Supplemental material for

New Methods for Side-Chain Protection of Cysteine.

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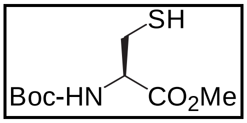
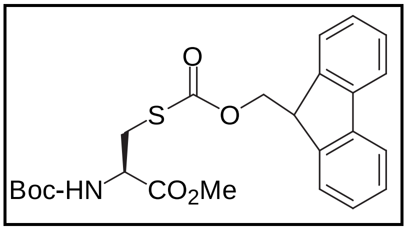
Experimental procedures and full characterization for compounds **1-14**.



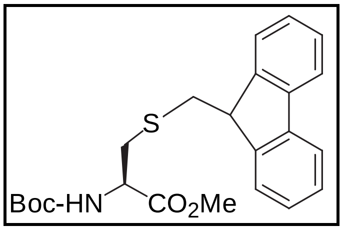
2-*tert*-Butoxycarbonylamino-3-mercapto-propionic acid methyl ester; Boc-Cys-OMe (1)

To a slurry of HCl-Cysteine methyl ester (844.5 mg, 4.92 mmol) in 15 mL of CH_2Cl_2 was added TEA (0.75 mL, 5.38 mmol) and stirred for 5 min. To this was added Boc_2O (1.1900 g, 5.45 mmol) as a solution in 5 mL of CH_2Cl_2. After stirring at room temp for 5 hours the reaction was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes, 25 x 190 mm) to give 1.0491 g (91%) of product as a clear oil (R_f = 0.44, 40% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41(m, 1H), 4.61(m, 1H), 3.79(s, 3H), 2.97(m, 2H), 1.53(s, 1H), 1.46(s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.40, 154.67, 79.85, 54.43, 52.26, 27.87, 26.90. MS calculated for $C_9H_{17}NO_4S$=235.0878; found (EIMS), 234.0802 (M^+).



2-*tert*-Butoxycarbonylamino-3-(9H-fluoren-9-ylmethoxycarbonylsulfanyl)-propionic acid methyl ester; Boc-Cys(Fmoc)-OMe (2)

To a solution of **1** (222.4 mg, 0.95 mmol) in 7 mL of CH_2Cl_2 was added FmocCl (271.5 mg, 1.05 mmol) and TEA (0.15 mL, 1.08 mmol). After stirring for 3 hours the reaction was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes, 25 x 190 mm) to give 425.9 mg (98%) of product as a white solid (R_f = 0.47, 40% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72(d, 2H, J=7.4 Hz), 7.67(d, 2H, J=7.4 Hz), 7.41(t, 2H, J=7.4 Hz), 7.33(t, 2H, J=7.4 Hz), 5.34(d, 1H, J=6.8 Hz), 4.56(m, 1H), 4.46(d, 2H, J=7.2 Hz), 4.08(t, 1H, J=6.6 Hz), 3.75(s, 3H), 3.44(m, 1H), 3.30(m, 1H), 1.44(s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.86, 170.43, 155.10, 143.22, 141.28, 127.98, 127.27, 125.19, 120.11, 80.30, 69.72, 53.22, 52.73, 46.66, 33.41, 28.31. MS calculated for $C_{24}H_{27}NO_4S$=457.1559; found (EIMS), 457.1554 (M).



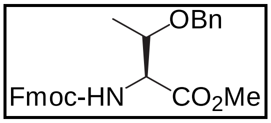
2-*tert*-Butoxycarbonylamino-3-(9H-fluoren-9-ylmethylsulfanyl)-propionic acid methyl ester; Boc-Cys(Fm)-OMe (3)

From **1**:

To a solution of **1** (80.2 mg, 0.34 mmol) in 3.5 mL of CH_2Cl_2 was added FmocOSu (125.6 mg, 0.37 mmol) and TEA (0.05 mL, 0.36 mmol). After stirring for 4 hours the reaction was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 25% EtOAc/hexanes, 25 x 170 mm) to give 130.2 mg (92%) of product as a clear oil.

