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# Lipase mediated enantiomer and diastereomer separation of 2,2′-[1,2- and 1,3-phenylenebis(oxy)]dicyclohexanols

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**Abstract**—Separation of diastereomeric and enantiomeric mixtures of 2,2′-[1,2- and 1,3-phenylenebis(oxy)]dicyclohexanols *rac*-**3a** and *meso*-**3a**, and *rac*-**3b** and *meso*-**3b**—resulting from the reactions of pyrocatechol **1a** and resorcinol **1b** with cyclohexene oxide **2**—were performed using acetylation catalyzed by the highly stereoselective *Candida antarctica* lipase B (Novozym 435). The absolute configurations of the resulting diols (*S*,*S*,*S*,*S*)-**3a**,**b**, monoacetates (*R*,*R*,*S*,*S*)-**4a**,**b** and diacetates (*R*,*R*,*R*,*R*)-**5a**,**b** were assigned on the basis of the steric analogy to the acetylation of racemic *trans*-2-phenoxycyclohexanol *rac*-**6** with the same enzyme resulting in the known acetate (−)-(*R*,*R*)-**7**.


## 1. Introduction

In organic and bioorganic chemistry, demand is increasing for convenient methods resulting in enantiomerically pure compounds. For the synthesis of various optically active molecules, asymmetric chemical reactions using chiral auxiliaries, among other methods, can be applied. The cyclohexanol-based chiral auxiliaries such as (+)- or (−)-menthol,[1] (−)-8-phenylmenthol,[2] (+)- or (−)-*trans*-2-phenylcyclohexanol[3] are useful in asymmetric transformations. Since the structurally related *trans*-2-aryloxycyclohexan-1-ol derivatives have also gained some interest as chiral auxiliaries in organic synthesis, various methods have been developed for their synthesis in enantiomerically pure form. For example, pig liver acetone powder (PLAP) was applied for the enantiomer selective hydrolysis of racemic *trans*-1-acetoxy-2-aryloxycyclohexanes to produce (−)-(*R*,*R*)-*trans*-2-aryloxycyclohexan-1-ols in high enantiomeric purities.[4] Hydrolysis of the corresponding racemic acetates can also be performed using other crude enzymes such as goat, chicken and bovine liver acetone powders resulting in the corresponding optically active 2-aryloxycyclohexan-1-ols.[5]

Although the enantioselective preparation of the 2-monosubstituted *trans*-cyclohexanol derivatives is well studied and the synthesis of the stereoisomeric mixtures of 2,2′-[1,2- or 1,3-phenylenebis(oxy)]dicyclohexanols is easy (Scheme 1), there are no examples describing the preparation of the pure diastereomers and enantiomers of diols **3a** and **3b**. These optically active compounds are potential chiral auxiliaries and can also serve as chiral building blocks in the synthesis of optically active crown ethers. Using such chiral units as precursors for highly substituted crown ether extractants will make crown ether molecules more rigid limiting their conformational flexibility and can thus affect their extraction or complexation properties.[6,7] For example, *meso*-2,2′-[1,2-phenylenebis(oxy)]dicyclohexanol *meso*-**3a** was structurally characterized and is a potential precursor for highly substituted crown ethers.[8] In addition, a diastereomeric and enantiomeric mixture of racemic and *meso*-diols can be separated into pure stereoisomers by the aid of a highly selective enzyme. For example, acetylation of a diastereomeric mixture of racemic and *meso*-2,6-bis (1-hydroxyethyl)pyridine with vinyl acetate and immobilized *Candida antarctica* lipase B (Novozym 435) resulted in a mixture of enantiopure (*S*,*S*)-diol, (*R*,*S*)-monoacetate and (*R*,*R*)-diacetate.[9] It can also be assumed that a highly selective enzyme retains its strict steric preference towards one of the local arrangements [either (1*S*,2*S*) or (1*R*,2*R*)] of the 2-*trans*-substituted cyclohexanols. In acetylation reactions with such an enzyme, the

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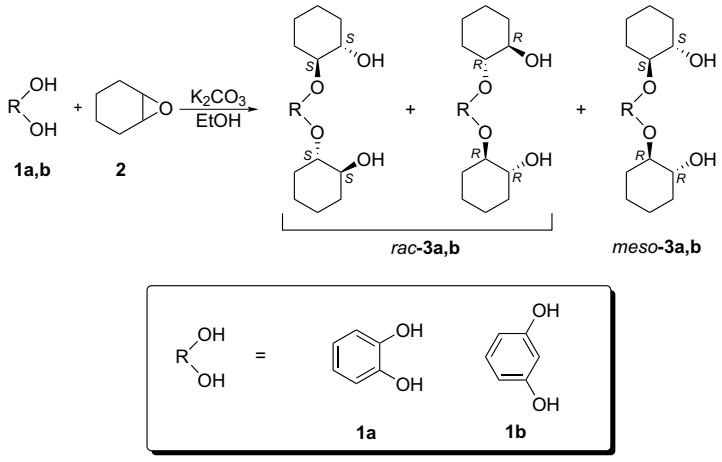
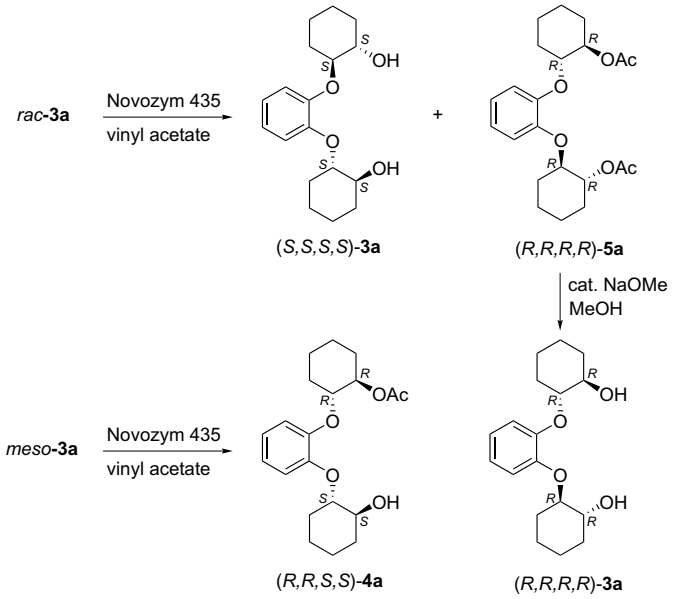



**Scheme 1.** Synthesis of diastereomeric and enantiomeric mixtures of 2,2′-[1,2- and 1,3-phenylenebis(oxy)]dicyclohexanols *rac*-**3a** and *meso*-**3a** and *rac*-**3b** and *meso*-**3b**.

racemates *rac*-**3a**,**b** should split into the intact diol (slowly reacting enantiomer) and diacetate (forming from the fast reacting diol enantiomer), whereas acetylation of the *meso*-diastereomers *meso*-**3a**,**b** should lead to a pure monoacetate enantiomer. Therefore, enzymatic acetylation of the stereoisomeric mixtures of 2,2′-[1,2- or 1,3-phenylenebis(oxy)]dicyclohexanols **3a** and **3b** with a highly selective enzyme was expected to result in mixtures of enantiopure diol, monoacetate and diacetate. Herein, we have synthesized from cyclohexene-oxide **2** and pyrocatechol **1a** or resorcinol **1b** the stereoisomeric mixtures of two aromatic bis-cyclohexanols **3a** and **3b** and developed efficient enzymatic methods for separation of their stereoisomers (diastereomers and enantiomers).

