Electronic Supplementary Information

Synthesis and Biological Evaluation of Analogs of AAL(S) for Use as Ceramide Synthase 1 Inhibitors

Hamish D. Toop, a Anthony S. Don, b Jonathan C. Morris*,a

a School of Chemistry, UNSW Australia, Sydney, NSW, Australia, 2052.
b Prince of Wales Clinical School, Faculty of Medicine, UNSW Australia, Sydney, NSW, Australia, 2052

Table of contents

1. Biological Experiments 1
2. General Experimental 2
3. Experimental 4
4. NMR Spectra 20
5. References 58
1. Biological Experiments

Ceramide Synthase 1 Activity Assays

CerS activity was assayed using extracts of HEK293 cells overexpressing human CerS1, CerS2, CerS5, or CerS6 as the source of enzyme, and fluorescent (2S,3R)-2-amino-18((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl) amino)octadecane-1-3-diol (NBD-dihydrosphingosine) substrate, as described. CerS4 was overexpressed in the astrocytoma cell line U251 rather than HEK293, as much higher levels of activity for this enzyme were achieved in U251 extracts. Briefly, 50 μL reactions containing 25 mM Hepes, pH 7.4, 25 mM KCl, 2 mM MgCl₂, 0.5 mM dithiothreitol, 0.01% (w/v) fatty acid poor BSA, 50 μM fatty acid-coenzyme A (CoA) substrate, and 5 μg CerS1-expressing HEK293 cell extract, were pre-incubated for 2 min with 10 μM test compounds, and reactions were started with the addition of 10 μM NBD-dihydrosphingosine substrate. For CerS1 and CerS4, C18:0-CoA substrate was used; for CerS2, C24:1-CoA was used; and for CerS5 and CerS6, C16:0-CoA was used. Reactions were stopped with addition of 200 μL methanol, stored at 4°C overnight, centrifuged at 21,800 × g for 15 min to pellet any precipitates, and 150 μL supernatant was transferred to glass HPLC vials with 400 μL fused glass inserts. Fluorescent NBD-dihydroceramide reaction products were quantified on a Thermo Surveyor HPLC with a Shimadzu RF-10AXL fluorescence detector, using reverse phase chromatography on a 3 × 150 mm Agilent XDB-C8 column, as described. The NBD-dihydrosphingosine was sourced from Avanti Polar Lipids, fatty acid-CoAs were from Sigma Aldrich, and fatty acid poor BSA was from SAFC Biosciences.

Product peak areas were quantified using Thermo XCalibur software. Results for each compound, as shown in Table 1, were derived from two independent assay runs, each run including three assays for each compound (i.e. n = 6). Results were normalised to the vehicle control (100% activity). Results for Figure 2 are derived from three assays for each ceramide synthase isoform (i.e. n = 3).

Cell Culture and Viability Assays

K562 cells (American Type Culture Collection) were cultured in RPMI medium containing 10% foetal bovine serum (FBS) and 2 mM L-glutamine. Cell culture reagents were purchased from Thermo Fisher Scientific. To assess the effect of compounds on cell viability, 2 × 10⁵ cells were seeded in 1 mL medium containing 1% FBS and incubated for
48 hours with test compounds at a final concentration of 10 μM. The cells were then incubated for 5 min with 1 µg/mL propidium iodide and transferred to flow cytometry tubes. Propidium iodide fluorescence was analysed on a Beckton Dickson FACS Scan II flow cytometer. Percentage viability refers to the percentage of propidium iodide negative cells. Results shown are the mean and standard error derived from three independent assays.

2. General Experimental

Melting points were obtained on OptiMelt Automated Melting Point System with Digital Image Processing Technology and are uncorrected. $^1$H NMR and $^{13}$C NMR were recorded at the Nuclear Magnetic Resonance Facility within the Mark Wainwright Analytical Centre at The University of New South Wales on a Bruker Avance III 300 (300 MHz), Bruker DPX 300 (300 MHz), Bruker Avance III 400 (400 MHz), Bruker Avance III 500 (500 MHz) or Bruker Avance III 600 (600 MHz), with data acquired and processed using TopSpin 3.0 software. Chemical shifts are expressed in parts per million (PPM) on the $\delta$ scale. Chemical shifts in (a) CDCl$_3$ were referenced relative to CHCl$_3$ (7.26 ppm) for $^1$HNMR and CHCl$_3$ (77.16 ppm) for $^{13}$CNMR, (b) MeOD were referenced relative to CH$_3$OH (3.31 ppm) for $^1$HNMR and CD$_3$OD (49.00 ppm) for $^{13}$CNMR, and (c) (CD$_3$)$_2$SO were referenced relative to (CH$_3$)$_2$SO (2.50 ppm) for $^1$HNMR and (CD$_3$)$_2$SO (39.52 ppm) for $^{13}$CNMR spectroscopy.[2] Infrared spectra were obtained on a ThermoNicolet Avatar 370 FT–IR spectrometer and are reported in wavenumbers (cm$^{-1}$). Spectra were recorded from thin films using NaCl plates. HRMS were performed at the Bioanalytical Mass Spectrometry Facility within the Mark Wainwright Analytical Centre at The University of New South Wales on an Orbitrap LTQ XL (Thermo Fisher Scientific, San Jose, Ca, USA) ion trap mass spectrometer using a nanospray (nano-electrospray) ionization source to generate ions from the analyte in solution. The instrument was calibrated with a standard calibration solution (as outlined in the instrument manual) on the day of analysis using direct infusion with the nanospray source. The instrument conditions were optimized for sensitivity on each compound of interest using LC tune software. The analysis was carried out in positive ion mode using the orbitrap FTMS analyser at a resolution of 100000. Samples, 5 μL, (1 µg/mL in methanol or acetonitrile), were injected into a glass needle and inserted into the nanospray source. Ions generated were measured over the mass range 150 to 2000. Data was acquired in full scan mode over 60 seconds. Data was analyzed using the Qual Browser feature in Xcaliber 2.1
Optical rotations (\(\alpha\)) were recorded on Rudolph Research Analytical Autopol 1 Automatic Polarimeter. Samples were prepared in 10 or 5 mL volumetric flasks at stated concentration (g/100 mL) in chloroform. Measurements were taken at 589 nm (sodium D line), at the stated temperature in a 1.0 or 0.5 dm path length optical cell. Values are reported as specific rotations ([\(\alpha\)]). The units of the specific rotation, (deg·mL)/(g·dm), are implicit and are not included with the reported value.

Unless otherwise stated all reactions were performed in flame dried glassware under an atmosphere of dry argon. Reaction temperatures refer to the external bath temperature. Concentration of solvents was performed under reduced pressure on a rotary evaporator after which, residual solvent was removed under high vacuum (~0.1 mm/Hg).

Reagents and solvents were purchased from commercial sources and used without further purification, unless stated below. Reagents and solvents used in reactions were purified according to well established procedures. In particular, tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone under an inert atmosphere of argon. N,N-Dimethylformamide (DMF) was dried sequentially over three batches of 4Å molecular sieves (3 × 24 h), before finally being stored over a fourth batch of 4Å molecular sieves, under argon. To remove residual N,N-dimethylamine from DMF, the solvent was evacuated (~0.1 mm/Hg) for at least 30 min prior to use. Methanol was distilled from magnesium and stored over 3Å molecular sieves, under argon. Triethylamine and dichloromethane were distilled from calcium hydride immediately prior to use. (S)-Schöllkopf (S)-4 reagent was distilled immediately before use (53 – 55°C at 0.1 mm/Hg). n-Butyllithium in hexanes was purchased from Sigma Aldrich and titrated using menthol and 2,2'-bipyridyl in THF as described by Eastham.

Analytical thin layer chromatography was conducted on Merck, aluminium-backed silica plates 60 F\(_{254}\) or silica gel 60 RP-C\(_{18}\) F\(_{254}\) plates and visualised using UV light and stained with a dip of either a potassium permanganate, vanillin or phosphomolybdic acid. Flash chromatography was routinely performed using Grace Davison Discovery Sciences, Davisil LC60A 40 – 63 micron silica gel, following published guidelines. Solvent was eluted using a Thomson SINGLE StEP pump at the flow rate recommended by the manufacturer (Thomson Instrument Company, Oceanside, Ca, USA). Deactivated silica gel was prepared
by washing a column packed with silica gel with neat triethylamine (5 column volumes). After drying, the column was washed with n-hexane to remove any residual triethylamine.
3. Experimental

2-(4'-t-Butyldimethylsilyloxyphenyl)ethanol (14)\(^{[6]}\)

(a) Tyrosol 12 (7.18 g, 51.94 mmol) was added as a solid in one portion to a solution of t-butyldimethylsilyl chloride (19.57 g, 129.84 mmol) and imidazole (8.84 g, 129.85 mmol) in dry DMF (50 mL) at room temperature. The solution was stirred for 12 h after which, water was added and the mixture extracted with \(n\)-hexane (× 3). The organic extracts were combined and washed with water and brine, then dried (\(\text{Na}_2\text{SO}_4\)). The solvent was removed under reduced pressure to afford the crude bis-TBS tyrosol compound 13 as a light yellow oil (17.62 g), which was used in the next step without further purification.

