1i***

Colourless liquid; yield 42%; purity 98% (GC); 99% ee (R_T = 23.16 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +0.8 (*c* 1.0, $CHCl_3$).

2.4.18. (S)-1-Chloro-3-(4-(3-oxobutyl)phenoxy)prop-2-yl acetate ***(S)-2i***

Colourless liquid; yield 45%; purity 98% (GC); 99% ee (R_T = 13.84 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +25.6 (*c* 1.0, $CHCl_3$).

2.5. General procedure for preparation of (±)-1-alkylamino-3-aryloxypropan-2-ols ***(±)-4*** *and* ***(±)-5*** *from* ***(±)-3***

To 3 mmol (±)-2-aryloxymethyloxirane **3** in 9 mL of amine (isopropylamine or *tert*-butylamine) 3 ml of water was added. The mixture was left at room temperature until disappearance of the oxirane was indicated by TLC (hexane–ethyl acetate, 6:4). After ~24 h an excess of amine was evaporated, residue diluted with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Organic layer was dried over anhydrous $MgSO_4$ and solvent was evaporated.

2.5.1. (±)-1-Isopropylamino-3-(4-ethyl-2-methoxyphenoxy) -propan-2-ol ***(±)-4b***

Yellow liquid; yield 96%; purity 99% (HPLC); ^{1}H NMR: δ 1.08 (d, 6H, *J* = 6.2 Hz, CH(C*H*$_3$)$_2$), 1.21 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$), 2.58 (q, 2H, *J* = 7.6 Hz, CH$_3$C*H*$_2$), 2.70–2.89 (m, 1H, C*H*(CH$_3$)$_2$), 2.73 (dd, 1H, *J* = 12.0 Hz, *J* = 7.1 Hz, C*H*$_2$NH), 2.86 (dd, 1H, *J* = 12.0 Hz, *J* = 4.0 Hz, C*H*$_2$NH), 3.25 (s (br), OH), 3.83 (s, 3H, C*H*$_3$OAr), 3.93–4.11 (m, 3H, OC*H*$_2$C*H*(OH)), 6.70 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.71 (s, 1H, Ar*H*), 6.83 (d, 1H, *J* = 8.0 Hz, Ar*H*); ^{13}C NMR: δ 14.0 (*C*H$_3$CH$_2$), 21.0 (CH(*C*H$_3$)$_2$), 26.7 (CH$_3$*C*H$_2$), 47.1 (*C*H$_2$NH or (*C*H(CH$_3$)$_2$), 47.8 (*C*H$_2$NH or (*C*H(CH$_3$)$_2$), 54.0 (O*C*H$_3$), 66.6 (*C*HOH), 71.5 (*C*H$_2$OAr), 110.2 (*C*6, Ar), 113.2 (*C*3, Ar), 118.0 (*C*5, Ar), 136.3 (*C*4, Ar), 144.5 (*C*1, Ar), 147.5 (*C*2, Ar); IR, (film), cm^{-1}: 3323, 3280, 3127, 2962, 1589, 1515, 1229; MS, *m*/*z* (%): 223 (12); 152 (38); 137 (8); 72 (100).

2.5.2. (±)-1-Isopropylamino-3-(2-nitrophenoxy)propan-2-ol ***(±)-4d***

Yellow solid; yield 90%; purity 97% (GC); ^{1}H NMR: δ 1.10 (d, 6H, *J* = 6.2 Hz, CH(C*H*$_3$)$_2$), 2.68 (s (br), OH), 2.76–2.93 (m, 1H, C*H*(CH$_3$)$_2$) 2.82 (dd, 1H, *J* = 12.3 Hz, *J* = 6.4 Hz, C*H*$_2$NH), 2.92 (dd, 1H, *J* = 12.1 Hz, *J* = 4.4 Hz, C*H*$_2$NH), 4.05 (qui, 1H, *J* = 5.2 Hz C*H*OH), 4.10–4.20 (m, 2H, C*H*$_2$OAr), 7.05 (t, 1H, *J* = 7.8 Hz, Ar*H*), 7.11 (d, 1H, *J* = 8.5 Hz, Ar*H*), 7.54 (t, 1H, *J* = 8.0 Hz, Ar*H*), 7.87 (d, 1H, *J* = 8.0 Hz, Ar*H*); ^{13}C NMR: δ 22.8 (CH(*C*H$_3$)$_2$), 48.8 (*C*H$_2$NH or (*C*H(CH$_3$)$_2$), 49.0 (*C*H$_2$NH or (*C*H(CH$_3$)$_2$), 67.9 (*C*HOH), 72.4 (*C*H$_2$OAr), 114.8 (*C*6, Ar), 120.6 (*C*4, Ar), 125.7 (*C*3, Ar), 134.3 (*C*5, Ar), 139.7 (*C*2, Ar), 152.3 (*C*1, Ar); IR, (film), cm^{-1}: 3265, 3076, 2964, 2943, 2904, 1612, 1582, 1518, 1287; MS, *m*/*z* (%): 239 (5); 210 (5); 73 (5); 72 (100); 56 (8); 41 (6).methylphenoxy)propan-

2.5.3. (±)-1-Isopropylamino-3-(2-isopropyl-5-methylphenoxy)-propan-2-ol ***(±)-4f***

