Supporting Information for *ChemBioChem* F 516

General Experimental Methods. Proton NMR spectra were run at 300 MHz on a Varian Gemini-300 or at 500 MHz on a Bruker AMX-500, and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. Electrospray mass spectra were recorded on a PE Biosystems Mariner or a Micromass-LCT spectrometer. Column chromatography was performed using Merck Kieselgel 60 (230-400 mesh) and analytical thin-layer chromatography was conducted with Merck Kieselgel 60 F_{254} plates. A Waters 600 or 600-Delta series HPLC was used for analytical and preparative HPLC, employing either a Phenomenex C18 reversed phase analytical column (5µ Luna 250 x 4.6 mm; Catalog No. 00G-4252-E0) or a Phenomenex C18 reversed phase semi-prep column (5µ Luna 250 x 21.2 mm; Catalog No. 00G-4273-P0). Analytical elutions were performed at a flow rate of 1 mL/min, and used either a gradient of 50%/50% to 0%/100% A/B over 20 min (method A), 70%/30% to 0%/100% A/B over 20 min (method B), or isocratic conditions of 10%/90% A/B (method C), 20%/80% A/B (method D), 30%/70% A/B (method E), 40%/60% A/B (method F), 50%/50% A/B (method G), 55%/45% A/B (method H), or 60%/40% A/B (method I), where A = H_20 - 0.1% TFA and B = CH_3CN - 0.1% TFA. For reactions performed under anhydrous conditions, glassware was either oven- or flame-dried and the reaction was run under a positive pressure of argon. Tetrahydrofuran was freshly distilled from sodium/benzophenone. The reported yields are the actual isolated yields or purified material

and are not optimised. Except where noted, reagents were purchased commercially and used without further purification. Petroleum ether had a boiling range of 40-60°. IUPAC nomenclature was used to name compounds via Autonom v2.1 (Under licence from Beilstein Information Systems in CS ChemDraw Ultra).

Enzyme Assay. Compounds **2a-q** (I) were evaluated in a mixed micelle colorimetric assay[1] utilizing a commercially available assay kit used (Cayman Chemical Company MI USA (Catalog No. 765001)) that included buffer (25 mM Tris-HCl at pH 7.5, 1mg/mL BSA, 0.3 mM Triton X-100, 100 mM KCl, 10 mM $CaCl_2$), substrate (1,2-bis(heptanoylthio)-1,2-dideoxy-*sn*-glycero-3-phosphorylcholine) and DTNB. Each well had a total volume of 225 µL, containing enzyme (110 ng hnps-PLA_2-IIa), 1,2-bis(heptanoylthio)-1,2-dideoxy-*sn*-glycero-3-phosphorylcholine (PC; final concentration 1.48 mM), Triton X-100 (T; final concentration 0.013 mM) and 5,5′-dithionitrobenzoic acid (DTNB; final concentration 0.44 mM), ± inhibitor. Concentration/response curves were generated for 60 min at 37 °C in a microtiter plate format at 414 nM. Recombinant hnps PLA_2-IIa obtained was found to be homogeneous by LCMS giving a molecular weight of 13,905 Da. Mole fractions ([I]/[I] + [PC] + [T])) for 50% inhibition, $X_i(50)$, were determined in triplicate.

Crystallography. Crystals were obtained by the sitting drop method at 20° C using conditions similar to those described by Cha *et al.*[2] 8 µL

of protein solution containing 20 mg/ml protein, was mixed with 8 μL of reservoir solution (4 - 4.5 M NaCl and 0.1 M $CaCl_2$). Inhibitor **2b** was added to the drop as a solid. Crystals appeared within one week and grew over 2-4 weeks to dimensions of 0.7 mm x 0.4 mm x 0.3 mm. Data were collected at 100K by flash freezing the crystal in a N_2 gas stream. A cryoprotectant solution of 4 M NaCl and 35% glucose was used. Data were measured on a Rigaku R-AXIS IIC imaging plate system using CuKα X-radiation (λ 1.54 Å) generated from a Rigaku RU-200 rotating anode generator (46 kV, 60mA). The data were integrated and reduced using DENZO and SCALEPACK, respectively.[3]

The enzyme-inhibitor complex crystallised in space group. The unit cell dimensions were $a = b = 75.11$ Å, and $c = 50.03$ Å, $\alpha = \beta = 90°$ and $\gamma = 120°$ with two molecules in the asymmetric unit. The structure was solved with molecular replacement using pdb1poe as the reference molecule. Statistics from data processing are given in Table 1.

Table 1. Crystallographic Data Processing

Resolution	2.2 Å
R_{sym}@	0.052
(in top shell)*	(0.274)
Completeness	91.5%
(in top shell)*	(60.0%)
I/σI	18.0
(in top shell)*	(3.2)
mosaicity	0.46
No. obs (I/σI > 1)	36,103
No. unique refls	14,678
Highest Resolution	2.28-2.20 Å
Resolution range	100-2.2 Å
No. protein atoms*	1884
No. inhibitor	86
No. waters	149
No. calcium atoms	4
R-factor^	0.227
(top shell)	(0.351)
R-free**	0.259
(top shell)	(0.386)
r.m.s. ideal bond	1.35°
r.m.s. ideal	22.75°
r.m.s. ideal	0.84°
% most favourable	92.2
% disallowed	0.0

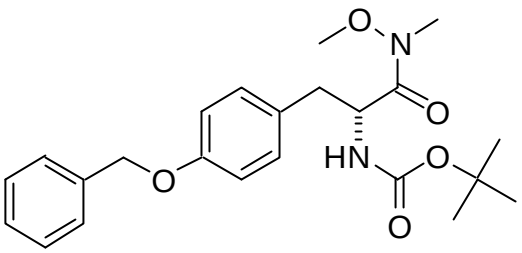
*including alternative conformations,

^$R = \Sigma \left| F_O - F_C \right| / \Sigma F_O$,

**Cross validation R-factor using 10% of data.

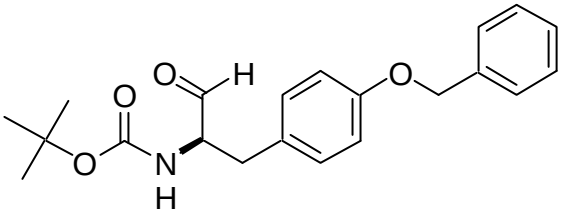
Syntheses.

Synthesis of (*R*)-[2-(4-Benzyloxy-phenyl)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester (4).



DIPEA (28.2 ml, 20.9 g, 162 mmol) was added to a stirred solution of **3** (20.0 g, 53.9 mmol), BOP (25.00 g, 56.5 mmol) and MeONHMe.HCl (5.52 g, 56.6 mmol) in DMF (300 mL). After stirring for 2 h the DMF was evaporated and the residue dissolved in EtOAc and washed with water, HCl (5 % aqueous), saturated $NaHCO_3$ solution, brine, then dried with Na_2SO_4 and evaporated to give **4** as a cream solid. This was ground to a powder (22.39 g, 100 %), mp 107.1-108.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.83 (dd, *J* = 6.2, 14.2 Hz, 1H), 3.00 (dd, *J* = 6.1, 13.6 Hz, 1H), 3.17 (s, 3H), 3.65 (s, 3H), 4.91 (br s, 1H), 5.04 (s, 2H), 5.15 (br d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.32-7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 157.7, 155.2, 137.1, 130.4, 128.9, 128.5, 127.9, 127.4, 114.7, 79.6, 70.0, 61.5, 51.6, 38.0, 32.1, 28.3.

Synthesis of (*R*)-[1-(4-Benzyloxy-benzyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (5).

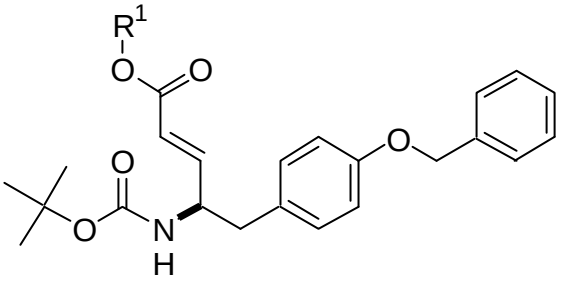


$LiAlH_4$ (916 mg, 24.1 mmol) was added cautiously and portionwise during 15 min to a stirred solution of **4** (10.00 g, 24.1 mmol) in THF (150 mL) at 0^o C under argon. The ice-bath was

removed and the mixture was stirred for 1 h, then poured onto a mixture of ice and $KHSO_4$ (1 *M*, aqueous). When the ice had melted the product was extracted into EtOAc. The combined extracts were washed with brine then dried (Na_2SO_4) and evaporated to give the aldehyde **5** as pale yellow crystals (8.51 g, 99 %), mp 100.3-101.7 °C. (An alternative workup procedure avoids evaporation of the EtOAc extract, where instead a solution of the crude aldehyde in EtOAc is used directly in the next step without prior evaporation). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.07 (m, 2H), 4.40 (m, 1H), 5.05 (s, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.33-7.45 (m, 5H), 9.63 (s, 1H), with one resonance obscured. ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 157.9, 155.4, 136.9, 130.3, 128.6, 128.0, 127.9, 127.4, 115.1, 80.2, 70.0, 60.8, 34.6, 28.3.

Synthesis of (*R*)-5-(4-Benzyloxy-phenyl)-4-tertbutoxycarbonylamino-pent-2-enoic acid methyl ester (6) (R^1 = Me)

A mixture of **5** (6.5 g, 0.018 mol) and $Ph_3P{=}CHCO_2Me$ (1 eq.) in dry THF (80 mL) was stirred at rt overnight. (Alternately, 1 eq. of $Ph_3P{=}CHCO_2Me$ can be added directly to an EtOAc solution of **5** as described above). Removal of the solvent *in vacuo* afforded a gummy residue (13.2 g) which was chromatographed (silica gel, 4:1 petroleum ether-EtOAc increasing to 1:1 petroleum ether-EtOAc toward completion) to yield **6** (R^1 = Me) (6.7 g, 89 %). ^{1}H NMR

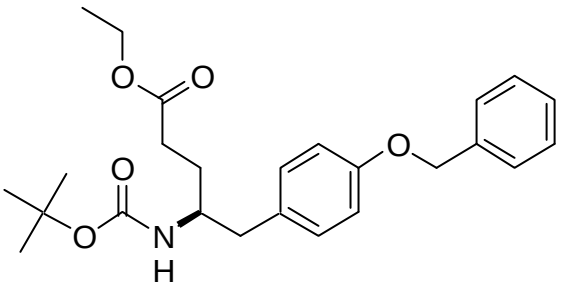


(300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.80 (m, 2H), 3.70 (s, 3H), 4.52 (br s, 2H), 5.05 (s, 2H), 5.83 (d, *J* = 15 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 15 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.28-7.48 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 157.9, 155.1, 148.2, 137.1, 130.6, 128.7, 128.1, 127.6, 120.8, 115.1, 80.0, 70.2, 52.6, 51.8, 40.1, 28.5, with one resonance obscured. ESMS m/z 412 $(M+H)^+$.

