Supporting Information

For

Cyclic Peptide Synthesis with Thioacids

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Compounds	Expt.	Spectra
***S*-(9-Fluorenylmethyl) *N*-*tert*-butoxycarbonyl-D-thiotryptophanate** (**1**)	SI-4	SI-14, 15
***S*-(9-Fluorenylmethyl) *N*-*tert*-butoxycarbonyl-L-leucyl-D-thiotryptophanate** (**2**)	SI-4	SI-16, 17
***S*-(9-Fluorenylmethyl) *N*-*tert*-butoxycarbonyl-D-valyl-L-leucyl-D-thiotryptophanate** (**3**)	SI-5	SI-18, 19
***S*-(9-Fluorenylmethyl) *N*-*tert*-butoxycarbonyl-L-alanyl-D-valyl-L-leucyl-D-thiotryptophanate** (**4**)	SI-5	SI-20, 21
***S*-(9-Fluorenylmethyl) *N*-fluorenylmethyloxycarbonyl-δ-*O*-*tert*-butyl-D-glutamyl-L-alanyl- D-valyl-L-leucyl-D-thiotryptophanate** (**5**)	SI-6	SI-22, 23
***cyclo*-(δ-*O*-*tert*-Butyl-D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-tryptophan)** (**6**)	SI-6	SI-24, 25
***cyclo*-(D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-tryptophan)** (**7**)	SI-7	SI-26, 27
***cyclo*-(L-phenylalanyl-D-tryptophanyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-L-proline)** (**8**)	SI-8	SI-28 to 30
L-363,301 [*cyclo*-(L-phenylalanyl-D-tryptophanyl-L-lysyl-L-threonyl-L-phenylalanyl-L-proline), **9**]	SI-8	SI-31 to 35 and 40
***cyclo*-(L-phenylalanyl-D-tryptophanyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**10**)	SI-9	SI-36 to 38
***cyclo*-(L-phenylalanyl-D-tryptophanyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**11**)	SI-9	SI-39 to 42
***cyclo*-[N^{ω}-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**)	SI-10	SI-43 to 49
***cyclo*-bis[N^{ω}-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**13**)	SI-10	SI-50 to 53
***cyclo*-(L-phenylalaninyl-L-serinyl-N^{ω}-*p*-toluenesulfonyl-L-arginyl-L-threonyl-L-leucyl-L-proline)** (**14**)	SI-11	SI-54, 55
***cyclo*-bis(L-alaninyl-L-tryptophanyl-glycinyl-L-phenylalanine)** (**15**)	SI-11	SI-56, 57

***S,S'*-Bis(2,4,6-trimethoxybenzyl) *N-tert*-butoxycarbonyl-L-dithioaspartate (16)**	SI-12	SI-58, 59
***S,S'*-Bis(2,4,6-trimethoxybenzyl) N^{α}-benzyloxycarbonyl-N^{ε}-fluorenylmethoxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-L-dithioaspartate (17)**	SI-12	SI-60, 61
***cyclo*-[N^{α}-benzyloxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-N^{γ}-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine] (20)**	SI-13	SI-62 to 67

***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-D-thiotryptophanate** (**1**). To a solution of Boc-D-Trp-OH (1.7 g, 5.7 mmol) and 9-fluorenylmethylthiol (1.0 g, 4.7 mmol) in CH_2Cl_2/DMF (5/1, 9.4 mL) were added EDCI (1.1 g, 5.7 mmol) and DMAP (29 mg, 0.24 mmol), and the reaction mixture was stirred for 1 h. The reaction was quenched with water (100 mL) and the mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (24 g, heptane/EtOAc = 9/1 to 4/1) gave a yellow foam (2.3 g, 98%). $[\alpha]^{24}_{D}$ = 61.3 (*c* = 4.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.78 (d *J* = 7.5 Hz, 2H), 7.63 (d *J* = 7.5 Hz, 1H), 7.59 (d *J* = 7.5 Hz, 2H), 7.42 (dd *J* = 7.5, 7.5 Hz, 2H), 7.34 (d *J* = 7.5 Hz, 2H), 7.33 (dd *J* = 7.5, 1.2 Hz, 1H), 7.21 (ddd *J* = 6.9, 6.9, 1.2 Hz, 1H), 7.14 (ddd *J* = 6.9, 6.9, 1.2 Hz, 1H), 6.79 (br s, 1H), 5.01 (d *J* = 8.1 Hz, 1H), 4.69 (dd *J* = 14.1, 6.0 Hz, 1H), 4.16 (t *J* = 6.0 Hz, 1H), 3.51 (d *J* = 6.0 Hz, 2H), 3.19 (d *J* = 5.7 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 155.2, 145.5, 145.5, 141.2, 141.1, 136.1, 127.7, 127.5, 127.3, 127.1, 124.9, 123.2, 123.0, 122.3, 119.9, 119.9, 119.8, 118.7, 111.3, 109.6, 80.3, 60.9, 46.7, 32.3, 28.3, 28.0; ESIHRMS: *m/z* calcd. for $C_{30}H_{30}N_2O_3SNa$ $(M + Na)^+$ 521.1875, found 521.1884.

***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-L-leucyl-D-thiotryptophanate** (**2**). **1** (750 mg, 1.50 mmol) Was dissolved in 40% TFA/CH_2Cl_2 (15 mL), and the solution was stirred for 15 min. The volatiles were removed *in vacuo*, and the residual TFA was removed by azeotropic distillation with toluene *in vacuo*. In another flask, Boc-Leu-OH (420 mg, 1.80 mmol) and HOBt.H_2O (350 mg, 2.25 mmol) were suspended in CH_2Cl_2/DMF (5/1, 3 mL), and EDCI (3.50 mg, 1.80 mmol) was added. The reaction mixture was stirred for 15 min, and DIPEA (260 μL, 1.50 mmol) was added, followed by a solution of the residue above in CH_2Cl_2/DMF (5/1, 12 mL). The reaction mixture was stirred for further 1 h, and then poured to water (100 mL). The mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (24 g, heptane/EtOAc = 9/1 to 2/1) gave a yellow syrup (670 mg, 73%). $[\alpha]^{23}_{D}$ = 25.0 (*c* = 4.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.76 (d *J* = 7.5 Hz, 2H), 7.58 (d *J* = 7.5 Hz, 1H), 7.57 (d *J* = 7.5 Hz, 2H), 7.41 (dd *J* = 7.5, 7.5 Hz, 2H), 7.36-7.30 (m, 3H), 7.16 (ddd *J* = 6.9, 1.2 Hz, 1H), 7.11 (ddd *J* = 6.9, 1.2 Hz, 1H), 6.84 (br d *J* = 3.9 Hz, 1H), 6.67 (br d *J* = 6.9 Hz, 1H), 4.94 (dd *J* = 13.8, 6.3 Hz, 1H), 4.94-4.80 (m, 1H), 4.18-4.00 (m, 1H), 4.11 (t *J* = 6.0 Hz, 1H), 3.51 (dd *J* = 13.5, 6.0 Hz, 1H), 3.43 (dd *J* = 13.5, 6.0 Hz, 1H), 3.17 (br d *J* = 3.6 Hz, 2H), 1.58-1.28 (m, 3H), 1.41 (s, 9H), 0.83 (d *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 172.6, 155.7, 145.4, 141.1, 136.2, 127.7, 127.4, 127.1, 124.8, 123.1, 122.3, 119.9, 119.8, 119.8, 118.5, 111.3, 109.4, 80.2, 59.5, 53.1, 46.6, 40.9, 32.3, 28.3, 28.0, 24.6, 22.8, 21.8; ESIHRMS: *m/z* calcd. for $C_{36}H_{41}N_3O_4SNa$ $(M + Na)^+$ 634.2715, found 634.2726.

***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-D-valyl-L-leucyl-D-thiotryptophanate** (**3**). **2** (500 mg, 0.82 mmol) Was dissolved in 40% TFA/CH_2Cl_2 (8.2 mL), and the solution was stirred for 15 min. The volatiles were removed *in vacuo*, and the residual TFA was removed by azeotropic distillation with toluene *in vacuo*. In another flask, Boc-D-Val-OH (210 mg, 0.96 mmol) and HOBt.H_2O (190 mg, 1.20 mmol) were suspended in CH_2Cl_2/DMF (5/1, 2.0 mL), and EDCI (190 mg, 0.96 mmol) was added. The reaction mixture was stirred for 15 min, and DIPEA (140 μL, 0.82 mmol) was added, followed by a solution of the residue above in CH_2Cl_2/DMF (5/1, 6.0 mL). The reaction mixture was stirred for further 1 h, and then poured to water (100 mL). The mixture was extracted with EtOAc, and the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (24 g, heptane/EtOAc = 9/1 to 2/1) gave a yellow syrup (480 mg, 83%). $[\alpha]^{23}_{D}$ = 8.1(*c* = 4.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.75 (d *J* = 7.5 Hz, 2H), 7.62-7.49 (m, 3H), 7.40 (dd *J* = 7.5, 7.5 Hz, 2H), 7.37-7.24 (m, 4H), 7.16 (dd *J* = 6.9, 6.9 Hz, 1H), 7.07 (dd *J* = 6.9, 6.9 Hz, 1H), 6.84 (br d *J* = 1.5 Hz, 1H), 6.76 (br d *J* = 8.1 Hz, 1H), 5.20 (br d, *J* = 7.2 Hz, 1H), 4.88 (dd *J* = 14.1, 6.0 Hz, 1H), 4.47-4.36 (m, 1H), 4.11 (t *J* = 6.0 Hz, 1H), 4.07-3.97 (m, 1H), 3.49 (dd *J* = 13.2, 6.0 Hz, 1H), 3.40 (dd *J* = 13.2, 6.0 Hz, 1H), 3.25 (dd *J* = 14.7, 6.0 Hz, 1H), 3.15 (dd *J* = 14.7, 6.0 Hz, 1H), 2.10 (dq, *J* = 12.0, 5.4 Hz, 1H), 1.46 (s, 9H), 1.55-1.35 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90-0.73 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 171.7, 171.6, 156.1, 145.4, 141.0, 136.2, 127.7, 127.5, 127.3, 127.1, 124.8, 123.3, 122.3, 119.9, 119.8, 119.7, 118.7, 111.4, 109.3, 80.3, 59.8, 59.1, 51.9, 46.5, 40.5, 32.5, 31.2, 28.3, 27.8, 24.6, 23.0, 21.4, 19.4, 17.3; ESIHRMS: *m/z* calcd. for $C_{41}H_{50}N_4O_5SNa$ $(M + Na)^+$ 733.3400, found 733.3412.

***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-L-alanyl-D-valyl-L-leucyl-D-thiotryptophanate** (**4**). **3** (400 mg, 0.56 mmol) Was dissolved in 40% TFA/CH_2Cl_2 (5.6 mL), and the solution was stirred for 15 min. The volatiles were removed *in vacuo*, and the residual TFA was removed by azeotropic distillation with toluene *in vacuo*. In another flask, Boc-Ala-OH (130 mg, 0.67 mmol) and HOBt.H_2O (130 mg, 0.85 mmol) were suspended in CH_2Cl_2/DMF (5/1, 1.4 mL), and EDCI (130 mg, 0.67 mmol) was added. The reaction mixture was stirred for 15 min, and DIPEA (98 μL, 0.56 mmol) was added, followed by a solution of the residue above in CH_2Cl_2/DMF (5/1, 4.2 mL). The reaction mixture was stirred for further 1 h, and then poured to water (100 mL). The mixture was extracted with EtOAc, and the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (24 g, heptane/EtOAc = 9/1 to 1/1) gave a yellow syrup (330 mg, 75%). $[\alpha]^{25}_{D}$ = 9.5 (*c* = 4.41, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 7.75 (d *J* = 7.8 Hz, 2H), 7.59 (d *J* = 7.2 Hz, 1H), 7.58 (d *J* = 7.2 Hz, 1H), 7.52 (d *J* = 7.8 Hz, 2H), 7.40 (dd *J* = 7.2, 7.2 Hz, 2H), 7.37-7.24 (m, 3H), 7.15 (dd *J* = 6.9, 6.9 Hz, 1H), 7.07 (dd *J* = 6.9, 6.9 Hz, 1H), 7.06-6.99 (m, 1H), 6.94 (br d *J* = 5.7 Hz, 1H), 6.89 (d *J* = 1.8 Hz, 1H), 5.27 (br d, *J* = 5.7 Hz, 1H), 5.20 (br s, 1H), 4.88 (dd *J* = 13.8, 7.2 Hz, 1H), 4.49-4.22 (m, 3H), 4.16-4.02 (m, 2H), 3.51

(dd J = 13.5, 6.0 Hz, 1H), 3.35 (dd J = 13.5, 6.0 Hz, 1H), 3.25-3.10 (m, 2H), 2.10 (dq, J = 12.0, 5.4 Hz, 1H), 1.61-1.03 (m, 3H), 1.47 (s, 9H), 1.21 (d, J = 7.2 Hz, 3H), 0.49 (d, J = 6.9 Hz, 3H), 1.20-0.70 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 176.5, 173.9, 172.4, 171.7, 155.6, 145.5, 141.0, 136.1, 127.7, 127.3, 127.1, 127.1, 124.8, 124.8, 123.4, 122.1, 119.9, 119.5, 118.5, 111.4, 109.5, 80.4, 80.1, 59.5, 58.5, 52.3, 50.4, 49.4, 46.6, 40.2, 32.5, 30.9, 28.3, 28.3, 27.4, 24.7, 22.9, 22.7, 21.3, 19.4, 18.2, 17.6, 14.2; ESIHRMS: *m/z* calcd. for $C_{44}H_{55}N_5O_6SNa$ $(M + Na)^+$ 804.3771, found 804.3766.

***S*-(9-Fluorenylmethyl) *N*-fluorenylmethyloxycarbonyl-δ-*O*-*tert*-butyl-D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-thiotryptophanate** (**5**). **4** (100 mg, 0.13 mmol) Was dissolved in 40% TFA/CH_2Cl_2 (1.3 mL), and the solution was stirred for 15 min. The volatiles were removed *in vacuo*, and the residual TFA was removed by azeotropic distillation with toluene *in vacuo*. In another flask, Boc-D-Glu(^{t}Bu)-OH (65 mg, 0.15 mmol) and HOBt.H_2O (29 mg, 0.19 mmol) were suspended in CH_2Cl_2/DMF (5/1, 0.33 mL), and EDCI (29 mg, 0.15 mmol) was added. The reaction mixture was stirred for 15 min, and DIPEA (22 μL, 0.13 mmol) was added, followed by a solution of the residue above in CH_2Cl_2/DMF (5/1, 1.0 mL). The reaction mixture was stirred for further 1 h, and then poured to water (10 mL). The mixture was extracted with EtOAc, and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (12 g, heptanes/EtOAc = 3/1 to CH_2Cl_2/MeOH) gave a yellow syrup (120 mg, 86%). $[\alpha]^{23}_{D}$ = 10.5 (c = 3.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 7.89-7.18 (m, 20H), 7.11 (dd J = 6.9, 6.9 Hz, 1H), 7.03 (dd J = 6.9, 6.9 Hz, 1H), 6.98-6.82 (m, 2H), 6.78 (br s, 1H), 6.11 (br s, 1H), 4.96-4.80 (m, 1H), 4.63-4.49 (m, 1H), 4.63-3.96 (m, 7H), 3.57-3.40 (m, 1H), 3.38-3.24 (m, 1H), 3.24-3.10 (m, 2H), 2.40-1.71 (m, 5H), 1.67-1.13 (m, 3H), 1.45 (s, 9H), 1.35-1.18 (m, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.0 Hz, 3H), 0.75 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 172.7, 172.6, 172.1, 171.4, 171.2, 162.7, 156.4, 145.5, 144.0, 143.6, 141.3, 141.0, 140.9, 136.1, 127.7, 127.6, 127.4, 127.1, 125.2, 124.8, 124.8, 123.6, 121.8, 119.9, 119.8, 119.2, 118.5, 111.4, 109.6, 80.9, 67.2, 60.0, 58.6, 54.3, 52.1, 48.9, 47.1, 46.6, 41.2, 36.5, 34.0, 32.4, 32.0, 32.0, 31.6, 31.5, 31.2, 29.7, 29.5, 29.4, 28.1, 27.2, 24.7, 22.8, 21.8, 19.3, 18.2, 14.2; MALDIHRMS: *m/z* calcd. for $C_{63}H_{72}N_6O_9SNa$ $(M + Na)^+$ 1111.4973, found 1111.4939.

