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Practical Two-Step Synthesis of an Enantiopure Aliphatic Terminal (*S*)-Epoxide Based on Reduction of Haloalkanones with "Designer Cells"

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Abstract: A practical biocatalytic method for the synthesis of aliphatic β-halogenated (*S*)-alcohols as epoxide precursors by means of an enantioselective reduction of the corresponding ketones with recombinant whole cells, bearing an alcohol dehydrogenase and a glucose dehydrogenase, was developed. The biotransformations operate at high substrate concentrations of up to 208 g/L, and afford the (*S*)-β-halohydrins with both high conversions of >95% and enantioselectivities of >99% *ee*. Base-induced cyclization of the β-halohydrin intermediates gave the desired (*S*)-epoxides in high yield and enantiomeric purity (>99% *ee*).

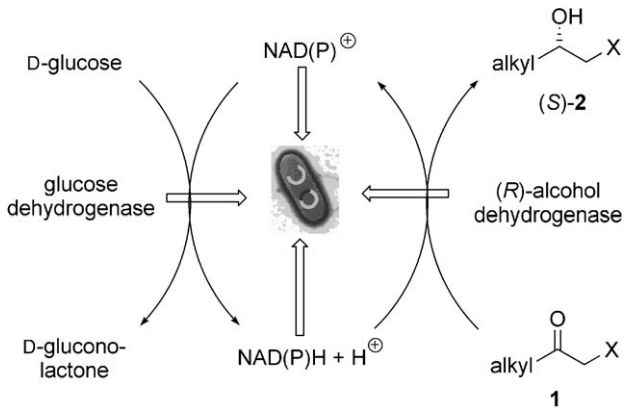
Keywords: alcohols; asymmetric catalysis; enzyme catalysis; epoxides; halohydrins; reduction

Introduction

Enantiomerically pure terminal (*S*)-epoxides are important chiral building blocks, widely used, e.g., as intermediates in the synthesis of pharmaceuticals.[1] Whereas numerous asymmetric transformations comprising chemocatalytic[2] and biocatalytic[3] techniques have been developed for the enantioselective synthesis of aromatic terminal epoxides, there is still comparatively little methodology available for the preparation of enantiomerically pure aliphatic terminal epoxides. In contrast to, e.g., allylic alcohols or conjugated *cis*-alkenes, the enantioselective epoxidation of terminal aliphatic alkenes still is a challenging task.[4] In early work, chiral ruthenium-porphyrin complexes in combination with pyridine *N*-oxides as oxidant gave 1-octene oxide with 6% conversion and 28% *ee*.[5a] Application of the Shi catalyst to vinylcyclohexane gave the epoxide in high yield and with 71% *ee*.[5b] Recently, significant advances were achieved in this area. Strukul et al. reported the asymmetric epoxidation of terminal alkenes with H_2O_2 catalyzed by pentafluorophenyl-Pt(II) complexes, with 1-octene oxide being formed in 88% yield and 79% *ee*.[5c] Katsuki et al. developed a Ti-based salen catalyst and reported 70% yield and 82% *ee* in the epoxidation of 1-octene with H_2O_2 as oxidant.[5d,e] Chemocatalytic kinetic resolution turned out to work efficiently when using short-chain aliphatic epoxides such as propylene oxide, but is limited by a maximum conversion of 50%.[6] High enantioselectivity of >99% *ee* was reported for the microbial epoxidation of hexadec-1-ene, but in combination with both low substrate concentration [≤5% (v/v)] and yield (41%).[7] Arnold et al. applied an engineered cytochrome P450 BM-3 enzyme to the epoxidation of several terminal aliphatic alkenes and achieved enantioselectivities between 55 and 83% *ee*.[8] In general, enantioselectivity in enzymatic epoxidation depends on the chain length and varies widely between 60 and >99% *ee*.[9] Furthermore, resolution using epoxide hydrolases is known for styrene oxides and aliphatic epoxides.[10] Nevertheless, terminal straight-chain aliphatic epoxides remain difficult substrates, in particular with respect to enantioselectivity. Very recently, Kroutil et al. reported an elegant chemoenzymatic approach for optically active terminal epoxides based on the asymmetric synthesis of β-halohydrins from α-haloketones using alcohol dehydrogenases (ADH) and subsequent cyclization.[11,12] The ADH-catalyzed reduction of 1-chloro-2-octanone

1a was combined with a cofactor-regeneration of NADH using 2-propanol.[11] Typically, the reductions were carried out at substrate concentrations of 8–18 g/L and gave good results for the (*R*)-alcohol (ADH from *Rhodococcus ruber*) with a conversion of >99% and >99% *ee*. In contrast, the (*S*)-1-chloro-2-octanol [(*S*)-**2a**] (ADH from *Pseudomonas fluorescens*) was formed with low enantioselectivity (52% *ee*), and the conversion did not exceed 63%.[11] A subsequent publication by Kroutil et al. describes the two-stage biocatalytic synthesis of highly enantiopure (*S*)-1-octene oxide, albeit at chemical yields of only 34% for each of the two steps.[13]

