CIAT with simultaneous epimerization at two stereocenters. Synthesis of substituted β-methyl-α-homophenylalanines.

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Experimental part

Remarks

Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian VXR-300 spectrometer (300 and 75.4 MHz, respectively) with TMS as internal standard. Elemental analyses were performed on analyzer NA 1500, Series 2, Carlo Erba Instruments. Optical rotations were measured on JASCO P-1020 or POLAR L-μP (IBZ Messtechnik) polarimeter, $[a]_D$ values are given in 10^{-1} deg.cm^2.g^{-1}. HPLC was carried out using a PU-4015/PU-4021 PYE UNICAM HPLC system, using C18 5 μm reverse phase column and a mixture acetonitrile/water/TEA 600:400:15 or 250:750:15, the pH was adjusted to 2.9-3.5 by H_3PO_4. Detector PU-4021 was set in SUM ABS mode, λ = 210-310 nm.

Diastereomer distribution in the CIAT process (Fig.1) was checked on Phenomenex Luna 5 μm, C18 250x4.6 mm ID column, eluent acetonitrile/water/TEA 250:750:15, the pH was adjusted to 3.5 by H_3PO_4, flow 0,7mL/min, inject 20 μL, t_R (min) 16.5 **4b**, 18.3, 25.8 and 26.4 the others diastereomers.

Enantiomeric purity of the final *anti*-2-amino-4-aryl-3-methylbutanoic acids **9a,b** was meassured using a chromatography system Pye Unicam with PU4225 UV detector and CROWNPAK CR (+) column (DAICEL). Detection was carried out at 210 nm. The mobile phase was a solution of $HClO_4$, pH=2.0, which was pumped through the system at 1.5 mL/min at room temperature. The amount injected was 20 μL. t_R (min) 26.2 **9a**, 20.7 (2*R*,3*S*)-enantiomer and 38.5 **9b**, 33.4 (2*R*,3*S*)-enantiomer. All HPLC data were collected and analysed using CSW 1.7 software (DATAAPEX).

1-(3-Iodo-4-methoxyphenyl)propan-1-one (1c)

Propionic anhydride (1.1 equiv., 47.0 mmol, 6.06 mL) was added to dried $LiClO_4$ (1.1 equiv., 47.0 mmol, 5.00 g) and the mixture was heated at 60 °C until $LiClO_4$ was dissolved. Then 1-iodo-2-methoxybenzene (42.7 mmol, 10.0 g) was added dropwise during 15 minutes. After stirring at 100 °C for 30 hours, the mixture was cooled to room temperature and dissolved in AcOEt (100 mL). The organic layer was treated with 5% $NaHCO_3$ (3-times 50 mL), dried over Na_2SO_4 and evaporated to dryness. The crude solid product was crystallised from *n*-hexane to give the ketone **1c** (7.50 g, 61%) as a white solid, mp 91-92 °C (from hexane-AcOEt) (lit.,[1] 95 °C from EtOH); (Found: C, 40.82; H, 3.83. $C_{10}H_{11}IO_2$ requires: C, 41.40; H, 3.82%); δ_H (300 MHz; $CDCl_3$; Me_4Si): 8.39 (1H, s, Ar-*H*), 7.95 (1H, d, *J* 8.5, Ar-*H*), 6.84 (1H, d, *J* 8.5, Ar-*H*), 3.94 (3H, s, C*H*$_3$O), 2.93 (2H, q, *J* 7.3, H-2), 1.21 (3H, t, *J* 7.3, H-1); δ_C (75 MHz, $CDCl_3$;

Me_4Si): 198.1 (C-1), 161.4, 139.7, 131.5, 130.0, 110.0, 85.8 (C-Ar), 56.5 (*C*H_3O), 31.4 (C-2), 8.2 (C-3).

(2*E*)-3-Methyl-4-oxo-4-phenylbut-2-enoic acid (2a)

To propiophenone **1a** (149 mmol, 20.00 g) and glyoxylic acid monohydrate (1.5 equiv., 224 mmol, 20.60 g) dissolved in dioxane (200 mL), 96%-H_2SO_4 (30 mL) was added dropwise with stirring. The resulting solution was stirred under reflux for 1.5 hour, cooled to room temperature and poured into water (500 mL). Mixture was extracted with AcOEt (3 × 100 mL), organic layer was repeatly extracted with 10% K_2CO_3 (3 × 70 mL). pH of water extract was adjusted to 2 and extracted with AcOEt (3 × 70 mL), the extract was dried over Na_2SO_4 and evaporated to dryness. Crude product (31.30 g) was crystallised from toluene-hexane to give acid **2a** (20.64 g, 73%, (*E*:*Z*) 96:4) as yellow solid, mp 104-106 °C (from toluene-hexane, (*E*:*Z*) 98:2 (lit.,[2] 99-100 °C from benzene-light petroleum) (lit.,[3] 102-103°C from EtOH-H_2O); δ_H (300 MHz; $CDCl_3$; Me_4Si): 7.46-7.83 (m, 5H, Ar-*H*), 6.16 (1H, q, *J* 1.5, H-2), 2.45 (3H, d, *J* 1.5, H-1′). δ_C (75 MHz, $CDCl_3$; Me_4Si): 197.6 (C-4), 171.1 (C-1), 154.7, 133.4, 129.7, 128.6, 123.8 (*C*-Ph, C-2, C-3), 15.9 (C-1′).