***cyclo*-(δ-*O*-*tert*-Butyl-D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-tryptophan)** (**6**). To a solution of **5** (25 mg, 0.023 mmol) in DMF (180 μL) was added piperidine (45 μL) at 0 ^{o}C. The reaction mixture was stirred for 15 min, then the volatiles were removed under high vacuum. The residual piperidine was removed by azeotropic distillation with toluene *in vacuo*, and the residue was dissolved in DMF (4.6 mL). 2,4-Dinitrofluorobenzene (3.4 μL, 0.027 mmol) was added to it, and the reaction mixture was stirred for 5 min. DMF was removed under high vacuum, and the residue was purified by silica gel chromatography (4 g, CH_2Cl_2/acetone = 9/1 to acetone only) to give a white foam (7.4 mg, 49%). $[\alpha]^{26}$

$_D$ = 3.2 (*c* = 0.509, DMF); ^{1}H NMR (500 MHz, DMF-d_7) δ 10.90 (br s, 1H), 8.75 (d *J* = 8.0 Hz, 1H), 8.61 (d *J* = 8.0 Hz, 1H), 8.53 (d *J* = 6.0 Hz, 1H), 7.68 (d *J* = 7.5 Hz, 1H), 7.66 (d *J* = 7.5 Hz, 1H), 7.48 (d *J* = 9.0 Hz, 1H), 7.40 (d *J* = 8.5 Hz, 1H), 7.31 (s, 1H), 7.10 (dd *J* = 7.0, 7.0 Hz, 1H), 7.02 (dd *J* = 7.0, 7.0 Hz, 1H), 4.59 (td *J* = 7.5, 7.5 Hz, 1H), 4.51 (tt *J* = 7.5, 1.5 Hz, 1H), 4.44 (td *J* = 7.0, 7.0 Hz, 1H), 4.26-4.16 (m, 2H), 3.45 (br s, 2H), 3.11 (dd *J* = 14.0, 11.5 Hz, 1H), 2.27 (dt *J* = 14.0, 11.5 Hz, 2H), 2.10-2.00 (m, 1H), 1.96-1.84 (m, 2H), 1.46 (s, 9H), 1.24 (d *J* = 11.5 Hz, 3H), 1.45-1.15 (m, 3H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 7.5 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 6.5 Hz, 3H),; ^{13}C NMR (125 MHz, DMF-d_7) δ 173.8, 173.4, 173.3, 173.0, 172.7, 171.9, 138.0, 128.5, 124.9, 122.0, 119.5, 119.2, 112.5, 112.1, 80.8, 59.0, 56.4, 53.9, 53.3, 48.7, 48.6, 40.1, 32.6, 32.0, 28.7, 28.6, 28.3, 25.3, 23.0, 22.9, 20.0, 18.9, 15.1; ESIHRMS: *m/z* calcd. for $C_{34}H_{50}N_6O_7Na$ $(M + Na)^+$ 677.3639, found 677.3642.

***cyclo*-(D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-tryptophan)** (**7**). **Procedure A**: **6** (8.0 mg, 0.0012 mmol) Was dissolved in TFA/CH_2Cl_2/Et_3SiH (5/4/1, v/v/v, 120 μL), and the reaction mixture was stirred for 2 h. The volatiles were removed *in vacuo*, and purification of the residue (4 g, CH_2Cl_2/acetone = 1/1 to acetone/ EtOH = 9/1) gave **7** as a yellowish syrup (4.1 mg, 56%). **Procedure B**: **5** (25.0 mg, 0.0023 mmol) Was dissolved in TFA/CH_2Cl_2/Et_3SiH (5/4/1, v/v/v, 230 μL), and the reaction mixture was stirred for 2 h. The residual TFA was removed by azeotropic distillation with toluene *in vacuo*. The residue was dissolved in DMF (180 μL), and piperidine (45 μL) was added at 0 ^{o}C. The reaction mixture was stirred for 15 min, then the volatiles were removed under high vacuum. The residual piperidine was removed by azeotropic distillation with toluene *in vacuo*, and the residue was dissolved in DMF (4.6 mL). $CsHCO_3$ (13.4 mg, 0.069 mmol) and 2,4-dinitrofluorobenzene (3.4 μL, 0.027 mmol) were added to it, and the reaction mixture was stirred for 5 min. DMF was removed under high vacuum and purification of the residue by silica gel chromatography (4 g, CH_2Cl_2/acetone = 1/1 to acetone/ EtOH = 9/1) gave **7** as a yellowish syrup (6.0 mg, 44%). $[\alpha]^{26}_D$ = -9.8 (*c* = 0.96, DMSO); lit. $[\alpha]^{20}_D$ = -10.0 (*c* = 1.00, DMSO); ^{1}H NMR (500 MHz, DMF-d_7) δ 11.26 (s, 1H), 9.09 (d *J* = 7.5 Hz, 1H), 8.81 (d *J* = 6.0 Hz, 1H), 8.75 (d *J* = 7.5 Hz, 1H), 8.02 (d *J* = 7.0 Hz, 1H), 7.88 (d *J* = 9.0 Hz, 1H), 7.83 (d *J* = 8.0 Hz, 1H), 7.60 (d *J* = 8.0 Hz 1H), 7.51 (s, 1H), 7.26 (dd *J* = 7.0, 7.0 Hz, 1H), 7.19 (dd *J* = 7.0, 7.0 Hz, 1H), 4.75 (dt *J* = 7.0, 7.0 Hz, 1H), 4.69-4.61 (m, 2H), 4.49 (td *J* = 7.0, 7.0 Hz, 1H), 4.35 (t *J* = 8.0 Hz, 1H), 3.61 (br d *J* = 9.0 Hz, 1H), 3.29 (dd *J* = 14.5, 11.5 Hz, 1H), 2.57-2.42 (m, 2H), 2.31-2.19 (m, 1H), 2.18-2.05 (m, 2H), 1.62-1.35 (m, 6H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.32-1.23 (m, 2H). 1.14-1.01 (m, 6H), 0.96 (d *J* = 6.0 Hz, 3H), 0.88 (d *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, DMF-d_7) δ 174.6, 172.9, 172.8, 172.5, 171.8, 171.1, 137.0, 127.5, 123.9, 120.9, 119.2, 118.4, 118.2, 116.8, 114.4, 111.5, 111.0, 121.5, 79.3, 69.2, 66.5, 58.7, 55.8, 52.6, 52.3, 48.0, 39.3, 46.0, 27.5, 27.3, 24.3, 21.9, 21.9, 19.0, 18.2, 14.4; ESIHRMS: *m/z* calcd. for $C_{30}H_{42}N_6O_7Na$ $(M + Na)^+$ 621.3013, found 621.3032.

***cyclo*-(L-phenylalanyl-D-tryptophanyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-L-proline)** (**8**) Fmoc-Phe-D-Trp-Lys(Cbz)-Thr-Phe- Pro-SFm (30 mg, 0.022 mmol) was dissolved in 20% piperidine in DMF (200 μL) and the reaction mixture was stirred for 15 min. Then, volatiles were removed *in vacuo*, followed by azeotropic removal of piperidine with toluene. To the solution of the residue in DMF (4.4 mL) was added Sanger's reagent (3.0 μL, 0.024 mmol). The reaction mixture was stirred for 5 min, and DMF was removed under high vacuum. Purification of the residue by preparative TLC (0.5 mm, $CHCl_3$/MeOH = 9/1) gave a white form (12.7 mg, 62%). $[\alpha]_D^{23}$ = -60.6 (*c* = 0.79, CH_3CN); ^{1}H NMR (500 MHz, CD_3CN) δ 9.44 (br. s), 7.61 (d, *J* = 7.5 Hz, 2H), 7.45-7.00 (m, 23H), 5.70 (br. s, 1H), 5.10 (s, 2H), 4.56 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 4.47 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 4.37-4.21 (m, 2H), 4.15 (br. s, 1H), 3.86 (br. s, 1H), 3.80-3.73 (m, 1H), 3.48 (d, *J* = 4.5 Hz, 1H), 3.34-3.24 (m, 1H), 3.22-2.86 (m, 7H), 1.95-0.80 (m, 13H); ^{1}H-^{1}H cosy showed five CON*H* cross peaks at δ 7.62, 7.22, 7.12, 7.03 and 6.99; ESIHRMS calcd for $C_{52}H_{60}N_8O_9Na$ $[M + Na]^+$ 963.4381, found 963.4512; LCMS: 5-65% B over 4.5 min with a flow rate of 0.7 mL/min and 215 nm UV detection, retention time = 3.70 min.

L-363,301 [*cyclo*-(L-phenylalanyl-D-tryptophanyl-L-lysyl-L-threonyl-L-phenylalanyl-L-proline), **9**] *cyclo*-[Phe-D-Trp-Lys(Cbz)-Thr- Phe-Pro] (15 mg, 0.016 mmol) was dissolved in THF/H_2O (3/1 v/v, 500 mL) and 20% Pd/C (15 mg) was added to it. The suspension was stirred for 12 h under H_2 atmosphere (balloon). The reaction mixture was filtrated through celite pad, and the filtrate was concentrated in vacuo. Purification of the residue by preparative TLC (0.5 mm, $CHCl_3$/MeOH = 3/1) gave L-363,301 (**9**, 9.0 mg, 70%) as colorless syrup. $[\alpha]_D^{24}$ = -148.0 (*c* = 0.20, CH_3OH); lit.[2] $[\alpha]_D^{22}$ = -23.6 (*c* = 1.0, CH_3OH); ^{1}H NMR (500 MHz, DMF-d_7) δ 11.11 (br s 1H), 8.71 (d *J* = 6.0 Hz, 1H, Lys), 8.44 (d *J* = 4.0 Hz, 1H, Phe^2), 8.39 (d *J* = 7.0 Hz, 1H, Trp), 7.63 (d *J* = 7.5 Hz, 1H), 7.50 (d *J* = 5.5 Hz, 1H, Phe^6), 7.49 (d *J* = 5.5 Hz, 1H), 7.45 (d *J* = 7.5 Hz, 1H), 7.40-7.10 (m, 10H), 7.25 (d *J* = 6.0 Hz, 1H, Thr), 7.06 (dd *J* = 7.0, 7.0 Hz, 1H), 6.97 (d *J* = 4.5 Hz, 1H), 4.75 (ddd, *J* = 8.0, 7.0, 6.5 Hz, 1H, Trp-α), 4.67 (dt, *J* = 5.5, 5.5 Hz, 1H, Phe^6-α), 4.44 (td *J* = 8.0, 7.0 Hz, 1H, Phe^2-α), 4.36 (dd *J* = 6.0, 3.5 Hz, 1H, Thr-α), 4.21 (br t *J* = 5.0 Hz, 1H, Thr-β), 3.99 (br s, 1H, Lys-α), 3.86 (br d *J* = 8.0 Hz, 1H, Pro-α), 3.40-3.32 (m, 2H), 3.19 (dd *J* = 9.0, 5.5 Hz, 1H, Phe^6-β), 3.13 (dd *J* = 14.0, 8.0 Hz, 1H, Trp-β), 3.10 (dd *J* = 9.0, 5.5 Hz, 1H, Phe^6-β), 3.07-2.98 (m, 1H), 3.30 (d *J* = 8.0 Hz, 2H, Phe^2-β), 2.86 (dd *J* = 9.0, 6.5 Hz, 1H, Trp-β), 1.94-1.00 (m, 12H), 1.09 (d *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMF-d_7) δ 172.3 (Trp), 171.9 (Lys), 171.2 (Phe^2), 170.4 (Pro), 170.2 (Thr), 169.6 (Phe^6), 137.4, 136.9, 136.7, 129.7, 129.5, 128.7, 127.9, 127.7, 127.1, 126.3, 124.0, 121.1, 121.0, 118.5, 118.4, 118.4, 111.5, 110.1, 67.5, 61.3, 56.4, 54.7, 54.7, 54.6, 54.0, 53.9, 46.1, 38.5, 37.2, 30.9, 30.7, 27.7, 23.2, 23.0, 22.5, 21.4, 17.5, 13.7; ESIHRMS calcd for $C_{44}H_{55}N_8O_7$ $[M + H]^+$ 807.4194, found 807.4283; LCMS: 5-15% B over 0.5 min then 15-35% B over 4.5 min with a flow rate of 0.7 mL/min and 215 nm UV detection,

retention time = 3.07 min; CD spectrum was recorded with 0.1 mg of **9** in 5 mM phosphate buffer (pH 7.4).

***cyclo*-(L-phenylalanyl-D-tryptophanyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**10**) Fmoc-Phe-D-Trp-Lys(Cbz)-Thr-Phe-D-Pro-SFm (100 mg, 0.073 mmol) was dissolved in 20% piperidine in DMF (700 μL) and the reaction mixture was stirred for 15 min. Then, volatiles were removed *in vacuo*, followed by azeotropic removal of piperidine with toluene. To the solution of the residue in DMF (14 mL) was added Sanger's reagent (10 μL, 0.080 mmol). The reaction mixture was stirred for 5 min, and DMF was removed under high vacuum. Purification of the residue by preparative TLC ($CHCl_3$/MeOH = 9/1) gave a white form (47.0 mg, 69%). $[\alpha]_D^{24}$ = 16.7 (*c* = 0.77, CH_3CN); ^{1}H NMR (500 MHz, CD_3CN) δ 9.44 (br. s), 7.64 (m, 3H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.38-6.83 (m, 21H), 5.68 (br. s, 1H), 5.09 (s, 2H), 4.55 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 1H), 4.52-4.46 (m, 1H), 4.44 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.41-4.35 (m, 1H), 4.17 (dt, *J* = 10.0, 5.0 Hz, 1H), 4.11-3.95 (m, 2H), 3.49 (t, *J* = 7.5 Hz, 1H), 3.12-2.95 (m, 6H), 2.91 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.80 (1H, *J* = 14.0, 6.0 Hz, 1H), 1.80-1.54 (m, 4H), 1.36-1.16 (m, 4H), 1.23 (d, *J* = 6.5 Hz, 3H), 0.88-0.70 (m, 2H); ^{1}H-^{1}H cosy showed five CON*H* cross peaks at δ 7.57, 7.55, 7.43, 7.08 and 6.87; ESIHRMS calcd for $C_{52}H_{60}N_8O_9Na$ $[M + Na]^+$ 963.4381, found 963.4534; LCMS: 5-65% B over 4.5 min with a flow rate of 0.7 mL/min and 215 nm UV detection, retention time = 3.42 min.