(b) The crude material (17.62 g) was dissolved in methanol (140 mL) and iodine (1.76 g, 10 wt/wt %, 6.94 mmol) was added. The solution was stirred at room temperature for 4 h. 10 % Aqueous sodium thiosulfate solution was added until the solution remained colourless. The methanol was removed under reduced pressure. The residue was extracted with diethyl ether (× 3). The organic extracts were combined and washed with water and brine, then dried (\(\text{Na}_2\text{SO}_4\)). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography on silica gel, eluting with 15 % ethyl acetate/\(n\)-hexane, to afford the product 14 as a clear colourless oil (12.56 g, 96 %) with all the analytical data matching that reported in the literature.\(^{[6]}\) \(^1\text{H NMR (300 MHz; CDCl}_3\)) \(\delta\) 0.19 (s, 6H), 0.98 (s, 9H), 1.42 (br s, 1H), 2.80 (t, \(J = 6.5\) Hz, 2H), 3.82 (br t, \(J = 6.5\) Hz, 2H), 6.76 – 6.81 (m, 2H), 7.06 – 7.10 (m, 2H).

2-(4'-t-Butyldimethylsilyloxyphenyl)-1-iodoethane (5)\(^{[7]}\)

(a) Methanesulfonyl chloride (0.34 mL, 4.39 mmol) was added dropwise to a solution of alcohol 14 (1.01 g, 4.00 mmol) and triethylamine (1.7 mL, 12.20 mmol) in dichloromethane (60 mL) at 0°C. The solution was stirred at 0°C for 15 min then the cold bath was removed and the solution stirred at room temperature for 3 h. The reaction mixture was poured onto brine and the organic layer was removed. The aqueous layer was extracted further with dichloromethane (× 2). The organic extracts were combined washed with brine, then dried (\(\text{Na}_2\text{SO}_4\)). The solvent was removed under reduced pressure to afford
the crude mesylate 15 as an orange residue (1.36 g), which was used in the next step without further purification.

(b) The crude material (1.36 g) was dissolved in acetone (30 mL) and sodium iodide (6.00 g, 40.02 mmol) was added in one portion. The solution was stirred at room temperature protected from light for 14 h. The acetone was removed under reduced pressure. The residue was diluted with water and extracted with dichloromethane (× 3). The organic extracts were combined and washed with water and brine, then dried (Na₂SO₄). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography on silica gel, eluting with 1 % ethyl acetate/n-hexane, to afford the product 5 as a clear colourless oil (1.13 g, 78 %) with all the analytical data matching that reported in the literature.\[^8\] H NMR (400 MHz; CDCl₃) δ 0.19 (s, 6H), 0.98 (s, 9H), 3.18 (t, J = 7.7 Hz, 2H), 3.82 (t, J = 7.7 Hz, 2H), 6.76 – 6.79 (m, 2H), 7.02 – 7.06 (m, 2H).

(2R,5S)-5-isopropyl-3,6-dimethoxy-2-(4′-t-butyldimethylsilyloxyphenethyl)-2,5-dihydropyrazine (16)

A solution of n-butyllithium in hexanes (3.4 mL, 2.4 M, 8.16 mmol) was added dropwise to a solution of freshly distilled (S)-Schöllkopf’s reagent (S)-4 (1.50 g, 8.15 mmol) in freshly distilled THF (8 mL) at -78°C (dry ice/acetone). The solution was stirred at -78°C for 15 min, where it had turned dark yellow. A solution of iodide 5 (2.81 g, 7.75 mmol) in freshly distilled THF (6 mL) at -78°C was added dropwise. The solution was stirred for a further 30 min at -78°C then allowed to slowly warm to -15°C over 4 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and allowed to warm to room temperature. The THF was removed under reduced pressure and the residue extracted with dichloromethane (× 4). The organic extracts were combined and dried (Na₂SO₄). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography on silica gel, eluting with 2 % ethyl acetate/n-hexane, to afford the product 16 as a clear colourless oil (2.89 g, 89 %). \[^{25}\] [α]D\textsubscript{25.0} = - 6 (c 0.5, CHCl₃); H NMR (300 MHz; CDCl₃) δ 0.18 (s, 6H), 0.70 (d, J = 6.8 Hz, 3H), 0.97 (s, 9H), 1.05 (d, J = 6.8 Hz, 3H), 1.90 – 2.02 (m, 1H), 2.07 – 2.18 (m, 1H), 2.27 (septd, J = 6.8, 3.3 Hz, 1H), 2.46 – 2.62 (m, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.95 (t, J = 3.3 Hz, 1H), 4.02 – 4.07 (m, 1H), 6.71 – 6.76 (m, 2H),
7.01 – 7.06 (m, 2H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) -4.3, 16.8, 18.3, 19.2, 25.9, 30.3, 31.9, 36.0, 52.50, 52.51, 55.1, 61.0, 119.9, 129.4, 134.9, 153.7, 163.7, 163.9; IR (NaCl, neat) 1697 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{23}\)H\(_{39}\)N\(_2\)O\(_3\)Si [M+Na]\(^+\) 419.2729, found 419.2710.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4’-t-butyldimethylsilyloxyphenethyl)-2-methyl-2,5-dihydropyrazine (6)

![Diagram](https://example.com/diagram.png)

A solution of \(n\)-butyllithium in hexanes (3.7 mL, 2.4 M, 8.88 mmol) was added dropwise to a solution of bis-lactim ether 16 (2.89 g, 6.90 mmol) in freshly distilled THF (25 mL) at -78°C (dry ice/acetone). The solution was stirred at -78°C for 15 min, where it had turned dark yellow. Methyl iodide (0.55 mL, 8.83 mmol) was added dropwise. The solution was stirred for a further 30 min at -78°C then allowed to slowly warm to -15°C over 4 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and allowed to warm to room temperature. The THF was removed under reduced pressure and the residue was extracted with dichloromethane (\(\times\) 4). The organic extracts were combined and dried (Na\(_2\)SO\(_4\)). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography on silica gel, eluting with 2 % ethyl acetate/n-hexane, to afford the product 7 as a clear colourless oil (2.85 g, 96 %). \([\alpha]_{D}^{25.3} = + 54\) (c 0.5, CHCl\(_3\)); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) 0.17 (s, 6H), 0.70 (d, \(J = 6.8\) Hz, 3H), 0.98 (s, 9H), 1.12 (d, \(J = 6.8\) Hz, 3H), 1.31 (s, 3H), 1.85 (td, \(J = 12.8, 5.0\) Hz, 1H), 2.08 (td, \(J = 12.9, 4.3\) Hz, 1H), 2.23 (td, \(J = 12.9, 4.3\) Hz, 1H), 2.32 – 2.46 (m, 2H), 3.70 (s, 3H), 3.71 (s, 3H), 3.71 (s, 3H), 3.94 (d, \(J = 3.3\) Hz, 1H), 6.71 – 6.75 (m, 2H), 6.99 – 7.02 (m, 2H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) -4.3, 17.1, 18.3, 19.7, 25.9, 28.7, 30.7, 30.9, 42.8, 52.4, 58.4, 60.5, 119.9, 129.3, 135.5, 153.6, 162.1, 165.7; IR (NaCl, neat) 1690 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{24}\)H\(_{41}\)N\(_2\)O\(_3\)Si [M+H]\(^+\) 433.2886, found 433.2887.

General procedure A for the one-pot TBS-deprotection/alkylation procedure

![Diagram](https://example.com/diagram.png)
Cesium fluoride (2 eq) was added in one portion to a solution of bis-lactim ether 6 (1 eq) in dry DMF (0.15 M) at room temperature. The solution was stirred for 15 min, where it had turned dark orange, before alkyl-halide (1.05 eq) was added dropwise. The solution was stirred at room temperature for 14 h. Water was added and the mixture was extracted with ethyl acetate (× 3). The organic extracts were combined and washed with water and brine, then dried (Na₂SO₄). The solvent was removed under reduced pressure and the crude material was purified, as indicated, to afford the product 7.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4′-methoxyphenethyl)-2-methyl-2,5-dihydropyrazine (7a)
Prepared using general procedure A using cesium fluoride (51 mg, 0.34 mmol), bis-lactim ether 6 (71 mg, 0.16 mmol), methyl iodide (22 μL, 0.35 mmol) and dry DMF (2 mL). The crude material was purified by flash chromatography on silica gel, eluting with 3 % ethyl acetate/n-hexane, to afford the product 7a as a clear colourless oil (54 mg, 98 %). [α]^{23.0}_{D} = + 3 (c 0.5, CHCl₃); ^1H NMR (300 MHz; CDCl₃) δ 0.71 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.32 (s, 3H), 1.86 (td, J = 12.8, 5.0 Hz, 1H), 2.09 (td, J = 12.8, 4.3 Hz, 1H), 2.26 (td, J = 12.8, 4.3 Hz, 1H), 2.33 – 2.49 (m, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 3.95 (d, J = 3.3 Hz, 1H), 6.80 – 6.84 (m, 2H), 7.07 – 7.11 (m, 2H); ^13C NMR (75 MHz; CDCl₃) δ 17.1, 19.7, 28.7, 30.7, 30.8, 43.0, 52.4, 55.4, 58.4, 60.5, 113.9, 129.3, 134.9, 157.8, 162.1, 165.7; IR (NaCl, neat) 1690 cm⁻¹; HRMS (ESI-MS): m/z calcd for C_{19}H_{29}N_{2}O_{3} [M+H]^+ 333.2178, found 333.2175.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4′-butoxyphenethyl)-2-methyl-2,5-dihydropyrazine (7b)
Prepared using general procedure A using cesium fluoride (67 mg, 0.44 mmol), bis-lactim ether 6 (95 mg, 0.2 mmol), 1-bromobutane (48 μL, 0.44 mmol) and dry DMF (2 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % ethyl acetate/n-hexane, to afford the product 7b as a clear colourless oil (58 mg, 71 %). [α]^{21.6}_{D} = + 4 (c 0.5, CHCl₃); ^1H NMR (300 MHz; CDCl₃) δ 0.70 (d, J = 6.8 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.30 (s, 3H), 1.42 – 1.54 (m, 2H), 1.70 – 1.90 (m, 3H), 2.08 (td, J = 12.8, 4.3 Hz, 1H), 2.24 (td, J = 12.8, 4.3 Hz, 1H), 2.32 – 2.47 (m, 2H), 3.70 (s, 3H), 3.71 (s, 3H), 3.91 – 3.95 (m, 3H), 6.78 – 6.83 (m, 2H), 7.04 – 7.07 (m, 2H); ^13C NMR (75 MHz; CDCl₃) δ 14.0, 17.1, 19.4, 19.7, 28.7, 30.7, 30.8, 31.5, 43.0, 52.4, 58.4, 60.5, 67.9,
114.5, 129.3, 134.7, 157.3, 162.1, 165.7; IR (NaCl, neat) 1691 cm⁻¹; HRMS (ESI-MS): m/z calcd for C₂₂H₃₅N₂O₃ [M+H]⁺ 375.2648, found 375.2645.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4'-heptoxyphenethyl)-2-methyl-2,5-dihydropyrazine (7c)