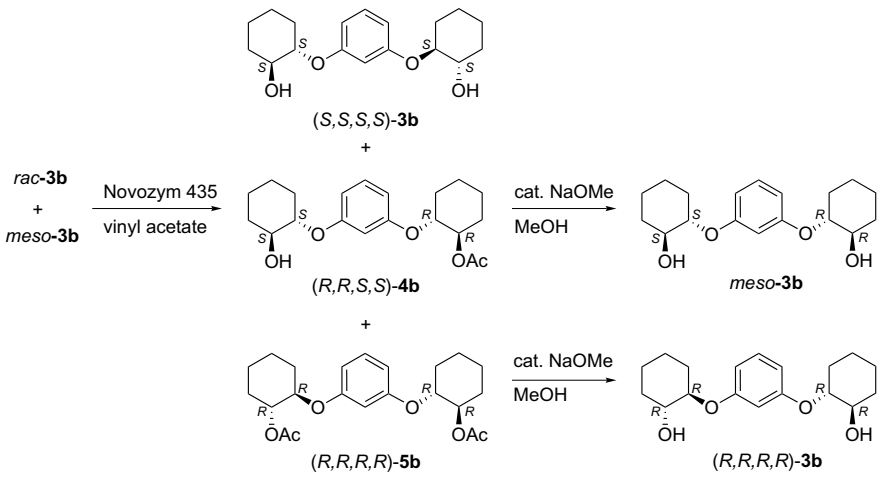
## 2. Results and discussion

The two target diols 2,2′-[1,2-phenylenebis(oxy)]dicyclohexanol **3a** and 2,2′-[1,3-phenylenebis(oxy)]dicyclohexanol **3b** were prepared by the ring opening reaction of cyclohexene oxide **2** with the proper phenolic diols **1a** or **1b**[10] (Scheme 1). As previously described,[8] the *meso*- and racemic forms of 2,2′-[1,2-phenylenebis(oxy)]dicyclohexanol (*meso*-**3a** and *rac*-**3a**) were separable by silica gel chromatography. On the other hand, the reaction of cyclohexene oxide **2** with **1b** resulted in a virtually inseparable mixture of racemic and *meso*-forms of 2,2′-[1,3-phenylenebis(oxy)]dicyclohexanols *rac*-**3b** and *meso*-**3b**. In our previous study on the enzymatic acetylation of the diastereomeric mixture (racemic and *meso*-isomers in a 1:1 ratio) of 2,6-bis(1-hydroxyethyl)pyridine resulting in a mixture of pure (*S*,*S*)-diol, (*R*,*S*)-monoacetate and (*R*,*R*)-diacetate in a ratio of 1:2:1,[9] the first task was to find a highly selective enzyme. In order to choose the most selective enzyme for acetylation of the bis-cyclohexanol substrates **3a** and **3b**, three series of test reactions were performed using (i) *rac*-**3a**, (ii) *meso*-**3a** and (iii) *rac*-**3b** and *meso*-**3b** in vinyl acetate in the presence of nine commercially available lipases and a crude esterase prepared in our laboratory (porcine liver acetone powder, PLAP). The progress of the enzymatic reactions was checked by TLC using chemically prepared monoacetates **4a** and **4b** and diacetates **5a** and **5b** as standards. Among the enzymes tested, only Novozym 435 converted the racemic *rac*-**3a** into its diacetate **5a** with a conversion of about 50%, and the *meso*-form *meso*-**3a** almost totally into monoacetate **4a** (Scheme 2). In the case of the stereoisomeric mixture *rac*-**3b** and *meso*-**3b**, enzymatic acetylation with Novozym 435 also led to diol **3b**, monoacetate **4b** and diacetate **5b** in the expected 1:2:1 ratio (Scheme 3). On the basis of the small scale test results, preparative scale separations of the stereomers of the two target diols **3a** and **b** were performed using only Novozym 435 as a catalyst.




**Scheme 2.** Novozym 435-catalyzed acetylation of the separated 2,2′-[1,2-phenylenebis-(oxy)]dicyclohexanol diastereomers *rac*-**3a** and *meso*-**3a**.

For deducing the absolute configuration of the stereoisomers of 2,2′-[1,2- or 1,3-phenylenebis(oxy)]dicyclohexanols **3a** and **3b**, the enzymatic acylation of their monocyclohexene oxide ring opening analogue *trans*-2-phenoxycyclohexanol *rac*-**6** has been used as a model. It can be assumed that




**Scheme 3.** Novozym 435-catalyzed acetylation of the diastereomeric and enantiomeric mixture of 2,2′-[1,3-phenylenebis(oxy)]dicyclohexanols *rac*-**3b** and *meso*-**3b**.

the highly selective *C. antarctica* lipase B (Novozym 435) retains its strict steric preference towards one of the local arrangements [either (1*S*,2*S*) or (1*R*,2*R*)] of the 2-*trans*-aryloxy-substituted cyclohexanol moiety in the acetylation of *rac*-**6** and also in the acetylation of the 2,2′-[1,2- or 1,3-phenylenebis(oxy)]dicyclohexanol stereoisomers **3a** and **3b** as only one of such units of diols **3a** or **3b** can fit into the active site at once. As the absolute configuration of (−)-*trans*-2-phenoxycyclohexan-l-ol (−)-**6** was assigned as (1*R*,2*R*)-**6** by copper catalyzed monophenylation of (−)-(1*R*,2*R*)-cyclohexanediol,[4] we performed the Novozym 435-catalyzed acetylation of *rac*-**6** to provide enantiomerically pure (+)-(1*S*,2*S*)-**6** and (−)-(1*R*,2*R*)-**7** (Scheme 4). It should be noted that the degree of enantiomer selectivity (*E*)[11] we could achieve in the Novozym 435-catalyzed acetylation ($E > 500$) was superior to that found in PLAP-catalyzed hydrolysis of *rac*-**7** ($E \sim 232$).[4] This experimentally observed strong preference of Novozym 435 towards the acetylation of the (1*R*,2*R*)-**6** enantiomer was also in full agreement with preliminary enantiomer selectivity calculations within the active site of this enzyme.[12] Based on these data, we assigned (+)-(1*R*,2*R*,1′*S*,2′*S*) absolute configuration to the optically active monoacetates **4a** and **4b** resulting from the enantiotope selective acetylation of *meso*-**3a** and *meso*-**3b** diastereomers and (−)-(1*R*,2*R*,1′*R*,2′*R*) absolute configuration to diacetates **5a** and **5b** forming from the faster reacting (1*R*,2*R*,1′*R*,2′*R*)-enantiomer of *rac*-**3a** and *rac*-**3b**.

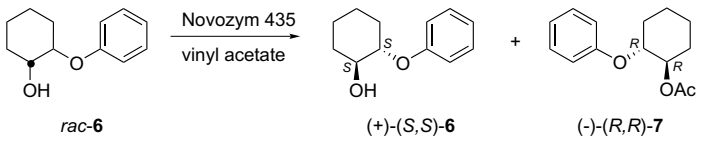
The high enantioselectivity of Novozym 435 was confirmed by preparative scale acetylation of *rac*-**3a** yielding virtually enantiopure diol (*S*,*S*,*S*,*S*)-**3a** and diacetate (*R*,*R*,*R*,*R*)-**5a** (Scheme 2 and Table 1). The hydrolysis of (*R*,*R*,*R*,*R*)-**5a** resulting in enantiopure (*R*,*R*,*R*,*R*)-**3a** (ee >99.5%) was also performed by this enzyme proving the (1*R*,2*R*)-stereopreference of the *C. antarctica* lipase B in hydrolysis as well. This strict (1*R*,2*R*)-stereopreference was observed in enantiotope selective (i.e., asymmetric) acetylation of the *meso*-diastereomer *meso*-**3a**, leading to exclusive formation of enantiopure (*R*,*R*,*S*,*S*)-**4a** (Scheme 2 and Table 1).