***cyclo*-(L-phenylalanyl-D-tryptophanyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**11**) *cyclo*-[Phe-D-Trp-Lys(Cbz)-Thr-Phe-D-Pro] (10 mg, 0.016 mmol) was dissolved in THF/H_2O (3/1 v/v, 500 mL) and 20% Pd/C (15 mg) was added to it. The suspension was stirred for 12 h under H_2 atmosphere (balloon). The reaction mixture was filtrated through celite pad, and the filtrate was concentrated in vacuo. Purification of the residue by preparative TLC ($CHCl_3$/MeOH = 3/1) gave **11** (6.7 mg, 79%) as colorless syrup. $[\alpha]_D^{24}$ = 9.9 (*c* = 0.45, CH_3OH); 1H NMR (500 MHz, CD_3OD) δ 7.46 (d *J* = 7.5 Hz, 1H), 7.38-7.15 (m, 11H), 7.10 (dd *J* = 7.5, 7.5 Hz, 1H), 7.02 (dd *J* = 7.5, 7.5 Hz, 1H), 6.95 (s, 1H), 4.56 (d *J* = 3.5 Hz, 1H), 4.52 (dd *J* = 10.0, 5.0 Hz, 1H), 4.44-4.36 (m, 2H), 4.20-4.10 (m, 2H), 4.03 (dd *J* = 11.0, 4.0 Hz, 1H), 3.68-3.57 (m, 2H), 3.15(dd *J* = 12.5, 5.0 Hz, 1H), 3.10-3.01 (m, 3H), 2.86 (dd *J* = 13.0, 9.5 Hz, 1H), 2.78 (dd *J* = 14.0, 5.5 Hz, 1H), 2.71 (dd *J* = 12.5, 9.0 Hz, 1H), 2.61-2.46 (m, 2H), 2.19-2.12 (m, 1H), 1.79-1.50 (m, 6H), 1.34-1.21 (m, 2H), 1.29 (d *J* = 6.5 Hz, 3H), 0.64-0.44 (m, 2H); ^{13}C NMR (125 MHz, DMF-d_7) δ 172.1, 171.8, 171.0, 170.9, 170.8, 171.2, 138.3, 137.5, 137.0, 129.7, 129.6, 129.5, 128.6, 128.3, 128.1, 128.0, 127.8, 127.0, 126.5, 124.0, 121.2, 121.1, 118.6, 118.5, 111.7, 109.9, 68.3, 68.2, 60.6, 60.5, 57.2, 56.9, 55.9, 55.9, 55.5, 54.5, 54.5, 54.4, 53.6, 47.0, 46.9, 46.8, 40.2, 38.4, 37.1, 37.1, 30.9, 28.3, 28.2, 26.9, 24.1, 22.8, 18.7; ESIHRMS calcd for $C_{44}H_{55}N_8O_7$ $[M + H]^+$ 807.4194, found 807.4269; LCMS: 5-15% B over 0.5 min then 15-35% B over 4.5 min with a flow rate of 0.7 mL/min and 215 nm UV detection, retention time = 2.85 min.

***cyclo*-[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**). To a solution of Fmoc-Arg(Pbf)-Thr-Leu-Pro-Phe-Ser-SFm (50 mg, 0.036 mmol) in DMF (280 μL) was added piperidine (70 μL) at 0 ^{o}C. The reaction mixture was stirred for 15 min, then the volatiles were removed under high vacuum. The residual piperidine was removed by azeotropic distillation with toluene *in vacuo*, and the residue was dissolved in DMF (7.2 mL). 2,4-Dinitrofluorobenzene (5.4 μL, 0.043 mmol) was added to it, and the reaction mixture was stirred for 5 min. DMF was removed under high vacuum, and the residue was purified by HPLC to give **12** as a colorless syrup (13 mg, 36%) and **13** as a colorless syrup (4.1 mg, 12 %). $[\alpha]^{26}_{D}$ = -83.6 (*c* = 0.88, MeOH); Our sample contains two conformers (*ea.* 2:1) at 25 ^{o}C. ^{1}H NMR (500 MHz, CD_3OD) δ 7.36–7.16 (m, 5H), 4.70-4.63 (m, 2H), 4.41-4.14 (m, 4H), 4.08-3.98 (m, 2.4H), 3.95 (dd *J* = 11.0, 5.0 Hz, 0.3H), 3.91 (dd *J* = 11.0, 5.0 Hz, 0.3H), 3.78-3.67 (m, 1H), 3.59-3.45 (m, 2H), 3.43-3.09 (m, 4H), 3.01 & 3.00 (each s, 2H), 2.59 & 2.58 (each s, 3H), 2.53-2.52 (each s, 3H), 2.09-2.08 (each s, 3H), 2.02-1.49 (m, 6H), 1.47 & 1.46 (each s, 6H), 1.38-1.29 (m, 0.7H), 1.27 (d *J* = 6.5 Hz, 1H), 1.21-1.15 (m, 0.3H), 1.14 (d *J* = 6.5 Hz, 2H), 1.04 (d *J* = 6.5 Hz, 2H), 1.01-0.91 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.5, 174.9, 174.6, 173.6, 173.2, 173.0, 172.3, 172.2, 172.1, 171.8, 159.9, 158.1, 140.1, 139.4, 139.2, 130.3, 130.2, 129.6, 129.4, 127.9, 127.6, 126.1, 118.5, 87.7, 69.2, 67.8, 63.6, 62.8, 62.4, 62.0, 60.4, 59.6, 59.1, 58.7, 57.7, 57.1, 55.9, 55.8, 53.3, 51.1, 48.4, 48.1, 44.0, 41.9, 41.4, 40.1, 38.3, 35.3, 32.4, 30.0, 29.3, 27.4, 27.3, 26.8, 25.9, 25.9, 28.7, 22.3, 21.6, 21.5, 21.1, 20.1, 19.6, 18.4; ^{1}H NMR (500 MHz, DMF-d_7 at 100 ^{o}C) δ 7.36–7.21 (m, 5H), 6.64 (br s, 1H), 6.58 (br s, 2H), 4.66-4.16 (m, 7H), 3.96-3.84 (m, 2H), 3.71-3.59 (m, 1H), 3.57-3.33 (m, 3H), 3.31-3.23 (m, 2H), 3.06 (s, 2H), 2.67 (s, 3H), 2.59 (s, 3H), 2.13 (s, 3H), 2.09-1.86 (m, 6H), 1.79-1.54 (m, 4H), 1.51 (s, 6H), 1.22 (d *J* = 6.0 Hz, 3H), 1.02 (d *J* = 6.5 Hz, 3H), 0.97 (d *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMF-d_7 at 100 ^{o}C) δ 174.0, 172.8, 172.6, 172.0, 171.9, 159.6, 158.4, 139.1, 133.6, 130.7, 129.6, 127.6, 126.1, 118.1, 87.7, 68.9, 63.6, 63.5, 63.0, 61.0, 57.7, 57.6, 48.4, 42.1, 29.4, 27.8, 30.2, 26.1, 24.5, 22.5, 19.8, 18.6, 13.0; ESIHRMS calcd for $C_{46}H_{68}N_9O_{11}S$ $[M + H]^+$ 954.4759, found 954.4806; LCMS: 5% B for 0.5 min then 5-100% B over 6.5 min with a flow rate of 0.6 mL/min and 215 nm UV detection, retention time = 5.50 min.

***cyclo*-bis[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**13**). $[\alpha]^{27}_{D}$ = -60.8 (*c* = 0.35, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.40–77.12 (m, 10H),4.99-4.92 (m, 1H), 4.79-4.71 (m, 1H), 4.64-4.54 (m, 1H), 4.49-4.07 (m, 11H), 4.05-3.95 (m, 1H), 3.93-3.75 (m, 3H), 3.69-3.54 (m, 1H), 3.52-3.36 (m, 3H), 3.27-3.30 (m, 7H), 3.03-2.92 (m, 4H), 2.63-2.45 (m, 12H), 2.23-1.99 (m 8H), 1.97-1.49 (m, 12H), 1.49-1.37 (m, 12H), 1.35-1.27 (m, 2H), 1.24-1.12 (m, 4H), 1.05-0.84 (m, 12H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.8, 175.1, 174.8, 174.6, 174.4, 174.0, 173.6, 173.6, 173.4, 173.3, 173.1, 172.9, 172.4,

172.4, 159.9, 158.2, 139.4, 139.4, 139.3, 139.0, 138.1, 134.3, 133.5, 133.5, 130.4, 130.3, 130.2, 130.1, 130.1, 129.6, 129.5, 128.4, 127.9, 127.7, 126.0, 118.5, 87.7, 69.8, 68.8, 68.7, 67.8, 63.2, 63.1, 62.9, 62.7, 62.4, 62.0, 61.9, 60.9, 60.7, 59.2, 58.5, 58.1, 57.8, 57.1, 56.8, 56.8, 56.7, 56.2, 54.4, 52.6, 51.2, 44.0, 41.6, 41.3, 41.1, 37.1, 36.2, 33.0, 32.7, 30.5, 30.1, 29.6, 29.5, 26.1, 25.9, 25.8, 25.3, 25.1, 24.2, 24.1, 23.9, 23.8, 22.4, 22.3, 22.1, 21.3, 21.0, 20.0, 19.6, 18.4, 26.2, 28.7, 12.5; MALDIHRMS calcd for $C_{92}H_{134}N_{18}NaO_{22}S_2$ $[M + Na]^+$ 1929.9259, found 1929.9225; LCMS: 5% B for 0.5 min then 5-100% B over 6.5 min with a flow rate of 0.6 mL/min and 215 nm UV detection, retention time = 6.28 min.

***cyclo*-(L-phenylalaninyl-L-serinyl-*N*$^{\omega}$-*p*-toluenesulfonyl-L-argininyl-L-threonyl-L-leucyl-L-proline)** (**14**). To a solution of Fmoc-Phe-Ser-Arg(Tos)-Thr-Leu-Pro-SFm (50 mg, 0.039 mmol) in DMF (280 μL) was added piperidine (70 μL) at 0 ^{o}C. The reaction mixture was stirred for 15 min, then the volatiles were removed under high vacuum. The residual piperidine was removed by azeotropic distillation with toluene *in vacuo*, and the residue was dissolved in DMF (7.7 mL). 2,4-Dinitrofluorobenzene (5.8 μL, 0.045 mmol) was added to it, and the reaction mixture was stirred for 5 min. DMF was removed under high vacuum, and the residue was purified by silica gel chromatography (4 g, CH_2Cl_2/acetone = 9/1 to actone/EtOH = 8/2) to give **14** as a colorless syrup (16 mg, 49%). $[\alpha]^{28}_{D}$ = -47.2 (*c* = 0.30, $CHCl_3$/MeOH = 3/1), ESIHRMS calcd for $C_{40}H_{58}N_9O_{10}S$ $[M + H]^+$ 856.4027, found 856.4005; LCMS: 5% B for 0.5 min then 5-100% B over 6.5 min with a flow rate of 0.6 mL/min and 215 nm UV detection, retention time = 5.77 min.

***cyclo*-bis(L-alaninyl-L-tryptophanyl-glycinyl-L-phenylalanine)** (**15**). To a solution of Fmoc-Ala-Trp-Gly-Phe-SFm (50 mg, 0.056 mmol) in DMF (450 μL) was added piperidine (110 μL) at 0 ^{o}C. The reaction mixture was stirred for 15 min, then the volatiles were removed under high vacuum. The residual piperidine was removed by azeotropic distillation with toluene *in vacuo*, and the residue was dissolved in DMF (11 mL). 2,4-Dinitrofluorobenzene (8.4 μL, 0.067 mmol) was added to it, and the reaction mixture was stirred for 5 min. DMF was removed under high vacuum, and the residue was purified by silica gel chromatography (4 g, CH_2Cl_2/acetone = 3/1 to CH_2Cl_2/MeOH = 9/1) to give a white foam (10 mg, 40%) $[\alpha]^{26}_{D}$ = -21.9 (*c* = 0.88, $CHCl_3$/MeOH = 3/1); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ = 3/1) δ 7.52-7.41 (m, 2H), 7.40-7.33 (m, 1H), 7.31-6.94 (m, 17H), 4.37 (br s, 4H), 3.87-3.75 (m, 2H), 3.70-3.48 (m, 4H), 3.27-3.12 (m, 2H), 2.95-2.75 (m, 4H), 1.25-1.10 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 174.2, 174.1, 171.9, 137.9, 130.4, 129.9, 128.6, 128.3, 124.6, 123.1, 120.4, 119.4, 112.9, 111.0, 56.8, 56.4, 51.6, 44.6, 38.4, 27.7, 17.6; ESIHRMS calcd for $C_{50}H_{54}N_{10}NaO_8$ $[M + Na]^+$ Exact Mass: 945.4024, found 945.4057.

***S,S'*-Bis(2,4,6-trimethoxybenzyl) *N*-*tert*-butoxycarbonyl-L-dithioaspartate** (**16**). To a solution of

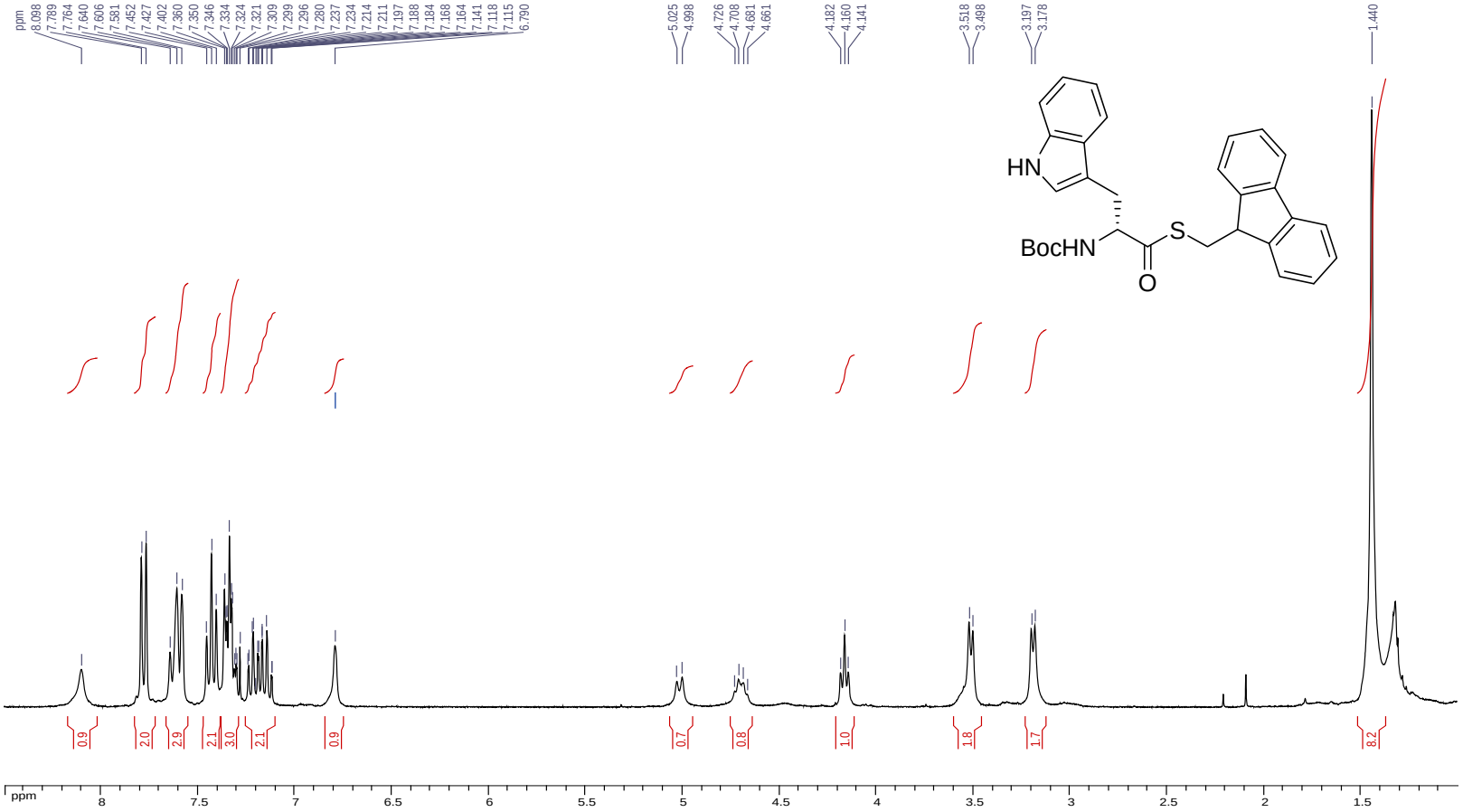
Boc-L-Asp-OH (1.0 g, 4.3 mmol), 2,4,6-trimethoxybenzylthiol (2.0 g, 9.3 mmol) and DIPEA (3.3 mL, 18.9 mmol) in CH_2Cl_2 (21 mL) was added PyBOP (4.9 g, 9.4 mmol). The reaction mixture was stirred for 1 h, and then the reaction was quenched with water (100 mL). The mixture was extracted with CH_2Cl_2 (50 mL x 3), and the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (40 g, heptane/EtOAc = 9/1 to 1/1) gave a white foam (2.7 g, 99%). $[\alpha]^{25}_D$ = 1.3 (*c* = 5.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (s, 4H), 5.63 (br d *J* = 9.6 Hz, 1H), 4.64 (ddd *J* = 9.6, 5.4, 4.2 Hz, 1H), 4.26 & 4.19 (ABq *J* = 12.0 Hz, 2H), 4.22 & 4.16 (ABq *J* = 12.3 Hz, 2H), 3.78 (s, 6H), 3.77 (s, 12H), 3.28 (dd, *J* = 16.2, 5.4 Hz, 1H), 3.00 (dd, *J* = 16.2, 4.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 197.4, 161.0, 160.9, 159.3, 159.2, 155.0, 104.5, 104.3, 90.5, 80.2, 57.2, 55.8, 55.3, 44.9, 28.3, 22.5, 22.3; ESIHRMS: *m/z* calcd. for $C_{29}H_{39}NO_{10}S_2Na$ $(M + Na)^+$ 648.1913, found 648.1912.

