Supporting Information

Design, Synthesis and Biological Activity of Isophthalic Acid Derivatives Targeted to the C1 Domain of Protein Kinase C

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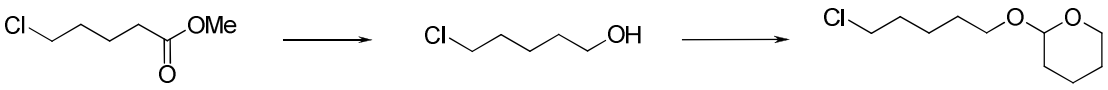
Contents

Syntheses and Characterisation of Compounds

All reagents were commercially available and were acquired from Fluka (Buchs, Switzerland) and Sigma-Aldrich (Schnelldorf, Germany). THF and Et_2O were distilled from sodium/benzophenone ketyl. $CHCl_3$ was distilled from CaH_2. Anhydrous DMF was from Fluka (Buchs, Switzerland) and was stored over molecular sieves (4 Å) under an inert atmosphere of dry argon. All reactions in anhydrous solvents were performed in flame-dried glassware under an inert atmosphere of dry argon. The progress of chemical reactions was monitored by thin-layer chromatography on silica gel 60-F_{254} plates acquired from Merck (Darmstadt, Germany) using phosphomolybdic acid stain (10% by weight in EtOH) or ninhydrin stain (1.5% by weight in EtOH). Flash SiO_2 column chromatography was performed with a Merck silica gel 60 (230-400 mesh) or with a Biotage High-Performance Flash Chromatography Sp^4-system (Uppsala, Sweden) using a 0.1-mm pathlength flow cell UV-detector/ recorder module (fixed wavelength: 254 nm), 12-mm or 25-mm flash cartridges, and the indicated mobile phase.

^1H NMR, ^{13}C NMR and DEPT spectra were recorded on a Varian Mercury 300 MHz or a Varian Unity 500 MHz spectrometer (Varian, Palo Alto, CA, USA) as solutions in $CDCl_3$, DMSO-d_6, CD_3OD or CD_2Cl_2. Deuterated solvents were purchased from Aldrich. Chemical shifts (δ) are given in parts per million (ppm) relative to the NMR solvent signals ($CDCl_3$ 7.26 and 77.21 ppm, DMSO-d_6 2.50 and 39.52 ppm, CD_3OD 3.31 and 49.00 ppm, CD_2Cl_2 5.32 and 53.80 ppm for ^1H and ^{13}C NMR, respectively). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quintet (qn) and m (multiplet). The synthesized compounds were analyzed

by HPLC-MS. HPLC-MS analyses were performed to determine the purity of all tested compounds by an HP1100 instrument with UV detector (λ 210 nm) and a Perkin Elmer Sciex API3000 triple-quadrupole LC/MS/MS mass spectrometer (Applied Biosystems/MDS Sciex, Concord, Canada) with a turbo ESI source. Signal separation was carried out by the use of an XTerra MS RP18 column (4.6 × 30 mm, 2.5 µm). High resolution mass spectra (HRMS) were run on a Q-TOF Micro (quadrupole time-of-flight) mass spectrometer (Waters/Micromass, Manchester, UK) with an ESI source in positive ion mode. The instrument was calibrated with an internal standard. The elemental analyses were conducted by Robertson-Microlit Laboratories (Madison, NJ, USA). Melting points were measured with an Electrothermal IA 9100 apparatus. Purity of all tested compounds was >95%. LogP values for the compounds were calculated using ChemBioDraw Ultra 11.0 (CambridgeSoft, Cambridge, MA, USA).

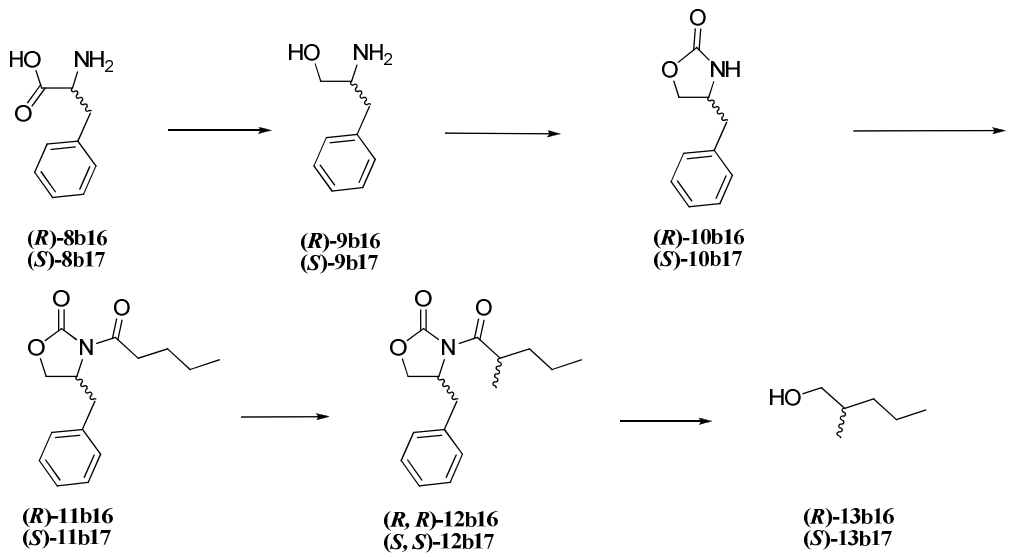


6 **7**

5-Chloropentan-1-ol (6). A solution of methyl 5-chlorovalerate (1.00 mL, 6.95 mmol) in dry THF (23 mL) was added dropwise to a solution of LAH (290 mg, 7.51 mmol, 1.1 equiv.) in THF (8 mL) and was stirred for 75 min. The reaction mixture was cooled to 0 °C on an ice-bath and 1 M H_2SO_4 (5.8 mL) was added to the reaction mixture. The resulting solution was stirred for 30 min and filtered. The precipitate

was washed with diethyl ether (25 mL). The filtrate was dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **6** as a clear liquid (570 mg, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 3.59 (dt, 4H, *J* 6.3, 26.7 Hz), 1.85-1.76 (m, 2H), 1.64-1.48 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 62.5, 45.1, 32.5, 32.0, 23.3.

2-[(5-Chloropentyl)oxy]tetrahydro-2*H*-pyran (7). DHP (630 μL, 6.87 mmol, 1.5 equiv.) was added to a solution consisting of **6** (570 mg, 4.65 mmol), PPTS (23 mg, 0.09 mmol, 0.02 equiv.) and DCM (17 mL) and the resulting mixture was stirred at rt for 22 h. DCM (40 mL) was added to the reaction mixture and it was washed with brine (20 mL), water (2×20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **7** as a colorless liquid, (911 mg, 95% yield). The compound **7** was used in the subsequent steps without further purification.



(2*R*)-2-Amino-3-phenylpropan-1-ol (9b16). A solution of D-phenylalanine (**8b16**) (16.5 g, 100 mmol) and THF (200 mL) was cooled to 0 °C on an ice bath and $NaBH_4$

(9.08 g, 240 mmol, 2.4 equiv.) was added in portions to the reaction mixture. A solution of I_2 (25.4 g, 100 mmol) in THF (50 mL) was added dropwise to the reaction mixture at 0 °C during 135 min. The resulting reaction mixture was stirred for 60 min during warming up to rt, refluxed overnight (19 h) and cooled to 0 °C on an ice bath. MeOH (50 mL) was added dropwise to the reaction mixture during 30 min and the resulting solution was stirred at rt for 1 h and evaporated *in vacuo* to give a grey oil. A solution of KOH (40 g) in water (200 mL) was added to the mixture and the resulting mixture was stirred at rt for 3 h. Water (40 mL) was added to the reaction mixture and it was extracted with DCM (3×100 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. Recrystallisation (toluene) gave **9b16** as a white solid (11.4 g, 75% yield). mp 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.31 (t, 2H, *J* 4.5 Hz), 7.23 (t, 1H, *J* 4.5 Hz), 7.19 (d, 2H, *J* 4.5 Hz), 3.64 (dd, 1H, *J* 2.4, 6.6 Hz), 3.39 (dd, 1H, *J* 4.5, 6.3 Hz), 3.13 (m, 1H), 2.80 (dd, 1H, *J* 3.3, 8.1 Hz), 2.54 (dd, 1H, *J* 5.4, 8.1 Hz), 1.88 (bs, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 138.8, 129.4, 128.8, 126.7, 66.6, 54.4, 41.2.

(2*S*)-2-Amino-3-phenylpropan-1-ol (9b17). A solution of L-phenylalanine (**8b17**) (33.0 g, 200 mmol) and THF (500 mL) was cooled to 0 °C on an ice bath and $NaBH_4$ (18.2 g, 480 mmol, 2.4 equiv.) was added in portions. A solution of I_2 (50.9 g, 200 mmol) in THF (100 mL) was added dropwise to the reaction mixture at 0 °C during 135 min. The resulting reaction mixture was stirred for 60 min during warming up to rt, refluxed overnight (16 h) and cooled to 0 °C on an ice bath. MeOH (100 mL) was added dropwise to the reaction mixture during 30 min and the resulting solution was stirred at rt for 1 h and evaporated *in vacuo* to give a grey oil. A solution of KOH (80

g) in water (400 mL) was added to the mixture and the resulting mixture was stirred at rt for 5 h. Water (200 mL) was added to the reaction mixture and it was extracted with DCM (3×250 mL). The combined organic layers were washed with water (200 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude **9b17** was obtained as a colorless oil which was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.35-18 (m, 5H), 3.64 (dd, 1H, *J* 4.2, 10.8 Hz), 3.40 (dd, 1H, *J* 7.2, 10.8 Hz), 3.17 (m, 1H), 2.80 (dd, 1H, *J* 5.1, 13.5 Hz), 2.53 (dd, 1H, *J* 9.0, 13.5 Hz), 2.04 (bs, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 138.9, 129.4, 128.8, 126.6, 66.4, 54.4, 41.0.

(4*R*)-4-Benzyl-1,3-oxazolidin-2-one (**10b16**). A mixture of **9b16** (16.6 g, 110 mmol), diethyl carbonate (26.7 g, 220 mmol, 2 equiv.) and potassium carbonate (1.52 g, 11 mmol, 0.1 equiv.) was heated at 130 °C using a distillation apparatus until no more EtOH was distilled off (2 h). After cooling to 0 °C on an ice bath, DCM (150 mL) and 1 M $NaHCO_3$ solution (75 mL) were added to the reaction mixture. The organic phase was collected, a saturated solution of $NaHCO_3$ (75 mL) was added to the organic phase and the mixture was stirred at rt for 1 h. The organic phase was collected, washed with brine (75 mL), dried over Na_2SO_4, filtered, evaporated *in vacuo* and recrystallized (hexane/EtOAc) to give **10b16** as a white solid (16.52 g, 85% yield). mp 86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.34 (t, 2H, *J* 4.5 Hz), 7.28 (t, 1H, *J* 4.5 Hz), 7.18 (d, 2H, *J* 5.2 Hz), 5.31 (bs, 1H), 4.47 (t, 1H, *J* 5.1 Hz), 4.16 (dd, 1H, *J* 3.3, 5.1 Hz), 4.09 (m, 1H), 2.92-2.84 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 144.2, 136.2, 129.3, 129.1, 127.5, 69.9, 54.0, 41.7.

(4*S*)-4-Benzyl-1,3-oxazolidin-2-one (10b17). The crude **9b17** was mixed with diethyl carbonate (47.2 g, 220 mmol, 2 equiv.) and potassium carbonate (2.79 g, 11 mmol, 0.1 equiv.) and the resulting mixture was heated at 130 °C using a distillation apparatus until no more EtOH was distilled off (2 h). After cooling to 0 °C on an ice bath, DCM (200 mL) and 1 M $NaHCO_3$ solution (200 mL) were added to the reaction mixture and the resulting mixture was stirred at rt for 15 min. The organic phase was collected, dried over Na_2SO_4, filtered and evaporated *in vacuo*. Toluene (100 mL) was added to the residue and the mixture was recrystallized at 0 °C. Evaporation *in vacuo* and recrystallization (hexane/EtOAc) gave **10b17** as a white solid (21.87 g, 62% yield for two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm}7.37-7.25 (m, 3H), 7.19-7.15 (m, 2H), 5.73 (bs, 1H), 4.47 (app. t, 1H), 4.17-4.04 (m, 2H), 2.88 (d, 2H, *J* 6.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 159.6, 136.1, 129.2, 127.4, 69.8, 54.0, 41.6; DEPT: 129.2 (CH), 127.4 (CH), 69.8 (CH_2), 54.0 (CH), 41.6 (CH_2).