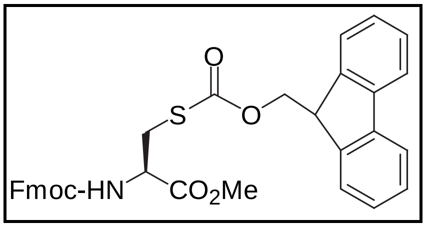
From **2**:

To a solution of **2** (109.8 mg, 0.24 mmol) in 2 mL of CH_2Cl_2 was added N-hydroxysuccinimide (33.6 mg, 0.29 mmol), and TEA (0.038 mL, 0.27 mmol). After stirring for 4.5 hours the solution was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes, 20 x 170 mm) to give 90.0 mg (91%) of product as a clear oil (R_f =0.48, 40% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74(d, 2H, J=7.4 Hz), 7.67(t, 2H, J=6.6 Hz), 7.39(t, 2H, J=7.4 Hz), 7.31(t, 2H, J=7.4 Hz), 5.34(d, 1H, J=7.4 Hz), 4.56(m, 1H), 4.08(t, 1H, J=6.6 Hz), 3.73(s, 3H), 3.09(d, 2H, J=6.6 Hz), 2.98(m, 2H), 1.44(s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.44, 155.05, 145.69, 140.96, 127.55, 126.97, 124.75, 119.84, 80.13, 53.37, 52.51, 46.85, 37.03, 35.48, 28.23. MS calculated for $C_{23}H_{27}NO_2S$=413.1661; found (EIMS), 413.1646 (M).



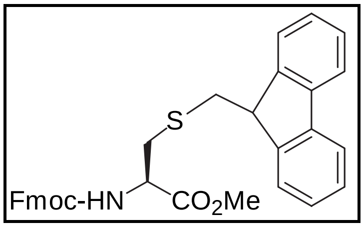
3-Benzyloxy-2-(9H-fluoren-9-ylmethoxycarbonylamino)-butyric acid methyl ester; Fmoc-Thr(OBn)-OMe (4)

To a solution of Fmoc-Threonine(OBn)-OH (223.8 mg, 0.52 mmol) in 2 mL of MeOH and 7 mL of toluene was added TMS-diazomethane (2.0 M in hexanes, 0.50 mL, 1.00 mmol) until a yellow color persisted. The reaction was stirred for an additional 20 minutes, concentrated *in vacuo*, and azeotrope with CH_2Cl_2 and EtOAc to obtain the methyl ester as a white solid. Recrystalization from EtOAc/hexanes gave 215.0 mg (93%) of product as a white solid (R_f = 0.41, 40% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75(d, 2H, J=7.4 Hz), 7.62(t, 2H, J=6.6 Hz), 7.42-7.24(m, 9H), 5.57(d, 1H, J=9.6 Hz), 4.58(d, 1H, J=11.8 Hz), 4.41(m, 4H), 4.24(t, 1H, J=7.4 Hz), 4.17(dq, 1H, J=2.2, 6.3 Hz), 3.68(s, 3H), 1.26(d, 3H, J=6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.06, 156.58, 143.79, 143.59, 141.12, 137.62, 128.24, 127.62, 127.52, 126.89, 124.99, 119.79, 73.98, 70.70, 67.06, 58.58, 52.19, 47.00, 16.04. MS calculated for $C_{27}H_{27}NO_5$=445.5; found (LSIMS), 468.2 (M+Na).



2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(9H-fluoren-9-ylmethoxycarbonyl sulfanyl)-propionic acid methyl ester; Fmoc-Cys(Fmoc)-OMe (5)

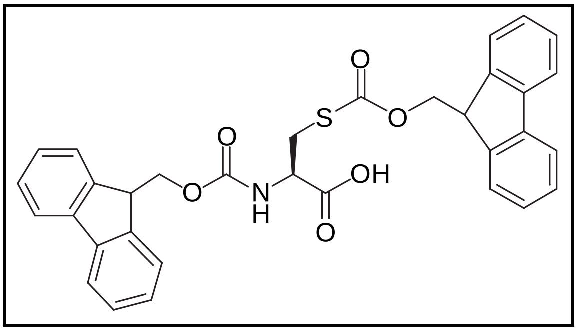
To a solution of HCl-Cysteine methyl ester (156.0 mg, 0.91 mmol) in 8 mL of CH_2Cl_2 was added FmocCl (496.5 mg, 1.92 mmol) and TEA (0.35 mL, 2.51 mmol). After stirring at room temp for 3.5 hours the reaction was diluted with 75 mL of CH_2Cl_2 and washed successively with 15 mL 1N $NaHCO_3$, 15 mL 1N $KHSO_4$, and 20 mL saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo,* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes, 25 x 200 mm) to give 403.3 mg (77%) of product as a white solid (R_f = 0.33, 40% EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.72(d, 4H, J=7.7 Hz), 7.54(m, 4H), 7.40-7.23(m, 8H), 5.72(d, 1H, J=8.1 Hz), 4.67(m, 1H), 4.40(m, 4H), 4.20(m, 2H), 3.74(s, 3H), 3.47(dd, 1H, J=14.3, 4.8 Hz), 3.30(dd, 1H, J=14.3, 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.37, 170.30, 155.55, 143.64, 143.58, 142.98, 142.95, 141.11, 127.82, 127.57, 127.08, 126.92, 124.99, 119.95, 119.84, 69.66, 67.11, 53.62, 52.73, 46.93, 46.42, 32.96. MS calculated for $C_{34}H_{29}NO_6S$=579.1716; found (EIMS), 579.1723 (M).



