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SUPPORTING INFORMATION

Title: Biocatalytic Racemization of (Hetero)Aryl-aliphatic α-Hydroxycarboxylic Acids by *Lactobacillus* spp. Proceeds via an Oxidation–Reduction Sequence

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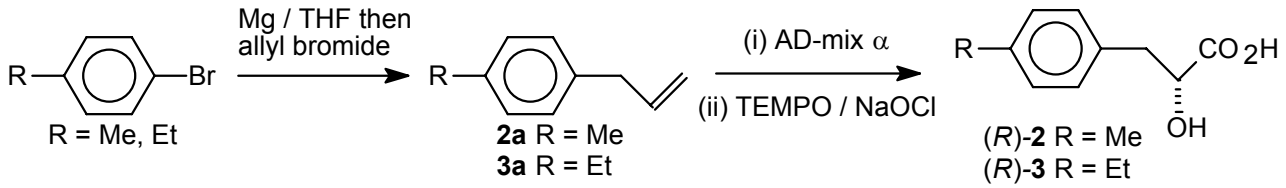
Synthesis of Substrates and Reference Material

General

NMR spectra were recorded in $CDCl_3$ using a Bruker AMX 360 at 360 (^1H) and 90 (^{13}C) MHz. Chemical shifts are reported relative to TMS (δ 0.00) and coupling constants (*J*) are given in Hz. TLC plates were run on silica gel Merck 60 (F_{254}) and compounds were visualized by spraying with Mo-reagent [$(NH_4)_6Mo_7O_{24}*4H_2O$ (100 g/L), $Ce(SO_4)_2*4H_2O$ (4 g/L) in H_2SO_4 (10%)]. The degree of conversion (expressed as % of racemization with 100% corresponding to the racemate) and enantiomeric excess were determined *via* HPLC or *via* GC on a chiral stationary phase. HPLC analyses were carried out on a Jasco HPLC-system (pumps PU-980, multiwavelength-detector MD-910, autosampler AS-950, degasser CMA-260) using a Chiralpak AD column (Daicel, 0.46 cm x 25 cm) and a Chiralpak OD-H column (Daicel, 0.46cm x 25 cm). GC analyses were carried out on a Varian 3800 gas chromatograph equipped with FID using a CP-Chirasil-Dex CB capillary column (25m x 0.32 mm x 0.25 μm film) and N_2 as carrier gas. Melting points were obtained on a Gallenkamp melting point apparatus MFB-595 in open capillary tubes. Optical rotation values ($[\alpha]_D^{20}$) were measured on a Perkin-Elmer polarimeter 341 at 589 nm (Na-line) in a 1 dm cuvette and are given in units of 10 deg cm^2 g^{-1}.

Synthesis of substrates and reference materials

General Procedure for the Synthesis of (*R*)-**2** and (*R*)-**3**.



Compounds (*R*)-**2**,**3** were obtained from the corresponding 1-bromo-4-alkylbenzene using the following procedure adapted from literature:[1] Alkylbenzene magnesium bromide was made from 1-bromo-4-alkylbenzene and magnesium in anhydrous THF. A solution of allyl bromide in anhydrous THF was added to the Grignard reagent. Heat was generated during this addition and refluxing was maintained for 30 min after the addition was complete. The reaction was quenched by hydrolysis and separation of the THF layer gave the corresponding 1-allyl-4-alkylbenzene.

1-Allyl-4-methylbenzene **2a**: 4-Tolylmagnesium bromide was made from 5.3 g (30.9 mmol) 4-bromtoluene, 1 g magnesium and 20 mL of freshly distilled THF. A solution of 4 g (33.1 mmol) allyl bromide in 5 mL THF was added and the mixture was refluxed for 30 min after the addition was complete. Hydrolysis, extraction with diethyl ether, drying over sodium sulfate and evaporation under vacuum gave **2a** as an orange oil (2.9 g, 72%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.37 (3H, s, CH_3), 3.41 (2H, d, J = 6.67 Hz, Ph-$\underline{CH_2}$), 5.10-5.16 (2H, m), 5.97-6.08 (1H, ddt, J_1 = 16.9 Hz, J_2 = 10.09 Hz, J_3 = 6.68 Hz), 7.16 (4H, s), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 21.3, 39.9, 115.6, 128.5, 129.1, 135.6, 137.0, 137.8.

1-Allyl-4-ethylbenzene **3a**: 4-Ethylbenzene magnesium bromide was made from 5.3 g (28.6 mmol) 1-brom-4-ethylbenzene, 1 g magnesium and 30 mL of freshly distilled THF. A solution of 4 g (33.1 mmol) allyl bromide in 5 mL THF was added and the mixture was refluxed for 30 min after the addition was complete. Hydrolysis, extraction with diethyl ether, drying over sodium sulfate and evaporation under vacuum gave **3a** as a brown oil (1.9 g, 54%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.28 (3H, t, J = 7.61 Hz, $CH_2\underline{CH_3}$), 2.67 (2H, q, J = 7.60 Hz, $\underline{CH_2}CH_3$) 3.40 (2H, d, J = 6.69 Hz, Ph-$\underline{CH_2}$), 5.08-5.15 (2H, m), 5.97-6.05 (1H, ddt, J_1 = 16.9 Hz, J_2 = 10.15 Hz, J_3 = 6.83 Hz), 7.16 (4H, s), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 15.7, 28.5, 39.9, 115.6, 127.9, 128.2, 137.7, 141.9.