Similarly, preparation of **6** (R^1 = Et) was achieved by reaction of $Ph_3P{=}CHCO_2Et$ and **5** using the above procedure; (83% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.40 (s, 9H), 2.84 (br d, *J* = 6.2 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.52 (br s, 2H), 5.05 (s, 2H), 5.86 (dd, *J* = 1.5, 15.7 Hz, 1H), 6.91 (dd, *J* = 4.8, 15.6 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.32-7.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 157.7, 154.9, 147.7, 137.0, 130.4, 128.6, 127.9, 127.4, 121.0, 115.1, 114.9, 79.8, 70.0, 60.4, 52.4, 40.0, 28.3, 14.2. ESMS m/z 426 $(M+H)^+$.

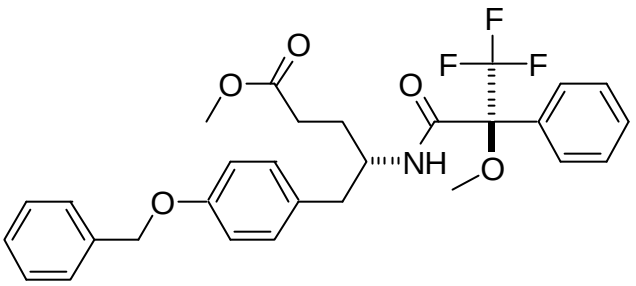
Synthesis of (*S*)-5-(4-Benzyloxy-phenyl)-4-*tert*-butoxycarbonylamino-pentanoic acid ethyl ester (7).

Compound **6** (R^1 = Et) (125 mg, 0.30 mmol) was hydrogenated over 10% Pd-C in EtOAc (30 mL). Removal of the catalyst (celite) and evaporation of the solvent afforded **7** in quantitative yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.40 (s,



9H), 1.47-1.67 (m, 1H), 1.76-1.92 (m, 1H), 2.26-2.44 (m, 2H), 2.61-2.82 (m, 2H), 3.69-3.85 (br m, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 4.30-4.43 (br d, *J* = 6.8 Hz, 1H), 5.03 (s, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.28-7.47 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 28.5, 29.3, 31.4, 41.1, 51.8, 60.6, 70.2, 79.4, 114.9, 127.6, 128.1, 128.7, 130.3, 130.6, 137.3, 155.7, 157.7, 173.8. ESMS m/z 428 $(M+H)^+$.

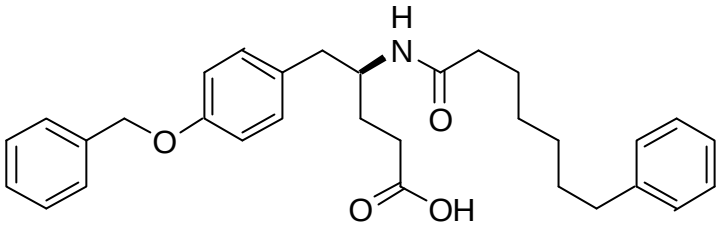
(2*R*,4*S*)-5-(4-Benzyloxy-phenyl)-4-(3,3,3-trifluoro-2-methoxy-2-phenyl-propionylamino)-pentanoic acid methyl ester



Compound **6** (R^1 = Me) was similarly hydrogenated over 10% Pd-C in EtOAc, and subsequently converted to the corresponding Mosher amide by sequential deprotection (TFA in CH_2Cl_2) and coupling (BOP/DIPEA/DMF) of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. After standard workup according to general procedure A, ^{1}H NMR analysis of the crude product provided a single set of signals: (500 MHz, $CDCl_3$) δ 1.71-1.82 (m, 1H), 1.94-2.05 (m, 1H), 2.33-2.47 (m, 2H), 2.71 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.83 (dd, *J* = 13.8, 6.5 Hz, 1H), 3.26 (s, 3H), 3.68 (s, 3H), 4.21-4.31 (m, 1H), 5.04 (s, 2H), 6.78 (d, *J* = 9.2 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 9.2 Hz, 2H), 7.14-7.48 (m, 10H).

General Procedure A: Preparation of compounds (2a)-(2g).

Example: synthesis of (*S*)-5-(4-Benzyloxy-phenyl)-4-(7-phenyl-heptanoylamino)-pentanoic acid (2b).

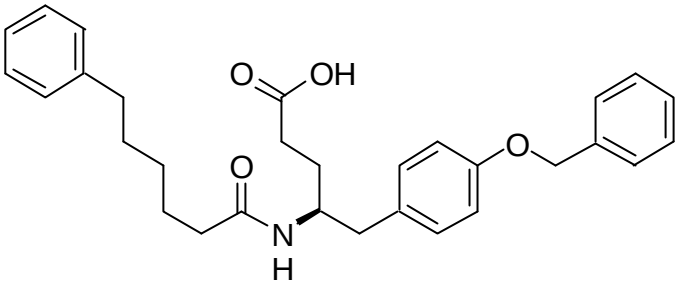


Compound **6** (R^1 = Me) (3.0 g, 0.0073 mol) was added to TFA (10 mL) at 0 °C with stirring. After 10 min, ice was added, and the mixture extracted into EtOAc. The extracts were washed with K_2CO_3 solution (20 % w/v) and brine, dried with $MgSO_4$, and evaporated to afford 2.23 g (98 %) of crude product. The crude material was dissolved in dry DMF (10 mL) and added dropwise to a solution of DIPEA (2.03 g, 2.74 mL, 0.0158 mol), 7-phenylhept-6-ene-oic acid (~1:1 mixture of *E*- and *Z*-isomers, 1.6 g, 0.0079 mol) and BOP (3.48 g, 0.0079 mol) in dry DMF (5 mL). After stirring overnight, the mixture was diluted with water (50 mL) and extracted with EtOAc. The organic phase was then washed with water, HCl (1 *M* aqueous), saturated $NaHCO_3$, and dried with $MgSO_4$. The solution was filtered, and the crude mixture hydrogenated over 10% Pd/C. The catalyst was removed by filtration through celite, and the solvent evaporated. The crude material was chromatographed (silica gel, 3:2 Et_2O-petroleum ether) to afford the methyl ester of **2b** as a colorless solid (1.98 g, 55 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (4H, m), 1.59 (5H, m), 1.84 (1H, m), 2.07 (2H, t, *J* = 7 Hz), 2.33 (2H, m), 2.58 (2H, t, *J* = 8 Hz), 2.68 (1H, dd, *J* = 8, 15 Hz), 2.76 (1H, dd, *J* = 8, 15 Hz), 3.63 (3H, s), 4.14 (1H, m), 5.01 (2H, s), 5.38 (1H, d, *J* = 9 Hz), 6.88 (2H, d,

J = 8 Hz), 7.07 (2H, d, *J* = 10 Hz), 7.11-7.48 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 172.9, 157.7, 142.8, 137.2, 130.5, 130.0, 128.7, 128.5, 128.4, 128.0, 127.6, 125.8, 114.9, 70.1, 51.9, 50.2, 40.6, 37.0, 36.0, 31.4, 31.1, 29.2, 29.1, 29.0, 25.8. ESMS m/z 502 $(M+H)^+$. A mixture of the methyl ester of **2b** (0.86 g, 1.7 mmol) and NaOH solution (4 *M*, 0.85 mL, 3.4 mmol) in MeOH-THF (1:1, 6 mL) was stirred at room temperature overnight. The solvent was removed, and the residue diluted with water. The solution was washed with Et_2O, acidified with 5 % aqueous HCl, and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4) and the solvent removed under reduced pressure to afford **2b** as a white solid (0.81 g, 98 %), m.p. 127.7-129.5 °C (EtOAc-petroleum). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21-1.34 (m, 4H), 1.47-1.70 (m, 5H), 1.85-1.96 (m, 1H), 2.03-2.15 (m, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.68-2.79 (m, 2H), 4.14-4.24 (m, 1H), 5.02 (s, 2H), 5.33 (br d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.12-7.44 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 173.7, 157.7, 142.6, 137.0, 130.3, 129.5, 128.6, 128.4, 128.2, 127.9, 127.5, 125.6, 114.9, 70.0, 49.9, 40.4, 36.8, 35.8, 31.2, 29.5, 29.0, 28.9, 25.6, with one resonance obscured. $[\alpha]_D^{26}$ = -3° (c 1.0, MeOH). ESHRMS $[M+H]^+$ for $C_{31}H_{37}NO_4$: Calcd. 488.2795 Found 488.2793. Retention time (rp-HPLC): 8.6 min (method D), 21.2 min (method A).

Also obtained in this fashion were the following:

(*S*)-5-(4-Benzyloxy-phenyl)-4-(6-phenyl-hexanoylamino)-pentanoic acid (2a).