2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(9H-fluoren-9-ylmethylsulfanyl)-propionic acid methyl ester; Fmoc-Cys(Fm)-OMe (6)

In CH_3CN: To a solution of **5** (31.5 mg, 0.054 mmol) in 0.5 mL of CH_3CN was added TEA (0.008 mL, 0.058 mmol). After stirring for 14 hours the reaction was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 30% EtOAc/hexanes, 10 x 120 mm) to give 23.9 mg (82%) of product as a clear oil.

In CH_2Cl_2: To a solution of **5** (87.2 mg, 0.15 mmol) in 3 mL of CH_2Cl_2 was added TEA (0.023 mL, 0.165 mmol). After stirring for 20 hours the reaction was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes, 20 x 150 mm) to give 30.1 mg (37%) of product as a clear oil (R_f = 0.36, 40% EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.75(m, 4H), 7.62(m, 4H), 7.41-7.25(m, 8H), 5.60(d, 1H, J=7.7 Hz), 4.60(m, 1H), 4.40(d, 2H, J=7.0 Hz), 4.22(m, 1H), 4.09(m, 1H), 3.74(s, 3H), 3.09(d, 2H, J=6.3 Hz), 2.99(m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.98, 155.50, 145.46, 143.53, 141.12, 140.88, 127.56, 127.47, 126.89, 124.91, 124.54, 119.82, 119.76, 67.01, 53.58, 52.55, 46.93, 46.72, 36.92, 35.34. MS calculated for $C_{33}H_{29}NO_4S$=535.63; found (LSIMS), 558 (M+Na).



2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(9H-fluoren-9-ylmethoxycarbonyl sulfanyl)-propionic acid; Fmoc-Cys(Fmoc)-OH (7)

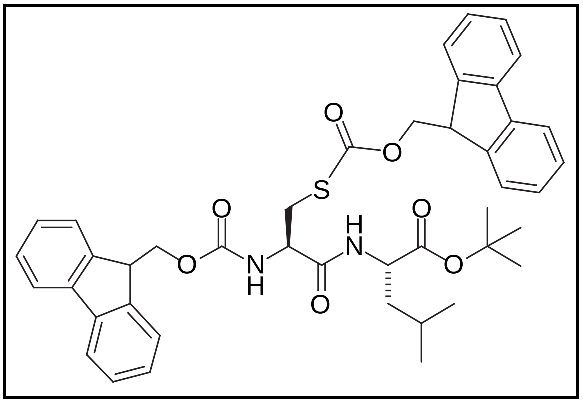
From HCl-Cysteine-OH-H_2O:

To a 0˚C solution of HCl-Cysteine-OH-H_2O (351.7 mg, 2.0 mmol) in 20 mL of 50% aqueous dioxane was added FmocCl (1.1976 g, 4.6 mmol) and adjusted to pH=7 by addition of 2N NaOH. Continuous adjustment to pH=7 with 2N NaOH was done for 5 hours at which point the reaction was concentrated *in vacuo* to remove dioxane. Acidification to pH=2 with 1N HCl was followed by extraction with CH_2Cl_2 (3x100 mL). The organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 94/5/1

CH_2Cl_2/MeOH/AcOH, 25 x 250 mm) to give a white foam. The product was recrystallized from EtOAc/hexanes to give 814.0 mg (72%) of product as a white solid.