(4*R*)-4-Benzyl-3-pentanoyl-1,3-oxazolidin-2-one (11b16). *n*-BuLi (2.5 M in hexane, 37.3 mL, 93.2 mmol) was added dropwise during 45 min to a solution of **10b16** (16.5 g, 93.2 mmol) in dry THF (200 mL) at -78 °C. Pentanoyl chloride (13.3 mL, 112 mmol, 1.12 equiv.) was added dropwise to the reaction mixture at -78 °C during 5 min. The resulting mixture was stirred for 15 min, allowed to warm up to rt and stirred for 1 h. A saturated solution of $NaHCO_3$ (200 mL) was added to the reaction mixture and the organic phase was collected. The aqueous phase was extracted with EtOAc (2×100 mL), all the organic phases were combined, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give **11b16** as a colorless oil (22.5 g, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.33 (t, 2H, *J* 4.5 Hz), 7.27 (t, 1H, *J* 4.5 Hz), 7.20 (d, 2H, *J* 4.5 Hz), 4.70-4.65 (m, 1H), 4.21-4.15 (m, 2H), 3.30 (dd, 1H, *J*

1.8, 8.1 Hz), 3.01-2.87 (m, 2H), 2.77 (dd, 1H, *J* 13.2, 6.6 Hz), 1.71-1.65 (m, 2H), 1.42 (sext, 2H, *J* 4.5 Hz), 0.96 (t, 3H, *J* 4.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 173.6, 153.6, 135.5, 129.6, 129.1, 127.5, 66.3, 55.3, 38.1, 35.4, 26.6, 22.5, 14.0.

(4*S*)-4-Benzyl-3-pentanoyl-1,3-oxazolidin-2-one (11b17). *n*-BuLi (1.5 M in hexane, 18.8 mL, 28.2 mmol) was added dropwise during 45 min to a solution of **10b17** (5.00 g, 28.2 mmol) in dry THF (100 mL) at -78 °C. Pentanoic anhydride (5.60 mL, 28.2 mmol, 1.12 equiv.) was added dropwise to the reaction mixture at -78 °C during 5 min. The resulting mixture was stirred for 15 min, allowed to warm up to rt and stirred for 1 h. A saturated solution of $NaHCO_3$ (60 mL) was added to the reaction mixture and the organic phase was collected. The aqueous phase was extracted with EtOAc (2×30 mL), the organic phases were combined, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the crude product as a colorless oil. The crude product was purified with flash SiO_2 chromatography (*n*-hexane/EtOAc, 10:1 → 5:1) and a colorless oil **11b17** was obtained (4.82 g, 65% yield). R_f 0.09 (*n*-hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.33 (t, 2H, *J* 4.5 Hz), 7.27 (t, 1H, *J* 4.5 Hz), 7.20 (d, 2H, *J* 4.5 Hz), 4.70-4.65 (m, 1H), 4.21-4.15 (m, 2H), 3.30 (dd, 1H, *J* 1.8, 8.1 Hz), 3.01-2.87 (m, 2H), 2.77 (dd, 1H, *J* 13.2, 6.6 Hz), 1.71-1.65 (m, 2H), 1.42 (sext, 2H, *J* 4.5 Hz), 0.96 (t, 3H, *J* 4.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 173.6, 153.6, 135.5, 129.6, 129.1, 127.5, 66.3, 55.3, 38.1, 35.4, 26.6, 22.5, 14.0.

(4*R*)-4-Benzyl-3-[(2*R*)-2-methylpentanoyl]-1,3-oxazolidin-2-one (12b16). Sodium *bis*(trimethylsilyl)amide (1 M in THF, 95.6 mL, 95.6 mmol, 1.11 equiv.) was added dropwise during 2 h to a solution of **11b16** (22.5 g, 86.1 mmol) in dry THF (95

mL) at -78 °C and stirred for 30 min. Iodomethane (26.9 mL, 431 mmol, 5 equiv.) was added dropwise during 5 min at -78 °C and the resulting mixture was stirred for 4 h at -78 °C. The reaction mixture was let to warm up to rt while saturated solution of NH_4Cl (165 mL) was added. The resulting mixture was evaporated *in vacuo*, extracted with DCM (2×150 mL) and washed with 1 M $KHSO_4$ solution (3×100 mL). The aqueous phases were combined and extracted with DCM (3×150 mL). The organic phases were washed with 1 M $KHSO_4$ solution (3×100 mL), combined with the first collected organic phase, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 10:1) to give **12b16** as a colorless oil (17.5 g, 74% yield). R_f 0.54 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.36-7.20 (m, 5H), 4.71-4.64 (m, 1H), 4.23-4.14 (m, 2H), 3.79-3.68 (m, 1H), 3.27 (dd, 1H, *J* 3.3, 13.2 Hz), 2.77 (dd, 1H, *J* 9.6, 13.5 Hz), 1.79-1.68 (m, 1H), 1.46-1.26 (m, 3H), 1.22 (d, 3H, *J* 6.9 Hz), 0.91 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 177.5, 153.2, 135.5, 129.6, 129.1, 127.5, 66.2, 55.5, 38.1, 37.6, 35.8, 20.6, 17.5, 14.3.

(4*S*)-4-Benzyl-3-[(2*S*)-2-methylpentanoyl]-1,3-oxazolidin-2-one (12b17). Sodium *bis*(trimethylsilyl)amide (1 M in THF, 12.5 mL, 12.5 mmol, 1.1 equiv.) was added dropwise during 2 h to a solution of **11b17** (2.97 g, 11.3 mmol) in dry THF (12 mL) at -78 °C and stirred for 30 min. Iodomethane (3.50 mL, 56.9 mmol, 5 equiv.) was added dropwise during 5 min at -78 °C and the resulting mixture was stirred for 5.5 h at -78 °C. The reaction mixture was let to warm up to rt while saturated solution of NH_4Cl (22 mL) was added. The resulting mixture was evaporated *in vacuo*, extracted with DCM (2×20 mL) and washed with 1 M $KHSO_4$ solution (3×15 mL). The aqueous phases were combined and extracted with DCM (3×20 mL), the organic

phase was washed with 1 M $KHSO_4$ solution (3×20 mL), combined with the first collected organic phase, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 15 → 20% of EtOAc) to give **12b17** a colorless oil (2.37 g, 75% yield). R_f 0.48 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.36-7.20 (m, 5H), 4.71-4.64 (m, 1H), 4.23-4.14 (m, 2H), 3.79-3.67 (m, 1H), 3.27 (dd, 1H, *J* 3.3, 13.5 Hz), 2.77 (dd, 1H, *J* 9.3, 13.5 Hz), 1.79-1.68 (m, 1H), 1.46-1.26 (m, 3H), 1.22 (d, 3H, *J* 6.9 Hz), 0.91 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 177.5, 153.3, 135.6, 129.6, 129.1, 127.5, 66.2, 55.6, 38.1, 37.6, 35.8, 20.6, 17.5, 14.3.

(2*R*)-2-Methyl-1-pentanol (13b16). A solution of lithium aluminum hydride (3.38 g, 89.1 mmol, 1.4 equiv.) in dry diethyl ether (120 mL) was added dropwise during 30 min to a solution of **12b16** (17.5 g, 63.7 mmol) in dry diethyl ether (200 mL) at 0 °C (ice bath) and stirred for 2 h at 0 °C. The reaction was quenched by the dropwise addition of brine (100 mL) during 20 min. The resulting mixture was stirred for 30 min on ice bath and filtered. The formed precipitate was washed with diethyl ether, the filtrate dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was placed at 5 °C, filtered and distilled twice to give **13b16** as a colorless liquid. bp 28 °C (22 mbar). ^{1}H NMR (300 MHz, CD_2Cl_2): δ_{ppm} 3.48-3.30 (m, 2H), 1.63-1.52 (m, 1H), 1.41-1.25 (m, 3H), 1.16-1.01 (m, 1H), 0.90-0.85 (m, 6H); ^{13}C NMR (75.4 MHz, CD_2Cl_2): δ_{ppm} 68.2, 35.6, 35.5, 20.2, 16.4, 14.2.

(2*S*)-2-Methyl-1-pentanol (13b17). A solution of lithium aluminum hydride (0.39 g, 10.2 mmol, 1.4 equiv.) in dry diethyl ether (17 mL) was added dropwise during 30 min to a solution of **12b17** (2.00 g, 7.26 mmol) in dry diethyl ether (20 mL) at 0 °C

(ice bath) and stirred for 2 h at 0 °C. The reaction was quenched by the dropwise addition of brine (10 mL) during 20 min. The resulting mixture was stirred for 30 min on ice bath and filtered. The formed precipitate was washed with diethyl ether, the filtrate cooled to 5 °C and filtered. The solid (4*S*)-4-benzyl-1,3-oxazolidin-2-one was washed with pentane and the filtrate cooled to 5 °C. The formed precipitate was filtered. This procedure was repeated twice to give **13b17** as a colorless liquid (560 mg, 75% yield). ^{1}H NMR (300 MHz, CD_2Cl_2): δ_{ppm} 3.47-3.30 (m, 2H), 1.63-1.52 (m, 1H), 1.41-1.25 (m, 3H), 1.16-1.01 (m, 1H), 0.90-0.85 (m, 6H); ^{13}C NMR (75.4 MHz, CD_2Cl_2): δ_{ppm} 68.2, 35.6, 35.5, 20.2, 16.4, 14.2.

Diethyl 5-(tetrahydropyran-2-yloxymethyl)isophthalate (3). A mixture of diethyl (5-hydroxymethyl)isophthalate (**2**) (5.72 g, 22.7 mmol), 3,4-dihydro-2*H*-pyran (5.54 mL, 61.3 mmol, 2.7 equiv.), pyridinium toluene-*p*-sulfonate (285 mg, 1.14 mmol, 0.05 equiv.) and 1,2-dichloroethane (50 mL) was stirred at room temperature for 6 h. The reaction mixture was quenched by the addition of cold water (50 mL), extracted with DCM (50 mL), washed with a saturated solution of $NaHCO_3$ (3×20 mL) and brine (3×20 mL). The organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **3** as a pale yellow oil (7.41 g, 97% yield). This oil was used without further purification and the full product analysis was carried out for the next product.

5-(Tetrahydropyran-2-yloxymethyl)isophthalic acid (4). A mixture of **3** (3.46 g, 10.3 mmol), a 10% solution of KOH (46.2 mL, 82.4 mmol, 8 equiv.) and MeOH (50 mL) was refluxed for 1 h. The solvents were evaporated *in vacuo* and the pH was adjusted with a 25% solution of $KHSO_4$ to 4.0. The white precipitate was filtered,

washed with water (10 mL), dissolved into a solution of EtOAc and THF (1:1, 3×50 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **4** as a white solid (2.45 g, 85% yield). This solid was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ_{ppm} 13.3 (bs, 2H), 8.39 (t, 1H, *J* 1.5 Hz), 8.13 (d, 2H, *J* 1.5 Hz), 4.80 (d, 1H, *J* 12.6 Hz), 4.72 (t, 1H, *J* 3.0 Hz), 4.59 (d, 1H, *J* 12.6 Hz), 3.82-3.75 (m, 1H), 3.52-3.45 (m, 1H), 1.80-1.62 (m, 2H), 1.58-1.48 (m, 4H); ^{13}C NMR (75.4 MHz, DMSO-d_6): δ_{ppm} 166.5, 139.8, 132.1, 131.3, 129.0, 97.7, 67.3, 61.4, 30.1, 25.0, 19.1.

A general procedure I, synthesis of the esters: *Bis*(4-*tert*-butylbenzyl) 5-(tetrahydropyran-2-yloxymethyl) isophthalate (5a1). A mixture of **4** (200 mg, 0.71 mmol), 4-*tert*-butylbenzyl bromide (390 mg, 2.13 mmol, 3 equiv.), K_2CO_3 (490 mg, 3.55 mmol, 5 equiv.) and KI (130 mg, 0.79 mmol, 1.1 equiv.) in dry DMF (4 mL) was heated at 110 °C for 2 h. The reaction mixture was cooled to rt and quenched by the addition of an ice water mixture (20 mL), extracted with EtOAc (3×20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **5a1** as a yellowish oil. This and the following crude diesters (**5a2-3**) were used in the subsequent deprotection step without further purification and the full product analysis was carried out for the products **1a1-3**.

***Bis*(3-chlorobenzyl) 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5a2).** A mixture of **4** (200 mg, 0.71 mmol), 3-chlorobenzyl bromide (210 μL, 1.57 mmol, 2.2 equiv.), K_2CO_3 (493 mg, 3.55 mmol, 5 equiv.) and KI (130 mg, 0.79 mmol, 1.1 equiv.) in dry DMF (4 mL) was heated at 110 °C for 100 min. The reaction mixture was cooled to rt and quenched by the addition of an ice water mixture (20 mL),

extracted with EtOAc (3×20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **5a2** as a red oil.

