Synthesis of Functional Ras-Lipoproteins and Fluorescent Derivatives

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Supporting Information

Experimental Procedures, analytical and spectroscopic data for all new compounds (69 pages).

Experimental

General Methods: Proton and carbon NMR spectra were recorded on Bruker AC-250, Bruker
AM-400 and Bruker DRX-500 spectrometers. NMR spectra were obtained in either
deuteriochloroform, deuterio methanol or deuteriochloroform/deuterio methanol mixture.
Proton and carbon spectra are reported in parts per million downfield from an internal
standard of Me₄Si. EI-MS and FAB-MS were recorded on a Finnigan MAT 90 machine,
MALDI-MS were recorded on a Voyager™ machine by PerSeptive Biosystems, applied
matrices are given for each particular compound. ESI-MS were recorded on a LCQ Ion Trap
instrument by Finnigan. Infrared Spectra were recorded on a Bruker IFS88 FTIR spectrometer
as a KBr disk. UV spectra were recorded on a Perkin Elmer UV/VIS spectrometer in

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methanol. Combustion analysis was carried out on a Heraeus CHN-Rapid analyser. Flash chromatography was carried out on columns packaged with Baker silica gel (30-60 μm). TLC was carried out on Kieselgel 60F254 aluminum sheets (Merck Darmstadt, Germany). All reagents were obtained from Fluka (Buchs, Switzerland), Aldrich (Steinheim, Germany) or Sigma (Deisenhofen, Germany). All solvents were dried and distilled using standard procedures.35

**Standard Peptide Coupling Conditions:**

Unless otherwise stated, all peptide coupling reactions were performed based on the following standard procedure: To a 1:1 (molar) solution of each coupling partner dissolved in CH₂Cl₂ (5 - 10 mL) at 0°C was added 1-hydroxybenzotriazole (HOBt) (1.5 equivalents), followed by ethyl-(dimethylamino)propylcarbodiimide (EDC) (1.2 equivalents). The reaction was warmed to room temperature and stirred for 18 h. The reaction mixture was then diluted with ethyl acetate (up to 50 – 100 mL) and was extracted with 0.5 M HCl (2 x 10 mL), 1 M NaHCO₃ (2 x 10 mL) and finally with brine solution (2 x 10 mL). The organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The product could then be isolated from the remaining residue by flash chromatography on silica gel using the solvent systems noted for each particular compound.

**Standard Fmoc Protecting Group Removal:**

To a solution of the protected peptide in CH₂Cl₂ (5 - 10 mL) at room temperature was added piperidine (1 - 2 mL). The reaction was warmed to room temperature and stirred for 18 h. After removing the solvent by azeotropic distillation with toluene (2 x 30 mL) and chloroform (30 mL), the product was isolated from the remaining residues by flash chromatography on silica gel using the solvent systems noted for each particular compound.
Standard Procedure for the Removal of Aloc Groups or Allyl Esters:

To a solution of the protected peptide in dry THF (5 - 10 mL) was added dimethylbarbituric acid (0.55 equivalents), followed by a catalytic amount of tetrakis(triphenylphosphine)palladium(0). The reaction was monitored by TLC, and was judged complete with the disappearance of starting material (generally 2 - 3 h). The solvent was then removed under reduced pressure. The product could be isolated from the remaining residue by the methods noted for each particular compound.

Standard Procedure of the Removal of Boc Groups or tert-Butyl Esters:

To a solution of the protected peptide in CH₂Cl₂ (5 mL) and thioanisole (0.5 mL) was added trifluoroacetic acid (2.5 - 5 mL). The reaction was then left to stir for 1 - 2 h at room temperature. The solvent was removed by azeotropic distillation with toluene (2 x 50 mL) and chloroform (50 mL). The desired product was isolated from the remaining residues by the methods noted for each particular compound.

(E,E)-8-O-(2-N-methyl-aminobenzoyl)-1-(tetrahydropyran)-3,7-dimethyl-2,6-octadiene (6a): A mixture of the anhydride 5 (440mg, 2.4 mmol) and DMAP (26 mg, 0.24 mmol), dissolved in dry DMF (2 mL), was heated to 65°C with stirring under an atmosphere of dry argon. A mixture of the alcohol 4a (620 mg, 2 mmol) and dry triethylamine (340 μL, 2.4 mmol), dissolved in dry DMF (2 mL), was then slowly added to the anhydride solution over a period of 40 min. The reaction was left stirring at this temperature for 3.5 hours, after which time TLC indicated the reaction was virtually complete. The solution was poured into a separatory funnel containing ethyl acetate (100 mL) and was washed once with 1:1 water/brine solution (10 mL) followed by brine (10mL). The combined aqueous phases were
back extracted 3 times with ethyl acetate (10 mL). The combined organic phases were dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification of the resulting oily residue by flash chromatography on silica gel with hexane/ethyl acetate (8:1), yielded 711 mg (75%) of the desired product 6a as a colorless oil, followed by 60 mg (10%) of starting material: \( R_f = 0.65 \) (hexane/ethyl acetate 3:1). UV (MeOH) \( \lambda_{max} \) 223 nm (\( \epsilon \) 29958), 256 nm (\( \epsilon \) 9960), 355 nm (\( \epsilon \) 7130). IR (KBr) \( \nu_{max} \) 3378, 2940 br s, 1682, 1607, 1581, 1520, 1239, 1128, 1085, 1023, 751 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.90 (dd, \( J = 1.6, 8.0 \) Hz, 1H, arom. CH); 7.67 (br s, 1H, NH); 7.34 (dd, \( J = 1.6, 7.1, 8.4 \) Hz, 1H, arom. CH); 6.62 (dd, \( J = 0.8, 8.4 \) Hz, 1H, arom. CH); 6.56 (dd, \( J = 0.8, 7.1, 8.0 \) Hz, 1H, arom. CH); 5.51 (dt, \( J = 1.0, 6.4 \) Hz, 1H, CH Ger); 5.38 (dt, \( J = 1.1, 7.4 \) Hz, 1H, CH Ger); 4.62 (s, 2H, CO₂CH₂); 4.61 (t, \( J = 3.6 \) Hz, 1H, OCHO); 4.23 (dd, \( J = 6.4, 11.7 \) Hz, 1H, CH₂O Ger); 4.01 (dd, \( J = 7.4, 11.7 \) Hz, 1H, CH₂O Ger); 3.87 (m, 1H, CH₂O THP); 3.49 (m, 1H, CH₂O THP); 2.87 (s, 3H, NHCH₃); 2.17-2.22 (m, 2H, CH₂ Ger); 2.07-2.10 (m, 2H, CH₂ Ger); 1.79-1.85 (m, 1H, CH₂a THP); 1.71 (s, 3H, CH₃ Ger); 1.69 (m, 1H partially obscured, CH₂b THP); 1.68 (s, 3H, CH₃ Ger); 1.47-1.60 (m, 4H, 2 * CH₂ THP). \(^{13}\)C NMR (125.6 MHz, CDCl₃): \( \delta \) 168.3 (CO₂); 152.0 (arom. quart. CNH); 139.4 (quart. C Ger); 134.5; 131.5 (2 * arom. CH); 130.6 (quart. C Ger); 128.6; 121.1 (2 * CH Ger); 114.3; 110.6 (2 * arom. CH); 110.0 (arom. quart. CO₂); 97.7 (CH THP); 69.6 (CO₂CH₂); 63.5 (CH₂O THP); 62.1 (CH₂O Ger); 39.0 (CH₂ Ger); 30.7 (CH₂ THP); 29.4 (NHCH₃); 26.0; 25.5; 19.6 (3 * CH₂ THP); 16.4; 14.0 (2 * CH₃ Ger). MS (El) \( m/z \) (rel. intensity) 387 (M⁺, 8.2), 302 (26), 151 (100), 134 (24), 105 (14), 85 (88). HRMS (El) \( m/z \): calcd for (M⁺) C₂₃H₃₃NO₄ 387.2409, found 387.2397. Anal. Calcd: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.54; H, 8.47; N, 3.90.

**(E,E)-8-O-(2-N-methyl-aminobenzoyl)-1-(tetrahydropyran)-3,7,11-trimethyl-2,6,10-dodecatriene (6b):** Compound 6b was prepared using alcohol 4b (500 mg, 1.5 mmol),
following the same procedures described for the synthesis of 6a. After chromatography 466 mg (66%) of 6b was obtained as a colorless oil, followed by 90 mg (18%) of starting material: $R_f = 0.74$ (hexane/ethyl acetate 4:1). UV (MeOH) $\lambda_{max}$ 195 nm ($e$ 60 244), 220 nm ($e$ 45 976), 253 nm ($e$ 14 394), 354 nm ($e$ 10 305). IR (KBr) $\nu_{max}$ 3378, 2939 br s, 1682, 1607, 1581, 1520, 1240, 1128, 1024, 750 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.92 (dd, $J = 1.6, 8.0$ Hz, 1H, arom. CH); 7.66 (br s, 1H, NH); 7.36 (ddd, $J = 1.6, 7.0, 8.4$ Hz, 1H, arom. CH); 6.65 (dd, $J = 1.0, 8.4$ Hz, 1H, arom. CH); 6.57 (ddd, $J = 1.0, 7.0, 8.0$ Hz, 1H, arom. CH); 5.51 (t, $J = 7.0$ Hz, 1H, CH Far); 5.36 (t, $J = 7.3$ Hz, 1H, CH Far); 5.12 (t, $J = 6.8$ Hz, 1H, CH Far); 4.60-4.80 (m, 3H, CO$_2$CH$_2$, OCHO); 4.23 (dd, $J = 6.4, 11.0$ Hz, 1H, CH$_2$O Far); 4.02 (dd, $J = 7.3, 11.8$ Hz, 1H, CH$_{2b}$O Far); 3.88 (m, 1H, CH$_2$O THP); 3.50 (m, 1H, CH$_{2b}$O THP); 2.89 (s, 3H, NHCH$_3$); 2.00-2.23 (m, 8H, 4 * CH$_2$ Far); 1.75-1.85 (m, 1H, CH$_2$a THP); 1.72 (s, 3H, CH$_3$ Far); 1.69 (m, 1H partially obscured, CH$_{2b}$ THP); 1.67 (s, 3H, CH$_3$ Far); 1.61 (s, 3H, CH$_3$ Far); 1.47-1.60 (m, 4H, 2 * CH$_2$ THP). $^{13}$C NMR (125.6 MHz, CDCl$_3$): $\delta$ 168.4 (CO$_2$); 152.0 (arom. quart. CNH); 140.1; 134.7 (2 * quart. C Far); 134.5; 131.5 (2 * arom. CH); 130.2 (quart. C Far); 129.0; 124.3; 120.7 (3 * CH Far); 114.3; 110.6 (2 * arom. CH); 110.0 (arom. quart. $\_\_CO_2$); 97.7 (CH THP); 69.8 (CO$_2$CH$_2$); 63.6 (CH$_2$O THP); 62.2 (CH$_2$O Far); 39.6; 39.1 (2 * CH$_2$ Far); 30.7 (CH$_2$ THP); 29.5 (NHCH$_3$); 26.4 (CH$_2$ Far); 26.3; 25.5; 19.6 (3 * CH$_2$ THP); 16.4; 16.0; 14.0 (3 * CH$_3$ Far). MS (El) $m/z$ (rel. intensity) 455 (M$^+$, 10), 370 (17), 167 (11), 152 (46), 151 (100), 149 (27), 134 (31), 85 (47). HRMS (El) $m/z$: calcd for (M$^+$) C$_{28}$H$_{44}$NO$_4$ 455.3036, found 455.3020. Anal. Calcd: C, 73.81; H, 9.07; N, 3.07. Found: C, 74.21; H, 9.10; N, 2.78.

(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7-dimethyl-2,6-octandien-1-ol (7a): Compound 6a (500 mg, 1.3 mmol) was dissolved in ethanol (5 mL). PPTS (36 mg, 0.14 mmol) was
added and the reaction was heated at 60°C for 3 hr. After this time, the solvent was removed under reduced pressure and the oily residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (3:1) as eluent, and yielded 362 mg (92%) of compound 7a as a colorless oil: \( R_f = 0.34 \) (hexane/ethyl acetate 3:1). UV (MeOH) \( \lambda_{max} \) 223 nm (\( \epsilon \) 36 325), 256 nm (\( \epsilon \) 11 857), 355 nm (\( \epsilon \) 8 497). IR (KBr) \( \nu_{max} \) 3379 br s, 2914 br s, 1680, 1607, 1581, 1520, 1242, 1128, 1087, 751 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.92 (dd, \( J = 1.6, 8.0 \) Hz, 1H, arom. CH); 7.60 (br s, 1H, NH); 7.37 (ddd, \( J = 1.6, 7.1, 8.5 \) Hz, 1H, arom. CH); 6.65 (dd, \( J = 1.0, 8.5 \) Hz, 1H, arom. CH); 6.58 (ddd, \( J = 1.0, 7.1, 8.5 \) Hz, 1H, arom. CH); 5.50 (dt, \( J = 1.3, 7.0 \) Hz, 1H, CH Ger); 5.40 (dt, \( J = 1.3, 6.8 \) Hz, 1H, CH Ger); 4.63 (s, 2H, CO\(_2\)CH\(_2\)); 4.12 (d, \( J = 6.8 \) Hz, 2H, CH\(_2\)O Ger); 2.89 (s, 3H, NHCH\(_3\)); 2.12-2.21 (m, 2H, CH\(_2\) Ger); 2.06-2.09 (m, 2H, CH\(_2\) Ger); 1.71 (s, 3H, CH\(_3\) Ger); 1.67 (s, 3H, CH\(_3\) Ger). \(^{13}\)C NMR (125.6 MHz, CDCl\(_3\)): \( \delta \) 168.4 (CO\(_2\)); 152.0 (arom. quart. CNH); 138.8 (quart. C Ger); 134.6; 131.5 (2 * arom. CH); 130.6 (quart. C Ger); 128.4; 123.9 (2 * CH Ger); 114.3; 110.7 (2 * arom. CH); 110.0 (arom. quart. CCO\(_2\)); 69.6 (CO\(_2\)CH\(_2\)); 59.2 (CH\(_2\)O Ger); 38.9 (CH\(_2\) Ger); 29.5 (NHCH\(_3\)); 25.9 (CH\(_2\) Ger); 16.2; 14.0 (2 * CH\(_3\) Ger). MS (El) \( m/z \) (rel. intensity) 303 (M\(^+\), 12), 151 (100), 134 (21), 105 (23). HRMS (El) \( m/z \): calcd for (M\(^+\)) C\(_{18}\)H\(_{25}\)NO\(_3\) 303.1834, found 303.1823. Anal. Calcd: C, 71.24; H, 8.31; N, 4.62. Found: C, 71.09; H, 8.31; N, 4.91.

\((E,E)-8-O-(2-N\text{-}methyl\text{-}aminobenzoyl)-3,7,11\text{-}trimethyl\text{-}2,6,10\text{-}dodecatrien\text{-}1\text{-}ol\) (7b):

Compound 7b was prepared using compound 6b (450 mg, 1.0 mmol), following the same procedures described for the synthesis of 7a. After chromatography 346 mg (92%) of 7b was obtained as a colorless oil. \( R_f = 0.38 \) (hexane/ethyl acetate 4:1). UV (MeOH) \( \lambda_{max} \) 195 nm (\( \epsilon \) 53 281), 220 nm (\( \epsilon \) 40 540), 253 nm (\( \epsilon \) 12 617), 354 nm (\( \epsilon \) 9 018). IR (KBr) \( \nu_{max} \) 3379 br s, 2915 br s, 1681, 1607, 1581, 1520, 1241, 1174, 1128, 1087, 751 cm\(^{-1}\). \(^1\)H NMR (500 MHz,
CDCl₃): δ 7.92 (dd, J = 1.6, 8.0 Hz, 1H, arom. CH); 7.65 (br s, 1H, NH); 7.37 (ddd, J = 1.6, 7.1, 8.5 Hz, 1H, arom. CH); 6.66 (dd, J = 1.0, 8.5 Hz, 1H, arom. CH); 6.58 (ddd, J = 1.0, 7.1, 8.0 Hz, 1H, arom. CH); 5.51 (dt, J = 1.3, 7.0 Hz, 1H, CH Far); 5.40 (dt, J = 1.2, 6.9 Hz, 1H, CH Far); 5.12 (dt, J = 1.2, 6.9 Hz, 1H, CH Far); 4.65 (s, 2H, CO₂CH₂); 4.14 (d, J = 6.9 Hz, 2H, CH₂O Far); 2.90 (s, 3H, NHCH₃); 2.02-2.20 (m, 8H, 4 * CH₂ Far); 1.72 (s, 3H, CH₃ Far); 1.66 (s, 3H, CH₃ Far); 1.61 (s, 3H, CH₃ Far). ¹³C NMR (125.6 MHz, CDCl₃): δ 168.5 (CO₂); 152.0 (arom. quart. CNH); 139.6; 134.8 (2 * quart. C Far); 134.6; 131.5 (2 * arom. CH); 130.2 (quart. C Far); 129.0; 124.2; 123.4 (3 * CH Far); 114.0; 110.7 (2 * arom. CH); 110.0 (arom. quart. CCO₂); 69.9 (CO₂CH₂); 39.5 (CH₂OH Far); 39.3; 39.0 (2 * CH₂ Far); 29.5 (NHCH₃); 26.3 (2 signals, 2 * CH₂ Far); 16.2; 16.0; 14.1 (3 * CH₃ Far). MS (EI) m/z (rel. intensity) 371 (M⁺, 10), 152 (36), 151 (100), 134 (20), 105 (14). HRMS (EI) m/z: calcd for (M⁺) C₂₃H₃₃NO₃ 371.2460, found 371.2449. Anal. Calcd: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.39; H, 8.95; N, 3.88.