In continuation of our studies on the use of tailor-made whole-cell biocatalysts for the preparation of optically active alcohols,[14,15] in the following we report a practical and efficient process for the highly enantioselective synthesis of aliphatic (*S*)-halohydrins, running at high substrate concentrations of >100 g/L. The cofactor is regenerated by means of an enzyme-coupled approach. The products (*S*)-**2** were subsequently converted to the corresponding epoxide. The concept for the synthesis of the β-halohydrins is shown in Scheme 1 and is based on the use of a recombinant whole-cell biocatalyst. In order to prepare the (*S*)-β-halohydrins (*S*)-**2**, we used our recently developed whole-cell catalyst, overexpressing an (*R*)-alcohol dehydrogenase from *L. kefir* (LK-ADH) and glucose dehydrogenase from *T. acidophilum* (TA-GDH).[14] The latter enzyme is needed for the in situ-regeneration of the cofactor NADPH *via* consumption of glucose under formation of gluconolactone, whereas the ADH catalyzes the reduction of **1** with consumption of the cofactor NADPH.

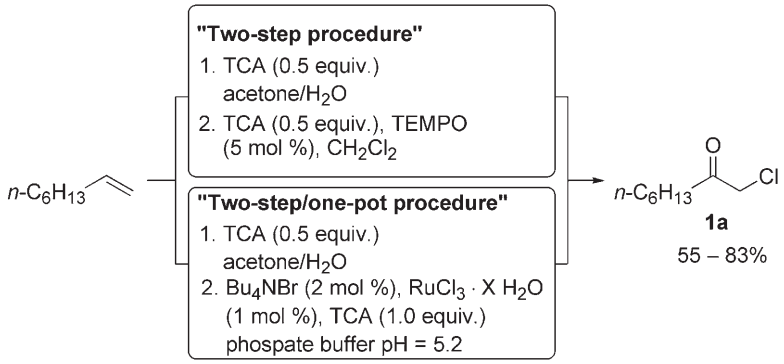


Scheme 1. Concept for an enzymatic reduction of α-halogenated ketones with recombinant whole-cell catalysts in biphasic media.

Results and Discussion

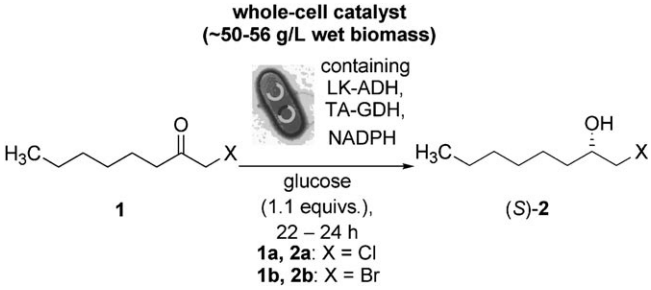
En route to the most challenging target (*S*)-1-octene oxide, 1-bromo-2-octanone (**1b**) and 1-chloro-2-octanone (**1a)** were needed as substrates. Ketone **1b** can be prepared in 42% yield by a two-step/one-pot procedure from 1-octene.[16] The latter method involves the use of over-stoichiometric amounts of NBS and Cr(VI) oxide. We therefore developed a practical synthesis of 1-chloro-2-octanone (**1a**) which avoids the use stoichiometric use of toxic metals. As shown in Scheme 2 (*top*), 1-chloro-2-octanone (**1a**) can be prepared from 1-octene in 83% yield by a two-step procedure, using trichloroisocyanuric acid and TEMPO (catalytic amount). Alternatively, a two-step/one-pot procedure using trichloroisocyanuric acid and $RuCl_3$ (catalytic amount) under phase-transfer conditions resulted in 55% yield for the haloketone **1a** (Scheme 2, *bottom*).

Initial screening reactions on 1-bromo-2-octanone (**1b**) revealed a high activity of the biocatalyst harbouring the (*R*)-ADH. A subsequent transformation on a preparative scale was done using a substrate concentration of 0.5 M, corresponding to 104 g/L. We were pleased to find that the biocatalytic reduction gave the desired β-halohydrin (*S*)-**2b** with high conversion (>95%) and excellent enantioselectivity (>99% *ee*; Table 1, entry 1). After extraction and isolation, the yield of (*S*)-**2b** was 76%. The purity of this material was sufficient for further conversion.



Scheme 2. Synthesis of 1-chloro-2-octanone (**1a**).

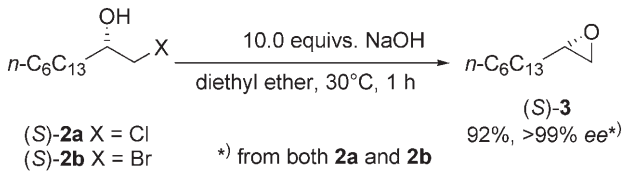
Table 1. Asymmetric biocatalytic reduction of 1-halogenated 2-octanones **1a**, **b** using a recombinant whole-cell catalyst.