A general procedure II, synthesis of the esters: Dihexyl 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b1). A mixture of **4** (250 mg, 0.89 mmol) and 1,1-carbonyldiimidazole (318 mg, 1.96 mmol, 2.2 equiv.) in dry DMF (2 mL) was stirred at room temperature for 1 h. 1-Hexanol (340 μL, 2.67 mmol, 3 equiv.), 4-(dimethylamino)pyridine (11 mg, 0.09 mmol, 0.1 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (332 μL, 1.78 mmol, 2 equiv.) were added to the reaction mixture that was stirred at 40 °C for 22 h. The reaction was quenched by the addition of an ice water mixture (10 mL) and extracted with EtOAc (3×20 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (2×20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude **5b1** as a yellow oil. This and the following crude diesters (**5b2-19**) were used in the subsequent deprotection step without further purification and the full product analysis was carried out for the products **1b1-19**.

***Bis*(2-methylpentyl) 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b2).** The general procedure II was used except that 2-methyl-1-pentanol (530 μL, 4.28 mmol, 3 equiv.) was used. The reaction mixture was stirred at 40 °C for 23 h. The crude **5b2** was obtained as a colorless oil after work up.

***Bis*[(2*R*)-2-methylpentyl)] 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b3).** The general procedure II was used except that (2*R*)-2-methyl-1-pentanol **(13b16)** (550 mg, 5.35 mmol, 3 equiv.) and DMF (2 mL) were used. The reaction

mixture was stirred at 40 °C for 21 h. The crude **5b3** was obtained as a yellow oil after work up.

***Bis*[(2*S*)-2-methylpentyl)] 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b4).** The general procedure II was used except that (2*S*)-2-methyl-1-pentanol **(13b17)** (270 mg, 2.67 mmol, 3 equiv.) and DMF (1 mL) were used. The reaction mixture was stirred at 40 °C for 24 h. The crude **5b4** was obtained as a yellow oil after work up.

***Bis*(3-methylpentyl) 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b5).** The general procedure II was used except that 3-methyl-1-pentanol (330 μL, 2.68 mmol, 3 equiv.) was used. The reaction mixture was stirred at 40 °C for 18 h. The crude **5b5** was obtained as a yellow oil after work up.

***Bis*(4-methylpentyl) 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b6).** The general procedure II was used except that 4-methyl-1-pentanol (340 μL, 2.68 mmol, 3 equiv.) was used. The reaction mixture was stirred at 40 °C for 18 h. The crude **5b6** was obtained as a yellow oil after work up.

***Bis*(2-ethylhexyl) 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b7).** The general procedure II was used except that 2-ethyl-1-hexanol (380 μL, 2.41 mmol, 3 equiv.) was used. The reaction mixture was stirred at 40 °C for 18 h. The crude **5b7** was obtained as a yellow oil after work up.

***Bis*(bicyclo[2.2.1]hept-2-ylmethyl) 5-(tetrahydropyran-2-yloxymethyl)-isophthalate (5b8).** The general procedure II was used except that 2-norbornanemethanol (360 μL, 2.68 mmol, 3 equiv.) was used. The reaction mixture

was stirred at 40 °C for 18 h. The crude **5b8** was obtained as a yellow oil after work up.

Dicyclohexylmethyl 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b9). The general procedure II was used except that DMAP was not used. Instead cyclohexylmethanol (440 μL, 3.56 mmol, 2 equiv.), CDI (580 mg, 3.56 mmol, 2 equiv.), DBU (660 μL, 3.56 mmol, 2 equiv.) and DMF (12.5 mL) were used. The reaction mixture was stirred at 40 °C for 19 h. DMAP (22 mg, 0.18 mmol, 0.1 equiv.) was added and the reaction mixture was stirred at 40 °C for 1 h. The crude **5b9** was obtained as a colorless oil after work up.

***Bis*(1-methylpentyl) 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b12).** The general procedure II was used except that DMAP was not used. Instead, 2-hexanol (180 μL, 1.43 mmol, 2 equiv.) and DMF (5 mL) were used. The reaction mixture was stirred at 40 °C for 19 h. The crude **5b12** was obtained as a yellowish oil after work up.

***Bis*(1-methylhexyl) 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b13).** The general procedure II was used except that DMAP was not used. Instead, 2-heptanol (510 μL, 3.56 mmol, 2 equiv.), CDI (580 mg, 3.56 mmol, 2.0 equiv.), DBU (660 μL, 3.56 mmol, 2 equiv.) and DMF (12.5 mL) were used. The reaction mixture was stirred at 40 °C for 18 h, DMAP (22 mg, 0.18 mmol, 0.1 equiv.) was added and the reaction mixture was stirred at 40 °C for 22 h. 2-Heptanol (100 μL, 0.64 mmol, 0.18 equiv) added and stirred for another 22 h. The crude **5b13** was obtained as an oil after work up.

***Bis*(decahydronaphthalen-2-yl) 5-(tetrahydropyran-2-yloxymethyl)-isophthalate (5b14).** The general procedure II was used except that DMAP was not used. Instead, decahydro-2-naphthol (430 μL, 2.68 mmol, 3 equiv.), DBU (400 μL, 2.68 mmol, 3 equiv.) and DMF (1 mL) were used. The reaction mixture was stirred at 40 °C for 43 h. The crude **5b14** was obtained as a colorless oil after work up.

***Bis*[(4a*S*,8a*S*)-decahydronaphthalen-1-yl] 5-(tetrahydropyran-2-yloxymethyl)-isophthalate (5b15).** The general procedure II was used except that *cis*-decahydro-1-naphthol (410 μL, 2.68 mmol, 3 equiv.), DBU (400 μL, 2.68 mmol, 3 equiv.) and DMF (1 mL) were used. The reaction mixture was stirred at 40 °C for 43 h. The crude **5b15** was obtained as a yellowish oil after work up.

***Bis*[(1*R*)-2,3-dihydro-1*H*-inden-1-yl] 5-(tetrahydropyran-2-yloxymethyl)-isophthalate (5b16).** The general procedure II was used except that (1*R*)-2,3-dihydro-1*H*-inden-1-ol (290 mg, 2.14 mmol, 3 equiv.) and DMF (0.8 mL) were used. The reaction mixture was stirred at 40 °C for 24 h. The crude **5b16** was obtained as a yellow liquid after work up.

***Bis*[5-(tetrahydro-2*H*-pyran-2-yloxy)pentyl] 5-(tetrahydropyran-2-yloxy-methyl)isophthalate (5b17).** The general procedure II was used except that **7** (325 mg, 1.57 mmol, 2.2 equiv.) and DMF (10 mL) were used. The reaction mixture was stirred for 95 min. The reaction mixture was cooled to rt and quenched by the addition of an ice water mixture (40 mL), extracted with EtOAc (2×40 mL), washed with saturated $NaHCO_3$ solution (2×15 mL), brine (2×15 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude **5b17** as a reddish oil.

***Bis*(tetrahydrofuran-3-ylmethyl) 5-(tetrahydropyran-2-yloxymethyl)-isophthalate (5b18).** The general procedure II was used except that tetrahydro-3-furanylmethanol (160 μL, 1.61 mmol, 3 equiv.), CDI (170 mg, 1.07, 2 equiv.), DMAP (3 mg, 0.03 mmol, 0.05 equiv.) and DMF (3.75 mL) were used. The reaction mixture was stirred at 40 °C for 41 h. The crude **5b18** was obtained as a colorless oil after work up.

***Bis*(3-ethoxypropyl) 5-(tetrahydropyran-2-yloxymethyl)isophthalate (5b19).** The general procedure II was used except that 3-ethoxy-1-propanol (370 μL, 3.21 mmol, 3 equiv.), CDI (350 mg, 2.14 mmol, 2 equiv.), DMAP (13 mg, 0.11 mmol, 0.1 equiv.), DBU (320 μL, 2.14 mmol, 2 equiv.) and DMF (7.5 mL) were used. The reaction mixture was stirred at 40 °C for 24 h. The crude **5b19** was obtained as a yellow liquid after work up.

A general procedure III, deprotection of the THP ethers: Dihexyl 5-(hydroxymethyl)isophthalate (1b1). A mixture of the crude **5b1** and Dowex 50W×8 (750 mg) in MeOH (8 mL) was stirred at 40 °C overnight. The Dowex 50W×8 was filtered off and the filtrate was evaporated *in vacuo*. The crude **1b1** was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1 → 2:1) to give **1b1** as a colorless oil (233 mg, 72% yield for two reaction steps). R_f 0.60 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.61 (s, 1H), 8.24 (s, 2H), 4.83 (d, 2H, *J* 6.0 Hz), 4.35 (app. t, 4H, *J* 7.0 Hz), 1.89 (app. t, 1H, *J* 6.0 Hz), 1.82-1.77 (m, 4H), 1.47–1.43 (m, 4H), 1.38–1.35 (m, 8H), 0.92 (app. t, 6H, *J* 6.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.1, 141.9, 132.1, 131.4, 130.0, 65.8, 64.5, 31.7, 28.8, 25.9, 22.8, 14.2. HRMS-ESI (*m/z*): $[M+HCOO^-]^-$ calcd 409.2226; found 409.2226.

***Bis*(4-*tert*-butylbenzyl) 5-(hydroxymethyl)isophthalate (1a1).** The general procedure III was followed except that **5a1** was used. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1 → 2:1) to give **1a1** as a white solid (157 mg, 45% yield for two reaction steps). R_f 0.47 (*n*-hexane/EtOAc, 2:1). mp 106.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.68–8.67 (m, 1H), 8.26–8.25 (m, 2H), 7.45–7.38 (m, 8H), 5.37 (s, 4 H), 4.80 (d, 2H, *J* 6.0 Hz), 1.79 (t, 1 H, *J* 6.0 Hz), 1.34 (s, 18H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.8, 164.9, 152.1, 151.7, 141.9, 132.9, 132.4, 131.2, 130.4, 128.5, 125.8, 67.2, 64.5, 34.8, 31.5; Anal. ($C_{31}H_{36}O_5$) C, H.

***Bis*(3-chlorobenzyl) 5-(hydroxymethyl)isophthalate (1a2).** The general procedure III was followed except that **5a2** was used and the reaction mixture was stirred for 6 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane:EtOAc, 2:1) to give **1a2** as a white solid (293 mg, 92% yield for two reaction steps). R_f 0.27 (*n*-hexane/EtOAc, 2:1). mp 99.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.66 (s, 1H), 8.28 (s, 2H), 7.45 (s, 2H), 7.34 (obsc. s, 6H), 5.37 (s, 4H), 4.83 (s, 2H), 1.86 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.5, 142.2, 137.4, 134.7, 132.6, 130.9, 130.3, 130.2, 128.8, 128.6, 126.6, 66.5, 64.4; Anal. ($C_{23}H_{18}Cl_2O_5$) C, H: calcd, 4.07; found, 3.86.

***Bis*(2-methylpentyl) 5-(hydroxymethyl)isophthalate (1b2).** The general procedure III was followed except that **5b2** was used and the reaction mixture was stirred for 18 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 2:1) to give **1b2** as a colorless oil (328 mg, 63% yield for two reaction steps). R_f 0.51 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (300

MHz, $CDCl_3$): δ_{ppm} 8.60 (app. t, 1H), 8.23 (m, 2H), 4.82 (d, 2H, *J* 0.9 Hz), 4.24 (dd, 2H, *J* 5.4, 10.5 Hz), 4.13 (dd, 2H, *J* 6.9, 10.5 Hz), 2.02-1.91 (m, 2H), 1.83 (bs, 1H), 1.51-1.20 (m, 8H), 1.02 (d, 6H, *J* 6.6 Hz), 0.92 (app. t, 6H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.0, 142.0, 132.1, 131.5, 129.9, 70.5, 64.5, 35.9, 32.6, 20.2, 17.2, 14.5. HRMS-ESI (*m/z*): $[M+HCOO^-]^-$ calcd 409.2226; found 409.2263.