(2*E*)-4-(4-Methoxyphenyl)-3-methyl-4-oxobut-2-enoic acid (2b)

According to the procedure described above (for 154 mmol, 25.20 g of **1b** used 21.20 g of glyoxylic acid monohydrate, 38 mL of 96% H_2SO_4, 220 mL of dioxane), **2b** (21.58 g, 64%, (*E*:*Z*) 85:15) has been obtained as a yellow solid, mp 132-134 °C (from toluene-heptane (*E*:*Z*) 98:2) (lit.,[2] 133-134 °C from benzene);.δ_H (300 MHz; d_6-DMSO; Me_4Si): 7.85 (2H, d, *J* 8.8, Ar-*H*), 7.04 (2H, d, *J* 8.8, Ar-*H*), 6.07 (1H, q, *J* 1.5, H-2), 3.91 (3H, s, CH_3O), 2.37 (3H, d, *J* 1.5, H-1′). δ_C (75 MHz, d_6-DMSO; Me_4Si): 197.5 (C-4), 167.8 (C-1), 165.5, 154.0, 133.6, 129.8, 125.0, 115.4 (*C*-Ar, C-2, C-3), 56.8 (*C*H_3O), 16.7 (C-1′).

(2*E*)-4-(3-Iodo-4-methoxyphenyl)-3-methyl-4-oxobut-2-enoic acid (2c)

An identical procedure to that described above was applied to the transformation of **1c** (for 4.5 mmol, 1.30 g of **1c** used 0.62 g glyoxylic acid monohydrate, 1.6 mL of 96% H_2SO_4, 15 mL of dioxane) to **2c**. Yellowish solid was obtained (0.79 g, 51%, (*E*:*Z*) 81:19), mp 173-178 °C (from H_2O (*E*:*Z*) 86:14) (Found: C, 41.70; H, 3.26. $C_{12}H_{11}IO$ requires C. 41.64, H 3.25%); δ_H (300 MHz; d_6-DMSO; Me_4Si): 12.85 (1H, br s, COO*H*), 8.15 (1H, d, *J* 1.8, Ar-*H*), 7.84 (1H, dd, *J* 8.6, *J* 1.8, Ar-*H*), 7.12 (1H, d, *J* 8.6, Ar-*H*), 6.00 (1H, br s, H-2), 3.93 (s, 3H, CH_3O), 2.26 (br s, 3H, H-1′); δ_C (75 MHz, d_6-DMSO; Me_4Si): 195.0 (C-4), 166.7 (C-1), 161.6, 149.9, 140.1, 132.3, 129.6, 125.3, 111.0, 86.5 (*C*-Ar, C-2, C-3), 56.9 (*C*H_3O), 15.2 (C-1′).

General procedure for the *aza*-Michael addition of amines to unsaturated acids 2

In the following typical procedure, to the suspension of acid **2a** (5.3 mmol, 1.00 g) in H_2O (25 mL), benzylamine (5.8 mmol, 1.1 eq, 0.63 mL) was added . The resulting mixture was stirred at 40°C for 7 days. After this time, the solid was filtered off, washed with Et_2O and dried to give amino acid **3a** (1.11 g, 70%, d.r. 97:3). The same procedure was used for the addition of benzylamine and (*S*)-PEA to the acids **2a-c** with only the slight modification of the solvent/substrate ratio.

***rac*-(2*S*,3*R*)-2-(Benzylamino)-3-methyl-4-oxo-4-phenyl-butanoic acid (3a)**

Off-white solid; mp 189-190 °C (from water, d.r. 97:3); (Found: C, 72.38; H, 6.53; N, 4.78. $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.44; N, 4.71%.); δ_H (300 MHz; d_6-acetone/DCl; Me_4Si): 7.38-7.71 (10H, m, Ar-*H*), 4.59-4.65 (1H, m, H-3), 4.56 (1H, d, *J* 13.2, H-1´´B), 4.38 (1H, d, *J* 13.2, H-1´´A), 4.24 (1H, d, *J* 3.7, H-2), 1.32 (3H, d, *J* 7.3, H-1´); δ_C (75 MHz, d_6-acetone/DCl; Me_4Si): 200.6 (C-4), 169.1 (C-1), 136.8, 135.0, 132.5, 131.6, 131.3, 130.7, 130.5, 130.1 (C-Ar), 61.0 (C-2), 52.4 (C-1´´), 43.5 (C-3), 13.3 (C-1´).

rac-(2*S*,3*R*)-2-(Benzylamino)-4-(4-methoxyphenyl)-3-methyl-4-oxobutanoic acid (3b)

According to the general procedure described above from 4.5 mmol (1.00 g of **2b** used 5.0 mmol) and 0.56 mL of benzylamine in 20 mL of H_2O at 40 °C for 7 days, **3b** (0.84 g, 57%, d.r. 90:10) was obtained as a white solid, mp 196-197°C (from water, d.r. 90:10); (Found: C, 69.60; H, 6.53; N, 4.20. $C_{19}H_{21}NO_4$ requires C, 69.71; H, 6.47; N, 4.28%.); δ_H (300 MHz; d_6-acetone/DCl; Me_4Si): 7.94 (2H, d, *J* 9.0, Ar-*H*), 7.67-7.71 (2H, m, Ph-*H*), 7.40-7.42 (3H, m, Ph-*H*), 6.96 (2H, d, *J* 9.0, Ar-*H*), 4.59-4.67 (1H, m, H-3), 4.55 (1H, d, *J* 13.2, H-1´´B), 4.38 (1H, d, *J* 13.2, H-1´´A), 4.24 (1H, d, *J* 4.3, H-2), 3.85 (3H, s, C*H*$_3$O), 1.31 (3H, d, *J* 7.3, H-1´). δ_C (75 MHz, d_6-acetone/DCl; Me_4Si): 199.2 (C-4), 169.3 (C-1), 165.6, 132.7, 132.6, 131.9, 131.3, 130.7, 129.4, 115.8 (*C*-Ar), 61.4 (C-2), 57.0 (*C*H$_3$O), 52.5 (C-1´), 43.1 (C-3), 14.0 (C-1´).