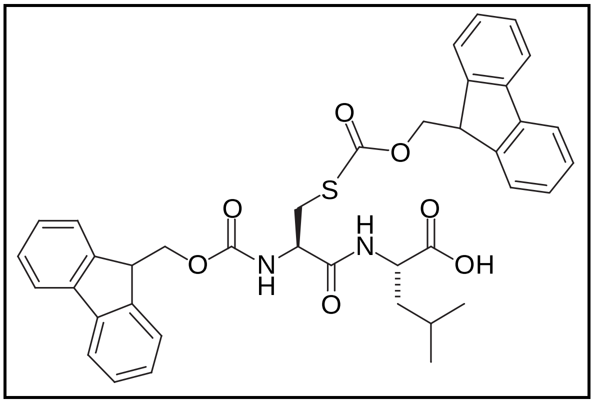
From **10**:

To a solution of **10** (622.0 mg, 1.03 mmol) in 15 mL of THF was added dimedone (322.7 mg, 2.30 mmol) and $Pd(PPh_3)_4$ (88.0 mg, 0.076 mmol). After stirring at room temp for 30 min the reaction was concentrated *in vacuo*, diluted with 75 mL of CH_2Cl_2, and washed successively with 1N $KHSO_4$ and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 94/5/1 CH_2Cl_2/MeOH/AcOH, 25 x 250 mm). Recrystallization from EtOAc/hexanes afforded 544.6 mg (94%) of product as an off white solid. (R_f =0.30, 94/5/1 CH_2Cl_2/MeOH/AcOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60(br s, 1H), 7.72(m, 4H), 7.61(d, 2H, J=7.7 Hz), 7.52(d, 2H, J=7.7 Hz), 7.34(m, 4H), 7.25(m, 4H), 5.70(d, 1H, J=6.8 Hz), 4.50(m, 1H), 4.42(d, 2H, J=7.0 Hz), 4.33(m, 1H), 4.27(m, 1H), 4.22(m, 2H), 3.56(dd, 1H, J=14.3, 4.4 Hz), 3.18(dd, 1H, J=14.3, 8.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.09, 170.55, 155.95, 143.48, 142.93, 141.08, 127.79, 127.57, 127.06, 126.92, 124.97, 119.92, 119.82, 69.71, 67.31, 53.81, 46.84, 46.38, 32.50. MS calculated for (M+Na) $C_{33}H_{27}NO_6S$=588.1457; found (HRLSIMS), 588.1479 (M+Na).



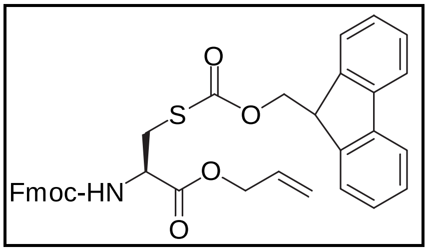
2-[2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(9H-fluoren-9-ylmethoxycarbonylsulfanyl)-propionylamino]-4-methyl-pentanoic acid *tert*-butyl ester; Fmoc-Cys(Fmoc)-Leu-O^{t}Bu (8)

To a 0˚C solution of **7** (102.5 mg, 0.18 mmol) and HOBt (36.6 mg, 0.27 mmol) in 2.5 mL of DMF was added EDCI (36.8 mg, 0.19 mmol). After stirring for 30 minutes HCl-Leu-O^{t}Bu (41.3 mg, 0.18 mmol) and DIEA (0.036 mL, 0.21 mmol) were added. The reaction was stirred at 0˚C for three hours and then at ambient temp for an additional 18 hours. This was diluted with EtOAc, washed with H_2O, 1N $KHSO_4$, and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes, 20 x 180 mm) to give 113.8 mg (87%) of product as a white solid (R_f = 0.46, 40% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72(d, 4H, J=7.4 Hz), 7.55(d, 4H, J=7.7 Hz), 7.42-7.23(m, 8H), 6.73(d, 1H, J=8.1 Hz), 5.80(d, 1H, J=8.1 Hz), 4.45(m, 4H), 4.35(m, 2H), 4.24(m, 2H), 3.42(dd, 1H, J=14.7, 4.1 Hz), 3.23(dd, 1H, J=14.7, 8.1 Hz), 1.63(m, 2H), 1.52(m, 1H), 1.45(s, 9H), 0.91(d, 6H, J=6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.60, 171.48, 169.37, 156.33, 143.74, 143.16, 141.28, 127.98, 127.75, 127.24, 127.10, 125.20, 125.14, 120.11, 120.00, 82.07, 69.91, 67.47, 60.42, 55.17, 51.75, 47.04, 46.58, 41.65, 33.46, 28.00, 24.97, 22.79, 22.12. MS calculated for (M+Na) $C_{43}H_{46}N_2O_7S$=757.2923; found (HRLSIMS), 757.2901 (M+Na).



