Supporting Information for

Chemoselective Nucleophilic Attack on N-Acyl Derivatives of (S)-Ethyl 4,4-Dimethyl Pyroglutamate (DMPG)

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General Methods.

^1H NMR spectra were acquired at 200 MHz, 300 MHz, 500 MHz and ^{13}C NMR were acquired at 50 MHz, 75 MHz and 125 MHz (unless otherwise indicated). Chemical shifts (δ) are reported in ppm relative to CDCl_3 (7.26 and 77.0 ppm). Mass spectra (MS) were determined at an ionizing voltage of 70 eV. All reactions were carried out in anhydrous solvents and under argon atmosphere. THF was distilled from sodium-benzophenone under argon. CH_2Cl_2 was distilled from P_2O_5 . Flash column chromatography was performed using silica gel Merck-60 (230-400 mesh).

General procedure for the reactions summarized in scheme 1.

Compounds **6** were obtained following the general procedure reported for **5**.¹

(S)-4,4-Dimethyl-N-propionyl ethyl pyroglutamate (5). Chromatography: *n*-hexane-EtOAc 8:2; yield: 71%; colorless oil; $[\alpha]_{\text{D}}^{21} = -29.4$ (*c* 1.40, CH_2Cl_2) {Lit. **5**,¹ $[\alpha]_{\text{D}}^{21} = -31.5$ (*c* 1.43 CH_2Cl_2)}; ^1H NMR (CDCl_3 , 200MHz) δ 4.57 (dd, *J* = 4.7, 9.2 Hz, 1H), 4.17 (c, *J* = 7.2Hz, 2H), 2.91 (c, *J* = 6.2Hz, 2H), 2.19 (dd, *J* = 9.7, 13.3 Hz, 1H), 1.89 (dd, *J* = 4.9, 13.1Hz, 1H), 1.23 (t, *J* = 7.2Hz, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.10 (t, *J* = 6.2Hz, 3H).

¹ Ezquerro, J.; Rubio, A.; Martín, J.; García Navío, J. L. *Tetrahedron: Asymmetry* **1997**, 8, 669.

(S)-N-But-2-enoyl-4,4-dimethyl ethyl pyroglutamate (6a).² Chromatography: *n*-hexane-EtOAc 9:1; yield: 72%; $[\alpha]_D^{21} = -32.6$ (c 0.40, CH₂Cl₂) {Lit. **6a**,² $[\alpha]_D^{21} = -34.5$ (c 0.31 CH₂Cl₂)}; ¹H NMR (CDCl₃, 200MHz) δ 7.28 (d, J= 15.4 Hz, 1H), 7.06-7.28 (m, 1H), 4.65 (dd, J= 5, 9.2 Hz, 1H), 4.21 (c, J= 7.2Hz, 2H), 2.23 (dd, J= 9.6, 13.4 Hz, 1H), 1.87-1.97 (m, 4H), 1.27 (t, J= 7.2Hz, 3H), 1.24 (s, 3H), 1.22 (s, 3H).

(S)-N-(3-Phenylpropionyl)-4,4-dimethyl ethyl pyroglutamate (6b). Chromatography: *n*-hexane-EtOAc 9:1; yield: 73%; colorless oil; $[\alpha]_D^{21} = -4.8^\circ$ (c 1.63, CDCl₃); IR (NaCl) 3402.6, 1743.7, 1679.5, 1456.3, 1377.8, 1300.0, 1204.2 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.21 (m, 5H), 4.63 (dd, J= 5.1, 9.5 Hz, 1H), 4.23 (c, J= 7.1 Hz, 2H), 3.29 (t, J= 8.7 Hz, 2H), 2.98 (t, J= 8.7Hz, 1H), 2.23 (dd, J= 9.5, 13.0 Hz, 1H), 1.94 (dd, J= 5.0, 13.0 Hz, 1H), 1.28 (t, J= 7.1 Hz, 3H), 1.24 (s, 3H), 1.22 (s, 3H); ¹³C-NMR (CDCl₃, 50MHz) δ 173.7, 171.4, 140.8, 128.6, 128.5, 126.4, 126.2, 61.8, 55.1, 42.7, 38.6, 36.3, 30.3, 25.9, 25.3, 14.3; MS (Electrospray) (M⁺ + Na⁺) 340.1 (M⁺ +1) 318.2; Anal.Calcd for C₁₆H₁₉NO₄: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.24; H, 6.71; N, 4.52.

(S)-N-(4-Phenyl-but-3-enoyl)-4,4-dimethyl ethyl pyroglutamate (6c). Chromatography: *n*-hexane-EtOAc 9:1; yield: 55%; colorless oil; $[\alpha]_D^{21} = -22.4^\circ$ (c 0.42, CHCl₃); IR (KBr) 3455.2, 2962.6, 2925.3, 2825.6, 2358.2, 2320.8, 1735.1, 1697.8, 1466.6, 1384.5, 1336.0, 1254.0, 1216.7, 1194.3, 1171.9, 1097.3 cm⁻¹; ¹H NMR (CDCl₃, 200MHz) δ 7.20-7.43 (m, 5H), 6.55 (d, J= 16.1Hz, 1H), 6.38 (dt, J= 5.6, 16.1 Hz, 1H), 4.65 (dd, J= 5, 8.8Hz, 1H), 4.24 (c, J= 7.1Hz, 2H), 3.91 (d, J= 6.4Hz, 2H), 2.27 (dd, J= 9.5, 13.3Hz, 1H), 1.98 (dd, J= 5.1, 13.3 Hz, 1H), 1.29 (t, J= 7.0Hz, 3H), 1.28 (s, 3H), 1.26 (s, 3H); MS (Electrospray) (M⁺+1) 330.1; (M⁺+Na⁺) 352.0; Anal.Calcd for C₁₉H₂₃NO₄: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.15; H, 7.16; N, 4.07.