***S,S'*-Bis(2,4,6-trimethoxybenzyl) *N*$^{\alpha}$-benzyloxycarbonyl-*N*$^{\varepsilon}$-fluorenylmethoxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-L-dithioaspartate** (**17**). Boc-D-Trp-Leu-Asp(STmob)-STmob (100 mg, 0.11 mmol) Was dissolved in 40% TFA/CH_2Cl_2 (1.1 mL), and the solution was stirred for 5 min. The volatiles were removed *in vacuo*, and the residual TFA was removed by azeotropic distillation with toluene *in vacuo*. In another flask, Cbz-L-Fmoc-OH (65 mg, 0.13 mmol) and HOBt.H_2O (25 mg, 0.16 mmol) were suspended in CH_2Cl_2 (270 μL), and EDCI (25 mg, 0.13 mmol) was added. The reaction mixture was stirred for 15 min, and DIPEA (14 μL, 0.11 mmol) was added, followed by a solution of the residue above in CH_2Cl_2 (810 μL). The reaction mixture was stirred for further 1 h, and then poured to water (10 mL). The mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (4 g, heptane/EtOAc = 9/1 to CH_2Cl_2/MeOH = 50/1) gave a colorless syrup (90 mg, 64%). $[\alpha]^{22}_D$ = 19.6 (*c* = 3.86, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 7.77 (d *J* = 7.2 Hz, 2H), 7.60 (d *J* = 4.2 Hz, 3H) 7.50-7.20 (m, 9H), 7.17 (m, 3H), 6.83 (br d *J* = 7.8 Hz, 1H), 6.09 (s, 2H), 6.07 (s, 2H), 5.62 (br d *J* = 4.5 Hz, 1H), 5.24-4.78 (m, 5H), 4.72-4.56 (m, 1H), 4.55-4.33 (m, 2H), 4.31-4.15 (m, 3H), 4.13-3.98 (m, 2H), 3.78 (s, 6H), 3.77 (s, 6H), 3.73 (s, 6H), 3.45-3.27 (m, 2H), 3.24-2.75 (m, 5H), 3.27 (dd *J* = 16.5, 6.0 Hz, 1H), 1.93-1.15 (m, 7H), 1.10-0.95 (m, 2H), 0.87 (d *J* = 6.6 Hz, 3H), 0.85 (d *J* = 6.6 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 198.5, 172.2, 171.9, 171.3, 161.0, 161.0, 159.2, 159.2, 156.6, 156.4, 144.0, 141.3, 136.2, 136.0, 128.5, 128.3, 128.2, 128.1, 128.0, 127.7, 127.1, 125.0, 123.5, 122.0, 120.0, 119.5, 118.3, 111.4, 110.1, 104.3, 103.8, 90.6, 90.6, 67.1, 66.5, 55.8, 55.3, 54.0, 51.9, 47.3, 44.2, 40.4, 40.2, 31.3, 29.5, 26.6, 24.6, 23.1, 22.6, 22.4, 22.2, 21.7; MALDIHRMS: *m/z* calcd. for $C_{70}H_{80}N_6O_{15}S_2Na$ $(M + Na)^+$ 1331.5015, found 1331.5071.

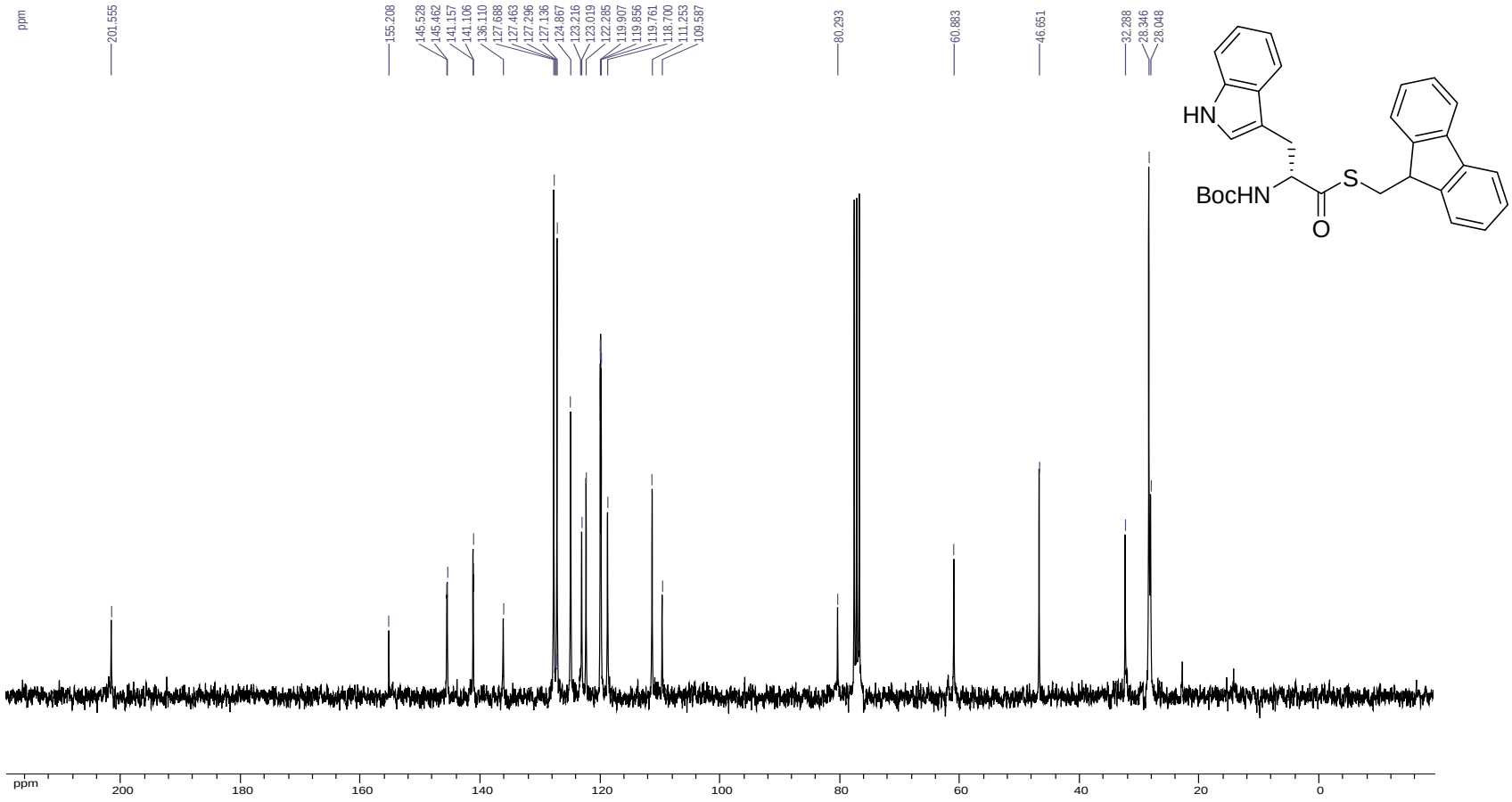
***cyclo*-[*N*$^{\alpha}$-benzyloxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-*N*$^{\gamma}$-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine]** (**20**). **17** (45 mg, 0.034 mmol) was dissolved in TFA/CH_2Cl_2/Et_3SiH

(4/5/1, 340 μL) and the reaction mixture was stirred for 2 h. The volatiles were removed by azeotropic distillation with toluene *in vacuo*. To a suspension of 2-acetamido-2-deoxy-β-D-glucopyranosylamine (9.0 mg, 0.041 mmol) and $CsHCO_3$ (20 mg, 0.10 mmol) in DMF (100 μL) was added a solution of the residue above in DMF (590 μL) dropwise over 20 min at -20 ^{o}C. The reaction mixture was warmed up to 0 ^{o}C, and stirred for 1 h. Piperidine (170 μL) was added to it, and the reaction mixture was stirred for further 15 min at the temperature, followed by removal of volatiles under high vacuum. The residue was dissolved in DMF (6.9 mL) and 2,4-dinitrofluorobenzene (5.1 μL, 0.041 mmol) was added to it. The reaction mixture was stirred for 5 min, and DMF was removed under high vacuum. The residue was dissolved in DMF (2 mL), and resulting cyclic peptides were triturated by Et_2O/heptane (1/1, 16 mL). The precipitate was purified by HPLC to give **19** (6.0 mg, 20%) as a yellowish form. $[\alpha]^{26}_{D}$ = -5.9 (*c* = 0.36, DMF); ^{1}H NMR (500 MHz, DMF-d_7) δ 10.84 (s, 1H), 8.65 (d J = 5.5 Hz, 1H, Leu), 8.26 (d *J* = 7.5 Hz, 1H, NHAc), 8.03 (d *J* = 8.5 Hz, 1H, Asn$^{\gamma}$), 8.01 (br s, 1H, Trp), 7.84 (d *J* = 9.0 Hz, 1H, Asn), 7.53-7.41 (m, 1H), 7.43 (d *J* = 8.0 Hz, 1H, Lys), 7.31-7.05 (m, 7H), 6.95 (dd *J* = 7.5, 7.5 Hz, 1H), 6.86 (dd *J* = 7.5, 7.5 Hz, 1H), 4.99 & 4.92 (ABq *J* = 12.5 Hz, 2H), 5.03-4.94 (m, 1H), 4.73 (dd *J* = 8.5, 8.5 Hz, 1H, H-1), 4.62 (dt *J* = 9.0, 7.0 Hz, 1H, Asn), 4.56-4.49 (m, 1H, Trp), 4.02-3.94 (m, 1H, Lys), 3.81 (td *J* = 6.5, 5.5 Hz, 1H, Leu), 3.67-3.30 (m, 8H), 3.20-3.14 (m, 2H, Lys$^{\delta}$), 2.68 (dd *J* = 15.0, 5.0 Hz, 1H), 2.66-2.49 (m, 2H), 2.42 (dd *J* = 15.0, 6.5 Hz, 1H), 1.74 (s, 3H), 1.66-0.55 (m, 9H), 0.60 (d *J* = 6.0 Hz, 3H), 0.51 (d *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, DMF-d_7) δ 174.1 (Trp), 172.9 (Lys), 172.2 (Leu), 171.7 (Ac), 170.8 (Asp), 170.6 (Asp$^{\gamma}$), 156.1, 137.5, 136.8, 128.5, 127.9, 127.7, 124.0, 121.1, 118.5, 118.4, 111.4, 109.6, 80.3, 79.0, 74.8, 71.3, 66.0, 61.7, 56.3, 55.4, 54.9, 53.4, 49.8, 39.8, 38.5, 37.7, 31.9, 27.6, 26.8, 24.2, 22.8, 22.3, 20.6, 20.4. The HMBC correlations observed between δ 8.03 and δ 170.6, δ 3.20-3.14 and δ 170.8, and δ 4.73 and δ 170.6 confirmed the regiochemistry of the ring-opening step of **18**. ESIHRMS: *m/z* calcd. for $C_{43}H_{58}N_8NaO_{12}$ $[M + Na]^+$ 901.4072, found 901.4076.

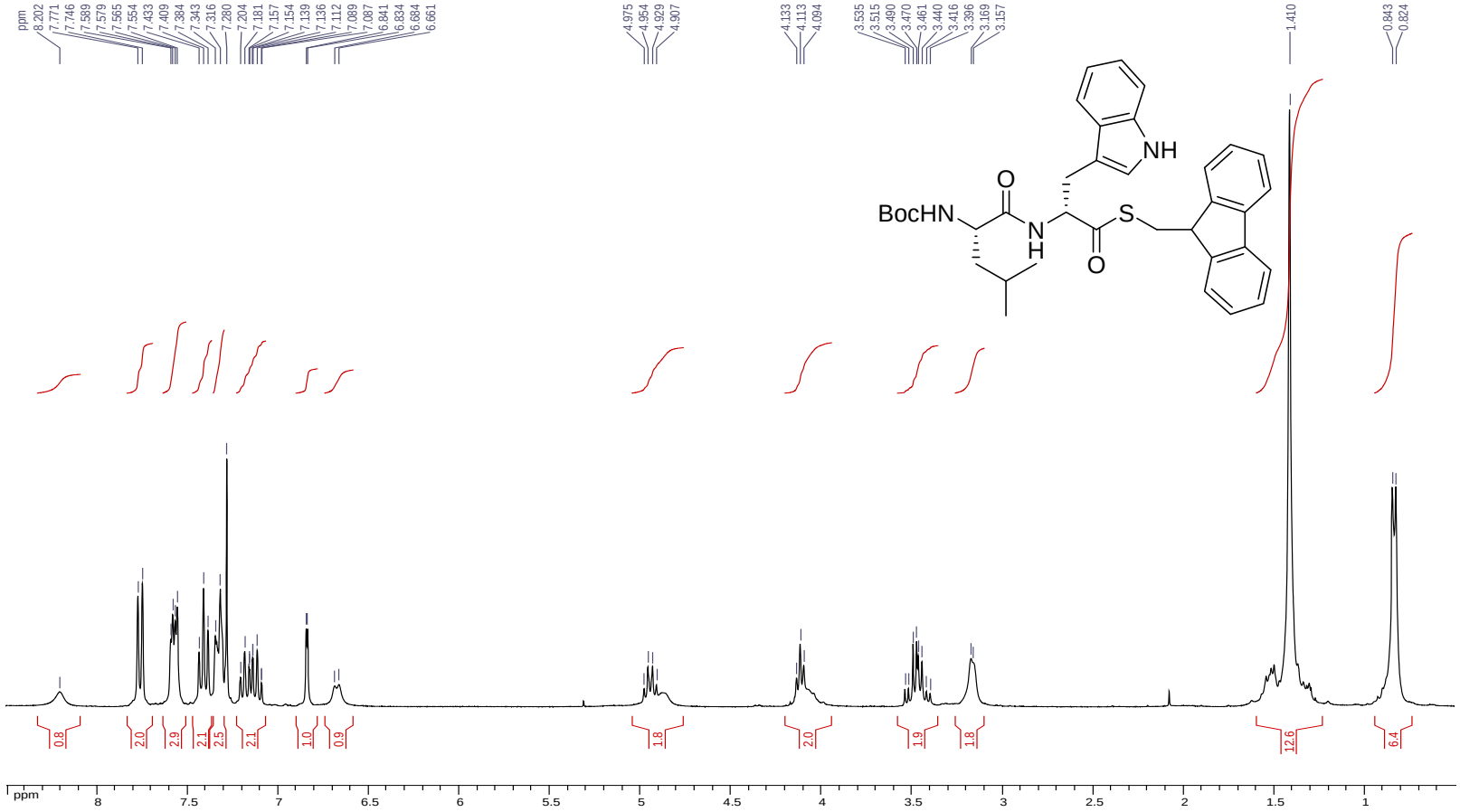
***S*-(9-Fluorenylmethyl) *N*-*tert*-butoxycarbonyl-D-thiotryptophanate (1)** ^{1}H NMR (300 MHz, $CDCl_3$)