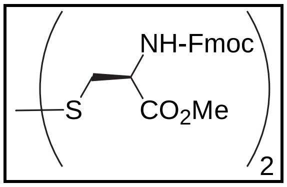
2-[2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(9H-fluoren-9-ylmethoxycarbonylsulfanyl)-propionylamino]-4-methyl-pentanoic acid; Fmoc-Cys(Fmoc)-Leu-OH (9)

To **8** (25.2 mg, 0.034 mmol) was added 4N HCl in dioxane (1.0 mL, 4.0 mmol). After stirring at room temp for 16 hours the reaction was concentrated *in vacuo* to give a clear oil. Purification by flash column chromatography (SiO_2, 5% MeOH/CH_2Cl_2, 10 x 150 mm) gave 18.0 mg (77%) of product as a white solid (R_f = 0.30, 94/5/1 CH_2Cl_2/MeOH/AcOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72(m, 4H), 7.53(d, 4H, J=7.0 Hz), 7.37(m, 4H), 7.28(m, 4H), 7.04(m, 1H), 6.03(d, 1H, J=7.9 Hz), 4.58(m, 2H), 4.43(m, 2H), 4.34(d, 2H, J=7.4 Hz), 4.22(m, 2H), 3.40(dd, 1H, J=14.7, 4.4 Hz), 3.19(dd, 1H, J=14.7, 8.1 Hz), 1.72(m, 3H), 0.91(d, 6H, J=5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.89, 171.61, 170.10, 156.54, 143.58, 143.07, 141.21, 127.93, 127.73, 127.20, 127.18, 127.05, 125.14, 125.06, 120.05, 119.96, 69.90, 67.57, 55.00, 51.06, 46.93, 46.51, 40.97, 33.21, 24.86, 22.74, 21.80. MS calculated for $C_{39}H_{38}N_2O_7S$=678.79; found (LSIMS), 699.6 (M+Na).



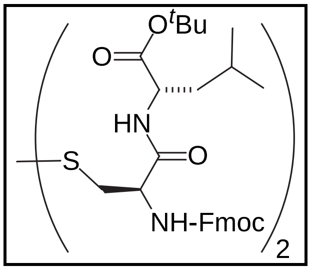
2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(9H-fluoren-9-ylmethoxycarbonylsulfanyl)-propionic acid allyl ester; Fmoc-Cys(Fmoc)-OAllyl (10)

A solution of Fmoc-Cysteine(S-Trt)-OH (999.4 mg, 1.71 mmol), allyl bromide (3.7 mL, 42.8 mmol), and DIEA (1.2 mL, 6.89 mmol) was refluxed for 40 min. This was allowed to cool, diluted with EtOAc, and washed with H_2O, 1N $KHSO_4$, and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting allyl ester was treated with a 7/2/1 mixture of CH_2Cl_2/TES/TFA for 40 minutes at which point the reaction was concentrated *in vacuo* and azeotrope with MeOH and Et_2O (2x). The resulting free thiol was dissolved in 16 mL of CH_2Cl_2 and treated with FmocCl (462.1 mg, 1.79 mmol) and DIEA (0.80 mL, 4.59 mmol). After stirring for 14 hrs, the reaction was concentrated *in vacuo*, diluted with EtOAc, and washed with H_2O, 1N $NaHCO_3$, 1N $KHSO_4$, and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, gradient 20-40% EtOAc/hexanes, 40 x 300 mm) to give 711.4 mg (69%, three steps) of product as a white solid (R_f = 0.50, 40% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68(d, 4H, J=7.4 Hz), 7.54(d, 2H, J=7.4 Hz), 7.49(d, 2H, J=7.4 Hz), 7.31(m, 4H), 7.25(m, 4H), 6.06(d, 1H, J=8.1 Hz), 5.86(m, 1H), 5.30(d, 1H, J=16.9 Hz), 5.18(d, 1H, J=10.7 Hz), 4.68(m, 1H), 4.62(d, 2H, J=5.5 Hz), 4.38(m 4H), 4.17(t, 2H, J=7.0 Hz), 3.50(dd, 1H, J=14.4, 4.4 Hz), 3.30(dd, 1H, J=14.4, 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.28, 169.61, 155.58, 143.64, 143.57, 142.97, 142.94, 141.10, 131.12, 127.80, 127.56, 127.07, 126.91, 124.98, 119.94, 119.82, 119.08, 69.65, 67.11, 66.43, 53.74, 46.90, 46.39, 32.92. MS calculated for $C_{36}H_{31}NO_6S$=605.68; found (LSIMS), 628.2 (M+Na).