rac-(2*S*,3*R*)-2-(Benzylamino)-4-(3-iodo-4-methoxyphenyl)-3-methyl-4-oxobutanoic acid (3c)

According to the above described general procedure (for 0.6 mmol, 0.20 g of **2c** used 0.6 mmol, 0.07 mL of benzylamine, 4 mL of H_2O at 40 °C, 7 days) **3c** (0.13 g, 50%, d.r. >99:1) was obtained as a white solid, mp 172-174 °C (from H_2O, d.r. >99:1); (Found C, 50.23; H, 4.60; N, 3.22; $C_{19}H_{20}INO_4$ requires C, 50.35; H, 4.45; N, 3.09%); δ_H (300 MHz; d_6-acetone/DCl; Me_4Si): 8.32 (1H, d, *J* 2.1, Ar-*H*), 8.13 (dd, 1H, *J* 8.5, *J* 1.7, Ar-*H*), 7.67-7.72 (m, 2H, Ph-*H*), 7.41-7.68 (3H, m, Ph-*H*), 7.06 (d, 1H, *J* 8.5, Ar-*H*), 4.64-4.68 (m, 1H, H-3), 4.54 (d, 1H, *J* 13.2, H-1´´B), 4.40 (1H, d, *J* 13.2, H-1´´A), 4.25 (1H, d, *J* 3.8, H-2), 3.97 (3H, s, C*H*$_3$O), 1.31 (3H, d, *J* 6.8, H-1´). δ_C (75 MHz, d_6-acetone/DCl; Me_4Si): 198.0, 169.2 (C-1), 163.8, 141.5, 133.1, 132.7, 132.0, 131.3, 130.8, 112.6, 87.6 (*C*-Ar), 61.4 (C-2), 58.3 (*C*H$_3$O), 52.5 (C-1´´), 43.2 (C-3), 13.7 (C-1´).

(2*S*,3*R*,1´´*S*)-3-Methyl-4-oxo-4-phenyl-2-[(1´´-phenylethyl)- amino]butanoic acid (4a)

According to general procedure from 5.3 mmol (1.00 g of **2a** used 5.8 mmol) and 0.74 mL of (*S*)-1-phenylethylamine in 20 mL of H_2O at 40 °C for 7 days, **4a** (1.14 g, 70%, d.r. >99:0:<1:0) was obtained as an off-white solid ; mp 197-198 °C (from H_2O, d.r. >99:0:<1:0); (Found: C, 73.19; H, 6.75; N, 4.58. $C_{19}H_{21}NO_3$ requires: C, 73.29; H, 6.80; N, 4.50%.); $[\alpha]_D^{25}$ +17.4 (c 1.0, MeOH:1 M HCl 3:1). δ_H (300 MHz; d_6-acetone/DCl; Me_4Si): 7.78-7.88 (4H, m, Ph-*H*), 7.33-7.54 (6H, m, Ph-*H*), 4.81-4.92 (1H, m, H-3), 4.60 (1H, q, *J* 6.8, H-1´´), 3.96 (1H, d, *J* 3.4, H-2), 1.97 (3H, d, *J* 6.8, H-2´´), 1.32 (3H, d, *J* 6.4, H-1´). δ_C (75 MHz, d_6-acetone/DCl; Me_4Si): 199.6 (C-4), 168.7 (C-1), 137.5, 137.2, 134.6, 131.3, 131.1, 130.5, 130.4, 130.1 (*C*-Ph), 61.2, 61.1 (C-2, C-1´´), 43.6 (C-3), 21.9 (C-2´´), 12.2 (C-1´).

(2*S*,3*R*,1´´*S*)-4-(4-Methoxyphenyl)-3-methyl-4-oxo-2-[(1´´-phenylethyl)amino]butanoic acid (4b)

According to general procedure from 13.6 mmol (3.00 g of **2b** used 15.0 mmol) and 1.9 mL of (*S*)-1-phenylethylamine in 21 mL of H_2O at 40 °C for 7 days, **4b** (2.80 g, 61%; d.r. >99:0:<1:0) was obtained as a white solid, mp 197-198 °C (from H_2O, d.r. >99:0:<1:0); (Found: C, 70.13;

H, 6.80; N, 4.15. $C_{20}H_{23}NO_4$ requires: C, 70.36; H, 6.65; N, 4.20%); $[\alpha]_D^{25}$ +43.2 (c 1.0, MeOH:1 M HCl 3:1). δ_H (300 MHz; d_6-acetone/DCl; Me_4Si): 7.91 (2H, d, *J* 8.1, Ar-*H*), 7.81-7.84 (2H, m, Ph-*H*), 7.38-7.49 (3H, m, Ph-*H*), 6.93 (2H, d, *J* 8.5, Ar-*H*), 4.81-4.91 (1H, m, H-3), 4.61 (1H, q, *J* 6.8, H-1´´), 3.97 (1H, d, *J* 3.0, H-2), 3.89 (3H, s, C*H*$_3$O), 1.95 (3H, d, *J* 6.4, H-2´´), 1.29 (3H, d, *J* 6.4, H-1´). δ_C (75 MHz, d_6-acetone/DCl; Me_4Si): 198.0 (C-4), 168.7 (C-1), 165.2, 137.3, 132.4, 131.3, 131.1, 130.3, 129.5, 115.7 (*C*-Ar), 61.4, 61.0 (C-2, C-1´´), 57.1 (*C*H$_3$O), 43.0 (C-3), 21.8 (C-2´´), 12.7 (C-1´).