Entry[a]	Product	Substrate input [g L^{-1}]	Conversion [%]	*ee* [%][b]
1	(*S*)-**2b**	104	>95	>99
2	(*S*)-**2b**	152	>95	>99
3	(*S*)-**2b**	208	>95	>99
4	(*S*)-**2a**	162	>95	>99

[a] For the general procedure, see Experimental Section.
[b] The enantiomeric excess (*ee*) was determined by chiral GC chromatography.

As a next step, process development was carried out, in particular with respect to an increase of volumetric productivity. Notably, increase of the substrate concentration did not have a negative impact on the reaction course. Thus, carrying out the whole-cell catalyzed reduction reactions at a substrate concentration of 0.75 M and 1.0 M (corresponding to a substrate input of 156 and 208 g/L, respectively) gave high conversions of >95% and enantioselectivities of >99% *ee* in both cases (Table 1, entries 2 and 3).

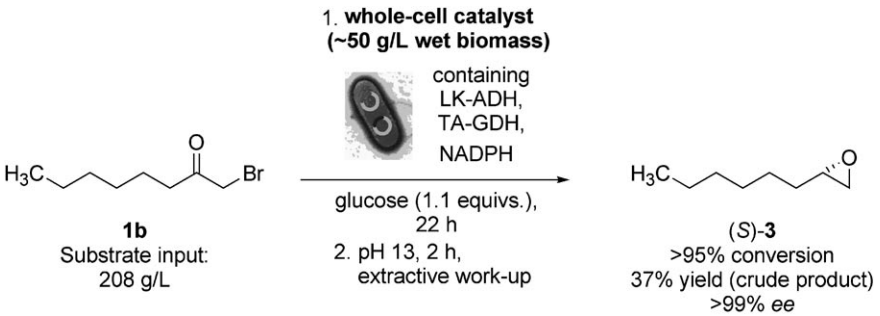


Scheme 3. Cyclization of the isolated β-halohydrins (*S*)-**2a** and (*S*)-**2b** to (*S*)-1-octene oxide (*S*)-**3**.

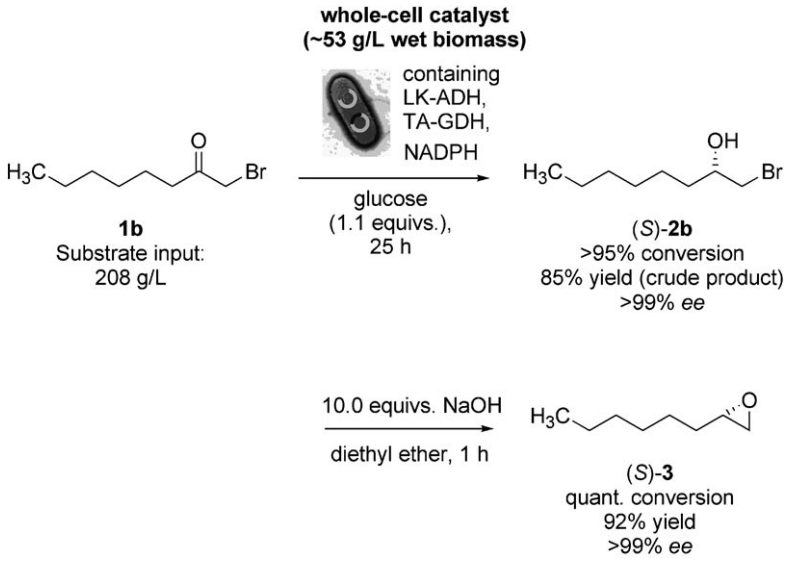
The analogous chloro ketone **1a** can serve as substrate as well. The reduction of **1a** affords >95% conversion and >99% *ee*[17-19] after a reaction time of 24 h, at a biocatalyst loading of ~53 g/L of wet biomass, and using a substrate concentration of 1.0 M (corresponding to 162 g/L). In general, the yields of isolated crude product, containing the desired product in good purity sufficient for further transformations, were high with, e.g., 82% and 88% for the biotransformations at a substrate concentration of 1.0 M (Table 1, entries 3 and 4).