(S)-N-(3-Phenylpropionyl)-4,4-ethyl pyroglutamate (6d). Chromatography: *n*-hexane-EtOAc 9:1; yield: 28%; yellow oil; $[\alpha]_D^{21} = -12.3$ (c 0.67, CHCl₃); IR (NaCl) 3416.1, 2975.6, 2214.0, 1747.8, 1656.7, 1490.6, 1444.9, 1322.7, 1201.6 cm⁻¹; ¹H NMR (CDCl₃, 200MHz) δ 7.71-7.65 (m, 2H), 7.45-7.32 (m, 3H), 4.69 (dd, J= 4.9, 9.5Hz, 1H), 4.25 (c, J= 7.0Hz, 2H), 2.29 (dd, J= 9.7, 13.6Hz, 1H),

² Ezquerro, J.; Prieto, L.; Avendaño, C.; Martos, J. L.; de la Cuesta, E. *Tetrahedron Lett.* **1999**, *40*, 1575.

2.00 (dd, $J = 4.9, 13.6\text{Hz}$, 1H), 1.33 (t, $J = 7.0\text{Hz}$, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (CDCl_3 , 50MHz) δ 177.9, 171.2, 170.4, 133.2, 130.7, 128.4, 119.8, 94.1, 61.8, 54.9, 42.3, 36.3, 25.6, 25.1, 14.0; MS (Electrospray) ($\text{M}^+ + 1$) 313.1; ($\text{M}^+ + \text{Na}^+$) 336.1; Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_4$: C, 68.77; H, 6.41; N, 4.46. Found: C, 68.45; H, 6.32; N, 4.39.

(S)-N-Benzoyl-4,4-dimethyl ethyl pyroglutamate (6e). Chromatography: *n*-hexane-EtOAc 9:1; yield: 45%; colorless oil; $[\alpha]_{\text{D}}^{21} = -49.8^\circ$ (c 0.95, CDCl_3); IR (NaCl) 3355.2, 2975.2, 1746.8, 1681.9, 1449.3, 1386.7, 1293.3, 120.6.26 cm^{-1} ; ^1H NMR (CDCl_3 , 300MHz) δ 7.49 (m, 5H), 4.89 (dd, $J = 6.4, 9.0\text{ Hz}$, 1H), 4.24 (c, $J = 7.0\text{ Hz}$, 2H), 2.35 (dd, $J = 9.0, 13.3\text{ Hz}$, 1H), 2.04 (dd, $J = 6.4, 13.3\text{ Hz}$, 1H), 1.28 (t, $J = 7.0\text{ Hz}$, 3H), 1.24 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (CDCl_3 , 75MHz) δ 178.5, 171.2, 170.9, 132.2, 129.1, 128.5, 127.9, 61.9, 55.8, 42.5, 36.7, 25.3, 14.3; MS (Electrospray) ($\text{M}^+ + \text{Na}^+$) 312.0, (M^+) 290.1; Anal. Calc for $\text{C}_{16}\text{H}_{20}\text{NO}_4$: C, 66.19; H, 6.94; N, 4.82. Found: C, 66.25; H, 6.64; N, 4.53.

(S)-N-(2-Phenylcyclopropanecarbonyl)-4,4-dimethyl ethyl pyroglutamate (6f). Chromatography: *n*-hexane-EtOAc 9:1; yield: 70%; colorless oil; IR (NaCl) 3102.5, 2975.7, 2873.6, 1739.2, 1682.9, 1458.00, 1405.1, 1209.3 cm^{-1} ; ^1H NMR (CDCl_3 , 300MHz) δ 7.24 (m, 5H), 4.65 (dd, $J = 5.6, 9.5\text{ Hz}$, 1H), 4.23 (dc, $J = 4.6, 7.1\text{ Hz}$, 2H), 3.61-3.72 (m, 1H), 2.73-2.62 (m, 1H), 2.24 (ddd, $J = 1.3, 9.5, 13.1\text{ Hz}$, 1H), 1.94 (ddd, $J = 2.8, 5.6, 13.1\text{ Hz}$, 1H), 1.72 (m, 2H), 1.28 (s, 3H), 1.26 (t, $J = 7.1\text{Hz}$, 3H), 1.24 (s, 3H); ^{13}C NMR (CDCl_3 , 75MHz) δ 179.6, 173.6, 170.9, 139.9, 128.2, 126.3, 126.2, 61.4, 55.3, 42.6, 35.8, 28.9, 25.6, 25.0, 24.2, 19.2, 14.0; MS (Electrospray) ($\text{M}^+ + \text{Na}^+$) 352.1 ($\text{M}^+ + 1$) 330.2; Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.96; H, 7.12; N, 4.13.