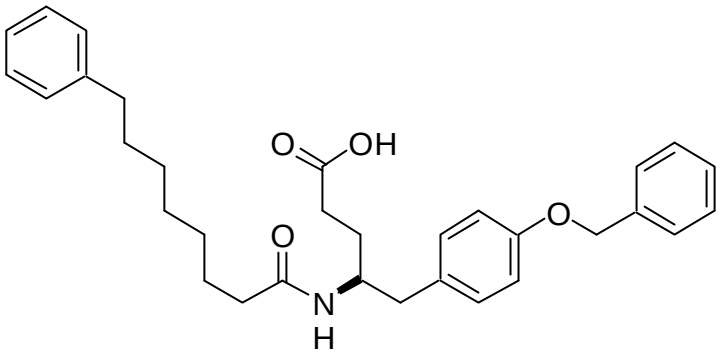


From 6-phenylhexanoic acid and **6** (R^1 = Et) to give the ethyl ester of **2a** (55% yield): chromatographed on silica gel using 50:40:10 petroleum ether-CH_2Cl_2-EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.28-1.90 (m, 9H), 2.11 (t, *J* = 7.4 Hz, 2H), 2.29-2.38 (m, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.71-2.77 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 5.03 (s, 2H), 5.55 (br d, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.16-7.44 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 172.8, 157.5, 142.4, 136.9, 130.3, 129.9, 128.5, 128.3, 128.2, 127.8, 127.4, 125.6, 114.7, 69.9, 60.5, 50.1, 40.3, 36.7, 35.6, 31.1, 31.0, 28.7, 28.6, 25.5, 14.1. ESMS m/z 502 $(M+H)^+$, 1003 $(2M+H)^+$. Hydrolysis of the ethyl ester of **2a** (18.2 mg, 0.036 mmol) with NaOH solution (4 *M*, 18 μL, 0.072 mmol) in MeOH-THF (1:1, 150 μL), followed by work up and purification by rp-hplc (method D) gave **2a** as a white powder (5.7 mg, 33%): ^{1}H NMR (500 MHz, d_6-DMSO) δ 1.04-1.75 (m, 8H), 1.89-2.05 (m, 2H), 2.05-2.27 (m, 2H), 2.40-2.68 (m, 4H), 3.80-3.94 (m, 1H), 5.02 (s, 2H), 6.88 (d, *J* = 7.6 Hz, 2H), 7.02-7.46 (m, 12H), 7.55 (br d, *J* = 8.3 Hz, 1H), 11.98 (br s, 1H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 174.3, 171.6, 156.7, 142.3, 137.2, 131.0, 130.1, 128.4, 128.2, 127.7, 127.6, 125.6, 114.3, 69.1, 49.3, 35.4, 35.1, 30.8, 30.5, 29.2, 28.1, 25.1.

$[\alpha]_D^{22}$ = -11° (c 0.17, MeOH). FABHRMS $[M+H]^+$ for $C_{30}H_{35}NO_4$: Calcd. 474.2637 Found 474.2645. Retention time (rp-HPLC): 7.1 min (method D), 19.6 min (method A).

(*S*)-5-(4-Benzyloxy-phenyl)-4-(8-phenyl-octanoylamino)-pentanoic acid (2c).

From 8-phenyloctanoic acid and **6** (R^1 = Et) to give the ethyl ester of **2c** (51% yield): chromatographed on silica gel using 50:40:10 petroleum ether-CH_2Cl_2-EtOAc.



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.27-1.55 (m, 10H), 2.06 (t, *J* = 7.4 Hz, 2H), 2.52 (t, *J* = 7.4 Hz, 2H), 2.74-2.79 (m, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 4.84-4.88 (m, 1H), (4.94, s, 2H), 5.80 (br d, *J* = 15.8 Hz, 1H), 6.00 (d, *J* = 8.2 Hz, 1H), 6.82-7.36 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 165.9, 157.5, 147.2, 142.5, 136.7, 130.1, 128.6, 128.3, 128.1, 128.0, 127.7, 127.2, 121.0, 114.7, 69.7, 60.2, 50.6, 39.3, 36.3, 35.7, 31.2, 29.0, 28.9, 28.1, 25.4, 14.0, with one resonance obscured. ESMS m/z 530 $(M+H)^+$, 1059 $(2M+H)^+$. Hydrolysis of the ethyl ester of **2c** (56.3 mg, 0.11 mmol) with NaOH solution (4 *M*, 53 μL, 0.22 mmol) in MeOH-THF (1:1, 0.3 mL) followed by workup and purification by rp-hplc (method C) gave **2c** a white powder (21.3 mg, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14-1.37 (m, 6H), 1.45-1.70 (m, 5H), 1.82-1.95 (m, 1H), 2.01-2.16 (m, 2H), 2.30-2.43 (m, 2H),

2.57 (t, *J* = 8.1 Hz, 2H), 2.66-2.78 (m, 2H), 4.14-4.23 (m, 1H), 5.01 (s, 2H), 5.45 (d, *J* = 9.0 Hz, 1H), 6.9 (d, J = 8.4 Hz, 2H), 7.0 (d, J = 8.4 Hz, 2H), 7.12-7.44 (m, 10H), with one resonance obscured. ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.5, 174.0, 157.8, 142.9, 137.1, 130.5, 129.7, 128.7, 128.5, 128.4, 128.1, 127.6, 125.7, 115.1, 70.2, 50.0, 40.5, 37.0, 36.1, 31.6, 31.4, 29.6, 29.3, 29.2, 25.8, with one resonance obscured. $[\alpha]_D^{22}$ = -5° (c 1.0, MeOH). ESHRMS $[M+H]^+$ for $C_{32}H_{39}NO_4$: Calcd. 502.2950 Found 502.2960. Retention time (rp-HPLC): 10.3 min (method D), 22.9 min (method A).

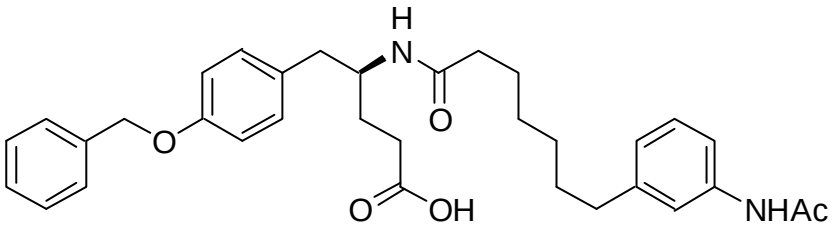
(*S*)-5-(4-Benzyloxy-phenyl)-4-[7-(2-methoxy-phenyl)-heptanoylamino]-pentanoic acid (2d).

From 7-(2-methoxy-phenyl)-heptanoic acid and **6** (R^1 = Me) to give the methyl ester of **2d** (53% yield): chromatographed on silica gel using 50:40:10 CH_2Cl_2-petroleum-EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 4H), 1.60 (m, 5H), 1.84 (m, 1H), 2.07 (t, *J* = 8 Hz, 2H), 2.28, (dd, *J* = 12, 7 Hz, 1H), 2.38 (dd, *J* = 12, 7 Hz, 1H), 2.57 (dd, *J* = 8 Hz, 2H), 2.67 (dd, *J* = 15, 7 Hz, 1H), 2.75 (dd, *J* = 15, 7 Hz, 1H), 3.62 (s, 3H), 3.78 (s, 3H), 4.11 (m, 1H), 4.99 (s, 2H), 5.28 (d, *J* = 9 Hz, 1H), 6.82 (t, *J* = 7 Hz, 1H); 6.87 (d, *J* = 7 Hz, 2H), 7.06 (d, *J* = 9 Hz, 2H), 7.07-7.42 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 29.0, 29.3, 29.4, 29.8, 29.9, 30.3, 31.1, 37.1, 40.6, 50.2, 51.9, 55.4, 70.2, 110.4, 115.0, 120.5, 127.0, 127.7, 128.1, 128.7,

129.9, 130.0, 130.6, 131.2, 137.2, 157.7, 173.1, 174.4. ESMS m/z 546 $(M+H)^+$, 1091 $(2M+H)^+$. Hydrolysis of the methyl ester of **2d** (148 mg, 0.27 mmol) with LiOH solution (4 *M*, 0.14 mL, 0.54 mmol) in MeOH-THF (1:1, 0.6 mL) gave, after workup, **2d** as a colourless solid (106 mg, 76%): ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.13-1.68 (m, 9H), 1.82-1.91 (m, 1H), 2.04-2.13 (m, 2H), 2.25-2.39 (m, 2H), 2.2-2.64 (m, 3H), 2.76 (dd, *J* = 13.8, 5.7 Hz, 1H), 3.77 (s, 3H), 4.02-4.12 (broad, m, 1H), 4.98 (s, 2H), 6.78-6.91 (m, 4H), 7.03-7.15 (m, 4H), 7.26-7.41 (m, 5H), with two resonances obscured. ^{13}C NMR (75 MHz, d_4-MeOH) δ 177.2, 176.1, 159.0, 139.0, 132.24, 132.20, 131.4, 130.9, 129.6, 128.9, 128.7, 128.1, 121.5, 115.9, 111.5, 71.1, 55.8, 51.7, 41.4, 37.4, 32.0, 31.3, 31.1, 30.4, 30.2, 27.2, with two resonances obscured. $[\alpha]_D^{22}$ = -5.3° (c 0.97, MeOH). ESHRMS $[M+H]^+$ for $C_{32}H_{39}NO_5$: Calcd. 518.2899 Found 518.2885. Retention time (rp-HPLC): 9.0 min (method D), 24.4 min (method B).

(*S*)-4-[7-(3-Acetylamino-phenyl)-heptanoylamino]-5-(4-benzyloxy-phenyl)-pentanoic acid (2e).

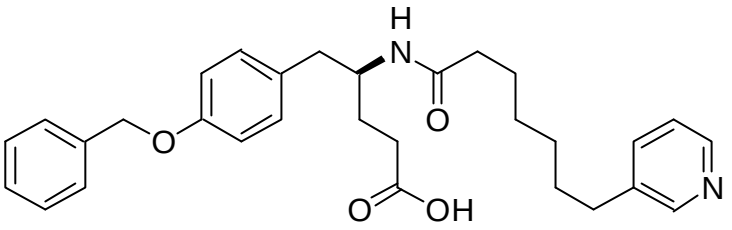
From 7-(3-acetylamino-phenyl)-heptanoic acid and **6** (R^1 = Et) to give the ethyl ester of **2e**



(36% yield): chromatographed on silica gel using 30:70 acetone-petroleum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.3 Hz, 3H) superimposed upon 1.19-1.37 (m, 3H), 1.48-1.95 (m, 7H), 2.03-2.20