Recently Kroutil et al. described the subsequent and quantitative cyclization of the halohydrin (*R*)-**2a** to the epoxide (*R*)-**3**, effected by the addition of 18.6 equivs. of powdered KOH during the biocatalytic reduction of **1a**.[11] In analogy to this protocol, the subsequent cyclization to (*S*)-1-octene oxide [(*S*)-**3**] was carried out for the isolated β-halohydrins (*S*)-**2a** and (*S*)-**2b**, with 10.0 equivs. of powdered NaOH in diethyl ether (Scheme 3). Within one hour, quantitative conversion of the halohydrins occurred, and the desired epoxide (*S*)-**3** was obtained in 92% yield in both cases. The expected absolute configuration of the resulting epoxide [(−)-*S*] was confirmed by comparison of the measured optical rotation with the literature value.[19]

As recently described by Kroutil and co-workers, the isolation of the intermediate β-halohydrin (*S*)-**2a** can be avoided in an alternative one-pot process.[11] We studied this concept using the recombinant whole-cell biocatalyst *E. coli* DSM14459, overexpressing an (*R*)-ADH from *L. kefir* and a GDH from *T. acidophilum* (Scheme 4). After formation of the β-halohydrin (*S*)-**2b** with high conversion, subsequent adjustment of the pH to 11 and stirring of the reaction mixture for 2 h, followed by an extractive work-up led to the desired epoxide (*S*)-**3**. In spite of a rapid cyclization and formation of the epoxide (*S*)-**3** with a high conversion of >95%, extractive isolation of the product under these conditions gave a yield of only 37% for the crude epoxide. Potential reasons for this low yield might be a lower efficiency of the extraction at high pH compared to the analogous work-up at low pH.



Scheme 4. Two step-one pot synthesis of the epoxide (*S*)-**3**.



Scheme 5. Gram-scale synthesis.

Further process development revealed that the synthesis of the epoxide (*S*)-**3** by means of two separated processes (reduction, epoxide cyclization) according to Scheme 5 is the method of choice. The efficiency of this two-step process was demonstrated in a multigram scale synthesis. The β-bromohydrin (*S*)-**2b** was prepared under optimized reaction conditions (according to Table 1, entry 3) at a substrate concentration of 1.0 M, corresponding to 208 g/L. The biocatalyst loading of the whole-cell catalyst of type *E. coli* DSM14459, overexpressing the (*R*)-alcohol dehydrogenase from *L. kefir* and glucose dehydrogenase from *T. acidophilum*, was ~53 g of wet biomass/L. After a reaction time of 25 h, a conversion of >95% and an enantioselectivity of >99% *ee* was obtained (Scheme 5). The β-halohydrin (*S*)-**2b** was isolated in 85% yield (crude product). The conversion of (*S*)-**2b** to the epoxide (*S*)-**3** was done in a subsequent step. The β-halohydrin (*S*)-**2b** was cyclized, as described above, with 10.0 equivs. of powdered NaOH in diethyl ether. The desired epoxide (*S*)-**3** resulted after 1.0 h in 92% yield (quantitative conversion) and with >99% *ee*.

Conclusions

In conclusion, a practical biocatalytic method for the synthesis of aliphatic terminal (*S*)-β-halohydrins by means of an enantioselective reduction of the corresponding ketones has been developed, which is based on the use of a recombinant, ADH-containing whole-cell catalyst. The biotransformations operate at a high substrate input of up to 208 g/L and lead to the formation of the desired (*S*)-alcohols with both high conversions of >95% and enantioselectivities of >99% *ee*. Subsequent cyclization of the β-halohydrins gave the corresponding (*S*)-epoxide. The two-step process with isolation of the β-halohydrin intermediate turned out to be superior to the one-pot process for the direct preparation of (*S*)-octene oxide, (*S*)-**3**, when using recombinant whole-cells as a catalyst. Extension of the reaction scope towards the synthesis of other types of aliphatic and enantiomerically pure terminal epoxides is planned.

Experimental Section

Materials

1-Octene, $RuCl_3 \cdot X H_2O$ and TEMPO were purchased from Aldrich, Bu_4NBr from Fluka, trichloroisocyanuric acid and NBS from Acros Organics, CrO_3 from Janssen Chimica. All chemicals were used without further purification. Solvents were distilled using standard techniques. Chromatographic separations were performed using silica gel 60 (0.040–0.063 mm/230–400 mesh ASTM) from Merck KGaA. For the preparation of the whole-cell catalyst of type *E. coli* DSM14459 [overexpressing the (*R*)-alcohol dehydrogenase from *L. kefir* and glucose dehydrogenase from *T. acidophilum*], see ref.[14]

Instrumentation

Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Bruker Avance DPX300 (300 MHz) NMR spectrometer. Chemical shifts for protons and carbon atoms are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual protons in the NMR solvent and carbon resonances of the solvent, respectively. FT-IR spectra were recorded on a Perkin–Elmer Par-

agon 1000 FT-IR spectrometer with the ATR technique. Data are reported as: wave number of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). GC analyses were performed using a HP 6890 Series instrument with a chiral stationary phase WCOT-FS CP-Chirasil-Dex CB: Octakis-(2,6-di-*O*-pentyl-3-*O*-butyryl)-γ-cyclodextrin capillary column and N_2 as carrier gas. For the measurements, (*S*)-**2a** and (*S*)-**2b** were silylated with *N*,*O*-bis(trimethylsilyl)acetamide (BSA). GC-MS analyses were performed using a HP 6890 Series instrument with a mass selective detector 5973. A HP-5 Crosslinked Methyl Silicone Gum capillary column was used as stationary phase, and helium as carrier gas. Optical rotations ([α]) were measured in silica glass cuvettes using a Perkin–Elmer 343plus instrument.