Separation of the stereomeric mixture of *rac*-**3b** and *meso*-**3b** was realized in one step by enzymatic acetylation with vinyl acetate using Novozym 435 lipase as a catalyst (Scheme 3). The reaction resulted in the formation of enantiopure products such as unreacted diol (*S*,*S*,*S*,*S*)-**3b** and diacetate (*R*,*R*,*R*,*R*)-**5b** from *rac*-**3b**, and (*R*,*R*,*S*,*S*)-**4b** forming from *meso*-**3b** (Table 1). This reaction proved the strict (1*R*,2*R*)-stereopreference of *C. antarctica* lipase B towards the stereoisomers of 2,2′-[1,3-phenylenebis(oxy)]-dicyclohexanols *rac*-**3b** and *meso*-**3b** as well. The further stereoisomers of **3b**, *meso*-**3b** and (*R*,*R*,*R*,*R*)-**3b**, were prepared in pure form by the chemical hydrolysis of the corresponding monoacetate (*R*,*R*,*S*,*S*)-**4b** and diacetate (*R*,*R*,*R*,*R*)-**5b**.

## 3. Conclusion

A simple synthesis of the stereoisomeric mixtures of 2,2′-[1,2- or 1,3-phenylenebis(oxy)]-dicyclohexanols **3a** and **3b** was developed to provide compounds, which in their stereoisomerically pure form, are potential chiral auxiliaries and can also serve as chiral building blocks in the synthesis of optically active crown ethers.

*C. antarctica* lipase B (Novozym 435) has been found as a highly stereoselective enzyme for the acetylation of these




**Scheme 4.** Novozym 435-catalyzed acetylation of racemic *trans*-2-phenoxycyclohexanol *rac*-**6**.

**Table 1.** Specific rotations and enantiomeric composition of stereoisomers **3**–**5a**,**b**, **6** and **7**

| Compound | Yield (%) | $[\alpha]_D^{25}$ | | | ee (%) |
|---|---|---|---|---|---|
| | | *c* 1, $CHCl_3$ | *c* 1, acetone | *c* 1, EtOH | |
| (*S*,*S*,*S*,*S*)-**3a** | 21 | +125.5 | +85.5 | +65.8 | 96[a] |
| (*R*,*R*,*R*,*R*)-**3a** | 75 | −130.6 | −89.0 | −68.5 | >99[b] |
| (*S*,*S*,*S*,*S*)-**3b** | 32 | +92.4 | +78.3 | +92.3 | >98[a] |
| (*R*,*R*,*R*,*R*)-**3b** | 75 | −93.3 | −79.3 | −92.9 | >99[b] |
| (*R*,*R*,*S*,*S*)-**4a** | 52 | +51.2 | +21.4 | +28.1 | >98[a] |
| (*R*,*R*,*S*,*S*)-**4b** | 43 | +34.5 | +18.8 | +25.7 | >98[a] |
| (*R*,*R*,*R*,*R*)-**5a** | 16 | −8.6 | −30.9 | −6.8 | >99[c] |
| (*R*,*R*,*R*,*R*)-**5b** | 34 | −3.1 | −8.8 | Not soluble | >99[c] |
| (*S*,*S*)-**6** | 44 | +90.8 | +43.9 | +69.5[d] | >99[f] |
| (*R*,*R*)-**7** | 38 | −5.2 | −15.2 | −10.0 | >99[f] |
| (*R*,*R*)-**6** | 84 | −82.9 | −54.1 | −74.9[e] | >99[f] |

[a] Ee was determined by 500 MHz $^1$H NMR using Pr shift reagent, see Section 4.16.
[b] Ee was determined by specific rotation compared to the (*S*,*S*,*S*,*S*)-**3a** or (*S*,*S*,*S*,*S*)-**3b**.
[c] Ee was deduced from hydrolysis to alcohols (*R*,*R*,*R*,*R*)-**3a** or (*R*,*R*,*R*,*R*)-**3b**.
[d] $[\alpha]_D^{25} = +72.7$ (*c* 1, MeOH); lit.:[4] = +66.1 (*c* 1.26, MeOH).
[e] $[\alpha]_D^{25} = -80.9$ (*c* 1, MeOH); lit.:[4] = −79.1 (*c* 0.86, MeOH).
[f] Ee was determined by GC on Hydrodex-β-6-TBDM column, see Section 4.1.3.

diols to provide an easy method for the separation of the stereoisomeric forms of **3a** or **3b** as enantiopure diols (*S*,*S*,*S*,*S*)-**3a** or **3b**, monoacetates (*R*,*R*,*S*,*S*)-**4a** or **4b** and diacetates (*R*,*R*,*R*,*R*)-**5a** or **5b**.

The Novozym 345-catalyzed acetylation of the racemic *trans*-2-phenoxycyclohexanol *rac*-**6** with the same enzyme resulting in the known acetate (−)-(*R*,*R*)-**7** proved to not only be a useful analogy to assign (+)-(1*R*,2*R*,1′*S*,2′*S*) absolute configuration to monoacetates **4a** and **4b** and (−)-(1*R*,2*R*,1′*R*,2′*R*) absolute configuration to diacetates **5a** and **5b** but also its enantiomer selectivity ($E > 500$) exceeded that found in PLAP-catalyzed hydrolysis of the corresponding racemic acetate *rac*-**7**.

## 4. Experimental

### 4.1. Materials and methods

**4.1.1. Reagents and solvents.** Vinyl acetate, acetic anhydride, cyclohexene oxide, pyrocatechol, resorcinol, sodium methoxide and triethylamine were purchased from Aldrich. All solvents were of analytical grade or freshly distilled. Praseodymium D-3-heptafluorobutyrylcamphorate was obtained from Alfa Aesar (Karlsruhe, Germany). Racemic *trans*-2-phenoxycyclohexanol *rac*-**6** and *trans*-2-phenoxycyclohexyl acetate *rac*-**7** are known compounds.[4]

**4.1.2. Biocatalysts.** Lipase AK, lipase AY and lipase PS were obtained from Amano Europe. Lipozyme IM 20, Lipozyme TL IM and Novozym 435 were products of Novozymes, Denmark. Lipase from *Pseudomonas fluorescens* was purchased from Fluka. PPL was obtained from Sigma. Pig liver acetone powder (PLAP) was prepared in our laboratory.

**4.1.3. Analytical methods.** NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz for $^1$H and 125 MHz for $^{13}$C; TMS; ppm on $\delta$ scale) in $CDCl_3$ if not stated otherwise. The $^1$H and $^{13}$C NMR signals were assigned on the basis of APT, HMQC, HMBC and COSY experiments. GC analyses for the enantiomer separation of **6** and **7** were carried out on HP 5890 instrument equipped with FID detector using $H_2$ as carrier gas (injector: 250 °C, detector: 250 °C, head pressure: 12 psi, 1:80 split ratio) on Hydrodex-β-6-TBDM (25 m × 0.25 mm × 0.25 μm film, Macherey & Nagel, No.: 21519/11) column. IR spectra were taken on a Specord 2000 spectrometer and the wave numbers are reported in $cm^{-1}$. Optical rotations were determined on a Perkin Elmer 241 polarimeter. TLC was carried out on Kieselgel 60 $F_{254}$ (Merck) sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates.