(m, 2H) superimposed upon 2.15 (s, 3H), 2.23-2.44 (m, 2H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.63-2.82 (m, 2H), 4.1 (q, *J* = 7.3 Hz, 2H) superimposed upon 4.04-4.23 (m, 1H), 5.02 (s, 2H), 5.55 (d, *J* = 8.9 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 7.15-7.47 (m, 9H), 7.53 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 24.8, 28.5, 28.9, 29.0, 30.9, 31.4, 35.7, 36.8, 40.6, 50.3, 60.8, 70.2, 115.0, 117.5, 120.1, 124.7, 127.7, 128.1, 128.8, 129.0, 130.2, 130.5, 137.2, 138.0, 143.7, 157.7, 168.6, 173.1, 174.0, with one resonance obscured. ESMS m/z 573 $(M+H)^+$. Hydrolysis of the ethyl ester of **2e** (107 mg, 0.19 mmol) with LiOH solution (4 *M*, 0.10 mL, 0.38 mmol) in MeOH-THF (1:1, 0.4 mL) gave, after workup, **2e** as an opaque gum (81 mg, 78%): ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.12-1.33 (m, 5H), 1.40-1.50 (m, 1H), 1.52-1.70 (m, 3H), 1.82-1.91 (m, 1H), 2.04-2.11 (m, 2H) superimposed upon 2.09 (s, 3H), 2.23-2.36 (m, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.62 (dd, *J* = 8.5, 13.8 Hz, 1H), 2.75 (dd, *J* = 5.7, 13.8 Hz, 1H), 4.01-4.11 (m, 1H), 4.98 (s, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.24-7.42 (m, 7H), with three resonances obscured. ^{13}C NMR (75 MHz, d_4-MeOH) δ 177.2, 175.9, 171.6, 158.9, 144.7, 139.9, 138.8, 132.2, 131.3, 129.8, 129.6, 128.9, 128.6, 125.5, 121.3, 118.6, 115.9, 71.0, 51.6, 41.4, 37.3, 36.8, 32.3, 31.9, 31.0, 29.9, 27.1, 24.0, with one resonance obscured. $[\alpha]_D^{22}$ = -2.6° (c 1.1, MeOH). ESHRMS $[M+H]^+$ for $C_{33}H_{40}N_2O_5$: Calcd. 545.3008 Found 545.2956. Retention time (rp-HPLC): 10.7 min (method F), 14.7 min (method A).

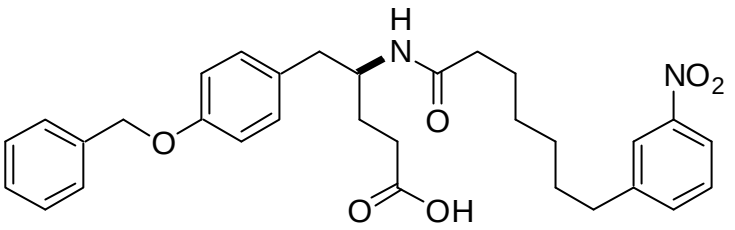
(*S*)-5-(4-Benzyloxy-phenyl)-4-(7-pyridin-3-yl-heptanoylamino)-pentanoic acid (2f).



From 7-pyridin-3-yl-heptanoic acid and **6** (R^1 = Me) to give the methyl ester of **2f** (26% yield): chromatographed on silica using 70:30 EtOAc-petroleum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14-1.42 (m, 4H), 1.46-1.94 (m, 5H), 1.82-1.95 (m, 1H), 2.08 (t, *J* = 8 Hz, 2H), 2.34 (m, 2H), 2.59 (t, *J* = 8 Hz, 2H), 2.69 (dd, *J* = 7, 14 Hz, 1H), 2.77 (dd, *J* = 7, 14 Hz, 1H), 3.65 (s, 3H), 4.07-4.22 (m, 1H), 5.03 (s, 2H), 5.36 (br d, *J* = 9 Hz, 1H), 6.90 (d, *J* = 9 Hz, 2H), 7.9 (d, *J* = 9 Hz, 2H), 7.17-7.52 (m, 7H), 8.42 (br s, 2H). ^{13}C NMR δ (75 MHz, $CDCl_3$) δ 25.7, 29.0, 29.1, 29.9, 31.0, 31.2, 33.1, 37.0, 40.6, 50.3, 51.9, 70.2, 115.0, 123.7, 127.7, 128.1, 128.8, 130.1, 130.6, 136.6, 137.2, 146.8, 149.4, 157.7, 172.9, 174.4, with one resonance obscured. ESMS m/z 503 $(M+H)^+$. Hydrolysis of the methyl ester of **2f** (66 mg, 0.13 mmol) with NaOH solution (1 *M*, 0.26 mL, 0.26 mmol) in MeOH-THF (1:1, 1.0 mL) gave, after workup, **2f** as white solid (61 mg, 95%): ^{1}H NMR (500 MHz, d_6-DMSO) δ 1.03-1.27 (m, 4H), 1.30-1.54 (m, 5H), 1.58-1.70 (m, 1H), 1.84-2.01 (m, 2H), 2.03-2.25 (m, 2H), 2.42-2.59 (m, 4H), 3.78-3.89 (br m, 1H), 4.98 (s, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 7.18-7.40 (m, 5H), 7.46-7.57 (m, 2H), 8.28-8.41 (m, 2H), with two resonances obscured. ^{13}C NMR (75 MHz, d_6-DMSO) δ 25.2, 28.2, 28.3, 29.3, 30.5, 32.1, 35.5, 49.4, 69.1, 114.3, 123.4, 127.6, 127.7, 128.4, 130.1, 131.1, 135.7, 137.2, 137.6, 147.0, 149.5, 156.7, 171.7, 174.3, with

two resonances obscured. $[\alpha]_D^{22}$ = -0.94° (c 1.0, DMSO). ESHRMS $[M+H]^+$ for $C_{30}H_{36}N_2O_4$: Calcd. 489.2746 Found 489.2745. Retention time (rp-HPLC): 13.7 min (method B), 11.7 min (method I).

(*S*)-5-(4-Benzyloxy-phenyl)-4-[7-(3-nitro-phenyl)-heptanoylamino]-pentanoic acid (2g).

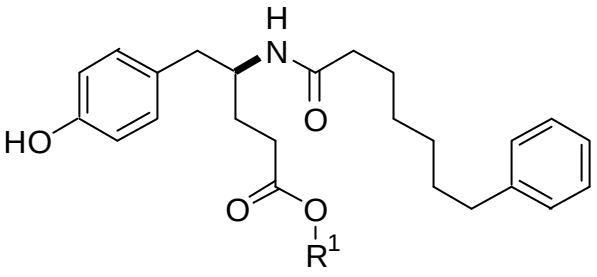


From 7-(3-nitro-phenyl)-heptanoic acid and **6** (R^1 = Me) to give the methyl ester of **2g** (55% yield): chromatographed on silica gel using 0.5% MeOH in CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 4H), 1.63 (m, 5H), 1.85 (m, 1H), 2.07 (t, *J* = 8 Hz, 2H), 2.32 (m, 2H), 2.67 (t, *J* = 8 Hz, 2H) superimposed upon 2.71 (m, 2H), 3.62 (s, 3H), 4.13 (m, 1H), 5.00 (s, 2H), 5.31 (br d, *J* = 9 Hz, 1H), 6.87 (d, *J* = 9 Hz, 2H), 7.05 (d, *J* = 9 Hz, 2H), 7.35 (m, 6H), 7.46 (m, 1H), 8.0 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 28.8, 28.9, 29.7, 30.8, 31.0, 35.5, 36.8, 40.4, 50.1, 51.7, 70.0, 114.8, 120.9, 123.2, 127.4, 127.9, 128.6, 129.1, 129.9, 130.4, 134.7, 137.0, 144.6, 157.6, 172.6, 174.2, with one resonance obscured. ESMS m/z 547 $(M+H)^+$. Hydrolysis of the methyl ester of **2g** (90 mg, 0.16 mmol) with NaOH solution (4 *M*, 80 μL, 0.33 mmol) in MeOH-THF (1:1, 1.0 mL) gave, after work up, **2g** as a hygroscopic white solid (83 mg, 94%): ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.11-1.23 (m, 2H), 1.23-1.33 (m, 2H), 1.40-1.50 (m, 2H), 1.53-1.70 (m, 3H), 1.82-1.91 (m, 1H), 2.02-2.12 (m, 2H), 2.24-2.36 (m, 2H), 2.61 (dd, *J* = 8.6, 13.8 Hz, 1H), 2.67 (t, *J* = 7.7 Hz, 2H), 2.75 (dd, *J* = 5.7, 13.8 Hz,

1H), 4.01-4.12 (m, 1H), 4.98 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.36 (m, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.96-8.03 (m, 2H), with two resonances obscured. ^{13}C NMR (125 MHz, d_4-MeOH) δ 177.1, 175.9, 158.8, 149.7, 146.3, 138.8, 136.0, 132.2, 131.3, 130.4, 129.5, 128.8, 128.5, 124.0, 121.8, 115.7, 71.0, 51.5, 41.2, 37.1, 36.3, 32.1, 31.8, 31.0, 29.9, 29.8, 26.9. $[\alpha]_D^{22}$ = -4.9° (c 0.64, MeOH). ESHRMS $[M+H]^+$ for $C_{31}H_{36}N_2O_6$: Calcd. 533.2644 Found 533.2619. Retention time (rp-HPLC): 12.8 min (method E), 20.1 min (method A).

Synthesis of (*S*)-5-(4-Hydroxy-phenyl)-4-(7-phenyl-heptanoylamino)-pentanoic acid methyl ester (8) (R^1 = Me)

Compound **2b** (R^1 = Me) (872 mg, 1.74 mmol) was hydrogenated over 10% Pd-C in THF (20 mL) containing HCl solution (1 *M*, 2.5 mL). The solution was filtered (Celite) and the bulk of the solvent removed under reduced pressure. The solution was diluted with water and extracted (EtOAc). The combined extracts were washed with water, brine and dried with $MgSO_4$. Evaporation of the solvent *in vacuo* afforded **8** (R^1 = Me) (702 mg, 98 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17-1.39 (m, 4H), 1.45-1.74 (m, 5H), 1.81-1.96 (m, 1H), 2.07 (t, *J* = 6.0 Hz, 2H), 2.25-2.46 (m, 2H), 2.54-2.59 (m, 2H), 2.63-2.73 (m, 2H), 3.64 (s, 3H), 4.10-4.25 (m, 1H), 5.51 (d, *J* = 9.0 Hz, 1H), 6.73 (d, *J*



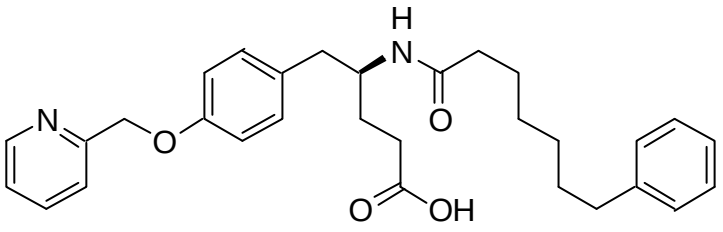
= 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.09-7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 173.7, 155.4, 142.9, 130.4, 128.8, 128.6, 128.4, 125.8, 115.6, 52.0, 50.6, 40.8, 37.0, 36.0, 31.4, 31.1, 29.3, 29.1, 29.0, 25.8. ESMS m/z 412 $(M+H)^+$.