1-Chloro-2-octanone (1a)

Preparation* via *a two-step procedure: 1-Octene (11.8 mL, 75.0 mmol, 1.00 equiv.) was dissolved in 188 mL acetone, 38.0 mL water, and trichloroisocyanuric acid (17.4 g, 75.0 mmol, 1.00 equiv.) was added. The mixture was stirred at room temperature for 1.0 h. The mixture was then filtered through celite, and the filtrate was extracted 3 times with 250 mL CH_2Cl_2. The organic phase was dried over Na_2SO_4, and the solvent was evaporated. The crude product was dissolved in 150 mL CH_2Cl_2 and cooled in an ice bath. Trichloroisocyanuric acid (17.4 g, 75.0 mmol, 1.00 equiv.) and TEMPO (0.59 g, 3.75 mmol, 0.05 equiv.) were added. The mixture was stirred with cooling for 10.0 min. Then the ice bath was removed and the mixture was stirred at room temperature for another 3.0 h. The mixture was then filtered through celite and the filtrate was washed successively with saturated aqueous $NaHSO_3$, saturated aqueous Na_2CO_3, aqueous HCl (1.0 M) and saturated aqueous NaCl (450 mL each). The organic phase was dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified by kugelrohr distillation (125 °C, 2.6 mbar) and column chromatography (silica gel, cyclohexane/CH_2Cl_2, 1:1). The ketone **1a** was obtained as colorless liquid; yield: 10.1 g (62.2 mmol, 83 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.88 (t, 3 H, $^3J_{H,H}$ = 6.9 Hz, H-8), 1.26–1.27 (m, 6 H, H-5-H-7), 1.54–1.64 (m, 2 H, H-4), 2.53–2.58 (t, 2 H, $^3J_{H,H}$ = 7.5 Hz, H-3), 4.06 (s, 2 H, H-1); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 13.9, 22.4, 23.5, 28.7, 31.4, 39.7, 48.2, 202.6; FT-IR (ATR-film): $\tilde{\nu}$ = 2948, 2921 (both s), 2853 (m), 1731, 1714 (both s), 1537, 1503 (both w), 1463, 1456, 1398, 1374 (all m), 1316, 1293, 1276, 1265, 1228, 1191, 1160 (all w), 1126 (m), 1102 (w), 1058 (m), 1011, 905, 888, (all w), 766, 725 (both m), 708, 650 cm^{-1} (both w); GC-MS [70 °C (3.00 min), 10 °C min^{-1}, 280 °C (10.0 min)]: τ_R = 9.01 min, *m*/*z* = 114/113, 105, 95, 92, 85, 77, 69, 57/55; GC [125 °C (20.0 min), 20 °C min^{-1}, 170 °C (5.00 min)]: τ_R = 11.47 min; DC: R_f = 0.51 (silica gel, cyclohexane/CH_2Cl_2, 1:1). Analytical data were in agreement with the literature reports.[20]

Preparation* via *a two-step/one-pot procedure: 1-Octene (3.14 mL, 20.0 mmol, 1.00 equiv.) was dissolved in 20.0 mL acetone and 0.40 mL water was added. The mixture was cooled in an ice bath, and trichloroisocyanuric acid (2.32 g, 10.0 mmol, 0.50 equiv.) dissolved in 30.0 mL acetone was added. Then Bu_4NBr (0.13 g, 0.40 mmol, 0.02 equiv.) dissolved in 4.00 mL water, 66.0 mL phosphate buffer (1.0 M, pH 5.2), $RuCl_3 \cdot X H_2O$ (~41 %) (0.13 g, 0.20 mmol, 0.01 equiv.) dissolved in 2.00 mL water and again trichloroisocyanuric acid (4.65 g, 20.0 mmol, 1.00 equiv.) dissolved in 20.0 mL acetone were added slowly. The pH value was kept at 5 by adding a K_2CO_3 solution (3.00 M) during the reaction. The mixture was stirred at room temperature for 1.0 h. 100 mL 2-propanol were added and the mixture was stirred again for 30.0 min. The mixture was filtered and the solvent was evaporated from the filtrate. The aqueous residue was extracted 3 times with 50.0 mL ethyl acetate. The combined organic phases were washed successively with saturated aqueous $NaHCO_3$ (2 × 300 mL) and water (300 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified by kugelrohr distillation (159 °C, 4.6 mbar), and the ketone **1a** was obtained as colorless liquid; yield: 1.78 g (10.9 mmol, 55 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.87 (t, 3 H, $^3J_{H,H}$ = 6.6 Hz, H-8), 1.26 (m, 6 H, H-5-H-7), 1.56–1.61 (m, 2 H, H-4), 2.53–2.58 (t, 2 H, $^3J_{H,H}$ = 7.4 Hz, H-3), 4.05 (s, 2 H, H-1); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 13.9, 22.4, 23.5, 28.7, 31.4, 39.6, 48.1, 202.7; FT-IR (ATR-film): $\tilde{\nu}$ = 2948, 2921, 2853, 1728, 1714 (all s), 1463, 1456, 1398, 1374 (all m), 1320, 1289, 1272, 1255, 1228, 1191, 1164 (all w), 1126 (m), 1099 (w), 1058 (m), 1007, 905, 888 (all w), 766, 725 (both m), 708, 654, 647 cm^{-1} (all w). GC-MS [70 °C (3.00 min), 10 °C min^{-1}, 280 °C (10.0 min)]: τ_R = 8.80 min, *m*/*z* = 114/113, 105, 95/92, 85, 77, 69, 57/55. GC [125 °C (20.0 min), 20 °C min^{-1}, 170 °C (5.00 min)]: τ_R = 11.51 min. Analytical data were in agreement with the literature reports.[20]