### 4.2. 2,2′-[1,2-Phenylenebis(oxy)]dicyclohexanol *rac*-3a and *meso*-3a

Cyclohexene oxide **2** (2.94 g, 30 mmol) was added to a mixture of pyrocatechol **1a** (1.1 g, 10 mmol) and potassium carbonate (4.14 g, 30 mmol) in ethanol (50 mL) and the resulting mixture was stirred at reflux for 15 h. The reaction mixture was filtered and washed with ethanol (2 × 20 mL). The combined filtrates were concentrated under reduced pressure to a volume of 15 mL and diluted with dichloromethane (50 mL). The resulting solution was washed with 5% HCl (30 mL) and brine (2 × 20 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel/hexane–acetone 10:1 to 10:2) to give *rac*-**3a** (0.820 g, 18%) and *meso*-**3a** (0.880 g, 19.5%) as white powders.

**4.2.1. Racemic (1*S**,2*S**,1′*S**,2′*S**)-2,2′-[1,2-phenylenebis-(oxy)]dicyclohexanol *rac*-3a.** Mp: 102–104 °C (acetonitrile); IR (KBr): 3450, 2962, 1590, 1448, 1418, 1356, 1290, 1226, 1118, 1080, 1018, 914; $^1$H NMR: 1.28 (2H, m, $H_5 + H_{5'}$), 1.31 (4H, m, $H_4 + H_{4'} + H_6 + H_{6'}$),

1.46 (2H, m, $H_3 + H_{3'}$), 1.71 (2H, m, $H_4 + H_{4'}$), 1.74 (2H, m, $H_5 + H_{5'}$), 2.08 (2H, m, $H_6 + H_{6'}$), 2.20 (2H, m, $H_3 + H_{3'}$), 3.64 (2H, br s, 2OH), 3.73 (2H, m, $H_1 + H_{1'}$), 3.82 (2H, br s, $H_2 + H_{2'}$), 6.96 (2H, m, $H_{Ar4} + H_{Ar5}$), 7.01 (2H, m, $H_{Ar3} + H_{Ar6}$); $^{13}$C NMR: 23.85 ($C_4 + C_{4'}$), 24.30 ($C_5 + C_{5'}$), 30.70 ($C_3 + C_{3'}$), 32.38 ($C_6 + C_{6'}$), 73.69 ($C_1 + C_{1'}$), 82.63 ($C_2 + C_{2'}$), 119.39 ($C_{Ar3} + C_{Ar6}$), 123.13 ($C_{Ar4} + C_{Ar5}$), 149.51 ($C_{Ar1} + C_{Ar2}$). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56, H, 8.55. Found: C, 70.53; H, 8.56.

#### 4.2.2. *meso*-(1*S*,2*S*,1′*R*,2′*R*)-2,2′-[1,2-Phenylenebis(oxy)]-dicyclohexanol *meso*-3a.

Mp: 112–115 °C (acetonitrile); IR (KBr): 3448, 2958, 1588, 1448, 1416, 1360, 1288, 1224, 1120, 1080, 1020, 912, 816; $^1$H NMR: 1.25 (2H, m, $H_5 + H_{5'}$), 1.33 (4H, m, $H_4 + H_{4'} + H_6 + H_{6'}$), 1.41 (2H, m, $H_3 + H_{3'}$), 1.74 (4H, m, $H_4 + H_{4'} + H_5 + H_{5'}$), 2.10 (2H, m, $H_6 + H_{6'}$), 2.24 (2H, m, $H_3 + H_{3'}$), 3.71 (4H, m, $H_1 + H_{1'} + H_2 + H_{2'}$), 3.88 (2H, br s, 2OH), 6.95 (2H, m, $H_{Ar4} + H_{Ar5}$), 6.99 (2H, m, $H_{Ar3} + H_{Ar6}$); $^{13}$C NMR: 24.00 ($C_4 + C_{4'}$), 24.15 ($C_5 + C_{5'}$), 30.02 ($C_3 + C_{3'}$), 32.33 ($C_6 + C_{6'}$), 73.41 ($C_1 + C_{1'}$), 86.30 ($C_2 + C_{2'}$), 118.95 ($C_{Ar3} + C_{Ar6}$), 122.74 ($C_{Ar4} + C_{Ar5}$), 149.08 ($C_{Ar1} + C_{Ar2}$). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56, H, 8.55. Found: C, 70.57; H, 8.49.

### 4.3. 2,2′-[1,3-Phenylenebis(oxy)]dicyclohexanols *rac*-3b and *meso*-3b

Cyclohexene oxide **2** (6 g, 61 mmol) was added to a mixture of resorcinol **1b** (2.2 g, 20 mmol) and potassium carbonate (6.94 g, 50 mmol) in ethanol (80 mL); the resulting mixture was stirred at reflux for 15 h. The reaction mixture was filtered and washed with ethanol (2 × 30 mL). The combined filtrates were concentrated under reduced pressure to a volume of 20 mL and diluted with dichloromethane (80 mL). The resulting solution was washed with 5% HCl (30 mL) and brine (2 × 20 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane–acetone 10:2) to give a mixture of *rac*-**3b** and *meso*-**3b** (4.2 g, 45%) as a white powder. Mp: 116–120 °C (hexane–acetone 10:2); IR (KBr): 3456, 2928, 2856, 1592, 1488, 1452, 1264, 1180, 1156, 1072, 1044, 832, 768. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56, H, 8.55. Found: C, 70.52; H, 8.51.

### 4.4. Racemic (1*R**,2*R**)-2-(2-{[(1*S**,2*S**)-2-hydroxycyclohexyl]oxy}phenoxy)cyclohexyl acetate *rac*-4a

*meso*-2,2′-[1,2-Phenylenebis(oxy)]dicyclohexanol *meso*-**3a** (300 mg, 0.65 mmol), acetic anhydride (100 mg, 0.98 mmol), triethylamine (10 mL) and DMAP (5 mg) were stirred at rt for 7 days. The reaction mixture was diluted with chloroform (20 mL) and washed with water (3 × 15 mL), 5% HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic solution was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane–acetone 10:1) to yield *rac*-**4a** (87 mg, 40%) as a colourless oil. IR (film): 3504, 2936, 2864, 1736, 1592, 1496, 1456, 1376, 1256, 1040, 748; $^1$H NMR: 1.28 (1H, m, $H_{5'}$), 1.34 (3H, m, $H_4 + H_{4'} + H_{6'}$), 1.44 (3H, m, $H_{3'} + H_5 + H_6$), 1.62 (1H, m, $H_3$), 1.75 (3H, m, $H_4 + H_{4'} + H_{5'}$), 1.78 (1H, m, $H_5$), 1.94 (3H, s, $CH_3$), 2.10 (2H, m, $H_6 + H_{6'}$), 2.20 (2H, m, $H_3 + H_{3'}$), 3.4 (1H, br s, OH), 3.76 (2H, m, $H_{1'} + H_{2'}$), 4.25 (1H, m, $H_2$), 5.07 (1H, m, $H_1$), 6.91 (1H, t, $H_{Ar5}$), 6.96 (1H, t, $H_{Ar4}$), 6.99 (1H, d, $H_{Ar6}$), 7.02 (1H, d, $H_{Ar3}$); $^{13}$C NMR: 21.11 (*C*$H_3$), 23.10 ($C_4$ or $C_5$), 23.14 ($C_4$ or $C_5$), 23.85 ($C_{5'}$), 24.16 ($C_{4'}$), 29.77 ($C_3$ or $C_6$), 29.84 ($C_3$ or $C_6$), 30.15 ($C_{3'}$), 32.12 ($C_{6'}$), 73.43 ($C_{1'}$), 74.60 ($C_1$), 79.03 ($C_2$), 85.69 ($C_{2'}$), 116.63 ($C_{Ar3}$), 118.45 ($C_{Ar6}$), 121.77 ($C_{Ar5}$), 122.36 ($C_{Ar4}$), 148.83 ($C_{Ar2}$), 149.24 ($C_{Ar1}$), 170.70 (*C*OO). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.00; H, 8.07.