General procedure for the preparation of (*R*)-2-hydroxy-3-(4-alkylphenyl)-propionic acids (*R*)-**2** and (*R*)-**3** from **2a** and **3a**.[2]

Olefin (**2a**, **3a**) was dissolved in *t*-BuOH:H_2O (1:1) and AD-mix α was added. The mixture was stirred at room temperature for 20h. Then, the reaction was quenched by adding sodium sulfite and stirred for 15 min. *t*-BuOH was removed under vacuum and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was removed under vacuum. The resulting residue was dissolved in acetonitrile and sodium phosphate buffer (0.1 M, pH 6.5). Then, TEMPO, sodium chlorite and diluted bleach (4% active chlorine) were added and

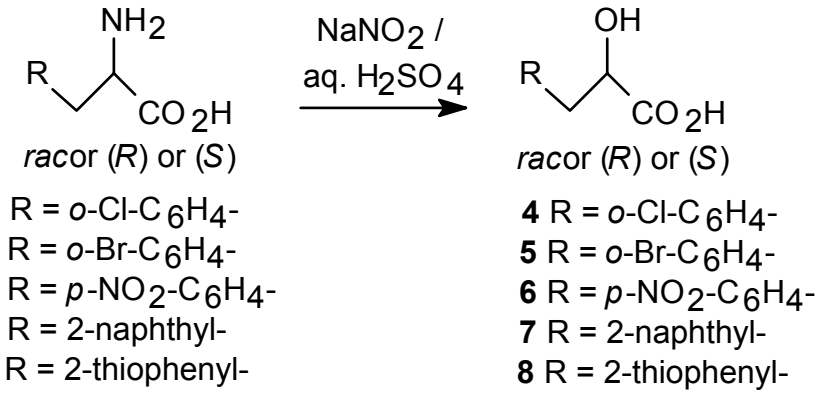
the mixture was heated to 55 °C. After five days, the reaction was allowed to cool to room temperature and water was added. The pH was set to 8 with 1N NaOH and cool aqueous sodium sulfite (0.4 g in 8 mL water) was added. The pH was lowered to 2 with 1N HCl and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, the solvent was removed by evaporation and the residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give enantiopure (*R*)-α-hydroxycarboxylic acids (*R*)-**2**,**3**.

(*R*)-2-Hydroxy-4-*p*-tolylpropionic acid (*R*)-**2**: 1-Allyl-4-methylbenzene **2a** (2.9 g, 21.9 mmol) was dissolved in *t*-BuOH/H_2O (1:1, 210 mL) and 32.1 g AD-mix α was added and stirred at room temperature for 20 h. The reaction was quenched by adding 10.9 g (86.4 mmol) sodium sulfite and stirred for 15 min. After extraction with ethyl acetate and evaporation to dryness, the residue was dissolved in acetonitrile (85 mL) and sodium phosphate buffer (0.1M, pH 6.5, 54 mL). Then 776 mg (4.97 mmol) TEMPO, 3.19 g (35.3 mmol) sodium chlorite and 2.2 mL diluted bleach were added and the mixture was heated to 55 °C. After five days, the reaction was allowed to cool to room temperature and water (100 mL) was added. The pH was set to 8 with 1N NaOH and cool aqueous sodium sulfite (5 g in 100 mL) was added. The pH was lowered to 2 with 1N HCl and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was removed by evaporation. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give (*R*)-**2** as brown crystals (2.29 g, 57%, e.e. >99%); mp = 125 °C; $[\alpha]_D^{20}$ +14.4 (*c* 1.0, EtOH)[3]; ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.06 (1H, s, OH), 2.34 (3H, s, CH_3), 3.48-3.69 (2H, ddd, J_1 = 47.27 Hz, J_2 = 10.98 Hz , J_3= 7.17 Hz, $\underline{CH_2}$CH-OH), 4.34 (1H, t, *J* = 7.17 Hz, $CH_2\underline{CH}$-OH), 7.13 (4H, s); ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 21.1, 39.3, 73.1, 129.1, 129.5, 134.5, 136.2, 173.4.

(*R*)-2-Hydroxy-3-(4-ethylphenyl)-propionic acid (*R*)-**3**: 1-Allyl-4-ethylbenzene **3a** (1.9 g, 13.1 mmol) was dissolved in *t*-BuOH/H_2O (1:1, 140 mL) and 21.1 g AD-mix α was added and allowed to stir at room temperature for 20h. The reaction was quenched by adding 7.14 g (56.7 mmol) sodium sulfite and stirred for 15 min. After extraction with ethyl acetate and evaporation to dryness, the resulting residue was dissolved in acetonitrile (56 mL) and sodium phosphate buffer (0.1 M, pH 6.5, 35 mL). Then 508 mg (3.25 mmol) TEMPO, 2.09 g (23.1 mmol) sodium chlorite and 1.5 mL diluted bleach were added and the mixture was heated to 55 °C. After five days, the reaction was allowed to cool to room temperature and water (66 mL) was added. The pH was set to 8 with 1N NaOH and cool aqueous sodium sulfite (3 g in 60 mL) was added. The pH was lowered to 2 with 1N HCl and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was removed by evaporation. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give (*R*)-**3** as dark red crystals (1.23 g, 44%, e.e. >99%); mp = 86 °C; $[\alpha]_D^{20}$ +40.3 (*c* 1.0, EtOH); ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.26 (3H, t, *J* = 5.22 Hz),