Yellow liquid; yield 93%; purity 99% (GC); ^{1}H NMR: δ 1.08 (d, 6H, *J* = 6.2 Hz, CH(C*H*$_3$)$_2$), 1.20 (d, 6H, *J* = 6.9 Hz, (C*H*$_3$)$_2$CH), 2.30 (s, 3H, C*H*$_3$Ar), 2.75 (dd, 1H, *J* = 12.0 Hz, *J* = 7.4 Hz, C*H*$_2$NH), 2.80 (sp, 1H, *J* = 6.2 Hz, C*H*(CH$_3$)$_2$), 2.91 (dd, 1H, *J* = 12.1 Hz, *J* = 3.8 Hz, C*H*$_2$NH), 3.27 (sp, 1H, *J* = 6.9 Hz, (CH$_3$)$_2$C*H*)), 3.92 (dd, 1H, *J* = 9.1 Hz, *J* = 5.4 Hz, C*H*$_2$OAr), 4.00 (dd, 1H, *J* = 9.1 Hz, *J* = 5.0 Hz, C*H*$_2$OAr), 4.02–4.10 (m, 1H, C*H*OH), 6.67 (s (br), 1H, Ar*H*), 6.74 (d, 1H, *J* = 7.7 Hz, Ar*H*), 7.08 (d, 1H, *J* = 7.7 Hz, Ar*H*); ^{13}C NMR: δ 19.6 (*C*H$_3$Ar), 21.0 ((*C*H$_3$)$_2$CH), 21.3 (CH(*C*H$_3$)$_2$), 24.9 ((CH$_3$)$_2$*C*H), 47.2 (*C*H$_2$NH or (*C*H(CH$_3$)$_2$), 48.0 (*C*H$_2$NH or (*C*H(CH$_3$)$_2$), 66.8 (*C*HOH), 69.0 (*C*H$_2$OAr), 110.7 (*C*6, Ar), 119.8 (*C*4, Ar), 124.1 (*C*3, Ar), 132.2 (*C*2, Ar), 134.6 (*C*5, Ar), 153.9 (*C*1, Ar); IR, (film), cm^{-1}: 3247, 2962, 2911, 2867, 2834, 1613, 1582, 1506, 1256; MS, *m*/*z* (%): 265 (7, M$^+$); 135 (4); 72 (100).

2.5.4. (±)-1-Isopropylamino-3-(4-(3-oxobutyl)phenoxy)propan-2-ol ***(±)-4h***

Colourless needles; m.p. 61 °C (hexane); yield 80%; purity 96% (HPLC); ^{1}H NMR: δ 1.09 (d, 6H, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 2.13 (s, 1H, C*H*$_3$CO), 2.46 (s (br), 1H, O*H*), 2.68–2.92 (m, 6H, ArC*H*$_2$C*H*$_2$, C*H*$_2$NH), 3.92–4.06 (m, 3H, OC*H*$_2$C*H*(OH)), 6.83 (ddd, 2H, *J* = 8.7 Hz, *J* = 2.5 Hz, *J* = 0.5 Hz, Ar*H*), 7.09 (ddd, 2H, *J* = 8.7 Hz, *J* = 2.5 Hz, *J* = 0.5 Hz, Ar*H*); ^{13}C NMR: δ 22.9 (CH(*C*H$_3$)$_2$), 28.8 (CO*C*H$_3$), 30.0 (Ar*C*H$_2$CH$_2$), 45.3 (ArCH$_2$*C*H$_2$), 48.8 (*C*H$_2$NH or (*C*H(CH$_3$)$_2$), 49.4 (*C*H$_2$NH or (*C*H(CH$_3$)$_2$), 68.4 (*C*HOH), 70.6 (*C*H$_2$OAr), 114.5 (*C*3, C5, Ar), 129.1 (*C*3, C5, Ar), 133.2 (*C*4, Ar), 157.0 (*C*1, Ar), 208.0 (*C*OCH$_3$); IR, (film), cm^{-1}: 3275, 2967, 2924, 2866, 2359, 1707, 1613, 1584, 1510, 1221; MS, *m*/*z* (%): 235 (8); 207 (6); 73 (6); 72 (100); 43 (11).

2.5.5. (±)-1-tert-Butylamino-3-(2-methoxyphenoxy)propan-2-ol ***(±)-5a***

White solid, m.p. 73–75 °C; yield 95%; purity 94% (HPLC); ^{1}H NMR: δ 1.11 (s, 9H, C(C*H*$_3$)$_3$), 2.72 (dd, 1H, *J* = 11.8 Hz, *J* = 6.1 Hz, C*H*$_2$NH), 2.84 (dd, 1H, *J* = 11.8 Hz, *J* = 4.1 Hz, C*H*$_2$NH), 3.86 (s, 3H, C*H*$_3$OAr), 3.93–4.09 (m, 1H, C*H*OH), 3.96 (dd, 1H, *J* = 8.8 Hz, *J* = 4.2 Hz, C*H*$_2$OAr), 4.05 (dd, 1H, *J* = 11.0 Hz, *J* = 4.8 Hz, C*H*$_2$OAr), 6.86–6.87 (m, 4H, Ar*H*) ^{13}C NMR: δ 26.9 (C(*C*H$_3$)$_3$), 45.3 (*C*H$_2$NH), 55.1 (*C*(CH$_3$)$_3$), 55.8 (O*C*H$_3$), 66.2 (*C*HOH), 72.3 (*C*H$_2$OAr), 112.0 (*C*6, Ar), 114.7 (*C*3, Ar), 121.0 (*C*5, Ar), 122.1 (*C*4, Ar), 147.9 (*C*1, Ar), 149.6 (*C*2, Ar); IR, (film), cm^{-1}: 3297, 3067, 2964, 1592, 1506, 1227; MS, *m*/*z* (%): 238 (21); 209 (22); 124 (9); 86 (100); 57 (14).