1-Bromo-2-octanone (1b)

1-Bromo-2-octanone **1b** was prepared following a literature procedure.[16] First, Jones reagent was prepared as follows: CrO_3 (8.70 g, 87.0 mmol, 1.30 equivs.) was dissolved in 9.00 mL water and 6.00 mL H_2SO_4 dissolved in 9.00 mL H_2O were added. The mixture was stirred for 10.0 min at room temperature. During this time 1-octene (10.5 mL, 66.9 mmol, 1.00 equiv.) was dissolved in 75.0 mL acetone and 3.00 mL water were added. The mixture was cooled in an ice bath and then the Jones reagent was added. During the next 10.0 min NBS (17.9 g, 100 mmol, 1.50 equivs.) was added. The ice bath was removed and the mixture was stirred at room temperature for another 3.0 h. Water was added and the mixture was extracted 3 times with 150 mL diethyl ether. The combined organic phases were washed 3 times with 450 mL water. The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by kugelrohr distillation (115 °C, 2.6 mbar) and column chromatography (silica gel, cyclohexane/CH_2Cl_2, 1:1). The ketone **1b** was obtained as a colorless liquid yield: 5.87 g (28.3 mmol, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.89 (t, 3 H, $^3J_{H,H}$ = 6.8 Hz, H-8), 1.28 (m, 6 H, H-5 to H-7), 1.55–1.65 (m, 2 H, H-4), 2.61–2.66 (t, 2 H, $^3J_{H,H}$ = 7.4 Hz, H-3), 3.87 (s, 2 H, H-1); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 13.9, 22.4, 23.7, 28.6, 31.4, 34.3, 39.7, 202.1; FT-IR (ATR-film): $\tilde{\nu}$ = 2948, 2925, 2854, 1712 (all s), 1465, 1403, 1374 (all m), 1204 (w), 1173 (m), 1116 (w), 1057 (m), 892, 722, 688, 628, 610 cm^{-1} (all w); GC-MS [70 °C (3.00 min), 10 °C min^{-1}, 280 °C (10.0 min)]: τ_R = 10.00 min, *m*/*z* (%) = 138/136, 123/121, 114/113, 97/95, 85, 69, 57/55; GC [125 °C (20.0 min), 20 °C min^{-1}, 170 °C (5.00 min)]: τ_R = 17.63 min;

DC: $R_f = 0.48$ (silica gel, cyclohexane/CH_2Cl_2 1 : 1). Analytical data were in agreement with the literature.[16]

General Procedure for the Enantioselective Biocatalytic Synthesis of (*S*)-1-Halo-2-octan-ols (*S*)-2 (According to the Reaction Shown in Table 1)

A Titrino reaction apparatus was filled with 20 mL of an aqueous buffer solution (0.2 M; adjusted to pH 7.0), the whole-cell catalyst of type *E. coli* DSM14459 [overexpressing the (*R*)-alcohol dehydrogenase from *L. kefir* and glucose dehydrogenase from *T. acidophilum*; cell concentration ~50–56 g of wet biomass/L], D-glucose (1.1 equivs. based on the amount of ketone) and 20 mmol (0.5 M), 30 mmol (0.75 M) or 40 mmol (1.0 M) of ketone **1** (see entries 1–4 in Table 1). Water was added until a volume of 40 mL is reached. The reaction mixture was stirred at room temperature for 22–24 h and the pH was maintained at ~6.5 by dosage of aqueous sodium hydroxide (5.0 M NaOH). After a reaction time of 22–24 h the conversion has been determined by means of HPLC-chromatography and NMR-spectroscopy, respectively. The work-up was carried out by lowering the pH to <3 with concentrated hydrochloric acid and addition of 3.0 g of the filter aid material Celite Hyflo Supercel to the reaction mixture, and subsequent filtration. The filter cake was washed with 3×50 mL of MTBE, and the aqueous phase was extracted accordingly with the resulting organic fractions. After drying over magnesium sulfate the collected organic phases were concentrated to dryness, delivering the desired optically active alcohols in a high purity, even as a crude product.