2.06 (1H, s, OH), 2.64 (2H, q, *J*= 7.53 Hz, $CH_3\underline{CH_2}$), 2.95-3.21 (4H, ddd, J_1 = 47.78 Hz, J_2 = 13.94 Hz, J_3 = 7.28 Hz, $\underline{CH_2}$CH-OH), 4.49 (2H, t, *J* = 4.07 Hz, $CH_2\underline{CH}$-OH), 7.17 (4H, s); ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 17.7, 30.7, 42.0, 73.3, 130.1, 136.6, 173.8.

Compounds *rac*-**4**-**8**, (*R*)-**4**-**8** and (*S*)-**4**-**8** were obtained by diazotation of the corresponding α-amino acid using the followed general procedure adapted from literature.[4]



*rac*or (*R*) or (*S*)

R = *o*-Cl-C_6H_4-
R = *o*-Br-C_6H_4-
R = *p*-NO_2-C_6H_4-
R = 2-naphthyl-
R = 2-thiophenyl-

*rac*or (*R*) or (*S*)

4 R = *o*-Cl-C_6H_4-
5 R = *o*-Br-C_6H_4-
6 R = *p*-NO_2-C_6H_4-
7 R = 2-naphthyl-
8 R = 2-thiophenyl-

Method A: α-Amino acid (6.05 mmol) was dissolved in H_2SO_4 (12 mL, 1M). The stirred solution was cooled to 0 °C and $NaNO_2$ (24 mmol) was added in small portions. The reaction was allowed to warm to room temperature and stirring was continued overnight. After dilution with water the aqueous phase was extracted with ethyl acetate (3 x 10 mL), the combined organic layers were washed with sat. aqueous $NaHCO_3$, dried over sodium sulfate and evaporated. Compounds *rac*-**4**-**8**, (*R*)-**4**-**8** and (*S*)-**4**-**8** were purified by flash chromatography.

rac- and (*S*)-3-(2-chlorophenyl)-2-hydroxypropionic acid *rac*-**4** and (*S*)-**4**: Method A was employed using *rac*- and L-2-chlorophenylalanine (1 g, 5.01 mmol), $NaNO_2$ (1.66 g) in H_2SO_4 (12 mL, 1M). The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give *rac*- and (*S*)-**4** as white crystals (670 mg, 67%, e.e. >99%); mp = 78 °C;[5] $[\alpha]_D^{20}$ +20.7 (*c* 1.0, EtOH); ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.07 (1H, s, OH), 3.01-3.47 (2H, ddd, J_1 = 42.41 Hz, J_2 = 10.35 Hz, J_3 = 3.83 Hz), 4.60 (1H, dd, J_1 = 4.15 Hz, J_2 = 4.19 Hz, C$\underline{H}$-OH), 7.21-7.44 (4H, m); ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 38.3, 69.9, 127.0, 128.7, 129.8, 132.0, 134.5, 146.8, 178.5.

rac- and (*S*)-3-(2-bromophenyl)-2-hydroxypropionic acid *rac*-**5** and (*S*)-**5**: Method A was employed using *rac*- and L-2-bromophenylalanine (0.5 g, 2.05 mmol), $NaNO_2$ (0.83 g) in H_2SO_4 (6 mL, 1M). The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give *rac*-**5** and (*S*)-**5** as white crystals (230 mg, 46%, e.e. >99%); mp = 136 °C; $[\alpha]_D^{20}$ +16.4 (*c* 1.0, EtOH); ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.08 (1H, s, OH), 2.49-3.33 (2H, ddd, J_1 = 23.62 Hz, J_2 = 8.87 Hz, J_3 = 4.12 Hz), 4.42 (1H, t, *J* = 4.17 Hz, C$\underline{H}$-OH), 7.16-7.38 (4H, m); ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 32.9, 69.8, 123.5, 128.6, 129.5, 131.7, 132.9, 141.4, 177.9.