Prepared using general procedure A using cesium fluoride (0.48 g, 3.15 mmol), bis-lactim ether 6 (0.67 g, 1.56 mmol), 1-bromoheptane (0.30 mL, 1.91 mmol) and dry DMF (10 mL). The crude material was purified by flash chromatography on silica gel, eluting with 5 % ethyl acetate/n-hexane, to afford the product 7c as a clear colourless oil (0.54 g, 88 %).

[α]^{26.7}_D = + 46 (c 0.5, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 0.70 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.25 – 1.47 (m, 11H), 1.71 – 1.81 (m, 2H), 1.85 (td, J = 12.9, 5.0 Hz, 1H), 2.08 (td, J = 12.9, 4.3 Hz, 1H), 2.23 (td, J = 12.9, 4.3 Hz, 1H), 2.32 – 2.47 (m, 2H), 3.70 (s, 3H), 3.71 (s, 3H), 3.92 (t, J = 6.6 Hz, 2H) 3.94 (d, J = 3.3 Hz, 1H), 6.78 – 6.82 (m, 2H), 7.04 – 7.07 (m, 2H); ¹³C NMR (75 MHz; CDCl₃) δ 14.2, 17.1, 19.7, 22.8, 26.2, 28.7, 29.2, 29.5, 30.7, 30.8, 31.9, 43.0, 52.4, 58.4, 60.5, 68.2, 114.5, 129.3, 134.7, 157.3, 162.1, 165.7; IR (NaCl, neat) 1691 cm⁻¹; HRMS (ESI-MS): m/z calcd for C₂₅H₄₁N₂O₃ [M+H]⁺ 417.3117, found 417.3094.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4'-octoxyphenethyl)-2-methyl-2,5-dihydropyrazine (7d)

Prepared using general procedure A using cesium fluoride (0.15 g, 0.99 mmol), bis-lactim ether 6 (0.21 g, 0.49 mmol), 1-bromoocctane (0.10 mL, 0.58 mmol) and dry DMF (3 mL). The crude material was purified by flash chromatography on silica gel, eluting with 5 % ethyl acetate/n-hexane, to afford the product 7d as a clear colourless oil (0.17 g, 81 %).

[α]^{25.1}_D = + 60 (c 0.5, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 0.70 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.23 – 1.47 (m, 13H), 1.71 – 1.81 (m, 2H), 1.85 (td, J = 12.8, 5.0 Hz, 1H), 2.08 (td, J = 12.8, 4.3 Hz, 1H), 2.24 (td, J = 12.8, 4.3 Hz, 1H), 2.32 – 2.48 (m, 2H), 3.70 (s, 3H), 3.71 (s, 3H), 3.90 – 3.95 (m, 3H), 6.78 – 6.83 (m, 2H), 7.04 – 7.07 (m, 2H); ¹³C NMR (75 MHz; CDCl₃) δ 14.2, 17.1, 19.7, 22.8, 26.2, 28.7, 29.4, 29.49, 29.52, 30.7, 30.8, 32.0, 43.0, 52.4, 58.4, 60.5, 68.2, 114.5, 129.3, 134.7, 157.3, 162.1, 165.7; IR (NaCl, neat) 1691 cm⁻¹; HRMS (ESI-MS): m/z calcd for C₂₆H₄₃N₂O₃ [M+H]⁺ 431.3274, found 431.3256.
(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4'-nonoxyphenethyl)-2-methyl-2,5-dihydropyrazine (7e)

Prepared using general procedure A using cesium fluoride (81 mg, 0.53 mmol), bis-lactim ether 6 (0.12 g, 0.27 mmol), 1-bromononane (0.10 mL, 0.54 mmol) and dry DMF (3 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % ethyl acetate/n-hexane, to afford the product 7e as a clear colourless oil (0.11 g, 89 %). 

\[ [\alpha]^{26.5}_{D} = +32 \, (c \, 0.5, \text{CHCl}_3); \]

\[ ^1H \text{ NMR (300 MHz; CDCl}_3) \delta 0.70 \, (d, J = 6.8 \, Hz, \, 3H), \, 0.89 \, (t, \, J = 6.8 \, Hz, \, 3H), \, 1.12 \, (d, \, J = 6.8 \, Hz, \, 3H), \, 1.23 - 1.49 \, (m, \, 12H), \, 1.31 \, (s, \, 3H), \, 1.71 - 1.81 \, (m, \, 2H), \, 1.85 \, (td, \, J = 12.8, \, 5.0 \, Hz, \, 1H), \, 2.08 \, (td, \, J = 12.8, \, 4.3 \, Hz, \, 1H), \, 2.24 \, (td, \, J = 12.8, \, 4.3 \, Hz, \, 1H), \, 2.32 - 2.48 \, (m, \, 2H), \, 3.70 \, (s, \, 3H), \, 3.71 \, (s, \, 3H), \, 3.90 - 3.95 \, (m, \, 3H), \, 6.78 - 6.83 \, (m, \, 2H), \, 7.04 - 7.07 \, (m, \, 2H); \]

\[ ^13C \text{ NMR (75 MHz; CDCl}_3) \delta 14.3, \, 17.1, \, 19.7, \, 22.8, \, 26.2, \, 28.7, \, 29.4, \, 29.5, \, 29.6, \, 29.7, \, 30.7, \, 30.8, \, 32.0, \, 43.0, \, 52.4, \, 58.4, \, 60.5, \, 68.2, \, 114.5, \, 129.3, \, 134.7, \, 157.3, \, 162.1, \, 165.7; \]

IR (NaCl, neat) 1691 cm\(^{-1}\); HRMS (ESI-MS): m/z calcd for C\(_{27}\)H\(_{45}\)N\(_2\)O\(_3\) [M+H]+ 445.3430, found 445.3418.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4'-decoxyphenethyl)-2-methyl-2,5-dihydropyrazine (7f)

Prepared using general procedure A using cesium fluoride (67 mg, 0.44 mmol), bis-lactim ether 6 (95 mg, 0.22 mmol), 1-bromodecane (92 \(\mu\)L, 0.44 mmol) and dry DMF (2 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % ethyl acetate/n-hexane, to afford the product 7f as a clear colourless oil (78 mg, 77 %). 

\[ [\alpha]^{21.9}_{D} = +4 \, (c \, 0.5, \text{CHCl}_3); \]

\[ ^1H \text{ NMR (300 MHz; CDCl}_3) \delta 0.70 \, (d, J = 6.8 \, Hz, \, 3H), \, 0.88 \, (t, \, J = 6.8 \, Hz, \, 3H), \, 1.12 \, (d, \, J = 6.8 \, Hz, \, 3H), \, 1.23 - 1.48 \, (m, \, 14H), \, 1.30 \, (s, \, 3H), \, 1.71 - 1.81 \, (m, \, 2H), \, 1.85 \, (td, \, J = 12.8, \, 5.0 \, Hz, \, 1H), \, 2.08 \, (td, \, J = 12.8, \, 4.3 \, Hz, \, 1H), \, 2.24 \, (td, \, J = 12.8, \, 4.3 \, Hz, \, 1H), \, 2.32 - 2.47 \, (m, \, 2H), \, 3.70 \, (s, \, 3H), \, 3.71 \, (s, \, 3H), \, 3.90 - 3.94 \, (m, \, 3H), \, 6.79 - 6.82 \, (m, \, 2H), \, 7.04 - 7.07 \, (m, \, 2H); \]

\[ ^13C \text{ NMR (75 MHz; CDCl}_3) \delta 14.3, \, 17.1, \, 19.7, \, 22.8, \, 26.2, \, 28.7, \, 29.4, \, 29.5, \, 29.6, \, 29.7, \, 30.7, \, 30.8, \, 32.0, \, 43.0, \, 52.4, \, 58.4, \, 60.5, \, 68.2, \, 114.5, \, 129.3, \, 134.7, \, 157.3, \, 162.1, \, 165.7; \]

IR (NaCl, neat) 1694 cm\(^{-1}\); HRMS (ESI-MS): m/z calcd C\(_{28}\)H\(_{47}\)N\(_2\)O\(_3\) [M+H]+ 459.3587, found 459.3587.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4'-dodecoxyphenethyl)-2-methyl-2,5-dihydropyrazine (7g)

Prepared using general procedure A using cesium fluoride (81 mg, 0.53 mmol), bis-lactim ether 6 (0.12 g, 0.27 mmol), 1-bromododecane (0.13 mL, 0.53 mmol) and dry DMF (3 mL).
The crude material was purified by flash chromatography on silica gel, eluting with 2 % ethyl acetate/n-hexane, to afford the product 7g as a clear colourless oil (0.13 g, 98 %). 