(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7-dimethyl-2,6-octandiene-1-chloride (8a): To a solution of N-chlorosuccinimide (30.5 mg, 0.23 mmol) in CH₂Cl₂ (1 mL), stirring at -40°C under an atmosphere of argon, was added dimethyl sulfide (18.5 uL, 0.28 mmol) dropwise. The reaction was then warmed to 0°C with an ice bath and kept at this temperature for 5 min. The reaction was then cooled back to -40°C and a solution of the alcohol 7a (63 mg, 0.21 mmol) in CH₂Cl₂ (2 mL), was added dropwise. The resulting milky white solution was then left stirring to warm to 0°C over 1 hr. The reaction was maintained at 0°C for another hour, after which time it was then warmed to room temperature for a further 15 min. The resulting clear yellow solution was poured into a separating funnel containing pentane (100 mL) and ice cold brine solution (20 mL). The layers were separated and the organic phase was washed
once more with ice cold brine solution. The combined aqueous phases were back extracted with pentane (2 x 20 mL). The combined organic phase was dried over Na₂SO₄, filtered and the solvent removed under reduced pressure, to yield the allylic chloride 8a as a pale yellow oil (62 mg, 92%): \( R_f = 0.63 \) (hexane/ethyl acetate 6:1). UV (MeOH) \( \lambda_{\text{max}} \) 219 nm (ε 44 908), 253 nm (ε 11 954), 353 nm (ε 8 432). IR (KBr) \( \nu_{\text{max}} \) 3379, 2933 br s, 1682, 1607, 1581, 1520, 1241, 1174, 1128, 1087, 844, 751 cm⁻¹. \(^1\)H NMR (500 MHz, CDCl₃): δ 7.92 (dd, \( J = 1.6, 8.0 \) Hz, 1H, arom. CH); 7.66 (br s, 1H, NH); 7.38 (ddd, \( J = 1.6, 7.1, 8.4 \) Hz, 1H, arom. CH); 6.66 (dd, \( J = 1.0, 8.4 \) Hz, 1H, arom. CH); 6.58 (ddd, \( J = 1.0, 7.1, 8.0 \) Hz, 1H, arom. CH); 5.43-5.49 (m, 2H, 2 * CH Ger); 4.63 (s, 2H, CO₂CH₂); 4.08 (d, \( J = 8.0 \) Hz, 2H, CH₂Cl Ger); 2.90 (s, 3H, NHCH₃); 2.18-2.21 (m, 2H, CH₂ Ger); 2.09-2.13 (m, 2H, CH₂ Ger); 1.73 (s, 3H, CH₃ Ger); 1.72 (s, 3H, CH₃ Ger). \(^13\)C NMR (125.6 MHz, CDCl₃): δ 168.4 (CO₂); 152.1 (arom. quart. CNH); 142.1 (quart. C Ger); 134.6; 131.5 (2 * arom. CH); 130.9 (quart. C Ger); 128.0; 120.7 (2 * CH Ger); 114.3; 110.7 (2 * arom. CH); 110.0 (arom. quart. CO₂); 69.6 (CO₂CH₂); 41.0 (CH₂Cl Ger); 38.8 (CH₂ Ger); 29.6 (NHCH₃); 25.8 (CH₂ Ger); 16.1; 14.1 (2 * CH₃ Ger). MS (EI) \( m/z \) (rel. intensity) 321 (M⁺, 19), 151 (100), 134 (30), 133 (17), 105 (32). HRMS (EI) \( m/z \): calcd for (M⁺) C₁₈H₂₄ClNO₂ 321.1495, found 321.1511. Anal. Calcd: C, 67.26; H, 7.53; N, 4.36. Found: C, 67.07; H, 7.61; N, 4.30.

(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7,11-trimethyl-2,6,10-dodecatriene-1-chloride (8b): Compound 8b was prepared using compound 7b (156 mg, 0.42 mmol) and following the same procedures described for the synthesis of 8a. The desired chloride 8b was obtained as a pale yellow oil 160 mg (92%): \( R_f = 0.38 \) (hexane/ethyl acetate 4:1). UV (MeOH) \( \lambda_{\text{max}} \) 194 nm (ε 35 708), 220 nm (ε 27 878), 253 nm (ε 7 618), 353 nm (ε 5176). IR (KBr) \( \nu_{\text{max}} \) 3376, 2915 br s, 1681, 1607, 1581, 1520, 1240, 1128, 1086, 846, 751, cm⁻¹. \(^1\)H NMR (500 MHz,
CDCl$_3$): $\delta$ 7.92 (dd, $J = 1.7$, 8.0 Hz, 1H, arom. CH); 7.65 (br s, 1H, NH); 7.37 (dd, $J = 1.7$, 7.1, 8.5 Hz, 1H, arom. CH); 6.66 (dd, $J = 0.9$, 8.5 Hz, 1H, arom. CH); 6.58 (ddd, $J = 0.9$, 7.1, 8.0 Hz, 1H, arom. CH); 5.51 (dt, $J = 1.0$, 7.0 Hz, 1H, CH Far); 5.44 (dt, $J = 1.2$, 8.0 Hz, 1H, CH Far); 5.11 (t, $J = 5.6$ Hz, 1H, CH Far); 4.63 (s, 2H, CO$_2$CH$_2$); 4.09 (apparent d, $J = 8.0$ Hz, 2H, CH$_2$Cl Far); 2.90 (s, 3H, NHCH$_3$); 2.02-2.19 (m, 8H, 4 * CH$_2$ Far); 1.72 (s, 6H, 2 * CH$_3$ Far); 1.61 (s, 3H, CH$_3$ Far). $^{13}$C NMR (125.6 MHz, CDCl$_3$): $\delta$ 168.5 (CO$_2$); 152.1 (arom. quart. CNH); 142.7; 135.1 (2 * quart. C Far); 134.6; 131.5 (2 * arom. CH); 130.3 (quart. C Far); 129.0; 123.9; 120.3 (3 * CH Far); 114.0; 110.7 (2 * arom. CH); 110.0 (arom. quart. CCO$_2$); 69.8 (CO$_2$CH$_2$); 41.1 (CH$_2$Cl Far); 39.4; 39.1 (2 * CH$_2$ Far); 29.5 (NHCH$_3$); 26.3; 26.1 (2 * CH$_2$ Far); 16.1; 16.0; 14.1 (3 * CH$_3$ Far). MS (EI) m/z (rel. intensity) 389 (M$^+$, 13), 217(9), 152 (10), 151 (100), 135 (41), 134 (48), 105 (12), 93 (11). HRMS (EI) m/z: calcd for (M$^+$) C$_{23}$H$_{32}$ClNO$_2$ 389.2122, found 389.2101. Anal. Calcd: C, 70.84; H, 8.27; N, 3.59. Found: C, 70.66; H, 8.25; N, 3.12.

$S$-Farnesyl-$L$-cysteine methyl ester (H-Cys(Far)-OMe) (20): H-Cys-(Far)-OMe 20 was synthesized as described previously.$^{21a}$

$S$-[(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7-dimethyl-2,6-octandiene]-L-cysteine methyl ester (H-Cys(Ger/Mant)-OMe) (9a): To a solution L-cysteine methyl ester hydrochloride (73.0 mg, 0.42 mmol) in dry liquid ammonia (10 mL), stirring vigorously at -40°C under an atmosphere of argon, was added a solution of the chloride 8a dissolved in dry THF (10 mL). The resulting clear solution was then left to slowly warm up overnight. After evaporation of the remaining solution the resulting white solid was dissolved in water (50 mL) and extracted with Et$_2$O (5x 20mL). The combined organic phase was dried over MgSO$_4$, filtered and the
solvent removed under reduced pressure to yield compound 9a as a pale yellow oil (142 mg, 89%). \( R_f = 0.53 \) (hexane/ethyl acetate 1:2). \( [\alpha]_D^{22} = +11.2 \) (c = 1.0, CH\(_3\)OH). UV (MeOH) \( \lambda_{\text{max}} \) 199 nm (c 29 653), 220 nm (c 31 033), 253 nm (c 9 106), 354 nm (c 6 220). IR (KBr) \( \nu_{\text{max}} \) 3379, 2925 br s, 1742, 1681, 1607, 1580, 1520, 1240 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.89 (dd, \( J = 1.6, 8.0 \) Hz, 1H, arom. CH); 7.62 (br d, \( J = 4.7 \) Hz, 1H, NH); 7.34 (ddd, \( J = 1.6, 7.0, 8.4 \) Hz, 1H, arom. CH); 6.62 (dd, \( J = 1.0, 8.4 \) Hz, 1H, arom. CH); 6.55 (ddd, \( J = 1.0, 7.0, 8.0 \) Hz, 1H, arom. CH); 5.47 (t, \( J = 7.0 \) Hz, 1H, CH Ger); 5.21 (t, \( J = 7.8 \) Hz, 1H, CH Ger); 4.60 (s, 2H, CO\(_2\)CH\(_2\)); 3.70 (s, 3H, OCH\(_3\)); 3.59 (dd, \( J = 4.7, 7.7 \) Hz, 1H, \( \alpha \)-CH Cys); 3.09-3.20 (m, 2H, \( \alpha \)-CH\(_2\) Ger); 2.86 (d, \( J = 4.7 \) Hz, 3H, NHCH\(_3\)); 2.83 (dd, \( J = 4.7, 13.5 \) Hz, 1H, \( \beta \)-CH\(_2\)a Cys); 2.64 (dd, \( J = 7.7, 13.5 \) Hz, 1H, \( \beta \)-CH\(_{2b}\) Cys); 2.00-2.20 (m, 4H, 2 \( \times \) CH\(_2\) Ger); 1.76 (s, 2H, NH\(_2\)); 1.69 (s, 3H, CH\(_3\) Ger); 1.64 (s, 3H, CH\(_3\) Ger). \(^{13}\)C NMR (125.6 MHz, CDCl\(_3\)): \( \delta \) 174.4 (CO\(_2\)Me); 168.3 (CO\(_2\)); 151.9 (arom. quart. CNH); 138.8 (quart. C Ger); 134.5; 131.4 (2 \( \times \) arom. CH); 130.6 (quart. C Ger); 128.3; 120.3 (2 \( \times \) CH Ger); 114.2; 110.6 (2 \( \times \) arom. CH); 110.0 (arom. quart. CCO\(_2\)); 69.5 (CO\(_2\)CH\(_2\)); 54.1 (\( \alpha \)-CH Cys); 52.1 (OCH\(_3\)); 38.9 (\( \alpha \)-CH\(_2\) Ger); 36.3 (\( \beta \)-CH\(_2\) Cys); 29.6 (CH\(_2\) Ger); 29.4 (NHCH\(_3\)); 26.0 (CH\(_2\) Ger); 16.0; 14.0 (2 \( \times \) CH\(_3\) Ger). MS (EI) \( m/z \) (rel. intensity) 420 (M\(^+\), 27), 151 (100), 134 (68), 105 (20), 88 (22). HRMS (EI) \( m/z \): calcd for (M\(^+\)) \( \text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_{4}\text{S} \) 420.2070, found 420.2083.

**S-[(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7,11-trimethyl-2,6,10-dodecatriene]-L-cysteine methyl ester (H-Cys(Far/Mant)-OMe)** (9b): Compound 9b was prepared using allyl chloride 8b (159 mg, 0.41 mmol) and following the same procedures described for the synthesis of 9a. The desired compound 9b was obtained as a pale yellow oil 190 mg (95%). \( R_f = 0.48 \) (hexane/ethyl acetate 1:2). \( [\alpha]_D^{22} = +9.0 \) (c = 1.0, CH\(_3\)OH). UV (MeOH) \( \lambda_{\text{max}} \) 195 nm (c 24 006), 219 nm (c 18 111), 253 nm (c 5 190), 354 nm (c 3 382). IR (KBr) \( \nu_{\text{max}} \) 3378, 2924
br s, 1742, 1682, 1607, 1581, 1520, 1239 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.90 (dd, J = 1.6, 8.0 Hz, 1H, arom. CH); 7.64 (br s, 1H, NH); 7.35 (ddd, J = 1.6, 7.0, 8.5 Hz, 1H, arom. CH); 6.64 (dd, J = 1.0, 8.5 Hz, 1H, arom. CH); 6.56 (ddd, J = 1.0, 7.0, 8.0 Hz, 1H, arom. CH); 5.49 (t, J = 7.0 Hz, 1H, CH Far); 5.21 (t, J = 7.8 Hz, 1H, CH Far); 5.10 (t, J = 6.8 Hz, 1H, CH Far); 4.61 (s, 2H, CO₂CH₂); 3.72 (s, 3H, OCH₃); 3.61 (dd, J = 4.7, 7.7 Hz, 1H, α-CH Cys); 3.10-3.20 (m, 2H, α-CH₂ Far); 2.89 (d, J = 4.7 Hz, 3H, NHCH₃); 2.86 (dd, J = 4.6, 13.5 Hz, 1H, β-CH₂a Cys); 2.66 (dd, J = 7.7, 13.5 Hz, 1H, β-CH₂b Cys); 2.00-2.20 (m, 8H, 4 * CH₂ Far); 1.80 (br s, 2H, NH₂); 1.70 (s, 3H, CH₃ Far); 1.64 (s, 3H, CH₃ Far); 1.59 (s, 3H, CH₃ Far.). ¹³C NMR (125.6 MHz, CDCl₃): δ 174.5 (CO₂Me); 168.4 (CO₂); 152.0 (arom. quart. CNH); 139.5; 134.8 (2 * quart. C Far); 134.5; 131.5 (2 * arom. CH); 130.2 (quart. C Far); 129.0; 124.2; 119.9 (3 * CH Far); 114.2; 110.6 (2 * arom. CH); 110.0 (arom. quart. CCO₂); 69.8 (CO₂CH₂); 54.2 (α-CH Cys); 52.1 (OCH₃); 39.5 (α-CH₂ Far); 39.0 (CH₂ Far); 36.4 (β-CH₂ Cys); 29.8 (CH₂ Far); 29.5 (NHCH₃); 26.4; 26.3 (2 * CH₂ Far); 16.1; 16.0; 14.0 (3 * CH₃ Far.). MS (EI) m/z (rel. intensity) 488 (M⁺, 5), 151 (100), 134 (31), 105 (10). HRMS (EI) m/z: calcd for (M⁺) C₂₇H₄₀N₂O₄S 488.2674, found 488.2709.

**Glycine allyl ester hydrotosylate (TosOH * H-Gly-OAll) (11):** TosOH * H-Gly-OAll 11 was synthesized as described previously.³⁶

**N-(9-Fluorenlymethyloxyxycarbonyl)-L-methionylglycine allyl ester (Fmoc-Met-Gly-OAll) (12):** To a solution of Fmoc-Met-OH 10 (636 mg, 1.71 mmol) in dry THF (10 mL) was added HOBt (463 mg, 3.42 mmol, 2 eq.). The reaction was cooled to 0°C, then dicyclohexylcarbodiimide (424 mg, 2.0 mmol, 1.2 eq.) was added. The reaction was left stirring for 1 h at 0°C, then a solution of TosOH * H-GlyOAll 11 (492 mg, 1.17 mmol) with
triethyl amine (238 µl, 1.71 mmol) in dry THF (5 mL) was added to the Fmoc-Met-OH solution. The reaction was left for 24 h after this time the reaction was diluted with ethyl acetate (100 mL) and extracted with 0.5M HCl (2 x 20 mL), then with NaHCO₃ (2 x 20 mL) and finally with brine solution (2 x 20 mL). The organic phase was dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification of the residue by flash chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent provided 481 mg (60%) of the desired dipeptide 12 as a white solid. Rf = 0.3 (hexane/ethyl acetate 2:1). [α]D₂²² = -8.8 (c = 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.76 (d, J = 7.2 Hz, 2H, arom. CH); 7.58 (d, J = 7.2 Hz, 2H, arom. CH); 7.40 (dd, J = 7.2, 7.2 Hz, 2H, arom. CH), 7.31 (dd, J = 7.2, 7.2 Hz, 2H, arom. CH); 6.70 (br, 1H, CONH); 5.90 (ddt, J = 5.9, 10.4, 17.2 Hz, 1H, CH=CH₂); 5.57 (d, J = 7.7 Hz, 1H, OCONH); 5.33 (dd, J = 1.3, 17.2 Hz, 1H, CH=CH₂); 4.64 (d, J = 5.9 Hz, 2H, OCH₂ All); 4.42 (d, J = 6.9 Hz, 2H, OCH₂ Fmoc); 4.40-4.44 (m, 1H, α-CH Met); 4.22 (t, J = 6.9 Hz, 1H, CH Fmoc); 4.11-4.15 (m, 1H, α-CH₂a Gly); 3.99-4.04 (m, 1H, α-CH₂b Gly); 2.56-2.61 (m, 2H, γ-CH₂ Met); 2.11 (s, 3H, SCh₃); 2.08-2.11 (m, 1H, β-CH₂a Met); 1.99-2.04 (m, 1H, β-CH₂b Met). ¹³C NMR (125.6 MHz, CDCl₃): δ 171.4; 169.1 (2 * C=O); 156.1 (OCONH); 143.8; 143.7; 141.3 (3 * arom. quart. C); 131.4 (CH=CH₂); 127.8; 127.1; 125.1; 120.0 (4 * arom. CH); 119.2 (CH=CH₂); 67.1 (OCH₂ Fmoc); 66.1 (OCH₂ All); 53.7 (α-CH Met); 47.2 (CH Fmoc); 41.3 (α-CH₂ Gly); 31.4; 30.0 (2 * CH₂ Met); 15.2 (SCh₃). HRMS (EI) m/z: for (M⁺) C₂₅H₂₈N₂O₅S, calcd 468.1719, found 468.1735. Anal. Calcd: C, 64.08; H, 6.02; N, 5.98. Found: C, 63.88; H, 6.03 N, 6.06.