(*S*)-1-Chloro-2-octanol [(*S*)-2a]

1.33 g of the crude product obtained by extraction of the asymmetric biocatalytic reduction of 1-chloro-2-octanone (**1a**) were subjected to kugelrohr distillation (117 °C, $7.2 \cdot 10^{-1}$ mbar). (*S*)-1-Chloro-2-octanol [(*S*)-**2a**] was obtained as a colorless liquid; yield: 1.23 g (7.45 mmol, 92 %; >99 % *ee*); $[\alpha]_D^{20}$: = −16.7° (*c* 1.00, EtOH); *ee* >99 %; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$–0.88 (3H, H-8), 1.29–1.51 (m, 10H, H-3-H-7), 2.27 (s, 1H, OH), 3.43–3.50 (dd, 1H, $^2J_{H,H}$ = 11.1 Hz, $^3J_{H,H}$ = 7.2 Hz, H-1$_a$), 3.59–3.64 (dd, 1H, $^2J_{H,H}$ = 11.1 Hz, $^3J_{H,H}$ = 3.3 Hz, H-1$_b$), 3.78–3.79 (m, 1H, H-2); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 25.4, 29.1, 31.7, 34.2, 50.5, 71.4; FT-IR (ATR-film): $\tilde{\nu} = 3369$, 2948, 2922, 2855 (all s), 1463, 1457, 1429, 1374 (all m), 1337, 1300, 1279, 1252, 1218, 1191, 1167 (all w), 1123 (m), 1050 (s), 966, 943, 892, 875, 848, 790 (all w), 739, 698 cm^{-1} (both m); GC-MS [70 °C (3.00 min), 10 °C min^{-1}, 280 °C (10.0 min)]: τ_R = 9.11 min, *m*/*z* = 115, 98/97, 81/79, 70/69, 57/56/55; GC [125 °C (20.0 min), 20 °C min^{-1}, 170 °C (5.00 min)]: τ_R = 13.40 min [(*S*)-product, major], τ_R = 13.85 min [(*R*)-product, minor]. The absolute configuration of the major enantiomer was assigned as (−)-*S*, based on comparison of the measured optical rotation with the literature values.[11,12a] Analytical data were in agreement with the literature.[12a]

(*S*)-1-Bromo-2-octanol [(*S*)-2b]

6.18 g of the crude product obtained by extraction of the asymmetric biocatalytic reduction of 1-bromo-2-octanone (**1b**) were subjected to kugelrohr distillation (129 °C, $7.4 \cdot 10^{-1}$ mbar). (*S*)-1-Bromo-2-octanol [(*S*)-**2b**] was obtained as a colorless liquid; yield: 5.49 g (26.3 mmol, 89 %; >99 % *ee*); $[\alpha]_D^{20}$: −14.8° (*c* 1.00, EtOH); *ee* >99 %; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$–0.90 (t, 3H, $^3J_{H,H}$ = 6.9 Hz, H-8), 1.28–1.56 (m, 10H, H-3-H-7), 2.16–2.17 (m, 1H, OH), 3.35–3.41 (dd, 1H, $^2J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 6.9 Hz, H-1$_a$), 3.52–3.56 (dd, 1H, $^2J_{H,H}$ = 10.4 Hz, $^3J_{H,H}$ = 3.2 Hz, H-1$_b$), 3.76–3.77 (m, 1H, H-2); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 25.6, 29.1, 31.7, 35.1, 40.7, 71.1; FT-IR (ATR-film): $\tilde{\nu} = 3390$, 2948, 2921, 2854 (all s), 1464, 1456, 1418, 1374 (all m), 1266 (w), 1219 (m), 1177, 1150 (both w), 1123, 1068 (both m), 1034 (s), 963, 936, 899, 868, 831, 790 (all w), 722 (m), 661 cm^{-1} (s); GC-MS [70 °C (3.00 min), 10 °C min^{-1}, 280 °C (10.0 min)]: τ_R = 10.35 min, *m*/*z* = 125/123, 115, 98/97, 81, 69, 57/56/55; GC [125 °C (20.0 min), 20 °C min^{-1}, 170 °C (5.00 min)]: τ_R = 19.05 min [(*S*)-product, major], τ_R = 19.64 min [(*R*)-product, minor]. The absolute configuration of the major enantiomer was assigned as (−)-*S*, based on comparison of the optical rotation for the (+)-*R* enantiomer. The (+)-*R* enantiomer was prepared by kinetic resolution of *rac*-1-octene oxide and nucleophilic ring opening of the (+)-*R* enantiomer by LiBr.[18] Analytical data were in agreement with the literature.[21]

(*S*)-1-Octene oxide [(*S*)-3]