General procedure for reaction of 6 with heteronucleophiles

To a solution of **6** (0.15 mmol) in the appropriate solvent (THF for morpholine and the corresponding alcohol for alkoxides) the heteronucleophile (0.165 mmol of morpholine and 0.15 mmol of the alkoxide) was added and the reaction mixture was refluxed for 24 h (morpholine) or stirred at room temperature for 1 h (alkoxides). Then the solvent was evaporated and the residue treated with CH_2Cl_2 . The organic phase washed with HCl (morpholine) or NaCl (alkoxydes), the solvent evaporated and the residue chromatographed on silica gel using hexane/EtOAc as eluent. Pyroglutamate **3** was recovered with a 3:7 mixture of solvents.

3-Phenylpropionic acid ethyl ester (7a).³ Chromatography: *n*-hexane-EtOAc 9:1; yield: 76%; colorless oil; 1H NMR ($CDCl_3$, 200MHz) δ 7.29-7.19 (m, 5H); 4.38 (c, $J = 7.1$ Hz, 2H), 2.96 (t, $J = 7.7$ Hz, 2H); 2.62 (t, $J = 7.9$ Hz, 2H); 1.30 (t, $J = 7.1$ Hz, 3H).

3-Phenylpropionic acid methyl ester (7b).⁴ Chromatography: *n*-hexane-EtOAc 9:1; yield: 94%; colorless oil; 1H NMR ($CDCl_3$, 200MHz) δ 7.2-7.4 (m, 5H); 3.68 (s, 3H); 2.97 (t, $J = 7.2$ Hz, 2H); 2.65 (t, $J = 7.2$ Hz, 2H).

³ Ahmad, M.S.; Baddeley, G. *J. Chem. Soc.* **1961**, 2520.

⁴ Semmelhack, M.F.; Stauffer, R.D.; Yamashita, A. *J. Org. Chem.* **1977**, 42, 3180.

1-Morpholin-4-yl-3-phenylpropan-1-one (7c).⁵ Chromatography: *n*-hexane-EtOAc 1:1; yield: 73%; colorless oil; ¹H NMR (CDCl₃, 200MHz) δ 7.1-7.4 (m, 5H); 3.63 (m, 4H); 3.64 (m, 2H); 3.36 (m, 2H); 3.00 (t, J= 7.7Hz, 2H); 2.62 (t, J=7.7Hz, 2H,).

4-Phenylbut-3-enoic acid methyl ester (7d).⁶ Chromatography: *n*-hexane-EtOAc 8:2; yield: 87%; colourless oil; ¹H NMR (CDCl₃, 200MHz) δ 7.22-7.38 (m, 5H); 6.48 (d, J= 11.7Hz, 1H); 6.24-6.35 (m, 1H); 3.77 (s, 3H); 3.25 (d, J= 4.0Hz, 2H).

Phenylpropyonic acid ethyl ester (7e).⁷ Chromatography: *n*-hexane-EtOAc 8:2; yield: 79%; colourless oil; ¹H NMR (CDCl₃, 200MHz) δ 7.54-7.58 (m, 2H); 7.31-7.43 (m, 3H); 4.28 (c, J= 7.1Hz, 2H); 1.34 (t, J= 7.0Hz, 3H).

Benzoic acid ethyl ester (7f).⁸ Chromatography: *n*-hexane-EtOAc 9:1; yield: 77%; colorless oil; ¹H NMR (CDCl₃, 200MHz) δ 8.06-8.02 (m, 2H); 7.56- 7.39 (m, 3H); 4.38 (c, J= 7.0Hz, 2H); 1.25 (t, J= 7.2Hz, 3H).

Morpholin-4-yl phenylmethanone (7g).⁵ Chromatography: *n*-hexane-EtOAc 1:1; yield: 64%; colourless oil; ¹H NMR (CDCl₃, 200MHz) δ 7.30-7.51 (m, 2H); 3.51-3.78 (m, 8H); 1.29 (s, 3H).

Morpholin-4-yl (2-phenyl-cyclopropyl) methanone (7h).⁹ Chromatography: *n*-hexane-EtOAc 7:3; yield: 73%; colourless oil; ¹H NMR (CDCl₃, 200MHz) δ 7.1-7.5 (m, 5H); 3.65 (m, 8H); 2.46-2.55 (m, 1H); 1.90-2.13 (m, 1H); 1.64-1.73 (m, 2H).