(2*S*,3*R*,1´´*R*)-2-[(2´´-Hydroxy-1´´-phenylethyl)amino]-3-methyl-4-oxo-4-phenylbutanoic acid (4a´)

To the suspension of acid **2a** (5.3 mmol, 1.00 g) in dichloromethane (10 mL), (*R*)-2-amino-2-phenylethanol (5.8 mmol, 1.1 eq, 0.79 g) was added. The resulting mixture was stirred at r.t for 14 days. After this time, the solid was filtered off, washed with Et_2O and dried to give aminoacid **4´a** (0.31 g, 18%, d.r. 1:99:0:0) as a white solid; mp 171-172 °C (from dichloromethane, d.r. 1:99:0:0); (Found : C, 69.98; H, 6.54; N, 4.33. $C_{19}H_{21}NO_4$ requires: C, 69.71; H, 6.47; N, 4.28%); $[\alpha]_D^{25}$ +7.6 (c 0.1, MeOH:1 M HCl 3:1); δ_H (300 MHz; d_6-acetone/DCl; Me_4Si): 7.40-7.83 (10H, m, Ph-*H*), 4.55-4.65 (2H, m, H-3, H-1´´), 4.36 (1H, dd, *J* 9.0, *J* 11.5, H-2´´B), 4.08 (1H, d, *J* 4.3, H-2), 3.95 (1H, dd, *J* 4.7, *J* 11.5, H-2´´A), 1.26 (3H, d, *J* 6.8, H-1´); δ_C (75 MHz, d_6-acetone/DCl; Me_4Si): 200.6 (C-4), 169.3 (C-1), 136.8, 135.0, 132.9, 131.8, 131.2, 131.1, 130.5, 130.1 (C-Ph), 67.5, 63.8 (C-1´´, C-2´´), 61.0 (C-2), 43.8 (C-3), 13.9 (C-1´).

(2*S*,3*R*,4*S*,1´´*S*)-4-Hydroxy-3-methyl-4-phenyl-2-[(1´´-phenylethyl)amino]butanoic acid (5a)

The suspension of acid **4a** (32.1 mmol, 10.00 g) in MeOH (500 mL) at 0-5 °C, $NaBH_4$ (96.3 mmol, 3 equiv., 3.64 g) was slowly added (2 h). The resulting mixture was stirred for additional 30 min., MeOH removed under reduced pressure and H_2O (500 mL) added. The pH of solution was adjusted to 6–6.5. A precipitate was filtered off, washed with Et_2O and dried to give hydroxy acid **5a** (9.10 g, 90%, **5a**/**6a** 92:8) as a white solid; mp 199-202 °C (from EtOH-H_2O **5a**/**6a** 92:8); (Found C 72.68, H 7.45, N, 4.50. $C_{19}H_{23}NO_3$ requires: C, 72.82; H, 7.40; N, 4.47 %); $[\alpha]_D^{25}$ -39.4 (c 1.0, 0.1 M NaOH); δ_H (300 MHz; NaOD/D_2O; Me_4Si): 6.89-7.46 (10H, m, Ph-*H*), 4.76 (1H, d, *J* 6.0, H-4), 3.59 (1H, q, *J* 6.4, H-1´´), 2.78 (1H, d, *J* 7.3, H-2), 2.04-2.16 (1H, m, H-3), 1.40 (3H, d, *J* 6.4, H-2´´), 0.72 (3H, d, *J* 6.8, H-1´); δ_C (75 MHz; NaOD/D_2O; Me_4Si): 183.3 (C-1), 146.6, 144.5, 131.7, 130.9, 130.6, 130.4, 130.2, 129.8 (C-Ar), 79.8 (C-4), 66.2, 59.6 (C-2, C-1´´), 44.3 (C-3), 25.8 (C-2´´), 14.9 (C-1´).

(2*S*,3*R*,4*S*,1´´*S*)-4-Hydroxy-4-(4-methoxyphenyl)-3-methyl-2-[(1´´-phenyletyl)amino]butanoic acid (5b)

According to the procedure above from 8.8 mmol (3.00 g) of **4b** and 3.5 equiv. (1.16 g) of $NaBH_4$ in 150 mL of MeOH for 3h, **5b** (1.88 g, 62%, **5b**/**6b** 95:5) has been obtained as a white solid, mp 225-230 °C (from EtOH-H_2O, **5b**/**6b** >99:1); (Found: C, 69.44; H, 7.40; N, 4.20. $C_{20}H_{25}NO_4$ requires: C, 69.95; H, 7.34; N, 4.13%); $[\alpha]_D^{25}$ -27.1 (c 1.0, 0.1 M NaOH); δ_H (300 MHz; NaOD/D_2O; Me_4Si): 7.24-7.38 (m, 5H, Ph-*H*), 6.89 (2H, d, *J* 8.5, Ar-*H*), 6.75 (2H, d, *J* 8.5, Ar-*H*), 4.64 (1H, d, *J* 6.8, H-4), 3.81 (3H, s, C*H*$_3$O), 3.56 (1H, q, *J* 6.4, H-1´´), 2.67 (1H, d, *J* 6.4, H-2), 1.99-2.11 (m, 1H, H-3), 1.37 (3H, d, *J* 6.4, H-2´´), 0.79 (3H, d, *J* 7.3, H-1´); δ_C (75 MHz; NaOD/D_2O; Me_4Si): 183.1 (C-1), 160.6, 146.5, 137.3, 131.6, 131.1, 130.3, 116.3 (C-Ar), 79.4 (C-4), 65.6, 59.6, 58.2 (*C*H$_3$O, C-2, C-1´´), 44.9 (C-3), 25.8 (C-2´´), 15.0 (C-1´).