Similarly, using the above procedure, compound **8** (R^1 = Et) was prepared from **2b** (R^1 = Et): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3H), 1.20-1.35 (m, 4H), 1.45-1.73 (m, 5H), 1.80-1.95 (m, 1H), 2.07 (t, *J* = 7.50 Hz, 2H), 2.22-2.42 (m, 2H), 2.55 (t, *J* = 7.7 Hz, 2H), 2.62-2.75 (m, 2H), 4.08 (m, 2H), 4.08-4.22 (m, 1H), 5.65-5.73 (d, *J* = 9.1 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4, 2H), 7.10-7.30 (m, 5H), 7.95-8.20 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 173.6, 155.4, 142.6, 130.1, 128.5, 128.3, 128.1, 126.8, 126.5, 115.4, 60.6, 50.3, 40.4, 36.7, 35.7, 31.1, 31.0, 28.9, 28.8, 25.5, 14.0. ESMS 426 $(M+H)^+$.

General Procedure B: Preparation of Compounds (2h)-(2p).

Example: synthesis of (*S*)-4-(7-phenyl-heptanoylamino)-5-[4-(pyridin-2-ylmethoxy)-phenyl]-pentanoic acid (2h).

A mixture of compound **8** (R^1 = Me) (889 mg, 2.16 mmol), 2-picolylchloride hydrochloride (570 mg, 3.47 mmol) and finely powdered anhydrous K_2CO_3 (1.45 g, 10.5 mmol) was stirred in dry DMF (7 mL) for 48 h. The mixture was poured onto water (40 mL) and extracted (EtOAc). The combined organic phases were successively washed with

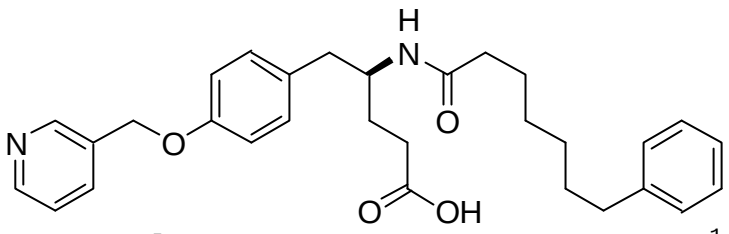


HCl solution (1 *M*, 30 mL), saturated $NaHCO_3$ solution, brine, and then dried with $MgSO_4$. Concentration of the solvent *in vacuo* afforded the methyl ester of **2h** (747 mg, 69 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15-1.40 (m, 4H); 1.40-1.70 (m, 5H); 1.73-1.85 (m, 1H); 2.08 (t, *J* = 7.6 Hz, 2H); 2.34 (m, 2H); 2.58 (t, *J* = 7.6 Hz, 2H); 2.69 (dd, *J* = 15, 6.9 Hz, 1H); 2.77 (dd, *J* = 15, 6.2 Hz, 1H); 3.64 (s, 3H); 4.06-4.21 (m, 1H); 5.17 (s, 2H); 5.37 (d, *J* = 9.3 Hz, 1H); 6.91 (d, *J* = 8.4 Hz, 2H); 7.10 (d, *J* = 8.4 Hz, 2H); 7.12-7.31 (m, 6H); 7.51 (d, *J* = 7.5 Hz, 1H); 7.71 (dt, *J* = 7.5, 1.6 Hz, 1H); 8.60 (m, *J* = 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 173.0, 157.5, 157.3, 149.4, 142.8, 137.0, 130.3, 125.8, 122.8, 121.5, 130.6, 128.5, 128.4, 115.0, 70.8, 51.9, 50.2, 40.6, 37.0, 36.0, 31.4, 31.1, 29.2, 29.1, 29.0, 25.8. ESMS m/z 503 $(M+H)^+$. The methyl ester of **2h** (707 mg, 1.41 mmol) was hydrolysed according to the method outlined in general procedure A to yield **2h** (608 mg, 89%) as a white solid: ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.12-1.31 (m, 4H), 1.40-1.50 (m, 2H), 1.50-1.69 (m, 3H), 1.81-1.91 (m, 1H), 2.01-2.12 (m, 2H), 2.23-2.36 (m, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.62 (dd, *J* = 8.5, 13 Hz, 1H), 2.75 (dd, *J* = 5.8, 13 Hz, 1H), 4.00-4.11 (m, 1H), 5.09 (s, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.06-7.25 (m, 7H), 7.29-7.37 (m, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.77-7.87 (m, 1H), 8.45-8.56 (m, 1H), with two resonances obscured. ^{13}C NMR (125 MHz, d_4-MeOH) δ 177.1, 175.9, 158.4, 149.7, 143.9, 139.0, 132.6, 131.4, 129.4, 129.2, 126.6, 124.4, 123.3, 115.7, 71.2, 51.5, 41.2, 37.2, 36.8, 32.5, 31.9, 30.9, 30.01, 29.97, 27.0, with one resonance obscured. $[\alpha]_D^{26}$ = -2° (c 1.0, MeOH). ESHRMS $[M+H]^+$ for $C_{30}H_{36}N_2O_4$: Calcd. 489.2746

Found 489.2745. Retention time (rp-HPLC): 9.1 min (method I), 14.6 min (method B).

Also obtained in this fashion was:

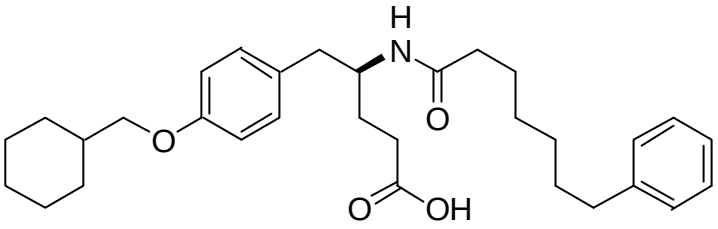
(*S*)-4-(7-Phenyl-heptanoylamino)-5-[4-(pyridin-3-ylmethoxy)-phenyl]-pentanoic acid (2i).



Prepared from **8** (R^1 = Me) (502 mg, 1.22 mmol) and 3-picolylchloride hydrochloride (300 mg, 1.83 mmol) to afford the methyl ester of **2i** (422 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14-1.42 (m, 4H), 1.46-1.94 (m, 6H), 2.09 (t, *J* = 9.0 Hz, 2H), 2.28-2.44 (m, 2H), 2.60 (t, *J* = 9.0 Hz, 2H), 2.70 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.76 (dd, J = 14.0, 6.0 Hz, 1H), 3.65 (s, 3H), 4.07-4.22 (m, 1H), 5.03 (s, 2H), 5.38 (d, *J* = 12 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 2H), 7.15-7.21 (m, 1H), 7.29-7.51 (m, 6H), 8.42 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 173.0, 157.3, 149.5, 149.1, 142.8, 135.5, 132.8, 130.6, 128.5, 128.4, 125.8, 123.7, 114.9, 67.7, 51.9, 50.3, 40.6, 37.0, 36.0, 31.4, 31.1, 29.2, 29.1, 29.0, 25.8, with one resonance obscured. ESMS m/z 503 $(M+H)^+$. The methyl ester of **2i** (360 mg, 0.72 mmol) was hydrolysed according to the method outlined in general procedure A to yield **2i** (299 mg, 85%) as a white solid: ^{1}H NMR (500 MHz, d_4-MeOH) δ 1.11-1.34 (m, 4H), 1.39-1.51 (m, 2H), 1.51-1.70 (m, 3H), 1.80-1.92 (m, 1H), 2.02-2.12 (m, 2H), 2.23-2.37 (m, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.63 (dd, *J* = 8.5,

14.0 Hz, 1H), 2.75 (dd, *J* = 5.8, 14.0 Hz, 1H), 3.99-4.13 (m, 1H), 4.86 (s, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.05-7.29 (m, 7H), 7.43 (dd, *J* = 5.0, 7.8 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 8.43-8.51 (m, 1H), 8.58 (br s, 1H), with two resonances obscured. ^{13}C NMR (125 MHz, d_4-MeOH) δ 177.1, 175.9, 158.4, 149.4, 149.2, 143.9, 137.5, 135.4, 132.6, 131.4, 129.4, 129.3, 126.6, 125.2, 115.7, 68.3, 51.5, 41.2, 37.2, 36.8, 32.5, 31.8, 30.9, 30.0, 29.9, 27.0. $[\alpha]_D^{22}$ = -3.2° (c 1.0, MeOH). ESHRMS $[M+H]^+$ for $C_{30}H_{36}N_2O_4$: Calcd. 489.2746 Found 489.2745. Retention time (rp-HPLC): 7.9 min (method I), 14.2 min (method B).

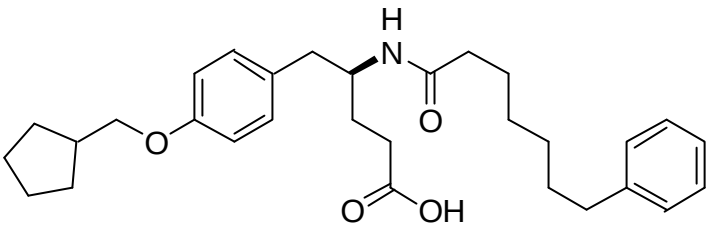
(*S*)-5-(4-Cyclohexylmethoxy-phenyl)-4-(7-phenyl-heptanoylamino)-pentanoic acid (2j)



Prepared from **8** (R^1 = Et) (200 mg, 0.47 mmol) and cyclohexylmethylbromide[5] (416 mg, 2.35 mmol) to afford the ethyl ester of **2j** (182 mg, 74%): chromatographed on silica gel using 1:3 EtOAc-petroleum ether. The ethyl ester of **2j** (180 mg, 0.35 mmol) was hydrolysed according to the method outlined in general procedure A to yield, after purification by rp-hplc (method D) **2j** (66 mg, 39 %) as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96-1.09 (m, 2H), 1.12-1.35 (m, 7H), 1.46-1.93 (m, 12H), 2.03-2.15 (m, 2H), 2.36 (d, *J* = 7.1 Hz, 2H), 2.58 (d, *J* = 7.7 Hz, 2H), 2.67-2.78 (m, 2H), 3.70 (d, *J* = 6.4 Hz, 2H), 4.12-4.23 (br m, 1H), 5.39 (d, *J* = 8.9 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 7.13-7.19 (m, 3H), 7.23-

7.29 (m, 2H), with one resonance obscured. ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 173.7, 158.2, 142.6, 130.2, 128.8, 128.4, 128.2, 125.6, 114.6, 73.5, 49.9, 40.3, 37.7, 36.8, 35.8, 31.2, 29.9, 29.5, 29.0, 28.9, 26.5, 25.8, 25.6, with one resonance obscured. $[\alpha]_D^{26}$ = -5.5° (c 0.51, MeOH). ESHRMS $[M+H]^+$ for $C_{31}H_{43}NO_4$: Calcd. 494.3263 Found 494.3249. Retention time (rp-HPLC): 11.9 min (method C), 27.7 min (method A).