\[ N-(9-\text{Fluorenylmethoxy} \text{carbonyl})-\text{L-} \text{methionyl} \text{glycine (Fmoc-Met-Gly-OH)} \] (13): The dipeptide Fmoc-Met-Gly-OH 13 is known in the literature²¹ but was synthesized using the
general allyl ester deprotection procedure given above using the fully protected dipeptide 12 (634 mg, 1.4 mmol). After completed reaction the solvent was removed under reduced pressure and the residue was taken up in 1 M NaHCO₃-solution (50 mL). The aqueous solution is washed with diethyl ether (2 * 40 mL), after adjusting pH 2 the desired product 13 is extracted with ethyl acetate (3 * 40 mL). Followed by drying with MgSO₄, filtering and removing the solvent under reduced pressure the material was obtained in virtually quantitative yield (577 mg, 1.4 mmol). A small amount of material was purified by flash chromatography on silica gel using ethyl acetate/acetic acid (95:5) to provide the desired compound 13 that was identical to the literature known derivative. Pale yellow solid. R_f = 0.15 (ethyl acetate/methanol 4:1). [α]₂²² = - 4.3 (c = 0.6, CHCl₃); [lit.: -2.5 (c = 0.3, CHCl₃)].¹¹ H NMR (250 MHz, CD₃OD): δ 7.77 (d, J = 7.2 Hz, 2H, arom. CH); 7.64-7.67 (m, 2H, arom. CH); 7.38 (t, J = 7.0 Hz, 2H, arom. CH); 7.29 (t, J = 7.0 Hz, 2H, arom. CH); 4.21-4.33 (m, 4H, α-CH Met, OCH₂, CH Fmoc); 3.96 (d, J = 17.7 Hz, 1H, α-CH₂ Gly); 3.85 (d, J = 17.7 Hz, 1H, α-CH₂ Gly); 2.50-2.55 (m, 2H, γ-CH₂ Met); 2.02-2.12 (m, 1H, β-CH₂ Met); 2.07 (s, 3H, SCH₃); 1.84-1.94 (m, 1H, β-CH₂ Met). HRMS (EI) m/z: calcd for (M⁺) C₂₂H₂₄N₂O₃S 428.1406, found 428.1390.

**L-Proline allyl ester hydrotosylate (TosOH * H-Pro-OAll)** (15): TosOH * H-Pro-OAll 15 was synthesized as described previously.³⁶

**N-tert-Butyloxycarbonyl-L-leucyl-L-proline allyl ester (Boc-Leu-Pro-OAll)** (16): To a solution of Boc-Leu-OH 14 (1 g, 4.33 mmol) and TosOH * H-Pro-OAll 15 (1.41 g, 4.33 mmol) in dry CH₂Cl₂ (20 mL) was added NEt₃ (630 μL, 4.54 mmol). The reaction was cooled to 0°C and EEDQ (1.6 g, 6.5 mmol, 1.5 equivalents) dissolved in dry CH₂Cl₂ (10 mL) was
added dropwise. The reaction was left for 24 h after which time the solvent was removed under reduced pressure, the residue was taken up in ethyl acetate (100 mL) and extracted with HCl (3 x 20 mL), then with sat. NaHCO₃ (2 x 20 mL) and finally with brine solution (1 x 20 mL). The organic phase was dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by flash chromatography on silica gel using hexane/ethyl acetate (3:1) as eluent, provided 1.4 g (84%) of the desired dipeptide 16 as a colorless oil. \( R_f = 0.3 \) (hexane/ethyl acetate 3:1). \([\alpha]_D^{22} = -72.7 \) (c = 1.1, CHCl₃). \(^1\)H NMR (400 MHz, CDCl₃): δ 5.89 (ddt, \( J = 5.7, 10.5, 17.2 \) Hz, 1H, CH=CH₂); 5.32 (dd, \( J = 1.4, 17.2 \) Hz, 1H, CH=CH₂a); 5.24 (dd, \( J = 1.1, 10.4 \) Hz, 1H, CH=CH₂b); 5.15 (d, \( J = 9.1 \) Hz, 1H, OCONH); 4.60-4.66 (m, 2H, OCH₂); 4.54-4.58 (m, 1H, α-CH); 4.45-4.50 (m, 1H, α-CH); 3.76-3.81 (m, 1H, δ-CH₂a Pro); 3.58-3.64 (m, 1H, δ-CH₂b Pro); 2.20-2.27 (m, 1H, β-CH₂a Pro); 1.97-2.09 (m, 3H, β-CH₂b Pro, γ-CH₂ Pro); 1.74-1.80 (m, 1H, γ-CH Leu); 1.49 (dd, \( J = 6.0, 6.0 \) Hz, 2H, β-CH₂ Leu); 1.42 (s, 9H, C(CH₃)₃); 0.99 (d, \( J = 6.5 \) Hz, 3H, 1 * ω-CH₃ Leu); 0.95 (d, \( J = 6.7 \) Hz, 3H, 1 * ω-CH₃ Leu). \(^1^\)C NMR (100.6 MHz, CDCl₃): δ 171.8; 171.6 (2 * C=O); 155.7 (OCONH); 131.8 (CH=CH₂); 118.5 (CH=CH₂); 79.4 (C(CH₃)₃); 65.6 (OCH₂); 58.7 (α-CH Pro); 50.2 (α-CH Leu); 46.7 (δ-CH₂ Pro); 42.0 (β-CH₂ Leu); 29.0 (β-CH₂ Pro); 28.3 (C(CH₃)₃); 24.9 (γ-CH₂ Pro); 24.5 (γ-CH Leu); 23.3; 21.7 (2 * ω-CH₃ Leu). HRMS (El) m/z: calcd for (M⁺) \( C_{19}H_{32}N_{2}O_5 \) 368.2311, found 368.2296. Anal. Calcd: C, 61.93; H, 8.75; N, 7.60. Found: C, 61.99; H, 8.77; N, 7.70.

L-Leucyl-L-proline allyl ester hydrotrifluoroacetate (TFA * H-Leu-Pro-OAll) (17): To cleave the Boc protecting group, Boc-Leu-Pro-OAll 16 (420 mg, 1.14 mmol) was dissolved in neat TFA (3 mL). The reaction was left to stir at room temperature for 1 h after which time TLC analysis determined the reaction to be complete. The solvent was removed under reduced
pressure by azeotropic distillation with toluene (4 x 50 mL). The resulting tacky white solid was used without further purification. \([\alpha]_D^{22} = -53.8\) (c = 1.0, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃): \(\delta 8.27\) (br, 3H, H₃N); 5.86 (ddt, J = 5.8, 10.4, 17.2 Hz, 1H, CH=CH₂); 5.30 (dd, J = 1.4, 17.2 Hz, 1H, CH=CH₂); 5.24 (dd, J = 1.2, 10.4 Hz, 1H, CH=CH₂); 4.62 (dd, J = 5.9, 13.2 Hz, 1H, OCH₂); 4.51-4.56 (m, 2H, OCH₂, \(\alpha\)-CH Pro); 4.18 (dd, J = 4.7, 9.0 Hz, 1H, \(\alpha\)-CH Leu); 3.70-3.75 (m, 1H, \(\delta\)-CH₂ Pro); 3.48-3.53 (m, 1H, \(\delta\)-CH₂ Pro); 2.22-2.29 (m, 1H, \(\beta\)-CH₂ Pro); 1.95-2.06 (m, 3H, \(\beta\)-CH₂ Pro, \(\gamma\)-CH₂ Pro); 1.85-1.91 (m, 1H, \(\gamma\)-CH Leu); 1.74-1.80 (m, 1H, \(\beta\)-CH₂ Leu); 1.58-1.63 (m, 1H, \(\beta\)-CH₂ Leu); 0.97 (d, J = 6.5 Hz, 3H, 1 * \(\omega\)-CH₃ Leu); 0.96 (d, J = 6.6 Hz, 3H, 1 * \(\omega\)-CH₃ Leu). \(^1\)C NMR (125.6 MHz, CDCl₃): \(\delta 171.2\); 168.6 (2 * C=O); 162.3; 162.0; 161.7; 161.5 (CF₃CO, \(J_{CF} = 34.7\) Hz); 131.7 (CH=CH₂); 120.1; 117.8; 115.4; 113.1 (CF₃CO, \(J_{CF} = 293.0\) Hz); 118.8 (CH=CH₂); 65.9 (OCH₂); 59.2 (\(\alpha\)-CH Pro); 50.3 (\(\alpha\)-CH Leu); 46.9 (\(\delta\)-CH₂ Pro); 40.0 (\(\beta\)-CH₂ Leu); 28.8 (\(\beta\)-CH₂ Pro); 24.8 (\(\gamma\)-CH₂ Pro); 24.0 (\(\gamma\)-CH Leu); 23.0; 21.7 (2 * \(\omega\)-CH₃ Leu). HRMS (EI) m/z: calc'd for (M-TFA)+ C₁₄H₂₄N₂O₅ 268.1787, found 268.1776. Anal. Calcd: C, 50.26; H, 6.59; N, 7.33. Found: C, 50.11; H, 6.46; N, 7.22.

\(N-(9\text{-Fluorenylmethoxycarbonyl})\)-methionylglycyl-L-leucyl-L-proline allyl ester (Fmoc-Met-Gly-Leu-Pro-OAll) (18): Coupling of the peptides Fmoc-Met-Gly-OH 13 (111 mg, 0.26 mmol) and TFA * H-Leu-Pro-OAll 17 (100 mg, 0.26 mmol) was performed using the standard coupling procedure except triethylamine (36 µL, 0.26 mmol, 1 eq.) was added to neutralize the trifluoroacetic acid. Purification of the resulting residue by flash chromatography on silica gel using ethyl acetate as eluent, yielded 152 mg (84%) of the desired tetrapeptide 18 as a white foam. \(R_f = 0.65\) (ethyl acetate/methanol 10:1). \([\alpha]_D^{22} = -47.5\) (c = 1.0, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃): \(\delta 7.68-7.71\) (m, 3H, 2 * arom. CH, CONH);
7.53 (d, J = 7.4 Hz, 2H, arom. CH); 7.35 (t, J = 7.4 Hz, 2H, arom. CH); 7.37 (br, 1H, CONH); 7.25 (t, J = 7.4 Hz, 2H, arom. CH); 6.14 (d, J = 8.2 Hz, 1H, OCONH); 5.83 (ddt, J = 5.7, 10.5, 17.1 Hz, 1H, CH=CH₂); 5.28 (dd, J = 1.4, 17.2 Hz, 1H, CH=CH₂a); 5.20 (dd, J = 1.0, 10.5 Hz, 1H, CH=CH₂b); 4.75 (ddd, J = 4.9, 8.7, 8.7 Hz, 1H, α-CH); 4.58 (dd, J = 5.8, 13.3 Hz, 1H, OCH₂a All); 4.49-4.54 (m, 2H, OCH₂b All, α-CH); 4.40-4.43 (m, 1H, α-CH); 4.31 (d, J = 5.2 Hz, 2H, OCH₂ Fmoc); 4.16 (br, 1H, CH Fmoc); 3.99 (dd, J = 5.3, 18.0 Hz, 1H, α-CH₂a Gly); 3.93 (dd, J = 5.2, 18.0 Hz, 1H, α-CH₂b Gly); 3.76-3.82 (m, 1H, δ-CH₂a Pro); 3.55-3.60 (m, 1H, δ-CH₂b Pro); 2.54 (t, J = 7.2 Hz, 2H, γ-CH₂ Met); 2.11-2.17 (m, 2H, β-CH₂a Met, β-CH₂b Pro); 2.06 (s, 3H, SCh₃); 1.91-2.05 (m, 4H, β-CH₂b Met, β-CH₂b Pro, γ-CH₂ Pro); 1.66-1.69 (m, 1H, γ-CH Leu); 1.51-1.58 (m, 2H, β-CH₂ Leu); 0.92 (d, J = 6.5 Hz, 3H, 1 * ω-CH₃ Leu); 0.89 (d, J = 6.7 Hz, 3H, 1 * ω-CH₃ Leu).¹³C NMR (125.6 MHz, CDCl₃): δ 171.8; 171.6; 171.4; 168.6 (4 * C=O); 156.3 (OCONH); 143.9; 143.7; 141.2; 141.2 (4 * quart. arom. C); 131.7 (CH=CH₂); 127.6; 127.0; 125.2; 125.1; 119.9 (5 * arom. CH); 118.5 (CH=CH₂); 67.0 (OCH₂ Fmoc); 65.6 (OCH₂ All); 58.9 (α-CH Pro); 53.9 (α-CH Met); 49.2 (α-CH Leu); 47.0 (CH Fmoc); 46.9 (δ-CH₂ Pro); 42.5 (α-CH₂ Gly); 41.1 (β-CH₂ Leu); 31.7; 30.0 (2 * CH₂ Met); 28.9 (β-CH₂ Pro); 24.8 (γ-CH₂ Pro); 24.5 (γ-CH Leu); 23.2; 21.8 (2 * ω-CH₃ Leu); 15.3 (SCH₃). HRMS (FAB; 3-NBA) m/z: calcd for (M+H)⁺ C₃₁H₄₁N₄O₇S 679.3165, found 679.3239.

**N-(9-Fluorenylmethyloxycarbonyl)-L-methionylglycyl-L-leucyl-L-proline (Fmoc-Met-Gly-Leu-Pro-OH) (19):** The allyl ester was removed from the protected tetrapeptide 18 (302 mg, 0.44 mmol) using the standard allyl deprotection method given above. After completed reaction the solvent was removed under reduced pressure. Purification of the compound by washing the residue with diethyl ether (3 x 10 mL) provided 250 mg (88%) of the desired
product 19 as a pale yellow solid. $R_f = 0.8$ (chloroform/methanol/water 35:10:1). $[\alpha]_D^{22} = -20.9$ ($c = 1.0, \text{CHCl}_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.40 (d, $J = 7.2$ Hz, 1H, CONH); 7.73 (d, $J = 7.5$ Hz, 2H, arom. CH); 7.57 (d, $J = 4.0$ Hz, 2H, arom. CH); 7.50 (br, 1H, CONH); 7.36-7.39 (m, 2H, arom. CH); 7.26-7.30 (m, 2H, arom. CH); 5.75 (d, $J = 8.1$ Hz, 1H, OCONH); 4.96-4.98 (m, 1H, $\alpha$-CH); 4.36-4.41 (m, 3H, OCH$_2$, $\alpha$-CH); 4.43-4.47 (m, 1H, $\alpha$-CH); 4.20 (t, $J = 6.8$ Hz, 1H, CH Fmoc); 4.03 (d, $J = 16.8$ Hz, 1H, $\alpha$-CH$_{2a}$ Gly); 3.96 (d, $J = 15.2$ Hz, 1H, $\alpha$-CH$_{2b}$ Gly); 3.77-3.80 (m, 1H, $\delta$-CH$_{2a}$ Pro); 3.62-3.64 (m, 1H, $\delta$-CH$_{2b}$ Pro); 2.49-2.51 (m, 2H, $\gamma$-CH$_2$ Met); 2.22-2.28 (m, 1H, $\beta$-CH$_{2a}$); 2.07-2.11 (m, 2H, $\beta$-CH$_2$); 2.06 (s, 3H, SCH$_3$); 1.96-2.04 (m, 3H, $\beta$-CH$_{2b}$, $\gamma$-CH$_2$ Pro); 1.65-1.67 (m, 1H, $\gamma$-CH Leu); 1.51-1.55 (m, 2H, $\beta$-CH$_2$ Leu); 0.95 (d, $J = 5.9$ Hz, 3H, 1 * $\omega$-CH$_3$ Leu); 0.92 (d, $J = 6.2$ Hz, 3H, 1 * $\omega$-CH$_3$ Leu). $^{13}$C NMR (125.6 MHz, CDCl$_3$): $\delta$ 173.5; 172.1; 171.7; 167.8 (4 * C=O); 156.0 (OCONH); 143.8; 143.6; 141.2 (3 * arom. quart. C); 127.7; 127.1; 125.1; 119.9 (4 * arom. CH); 67.1 (OCH$_2$); 59.2 ($\alpha$-CH Pro); 53.9 ($\alpha$-CH Met); 49.0 ($\alpha$-CH Leu); 47.6 ($\delta$-CH$_2$ Pro); 47.1 (CH Fmoc); 42.7 ($\alpha$-CH$_2$ Gly); 42.5 ($\beta$-CH$_2$ Leu); 31.8; 30.0 (2 * CH$_2$ Met); 28.9 ($\beta$-CH$_2$ Pro); 25.1 ($\gamma$-CH$_2$ Pro); 24.4 ($\gamma$-CH Leu); 23.2; 22.1 (2 * $\omega$-CH$_3$ Leu); 15.26 (SCH$_3$). HRMS (FAB; 3-NBA) $m/z$: calcld for (M+H)$^+$ C$_{33}$H$_{45}$N$_4$O$_7$S 639.2852, found 639.2919.