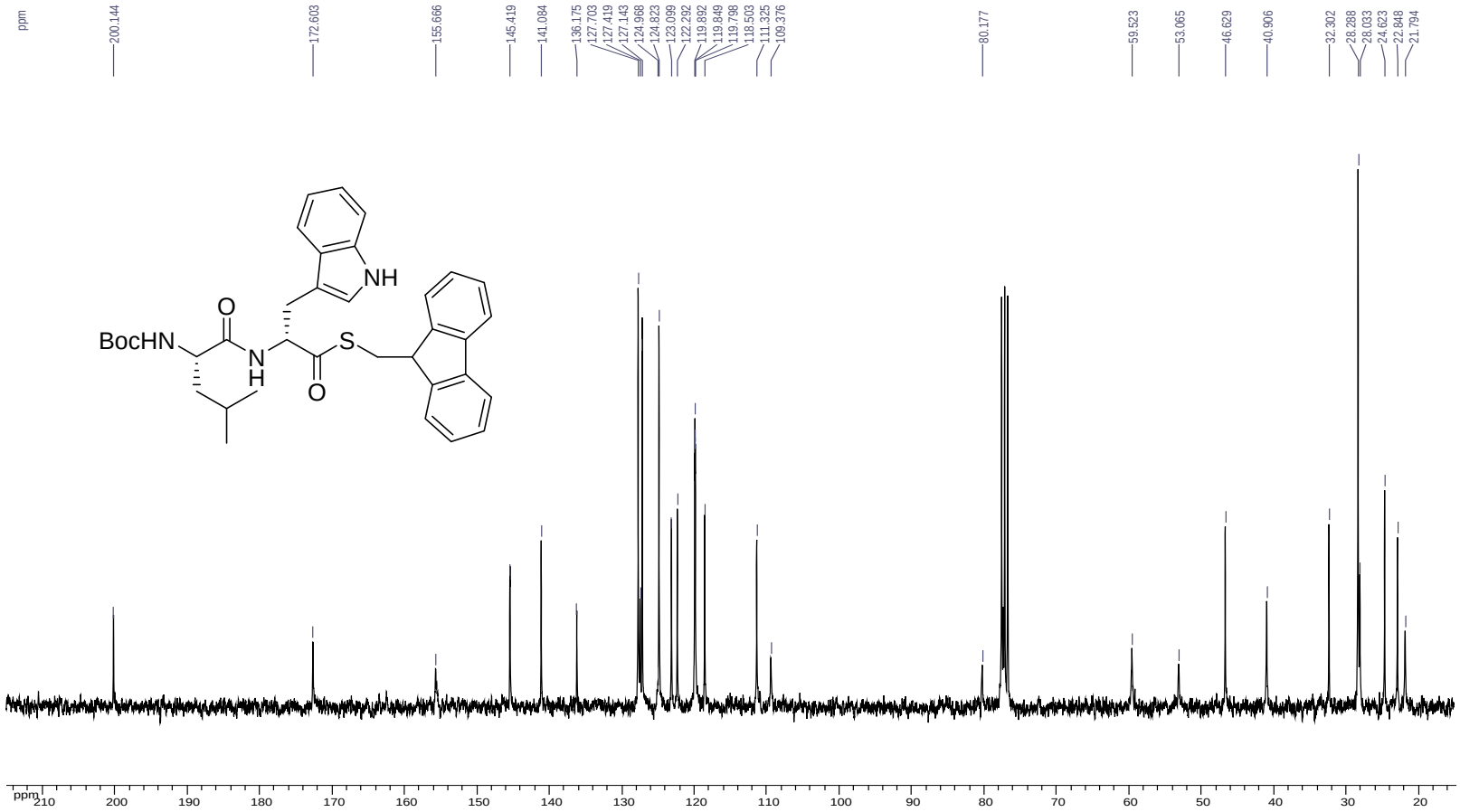
***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-D-thiotryptophanate (1)** ^{13}C NMR (75 MHz, $CDCl_3$)



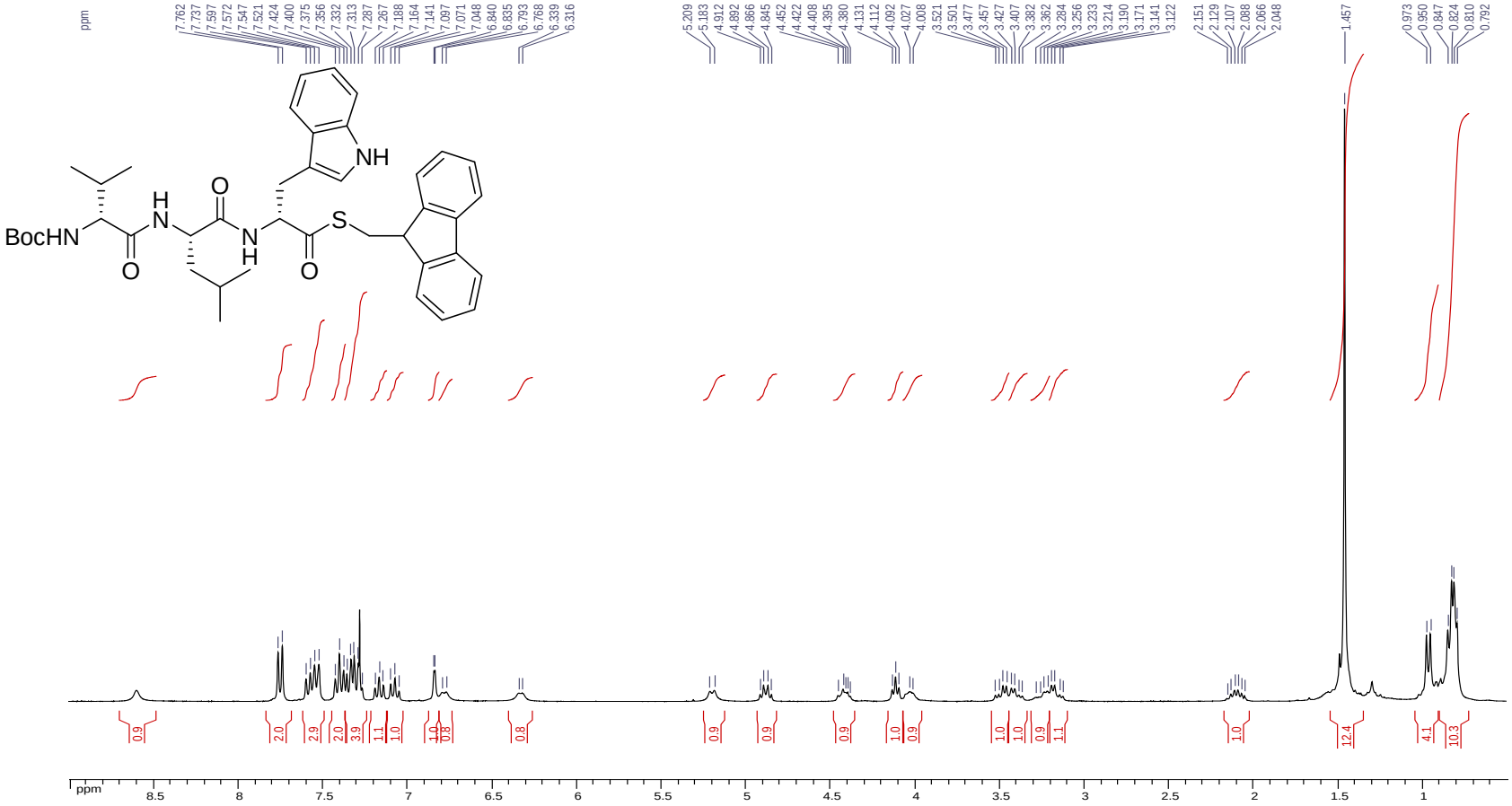
***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-L-leucyl-D-thiotryptophanate** (**2**) ^{1}H NMR (300 MHz, $CDCl_3$)



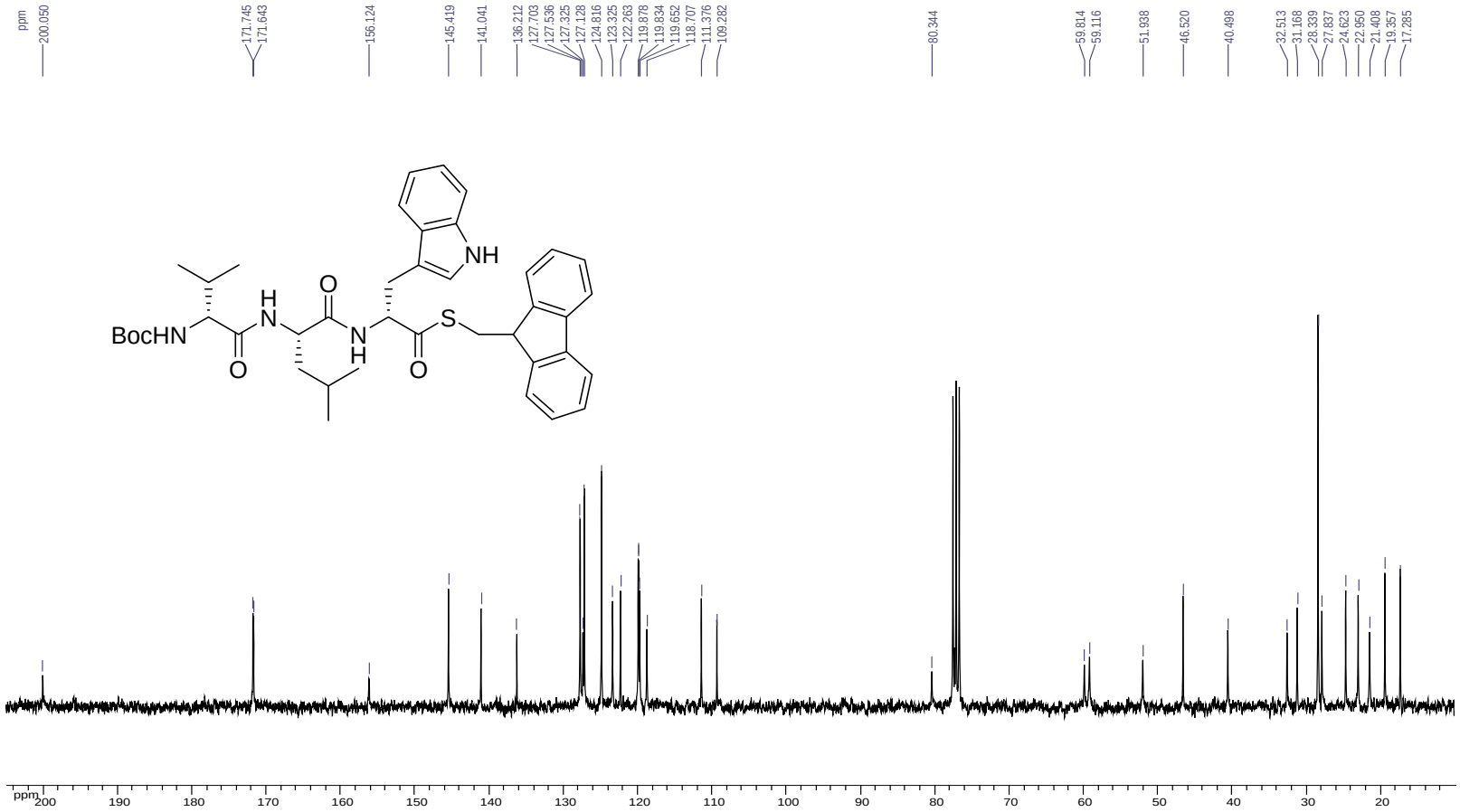
***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-L-leucyl-D-thiotryptophanate** (**2**) ^{13}C NMR (75 MHz, $CDCl_3$)



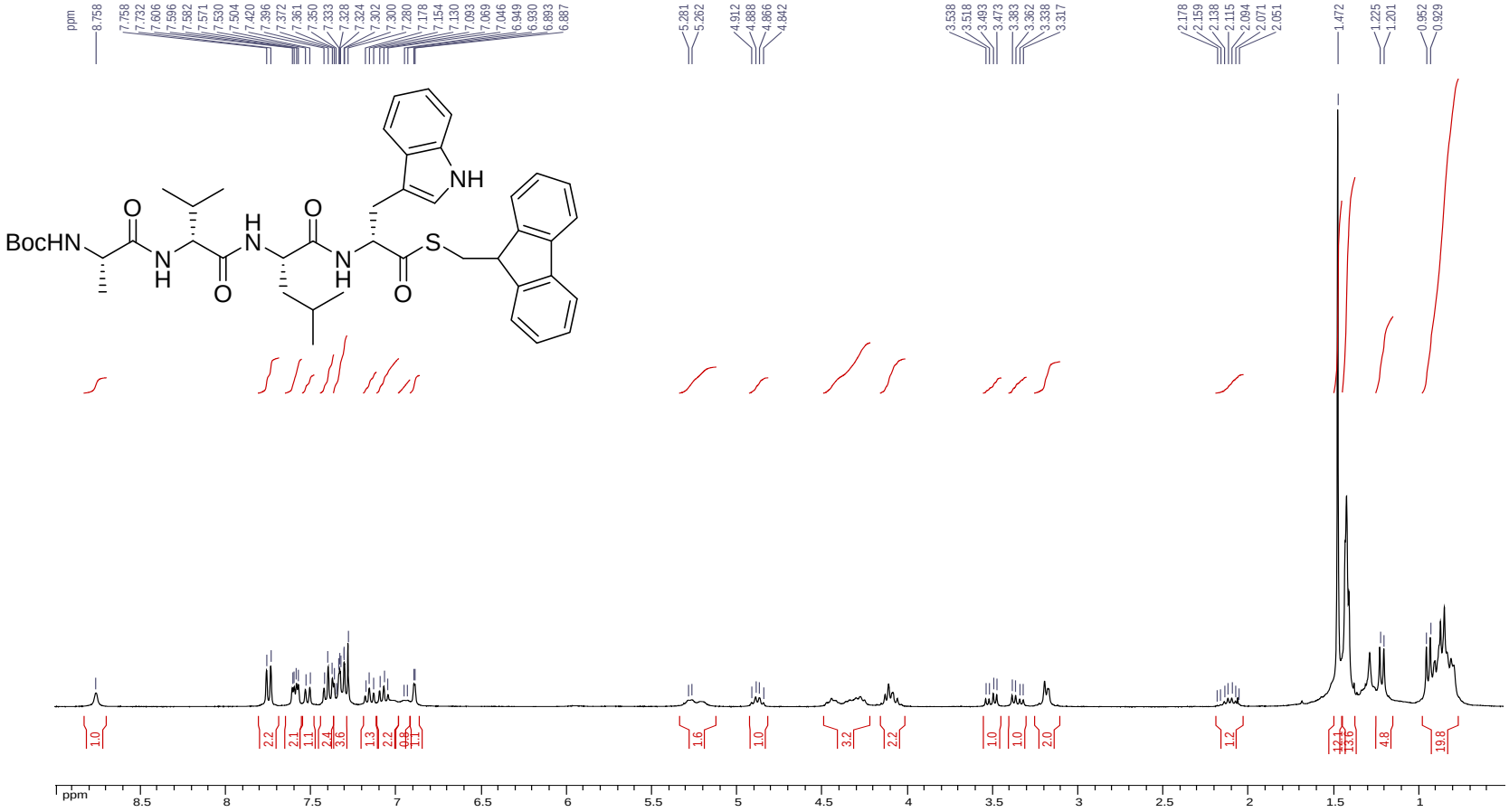
***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-D-valyl-L-leucyl-D-thiotryptophanate** (**3**) ^{1}H NMR (300 MHz, $CDCl_3$)