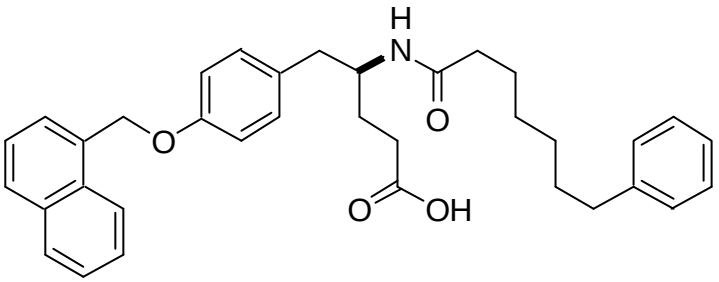
(*S*)-5-(4-Cyclopentylmethoxy-phenyl)-4-(7-phenyl-heptanoylamino)-pentanoic acid (2k)



Prepared from **8** (R^1 = Et) (200 mg, 0.47 mmol) and cyclopentylmethyl bromide[5] (123 mg, 0.76 mmol) to afford the ethyl ester of **2k** (184 mg, 76 %): chromatographed on silica gel using 1:3 EtOAc-petroleum ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.3 Hz, 3H) superimposed upon 1.19-1.94 (m, 18H), 2.04-2.14 (m, 2H), 2.22-2.45 (m, 3H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.65- 2.84 (m, 2H), 3.79 (d, *J* = 7.1 Hz, 2H), 4.05-4.20 (m, 3H), 5.35 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 2H), 7.07 (*J* = 8.3 Hz, 2H), 7.15-7.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 173.6, 155.4, 142.6, 130.1, 128.3, 128.1, 125.5, 115.4, 60.6, 50.4, 40.5, 36.7, 35.7, 31.11, 31.08, 28.9, 28.8, 25.5, 14.1, with six resonances obscured. ESMS 508 $(M+H)^+$. The ethyl ester of **2k** (180 mg, 0.36 mmol) was hydrolysed according to the method outlined in general procedure A to yield, after purification by rp-hplc (method D), **2k** (74 mg, 43%) as a white

powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18-1.98 (m, 18H), 2.05-2.16 (m, 2H), 2.23-2.43 (m, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.70 (dd, *J* = 6.7, 14.0 Hz, 1H), 2.77 (dd, *J* = 6.4, 14.0 Hz, 1H), 3.79 (d, *J* = 7.0 Hz, 2H), 4.13-4.23 (m, 1H), 5.33 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 7.14-7.20 (m, 2H), 7.24-7.30 (m, 3H), with one resonance obscured. ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 173.9, 158.2, 142.6, 130.2, 128.7, 128.4, 128.2, 125.6, 114.6, 72.3, 49.8, 40.4, 39.1, 36.8, 35.9, 31.3, 31.2, 30.0, 29.5, 29.0, 28.9, 25.5, 25.4. $[\alpha]_D^{26}$ = -5.3° (c 0.52, MeOH). ESHRMS $[M+H]^+$ for $C_{80}H_{41}NO_4$: Calcd. 480.3106 Found 480.3101. Retention time (rp-HPLC): 15.5 min (method D), 25.4 min (method A).

Synthesis of 5-[4-(Naphthalen-1-ylmethoxy)-phenyl]-4(7-phenyl-heptanoylamino)-pentanoic acid (2l)

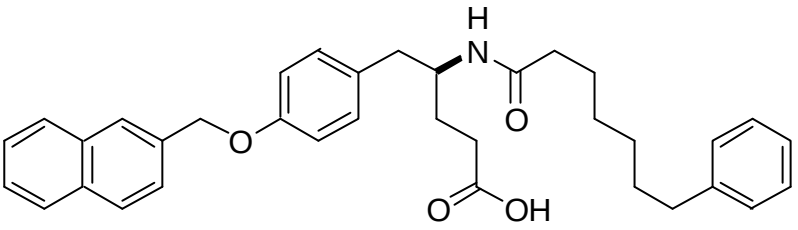


Prepared from **9** (R^1 = Et) (200 mg, 0.47 mmol) and 1-chloromethylnapthalene (90% purity; remainder 2-chloromethylnapthalene) (134mg, 0.76 mmol) to afford the ethyl ester of **2l** (215 mg, 81%) as a 90:10 mixture of 1- and 2-napthylmethyl isomers. ESMS 566 $(M+H)^+$. The crude 90:10 mixture of ethyl esters (200 mg, 0.35 mmol) was hydrolysed according to the method outlined in general procedure A to yield, after purification by rp-hplc (method E), compound **2l** (130 mg, 52%) as a white powder: ^{1}H NMR (125 MHz, $CDCl_3$) δ 1.23-1.38 (m, 4H), 1.50-1.72 (m, 5H), 1.87-1.98 (m, 1H), 2.05-

2.18 (m, 2H), 2.40 (t, *J* = 6.9 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.71-2.82 (m, 2H), 4.17-4.28 (br m, 1H), 5.40 (d, *J* = 8.5 Hz, 1H), 5.45 (s, 2H), 6.99 (d, *J* = 9.4 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.13-7.20 (m, 3H), 7.21-7.29 (m, 2H), 7.43-7.62 (m, 4H), 7.83-7.94 (m, 2H), 8.00-8.08 (m, 1H), with one resonance obscured. ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 173.8, 157.7, 142.6, 133.8, 132.2, 131.5, 130.3, 129.5, 129.0, 128.7, 128.4, 128.2, 126.6, 126.4, 125.9, 125.6, 125.3, 123.7, 115.0, 68.7, 49.8, 40.4, 36.8, 35.8, 31.2, 29.6, 29.0, 28.9, 25.5. $[\alpha]_D^{26}$ = -6.4° (c 1.0, MeOH). ESHRMS $[M+H]^+$ for $C_{35}H_{39}NO_4$: Calcd. 538.2950 Found 538.2956. Retention time (rp-HPLC): 13.2 min (method D), 24.3 min (method A).

(S)-5-[4-(Naphthalen-2-ylmethoxy)-phenyl]-4-(7-phenyl-heptanoylamino)-pentanoic acid (2m)

Prepared from **8** (R^1 = Et) (200 mg, 0.47 mmol) and 2-chloromethylnapthalene (137 mg, 0.78 mmol) to afford

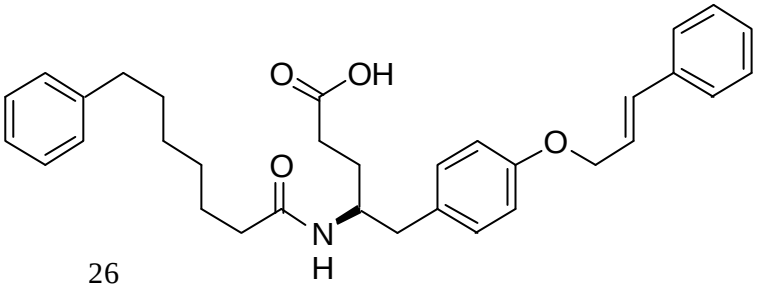


the ethyl ester of **2m** (230 mg, 87%): chromatographed on silica gel using 1:2 EtOAc-petroleum ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3H), 1.15-1.40 (m, 4H), 1.47-1.73 (m, 5H), 1.78-1.92 (m, 1H), 2.07 (t, *J* = 7.6 Hz, 2H), 2.21-2.45 (m, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.64-2.82 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 2H) superimposed upon 4.05-4.22 (m, 1H), 5.19 (s, 2H), 5.34 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.13-7.32 (m, 5H), 7.45-7.54

(m, 3H), 7.80-7.91 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 172.7, 157.5, 142.6, 134.5, 133.3, 133.0, 130.4, 130.0, 128.5, 128.4, 128.2, 127.9, 127.7, 126.3, 126.2, 126.0, 125.6, 125.3, 114.8, 70.1, 60.5, 50.1, 40.4, 36.9, 35.9, 31.3, 31.2, 29.0, 28.9, 28.7, 25.6, 14.2. ESMS 566 $(M+H)^+$. The ethyl ester of **2m** (200 mg, 0.35 mmol) was hydrolysed according to the method outlined in general procedure A to yield, after purification by rp-hplc (method E), compound **2m** (40 mg, 21%) as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20-1.36 (m, 4H), 1.50-1.72 (m, 5H), 1.85-2.00 (m, 1H), 2.03- 2.20 (m, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.68-2.81 (m, 2H), 4.15-4.26 (m, 1H), 5.19 (s, 2H), 5.40 (d, *J* = 9.3 Hz, 1H), 6.95 (d, *J* = 9.5 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.12- 7.19 (m, 3H), 7.21-7.30 (m, 2H), 7.46-7.56 (m, 3H), 7.81-7.91 (m, 4H), with one resonance obscured. ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 174.0, 157.9, 142.8, 134.6, 133.5, 133.2, 130.5, 129.6, 128.6, 128.4, 128.1, 128.0, 126.5, 126.4, 126.3, 125.8, 125.5, 115.2, 70.4, 50.0, 40.6, 36.9, 36.0, 31.4, 29.9, 29.2, 29.1, 25.7, with two resonances obscured. $[\alpha]_D^{26}$ = -5.6° (c 1.0, MeOH). ESHRMS $[M+H]^+$ for $C_{35}H_{39}NO_4$: Calcd. 538.2950 Found 538.2956. Retention time (rp-HPLC): 13.6 min (method D), 24.6 min (method A).