$N$-(9-Fluorenylmethoxycarbonyl)-L-methionylglycyl-L-leucyl-L-prolyl-S-farnesyl-L-cysteine methyl ester (Fmoc-Met-Gly-Leu-Pro-Cys(Far)-OMe) (21c): Fmoc-Met-Gly-Leu-Pro-Cys(Far)-OMe 2c is a literature known compound. For this study however, the compound was prepared via a different method using the tetrapeptide 19 (589 mg, 0.9 mmol) and H-Cys(Far)-OMe 20 (360 mg, 1 mmol, 1.1 eq.), and the standard coupling reaction given above. Purification by flash chromatography on silica gel using ethyl acetate as eluent, provided 673 mg (76%) of the pentapeptide 21c as a white foam. $R_f = 0.65$ (ethyl
acetate/methanol 10:1). \([\alpha]_D^{22} = -51.6 \, (c = 1.0, \text{CHCl}_3); \) \([\text{lit.}: -46.0 \, (c = 1.0, \text{CHCl}_3)]\).^{21a} \(1^H\) NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.95 (d, \(J = 8.1\) Hz, 1H, CONH); 7.72-7.74 (m, 3H, 2 * arom. CH, CONH); 7.56 (d, \(J = 7.4\) Hz, 2H, arom. CH); 7.37 (br, 1H, CONH); 7.34 (t, \(J = 7.5\) Hz, 2H, arom. CH); 7.27 (t, \(J = 7.4\) Hz, 2H, arom. CH); 5.91 (d, \(J = 7.9\) Hz, 1H, OCONH); 5.14 (t, \(J = 7.6\) Hz, 1H, CH Far); 5.08 (t, \(J = 6.8\) Hz, 2H, 2 * CH Far); 4.88-4.90 (m, 1H, \(\alpha\)-CH); 4.61-4.67 (m, 2H, 2 * \(\alpha\)-CH); 4.43-4.45 (m, 1H, \(\alpha\)-CH); 4.37-4.39 (m, 2H, OCH\(_2\)); 4.18 (t, \(J = 6.8\) Hz, 1H, CH Fmoc); 4.12-4.16 (m, 2H, \(\alpha\)-CH\(_2\) Gly); 3.84-3.87 (m, 1H, \(\delta\)-CH\(_{2b}\) Pro); 3.70 (s, 3H, OCH\(_3\)); 3.66-3.68 (m, 1H, \(\delta\)-CH\(_{2b}\) Pro); 3.16 (dd, \(J = 8.3, 13.3\) Hz, 1H, \(\alpha\)-CH\(_{2a}\) Far); 3.01 (dd, \(J = 7.1, 13.2\) Hz, 1H, \(\alpha\)-CH\(_{2b}\) Far); 2.89 (dd, \(J = 4.7, 13.9\) Hz, 1H, \(\beta\)-CH\(_{2a}\) Cys); 2.67 (dd, \(J = 7.5, 13.8\) Hz, 1H, \(\beta\)-CH\(_{2b}\) Cys); 2.51-2.54 (m, 2H, \(\gamma\)-CH\(_2\) Met); 2.07 (s, 3H, SCH\(_3\)); 1.99-2.17 (m, 10H, 2 * CH\(_2\) Far, \(\beta\)-CH\(_2\) Met, \(\beta\)-CH\(_2\) Pro, \(\gamma\)-CH\(_2\) Pro); 1.95-1.97 (m, 4H, 2 * CH\(_2\) Far); 1.67 (s, 3H, CH\(_3\) Far); 1.65-1.70 (m, 1H, \(\gamma\)-CH Leu); 1.64 (s, 3H, CH\(_3\) Far); 1.59 (s, 3H, CH\(_3\) Far); 1.58 (s, 3H, CH\(_3\) Far); 1.54-1.59 (m, 2H, \(\beta\)-CH\(_2\) Leu); 0.92 (t, \(J = 6.7\) Hz, 6H, 2 * \(\omega\)-CH\(_3\) Leu). \(1^H\) NMR (125.6 MHz, CDCl\(_3\)): \(\delta\) 172.0; 171.7; 171.6; 171.2; 168.3 (5 * C=O); 156.2 (OCONH); 143.8; 143.6; 141.2 (3 * arom. quart. C); 139.8; 135.3; 131.2 (3 * quart. C Far); 127.7; 127.0; 125.1 (3 * arom. CH); 124.3; 123.7 (2 * CH Far); 119.9 (arom. CH), 119.6 (CH Far); 67.0 (OCH\(_2\)); 59.8 (\(\alpha\)-CH Pro); 53.9 (\(\alpha\)-CH Met); 52.4 (OCH\(_3\)); 52.1 (\(\alpha\)-CH Cys); 48.8 (\(\alpha\)-CH Leu); 47.6 (\(\delta\)-CH\(_2\) Pro); 47.1 (CH Fmoc); 43.0 (\(\alpha\)-CH\(_2\) Gly); 41.7 (\(\beta\)-CH\(_2\) Leu); 39.7 (\(\alpha\)-CH\(_2\) Far); 32.6 (\(\beta\)-CH\(_2\) Cys); 32.0; 30.1 (2 * CH\(_2\) Met); 29.4 (CH\(_2\) Far); 28.6 (\(\beta\)-CH\(_2\) Pro); 26.7; 26.5 (2 * CH\(_2\) Far); 25.7 (CH\(_3\) Far); 24.8 (\(\gamma\)-CH\(_2\) Pro); 24.5 (\(\gamma\)-CH Leu); 23.2; 22.0 (2 * \(\omega\)-CH\(_3\) Leu); 17.7; 16.1; 16.0 (3 * CH\(_3\) Far); 15.3 (SCH\(_3\)). MS (FAB; 3-NBA) \(m/z\): found 960.5 (M+H)\(^+\), 982.5 (M+Na)\(^+\).
N-(9-Fluorenylmethyloxycarbonyl)-L-methionylglycyl-L-leucyl-L-prolyl-S-[(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7-dimethyl-2,6-octandiene]-L-cysteine methyl ester (Fmoc-Met-Gly-Leu-Pro-Cys(Ger/Mant)-OMe) (21a): This compound was prepared utilizing the standard peptide coupling procedure with the tetrapeptide 19 (250 mg, 0.39 mmol) and the lipitated cysteine 9a (164 mg, 0.39 mmol). Purification by flash chromatography on silica gel starting with ethyl acetate, followed by ethyl acetate/methanol (95:5) as eluent, yielded 272 mg (68%) of the desired product 21a as a colorless oil. Rf = 0.6 (ethyl acetate). [α]D²² = -52.9 (c = 1.0, CH₃OH).¹H NMR (500 MHz, CDCl₃): δ 7.91 (dd, J = 1.6, 8.0 Hz, 1H, arom. CH Mant); 7.75 (d, J = 7.5 Hz, 2H, arom. CH Fmoc); 7.58 (d, J = 7.4 Hz, 2H, arom. CH Fmoc); 7.35-7.47 (m, 4H, 2 * arom. CH Fmoc, arom. CH Mant, CONH); 7.30 (m, 2H, arom. CH Fmoc); 7.03 (br s, 1H, CONH); 6.92 (br s, 1H, CONH); 6.67 (d, J = 8.4 Hz, 1H, arom. CH Mant); 6.59 (t, J = 8.0 Hz, 1H, arom. CH Mant); 5.62 (d, J = 7.7 Hz, 1H, OCONH); 5.48 (t, J = 6.9 Hz, 1H, CH Ger); 5.15 (t, J = 7.9 Hz, 1H, CH Ger); 4.81-4.84 (m, 1H, α-CH); 4.60-4.68 (m, 2H, 2 * α-CH), 4.63 (s, 2H, CO₂CH₂); 4.30-4.47 (m, 3H, OCH₂ Fmoc, α-CH); 4.21 (t, J = 6.6 Hz, 1H, CH Fmoc); 3.90-4.13 (m, 2H, α-CH₂ Gly); 3.75-3.79 (m, 1H, δ-CH₂a Pro); 3.72 (s, 3H, OCH₃); 3.61-3.64 (m, 1H, δ-CH₂b Pro); 3.16 (dd, J = 8.1, 13.3 Hz, 1H, α-CH₂a Ger); 3.06 (dd, J = 7.4, 13.3 Hz, 1H, α-CH₂b Ger); 2.92 (dd, J = 4.7, 13.8 Hz, 1H, β-CH₂a Cys); 2.90 (s, 3H, NHCH₃); 2.72 (dd, J = 6.9, 13.8 Hz, 1H, β-CH₂b Cys); 2.54 (br s, 2H, γ-CH₂ Met); 2.09 (s, 3H, SCH₃); 1.90-2.30 (m, 8H, 2 * CH₂ Ger, β-CH₂ Met, β-CH₂ Pro); 1.71 (s, 3H, CH₃ Ger); 1.65 (s, 3H, CH₃ Ger); 1.50-1.71 (m, 5H, γ-CH₂ Pro, β-CH₂ Leu, γ-CH Leu); 0.94 (d, J = 6.5 Hz, 3H, 1 * ω-CH₃ Leu); 0.91 (d, J = 6.5 Hz, 3H, 1 * ω-CH₃ Leu).¹³C NMR (125.6 MHz, CDCl₃): δ 171.8; 171.6; 171.1; 168.3; 168.2 (5 * C=O); 156.1 (OCONH); 151.9 (arom. quart. CNH); 143.7; 143.5; 141.1 (3 * quart. C Fmoc); 139.1 (quart. C Ger); 134.5; 131.4 (2 * arom. CH); 130.5 (quart. C Ger); 128.3 (CH Ger); 127.6; 126.9; 125.0 (3 * arom.
N-(9-Fluorenylmethoxy carbonyl)-L-methionylglycyl-L-leucyl-L-prolyl-S-[(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7,11-trimethyl-2,6,10-dodecatriene]-L-cysteine methyl ester (Fmoc-Met-Gly-Leu-Pro-Cys(Far/Mant)-OMe) (21b): This compound was prepared utilizing the standard peptide coupling procedure with tetrapeptide 19 (250 mg, 0.3 mmol) and the lipidated cysteine 9b (160 mg, 0.33 mmol). Purification by flash chromatography on silica gel starting with ethyl acetate, followed by ethyl acetate/methanol (95:5) as eluent, yielded 230 mg (63%) of the desired product 21b as a colorless oil. $R_f = 0.44$ (ethyl acetate). $[\alpha]_D^{22} = -46.1$ (c = 1.0, CH$_3$OH). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.92 (dd, J = 1.6, 8.0 Hz, 1H, arom. CH Mant); 7.75 (d, J = 7.5 Hz, 2H, arom. CH Fmoc); 7.65 (br s, 1H, NH); 7.58 (d, J = 7.2 Hz, 2H, arom. CH Fmoc); 7.35-7.43 (m, 4H, 2 * arom. CH Fmoc, arom. CH Mant, CONH); 7.30 (t, J = 7.4 Hz, 2H, arom. CH Fmoc); 7.02 (br s, 1H, CONH); 6.66 (d, J = 8.5 Hz, 1H, arom. CH Mant); 6.58 (t, J = 8.0 Hz, 1H, arom. CH Mant); 5.62 (d, J = 7.4 Hz, 1H, OCONH); 5.50 (t, J = 7.0 Hz, 1H, CH Far); 5.16 (t, J = 8.1 Hz, 1H, CH Far); 5.10 (t, J = 6.5 Hz, 1H, CH Far); 4.81-4.84 (m, 1H, $\alpha$-CH); 4.62-4.67 (m, 2H, 2 * $\alpha$-CH), 4.63 (s, 2H, CO$_2$CH$_2$); 4.35-4.50 (m, 3H, Fmoc OCH$_2$, $\alpha$-CH); 4.21 (t, J = 6.6 Hz, 1H, Fmoc CH); 3.90-4.10 (m, 2H, $\alpha$-CH$_2$ Gly);
3.75-3.79 (m, 1H, δ-CH₂ Pro); 3.71 (s, 3H, OCH₃); 3.61-3.65 (m, 1H, δ-CH₂ Pro); 3.16 (dd, J = 8.2, 13.1 Hz, 1H, α-CH₂ Far); 3.06 (dd, J = 7.2, 13.0 Hz, 1H, α-CH₂ Far); 2.93 (dd, J = 4.8, 13.8 Hz, 1H, β-CH₂ Cys); 2.90 (s, 3H, NHCH₃); 2.72 (dd, J = 7.0, 13.8 Hz, 1H, β-CH₂ Cys); 2.54 (br s, 2H, γ-CH₂ Met); 2.09 (s, 3H, SCH₃); 1.94-2.30 (m, 12H, 4 * CH₂ Far, β-CH₂ Met, β-CH₂ Pro); 1.72 (s, 3H, CH₃ Far); 1.66-1.68 (m, partially obscured, 3H, γ-CH₂ Pro, γ-CH Leu); 1.64 (s, 3H, CH₃ Far); 1.60 (s, 3H, CH₃ Far); 1.53-1.59 (m, 2H, β-CH₂ Leu); 0.94 (d, J = 6.4 Hz, 3H, 1 * ω-CH₃ Leu); 0.91 (d, J = 6.4 Hz, 3H, 1 * ω-CH₃ Leu). ¹³C NMR (125.6 MHz, CDCl₃): δ 171.8; 171.6; 171.1; 168.3; 168.2 (5 * C=O); 156.1 (OCONH); 151.9 (arom. quart. CNH); 143.7; 143.5; 141.1 (3 * arom. quart. C Fmoc); 139.7; 134.6 (2 * quart. C Far); 134.4; 131.4 (2 * arom. CH Mant); 130.1 (quant. C Far); 128.8 (CH Far); 127.6; 126.9; 125.0 (3 * arom. CH Fmoc); 124.1; 119.8 (2 * CH Far); 119.5 (arom. CH Fmoc), 114.1; 110.6 (2 * arom. CH Mant); 109.9 (arom. quart. CCO₂); 69.7 (CO₂CH₂); 66.9 (OCH₂ Fmoc); 59.6 (α-CH Pro); 53.7 (α-CH Met); 52.2 (OCH₃); 52.1 (α-CH Cys); 48.6 (α-CH Leu); 47.4 (δ-CH₂ Pro); 47.0 (CH Fmoc); 42.8 (α-CH₂ Gly); 41.7 (β-CH₂ Leu); 39.5 (α-CH₂ Far); 38.9 (CH₂ Far); 32.5 (β-CH₂ Cys); 32.0 (CH₂ Met); 29.9 (2 signals overlapped, CH₂ Far, CH₂ Met); 29.4 (NHCH₃); 28.5 (β-CH₂ Pro); 26.4; 26.2 (2 * CH₂ Ger); 24.7 (γ-CH₂ Pro); 24.4 (γ-CH Leu); 23.1; 21.9 (2 * ω-CH₃ Leu); 16.0; 15.9 (2 * CH₃ Far); 15.1 (SCH₃); 13.9 (CH₃ Far). MS (FAB; 3-NBA) m/z: found 1109.0 (M+H)⁺.