2.5.6. (±)-1-tert-Butylamino-3-(4-ethyl-2-methoxyphenoxy)-propan-2-ol ***(±)-5b***

Yellow liquid; yield 96%; purity 99% (HPLC); ^{1}H NMR: δ 1.10 (s, 9H, C(C*H*$_3$)$_3$), 1.21 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$), 2.58 (q, 2H, *J* = 7.6 Hz, CH$_3$C*H*$_2$), 2.71 (dd, 1H, *J* = 11.6 Hz, *J* = 5.6 Hz, C*H*$_2$NH), 2.83 (dd, 1H, *J* = 11.4 Hz, *J* = 3.6 Hz, C*H*$_2$NH), 3.84 (s, 3H, C*H*$_3$OAr), 3.96–4.03 (m, 3H, OC*H*$_2$C*H*(OH)), 6.71 (d, 1H, *J* = 6.7 Hz, Ar*H*), 6.73 (s, 1H, Ar*H*), 6.85 (d, 1H, *J* = 8.5 Hz, Ar*H*); ^{13}C NMR: δ 15.7 (*C*H$_3$CH$_2$), 28.4 (CH$_3$*C*H$_2$), 28.9 (C(*C*H$_3$)$_3$), 44.7 (*C*H$_2$NH), 50.0 (*C*(CH$_3$)$_3$), 55.7 (O*C*H$_3$), 68.5 (*C*HOH), 73.1 (*C*H$_2$OAr), 111.8 (*C*6, Ar), 114.7 (*C*3, Ar), 119.6 (*C*5, Ar), 137.8 (*C*4, Ar), 146.2 (*C*1, Ar), 149.5 (*C*2, Ar); IR, (film), cm^{-1}: 3305, 3118, 2964, 1588, 1514, 1229; MS, *m*/*z* (%): 266 (16); 237 (19); 152 (17); 137 (10); 86 (100); 71 (9); 57 (12).

2.5.7. (±)-1-tert-Butylamino-3-(2-nitrophenoxy)propan-2-ol ***(±)-5d***

Yellow solid; yield 85%; purity 90% (GC); ^{1}H NMR: δ 1.15 (s, 9H, C(C*H*$_3$)$_3$), 2.81 (dd, 1H, *J* = 12.0 Hz, *J* = 6.5 Hz, C*H*$_2$NH), 2.92 (dd, 1H, *J* = 12.1 Hz, *J* = 4.5 Hz, C*H*$_2$NH), 4.00 (qui, 1H, *J* = 5.3 Hz, C*H*OH), 4.12–4.22 (m, 2H, C*H*$_2$OAr), 7.05 (t, 1H, *J* = 7.5 Hz, Ar*H*), 7.12 (d, 1H, *J* = 8.0 Hz, Ar*H*), 7.54 (t, 1H, *J* = 7.5 Hz, Ar*H*), 7.88 (d, 1H, *J* = 8.0 Hz, Ar*H*); ^{13}C NMR: δ 28.9 (C(*C*H$_3$)$_3$), 44.3 (*C*H$_2$NH), 50.2 (*C*(CH$_3$)$_3$), 68.0 (*C*HOH), 72.4 (*C*H$_2$OAr), 114.7 (*C*6, Ar), 120.5 (*C*4, Ar), 125.6 (*C*3, Ar), 134.2 (*C*5, Ar), 139.6 (*C*2, Ar), 152.3 (*C*1, Ar); IR, (film), cm^{-1}: 3289, 3094, 2959, 2867, 1609, 1581, 1520, 1259; MS, *m*/*z* (%): 253 (37); 224 (6); 86 (100); 71 (8); 70 (14); 57 (21); 41 (10).

2.5.8. (±)-1-tert-Butylamino-3-(2-isopropyl-5-methylphenoxy)-propan-2-ol ***(±)-5f***

Yellow liquid; yield 90%; purity 99.2% (GC); ^{1}H NMR: δ 1.18 (s, 9H, C(C*H*$_3$)$_3$), 1.27 (d, 6H, *J* = 6.9 Hz, (C*H*$_3$)$_2$CH), 2.37 (s, 3H, C*H*$_3$Ar), 2.80 (dd, 1H, *J* = 11.8 Hz, *J* = 6.9 Hz C*H*$_2$NH), 2.95 (dd, 1H, *J* = 11.8 Hz, *J* = 3.8 Hz, C*H*$_2$NH), 3.33 (sp, 1H, *J* = 6.9 Hz, (CH$_3$)$_2$C*H*), 3.96–4.11 (m, 3H, OC*H*$_2$C*H*(OH)), 6.74 (s, 1H, Ar*H*), 6.81 (d, 1H, *J* = 7.5 Hz, Ar*H*), 7.14 (d, 1H, *J* = 7.7 Hz, Ar*H*); ^{13}C NMR: δ 19.6 (*C*H$_3$Ar), 21.0 ((CH$_3$)$_2$CH),

24.9 ($(CH_3)_2CH$), 27.3 ($C(CH_3)_3$), 43.3 (CH_2NH), 48.6 ($C(CH_3)_3$), 67.0 (*C*HOH), 68.9 (CH_2OAr), 110.7 (*C*6, Ar), 119.7 (*C*4, Ar), 124.1 (*C*3, Ar), 132.2 (*C*2, Ar), 134.6 (*C*5, Ar), 154.0 (*C*1, Ar); IR, (film), cm^{-1}: 3259, 3118, 2964, 2920, 2869, 1612, 1582, 1506, 1252; MS, *m*/*z* (%): 279 (10, M^+); 264 (19); 135 (6); 125 (8); 116 (6); 91 (7); 86 (100); 57 (11); 41 (6).