3-(But-2-enoyl ethoxycarbonyl amino)-2,2-dimethyl propionic acid ethyl ester (8). Chromatography: *n*-hexane-EtOAc 7:3; yield: 67%; colorless oil; [α]_D²¹ = -2.2° (c 0.12, CHCl₃); IR (KBr) 3373.1, 2962.6, 2865.6, 1709.0, 1533.7, 1462.8, 1388.8, 1365.9, 1265.1, 1205.5, 1134.6, 1093.6 cm⁻¹; ¹H NMR (CDCl₃, 200MHz) δ 6.72-6.90 (m, 1H), 6.26 (d, J= 10.5Hz, 1H), 5.75 (dd, J= 1.5, 15.1Hz, 1H), 4.60-4.72 (m, 1H), 4.21 (c, J= 7.0Hz, 2H), 4.18 (c, J= 7.1Hz, 2H), 2.31 (dd, J= 8.5, 13.1Hz, 1H), 2.04 (dd, J= 6.4, 13.1Hz, 1H), 1.27 (t, J= 7.1Hz, 3H), 1.26 (t, J= 7.1Hz, 3H), 1.17 (s, 3H), 1.15 (s, 3H); ¹³C NMR (CDCl₃, 50MHz) δ 178.0,

⁵ Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis*, **1983**, 474.

⁶ Heck, R.F. *J. Am. Chem. Soc.* **1971**, 93, 6896.

⁷ Newman, M.S.; Merrill, S.H. *J. Am. Chem. Soc.* **1955**, 77, 5549.

⁸ Bost, R.W.; Starnes, P.K.; Wood, E.L. *J. Am. Chem. Soc.* **1951**, 73, 1968.

⁹ Teotino, U.M.; Bella, D.D.; Gandini, A.; Beneli, G. *J. Med. Chem.* **1967**, 10, 1091.

172.4, 165.3, 140.7, 124.4, 61.7, 61.5, 49.8, 41.1, 40.1, 27.7, 24.9, 24.7, 14.2, 14.1; MS ($M^+ + Na^+$) 322.2; ($M^+ + 1$) 300.2; Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.63; H, 8.05; N, 4.19.

General procedure for reaction of 6 with Grignard reagents

To a solution of **6** (0.15 mmol) in THF at -40°C the Grignard reagent (0.15 mmol) was added and the reaction mixture was stirred for 5 h, then treated with NH_4Cl solution and extracted with CH_2Cl_2 . The residue obtained after evaporation of the solvent was chromatographed on silica gel using hexane/EtOAc as eluent (9:1) for isolation of ketones. Pyroglutamate **3** was recovered with a 3:7 mixture of solvents.

1,3-Diphenylpropan-1-one (7j).¹⁰ Chromatography: *n*-hexane-EtOAc 9:1; yield: 85%; colourless oil; ^1H NMR (CDCl_3 , 200MHz) δ 7.93-7.96 (m, 2H); 7.52-7.59 (m, 1H); 7.41-7.49 (m, 2H); 7.13-7.28 (m, 5H); 3.31 (t, $J = 5.5\text{Hz}$, 2H); 3.08 (t, $J = 5.5\text{Hz}$, 2H).

1,3-Diphenylpropynone (7k).¹¹ Chromatography: *n*-hexane-EtOAc 9:1; yield: 88%; yellow oil; ^1H NMR (CDCl_3 , 300MHz) δ 8.20-8.26 (m, 1H); 7.64-7.72 (m, 2H); 7.38-7.54 (m, 4H); 7.22-7.36 (m, 3H).

¹⁰ French, H.E.; Sears, K. *J. Am. Chem. Soc.* **1951**, *73*, 469.

¹¹ Livingston, R.C.; Rovert, C.; Cox, L.R.; Gramlich, V.; Diederich, F. *Angew. Chem. Int. Ed. En.* **2001**, *40*, 2334.

Diphenyl metanone (7l).¹² Chromatography: *n*-hexane-EtOAc 9:1; yield: 85%; white solid; ¹H NMR (CDCl₃, 200MHz) δ 7.77 (dd, J= 1.5, 7.0Hz, 4H); 7.57 (dt, J= 1.3, 7.7Hz); 7.45 (dd, J= 7.0, 7.7Hz, 4H).

Phenyl (2-phenylcyclopropyl) propenone (7m).¹³ Chromatography: *n*-hexane-EtOAc 9:1; yield: 77%; colourless oil; ¹H NMR (CDCl₃, 200MHz) δ 8.00-8.03 (m, 2H); 7.40-7.61 (m, 3H); 7.417-7.40 (m, 5H); 2.92 (ddd, J= 4.1, 5.1, 7.9Hz, 1H); 2.72 (ddd, J= 4.1, 6.5, 9.0Hz, 1H); 1.94 (ddd, J= 4.1, 5.1, 9.0 Hz, 1H); 1.57 (ddd, J= 4.1, 6.6, 8.2 Hz, 1H).

1-(2-Phenylcyclopropyl) propan-1-one (7n).¹⁴ Chromatography: *n*-hexane-EtOAc 9:1; yield: 76%; colourless oil; ¹H NMR (CDCl₃, 300 MHz) δ 7.08-7.18 (m, 2H); 7.21-7.34 (m, 3H); 2.65 (c, J= 7.2 Hz, 2H); 2.52 (ddd, J= 4.1, 5.1, 7.9 Hz, 1H); 2.21 (ddd, J= 4.1, 6.5, 9.0 Hz, 1H); 1.66 (ddd, J= 4.1, 5.1, 9.0 Hz, 1H); 1.39 (ddd, J= 4.1, 6.6, 8.2 Hz, 1H); 1.12 (t, J= 7.2 Hz, 3H).