### 4.5. Racemic (1*S**,2*S**,1′*S**,2′*S**)-2,2′-diacetoxy-[1,2-phenylenebis(oxy)]dicyclohexane *rac*-5a

Racemic 2,2′-[1,2-phenylenebis(oxy)]dicyclohexanol *rac*-**3a** (200 mg, 0.65 mmol), acetic anhydride (133 mg, 1.30 mmol), triethylamine (10 mL) and DMAP (5 mg) were stirred at rt for 7 days. The reaction mixture was diluted with chloroform (20 mL) and washed with water (3 × 15 mL), 5% HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic solution was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane–acetone 10:2) to give *rac*-**5a** (96 mg, 40%) as a colourless oil. IR (film): 3480, 2936, 2864, 1736, 1496, 1456, 1372, 1244, 1040, 752; $^1$H NMR: 1.32 (2H, m, $H_4 + H_{4'}$), 1.41 (4H, m, $H_5 + H_{5'} + H_6 + H_{6'}$), 1.57 (2H, m, $H_3 + H_{3'}$), 1.72 (4H, m, $H_4 + H_{4'} + H_5 + H_{5'}$), 1.93 (6H, s, $2CH_3$), 2.07 (4H, m, $H_3 + H_{3'} + H_6 + H_{6'}$), 4.20 (2H, m, $H_2 + H_{2'}$), 4.97 (1H, m, $H_1 + H_{1'}$), 6.89 (2H, m, $H_{Ar4} + H_{Ar5}$), 6.97 (2H, m, $H_{Ar3} + H_{Ar6}$); $^{13}$C NMR: 21.22 (2*C*$H_3$), 22.96 ($C_4 + C_{4'} + C_5 + C_{5'}$), 29.56 ($C_3 + C_{3'}$ or $C_6 + C_{6'}$), 29.85 ($C_3 + C_{3'}$ or $C_6 + C_{6'}$), 74.62 ($C_1 + C_{1'}$), 78.70 ($C_2 + C_{2'}$), 118.38 ($C_{Ar3} + C_{Ar6}$), 122.05 ($C_{Ar4} + C_{Ar5}$), 149.25 ($C_{Ar1} + C_{Ar2}$), 170.36 (2 *C*OO). Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.75; H, 7.71.

### 4.6. Chemical acetylation of 2,2′-[1,3-Phenylenebis(oxy)]dicyclohexanols *rac*-3b and *meso*-3b

A diastereomeric mixture of *rac*-**3b** and *meso*-**3b** (200 mg, 0.65 mmol), acetic anhydride (102 mg, 1.00 mmol) and DMAP (5 mg) were added to triethylamine (10 mL) and the resulting mixture was stirred at rt for 7 days. The reaction mixture was diluted with chloroform (20 mL) and washed with water (3 × 15 mL), 5% HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic solution was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane–acetone 10:0.5 to 10:2) to give *rac*-**4b** and *meso*-**4b** (43 mg, 19%) and *rac*-**5b** and *meso*-**5b** (66 mg, 26%) as colourless oils.

The monoacetates *rac*-**4b** and *meso*-**4b** and diacetates *rac*-**5b** and *meso*-**5b** were prepared as standards for TLC analyses and therefore no detailed spectral characterization of the diastereomeric mixtures was performed.

### 4.7. Screening the enzymatic acetylation of racemic and *meso*-2,2′-[1,2-phenylenebis(oxy)]dicyclohexanols *meso*-3a and *rac*-3a and 2,2′-[1,3-phenylenebis(oxy)]dicyclohexanols *rac*-3b and *meso*-3b

Enzymes (20 mg, listed in Section 4.1.2) were added to solutions of racemic and *meso*-forms of 2,2′-[1,2-phenylenebis(oxy)]dicyclohexanol *rac*-**3a**/*meso*-**3a**, and to 2,2′-[1,3-phenylenebis(oxy)]dicyclohexanol *rac*-**3b** + *meso*-**3b** (20 mg, each diol with each enzyme) in vinyl acetate (1 mL). The resulting suspensions were shaken at rt/1000 rpm in a sealed glass vial for 5 days. The progress of the reactions was checked by TLC (hexane–acetone 10:4) using chemically prepared monoacetate *rac*-**4a**,**b** and diacetate *rac*-**5a**,**b** standards.

### 4.8. Novozym 435 catalyzed acetylation of racemic 2,2′-[1,2-phenylenebis(oxy)]dicyclohexanol *rac*-3a

Racemic diol *rac*-**3a** (400 mg, 1.52 mmol) and Novozym 435 (400 mg) were added to vinyl acetate (25 mL) and the resulting mixture was shaken at rt for 9 days. After removing the enzyme by filtration, vinyl acetate was evaporated off under reduced pressure and the residue was purified by column chromatography (silica gel/hexane–acetone 10:0.5 to 10:4) to yield (*S*,*S*,*S*,*S*)-**3a** (83 mg, 21%) as a white powder and (*R*,*R*,*R*,*R*)-**5a** (79 mg, 16%) as colourless oil.

**4.8.1. (1*S*,2*S*,1′*S*,2′*S*)-2,2′-[1,2-Phenylenebis(oxy)]dicyclohexanol (*S*,*S*,*S*,*S*)-3a.** Mp: 108–110 °C; $[\alpha]_D^{25} = +125.5$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = +85.5$ (*c* 1.0, acetone); $[\alpha]_D^{25} = +65.8$ (*c* 1.0, EtOH); IR, $^1H$ and $^{13}C$ NMR data were indistinguishable from the spectra of *rac*-**3a**.

**4.8.2. 1,2-Phenylenebis[oxy(1*R*,2*R*)cyclohexane-2,1-diyl] diacetate (*R*,*R*,*R*,*R*)-5a.** $[\alpha]_D^{25} = -8.6$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = -30.9$ (*c* 1.0, acetone); $[\alpha]_D^{25} = -6.8$ (*c* 1.0, EtOH); IR, $^1H$ and $^{13}C$ NMR data were indistinguishable from the spectra of *rac*-**5a**.

### 4.9. (1*R*,2*R*,1′*R*,2′*R*)-2,2′-[1,2-Phenylenebis(oxy)]dicyclohexanol (*R*,*R*,*R*,*R*)-3a

A solution of diacetate (*R*,*R*,*R*,*R*)-**5a** (40 mg, 1.21 mmol) and sodium methoxide (4 mg) in methanol (2 mL) was stirred at rt for 48 h. The resulting mixture was diluted with dichloromethane (20 mL) and washed with 5% HCl (25 mL) and satd $Na_2CO_3$ solution (2 × 5 mL) and dried over $K_2CO_3$. After concentrating under reduced pressure, the residue was purified by column chromatography (silica gel/hexane–acetone 10:4) to yield (*R*,*R*,*R*,*R*)-**3a** (25 mg, 75%) as a white powder. Mp: 107–110 °C (acetonitrile); $[\alpha]_D^{25} = -130.6$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = -89.0$ (*c* 1.0, acetone); $[\alpha]_D^{25} = -68.5$ (*c* 1.0, EtOH); IR, $^1H$ and $^{13}C$ NMR data were indistinguishable from the spectra of *rac*-**3a**.

### 4.10. Novozym 435 catalyzed acetylation of *meso*-2,2′-[1,2-phenylenebis(oxy)]dicyclohexanol *meso*-3a

*meso*-Diol *meso*-**3a** (400 mg, 1.52 mmol) and Novozym 435 (400 mg) were added to vinyl acetate (25 mL) and the resulting mixture was shaken at rt for 7 days. After removing the enzyme by filtration, vinyl acetate was evaporated off under reduced pressure and the residue was purified by column chromatography (silica gel/hexane–acetone 10:0.5) to yield (*R*,*R*,*S*,*S*)-**4a** (227 mg, 52%) as a colourless oil.