2.5.9. (±)-1-tert-Butylamino-3-(4-(3-oxobutyl)phenoxy) propan-2-ol ***(±)-5h***

Colourless needles; yield 77%; purity 98.6% (HPLC); m.p. 59–60 °C (hexane); ^{1}H NMR: δ 1.12 (s, 9H, $C(CH_3)_3$), 2.13 (s, 1H, CH_3CO), 2.48 (s (br), 1H, O*H*), 2.64–2.89 (m, 6H, $ArCH_2CH_2$, CH_2NH), 3.92–3.97 (m, 3H, $OCH_2CH(OH)$), 6.84 (ddd, 2H, *J* = 8.7 Hz, *J* = 2.5 Hz, *J* = 0.5 Hz, Ar*H*), 7.09 (ddd, 2H, *J* = 8.7 Hz, *J* = 2.5 Hz, *J* = 0.5, Hz, Ar*H*); ^{13}C NMR: δ 27.1 ($COCH_3$), 27.3 ($C(CH_3)_3$), 28.3 ($ArCH_2CH_2$), 43.0 ($ArCH_2CH_2$), 43.6 (CH_2NH), 48.5 ($C(CH_3)_3$), 67.0 (*C*HOH), 68.9 (CH_2OAr), 112.8 (*C*3, C5, Ar), 127.4 (*C*3, C5, Ar), 131.5 (*C*4, Ar), 155.4 (*C*1, Ar), 206.3 ($COCH_3$); IR, (film), cm^{-1}: 3130, 2969, 2930, 2871, 1704, 1614, 1584, 1511, 1221; MS, *m*/*z* (%): 278 (20); 249 (11); 207 (15); 86 (100); 57 (15); 43 (13).

2.6. General procedure for preparation of (S)-1-alkylamino-3-aryloxypropan-2-ols ***(S)-4***, ***(S)-5*** *from* ***(R)-1***

To 3 mmol bromopropanol (*R*)-**1a** or chloropropanol (*R*)-**1c**, **1e**, **1g**, **1i**, 9 mL amine (isopropylamine or *tert*-butylamine) and 3 mL water was added. The mixture was left at room temperature until disappearance of substrate was indicated by TLC. Then excess amine was evaporated, residue diluted with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Organic layer was dried over anhydrous $MgSO_4$ and solvent was evaporated.

2.6.1. (S)-3-(4-Ethyl-2-methoxyphenoxy)-1-isopropylamino-propan-2-ol ***(S)-4b***

Colourless liquid; yield 92%; purity 98% (GC); 98% ee (R_T = 13.60 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +2.8 (*c* 1.0, $CHCl_3$).

2.6.2. (S)-1-Isopropylamino-3-(2-nitrophenoxy)propan-2-ol ***(S)-4d***

Yellow solid; yield 70%; purity 90% (GC); 91% ee (R_T = 11.26 min; hexane/iPrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = −21.4 (*c* 2.5, $CHCl_3$).

2.6.3. (S)-1-Isopropylamino-3-(2-isopropyl-5-methylphenoxy)-propan-2-ol ***(S)-4f***

Colourless liquid; yield 79%; purity 98% (GC); 99% ee (R_T = 11.34 min; hexane/i-PrOH 95:5, 0.6 ml/min); $[\alpha]_D$ = −11.8 (*c* 7.6, $CHCl_3$).

2.6.4. (S)-1-Isopropyloamino-3-(4-(3-oxobutyl) phenoxy)-propan-2-ol ***(S)-4h***

White crystals; m.p. 63 °C yield 68%; purity 97% (GC); 99% ee (R_T = 35.74 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = −11.0 (*c* 1.0, $CHCl_3$).

2.6.5. (S)-1-tert-Butylamino-3-(2-methoxyphenoxy) propan-2-ol ***(S)-5a***

White solid; m.p. 74–76 °C; yield 82%; purity 98% (GC); 90% ee (R_T = 43.88 min; i-PrOH/hexane 6:4, 0.5 mL/min); $[\alpha]_D$ = −0.9 (*c* 1.0, $CHCl_3$).

2.6.6. (S)-1-tert-Butylamino-3-(4-ethyl-2-methoxyphenoxy) propan-2-ol ***(S)-5b***

Colourless liquid; yield 92%; purity 99% (GC); 99% ee (R_T = 16.66 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = −2.9 (*c* 1.0, $CHCl_3$).

2.6.7. (S)-1-tert-Butylamino-3-(2-nitrophenoxy)propan-2-ol ***(S)-5d***

Yellow solid; yield 66%; purity 91% (GC); 90% ee (R_T = 10.74 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = −28.0 (*c* 3.1, $CHCl_3$).

2.6.8. (S)-1-tert-Butylamino-3-(2-isopropyl-5-methylphenoxy)-propan-2-ol ***(S)-5f***

Colourless liquid; yield 92%; purity 99% (GC); 99% ee (R_T = 11.60 min; hexane/i-PrOH 95:5, 0.6 mL/min); $[\alpha]_D$ = −13.4 (*c* 3.0, $CHCl_3$).

2.6.9. (S)-1-tert-Butyloamino-3-(4-(3-oxobutyl) phenoxy)-propan-2-ol ***(S)-5h***

White crystals; m.p.79 °C yield 60%; purity 99% (GC); 99% ee (R_T = 32.04 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = −7.3 (*c* 1.0, $CHCl_3$).