(2*S*,3*R*,4*R*,1´´*S*)-4-Hydroxy-3-methyl-4-phenyl-2-[(1´´-phenylethyl)amino]butanoic acid (6a)

To a presonicated (1 min) stirred suspension of acid **4a** (3.2 mmol, 1.00 g) and $MnCl_2.4H_2O$ (0.6 mmol, 0.2 eq, 0.13 g) in MeOH (50 mL) at 0-5°C, $NaBH_4$ (6.4 mmol, 2 equiv., 0.24 g) was slowly added (20 min). The resulting mixture was stirred additionaly for 30 min. MeOH was removed under reduced pressure, 3% solution of K_2CO_3 (70 mL) was added. After 30 min of stirring brown solid was filtered off and discarded. The pH of filtrate was adjusted to 6–6.5. The precipitate was filtered off, washed with Et_2O and dried to give a hydroxyacid **6a** (0.68 g, 68%, **6a**/**5a** 94:6) as a white solid, mp 221-225 °C (from EtOH-H_2O **6a**/**5a** >99:1); (Found C 72.45, H 7.44, N, 4.50. $C_{19}H_{23}NO_3$ requires: C, 72.82; H, 7.40; N, 4.47%); $[\alpha]_D^{25}$ -50.7 (c 1.0, 0.1 M NaOH); δ_H (300 MHz; NaOD/D_2O; Me_4Si): 7.18-7.46 (10H, m, Ph-*H*), 4.30 (1H, d, *J* 8.5, H-4), 3.68 (1H, q, *J* 6.4, H-1´´), 2.87 (1H, d, *J* 8.5, H-2), 1.94 (1H, m, H-3), 1.40 (3H, d, *J* 6.4, H-2´´), 0.52 (3H, d, *J* 6.8, H-1´); δ_C (75 MHz; NaOD/D_2O; Me_4Si): 183.3 (C-1), 146.3, 145.0, 131.7, 131.3, 130.7, 130.5, 130.2, 130.1 (C-Ar), 83.0 (C-4), 59.5, 69.4 (C-2, C-1´´), 43.9 (C-3), 26.2 (C-2´´), 15.8 (C-1´).

(2*S*,3*R*,4*R*,1´´*S*)-4-Hydroxy-4-(4-methoxyphenyl)-3-methyl-2-[(1´´-phenylethyl)amino]butanoic acid (6b)

According to procedure above (for 2.9 mmol, 1.00 g of **4b** used 0.6 mmol, 0.13 g of $MnCl_2.4H_2O$, 5.9 mmol, 0.22 g of $NaBH_4$, 50 mL of MeOH) **6b** (0.71 g, 71%, **6b**/**5b** 85:15) was obtained as a white solid; mp 213-214 °C (from EtOH-H_2O d.r. 70:30); (Found C 69.56, H 7.37, N 4.13; $C_{20}H_{25}NO_4$ requires: C, 69.95; H, 7.34; N, 4.08 %); $[\alpha]_D^{25}$ -18.4 (c 1.0, 0.1M NaOH); δ_H (300 MHz; NaOD/D_2O; Me_4Si): 7.32-7.45 (5H, m, Ph-*H*), 7.18 (2H, d, *J* 8.5, Ar-*H*), 6.91 (2H, d, *J* 8.5, Ar-*H*), 4.29 (1H, d, *J* 8.1, H-4), 3.81 (3H, s, C*H*$_3$O), 3.67 (1H, q, *J* 6.4, H-1´´), 2.84 (1H, d, *J* 8.1, H-2), 1.91 (1H, m, H-3), 1.38 (3H, d, *J* 6.4, H-2´´), 0.56 (3H, d, *J* 6.8, H-1´); δ_C (75 MHz; NaOD/D_2O; Me_4Si): 183.4 (C-1), 161.0, 146.4, 137.9, 131.6, 131.1, 130.3, 130.1, 116.6 (C-Ar), 82.1 (C-4), 69.4, 59.5, 58.1, (C-2, C-1´´, *C*H_3O), 44.2 (C-3), 26.2 (C-2´´), 15.8 (C-1´).

(2*S*,3*R*,4S)-2-amino-4-hydroxy-4-(4-methoxyphenyl)-3-methylbutanoic acid (7b)

According to the procedure above from 6.9 mmol (2.37 g) of **5b** in 125 mL of MeOH and 25 mL of H_2O and 0.35 g of Pd/C at r.t for 7 h, **7b** (1.39 g, 84%, **7b**/**8b** >95:5) was obtained as a white solid; mp 222-223 °C (from EtOH-H_2O, **7b**/**8b** >98:2); (Found: C 60.33, H 7.18, N, 5.82. $C_{12}H_{17}NO_4$ requires: C, 60.24; H, 7.16; N, 5.85 %); $[\alpha]_D^{25}$ -9.6 (c 1.0, 0.1 M NaOH). δ_H (300 MHz; NaOD/D_2O; Me_4Si): 7.35 (2H, d, *J* 9.0, H-Ar), 7.03 (d, 2H, *J* 9.0, H-Ar); 4.95 (1H, d, *J* 4.7, H-4); 3.85 (3H, s, C*H*$_3$O); 3.26 (1H, d, *J* 5.6, H-2); 1.96-2.07 (1H, m, H-3); 0.82 (3H, d, *J* 6.8, H-1´). δ_C (75 MHz; NaOD/D_2O; Me_4Si): 184.8 (C-1), 160.7, 138.6, 130.4, 116.7 (C-Ar), 77.2 (C-4), 62.3 (C-2), 58.3 (*C*H_3O), 46.8 (C-3), 12.3 (C-1´).