(*S*)-4-(7-Phenyl-heptanoylamino)-5-[4-(3-phenyl-propenyloxy)-phenyl]-pentanoic acid (2n)

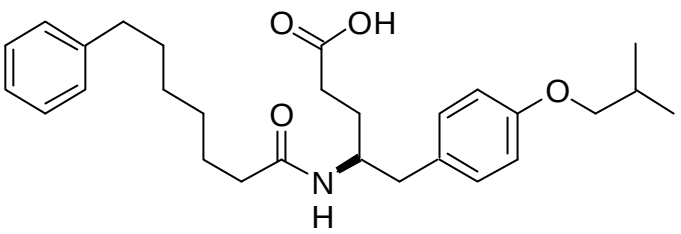
Prepared from **8** (R^1 = Et) (200 mg, 0.47 mmol) and



cinnamyl bromide (149 mg, 0.76 mmol) to afford the ethyl ester of **2n** (153 mg, 60%): chromatographed on silica gel using 3:5 EtOAc-petroleum ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.4 Hz, 3H) superimposed upon 1.20-1.42 (m, 4H), 1.45- 1.76 (m, 5H) 1.78-1.96 (m, 1H), 2.08 (t, *J* = 7.59, 2H), 2.24-2.48 (m, 2H), 2.59 (t, *J* = 7.68, 2H), 2.65-2.84 (m, 2H), 4.10 (q, *J* = 7.14, 2H), overlapped with 4.05-4.24 (m, 1H), 4.66 (d, *J* = 5.6 Hz, 2H), 5.35 (d, *J* = 8.3 Hz, 1H), 6.40 (dt, *J* = 16.0, 5.8 Hz, 1H), 6.72, (d, *J* = 16.0 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.14-7.22 (m, 2H), 7.24-7.48 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 172.7, 157.3, 142.7, 136.4, 133.0, 130.4, 129.9, 128.6, 128.4, 128.2, 128.1, 126.6, 125.6, 124.5, 114.7, 68.6, 60.6, 50.1, 40.4, 36.9, 35.9, 31.3, 31.2, 29.1, 29.0, 28.7, 25.6, 14.2. ESMS 542 $(M+H)^+$. The ethyl ester of **2n** (145 mg, 0.27 mmol) was hydrolysed according to the method outlined in general procedure A to yield, after purification by rp-hplc (method C) **2n** (47 mg, 34%) as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20-1.34 (m, 4H), 1.47-1.71 (m, 5H), 1.90-1.96 (br m, 1H), 2.03-2.15 (m, 2H), 2.33-2.46 (br m, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.68-2.80 (m, 2H), 4.14-4.25 (br m, 1H), 4.65 (d, *J* = 5.8 Hz , 2H), 5.36 (br d, *J* = 8.4 Hz, 1H), 6.39 (dt, *J* = 16.0, 5.8 Hz, 1H), 6.71 (d, *J* = 16.0 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.13-7.19 (m, 3H), 7.22-7.30 (m, 3H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.38-7.42 (m, 2H), with one resonance obscured. ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 157.5, 142.6, 136.4, 133.0, 130.3, 129.4, 128.6, 128.4, 128.3, 127.9, 126.6, 125.6, 124.4, 114.8, 68.6, 49.8, 40.3, 36.8, 35.9, 31.2, 29.6,

29.0, 28.9, 25.6, with two resonances obscured. $[\alpha]_D^{26}$ = -5.3° (c 1.0, MeOH). ESHRMS $[M+H]^+$ for $C_{33}H_{39}NO_4$: Calcd. 514.2950 Found 514.2960. Retention time (rp-HPLC): 11.5 min (method D), 23.6 min (method A).

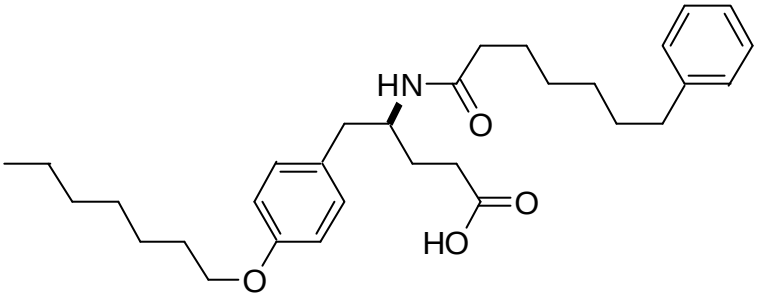
(*S*)-5-(4-Isobutoxy-phenyl)-4-(7-phenyl-heptanoylamino)-pentanoic acid (2o)



Prepared from **8** (R^1 = Et) (200 mg, 0.47 mmol) and 1-bromo-2-methylpropane (104 mg, 0.76 mmol) to afford the ethyl ester of **2o** (206 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.8 Hz, 6H), 1.18-1.40 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.46-1.74 (m, 5H), 1.79-1.92 (m, 1H), 2.05-2.11 (m, 3H), 2.22-2.44 (m, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.63-2.82 (m, 2H), 3.70 (d, *J* = 5.5 Hz, 2H), 4.09 (q, *J* = 7.0 Hz, 2H) superimposed upon 4.04-4.20 (m, 1H), 5.35 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.13-7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 172.7, 158.0, 142.7, 130.3, 129.3, 128.5, 128.4, 128.2, 125.6, 114.4, 74.4, 60.5, 50.1, 40.3, 36.9, 35.9, 31.2, 29.0, 28.9, 28.6, 28.3, 25.6, 19.3, 14.2. ESMS 482 $(M+H)^+$. The ethyl ester of **2o** (200 mg, 0.42 mmol) was hydrolysed according to the method outlined in general procedure A to yield, after purification by rp-hplc (method D) **2o** (111 mg, 49%) as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.4 Hz, 6H), 1.19-1.37 (m, 4H), 1.45-1.70 (m, 5H), 1.85-1.97 (m, 1H), 2.00-2.15 (m, 3H), 2.31-2.45 (br m, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.67-2.80 (m,

2H), 3.68 (d, *J* = 6.5 Hz, 2H), 4.12- 4.25 (br m, 1H), 5.32 (d, *J* = 8.9 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.13-7.20 (m, 2H), 7.23-7.30 (m, 3H), with one resonance obscured. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 173.9, 158.2, 142.6, 130.2, 128.7, 128.4, 128.3, 125.6, 114.6, 74.42, 49.8, 40.4, 36.8, 35.8, 31.3, 31.2, 30.0, 28.94, 2.87, 28.3, 25.5, 19.3. $[\alpha]_D^{26}$ = -3.5° (c 0.91, MeOH). ESHRMS $[M+H]^+$ for $C_{28}H_{39}NO_4$: Calcd. 454.2950 Found 454.2954. Retention time (rp-HPLC): 10.9 min (method D), 23.1 min (method A).

(*S*)-5-(4-Heptyloxy-phenyl)-4-(7-phenyl-heptanoylamino)-pentanoic acid (2p)

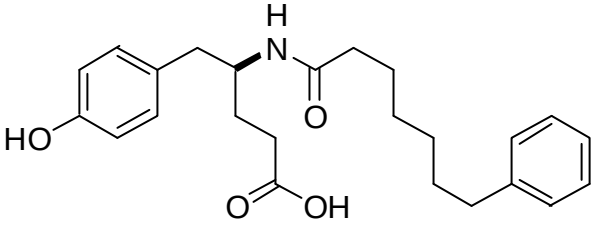


Prepared from **8** (R^1 = Et) (200 mg, 0.47 mmol) and 1-bromoheptane (136 mg, 0.76 mmol) to afford the ethyl ester of **2p** (169 mg, 68%): chromatographed on silica gel using 1:3 EtOAc-petroleum ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H) superimposed upon 1.20-1.68 (m, 17H), 1.71-1.79 (m, 3H), 2.08 (t, *J* = 7.5 Hz, 2H), 2.23-2.44 (m, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.64-2.82 (m, 2H), 3.90 (t, *J* = 6.6 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H) superimposed upon 4.01-4.20 (m, 1H), 5.35 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 7.13-7.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 172.7, 157.8, 142.6, 130.3, 129.3, 128.4, 128.2, 125.6, 114.4, 67.9, 60.5, 50.1, 40.3, 36.9, 35.9, 31.8, 31.2,

29.3, 29.1, 28.9, 28.7, 26.0, 25.6, 22.6, 14.2, 14.1, with two resonances obscured. ESMS 524 $(M+H)^+$. The ethyl ester of **2p** (165 mg, 0.32 mmol) was hydrolysed according to the method outlined in general procedure A to yield, after purification by rp-hplc (method D), **2p** (73 mg, 47%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.20-1.68 (m, 17H), 1.71-1.79 (m, 2H), 1.86-1.95 (m, 1H), 2.04-2.15 (m, 2H), 2.32-2.41 (m, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.71 (dd, *J* = 14.2, 6.4 Hz, 1H) superimposed upon 2.76 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.90 (t, *J* = 6.6 Hz, 2H), 4.14- 4.23 (br m, 1H), 5.35 (d, *J* = 9.0, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 7.13-7.19 (m, 2H), 7.24-7.30 (m, 3H), with one resonance obscured. ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 173.8, 158.1, 142.6, 130.2, 128.8, 128.4, 128.3, 125.6, 114.6, 68.0, 49.8, 40.35, 36.8, 35.9, 31.8, 31.3, 31.2, 29.9, 29.3, 29.1, 29.0, 28.9, 26.0, 25.6, 22.6, 14.0. $[\alpha]_D^{26}$ = -4.5° (c 0.71, MeOH). ESHRMS $[M+H]^+$ for $C_{31}H_{45}NO_4$: Calcd. 496.3419 Found 496.3399. Retention time (rp-HPLC): 14.5 min (method C), 29.1 min (method A).

