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Chemoenzymatic Protocol for the Synthesis of Enantiopure β-Blocker (*S*)-Bisoprolol

Lucas Bocquin and Elisabeth Egholm Jacobsen *

Department of Chemistry, Norwegian University of Science and Technology, Høgskoleringen 5, 7491 Trondheim, Norway
* Correspondence: elisabeth.e.jacobsen@ntnu.no

Abstract: The β-blocker (*S*)-bisoprolol hemifumarate has been synthesised in 96% enantiomeric excess with 19% total yield in a six-step synthesis. A transesterification reaction of the racemic chlorohydrin 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol catalysed by lipase B from *Candida antarctica* resulted in the *R*-chlorohydrin in high enantiomeric purity. Reaction of this building block with isopropylamine in methanol gave (*S*)-bisoprolol, and further reaction with fumaric acid gave (*S*)-bisoprolol fumarate in 96% ee. Specific rotation value confirmed the absolute configuration of the enantiopure drug.

Keywords: (*S*)-bisoprolol; enantiopure building blocks; *Candida antarctica* lipase B; chiral chromatography

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1. Introduction

Bisoprolol is a β_1-selective β-blocker used among other β-blockers in the treatment of hypertension and heart failure. The drug is mostly sold as a hemifumarate salt under the brand name Zebeta and is one of the ten most prescribed β-blockers in the USA [1]. Due to the negative side effects of β_2-selective β-blockers, β_1-selective β-blockers are preferred in most treatments. Most of the clinically approved β-blockers nevertheless have a relatively low β_1-selectivity, and more effort into the development and synthesis of β_1-selective β-blockers is therefore needed [2].

The *S*-enantiomer of bisoprolol (Figure 1) has about 30 to 80 times greater β-blocking activity than its *R*-enantiomer [3]. However, the drug is currently mostly sold as a racemic mixture [4]. Even if the *R*-enantiomer does not lead to any serious side effects, it can be considered unnecessary and potentially harmful to the patient [5].

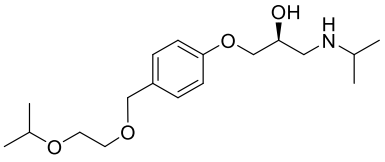


Figure 1. Structure of (*S*)-bisoprolol.

Most of the reported syntheses of (*S*)-bisoprolol use stoichiometric amounts of expensive commercial enantiopure reactants, such as (*R*)-epichlorohydrin, (*R*)-epoxypropanol, (*S*)-glycidyl tosylate, and (*S*)-glycidyl nosylate [6–9]. Syntheses of (*S*)-bisoprolol by use of chiral non-biological or biological catalysts without the use of enantiopure reagents in stoichiometric amounts have not been reported. Sheldon and Woodley have, in a review article in 2018, described the benefits of use of biocatalysis in the development of green and sustainable methods in the synthesis of biologically active compounds [10]. We present here a chemoenzymatic protocol for the synthesis of enantiopure (*S*)-bisoprolol and its hemifumarate salt. We have previously developed and reported efficient synthesis

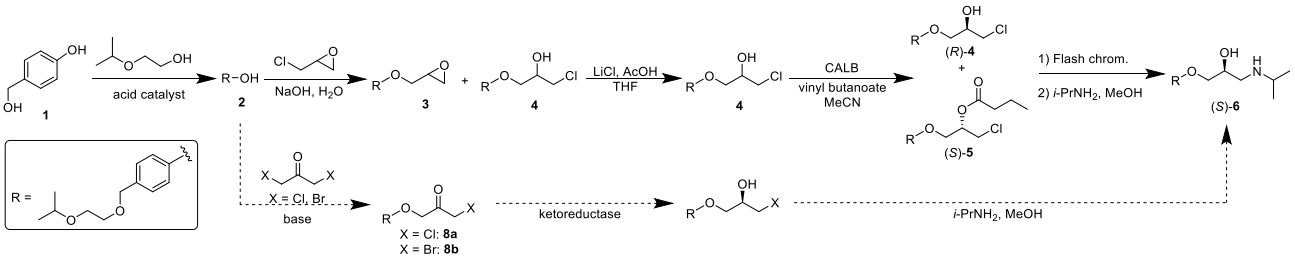
protocols for the syntheses of enantiopure *β*-adrenergic receptor blockers and their chiral building blocks using *Candida antarctica* lipase B (CALB) as the chiral catalyst [11–13].