Fmoc-Cys-OMe disulfide (11)

To a solution of **5** (49.5 mg, 0.085 mmol) in 1 mL of CH_2Cl_2 and 0.5 mL of MeOH was added TEA (0.12 mL, 0.86 mmol) and a solution of I_2 (100mg/1mL, 0.66 mL, 0.26 mmol). After stirring for 8 hrs, the reaction was concentrated *in vacuo*, diluted with EtOAc, and washed with H_2O, 1N $NaHCO_3$, 1N $KHSO_4$, and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes, 15 x 150 mm) to give 22.7 mg (75%) of product as a white solid (R_f = 0.19, 40% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75(d, 4H, J=7.4 Hz), 7.59(d, 4H, J=6.6 Hz), 7.39(t, 4H, J=7.4 Hz), 7.30(dt, 4H, J=7.4, 1.1 Hz), 5.73(d, 2H, J=7.7 Hz), 4.68(m, 2H), 4.41(m, 4H), 4.21(m, 2H), 3.76(s, 6H), 3.18(ABX d, 4H, J=4.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.77, 155.64, 143.73, 143.62, 141.27, 127.71, 127.06, 125.06, 119.97, 67.21, 53.20, 52.81, 47.05, 41.09. MS calculated for $C_{38}H_{36}N_2O_8S_2$=712.80; found (Maldi), 735.4 (M+Na), 751.3 (M+K).

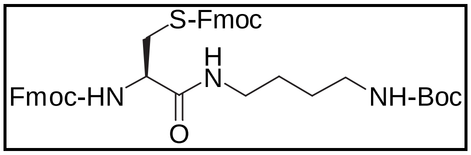


2-[3-[2-(1-tert-Butoxycarbonyl-3-methyl-butylcarbamoyl)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-ethyldisulfanyl]-2-(9H-fluoren-9-ylmethoxycarbonylamino)-propionylamino]-4-methyl-pentanoic acid *tert*-butyl ester (12)

To a solution of **8** (38.3 mg, 0.052 mmol) in 3 mL of CH_3CN was added TEA (0.30 mL, 2.15 mmol) and benzyl mercaptan (0.15 mL, 1.28 mmol). The reaction was stirred at room temp for 50 minutes at which point the reaction was concentrated *in vacuo* to give a clear oil. This was purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes, 10 x 150 mm) to give 12.0 mg (45%) of product as a clear oil (R_f = 0.36, 40% EtOAc/hexanes). Reported for monomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.76(d, 2H, J=7.4 Hz), 7.59(d, 2H, J=7.7 Hz), 7.41(t, 2H, J=7.4 Hz), 7.32(t, 2H, J=7.4Hz), 6.51(d, 1H, J=6.6 Hz), 5.75(m, 1H), 4.50(m, 4H), 4.23(t, 1H, J=7.2 Hz), 3.05(m, 1H), 2.75(m, 1H), 1.63(m, 3H), 1.46(s, 9H), 0.94(d, 6H, J=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.57, 169.15, 155.88, 143.74, 143.63, 141.35, 127.81, 127.12, 125.07, 125.00, 120.06, 82.23, 67.23, 56.10, 51.79, 47.15, 41.55, 27.98, 27.12, 24.98, 22.77, 22.02. MS calculated for $C_{66}H_{56}N_2O_8S_2$=1023.28; found (MaldiMS), 1045.5 (M+Na).