***Bis*[(2*R*)-methylpentyl] 5-(hydroxymethyl)isophthalate (1b3).** The general procedure III was followed except that **5b3** was used and the reaction mixture was stirred for 20 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1) to give **1b3** as a colorless oil (250 mg, 39% yield for two reaction steps). R_f 0.07 (*n*-hexane/ EtOAc, 8:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 8.61 (s, 1H), 8.23 (m, 2H), 4.82 (s, 2H), 4.24 (dd, 2H, *J* 6.0, 10.5 Hz), 4.13 (dd, 2H, *J* 6.9, 10.5 Hz), 2.02-1.91 (m, 2H), 1.80 (bs, 1H), 1.50-1.22 (m, 8H), 1.02 (d, 6H, *J* 6.6 Hz), 0.92 (t, 6H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.0, 142.0, 132.1, 131.5, 129.9, 70.5, 64.5, 35.9, 32.6, 20.2, 17.2, 14.4. HRMS-ESI (*m/z*): $[M+HCOO^-]^-$ calcd 409.2226; found 409.2255.

***Bis*[(2*S*)-methylpentyl)] 5-(hydroxymethyl)isophthalate (1b4).** The general procedure III was followed except that **5b4** was used and the reaction mixture was stirred for 21 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1) to give **1b4** as a colorless oil (171 mg, 53% yield for two reaction steps). R_f 0.04 (*n*-hexane/EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.58 (app. t, 1H), 8.21 (app. d, 2H), 4.80 (s, 2H), 4.23 (dd, 2H, *J* 5.7, 10.8 Hz), 4.12 (dd, 2H, *J* 6.9, 10.8 Hz), 2.22 (bs, 1H), 2.01-1.90 (m, 2H), 1.50-1.21 (m, 8H), 1.01 (d, 6H, *J* 6.9 Hz), 0.92 (t, 6H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$):

δ_{ppm} 166.0, 142.1, 132.1, 131.4, 129.9, 70.5, 64.5, 35.8, 32.6, 20.2, 17.2, 14.4. HRMS-ESI (*m/z*): $[M+HCOO^-]^-$ calcd 409.2226; found 409.2256.

***Bis*(3-methylpentyl) 5-(hydroxymethyl)isophthalate (1b5).** The general procedure III was followed except that **5b5** was used and the reaction mixture was stirred for 23 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1 → 4:1) to give **1b5** as a white solid (165 mg, 51% yield for two reaction steps). R_f 0.04 (*n*-hexane/EtOAc, 8:1). mp 74.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.54 (app. t, 1H), 8.19 (app. t, 2H), 4.78 (s, 2H), 4.42-4.29 (m, 4H), 2.41 (s, 1H), 1.86-1.74 (m, 2H), 1.63-1.49 (m, 4H), 1.47-1.34 (m, 2H), 1.30-1.15 (m, 2H), 0.94 (d, 6H, *J* 6.3 Hz), 0.89 (t, 6H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.0, 142.1, 132.1, 131.3, 129.8, 64.4, 64.3, 35.2, 31.7, 29.5, 19.3, 11.4; DEPT: 132.1 (CH), 129.8 (CH), 64.4 (CH_2), 64.3 (CH_2), 35.2 (CH_2), 31.7 (CH), 29.6 (CH_2), 19.3 (CH_3), 11.4 (CH_3); Anal. ($C_{21}H_{32}O_5$) C: calcd, 69.20; found, 70.83; H: calcd, 8.85; found, 7.96.

***Bis*(4-methylpentyl) 5-(hydroxymethyl)isophthalate (1b6).** The general procedure III was followed except that **5b6** was used and the reaction mixture was stirred for 23 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1 → 4:1) to give **1b6** as a colorless oil (263 mg, 81% yield for two reaction steps). R_f 0.14 (*n*-hexane/EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.59 (app. t, 1H), 8.22 (m, 2H), 4.81 (s, 2H), 4.33 (t, 4H, *J* 6.9 Hz), 1.86 (bs, 1H), 1.84-1.74 (m, 4H), 1.69-1.55 (m, 2H), 1.35-1.28 (m, 4H), 0.92 (d, 12H, *J* 6.6 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.0, 141.9, 132.1, 131.4, 130.0, 66.1, 64.5, 35.2, 27.9, 26.8, 22.7; DEPT: 132.1 (CH), 130.0 (CH), 66.1 (CH_2), 64.5

(CH_2), 35.2 (CH_2), 27.9 (CH), 26.8 (CH), 22.7 (CH_3); Anal. ($C_{21}H_{32}O_5$) C, H: calcd, 8.85; found, 9.14.

***Bis*(2-ethylhexyl) 5-(hydroxymethyl)isophthalate (1b7).** The general procedure III was followed except that **5b7** and THF co-solvent (3 mL) were also used and the reaction mixture was stirred for 24 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 10:1) to give **1b7** as a colorless oil (216 mg, 64% yield for two reaction steps). R_f 0.28 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.58-8.57 (m, 1H), 8.22 (m, 2H), 4.81 (s, 4H), 4.28-4.25 (m, 4H), 2.02 (s, 1H), 1.79-1.67 (m, 2H), 1.54-1.25 (m, 16H), 0.97-0.87 (m, 12H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.1, 142.0, 132.1, 131.4, 129.9, 67.9, 64.5, 39.1, 30.7, 29.2, 24.1, 23.2, 14.2, 11.3; DEPT: 132.1 (CH), 129.9 (CH), 67.9 (CH_2), 64.5 (CH_2), 39.1 (CH), 30.7 (CH_2), 29.2 (CH_2), 24.1 (CH_2), 23.2 (CH_2), 14.2 (CH_3), 11.3 (CH_3); Anal. ($C_{25}H_{40}O_5$) C, H: calcd, 9.59; found, 9.83.

***Bis*(bicyclo[2.2.1]hept-2-ylmethyl) 5-(hydroxymethyl)isophthalate (1b8).** The general procedure III was followed except that **5b8** and THF co-solvent (1 mL) were used and the reaction mixture was stirred for 23 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1 → 4:1) to give **1b8** as a white solid (199 mg, 54% yield for two reaction steps). R_f 0.06 (*n*-hexane/EtOAc, 8:1). mp 80.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.54 (app. t, 1H), 8.18 (app. t, 2H), 4.78 (s, 2H), 4.36 (dd, 2H, *J* 6.6, 11.1 Hz), 4.19 (app. dd, 2H, *J* 9.3, 11.1 Hz), 4.05 (d, 1H, 7.5 Hz), 2.46 (s, 1H), 2.36-2.22 (m, 4H) 1.97-1.88 (m, 1H), 1.82-1.72 (m, 2H), 1.59-1.09 (m, 12H), 0.81-0.73 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.1, 166.0, 142.1, 132.1, 131.3, 129.9, 68.8, 67.5, 64.4, 41.2, 39.9, 38.9, 38.7, 38.6,

36.8, 36.4, 35.4, 34.2, 33.7, 30.0, 29.8, 29.0, 22.8; DEPT: 132.1 (CH), 129.9 (CH), 68.8 (CH_2), 67.5 (CH_2), 64.4 (CH_2), 41.2 (CH), 39.9 (CH_2), 38.9 (CH), 38.7 (CH), 38.6 (CH), 36.8 (CH), 36.4 (CH), 35.4 (CH_2), 34.2 (CH_2), 33.7 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.0 (CH_2), 22.8 (CH_2); Anal. ($C_{25}H_{32}O_5$) C, H: calcd, 7.82; found, 7.62.

Dicyclohexylmethyl 5-(hydroxymethyl)isophthalate (1b9). The general procedure III was followed except that **5b9** was used. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 2:1) to give **1b9** as a white solid (242 mg, 35% yield for two reaction steps). R_f 0.38 (*n*-hexane/EtOAc, 2:1). mp 81.9-82.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.61 (s, 1H), 8.23 (s, 2H), 4.83 (s, 2H), 4.17 (d, 4H, *J* 6.5 Hz), 1.86–1.70 (m, 8H), 1.34–1.20 (m, 8H), 1.12–1.07 (m, 4H), 0.98–0.90 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.0, 142.0, 132.1, 131.5, 130.0, 70.7, 64.6, 37.4, 30.0, 26.6, 25.9; Anal. ($C_{23}H_{32}O_5$) C, H.

***Bis*(1-methylpentyl) 5-(hydroxymethyl)isophthalate (1b12).** The general procedure III was followed except that except that **5b12** was used. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 2:1) to give **1b12** as a colorless oil (81 mg, 31% yield for two reaction steps). R_f 0.25 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.56 (s, 1H), 8.19 (s, 2H), 5.15 (sext, 2H, *J* 6.3 Hz, CH), 4.80 (s, 2H), 2.38 (bs, 1H), 1.80–1.53 (m, 4H), 1.42–1.24 (m, 14H), 0.89 (t, 6H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.7, 141.9, 132.0, 131.7, 129.9, 72.6, 64.4, 35.8, 27.8, 22.7, 20.2, 14.1; Anal. ($C_{21}H_{32}O_5$) C: calcd, 69.20; found, 70.83; H: calcd, 8.85; found, 7.96.

***Bis*(1-methylhexyl) 5-(hydroxymethyl)isophthalate (1b13).** The general procedure III was followed except that **5b13** was used. The crude product was

purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 2:1) to give **1b13** as a colorless oil (56 mg, 8% yield for two reaction steps). R_f 0.50 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.58 (app. t, 1H), 8.21 (app d, 2H), 5.24-5.13 (sext, 2H, *J* 6.3Hz), 4.81 (s, 2H), 1.89 (bs, 1H), 1.82–1.55 (m, 5H), 1.44–1.27 (m, 18H, *J* 6.3Hz), 0.88 (t, 6H, *J* 6.8 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.6, 141.8, 132.0, 131.8, 130.0, 72.6, 64.6, 36.1, 31.8, 25.3, 22.7, 20.2, 14.2. HRMS-ESI (*m/z*): $[M+HCOO^-]^-$ calcd 437.2539; found 437.2520.

***Bis*(decahydronaphthalen-2-yl) 5-(hydroxymethyl)isophthalate (1b14).** The general procedure III was followed except that **5b14** was used and the reaction mixture was stirred for 20 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1) to give **1b14** as a white solid (296 mg, 71% yield for two reaction steps). R_f 0.08 (*n*-hexane/EtOAc, 8:1). mp 68.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.55 (app. d, 1H), 8.18 (s, 2H), 5.21 (bs, 1H), 4.99-4.92 (m, 1H), 4.78 (s, 2H), 2.11-0.89 (m, 32H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.5, 141.9, 132.0, 131.9, 130.0, 74.7, 72.0, 64.6, 43.0, 42.5, 41.3, 39.3, 37.8, 37.6, 35.5, 35.1, 34.8, 33.9, 33.4, 32.1, 31.9, 31.8, 31.6, 30.5, 28.7, 27.1, 26.8, 26.4, 25.5, 22.9, 14.3; Anal. ($C_{29}H_{40}O_5$) C: calcd, 74.33; found, 66.17; H: calcd, 8.60; found, 7.92.

***Bis*[(4a*S*,8a*S*)-decahydronaphthalen-1-yl] 5-(hydroxymethyl)isophthalate (1b15).** The general procedure III was followed except that **5b15** was used and the reaction mixture was stirred for 20 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1) to give **1b15** as a white solid (239 mg, 57% yield for two reaction steps). R_f 0.06 (*n*-hexane/EtOAc, 8:1). mp 75.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.56 (app. t, 1H, *J* 1.5 Hz), 8.19 (app. d, 2H, *J* 0.9),

5.08-5.02 (m, 2H), 4.80 (s, 2H), 2.11 (bs, 2H), 1.87-1.35 (m, 26H), 1.26–1.21 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.3, 141.9, 132.0, 131.8, 130.0, 64.5, 40.3, 40.3, 35.7, 31.8, 26.3, 26.1, 24.7, 24.3, 21.5, 20.3; Anal. ($C_{29}H_{40}O_5$) C, H: calcd, 8.60; found, 8.88.

***Bis*[(1*R*)-2,3-dihydro-1*H*-inden-1-yl] 5-(hydroxymethyl)isophthalate (1b16).** The general procedure III was followed except that **5b16** and co-solvent THF (2 mL) were used and the reaction mixture was stirred for 21 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 8:1) to give **1b16** as a white solid (100 mg, 32% yield for two reaction steps). R_f 0.29 (*n*-hexane/EtOAc, 2:1). mp 86.9-87.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.57 (app. t, 1H), 8.18 (app. t, 2H), 7.47 (d, 2H, *J* 7.5 Hz), 7.31 (d, 4H, *J* 3.6 Hz), 7.26-7.19 (m, 2H), 6.45 (dd, 2H, *J* 4.2, 6.9 Hz), 4.73 (s, 2H), 3.24-3.14 (m, 2H), 2.98-2.89 (m, 2H), 2.67–2.55 (m, 2H), 2.29–2.19 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.9, 144.7, 141.9, 141.0, 132.2, 131.3, 130.2, 129.3, 126.9, 125.9, 125.0, 79.6, 64.3, 32.5, 30.4; Anal. ($C_{23}H_{36}O_5$) C: calcd, 70.38; found, 74.95; H: calcd, 9.24; found, 5.57.