We show here that the chiral chlorohydrin building block for the synthesis of (*S*)-bisoprolol can be obtained in high enantiomeric excess by using CALB as the catalyst in kinetic resolution of the corresponding racemic chlorohydrin. The yield for this step is however limited to 50% unless techniques such as dynamic kinetic resolution or Mitsunobu esterification are used [14]. Other types of enzymatic processes, such as asymmetrisation of a ketone precursor catalysed by a ketoreductase, could also overcome the limitation of 50% yield compared to the kinetic resolution of the racemic halohydrin.

2. Results and Discussion

2.1. Synthesis of 4-((2-isopropoxyethoxy)methyl)phenol, **2**

4-((2-Isopropoxyethoxy)methyl)phenol (**2**) was synthesized from 4-(hydroxymethyl)phenol (**1**) and 2-isopropoxyethan-1-ol in the presence of a silica sulfuric acid as the acid catalyst, with a yield of 75% (Scheme 1). This solid catalyst has been chosen because it can be filtered off and reused after use and because it leads to the formation of fewer byproducts than when concentrated sulfuric acid is used for this synthesis step [15].



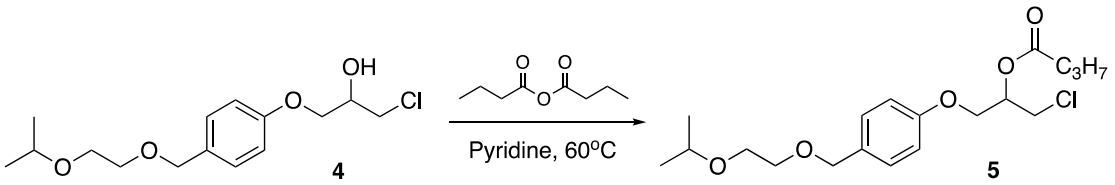
Scheme 1. Synthesis of (*S*)-bisoprolol, (*S*)-**6** from diol **1**, where in the last step, (*R*)-**4** is converted to (*S*)-**6**. The dashed arrows indicate a possible, but by us unsuccessful, synthesis pathway with assymmetrisation of the corresponding haloketones **8a** and **8b** with a ketoreductase as the chiral catalyst.

2.2. Synthesis of 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol, **4**

Racemic chlorohydrin **4** has been synthesized from 4-((2-isopropoxyethoxy)methyl)phenol (**2**) and epichlorohydrin in 63% yield and in 99% purity (Scheme 1). Deprotonation of 4-((2-isopropoxyethoxy)methyl)phenol (**1**) and its subsequent attack on epichlorohydrin gave a mixture of racemic chlorohydrin **4** and epoxide **3**. Reaction with lithium chloride gave racemic chlorohydrin **4** via ring opening of epoxide **3**.

2.3. Synthesis of 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-yl butanoate, **5**

A derivatisation reaction of racemic chlorohydrin **4** was performed in order to form butanoic ester **5** for determination of the retention times of its *R*- and *S*-enantiomers on the chiral HPLC column. Pyridine and butanoic anhydride were added to a solution of **4** in hexane, and the mixture was heated to 60 °C for 1 h (Scheme 2) before work up. The enantiomers of **5** was separated on chiral HPLC.



Scheme 2. Synthesis of racemic 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-yl butanoate (**5**) from 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol (**4**).