**4.10.1. (1*R*,2*R*)-2-(2-{[(1*S*,2*S*)-2-Hydroxycyclohexyl]oxy}-phenoxy)cyclohexyl acetate (*R*,*R*,*S*,*S*)-4a.** $[\alpha]_D^{25} = +51.2$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = +21.4$ (*c* 1.0, acetone); $[\alpha]_D^{25} = +28.4$ (*c* 1.0, EtOH); IR, $^1H$ and $^{13}C$ NMR data were indistinguishable from the spectra of *rac*-**4a**.

### 4.11. Novozym 435 catalyzed acetylation of the diastereomeric mixture of 2,2′-[1,3-phenylenebis(oxy)]dicyclohexanols *rac*-3b and *meso*-3b

A diastereomeric mixture of *rac*-**3b** and *meso*-**3b** (350 mg, 1.15 mmol) and Novozym 435 (350 mg) were added to vinyl acetate (25 mL) and the resulting mixture was shaken at rt for 10 days. After removing the enzyme by filtration, vinyl acetate was evaporated off under reduced pressure and the residue was purified by column chromatography (silica gel/hexane–acetone 10:0.5 to 10:4) to yield (*S*,*S*,*S*,*S*)-**3b** (102 mg, 30%), (*R*,*R*,*S*,*S*)-**4b** (157 mg, 41%) and (*R*,*R*,*R*,*R*)-**5a** (128 mg, 31%) as white powders.

**4.11.1. (1*S*,2*S*,1′*S*,2′*S*)-2,2′-[1,3-Phenylenebis(oxy)]dicyclohexanol (*S*,*S*,*S*,*S*)-3b.** Mp 126–128 °C (hexane–acetone 10:2); $[\alpha]_D^{25} = +92.4$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = +78.3$ (*c* 1.0, acetone); $[\alpha]_D^{25} = +92.3$ (*c* 1.0, EtOH); IR (KBr): 3432, 2944, 2864, 1592, 1488, 1456, 1264, 1160, 1040, 776; $^1H$ NMR: 1.33 (6H, m, $H_3 + H_{3'} + H_4 + H_{4'} + H_5 + H_{5'}$), 1.41 (2H, m, $H_6 + H_{6'}$), 1.77 (4H, m, $H_4 + H_{4'} + H_5 + H_{5'}$), 2.12 (2H, m, $H_6 + H_{6'}$), 2.18 (2H, m, $H_3 + H_{3'}$), 2.52 (2H, br s, 2OH), 3.72 (2H, m, $H_1 + H_{1'}$), 4.00 (2H, m, $H_2 + H_{2'}$), 6.57 (1H, s, $H_{Ar2}$), 6.58 (2H, d, $J \sim 7.5$ Hz, $H_{Ar4,6}$), 7.17 (1H, t, $J \sim 7.5$ Hz, $H_{Ar5}$); $^{13}C$ NMR: 23.88 ($C_4 + C_{4'}$ or $C_5 + C_{5'}$), 23.98 ($C_4 + C_{4'}$ or $C_5 + C_{5'}$), 29.22 ($C_6 + C_{6'}$), 32.05 ($C_3 + C_{3'}$), 73.40 ($C_1 + C_{1'}$), 82.19 ($C_2 + C_{2'}$), 101.96 ($C_{Ar2}$), 108.87 ($C_{Ar4} + C_{Ar6}$), 129.99 ($C_{Ar5}$), 159.16 ($C_{Ar1} + C_{Ar3}$). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56, H, 8.55. Found: C, 70.58; H, 8.52.

**4.11.2. (1*R*,2*R*)-2-(3-{[(1*S*,2*S*)-2-Hydroxycyclohexyl]oxy}-phenoxy)cyclohexyl acetate (*R*,*R*,*S*,*S*)-4b.** Mp 56–58 °C (hexane); $[\alpha]_D^{25} = +34.5$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = +18.8$ (*c* 1.0, acetone); $[\alpha]_D^{25} = +25.7$ (*c* 1.0, EtOH); IR (film): 3488, 2928, 2864, 1720, 1600, 1492, 1376, 1256, 1144, 1064, 1040, 844, 768; $^1H$ NMR: 1.30 (1H, m, $H_{6'}$), 1.33 (2H, m, $H_{4'} + H_{5'}$), 1.38 (3H, m, $H_4 + H_5 + H_{3'}$), 1.42 (1H, m, $H_3$ or $H_6$), 1.53 (1H, m, $H_3$ or $H_6$), 1.72 (2H, m, $H_4 + H_5$), 1.75 (2H, m, $H_{4'} + H_{5'}$), 1.96 (3H, s, $CH_3$), 2.04 (1H, m, $H_3$ or $H_6$), 2.09 (2H, m, ($H_3$ or $H_6$) + $H_{3'}$), 2.16 (1H, m, $H_{6'}$), 2.3 (1H, br s, OH), 3.70 (1H, m, $H_{2'}$), 3.98 (1H, m, $H_{1'}$), 4.20 (1H, m, $H_2$), 4.96 (1H, m, $H_1$), 6.53 (2H, m, $H_{Ar4} + H_{Ar6}$), 6.55 (1H, m, $H_{Ar2}$), 7.14 (1H, m, $H_{Ar5}$); $^{13}C$ NMR: 21.17 ($CH_3$), 22.90 ($C_4$ or $C_5$), 23.00 ($C_4$ or $C_5$), 23.84 ($C_{4'}$ or $C_{5'}$), 23.92 ($C_{4'}$ or $C_{5'}$), 29.19

($C_{6'}$), 29.59 (2C: $C_3$ and $C_6$), 31.99 ($C_{3'}$), 73.31 ($C_{2'}$), 73.93 ($C_1$), 77.25 ($C_2$), 82.06 ($C_{1'}$), 104.83 ($C_{Ar2}$), 108.75 ($C_{Ar6}$), 108.92 ($C_{Ar4}$), 129.84 ($C_{Ar5}$), 159.07 ($C_{Ar3}$), 159.52 ($C_{Ar1}$), 170.51 (*C*OO). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.77; H, 8.13.

#### 4.11.3. 1,3-Phenylenebis[oxy(1*R*,2*R*)cyclohexane-2,1-diyl] diacetate (*R*,*R*,*R*,*R*)-5b.

Mp 118–120 °C (hexane); $[\alpha]_D^{25} = -3.1$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = -8.8$ (*c* 1.0, acetone); IR (film): 2944, 2872, 1736, 1588, 1488, 1368, 1272, 1236, 1184, 1156, 1048; $^1$H NMR: 1.38 (4H, m, $H_4 + H_{4'} + H_5 + H_{5'}$), 1.44 (2H, m, $H_3 + H_{3'}$), 1.52 (2H, m, $H_6 + H_{6'}$), 1.73 (4H, m, $H_4 + H_{4'} + H_5 + H_{5'}$), 1.95 (6H, s, $2CH_3$), 2.10 (4H, m, $H_3 + H_{3'} + H_6 + H_{6'}$), 4.19 (2H, m, $H_2 + H_{2'}$), 4.96 (2H, m, $H_1 + H_{1'}$), 6.51 (1H, m, $H_{Ar2}$), 6.52 (2H, m, $H_{Ar4} + H_{Ar6}$), 7.12 (1H, m, $H_{Ar5}$); $^{13}$C NMR: 21.14 (2*C*$H_3$), 22.99 ($C_4 + C_{4'}$ or $C_5 + C_{5'}$), 23.10 ($C_4 + C_{4'}$ or $C_5 + C_{5'}$), 29.66 ($C_3 + C_{3'} + C_6 + C_{6'}$), 74.04 ($C_1 + C_{1'}$), 77.53 ($C_2 + C_{2'}$), 104.73 ($C_{Ar2}$), 108.71 ($C_{Ar4} + C_{Ar6}$), 129.67 ($C_{Ar5}$), 159.42 ($C_{Ar1} + C_{Ar3}$), 170.43 (2*C*OO). Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.61; H, 7.77.

