Supplementary Information

Episulfonium-ion mediated cyclic peptide and triazine synthesis

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Experimental

All solvents were BOC standard grade and distilled before use. THF was distilled from sodium wire with benzophenone as an indicator. Ether, acetonitrile and dichloromethane were distilled from calcium hydride. Toluene was also distilled from calcium hydride and stored over 4Å molecular sieves. Pyridine, *N,N*-dimethylformamide, triethylamine and diisopropylamine were dried and stored over 4Å molecular sieves. TFA was used under nitrogen and stored in a dessicator over anhydrous potassium hydroxide. *n*-Butyllithium was titrated against L-menthol using *N*-(4-phenylbenzylidene)benzylamine as indicator before use. pH 2 Sulfate buffer was prepared by dissolving sodium sulfate (1.5 mol) and sulfuric acid (0.5 mol) in distilled water to give a total volume of 2000 cm^3. For reactions conducted under anhydrous conditions, all glassware was dried overnight in an oven (120°C) and allowed to cool under a vacuum with the reactions being carried out under an argon or nitrogen atmosphere. Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). Thin layer chromatography was carried out on commercially available pre-coated glass-backed plates (Merck Kieselgel $60F_{254}$). Proton and carbon NMR spectra were recorded on Bruker Avance DPX400 (5 mm QNP probe) and Bruker Avance DPX500 (5 mm dual ^{13}C-^{1}H cryo probe) Fourier Transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane. ^{1}H chemical shifts are rounded to the nearest 0.01ppm and ^{13}C chemical shifts are rounded to the nearest 0.1ppm. Coupling constants (*J*) are given in Hertz (Hz) and are quoted to the nearest 0.5 Hz. Carbon NMR spectra were recorded with broadband proton decoupling and were recorded with APT or DEPT. Complex ^{1}H and ^{13}C spectra were assigned on the basis of ^{1}H, COSY, ^{13}C, APT or DEPT, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC as relevant. LC-MS was run on a Waters Alliance LC/MS system consisting of a Water 2795 Separations Module, a Waters 2996 Photodiode Array Detector and a Waters Micromass ZQ on a C18 analytical Reverse Phase Supercosil™ ABZ+PLUS column (3.3 cm x 4.6 mm, 3 μm) using the following gradient: 0.00-0.70 min 100% solvent A, 0.70-4.20 min 100% solvent A to 100 % solvent B, 4.20-7.70 min 100% solvent B, 7.70-8.00 min solvent B to solvent A (solvent A: 10 mM ammonium acetate in water containing 0.1% formic acid; solvent B: 95% acetonitrile in water) with a flow rate of 1 cm^3/min. EI and LSIMS mass spectra were recorded on a Kratos concept 1H double focusing magnetic sector instrument using a MACH 3 data system. +ESI mass spectra were recorded using a Bruker Bio-Apex II FT-ICR instrument or a Micromass Q-Tof 1 machine. Melting points were measured on a microscope hot stage melting point apparatus (C. Reichert Optische Werke AG) and are uncorrected. Film phase infrared spectra were recorded using a Perkin Elmer Spectrum One (FT-IR) spectrophotometer with a universal ATR sampling accessory.

3-Hydroxy-4-methyl-4-(phenylthio)pentanoic acid 23: a solution of diisopropylamine (117 mmol) in THF (500 cm^3) under nitrogen was cooled to –78 °C before the dropwise addition of *n*-butyllithium (117 mmol, 2.5 mol dm^{-3} in hexanes). The mixture was stirred for 20 minutes to give the pale yellow LDA solution. Ethyl acetate (112 mmol) was added and the reaction was stirred for 20 minutes. 2-Methyl-2-phenylsulfanylpropional[1] (20.0 g, 111.1 mmol) in THF (20 cm^3) was added dropwise and the solution was stirred for a further 30 minutes before allowing warming to room temperature over three hours. Saturated ammonium chloride solution (100 cm^3) was added and the solvent was evaporated under reduced pressure. The remaining aqueous phase was extracted with ethyl acetate (2 x 200 cm^3) and the combined organic extracts were washed with saturated sodium bicarbonate solution (2 x 100 cm^3) and brine (100 cm^3), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:20 to 1:4) to give *ethyl 3-hydroxy-4-methyl-4-(phenylthio)pentanoate* as a pale yellow oil (14.4 g, 53.6 mmol, 48%); R_f (EtOAc–hexane 1:4) 0.22; δ_H (500 MHz; $CDCl_3$) 7.55-7.50 (2 H, m, *o*-Ph), 7.36-7.29 (3 H, m, *m* and *p*-Ph), 4.15 (2 H, q, *J* 7.0, OC$\underline{H}_2$Me), 3.88 (1 H, dt, *J* 10.0, 3.0, C$\underline{H}$OH), 3.19 (1 H, d, *J* 2.0, OH), 2.73 (1 H, dd, *J* 15.5 and 2.0, C$\underline{H}_A$H$_B$CO$_2$), 2.47 (1 H, dd, *J* 15.5 and 10.5, CH$_A\underline{H}_B$CO$_2$), 1.25 (3 H, t, *J* 7.0, CH$_2\underline{Me}$), 1.24 (3 H, s, C$\underline{Me}_A$Me$_B$), 1.19 (3 H, s, CMe$_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 172.8 (CO_2), 137.5 (*o*-Ph), 130.4 (*i*-

Ph), 129.2 (*p*-Ph), 128.7 (*m*-Ph), 72.7 (CHOH), 60.8 ($\underline{C}H_2Me$), 53.2 ($S\underline{C}Me_2$), 36.6 ($\underline{C}H_2CO_2$), 24.6 ($C\underline{Me}_AMe_B$), 23.8 ($CMe_A\underline{Me}_B$) and 14.1 ($CH_2\underline{Me}$); m/z = 291.10280 ($C_{14}H_{20}O_3Na$ requires *M+Na*, 291.10309, dev. -1.09 ppm); ν_{max} ($CDCl_3$/cm^{-1}) 3500 (broad OH), 1724 (CO). The ester (14.4 g, 53.6 mmol) was dissolved in methanol (200 cm^3) and water (20 cm^3). Potassium hydroxide (3.30 g, 59.0 mmol) was added and the reaction was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and saturated sodium bicarbonate solution (100 cm^3), water (100 cm^3) and a hexane and ethyl acetate mixture (1:1 ratio, 200 cm^3) were added. The organic layer was subsequently separated and discarded. The aqueous phase was extracted with further portions of ethyl acetate and hexane (1:1 ratio, 2 x 100 cm^3) and each organic phase was discarded. The aqueous phase was acidified with pH 2 sulfate buffer (200 cm^3) and hydrochloric acid as required to bring the pH of the solution to pH 2 before extracting with diethylether (2 x 200 cm^3) and ethyl acetate (200 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give a pale yellow solid (12.8 g, 52.5 mmol, 98%); δ_H (500 MHz; $CDCl_3$) 7.53-7.50 (2 H, m, *o*-Ph), 7.39-7.33 (3 H, m, *m*-Ph and *p*-Ph), 3.84 (1 H, dd, *J* 10.5 and 2.5, C$\underline{H}$OH), 2.73 (1 H, dd, *J* 16.0 and 2.5, $C\underline{H}_AH_B$), 2.52 (1 H, dd, *J* 15.5 and 10.5, $CH_A\underline{H}_B$), 1.27 (3 H, s, $C\underline{Me}_AMe_B$), 1.21 (3 H, s, $CMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 176.0 (CO), 137.5 (*o*-Ph), 129.9 (*i*-Ph), 129.4 (*p*-Ph), 128.9 (*m*-Ph), 72.2 (CHOH), 53.4 ($S\underline{C}Me_2$), 36.0 ($\underline{C}H_2CO$), 24.9 ($C\underline{Me}_AMe_B$), 23.1 (CMe_AMe_B); m/z = 263.07039 ($C_{12}H_{16}O_3SNa$ requires *M+Na*, 263.07123, dev. 2.27 ppm); ν_{max} ($CDCl_3$/ cm^{-1}) 3300 (broad OH), 1713 (CO); m.p. (EtOAc/Hexane) 105-108 ^oC.

3-Hydroxy-4-methyl-4-phenylsulfanyl-pentanamide 7: carboxylic acid **23** (1.00 g, 4.20 mmol) was dissolved in THF (50 cm^3) under a nitrogen atmosphere at room temperature. To the rapidly stirring solution was added *N*-hydroxy-succinimide (0.51 g, 4.41 mmol) followed by dicyclohexylcarbodimide (0.91 g, 4.41 mmol) and stirring was continued overnight. The dicyclohexyl-urea precipitate was filtered out under gravity and the filter was washed with THF (10 cm^3). Concentrated ammonia (3.0 cm^3) was added to the THF solution of activated acid and the mixture was stirred overnight. The solution was filtered and the solvent was evaporated under reduced pressure. The solid residue was dissolved in ethyl acetate (50 cm^3), filtered under gravity and washed with saturated sodium bicarbonate solution (2 x 50 cm^3), pH 2 sulfate buffer (2 x 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:1) to give the *amide* as white crystals (925 mg, 92 %); R_f (EtOAc-hexanes 1:1) 0.21; δ_H (500 MHz; $CDCl_3$) 7.52-7.47 (2 H, m, *o*-Ph), 7.40-7.36 (1 H, m, *p*-Ph), 7.35-7.31 (2 H, m, *m*-Ph), 6.31 (1 H, br s, NH), 5.63 (1 H, br s, NH), 3.77 (1 H, s, OH), 3.74 (1 H, d, *J* 10.5, C$\underline{H}$OH), 2.51 (1 H, d, *J* 15.0, $C\underline{H}_AH_B$), 2.37 (1 H, dd, *J* 15.0 and 10.5, $CH_A\underline{H}_B$), 1.24 (3 H, s, $C\underline{Me}_AMe_B$), 1.21 (3 H, s, $CMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 174.5 (CO), 137.4 (*o*-Ph), 130.0 (*i*-Ph), 129.4 (*p*-Ph), 128.9 (*m*-Ph), 72.3 (CHOH), 54.0 ($S\underline{C}Me_2$), 37.7 (CH_2), 25.0 ($CMe_A\underline{Me}_B$), 22.9 ($C\underline{Me}_AMe_B$); *m/z* = 262.08850 ($C_{12}H_{17}NO_2SNa$ requires *M+Na* = 262.0878, dev. 2.88); ν_{max} ($CHCl_3$ / cm^{-1}) 3413 (NH), 3350 (broad OH), 1662 (CO); m.p. (EtOAc/Hexane) 97-101 ^oC.

2,4,6-Tris-(2'-phenylsulfanyl-3'-hydroxyl-3'-methyl-but-1-yl)-1,3,5-triazine 42: amide **7** (24 mg, 0.10 mmol) was added to a mixture of toluene (0.9 cm^3) and TFA (0.1 cm^3) under nitrogen. An oven-dried air condenser was cooled under a stream of nitrogen and attached to the reaction flask before being fitted with an argon balloon. The reaction mixture was heated to 40 ^oC overnight. After the reaction was allowed to cool to room temperature saturated sodium bicarbonate solution (5 cm^3) was added, followed by ethyl acetate (5 cm^3). The aqueous layer was extracted with ethyl acetate (2 x 5 cm^3) and the combined organic phases were washed with saturated sodium bicarbonate (2 x 10 cm^3) and brine (10 cm^3), dried (Na_2SO_4) and evaporated to yield the crude reaction residue. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:1) to give the trimer as a white solid (20 mg, 92%) with three spin system environments in a ratio of 8:4:3 (e1:e2:e3); R_f (EtOAc) 0.49; δ_H (500 MHz, $CDCl_3$) 7.32-7.28 (6 H, m, *o*-Ph), 7.19-7.08 (9H, m, *m* and *p*-Ph), 3.90 (1 H, dd, *J* 9.5 and 4.5, e2 SC$\underline{H}$), 3.86 (1 H, dd, *J* 10.0 and 4.5, e1 SC$\underline{H}$), 3.85 (1 H, dd, *J* 10.5 and 4.5, e3 SC$\underline{H}$), 3.32 (1 H, dd, *J* 15.5 and 4.5, e2 $C\underline{H}_AH_B$), 3.22 (1 H, dd, *J* 15.5 and 4.0, e3 $C\underline{H}_AH_B$), 3.18 (1 H, dd, *J* 15.5 and 4.0, e1 $C\underline{H}_AH_B$), 3.00 (1 H, dd, *J* 15.5 and 9.5, e2 $CH_A\underline{H}_B$), 2.96 (1 H, dd, *J* 15.5 and 10.5, e3 $CH_A\underline{H}_B$), 2.94 (1 H, dd, *J* 15.5 and 10.0, e1 $CH_A\underline{H}_B$), 2.73 (1 H, br s, e2 OH), 2.69 (1 H, br s, e3 OH), 2.66 (1 H, br s, e1 OH), 1.36 (3 H, s, e2 $C\underline{Me}_AMe_B$), 1.35 (3 H, s, e3, $C\underline{Me}_AMe_B$), 1.34 (6 H, s, e1 $C\underline{Me}_AMe_B$ and e2 $CMe_A\underline{Me}_B$), 1.32 (3 H, s, e3 $CMe_A\underline{Me}_B$), 1.31 (3 H, s, e1 $CMe_A\underline{Me}_B$); δ_C (125 MHz, $CDCl_3$) 176.7 (CN e2), 176.8 (CN e1 and e3), 136.6 (*i*-Ph, e3), 136.5 (*i*-Ph, e1), 136.4 (*i*-Ph, e2), 130.9 (*o*-Ph, e3), 130.8 (*o*-Ph, e1), 130.7 (*o*-Ph, e2), 128.8 (*m*-Ph, e1, e2 and e3), 126.7 (*p*-Ph e3), 126.6 (*p*-Ph e1), 126.6 (*p*-Ph e2), 73.2 and 73.1 ($\underline{C}Me_2$ e1, e2 and e3), 59.9 (SCH e3), 59.6 (SCH e1 and e2), 41.2 (CH_2 e3), 41.1 (CH_2 e2), 41.0 (CH_2 e1), 27.7 ($CMe_A\underline{Me}_B$ e2), 27.6 ($CMe_A\underline{Me}_B$ e1), 27.5 ($CMe_A\underline{Me}_B$ e3), 26.7

($C\underline{Me}_AMe_B$ e3), 26.6 ($C\underline{Me}_AMe_B$ e1), 26.6 ($C\underline{Me}_AMe_B$ e2); *m/z* = 686.25220 ($C_{36}H_{45}N_3O_3S_3Na$ requires *M+Na*, 686.2515, dev. 2.36 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 1538 (CN); m.p. (EtOAc/Hexane) 135-138 °C.