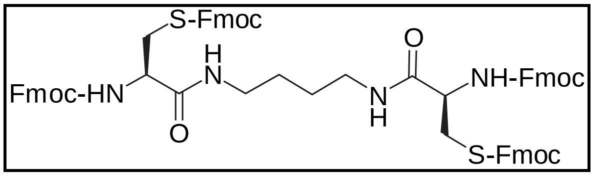
Boc-DAB (13)

To a solution of DAB (3.35 g, 38.0 mmol) in 35 mL of $CHCl_3$ was added a solution of Boc_2O (1.59 g, 7.3 mmol) in 15 mL of $CHCl_3$ over 4 hrs. After stirring for an additional 14 hrs, the resulting slurry was diluted with CH_2Cl_2 and washed with 1N $NaHCO_3$ (2x). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 1.37 g (quant) of product as a clear oil (R_f = 0.10, 10% MeOH/$CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 4.88(br s, 1H), 3.12(m, 2H), 2.72(m, 2H), 1.49(m, 4H), 1.45(s, 9H), 1.18(m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.79, 41.54, 40.11, 30.64, 28.14, 27.19. MS calculated for $C_9H_{20}N_2O_2$=188.27; found (ESIMS), 189.2 (M+H).



Fmoc-Cys(Fmoc)-DAB-Boc (14)

To a 0˚C solution of Fmoc-Cys(Fmoc)OH (101.6 mg, 0.18 mmol) and HOBt (36.2 mg, 0.27 mmol) in 1.2 mL of DMF was added EDCI (38.0 mg, 0.20 mmol). After stirring for 30 minutes a solution of Boc-DAB in 0.8 mL of DMF was added. The reaction was stirred at 0˚C for three hours and then at ambient temp for an additional 14 hours. This was diluted with EtOAc, washed with H_2O, 1N $NaHCO_3$, 1N $KHSO_4$, and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 2% MeOH/CH_2Cl_2, 20 x 200 mm) to give 91.4 mg (69%) of product as a white solid (R_f = 0.46, 5% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$/MeOH-d_4) δ 7.74(m, 4H), 7.55(m, 4H), 7.36(m, 4H), 7.27(m, 4H), 6.47(d, 1H, J=8.5 Hz), 4.45-4.32(m, 5H), 4.22(m, 2H), 3.44(s, 2H), 3.37(overlap dd, 1H), 3.20(m, 3H), 3.07(m, 2H), 1.48(m, 4H), 1.42(s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$/MeOH-d_4) δ 170.96, 169.96, 156.33, 143.49, 143.39, 142.86, 140.98, 127.71, 127.50, 126.96, 126.83, 124.88, 119.83, 119.71, 79.06, 69.47, 66.97, 54.50, 46.77, 46.29, 39.64, 39.08, 33.11, 28.10, 26.94, 26.06. MS calculated for $C_{42}H_{45}N_3O_7S$=735.87; found (ESIMS), 736.4 (M).



Fmoc-Cys(Fmoc)-DAB-Cys(Fmoc)-Fmoc (15)

Fmoc-Cys(Fmoc)-DAB-Boc (345.0 mg, 0.47 mmol) was dissolved in 10 mL of 4N HCl in dioxane. After stirring for 1.5 hr, the reaction was concentrated *in vacuo* and azeotrope to a white solid with MeOH and Et_2O. The HCl salt was used without further purification.

To a 0˚C solution of Fmoc-Cys(Fmoc)-OH (267.8 mg, 0.47 mmol) and HOBt (102.3 mg, 0.76 mmol) in 3 mL of DMF was added EDCI (98.5 mg, 0.51 mmol). After stirring for 40 minutes a solution of the HCl salt from above in 2.5 mL of DMF and DIEA (0.094 mL, 0.54 mmol) were added. The reaction was stirred at 0˚C for three hours and then at ambient temp for an additional 15 hours. This was diluted with EtOAc, washed with H_2O, 1N $NaHCO_3$, 1N $KHSO_4$, and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 2% MeOH/$CHCl_3$, 25 x 300 mm) to give 392.4 mg (71%) of product as a white solid (R_f = 0.32, 5% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07(d, 1H, J=5.2 Hz), 8.04(d, 1H, J=5.5 Hz), 7.88(m, 8H), 7.70(m, 6H), 7.57(m, 4H), 7.36(m, 8H), 7.28(m, 8H), 4.51(d, 4H, J=7.0 Hz), 4.31(m, 4H), 4.19(m, 6H), 3.24(dd, 2H, J=12.8, 4.8 Hz), 3.02(m, 6H), 1.38(m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.86, 169.30, 155.84, 143.75, 143.16, 140.73, 129.32, 127.83, 127.66, 127.20, 127.06, 125.29, 124.97, 124.84, 120.25, 120.12, 68.58, 65.83, 54.02, 46.60, 46.14, 32.91, 26.28. MS calculated for $C_{70}H_{62}N_4O_{10}S_2$=1183.36; found (ESIMS), 1183.4 (M).