1-(2-Phenylcyclopropyl) butan-1-one (7o).¹⁵ Chromatography: *n*-hexane-EtOAc 9:1; yield: 64%; colourless oil; ¹H NMR (CDCl₃, 300 MHz) δ 7.25 (dt, J= 1.5, 7.6 Hz, 2H); 7.14 (dt, J= 1.9, 7.5 Hz, 1H); 7.07 (d, J= 7.1 Hz, 2H); 2.57 (c, J= 7.2 Hz, 2H); 2.49 (ddd, J= 4.1, 5.1, 7.9 Hz, 1H); 2.19 (ddd, J= 4.1, 6.5, 9.0 Hz, 1H); 1.91-1.97 (m, 3H); 1.63-1.70 (m, 1H); 0.88 (t, J= 7.2 Hz, 3H).

1-(2-Phenylcyclopropyl) propenone (7p). Chromatography: *n*-hexane-EtOAc 9:1; yield: 65%; colorless oil; IR (NaCl) 3429.4, 2360.0, 2341.8, 1645.2, 1496.8, 1456.6, 1399.2, 1091.6 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.04-7.32 (m, 5H), 5.95 (ddd, J= 3.8, 10.7, 17.3 Hz, 1H), 5.32 (ddd, J= 1.2, 4.3, 17.3 Hz, 1H), 5.14 (ddd, J= 1.3, 2.6, 10.5 Hz, 1H), 3.61-3.66 (m, 1H), 2.61-2.70 (m, 1H), 1.69-1.75 (m, 1H), 1.38-1.43 (m, 1H); MS (QI) *m/z* 173 (M⁺+1); Anal.Calcd for C₁₂H₁₂O: C, 83.69; H, 7.02. Found: C, 83.27; H, 6.87.

1-(2-Phenylcyclopropyl)-but-3-en-1-one (7q). Chromatography: *n*-hexane-EtOAc 9:1; yield: 63%; colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 7.06-7.30 (m, 5H), 5.77-6.03 (m, 1H), 5.04-5.31 (m, 2H), 2.36 (d, J= 7.7 Hz, 2H), 1.95 (dt, J= 5.1, 9.2 Hz, 1H), 1.02-1.57 (m, 2H), 0.81-0.88 (m, 1H); ¹³C NMR (CDCl₃, 75

¹² Adams, R.; Tarbell, D.S. *J. Am. Chem. Soc.* **1938**, *60*, 1260.

¹³ Tanner, D.D.; Chen, J.J.; Luelo, C.; Peters, P.M. *J. Am. Chem. Soc.* **1992**, *114*, 713.

¹⁴ Toy, P.H.; Newcomb, M.; Hollemberg, P.F. *J. Am. Chem. Soc.* **1998**, *120*, 7719

¹⁵ Portnoy, N.A.; Yong, K.S.; Aguiar, A.M. *Tetrahedron Lett.* **1971**, *27*, 2559.

MHz) δ 166.3, 143.2, 133.8, 128.3, 125.8, 125.3, 118.9, 45.4, 31.3, 18.4, 11.1;
MS (QI) m/z 187 ($M^+ + 1$).

General procedure for the reactions summarized in scheme 3

Aldols **9** obtained following the procedure described,¹ were stirred in CH_2Cl_2 in the presence of DBU (1.1 mmol) for 12 h at room temperature. Then, a K_2CO_3 solution was added and chiral auxiliary was isolated by extraction with CH_2Cl_2 . The aqueous phase was acidified with 1N HCl, extracted with EtOAc and the solvent removed under reduced pressure. The residue containing the hydroxy acid **11** was dissolved in DMF and K_2CO_3 (1.1 equiv) and benzyl bromide (1.1 equiv) were added. The solution was stirred for 4 h at r.t. Then, EtOAc was added and the organic phase washed with a NaCl solution. After removal of the solvent the esters **12a-c** were isolated by column chromatography using hexane/EtOAc (9:1) as eluent.

(2S)-N-[2R,3R-(3-Hydroxy-2-methyl-3-phenylpropionyl)]-4,4-dimethyl ethyl pyroglutamate (9a).¹ Chromatography: *n*-hexane-EtOAc 7:3; yield: 71%;

¹ Ezquerro, J.; Rubio, A.; Martín, J.; García Navío, J. L. *Tetrahedron: Asymmetry* **1997**, 8, 669.

$[\alpha]_D^{21} = -11.2$ (*c* 1.25, CH₂Cl₂) {Lit¹ (**9a**) $[\alpha]_D^{21} = -12.8$ (*c* 1.25, CH₂Cl₂)}; ¹H NMR (CDCl₃, 200 MHz) δ 7.20-7.37 (m, 5H), 5.06 (d, *J* = 3.6 Hz, 1H), 4.55 (dd, *J* = 5.1, 9.5 Hz, 1H), 4.06-4.25 (m, 3H), 3.22 (s, 1H), 2.20 (dd, *J* = 9.5, 13.2 Hz, 1H), 1.88 (dd, *J* = 5.4, 13.5 Hz, 1H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.14 (d, *J* = 6.6 Hz, 3H)