Hydroxy-nitrile **1** was reacted in an analogous fashion (except that the reaction solvent mixture TFA / hexanes 1:5 v/v was used) to give triazine **2** in 63% yield. In incomplete reactions, **5,5-dimethyl-4-phenylsulfanyl-dihydro-furan-2-imine 9** was observed as an unstable intermediate which hydrolysed in air or during silica column chromatography: δ_H (500 MHz; $CDCl_3$) 7.49-7.44 (2 H, m, *o*-Ph), 7.32-7.27 (2 H, m, *m*-Ph), 7.15-7.07 (1 H, m, *p*-Ph), 3.62 (1 H, dd, *J* 10.5 and 8.0, SCH), 3.01 (1 H, dd, *J* 17.0 and 8.0, $C\underline{H}_AH_B$), 2.75 (1 H, dd, *J* 17.0 and 10.5, $CH_A\underline{H}_B$), 1.40 (3 H, s, $C\underline{Me}_AMe_B$), 1.37 (3 H, s, $CMe_A\underline{Me}_B$);
δ_C (125 MHz; $CDCl_3$) 176.6 (CON), 136.5 (*i*-Ph), 131.1 (*o*-Ph), 129.4 (*m*-Ph), 127.8 (*p*-Ph), 87.4 ($O\underline{C}Me_2$), 53.7 (SCH), 37.1 (CH_2), 29.6 ($CMe_A\underline{Me}_B$), 23.0 ($C\underline{Me}_AMe_B$); *m/z* = 221.08818 ($C_{12}H_{15}NOS$ requires *M+*, 221.08743, dev. 3.34 ppm).

Hydrolysis of imide **9** produces the previously reported lactone[2] **5,5-dimethyl-4-phenylsulfanyl-dihydro-furan-2-one 3** and **4-hydroxy-4-methyl-3-phenylsulfanyl-pentanamide 8**: R_f (EtOAc) 0.10; δ_H (500 MHz; $CDCl_3$) 7.50-7.47 (2 H, m, *o*-Ph), 7.29-7.24 (2 H, m, *m*-Ph), 7.22-7.18 (1 H, m, *p*-Ph), 5.56 (1 H, br s, NH), 5.37 (1 H, br s, NH), 3.63 (1 H, dd, *J* 8.0 and 5.0, SCH), 2.82 (1 H, dd, *J* 15.5 and 5.0, $C\underline{H}_AH_B$), 2.69 (1 H, br s, OH), 2.48 (1 H, dd, *J* 16.0 and 8.0, $CH_A\underline{H}_B$), 1.33 (3 H, s, $C\underline{Me}_AMe_B$), 1.32 (3 H, s, $CMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 173.6 (CON), 134.7 (*o*-Ph), 131.1 (*p*-Ph), 129.1 (*m*-Ph), 127.0 (*i*-Ph), 73.1 ($O\underline{C}Me_2$), 57.7 (SCH), 38.3 (CH_2), 27.9 $CMe_A\underline{Me}_B$), 26.6 ($C\underline{Me}_AMe_B$); *m/z* = 262.08720 ($C_{12}H_{17}NO_2Na$ requires *M+Na*, 262.0878, dev. –2.30 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3320 (broad, OH and NH), 1671 (CO); m.p. (EtOAc/Hexane) 129.0-131.4°C.

2-Methyl-2-(4-methylphenylsulfanyl)-propionaldehyde[3] **12**: 4-Methylbenzenethiol (23.8 g, 0.22 mol) was dissolved in dry pentane (200 cm^3) and stirred with dry triethylamine (1.00 cm^3) under argon before cooling to 0 °C. Sulfuryl chloride (28.5 g, 0.21 mol) was added slowly over a period of one hour, and the resulting mixture was stirred for one hour at 0 °C and then for two hours at room temperature to yield a deep red solution to which was added THF (200 cm^3). This mixture was slowly transferred to a solution of trimethyl-(2-methyl-propenyloxy)-silane (25.0 g 0.20 mol) in THF (200 cm^3) stirred at –78 °C under argon. The reaction mixture was stirred for three hours before water (200 cm^3) was added and the resulting aqueous phase was extracted with ether (3 x 100 cm^3). The combined organic extracts were washed with dilute hydrochloric acid (1 M, 2 x 250 cm^3), saturated sodium bicarbonate solution (3 x 100 cm^3) and brine (100 cm^3), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to yield the aldehyde as a pale yellow oil (35.8 g, 92 %); δ_H (500 MHz; $CDCl_3$) 9.25 (1 H, s, CHO), 7.26 (2 H, d, *J* 8.0, *o*-Ph), 7.10 (2 H, d, *J* 8.0, *m*-Ph), 2.32 (3 H, s, Ph$\underline{Me}$), 1.30 (6 H, s, $C\underline{Me}_2$); δ_C (125 MHz; $CDCl_3$) 195.3 (CHO), 139.9 (*i*-Ph), 136.9 (*o*-Ph), 129.8 (*m*-Ph), 126.2 (*p*-Ph), 55.3 ($S\underline{C}Me_2$), 21.2 (Ph$\underline{Me}$), 21.1 ($SC\underline{Me}_2$); *m/z* = 217.06610 ($C_{11}H_{14}OSNa$ requires *M+Na* = 217.06630, dev. –1.10 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 1712 (CO), 1492 (Ph), 1457 (Ph).

2-(4-Butyl-phenylsulfanyl)-2-methyl-propionaldehyde 13: 4-butylbenzenethiol (4.80 g, 28.9 mmol) was dissolved in dry pentane (50 cm^3) and stirred with dry triethylamine (1.00 cm^3) under argon before cooling to 0 °C. Sulfuryl chloride (4.10 g, 30.4 mmol) was added slowly over a period of one hour, and the resulting mixture was stirred for one hour at 0 °C and then for two hours at room temperature to yield a deep red solution to which was added THF (50 cm^3). This mixture was slowly transferred to a solution of trimethyl-(2-methyl-propenyloxy)-silane (4.16 g, 28.9 mmol) in THF (50 cm^3) stirred at –78 °C under argon. The reaction mixture was stirred for three hours before water (50 cm^3) was added and the resulting aqueous phase was extracted with ether (3 x 25 cm^3). The combined organic extracts were washed with dilute hydrochloric acid (1 M, 2 x 50 cm^3), saturated sodium bicarbonate solution (3 x 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to yield the *aldehyde* as a pale yellow oil (5.40 g, 79 %); δ_H (500 MHz; $CDCl_3$) 9.33 (1 H, s, CHO), 7.28 (2 H, d, *J* 8.0, *o*-Ph), 7.10 (2 H, d, *J* 8.0, *m*-Ph), 2.57 (1 H, t, *J* 8.0, $ArC\underline{H}_2$), 1.60-1.52 (2 H, m, $ArCH_2C\underline{H}_2$), 1.32 (2 H, sextet, *J* 7.5, $C\underline{H}_2Me$), 1.30 (6 H, s, $SCMe_2$), 0.91 (3 H, t, *J* 7.5, $CH_2\underline{Me}$); δ_C (125 MHz; $CDCl_3$) 195.4 (CHO), 144.8 (*p*-Ph), 136.9 (*o*-Ph), 129.1 (*m*-Ph), 126.4 (*i*-Ph), 55.3 ($S\underline{C}Me_2$), 35.4 ($Ar\underline{C}H_2$), 33.3 ($ArCH_2\underline{C}H_2$), 22.3 ($\underline{C}H_2Me$), 21.1 ($C\underline{Me}_2$) 13.9 ($CH_2\underline{Me}$); *m/z* = 236.12426 ($C_{14}H_{20}OS$ requires *M+* = 236.12348, dev. 3.68 ppm); ν_{max} (neat / cm^{-1}) 1712, (CO), 1596 (Ph), 1489 (Ph), 1458 (Ph).

3-Hydroxy-4-methyl-4-(4'-methylphenyl)sulfanyl-pentanamide 14: a solution of diisopropylamine (25.8 mmol) in THF (250 cm^3) under nitrogen was cooled to –78 °C before the dropwise addition of *n*-butyllithium (25.8 mmol, 2.5 M in hexanes). The mixture was stirred for 20 minutes to give the pale yellow LDA solution. Ethyl acetate (2.38 g, 27.1 mmol) was added and the reaction was stirred for 20 minutes. 2-Methyl-2-(4-methylphenyl)sulfanylpropional **12** (5.00 g, 25.8 mmol) in THF (10 cm^3) was added dropwise and the solution was stirred for a further 30 minutes before allowing warming to room temperature over three hours. Saturated ammonium chloride solution (50 cm^3) was added and the organic solvent was evaporated under reduced pressure. The remaining aqueous phase was extracted with ethyl acetate (3 x 50 cm^3) and the combined organic extracts were washed with saturated sodium bicarbonate solution (100 cm^3) and brine (100 cm^3), dried (Na_2SO_4) and were evaporated under reduced pressure to give *ethyl 3-hydroxy-4-methyl-4-(4'-methylphenylthio)pentanoate* as a yellow oil (6.48 g, 89 %); δ_H (500 MHz; $CDCl_3$) 7.39 (2 H, dt, *J* 8.0 and 2.0, *o*-Ph), 7.13 (2 H, d, *J* 8.0, *m*-Ph), 4.16 (2 H, q, *J* 7.0, C$\underline{H}_2$Me), 3.86 (1 H, dt, *J* 10.5 and 2.5, C$\underline{H}$OH), 3.15 (1 H, d, *J* 2.5, OH), 2.70 (1 H, dd, *J* 15.5 and 2.0, C$\underline{H}_A$H$_B$), 2.46 (1 H, dd, *J* 15.5 and 10.5, CH$_A\underline{H}_B$), 2.34 (3 H, s, Ph$\underline{Me}$), 1.26 (3 H, t, *J* 7.0, CH$_2\underline{Me}$), 1.24 (3 H, s, C$\underline{Me}_A$Me$_B$), 1.18 (3 H, s, CMe$_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 172.7 (CO_2), 139.4 (*i*-Ph), 137.4 (*o*-Ph), 129.6 (*m*-Ph), 126.8 (*p*-Ph), 72.6 (CHOH), 60.8 ($\underline{C}H_2$Me), 53.0 (S$\underline{C}$Me$_2$), 36.5 (CH_2), 24.7 (CMe$_A\underline{Me}_B$), 23.6 (C$\underline{Me}_A$Me$_B$), 21.2 (Ph$\underline{Me}$), 14.2 (CH$_2\underline{Me}$); *m/z* = 305.11820 ($C_{15}H_{22}O_3SNa$ requires *M+Na* = 305.11873, dev. –1.86 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3500 (br OH), 1732 (CO), 1492 (Ph), 1461 (Ph). The ester (3.00 g, 10.6 mmol) was dissolved in methanol (25 cm^3) and water (2.5 cm^3). Potassium hydroxide (0.65 g, 11.7 mmol) was added and the reaction was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and saturated sodium bicarbonate solution (20 cm^3), water (20 cm^3) and a hexane and ethyl acetate mixture (1:1 ratio, 50 cm^3) were added. The organic layer was separated and discarded. The aqueous phase was extracted with further portions of ethyl acetate and hexane (1:1 ratio, 2 x 20 cm^3) and each organic phase was discarded. The aqueous phase was acidified with pH 2 sulfate buffer (20 cm^3) and hydrochloric acid as required to bring the pH of the solution to pH 2 before extracting with diethylether (2 x 500 cm^3) and ethyl acetate (50 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give *3-hydroxy-4-methyl-4-(4'-methylphenylthio) pentanoic acid* as an amorphous off white solid (2.41 g, 9.48 mmol, 89 %); δ_H (500 MHz; $CDCl_3$) 7.38 (2 H, dt, *J* 8.0 and 2.0, *o*-Ph), 7.14 (2 H, dd, *J* 8.0 and 0.5, *m*-Ph), 3.83 (1 H, dd, *J* 10.5 and 2.5, C$\underline{H}$OH), 2.71 (1 H, dd, *J* 15.5 and 2.5, C$\underline{H}_A$H$_B$), 2.49 (1 H, dd, *J* 15.5 and 10.5, CH$_A\underline{H}_B$), 2.35 (3 H, s, Ph$\underline{Me}$), 1.25 (3 H, s, C$\underline{Me}_A$Me$_B$), 1.20 (3 H, s, CMe$_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 176.3 (CO_2), 139.7 (*p*-Ph), 137.4 (*o*-Ph), 129.7 (*m*-Ph), 126.3 (*i*-Ph), 72.1 (CHOH), 53.1 (S$\underline{C}$Me$_2$), 36.0 (CH_2), 24.8 (CMe$_A\underline{Me}_B$), 22.9 (C$\underline{Me}_A$Me$_B$), 21.2 (Ph$\underline{Me}$); *m/z* = 277.08740 ($C_{13}H_{19}O_3SNa$ requires *M+Na* = 277.08743, dev. –0.24 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3450 (br OH), 1708 (CO), 1492 (Ph). The carboxylic acid (2.40 g, 9.40 mmol) was dissolved in THF (100 cm^3) under a nitrogen atmosphere at room temperature. To the rapidly stirring solution was added *N*-hydroxy-succimide (1.14 g, 9.90 mmol) followed by dicyclohexylcarbodimide (2.04 g, 9.90 mmol) and stirring was continued overnight. The dicyclohexyl-urea precipitate was filtered out under gravity and the filter was washed with THF (25 cm^3). Concentrated ammonia (5.0 cm^3) was added and the mixture was stirred overnight. The solution was filtered and the solvent was evaporated under reduced pressure. The residue was suspended in ethyl acetate (50 cm^3), filtered and washed with saturated sodium bicarbonate solution (2 x 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexane 1:2 to EtOAc-MeOH 9:1) to give *3-hydroxy-4-methyl-4-(4'-methylphenyl)sulfanyl-pentanamide* **14** as off white plates (1.48 g, 5.85 mmol, 62 %); R_f (EtOAc) 0.26; δ_H (500 MHz; $CDCl_3$) 7.27 (2 H, d, *J* 8.0, *o*-Ph), 7.14 (2 H, d, *J* 8.0, *m*-Ph), 6.30 (1 H, br s, N$\underline{H}_A$H$_B$), 5.38 (1 H, br s, NH$_A\underline{H}_B$), 3.72 (1 H, dt, *J* 11.0 and 2.0, C$\underline{H}$OH), 3.70 (1 H, d, *J* 1.5, OH), 2.47 (1 H, d, *J* 15.0, C$\underline{H}_A$H$_B$), 2.36 (1 H, dd, *J* 15 and 11.0, CH$_A\underline{H}_B$), 2.35 (3 H, s, Ph$\underline{Me}$), 1.23 (3 H, s, C$\underline{Me}_A$Me$_B$), 1.20 (3 H, s, CMe$_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 174.3 (CON), 139.7 (*p*-Ph), 137.2 (*o*-Ph), 129.7 (*m*-Ph), 126.3 (*i*-Ph), 72.1 (CHOH), 53.9 (S$\underline{C}$Me$_2$), 37.2 (CH_2), 25.1 (CMe$_A\underline{Me}_B$), 22.5 (C$\underline{Me}_A$Me$_B$), 21.1 (Ph$\underline{Me}$); *m/z* = 276.10390 ($C_{13}H_{19}NO_2SNa$ requires *M+Na* = 276.10342, dev. 1.62 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3350 (br OH), 1661 (CO), 1492 (Ph); m.p. (EtOAc/Hexane) 88.7-89.9 °C.