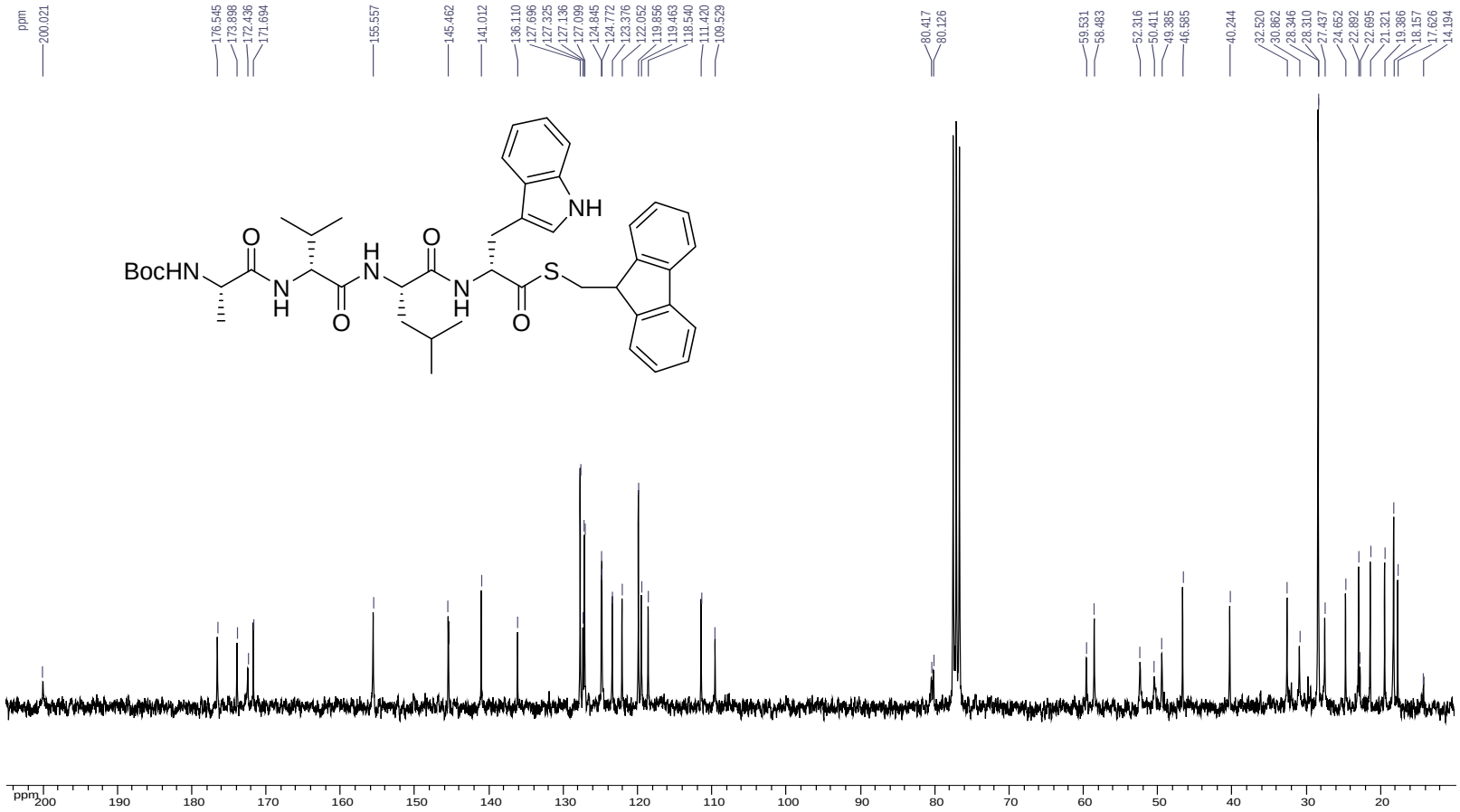
***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-D-valyl-L-leucyl-D-thiotryptophanate** (**3**) ^{13}C NMR (75 MHz, $CDCl_3$)



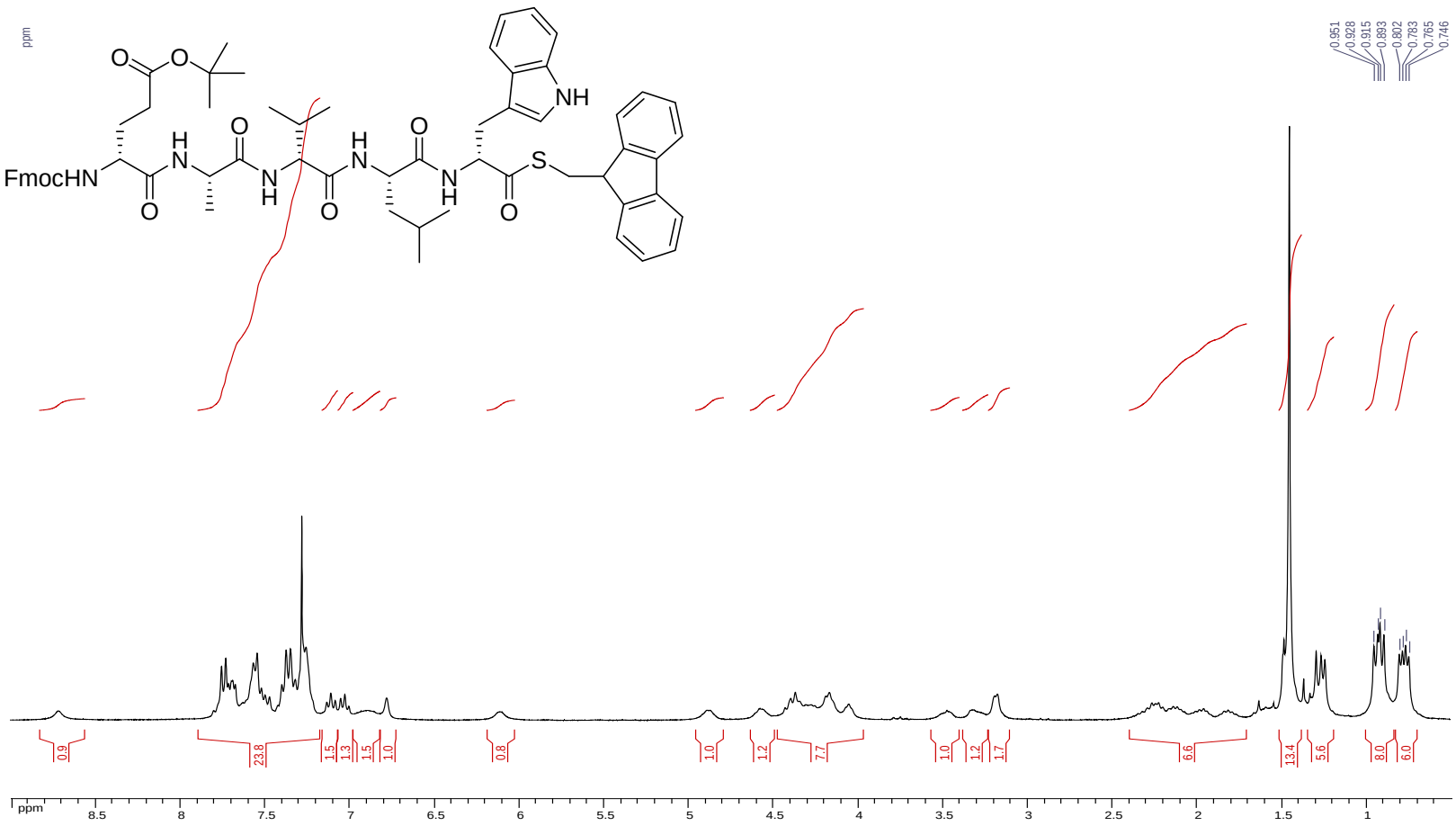
***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-L-alanyl-D-valyl-L-leucyl-D-thiotryptophanate (4)** ^{1}H NMR (300 MHz, $CDCl_3$)



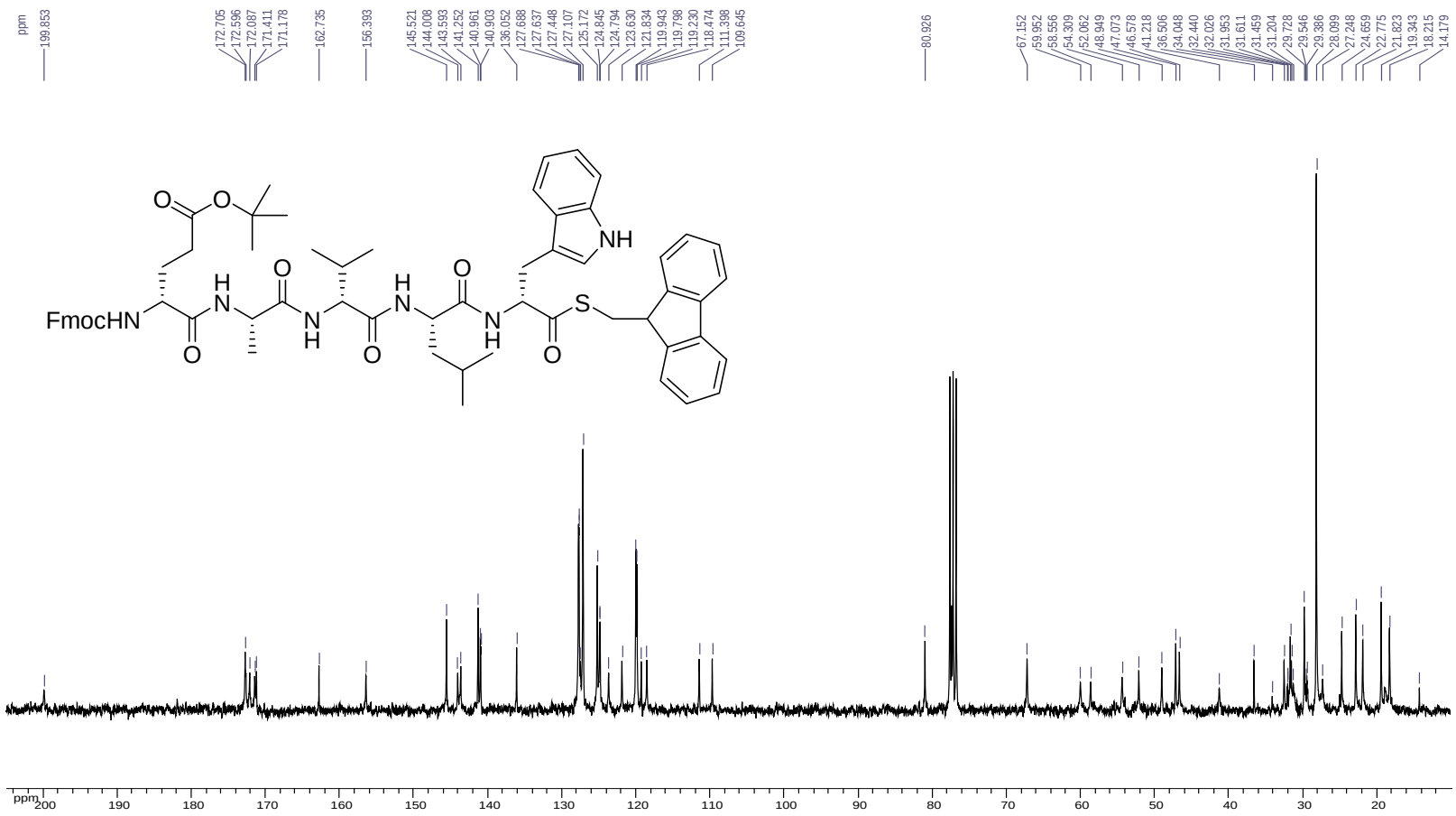
***S*-(9-Fluorenylmethyl) *N-tert*-butoxycarbonyl-L-alanyl-D-valyl-L-leucyl-D-thiotryptophanate (4)** ^{13}C NMR (75 MHz, $CDCl_3$)



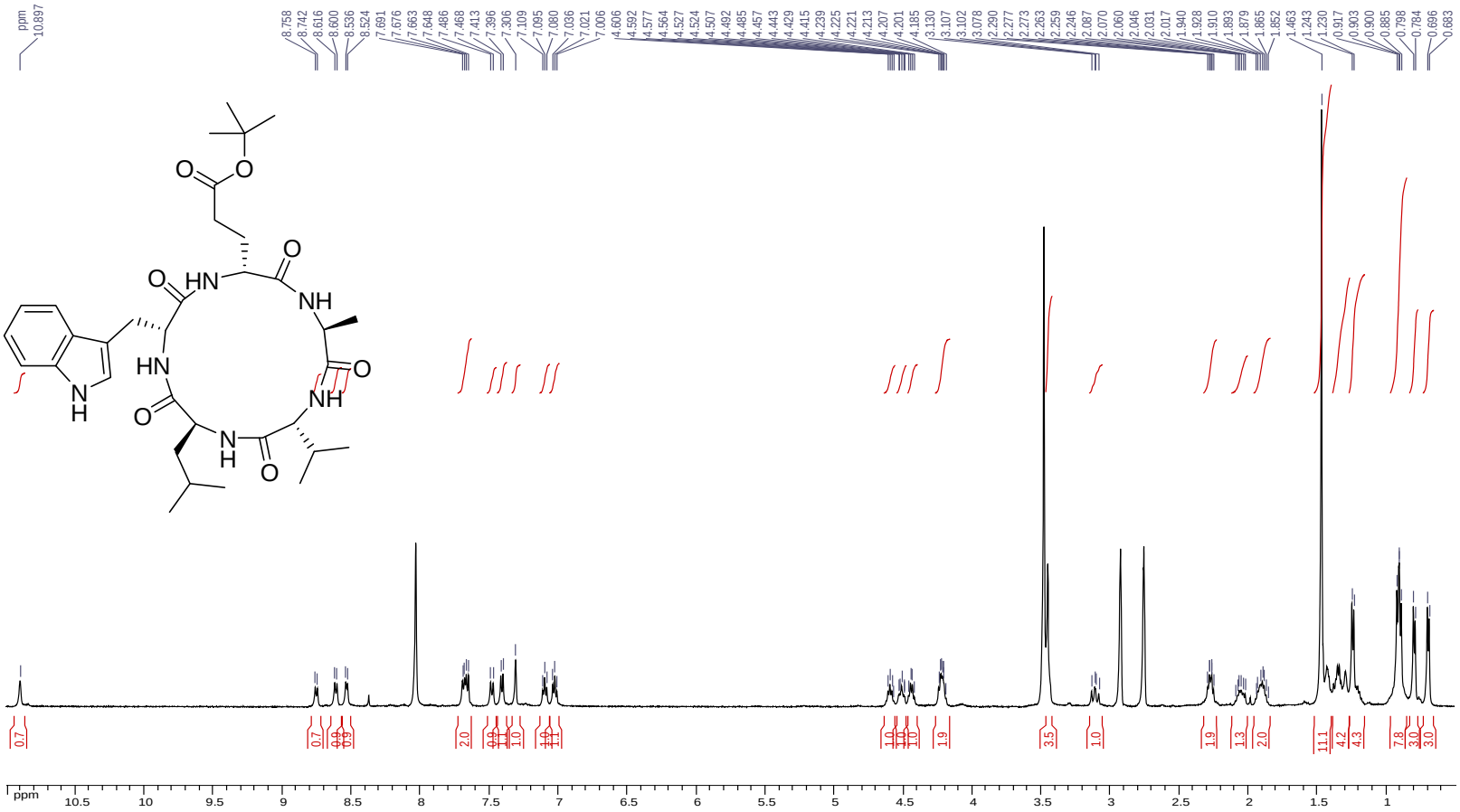
***S*-(9-Fluorenylmethyl) *N*-fluorenylmethyloxycarbonyl-δ-*O*-*tert*-butyl-D-glutamyl-L-alanyl- D-valyl-L-leucyl-D-thiotryptophanate** (**5**) ^{1}H NMR (300 MHz, $CDCl_3$)