***Bis*(5-hydroxypentyl) 5-(hydroxymethyl)isophthalate (1b17).** The general procedure III was followed except that **5b17** was used and the reaction mixture was stirred for 24 h. The crude product was purified with flash SiO_2 column chromatography ($CHCl_3$/MeOH, 10:1) to give **1b17** as a colorless oil (145 mg, 55% yield for two reaction steps). R_f 0.23 ($CHCl_3$/MeOH, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.54 (s, 1H), 8.19 (app. t, 2H), 4.78 (s, 2H), 4.35 (t, 4H, *J* 6.6 Hz), 3.67 (t, 4H, *J* 6.3 Hz), 2.16 (bs, 3H) 1.81 (app. qn, 4H), 1.70–1.48 (m, 8H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.0, 142.2, 132.1, 131.2, 129.9, 65.6, 64.3, 62.8, 32.4,

28.6, 22.6; Anal. ($C_{19}H_{28}O_7$) C: calcd, 61.94; found, 59.58; H: calcd, 7.66; found, 7.33.

***Bis*(tetrahydrofuran-3-ylmethyl) 5-(hydroxymethyl)isophthalate (1b18).** The general procedure III was followed except that **5b18** was used and the reaction mixture was stirred for 19 h. The crude product was purified with flash SiO_2 column chromatography ($CHCl_3$/MeOH, 20:1 → 4:1) to give **1b18** as a colorless oil (20 mg, 10% yield for two reaction steps). R_f 0.32 ($CHCl_3$/MeOH, 20:1) ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.55 (t, 1H, *J* 1.8 Hz) , 8.22-8.21 (m, 2H), 4.81 (s, 2H), 4.36 (dd, 2H, *J* 6.6, 10.8 Hz), 4.25 (dd, 2H, *J* 7.8, 10.8 Hz), 3.95-3.88 (m, 4H), 3.83-3.75 (m, 2H), 3.71-3.66 (m, 2H), 2.81-2.67 (m, 2H), 2.36 (bs, 1H), 2.18-1.68 (m, 2H), 1.79-1.68 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.8, 142.3, 132.3, 131.0, 130.0, 70.7, 67.9, 67.0, 64.3, 38.5, 29.2; Anal. ($C_{19}H_{24}O_7$) C: calcd, 62.63; found, 61.95; H: calcd, 6.64; found, 6.78.

***Bis*(3-ethoxypropyl) 5-(hydroxymethyl)isophthalate (1b19).** The general procedure III was followed except that **5b19** was used and the reaction mixture was stirred for 17 h. The crude product was purified with flash SiO_2 column chromatography ($CHCl_3$/MeOH, 20:1 → 4:1) to give **1b19** as a colorless oil (18 mg, 4.5% yield). R_f 0.23 ($CHCl_3$/MeOH, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.56 (app. t, 1H), 8.21 (app. t, 2H), 4.79 (s, 2H), 4.44 (t, 4H, *J* 6.3 Hz), 3.57 (t, 4H, *J* 6.3 Hz), 3.49 (q, *J* 7.2 Hz), 2.31 (bs, 1H), 2.05 (qn, 4H, *J* 6.3 Hz), 1.19 (t, 6H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.9, 142.1, 132.2, 131.7, 129.9, 67.2, 66.5, 64.4, 63.0, 29.3, 15.4; Anal. ($C_{25}H_{40}O_5$) C, H: calcd, 9.59; found, 9.83.

5-Hydroxymethylisophthalic acid (1b20). A mixture of diethyl isophthalate (**2**) (250 mg, 1.28 mmol), a 10% solution of KOH (5.71 mL, 10.2 mmol, 8 equiv.) and MeOH (5 mL) was refluxed for 2 h. The solvents were evaporated *in vacuo*, water (20 mL) added to the residue and the solution was washed with EtOAc (2×20 mL). The pH of the aqueous phase was adjusted to 1 with 1 M HCl solution. The mixture was extracted with EtOAc (3×20 mL), washed with brine (4×20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **1b20** as a white solid (170 mg, 87% yield). mp 271.5-272.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ_{ppm} 13.20 (bs, 2H), 8.35 (s, 1H), 8.12 (s, 2H, *J* 1.5 Hz), 5.45 (bs, 1H), 4.62 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.7, 143.9, 131.1, 131.1, 128.4, 62.0; Anal. ($C_{19}H_{24}O_7$) C: calcd, 55.11; found, 54.60; H: calcd, 4.11; found, 3.58.

A general procedure IV, synthesis of esters: *Bis*(2-methylpentyl) isophthalate (15a). A mixture of isophthalic acid (**14a**) (200 mg, 1.20 mmol) and CDI (390 mg, 2.41 mmol, 2 equiv.) in dry DMF (8 mL) was stirred at room temperature for 1 h. 2-Methyl-1-pentanol (450 μL, 3.61 mmol, 3 equiv.), DMAP (7 mg, 0.06 mmol, 0.05 equiv.) and DBU (360 μL, 2.41 mmol, 2 equiv.) were added to the reaction mixture that was stirred at 40 °C for 20 h. The reaction was quenched by the addition of an ice water mixture (10 mL) and the resulting mixture was extracted with EtOAc (3×20 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (2×20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1) to give **15a** as a colorless oil (42 mg, 11% yield). R_f 0.57 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.69 (t, 1H, *J* 1.8 Hz), 8.30

(dd, 2H, *J* 1.8, 7.8 Hz), 7.54 (t, 1H, *J* 7.8 Hz), 4.24 (dd, 2H, *J* 5.7, 10.5 Hz), 4.14 (dd, 2H, *J* 6.6, 10.5 Hz), 2.02-1.91 (m, 2H), 1.52-1.20 (m, 8H), 1.03 (d, 6H, *J* 6.6 Hz), 0.93 (app. t, 6H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.1, 133.9, 131.2, 130.8, 128.8, 70.4, 35.9, 32.7, 20.2, 17.2, 14.5; Anal. ($C_{20}H_{30}O_4$) C: calcd, 71.82; found, 71.33; H: calcd, 9.04; found, 10.06.

***Bis*(2-methylpentyl) 5-methylisophthalate (15b).** The general procedure IV for the synthesis of **15a** was used except that 5-methylisophthalic acid (**14b**) (220 mg, 1.20 mmol) was used. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1) to give **15b** as a colorless oil (116 mg, 28% yield). R_f 0.90 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.48 (bs, 1H), 8.03 (app. t, 2H), 4.23 (dd, 2H, *J* 5.7, 10.8 Hz), 4.12 (dd, 2H, *J* 6.6, 10.8 Hz), 2.46 (s, 3H), 2.01-1.91 (m, 2H), 1.51-1.19 (m, 8H), 1.02 (d, 6H, *J* 7.2 Hz), 0.92 (app. t, 6H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.3, 138.8, 134.5, 131.1, 128.1, 70.4, 35.9, 32.6, 21.4, 20.2, 17.2, 14.5; Anal. ($C_{21}H_{32}O_4$) C, H: calcd, 9.26; found, 9.46.

Methyl (2-methylpentyl) isophthalate (15c). The general procedure IV for the synthesis of **15a** was used except that monomethyl isophthalate (**14c**) (220 mg, 1.20 mmol) was used and the reaction mixture was stirred for 19 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 19:1 → 3:2) to give **15c** as a colorless oil (240 mg, 76% yield). R_f 0.55 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.69 (app. t, 1H, *J* 1.8 Hz), 8.23 (app. dd, 2H, *J* 1.8, 7.8 Hz), 7.53 (app. t, 1H, *J* 7.8 Hz), 4.24 (dd, 2H, *J* 6.0, 10.8 Hz), 4.13 (dd, 2H, *J* 6.9 and 10.8 Hz), 3.95 (s, 3H), 2.02-1.92 (m, 1H), 1.49-1.19 (m, 4H), 1.02 (d, 3H, *J* 6.9

Hz), 0.93 (app. t, 6H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.5, 166.1, 134.0, 133.9, 131.2, 130.9, 130.8, 128.8, 70.5, 52.6, 35.9, 32.7, 20.2, 17.2, 14.5; DEPT 134.0 (CH), 133.9 (CH), 130.9 (CH), 128.8 (CH), 70.5 (CH_2), 52.6 (CH_3), 35.9 (CH_2), 32.7 (CH), 20.2 (CH_2), 17.2 (CH_3), 14.5 (CH_3); Anal. ($C_{15}H_{20}O_4$) C, H.

***Bis*(2-methylpentyl) 5-nitroisophthalate (15d).** The general procedure IV for the synthesis of **15a** was used except that 5-nitroisophthalic acid (**14d**) (510 mg, 2.41 mmol) was used. The reaction mixture was stirred for 21 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1) to give **15d** as a yellow oil (329 mg, 36% yield). R_f 0.79 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 9.01 (d, 1H, *J* 1.5 Hz), 8.97 (app. t, 2H), 4.30 (dd, 2H, *J* 6.0, 10.8 Hz), 4.20 (dd, 2H, *J* 6.9, 10.8 Hz), 2.05-1.95 (m, 2H), 1.48-1.21 (m, 8H), 1.04 (d, 6H, *J* 6.6 Hz), 0.94 (app. t, 6H, *J* 7.2 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 164.0, 148.7, 135.9, 133.1, 128.2, 71.4, 35.8, 32.6, 20.2, 17.2, 14.4; Anal. ($C_{20}H_{29}NO_6$) C, H: calcd, 7.70; found, 7.49, N: calcd, 3.69; found 3.56.

***Bis*(3-trifluoromethylbenzyl) 5-nitroisophthalate (15e).** A mixture of 5-nitroisophthalic acid (**14e**) (510 mg, 2.41 mmol), 3-(trifluoromethyl)benzyl chloride (1.120 g, 7.23 mmol, 3 equiv.), K_2CO_3 (1670 mg, 12.1 mmol, 5 equiv.) and KI (440 mg, 2.69 mmol, 1.1 equiv.) in dry DMF (9 mL) was heated at 80 °C for 2 h. The reaction mixture was cooled to rt and quenched by the addition of an ice water mixture (30 mL) and extracted with EtOAc (3×50 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 5:1 → 4:1) to give **15e** as a yellow oil (433 mg, 34% yield). R_f 0.37 (*n*-hexane/EtOAc, 5:1). ^{1}H

NMR (300 MHz, $CDCl_3$): δ_{ppm} 9.05 (app. t, 1H), 9.02 (app. d, 2H, *J* 1.5 Hz), 7.72 (s, 2H), 7.66 (app. t, 4H), 7.55 (app. t, 2H), 5.49 (s, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 163.6, 148.7, 136.2, 136.1, 132.5, 132.1, 132.1, 131.7, 131.2, 129.6, 128.7, 125.9, 125.9, 125.8, 125.6, 125.6, 125.5, 122.2, 67.3.

Monomethyl isophthalate (17). A mixture of NaOH (430 mg, 10.8 mmol, 1.05 equiv.) in MeOH (4 mL) was added dropwise during 10 min to a solution of dimethyl isophthalate (**16**) (2.0 g, 10.3 mmol) and acetone (20 mL). The resulting mixture was stirred at rt for 21 h. NaOH (40 mg, 1.00 mmol, 0.1 equiv.) was added to the reaction mixture and it was stirred for 4 h at rt. The solvents were evaporated *in vacuo*, water (40 mL) was added to the residue and the pH adjusted to 1 with concentrated HCl solution. The formed precipitate was filtered, washed with water (4×10 mL) and dried *in vacuo* to give **17** as a white solid (1.81 g, 98% yield). ^1H NMR (300 MHz, DMSO-d_6): δ_{ppm} 13.32 (bs, 1H), 8.49 (app. t, 1H), 8.21-8.17 (m, 2H), 7.67 (app. t, 1H), 3.89 (s, 3H); ^{13}C NMR (75.4 MHz, DMSO-d_6): δ_{ppm} 166.4, 165.5, 133.8, 133.2, 131.3, 130.0, 129.7, 129.4, 52.4.

Methyl 3-(hydroxymethyl)benzoate (18). A solution of borane dimethyl sulfide complex ($BH_3{\cdot}SMe_2$) (4.2 mL, 44.2 mmol, 4.4 equiv.) in dry THF (28 mL) was added dropwise during 1 h to a solution of **17** (1.81 g, 10.0 mmol) in dry THF (45 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min, at rt for 4 h and finally cooled to 0 °C. Ice (100 mL) was added to the reaction mixture. The resulting mixture was washed with brine (20 mL) and extracted with diethyl ether (3×30 mL). The combined organic phases were washed with a 3% solution of H_2O_2 (10 mL), a saturated solution of $NaHCO_3$ (3×15 mL), brine (2×20 mL), dried over Na_2SO_4,

filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 2:1) to give **18** as a colorless oil (486 mg, 29% yield). R_f 0.09 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.03 (t, 1H, *J* 1.8 Hz), 7.97-7.94 (m, 1H), 7.59-7.56 (app. d, 1H), 7.46-7.41 (app. t, 1H), 4.75 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 167.2, 141.4, 131.6, 130.6, 129.0, 128.9, 128.2, 65.0, 52.4.