3-Hydroxy-4-methyl-4-(4'-butylphenyl)sulfanyl-pentanamide 15: a solution of diisopropylamine (15 mmol) in THF (150 cm^3) under nitrogen was cooled to –78 °C before the dropwise addition of *n*-butyllithium (15 mmol, 2.5 M in hexanes). The mixture was stirred for 20 minutes to give the pale yellow LDA solution. Ethyl acetate (1.39 g, 15.8 mmol) was added and the reaction was stirred for 20 minutes. 2-Methyl-2-(4-butylphenyl)sulfanylpropional **13** (3.54 g, 15.0 mmol) in THF (5 cm^3) was added dropwise and the solution was stirred for a further 30 minutes before allowing warming to room temperature over three hours. Saturated ammonium chloride solution (50 cm^3) was added and the

organic solvent was evaporated under reduced pressure. The remaining aqueous phase was extracted with ethyl acetate (3 x 50 cm^3) and the combined organic extracts were washed with saturated sodium bicarbonate solution (100 cm^3) and brine (100 cm^3), dried (Na_2SO_4) and were evaporated under reduced pressure to give crude *ethyl 3-hydroxy-4-methyl-4-(4'-butylphenylthio)pentanoate* as a yellow oil; δ_H (500 MHz; $CDCl_3$) 7.41 (2 H, d, *J* 8.0, *o*-Ph), 7.13 (2 H, d, *J* 8.0, *m*-Ph), 4.16 (2 H, q, *J* 7.0, OCH_2), 3.88 (1 H, dd, *J* 10.5 and 2.5, C<u>H</u>OH), 3.15 (1 H, br s, OH), 2.71 (1 H, dd, *J* 15.5 and 2.5, C<u>H</u>$_A$H$_B$CO$_2$), 2.60 (1 H, t, *J* 8.0, ArC<u>H</u>$_2$), 2.46 (1 H, dd, *J* 15.5 and 10.5, CH$_A$<u>H</u>$_B$CO$_2$), 1.62-1.55 (2 H, m, ArCH$_2$C<u>H</u>$_2$), 1.34 (2 H, sextet, *J* 7.5, C<u>H</u>$_2$Me), 1.24 (3 H, t, *J* 7.0, OCH$_2$<u>Me</u>), 1.24 (3 H, s, C<u>Me</u>$_A$Me$_B$), 1.19 (3 H, s, CMe$_A$<u>Me</u>$_B$), 0.92 (3 H, t, *J* 7.5, CH$_2$<u>Me</u>); δ_C (125 MHz; $CDCl_3$) 172.8 (CO_2), 144.4 (*p*-Ph), 137.4 (*o*-Ph), 128.9 (*m*-Ph), 126.9 (*i*-Ph), 72.6 (CHOH), 60.8 (OCH_2), 53.1 (S<u>C</u>Me$_2$), 36.5 (<u>C</u>H$_2$CO), 35.3 (Ar<u>C</u>H$_2$), 33.4 (ArCH$_2$<u>C</u>H$_2$), 24.7 (CMe$_A$<u>Me</u>$_B$), 23.6 (C<u>Me</u>$_A$Me$_B$), 22.3 (CH$_2$<u>C</u>H$_2$Me), 14.2 (OCH$_2$<u>Me</u>) 13.9 (CH$_2$CH$_2$<u>Me</u>); ν_{max} (CH_2Cl_2 / cm^{-1}) 3500 (br OH), 1733 (CO), 1597 (Ph), 1463 (Ph). The crude ester was dissolved in methanol (100 cm^3) and water (10 cm^3). Potassium hydroxide (0.93 g, 16.5 mmol) was added and the reaction was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and saturated sodium bicarbonate solution (50 cm^3), water (50 cm^3) and a hexane and ethyl acetate mixture (1:1 ratio, 100 cm^3) were added. The organic layer was subsequently separated and discarded. The aqueous phase was extracted with further portions of ethyl acetate and hexane (1:1 ratio, 2 x 50 cm^3) and each organic phase was discarded. The aqueous phase was acidified with pH 2 sulfate buffer (50 cm^3) and hydrochloric acid as required to bring the pH of the solution to pH 2 before extracting with diethylether (2 x 50 cm^3) and ethyl acetate (50 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give the *3-hydroxy-4-methyl-4-(4'-butylphenylthio) pentanoic acid* as an amorphous off white solid (3.70 g, 83 % over 2 steps); δ_H (500 MHz; $CDCl_3$) 7.40 (2 H, d, *J* 8.0, *o*-Ph), 7.14 (2 H, d, *J* 8.0, *m*-Ph), 3.84 (1 H, dd, *J* 10.5 and 2.0, C<u>H</u>OH), 2.72 (1 H, dd, *J* 15.5 and 1.5, C<u>H</u>$_A$H$_B$), 2.60 (1 H, t, *J* 8.0, ArC<u>H</u>$_2$), 2.49 (1 H, dd, *J* 15.5 and 10.5, CH$_A$<u>H</u>$_B$), 1.62-1.55 (2 H, m, ArCH$_2$C<u>H</u>$_2$), 1.34 (2 H, sextet, *J* 7.5, C<u>H</u>$_2$Me), 1.25 (3 H, s, C<u>Me</u>$_A$Me$_B$), 1.20 (3 H, s, CMe$_A$<u>Me</u>$_B$), 0.92 (3 H, t, *J* 7.5, CH$_2$<u>Me</u>); δ_C (125 MHz; $CDCl_3$); 176.6 (CO_2), 144.6 (*p*-Ph), 137.3 (*o*-Ph), 129.0 (*m*-Ph), 126.5 (*i*-Ph), 72.2 (CHOH), 53.2 (S<u>C</u>Me$_2$), 36.1 (<u>C</u>H$_2$CO), 35.3 (Ar<u>C</u>H$_2$), 33.3 (ArCH$_2$<u>C</u>H$_2$), 24.8 (CMe$_A$<u>Me</u>$_B$), 23.0 (C<u>Me</u>$_A$Me$_B$), 22.3 (<u>C</u>H$_2$Me), 13.9 (CH$_2$<u>Me</u>); *m/z* = 319.1333 ($C_{16}H_{24}O_3SNa$ requires *M+Na* = 319.1344, dev. –3.4 ppm); ν_{max} (CH_2Cl_2 / cm^{-1}) 3420 (br OH), 1709 (CO), 1597 (Ph), 1488 (Ph), 1460 (Ph). The carboxylic acid (3.70 g, 12.5 mmol) was dissolved in THF (120 cm^3) under a nitrogen atmosphere at room temperature. To the rapidly stirring solution was added *N*-hydroxy-succimide (1.51 g, 13.1 mmol) followed by dicyclohexylcarbodimide (2.70 g, 13.1 mmol) and stirring was continued overnight. The dicyclohexyl-urea precipitate was filtered out under gravity and the filter was washed with THF (30 cm^3). Concentrated ammonia (5.0 cm^3) was added and the mixture was stirred overnight. The solution was filtered and the solvent was evaporated under reduced pressure. The residue was suspended in ethyl acetate (75 cm^3), filtered and washed with pH 2 sulfate buffer (2 x 50 cm^3), saturated sodium bicarbonate solution (2 x 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:2 to neat EtOAc) to give the *3-hydroxy-4-methyl-4-(4'-butylphenyl)sulfanyl-pentanamide* **15** as an amorphous white solid (1.81 g, 6.1 mmol, 49 %), R_f (EtOAc) 0.28; δ_H (500 MHz; $CDCl_3$) 7.39 (2 H, d, *J* 8.0, *o*-Ph), 7.13 (2 H, d, *J* 8.0, *m*-Ph), 6.35 (1 H, br s, N<u>H</u>$_A$H$_B$), 5.55 (1 H, br s, NH$_A$<u>H</u>$_B$), 3.77 (1 H, s, OH), 3.73 (1 H, dd, *J* 10.5 and 2.0, C<u>H</u>OH), 2.59 (1 H, t, *J* 8.0, ArC<u>H</u>$_2$), 2.48 (1 H, dd, *J* 15.0 and 2.0, C<u>H</u>$_A$H$_B$CO$_2$), 2.36 (1 H, dd, *J* 15.0 and 10.5, CH$_A$<u>H</u>$_B$CO$_2$), 1.62-1.54 (2 H, m, ArCH$_2$C<u>H</u>$_2$), 1.34 (2 H, sextet, *J* 7.5, C<u>H</u>$_2$Me), 1.23 (3 H, s, C<u>Me</u>$_A$Me$_B$), 1.19 (3 H, s, CMe$_A$<u>Me</u>$_B$), 0.91 (3 H, t, *J* 7.5, CH$_2$<u>Me</u>); δ_C (125 MHz; $CDCl_3$) 174.5 (CON), 144.6 (*p*-Ph), 137.3 (*o*-Ph), 129.0 (*m*-Ph), 126.5 (*i*-Ph), 72.1 (CHOH), 53.9 (S<u>C</u>Me$_2$), 37.3 (<u>C</u>H$_2$CO), 35.3 (Ar<u>C</u>H$_2$), 33.3 (ArCH$_2$<u>C</u>H$_2$), 25.0 (CMe$_A$<u>Me</u>$_B$), 22.6 (C<u>Me</u>$_A$Me$_B$), 22.3 (<u>C</u>H$_2$Me), 13.9 (CH$_2$<u>Me</u>); *m/z* = 318.1508 ($C_{16}H_{25}NO_2SNa$ requires *M+Na* = 318.1504, dev. 1.3 ppm); ν_{max} (cm^{-1}) 3330 (OH), 3189 (NH), 1668 (CO), 1489 (Ph), 1436 (Ph); m.p. (EtOAc/Hexane) 32.3-33.4 ^oC.

2,4,6-Tris-(2'-[4''-methyl-phenylsulfanyl]-3'-hydroxyl-3'-methyl-but-1-yl)-1,3,5-triazine 16: amide **14** (0.4 mmol) was added to a mixture of toluene (3.6 cm^3) and TFA (0.37 cm^3). An oven dried air condenser was cooled under a stream of nitrogen and attached to the reaction flask before being fitted with an argon balloon. The reaction mixture was heated to 40 ^oC overnight. After the reaction was allowed to cool to room temperature saturated sodium bicarbonate solution (20 cm^3) was added, followed by ethyl acetate (20 cm^3). The aqueous layer was extracted with ethyl acetate (2 x 10 cm^3) and the combined organic phases were washed with saturated sodium bicarbonate (2 x 20 cm^3) and brine (20 cm^3), dried (Na_2SO_4) and evaporated to yield the crude reaction residue. The residue was chromatographed (SiO_2, eluting with EtOAc-hexane 1:10 to neat EtOAc) to give the *triazine* as a white

solid (62 mg, 0.26 mmol, 65%) with three spin system environments in a ratio of 5:2:1 (e1:e2:e3); R_f (EtOAc) 0.52; δ_H (500 MHz; $CDCl_3$) 7.20-7.16 (6 H, m, *o*-Ph), 6.96 (2 H, d, *J* 8.0, *m*-Ph e3), 6.93 (2 H, d, *J* 8.0, *m*-Ph e1), 6.90 (2 H, d, *J* 8.0, *m*-Ph e2), 3.84 (1 H, dd, *J* 9.5 and 4.5, SCH e2), 3.79 (1 H, dd, *J* 10.0 and 4.5, SCH e1), 3.78 (1 H, dd, *J* 10.0 and 3.5, SCH e3), 3.33 (1 H, dd, *J* 15.5 and 4.5, $C\underline{H}_AH_B$ e2), 3.20 (1 H, dd, *J* 15.5 and 4.0, $C\underline{H}_AH_B$ e3), 3.16 (1 H, dd, *J* 15.5 and 4.5, $C\underline{H}_AH_B$ e1), 2.99 (1 H, dd, *J* 15.5 and 10.0, $CH_A\underline{H}_B$ e2), 2.97 (1 H, dd, *J* 15.5 and 10.5, $CH_A\underline{H}_B$ e3), 2.93 (1 H, dd, *J* 15.5 and 10.0, $CH_A\underline{H}_B$ e1), 2.85 (1 H, br s, OH e2), 2.81 (1 H, br s, OH e3), 2.78 (1 H, br s, OH e1), 2.22 (6 H, s, Ph$\underline{Me}$ e1 and e3), 2.21 (3 H, s, Ph$\underline{Me}$ e2), 1.35 (3 H, s, $C\underline{Me}_AMe_B$ e2), 1.34 (6 H, s, $CMe_A\underline{Me}_B$ e2 and $C\underline{Me}_AMe_B$ e3), 1.33 (3 H, s, $C\underline{Me}_AMe_B$ e1), 1.31 (3 H, s, $CMe_A\underline{Me}_B$ e3), 1.31 (3 H, s, $CMe_A\underline{Me}_B$ e1); δ_C (125 MHz; $CDCl_3$) 176.7 (CN e2 and e3), 176.6 (CN e1), 136.8 (*p*-Ph e3), 136.7 (*p*-Ph e1), 136.6 (*p*-Ph e2), 132.8 (*i*-Ph e3), 132.7 (*i*-Ph e1), 132.6 (*i*-Ph e2), 131.5 (*m*-Ph e3), 131.3 (*m*-Ph e1), 131.3 (*m*-Ph e2), 129.6 (*o*-Ph e3), 129.6 (*o*-Ph e1), 129.6 (*o*-Ph e2), 73.2 ($Me_2\underline{C}$ e1), 73.1 ($Me_2\underline{C}$ e2 and e3), 73.1 ($Me_2\underline{C}$ e1), 60.4 (SCH e2), 60.4 (SCH e3), 60.3 (SCH e1), 41.2 (CH_2 e2), 41.1 (CH_2 e3), 41.0 (CH_2 e1), 27.7 ($CMe_A\underline{Me}_B$ e2), 27.5 ($CMe_A\underline{Me}_B$ e1), 27.4 ($CMe_A\underline{Me}_B$ e3), 26.7 ($C\underline{Me}_AMe_B$ e1), 26.7 ($C\underline{Me}_AMe_B$ e3), 26.6 ($C\underline{Me}_AMe_B$ e2), 21.0 (Ph$\underline{Me}$ e3), 20.9 (Ph$\underline{Me}$ e1 and e2); Accurate mass, *m/z* = 728.29765 ($C_{39}H_{51}N_3O_3S_3Na$ requires *M+Na* = 728.29848, dev. 1.13 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3410 (OH), 1540 (CN), 1492 (Ph).

Also isolated from this reaction was **5,5-dimethyl-4-(4'-methylphenylsulfanyl)-dihydro-furan-2-one 18** as a pale yellow oil (11 mg, 12%); R_f (EtOAc:Hexane, 1:4) 0.29; δ_H (500 MHz; $CDCl_3$) 7.33 (2 H, dt, *J* 8.0 and 1.5, *o*-Ph), 7.13 (2 H, d, *J* 8.0, *m*-Ph), 3.63 (1 H, dd, *J* 10.5 and 8.0, SCH), 2.88 (1 H, dd, *J* 17.5 and 8.0, $C\underline{H}_AH_B$), 2.66 (1 H, dd, *J* 17.5 and 10.5, $CH_A\underline{H}_B$), 2.33 (3 H, s, Ph$\underline{Me}$), 1.46 (3 H, s, $C\underline{Me}_AMe_B$), 1.40 (3 H, s, $CMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 173.5 (CO_2), 138.5 (*p*-Ph), 132.9 (*o*-Ph), 130.2 (*m*-Ph), 129.7 (*i*-Ph), 87.0 ($\underline{C}Me_2$), 53.1 (SCH), 36.9 (CH_2), 27.4 ($CMe_A\underline{Me}_B$), 23.0 ($C\underline{Me}_AMe_B$), 21.1 (Ph$\underline{Me}$); *m/z* = 259.07740 ($C_{13}H_{16}O_2SNa$ requires *M+Na* = 259.07687, dev. 1.92 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 1766 (CO), 1493 Ph), 1457 (Ph).