2.7. General procedure for preparation of (R)-1-alkylamino-3-aryloxypropan-2-ols ***(R)-4***, ***(R)-5*** *from* ***(S)-2***

To 3 mmol (*S*)-**2a**, **2c**, **2e**, **2g**, **2i** in 9 mL of amine (isopropylamine or *tert*-butylamine), 6 mmol NaOH and 3 mL water was added. The mixture was left at room temperature until disappearance of substrate was indicated by TLC. Then excess of amine was evaporated, residue diluted with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Organic layer was dried over anhydrous $MgSO_4$ and solvent was evaporated.

2.7.1. (R)-3-(4-Ethyl-2-methoxyphenoxy)-1-isopropylamino-propan-2-ol ***(R)-4b***

Colourless liquid; yield 92%; purity 97% (GC); 90% ee (R_T = 7.65 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = −2.9 (*c* 1.0, $CHCl_3$).

2.7.2. (R)-1-Isopropylamino-3-(2-nitrophenoxy)propan-2-ol ***(R)-4d***

Yellow solid; yield 69%; purity 89% (GC); 93% ee (R_T = 10.71 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +25.9 (*c* 4.6, $CHCl_3$).

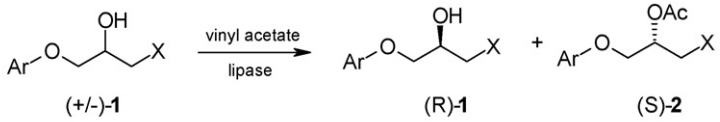
2.7.3. (R)-1-Isopropylamino-3-(2-isopropyl-5-methylphenoxy)-propan-2-ol ***(R)-4f***

Colourless liquid; yield 98%; purity 97% (GC); 85% ee (R_T = 10.24 min; hexane/i-PrOH 95:5, 0.6 mL/min); $[\alpha]_D$ = +9.7 (*c* 6.3, $CHCl_3$).

Table 1
Lipase-catalyzed acetylation of **1a** with vinyl acetate in hexane at 40 °C.

Enzyme	Time (h)	Conversion (%)	Substrate **1a**		E[a]
			Config.	ee_s (%)	
Lipozyme® RM	72	14	R	10	5
Novozym® 435	24	100	–	–	1
Lipozyme® TL	48	26	R	30	**15**
M. racemosus	72	0	–	–	–
M. circinelloides	72	0	–	–	–
Lipase A	48	3	R	1	2
Lipase AY	48	23	S	6	2
Acylase	48	23	R	6	2
Porcine pancreas lipase	48	5	R	1	~1
Lipase *C. cylindracea*	48	19	S	5	2
Lipase *C. rugosa*	48	19	S	6	2

[a] Calculated from ee_s and conversion according to ref. [23].



a: Ar = 2-methoxyphenyl, X = Br
b: Ar = 4-ethyl-2-methoxyphenyl, X = Br
c: Ar = 4-ethyl-2-methoxyphenyl, X = Cl
d: Ar = 2-nitrophenyl, X = Br
e: Ar = 2-nitrophenyl, X = Cl
f: Ar = 2-isopropyl-5-methylphenyl, X = Br
g: Ar = 2-isopropyl-5-methylphenyl, X = Cl
h: Ar = 4-(3-oxobutyl)phenyl, X = Br
i: Ar = 4-(3-oxobutyl)phenyl, X = Cl

Scheme 1. Enantioselective acetylation of (±)-3-aryloxy-1-halogenpropan-2-ols **1a**–**i** by lipases.

2.7.4. (R)-1-Isopropyloamino-3-(4-(3-oxobutyl) phenoxy)-propan-2-ol ***(R)-4h***

White crystals; m.p. 64–65 °C; yield 60%; purity 98% (GC); 99% ee (R_T = 16.45 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D^{20}$ = +11.1 (*c* 1.0, $CHCl_3$).

2.7.5. (R)-1-tert-Butylamino-3-(2-methoxyphenoxy)propan-2-ol ***(R)-5a***

Yellow solid; m.p. 73–76 °C; yield 94%; purity 99% (GC); 90% ee (R_T = 8.75; i-PrOH/hexane 6:4, 0.5 mL/min); $[\alpha]_D$ = +0.9 (*c* 1.0, $CHCl_3$).

2.7.6. (R)-1-tert-Butylamino-3-(4-ethyl-2-methoxyphenoxy)-propan-2-ol ***(R)-5b***

Colourless liquid; yield 92%; purity 98% (GC); 93% ee (R_T = 7.35 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +1.0 (*c* 1.2, $CHCl_3$).

2.7.7. (R)-1-tert-Butylamino-3-(2-nitrophenoxy)propan-2-ol ***(R)-5d***

Yellow solid; yield 72%; purity 91% (GC); 89% ee (R_T = 9.97 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +31.9 (*c* 1.0, $CHCl_3$).

2.7.8. (R)-1-tert-Butylamino-3-(2-isopropyl-5-methylphenoxy) propan-2-ol ***(R)-5f***

Colourless liquid; yield 98%; purity 99% (GC); 88% ee (R_T = 9.87 min; hexane/i-PrOH 95:5; 0.6 mL/min); $[\alpha]_D$ = +12.5 (*c* 4.2, $CHCl_3$).

2.7.9. (R)-1-tert-Butylamino-3-(4-(3-oxobutyl) phenoxy)propan-2-ol ***(R)-5h***

White crystals; m.p. 77–78 °C yield 65%; purity 98% (GC); 99% ee (R_T = 13.94 min; hexane/i-PrOH 8:2, 0.6 mL/min); $[\alpha]_D$ = +7.2 (*c* 1.0, $CHCl_3$).