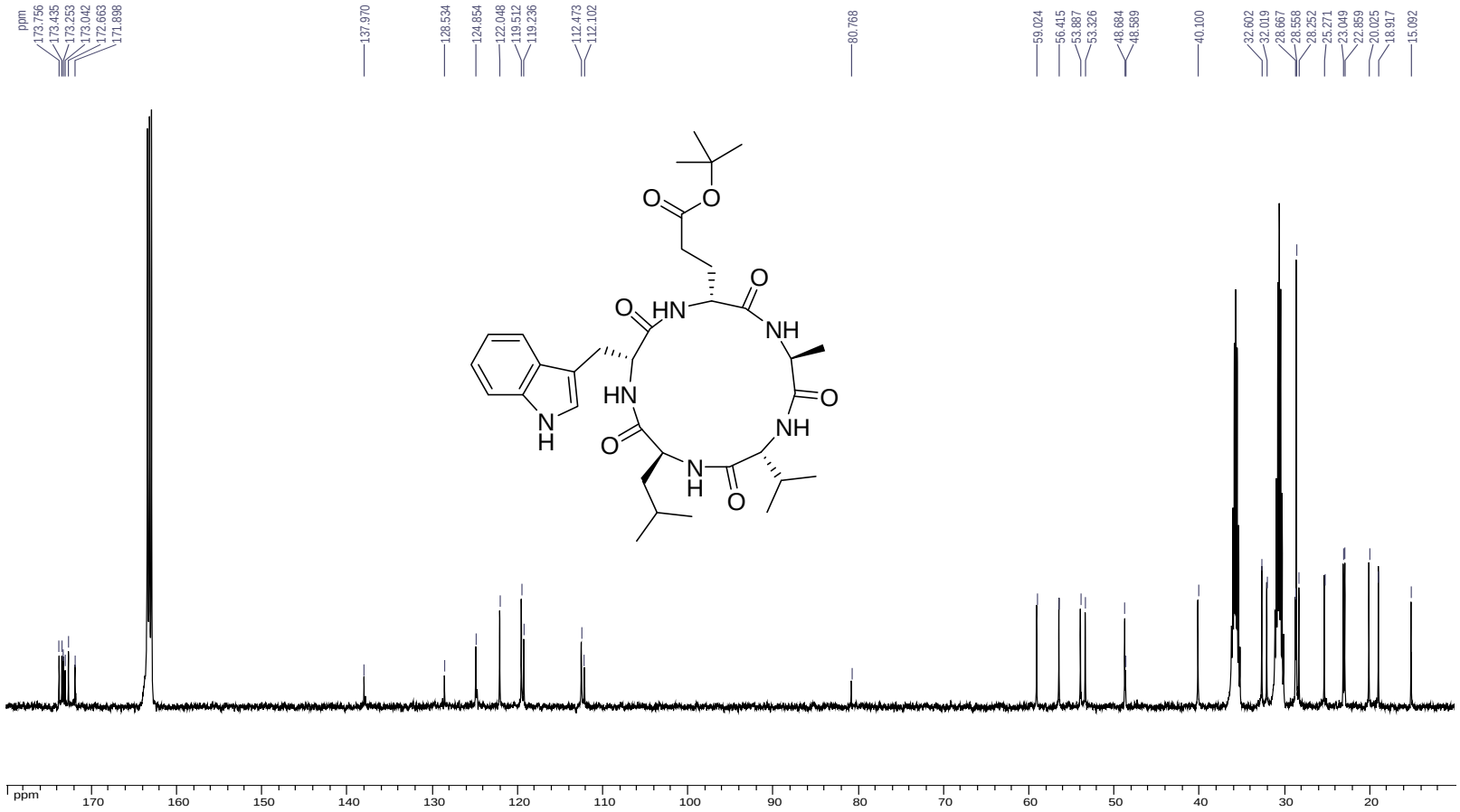
***S*-(9-Fluorenylmethyl) *N*-fluorenylmethyloxycarbonyl-δ-*O*-*tert*-butyl-D-glutamyl-L-alanyl- D-valyl-L-leucyl-D-thiotryptophanate** (**5**) ^{13}C NMR (75 MHz, $CDCl_3$)



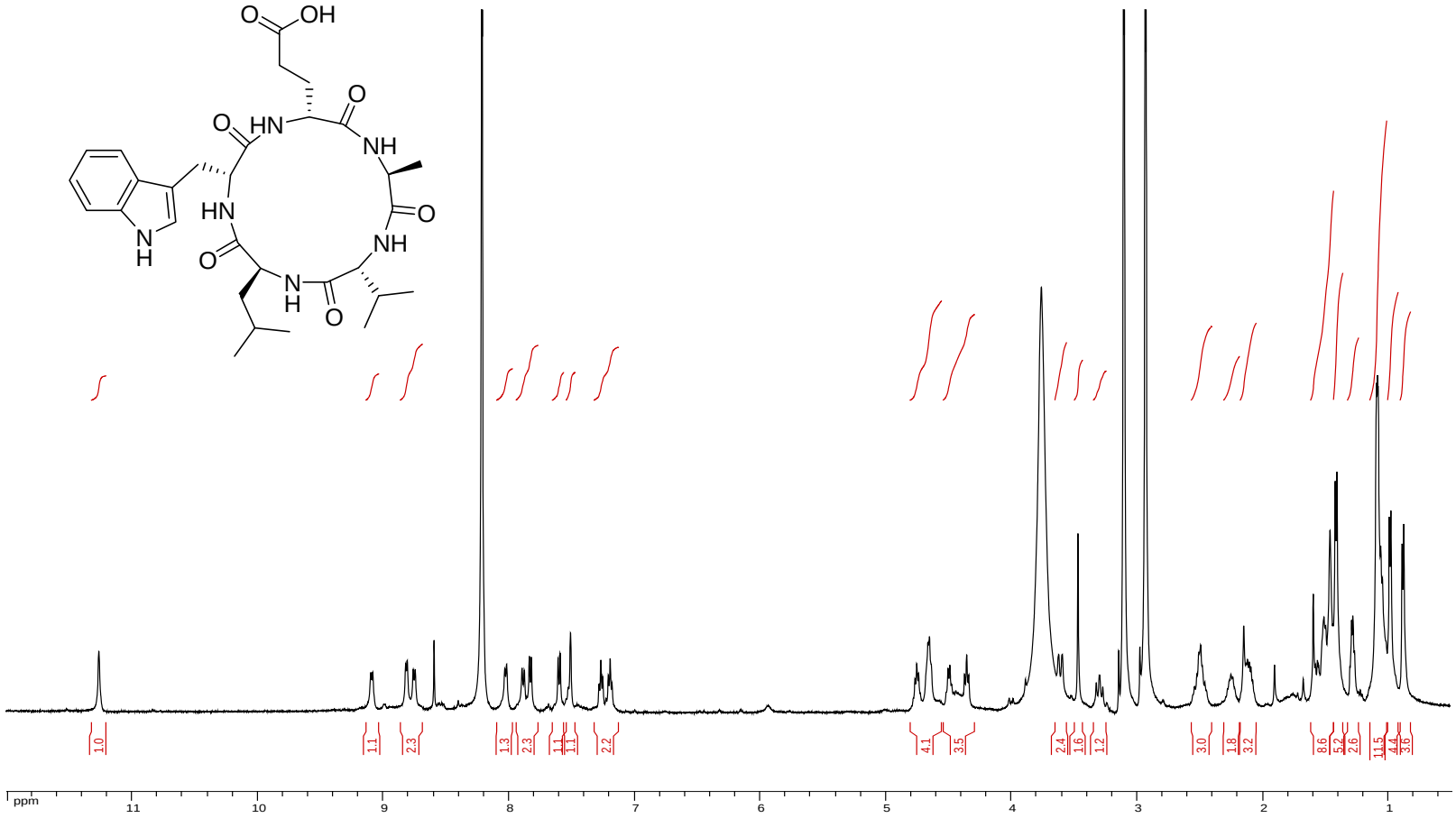
***cyclo*-(δ-*O*-*tert*-Butyl-D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-tryptophan)** (**6**) ^{1}H NMR (500 MHz, DMF-d_7)



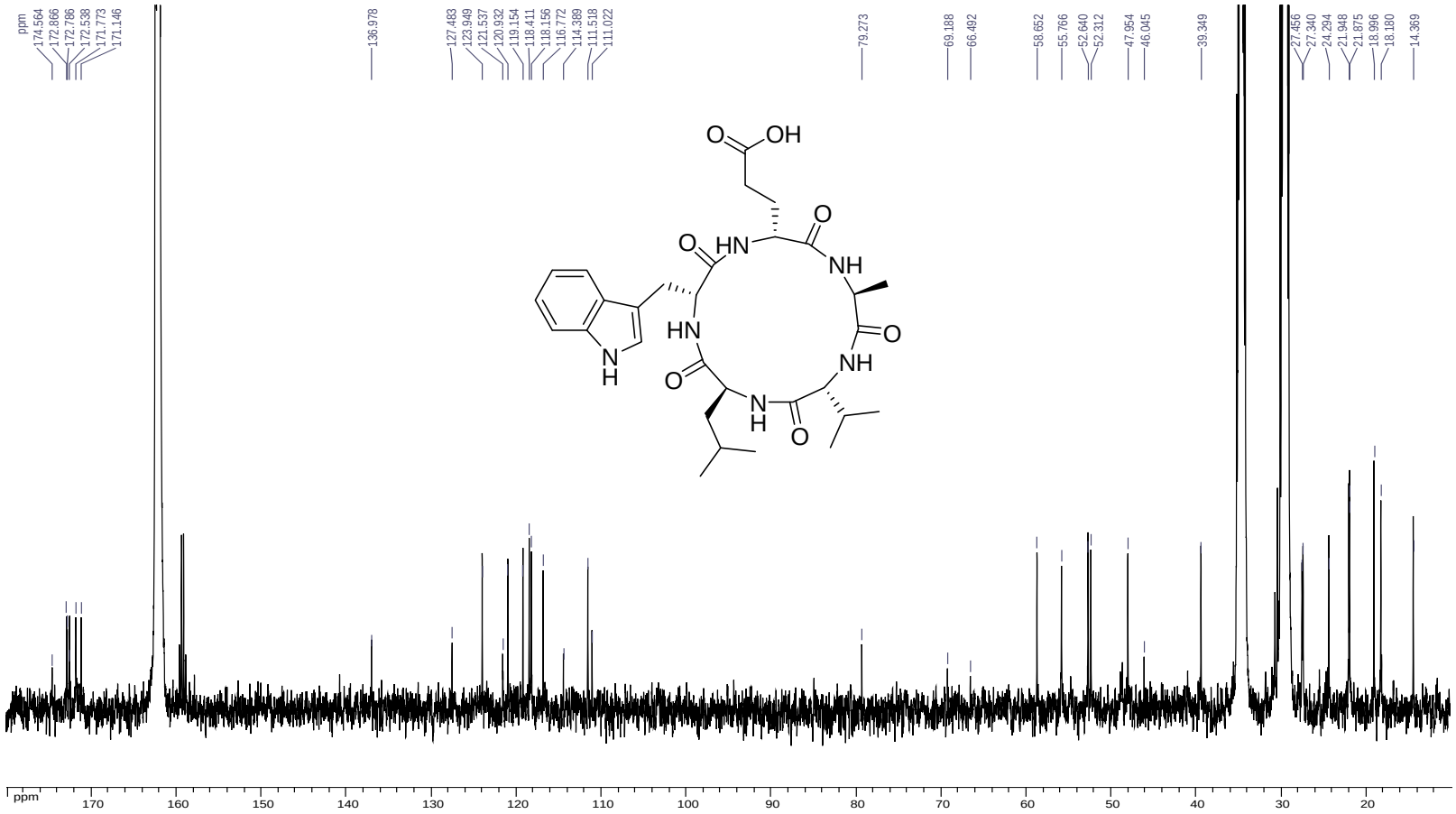
***cyclo*-(δ-*O*-*tert*-Butyl-D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-tryptophan)** (**6**) ^{13}C NMR (125 MHz, DMF-d_7)



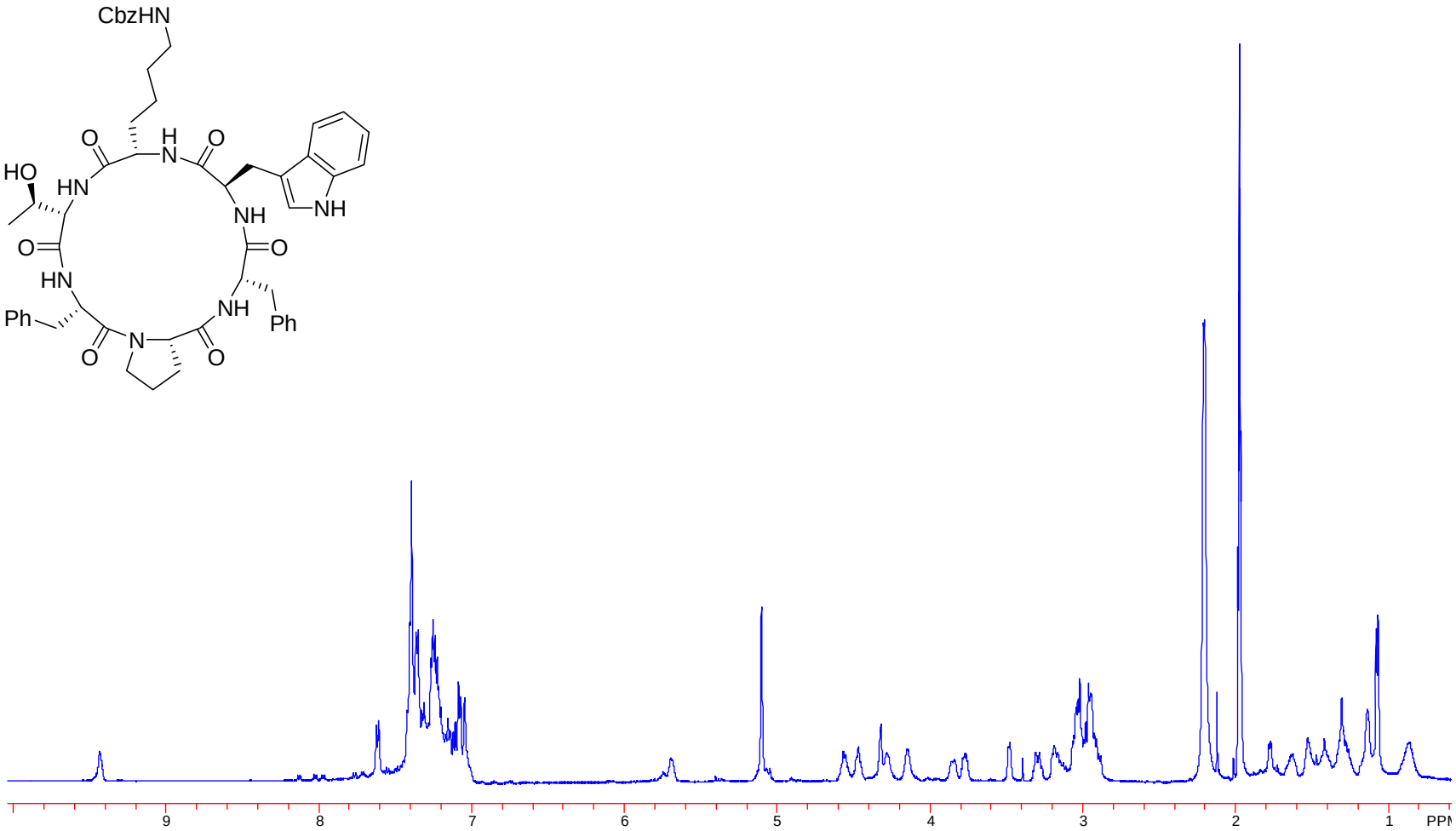
***cyclo*-(D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-tryptophan)** (**7**) ^{1}H NMR (500 MHz, DMF-d_7)