(2*S*,3*R*,4*R*)-2-Amino-4-hydroxy-3-methyl-4-phenylbutanoic acid (8a)

To the solution of acid **6a** (9.6 mmol, 3.00 g) and HBr (9.6 mmol, 1 equiv., 1.61 g of 48% solution) in MeOH (150 mL) H_2O (30 mL) and Pd/C (0.60 g) were added. Heterogenous mixture was stirred in atmosphere of H_2 (1.1 atm.) at r.t. After reaction was finished (HPLC-monitoring, typically 6-10 h) the catalyst was filtered off. The pH of the filtrate was adjusted to 6-6.5. The resulting precipitate was filtered off, washed with Et_2O and dried to give acid **8a** (1.20 g, 60%, **8a**/**7a** 91:9) as a white solid; mp 213-215 °C (from EtOH-H_2O); (Found: C, 63.41; H, 7.28; N, 6.72. $C_{11}H_{15}NO_3$ requires: C 63.14, H 7.23; N, 6.69%); $[\alpha]_D^{25}$ +21.9 (c 1.0, 0.1 M NaOH). δ_H (300 MHz; NaOD/D_2O; Me_4Si): 7.28-7.48 (5H, m, Ph-*H*), 4.68 (1H, d, *J* 8.1,

H-4), 3.40 (1H, d, *J* 5.6, H-2), 2.04-2.15 (1H, m, H-3), 0.71 (3H, d, *J* 6.8, H-1′). δ_C (75 MHz; NaOD/D_2O; Me_4Si): 184.6 (C-1), 145.8, 131.4, 130.6, 129.8 (C-Ar), 80.3 (C-4), 61.0 (C-2), 46.4 (C-3), 15.2 (C-1′).

(2*S*,3*R*,4*R*)-2-amino-4-hydroxy-4-(4-methoxyphenyl)-3-methylbutanoic acid (8b)

According to the procedure above from 5.1 mmol (1.74 g) of **6b** and 0.86 g of 48% water solution of HBr in 80 mL of MeOH and 16 mL of H_2O at r.t for 7 h, **8b** (0.89 g, 76%, **8b**/**7b** 88:12) was obtained as a white solid; mp 204-206 °C (from EtOH-H_2O, **8b**/**7b** 95:5); (Found: C 60.21, H 7.21, N, 5.87; $C_{12}H_{17}NO_4$ requires: C, 60.24; H, 7.16; N, 5.85 %); $[\alpha]_D^{25}$ +26.4 (c 1.0, 0.1 M NaOH). δ_H (300 MHz; NaOD/D_2O; Me_4Si): 7.34 (2H, d, *J* 8.2, Ar-*H*), 7.00 (2H, d, *J* 8.9, Ar-*H*), 4.62 (1H, d, *J* 8.2, H-4), 3.82 (3H, s, C*H*$_3$O), 3.41 (1H, d, *J* 4.8, H-2), 1.97-2.12 (1H, m, H-3), 0.70 (3H, d, *J* 6.9, H-1′). δ_C (75 MHz; NaOD/D_2O; Me_4Si): 184.3 (C-1), 160.5, 137.9, 130.6, 116.2 (C-Ar), 79.2 (C-4), 60.6 (C-2), 57.7 (*C*H_3O), 46.0 (C-3), 14.8 (C-1′).

(2*S*,3*R*)-2-Amino-3-metyl-4-phenylbutanoic acid (9a)

To the solution of acid **4a** (3.2 mmol, 1.00 g) and HBr (9.6 mmol, 3 equiv., 1.63 g of 48% solution) in EtOH-H_2O (20 mL, 4 mL), Pd/C (20% of weight, 0.20 g) was added. The resulting heterogeneous mixture was stirred in the atmosphere of H_2 (1.1 atm.) at 40 °C. After reaction was finished (HPLC-monitoring, typically 24 h) the catalyst was filtered off. The pH of the filtrate was adjusted to 6-6.5. The precipitate was filtered off, washed with Et_2O and dried to give the carboxylic acid **9a** (0.38 g, 61%, d.r. >95:5) as an off-white solid; mp 204-206 °C (EtOH-H_2O, d.r. >98:2, ee 99%) (lit.,[4] 185-187 °C); (Found: C, 68.26; H, 7.85; N, 7.28. $C_{11}H_{15}NO_2$ requires: C, 68.37; H, 7.82; N, 7.25 %); $[\alpha]_D^{25}$ +13.1 (c 0.12, H_2O) (lit.,[4] -13 (c 0.11, H_2O, for (2*R*,3*S*)-enantiomer). NMR spectral dates are in agreement with published data.[4]

(2*S*,3*R*)-2-Amino-4-(4-methoxyphenyl)-3-methylbutanoic acid (9b)

According to the procedure above from 3.5 mmol (1.20 g) of **4b**, **9b** (0,39 g, 49%, d.r. >96:4, ee 98 %) was obtained as a white solid; mp 214-216 °C (from EtOH-H_2O, d.r. >95:5); (Found: C, 64.17; H, 7.73; N, 6.29; $C_{12}H_{17}NO_3$ requires: C, 64.55; H, 7.67; N, 6.27%); $[\alpha]_D^{25}$ +16.6 (c 0.12; H_2O); δ_H (300 MHz; NaOD/D_2O; Me_4Si): 7.23 (2H, d, *J* 9.0, Ar-*H*), 6.97 (2H, d, *J* 8.5, Ar-*H*), 3.83 (3H, s, C*H*$_3$O), 3.19 (1H, d, *J* 5.1, H-2), 2.76 (1H, dd, *J* 13.2, *J* 3.8, H-4B), 2.32 (1H, dd, *J* 13.2, *J* 10.7, H-4A), 1.94-2.07 (1H, m, H-3), 0.80 (3H, d, *J* 6.8, H-1′); δ_C (75 MHz; NaOD/D_2O; Me_4Si): 185.2 (C-1), 159.6, 136.7, 133.1, 116.6 (C-Ar), 63.9 (C-2), 58.2 (*C*H_3O), 42.1, 39.5 (C-3, C-4), 18.0 (C-1′).