\([\alpha]^{26.5}_D = + 32\) (c 0.5, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 0.70 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.27 – 1.49 (m, 18H), 1.31 (s, 3H), 1.71 – 1.81 (m, 2H), 1.85 (td, J = 12.8, 5.0 Hz, 1H), 2.08 (td, J = 12.8, 4.3 Hz, 1H), 2.24 (td, J = 12.8, 4.3 Hz, 1H), 2.32 – 2.48 (m, 2H), 3.70 (s, 3H), 3.71 (s, 3H), 3.90 – 3.95 (m, 3H), 6.78 – 6.83 (m, 2H), 7.04 – 7.07 (m, 2H); ¹³C NMR (75 MHz; CDCl₃) δ 14.3, 17.1, 19.7, 22.8, 26.2, 28.7, 29.5, 29.6, 29.7, 29.75, 29.79, 29.81, 30.7, 30.8, 32.1, 43.0, 52.4, 58.4, 60.5, 68.2, 114.5, 129.3, 134.7, 157.4, 162.1, 165.7; IR (NaCl, neat) 1691 cm⁻¹; HRMS (ESI-MS): m/z calcd for C₂₈H₄₇N₂O₃ [M+H]⁺ 487.3900, found 487.3883.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4'-benzyloxyphenethyl)-2-methyl-2,5-dihydropyrazine (7h)

Prepared using general procedure A using cesium fluoride (0.14 g, 0.89 mmol), bis-lactim ether 6 (0.19 g, 0.44 mmol), benzylbromide (0.11 mL, 0.92 mmol) and dry DMF (4 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % ethyl acetate/n-hexane, to afford the product 7h as a clear colourless oil (0.15 g, 83 %). 

\([\alpha]^{22.3}_D = + 4\) (c 0.5, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 0.71 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.31 (s, 3H), 1.86 (td, J = 12.8, 5.0 Hz, 1H), 2.09 (td, J = 12.8, 4.3 Hz, 1H), 2.25 (td, J = 12.8, 4.3 Hz, 1H), 2.33 – 2.49 (m, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 3.95 (d, J = 3.3 Hz, 1H), 5.04 (s, 2H), 6.87 – 6.92 (m, 2H), 7.07 – 7.10 (m, 2H), 7.29 – 7.45 (m, 5H); ¹³C NMR (75 MHz; CDCl₃) δ 17.1, 19.7, 28.7, 30.7, 30.8, 42.9, 52.4, 58.4, 60.5, 70.2, 114.8, 127.6, 128.0, 128.7, 129.4, 135.2, 137.4, 157.0, 162.1, 165.7; IR (NaCl, neat) 1694 cm⁻¹; HRMS (ESI-MS): m/z calcd for C₂₅H₃₃N₂O₃ [M+H]⁺ 409.2491, found 409.2490.

(2S,5S)-5-Isopropyl-3,6-dimethoxy-2-(4'-cyclohexylbutoxyphenyl)-2-methyl-2,5-dihydropyrazine (7i)

Prepared using general procedure A using cesium fluoride (0.15 g, 0.97 mmol), bis-lactim ether 6 (0.21 g, 0.48 mmol), (0.13 g, 0.59 mmol) and dry DMF (3 mL). The crude material was purified by flash chromatography on silica gel, eluting with 5 % ethyl acetate/n-hexane, to afford the product 7i as a clear colourless oil (0.19 g, 88 %). 

\([\alpha]^{25.1}_D = + 50\) (c 0.5, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 0.70 (d, J = 6.8 Hz, 3H), 0.82 – 0.92 (m, 2H), 1.12 (d, J = 6.8 Hz, 3H), 1.15 – 1.28 (m, 6H), 1.31 (s, 3H), 1.40 – 1.50 (m, 2H), 1.58 – 1.79 (m, 8H), 1.85 (td, J = 12.8, 5.0 Hz, 1H), 2.08 (td, J = 12.8, 4.3 Hz, 1H), 2.24 (td, J = 12.8, 4.3 Hz, 1H),
2.32 – 2.48 (m, 2H), 3.70 (s, 3H), 3.71 (s, 3H), 3.90 – 3.95 (m, 3H), 6.78 – 6.83 (m, 2H), 7.04 – 7.07 (m, 2H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) 17.1, 19.7, 23.5, 26.6, 26.9, 28.7, 29.8, 30.7, 30.8, 33.5, 37.4, 37.8, 43.0, 52.4, 58.4, 60.5, 68.2, 114.5, 129.3, 134.7, 157.4, 162.1, 165.7; IR (NaCl, neat) 1692 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{28}\)H\(_{45}\)N\(_2\)O\(_3\) [M+H]\(^+\) 457.3430, found 457.3419.

\((2S,5S)-5\text{-Isopropyl-3,6-dimethoxy-2-}(4'\text{-hydroxyphenethyl})\text{-2-methyl-2,5-dihydropyrazine (17)}\)

Cesium fluoride (72 mg, 0.47 mmol) was added in one portion to a solution of bis-lactim ether 6 (0.10 g, 0.24 mmol) in dry DMF (3 mL) at room temperature. The solution was stirred for 13 h. Water was added and the mixture was extracted with ethyl acetate (\(\times\) 3). The organic extracts were combined and washed with water and brine, then dried (Na\(_2\)SO\(_4\)). The solvent was removed under reduced pressure and the crude material purified by flash chromatography on silica gel, eluting with 10% ethyl acetate/\(n\)-hexane, to afford the product 17 as a clear colourless oil (57 mg, 76%). \([\alpha]^{21.7}_D\) = + 4 (c 0.5, CHCl\(_3\)); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) 0.72 (d, \(J = 6.8\) Hz, 3H), 1.12 (d, \(J = 6.8\) Hz, 3H), 1.34 (s, 3H), 1.86 (td, \(J = 12.9, 4.9\) Hz, 1H), 2.09 (td, \(J = 12.9, 4.3\) Hz, 1H), 2.23 (td, \(J = 12.9, 4.3\) Hz, 1H), 2.33 – 2.47 (m, 2H), 3.72 (s, 6H), 3.97 (d, \(J = 3.3\) Hz, 1H), 6.04 (s, 1H), 6.71 – 6.75 (m, 2H), 6.99 – 7.01 (m, 2H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) 17.2, 19.7, 28.7, 30.8, 42.7, 52.5, 52.6, 58.6, 60.6, 115.4, 129.5, 134.5, 153.9, 162.6, 165.7; IR (NaCl, neat) 1691, 3349 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{18}\)H\(_{27}\)N\(_2\)O\(_3\) [M+H]\(^+\) 319.2022, found 319.2016.

\((2S,5S)-5\text{-Isopropyl-3,6-dimethoxy-2-}(4'\text{-2'-(2'-methoxyethoxy)ethoxyphenethyl})\text{-2-methyl-2,5-dihydropyrazine (7j)}\)

1-Bromo-2-(2-methoxyethoxy)ethane (74 \(\mu\)L, 0.55 mmol) was added dropwise to a suspension of bis-lactim ether 17 (0.12 g, 0.36 mmol) and potassium carbonate (0.15 g, 1.09 mmol) in dry DMF (3 mL). The suspension was stirred at room temperature for 15 h
then 60°C for 6 h. The solution was allowed to cool to room temperature and water was added. The solution was extracted with ethyl acetate (× 3). The organic extracts were combined and washed with water and brine, then dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography on silica gel, eluting with 15 % ethyl acetate/n-hexane, to afford the product 7j as a clear colourless oil (68 mg, 44 %). $[\alpha]_{D}^{24.6} = +54$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) δ 0.70 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.30 (s, 3H), 1.84 (td, $J = 12.9$, 5.0 Hz, 1H), 2.07 (td, $J = 12.9$, 4.4 Hz, 1H), 2.23 (td, $J = 12.9$, 4.4 Hz, 1H), 2.32 – 2.47 (m, 2H), 3.39 (s, 3H), 3.56 – 3.59 (m, 2H), 3.70 – 3.73 (m, 8H), 3.82 – 3.86 (m, 2H), 3.72 (s, 6H), 3.93 (d, $J = 3.3$ Hz, 1H), 4.09 – 4.13 (m, 2H), 6.79 – 6.84 (m, 2H), 7.03 – 7.08 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) δ 17.1, 19.7, 28.7, 30.7, 30.8, 42.9, 52.4, 58.4, 59.2, 60.5, 67.6, 70.0, 70.9, 72.1, 114.6, 129.3, 135.1, 157.0, 162.1, 165.7; IR (NaCl, neat) 1691 cm$^{-1}$; HRMS (ESI-MS): m/z calcd for C$_{23}$H$_{37}$N$_2$O$_5$ [M+H]$^+$ 421.2703, found 421.2695.
A solution of TFA (50 eq) in water (200 % vol/vol of TFA) was added dropwise to a solution of bis-lactim ether 7 (1 eq) in acetonitrile (0.03 M). The solution was stirred at room temperature for 4 h after which the acetonitrile was removed under reduced pressure. The residue was diluted with water and neutralised with portions of solid sodium bicarbonate, then extracted with dichloromethane (× 4). The organic extracts were combined and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure and the crude material was purified, as indicated, to afford the product 18.