3. Results and discussion

Synthesis of racemic 3-aryloxy-1-halogenopropan-2-ols **1a**–**i** by regioselective cleavage of 2-aryloxymethyloxiranes prepared from corresponding phenols and epichlorohydrin has been described elsewhere [22]. For resolutions of known β-blockers precursors lipase PS (*Pseudomonas cepacia*) was found the most enantioselective [8–12]. However this enzyme showed low activity and moderate selectivity for substrates with 2-substituted phenyl ring [13]. Moreover at present new enzyme preparations appeared which were not used in previous studies. Expecting some differences in enzyme activity and enantioselectivity with respect to substituents at stereogenic centre, we prepared chloro- and bromoalcohol from each 2-aryloxymethyloxirane. As we were going to resolve these substrates by lipase-catalyzed acylation with enol esters, racemic acetates **2a**–**i** were also prepared by treating halogenopropanols **1a**–**i** with acetic anhydride in the presence of pyridine. For monitoring enzymatic reaction progress and enantiomeric excess determination HPLC analysis on a chiral support was employed. Using Chiralcel OD column, excellent enantiomers resolution of all halogenopropanols and their acetates was achieved.

1-Bromo-3-(2-methoxyphenoxy)propan-2-ol (**1a**) was chosen as a model substrate for testing enzymes activity and enantioselectivity. In preliminary screening, eleven enzyme preparations were used: eight commercial lipases and one acylase as well as two non-commercial lipases (*Mucor racemosus* and *Mucor circinelloides*) as acetone-dried whole-cell preparations. Reactions were carried out in hexane at 40 °C because of rather low substrate solubility at room temperature. In a typical experiment, vials containing 0.5 mmol aryloxyhalogenopropanol **1a**, 2 mmol vinyl acetate and 50 mg enzyme in 2.5 ml hexane were placed in a thermostatic shaker and the reaction progress was monitored by HPLC. From the conversion level and enantiomeric excess of remaining substrate **1a**, enantioselectivity *E* was determined (Table 1).

We found eight active lipases with the most active one – Novozym 435® – lacking any enantioselectivity. When more sterically hindered isopropenyl acetate was used as an acyl donor for Novozym® 435, a lower reaction rate was observed while enantioselectivity was only slightly improved and ranged 2–3 at conversion below 50%. The highest enantioselectivity (E = 15) has been found for Lipozyme® TL (immobilized *Thermomyces lanuginosus* lipase). This is noteworthy that lipases *C. rugosa* (formerly classified as *C.*

Table 2
The solvent effect on lipase-catalyzed acetylation of **1a** with vinyl acetate.

Lipase	Chloroform		Toluene		*tert*-Butyl methyl ether	
	Conversion/time (%/h)	E^a	Conversion/time (%/h)	E^a	Conversion/time (%/h)	E^a
Lipozyme® RM	0/72	–	6/72	4	28/96	8
Novozym® 435	28/72	2	85/24	2	36/6	2
Lipozyme® TL	8/72	**10**	49/168	**53**	55/24	**50**
Lipase AY	0/72	–	7/72	5	19/96	6
Lipase *C. rugosa*	3/72	3	5/72	4	10/96	6

[a] Calculated from ee_s and conversion according to ref. [23].