Also isolated from this reaction was **4-hydroxy-4-methyl-3-(4'-methylphenylsulfanyl)-pentanamide 20** as an amorphous white solid (15 mg, 15%); R_f (EtOAc) 0.10; δ_H (500 MHz; $CDCl_3$) 7.39-7.36 (2 H, d, *J* 8.0, *o*-Ph), 7.10-7.07 (2 H, d, *J* 8.0, *m*-Ph), 5.62 (1 H, br s, $N\underline{H}_AH_B$), 5.46 (1 H, br s, $NH_A\underline{H}_B$), 3.54 (1 H, dd, *J* 8.0 and 5.0, SCH), 2.79 (1 H, dd, *J* 15.5 and 5.0, $C\underline{H}_AH_B$), 2.47 (1 H, dd, *J* 15.5 and 8.0, $CH_A\underline{H}_B$), 2.30 (3 H, s, Ph$\underline{Me}$), 1.32 (3 H, s, $C\underline{Me}_AMe_B$), 1.31 (3 H, s, $CMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 173.8 (CON), 137.3 (*p*-Ph), 132.1 (*i*-Ph), 131.7 (*o*-Ph), 129.9 (*m*-Ph), 73.1 ($O\underline{C}Me_2$), 58.3 (SCH), 38.3 (CH_2), 27.9 ($C\underline{Me}_AMe_B$), 26.6 ($CMe_A\underline{Me}_B$), 21.0 (Ph$\underline{Me}$); *m/z* = 253.11361 ($C_{13}H_{19}NO_2$ requires *M*+ 253.11365, dev. –0.18 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3340 (br OH), 1670 (CO), 1492 (Ph), 1457 (Ph).

2,4,6-Tris-(2'-[4''-butyl-phenylsulfanyl]-3'-hydroxyl-3'-methyl-but-1-yl)-1,3,5-triazine 17: amide **15** (0.20 mmol) was added to a mixture of toluene (1.8 cm^3) and TFA (0.18 cm^3). An oven dried air condenser was cooled under a stream of nitrogen and attached to the reaction flask before being fitted with an argon balloon. The reaction mixture was heated to 40 °C overnight. After the reaction was allowed to cool to room temperature saturated sodium bicarbonate solution (10 cm^3) was added, followed by ethyl acetate (10 cm^3). The aqueous layer was extracted with ethyl acetate (2 x 10 cm^3) and the combined organic phases was washed with saturated sodium bicarbonate (2 x 20 cm^3) and brine (20 cm^3), dried (Na_2SO_4) and evaporated to yield the crude reaction residue. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:10 to neat EtOAc) to give the trimer as an amorphous white solid (24 mg, 44%) with spin system environments in a 4:2;1 ratio (e1:e2:e3); R_f (EtOAc) 0.68; δ_H (500 MHz; $CDCl_3$) 7.21 (2 H, d, *J* 8.5, *o*-Ph e3), 7.20 (2 H, d, *J* 8.0, *o*-Ph e1), 7.19 (2 H, d, *J* 8.0, *o*-Ph e2), 6.96 (2 H, d, *J* 8.5, *m*-Ph e3), 6.94 (2 H, d, *J* 8.0, *m*-Ph e1), 6.90 (2 H, d, *J* 8.0, *m*-Ph e2), 3.84 (1 H, dd, *J* 10.0 and 4.5, SCH e2), 3.82 (2 H, dd, *J* 10.0 and 4.5, SCH e1 and e3), 3.34 (1 H, dd, *J* 15.5 and 4.5, $C\underline{H}_AH_BCN$ e2), 3.22 (1 H, dd, *J* 15.5 and 4.5, $C\underline{H}_AH_BCN$ e3), 3.18 (1 H, dd, *J* 15.5 and 4.5, $C\underline{H}_AH_BCN$ e1), 3.01 (1 H, dd, *J* 15.5 and 10.0, $CH_A\underline{H}_BCN$ e2), 2.99 (1 H, dd, *J* 15.5 and 10.5, $CH_A\underline{H}_BCN$ e3), 2.95 (1 H, dd, *J* 15.5 and 10.0, $CH_A\underline{H}_BCN$ e1), 2.83 (1 H, s, OH e2), 2.78 (1 H, s, OH e3), 2.77 (1 H, s, OH e1), 2.50-2.44 (6 H, m, $ArC\underline{H}_2$), 1.53-1.45 (6 H, m, $ArCH_2C\underline{H}_2$), 1.36 (3 H, s, $C\underline{Me}_AMe_B$ e2), 1.35 (3 H, s, $C\underline{Me}_AMe_B$ e3), 1.34 (3 H, s, $C\underline{Me}_AMe_B$ e1), 1.33 (3 H, s, $CMe_A\underline{Me}_B$ e2), 1.31 (3 H, s, $CMe_A\underline{Me}_B$ e3), 1.31 (3 H, s, $CMe_A\underline{Me}_B$ e1), 1.32-1.24 (6 H, m, $C\underline{H}_2Me$), 0.89 (6 H, t, *J* 7.5, $CH_2\underline{Me}$ e1 and e2), 0.88 (3 H, t, *J* 7.5, $CH_2\underline{Me}$ e3); δ_C (125 MHz; $CDCl_3$) 176.8 (CN e2), 176.7 (CN e3), 176.6 (CN e1), 141.8 (*p*-Ph e3), 141.7 (*p*-Ph e1), 141.7 (*p*-Ph e2), 132.9 (*i*-Ph e1 and e3), 132.8 (*i*-Ph e2), 131.4 (*o*-Ph e3), 131.3 (*o*-Ph e2), 131.2 (*o*-Ph e1), 129.0 (*m*-Ph), 73.1 ($\underline{C}Me_2$ e2 and e3), 73.1 ($\underline{C}Me_2$ e1), 60.3 (SCH e2), 60.3 (SCH e3), 60.2 (SCH e1), 41.2 ($\underline{C}H_2CN$ e2), 41.2 ($\underline{C}H_2CN$ e3), 41.1 ($\underline{C}H_2CN$ e1), 35.1 ($Ar\underline{C}H_2$), 33.4 ($ArCH_2\underline{C}H_2$), 27.6 ($CMe_A\underline{Me}_B$ e2), 27.5 ($CMe_A\underline{Me}_B$ e1), 27.4

($CMe_A\underline{Me}_B$ e3), 26.7 ($C\underline{Me}_AMe_B$ e1 and e3), 26.7 ($C\underline{Me}_AMe_B$ e2), 22.3 ($\underline{C}H_2Me$ e1 and e3), 22.3 ($\underline{C}H_2Me$ e2), 13.9 ($CH_2\underline{Me}$); *m/z* = 854.4440 ($C_{48}H_{69}N_3O_3S_3Na$ requires *M+Na* = 854.4399, dev. 4.8 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 1541 (CN), 1494 (Ph); m.p. (EtOAc/Hexane) 62.5-65.1 °C.

Also isolated from this reaction was **5,5-dimethyl-4-(4'-butylphenylsulfanyl)-dihydro-furan-2-one 19** as a pale yellow oil (7 mg, 0.03 mmol, 15 %), R_f (EtOAc:Hexane, 1:4) 0.32; δ_H (500 MHz; $CDCl_3$) 7.35 (2 H, d, *J* 8.0, *o*-Ph), 7.14 (2 H, d, *J* 8.0, *m*-Ph), 3.64 (1 H, dd, *J* 10.5 and 8.0, SCH), 2.88 (1 H, dd, *J* 17.5 and 8.0, $C\underline{H}_AH_BCO_2$), 2.67 (1 H, dd, *J* 17.5 and 10.5, $CH_A\underline{H}_BCO_2$), 2.58 (1 H, t, *J* 7.5, $ArC\underline{H}_2$), 1.60-1.53 (2 H, m, $ArCH_2C\underline{H}_2$), 1.46 (3 H, s, $C\underline{Me}_AMe_B$), 1.41 (3 H, s, $CMe_A\underline{Me}_B$), 1.33 (2 H, sextet, *J* 7.5, $C\underline{H}_2Me$), 0.91 (3 H, t, *J* 7.5, $CH_2\underline{Me}$); δ_C (125 MHz; $CDCl_3$) 173.6 (CO_2), 143.5 (*i*-Ph), 132.9 (*o*-Ph), 129.9 (*p*-Ph), 129.5 (*m*-Ph), 87.0 ($O\underline{C}Me_2$), 53.1 (SCH), 37.0 ($\underline{C}H_2CO$), 35.2 ($Ar\underline{C}H_2$), 33.4 ($ArCH_2\underline{C}H_2$), 27.4 ($CMe_A\underline{Me}_B$), 23.0 ($C\underline{Me}_AMe_B$), 22.2 ($\underline{C}H_2Me$), 13.9 ($CH_2\underline{Me}$); Accurate mass, *m/z* = 279.1403 ($C_{16}H_{23}O_2S$ requires *M+H* = 279.1419, dev. –5.7 ppm); ν_{max} (CH_2Cl_2 / cm^{-1}) 1772 (CO), 1494 (Ph), 1465 (Ph).

Also isolated from this reaction was **4-hydroxy-4-methyl-3-(4-methylphenylsulfanyl)-pentanamide 21** as an amorphous pale yellow solid (18 mg, 0.06 mmol, 30 %), R_f (EtOAc) 0.26; δ_H (500 MHz; $CDCl_3$) 7.39 (2 H, d, *J* 8.0, *o*-Ph), 7.09 (2 H, d, *J* 8.0, *m*-Ph), 5.63 (1 H, br s, $N\underline{H}_AH_B$), 5.47 (1 H, br s, $NH_A\underline{H}_B$), 3.55 (1 H, dd, *J* 8.0 and 5.0, $C\underline{H}SPh$), 2.82 (1 H, br s, OH), 2.79 (1 H, dd, *J* 15.5 and 5.0, $C\underline{H}_AH_BCO$), 2.55 (1 H, t, *J* 8.0, $ArC\underline{H}_2$), 2.48 (1 H, dd, *J* 15.5 and 8.0, $CH_A\underline{H}_BCO$), 1.58-1.52 (2 H, m, $ArCH_2C\underline{H}_2$), 1.35-1.29 (2 H, m, $C\underline{H}_2Me$), 1.32 (3 H, s, $C\underline{Me}_AMe_B$), 1.32 (3 H, s, $CMe_A\underline{Me}_B$), 0.98 (3 H, t, *J* 7.5, $CH_2\underline{Me}$); δ_C (125 MHz; $CDCl_3$) 173.8 (CO), 142.2 (*i*-Ph), 132.3 (*p*-Ph), 131.6 (*o*-Ph), 129.3 (*m*-Ph), 73.1 ($O\underline{C}Me_2$), 58.2 (SCH), 38.4 ($\underline{C}H_2CO$), 35.2 ($Ar\underline{C}H_2$), 33.4 ($ArCH_2\underline{C}H_2$), 27.9 ($C\underline{Me}_AMe_A$), 26.6 ($CMe_A\underline{Me}_B$), 22.3 ($\underline{C}H_2Me$), 13.9 ($CH_2\underline{Me}$); *m/z* = 318.1510 ($C_{16}H_{25}NO_2SNa$ requires *M+Na* = 318.1504, dev. 2.0 ppm); ν_{max} (CH_2Cl_2 / cm^{-1}) 3348 (OH), 3171 (NH), 1678 (CO), 1491 (Ph), 1464 (Ph), 1437 (Ph); m.p. (EtOAc/Hexane) 113.3-116.0 °C.

***tert*-Butyl-4-(3'-hydroxy-4'-methyl-4'-phenylsulfanyl-pentanoylamino)-4-methyl-pentanoate 24**: acid **23** (2.69 g, 11.2 mmol) was dissolved in THF (100 cm^3) under a nitrogen atmosphere at room temperature. To the rapidly stirring solution was added HOBt (1.51 g, 11.2 mmol), followed by DCC (2.31 g, 11.2 mmol) and stirring was continued overnight. DCU precipitate was filtered out under gravity and the filter was washed with THF (10 cm^3) to give the required solution of the activated acid. A solution of amino ester[4] **22** (2.10 g, 11.2 mmol) in THF (5 cm^3) and triethylamine (2.26 g, 22.4 mmol) was added and the mixture was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (150 cm^3), filtered and washed with pH 2 sulfate buffer (2 x 100 cm^3), saturated sodium bicarbonate solution (2 x 100 cm^3) and brine (100 cm^3), dried (Na_2SO_4) and was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:10 to 1:1) to give the *ester* as a highly viscous pale yellow oil (3.60 g, 8.8 mmol, 79%), R_f (EtOAc-hexanes, 1:1) 0.51; δ_H (500 MHz; $CDCl_3$) 7.53-7.49 (2 H, m, *o*-Ph), 7.39-7.28 (3 H, m, *m* and *p*-Ph), 6.12 (1 H, br s, NH), 3.96 (1 H, dd, *J* 2.0 and 0.5, OH), 3.75 (1 H, dt, *J* 10.5 and 2.0, $C\underline{H}OH$), 2.44 (1 H, ddd, *J* 15.0, 1.5 and 1.0, $C\underline{H}_AH_BCON$), 2.26 (1 H, dd, *J* 15.0 and 10.5, $CH_A\underline{H}_BCON$), 2.25 (2 H, t, *J* 7.5, $C\underline{H}_2CO_2{}^tBu$), 2.05-1.89 (2 H, m, $NCMe_2C\underline{H}_2$), 1.44 (9 H, s, ^tBu), 1.33 (3 H, s, $NC\underline{Me}_AMe_B$), 1.31 (3 H, s, $NCMe_A\underline{Me}_B$), 1.23 (3 H, s, $SC\underline{Me}_AMe_B$), 1.19 (3 H, s, $NCMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 173.4 (CON), 171.6 ($\underline{C}O_2{}^tBu$), 137.5 (*o*-Ph), 130.3 (*i*-Ph), 129.2 (*p*-Ph), 128.8 (*m*-Ph), 80.6 ($\underline{C}Me_3$), 72.9 (CHOH), 53.7 ($N\underline{C}Me_2$), 53.3 ($S\underline{C}Me_2$), 38.4 ($\underline{C}H_2CON$), 35.1 ($NCMe_2\underline{C}H_2$), 30.6 ($\underline{C}H_2CO_2{}^tBu$), 28.1 ($C\underline{Me}_3$), 26.7 ($NCMe_A\underline{Me}_B$), 26.6 ($NC\underline{Me}_AMe_B$), 24.8 ($SCMe_A\underline{Me}_B$), 23.5 ($SC\underline{Me}_AMe_B$); *m/z* = 432.2201 ($C_{22}H_{35}NO_4SNa$ requires *M+Na* = 432.2185, dev. 3.8 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3335 (br OH), 1728 ($CO_2{}^tBu$), 1647 (CONH), 1474 (Ph), 1439 (Ph).