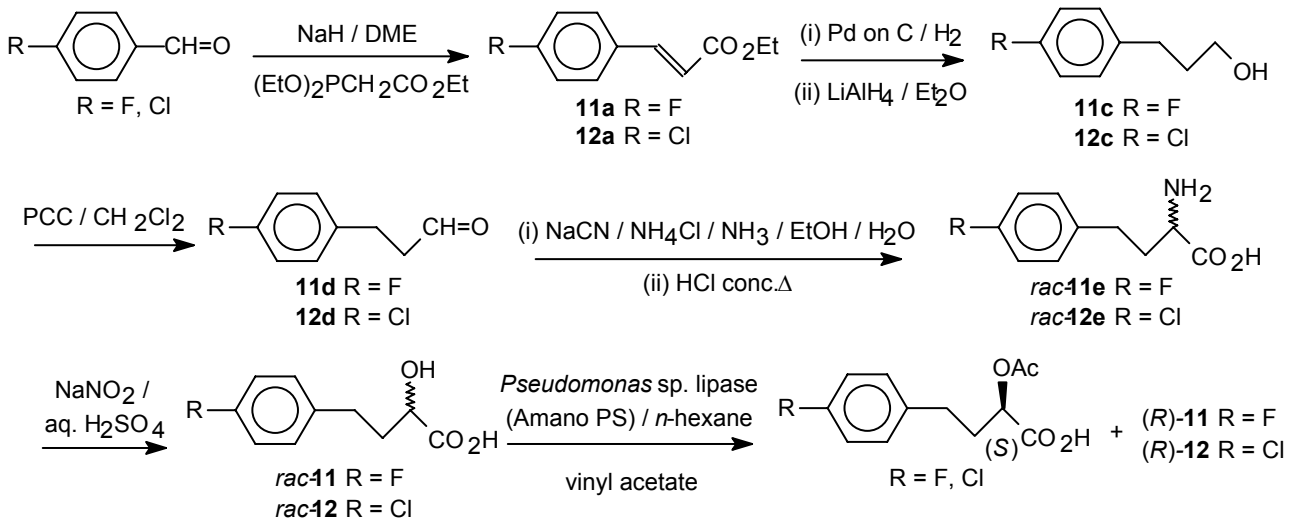
rac- and (*S*)-3-(4-nitrophenyl)-2-hydroxypropionic acid *rac*-**6** and (*S*)-**6**: Method A was employed using *rac*- and L-4-nitrophenylalanine (1 g, 4.38 mmol), $NaNO_2$ (1.66 g) in H_2SO_4 (12 mL, 1M). The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give *rac*-**6** and (*S*)-**6** as light yellow crystals (547 mg, 55%, e.e. >99%); mp = 111 °C;[6] $[\alpha]_D^{20}$ –17.4 (*c* 1.0, EtOH);[6] ^{1}H-NMR: (360 MHz, DMSO) δ = 2.08 (1H, s, OH), 2.90-3.14 (2H, ddd, J_1 = 43.94 Hz, J_2 = 9.56 Hz, J_3 = 4.22 Hz), 4.23 (1H, t, *J* = 4.26 Hz, C<u>H</u>-OH), 7.52 (2H, d, *J* = 8.6 Hz), 8.13 (2H, d, *J* = 8.5 Hz), 12.1 (1H, s, COO<u>H</u>); ^{13}C-NMR: (90 MHz, DMSO) δ = 39.9, 70.8, 123.8, 131.2, 146.6, 175.2.

rac- and (*S*)-2-hydroxy-3-naphth-2-ylpropionic acid *rac*-**7** and (*S*)-**7**: Method A was employed using *rac*- and L-3-(2-naphthyl)-alanine (1 g, 4.65 mmol), $NaNO_2$ (1.66 g) in H_2SO_4 (12 mL, 1M). The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give *rac*-**7** and (*S*)-**7** as yellow crystals (589 mg, 59%, e.e. >99%); mp = 134 °C; $[\alpha]_D^{20}$ +25.3 (*c* 1.0, EtOH);[7] ^{1}H-NMR: (360 MHz, DMSO) δ = 2.07 (1H, s, OH), 2.69-3.43 (2H, ddd, J_1 = 41.24 Hz, J_2 = 8.20 Hz, J_3 = 4.19 Hz), 4.28 (1H, t, *J* = 4.23 Hz, C<u>H</u>-OH), 7.43-7.88 (7H, m), ^{13}C-NMR: (90 MHz, DMSO) δ = 40.7, 72.9, 127.1, 127.3, 127.5, 128.0, 128.6, 129.1, 131.8, 134.2, 135.8, 138.9, 176.5.

rac- and (*R*)-2-hydroxy-3-thiophen-2-ylpropionic acid *rac*-**8** and (*S*)-**8**: Method A was employed using *rac*- and D-3-(2-thienyl)-alanine (1 g, 5.84 mmol), $NaNO_2$ (1.66 g) in H_2SO_4 (12 mL, 1M). The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give *rac*-**8** and (*S*)-**8** as white crystals (391 mg, 39%, e.e. >99%); mp = 128 °C; $[\alpha]_D^{20}$ –3.3 (*c* 0.2, EtOH); ^{1}H-NMR: (360 MHz, DMSO) δ = 2.09 (1H, s, OH), 2.87-3.29 (2H, ddd, J_1 = 23.54 Hz, J_2 = 8.85 Hz, J_3 = 4.12 Hz), 4.27 (1H, t, *J*= 4.17 Hz, C<u>H</u>-OH), 6.60-6.91 (3H, m), ^{13}C-NMR: (90 MHz, DMSO) δ = 31.9, 74.2, 124.2, 127.1, 127.6, 138.3, 175.1.

(*S*)-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (*S*)-**9**: mp = 121 °C; $[\alpha]_D^{20}$ +11.5 (*c* 1.8, EtOH). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.18 (1H, s), 3.17 (3H, s), 5.11 (1H, s), 7.37-7.44 (10H, m), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 52.9, 73.7, 85.6, 127.9, 128.8, 129.7, 136.3, 137.5, 178.4.