Methyl 3-(tetrahydropyran-2-yloxymethyl)benzoate (19). A mixture of **18** (480 mg, 2.86 mmol), DHP (310 μL, 3.44 mmol, 1.2 equiv.), PPTS (70 mg, 0.29 mmol, 0.1 equiv.) and DCE (12 mL) was stirred at room temperature for 16 h. The reaction mixture was evaporated *in vacuo* and DCM (50 mL) and water (50 mL) were added to the residue. The resulting mixture was extracted with DCM (50 mL), washed with a saturated solution of $NaHCO_3$ (3×30 mL) and brine (3×20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **19** as a colorless oil (710 mg, 99% yield). This oil was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.04-8.03 (m, 1H), 7.97-7.94 (m, 1H), 7.59-7.56 (app. d, 1H), 7.45-7.39 (app. t, 1H), 4.82 (d, 1H, *J* 12.3 Hz), 4.72 (t, 1H, *J* 3.6 Hz), 4.54 (d, 1H, *J* 12.0 Hz), 3.95-3.84 (m, 4H), 3.59-3.52 (m, 1H), 1.94-1.51 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 167.2, 139.0, 132.4, 130.5, 129.0, 128.9, 128.6, 98.1, 94.8, 68.5, 63.6, 63.1, 62.3, 52.3, 31.1, 30.9, 30.7, 25.6, 20.0, 19.5.

3-(Tetrahydropyran-2-yloxymethyl)benzoic acid (20). A mixture of **19** (720 mg, 2.86 mmol), a 10% solution of KOH (8.7 mL, 11.4 mmol, 4 equiv.) and MeOH (14 mL) was refluxed at 90 °C for 17 h. The reaction mixture was evaporated *in vacuo* and water (20 mL) was added to the residue. The resulting mixture was washed with

EtOAc (3×20 mL), cooled to 0 °C on ice bath and the pH was adjusted to 4.0 with a 25% solution of $KHSO_4$. The resulting mixture was extracted with DCM (3×30 mL), the combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **20** as a colorless oil (452 mg, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.11 (s, 1H), 8.03 (d, 1H, *J* 7.5 Hz), 7.63 (d, 1H, *J* 7.8 Hz) 7.46 (t, 1H, *J* 7.8 Hz), 4.85 (d, 1H, *J* 12.3 Hz), 4.75 (t, 1H, *J* 3.6 Hz), 4.56 (d, 1H, *J* 12.0 Hz), 3.97-3.89 (m, 1H), 3.61-3.54 (m, 1H), 1.92-1.53 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 171.9, 139.1, 133.2, 129.7, 129.6, 129.5, 128.7, 98.2, 68.5, 62.3, 30.7, 25.6, 21.2, 19.4.

A general procedure V, synthesis of esters: Hexyl 3-(tetrahydropyran-2-yloxymethyl)benzoate (21a). A mixture of **20** (110 mg, 0.48 mmol) and CDI (93 mg, 0.57 mmol, 1.2 equiv.) in dry DMF (3.20 mL) was stirred at room temperature for 1 h. 1-Hexanol (90 μL, 0.73 mmol, 1.5 equiv.), DMAP (6 mg, 0.05 mmol, 0.1 equiv.) and DBU (72 μL, 0.48 mmol, 1 equiv.) were added to the reaction mixture that was stirred at 40 °C for 21 h. The reaction was quenched with the addition of an ice water mixture (10 mL) and the resulting mixture was extracted with EtOAc (3×20 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (2×20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude **21a** as a colorless oil. The crude ester was used in the subsequent deprotection step without further purification and the full product analysis was carried out for the product (**22a**).

2-Methylpentyl 3-(tetrahydropyran-2-yloxymethyl)benzoate (21b). The general procedure V for the synthesis of **21a** was used except that 2-methyl-1-pentanol (90

μL, 0.73 mmol, 1.5 equiv.) was used. After work up a colorless oil (**21b**) could be obtained. The crude ester was used in the subsequent deprotection step without further purification and the full product analysis was carried out for the product (**22b**).

1-Ethylpentyl 3-(tetrahydropyran-2-yloxymethyl)benzoate (21c). The general procedure V for the synthesis of **21a** was used except that 3-heptanol (102 μL, 0.73 mmol, 1.5 equiv.) was used. After work up a colorless oil (**21c**) could be obtained. The crude ester was used in the subsequent deprotection step without further purification and the full product analysis was carried out for the product (**22c**).

A general procedure VI, deprotection of the THP ethers: Hexyl 3-(hydroxymethyl)benzoate (22a). A mixture of the crude **21a** and Dowex 50W×8 (300 mg) in MeOH (3 mL) was stirred at 40 °C for 17 hours. The Dowex 50W×8 was filtered off and the filtrate was evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 1:1) to give **22a** as a colorless oil (85 mg, 75% yield for two steps). R_f 0.11 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.02 (s, 1H), 7.97-7.93 (m, 1H), 7.57-7.55 (m, 1H) 7.42 (t, 1H, *J* 7.8 Hz), 4.73 (s, 2H), 4.30 (t, 2H, *J* 6.9 Hz), 1.80-1.71 (m, 2H), 1.46-1.22 (m, 6H), 0.87 (t, 3H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 171.9, 139.1, 133.2, 129.7, 129.6, 129.5, 128.7, 98.2, 68.5, 62.3, 30.7, 25.6, 21.2, 19.4.

2-Methylpentyl 3-(hydroxymethyl)benzoate (22b). The general procedure VI was followed except that **21b** was used. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 2:1) to give **22b** as a colorless oil (77 mg, 68% yield for two steps). R_f 0.19 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300

MHz, $CDCl_3$): δ_{ppm} 7.99 (s, 1H), 7.95-7.16 (m, 1H), 7.54 (d, 1H, *J* 7.5 Hz), 7.40 (t, 1H, *J* 7.5 Hz), 4.71 (s, 2H), 4.18 (dd, 1H, *J* 5.7, 10.8 Hz), 4.07 (dd, 1H, *J* 6.9, 10.8 Hz), 1.98-1.87 (m, 2H), 1.47-1.14 (m, 4H), 1.00 (d, 3H, *J* 6.6 Hz), 0.91 (t, 3H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.9, 141.5, 131.5, 130.8, 128.8, 128.7, 128.0, 70.2, 64.8, 35.8, 32.6, 20.1, 17.1, 14.4.

1-Ethylpentyl 3-(hydroxymethyl)benzoate (22c). The general procedure VI was followed except that **21c** was used. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 2:1) to give **22c** as a colorless oil (78 mg, 65% yield for two steps). R_f 0.25 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.81-7.94 (m, 3H), 7.56-7.53 (m, 1H), 7.41 (t, 1H, *J* 7.8 Hz), 5.10-5.02 (m, 1H), 4.72 (s, 2H), 2.45 (bs, 1H), 1.73-1.64 (m, 4H), 1.33-1.31 (m, 4H), 0.95-0.85 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 166.6, 141.4, 131.4, 131.2, 128.9, 128.7, 128.0, 76.5, 64.9, 33.5, 27.7, 27.2, 22.8, 14.1, 9.8.

A general procedure VII, synthesis of the amides: *N,N'-Bis*[3-(trifluoromethyl)benzyl] 5-(tetrahydropyran-2-yloxymethyl)isophthalamide (23a). To a solution of **4** (250 mg, 0.89 mmol) and DIPEA (340 μL, 1.96 mmol, 2.2 equiv.) in dry DCM (5 mL) was added EDC (380 mg, 1.96 mmol, 2.2 equiv.) and HOBt (270 mg, 1.96 mmol, 2.2 equiv.). The reaction mixture was stirred at rt for 30 min. 3-(Trifluoromethyl)benzylamine (281 μL, 1.96 mmol, 2.2 equiv.) was added to the reaction mixture and it was stirred at rt for 3 h and at 40 °C for 40 min. DCM (30 mL) was added to the reaction mixture and the organic phase was washed with saturated $NaHCO_3$ solution (3×15 mL), 1 M HCl solution (2×10 mL), water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the

crude **23a** as a yellow oil. The crude diamide was used in the subsequent deprotection step without further purification and the full product analysis was carried out for the product (**24a**).

***N,N′*-Dihexyl 5-(tetrahydropyran-2-yloxymethyl)isophthalamide (23b).** The general procedure VII was followed except that hexylamine (180 μL, 1.37 mmol) and DCM (5 mL) were used. The reaction mixture was stirred at 40 °C for 23 h and after work up a colorless oil (**23b**) was obtained. The crude diamide was used in the subsequent deprotection step without further purification and the full product analysis was carried out for the product (**24b**).

***N,N′-Bis*[3-(trifluoromethyl)benzyl] 5-(hydroxymethyl)isophthalamide (24a).** The general procedure III was followed except that **23a** was used and the reaction mixture was stirred for 23 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 2:1 → 0:1) to give **24a** as a white solid (179 mg, 39% yield for two steps). R_f 0.49 (EtOAc). mp 170.5-171.6 °C; ^{1}H NMR (300 MHz, CD_3OD): δ_{ppm} 8.25 (app. t, 1H), 8.03 (t, 2H, *J* 0.9 Hz), 7.67 (s, 2H), 7.63 (d, 2H, *J* 7.2 Hz), 7.58-7.49 (m, 4H), 4.72 (s, 2H), 4.64 (s, 4H); ^{13}C NMR (75.4 MHz, CD_3OD): δ_{ppm} 169.4, 144.4, 141.6, 136.1, 132.4, 130.4, 129.7, 126.2, 125.3, 125.0, 125.0, 64.3, 44.2; Anal. ($C_{25}H_{20}F_6N_2O_3$) C, H: calcd, 3.95; found, 3.92; N: calcd, 5.49; found, 5.43.

***N,N′*-Dihexyl 5-(hydroxymethyl)isophthalamide (24b).** The general procedure III was followed except that **23b** was used and the reaction mixture was stirred for 24 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 1:1 → 0:1) to give **24b** as a white solid (62 mg, 28% yield for two

steps). R_f 0.40 (EtOAc). mp 119.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.91 (bs, 1H), 7.72 (d, 2H, *J* 1.5 Hz), 6.74 (t, 2H, *J* 5.7 Hz), 4.60 (s, 2H), 3.39 (dd, 4H, *J* 7.2, 13.2 Hz), 3.02 (bs, 1H), 1.63-1.54 (m, 4H), 1.40-1.25 (m, 12H), 0.88 (t, 6H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 167.3, 142.5, 135.2, 128.1, 124.4, 64.1, 40.5, 31.7, 29.7, 26.9, 22.8, 14.2; Anal. ($C_{21}H_{34}N_2O_3$) C: calcd, 69.58, found, 66.23, H: calcd, 9.45; found, 9.16; N: calcd, 7.73; found, 7.36.

3,5-Diheptanamidobenzyl heptanoate (26). To a mixture of 3,5-aminobenzyl alcohol dihydrochloride (**25**) (422 mg, 2 mmol) and dry pyridine (20 mL) in dry DCM (20 mL) was added heptanoyl chloride (620 μL, 4 mmol, 2 equiv.). The reaction mixture was stirred at rt for 20 h. The reaction mixture was evaporated *in vacuo*, EtOAc (30 mL) was added to the residue and the resulting mixture was washed with a 4 M HCl solution (3×30 mL), a saturated $NaHCO_3$ solution (3×30 mL), brine (2×20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 2:1) to give **26** as a white solid (160 mg, 17% yield). R_f 0.89 (*n*-hexane/EtOAc, 1:1). mp 104.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.76 (s, 3H), 7.52 (s, 2H), 7.29 (app. d, 2H), 5.00 (s, 2H), 2.30 (m, 6H), 1.73-1.56 (m, 6H), 1.39-1.23 (m, 18H), 0.90-0.84 (m, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 174.0, 172.0, 138.9, 137.9, 115.0, 110.8, 100.3, 65.9, 38.0, 34.4, 31.7, 31.6, 29.1, 29.0, 25.7, 25.0, 22.7, 14.2.