L-Methionylglycyl-L-leucyl-L-prolyl-S-farnesyl-L-cysteine methyl ester (H-Met-Gly-Leu-Pro-Cys(Far)-OMe) (22c): H-Met-Gly-Leu-Pro-Cys-(Far)-OMe 22c was synthesized as described previously.²¹a
L-Methionylglycyl-L-leucyl-L-prolyl-S-[(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7-
dimethyl-2,6-octandienyl]-L-cysteine methyl ester (H-Met-Gly-Leu-Pro-Cys(Ger/Mant)-
OMe) (22a): This compound was prepared utilizing the standard Fmoc deprotection
procedure using the pentapeptide 21a (130 mg, 0.125 mmol). Purification by flash
chromatography on silica gel starting with ethyl acetate, followed by ethyl acetate/methanol
(80:20), yielded 95 mg (93%) of the desired product 22a as a colorless oil. \( R_f = 0.2 \) (ethyl
acetate/methanol 95:5). \([\alpha]_D^{22} = -43.1 \) (c = 1.0, CH\(_2\)OH). \(^1\)H NMR (500 MHz, CDCl\(_3\)/CD\(_2\)OD
5:1): \( \delta \) 7.83 (dd, \( J = 1.5, 8.0 \) Hz, 1H, arom. CH); 7.70 (d, \( J = 7.7 \) Hz, 1H, CONH); 7.56 (d, \( J = 7.5 \) Hz, 1H, CONH); 7.29-7.32 (m, 2H, arom. CH, CONH); 6.60 (d, \( J = 8.4 \) Hz, 1H, arom.
CH); 6.51 (t, \( J = 7.5 \) Hz, 1H, arom. CH); 5.43 (t, \( J = 6.6 \) Hz, 1H, CH Ger); 5.13 (t, \( J = 7.2 \) Hz,
1H, CH Ger); 4.61 (m, 1H, \( \alpha-\)CH); 4.55 (s, 3H, \( \alpha-\)CH, CO\(_2\)CH\(_2\)); 4.46-4.49 (m, 1H, \( \alpha-\)CH);
4.04 (obscured by MeOH, 2H, \( \alpha-\)CH\(_2\) Gly); 3.72-3.76 (m, 1H, \( \delta-\)CH\(_{2a}\) Pro); 3.68 (s, 3H,
OCH\(_3\)); 3.51-3.55 (m, 1H, \( \delta-\)CH\(_{2b}\) Pro); 3.28 (br, 1H, \( \alpha-\)CH Met); 3.12 (dd, \( J = 8.3, 13.6 \) Hz,
1H, \( \alpha-\)CH\(_{2a}\) Ger); 3.04 (m, 1H, \( \alpha-\)CH\(_{2b}\) Ger); 2.88 (dd, \( J = 5.0, 13.7 \) Hz, 1H, \( \beta-\)CH\(_{2a}\) Cys);
2.83 (s, 3H, NHCH\(_3\)); 2.72 (dd, \( J = 7.0, 13.8 \) Hz, 1H, \( \beta-\)CH\(_{2b}\) Cys); 2.55 (t, \( J = 7.4 \) Hz, 2H, \( \gamma-
CH\(_2\) Met); 1.91-2.12 (m, 10H, 2 * CH\(_2\) Ger, \( \beta-\)CH\(_2\) Met, \( \beta-\)CH\(_2\) Pro, \( \gamma-\)CH\(_2\) Pro); 2.06 (s, 3H,
SCH\(_3\)); 1.76 (m, 1H, \( \gamma-\)CH Leu); 1.65 (s, 3H, CH\(_3\) Ger); 1.60 (s, 3H, CH\(_3\) Ger); 1.40-1.65 (m,
2H, \( \beta-\)CH\(_2\) Leu); 0.88 (d, \( J = 5.2 \) Hz, 6H, 2 * \( \omega-\)CH\(_3\) Leu). \(^13\)C NMR (125.6 MHz, CDCl\(_3\)): \( \delta \)
172.9; 171.9; 171.5; 169.5; 169.4; 168.7 (6 * C=O); 152.2 (arom. quart. CNH); 139.7 (quart. 
C Ger); 134.9; 131.7 (2 * arom. CH); 130.8 (quart. C Ger); 128.6; 120.1 (2 * CH Ger); 114.6;
111.0 (2 * arom. CH); 110.1 (arom. quart. CO\(_2\)); 69.9 (CO\(_2\)CH\(_2\)); 60.2 (\( \alpha-\)CH Pro); 52.8 (\( \alpha-\)
CH Met); 52.7 (OCH\(_3\)); 52.3 (\( \alpha-\)CH Cys); 49.8 (\( \alpha-\)CH Leu); 47.5 (\( \delta-\)CH\(_2\) Pro); 42.7 (\( \alpha-\)CH
Gly); 40.6 (\( \beta-\)CH\(_2\) Leu); 39.2 (\( \alpha-\)CH\(_2\) Ger); 32.9 (\( \beta-\)CH\(_2\) Cys); 30.4 (CH\(_2\) Met); 29.8 (CH\(_2\)
Ger); 29.5 (NHCH\(_3\)); 29.2 (CH\(_2\) Met); 28.4 (\( \beta-\)CH\(_2\) Pro); 26.3 (CH\(_2\) Ger); 25.0 (\( \gamma-\)CH\(_2\) Pro);
24.8 (γ-CH Leu); 23.3; 21.5 (2 * ω-CH3 Leu); 16.1 (CH3 Ger); 15.0 (SCH3); 14.1 (CH3 Ger).

HRMS (FAB; 3-NBA) m/z: calcd for (M+H)+ C48H62N6O8S2 819.4218, found 819.4149.

L-Methionylglycyl-L-leucyl-L-prolyl-S-[(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7,11-trimethyl-2,6,10-dodecatriene]-L-cysteine methyl ester (H-Met-Gly-Leu-Pro-Cys(Far/Mant)-OMe) (22b): This compound was prepared utilizing the standard Fmoc deprotection procedure using the pentapeptide 21b (100 mg, 0.09 mmol). Purification on silica gel using ethyl acetate, followed by ethyl acetate/methanol (90:10) as eluents, yielded 75 mg (94%) of the desired product 22b as a colorless oil. Rf = 0.23 (ethyl acetate/methanol 9:1). [α]D22 = -45.1 (c = 1.0, CH3OH). 1H NMR (500 MHz, CDCl3): δ 7.80-7.94 (m, 3H, arom. CH, 2 * CONH); 7.70 (d, J = 4.9 Hz, 1H, NH); 7.63 (br s, 1H, CONH); 7.35 (t, J = 7.4 Hz, 1H, arom. CH); 6.64 (d, J = 8.5 Hz, 1H, arom. CH); 6.56 (t, J = 7.6 Hz, 1H, arom. CH); 5.48 (t, J = 6.9 Hz, 1H, CH Far); 5.14 (t, J = 7.5 Hz, 1H, CH Far); 5.09 (t, J = 6.6 Hz, 1H, CH Far); 4.94 (br s, 1H, α-CH); 4.67-4.70 (m, 1H, α-CH); 4.61 (s, 2H, CO2CH2); 4.55-4.58 (m, 1H, α-CH); 4.11-4.16 (m, 2H, α-CH2 Gly); 3.83-3.86 (m, 1H, δ-CH2a Pro); 3.69 (s, 3H, OCH3); 3.63-3.66 (m, 1H, δ-CH2b Pro); 3.50 (dd, J = 4.5, 8.3 Hz, 1H, α-CH Met); 3.16 (dd, J = 8.5, 13.1 Hz, 1H, α-CH2a Far); 3.01 (dd, J = 6.9, 13.1 Hz, 1H, α-CH2b Far); 2.80 (d, J = 4.9 Hz, 3H, NHCH3); 2.70-2.89 (m, 1H, β-CH2a Cys); 2.65 (dd, J = 8.0, 13.8 Hz, 1H, β-CH2b Cys); 2.55-2.60 (m, 2H, γ-CH2 Met); 2.08 (s, 3H, SCh3); 1.90-2.20 (m, 16H, NH2, 4 * CH2 Far, β-CH2 Met, β-CH2 Pro, γ-CH2 Pro); 1.70 (s, 3H, CH3 Far); 1.63 (s, 3H, CH3 Far); 1.58 (s, 3H, CH3 Far); 1.55-1.70 (m, partially obscured, 3H, β-CH2 Leu, γ-CH Leu); 0.94 (m, 6H, 2 * ω-CH3 Leu). 13C NMR (125.6 MHz, CDCl3): δ 175.3; 171.8; 171.2; 168.5; 168.4 (5 * C=O); 152.0 (arom. quart. CNH); 139.8; 134.8 (2 * quart. C Far); 134.6; 131.5 (2 * arom. CH); 130.2 (quart. C Far); 129.0; 124.2; 119.6 (3 * CH Far); 114.2; 110.6 (2 * arom. CH); 110.0 (arom.
quart. CO$_2$); 69.8 (CO$_2$CH$_2$); 59.7 (α-CH Pro); 54.3 (α-CH Met); 52.3 (2 signals overlapped, OCH$_3$, α-CH Cys); 48.4 (α-CH Leu); 47.6 (δ-CH$_2$ Pro); 42.8 (α-CH$_2$ Gly); 42.1 (β-CH$_2$ Leu); 39.6 (α-CH$_2$ Far); 39.1 (CH$_2$ Far); 34.0 (β-CH$_2$ Cys); 32.4 (CH$_2$ Met); 30.6 (CH$_2$ Far); 29.5 (2 signals overlapped, CH$_2$ Met, NHCH$_3$); 29.5 (β-CH$_2$ Pro); 26.5; 26.3 (2 * CH$_2$ Far); 24.7 (γ-CH$_2$ Pro); 24.5 (γ-CH Leu); 23.3; 22.0 (2 * ω-CH$_3$ Leu); 16.1; 16.0 (2 * CH$_3$ Far); 15.3 (SCH$_3$); 14.0 (CH$_3$ Far). HRMS (FAB; 3-NBA) $m/z$: calcd for (M+H)$^+$ C$_{43}$H$_{71}$N$_6$O$_8$S$_2$ 887.4775, found 887.4904.

$N$-(6-Maleimidocaproyl)-L-methionylglycyl-L-leucyl-L-prolyl-S-farnesyl-L-cysteine methyl ester (MIC-Met-Gly-Leu-Pro-Cys(Far)-OMe) (41c): This compound was prepared following the standard coupling procedure using the pentapeptide 22c (57 mg, 0.08 mmol) and maleimidocaproic acid 3 (18 mg, 0.09 mmol, 1.1eq.). The compound was purified by flash chromatography on silica gel starting with ethyl acetate, followed by ethyl acetate/methanol (10:1) as eluents, furnished 56 mg (78%) of the desired target molecule 41c as a colorless amorphous solid. $R_f$ = 0.35 (ethyl acetate). $[α]$$_D$$^{22}$ = -149.0 ($c$ = 0.5, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.76 (d, $J$ = 8.5 Hz, 1H, CONH); 7.63 (d, $J$ = 7.5 Hz, 1H, CONH); 7.29 (t, $J$ = 4.8 Hz, 1H, CONH); 6.69 (s, 2H, CH=CH MIC); 6.65 (d, $J$ = 7.7 Hz, 1H, CONH); 5.17 (t, $J$ = 7.6 Hz, 1H, CH Far); 5.07-5.09 (m, 2H, 2 * CH Far); 4.83-4.88 (m, 1H, α-CH); 4.64-4.68 (m, 3H, 3 * α-CH); 4.09 (dd, $J$ = 5.0, 17.4 Hz, 1H, α-CH$_2$a Gly); 4.04 (dd, $J$ = 5.1, 17.4 Hz, 1H, α-CH$_2$b Gly); 3.84-3.88 (m, 1H, δ-CH$_2$a Pro); 3.74 (s, 3H, OCH$_3$); 3.64-3.68 (m, 1H, δ-CH$_2$b Pro); 3.50 (t, $J$ = 7.2 Hz, 2H, NCH$_2$ MIC); 3.18 (dd, $J$ = 8.4, 13.2 Hz, 1H, α-CH$_2$a Far); 3.05 (dd, $J$ = 7.2, 13.2 Hz, 1H, α-CH$_2$b Far); 2.92 (dd, $J$ = 6.7, 13.8 Hz, 1H, β-CH$_2$a Cys); 2.70 (dd, $J$ = 7.3, 13.8 Hz, 1H, β-CH$_2$b Cys); 2.48-2.52 (m, 2H, γ-CH$_2$ Met); 2.20-2.26 (m, 3H, α-CH$_2$ MIC, β-CH$_2$a Met); 2.09 (s, 3H, SCH$_3$); 2.01-2.16 (m, 9H, β-CH$_2$b Met, β-CH$_2$
Pro, γ-CH₂ Pro, 2 * CH₂ Far); 1.91-1.98 (m, 4H, 2 * CH₂ Far); 1.68 (s, 3H, CH₃ Far); 1.66 (s, 3H, CH₃ Far); 1.60 (s, 6H, 2 * CH₃ Far); 1.52-1.73 (m, 7H, 2 * CH₂ MIC, β-CH₂ Leu, γ-CH Leu); 1.26-1.34 (m, 2H, CH₂ MIC); 0.94 (t, J = 7.0 Hz, 6H, 2 * ω-CH₃ Leu). ¹³C NMR (125.6 MHz, CDCl₃): δ 173.0; 172.2; 171.7; 171.4; 171.2; 170.8; 168.3 (7 * C=O); 139.9; 135.3 (2 * quart. C Far); 134.1 (CH=CH MIC); 131.3 (quart. C Far); 124.3; 123.7; 119.6 (3 * CH Far); 59.8 (α-CH Pro); 52.4 (OCH₃); 52.1; 52.0 (α-CH Met, α-CH Cys); 48.9 (α-CH Leu); 47.5 (δ-CH₂ Pro); 42.9 (α-CH₂ Gly); 41.7 (β-CH₂ Leu); 39.7 (α-CH₂ Far); 37.6 (NCH₂ MIC); 36.1 (α -CH₂ MIC); 32.8 (β-CH₂ Cys); 31.8; 30.1 (2 * CH₂ Met); 29.5 (CH₂ Far); 28.3; 28.2 (β-CH₂ Pro, CH₂ MIC); 26.7; 26.5 (2 * CH₂ Far); 26.3 (CH₂ MIC); 25.7 (CH₃ Far); 24.9; 24.8 (CH₂ MIC, γ-CH₂ Pro); 24.6 (γ-CH Leu); 23.3; 21.9 (2 * ω-CH₃ Leu); 17.7; 16.1; 16.0 (3 * CH₃ Far); 15.3 (SCH₃). HRMS (FAB; 3-NBA) m/z: calcd for (M+H)⁺ C₄₇H₇₅N₆O₂S₂ 931.5037, found 931.4871.

N-(6-Maleimidocaproyl)-L-methionylglycyl-L-leucyl-L-prolyl-S-[(E,E)-8-O-(2-N-methylaminobenzoyl)-3,7-dimethyl-2,6-octadiene]-L-cysteine methyl ester (MIC-Met-Gly-Leu-Pro-Cys(Ger/Mant)-OMe) (41a): This compound was prepared following the standard coupling procedure using the pentapeptide 22a (64 mg, 0.08 mmol) and maleimidocaproic acid 3 (18 mg, 0.09 mmol, 1.1 eq.). The compound was purified by flash chromatography on silica gel starting with ethyl acetate, followed by ethyl acetate/methanol (98:2), and furnished 44 mg (55%) of the desired target molecule 41a as a colorless oil. Rf = 0.33 (ethyl acetate/methanol 98:2). [α]D²² = -41.6 (c = 1.0, CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃): δ 7.90 (dd, J = 1.6, 8.0 Hz, 1H, arom. CH); 7.58-7.62 (m, 2H, CONH, NH); 7.57 (d, J = 7.6 Hz, 1H, arom. CH); 7.36 (m, 1H, arom. CH); 7.24 (br s, 1H, CONH); 6.67 (s, 2H, CH=CH MIC); 6.64 (d, J = 8.5 Hz, 1H, arom. CH); 6.55-6.57 (m, 2H, arom. CH, CONH); 5.46-5.49 (m, 1H, CH
Ger); 5.17 (t, J = 8.2 Hz, 1H, CH Ger); 4.83 (dt, J = 4.4, 9.1 Hz, 1H, α-CH); 4.59-4.66 (m, 3H, 3 * α-CH); 4.61 (s, 2H, CO₂CH₂); 4.00-4.06 (m, 2H, α-CH₂ Gly); 3.80-3.84 (m, 1H, δ-CH₂a Pro); 3.71 (s, 3H, OCH₃); 3.62-3.66 (m, 1H, δ-CH₂b Pro); 3.48 (t, J = 7.2 Hz, 2H, NCH₂ MIC); 3.16 (dd, J = 8.3, 13.2 Hz, 1H, α-CH₂a Ger); 3.04 (dd, J = 7.2, 13.2 Hz, 1H, α-CH₂b Ger); 2.90 (partially obscured, 1H, β-CH₂a Cys); 2.89 (d, J = 4.8 Hz, 3H, NHCH₃); 2.70 (dd, J = 7.3, 13.8 Hz, 1H, β-CH₂b Cys); 2.50-2.55 (m, 2H, γ-CH₂ Met); 2.12-2.25 (m, 3H, β-CH₂a Met, α-CH₂ MIC); 2.08 (s, 3H, SCH₃); 1.72-2.11 (m, 9H, 2 * CH₂ Ger, β-CH₂b Met, β-CH₂ Pro, γ-CH₂ Pro); 1.70 (s, 3H, CH₃ Ger); 1.65 (s, 3H, CH₃ Ger); 1.50-1.70 (m, 6H, 2 * CH₂ MIC, γ-CH Leu, β-CH₂a Leu); 1.23-1.31 (m, 3H, CH₂ MIC, β-CH₂b Leu); 0.93 (d, J = 6.5 Hz, 3H, 1 * ω-CH₃ Leu); 0.91 (d, J = 6.5 Hz, 3H, 1 * ω-CH₃ Leu). ¹³C NMR (125.6 MHz, CDCl₃): δ 173.1; 172.3; 171.7; 171.3; 171.2; 170.9 (2 signals overlapped); 168.4; 168.4 (9 * C=O); 152.1 (arom. quart. CNH); 139.4 (quart. C Ger); 134.6 (arom. CH); 134.1 (CH=CH MIC); 131.5 (arom. CH); 130.7 (quart. C Ger); 128.4; 120.0 (2 * CH Ger); 114.3; 110.7 (2 * arom. CH); 110.0 (arom quart. C=O₂); 69.7 (CO₂CH₂); 59.8 (α-CH Pro); 52.5; 52.2 (α-CH Met, α-CH Cys); 52.0 (OCH₃); 48.9 (α-CH Leu); 47.5 (δ-CH₂ Pro); 42.9 (α-CH₂ Gly); 41.7 (β-CH₂ Leu); 39.1 (α-CH₂ Ger); 37.6 (NCH₂ MIC); 36.1 (α-CH₂ MIC); 32.9 (β-CH₂ Cys); 31.5; 30.1 (3 signals 2 * CH₂ Met, CH₂ Ger); 29.5 (NHCH₃); 28.2 (2 signals overlapped, CH₂ MIC, β-CH₂ Pro); 26.3 (CH₂ Ger); 26.2 (CH₂ MIC); 24.9; 24.8 (γ-CH₂ Pro, CH₂ MIC); 24.6 (γ-CH Leu); 23.3; 21.9 (2 * ω-CH₃ Leu); 16.1 (CH₃ Ger); 15.3 (SCH₃); 14.0 (CH₃ Ger).