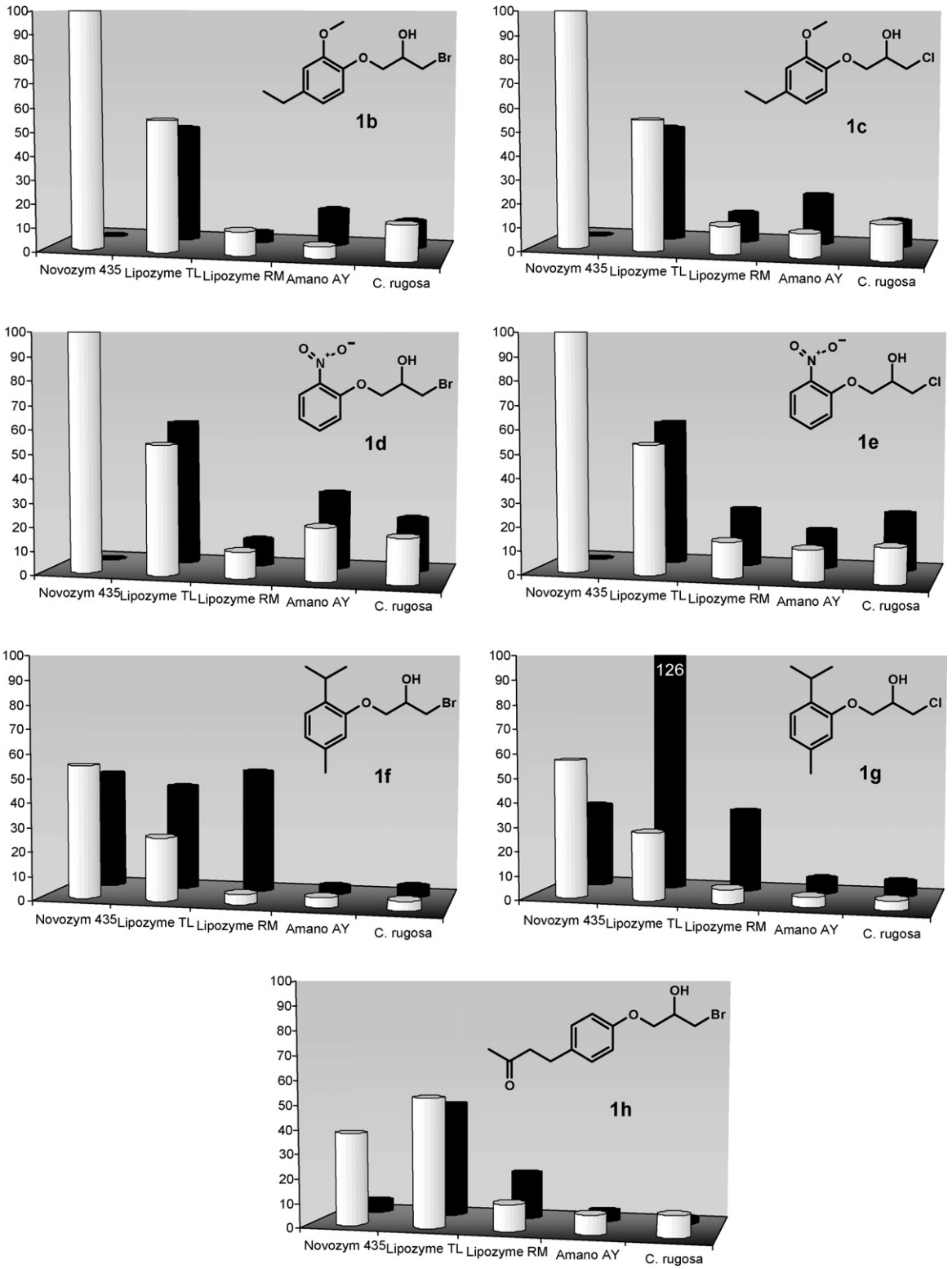


Fig. 1. Activity and enantioselectivity of lipases for resolution of (±)-3-aryloxy-1-halogenopropan-2-ols **1b**–**h** by acylation with vinyl acetate in *tert*-butyl methyl ether at 25 °C; white bar—activity measured as substrate conversion (%) at 24 h reaction time; black bar—enantioselectivity ratio *E*.

cylindracea) and Amano AY (*C. rugosa*) exerted enantiopreference opposite to the other enzymes tested in our study, and, moreover it was contrary to the Kazlauskas substrate model for this enzyme [24,25]. We established that all the lipases used in our study, except *C. rugosa*, acetylated (*S*)-aryloxybromopropanol **1a** faster than (*R*)-enantiomer (Scheme 1).

Because of low substrate solubility in hexane and frequently observed influence of the solvent on the reaction rate and enzyme enantioselectivity we also performed the acetylation of **1a** with vinyl acetate at 25 °C in chloroform, toluene and *tert*-butyl methyl ether using five lipases of the highest activity from preliminary screening (Table 2). We found a very slow reaction in chloroform,

with two lipases completely inactive in that solvent. In toluene or *tert*-butyl methyl ether all five enzymes were active, but in ether the reaction proceeded faster. Moreover, in all the solvents, Lipozyme® TL showed a significantly higher enantioselectivity than other lipases.

In order to determine the scope of the applicability of this resolution method to other substrates of similar structure but different substitution pattern in the phenyl ring, aryloxyhalogenopropanols **1b**–**h** were treated with vinyl acetate in *tert*-butyl methyl ether at 25 °C, in the presence of five the most active lipases for 24 h (Fig. 1). Conversion determined by HPLC analysis was used as a measure of enzyme activity, and enantioselectivity was calculated as previously from the enantiomeric excess of the remaining substrate and conversion.

All the lipases studied accepted chloro- and bromopropanols as substrates. We did not find large differences either in reaction rates or in enantioselectivity for bromo vs. chloro analogues (**1b** vs. **1c**; **1d** vs. **1e**, Fig. 1), which implies that size of the halogenomethyl group does not play a role when the substrate is accommodated in a lipase active site. However, in most cases, the reaction rate and enantioselectivity are slightly in favor of chloropropanols. This is in agreement with Schneider's results for lipase PS [13]. Exceptionally high enantioselectivity ($E = 126$) was observed for chloro derivative **1g** vs. bromo analogue **1f** for Lipozyme TL® at low conversion. However at 50% conversion, enantioselectivity for chloro- **1g** and bromopropanol **1f** was found to be 88 and 82, respectively. The most active lipase—Novozym® 435 accepted all aryloxyhalogenopropanols but was not enantioselective for phenyl substituted with medium-sized groups at 2-, 4- or both positions (substrates **1a**–**e**, **1h**). For halogenopropanols **1f**, **1g** with bulky isopropyl group at position 2 and methyl at position 5, Novozym® 435 was found less enantioselective than Lipozyme® TL, but reactions proceeded faster. For resolution of **1h**, **1i** (phenyl substituted with 3-oxobutyl chain at position 4) Lipozyme® TL revealed a higher activity as well as a higher enantioselectivity than Novozym 435®.

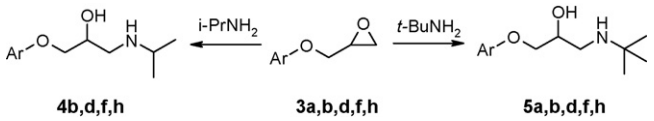
It is interesting to note that for substrates **1f**, **1g** switching of lipase *C. rugosa* enantiopreference from (*R*) to (*S*) was observed.

Preparative resolutions of substrates **1a**–**e**, **1h**, **1i** on 10 mmole substrate (2–3 g) were conducted in the presence of Lipozyme® TL, while halogenoalcohols **1f**, **1g** were resolved by Novozym® 435 (Table 3). The resolution of substrates **1a**, **1d**, **1e** was conducted in a single step and terminated at a conversion close to 50%, while **1b**, **1c**, **1f**, **1g**, **1h**, **1i** were resolved in two-step procedure. In the first step, resolution was terminated at ca. 45% conversion by enzyme filtration. Acetate and alcohol were separated by column chromatography and enantiomerically enriched alcohol was again subjected to the operation of lipase until a conversion of ca. 10% was achieved which provided for ca. 55% of overall conversion. This

Table 3
Preparative resolution of **1a**–**i** by Lipozyme® TL catalyzed acetylation.