Methyl 4-(3'-hydroxy-4'-methyl-4'-phenylsulfanyl-pentanoylamino)-4-methyl-pentanoate 25: ester **24** (3.60 g, 8.56 mmol) was dissolved in methanol (100 cm^3) under nitrogen. Thionyl chloride (0.30 g, 2.5 mmol) was added and the solution was heated to 40 °C for two days before the addition of saturated sodium bicarbonate solution (40 cm^3). The organic solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (100 cm^3) and washed with saturated sodium bicarbonate solution (2 x 100 cm^3) and brine (100 cm^3), dried (Na_2SO_4) and was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:4 to 1:1) to give the *ester* as a pale yellow oil (2.17 g, 5.91 mmol, 69%), R_f (EtOAc-hexanes, 1:1) 0.44; δ_H (500 MHz; $CDCl_3$) 7.52-7.49 (2 H, m, *o*-Ph), 7.39-7.35 (1 H, m, *p*-Ph), 7.35-7.30 (2 H, m, *m*-Ph), 6.02 (1 H, br s, NH), 3.85 (1 H, s, OH), 3.74 (1 H, dt, *J* 10.5 and 2.0, $C\underline{H}OH$), 3.67 (3 H, s, OMe), 2.43 (1 H, dd, *J* 15.0 and 1.5, $C\underline{H}_AH_BCON$), 2.33 (2 H, t, *J* 8.0, $C\underline{H}_2CO_2Me$), 2.25 (1 H, dd, *J* 15.0 and 10.5,

$CH_A\underline{H}_BCON$), 2.12-2.06 (1 H, m, $NCMe_2C\underline{H}_AH_B$), 1.98-2.04 (1 H, m, $NCMe_2CH_A\underline{H}_B$), 1.33 (3 H, s, $NC\underline{Me}_AMe_B$), 1.30 (3 H, s, $NCMe_A\underline{Me}_B$), 1.23 (3 H, s, $SC\underline{Me}_AMe_B$), 1.19 (3 H, s, $SCMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 174.4 (CONH), 172.4 ($\underline{C}O_2Me$), 137.4 (*o*-Ph), 130.3 (*i*-Ph), 129.2 (*p*-Ph), 128.8 (*m*-Ph), 72.9 (CHOH), 53.8 ($N\underline{C}Me_2$), 53.2 ($S\underline{C}Me_2$), 51.8 (OMe), 38.6 ($\underline{C}H_2CON$), 34.7 ($NCMe_2\underline{C}H_2$), 29.3 ($\underline{C}H_2CO_2Me$), 26.9 ($NCMe_A\underline{Me}_B$), 26.8 ($NC\underline{Me}_AMe_B$), 24.8 ($SCMe_A\underline{Me}_B$), 24.0 ($SC\underline{Me}_AMe_B$); *m/z* = 390.1703 ($C_{19}H_{29}NO_4SNa$ requires *M+Na* = 390.1717, dev. –3.2 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3320 (br OH), 1736 (CO_2Me), 1647 (CONH), 1438 (Ph).

4-(3'-Hydroxy-4'-methyl-4'-phenylsulfanyl-pentanoylamino)-4-methyl-pentanoic acid 26: ester **25** (2.17 g, 5.91 mmol) was dissolved in methanol (50 cm^3) and water (10 cm^3). Potassium hydroxide (0.40 g, 7.09 mmol) was added and the reaction was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and saturated sodium bicarbonate solution (50 cm^3), water (50 cm^3) and a hexane and ethyl acetate mixture (1:1 ratio, 100 cm^3) were added. The organic layer was subsequently separated and discarded. The aqueous phase was extracted with further portions of ethyl acetate and hexane (1:1 ratio, 2 x 100 cm^3) and each organic phase was discarded. The aqueous phase was acidified with pH 2 sulfate buffer (200 cm^3) and hydrochloric acid as required to bring the pH of the solution to pH 2 before extracting with diethylether (2 x 200 cm^3) and ethyl acetate (200 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give the *acid* as an amorphous white solid (1.70 g, 4.82 mmol, 82%); δ_H (500 MHz; $CDCl_3$) 7.52-7.49 (2 H, m, *o*-Ph), 7.39-7.28 (3 H, m, *m* and *p*-Ph), 6.00 (1 H, br s, NH), 3.78 (1 H, dd, *J* 10.5 and 2.0, C<u>H</u>OH), 2.47 (1 H, dd, *J* 14.5 and 2.0, $C\underline{H}_AH_BCON$), 2.35 (2 H, t, *J* 8.0, $C\underline{H}_2CO_2H$), 2.25 (1 H, dd, *J* 14.5 and 10.5, $CH_A\underline{H}_BCON$), 2.19 (1 H, dt, *J* 14.5 and 8.0, $NCMe_2C\underline{H}_AH_B$), 2.00-1.94 (1 H, m, $NCMe_2CH_A\underline{H}_B$), 1.35 (3 H, s, $NC\underline{Me}_AMe_B$), 1.29 (3 H, s, $NCMe_A\underline{Me}_B$), 1.23 (3 H, s, $SC\underline{Me}_AMe_B$), 1.19 (3 H, s, $SCMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 177.5 (CO_2H), 171.8 (CONH), 137.4 (*o*-Ph), 130.2 (*i*-Ph), 129.3 (*p*-Ph), 128.8 (*m*-Ph), 72.9 (CHOH), 53.8 ($N\underline{C}Me_2$), 53.3 ($S\underline{C}Me_2$), 38.8 ($\underline{C}H_2CON$), 34.2 ($NCMe_2\underline{C}H_2$), 29.1 ($\underline{C}H_2CO_2Me$), 27.1 ($NCMe_A\underline{Me}_B$), 27.0 ($NC\underline{Me}_AMe_B$), 24.9 ($SCMe_A\underline{Me}_B$), 23.4 ($SC\underline{Me}_AMe_B$); *m/z* = 354.1736 ($C_{18}H_{28}NO_4S$ requires *M+H* = 354.1739, dev. –0.9 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3727 (NH), 3340 (br OH), 1711 (CO_2H), 1648 (CONH), 1439 (Ph).

3-Hydroxy-4-methyl-4-phenylsulfanyl-(3'-carbamoyl-1',1'-dimethyl-propyl)-pentanamide 27: acid **26** (300 mg, 0.85 mmol) was dissolved in THF (10 cm^3) under a nitrogen atmosphere at room temperature. To the stirred solution was added HOBt (120 mg, 0.89 mmol), followed by CDI (145 mg, 0.89 mmol) and stirring was continued overnight to give the required solution of the activated acid. Concentrated ammonia (2 cm^3) was added and the mixture was stirred at room temperature overnight before the organic solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of ethyl acetate (50 cm^3) and methanol (10 cm^3) and washed with saturated sodium bicarbonate solution (2 x 50 cm^3), pH 2 sulfate buffer (2 x 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and was evaporated to yield the *amide* as white platelets (155 mg, 0.61 mmol, 72%); δ_H (500 MHz; D_6-DMSO) 7.56-7.53 (2 H, m, *o*-Ph), 7.43-7.33 (4 H, m, *m* and *p*-Ph, NH), 7.21 (1 H, s, NH) 6.70 (1 H, s, NH), 5.03 (1 H, d, *J* 5.5, OH), 3.77 (1 H, ddd, *J* 9.5, 5.5 and 2.0, C<u>H</u>OH), 2.61 (1 H, dd, *J* 14.0 and 2.0, $C\underline{H}_AH_BCONH_2$), 2.22 (1 H, dd, *J* 14.0 and 10.0, $CH_A\underline{H}_BCONH_2$), 2.35 (2 H, t, *J* 8.0, $C\underline{H}_2CO_2H$), 2.09-1.97 (2 H, m, $\underline{C}H_2CONH_2$), 1.90-1.77 (2 H, m, $NCMe_2C\underline{H}_2$), 1.22 (3 H, s, $NC\underline{Me}_AMe_B$), 1.20 (3 H, s, $NCMe_A\underline{Me}_B$), 1.11 (3 H, s, $SC\underline{Me}_AMe_B$), 1.09 (3 H, s, $SCMe_A\underline{Me}_B$); δ_C (125 MHz; D_6-DMSO) 174.8 ($CONH_2$), 171.1 (CONH), 137.5 (*o*-Ph), 131.4 (*i*-Ph), 129.0 (*p*-Ph), 128.8 (*m*-Ph), 72.9 (CHOH), 52.8 ($N\underline{C}Me_2$), 52.3 ($S\underline{C}Me_2$), 39.2 ($\underline{C}H_2CONH_2$), 35.4 ($NCMe_2\underline{C}H_2$), 30.4 ($\underline{C}H_2CONH_2$), 26.7 and 26.7 ($NCMe_2$), 25.9 ($SC\underline{Me}_AMe_B$), 23.5 ($SCMe_A\underline{Me}_B$); *m/z* = 353.1892 ($C_{18}H_{29}N_2O_3S$ requires *M+H* = 353.1899, dev. –1.9 ppm); ν_{max} (neat / cm^{-1}) 3411 (OH), 3319 (NH), 3198 (NH), 1672 (CONH), 1644 ($CONH_2$), 1524 (Ph), 1438 (Ph); m.p. (EtOAc/Hexane) 199.8-201.1 ^oC.

***tert*-Butyl 4-[4'-(3''-hydroxy-4''-methyl-4''-phenylsulfanyl-pentanoylamino)-4'-methyl-pentanoylamino]-4-methyl-pentanoate 28**: acid **26** (1.40 g, 4.0 mmol) was dissolved in THF (50 cm^3) under a nitrogen atmosphere at room temperature. To the rapidly stirring solution was added HOBt (562 mg, 4.2 mmol), followed by DCC (858 mg, 4.2 mmol) and stirring was continued overnight. DCU precipitate was filtered out under gravity and the filter was washed with THF (2 cm^3) to give the required solution of the activated acid. A solution of amino ester[4] **22** (779 mg, 4.2 mmol) in THF (5 cm^3) and triethylamine (808 mg, 8.0 mmol) was added and the mixture was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (50 cm^3), filtered and washed with pH 2 sulfate buffer (2 x 50 cm^3), saturated sodium bicarbonate solution (2 x 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexane 1:4 to 4:1) to

give the *ester* as a highly viscous pale yellow oil (1.40 g, 2.7 mmol, 67%), R_f (EtOAc-Hexane, 1:1) 0.45; δ_H (500 MHz; $CDCl_3$) 7.53-7.50 (2 H, m, *o*-Ph), 7.37-7.33 (1 H, m, *p*-Ph), 7.33-7.29 (2 H, m, *m*-Ph), 6.62 (1 H, br s, NH), 5.90 (1 H, br s, NH), 3.78 (1 H, dd, *J* 10.5 and 2.0, C<u>H</u>OH), 2.49 (1 H, dd, *J* 14.5 and 2.0, CHOHC<u>H</u>$_A$H$_B$), 2.25 (1 H, dd, *J* 14.5 and 10.5, CHOHCH$_A$<u>H</u>$_B$), 2.24 (2 H, t, *J* 7.5, C<u>H</u>$_2$CO$_2$^{t}Bu), 2.17-2.13 (2 H, m, CH$_2$C<u>H</u>$_2$CONH), 1.97 (1 H, dt, *J* 14.0 and 7.0, C<u>H</u>$_A$H$_B$CH$_2$CONH), 1.92 (2 H, t, *J* 7.5, C<u>H</u>$_2$CH$_2$CO$_2$^{t}Bu), 1.90 (1 H, dt, *J* 14.0 and 7.0, CH$_A$<u>H</u>$_B$CH$_2$CONH), 1.42 (9 H, s, CMe$_3$), 1.33 (3 H, s, NCMe), 1.31 (3 H, s, NCMe), 1.30 (3 H, s, NCMe), 1.30 (3 H, s, NCMe), 1.23 (3 H, s, SC<u>Me</u>$_A$Me$_B$), 1.19 (3 H, s, SCMe$_A$<u>Me</u>$_B$); δ_C (125 MHz; $CDCl_3$) 173.6 (CONH), 173.0 (CONH), 171.9 (CO$_2$^{t}Bu), 137.5 (*o*-Ph), 130.7 (*i*-Ph), 129.1 (*p*-Ph), 128.3 (*m*-Ph), 80.7 (<u>C</u>Me$_3$), 73.3 (CHOH), 53.5 and 53.4 and 53.3 (N<u>C</u>Me$_2$ x2 and S<u>C</u>Me$_2$), 38.5 (CHOH<u>C</u>H$_2$), 36.3 (<u>C</u>H$_2$CH$_2$CO$_2$^{t}Bu), 35.4 (<u>C</u>H$_2$CH$_2$CONH), 32.4 (<u>C</u>H$_2$CONH), 30.6 (<u>C</u>H$_2$CO$_2$^{t}Bu), 28.0 (C<u>Me</u>$_3$), 26.8 and 26.6 and 26.5 and 26.5 (NC<u>Me</u>$_2$ x 2), 24.8 (SCMe$_A$<u>Me</u>$_B$), 24.0 (SC<u>Me</u>$_A$Me$_B$); *m/z* = 545.3039 ($C_{28}H_{46}N_2O_5SNa$ requires *M+Na* = 545.3025, dev. –2.5 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3310 (br OH), 1727 (CO$_2$^{t}Bu), 1644 (CONH), 1451 (Ph), 1439 (Ph).