(2S)-N-[2R,3S-(3-Hydroxy-2-methyl heptanoyl)]-4,4-dimethyl ethyl pyroglutamate (9b). Chromatography: *n*-hexane-EtOAc 8:2; yield: 73%; $[\alpha]_D^{21} = -29.6$ (*c* 1.25, CH₂Cl₂); IR (NaCl) 3482.4, 2976.6, 2937.1, 2876.6, 1744.4, 1695.8, 1458.2, 1376.9, 1292.9, 1241.6, 1209.2, 1148.0 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.64 (dd, *J* = 5.1, 9.7 Hz, 1H), 4.11-4.27 (m, 2H), 3.88-3.91 (m, 1H), 3.77 (dc, *J* = 2.3, 7.0 Hz, 1H), 2.94 (s, 1H), 2.22 (dd, *J* = 9.5, 13.3 Hz, 1H), 1.93 (dd, *J* = 4.9, 13.3 Hz, 1H), 1.12-1.34 (m, 12H), 0.80-0.94 (m, 6H); ¹³C NMR (CDCl₃, 50 MHz) δ 178.8, 170.8, 71.0, 61.7, 55.0, 54.4, 43.1, 42.7, 35.8, 33.4, 28.2, 25.7, 25.1, 22.7, 14.1, 10.0; MS (Electrospray) (*M*⁺+Na⁺) 352.2; (*M*⁺+1) 330.1; Anal.Calcd for C₁₇H₂₉NO₅: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.18; H, 8.75; N, 4.07.

(2S)-N-[2R,3S(3-Hydroxy-2-methyl undecanoyl)]-4,4-dimethyl ethyl pyroglutamate (9c). Chromatography: *n*-hexane-EtOAc 8:2; yield: 76%; colorless oil; $[\alpha]_D^{21} = -20.8^\circ$ (*c* 1.25, CH₂Cl₂); IR (NaCl) 3521.2, 2928.8, 2856.1, 1746.7, 1698.0, 1459.6, 1377.0, 1241.64, 1208.78, 1147.54 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.64 (dd, *J* = 4.9, 9.5 Hz, 1H), 4.12-4.28 (m, 2H), 3.90-3.94 (m, 1H), 3.77 (dc, *J* = 2.4, 7.1 Hz, 1H), 2.93 (d, *J* = 2.7 Hz, 1H), 2.23 (dd, *J* = 9.5, 13.4 Hz, 1H), 1.93 (dd, *J* = 4.9, 13.4 Hz, 1H), 1.17-1.30 (m, 23H), 0.85 (t, *J* = 7.0, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 179.0, 171.5, 171.0, 71.1, 61.7, 55.0, 43.1, 42.7, 35.8, 33.7, 31.8, 29.6, 29.5, 29.3, 26.0, 25.6, 25.1, 22.6, 14.1, 9.9; MS (Electrospray) (*M*⁺+1) 384.3; (*M*⁺+Na⁺) 406.2; Anal.Calcd for C₂₁H₃₇NO₅: C, 65.77; H, 9.72; N, 3.65. Found: C, 65.29; H, 9.58; N, 3.39.

(2R, 3R)-3-Hydroxy-2-methyl-3-phenyl propionic acid benzyl ester (12a). Chromatography: *n*-hexane-EtOAc 9:1; yield: 87%; colorless oil; $[\alpha]_D^{21} = -10.0^\circ$ (*c* 0.02, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.27-7.35 (m, 10H, H arom); 5.11 (s, 2H, CH₂-O); 2.82-2.88 (m, 1H, CH-CH₃); 1.54 (s, 1H, OH); 1.30 (d, 1H, *J* =

7.2 Hz, CH-OH); 1.16 (d, 3H, J= 6.9 Hz, CH₃); ¹³C NMR (CDCl₃, 125 MHz) δ 175.7, 141.5, 135.8, 128.8, 128.5, 128.3, 127.7, 126.2, 73.9, 66.7, 46.7, 11.1.

HRMS (m/z): Calculate for C₁₇H₁₈O₃ (M⁺): 271.1329. Found: 271.1328

(2R,3S)-3-Hydroxy-2-methyl heptanoic acid benzyl ester (12b).

Chromatography: *n*-hexane-EtOAc 9:1; yield: 92%; colorless oil; [α]_D²¹ = -6.0° (c 0.04, CH₂Cl₂); e.e. > 98%; ¹H NMR (CDCl₃, 500 MHz) δ 7.32-7.39 (m, 5H), 3.90 (dd, J= 3.5, 8.2 Hz, 1H), 2.58 (dc, J= 3.5, 7.3 Hz, 1H), 2.40 (s, 1H), 1.23-1.56 (m, 6H), 1.20 (d, J= 7.2 Hz, 3H), 0.89 (t, J= 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 176.2, 136.0, 128.8, 128.5, 128.4, 72.0, 66.6, 44.5, 33.7, 28.3, 22.8, 14.2, 10.8. **HRMS** (m/z): Calculate for C₁₅H₂₂O₃ (M⁺): 251.1641. Found: 251.1639

(2R,3S)-3-Hydroxy-2-methyl undecanoic acid benzyl ester (12c).