### 4.12. (1*R*,2*R*,1′*R*,2′*R*)-2,2′-[1,3-Phenylenebis(oxy)]dicyclohexanol (*R*,*R*,*R*,*R*)-3b

A solution of (*R*,*R*,*R*,*R*)-**5b** (40 mg, 1.21 mmol) and sodium methoxide (4 mg) in methanol (2 mL) was stirred at rt for 48 h. The resulting mixture was diluted with dichloromethane (20 mL) and washed with 5% HCl (20 mL) and satd $Na_2CO_3$ solution (2 × 5 mL) and dried over $K_2CO_3$. After concentrating under reduced pressure, the residue was purified by column chromatography (silica gel/hexane–acetone 10:4) to yield (*R*,*R*,*R*,*R*)-**3b** (26 mg, 78%) as a white powder. Mp 128–129 °C (hexane–acetone 10:4); $[\alpha]_D^{25} = -93.3$ (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = -79.3$ (*c* 1.0, acetone); $[\alpha]_D^{25} = -92.9$ (*c* 1.0, EtOH); IR, $^1$H and $^{13}$C NMR data were indistinguishable from the spectra of *rac*-**3b**.

### 4.13. *meso*-2,2′-[1,3-Phenylenebis(oxy)]dicyclohexanol *meso*-3b

A solution of monoacetate (*R*,*R*,*S*,*S*)-**4b** (80 mg, 0.232 mmol) and sodium methoxide (6 mg) in methanol (4 mL) was stirred at rt for 48 h. The resulting mixture was diluted with dichloromethane (30 mL) and washed with 5% HCl (30 mL) and satd $Na_2CO_3$ solution (2 × 10 mL) and dried over $K_2CO_3$. After concentrating under reduced pressure, the residue was purified by column chromatography (silica gel/hexane–acetone 10:4) to yield *meso*-**3b** (50 mg, 72%) as a white semisolid. IR (nujol): 3448, 1586, 1256, 1154, 1036; $^1$H NMR: 1.30 (6H, m, $H_3 + H_{3'} + H_4 + H_{4'} + H_5 + H_{5'}$), 1.39 (2H, m, $H_6 + H_{6'}$), 1.74 (4H, m, $H_4 + H_{4'} + H_5 + H_{5'}$), 2.09 (2H, m, $H_6 + H_{6'}$), 2.15 (2H, m, $H_3 + H_{3'}$), 2.57 (2H, br s, 2OH), 3.70 (2H, m, $H_1 + H_{1'}$), 3.98 (2H, m, $H_2 + H_{2'}$), 6.54 (2H, br s, $H_{Ar4,6}$), 6.56 (1H, br s, $H_{Ar2}$), 7.15 (1H, t, $J \sim 8$ Hz, $H_{Ar5}$); $^{13}$C NMR: 23.88 ($C_4 + C_{4'}$ or $C_5 + C_{5'}$), 23.95 ($C_4 + C_{4'}$ or $C_5 + C_{5'}$), 29.20 ($C_6 + C_{6'}$), 30.05 ($C_3 + C_{3'}$), 73.38 ($C_1 + C_{1'}$), 82.19 ($C_2 + C_{2'}$), 105.09 ($C_{Ar2}$), 108.88 ($C_{Ar4} + C_{Ar6}$), 129.98 ($C_{Ar5}$) 159.13 ($C_{Ar1} + C_{Ar3}$). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56, H, 8.55. Found: C, 70.61; H, 8.48.

### 4.14. Racemic (1*R**,2*R**)-2-(3-{[(1*S**,2*S**)-2-hydroxycyclohexyl]oxy}phenoxy)cyclohexyl acetate *rac*-4b

*meso*-2,2′-[1,3-Phenylenebis(oxy)]dicyclohexanol *meso*-**3b** (30 mg, 0.098 mmol), acetic anhydride (24 mg, 0.24 mmol), triethylamine (1.2 mL) and DMAP (1 mg) were stirred at rt for 7 days. The reaction mixture was diluted with chloroform (10 mL) and washed with water (3 × 5 mL), 5% HCl solution (3 mL), saturated $NaHCO_3$ solution (3 mL) and brine (3 mL). The organic solution was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane–acetone 10:2) to yield *rac*-**4b** (17 mg, 50%) as colourless oil. $^1$H and $^{13}$C NMR spectra of *rac*-**4b** were identical to the spectra of pure enantiomer (*R*,*R*,*S*,*S*)-**4b**.

### 4.15. Novozym 435 catalyzed acetylation of racemic *trans*-2-phenoxycyclohexanol *rac*-6

Racemic alcohol *rac*-**6** (500 mg, 2.6 mmol) and Novozym 435 (500 mg) were added to vinyl acetate (25 mL) and the resulting mixture was shaken at rt for 3 h. After removing the enzyme by filtration, vinyl acetate was evaporated off under reduced pressure and the residue was purified by column chromatography (silica gel/toluene–ethylacetate 10:0.2 to 10:0.4) to yield (*S*,*S*)-**6** (220 mg, 44%) as a white powder and (*R*,*R*)-**7** (230 mg, 38%) as colourless oil.

#### 4.15.1. (+)-(1*S*,2*S*)-2-Phenoxycyclohexanol (1*S*,2*S*)-6.

Mp 82–83 °C (hexane), lit.:[13] 82 °C (hexane); $[\alpha]_D^{25} = +90.8$ (*c* 1, $CHCl_3$), $= +43.9$ (*c* 1, acetone), $= +69.5$ (*c* 1, EtOH), +72.7 (*c* 1, MeOH) (ee > 99% by GC), lit.:[4] +66.1 (*c* 1.26, MeOH); $^1$H NMR: 1.35 (3H, m, $H_3 + H_4 + H_5$), 1.42 (1H, m, $H_6$), 1.78 (2H, m, $H_4 + H_5$), 2.13 (1H, m, $H_6$), 2.18 (1H, m, $H_3$), 2.56 (1H, s, OH), 3.74 (1H, m, $H_1$), 4.03 (1H, m, $H_2$), 6.98 (2H, d, $J \sim 8$ Hz, $H_{Ar2,6}$), 6.99 (1H, t, $J \sim 8$ Hz, $H_{Ar4}$), 7.31 (2H, t, $J \sim 8$ Hz, $H_{Ar3,5}$); $^{13}$C NMR: 23.85 ($H_4$ or $H_5$), 23.92 ($H_4$ or $H_5$), 29.14 ($H_3$), 32.00 ($H_6$), 73.34 ($H_1$), 82.13 ($H_2$), 116.34 ($H_{Ar2,6}$), 121.20 ($H_{Ar4}$), 129.48 ($H_{Ar3,5}$), 157.80 ($H_{Ar1}$). IR, $^1$H and $^{13}$C NMR data agree well with the published spectra[4] of (1*S*,2*S*)-**6**.