Methyl 4-[4'-(3''-hydroxy-4''-methyl-4''-phenylsulfanyl-pentanoylamino)-4'-methyl-pentanoylamino]-4-methyl-pentanoate 29: ester **28** (1.40 g, 2.68 mmol) was dissolved in methanol (30 cm^3) under nitrogen. Concentrated aqueous HCl (0.20 cm^3) was added and the solution was stirred at ambient temperature for 24 hours before the addition of saturated sodium bicarbonate solution (40 cm^3). The organic solvent was evaporated and the residue was dissolved in ethyl acetate (50 cm^3) and washed with saturated sodium bicarbonate solution (2 x 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexane 1:4 EtOAc) to give the *ester* as a pale yellow oil (0.80 g, 1.67 mmol, 62%), R_f (EtOAc-Hexane, 1:1) 0.11; δ_H (500 MHz; $CDCl_3$) 7.53-7.50 (2 H, m, *o*-Ph), 7.38-7.34 (1 H, m, *p*-Ph), 7.33-7.30 (2 H, m, *m*-Ph), 6.51 (1 H, br s, NH), 5.76 (1 H, br s, NH), 4.07 (1 H, dd, *J* 2.5 and 0.5, OH), 3.79 (1 H, dt, *J* 10.5 and 2.5, C<u>H</u>OH), 3.65 (3 H, s, OMe), 2.49 (1 H, ddd, *J* 14.5, 2.5 and 0.5, CHOHC<u>H</u>$_A$H$_B$), 2.32 (2 H, t, *J* 7.5, C<u>H</u>$_2$CO$_2$Me), 2.25 (1 H, dd, *J* 14.5 and 10.5, CHOHCH$_A$<u>H</u>$_B$), 2.17-2.13 (2 H, m, CH$_2$C<u>H</u>$_2$CONH), 2.05-1.97 (3 H, m, C<u>H</u>$_A$H$_B$CH$_2$CONH and C<u>H</u>$_2$CH$_2$CO$_2$Me), 1.94-1.86 (1 H, m, CH$_A$<u>H</u>$_B$CH$_2$CONH), 1.34 (3 H, s, NCMe), 1.31 (6 H, s, NCMe x2), 1.29 (3 H, s, NCMe), 1.23 (3 H, s, SC<u>Me</u>$_A$Me$_B$), 1.19 (3 H, s, SCMe$_A$<u>Me</u>$_B$); δ_C (125 MHz; $CDCl_3$) 174.6 (CONH), 173.0 (CONH), 171.9 (CO$_2$Me), 137.5 (*o*-Ph), 130.6 (*i*-Ph), 129.1 (*p*-Ph), 128.7 (*m*-Ph), 73.3 (CHOH), 53.5 and 53.4 and 53.2 (N<u>C</u>Me$_2$ x2 and S<u>C</u>Me$_2$), 51.8 (OMe), 38.6 (CHOH<u>C</u>H$_2$), 36.2 (<u>C</u>H$_2$CH$_2$CONH), 35.0 (<u>C</u>H$_2$CH$_2$CO$_2$Me), 32.4 (<u>C</u>H$_2$CONH), 29.3 (<u>C</u>H$_2$CO$_2$Me), 26.9 and 26.8 and 26.7 and 26.7 (NC<u>Me</u>$_2$ x 2), 24.8 (SCMe$_A$<u>Me</u>$_B$), 23.9 (SC<u>Me</u>$_A$Me$_B$); *m/z* = 503.2578 ($C_{25}H_{40}N_2O_5SNa$ requires *M+Na* = 503.2556, dev. 4.5 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3300 (br OH), 1737 (CO$_2$Me), 1644 (CONH), 1545 (Ph), 1439 (Ph).

4-[4'-(3''-Hydroxy-4''-methyl-4''-phenylsulfanyl-pentanoylamino)-4'-methyl-pentanoylamino]-4-methyl-pentanoic acid 30: ester **23** (800 mg, 1.67 mmol) was dissolved in methanol (20 cm^3) and water (2 cm^3). Potassium hydroxide (112 mg, 2.00 mmol) was added and the reaction was stirred at room temperature overnight. The excess solvent was evaporated under reduced pressure and saturated sodium bicarbonate solution (10 cm^3), water (10 cm^3) and a hexane and ethyl acetate mixture (1:1 ratio, 20 cm^3) were added. The organic layer was subsequently separated and discarded. The aqueous phase was extracted with further portions of ethyl acetate and hexane (1:1 ratio, 2 x 20 cm^3) and each organic phase was discarded. The aqueous phase was acidified with pH 2 sulfate buffer (40 cm^3) and hydrochloric acid as required to bring the pH of the solution to pH 2 before extracting with diethylether (2 x 50 cm^3) and ethyl acetate (50 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give the *acid* as a highly viscous pale yellow oil (575 mg, 1.23 mmol, 74%); δ_H (500 MHz; $CDCl_3$) 7.55-7.51 (2 H, m, *o*-Ph), 7.38-7.30 (3 H, m, *m* and *p*-Ph), 6.11 (1 H, br s, NH), 5.75 (1 H, br s, NH), 3.79 (1 H, dd, *J* 10.5 and 2.0, C<u>H</u>OH), 2.66 (1 H, dd, *J* 14.5 and 2.0, CHOHC<u>H</u>$_A$H$_B$), 2.44-2.34 (2 H, m, C<u>H</u>$_2$CO$_2$H), 2.33 (1 H, dd, *J* 14.5 and 10.5, CHOHCH$_A$<u>H</u>$_B$), 2.25-2.18 (1 H, m, CH$_2$C<u>H</u>$_A$H$_B$CONH), 2.11-1.87 (5 H, m, CH$_2$CH$_A$<u>H</u>$_B$CONH, C<u>H</u>$_2$CH$_2$CONH and C<u>H</u>$_2$CH$_2$CO$_2$Me), 1.38 (3 H, s, NCMe), 1.34 (3 H, s, NCMe), 1.33 (3 H, s, NCMe), 1.23 (3 H, s, SC<u>Me</u>$_A$Me$_B$), 1.23 (3 H, s, NCMe), 1.21 (3 H, s, SCMe$_A$<u>Me</u>$_B$); δ_C (125 MHz; $CDCl_3$) 177.5 (CO$_2$H), 172.9 (CONH), 172.9 (CONH), 137.5 (*o*-Ph), 130.6 (*i*-Ph), 129.1 (*p*-Ph), 128.7 (*m*-Ph), 73.0 (CHOH), 54.0 and 53.5 and 53.3 (N<u>C</u>Me$_2$ x2 and S<u>C</u>Me$_2$), 39.6 (CHOH<u>C</u>H$_2$), 35.4 and 35.3 (<u>C</u>H$_2$CH$_2$CONH and <u>C</u>H$_2$CH$_2$CO$_2$H), 32.6 (<u>C</u>H$_2$CONH), 29.8 (<u>C</u>H$_2$CO$_2$H), 27.4 and 27.3 and 26.8 and 26.6 (NC<u>Me</u>$_2$ x 2), 24.7 (SCMe$_A$<u>Me</u>$_B$), 24.3 (SC<u>Me</u>$_A$Me$_B$); *m/z* = 489.2401 ($C_{24}H_{38}N_2O_5SNa$ requires *M+Na* = 489.2399, dev. 0.5 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3325 (br OH), 1710 (CO$_2$H), 1647 (CONH), 1548 (Ph), 1453 (Ph).

4-[4'-(3''-Hydroxy-4''-methyl-4''-phenylsulfanyl-pentanoylamino)-4'-methyl-pentanoylamino]-4-methyl-pentanamide 31: acid **30** (300 mg, 0.54 mmol) was dissolved in THF (10 cm^3) under a nitrogen atmosphere at room temperature. To the stirred solution was added CDI (125 mg, 0.77 mmol) and stirring was continued overnight to give the required solution of the activated acid. Concentrated ammonia (2 cm^3) was added and the mixture was stirred overnight. The organic solvent was evaporated under reduced pressure and the residue was suspended in a mixture of ethyl acetate and hexane (1:1 mixture, 20 cm^3) and the solid was obtained by filtration. The solid was suspended in the same solvent mixture and the process repeated. The solid was suspended in saturated sodium bicarbonate solution (20 cm^3) and was filtered. This process was repeated twice. The solid was washed on the filter with toluene (3 x 20 cm^3), suspended in toluene (20 cm^3) and the solvent was evaporated under reduced pressure to yield the *amide* as a white amorphous solid (189 mg, 0.34 mmol, 63 %); δ_H (500 MHz; D_6-DMSO) 7.56-7.53 (2 H, m, *o*-Ph), 7.43-7.35 (4 H, m, *m* and *p*-Ph, NH), 7.23 (1 H, br s, NH), 6.70 (1 H, br s, NH), 5.02 (1 H, d, *J* 5.5, OH), 3.78 (1 H, ddd, *J* 10.0, 5.5 and 2.0, C<u>H</u>OH), 2.62 (1 H, dd, *J* 14.5 and 2.0, CHOHC<u>H</u>$_A$H$_B$), 2.21 (1 H, dd, *J* 14.5 and 10.0, CHOHCH$_A$<u>H</u>$_B$), 2.04-1.97 (4 H, m, C<u>H</u>$_2$CONH and C<u>H</u>$_2$CONH$_2$), 1.84-1.78 (4 H, m, C<u>H</u>$_2$CH$_2$CONH and C<u>H</u>$_2$CH$_2$CONH$_2$), 1.21 (6 H, s, NCMe x2), 1.19 (6 H, s, NCMe x2), 1.11 (3 H, s, SC<u>Me</u>$_A$Me$_B$), 1.09 (3 H, s, SCMe$_A$<u>Me</u>$_B$); δ_C (125 MHz; D_6-DMSO) 174.7 ($CONH_2$), 172.1 (CONH), 171.1 (CONH), 137.5 (*o*-Ph), 131.4 (*i*-Ph), 129.0 (*p*-Ph), 128.8 (*m*-Ph), 72.9 (CHOH), 52.8 and 52.4 and 52.1 (N<u>C</u>Me$_2$ x2 and <u>C</u>SPh), 39.0 (CHOH<u>C</u>H$_2$), 35.8 (<u>C</u>H$_2$CH$_2$CONH$_2$), 35.4 (<u>C</u>H$_2$CH$_2$CONH), 31.4 (<u>C</u>H$_2$CONH$_2$), 30.4 (<u>C</u>H$_2$CONH), 26.6 and 26.6 and 26.5 and 26.5 (NC<u>Me</u>$_2$ x 2), 25.9 (SC<u>Me</u>$_A$Me$_B$), 23.5 (SCMe$_A$<u>Me</u>$_B$); *m/z* = 466.2739 ($C_{24}H_{40}N_3O_4S$ requires *M+H* = 466.2740, dev. –0.2 ppm); ν_{max} (cm^{-1}) 3299 (OH or NH), 3208 (OH or NH), 1645 (CONH), 1619 ($CONH_2$), 1550 (Ph), 1439 (Ph); m.p. (EtOAc/Hexane) 206.3-209.9 ^oC.

***N*-(1'-Carbamoyl-1'-methyl-ethyl)-3-hydroxy-4-methyl-4-phenylsulfanyl-pentanamide 32**: acid **23** (480 mg, 2.0 mmol) was dissolved in THF (20 cm^3) under a nitrogen atmosphere at room temperature. To the rapidly stirring solution was added NHS (412 mg, 2.0 mmol), followed by DCC (270 mg, 2.0 mmol) and stirring was continued overnight. DCU precipitate was filtered out under gravity and the filter was washed with THF (5 cm^3) to give the required solution of the activated acid. A solution of 2-amino isobutyric acid (206 mg, 2.0 mmol) and potassium carbonate (552 mg, 4.0 mmol) in water (3 cm^3) was added and the mixture was stirred at room temperature overnight. The mixture was filtered through a thin pad of celite and the organic solvent was evaporated under reduced pressure. Saturated sodium bicarbonate solution (10 cm^3) was added and the aqueous phase was washed with a mixture of ethyl acetate and hexanes (1:1 mixture, 2 x 30 cm^3). The aqueous phase was acidified with pH 2 sulfate buffer (30 cm^3) and dilute hydrochloric acid (3 N solution) to bring the solution to pH 2 before extraction with diethylether (2 x 50 cm^3) and ethyl acetate (50 cm^3). The combined organic extracts were washed with brine (100 cm^3), dried (Na_2SO_4) and were evaporated under reduced pressure. The residue was dissolved in methanol (20 cm^3) and concentrated hydrochloric acid (0.1 cm^3) and was stirred at room temperature overnight. The organic solvent was evaporated and the residue was dissolved in ethyl acetate (50 cm^3) and washed with saturated sodium bicarbonate solution (2 x 50 cm^3) and brine (50 cm^3), dried (Na_2SO_4) and was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:10 to 1:1) to give the *ester* as a pale oil (385 mg, 1.13 mmol, 57%), R_f (EtOAc-hexanes, 1:1) 0.57; δ_H (400 MHz; $CDCl_3$) 7.53-7.49 (2 H, *o*-Ph), 7.39-7.29 (3 H, m, *m* and *p*-Ph), 6.62 (1 H, br s, NH), 3.79 (1 H, dt, *J* 10.0 and 2.0, C<u>H</u>OH), 3.77 (1 H, br s, OH), 3.73 (3 H, s, OMe), 2.55-2.50 (1 H, m, C<u>H</u>$_A$H$_B$), 2.34 (1 H, dd, *J* 15.0 and 10.0, CH$_A$<u>H</u>$_B$), 1.55 (3 H, s, NC<u>Me</u>$_A$Me$_B$), 1.54 (3 H, s, NCMe$_A$<u>Me</u>$_B$), 1.24 (3 H, s, SC<u>Me</u>$_A$Me$_B$), 1.20 (3 H, s, SCMe$_A$<u>Me</u>$_B$). The ester (385 mg, 1.13 mmol) was dissolved in methanol (10 cm^3) and water (1 cm^3). Potassium hydroxide (76 mg, 1.36 mmol) was added and the reaction was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and saturated sodium bicarbonate solution (5 cm^3), water (5 cm^3) and a hexane and ethyl acetate mixture (1:1 ratio, 10 cm^3) were added. The organic layer was subsequently separated and discarded. The aqueous phase was extracted with further portions of ethyl acetate and hexane (1:1 ratio, 2 x 10 cm^3) and each organic phase was discarded. The aqueous phase was acidified with pH 2 sulfate buffer (20 cm^3) and hydrochloric acid as required to bring the pH of the solution to pH 2 before extracting with diethylether (2 x 25 cm^3) and ethyl acetate (25 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give 2-(3-hydroxy-4-methyl-4-[phenylthio]pentanamido)-2-methylpropanoic acid as a pale oil (367 mg, 1.13 mmol, 99%), obtained as a mixture of two rotamers in a ratio of three to one (r_1:r_2); δ_H (500 MHz; $CDCl_3$) 7.53-7.47 (4 H, m, *o*-Ph r_1 and r_2), 7.37-7.27 (6 H, m, *m* and *p*-Ph r_1 and r_2), 7.01 (1 H, br s, NH r_1), 3.87 (1 H, dd, *J* 10.5 and 2.5, C<u>H</u>OH r_2), 3.79 (1 H, dd, *J* 10.5 and 2.0, C<u>H</u>OH r_1), 2.75 (1 H, dd, *J* 16.0 and 2.5, C<u>H</u>$_A$H$_B$ r_2), 2.57 (1 H, dd, *J* 15.0 and 2.0, C<u>H</u>$_A$H$_B$ r_1), 2.52 (1 H, dd, *J* 16.0 and 10.5, CH$_A$<u>H</u>$_B$ r_2), 2.39 (1 H, dd, *J* 15.0 and 10.5, CH$_A$<u>H</u>$_B$ r_1), 1.57