**Methyl (2S)-2-amino-4-(4'-methoxyphenyl)-2-methylbutanoate (18a)**

Prepared using general procedure B using TFA (1 mL), water (2 mL) bis-lactim ether 7a (67 mg, 0.20 mmol) and acetonitrile (6 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18a as a clear colourless oil (46 mg, 96 %). $[^\alpha]_{25.6}^D = + 12$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) δ 1.36 (s, 3H), 1.74 (s, 2H), 1.79 – 1.90 (m, 1H), 1.95 – 2.05 (m, 1H), 2.40 – 2.50 (m, 1H), 2.54 – 2.65 (m, 1H), 3.70 (s, 3H), 3.77 (s, 3H), 6.79 – 6.84 (m, 2H), 7.06 – 7.10 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) δ 26.6, 29.9, 43.2, 52.4, 55.4, 57.9, 114.0, 129.4, 133.7, 158.0, 178.1; IR (NaCl, neat) 1729, 3315, 3372 cm$^{-1}$; HRMS (ESI-MS): m/z calcd for C$_{13}$H$_{20}$NO$_3$ [M+H]$^+$ 238.1443, found 238.1438.

**Methyl (2S)-2-amino-4-(4'-butoxyphenyl)-2-methylbutanoate (18b)**

Prepared using general procedure B using TFA (1 mL), water (2 mL) bis-lactim ether 7b (58 mg, 0.16 mmol) and acetonitrile (6 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18b as a clear colourless oil (41 mg, 95 %). $[^\alpha]_{23.5}^D = + 12$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) δ 0.96 (t, $J = 7.3$ Hz, 3H), 1.36 (s, 3H), 1.41 – 1.54 (m, 2H), 1.69 (br s, 2H), 1.72 – 1.79 (m, 2H), 1.81 – 1.90 (m, 2H), 1.95 – 2.05 (m, 1H), 2.40 – 2.50 (m, 1H), 2.54 – 2.64 (m, 1H), 3.70 (s, 3H), 3.92 (t, $J = 6.5$ Hz, 2H), 6.78 – 6.83 (m, 2H), 7.04 – 7.09 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) δ 14.0, 19.4, 26.7, 29.9, 31.5, 43.2, 52.3, 57.9, 67.8, 114.6, 129.3, 133.5,
Methyl (2S)-2-amino-4-(4’-heptyloxyphenyl)-2-methylbutanoate (18c)
Prepared using general procedure B using TFA (10 mL), water (20 mL), bis-lactim ether 7c (0.84 g, 2.02 mmol) and acetonitrile (55 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18c as a clear colourless oil (0.56 g, 87 %). \([\alpha]^{23.3}_{D} = + 4 \text{ (c 0.5, CHCl}_3\); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) 0.88 (t, \(J = 6.8\) Hz, 3H), 1.25 – 1.48 (m, 8H), 1.36 (s, 3H), 1.71 – 1.80 (m, 4H), 1.85 (td, \(J = 12.6, 5.5\) Hz, 1H), 2.00 (td, \(J = 12.6, 5.1\) Hz, 1H), 2.23 (td, \(J = 12.6, 5.1\) Hz, 1H), 2.58 (td, \(J = 12.6, 5.5\) Hz, 1H), 3.70 (s, 3H), 3.91 (t, \(J = 6.6\) Hz, 2H), 3.94 (d, \(J = 3.3\) Hz, 1H), 6.78 – 6.82 (m, 2H), 7.04 – 7.09 (m, 2H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) 14.2, 22.7, 26.1, 29.2, 29.4, 29.8, 29.9, 31.9, 43.2, 52.27, 52.33, 57.9, 68.1, 114.6, 129.3, 133.5, 157.5, 178.1; IR (NaCl, neat) 1732, 3314, 3378 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{16}\)H\(_{26}\)NO\(_3\) [M+H]\(^+\) 280.1913, found 280.1913.

Methyl (2S)-2-amino-4-(4’-octoxyphenyl)-2-methylbutanoate (18d)
Prepared using general procedure B using TFA (3 mL), water (6 mL) bis-lactim ether 7d (0.17 g, 0.40 mmol) and acetonitrile (8 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18d as a clear colourless oil (95 mg, 64 %). \([\alpha]^{27.9}_{D} = + 16 \text{ (c 0.5, CHCl}_3\); \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 0.88 (t, \(J = 6.8\) Hz, 3H), 1.26 – 1.46 (m, 10H), 1.35 (s, 3H), 1.68 (br s, 2H), 1.71 – 1.78 (m, 2H), 1.80 – 1.88 (m, 1H), 1.96 – 2.03 (m, 1H), 2.40 – 2.48 (m, 1H), 2.54 – 2.62 (m, 1H), 3.69 (s, 3H), 3.90 (t, \(J = 6.6\) Hz, 2H), 6.78 – 6.81 (m, 2H), 7.05 – 7.07 (m, 2H); \(^{13}\)C NMR (100 MHz; CDCl\(_3\)) \(\delta\) 14.2, 22.7, 26.1, 29.2, 29.4, 29.8, 29.9, 31.9, 43.2, 52.27, 52.33, 57.9, 68.1, 114.6, 129.3, 133.5, 157.5, 178.1; IR (NaCl, neat) 1732, 3314, 3378 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{20}\)H\(_{34}\)NO\(_3\) [M+H]\(^+\) 322.2382, found 322.2382.

Methyl (2S)-2-amino-4-(4’-nonoxyphenyl)-2-methylbutanoate (18e)
Prepared using general procedure B using TFA (2 mL), water (4 mL) bis-lactim ether 7e (0.11 g, 0.24 mmol) and acetonitrile (7 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18e as a clear colourless oil (55 mg, 66 %). \([\alpha]^{26.3}_{D} = + 12 \text{ (c 0.5, CHCl}_3\); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) 0.88 (t, \(J = 6.8\) Hz, 3H), 1.27 – 1.48 (m, 12H), 1.36 (s, 3H), 1.71 – 1.90 (m, 5H), 1.95 – 2.05

157.5, 178.1; IR (NaCl, neat) 1732, 3310, 3378 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{16}\)H\(_{26}\)NO\(_3\) [M+H]\(^+\) 280.1913, found 280.1913.
(m, 1H), 2.40 – 2.50 (m, 1H), 2.54 – 2.64 (m, 1H), 3.70 (s, 3H), 3.91 (t, J = 6.6 Hz, 2H), 6.78 – 6.83 (m, 2H), 7.04 – 7.09 (m, 2H); 13C NMR (75 MHz; CDCl3) δ 14.2, 22.8, 26.2, 26.6, 29.37, 29.43, 29.5, 29.7, 29.9, 32.0, 43.2, 52.3, 57.9, 68.1, 114.6, 129.3, 133.5, 157.5, 178.1; IR (NaCl, neat) 1732, 3314, 3379 cm⁻¹; HRMS (ESI-MS): m/z calcd for C21H36NO3 [M+H]+ 350.2695, found 350.2685.

Methyl (2S)-2-amino-4-(4'-decoxyphenyl)-2-methylbutanoate (18f)
Prepared using general procedure B using TFA (1 mL), water (2 mL) bis-lactim ether 7f (78 mg, 0.17 mmol) and acetonitrile (6 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18f as a clear colourless oil (54 mg, 91 %). [α]23.6 = +12 (c 0.5, CHCl3); 1H NMR (300 MHz; CDCl3) δ 0.88 (t, J = 6.8 Hz, 3H), 1.27 – 1.48 (m, 14H), 1.36 (s, 3H), 1.71 – 1.79 (m, 4H), 1.80 – 1.90 (m, 1H), 1.95 – 2.05 (m, 1H), 2.40 – 2.50 (m, 1H), 2.54 – 2.64 (m, 1H), 3.70 (s, 3H), 3.91 (t, J = 6.6 Hz, 2H), 6.78 – 6.83 (m, 2H), 7.04 – 7.09 (m, 2H); 13C NMR (75 MHz; CDCl3) δ 14.2, 22.8, 26.2, 26.6, 29.4, 29.5, 29.66, 29.69, 29.91, 32.0, 43.2, 52.3, 57.9, 68.1, 114.6, 129.3, 133.5, 157.5, 178.1; IR (NaCl, neat)1733, 3326, 3380 cm⁻¹; HRMS (ESI-MS): m/z calcd for C22H38NO3 [M+H]+ 364.2852, found 364.2849.

Methyl (2S)-2-amino-4-(4'-dodecoxyphenyl)-2-methylbutanoate (18g)
Prepared using general procedure B using TFA (2 mL), water (4 mL) bis-lactim ether 7g (0.13 g, 0.27 mmol) and acetonitrile (7 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18g as a clear colourless oil (56 mg, 54 %). [α]26.3 = +12 (c 0.5, CHCl3); 1H NMR (300 MHz; CDCl3) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26 – 1.48 (m, 18H), 1.36 (s, 3H), 1.71 – 1.90 (m, 5H), 1.95 – 2.05 (m, 1H), 2.40 – 2.50 (m, 1H), 2.54 – 2.64 (m, 1H), 3.70 (s, 3H), 3.91 (t, J = 6.6 Hz, 2H), 6.78 – 6.83 (m, 2H), 7.04 – 7.09 (m, 2H); 13C NMR (75 MHz; CDCl3) δ 14.2, 22.8, 26.2, 26.6, 29.4, 29.5, 29.7, 29.75, 29.77, 29.9, 32.0, 43.2, 52.3, 57.9, 68.1, 114.6, 129.3, 133.5, 157.5, 178.1; IR (NaCl, neat)1732, 3326, 3380 cm⁻¹; HRMS (ESI-MS): m/z calcd for C24H42NO3 [M+H]+ 392.3165, found 392.3154.