Preparation starting from (S)-1-Chloro-2-octanol [(S)-2a]: (*S*)-1-Chloro-2-octanol [(*S*)-**2a**] (0.88 g, 5.33 mmol, 1.00 equiv.) was dissolved in 3.00 mL diethyl ether, and sodium hydroxide (2.13 g, 53.3 mmol, 10.0 equivs.) was added. The mixture was stirred for one hour at 30 °C. Then the solvent was evaporated and the crude product was purified by bulb-to-bulb distillation (60 °C, 3.00 mbar). The epoxide (*S*)-**3** was obtained as colorless liquid; yield: 0.63 g (4.90 mmol, 92 %; >99 % *ee*); $[\alpha]_D^{20}$: −15.0° (*c* 1.00, EtOH); *ee* > 99 % {Lit.[19] $[\alpha]_D^{23}$: −14.0° (*c* 2.10, EtOH); *ee* >97 %}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$–0.90 (t, 3H, $^3J_{H,H}$ = 6.8 Hz, H-8), 1.24–1.53 (m, 10H, H-3-H-7), 2.44–2.46 (dd, 1H, $^2J_{H,H}$ = 5.1 Hz, $^3J_{H,H}$ = 2.7 Hz, H-1$_a$), 2.72–2.75 (dd, 1H, $^2J_{H,H}$ = 5.0 Hz, $^3J_{H,H}$ = 4.1 Hz, H-1$_b$), 2.86–2.92 (m, 1H, H-2); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 25.9, 29.1, 31.7, 32.5, 47.1, 52.4; FT-IR (ATR-film): $\tilde{\nu} = 2948$, 2921, 2846 (all s), 1466, 1456, 1449 (all m), 1408, 1378, 1296, 1255, 1221, 1191, 1126, 1099, 1079, 1055, 1024, 929 (all w), 916 (m), 882 (w), 831 (m), 814, 759 (both w), 729 (m), 678 cm^{-1} (w); GC-MS [70 °C (3.00 min), 10 °C min^{-1}, 280 °C (10.0 min)]: τ_R = 5.82 min, *m*/*z* = 99, 85/81, 71/70/69/68/67, 58/57/56/55; GC [60 °C (48.0 min), 5 °C min^{-1}, 120 °C (35.0 min), 15 °C min^{-1}, 180 °C (3.00 min)]: τ_R = 33.55 min [(*R*)-product, minor], τ_R = 34.36 min [(*S*)-product, major]. The absolute configuration of the major enantiomer was assigned as (−)-*S*, based on comparison of the measured optical rotation with the literature value.[19] Analytical data were in agreement with the literature.[22]

Preparation starting from (S)-1-Bromo-2-octanol [(S)-2b]: (*S*)-1-Bromo-2-octanol [(*S*)-**2b**] (5.12 g, 24.5 mmol, 1.00 equiv.) was dissolved in 15.0 mL diethyl ether, and sodium hydroxide (9.80 g, 0.24 mol, 10.0 equivs.) was added. The mixture was stirred for one hour at 30 °C. Then the solvent was evaporated and the crude product was purified by bulb-to-bulb distillation (55 °C, 2.00 mbar). The epoxide (*S*)-**3** was obtained as colorless liquid; yield: 2.89 g (22.5 mmol,

92%; >99% *ee*; $[\alpha]_D^{20}$: −15.1° (*c* 1.00, EtOH); *ee* >99% {Lit.[19] $[\alpha]_D^{23}$: −14.0° (*c* 2.10, EtOH); *ee* >97%}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.89 (t, 3H, $^3J_{H,H}$ = 6.8 Hz, H-8), 1.24–1.52 (m, 10H, H-3-H-7), 2.43–2.46 (dd, 1H, $^2J_{H,H}$ = 5.0 Hz, $^3J_{H,H}$ = 2.9 Hz, H-1$_a$), 2.71–2.74 (dd, 1H, $^3J_{H,H}$ = 3.9 Hz, $^2J_{H,H}$ = 5.1 Hz, H-1$_b$), 2.86–2.92 (m, 1H, H-2); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.9, 29.1, 31.7, 32.5, 47.1, 52.4; FT-IR (ATR-film): $\tilde{\nu}$ = 3037 (w), 2948, 2921, 2853 (all s), 1480 (w), 1463, 1456 (both m), 1408, 1374, 1327, 1303, 1255, 1221, 1191, 1126, 1070, 1048, 990, 929 (all w), 916 (m), 885 (w), 831 (s), 780, 756, 735, 722 cm^{-1} (all w); GC-MS [70°C (3.00 min), 10°C min^{-1}, 280°C (10.0 min)]: τ_R = 5.82 min, *m*/*z* = 99, 85/81, 71/70/69/68/67, 58/57/56/55; GC [60°C (48.0 min), 5°C min^{-1}, 120°C (35.0 min), 15°C min^{-1}, 180°C (3.00 min)]: τ_R = 33.92 min [(*R*)-product, minor], τ_R = 34.70 min [(*S*)-product, major]. The absolute configuration of the major enantiomer was assigned as (−)-*S*, based on comparison of the measured optical rotation with the literature value.[19] Analytical data were in agreement with the literature.[22]

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