(6 H, s, NC<u>Me</u>$_A$Me$_B$ r_1 and r_2), 1.54 (3 H, s, NCMe$_A$<u>Me</u>$_B$ r_1), 1.48 (3 H, s, NCMe$_A$<u>Me</u>$_B$ r_2), 1.27 (3 H, s, SC<u>Me</u>$_A$Me$_B$ r_2), 1.22 (3 H, s, SC<u>Me</u>$_A$Me$_B$ r_1), 1.21 (3 H, s, SCMe$_A$<u>Me</u>$_B$ r_2), 1.18 (3 H, s, SCMe$_A$<u>Me</u>$_B$ r_1); δ_C (125 MHz; $CDCl_3$) 175.7 (CO_2H r_1), 170.9 (CONH r_1), 137.5 (*o*-Ph r_1), 137.4 (*o*-Ph r_2), 131.3 (*i*-Ph r_1), 131.2 (*i*-Ph r_2), 129.2 (*p*-Ph r_2), 129.1 (*p*-Ph r_1), 128.8 (*m*-Ph r_2), 128.8 (*m*-Ph r_1), 72.6 (CHOH r_1), 72.1 (CHOH r_2), 54.3 (N<u>C</u>Me$_2$ r_2), 54.8 (N<u>C</u>Me$_2$ r_1), 52.8 (S<u>C</u>Me$_2$ r_1), 52.6 (S<u>C</u>Me$_2$ r_2), 38.2 (CH_2 r_2), 37.9 (CH_2 r_1), 26.0 (SC<u>Me</u>$_A$Me$_B$ r_2), 25.9 (SC<u>Me</u>$_A$Me$_B$ r_1), 25.5 (NCMe$_A$<u>Me</u>$_B$ r_2), 25.4 (NCMe$_A$<u>Me</u>$_B$ r_1), 24.8 (NC<u>Me</u>$_A$Me$_B$ r_1 and r_2), 23.4 (SCMe$_A$<u>Me</u>$_B$ r_1), 23.1 (SCMe$_A$<u>Me</u>$_B$ r_2); *m/z* = 348.1252 ($C_{16}H_{23}NO_4SNa$ requires *M+Na* = 348.1246, dev. 2.0 ppm); ν_{max} (CH_2Cl_2 / cm^{-1}) 3250 (br OH and NH), 1710 (CO_2H), 1645 (CONH), 1470 (Ph); m.p. (EtOAc/ Hexanes) 93.6-95.5 °C. The acid (367 mg, 1.13 mmol) was dissolved in THF (10 cm^3) under a nitrogen atmosphere at room temperature. To the stirred solution was added HOBt (1.36 mmol), followed by CDI (221 mg, 1.36 mmol) and stirring was continued overnight to give the required solution of the activated acid. Concentrated ammonia (2 cm^3) was added and the mixture was stirred at room temperature overnight. The organic solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (25 cm^3) and washed with saturated sodium bicarbonate solution (2 x 25 cm^3), pH 2 sulfate buffer (2 x 25 cm^3) and brine (25 cm^3), dried (Na_2SO_4) and was evaporated under reduced pressure. The crude solid was recrystallised from ethyl acetate and hexane to yield the *amide* as white plates (142 mg, 0.43 mmol, 22% from **23**); δ_H (500 MHz; D_6-DMSO) 7.87 (1 H, s, CONH), 7.56-7.53 (2 H, m, *o*-Ph), 7.43-7.35 (3 H, m, *p* and *m*-Ph), 6.94 (1 H, s, N<u>H</u>$_A$H$_B$), 6.82 (1 H, s, NH$_A$<u>H</u>$_B$), 5.07 (1 H, d, *J* 5.5, OH), 3.77 (1 H, ddd, *J* 10.0, 5.5 and 2.0, C<u>H</u>OH), 2.68 (1 H, dd, *J* 14.0 and 2.0, C<u>H</u>$_A$H$_B$), 2.28 (1 H, dd, *J* 14.0 and 10.0, CH$_A$<u>H</u>$_B$), 1.35 (3 H, s, NC<u>Me</u>$_A$Me$_B$), 1.33 (3 H, s, NCMe$_A$<u>Me</u>$_B$), 1.12 (3 H, s, SC<u>Me</u>$_A$Me$_B$), 1.11 (3 H, s, SCMe$_A$<u>Me</u>$_B$); δ_C (125 MHz; D_6-DMSO) 176.6 ($CONH_2$), 171.1 (CONH), 137.5 (*o*-Ph), 131.3 (*i*-Ph), 129.0 (*p*-Ph), 128.8 (*m*-Ph), 73.2 (CHOH), 55.9 (N<u>C</u>Me$_2$), 52.7 (S<u>C</u>Me$_2$), 38.9 (CH_2) 25.9 (SC<u>Me</u>$_A$Me$_B$), 25.6 (NCMe$_A$<u>Me</u>$_B$), 25.1 (NC<u>Me</u>$_A$Me$_B$), 23.4 (SCMe$_A$<u>Me</u>$_B$); *m/z* = 325.1581 ($C_{16}H_{25}N_2O_3S$ requires *M+H* = 325.1586, dev. –1.5 ppm); ν_{max} (cm^{-1}) 3410 (NH), 3316 (NH), 3196 (OH), 1671 ($CONH_2$), 1643 (CONH), 1453 (Ph), 1438 (Ph); m.p. (EtOAc/ Hexanes) 197.5-199.6 °C;

4-(5',5'-Dimethyl-5*H*-furan-2'-ylideneamino)-4-methyl-pentanamide 36: amide **27** (70 mg, 0.20 mmol) was dissolved in toluene (2.0 cm^3) and TFA (0.2 cm^3) and the reaction was stirred at 40 °C overnight. After the reaction was allowed to cool to room temperature saturated sodium bicarbonate (300 mg, 3.6 mmol) and water (1 cm^3) was added and the mixture was evaporated under reduced pressure with further portions of toluene (2 x 5 cm^3). The residue was dissolved in methanol (2 cm^3) and absorbed onto celite. The dry celite mixture was chromatographed (SiO_2, eluting with EtOAc-hexane 1:4 to neat methanol) to give the *cyclic imidate* as an amorphous white solid (30 mg, 0.14 mmol, 67%), R_f (EtOAc:MeOH, 10:1) 0.01; δ_H (500 MHz; CD_3OD) 7.05 (1 H, d, *J* 5.5, COCHC<u>H</u>), 5.98 (1 H, d, *J* 5.5, COC<u>H</u>CH), 2.24-2.18 (2 H, m, $CH_2C\underline{H}_2CO$), 1.97-1.90 (2 H, m, $C\underline{H}_2CH_2CO$), 1.45 (6 H, s, C<u>Me</u>$_2$), 1.28 (6 H, s, C<u>Me</u>$_2$); δ_C (125 MHz; CD_3OD) 179.5 ($CONH_2$), 164.8 (CN), 153.7 (<u>C</u>HCHCN), 123.4 (CH<u>C</u>HCN), 92.9 (O<u>C</u>Me$_2$), 56.8 (<u>C</u>Me$_2$), 39.2 ($\underline{C}H_2CH_2CO$), 32.0 ($CH_2\underline{C}H_2CO$), 27.7 (C<u>Me</u>$_2$), 26.2 (C<u>Me</u>$_2$); *m/z* = 225.1606 ($C_{12}H_{21}N_2O_2$ requires *M+H* = 225.1603, dev. 1.5 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3336 (NH), 3189 (NH), 1667 (CO), 1461 (Ph). Lactone **3** (10.3 mg, 23%) was also recovered fron this reaction.

In a repeat of the reaction amide **27** (4.0 mmol) was reacted to give crude **4-phenylsulfanyl-5,5,10,10-tetramethyl-[1,6]diazecane-2,7-dione 34** (108 mg, 8%). This product was treated with Raney nickel (1.0 g) in ethanol (5 cm^3) and acetone (5 cm^3) at room temperature for two hours. The mixture was filtered through a pad of celite (approx 1 cm^3 thick) and washed on the filter with further portions of ethanol (2 x 20 cm^3). The filtrate was evaporated under reduced pressure and the residue was suspended in toluene (20 cm^3). The organic solvent was evaporated under reduced pressure to yield a residue which was chromatographed (SiO_2, eluting with EtOAc-hexane 1:2 to neat methanol) to give **5,5,10,10-tetramethyl-[1,6]diazecane-2,7-dione**[5] **35** as an amorphous white solid (42 mg, 0.18 mmol, 40 %), R_f (EtOAc) 0.04; δ_H (500 MHz; CD_3OD) 2.38 (4 H, t, *J* 8.0, $CH_2C\underline{H}_2CO$), 1.92 (4 H, t, *J* 8.0, $C\underline{H}_2CH_2CO$), 1.26 (12 H, s, CMe_2); δ_C (125 MHz; CD_3OD) 179.5 (CO), 58.3 (<u>C</u>Me$_2$), 36.1 ($\underline{C}H_2CH_2CO$), 31.6 ($CH_2\underline{C}H_2CO$), 29.0 (C<u>Me</u>$_2$); *m/z* = 249.1578 ($C_{12}H_{22}N_2O_2Na$ requires *M+Na* = 249.1579, dev. –0.6 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3430 (br NH), 1668 (CO).

4-[4'-(5'',5''-Dimethyl-4''-phenylsulfanyl-dihydro-furan-2''-ylideneamino)-4'-methyl-pentanoylamino]-4-methyl-pentanamide 37: amide **31** (93 mg, 0.20 mmol) was dissolved in toluene (2.0 cm^3) and TFA (0.2 cm^3) and the reaction stirred at 40 °C overnight. After the reaction was allowed to cool saturated sodium bicarbonate (300 mg, 3.6 mmol) and water (1 cm^3) was added and the mixture was evaporated under reduced pressure and dried with further portions of toluene (2 x 5 cm^3). The

residue was dissolved in methanol (2 cm^3) and absorbed onto celite, which was chromatographed (SiO_2, eluting with EtOAc to EtOAc:MeOH 6:4) to give the *cyclic imidate* as a white solid (80 mg, 0.18 mmol, 89%), R_f (EtOAc-MeOH 10:1) 0.04; δ_H (500 MHz; CD_3OD) 7.56-7.53 (2 H, m, *o*-Ph), 7.42-7.35 (3 H, m, *m* and *p*-Ph), 4.13 (1 H, dd, *J* 9.5 and 8.0, SCH), 3.61 (1 H, dd, *J* 18.0 and 8.0, $SCHC\underline{H}_AH_B$), 3.39 (1 H, dd, *J* 18.0 and 9.5, $SCHCH_A\underline{H}_B$), 2.27 (2 H, t, *J* 7.5, $CH_2C\underline{H}_2CO$ A), 2.22-2.18 (2 H, m, $CH_2C\underline{H}_2CO$ B), 2.10 (4 H, m, $C\underline{H}_2CH_2CO$ x2), 1.68 (3 H, s, Me_A), 1.62 (3 H, s, Me_B), 1.43 (3 H, s, Me_C), 1.42 (3 H, s, Me_D), 1.30 (6 H, s, Me_E and Me_F); δ_C (125 MHz; CD_3OD) 179.1 ($CONH_2$), 178.1 (CONH), 174.6 (OCN), 138.9 (*i*-Ph), 133.8 (*o*-Ph), 130.7 (*m*-Ph), 129.7 (*p*-Ph), 103.6 ($O\underline{C}Me_2$), 60.5 and 54.8 ($N\underline{C}Me_2$ x2), 52.6 ($\underline{C}HSPh$), 40.1 ($CH\underline{C}H_2$), 36.6 and 36.2 ($\underline{C}H_2CH_2CO$ x2), 32.0 ($CH_2\underline{C}H_2CO$ A), 31.7 ($CH_2\underline{C}H_2CO$ B), 27.0 and 27.0 (Me_E and Me_F), 26.9 (Me_B), 26.2 and 26.1 (Me_C and Me_D), 23.0 (Me_A); *m/z* = 448.2634 ($C_{24}H_{38}N_3O_4S$ requires *M+H* = 448.2634, dev. 0.1 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3313 (NH), 1658 (CO), 1541 (CN), 1440 (Ph).

3,3,8,8-Tetramethyl-7-phenylsulfanyl-[1,4]diazocane-2,5-dione 38: amide **32** (32 mg, 0.1 mmol) was dissolved in toluene (1.0 cm^3) and TFA (0.1 cm^3) and the reaction stirred at 40 °C for seven days. After the reaction was allowed to cool a mixture of ethyl acetate and dichloromethane (10:1 mixture, 50 cm^3) was added. The mixture was washed with saturated sodium bicarbonate solution (2 x 20 cm^3) and brine (20 cm^3), dried (Na_2SO_4) and was evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:5 to methanol-ethyl acetate 1:10) to give *the bis-lactam* as an amorphous white solid (2 mg, 0.007 mmol, 7%), R_f (EtOAc) 0.20; δ_H (500 MHz; $CDCl_3$) 7.48-7.45 (2 H, m, *o*-Ph), 7.35-7.28 (3 H, m *m* and *p*-Ph), 3.75 (1 H, dd, *J* 10.5 and 8.0, SCH), 2.97 (1 H, dd, *J* 17.5 and 8.0, $C\underline{H}_AH_B$), 2.66 (1 H, dd, *J* 17.5 and 10.5, $CH_A\underline{H}_B$), 1.55 (3 H, s, Me_A), 1.44 (3 H, s, Me_B), 1.31 (6 H, s, Me_C and Me_D); δ_C (125 MHz; $CDCl_3$) 182.8 ($N\underline{C}OCMe_2$), 164.1 ($N\underline{C}OCH_2$), 133.6 (*i*-Ph), 132.4 (*o*-Ph), 129.4 (*m*-Ph), 128.0 (*p*-Ph), 75.4 ($\underline{C}Me_2CO$), 61.2 ($\underline{C}Me_2CH$), 58.1 (SCH), 31.6 (CH_2), 34.9 (Me_A), 23.9 and 23.9 (Me_C and Me_D), 21.4 (Me_B); *m/z* = 307.1490 ($C_{16}H_{23}N_2O_2S$ requires *M+H* = 307.1480, dev. 3.3 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 1723 (CO), 1666 (CO), 1439 (Ph).

2-(5',5'-Dimethyl-4'-phenylsulfanyl-dihydro-furan-2'-ylideneamino)-2-methyl-propionamide 39 was also obtained as an amorphous white solid (10 mg, 0.033 mmol, 33%), R_f (EtOAc) 0.08; δ_H (500 MHz; $CDCl_3$) 7.47 (1 H, br s, $N\underline{H}_AH_B$), 7.44-7.41 (2 H, m, *o*-Ph), 7.33-7.25 (3 H, m, *m* and *p*-Ph), 5.33 (1 H, br s, $NH_A\underline{H}_B$), 3.54 (1 H, dd, *J* 10.5 and 8.0, SCH), 2.95 (1 H, dd, *J* 17.0 and 8.0, $C\underline{H}_AH_B$), 2.72 (1 H, dd, *J* 17.0 and 10.5, $CH_A\underline{H}_B$), 1.44 (3 H, s, Me_A), 1.43 (3 H, s, Me_B), 1.39 (s H, s, Me_C), 1.38 (3 H, s, Me_D); δ_C (125 MHz; $CDCl_3$); 180.9 (CON), 158.5 (CN), 134.0 (*i*-Ph), 132.0 (*o*-Ph), 129.3 (*m*-Ph), 127.7 (*p*-Ph), 88.1 ($O\underline{C}Me_2$), 60.9 ($N\underline{C}Me_2$), 52.6 (SCH), 38.9 (CH_2), 37.6 (Me_D), 24.0 and 23.9 (Me_A and Me_B), 22.9 (Me_C); *m/z* = 329.1312 ($C_{16}H_{22}N_2O_2SNa$ requires *M+Na* = 329.1300, dev. 3.7 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 1681 ($CONH_2$), 1568 (CN), 1492 (Ph), 1422 (Ph); m.p. (EtOAc/ Hexanes) 156.3-158.7 °C.