#### 4.15.2. (−)-(1*R*,2*R*)-2-Phenoxycyclohexyl acetate (1*R*,2*R*)-7.

$[\alpha]_D^{25} = -82.9$ (*c* 1, $CHCl_3$), $= -54.1$ (*c* 1, acetone), $= -74.9$ (*c* 1, EtOH) (ee >99% by GC); $^1$H NMR: 1.38 (1H, m, $H_4$ or $H_5$), 1.46 (2H, m ($H_4$ or $H_5$) + $H_6$), 1.58 (1H, m, $H_3$), 1.77 (2H, m, $H_4 + H_5$), 1.96 (3H, s, $-CH_3$), 2.08 (1H, m, $H_6$), 2.16 (1H, m, $H_3$), 4.25 (1H, m, $H_2$), 5.01 (1H, m, $H_1$), 6.96 (1H, t, $J \sim 8$ Hz, $H_{Ar4}$), 6.98 (2H, d, $J \sim 8$ Hz, $H_{Ar2,6}$), 7.29 (2H, t, $J \sim 8$ Hz, $H_{Ar3,5}$); $^{13}$C NMR: 21.02 (*C*$H_3$), 22.94 ($H_4$ or $H_5$), 23.03 ($H_4$ or $H_5$), 29.62 ($H_3$ or $H_6$), 29.67 ($H_3$ or $H_6$), 74.09 ($H_1$), 77.56 ($H_2$), 116.26 ($H_{Ar2,6}$), 120.94 ($H_{Ar4}$), 129.30 ($H_{Ar3,5}$), 158.24 ($H_{Ar1}$), 170.36 (*C*OO). IR, $^1$H and $^{13}$C NMR data agree well with the published spectra[4] of (1*R*,2*R*)-**7**.

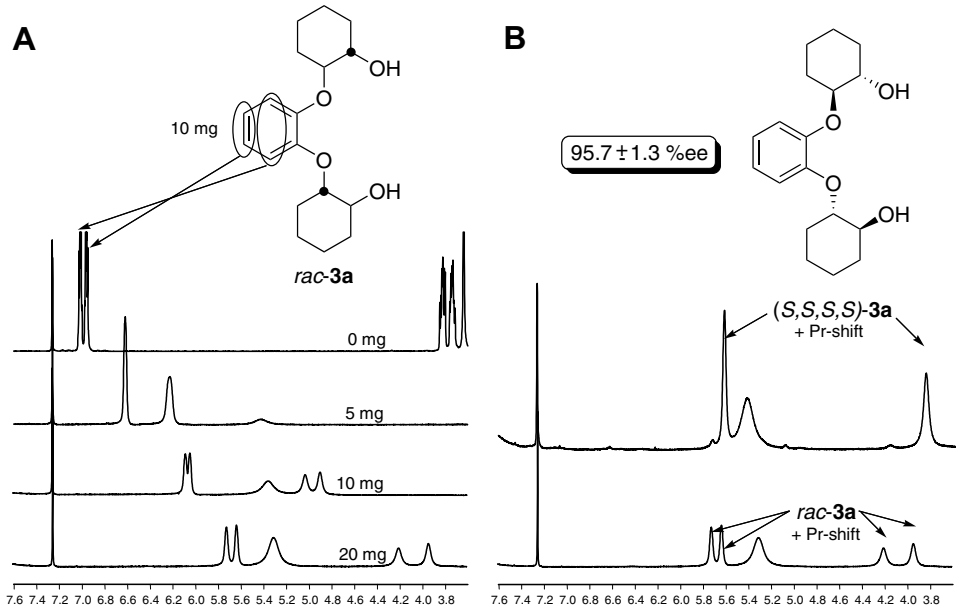



**Figure 1.**

### 4.16. Determination of the enantiomeric composition of the optically active (*S*,*S*,*S*,*S*)-3a, (*S*,*S*,*S*,*S*)-3b, (*R*,*R*,*S*,*S*)-4a and (*R*,*R*,*S*,*S*)-4b

The enantiomeric compositions of the optically active (*S*,*S*,*S*,*S*)-**3a**, (*S*,*S*,*S*,*S*)-**3b**, (*R*,*R*,*S*,*S*)-**4a** and (*R*,*R*,*S*,*S*)-**4b** were determined by $^1$H NMR using praseodymium D-3-heptafluorobutyryl-camphorate shift reagent as indicated in Figure 1. $^1$H NMR spectra of the optically active [(*S*,*S*,*S*,*S*)-**3a**,**b** and (*R*,*R*,*S*,*S*)-**4a**,**b**] or racemic [*rac*-**3a**,**b** and *rac*-**4a**,**b**] compound (10 mg) in $CDCl_3$ (600 μL) were taken in the presence of increasing amounts of the shift reagent (2–25 mg). The ee values determined by praseodymium shift reagent are listed in Table 1.

**4.16.1. Enantiomeric composition of (*S*,*S*,*S*,*S*)-3a.** By adding a Pr shift reagent to the *rac*-**3a** sample, the 6.96 ppm (2H, m, $H_{Ar4} + H_{Ar5}$) and 7.01 ppm (2H, m, $H_{Ar3} + H_{Ar6}$) signals were separated into two pairs of signals (in 1:1 ratio, each). By adding 20 mg of Pr shift reagent, the signal at 6.96 ppm shifted to 5.63 and 5.72 ppm, whereas the signal at 7.01 ppm shifted to 3.9 and 4.2 ppm. When the optically active (*S*,*S*,*S*,*S*)-**3a** was treated with 20 mg of Pr shift reagent major signals were detected at 5.75 and 4.02 ppm, along with minor signals at 5.67 and 4.28 ppm (Fig. 1). From the ratio of these signals, 95.7% ee was calculated for (*S*,*S*,*S*,*S*)-**3a**.

**4.16.2. Enantiomeric composition of (*S*,*S*,*S*,*S*)-3b.** By adding a Pr shift reagent to *rac*-**3b** [prepared by mixing (*S*,*S*,*S*,*S*)-**3b** and (*R*,*R*,*R*,*R*)-**3b** in 1:1 (w/w) ratio], the 6.57 ppm (1H, s, $H_{Ar2}$) signal separated into signals in 1:1 ratio (5 mg of Pr shift reagent: 6.03 and 5.94 ppm; 10 mg of Pr shift reagent: 5.82 and 5.73 ppm). Adding a Pr shift reagent to the sample of optically active (*S*,*S*,*S*,*S*)-**3b**, only a single peak could be observed (5 mg of Pr shift reagent: 6.04 ppm; 10 mg of Pr shift reagent: 5.23 ppm).

**4.16.3. Enantiomeric composition of (*R*,*R*,*S*,*S*)-4a.** By adding a Pr shift reagent to *rac*-**4a** (for preparation, see Section 4.4), the 6.99 ppm (1H, d, $H_{Ar6}$) and 7.02 ppm (1H, d, $H_{Ar3}$) signals were gradually separated into two pairs of signals (in 1:1 ratio, each). By adding 20 mg of Pr shift reagent to the racemic sample, the signal at 6.99 ppm shifted to 5.04 and 5.18 ppm, whereas the signal at 7.02 ppm shifted to 4.34 and 4.52 ppm. When the optically active (*R*,*R*,*S*,*S*)-**4a** was treated with 20 mg of Pr shift reagent, signals were detected only at 4.86 and 4.08 ppm, without observable peaks of the minor enantiomer.

**4.16.4. Enantiomeric composition of (*R*,*R*,*S*,*S*)-4b.** By adding a Pr shift reagent to *rac*-**4b** (for preparation, see Section 4.14), the 6.53 ppm (1H, m, $H_{Ar2}$) signal separated into signals in 1:1 ratio (5 mg of Pr shift reagent: 5.86 and 5.98 ppm; 10 mg of Pr shift reagent: 5.14 and 5.37 ppm). Adding Pr shift reagent to the sample of optically active (*R*,*R*,*S*,*S*)-**4b**, only a single peak could be observed (5 mg of Pr shift reagent: 5.09 ppm; 10 mg shift reagent: 4.38 ppm).

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