2.4. Synthesis of (*R*)-**4** by CALB-Catalysed Kinetic Resolution of Chlorohydrin **4**

Kinetic resolution of chlorohydrin **4** was catalysed by lipase B from *Candida antarctica* (CALB) in dry acetonitrile with vinyl butanoate as the acyl donor. This gave an *E*-value of 52 (calculated using E&K Calculator, 2.1b0 PPC) [16] (Figure 2) and an enantiomeric excess (ee) of 99% for *R*-chlorohydrin (*R*)-**4**. As seen from the graph, there is always possible to obtain 100% ee of the remaining substrate (blue line and blue squares for experimental ee-values) even when the ester product (red line and red circles for experimental ee values) is not obtained in 100%ee. The blue and the red curves are generated from the experimental values of ee_S and ee_P, respectively. The reaction time for the transesterification reaction of (*R*)-**4** was 25 h. The use of acetonitrile as the solvent in these kinetic resolutions makes the syntheses greener than previous reports on similar reactions using toluene [17], while maintaining a high selectivity in the synthesis of *R*-chlorohydrin (*R*)-**4**. The ester product (*S*)-1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-yl butanoate ((*S*)-**5**) was obtained in 51% yield, 75% ee and with 68% purity (^{1}H NMR). Optical rotation measurement was not performed.

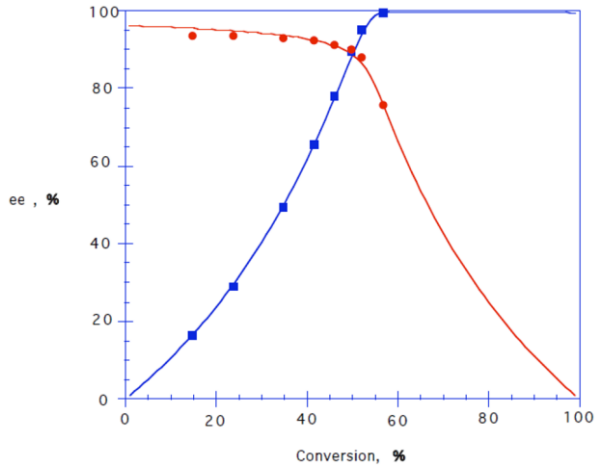
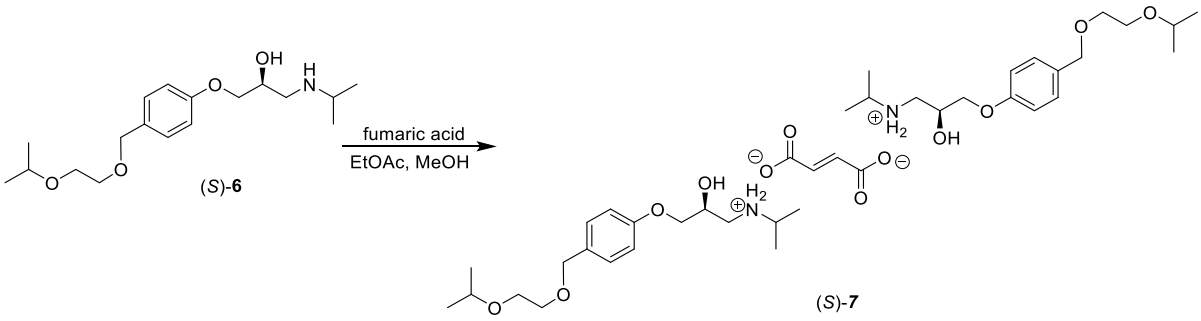


Figure 2. Graphical representation of kinetic resolution of chlorohydrin **4** with CALB in dry acetonitrile with vinyl butanoate as acyl donor. ee_S (blue squares, ee of the substrate (*R*)-**4**) and ee_F (red circles, ee of the ester product (*S*)-**5**) in percent plotted against conversion in percent. The blue and the red curves are generated from the experimental values of ee_S and ee_P, respectively. The *E*-value was calculated to 52. *E*-values are calculated using E&K Calculator 2.1b0 PPC [16].