Compounds *rac*-**11**,**12** and (*S*)-**11**,**12** were obtained from the corresponding benzaldehydes using the followed procedure adapted from literature.[8]



Ethyl 3-(4-halophenyl)-prop-2-enoate **11a**, **12a**: To a slurry of sodium hydride in dimethoxyethane under a nitrogen atmosphere was added dropwise triethyl phosphonoacetate and the reaction stirred at room temperature for 1 h. 4-Halobenzaldehyde was then added and the reaction was stirred for 20 h. Water was then added, dropwise at first, and the products were extracted with diethyl ether. The combined organic phase was dried, filtered and concentrated under reduced pressure to give the corresponding propenoates.

Ethyl 3-(4-fluorophenyl)-prop-2-enoate **11a**: Sodium hydride (5.3 g, 1.32 mol) in 400 mL dimethoxyethane was treated with triethyl phosphonoacetate (16 mL, 80 mmol) and *p*-fluorobenzaldehyde (14 mL, 0.13 mol). Water (170 mL) was then added and extracted with diethyl ether to give **11a** (14.5 g, 93%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.33 (3H, t, *J* = 7.10 Hz, $COCH_2\underline{CH_3}$), 4.26 (2H, q, *J* = 7.14 Hz, $CO\underline{CH_2}CH_3$), 6.36 (1H, d, *J* = 14.4 Hz), 7.21 (2H, t, *J* = 8.55 Hz), 7.49 (2H, q, *J* = 5.41 Hz), 7.62 (1H, d, *J* = 16.0 Hz), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 14.3, 60.5, 116.5, 118.0, 129.9, 132.2, 143.2, 164.9, 166.8.

Ethyl 3-(4-chlorophenyl)-prop-2-enoate **12a**: Sodium hydride (3.2 g, 0.80 mol) in 400 mL dimethoxyethane was treated with triethyl phosphonoacetate (16 mL, 80 mmol) and *p*-chlorobenzaldehyde (11.5 g, 81.8 mmol). Water (200 mL) was then added and extracted with diethyl ether to give **12a** (15.8 g, 94%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.29 (3H, t, *J* = 7.20 Hz, $COCH_2\underline{CH_3}$), 4.24 (2H, q, *J* = 7.19 Hz, $CO\underline{CH_2}CH_3$), 6.38 (1H, d, *J* = 15.9 Hz), 7.33-7.43 (4H, dd, J_1 = 36.23 Hz, J_2 = 8.47 Hz), 7.60 (1H, d, *J* = 16.0 Hz), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 14.4, 61.7, 119.0, 129.5, 130.9, 135.2, 136.4, 143.0, 166.8.

Ethyl 3-(4-halophenyl)-propionate **11b**, **12b**: To a solution of ethyl 3-(4-halophenyl)-prop-2-enoate **11a** and **12a** in ethyl acetate was added 10% palladium on charcoal and the reaction was placed under a hydrogen atmosphere (1 bar). The reaction was then stirred vigorously until uptake of hydrogen ceased, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give the corresponding propanoates.

Ethyl 3-(4-fluorophenyl)-propanoate **11b**: Ethyl 3-(4-fluorophenyl)-prop-2-enoate **11a** (14.5 g, 74.5 mmol) was dissolved in 250 mL ethyl acetate and 800 mg Pd on charcoal was added to give ethyl 3-(4-fluorophenyl)-propanoate **11b** (10.3 g, 94%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.26 (3H, t, *J* = 7.15 Hz, $CH_2\underline{CH_3}$), 2.59 (2H, t, *J* = 7.84 Hz, $\underline{CH_2}$-CH), 2.92 (2H, t, *J* = 7.61 Hz, Ph-$\underline{CH_2}$), 4.13 (2H, q, *J* = 7.14 Hz, $\underline{CH_2}CH_3$), 6.97 (2H, t, *J* = 8.68 Hz), 7.15 (2H, q, *J* = 5.58 Hz), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 14.2, 30.1, 36.0, 60.5, 115.2, 128.6, 129.7, 136.2, 152.8, 172.7.

Ethyl 3-(4-chlorophenyl)-propanoate **12b**: Ethyl 3-(4-chlorophenyl)-prop-2-enoate **12a** (15.5 g, 73.3 mmol) was dissolved in 300 mL ethyl acetate and 800 mg Pd on charcoal was added to give ethyl 3-(4-chlorophenyl)-propanoate **12b** (13.6 g, 87%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.24 (3H, t, *J* = 7.09 Hz, $CH_2\underline{CH_3}$), 2.61 (2H, t, *J* = 7.55 Hz, $\underline{CH_2}$-CH), 2.93 (2H, t, *J* = 7.59 Hz, Ph-$\underline{CH_2}$), 4.14 (1H, q, *J* = 7.12 Hz, $\underline{CH_2}CH_3$), 7.14-7.23 (4H, dd, J_1 = 21.39 Hz, J_2 = 8.33 Hz), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 14.1, 30.2, 35.7, 60.5, 128.6, 129.7, 130.3, 136.4, 172.6.

3-(4-Halophenyl)-propan-1-ol **11c**, **12c**: To a slurry of lithium aluminium hydride in dry diethyl ether under a nitrogen atmosphere was added dropwise ethyl 3-(4-halophenyl)-propionate **11b** and **12b** and the reaction then stirred for 20 h. The reaction was then quenched by slow addition of water and then stirred for 1h. The aluminium salts were then filtered off and washed thoroughly with diethyl ether. The organic fraction was dried over sodium sulfate and concentrated under reduced pressure to give the corresponding alcohol.