Chromatography: *n*-hexane-EtOAc 9:1; yield: 90%; colorless oil; [α]_D²¹ = -9.0° (c 0.05, CH₂Cl₂); e.e. > 98%; ¹H NMR (CDCl₃, 500 MHz) δ 7.32-7.39 (m, 5H), 5.15 (s, 2H), 3.90 (m, 1H), 2.58 (dc, J= 3.5, 6.9 Hz, 1H), 2.41 (s, 1H), 1.29-1.62 (m, 14H), 1.20 (d, J= 7.25 Hz, 3H), 0.88 (t, J= 6.6 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 176.2, 136.0, 128.8, 128.5, 128.3, 72.0, 66.6, 44.5, 34.0, 32.0, 29.7, 29.7, 29.4, 26.2, 22.8, 14.3, 10.8. **HRMS** (m/z): Calculate for C₁₉H₃₀O₃ (M⁺): 307.2265. Found: 307.2278

General procedure for the reactions summarized in scheme 4

(2S)-N-(1-Hydroxy-3-phenylpropyl)-4,4-dimethyl ethyl pyroglutamate (13).

To a solution of **6b** (60 mg, 0.19 mmol) in THF (3 mL) was added DIBAL-H (1M, toluene) (0.19 mL) under argon at -40°C. The reaction mixture was stirred at room temperature for 2 h and then treated with a saturated solution of NaCl (5 mL) and extracted with CH₂Cl₂ (3x10 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The crude was purified by chromatography (hexane/EtOAc 8:2) yielding 46.1 mg (76%) of **13** as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.17-7.29 (m, 5H); 5.19-5.26 (m, 1H); 4.15-4.26 (m, 3H); 3.77 (d, 1H J=3.0 Hz); 2.64-2.87 (m, 4H); 2.21 (dd, 1H, J=6.0, 9.0 Hz); 1.97 (dd, 1H, J=3.0, 9.0 Hz); 1.24 (t, 3H, J=7.3 Hz); 1.18 (s, 3H); 1.16 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 181.5, 173.4, 141.1, 128.5, 128.4, 126.0, 78.6, 61.7, 55.2, 40.7, 39.0, 34.9, 31.7, 25.7, 25.2, 14.0. IR (NaCl): 3436.0, 1745.0, 1208.2, 1031.2 cm⁻¹. MS (Electrospray) (M⁺+1) 319.1; (M⁺+Na⁺) 342.0; Anal.Calcd for C₁₈H₂₅NO₄: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.57; H, 7.74; N, 4.02.

3-Phenylpropionaldehyde (14). To a solution of **6b** (60 mg, 0.19 mmol) in THF (3 mL) was added DIBAL-H (1M, toluene) (0.19 mL) under argon at -40°C. The reaction mixture was stirred at room temperature for 2 h, then treated with 1N HCl, stirred for 12 h at room temperature and extracted with CH₂Cl₂ (3x10 mL). The organic phase washed with a saturated solution of NaCl, dried (MgSO₄) and concentrated in vacuo. The crude was purified by chromatography (hexane/EtOAc 9:1) yielding **14** (52%)¹⁶ and recovering **3** (60%). ¹H NMR (300 MHz, CDCl₃) δ (ppm). ¹H NMR (200 MHz, CDCl₃) δ (ppm): 9.80 (s, 1H); 7.13-7.38 (m, 5H); 2.95 (t, 2H, J=6.9 Hz); 2.78 (t, 2H, J=6.9 Hz).

(2S)-4,4-Dimethyl-N-(3-phenylpropenyl) ethyl pyroglutamate (15). To a solution of **6b** (60 mg, 0.19 mmol) in THF (3 mL) was added DIBAL-H (1M, toluene) (0.19 mL) under argon at -40°C. The reaction mixture was stirred at room temperature for 2 h and then treated with a saturated solution of NaCl (5 mL) and extracted with CH₂Cl₂ (3x10 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The crude without further purification was dissolved in CH₂Cl₂, treated with TFA and the mixture stirred for 12 at room

¹⁶ Herbert, R. B.; Kattah, A. E.; Knagg, E. *Tetrahedron*, **1999**, *46*, 7119.

temperature. The mixture was neutralized with a saturated aqueous solution of NaHCO_3 and the aqueous phase extracted with CH_2Cl_2 (3x10 mL). The organic phase washed with a saturated solution of NaCl , dried (MgSO_4) and concentrated in vacuo. The crude was purified by chromatography (hexane/EtOAc 9:1) yielding 0.50 mg of **15** (87%) as a colorless oil. $[\alpha]_D^{21} = -4.1^\circ$ (c 0.95, CHCl_3) ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.25-7.30 (m, 2H); 7.15-7.20 (m, 3H); 6.96 (d, 1H, $J=14.6$ Hz); 4.95 (dt, 1H $J=7.1$ and 14.5 Hz); 4.28 (dd, 1H, $J=3.3$ and 9.9 Hz); 4.15 (q, 2H, $J=7.1$ Hz); 3.38 (d, 2H, $J=7.1$ Hz); 2.28 (dd, 1H, $J=9.9$ and 13.4 Hz); 2.02 (dd, 1H, $J=3.3$ and 13.4 Hz); 1.24 (s, 3H); 1.21 (s, 3H); 1.18 (t, 3H, $J=7.1$) ^{13}C NMR (75 MHz, CDCl_3) δ (ppm); 177.7, 171.8, 139.6, 128.4, 128.3, 124.3, 111.3, 61.6, 55.8, 40.5, 37.9, 36.5, 26.3, 25.5, 14.0. IR (NaCl): 3355.3, 2972.5, 1745.1, 1703.1, 1455.5, 1391.4, 1336.0, 1203.1, 1134.2, 1029.3 cm^{-1} . MS (Electrospray) (M^++1) 301.1; (M^++Na^+) 324.0; Anal.Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.62; H, 7.57; N, 4.37.