HRMS (FAB; 3-NBA) m/z: calcd for (M+H)⁺ C₅₀H₇₄N₇O₁₁S₂ 1012.489, found 1012.465.

N-(6-Maleimidocaproyl)-L-methionylglycyl-L-leucyl-L-prolyl-S-[(E,E)-8-O-(2-N-methylaminobenzoyl)-3,7,11-trimethyl-2,6,10-dodecatriene]-L-cysteine methyl ester (MIC-Met-Gly-Leu-Pro-Cys(Far/Mant)-OMe) (41b): This compound was prepared following the
standard coupling procedure using the pentapeptide 22b (72 mg, 0.085 mmol) and maleimidocaproic acid 3 (19 mg, 0.09 mmol, 1.1 eq.). The compound was purified by flash chromatography on silica gel using gradient elution starting with ethyl acetate, followed by ethyl acetate/methanol (98:2) and finally with ethyl acetate/methanol (95:5). The last eluent provided the desired target molecule 41b, 63.9 mg (73%), as a colorless oil. \( R_f = 0.54 \) (ethyl acetate/methanol 98:2). [\( \alpha \)]\textsubscript{D}\textsuperscript{22} = -39.2 (c = 1.0, CH\textsubscript{3}OH). \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 7.91 (d, \( J = 8.0 \) Hz, 1H, arom. CH) 7.64 (br s, 1H, NH); 7.46 (d, \( J = 7.5 \) Hz, 1H, CONH); 7.37 (t, \( J = 8.5 \) Hz, 1H, arom. CH); 7.20 (br s, 1H, CONH); 7.10 (br s, 1H, CONH); 6.68 (s, 2H, CH=CH MIC); 6.66 (d, \( J = 8.5 \) Hz, 1H, arom. CH); 6.57 (t, \( J = 8.0 \) Hz, 1H, arom. CH); 6.49 (br s, 1H, CONH); 5.50 (t, \( J = 6.5 \) Hz, 1H, CH Far); 5.16 (t, \( J = 7.7 \) Hz, 1H, CH Far); 5.10 (t, \( J = 6.6 \) Hz, 1H, CH Far); 4.79-4.82 (m, 1H, \( \alpha \)-CH); 4.58-4.72 (m, 3H, 3 \( \times \) \( \alpha \)-CH); 4.63 (s, 2H, CO\textsubscript{2}CH\textsubscript{2}); 4.08 (dd, \( J = 5.3 \), 16.9Hz, 1H, \( \alpha \)-CH\textsubscript{2a} Gly); 3.94 (dd, \( J = 4.9 \), 16.9 Hz, 1H, \( \alpha \)-CH\textsubscript{2b} Gly); 3.78-3.82 (m, 1H, \( \delta \)-CH\textsubscript{2a} Pro); 3.73 (s, 3H, OCH\textsubscript{3}); 3.60-3.63 (m, 1H, \( \delta \)-CH\textsubscript{2b} Pro); 3.50 (t, \( J = 7.1 \) Hz, 2H, NCH\textsubscript{2} MIC); 3.04-3.24 (m, 2H, \( \alpha \)-CH\textsubscript{2} Far); 2.94 (dd, \( J = 4.7 \), 13.7Hz, 1H, \( \beta \)-CH\textsubscript{2a} Cys); 2.90 (s, 3H, NHCH\textsubscript{3}); 2.73 (dd, \( J = 6.9 \) Hz, 13.7 Hz, 1H, \( \beta \)-CH\textsubscript{2b} Cys); 2.54 (m, 2H, \( \gamma \)-CH\textsubscript{2} Met); 2.10 (s, 3H, S\textsubscript{CH\textsubscript{3}}); 1.81-2.29 (m, 16H, 4 \( \times \) CH\textsubscript{2} Far, \( \alpha \)-CH\textsubscript{2} MIC, \( \beta \)-CH\textsubscript{2} Met, \( \beta \)-CH\textsubscript{2} Pro, \( \gamma \)-CH\textsubscript{2} Pro); 1.71 (s, 3H, CH\textsubscript{3} Far); 1.65 (s, 3H, CH Far); 1.60 (s, 3H, CH\textsubscript{3} Far); 1.50-1.73 (m, 6H, 2 \( \times \) CH\textsubscript{2} MIC, \( \beta \)-CH\textsubscript{2a} Leu, \( \gamma \)-CH Leu); 1.25-1.33 (m, 3H, CH\textsubscript{2} MIC, \( \beta \)-CH\textsubscript{2b} Leu); 0.95 (d, \( J = 6.4 \) Hz, 3H, 1 \( \times \) \( \omega \)-CH\textsubscript{3} Leu); 0.92 (d, \( J = 6.4 \) Hz, 3H, 1 \( \times \) \( \omega \)-CH\textsubscript{3} Leu).

\(^1\)C NMR (125.6 MHz, CDCl\textsubscript{3}): \( \delta \) 173.0; 172.2; 171.6; 171.3; 171.2; 170.8 (2 signals overlapped); 168.4; 168.3 (9 \( \times \) C=O); 152.0 (arom. quart. CNH); 139.9; 134.8 (2 \( \times \) quart. C Far); 134.6 (arom. CH); 134.0 (CH=CH MIC); 131.5 (arom. CH); 130.2 (quart. C Far); 128.9; 124.1; 119.5 (3 \( \times \) CH Far); 114.2; 110.6 (2 \( \times \) arom. CH); 110.0 (arom. quart. CCO\textsubscript{2}); 69.8 (CO\textsubscript{2}CH\textsubscript{2}); 59.8 (\( \alpha \)-CH Pro); 52.4 (OCH\textsubscript{3}); 52.2; 52.0 (\( \alpha \)-CH Met, \( \alpha \)-CH Cys); 48.9 (\( \alpha \)-CH
Leu); 47.4 (δ-CH2 Pro); 42.9 (α-CH2 Gly); 41.6 (β-CH2 Leu); 39.6 (α-CH2 Far); 39.0 (CH2 Far); 37.5 (NCH2 MIC); 36.1 (α-CH2 MIC); 32.8 (β-CH2 Cys); 31.6; 30.1 (2 * CH2 Met); 29.5 (NHCH3); 28.2 (2 signals overlapped, CH2 MIC, β-CH2 Pro); 26.5; 26.3; 26.2 (CH2 Far, 2 * CH2 MIC); 24.9; 24.8 (γ-CH2 Pro, CH2 MIC); 24.6 (γ-CH Leu); 23.3; 21.9 (2 * ω-CH3 Leu); 16.1; 16.0 (2 * CH3 Far); 15.2 (SCH3); 14.0 (CH3 Far). HRMS (FAB; 3-NBA) m/z: calcd for (M+H)+ C55H82N7O11S2 1080.551, found 1080.516.

L-Cystine bis-(allyl ester) bis-(hydrotosylate) [(TosOH *(H-Cys-OAll)2]: (TosOH *(H-Cys-OAll)2 was synthesized as described previously.37

Bis-(N-tert-Butyloxycarbonylglycyl)-L-cystine bis-(allyl ester) [(Boc-Gly-Cys-OAll)2] (23a): (Boc-Gly-Cys-OAll)2 23a was synthesized as described previously.13c

L-Cystine bis-(tert-butyl ester) [(H-Cys-O'Bu)2]: (H-Cys-O'Bu)2 was synthesized as described previously.38

Bis-(N-Allyloxycarbonylglycyl)-L-cystine bis-(tert-butyl ester) [(Aloc-Gly-Cys-O'Bu)2] (23b): The standard coupling procedure were used to synthesize (Aloc-Gly-Cys-O'Bu)2 23b using Aloc-Gly-OH (1.2 g, 9 mmol) and (H-Cys-O'Bu)2 (1.128 g, 3.2 mmol) Purification by flash chromatography on silica gel using ethyl acetate as eluent yielded 1.50 g (74%) of the desired product 23b as a white foam. Rf = 0.2 (hexane/ethyl acetate 1:1). [α]D22 = -46.5 (c = 0.7, CH3OH). 1H NMR (500 MHz, CDCl3): δ 7.14 (d, J = 6.9 Hz, 2H, 2 * CONH); 5.58-5.95 (m, 4H, 2 * OCONH, CH=CH2); 5.30 (dd, J = 0.9, 17.2 Hz, 2H, CH=CH2a); 5.20 (dd, J = 1.1, 10.4 Hz, 2H, CH=CH2b); 4.71 (dd, J = 5.3, 12.4 Hz, 2H, 2 * α-CH Cys), 4.58 (d, J = 5.4 Hz,
4H, 2 * OCH₃); 3.85-4.01 (m, 4H, 2 * α-CH₂ Gly); 3.15 (d, J = 5.1 Hz, 4H, 2 * β-CH₂ Cys); 1.45 (s, 18H, C(CH₃)₃). ¹³C NMR (125.6 MHz, CDCl₃): δ 169.5; 168.9 (4 * C=O); 156.6 (2 * OCONH); 132.6 (2 * CH=CH₂); 117.6 (2 * CH=CH₂); 82.9 (2 * C(CH₃)₃); 65.8 (2 * OCH₂); 52.5 (2 * α-CH Cys); 44.2 (2 * α-CH₂ Gly); 41.1 (2 * β-CH₂ Cys); 27.8 (2 * C(CH₃)₃). MS (EI) m/z (rel. intensity) 634 (M⁺, 0.5), 332 (17), 174 (43), 151 (90), 142 (39), 118 (100), 57 (28), 41 (29). HRMS (EI) m/z: calcd for (M⁺) C₂₅H₄₂N₄O₁₀S₂ 634.2342, found 634.2322. Anal. Calcd: C, 49.20; H, 6.67; N, 8.83. Found: C, 49.05; H, 6.56; N, 8.79.

*N-tert-Butyloxycarbonylglycyl-S-palmitoyl-L-cysteine allyl ester* (Boc-Gly-Cys(Pal)-OAll) (24a): Boc-Gly-Cys(Pal)-OAll 24a was synthesized as described previously.¹³c

*N-tert-Butyloxycarbonylglycyl-S-palmitoyl-L-cysteine* (Boc-Gly-Cys(Pal)-OH) (32): Boc-Gly-Cys(Pal)-OH 32 was synthesized as described previously.¹³c

Glycyl-S-palmitoyl-L-cysteine Hydrotrifluoroacetate (TFA * H-Gly-Cys(Pal)-OH) (35): TFA * H-Gly-Cys(Pal)-OH 35 was synthesized as described previously.¹³c

*N-(6-Maleimidocaproyl)-glycyl-S-palmitoyl-L-cysteine* (MIC-Gly-Cys(Pal)-OH) (29): To a solution of maleimidocaproylic acid 3 (44 mg, 0.2 mmol) in 10 mL CH₂Cl₂ (10 mL) were added HOBT (28 mg, 0.2 mmol) and EDC (39 mg, 0.2 mmol) at room temperature. After 30 min this solution was poured into a mixture of the dipeptide 35 (93 mg, 0.2 mmol) and triethylamine (53.1 µL, 0.4 mmol, 2 eq.) in CH₂Cl₂ (7 mL) with trifluoroethanol (3 mL). After stirring for 15 h at room temperature, this solution was poured into CH₂Cl₂ (100 mL), washed with 0.5 M HCl (3 x 50 mL) and brine (50 mL). The solution was dried over MgSO₄, and the
solvent was removed under reduced pressure. The crude compound was purified by flash chromatography on silica gel using gradient elution starting with ethyl acetate, followed by ethyl acetate/methanol (10:1), and finally ethanol and furnished 66 mg (62%) of the desired compound 29 as a colorless amorphous solid. \( R_f = 0.65 \) (chloroform/methanol/water 35:10:1). 
\[ \alpha \] \(_D\) = -10.7 (c = 1.4, CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)/CD\(_3\)OD 5:1): \( \delta \) 6.74 (s, 2H, CH=CH MIC); 4.33-4.37 (m, 1H, \( \alpha \)-CH Cys); 3.96 (d, \( J = 16.4 \) Hz, 1H, \( \alpha \)-CH\(_2\)a Gly); 3.73 (d, \( J = 16.5 \) Hz, 1H, \( \alpha \)-CH\(_2b\) Gly); 3.51 (t, \( J = 7.2 \) Hz, 2H, NCH\(_2\) MIC); 3.42-3.46 (m, 1H, \( \beta \)-CH\(_2\)a Cys); 3.19 (dd, \( J = 9.5, 13.8 \) Hz, 1H, \( \beta \)-CH\(_2b\) Cys); 2.55 (t, \( J = 7.5 \) Hz, 2H, \( \alpha \)-CH\(_2\) Pal); 2.30 (t, \( J = 7.5 \) Hz, 2H, \( \alpha \)-CH MIC); 1.57-1.71 (m, 6H, \( \beta \)-CH\(_2\) Pal, 2 * CH\(_2\) MIC); 1.26 (s, br, 24H, (CH\(_2\))\(_{12}\) Pal); 1.26-1.36 (m, 2H, CH\(_2\) MIC); 0.88 (t, \( J = 6.8 \) Hz, 3H, \( \omega \)-CH\(_3\) Pal). \(^{13}\)C NMR (125.6 MHz, CDCl\(_3\)/CD\(_3\)OD 5:1): \( \delta \) 201.0 (COSC); 177.2; 175.4; 171.4; 171.0 (4 * C=O); 134.4 (CH=CH MIC); 55.2 (\( \alpha \)-CH Cys); 44.2 (\( \beta \)-CH\(_2\) Cys); 43.2 (\( \alpha \)-CH\(_2\) Gly); 37.8 (NCH\(_2\) MIC); 35.9 (\( \alpha \)-CH\(_2\) MIC); 32.1; 30.5; 29.9; 29.7; 29.6; 29.3; 28.5; 26.5; 25.8; 25.1; 22.9 (8 * CH\(_2\) Pal, 3 * CH\(_2\) MIC); 14.2 (\( \omega \)-CH\(_3\) Pal). MS (MALDI; DHBA) \( m/z \): calcd for (M+H)+ \( C_{31}H_{52}N_{3}O_{7}S \) 610.35, found 610.30.

**N-(6-Maleimidocaproyl)-glycyl-S-palmitoyl-L-cysteyl-L-methionylglycyl-L-leucyl-L-prolyl-S-farnesyl-L-cysteine methyl ester (MIC-Gly-Cys(Pal)-Met-Gly-Leu-Pro-Cys(Far)-OMe) (43c)**: This compound was prepared following the standard coupling procedure using the pentapeptide 22e (42 mg, 0.06 mmol) and MIC-Gly-Cys(Pal)-OH 29 (35 mg, 0.06 mmol). The compound was purified by size exclusion chromatography on Sephadex LH 20 with chloroform/methanol (1:1) and furnished 36 mg (48%) of the desired target molecule 43c as a colourless amorphous solid. \( R_f = 0.65 \) (ethyl acetate/methanol 10:1). \( \alpha \) \( _D \) = -60.8 (c = 1.4, CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 8.00 (d, \( J = 6.7 \) Hz, 1H, CONH);
7.66 (d, J = 7.6 Hz, 1H, CONH); 7.55 (d, J = 7.6 Hz, 1H, CONH); 7.52 (t, J = 7.0 Hz, 1H, CONH); 7.12 (d, J = 7.4 Hz, 1H, CONH); 6.69 (s, 2H, CH=CH MIC); 6.57 (br, 1H, CONH); 5.15 (t, J = 8.0 Hz, 1H, CH Far); 5.08-5.10 (m, 2H, 2 * CH Far); 4.75-4.78 (m, 1H, α-CH Leu); 4.70-4.73 (m, 1H, α-CH CysFar); 4.56-4.60 (m, 2H, α-CH Pro, α-CH CysPal); 4.38 (dd, J = 7.7, 16.9 Hz, 1H, α-CH2a Gly); 4.29-4.33 (m, 1H, α-CH Met); 3.96 (dd, J = 4.4, 16.6 Hz, 1H, α-CH2a Gly’); 3.81-3.87 (m, 2H, α-CH2b Gly’, δ-CH2a Pro); 3.75 (s, 3H, OCH3); 3.56-3.61 (m, 2H, α-CH2b Gly, δ-CH2b Pro); 3.51 (t, J = 7.1 Hz, 2H, NCH2 MIC); 3.20-3.27 (m, 2H, β-CH2 CysPal); 3.15 (dd, J = 8.2, 13.2 Hz, 1H, α-CH2a Far); 3.05 (dd, J = 7.3, 13.2 Hz, 1H, α-CH2b Far); 2.95 (dd, J = 4.7, 13.7 Hz, 1H, β-CH2a CysFar); 2.72 (dd, J = 6.3, 13.7 Hz, 1H, β-CH2b CysFar); 2.52-2.64 (m, 4H, α-CH2 Pal, γ-CH2 Met); 2.40-2.45 (m, 1H, β-CH2a Met); 2.30-2.33 (m, 1H, β-CH2a Pro); 2.24 (t, J = 7.5 Hz, 2H, α-CH2 MIC); 2.10 (s, 3H, SCH3); 2.00-2.17 (m, 10H, β-CH2b Met, β-CH2b Pro, γ-CH2 Pro, 3 * CH2 Far); 1.95-1.98 (m, 2H, CH2 Far); 1.82-1.86 (m, 1H, γ-CH Leu); 1.71-1.77 (m, 1H, β-CH2a Leu); 1.68 (s, 3H, CH3 Far); 1.66 (s, 3H, CH3 Far); 1.60 (s, 6H, 2 * CH3 Far); 1.57-1.65 (m, 6H, β-CH2 Pal, 2 * CH2 MIC); 1.43-1.47 (m, 1H, β-CH2b Leu); 1.25 (br, 26H, (CH2)12 Pal, CH2 MIC); 0.94 (t, J = 7.1 Hz, 6H, 2 * ω-CH3 Leu); 0.88 (t, J = 7.0 Hz, 3H, ω-CH3 Pal). MS (FAB; 3-NBA) m/z: found 1328.9 (M+H)+.