2.5. Synthesis of (*S*)-bisoprolol, (*S*)-**6**, and (*S*)-bisoprolol hemifumarate, (*S*)-**7**

R-Chlorohydrin (*R*)-**4** was converted to (*S*)-bisoprolol ((*S*)-**6**) with 91% yield by reacting it with isopropylamine in methanol. Further reaction of (*S*)-**6** with fumaric acid gave (*S*)-bisoprolol hemifumarate ((*S*)-**7**) with an ee of 96% in 99% yield, see Scheme 3 and Table 1. The ee of (*S*)-**7** is slightly lower than the ee of (*R*)-**4**. One reason could be detection errors of the chromatographic separation. Another reason would be that small amounts of (*S*)-**5** were present after separation of (*R*)-**4** and (*S*)-**5** on the silica column after the batch transesterification reaction of **4** with CALB. When sodium chloride solution was added, (*S*)-**5** was hydrolysed to (*S*)-**4**, thus lowering the ee of the final product. We do not observe (*S*)-**5** in the HPLC chromatogram of the transesterification of **4** after separation of the enantiomers, which could be due to low concentration of the sample, since we observe the *R*-enantiomer of the hemifumaric salt of bisoprolol in the final chromatogram of (*S*)-**7** giving 96%ee; see Supplementary Materials for chromatogram. As mentioned, 100% ee of the remaining alcohols in such transesterification reactions is always possible to obtain; the only drawback is that the yield will be lower, see Figure 2. Based on this, it is possible to obtain 99% ee of the final drug when the remaining alcohol is the building block, however, the total yield must be sacrificed.



Scheme 3. Synthesis of (*S*)-bisoprolol hemifumarate, (*S*)-**7** in 96% ee, from (*S*)-bisoprolol ((*S*)-**6**) and fumaric acid.

Table 1. *E*-values, ee-values, and yields of the enantiopure chlorohydrin (*R*)-**4** and the drug (*S*)-**7**. The kinetic resolutions were catalysed via CALB from syncozymes in dry acetonitrile. Specific rotations $[\alpha]_D^T$ were determined at 20 °C in methanol with *c* = 1. For additional parameters, see Materials and Methods. The yields for each compound in the table are for each reaction step. The overall yield for (*S*)-bisoprolol hemifumarate ((*S*)-**7**) is 19%.

Compound	ee (%)	Yield (%)	Specific Rotation	*E*-Value
(*R*)-**4**	99	44	$[\alpha]_D^{20} = -17.0$ (*c* 1.0, MeOH)	52
(*S*)-**7**	96	99	$[\alpha]_D^{20} = -17.0$ (*c* 1.0, MeOH)	-

*2.6. Specific Rotation of (R)-**4** and (S)-**7***

Specific rotation of chlorohydrin (*R*)-**4** in 99% ee is determined to $[\alpha]_D^{20} = -17.0$ (*c* 1.0, MeOH), which has not been reported previously. Specific rotation of (*S*)-bisoprolol hemifumarate has been reported by Kitaori et al. to be $[\alpha]_D^{20} = -20.6$ (*c* 1.0, MeOH) [9]. The authors do not report any corresponding ee value. We have synthesized (*S*)-bisoprolol hemifumarate ((*S*)-**7**) from (*S*)-bisoprolol and fumaric acid with an ee of 96% and the specific rotation is $[\alpha]_D^{20} = -17.0$ (*c* 1.0, MeOH), which is consistent with Kitaori et al.

*2.7. Unsuccessful Synthesis of 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-one, **8a**, and 1-bromo-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-one, **8b***

The synthesis pathway of (*S*)-bisoprolol ((*S*)-**6**) using a ketoreductase as catalyst in asymmetrisation of the corresponding haloketones is illustrated by the dashed arrows in Scheme 1. This pathway towards enantiopure building blocks for (*S*)-bisoprolol is one step shorter than the synthesis pathway, in which CALB is used as a catalyst in the transesterification of **4**. In asymmetrisations of ketones catalysed by ketoreductases the maximum yield would be 100%.