Methyl (2S)-2-amino-4-(4'-benzyloxyphenyl)-2-methylbutanoate (18h)
Prepared using general procedure B using TFA (1.5 mL), water (3 mL) bis-lactim ether 7h (0.15 g, 0.37 mmol) and acetonitrile (10 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18h as a clear
colourless oil (98 mg, 85 %). $[\alpha]^{23.5}_{D} = + 12$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 1.38 (s, 3H), 1.70 (br s, 2H), 1.81 – 1.91 (m, 1H), 1.97 – 2.07 (m, 1H), 2.42 – 2.52 (m, 1H), 2.56 – 2.67 (m, 1H), 3.70 (s, 3H), 6.88 – 6.93 (m, 2H), 7.07 – 7.12 (m, 2H), 7.29 – 7.45 (m, 5H); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 26.6, 29.9, 43.1, 52.3, 57.8, 70.1, 114.9, 127.5, 127.9, 128.6, 129.3, 134.0, 137.2, 157.1, 178.0; IR (NaCl, neat) 1733 cm$^{-1}$; HRMS (ESI-MS): m/z calcd for C$_{19}$H$_{24}$NO$_3$ [M+H]$^+$ 314.1756, found 314.1754.

Methyl (2S)-2-amino-4-(4'-cyclohexylbutoxyphenyl)-2-methylbutanoate (18i)

Prepared using general procedure B using TFA (3 mL), water (6 mL) bis-lactim ether 7i (0.19 g, 0.43 mmol) and acetonitrile (9 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18i as a clear colourless oil (85 mg, 55 %). $[\alpha]^{27.9}_{D} = + 16$ (c 0.5, CHCl$_3$); $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 0.81 – 0.92 (m, 2H), 1.10 – 1.26 (m, 6H), 1.35 (s, 3H), 1.39 – 1.47 (m, 2H), 1.61 – 1.76 (m, 9H), 1.80 – 1.88 (m, 1H), 1.95 – 2.03 (m, 1H), 2.40 – 2.48 (m, 1H), 2.54 – 2.62 (m, 1H), 3.69 (s, 3H), 3.90 (t, $J$ = 6.6 Hz, 2H), 6.78 – 6.80 (m, 2H), 7.04 – 7.07 (m, 2H); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$ 23.4, 26.5, 26.6, 26.8, 29.7, 29.9, 33.4, 27.3, 37.7, 43.2, 52.2, 57.8, 68.1, 114.5, 129.2, 133.4, 157.5, 178.1; IR (NaCl, neat) 1732, 3315, 3377 cm$^{-1}$; HRMS (ESI-MS): m/z calcd for C$_{22}$H$_{36}$NO$_3$ [M+H]$^+$ 362.2695, found 362.2673.

Methyl (2S)-2-amino-4-(4'-(2'-(2'-(methoxyethoxy)ethoxy)phenyl)-2-methylbutanoate (18j)

Prepared using general procedure B using TFA (1 mL), water (2 mL) bis-lactim ether 7j (68 mg, 0.16 mmol) and acetonitrile (6 mL). The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 18j as a clear colourless oil (37 mg, 71 %). $[\alpha]^{24.0}_{D} = + 16$ (c 0.5, CHCl$_3$); $^1$H NMR (500 MHz; CDCl$_3$) $\delta$ 1.35 (s, 3H), 1.75 (br s, 2H), 1.80 – 1.86 (m, 1H), 1.95 – 2.01 (m, 1H), 2.40 – 2.46 (m, 1H), 2.54 – 2.60 (m, 1H), 3.37 (s, 3H), 3.54 – 3.56 (m, 2H), 3.68 – 3.70 (m, 5H), 3.81 – 3.83 (m, 2H), 4.08 – 4.10 (m 2H), 6.80 – 6.83 (m, 2H), 7.04 – 7.06 (m, 2H); $^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$ 26.6, 29.9, 43.1, 52.3, 57.8, 59.1, 67.5, 69.9, 70.8, 72.0, 114.7, 129.3, 133.9, 157.1, 178.1; IR (NaCl, neat) 1730, 3310, 3374 cm$^{-1}$; HRMS (ESI-MS): m/z calcd for C$_{17}$H$_{28}$NO$_5$ [M+H]$^+$ 326.1968, found 326.1967.

General Procedure C for the preparation of aminoalcohols 11
Lithium aluminium hydride (1.5 eq) was added as a solid in one portion to a solution of aminoester 18 (1 eq) in freshly distilled THF (0.05 M) at 0°C. The solution was stirred at 0°C for 20 min then the cold bath was removed and the solution stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous sodium sulfate solution and the mixture was extracted with ethyl acetate (× 4). The organic extracts were combined and washed with saturated aqueous sodium bicarbonate solution, water and brine, then dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure and the crude material was purified, as indicated, to afford the product 11.

(2S)-2-Amino-4-(4'-methoxyphenyl)-2-methyl-1-butanol (11a)
Prepared using general procedure C using lithium aluminium hydride (14 mg, 0.36 mmol), aminoester 18a (46 mg, 0.19 mmol) and freshly distilled THF (2 mL). The crude material was recrystallised (EtOH/n-hexane) to afford the product 11a as a clear colourless oil (36 mg, 88%). $[\alpha]_{D}^{25.6} = +2$ (c 0.5, MeOH); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 1.14 (s, 3H), 1.62 – 1.74 (m, 2H), 2.33 (br s, 3H), 2.59 (t, $J$ = 8.5 Hz, 2H), 3.34 (d, $J$ = 10.6 Hz, 1H), 3.40 (d, $J$ = 10.6 Hz, 1H), 3.78 (s, 3H), 6.81 – 6.84 (m, 2H), 7.09 – 7.12 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 24.3, 29.4, 42.1, 53.5, 55.4, 70.1, 114.0, 129.3, 134.3, 157.9; IR (NaCl, neat) 3445 cm$^{-1}$; HRMS (ESI-MS): $m/z$ calcd for C$_{12}$H$_{20}$NO$_2$ [M+H]$^+$ 210.1494, found 210.1491.

(2S)-2-Amino-4-(4'-butoxyphenyl)-2-methyl-1-butanol (11b)
Prepared using general procedure C using lithium aluminium hydride (8 mg, 0.21 mmol), aminoester 18b (41 mg, 0.15 mmol) and freshly distilled THF (2 mL). The crude material was purified by flash chromatography on silica gel, eluting with 3 % methanol/6 % triethylamine/dichloromethane, to afford the product 11b as a clear colourless oil (25 mg, 68%). $[\alpha]_{D}^{25.5} = -2$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 0.96 (t, $J$ = 7.3 Hz, 3H), 1.14 (s, 3H), 1.41 – 1.54 (m, 2H), 1.63 – 1.79 (m, 4H), 2.55 – 2.61 (m, 6H), 3.35 (d, $J$ = 10.7 Hz, 1H), 3.41 (d, $J$ = 10.7 Hz, 1H), 3.92 (t, $J$ = 6.5 Hz, 2H), 6.78 (m, 2H), 7.06 – 7.11 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 14.0, 19.4, 24.2, 29.4, 31.5, 41.9, 53.7, 67.8, 69.8, 114.6, 129.2, 134.1, 157.5; IR (NaCl, neat) 3386 cm$^{-1}$; HRMS (ESI-MS): $m/z$ calcd for C$_{15}$H$_{26}$NO$_2$ [M+H]$^+$ 252.1964, found 252.1963.
AAL(S) (3)[9]

Prepared using general procedure C using lithium aluminium hydride (0.10 g, 2.69 mmol), aminoester 18c (0.58 g, 1.80 mmol) and freshly distilled THF (18 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % methanol/5 % triethylamine/dichloromethane, to afford the product 3 as a white solid (0.45 g, 86 %) with all the analytical data matching that reported in the literature.[9] $[^{[\alpha]}]^{24.9}_D = + 4$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 0.89 (t, $J = 6.8$ Hz, 3H), 1.14 (s, 3H), 1.26 – 1.37 (m, 6H), 1.41 – 1.46 (m, 2H), 1.62 – 1.78 (m, 6H), 2.56 – 2.61 (m, 2H), 3.34 (d, $J = 10.5$ Hz, 1H), 3.39 (d, $J = 10.5$ Hz, 1H), 3.92 (t, $J = 6.6$ Hz, 2H), 6.80 – 6.82 (m, 2H), 7.08 – 7.10 (m, 2H); HRMS (ESI-MS): $m/z$ calcd for C$_{18}$H$_{32}$NO$_2$ [M+H]$^+$ 294.2433, found 294.2429.

(2S)-2-Amino-4-(4'-octoxyphenyl)-2-methyl-1-butanol (11d)

Prepared using general procedure C using lithium aluminium hydride (16 mg, 0.42 mmol), aminoester 18d (95 mg, 0.28 mmol) and freshly distilled THF (2 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % methanol/5 % triethylamine/dichloromethane, to afford the product 11d as a clear colourless oil (55 mg, 63 %). $[^{[\alpha]}]^{26.9}_D = + 6$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 0.88 (t, $J = 6.8$ Hz, 3H), 1.11 (s, 3H), 1.28 – 1.46 (m, 10H), 1.60 – 1.80 (m, 4H), 2.24 (br s, 3H), 2.54 – 2.60 (m, 2H), 3.32 (d, $J = 10.6$ Hz, 1H), 3.38 (d, $J = 10.6$ Hz, 1H), 3.91 (t, $J = 6.6$ Hz, 2H), 6.78 – 6.83 (m, 2H), 7.06 – 7.11 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 14.2, 22.8, 24.5, 26.2, 29.3, 29.4, 29.5, 31.9, 42.2, 53.2, 68.1, 70.2, 114.6, 129.2, 134.2, 157.4; IR (NaCl, neat) 3184, 3264, 3333 cm$^{-1}$; HRMS (ESI-MS): $m/z$ calcd for C$_{19}$H$_{34}$NO$_2$ [M+H]$^+$ 308.2589, found 308.2572.