**N-tert-Butyloxycarbonylglycyl-S-hexadecyl-L-cysteine allyl ester (Boc-Gly-Cys(HD)-OAll)** (25a): Boc-Gly-Cys(HD)-OAll 25a was synthesized as described previously.13c

**N-Allyloxycarbonylglycyl-S-hexadecyl-L-cysteine tert-butyl ester (Aloc-Gly-Cys(HD)-O’Bu)** (25b): The disulfide bridge in compound 23b was cleaved with DTT as has been previously reported.13c The resulting free thiol (1.4 g) was dissolved in dry DMF (12 mL) and...
the reaction was cooled to 0°C. Diisopropylethyl amine (1.2 mL, 3 eq.) was added to the solution followed by hexadecylbromide (3.5 mL, 5 eq.). The reaction was left to stir at room temperature for 5 days. After TLC had confirmed the consumption of virtually all starting material, the solvent was removed under reduced pressure. The resulting residue was taken up into ethyl acetate, filtered and the solvent removed under reduced pressure. The resulting orange oil was purified by flash chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent to yield 1.8 g (75%) of the desired compound 25b as a colorless oil. $R_f = 0.5$ (hexane/ethyl acetate 2:1). $[\alpha]_D^{22} = -13.8$ (c = 1.0, CH$_2$OH). $^1$H NMR (500 MHz, CDCl$_3$): δ 6.72 (br s, 1H, CONH); 5.87-5.94 (m, 1H, CH=CH$_2$); 5.41 (br s, 1H, OCONH); 5.31 (dd, J = 1.3, 17.2 Hz, 1H, CH=CH$_2$); 5.21 (dd, J = 1.3, 10.4 Hz, 1H, CH=CH$_2$); 4.68 (dt, J = 5.0, 7.5 Hz, 1H, α-CH Cys); 4.59 (d, J = 5.5 Hz, 2H, OCH$_2$); 3.89-3.94 (m, 2H, α-CH$_2$ Gly); 2.96 (m, 2H, β-CH$_2$ Cys); 2.50 (m, 2H, α-CH$_2$ HD); 1.53 (m, 2H, β-CH$_2$ HD); 1.47 (s, 9H, C(CH$_3$)$_3$); 1.24 (br s, 26H, (CH$_2$)$_{13}$ HD); 0.87 (t, J = 6.9 Hz, 3H, ω-CH$_3$ HD). $^{13}$C NMR (125.6 MHz, CDCl$_3$): δ 169.6; 168.9 (2 * C=O); 156.4 (OCONH); 132.6 (CH=CH$_2$); 117.6 (CH=CH$_2$); 82.6 (C(CH$_3$)$_3$); 65.8 (OCH$_2$); 52.5 (α-CH Cys); 44.3 (α-CH$_2$ Gly); 34.2 (β-CH$_2$ Cys); 32.8; 31.8; 29.6; 29.6; 29.5; 29.4; 29.3; 29.1; 28.5 (13 * CH$_2$ HD); 27.9 (C(CH$_3$)$_3$); 22.6 (CH$_2$ HD); 14.0 (ω-CH$_3$ HD). Anal. Calcd: C, 64.17; H, 10.03; N, 5.16. Found: C, 64.23; H, 9.60; N, 5.05.

*N-tert-Butyloxycarbonylglycyl-S-hexadecyl-L-cysteine (Boc-Gly-Cys(HD)-OH)* (33): Boc-Gly-Cys(HD)-OH 33 was synthesized as described previously.$^{13c}$

**Glycyl-S-hexadecyl-L-cysteine hydrotrifluoroacetate (TFA * H-Gly-Cys(HD)-OH)** (36):

TFA * H-Gly-Cys(Pal)-OH 36 was synthesized as described previously.$^{13c}$
N-(6-Maleimidocaproyl)-glycyl-S-hexadecyl-L-cysteine tert-butyl ester (MIC-Gly-Cys(HD)-O'Bu) (39): Removal of the Aloc protecting group from the dipeptide 25b was achieved following the standard Aloc deprotection procedure, however dimethylmalonate (0.17 mL, 8 eq.) was utilized instead of dimethylbarbituric acid as scavenger, using 100 mg (0.2 mmol) of 25b. Purification by flash chromatography on silica gel starting with ethyl acetate, followed by ethyl acetate/methanol (20:1) provided the desired free amine 37 as colorless oil, which was used immediately without further identification. The free amine 37 (63 mg, 0.144 mmol) was coupled with maleimidocaproic acid (35.5 mg, 0.16 mmol, 1.1 eq.) using the standard coupling procedure. The resulting orange oil was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:3) as eluent to yield 64 mg (51% over two steps) of the desired compound 39 as a colorless oil. $R_f = 0.69$ (hexane/ethyl acetate 1:3). $[\alpha]_D^{22} = -10.4$ (c = 1.0, CH$_2$OH). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.67 (s, 3H, CONH, CH=CH); 6.24 (br s, 1H, CONH); 4.65 (dt, $J = 5.1$, 7.5 Hz, 1H, $\alpha$-CH Cys); 3.98 (t, $J = 4.9$ Hz, 2H, $\alpha$-CH$_2$ Gly); 3.50 (t, $J = 7.2$ Hz, 2H, NCH$_2$ MIC); 2.95 (m, 2H, $\beta$-CH$_2$ Cys); 2.50 (m, 2H, $\alpha$-CH$_2$ HD); 2.23 (t, $J = 7.5$ Hz, 2H, $\alpha$-CH$_2$ MIC); 1.50-1.70 (m, 6H, $\beta$-CH$_2$ HD, 2 * CH$_2$ MIC); 1.47 (s, 9H, C(CH$_3$)$_3$); 1.24 (br s, 28H, CH$_2$ MIC, (CH$_2$)$_{13}$ HD); 0.87 (t, $J = 7.0$ Hz, 3H, $\omega$-CH$_3$ HD). $^{13}$C NMR (125.6 MHz, CDCl$_3$): $\delta$ 173.2; 171.0; 170.7; 169.5; 168.9 (5 * C=O); 134.0 (CH=CH MIC); 82.6 (C(CH$_3$)$_3$); 52.6 ($\alpha$-CH Cys); 42.9 ($\alpha$-CH$_2$ Gly); 37.5 (NCH$_2$ MIC); 35.9 ($\alpha$-CH$_2$ MIC); 34.1 ($\beta$-CH$_2$ Cys); 32.7; 31.8; 29.6 (3 signals overlapped); 29.6 (2 signals overlapped); 29.5; 29.5; 29.4; 29.2; 29.1; 28.7; 28.1 (15 * CH$_2$ MIC, HD); 27.9 (C(CH$_3$)$_3$); 26.2; 24.9; 22.6 (3 * CH$_2$, HD, MIC); 14.0 ($\omega$-CH$_3$ HD). MS (FAB; 3-NBA) m/z: found 652.4273 (M+H)$^+$. 
N-(6-Maleimidocaproyl)-glycyl-S-hexadecyl-L-cysteine (MIC-Gly-Cys(HD)-OH) (30): To a solution of maleimidocaproic acid 3 (21 mg, 0.1 mmol) in 10 mL CH₂Cl₂ (10 mL) was added HOBt (13 mg, 0.1 mmol) and EDC (19 mg, 0.1 mmol) at room temperature. After 30 min this solution was poured into a mixture of the dipeptide 36 (50 mg, 0.1 mmol) and triethylamine (27 μL, 0.2 mmol, 2 eq.) in CH₂Cl₂ (7 mL) with trifluoroethanol (3 mL). After stirring for 15 h at room temperature, this solution was poured into CH₂Cl₂ (100 mL), washed with 0.5 M HCl (3 x 50 mL) and brine (50 mL). The solution was dried over MgSO₄, and the solvent was removed under reduced pressure. The crude compound was purified by flash chromatography on silica gel starting with ethyl acetate, followed by ethyl acetate/methanol (10:1) to furnish 39 mg (67%) of the desired compound 30 as a colorless amorphous solid. Alternatively deprotection of the tert-butyl ester from compound 39 could be achieved by treatment with TFA using the standard tert-butyl deprotection strategy above, and furnished the desired compound 30 without further purification in quantitative yield. \( R_f = 0.7 \) (chloroform/methanol/water 35:10:1). \([\alpha]_{D}^{22} = +14.6 \) (c = 0.6, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃/CD₃OD 5:1): \( \delta \) 6.73 (s, 2H, CH=CH MIC); 4.67 (dd, \( J = 5.1, 5.1 \) Hz, 1H, \( \alpha\)-CH Cys); 3.96 (d, \( J = 16.8 \) Hz, 1H, \( \alpha\)-CH₂a Gly); 3.88 (d, \( J = 16.8 \) Hz, 1H, \( \alpha\)-CH₂b Gly); 3.52 (t, \( J = 7.2 \) Hz, 2H, NCH₂ MIC); 3.03 (dd, \( J = 4.9, 13.9 \) Hz, 1H, \( \beta\)-CH₂b Cys); 2.92 (dd, \( J = 6.5, 13.8 \) Hz, 1H, \( \beta\)-CH₂b Cys); 2.54 (t, \( J = 7.4 \) Hz, 2H, \( \alpha\)-CH₂ HD); 2.26 (t, \( J = 7.5 \) Hz, 2H, \( \alpha\)-CH₂ MIC); 1.46-1.71 (m, 6H, \( \beta\)-CH₂ HD, 2 * CH₂ MIC); 1.33-1.37 (m, 2H, CH₂ MIC); 1.26 (s, br, 26H, \( (CH₂)_{13} \) HD); 0.88 (t, \( J = 6.8 \) Hz, 3H, \( \omega\)-CH₃ HD). \(^13\)C NMR (125.6 MHz, CDCl₃/CD₃OD 5:1): \( \delta \) 174.3; 172.5; 171.0; 169.4 (4 * C=O); 134.0 (CH=CH MIC); 51.9 (\( \alpha\)-CH Cys); 42.5 (\( \alpha\)-CH₂ Gly); 37.4 (NCH₂ MIC); 35.7 (\( \alpha\)-CH₂ MIC); 33.6 (\( \beta\)-CH₂ Cys); 32.4; 31.8; 29.6; 29.4; 29.3; 29.2; 29.1; 28.7; 28.1; 26.1; 24.9; 22.5 (9 * CH₂ HD, 3 * CH₂ MIC); 13.88 (\( \omega\)-CH₃ HD). MS (FAB; 3-NBA) \( m/z \): found 596.2 (M+H)^+.
N-(6-Maleimidocaproyl)-glycyl-S-hexadecyl-L-cysteinylglycyl-L-leucyl-L-prolyl-S-farnesyl-L-cysteine methylester (MIC-Gly-Cys(HD)-Met-Gly-Leu-Pro-Cys(Far)-OMe) (44c): This compound was prepared utilizing the standard coupling procedure using the pentapeptide 22c (63 mg, 0.85 mmol) and MIC-Gly-Cys(HD)-OH 30 (51 mg, 0.85 mmol). The compound was purified by flash chromatography on silica gel using gradient elution, starting with ethyl acetate, followed by ethyl acetate/methanol (10:1) and furnished 84 mg (75%) of the desired target molecule 44c as a colorless amorphous solid. 

$R_f = 0.4$ (ethyl acetate/methanol 10:1). $[\alpha]_D^{22} = -57.3$ (c = 0.4, CHCl$_3$). 

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.94 (d, $J = 7.0$ Hz, 1H, CONH); 7.58 (d, $J = 7.6$ Hz, 1H, CONH); 7.53 (d, $J = 7.4$ Hz, 1H, CONH); 7.37 (s, br, 1H, CONH); 7.22 (d, $J = 8.1$ Hz, 1H, CONH); 6.69 (s, 2H, CH=CH MIC); 6.66 (s, br, 1H, CONH); 5.16 (t, $J = 7.4$ Hz, 1H, CH Far); 5.07-5.09 (m, 2H, 2 * CH Far); 4.74-4.79 (m, 1H, α-CH Leu); 4.68-4.72 (m, 1H, α-CH Cys$_{Far}$); 4.58-4.61 (m, 1H, α-CH Pro); 4.53-4.57 (m, 1H, α-CH Cys$_{HD}$); 4.38 (dd, $J = 7.8$, 17.0 Hz, 1H, α-CH$_{2a}$ Gly); 4.28 (br, 1H, α-CH Met); 3.91-4.00 (m, 2H, α-CH$_2$ Gly’); 3.84-3.90 (m, 1H, δ-CH$_{2a}$ Pro); 3.75 (s, 3H, OCH$_3$); 3.55-3.61 (m, 2H, δ-CH$_{2b}$ Pro, α-CH$_{2b}$ Gly); 3.51 (t, $J = 7.1$ Hz, 2H, NCH$_2$ MIC); 3.16 (dd, $J = 8.3$, 13.2 Hz, 1H, α-CH$_{2a}$ Far); 3.06 (dd, $J = 7.4$, 13.2 Hz, 1H, α-CH$_{2b}$ Far); 2.94 (dd, $J = 4.8$, 13.8 Hz, 1H, β-CH$_{2a}$ Cys$_{Far}$); 2.90 (dd, $J = 5.2$, 13.5 Hz, 1H, β-CH$_{2a}$ Cys$_{HD}$); 2.83 (dd, $J = 5.5$, 13.5 Hz, 1H, β-CH$_{2b}$ Cys$_{HD}$); 2.71 (dd, $J = 6.5$, 13.8 Hz, 1H, β-CH$_{2b}$ Cys$_{Far}$); 2.56-2.67 (m, 2H, γ-CH$_2$ Met); 2.52 (t, $J = 7.4$ Hz, 2H, α-CH$_2$ HD); 2.38-2.43 (m, 1H, β-CH$_{2a}$ Met); 2.29-2.32 (m, 1H, β-CH$_{2a}$ Pro); 2.23 (t, $J = 7.5$ Hz, 2H, α-CH$_2$ MIC); 2.19-2.22 (m, 1H, β-CH$_{2b}$ Met); 2.08 (s, 3H, SCh$_3$); 2.03-2.11 (m, 9H, β-CH$_{2b}$ Pro, γ-CH$_2$ Pro, 3 * CH$_2$ Far); 1.95-1.99 (m, 2H, CH$_2$ Far); 1.71-1.82 (m, 2H, β-CH$_{2a}$ Leu, γ-CH Leu); 1.68 (s, 3H, CH$_3$ Far); 1.66 (s, 3H, CH$_3$ Far); 1.60 (s, 6H, 2 * CH$_3$ Far); 1.51-1.66 (m, 6H, β-
CH$_2$ HD, 2 * CH$_2$ MIC; 1.43-1.47 (m, 1H, β-CH$_2$β Leu); 1.28-1.34 (m, 2H, CH$_2$ MIC); 1.25 (s, br, 26H, (CH$_2$)$_{13}$ HD); 0.94 (t, J = 6.6 Hz, 6H, 2 * ω-CH$_3$ Leu); 0.88 (t, J = 6.9 Hz, 3H, ω-CH$_3$ HD). $^{13}$C NMR (125.6 MHz, CDCl$_3$): δ 174.4; 173.0; 171.4; 171.2; 170.9; 170.8; 170.2; 169.3 (8 * C=O); 140.0; 135.4 (2 * quart. C Far); 134.1 (CH=CH MIC); 131.3 (quart. C Far); 124.3; 123.7; 119.6 (3 * CH Far); 59.9 (α-CH Pro); 53.2; 52.9 (2 * α-CH Cys); 52.5 (OCH$_3$); 52.0 (α-CH Met); 49.1 (α-CH Leu); 47.4 (δ-CH$_2$ Pro); 43.7; 43.1 (2 * α-CH$_2$ Gly); 40.9 (β-CH$_2$ Leu); 39.7 (α-CH$_2$Far); 37.5 (NCH$_2$ MIC); 35.8 (α-CH$_2$ MIC); 33.0; 32.9; 31.9; 30.4; 29.7; 29.7; 29.6; 29.4; 29.3; 28.9; 28.3; 28.1 (2 * β-CH$_2$ Cys, β-CH$_2$ Met, γ-CH$_2$ Met, β-CH$_2$ Pro, CH$_2$ Far, CH$_2$ MIC, 5 * CH$_2$ HD); 26.7; 26.5 (2 * CH$_2$ Far); 26.3 (CH$_2$ MIC); 25.7 (CH$_3$ Far); 24.9; 24.8 (CH$_2$ MIC, γ-CH$_2$ Pro); 24.6 (γ-CH Leu); 23.3 (ω-CH$_3$ Leu); 22.7 (CH$_2$ HD); 21.8 (ω-CH$_3$ Leu); 17.7; 16.1; 16.0 (3 * CH$_3$ Far); 15.1 (SCH$_3$); 14.1 (ω-CH$_3$ HD). MS (FAB; 3-NBA) m/z: found 1315.9 (M+H)$^+$, 1338.2 (M+Na)$^+$. 