However, attempts to synthesise 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-one (**8a**) and 1-bromo-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-one (**8b**) from 4-((2-isopropoxyethoxy)methyl)phenol (**2**) and 1,3-dichloropropan-2-one or 1,3-dibromopropan-2-one were not successful. 1,3-Dichloropropan-2-one and 1,3-dibromopropan-2-one were not stable in most of the basic environments tested (potassium carbonate, sodium bicarbonate, sodium hydroxide, and sodium ethoxide). Since both the reaction mixtures turned black after a few hours of reaction time, a polymerization reaction has probably taken place, and further asymmetrisations were not possible to perform.

3. Materials and Methods

3.1. Chemicals and Solvents

All chemicals used in this project are commercially available, of analytical grade, and were purchased from Sigma-Aldrich Norway (Oslo, Norway) or vwr Norway (Oslo, Norway).

HPLC grades of solvents were used for the HPLC-analyses. Dry MeCN was acquired from a solvent purifier, MBraun MD-SPS800 (München, Germany), and stored in a flask containing molecular sieves (4 Å).

3.2. TLC Analyses and Column Chromatography

TLC analyses were performed on Merck silica 60 F_{254} and detection with UV at λ = 254 nm. Flash chromatography was performed using silica gel from Sigma-Aldrich Norway (Oslo, Norway) (pore size 60 Å, 230–400 mesh particle size, 40–63 μm particle size).

3.3. Enzymes

Candida antarctica Lipase B (CALB) (activity ≥ 10,000 PLU/g, lot#20170315) immobilised at high hydrophobic macro porous resin, produced in fermentation with genetically modified *Pichia pastoris*, was a gift from SyncoZymes Co, Ltd. (Shanghai, China). The enzyme reactions were performed in a New Brunswick G24 Environmental Incubator Shaker from New Brunswick Co. (Edison, NJ, USA).

3.4. Chiral HPLC Analyses

All chiral HPLC analyses were performed on Agilent HPLC systems 1100 and 1200: manual injector (Rheodyne 77245i/Agilent 10 mL loop (Agilent 1100)), an autosampler (Agilent 1200), and a variable wavelength detector (VWD) set to 254 nm. Separations of enantiomers were performed on a Chiralcel OD-H column (250 mm × 4.6 mm ID, 5 μm particle size, Daicel, Chiral Technologies Europe, Gonthier d'Andernach, Illkirch, France). Chlorohydrin **4** enantiomers: (*n*-hexane:i-PrOH, 90:10), flow 1 mL/min, t_R((*R*)-**4**) = 14.81 min, t_R((*S*)-**4**) = 15.93 min, R_S((*S*)/(*R*)-**4**) = 1.63. Ester **5** enantiomers: (*n*-hexane:*i*-PrOH, 96:4), flow 1 mL/min, t_R((*R*)-**5**) = 11.23 min, t_R((*S*)-**5**) = 12.33 min, R_S((*S*)/(*R*)-**5**) = 1.89. Bisoprolol hemifumarate (**7**) enantiomers: (*n*-hexane:i-PrOH:Et_2NH (90:9.8:0.2), flow 1 mL/min, t_R((*R*)-**7**) = 7.92 min and t_R((*S*)-**7**) = 11.8 min, R_S((*S*)/(*R*)-**7**) = 7.02. Selected chromatograms can be found in the Supplementary Materials.

3.5. Optical Rotation

Optical rotation values were performed with an Anton Paar MCP 5100 polarimeter from Dipl. Ing. Houm AS (Oslo, Norway), wavelength of 589 nm (D). See single enantiomers for specific rotation values.

3.6. Absolute Configurations

Specific rotation values of chlorohydrin (*R*)-**4** has not been reported previously, and its absolute configuration was determined through the enantioselectivity of CALB, which we have reported previously [14,18]. Absolute configuration of (*S*)-bisoprolol hemifumarate (*S*)-**7** was determined by comparing its measured specific rotation to previously reported data [9].

3.7. NMR Analyses

NMR analyses were recorded on a Bruker 600 MHz Avance III HD instrument equipped with a 5 mm cryogenic CP-TCI Z-gradient probe operating at 600 MHz for ^{1}H and 151 MHz for ^{13}C (Bruker, Rheinstetten, Germany). Chemical shifts are in ppm relative to TMS (or $CHCl_3$ shift), and coupling constants are in hertz (Hz). The spectroscopic data were analysed with Mestrelab Research software MestReNova 14.2.0-26256.