(2S)-2-Amino-4-(4'-nonoxyphenyl)-2-methyl-1-butanol (11e)

Prepared using general procedure C using lithium aluminium hydride (12 mg, 0.32 mmol), aminoester 18e (55 mg, 0.16 mmol) and freshly distilled THF (3 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % methanol/5 % triethylamine/dichloromethane, to afford the product 11e as a clear colourless oil (23 mg, 45 %). $[^{[\alpha]}]^{26.6}_D = + 4$ (c 0.5, CHCl$_3$); $^1$H NMR (600 MHz; CDCl$_3$) $\delta$ 0.88 (t, $J = 6.8$ Hz, 3H), 1.14 (s, 3H), 1.27 – 1.35 (m, 10H), 1.41 – 1.46 (m, 2H), 1.62 – 1.78 (m, 4H), 2.10 (br s, 1H), 2.13 (br, s, 3H), 2.57 – 2.59 (m, 2H), 3.34 (d, $J = 10.6$ Hz, 1H), 3.39 (d, $J = 10.6$ Hz, 1H), 3.91 (t, $J = 6.6$ Hz, 2H), 6.80 – 6.82 (m, 2H), 7.08 – 7.09 (m, 2H); $^{13}$C NMR (150 MHz; CDCl$_3$) $\delta$ 14.3, 22.8, 24.4, 26.2, 29.4, 29.5, 29.6, 29.7, 32.0, 42.1, 53.4, 68.2, 70.1, 114.7, 129.2,
(2S)-2-Amino-4-(4'-decoxyphenyl)-2-methyl-1-butanol (11f)
Prepared using general procedure C using lithium aluminium hydride (9 mg, 0.24 mmol), aminoester 18f (54 mg, 0.16 mmol) and freshly distilled THF (2 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % methanol/4 % triethylamine/dichloromethane, to afford the product 11f as a clear colourless oil (36 mg, 69 %). $[\alpha]_{D}^{25.5} = -2 \ (c \ 0.5, CHCl_3)$; $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 0.88 (t, $J = 6.8$ Hz, 3H), 1.12 (s, 3H), 1.27 – 1.48 (m, 14H), 1.58 – 1.80 (m, 4H), 2.32 (br s, 3H), 2.55 – 2.60 (m, 2H), 3.33 (d, $J = 10.6$ Hz, 1H), 3.39 (d, $J = 10.6$ Hz, 1H), 3.91 (t, $J = 6.6$ Hz, 2H), 6.78 – 6.83 (m, 2H), 7.06 – 7.11 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 14.2, 22.8, 24.4, 26.2, 29.45, 29.53, 29.68, 29.70, 32.0, 42.1, 53.4, 68.2, 70.1, 114.6, 129.2, 134.2, 157.5; IR (NaCl, neat) 3177, 3264, 3333 cm$^{-1}$; HRMS (ESI-MS): m/z calcd for C$_{21}$H$_{38}$NO$_2$ [M+H]$^+$ 336.2903, found 336.2899.

(2S)-2-Amino-4-(4'-dodecoxyphenyl)-2-methyl-1-butanol (11g)
Prepared using general procedure C using lithium aluminium hydride (11 mg, 0.29 mmol), aminoester 18g (56 mg, 0.14 mmol) and freshly distilled THF (3 mL). The crude material was purified by flash chromatography on silica gel, eluting with 1 % methanol/5 % triethylamine/dichloromethane, to afford the product 11g as a clear colourless oil (29 mg, 56 %). $[\alpha]_{D}^{26.6} = +4 \ (c \ 0.5, CHCl_3)$; $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 0.88 (t, $J = 6.8$ Hz, 3H), 1.13 (s, 3H), 1.26 – 1.36 (m, 16H), 1.41 – 1.46 (m, 2H), 1.58 – 1.78 (m, 4H), 2.13 (br s, 3H), 2.56 – 2.59 (m, 2H), 3.34 (d, $J = 10.6$ Hz, 1H), 3.39 (d, $J = 10.6$ Hz, 1H), 3.91 (t, $J = 6.6$ Hz, 2H), 6.80 – 6.82 (m, 2H), 7.08 – 7.09 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 14.3, 22.8, 24.5, 26.2, 29.47, 29.48, 29.6, 29.72, 29.74, 29.77, 29.80, 32.1, 42.2, 53.4, 68.2, 70.2, 114.6, 129.2, 134.2, 157.5; IR (NaCl, neat) 3176, 3264, 3333 cm$^{-1}$; HRMS (ESI-MS): m/z calcd for C$_{23}$H$_{42}$NO$_2$ [M+H]$^+$ 364.3216, found 364.3208.

(2S)-2-Amino-4-(4'-benzyloxyphenyl)-2-methyl-1-butanol (11h)
Prepared using general procedure C using lithium aluminium hydride (18 mg, 0.47 mmol), aminoester 18h (98 mg, 0.31 mmol) and freshly distilled THF (3 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % methanol/4 %
triethylamine/dichloromethane, to afford the product 11h as a clear colourless oil (61 mg, 69%). \([\alpha]^{25.5}_D = -2 \) (c 0.5, CHCl\(_3\)); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) 1.13 (s, 3H), 1.58 – 1.76 (m, 2H), 2.07 (br s, 3H), 2.55 – 2.64 (m, 2H), 3.33 (d, \(J = 10.6\) Hz, 1H), 3.39 (d, \(J = 10.6\) Hz, 1H), 5.04 (s, 2H), 6.88 – 6.93 (m, 2H), 7.09 – 7.14 (m, 2H), 7.29 – 7.45 (m, 5H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) 24.6, 29.5, 42.2, 53.1, 70.2, 70.3, 115.0, 127.6, 128.0, 128.7, 129.3, 134.8, 137.3, 157.1; IR (NaCl, neat) 3425 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C \([\text{M+H}]^+\) 286.1807, found 286.1807.

(2S)-2-Amino-4-(4'-cyclohexylbutoxyphenyl)-2-methyl-1-butanol (11i)

Prepared using general procedure C using lithium aluminium hydride (14 mg, 0.37 mmol), aminoester 18i (85 mg, 0.24 mmol) and freshly distilled THF (2 mL). The crude material was purified by flash chromatography on silica gel, eluting with 2 % methanol/5 % triethylamine/dichloromethane, to afford the product 11i as a clear colourless oil (26 mg, 33%). \([\alpha]^{26.9}_D = +6 \) (c 0.5, CHCl\(_3\)); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) 0.85 – 0.92 (m, 2H), 1.12 (s, 3H), 1.15 – 1.30 (m, 7H), 1.39 – 1.50 (m, 2H), 1.62 – 1.78 (m, 9H), 1.99 (br s, 3H), 2.55 – 2.61 (m, 2H), 2.72 – 2.83 (m, 4H), 3.38 (s, 3H), 3.55 – 3.58 (m, 2H), 3.69 – 3.73 (m, 2H), 3.82 – 3.85 (m, 2H), 4.08 – 4.11 (m, 2H), 6.80 – 6.83 (m, 2H), 6.92 – 6.95 (m, 2H), 7.07 – 7.10 (m, 2H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) 23.5, 26.5, 26.9, 29.5, 29.8, 33.5, 37.3, 37.7, 68.2, 114.6, 129.2, 134.2, 157.5; IR (NaCl, neat) 3169, 3268, 3332 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{21}\)H\(_{36}\)NO\(_2\) \([\text{M+H}]^+\) 334.2746, found 334.2729.

(2S)-2-Amino-4-(4'-2'-(2'-methoxyethoxy)ethoxy)phenyl)-2-methyl-1-butanol (11j)

Prepared using general procedure C using lithium aluminium hydride (6 mg, 0.16 mmol), aminoester 18j (36 mg, .11 mmol) and freshly distilled THF (2 mL). The crude material was purified by flash chromatography on silica gel, eluting with 5 % methanol/5 % triethylamine/dichloromethane, to afford the product 11j as a clear colourless oil (25 mg, 78%). \([\alpha]^{25.5}_D = +2 \) (c 0.5, CHCl\(_3\)); \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) 1.14 (s, 3H), 1.63 – 1.77 (m, 2H), 2.54 – 2.60 (m, 2H), 2.72 – 2.83 (m, 4H), 3.38 (s, 3H), 3.55 – 3.58 (m, 2H), 3.60 – 3.73 (m, 2H), 3.82 – 3.85 (m, 2H), 4.08 – 4.11 (m, 2H), 6.80 – 6.83 (m, 2H), 6.92 – 6.95 (m, 2H), 7.07 – 7.10 (m, 2H); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) 23.9, 29.4, 41.6, 53.9, 59.2, 67.5, 69.6, 69.9, 70.8, 72.0, 114.7, 129.2, 134.4, 157.1; IR (NaCl, neat) 3286, 3349 cm\(^{-1}\); HRMS (ESI-MS): \(m/z\) calcd for C\(_{16}\)H\(_{28}\)NO\(_4\) \([\text{M+H}]^+\) 298.2018, found 298.2018.