3-(4-Fluorophenyl)-propan-1-ol **11c**: To a slurry of $LiAlH_4$ (2.50 g, 65.8 mmol) in 200 mL dry diethyl ether was added dropwise ethyl 3-(4-fluorophenyl)-propanoate **11b** (10.4 g, 52.7 mmol) to give 3-(4-fluorophenyl)-propan-1-ol **11c** (6.61 g, 81%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.83 (2H, m), 2.32 (1H, s), 2.65 (2H, t, *J* = 7.53 Hz), 3.61 (2H, t, *J* = 6.43 Hz), 6.94 (2H, t, *J* = 6.71 Hz), 7.04 (2H, t, *J* = 6.77 Hz), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 31.4, 34.3, 61.9, 115.1, 129.7, 135.6, 162.6.

3-(4-Chlorophenyl)-propan-1-ol **12c**: To a slurry of $LiAlH_4$ (3.01g, 79.8 mmol) in 200 mL dry diethyl ether was added dropwise ethyl 3-(4-chlorophenyl)-propanoate **12b** (13.57 g, 63.8 mmol) to give 3-(4-chlorophenyl)-propan-1-ol **12c** (4.75 g, 86%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.85 (2H, m), 2.32 (1H, s), 2.68 (2H, t, *J* = 7.49 Hz), 3.65 (2H, t, *J* = 6.37 Hz), 7.11-7.24 (4H, dd, J_1 = 27.48 Hz, J_2 = 8.43 Hz), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 31.4, 34.0, 61.9, 128.5, 129.2, 140.2.

3-(4-Halophenyl)-propanal **11d**, **12d**: To a solution of 3-(4-halophenyl)-propan-1-ol **11c** and **12c** in dichloromethane was added in one portion pyridinium chlorochromate and the reaction was stirred

at room temperature for 20 h. Diethyl ether was then added and the organic phase was passed through a column of Florisil eluting the column with diethyl ether. The eluent was then concentrated under reduced pressure to give the corresponding aldehyde.

3-(4-Fluorophenyl)-propanal **11d**: To a solution of 3-(4-fluorophenyl)-propan-1-ol **11c** (4.71 g, 30.6 mmol) in 125 mL dichloromethane was added pyridinium chlorochromate (9.88 g, 45.8 mmol) in one portion to give 3-(4-fluorophenyl)-propanal **11d** (2.93 g, 63%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.78 (2H, q, *J* = 7.41 Hz), 2.93 (2H, t, *J* = 7.24 Hz), 6.94 (2H, t, *J* = 8.65 Hz), 7.19 (2H, t, *J* = 8.35 Hz), 9.83 (1H, s), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 29.7, 45.3, 115.7, 129.5, 132.2, 162.0, 202.3.

3-(4-Chlorophenyl)-propanal **12d**: To a solution of 3-(4-chlorophenyl)-propan-1-ol **12c** (5.26 g, 30.7 mmol) in 100 mL dichloromethane was added pyridinium chlorochromate (9.93 g, 46.1 mmol) in one portion to give 3-(4-chlorophenyl)-propanal **12d** (3.21 g, 62%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.78 (2H, q, *J* = 7.39 Hz), 2.92 (2H, t, *J* = 7.40 Hz), 7.12-7.23 (4H, dd, J_1 = 23.63 Hz, J_2 = 8.33 Hz), 9.81 (1H, s), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 30.0, 45.1, 128.7, 129.7, 132.8, 141.0, 201.0.

rac-2-Amino-4-(4-halophenyl)-butanoic acid *rac*-**11e**, *rac*-**12e**: To a solution of 3-(4-halophenyl)-propanal **11d** and **12d** in a mixture of ethanol and water were added sodium cyanide, ammonium chloride and conc. ammonia solution and the reaction mixture was stirred at room temperature for 24 h. Then the reaction mixture was concentrated under reduced pressure to dryness. Hydrochloric acid (6N) was then added and the reaction was heated under reflux for 6 h. After cooling, the mixture was again concentrated to dryness and water was added. The resulting acidic solution was then neutralised with 2M potassium hydroxide solution. The precipitate which formed was filtered off and washed with both water and ethyl acetate to give the desired α-amino acid as a racemate.

rac-2-Amino-4-(4-fluorophenyl)-butanoic acid *rac*-**11e**: 3-(4-Fluorophenyl)-propanal **11d** (2.93 g, 19.3 mmol) was dissolved in 100 mL ethanol and 25 mL water. NaCN (1.04 g, 21.2 mmol), NH_4Cl (1.13 g, 21.2 mmol) and aqu. NH_3 conc. (20 mL) were then added to give *rac*-2-amino-(4-fluorophenyl)-butanoic acid *rac*-**11e** (417 mg, 11%). ^{1}H-NMR: (360 MHz, DMSO) δ = 2.06 (2H, s, NH_2), 2.14 (2H, q, *J* = 4.28 Hz), 2.37 (2H, t, *J* = 6.60 Hz), 3.27 (1H, t, *J* = 4.19 Hz), 6.95 (2H, t, *J* = 8.48 Hz), 7.09 (2H, q, *J* = 5.59 Hz), ^{13}C-NMR: (90 MHz, DMSO) δ = 29.4, 33.4, 52.2, 115.1, 129.8, 132.6, 161.5, 173.6.