^{1}H- and ^{13}C NMR spectra can be found in the Supplementary Materials.

3.8. Synthesis Protocols

3.8.1. Silica Sulfuric Acid Catalyst

To a mixture of SiO_2 (10 g) in acetone (30 mL) was slowly added concentrated sulfuric acid (95%, 6.5 mL). The solution was stirred for 1 h at rt, and the solvent was then removed under reduced pressure. The black paste obtained was placed in an oven at 180 °C

overnight, and the obtained solid was crushed into a fine powder. The powder was then stored in a desiccator.

3.8.2. 4-((2-Isopropoxyethoxy)methyl)phenol, **2**

To a solution of 2-isopropoxyethan-1-ol (26.0 mL, 23.5 g, 0.23 mol) at 0 °C were added Silica Sulfuric Acid catalyst (2.01 g) and 4-(hydroxymethyl)phenol (**1**) (1.99 g, 16.0 mmol). The reaction mixture was stirred for 24 h at rt, filtered, and the black filtrate was concentrated under reduced pressure. EtOAc (20 mL) was added, and the solution was washed with a saturated NaCl solution (3 × 15 mL). The aqueous phase was then extracted with EtOAc (15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The obtained product was purified using flash chromatography (*n*-pentane:EtOAc, 7:3, *v*/*v*) to give 4-((2-isopropoxyethoxy)methyl)phenol (**2**) as a slightly red oil (2.56 g, 12.2 mmol, 99% purity (^{1}H-NMR), 75% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22–7.13 (m, 2H), 6.82–6.72 (m, 2H), 6.02 (s, 1H), 4.48 (s, 2H), 3.72–3.58 (m, 5H), 1.20 (d, *J* = 5.9 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.55, 129.75, 129.74, 115.26, 73.11, 72.21, 69.34, 67.48, 22.01.

3.8.3. 1-Chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol, **4**

To a solution of NaOH (80 mg, 2.00 mmol) in distilled H_2O (2 mL) was added 4-((2-isopropoxyethoxy)methyl)phenol (**2**) (209 mg, 0.99 mmol). The reaction mixture was stirred for 1 min, and 2-(chloromethyl)oxirane (epichlorohydrin) (157 µL, 185 mg, 2.00 mmol) was added. The mixture was stirred at rt for 48 h. Distilled H_2O (5 mL) was then added, and the product was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with a saturated NaCl solution (15 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure, yielding 241 mg of a mixture mainly composed of 2-((4-((2-isopropoxyethoxy)methyl)phenoxy)methyl)oxirane (**3**) and 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol (**4**) (^{1}H-NMR) as a slightly yellow oil.

The obtained mixture (238 mg) was dissolved in THF (1 mL). AcOH (153 µL, 161 mg, 2.68 mmol) and LiCl (116 mg, 2.74 mmol) were added. The reaction mixture was stirred at rt for 24 h. The solution was then concentrated under reduced pressure. The obtained product was dissolved in EtOAc (10 mL) and washed with distilled H_2O (10 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with a saturated NaCl solution (15 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified using flash chromatography (*n*-pentane:EtOAc, 7:3, *v*/*v*) yielding 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol (**4**) as a colourless oil (188 mg, 0.62 mmol, 99% purity (^{1}H-NMR), 63% yield). TLC (*n*-pentane:EtOAc, 7:3, *v*/*v*): R_f (**4**) = 0.45. Chiral HPLC eluent: hexane:*i*-PrOH (90:10), flow 1 mL/min. t_R((*R*)-**4**) = 14.81 min and t_R((*S*)-**4**) = 15.93 min. R_S((*S*)/(*R*)-**4**) = 1.63. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 6.93–6.89 (m, 2H), 4.54 (s, 2H), 4.24 (h, *J* = 5.5 Hz, 1H), 4.13–4.08 (m, 2H), 3.82–3.73 (m, 2H), 3.66–3.60 (m, 5H), 2.57 (d, *J* = 5.9 Hz, 1H), 1.20 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.79, 131.40, 129.41, 114.45, 72.78, 71.94, 69.87, 69.54, 68.59, 67.47, 45.98, 22.09.