***N*-(1'-amino-2'-methyl-1'-oxopropan-2'-yl)-4-hydroxy-4-methyl-3-(phenylthio)pentanamide 40** was also obtained, but could not be purified completely: δ_H (500 MHz; $CDCl_3$) 7.57 (1 H, br s, CONH), 7.48-7.45 (2 H, m, *o*-Ph), 7.31-7.26 (2 H, m, *m*-Ph), 7.23-7.19 (1 H, m, *p*-Ph), 6.58 (1 H, br s, $N\underline{H}_AH_B$), 6.35 (1 H, br s, $NH_A\underline{H}_B$), 3.63 (1 H, dd, *J* 8.5 and 5.0, $C\underline{H}SPh$), 2.78 (1 H, dd, *J* 15.0 and 5.0, $C\underline{H}_AH_BCO$), 2.45 (1 H, dd, *J* 15.0 and 8.5, $CH_A\underline{H}_BCO$), 1.55 (3 H, s, $NC\underline{Me}_AMe_B$), 1.51 (3 H, s, $NCMe_A\underline{Me}_B$), 1.33 ($OC\underline{Me}_AMe_B$), 1.30 ($OCMe_A\underline{Me}_B$); δ_C (125 MHz; $CDCl_3$) 176.7 ($CONH_2$), 171.3 (CONH), 135.6 (*i*-Ph), 130.9 (*o*-Ph), 129.2 (*m*-Ph), 127.1 (*p*-Ph), 73.4 ($O\underline{C}Me_2$), 58.4 (SCH), 57.4 ($N\underline{C}Me_2$), 39.3 (CH_2), 27.9 ($OC\underline{Me}_AMe_B$), 26.6 ($OCMe_A\underline{Me}_B$), 25.7 ($NCMe_A\underline{Me}_B$), 25.2 ($NC\underline{Me}_AMe_B$); *m/z* = 347.1415 ($C_{16}H_{24}N_2O_2SNa$ requires *M+Na* = 347.1405, dev. 2.8 ppm); ν_{max} (CH_2Cl_2 / cm^{-1}) 3330 (br OH or NH), 1660 (CO), 1460 (Ph).

2-(5,5-Dimethyl-5*H*-furan-2-ylideneamino)-2-methyl-propionamide 41 was also obtained as an amorphous white solid (7 mg, 0.036 mmol, 36%), R_f (EtOAc) 0.03; δ_H (500 MHz; $CDCl_3$) 6.77 (1 H, d, *J* 5.5, $C\underline{H}CHCN$), 5.92 (1 H, d, *J* 5.5, $CHC\underline{H}CN$), 1.50 (6 H, s, $NC\underline{Me}_2$), 1.42 (6 H, s, $OC\underline{Me}_2$); δ_C (125 MHz; $CDCl_3$); 181.1 ($CONH_2$), 161.9 (CN), 150.9 ($\underline{C}HCHCN$), 123.9 ($CH\underline{C}HCN$), 90.6 ($O\underline{C}Me_2$), 60.9 ($N\underline{C}Me_2$), 26.1 ($OC\underline{Me}_2$), 24.0 ($NC\underline{Me}_2$); *m/z* = 197.1275 ($C_{10}H_{17}N_2O_2$ requires *M+H* = 197.1290, dev. –0.8 ppm); ν_{max} (cm^{-1}) 1682 ($CONH_2$), 1568 (CN), 1493 (CC); m.p. (EtOAc/ Hexanes) 164.6-166.9 °C.

5,5-dimethyl-4-phenylsulfanyl-dihydro-furan-2-one 3 was also obtained (5 mg, 23%).

2,4,6-Tris-(3'-hydroxyl-3'-methyl-but-1'-ene)-1,3,5-triazine 43: a suspension of sodium hydride (2.0 mg, 0.08 mmol) in THF (1 cm^3) under nitrogen was cooled to 0 °C. Trimer **42** (16 mg, 0.02 mmol) in THF (0.5 cm^3) was added dropwise and the mixture stirred for two hours before the addition of

saturated sodium bicarbonate solution (1 cm^3). The mixture was extracted with ethyl acetate (3 x 5 cm^3) and the combined organic extracts were washed with saturated sodium bicarbonate solution (10 cm^3) and brine (10 cm^3), dried (Na_2SO_4) and was evaporated under reduced pressure to yield the *triene* as a white solid (7 mg, 0.02 mmol, >95 %); δ_H (500 MHz; d_6-DMSO) 7.42 (3 H, d, *J* 15.5, CNCHC<u>H</u>), 6.46 (3 H, d, *J* 15.5, CNC<u>H</u>CH), 4.98 (3 H, s, OH), 1.28 (18 H, s, Me); δ_C (125 MHz; D_6-DMSO) 171.2 (CN), 154.0 (CNCHC<u>H</u>), 124.5 (CNC<u>H</u>CH), 69.9 (<u>C</u>Me_2), 29.8 (C<u>Me</u>$_2$); *m/z* = 356.1945 ($C_{18}H_{27}N_3O_3SNa$ requires *M+Na* = 356.1950, dev. –1.6 ppm); ν_{max} (cm^{-1}) 3325 (br OH), 1652 (CC), 1519 (CN); m.p. (EtOAc/Hexane) 118.7-120.6 °C.

1-(4',6'-Dimethyl-[1,3,5]triazin-2'-yl)-3-methyl-3-phenylsulfanyl-butan-2-ol 45: 2,4,6-trimethyl-1,3,5-triazine[6] (400 mg, 3.30 mmol) was dissolved in diethylether (10 cm^3) and cooled to –78 °C. *n*-Butyllithium (0.50 cm^3, 4.7 mol dm^{-3} solution in hexanes, 3.30 mmol) was added dropwise and the solution warmed to 0 °C and stirred for 20 minutes. After cooling to –78 °C a solution of 2-methyl-2-phenylsulfanylpropional (590 mg, 3.30 mmol) in diethylether (2 cm^3) was added dropwise and the solution allowed to warm to room temperature over the period of 30 minutes before the addition of water (2 cm^3). The aqueous phase was separated and extracted with ethyl acetate (2 x 25 cm^3) and the combined organic extracts were washed with brine (25 cm^3), dried (Na_2SO_4) and were evaporated under reduced pressure. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:10 to 1:1) to give the *triazine* as white platelets (574 mg, 1.89 mmol, 49%), R_f (EtOAc:Hexanes, 1:1) 0.13; δ_H (500 MHz; $CDCl_3$) 7.57-7.53 (2 H, m, *o*-Ph), 7.37-7.34 (1 H, m, *p*-Ph), 7.33-7.29 (2 H, m, *m*-Ph), 4.01 (1 H, dd, *J* 10.5 and 2.0, C<u>H</u>OH), 3.32 (1 H, dd, *J* 15.0 and 2.0, C<u>H</u>$_A$H$_B$), 3.01 (1 H, dd, *J* 15.0 and 10.5, CH$_A$<u>H</u>$_B$), 2.62 (6 H, s, NC<u>Me</u> x2), 1.33 (3 H, s, SC<u>Me</u>$_A$Me$_B$), 1.30 (3 H, s, SCMe$_A$<u>Me</u>$_B$); δ_C (125 MHz; $CDCl_3$) 177.4 (N<u>C</u>CH$_2$), 176.0 (N<u>C</u>Me x2), 137.7 (*o*-Ph), 130.8 (*i*-Ph), 129.0 (*p*-Ph), 128.6 (*m*-Ph), 74.6 (CHOH), 53.2 (S<u>C</u>Me$_2$), 40.0 (CH$_2$), 25.5 (NC<u>Me</u> x2), 24.7 (SCMe$_A$<u>Me</u>$_B$), 24.5 (SC<u>Me</u>$_A$Me$_B$); *m/z* = 304.1474 ($C_{16}H_{22}N_3OS$ requires *M+H* = 304.1484, dev. –3.2 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3400 (br OH), 1540 (CN) 1440 (Ph); m.p. (EtOAc/ Hexanes) 98.2-100.4 °C;

2,4-Dimethyl-6-(3'-methyl-3'-phenylsulfanyl-but-1'-enyl)-[1,3,5]triazine 47: triazine **45** (60 mg, 0.20 mmol) was dissolved in a mixture of toluene (2.0 cm^3) and TFA (0.2 cm^3) and the reaction was heated at 40 ºC overnight. After the reaction was allowed to cool to room temperature saturated sodium bicarbonate solution (5 cm^3) was added, followed by ethyl acetate (5 cm^3). The aqueous layer was extracted with ethyl acetate (2 x 5 cm^3) and the combined organic phases was washed with saturated sodium bicarbonate (2 x 10 cm^3) and brine (10 cm^3), dried (Na_2SO_4) and evaporated to yield the crude reaction residue. The residue was chromatographed (SiO_2, eluting with EtOAc-hexanes 1:10 to neat EtOAc) to give *the triazine* as an off white amorphous solid (18 mg, 0.06 mmol, 32%); R_f (EtOAc:hexanes, 1:1) 0.42; δ_H (500 MHz; $CDCl_3$) 7.53 (1 H, d, *J* 15.5, CHC<u>H</u>CMe$_2$), 7.42-7.38 (2 H, m, *o*-Ph), 7.32-7.27 (1 H, m, *p*-Ph), 7.25-7.21 (2 H, m, *m*-Ph), 5.92 (1 H, d, *J* 15.5, C<u>H</u>CHCMe$_2$), 2.58 (6 H, s, NC<u>Me</u> x2), 1.46 (6 H, s, C<u>Me</u>$_2$); δ_C (125 MHz; $CDCl_3$) 175.9 (N<u>C</u>Me x2), 170.7 (N<u>C</u>CH), 150.9 (CH<u>C</u>HCMe$_2$), 127.3 (*o*-Ph), 131.4 (*i*-Ph), 129.1 (*p*-Ph), 128.5 (*m*-Ph), 124.7 (<u>C</u>HCHCMe$_2$), 49.5 (S<u>C</u>Me$_2$), 27.1 (SC<u>Me</u>$_2$), 25.6 (NC<u>Me</u> x2); Accurate mass, *m/z* = 286.1368 ($C_{16}H_{20}N_3S$ requires *M+H* = 286.1378, dev. –3.3 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 1640 (CC), 1530 (CN), 1470 (Ph), 1440 (Ph).

***N*-(5,5-Dimethyl-4-phenylsulfanyl-dihydro-furan-2-ylidene)-acetamidine 46** was also obtained as an off white amorphous solid (10 mg, 0.04 mmol, 19%); R_f (EtOAc) 0.05; δ_H (500 MHz; $CDCl_3$) 7.43-7.40 (2 H, m, *o*-Ph), 7.31-7.28 (2 H, m, *m*-Ph), 7.27-7.23 (1 H, m, *p*-Ph), 3.55 (1 H, dd, *J* 9.5 and 8.0, SCH), 3.37-3.20 (1 H, br s, C<u>H</u>$_A$H$_B$), 2.94 (1 H, dd, *J* 18.0 and 9.5, CH$_A$<u>H</u>$_B$), 2.13 (3 H, s, CN<u>Me</u>), 1.33 (3 H, s, C<u>Me</u>$_A$Me$_B$), 1.32 (3 H, s, CMe$_A$<u>Me</u>$_B$); δ_C (125 MHz; $CDCl_3$) 134.4 (*i*-Ph), 131.8 (*o*-Ph), 129.2 (*m*-Ph), 127.5 (*p*-Ph), 53.3 (SCH), 41.5 (CH$_2$), 28.4 (C<u>Me</u>$_A$Me$_B$), 26.4 (CNMe), 23.9 (CMe$_A$<u>Me</u>$_B$), other peaks not found due to broadening; *m/z* = 263.1210 ($C_{14}H_{19}N_2OS$ requires *M+H* = 263.1218, dev. –3.1 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 3250 (br NH), 1680 (CN), 1640 (CN), 1540 (Ph), 1480 (Ph), 1440 (Ph).

2,4-*bis*-(3'-methyl-3'-phenylsulfanyl-but-1'-enyl)-6-methyl-[1,3,5]triazine 49 was also obtained as a pale oil (5 mg, 0.01 mmol, 6%); R_f (EtOAc:hexanes, 1:1) 0.68; δ_H (500 MHz; $CDCl_3$) 7.56 (2 H, d, *J* 15.5, CHC<u>H</u>CMe$_2$), 7.45-7.42 (4 H, m, *o*-Ph), 7.35-7.31 (2 H, m, *p*-Ph), 7.29-7.26 (4 H, m, *m*-Ph), 6.01 (2 H, d, *J* 15.5, C<u>H</u>CHCMe$_2$), 2.62 (3 H, s, NC<u>Me</u>), 1.49 (12 H, s, SC<u>Me</u>$_2$); δ_C (125 MHz; $CDCl_3$) 175.7 (N<u>C</u>Me), 170.6 (N<u>C</u>CH), 151.2 (CH<u>C</u>HCMe$_2$) 137.4 (*o*-Ph), 131.4 (*i*-Ph), 129.2 (*p*-Ph), 128.5 (*m*-Ph), 124.4 (<u>C</u>HCHCMe$_2$), 49.6 (S<u>C</u>Me$_2$), 27.1 (SC<u>Me</u>$_2$), 25.4 (NC<u>Me</u>); *m/z* = 448.1870 ($C_{26}H_{30}N_3S_2$ requires *M+H* = 448.1881, dev. –2.5 ppm); ν_{max} ($CHCl_3$ / cm^{-1}) 1640 (CC), 1520 (CN) 1470 (Ph), 1440 (Ph).

Crystal Data for **42**: $C_{36}H_{45}N_3O_3S_3.1/2(H_2O)$, M= 672.94, triclinic, space group P-1, a = 12.2457(2), b = 13.6867(3), c = 22.7701(5) Å, α= 83.977(1)°, β= 80.763 (1)°, γ = 75.344 (1)° U = 3636.02(13) $Å^3$, Z = 4, μ(Mo-Kα) = 0.243 mm^{-1}, 39905 reflections measured at 120(2)K using an Oxford Cryosystems Cryostream cooling apparatus, 16301 unique (Rint = 0.088); R1 = 0.071, wR2 = 0.167 [I>2σ(I)]. The structure was solved with SHELXS-97, and refined with SHELXL-97.[7]

References

1 M. D. Eastgate, D. J. Fox, T. J. Morley, and S. Warren, *Synthesis*, 2002, 2124.

2 P. Brownbridge, E. Egert, P. G. Hunt, O. Kennard, and S. Warren, *J. Chem. Soc.: Perkin Trans. I*, 1981, 2751.

3 J. H. Youn, R. Herrmann, and I. Ugi, *Synthesis*, 1987, 159.

4 G. R. Newkome, C. N. Moorefield, and J. D. Epperson, *Eur. J. Org. Chem.*, 2003, 3666.

5 J. W. Ducker and M. J. Gunter, *Aust. J. Chem.*, 1968, **21**, 2809.

6 F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, 1961, **26**, 2778.

7 G. M. Sheldrick, 'ref 13 ver. SHELXS-97/SHELXL-97', University of Göttingen, Germany, 1997.