rac-2-Amino-4-(4-chlorophenyl)-butanoic acid *rac*-**12e**: 3-(4-Chlorophenyl)-propanal **12d** (3.21 g, 19.0 mmol) was dissolved in 120 mL ethanol and 30 mL water. NaCN (1.03 g, 20.9 mmol), NH_4Cl (1.12 g, 20.9 mmol) and aqu. NH_3 conc. (20 mL) were then added to give *rac*-2-amino-(4-chlorophenyl)-butanoic acid *rac*-**12e** (1.29 g, 32%). ^{1}H-NMR: (360 MHz, DMSO) δ = 2.02 (2H, s, NH_2), 2.14 (2H, q, *J* = 4.87 Hz), 2.53 (2H, t, *J* = 4.83 Hz), 3.16 (1H, t, *J* = 6.27 Hz), 7.04-7.20 (4H,

dd, J_1 = 33.60 Hz, J_2 = 6.58 Hz), ^{13}C-NMR: (90 MHz, DMSO) δ = 29.4, 31.4, 52.2, 129.2, 129.9, 132.4, 135.6, 171.6.

rac-2-Hydroxy-4-(4-fluorophenyl)-butanoic acid *rac*-**11**: Method A was employed using *rac*-2-amino-4-(4-fluorophenyl)-butanoic acid *rac*-**11e** (417 mg, 2.11 mmol), $NaNO_2$ (5.82 g) in H_2SO_4 (3 mL, 1M). The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give *rac*-2-hydroxy-4-(4-fluorophenyl)-butanoic acid *rac*-**11** as yellow crystals (160 mg, 38%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.04 (3H, q, J = 6.07 Hz), 2.63 (2H, t, J = 6.06 Hz), 4.13 (1H, t, J = 6.10 Hz), 6.85 (2H, t, J = 8.78 Hz), 7.10 (2H, m); ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 29.0, 34.5, 71.1, 114.6, 130.1, 136.9, 162.5, 171.3.

rac-2-Hydroxy-4-(4-chlorophenyl)-butanoic acid *rac*-**12**: Method A was employed using *rac*-2-amino-4-(4-chlorophenyl)-butanoic acid *rac*-**12e** (1.29 g, 6.95 mmol), $NaNO_2$ (2.14 g) in H_2SO_4 (15 mL, 1M). The residue was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to give *rac*-2-hydroxy-4-(4-chlorophenyl)-butanoic acid *rac*-**12** as yellow crystals (284 mg, 20%). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.05 (3H, m), 3.01 (2H, t, J = 4.98 Hz), 4.27 (1H, t, J = 5.21 Hz), 7.14-7.30 (4H, dd, J_1 = 38.90 Hz, J_2 = 8.28 Hz), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 28.3, 31.2, 62.0, 128.9, 129.7, 130.6, 136.5, 169.8.

(*R*)-2-Hydroxy-4-(4-halophenyl)-butanoic acid (*R*)-**11**, (*R*)-**12** were obtained by lipase-catalyzed kinetic resolution in analogy to a known procedure[9] with minor modifications: *rac*-2-Hydroxy-4-(4-halophenyl)-butanoic acid *rac*-**11**,**12** were dissolved in *n*-hexane, vinyl acetate and lipase (Amano PS) were added and the mixture was vigorously stirred at 30 °C until a conversion of 50% was reached after 48 h. Then the enzyme was removed by filtration and the solvent was evaporated under reduced pressure. Flash chromatography (CH_2Cl_2/MeOH 9:1) yielded optically pure (*R*)-2-hydroxy-4-(4-halophenyl)-butanoic acid (*R*)-**11** and (*R*)-**12** as the remaining substrate enantiomer (slightly yellow crystals).

(*R*)-2-Hydroxy-4-(4-fluorophenyl)-butanoic acid (*R*)-**11**: *rac*-2-Hydroxy-4-(4-fluorophenyl)-butanoic acid *rac*-**11** (160 mg, 1 mmol) was dissolved in *n*-hexane (6 mL), vinyl acetate (1 mL) and lipase (Amano PS, 70 mg) were added. Flash chromatography (CH_2Cl_2/MeOH 9:1) yielded optically pure (*R*)-2-hydroxy-4-(4-fluorophenyl)-butanoic acid (*R*)-**11** (76 mg, 95%, e.e. >99%); mp 172 °C; $[\alpha]_D^{20}$ –33.1 (*c* 1.7, EtOH) ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.04 (3H, q, J = 6.07 Hz), 2.63 (2H, t, J = 6.06 Hz), 4.13 (1H, t, J = 6.10 Hz), 6.85 (2H, t, J = 8.78 Hz), 7.10 (2H, m); ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 29.0, 34.5, 71.1, 114.6, 130.1, 136.9, 162.5, 171.3.