***N,N'*-[5-(hydroxymethyl)-1,3-phenylene]diheptanamide (27).** The compound **26** (131 mg, 0.28 mmol) was hydrolysed using EtOH (10 mL) and a 10% KOH solution (310 μL, 0.56 mmol, 2 equiv.). The reaction mixture was stirred at rt for 3.5 h and

evaporated *in vacuo*. EtOAc (40 mL) and a saturated solution of $NaHCO_3$ (20 mL) were added to the residue, the organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **27** as a white solid (124 mg, 95% yield). R_f 0.13 (*n*-hexane/EtOAc, 1:1). mp 162.5 °C; ^{1}H NMR (300 MHz, CD_3OD): δ_{ppm} 7.77 (t, 1H, *J* 1.8 Hz), 7.32 (d, 2H, *J* 1.8 Hz), 4.56 (s, 2H), 2.36 (t, 4H, *J* 7.5 Hz), 1.74-1.64 (qn, 4H, *J* 7.5 Hz), 1.44-1.29 (m, 12H), 0.92 (t, 6H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, CD_3OD): δ_{ppm} 174.8, 144.1, 140.3, 115.4, 112.1, 65.0, 38.0, 32.7, 30.0, 26.9, 23.6, 14.4; DEPT 115.4 (CH), 112.1 (CH), 65.0 (CH_2), 38.0 (CH_2), 32.7 (CH_2), 30.0 (CH_2), 26.9 (CH_2), 23.6 (CH_2), 14.4 (CH_3); Anal. ($C_{21}H_{34}N_2O_3$) C: calcd, 69.58, found, 69.26, H: calcd, 9.45; found, 9.30; N: calcd, 7.73; found, 7.52.

Methyl 3,5-diaminobenzoate (29). A mixture of methyl 3,5-dinitrobenzoate (**28**) (900 mg, 4 mmol), 10% Pd/C (20 mg), EtOAc (20 mL) and EtOH (10 mL) was hydrogenated for 22 h. The reaction mixture was filtered through a pad of Celite 545, the pad was washed with MeOH and EtOAc and the filtrate was evaporated *in vacuo* to give **29** as a brown solid (656 mg, 99% yield). mp 130.1-130.6 °C; ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ_{ppm} 6.42 (d, 2H, *J* 1.2 Hz), 6.32 (t, 1H, *J* 1.2 Hz), 3.82 (s, 3H); ^{13}C NMR (75.4 MHz, DMSO-*d*$_6$): δ_{ppm} 167.3, 149.3, 130.5, 103.6, 51.5; DEPT 103.6 (CH), 51.5 (CH_3).

Methyl 3,5-diheptanoylaminobenzoate (30). Heptanoyl chloride (410 μL, 2.65 mmol, 2.2 equiv.) was added dropwise under argon to a solution of **29** (200 mg, 1.20 mmol), DIPEA (453 μL, 2.65 mmol, 2.2 equiv.) and DCM (2 mL) and the reaction mixture was stirred at rt for 21 h. The reaction was quenched by the addition of DCM (15 mL) and an ice water mixture (10 mL), the resulting mixture was washed with

water (2×10 mL), 1 M HCl solution (3×10 mL), saturated $NaHCO_3$ solution (3×10 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 2:1) to give **30** as a yellow oil (226 mg, 48% yield). R_f 0.34 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 8.40 (bs, 2H), 8.03 (s, 1H), 7.89 (s, 2H), 3.81 (s, 3H), 2.32 (t, 4H, *J* 7.5 Hz), 1.65 (qn, 4H, *J* 7.5 Hz), 1.32-1.24 (m, 12H), 0.83 (t, 6H, *J* 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 172.6, 167.0, 138.9, 131.1, 117.0, 116.4, 52.4, 37.7, 31.7, 29.1, 25.7, 22.6, 14.1; Anal. ($C_{22}H_{34}N_2O_3$) C: calcd, 67.66, found, 67.30, H: calcd, 8.78; found, 8.63; N: calcd, 7.17; found, 7.05.

Methyl 3-(hydroxymethyl)-5-nitrobenzoate (32). $BH_3{\cdot}SMe_2$ (2.53 mL, 26.6 mmol, 2 equiv.) was added dropwise to a solution of 5-nitroisophthalic acid monomethyl ester (**31**) (3.00 g, 13.3 mmol) in dry THF (75 mL) during 10 min at 0 °C. The reaction mixture was stirred at rt for 19 h, at 60 °C for 2 h, the reaction was quenched with the addition of a solution of acetic acid and water (800 μL, 1:1) and the resulting mixture was stirred for 40 min. A saturated solution of $NaHCO_3$ (5 mL) was added to the mixture and it was evaporated *in vacuo*. EtOAc (50 mL) was added to the residue and it was washed with saturated $NaHCO_3$ solution (3×25 mL) and brine (2×20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 1:1) to give **32** as a white solid (2.41 g, 86% yield). R_f 0.40 (*n*-hexane/EtOAc, 1:1) mp 78.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.76 (dd, 1H, *J* 1.5, 2.1 Hz), 8.45-8.44 (m, 1H), 8.36-8.34 (m, 1H), 4.89 (d, 2H, *J* 0.6 Hz), 3.98 (s, 3H), 2.02 (bs, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.2, 148.7, 143.7, 133.3, 132.1, 125.5, 123.7, 63.7, 53.1;

DEPT 148.7, 143.7, 133.3 (CH), 132.1, 125.5 (CH), 123.7 (CH), 63.7 (CH_2), 53.1 (CH_3).

Methyl 3-(tetrahydropyran-2-yloxymethyl)-5-nitrobenzoate (33). A solution of **32** (1.99 g, 9.44 mmol), DHP (1.72 mL, 18.9 mmol, 2 equiv.), PPTS (240 mg, 0.94 mmol, 0.1 equiv.) and DCE (20 mL) was stirred for 25 h. The reaction was quenched by the addition of water (60 mL). The resulting mixture was extracted with DCM (3×60 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (3×60 mL) and brine (2×60 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **33** as a yellow solid (2.76 g, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.74 (app. t, 1H), 8.42-8.41 (m, 1H), 8.32 (s, 1H), 4.90 (d, 1H, *J* 13.2 Hz), 4.74 (t, 1H, *J* 3.3 Hz), 4.61 (d, 1H, *J* 12.6 Hz), 3.97 (s, 3H), 3.90-3.83 (m, 1H), 3.60-3.52 (m, 1H), 1.89-1.50 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 165.1, 148.6, 141.6, 134.1, 131.9, 126.3, 123.6, 98.6, 94.8, 67.4, 63.1, 62.5, 53.0, 30.8, 30.5, 25.6, 25.5, 19.9, 19.4; DEPT 134.1 (CH), 131.9, 126.3 (CH), 123.6 (CH), 98.6 (CH), 94.8 (CH), 67.4 (CH_2), 63.1 (CH_2), 62.5 (CH_2), 53.0 (CH_3), 30.8 (CH_2), 30.5 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 19.9 (CH_2), 19.4 (CH_2).

Methyl 3-(tetrahydropyran-2-yloxymethyl)-5-aminobenzoate (34). A mixture of **33** (2.80 g, 9.47 mmol) in EtOH (20 mL) and THF (10 mL) was hydrogenated with 10% Pd/ C (20 mg) at rt for 23 h and filtered through a pad of Celite 545. The pad was washed with MeOH and THF and the filtrate was evaporated *in vacuo* to give the crude **34** as a brownish liquid (2.51 g, quant. yield). The amine was used in the next reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.44 (s, 1H), 7.30 (s, 1H), 6.93 (s, 1H), 4.77 (d, 1H, *J* 12 Hz), 4.74 (t, 1H, *J* 3.5 Hz), 4.49 (d, 1H, *J*

12.5 Hz), 3.96-3.94 (m, 1H), 3.92 (s, 3H), 3.83 (bs, 2H), 3.61-3.57 (m, 1H), 1.94-1.57 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 167.3, 146.8, 139.8, 131.4, 119.3, 118.8, 115.2, 98.1, 68.6, 62.4, 52.3, 30.7, 25.7, 19.6; DEPT 119.2 (CH), 118.8 (CH), 115.2 (CH), 98.0 (CH), 68.6 (CH_2), 62.4 (CH_2), 52.4 (CH_3), 30.7 (CH_2), 25.6 (CH_2), 19.5 (CH_2).

A general procedure VIII, synthesis of the amides: Methyl 3-(undec-10-enoylamino)-5-(tetrahydropyran-2-yloxymethyl)benzoate (35a). To a solution of undecylenic acid (250 μL, 1.24 mmol, 1.1 equiv.) and DIPEA (213 μL, 1.24 mmol, 1.1 equiv.) in dry DCM (9 mL) was added EDC (238 mg, 1.24, 1.1 equiv.) and HOBt (168 mg, 1.24 mmol, 1.1 equiv.). The reaction mixture was stirred at rt for 30 min and **34** (300 mg, 1.13 mmol) was added to the reaction mixture. The resulting mixture was stirred at 40 °C for 21 h and DCM (30 mL) was added to the reaction mixture. The organic phase was washed with saturated $NaHCO_3$ solution (3×15 mL), 1 M HCl solution (2×10 mL), water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 11:1 → 1:2) to give **35a** as a colorless oil (245 mg, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.01 (s, 1H), 7.89 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 5.85-5.71 (m, 2H), 5.00-4.88 (m, 2H), 4.76 (d, 1H, *J* 12.6 Hz), 4.69 (t, 1H, *J* 3.3 Hz), 4.48 (d, 1H, *J* 12.6 Hz), 3.92-3.84 (m, 4H), 3.56-3.49 (m, 1H), 2.38-2.29 (m, 2H), 2.05-1.97 (m, 2H), 1.88-1.48 (m, 6H), 1.34-1.25 (m, 12H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 171.7, 166.9, 140.0, 139.3, 138.6, 131.0, 124.4, 123.6, 119.9, 114.3, 98.2, 68.4, 62.3, 52.4, 37.8, 34.0, 33.9, 30.6, 29.5, 29.4, 29.4, 29.3, 29.2, 29.0, 25.7, 25.5, 24.9, 19.4.

Methyl 3-(nonanoylamino)-5-(tetrahydropyran-2-yloxymethyl)benzoate (35b). The general procedure VIII was followed except that nonanoic acid (340 μL, 2.49 mmol, 1.1 equiv.) was used and the reaction was stirred at 40 °C for 22 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 11:1 → 1:2) to give **35b** as a colorless oil (531 mg, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.01 (s, 1H), 7.88 (s, 1H), 7.75 (s, 1H), 7.63 (s, 1H), 4.77 (d, 1H, *J* 12.3 Hz), 4.69 (t, 1H, *J* 3.6 Hz), 4.49 (d, 1H, *J* 12.3 Hz), 3.93-3.85 (m, 4H), 3.57-3.50 (m, 1H), 2.38-2.30 (m, 2H), 1.90-1.50 (m, 8H), 1.30-1.25 (m, 10H), 0.86 (t, 3H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 171.9, 166.9, 140.0, 138.6, 131.0, 124.4, 123.6, 119.9, 98.2, 68.4, 62.4, 52.4, 37.9, 34.0, 32.0, 30.7, 29.5, 29.4, 29.4, 29.3, 29.3, 25.7, 25.6, 24.9, 22.8, 19.5, 14.2; DEPT 140.0, 138.6, 131.0, 124.4 (CH), 123.6 (CH), 119.9 (CH), 98.2 (CH), 68.4 (CH_2), 62.4 (CH_2), 52.4 (CH_3), 37.9 (CH_2), 34.0 (CH_2), 32.0 (CH_2), 30.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 24.9 (CH_2), 22.8 (CH_2), 19.5 (CH_2), 14.2 (CH_3).

Methyl 3-(heptanoylamino)-5-(tetrahydropyran-2-yloxymethyl)benzoate (35c). The general procedure VIII was followed except that heptanoic acid (177 μL, 1.24 mmol, 1.1 equiv.) was used and the reaction was stirred at 40 °C for 22 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 11:1 → 1:2) to give **35c** as a yellow oil (178 mg, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.00 (s, 1H), 7.88 (s, 1H), 7.77 (s, 1H), 7.28 (s, 1H), 4.79 (d, 1H, *J* 12.3 Hz), 4.71 (t, 1H, *J* 3.6 Hz), 4.51 (d, 1H, *J* 12.3 Hz), 3.94-3.87 (m, 4H), 3.59-3.52 (m, 1H), 2.37 (t, 2H, *J* 7.5 Hz), 1.91-1.52 (m, 8H), 1.42-1.26 (m, 6H), 0.89 (t, 3H, *J* 6.9 Hz);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 171.7, 166.9, 140.1, 138.5, 131.1, 124.6, 123.5, 119.9, 98.3, 68.4, 62.4, 52.4, 38.0, 31.7, 30.7, 29.1, 25.7, 25.6, 22.7, 19.5, 14.2.