Experimental procedure for High Performance Liquid Chromatography:

Materials

HPLC grade hexane and ethanol were purchased from Merck (Darmstadt, Germany). Isopropanol was supplied by LabScan (Dublin, Ireland). Spectrophotometric grade trifluoroacetic acid (TFA) was obtained from Sigma-Aldrich.

Chromatography was performed on the following polysaccharide chiral stationary phases: CHIRALPAK AD [amylose tris (3,5-dimethyl-phenyl carbamate)], CHIRALPAK AS [amylose tris ((S)-1-phenylethyl carbamate)], CHIRALCEL OD [cellulose tris (3,5-dimethylphenyl carbamate)] and CHIRALCEL OJ [cellulose tris (4-methyl benzoate)] columns. The columns dimensions were 250 x 4.6 mm. with the enantioselective phase coated onto a 10 μm silica-gel substrate. All columns were purchased from Chiral Technologies (Illkirch-Cedex, France)

Instrumentation

All the analytical studies were performed on an HP series 1100 system (Agilent, Waldbronn, Germany) driven by ChemStation 9.01 [®] software. This system was

composed of a quaternary pump, an autosampler, a mobile phase degasser, a diode array detector and an Agilent MSD 1100 SL single quadrupole mass spectrometer (APCI). Connections from the autosampler to column inlet and from column outlet to detectors were made with 0.005" i.d.. Polyether ether ketone (PEEK) connections were made as short as possible in order to minimize dead volume. A Cheminert® HPLC 8 column selector (VALCO), controlled via remote logic level signal, was coupled in series to the HPLC system in order to perform overnight chiral screening under 8 different conditions.

Chromatographic conditions

All the screening experiments were conducting by using those polysaccharide chiral stationary phases under normal phase conditions.¹⁶

With the change to a new mobile phase and / or column, there was a 30 min equilibration step under the new conditions to ensure that traces of the previous mobile phase had no influence on the new chromatographic experiment.

Experiments were carried out at room temperature. An UV (DAD) detector monitored the eluent, and the absorbance spectra (210-400 nm) were collected continuously during the course of each run. Chromatograms were recorded at 215 and 254 nm signals.

Chromatographic conditions were as follows:

1. *Gradient elution*: Mobile phase consisted on mixtures of hexane-TFA 0.05% (A) and an alcohol (B; either IPA or EtOH). Elution was carried out using a linear gradient starting from 20 to 60 % alcohol over 15 min. This latter solvent composition was held for 2 min and the return to the initial conditions was performed within 3 min. After 5 min of isocratic equilibration, the next sample was injected. The flow rate was held constant at 0.75 ml min⁻¹ on all column types and gradients. For comparison purposes, identical experiments were performed under neutral conditions after removing acidic modifier (TFA) from hexane. For Chiralpak AD there is a restriction on the use of hexane/ethanol mixtures from 85/15 to 40/60 due to UV absorption and stability issues (polymer leakage). This column was not included in the hexane/ethanol

¹⁶ De la Puente, M.L.; White, C.T.; Rivera-Sagredo, A.; Reilly, J.; Burton, K.; Harvey G. *J. Chromatogr. A*, **2003**, 983, 101.

gradient studies. Analysis of results so obtained confirmed ee > 98% for compounds 12a and 12b.

2. Isocratic elution: Gradient analysis of compound 12c indicated ee > 98%. However, the presence of an impurity showing identical retention time (5.2 min) than the one corresponding to the possible second isomer prompted us to perform isocratic elution. Mobile phase consisted on a 95/5 mixture of hexane-TFA 0.05%/ ethanol. The rest of chromatographic parameters were kept as above indicated. Results so obtained confirmed ee > 98%.

Confirmation of all results was performed by comparison of HPLC data yielded by compounds **12a**, **12b** and **12c**, and previous data generated by analysis of the corresponding mixtures of isomers under identical HPLC conditions.

Representative Chromatograms

Representative chromatograms for the resolution of compounds **12a**, **12b** and **12c**:

Chromatographic conditions: column, Chiralpak AS; mobile phase, Hexane-0.05%TFA (A) / IPA (B); gradient from 20 to 60%B in 15 min; flow rate, 0.75 ml/min.; detection, 215 nm.

Spectrum of 500 MHz for 9a

Spectrum of 500 MHz for 9b

Spectrum of 500 MHz for 9c

Spectrum of 500 MHz for 12a

Spectrum of 500 MHz for 12b

Spectrum of 500 MHz for 12c

NMR study of 9c conversion