3.8.4. Synthesis of 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-yl butanoate, **5**, from 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol, **4**

To a solution of 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol (**4**) (5 mg, 0.02 mmol) in hexane (0.5 mL) was added pyridine (one drop) and butanoic anhydride (one drop). The reaction mixture was heated at 60 °C for 1 h. Hexane (3 mL) was then added, and the solution was washed with distilled H_2O (5 × 0.5 mL). The organic phase was then dried over anhydrous $MgSO_4$ and filtered before the solvents and excess butanoic anhydride/acid and the solvent were removed under reduced pressure.

3.8.5. Synthesis of chlorohydrin (*R*)-**4** and (*S*)-**5** by CALB catalysed kinetic resolution of 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol, **4**

To a solution of 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol (**4**) (303 mg, 1.00 mmol) dissolved in dry MeCN (24 mL) were added activated molecular sieves (4 Å), vinyl butanoate (623 µL, 556 mg, 4.86 mmol) and CALB (746 mg). The mixture was placed in an incubator shaker (38 °C, 200 rpm.) for 25 h. Enzymes and molecular sieves were filtered off, and solvents were removed invacuo. The obtained product was dissolved in EtOAc (15 mL) and was washed with a saturated NaCl solution (2 × 10 mL). The solution was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. (*R*)-1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol ((*R*)-**4**) and (*S*)-1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-yl butanoate ((*S*)-**5**) were separated using flash chromatography (*n*-pentane: EtOAc, 7:3, *v/v*). (*R*)-1-Chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol ((*R*)-**4**) was obtained as a colourless oil (134 mg, 0.44 mmol, 82% purity (^{1}H-NMR), 44% yield, ee = 99% (chiral HPLC)). $[\alpha]_D^{20} - 7$ (c 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 6.91–6.87 (m, 2H), 4.51 (s, 2H), 4.21 (q, *J* = 5.1 Hz, 1H), 4.12–4.05 (m, 2H), 3.80–3.70 (m, 2H), 3.66–3.53 (m, 5H), 2.51 (d, *J* = 5.9 Hz, 1H), 1.17 (d, *J* = 6.1 Hz, 6H). (*S*)-1-Chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-yl butanoate ((*S*)-**5**) was obtained as a colourless oil (191 mg, 0.51 mmol, 51% yield, 68% purity (^{1}H-NMR)). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30–7.25 (m, 2H), 6.92–6.85 (m, 2H), 5.34 (p, *J* = 5.1 Hz, 1H), 4.51 (s, 2H), 4.20–4.12 (m, 2H), 3.85 (dd, *J* = 11.7, 5.0 Hz, 1H), 3.78 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.65–3.55 (m, 5H), 2.41–2.30 (m, 2H), 1.73–1.63 (m, 2H), 1.17 (d, *J* = 6.1 Hz, 6H), 1.00–0.94 (m, 3H). ^{13}C data similar as for **4**.

3.8.6. (*S*)-Bisoprolol, (*S*)-**6**

To a mixture of (*R*)-1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-ol ((*R*)-**4**) (40 mg, 0.13 mmol) in MeOH (2.5 mL) was added *i*-$PrNH_2$ (0.16 mL, 1.82 mmol). The mixture was stirred under reflux for 25 h, and was then concentrated under reduced pressure. The obtained product was dissolved in EtOAc (20 mL) and washed with distilled H_2O (10 mL). The aqueous phase was extracted with EtOAc (10 mL), and the combined organic layers were washed with saturated NaCl solution (5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give (*S*)-bisoprolol ((*S*)-**6**) as a white solid (39 mg, 0.12 mmol, 91% purity (^{1}H-NMR), 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21–7.18 (m, 2H), 6.83–6.80 (m, 2H), 4.44 (s, 2H), 3.96–3.87 (m, 3H), 3.58–3.49 (m, 5H), 2.82 (dd, *J* = 12.2, 3.7 Hz, 1H), 2.76 (p, *J* = 6.3 Hz, 1H), 2.66 (dd, *J* = 12.1, 7.4 Hz, 1H), 1.10 (d, *J* = 6.1 Hz, 6H), 1.02 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.28, 130.93, 129.35, 114.43, 72.85, 71.91, 70.56, 69.47, 68.50, 67.48, 49.19, 48.94, 23.19, 23.05, 22.09.