Methyl 3-(2,2-dimethylpropanoylamino)-5-(tetrahydropyran-2-yloxymethyl)-benzoate (35d). The general procedure VIII was followed except that pivalic acid (257 mg, 2.49 mmol, 1.1 equiv) was used and the reaction was stirred at 40 °C for 23 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 11:1 → 0:1) to give **35d** as a yellow oil (116 mg, 15% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.03 (t, 1H, *J* 1.8 Hz), 7.88 (app. t, 1H), 7.78 (s, 1H), 7.42 (bs, 1H), 4.80 (d, 1H, *J* 12.0 Hz), 4.71 (t, 1H, *J* 3.6 Hz), 4.51 (d, 1H, *J* 12.0 Hz), 3.94-3.87 (m, 4H), 3.59-3.52 (m, 1H), 1.91-1.52 (m, 6H), 1.32 (s, 9H);^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 177.0, 166.9, 140.0, 138.5, 131.0, 124.6, 123.8, 120.2, 98.2, 68.4, 62.4, 52.4, 39.8, 30.6, 27.7, 25.5, 19.5.

Methyl 3-(acetylamino)-5-(tetrahydropyran-2-yloxymethyl)benzoate (35e). The general procedure VIII was followed except that acetic acid (71 μL, 1.24 mmol, 1.1 equiv) was used and the reaction was stirred at 40 °C for 21 h. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 0:1) to give **35e** as a yellow oil (44 mg, 13% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.89 (s, 2H), 7.88 (s, 1H), 7.74 (s, 1H), 4.77 (d, 1H, *J* 12.6 Hz), 4.69 (t, 1H, *J* 3.9 Hz), 4.48 (d, 1H, *J* 12.3 Hz), 3.93-3.85 (m, 4H), 3.57-3.50 (m, 1H), 2.17 (s, 3H), 1.88-1.49 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 169.0, 166.9, 140.1, 138.6, 131.0, 124.5, 123.7, 120.0, 98.3, 68.4, 62.4, 52.4, 30.7, 25.5, 24.6, 19.5.

Methyl 3-(undec-10-enoylamino)-5-(hydroxymethyl)benzoate (36a). A mixture of **35a** (38 mg, 0.09 mmol) and Dowex 50W×8 (210 mg) in MeOH (3 mL) was

stirred at 40 °C for 21 h. The Dowex 50W×8 was filtered off and the filtrate was evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 2:1 → 0:1) to give **36a** as a yellow solid (28 mg, 92% yield). R_f 0.11 (*n*-hexane/EtOAc, 2:1). mp 82.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.94 (s, 1H), 7.85 (s, 1H), 7.75 (s, 1H), 7.71 (s, 1H), 5.84-5.75 (m, 1H), 5.00-4.96 (m, 1H), 4.93-4.91 (m, 1H), 4.66 (s, 2H), 3.88 (s, 3H), 2.43 (bs, 1H), 2.35 (t, 2H, *J* 7.5 Hz), 2.02 (q, 2H, *J* 7.0 Hz), 1.70 (qn, 2H, *J* 7.5 Hz), 1.36-1.28 (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 172.0, 166.9, 142.6, 139.3, 138.6, 131.2, 123.7, 122.8, 120.0, 114.4, 64.7, 52.5, 37.9, 34.0, 29.5, 29.5, 29.4, 29.3, 29.1, 25.7; DEPT 139.3 (CH), 123.7 (CH), 122.8 (CH), 120.0 (CH), 114.4 (CH_2), 64.7 (CH_2), 52.5 (CH_3), 37.9 (CH_2), 34.0 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 25.7 (CH_2); Anal. ($C_{20}H_{29}NO_4$) C, H: calcd, 8.41; found, 8.32; N: calcd, 4.03; found, 3.84.

Methyl 3-(nonanoylamino)-5-(hydroxymethyl)benzoate (36b). A mixture of **35b** (99 mg, 0.24 mmol) and Dowex 50W×8 (530 mg) in MeOH (6 mL) was stirred at 40 °C for 21 h. The Dowex 50W×8 was filtered off and the filtrate was evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 2:1 → 1:1) to give **36b** as a white solid (57 mg, 73% yield). R_f 0.12 (*n*-hexane/EtOAc, 2:1). mp 93.8-94.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.99 (s, 1H), 7.95 (s, 1H), 7.82 (s, 1H), 7.67 (s, 1H), 4.63 (s, 2H), 3.86 (s, 3H), 2.72 (bs, 1H), 2.34 (t, 2H, *J* 7.8 Hz), 1.69 (qn, 2H, *J* 7.5 Hz), 1.40-1.18 (m, 10H), 0.86 (t, 3H, *J* 6.6 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 172.4, 167.0, 142.6, 138.6, 130.9, 123.6, 123.0, 120.1, 64.5, 52.5, 37.8, 32.0, 29.5, 29.5, 29.3, 25.7, 22.8, 14.2; DEPT 123.7

(CH), 123.1 (CH), 120.2 (CH), 62.6 (CH_2), 52.5 (CH_3), 37.8 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 25.8 (CH_2), 22.9 (CH_2), 14.2 (CH_3); Anal. ($C_{18}H_{27}NO_4$) C: calcd, 67.26; found, 66.99; H: calcd, 8.47; found, 8.41; N: calcd, 4.36; found, 4.23.

Methyl 3-(heptanoylamino)-5-(hydroxymethyl)benzoate (36c). A mixture of **35c** (178 mg, 0.47 mmol) and Dowex 50W×8 (500 mg) in MeOH (5 mL) was stirred at 40 °C for 19 h. The Dowex 50W×8 was filtered off and the filtrate was evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 1:1) to give **36c** as a white solid (94 mg, 68% yield). R_f 0.11 (*n*-hexane/EtOAc, 2:1). mp 96.5-97.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.08 (s, 1H), 7.95 (s, 1H), 7.80 (s, 1H), 7.66 (s, 1H), 4.61 (s, 2H), 3.86 (s, 3H), 2.85 (bs, 1H), 2.34 (t, 2H, *J* 7.5 Hz), 1.68 (qn, 2H, *J* 7.5 Hz), 1.37-1.25 (m, 6H), 0.86 (t, 3H, *J* 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 172.5, 167.1, 142.6, 138.6, 130.9, 123.6, 123.0, 120.1, 64.5, 52.5, 37.7, 31.7, 29.1, 25.7, 22.7, 14.2; Anal. ($C_{16}H_{23}NO_4$) C, H: calcd, 7.90; found, 7.79; N: calcd, 4.77; found, 4.74.

Methyl 3-(2,2-dimethylpropanoylamino)-5-(hydroxymethyl)benzoate (36d). A mixture of **35d** (116 mg, 0.33 mmol) and Dowex 50W×8 (500 mg) in MeOH (5 mL) was stirred at 40 °C for 24 h. The Dowex 50W×8 was filtered off and the filtrate was evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 4:1 → 1:1) to give **36d** as a white solid (68 mg, 77% yield). R_f 0.31 (*n*-hexane/EtOAc, 1:1). mp 130.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.92 (s, 1H), 7.85 (s, 1H), 7.71-7.70 (m, 1H), 7.62 (bs, 1H), 4.66 (s, 2H), 3.88 (s, 3H), 2.60 (bs, 1H), 1.31 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm}

177.3, 166.9, 142.6, 138.5, 131.0, 123.7, 123.2, 120.4, 64.6, 52.4, 39.8, 27.7; Anal. ($C_{14}H_{19}NO_4$) C: calcd, 63.38; found, 62.61; H: calcd, 7.22; found, 6.91; N: calcd, 5.28; found, 5.09.

Methyl 3-(acetylamino)-5-(hydroxymethyl)benzoate (36e). A mixture of **35e** (43 mg, 0.14 mmol) and Dowex 50W×8 (500 mg) in MeOH (5 mL) was stirred at 40 °C for 24 h. The Dowex 50W×8 was filtered off and the filtrate was evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 1:1 → 0:1) to give **36e** as a white solid (28 mg, 89% yield). R_f 0.48 (EtOAc). mp 149.9-150.1 °C; ^{1}H NMR (300 MHz, CD_3OD): δ_{ppm} 8.14 (t, 1H, *J* 1.8 Hz), 7.81 (app. t, 1H), 7.75 (t, 1H, *J* 1.8 Hz), 4.63 (s, 2H), 3.90 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75.4 MHz, CD_3OD): δ_{ppm} 171.8, 168.3, 144.4, 140.4, 132.0, 124.2, 123.7, 120.7, 64.5, 52.7, 23.8; DEPT 124.2 (CH), 123.7 (CH), 120.7 (CH), 64.5 (CH_2), 52.7 (CH_3), 23.8 (CH_3); Anal. ($C_{11}H_{13}NO_4$) C, H: calcd, 5.87; found, 5.60; N: calcd, 6.27; found, 6.13.

Monomethyl 5-(tetrahydropyran-2-yloxymethyl)isophthalate (37). A mixture of **3** (230 mg, 0.69 mmol), KOH (39 mg, 0.69 mmol, 1 equiv.) and MeOH (3 mL) was stirred at 40 °C for 20 h. The solvent was evaporated *in vacuo*, water (50 mL) was added to the residue and the resulting mixture was washed with DCM (50 mL). The aqueous phase was cooled to 0 °C on ice bath and the pH adjusted to 4.0 with 25% $KHSO_4$ solution. The resulting mixture was extracted with EtOAc (2×50 mL) and evaporated *in vacuo* to give **37** as an oil (137 mg, 65% yield). NMR studies showed a mixture of ethyl and methyl ester (~15% and 85% respectively). This was used in the next reaction without of further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 11.76

(bs, 1H), 8.67 (app. t, 1H), 8.28 (dd, 2H, *J* 1.5, 4.8 Hz), 4.88 (d, 1H, *J* 12.3 Hz), 4.77 (t, 1H, *J* 3.3 Hz), 4.56 (d, 1H, *J* 12.6 Hz), 3.95 (s, 3H), 3.93-3.88 (m, 1H), 3.62-3.55 (m, 1H), 1.93-1.54 (m, 6H), 1.42.

Methyl 5-(tetrahydropyran-2-yloxymethyl)-*N*-[3-(trifluoromethyl)benzyl]-isophthalamate (38). To a mixture of **37** (140 mg, 0.47 mmol) and DIPEA (90 μL, 0.51 mmol, 1.1 equiv.) in dry DCM (15 mL) was added EDC (100 mg, 0.51 mmol, 1.1 equiv.) and HOBt (70 mg, 0.51 mmol, 1.1 equiv.). The reaction mixture was stirred at rt for 30 min. 3-(Trifluoromethyl)benzylamine (70 μL, 0.51 mmol, 1.1 equiv.) was added to the reaction mixture and the resulting mixture was stirred at rt for 160 min and at 40 °C for 40 min. DCM (30 mL) was added to the reaction mixture and the organic phase was washed with saturated $NaHCO_3$ solution (3×15 mL), 1 M HCl solution (2×10 mL), water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude **38** as a yellowish oil. The crude product was used in the next reaction without further purification and the full product analysis was carried out for the product (**39**).

Methyl 5-(hydroxymethyl)-*N*-[3-(trifluoromethyl)benzyl]isophthalamate (39). A mixture of the crude **38** and Dowex 50W×8 (750 mg) in MeOH (8 mL) was stirred at 40 °C for 23 h. The Dowex 50W×8 was filtered off and the filtrate was evaporated *in vacuo*. The crude product was purified with flash SiO_2 column chromatography (*n*-hexane/EtOAc, 2:1 → 0:1) to give **39** as a colorless oil. NMR showed ~16% ethyl ester and 84% methyl ester (71 mg, 41% yield for two steps). R_f 0.04 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.22-8.20 (m, 1H), 8.02 (s, 1H), 7.97 (s, 1H), 7.56 (s, 1H), 7.51 (d, 2H, *J* 7.8 Hz), 7.42 (t, 1H, *J* 7.5 Hz), 7.25-

7.23 (m, 1H), 4.65 (s, 2H), 4.62 (s, 2H), 3.86 (s, 2.44H), 3.15 (bs, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_{ppm} 167.0, 166.5, 166.0, 142.6, 142.5, 139.2, 134.6, 131.4, 131.1, 130.9, 130.7, 130.1, 130.0, 129.4, 126.9, 125.9, 124.8, 124.7, 124.7, 124.6, 124.6, 124.5, 122.3, 118.7, 64.0, 61.7, 52.6, 43.8; Anal. ($C_{19}H_{18}F_3NO_4$) C: calcd, 59.84; found, 59.58; H: calcd, 4.76; found, 4.56; N: calcd, 3.67; found, 3.62.