General procedure for the lactonisation of hydroxyacids

Acid **6a** (1.6 mmol, 0.50 g) was suspended in water (6 mL), MeOH (0.2 mL) and conc. HCl (12 mL) were added. The resulting mixture was stirred at 40 °C. After 24 hours the resulting solid was filtered off and dried to obtain lactone **11a** (0.39 g, 74%, **11a**/**10a** 97:3) as a white solid.

(3*S*,4*R*,5*R*,1′′*S*)-4-Methyl-5-phenyl-3-(1′′-phenylethylamino)-dihydrofuran-2(3*H*)-one hydrochloride (11a)

The product melted at mp 199-204 °C (from CH_3CN-HCl, **11a**/**10a** >99:1); (Found: C, 68.36; H, 6.70; N, 4.24. $C_{19}H_{22}ClNO_2$ requires: C, 68.77; H, 6.68; N, 4.22 %.); $[\alpha]_D^{25}$ -99.5 (c 0.5, MeOH); δ_H (300 MHz; d_6-DMSO; Me_4Si): 7.22-7.72 (10H, m, Ph-*H*), 5.64 (1H, d, *J* 5.1, H-5), 4.83 (1H, q, *J* 6.6, H-1′′), 3.64 (d, 1H, *J* 8.1, H-3), 2.72-2.84 (1H, m, H-4), 1.74 (3H, d, *J* 6.6, H-2′′), 1.29 (3H, d, *J* 7.3, H-1′); δ_C (75 MHz; d_6-DMSO; Me_4Si): 170.6 (C-2), 137.1, 136.0,

129.3, 129.1, 128.9, 128.7, 125.8 (C-Ar), 85.3 (C-5), 57.0, 53.9 (C-3, C-1´´), 19.9 (C-2´´), 12.8 (C-1´), signal for C-4 overlaped by signal of d_6-DMSO.

(3*S*,4*R*,5*S*,1´´*S*)-4-Methyl-5-phenyl-3-(1´´-phenylethylamino)-dihydrofuran-2(3*H*)-one hydrochloride (10a)

According to the general procedure from 6.4 mmol (2.00 g) of **5a**in 60 mL of 3 M HCl and 0.6 mL of MeOH at r.t for 24h, **10a** (1.90 g, 90%, **10a**/**11a** 95:5) was obtained as a white solid, mp 186-190 °C (from CH_3CN-HCl, **10a**/**11a** >99:1); (Found: C 69.10, H 6.81, N, 4.25. $C_{19}H_{22}ClNO_2$ requires: C 68.77, H 6.68; N, 4.22 %.); $[\alpha]_D^{25}$ -53.3 (c 1.0, MeOH); δ_H (300 MHz; d_6-DMSO; Me_4Si): 5.78 (1H, d, *J* 4.4, H-5); (10H, m, H-Ph); 4.90 (1H, m, H-1´´); 4.28 (1H, d, *J* 6.6, H-3); 3.10-3.22 (1H, m, H-4); 1.74 (3H, d, *J* 6.6, H-2´´); 0.71 (3H, d, *J* 7.3, H-1´); δ_C (75 MHz; d_6-DMSO; Me_4Si): 170.9 (C-2), 134.8, 129.1, 129.0, 128.5, 128.0, 125.0 (C-Ar), 80.5 (C-5); 56.8, 57.1 (C-3, C-1´´); 38.0 (C-4); 20.1 (C-2´´); 9.3 (C-1´).

(3*S*,4*R*,5*S*,1´´*S*)-5-(4-methoxyphenyl)-4-methyl-3-[(1´´-phenylethyl)amino]dihydrofuran-2(3*H*)-one hydrochloride (10b)

According to the general procedure (for 2.9 mmol, 1.00 g of **5b** used 80 mL 3 M HCl, 2 mL of MeOH at r.t, 4 h) **10b** (0.85 g, 89%, **10b**/**11b** 95:5) was obtained as a white solid; mp 194-200 °C (from CH_3CN-HCl, **10b**/**11b** >99:1); (Found: C, 66.22, H, 6.72; N, 3.96. $C_{20}H_{24}ClNO_3$ requires: C 66.38, H 6.69, N 3.87 %.); $[\alpha]_D^{25}$ -55.0 (c 1.0, MeOH); δ_H (300 MHz; d_6-DMSO; Me_4Si): 7.42-7.72 (5H, m, Ph*H*), 7.13 (2H, d, *J* 8.8, Ar*H*), 6.95 (2H, d, *J* 8.8, Ar*H*), 5.70 (1H, d, *J* 4.4, H-5), 4.88 (1H, q, *J* 6.6., H-1´´), 4.26 (1H, d, *J* 6.6, H-3), 3.73 (3H, s, C*H*$_3$O), 3.05-3.11 (1H, m, H-4), 1.71 (3H, d, *J* 6.6, H-2´´), 0.69 (3H, d, *J* 7.3, H-1´); δ_C (75 MHz; d_6-DMSO; Me_4Si): 171.0 (C-2), 159.1, 136.3, 129.3, 129.2, 128.6, 126.7, 126.6, 114.1 (C-Ar), 80.7 (C-5), 57.2, 56.9, 55.2 (C-3, C-1´´, *C*H_3O), 38.3 (C-4), 20.1 (C-2´´), 9.5 (C-1´).