Substrate	Conversion/time (%/h)	(*R*)-**1** ee (%)	(*S*)-**2** ee (%)	*E*[a]
(±)-**1a**	50/24	91	92	67
(±)-**1b**	44/48; 55/120	99	97	71
(±)-**1c**	49/48; 53/96	99	95	99
(±)-**1d**	48/72	86	91	75
(±)-**1e**	49/72	89	92	78
(±)-**1f**[b]	47/24; 53/48	98	n.d.	77
(±)-**1g**[b]	47/24; 57/48	99	n.d.	82
(±)-**1h**	45/96; 55/144	>99	>99	64
(±)-**1i**	45/96; 58/144	>99	>99	64

n.d., not determined (enantiomers not resolved by HPLC).
[a] Calculated from ee_s and conversion ≤0.50.
[b] Novozym® 435 was used for resolution.



Scheme 2. Synthesis of (±)-1-alkylamino-3-aryloxypropan-2-ols (±)**-4** and (±)**-5**.

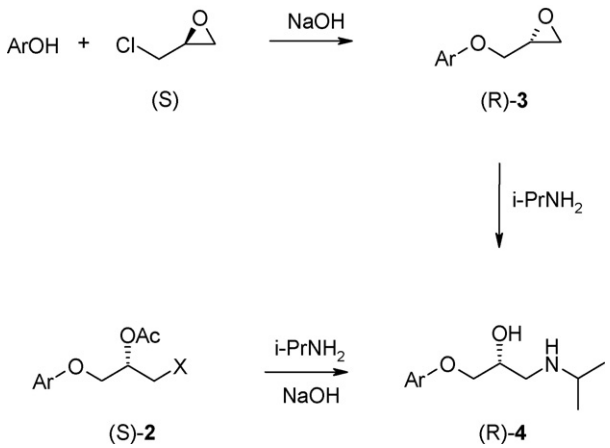
manipulation resulted in somewhat lower yield, but enantiomeric excess 99% for both enantiomers was attained—from the first step acetate (*S*)-**2**, while from the second step halogenopropanol (*R*)-**1**.

Subsequently, we decided to use resolved enantiomers as chiral building blocks for the synthesis of new potential β-receptor antagonists by halogen substitution with alkyl amines. At first from 2-aryloxy-methyloxiranes **3**, racemic 3-aryloxy-1-isopropylaminopropan-2-ols **4** and 3-aryloxy-1-*tert*-butylaminopropan-2-ols **5** were obtained by nucleophilic oxirane cleavage with isopropylamine and *tert*-butylamine, respectively (Scheme 2).

A similar protocol was applied for the nucleophilic substitution of optically active halogenopropanols (*R*)-**1** and halogenopropanols acetates (*S*)-**2** with isopropylamine and *tert*-butylamine. Alkylamination of halogenopropanol acetates (*S*)-**2** was conducted in the presence of sodium hydroxide for the simultaneous hydrolysis of the acetate group. A series of new 1-alkylamino-3-aryloxypropan-2-ols in both enantiomeric forms was synthesized as a proof of usefulness of these new building blocks for constructing aryloxypropanolamines containing structurally variable amine part. The high enantiomeric excess of halogenopropanol is preserved during subsequent amination reaction yielding a final product with high ee. This is not the case when epichlorohydrin enantiomers are used as synthons for 2-aryloxymethyloxirane preparation, because of a concomitant significant decrease in enantiomeric purity in this step [26].

Unambiguous assignment of 3-aryloxyhalogenopropan-2-ol absolute configuration preferred by all the lipases studied (except *C. rugosa* for **1a**–**e**, **1h**, **1i**) during the acetyl transfer reaction was confirmed by the preparation of (*R*)-2-aryloxymethyloxiranes from (S)-epichlorohydrin and respective phenols, and a subsequent oxirane opening with isopropylamine.

For all the compounds studied, the same enantiomer of 1-isopropylamino-3-aryloxypropan-2-ol was obtained from (S)-epichlorohydrin and a respective acetate of halogenopropanol (*S*)-**2** (Scheme 3).



Scheme 3. Assignment of Lipozyme® TL enantiopreference in acetylation of 3-aryloxy-1-halogenopropan-2-ols **1a**–**i** with vinyl acetate.

4. Conclusions

The resolution of racemic 3-aryloxy-1-halogenopropan-2-ols by lipase-catalyzed acyl transfer provides access to both enantiomers of versatile intermediates for synthesis of new β-receptors antagonists. Inexpensive commercial lipase Lipozyme® TL exhibits high activity and enantioselectivity for a broad range of aryloxyhalogenopropanols yielding at 50% conversion, both enantiomers of ee exceeding 90%.

For substrates with more bulky aryloxy substituent Novozym® 435 exhibits higher activity and comparable to Lipozyme® TL enantioselectivity. When very high enantiomeric purity is required, two-step resolution might be considered.

3-Aryloxy-1-chloropropan-2-ols are slightly favored as substrates for resolution over bromo analogues. Resolved enantiomers of aryloxyhalogenopropanols can serve as versatile building blocks for the preparation of numerous aryloxypropanolamine derivatives with a structurally varying amine part (the third generation β-blockers) with excellent yield and high enantiomeric excess.

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