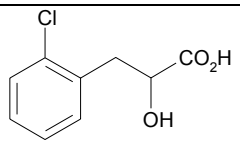
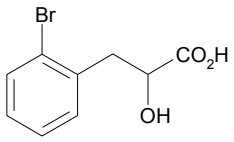
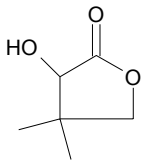
(*R*)-2-Hydroxy-4-(4-chlorophenyl)-butanoic acid (*R*)-**12**: *rac*-2-Hydroxy-4-(4-chlorophenyl)-butanoic acid *rac*-**12** (284 mg, 1.41 mmol) was dissolved in *n*-hexane (7.4 mL), vinyl acetate (1.4 mL) and lipase (Amano PS, 96 mg) were added. Flash chromatography (CH_2Cl_2/MeOH 9:1) yielded optically pure (*R*)-2-hydroxy-4-(4-chlorophenyl)-butanoic acid (*R*)-**11** (130 mg, 89%, e.e.

>99%); mp = 148 °C; $[\alpha]_D^{20}$ –25.6 (*c* 0.8, EtOH). ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 2.05 (3H, m), 3.01 (2H, t, *J* = 4.98 Hz), 4.27 (1H, t, *J* = 5.21 Hz), 7.14-7.30 (4H, dd, J_1 = 38.90 Hz, J_2 = 8.28 Hz), ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 28.3, 31.2, 62.0, 128.9, 129.7, 130.6, 136.5, 169.8.

(*R*)-3-hydroxy-4,4-dimethyl-tetrahydrofuran-2-one (pantolactone) *rac*-**13** and (*S*)-**13**: mp = 86 °C;[10] $[\alpha]_D^{20}$ –19.3 (*c* 1.7, EtOH).[11] ^{1}H-NMR: (360 MHz, $CDCl_3$) δ = 1.07 (3H, s), 1.21 (3H, s), 2.04 (1H, s, OH), 3.95-4.03 (2H, dd, J_1 = 17.56 Hz, J_2 = 8.89 Hz), 4.16 (1H, s), , ^{13}C-NMR: (90 MHz, $CDCl_3$) δ = 18.8, 22.8, 75.7, 76.5, 175.2.

Analytical Procedures

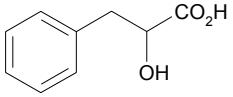
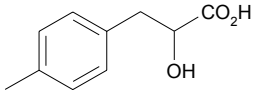
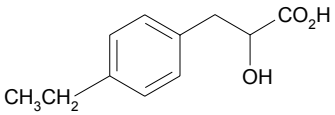
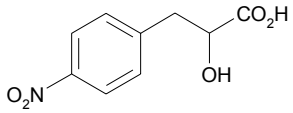
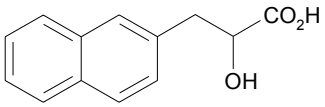
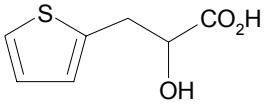
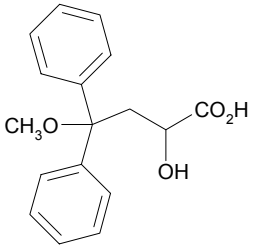
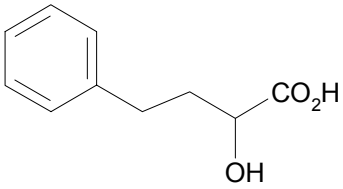
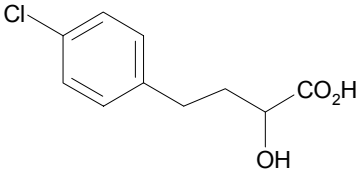
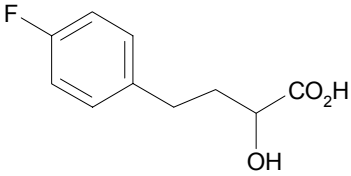
Table 1. GC-Analyses using a chiral stationary phase.

Substrate	Compound	Conditions[a,b]	t_R [min]	
			R	*S*
4		[a]	6.0	6.6
5		[a]	8.6	8.8
13		[b]	6.1	5.8

[a] Column CP-Chiralsil Dex CB, 12.0 psi H_2 at 80 °C to 150 °C, heat rate 5 °C min^{-1}; to 170 °C, heat rate 10 °C min^{-1}.

[b] Column CP-Chiralsil Dex CB, 12.0 psi H_2 at 110 °C, heat rate 2.5 °C min^{-1} to 120 °C; heat rate 10 °C min^{-1} to 200 °C; hold 1 min.

Table 2. HPLC-Analyses using a chiral stationary phase.

Substrate	Compound	Conditions[a,b,c]	t_R [min]	
			R	*S*
1		[a]	20.8	24.7
2		[b]	11.9	8.5
3		[a]	9.2	12.8
6		[b]	14.0	16.8
7		[b]	14.8	16.5
8		[b]	27.2	23.1
9		[c]	13.5	11.7
10		[a]	20.8	21.8
11		[a]	21.0	19.8
12		[b]	25.8	23.9

[a] Column Chiralpak AD, heptane/*i*-propanol/TFA (90/10/0.1), 18 °C, flow 0.5 mL min^{-1}. [b] Column Chiralpak AD, heptane/*i*-propanol/TFA (90/10/0.1), 18 °C, flow 0.3 mL min^{-1}. [c] Column Chiralpak OD-H, heptane/*i*-propanol/formic acid (95/5/0.5), 18 °C, flow 0.8 mL min^{-1}.

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