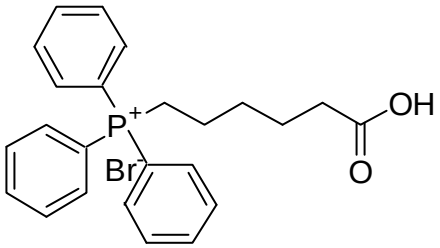
(*S*)-5-(4-Hydroxy-phenyl)-4-(7-phenyl-heptanoylamino)-pentanoic acid (2q)

Compound **8** (R^1 = Et) (200 mg, 0.47 mmol) was hydrolysed according to the method outlined in general procedure A to yield, after purification by rp-hplc (method D), **2q** as a white powder (97 mg, 52%). ^{1}H NMR (500 MHz,



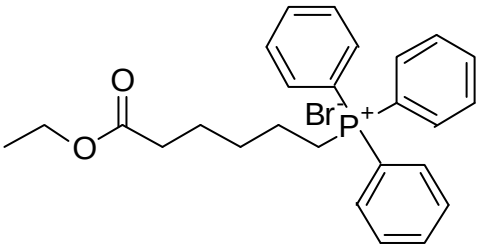
95:5 $CDCl_3$-DMSO-d_6) δ 0.92-1.05 (m, 4H), 1.19-1.34 (m, 5H), 1.43-1.53 (m, 1H), 1.78 (t, *J* = 7.3 Hz, 2H), 1.88-2.03 (m, 2H), 2.27 (t, *J* = 8.0 Hz, 2H) superimposed upon 2.29 (dd, *J* = 13.9, 7.4 Hz 1H), 2.39 (dd, *J* = 13.9, 6.4. Hz, 1H), 3.65-3.76 (m, 1H), 6.38 (s, 1H) superimposed upon 6.40 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 9.3 Hz, 2H), 6.02-6.86 (m, 3H), 6.91-6.96 (m, 2H), 8.39 (s, 1H), with one resonance obscured. ^{13}C NMR (75 MHz, 95:5 $CDCl_3$-DMSO-d_6) δ 175.8, 173.3, 156.1, 143.0, 130.6, 129.0, 128.7, 128.5, 125.9, 115.6, 50.4, 36.8, 36.1, 31.6, 31.5, 29.4, 29.3, 26.0, with two resonances obscured. $[\alpha]_D^{26}$ = -2.6° (c 1.0, MeOH). ESHRMS $[M+H]^+$ for $C_{24}H_{31}NO_4$: Calcd. 398.2324 Found 398.2345. Retention time (rp-HPLC): 18.0 min (method B), 15.1 min (method G).

Synthesis of (5-carboxypentyl)triphenylphosphonium bromide



6-bromohexanoic acid (50 g, 0.26 mol) and triphenylphosphine (67.2 g, 0.26 mol) were heated at 140 °C under argon. After 16 h, a glassy solid was obtained. Recrystallisation from $CHCl_3$/ether (a seed crystal was added to aid crystallization) afforded pure title compound as a white solid, (95.7 g, 82%).

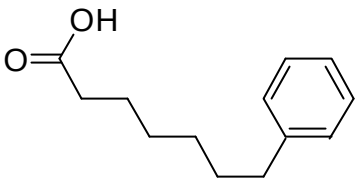
Synthesis of (5-Ethoxycarbonyl-pentyl)-triphenyl-phosphonium bromide



Ethyl 6-bromohexanoate (73 g, 0.32 mol) and triphenylphosphine (82.8 g, 0.32 mol) were heated at 90° C under argon. After 16 h, a translucent amorphous solid was obtained. The material was stored under vacuum over P_2O_5, and used without further purification.

General procedure C: Preparation of Substituted and Unsubstituted Phenylalkanoic Acids.

Example: synthesis of 7-phenylheptanoic acid.

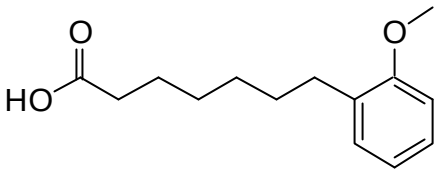


Benzaldehyde (6.63g, 0.062 mol, 6.35 mL) in dry THF (20 mL) was added dropwise to a suspension of NaH (60 % dispersion, 5.51 g, 0.138 mol) and (5-carboxypentyl)triphenylphosphonium bromide (30 g, 0.066 mol) in dry THF (260 mL). After stirring overnight, the solvent was removed, and the residue suspended in water (300 mL). The solution was made alkaline (pH 12-14) with NaOH solution (4 *M*) and extracted with EtOAc. The basic solution was then acidified (conc. HCl), extracted with Et_2O, and the combined extracts washed with brine and dried with $MgSO_4$. Removal of the solvent afforded 16.5 g of crude product which was purified by chromatography (silica gel, 1:5 EtOAc-petroleum ether, increasing to 1:1 EtOAc-petroleum ether toward completion) to give 7-phenyl-hept-6-enoic acid (*ca*. 1:1 mixture of *E*- and *Z*-isomers; 10.81g, 85 %). Hydrogenation of this mixture using 10% Pd-C in EtOAc afforded the title compound as a pale yellow oil (quantitative): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (m, 4H), 1.61 (m, 4H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 7.20 (m, 5H), 11.57 (br s, 1H). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 24.7, 29.0, 31.4, 34.2, 36.0, 125.7, 128.4, 128.5, 142.7, 180.8.

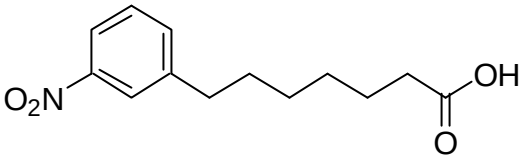
Also obtained in this fashion was:

7-(2-Methoxy-phenyl)-heptanoic acid.



Prepared from 2-methoxybenzaldehyde (5.0 g, 36.8 mmol) and (5-carboxypentyl)triphenylphosphonium bromide (16.8g, 36.8 mmol) to give the title compound (86% yield): chromatographed on silica gel using 1:3 EtOAc-petroleum ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (m, 4H), 1.70 (m, 4H), 2.41 (t, *J* = 8 Hz, 2H), 2.64 (t, *J* = 8 Hz, 2H), 3.84 (s, 3H), 6.80 (m, 3H), 7.24 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 29.0, 31.3, 34.2, 36.0, 55.2, 111.0, 114.3, 121.0, 129.3, 144.4, 159.7, 180.6.

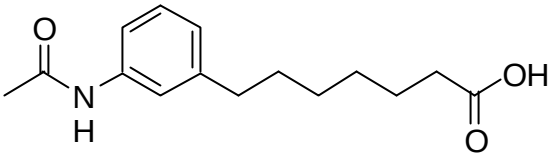
7-(3-Nitro-phenyl)-heptanoic acid.



Prepared from *m*-nitro benzaldehyde (5.0g, 33.1 mmol) and (5-carboxypentyl)triphenylphosphonium bromide (15.9 g, 34.8 mmol) to give, after hydrogenation, 7-(3-amino-phenyl)-heptanoic acid (52% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (m, 4H), 1.65 (m, 4H), 2.35 (t, *J* = 8 Hz, 2H), 2.52 (t, *J* = 8 Hz), 6.53 (m, 2H), 6.60 (d of mult, 1H), 7.07 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 29.0, 31.2, 34.2, 36.0, 113.0, 115.7, 119.3, 129.3, 144.1, 146.1, 179.9. ESMS m/z 222 $(M+H)^+$. Oxidation[6] of 7-(3-amino-phenyl)-heptanoic acid with oxone in aqueous acetone gave the title compound (31% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (m, 4H), 1.63 (m, 4H), 2.33 (t, *J* = 7 Hz, 2H), 2.69 (t, *J* = 8 Hz, 2H), 7.44 (m, 2H), 8.02 (m,

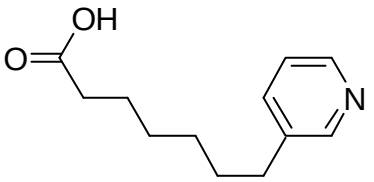
2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 28.88, 28.93, 31.0, 34.1, 35.6, 121.1, 123.3, 129.3, 134.9, 144.7, 148.5, 180.2.

7-(3-Acetylamino-phenyl)-heptanoic acid.



Prepared from *N*-(3-formyl-phenyl)-acetamide[7] (5.93 g, 36.3 mmol) and (5-carboxypentyl)triphenylphosphonium bromide (17.45 g, 38.2 mmol) to give the title compound (25% yield): ^{1}H NMR (300 MHz, Acetone-*d*6) δ 1.36 (m, 4H), 1.62 (m, 4H), 2.06 (s, 3H), 2.28 (t, *J* = 7 Hz, 2H), 2.57 (t, *J* = 7 Hz, 2H), 6.88 (d, *J* = 8 Hz, 1H), 7.17 (t, *J* = 8 Hz, 1H), 7.46 (d, 1H) overlapped with 7.48 (s, 1H), 9.08 (br s, 1H). ^{13}C NMR (75 MHz, Acetone-*d*6) δ 24.4, 25.6, 32.1, 34.2, 36.6, 117.4, 120.0, 124.2, 129.4, 140.5, 144.1, 168.9, 174.8.

7-Pyridin-3-yl-heptanoic acid.



Prepared from (5-ethoxycarbonyl-pentyl)-triphenyl-phosphonium bromide (156 g, 0.32 mol) and 3-pyridinecarboxaldehyde (30.8 g, 27.1 ml, 0.29 mol) to give 33.2 g (49%) of 7-pyridin-3-yl-hept-6-enoic acid ethyl ester (as mixture of *E*- and *Z*-isomers): purified by distillation and isolated as a yellow liquid (b.p.$_{0.2}$ 134-138°C). ESMS m/z 234 $(M+H)^+$. Hydrogenation of this mixture over 10% Pd-C in MeOH gave 7-pyridin-3-yl-heptanoic acid ethyl ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 6 Hz, 3H), 1.29-1.44 (m, 4H), 1.51-1.72 (m, 4H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.60

(t, *J* = 7.5 Hz, 2H), 4.12 (q, *J* = 6 Hz, 2H), 7.20 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.47 (m, 1H), 8.38-8.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 24.9, 28.9, 29.0, 31.0, 33.0, 34.4, 60.3, 123.3, 135.9, 137.9, 147.3, 150.1, 173.8. ESMS m/z 235 $(M+H)^+$. 7-Pyridin-3-yl-heptanoic acid ethyl ester (5.0g, 21 mmol) was hydrolysed according to the method outlined in general procedure A to afford the title compound (3.56 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30-1.45 (m, 4H), 1.57-1.71 (m, 4H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.50-7.61 (m, 1H), 8.39-8.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 28.9, 29.0, 30.9, 33.0, 34.7, 123.8, 137.2, 138.7, 145.8, 148.4, 177.9. ESMS m/z 207 $(M+H)^+$.

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