(2S)-t-Butyl(1-hydroxy-4-(4'-heptyloxyphenyl)-2-methylbutan-2-yl)carbamate (19)
Di-t-butyl dicarbonate (0.46 g, 2.10 mmol) was added as a solid in one portion to a mixture of AAL(S) (3) (0.45 g, 1.54 mmol) in saturated aqueous sodium bicarbonate solution (25 mL) and ethyl acetate (20 mL). The mixture was stirred vigorously and heated at 60°C for 6.5 h then allowed to cool to room temperature. The solution was diluted with water and extracted with ethyl acetate (× 3). The organic extracts were combined and washed with brine, then dried (Na₂SO₄). The solvent was removed under reduce pressure and the crude material purified by flash chromatography on silica gel, eluting with 30 % ethyl acetate/n-hexane, to afford the product 19 as a white solid (0.51 g, 83 %). \( \left[ \alpha \right]_{D}^{25.6} = +2 \) (c 0.5, CHCl₃); \( \delta \) H NMR (300 MHz; CDCl₃) \( \delta \) 0.88 (t, \( J = 6.8 \) Hz, 3H), 1.22 (s, 3H), 1.26 – 1.47 (m, 8H), 1.43 (s, 9H), 1.71 – 1.89 (m, 3H), 2.02 (td, \( J = 12.8, 5.2 \) Hz, 1H), 2.46 – 2.67 (m, 2H), 3.61 – 3.73 (m, 2H), 3.92 (t, \( J = 6.6 \) Hz, 2H), 4.21 (br s, 1H), 4.63 (br s, 1H), 6.77 – 6.84 (m, 2H), 7.087 – 7.11 (m, 2H); \( \delta \) C NMR (100 MHz; CDCl₃) \( \delta \) 14.2, 22.7, 23.0, 26.2, 28.5, 29.2, 29.3, 29.5, 31.9, 38.7, 57.1, 68.2, 69.8, 80.0, 114.7, 129.3, 133.9, 156.3, 157.5; IR (NaCl, neat) 1678, 3077, 3278 cm⁻¹; HRMS (ESI-MS): \( m/z \) calcld for C₂₃H₃₉NO₄Na [M+Na]⁺ 416.2777, found 416.2776. Spectroscopic data matched those reported in the literature.[10]

**(2S)-4-(4’-Heptyloxyphenyl)-1-methoxy-2-methylbutan-2-amine (8)**

Methyl iodide (11 μL, 0.18 mmol) was added dropwise to a solution of Boc-AAL(S) 19 (14 mg, 34 μmol) and tetra-n-butylammonium sulfate (2 mg, 5.9 μmol) in 50 % aqueous sodium hydroxide solution (0.3 mL) and THF (0.3 mL) at room temperature. The solution was stirred at room temperature for 72 h. The reaction solution was diluted with water and extracted with ethyl acetate (× 3). The organic extracts were combined and washed with water and brine, then dried (Na₂SO₄). The solvent was removed under reduced pressure. The crude material was dissolved in acetonitrile (1 mL) and 2 M aqueous hydrochloric acid solution (2 mL) was added. The suspension was heated at reflux for 9 h. The solution was cooled and the acetonitrile was removed under reduced pressure. The residue was diluted with water and neutralised with solid sodium bicarbonate before being extracted with ethyl acetate (× 3). The organic extracts were combined and washed with water and brine, then
dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure and the crude material purified by flash chromatography on silica gel, eluting with 1 % triethylamine/ethyl acetate, to afford the product 8 as a colourless gum (9 mg, 82 %). $\left[\alpha\right]^{24.4}_D = + 4$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.11 (s, 3H), 1.26 – 1.44 (m, 12H), 1.63 – 1.81 (m, 4H), 2.50 – 2.65 (m, 2H), 2.74 (br s, 1H), 3.15 (d, $J = 8.7$ Hz, 1H), 3.20 (d, $J = 8.7$ Hz, 1H), 3.36 (s, 3H), 3.92 (t, $J = 6.6$ Hz, 2H), 6.78 – 6.83 (m, 2H), 7.07 – 7.12 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) δ 14.2, 22.8, 25.1, 26.2, 29.2, 29.5, 29.6, 31.9, 42.5, 52.3, 59.4, 68.2, 81.9, 114.6, 129.3, 134.7, 157.4; IR (NaCl, neat) 3305, 3368 cm$^{-1}$; HRMS (ESI-MS): $m/z$ calcld for C$_{19}$H$_{34}$NO$_2$ [M+H]$^+$ 308.2589, found 308.2587.

$\left(2S\right)$-2-(Dimethylamino)-4-(4'-heptyloxyphenyl)-2-methylbutanol (9)

Sodium cyanoborohydride (42 mg, 0.67 mmol) was added as a solid in one portion to a solution of AAL(S) (3) (49 mg, 0.17 mmol), paraformaldehyde (20 mg, 0.67 mmol) and acetic acid (0.2 mL) in acetonitrile (2 mL) at 0°C. The solution was stirred for 15 min. at 0°C then room temperature for 3 h. After diluting the solution with saturated aqueous sodium bicarbonate solution the acetonitrile was removed under reduced pressure. The resulting solution was extracted with ethyl acetate ($\times$ 3). The organic extracts were combined and washed with water and brine, then dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure and the crude material purified by flash chromatography in silica gel, eluting with 1 % methanol/1 % triethylamine/dichloromethane, to afford the product 9 as a clear colourless oil (29 mg, 54 %). $\left[\alpha\right]^{25.5}_D = -2$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz; CDCl$_3$) δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.06 (s, 3H), 1.26 – 1.49 (m, 9H), 1.64 – 1.70 (m, 2H), 1.72 – 1.81 (m, 2H), 2.28 (s, 6H), 2.51 – 2.57 (m, 2H), 2.74 (br s, 1H), 3.41 (d, $J = 10.6$ Hz, 1H), 3.49 (d, $J = 10.6$ Hz, 1H), 3.92 (t, $J = 6.6$ Hz, 2H), 6.79 – 6.84 (m, 2H), 7.06 – 7.11 (m, 2H); $^{13}$C NMR (75 MHz; CDCl$_3$) δ 14.2, 17.6, 22.7, 26.2, 29.2, 29.5, 30.1, 31.9, 36.7, 38.1, 59.3, 65.8, 68.2, 114.6, 129.2, 134.6, 157.5; IR (NaCl, neat) 3406 cm$^{-1}$; HRMS (ESI-MS): $m/z$ calcld for C$_{20}$H$_{36}$NO$_2$ [M+H]$^+$ 322.2746, found 322.2746.

$\left(2S\right)$-N-(4-(4'-Heptyloxyphenyl)-1-hydroxy-2-methylbutan-2-yl)acetamide (10)
Acetyl chloride (10 μL, 0.14 mmol) was added dropwise to a solution of AAL(S) (3) (42 mg, 0.14 mmol) and triethylamine (60 μL, 0.43 mmol) in dichloromethane (3 mL) at 0°C. The solution was stirred at 0°C for 2 h. before being quenched with saturated aqueous sodium bicarbonate solution. The mixture was extracted with dichloromethane (× 3). The organic extracts were combined and washed with saturated aqueous sodium bicarbonate solution, water and brine, then dried (Na₂SO₄). The solvent was removed under reduced pressure and the crude material purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the product 10 as a clear colourless gum (17 mg, 35 %). $\left[\alpha\right]^{26.9}_D = -10$ (c 0.5, CHCl₃); $^1$H NMR (300 MHz; CDCl₃) δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.26 (s, 3H), 1.28 – 1.46 (m, 8H), 1.69 – 1.80 (m, 2H), 1.84 – 1.97 (m, 1H), 1.91 (s, 3H), 2.01 – 2.11 (m, 1H), 2.47 – 2.58 (m, 1H), 2.61 -2.71 (m, 1H), 3.61 – 3.70 (m, 2H), 3.91 (t, $J = 6.6$ Hz, 2H), 4.93 (br s, 1H), 5.50 (br s, 1H), 6.80 – 6.84 (m, 2H), 7.06 – 7.11 (m, 2H); $^{13}$C NMR (75 MHz; CDCl₃) δ 14.2, 22.7, 23.0, 24.1, 26.1, 29.2, 29.3, 29.4, 31.9, 38.4, 59.1, 68.2, 69.7, 114.8, 129.3, 133.6, 157.6, 171.4; IR (NaCl, neat) 1742, 3089, 3191, 3288 cm⁻¹; HRMS (ESI-MS): m/z calcd for C$_{20}$H$_{33}$NO$_3$Na [M+Na]$^+$ 358.2358, found 358.2336.
4. NMR Spectra

18/01/2011 HDTD054_2; 300 MHz; CDCl3

04/07/2011 HDTG002_1; 400 MHz; CDCl3
10/07/2011 HDTG013_1; 300 MHz, CDCl3

H2C10O

\[
\begin{align*}
\text{N} & \quad \text{Me} \\
\text{N} & \quad \text{OMe} \\
\text{O} & \quad \text{OMe} \\
\text{N} & \quad \text{Pr}
\end{align*}
\]

\(7f\)

10/07/2011 HDTG013_1; 300 MHz, CDOD

H2C10O

\[
\begin{align*}
\text{N} & \quad \text{Me} \\
\text{N} & \quad \text{OMe} \\
\text{O} & \quad \text{OMe} \\
\text{N} & \quad \text{Pr}
\end{align*}
\]

\(7f\)
$H_2C=O$

$7g$

11/01/2012 HDTI007_1; 300 MHz; CDC3

$H_2C=O$

$7g$
MeO – O – O – 4-MeO
N
O

29/08/2011 HDTG052_1; 300 MHz; CDCl3

MeO – O – O – 4-MeO
N
O

29/08/2011 HDTG052_1; 300 MHz; CDCl3
05/09/2011 HDTG059_1; 300 MHz; CDCl3

MeO—O—O—Me

11j

05/09/2011 HDTG059_1; 300 MHz; CDCl3

MeO—O—O—Me

11j
5. References