$N$-(6-Maleimidocaproyl)-glycyl-$S$-hexadecyl-$L$-cysteyl-$L$-methionylglycyl-$L$-leucyl-$L$-prolyl-$S$-[(E,E)-8-O-(2-$N$-methyl-aminobenzoyl)-3,7-dimethyl-2,6-octandiene]-$L$-cysteine methyl ester (MIC-Gly-Cys(HD)-Met-Gly-Leu-Pro-Cys(Ger/Mant)-OMe) (44a): This compound was prepared utilizing the standard coupling procedure with the pentapeptide 22a (27 mg, 0.033 mmol) and MIC-Gly-Cys(HD)-OH 30 (20 mg, 0.033 mmol). The compound was purified by flash chromatography on silica gel using gradient elution starting with ethyl acetate, followed by ethyl acetate/methanol (98:2) and furnished 25.5 mg (52%) of the desired target molecule 44a as a colorless oil. $R_f = 0.63$ (ethyl acetate/methanol 98:2). $[α]_D^{22} = -56.3$ ($c = 1.0$, CH$_2$Cl$_2$). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.91 (dd, J = 1.5, 7.9 Hz, 2H, arom. CH, CONH); 7.63 (br s, 1H, NH); 7.55 (d, J = 7.5 Hz, 1H, CONH); 7.37 (t, J = 6.9 Hz, 2H, arom. CH, CONH); 7.20 (d, J = 7.9 Hz, 1H, CONH); 6.68 (s, 2H, CH=CH MIC); 6.66-6.68 (m, 1H,
arom. CH); 6.58 (t, J = 7.9 Hz, 1H, arom. CH); 5.49 (t, J = 6.5 Hz, 1H, CH Ger); 5.17 (t, J = 7.7 Hz, 1H, CH Ger); 4.74-4.78 (m, 1H, α-CH Leu); 4.69-4.72 (m, 1H, α-CH CysGer); 4.62 (s, 2H, CO₂CH₂); 4.51-4.59 (m, 2H, α-CH Cys₃₅HD α-CH Pro); 4.37 (dd, J = 7.7, 17.0 Hz, 1H, δ-CH₂a Gly); 4.27 (br, 1H, α-CH Met); 3.91-3.96 (m, 2H, α-CH₂ Gly'); 3.85-3.88 (m, 1H, δ-CH₂a Pro); 3.74 (s, 3H, OCH₃); 3.54-3.73 (m, 2H, δ-CH₂b Pro, α-CH₂b Gly); 3.50 (t, J = 7.1 Hz, 2H, NCH₂ MIC); 3.16 (dd, J = 8.2, 13.3 Hz, 1H, α-CH₂a Ger); 3.05 (dd, J = 4.5, 13.3 Hz, 1H, α-CH₂b Ger); 2.90 (d, J = 4.9 Hz, 3H, NHCH₃); 2.81-2.96 (m, 3H, β-CH₂a CysGer, β-CH₂ Cys₃₅HD); 2.71 (dd, J = 6.6, 13.7 Hz, 1H, β-CH₂b CysGer); 2.55-2.67 (m, 2H, γ-CH₂ Met); 2.52 (t, J = 7.4 Hz, 2H, α-CH₂ HD); 1.98-2.41 (m, 12H, 2 * CH₂ Ger, α-CH₂ MIC, β-CH₂ Met, β-CH₂ Pro, γ-CH₂ Pro); 2.08 (s, 3H, SCH₃); 1.72 (s, 3H, CH₃ Ger); 1.66 (s, 3H, CH₃ Ger); 1.42-1.80 (m, 9H, 2 * CH₂ MIC, β-CH₂ HD, γ-CH Leu, β-CH₂ Leu); 1.24 (br s, 28H, CH₂ MIC, (CH₂)₁₃); 0.93 (t, J = 6.4 Hz, 6H, 2 * ω-CH₃ Leu); 0.87 (t, J = 6.9 Hz, 3H, ω-CH₃ HD). ¹³C NMR (125.6 MHz, CDCl₃): δ 174.9; 173.4; 171.4; 171.2; 171.1; 170.9 (2 signals overlapped); 170.8; 170.6; 169.7; 168.5 (11 * C=O); 152.1 (arom. quart. CNH); 139.5 (quart. C Ger); 134.7 (arom. CH); 134.1 (CH=CH MIC); 131.5 (arom. CH); 130.8 (quart. C Ger); 128.4; 120.0 (2 * CH Ger); 114.3; 110.7 (2 * arom. CH); 110.0 (arom. quart. CCO₂); 69.7 (CO₂CH₂); 60.1 (α-CH Pro); 53.4; 53.1 (α-CH Met, α-CH Cys); 52.6 (OCH₃); 51.9 (α-CH Cys); 49.1 (α-CH Leu); 47.4 (δ-CH₂ Pro); 44.0; 43.0 (2 * α-CH₂ Gly); 40.6 (β-CH₂ Leu); 39.1 (α-CH₂ Ger); 37.6 (NCH₂ MIC); 35.9 (α-CH₂ MIC); 33.2; 32.7; 32.7; 31.9; 30.6; 29.7 (2 * β-CH₂ Cys, 2 * CH₂ Met, CH₂ Ger, 9 * CH₂ HD); 29.6 (NHCH₃); 29.6; 29.4; 29.3; 28.9; 28.5; 28.2; 27.8; 26.3; 26.2; 25.0; 24.9 (3 * CH₂ MIC, 5 * CH₂ HD, CH₂ Ger, β-CH₂ Pro, γ-CH₂ Pro); 24.6 (γ-CH Leu); 23.3 (1 * ω-CH₃ Leu); 22.7 (CH₂ HD); 21.7 (1 * ω-CH₃ Leu); 16.1 (CH₃ Ger); 15.0 (SCH₃); 14.2 (CH₃ Ger); 14.1 (ω-CH₃ HD). MS (FAB; 3-NBA) m/z: found 1396.0 (M+H)⁺.
N-(6-Maleimidocaproyl)-glycyl-S-hexadecyl-L-cysteyl-L-methionylglycyl-L-leucyl-L-prolyl-S-[(E,E)-8-O-(2-N-methyl-aminobenzoyl)-3,7,11-trimethyl-2,6,10-dodecatriene]-L-cysteine methyl ester (MIC-Gly-Cys(HD)-Met-Gly-Leu-Pro-Cys(Far/Mant)-OMe) (44b):

This compound was prepared utilizing the standard coupling procedure with the pentapeptide 22b (29.4 mg, 0.033 mmol) and MIC-Gly-Cys(HD)-OH 30 (20 mg, 0.033 mmol). The compound was purified by flash chromatography on silica gel using gradient elution starting with ethyl acetate, followed by ethyl acetate/methanol (98:2), and finally the compound was eluted from the column with ethyl acetate/methanol (95:5). After purification a total of 35 mg (72%) of the desired target molecule 44b was obtained as a colorless oil. \( R_f = 0.54 \) (ethyl acetate/methanol 98:2). \( [\alpha]_D^{22} = -46.38 \) (c = 1.0, CH\(_2\)Cl\(_2\)). \( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta \)

7.90 (m, 2H, arom. CH, CONH) 7.64 (br s, 1H, NH); 7.55 (d, \( J = 7.6 \) Hz, 1H, CONH); 7.52 (d, \( J = 7.9 \) Hz, 1H, CONH); 7.36-7.38 (m, 1H, arom. CH); 7.19 (d, \( J = 8.3 \) Hz, 1H, CONH); 6.68 (s, 2H, CH=CH MIC); 6.65-6.68 (m, 2H, arom. CH, CONH); 6.57 (d, \( J = 7.5 \) Hz, 1H, arom. CH); 5.50 (t, \( J = 7.0 \) Hz, 1H, CH Far); 5.15 (t, \( J = 8.3 \) Hz, 1H, CH Far); 5.10 (t, \( J = 6.6 \) Hz, 1H, CH Far); 4.73-4.77 (m, 1H, \( \alpha\)-CH Leu); 4.68-4.72 (m, 1H, \( \alpha\)-CH Cys\(_{\text{Far}}\)); 4.63 (s, 2H, CO\(_2\)CH\(_2\)); 4.51-4.59 (m, 2H, \( \alpha\)-CH Cys\(_{\text{HD}}\), \( \alpha\)-CH Pro); 4.38 (dd, \( J = 7.9, 17.0 \) Hz, 1H, \( \alpha\)-CH\(_2\)a Gly); 4.26 (br, 1H, \( \alpha\)-CH Met); 3.92-3.96 (m, 2H, \( \alpha\)-CH\(_2\) Gly); 3.85-3.88 (m, 1H, \( \delta\)-CH\(_2\)a Pro); 3.74 (s, 3H, OCH\(_3\)); 3.54-3.73 (m, 2H, \( \delta\)-CH\(_{2b}\) Pro, \( \alpha\)-CH\(_{2b}\) Gly); 3.50 (t, \( J = 7.1 \) Hz, 2H, NCH\(_2\) MIC); 3.16 (dd, \( J = 8.3, 13.1 \) Hz, 1H, \( \alpha\)-CH\(_{2a}\) Far); 3.06 (dd, \( J = 7.3, 13.1 \) Hz, 1H, \( \alpha\)-CH\(_{2b}\) Far); 2.90 (d, \( J = 3.4 \) Hz, 3H, NHCH\(_3\)); 2.81-3.00 (m, 3H, \( \beta\)-CH\(_{2a}\) Cys\(_{\text{Far}}\), \( \beta\)-CH\(_2\) Cys\(_{\text{HD}}\)); 2.71 (dd, \( J = 6.5, 13.8 \) Hz, 1H, \( \beta\)-CH\(_{2b}\) Cys\(_{\text{HD}}\)); 2.55-2.67 (m, 2H, \( \gamma\)-CH\(_2\) Met); 2.52 (t, \( J = 7.4 \) Hz, 2H, \( \alpha\)-CH\(_2\) HD); 1.98-2.43 (m, 16H, 4 * CH\(_2\) Far, \( \alpha\)-CH\(_2\) MIC, \( \beta\)-CH\(_2\) Met, \( \beta\)-CH\(_2\) Pro, \( \gamma\)-CH\(_2\) Pro); 2.08 (s, 3H, SCH\(_3\)); 1.72 (s, 3H, CH\(_3\) Far); 1.65 (s, 3H, CH\(_3\) Far); 1.60 (s, 3H, CH\(_3\) Far).
Far); 1.42-1.80 (m, 9H, 2 * CH₂ MIC, β-CH₂ HD, γ-CH Leu, β-CH₂ Leu); 1.24 (br s, 28H, CH₂ MIC, (CH₂)₁₃ HD); 0.93 (t, J = 6.7 Hz, 6H, 2 * ω-CH₃ Leu); 0.87 (t, J = 6.9 Hz, 3H, ω-CH₃ HD). ¹³C NMR (125.6 MHz, CDCl₃): δ 174.7; 174.6; 173.2; 171.4; 171.2; 171.0; 170.9 (2 signals overlapped); 170.6; 169.6; 168.5 (11 * C=O); 152.0 (arom. quart. CNH); 140.0; 134.9 (2 * quart. C Far); 134.6 (arom. CH); 134.1 (CH=CH MIC); 131.5 (arom. CH); 130.3 (quart. C Far); 129.0; 124.1; 119.5 (3 * CH Far); 114.3; 110.7 (2 * arom. CH); 110.0 (arom. quart. CCO₂); 69.8 (CO₂CH₂); 60.0 (α-CH Pro); 53.3; 53.1 (α-CH Met, α-CH Cys); 52.1 (OCH₃); 51.9 (α-CH Cys); 49.1 (α-CH Leu); 47.4 (δ-CH₂ Pro); 43.8; 43.0 (2 * α-CH₂ Gly); 40.6 (β-CH₂ Leu); 39.6 (α-CH₂ Far); 39.1 (CH₂ Far); 37.5 (NCH₂ MIC); 35.8 (α-CH₂ MIC); 33.0; 32.7; 31.9; 31.9; 30.5; 30.3; 29.7; 29.6 (2 * β-CH₂ Cys, 2 * CH₂ Met, CH₂ Far, 9 * CH₂ HD); 29.5 (NHCH₃); 29.3; 29.3; 28.9; 28.7; 27.9; 26.5; 26.3; 26.2; 24.9 (3 * CH₂ MIC, 2 * CH₂ HD, 2 * CH₂ Far, β-CH₂ Pro, γ-CH₂ Pro); 24.6 (γ-CH Leu); 23.3 (1 * ω-CH₃ Leu); 22.7 (CH₂ HD); 22.7 (1 * ω-CH₃ Leu); 16.1; 16.0 (2 * CH₃ Far); 15.0 (SCH₃); 14.1 (CH₃ Far); 14.0 (ω-CH₃ HD). MS (FAB; 3-NBA) m/z: found 1464 (M+H)+.

**N- Allyloxy carbonyl glycyl-S- tert - butyl thio-L- cysteine tert - butyl ester (Aloc-Gly-Cys(S′Bu)-O′Bu) (26b):** To a mixture of the disulfide 22b (500 mg, 0.79 mmol) in dioxane (32 mL) was added triethylamine (0.25 mL) followed by tert - butanethiol (0.63 mL). The reaction was left to stir in air for 5 days. After this time the solvent was removed under reduced pressure. The resulting orange oil was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:1) as eluent, and provided the desired dipeptide 26b, 385 mg (60%) as a colorless oil. *R*ᵣ = 0.7 (hexane/ethyl acetate 1:1). [α]₀²² = -34.3 (c = 1.0, CH₂Cl₂).

¹H NMR (500 MHz, CDCl₃): δ 6.95 (d, J = 7.0 Hz 1H, CONH); 5.86-5.92 (m, 1H, CH=CH₂); 5.60 (t, J = 5.2 Hz 1H, OCONH); 5.28 (dd, J = 1.4, 17.2 Hz, 1H, CH=CH₂); 5.18
(dd, J = 1.3, 10.5 Hz, 1H, CH=CH$_2$); 4.74 (dt, J = 5.0, 7.5 Hz, 1H, α-CH Cys); 4.56 (d, J = 5.4 Hz, 2H, OCH$_2$); 3.91 (d, J = 5.0 Hz 2H, α-CH$_2$ Gly); 3.20 (dd, J = 4.6, 13.7 Hz 1H, β-CH$_{2a}$ Cys); 3.10 (dd, J = 5.3, 13.7 Hz 1H, β-CH$_{2b}$ Cys); 1.45 (s, 9H, OC(CH$_3$)$_3$); 1.28 (s, 9H, SC(CH$_3$)$_3$). $^{13}$C NMR (125.6 MHz, CDCl$_3$): δ 169.0; 168.8 (2 * C=O); 156.4 (OCNH); 132.6 (CH=CH$_2$); 117.8 (CH=CH$_2$); 83.0 (OC(CH$_3$)$_3$); 66.0 (OCH$_2$); 52.9 (α-CH Cys); 48.2 (SC(CH$_3$)$_3$); 44.4 (α-CH$_2$ Gly); 42.6 (β-CH$_2$ Cys); 29.7 (SC(CH$_3$)$_3$); 28.0 (OC(CH$_3$)$_3$). HRMS (FAB; 3-NBA) m/z: calcd for (M+H)$^+$ C$_{17}$H$_{31}$N$_2$O$_5$S$_2$ 407.1674, found 407.1608.

**Glycyl-S-tert-butylthio-L-cysteine tert-butylester (H-Gly-Cys(S'Bu)-O'Bu) (38):** Removal of the Aloc protecting group was achieved using the standard Aloc deprotection procedure given above. Purification by flash chromatography on silica gel using ethyl acetate/hexane (5:1), followed by ethyl acetate as eluents and provided 80 mg (41%) of the desired compound 38 as a white amorphous solid. $^1$H NMR (250 MHz, CD$_3$OD): δ 7.92 (d, J = 7.5 Hz, 1H, CONH); 4.72-4.76 (m, 1H, α-CH Cys); 3.36 (s, 2H, α-CH$_2$ Gly); 3.21 (dd, J = 4.7, 13.5 Hz, 1H, β-CH$_{2a}$ Cys); 3.12 (dd, J = 5.4, 13.5 Hz, 1H, β-CH$_{2b}$ Cys); 1.82 (br s, 2H, NH$_2$); 1.45 (s, 9H, OC(CH$_3$)$_3$); 1.28 (s, 9H, SC(CH$_3$)$_3$). $^{13}$C NMR (125.6 MHz, CDCl$_3$): δ 172.4; 169.3 (2 * C=O); 82.7 (OC(CH$_3$)$_3$); 52.4 (α-CH Cys); 48.0 (SC(CH$_3$)$_3$); 44.6 (α-CH$_2$ Gly); 43.1 (β-CH$_2$ Cys); 29.7 (SC(CH$_3$)$_3$); 28.0 (OC(CH$_3$)$_3$).

**N-(6-Maleimidocaproyl)-glycyl-S-tert-butylthio-L-cysteine tert-butyl ester (MIC-Gly-Cys(S'Bu)-O'Bu) (40):** The free amine 38 (80 mg, 0.25 mmol) was coupled with maleimidocaproic acid (57 mg, 0.27 mmol, 1.1 eq.) following the standard coupling procedure given above. The compound was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:3) to yield 77 mg (60%) of the desired compound 40 as a colorless oil.