(3*S*,4*R*,5*R*,1´´*S*)-5-(4-methoxyphenyl)-4-methyl-3-[(1´´-phenylethyl)amino]dihydrofuran-2(3*H*)-one (11b)

To the suspension of acid **6b** (5.8 mmol, 2.00 g) in DCM (30 mL), DCC (6.4 mmol, 1.1 equiv., 1.32 g) was addded. The resulting mixture was stirred at r.t. After 16 h of contact, the unsoluble solid was filtered off and the filtrate evaporated to dryness (yellow solid, 1.85 g). The crude product was then purified by column chromatography (AcOEt:heptane 1:7) to give the title compounds **11b** (0.98 g, 50%, **11b**/**10b** 98:2, R_f 0.33 AcOEt-heptane 1:3) and **10b** (0.17 g, 9%, **10b**/**11b** 99:1, R_f 0.40 AcOEt-heptane 1:3). White solid, mp 102-103 °C (from AcOEt-heptane **11b**/**10b** >99:1); (Found: C, 73.25; H, 7.15; N, 4.35. $C_{20}H_{23}NO_3$ requires: C, 73.82; H, 7.12; N, 4.30%.); $[\alpha]_D^{25}$ -111.7 (c 1.0, $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si): 7.22-7.37 (5H, m, Ph*H*), 7.12 (2H, d, *J* 8.8, H-Ar), 6.86 (2H, d, *J* 8.8, H-Ar), 5.09 (1H, d, *J* 4.7, H-5), 4.14 (1H, q, *J* 6.4, H-1´´), 3.79 (3H, s, C*H*$_3$O), 3.36 (1H, d, *J* 7.0, H-3), 2.19-2.30 (1H, m, H-4), 1.40 (3H, d, *J* 6.4, H-2´´), 1.07 (3H, d, *J* 7.0, H-1´); δ_C (75 MHz; $CDCl_3$; Me_4Si): 176.9 (C-2), 159.6, 144.4, 129.9, 128.4, 127.3, 127.0, 126.8, 114.0 (C-Ar), 85.2 (C-5), 57.4, 56.7, 55.3, (C-3, C-1´´, *C*H_3O), 41.9 (C-4), 24.3 (C-2´´), 12.1 (C-1´).

(3*S*,4*R*,5*S*)-*tert*-Butyl [5-(4-methoxyphenyl)-4-methyl-2-oxotetrahydrofuran-3-yl]carbonate (12b)

Acid **7b** (1.6 mmol, 0.38 g) was suspended in conc. HCl (5 mL) and the resulting mixture was stirred at r.t. After 1h, the mixture was evaporated *in vacuo* and dried (0.41 g, d.r. 98:2, ~100%). The crude lactone was suspended in dioxane (10 mL), Et_3N (3.3 mmol, 2.1 equiv.,

0.45 mL) and Boc_2O (2.1 mmol, 1.3 equiv., 0.45 g) were added. The resulting mixture was stirred at r.t for 20 h and the solvant was removed *in vacuo* before addition of AcOEt (25 mL). The resulting mixture was extracted with water (2× 10mL). Organic layer was dried (Na_2SO_4), filtered and evaporated *in vacuo* (pale-yellow oil, 0.56 g). The crude product was crystallised from Et_2O-heptane (2mL-8mL) to give the title compound **12b** (0.26 g, 50%) as a white solid, mp 111-113 °C (from AcOEt-heptane) (lit.,[5] 103-105 °C); (Found: C, 63.48; H, 7.25; N, 4.39. $C_{17}H_{23}NO_5$ requires: C, 63.54; H, 7.21; N, 4.36%.); $[\alpha]_D^{25}$ +40.0 (c 0.83, $CHCl_3$) (lit.,[5] +26.5° c 0.82, $CHCl_3$). The NMR spectral dates are in agreement with reported data.[5]

(3*S*,4*R*,5*S*)-*tert*-Butyl [5-(4-methoxyphenyl)-4-methyl-2-oxotetrahydrofuran-3-yl]carbonate (13b)

To the suspension of **6b** (1.4 mmol, 0.33 g) in DCM (15 mL) was added Et_3N (4.1 mmol, 3 equiv., 0.58 mL) and Boc_2O (3.4 mmol, 2.5 equiv., 0.75 g). The resulting mixture was stirred at 30 °C. After 2 h of the reaction the mixture was extracted with 10% solution of K_2CO_3 (3 × 10mL). Aqueous phase, adjusted to pH 2.5, was extracted with AcOEt (3 × 10 mL). Combined organic layers were dried (Na_2SO_4), filtered and evaporated *in vacuo* (white solid, 0.18 g). The residue was dissolved in DCM (6 mL), DCC was added (0.5 mmol, 1 equiv., 0.11 g). After 5 min of stirring at r.t, the unsoluble solid was filtered off and the filtrate dried (Na_2SO_4) and then evaporated *in vacuo* to give a colourless oil (0.20 g) as **13b**/**12b** in 81:19 ratio. The mixture of diastereomers was separated by column chromatography (AcOEt-heptane 1:7). It was obtained **13b** (0.12 g, 28%, **13b**/**12b** 98:2, R_f 0.49 AcOEt-cyclohexane 1:2) and **12b** (0.02 g, 5%, **12b**/**13b** 99:1, R_f 0.58 AcOEt-cyclohexane 1:2). White solid, mp 146-148 °C (from AcOEt-heptane, **13b**/**12b** >99:1) (lit.,[5] 140-142 °C (from *n*-hexane-Et_2O); $[\alpha]_D^{25}$ -49.8 (c 0.06, $CHCl_3$) (lit.,[5] -22.3 (c 0.56, $CHCl_3$)). The NMR spectral data are in agreement with those reported in the literature.[5]

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