3.8.7. (*S*)-Bisoprolol Hemifumarate, (*S*)-**7**

(*S*)-Bisoprolol ((*S*)-**6**) (10.0 mg, 0.31 mmol) was then dissolved in EtOAc (15 µL) and MeOH (145 µL) and heated to 50 °C. Fumaric acid (1.8 mg, 15 µmol) was added. The reaction was run for 1 h, and the solvent was removed under reduced pressure to give (*S*)-bisoprolol hemifumarate ((*S*)-**7**) as a white solid (11.8 mg, 0.15 mmol, 90% purity (^{1}H-NMR), 99% yield, ee > 96% (chiral HPLC)). $[\alpha]_D^{20} - 17.0$ (c 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.3 Hz, 4H), 6.87–6.83 (m, 4H), 6.65 (s, 2H), 4.52 (dt, *J* = 11.6, 6.1 Hz, 2H), 4.48 (s, 4H), 4.04 (dd, *J* = 9.6, 4.3 Hz, 2H), 3.97 (dd, *J* = 9.7, 6.1 Hz, 2H), 3.63–3.54 (m, 11H), 3.28 (p, *J* = 6.5 Hz, 2H), 3.14 (t, *J* = 11.2 Hz, 2H), 3.04 (dd, *J* = 12.1, 2.8 Hz, 2H), 1.36 (d, *J* = 6.5 Hz, 6H), 1.32 (d, *J* = 6.5 Hz, 6H), 1.16 (d, *J* = 6.1 Hz, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.28, 157.99, 136.16, 131.10, 129.37, 114.38, 72.80, 71.92, 70.11, 69.51, 67.46, 65.25, 50.63, 48.29, 22.09, 19.60, 19.06.

3.8.8. Attempts to Synthesize 1-chloro-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-one (**8a**)

To a solution of 4-((2-isopropoxyethoxy)methyl)phenol (25 mg, 0.12 mmol) in dry MeCN (5 mL) was added K_2CO_3 (67 mg, 0.34 mmol). 1,3-Dichloropropan-2-one (11 µL at 45 °C, 15 mg, 0.12 mmol) diluted in MeCN (5 mL) was added dropwise over 30 min. The reaction mixture was stirred at rt for 24 h, filtered, and concentrated under reduced pressure. EtOAc (15 mL) was added, and the solution was washed with distilled H_2O (3 × 10 mL) and with a saturated NaCl solution (10 mL). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to give a brown paste (31 mg) that did not contain compound **8a** in significant amounts (^{1}H-NMR). A similar procedure was used in order to synthesise 1-bromo-3-(4-((2-isopropoxyethoxy)methyl)phenoxy)propan-2-one (**8b**). However, this was also unsuccessful.

4. Conclusions

A six-step synthesis of (*S*)-bisoprolol hemifumarate with 19% overall yield and 96% ee has been performed starting from 4-(hydroxymethyl)phenol and 2-isopropoxyethan-1-ol. Specific rotation of (*S*)-bisoprolol hemifumarate has been determined to be $[\alpha]_D^{20} = -17$ (*c* 1.0, MeOH), consistent with previously reported data [9]. CALB catalysed kinetic resolution of chlorohydrin **4** is an efficient method of obtaining enantiopure building block (*R*)-**4**. The yield of this enzymatic step is limited to 50% but could be increased further by the use of special techniques, such as dynamic kinetic resolution [11].

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal13010054/s1, ^{1}H and ^{13}C NMR spectra and relevant chiral HPLC chromatograms.

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