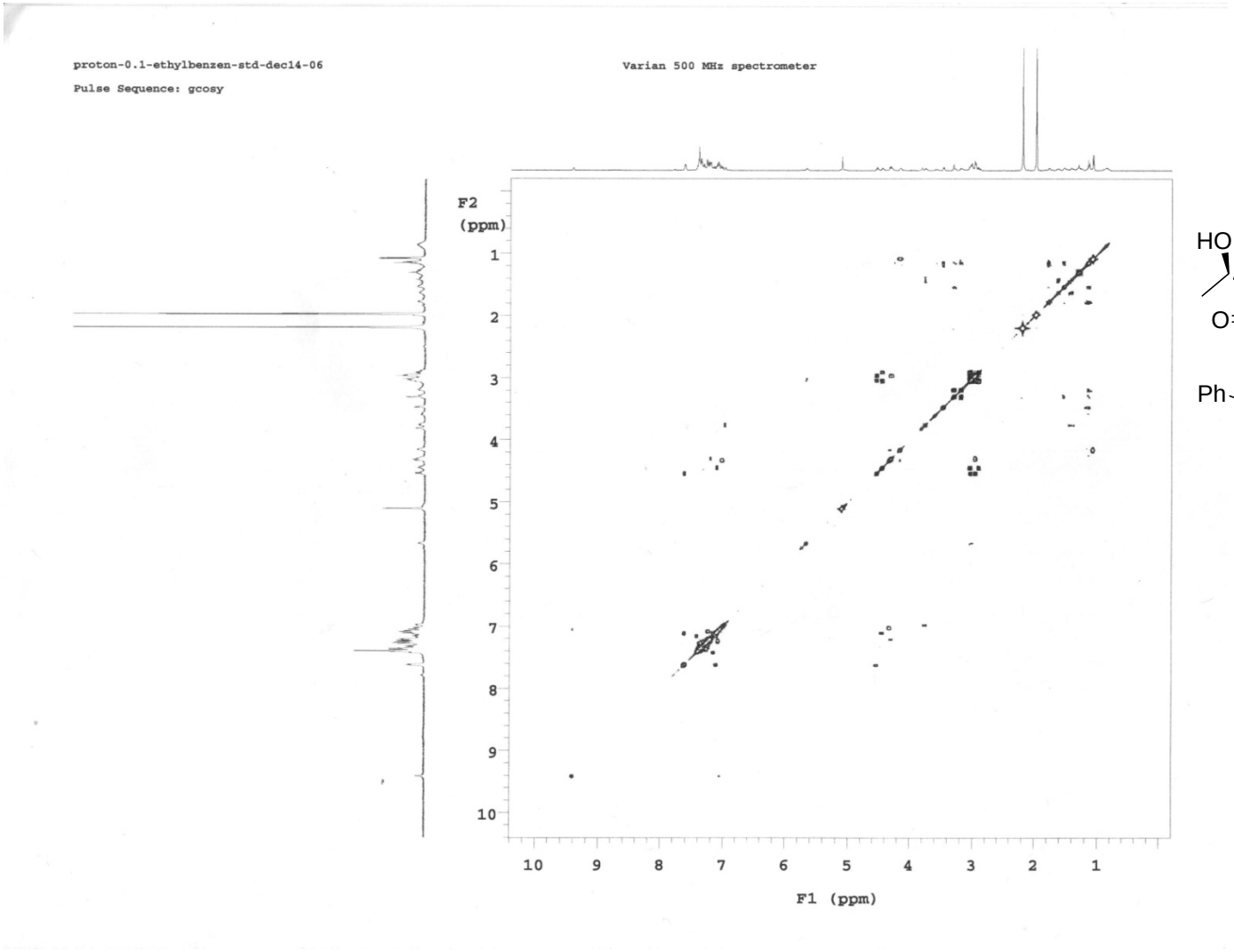
***cyclo*-(D-glutamyl-L-alanyl-D-valyl-L-leucyl-D-tryptophan)** (**7**) ^{13}C NMR (125 MHz, DMF-d_7)

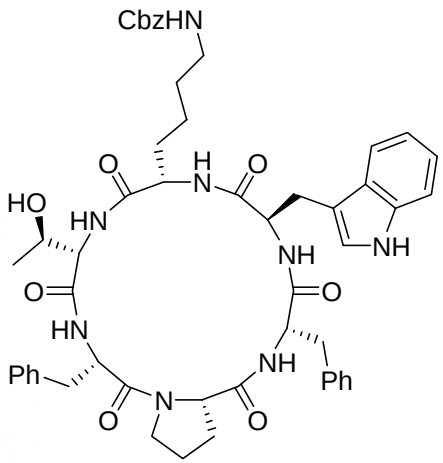


***cyclo*-(L-phenylalanyl-D-tryptophanyl-*N*$^{\varepsilon}$-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-L-proline)** (**8**, ^{1}H NMR, 500 MHz, CD_3CN)

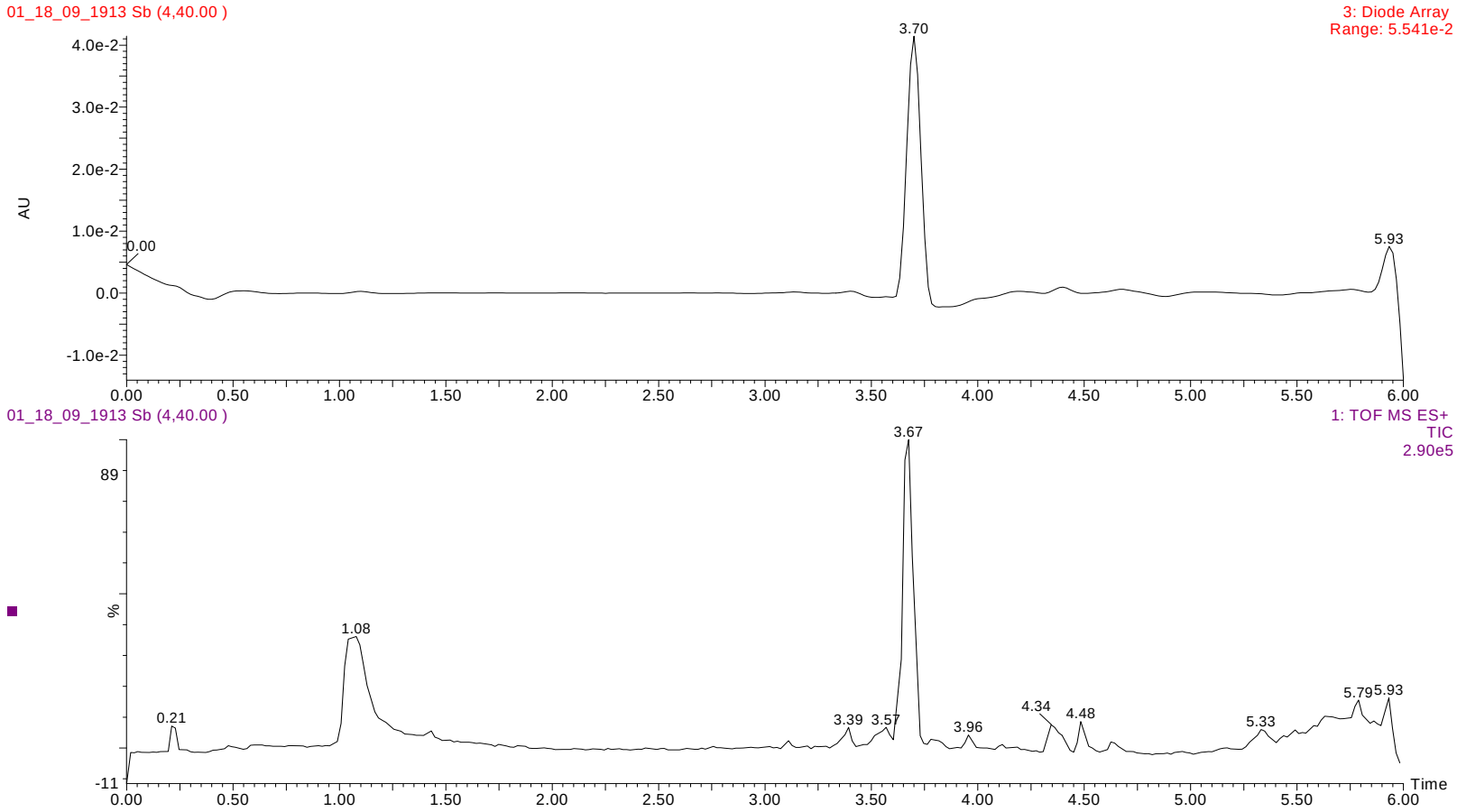


***cyclo*-(L-phenylalanyl-D-tryptophanyl-*N*$^{\varepsilon}$-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-L-proline)** (**8**, ^{1}H-^{1}H cosy, 500 MHz, CD_3CN)

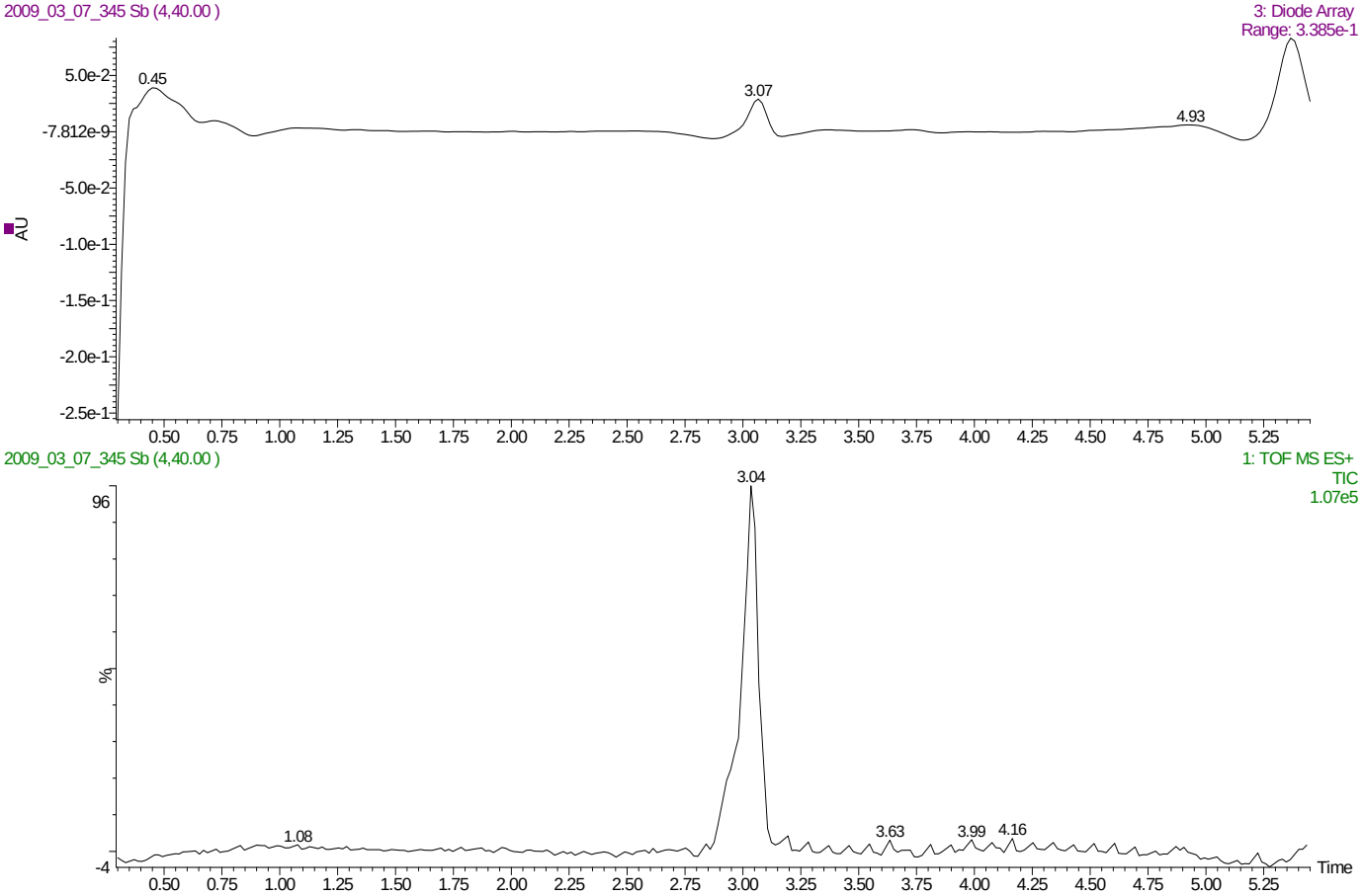




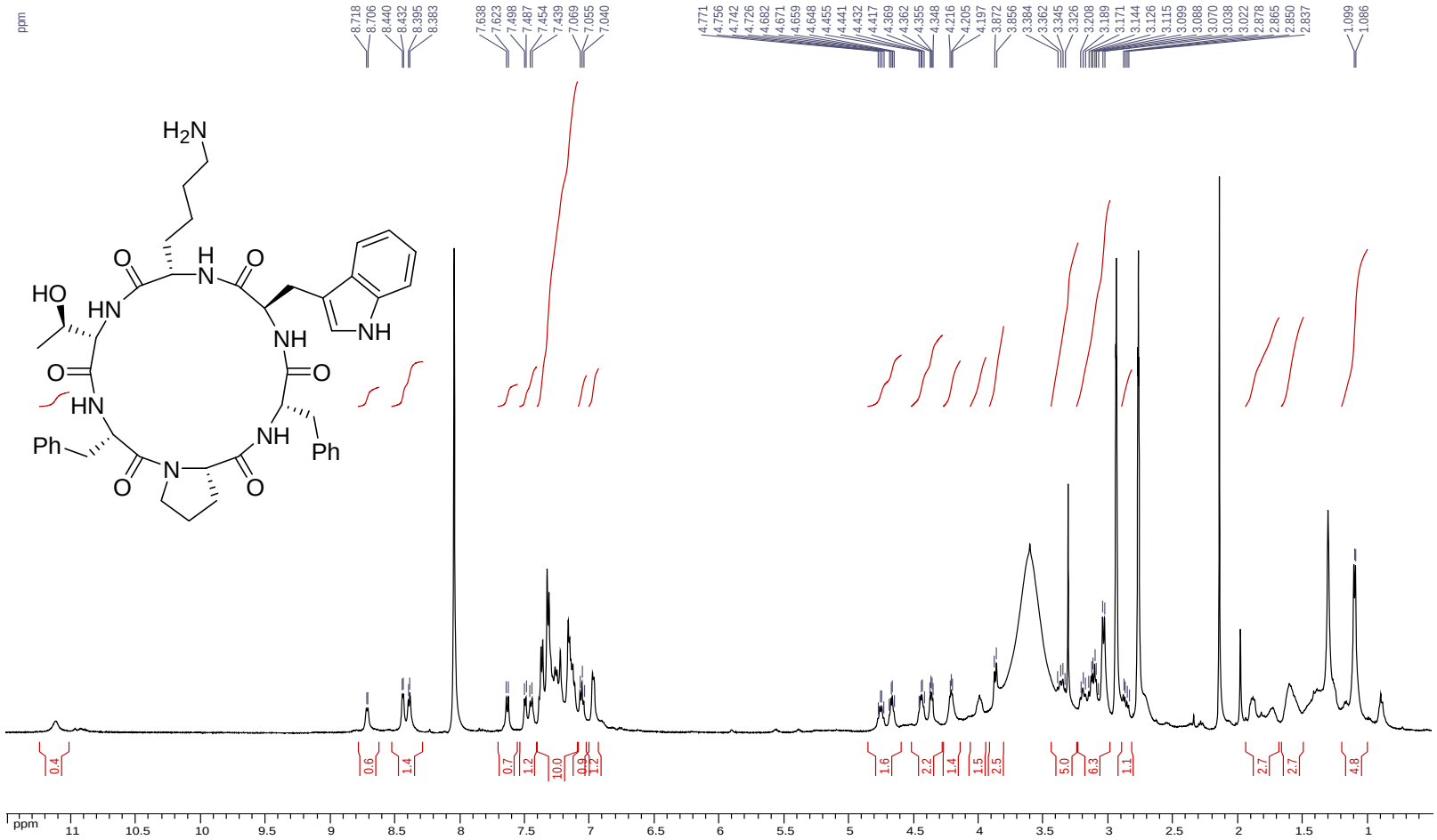
***cyclo*-(L-phenylalanyl-D-tryptophanyl-*N*$^{\varepsilon}$-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-L-proline)** (**8**, LCMS analysis, top; UV spectrum, bottom; TIC)



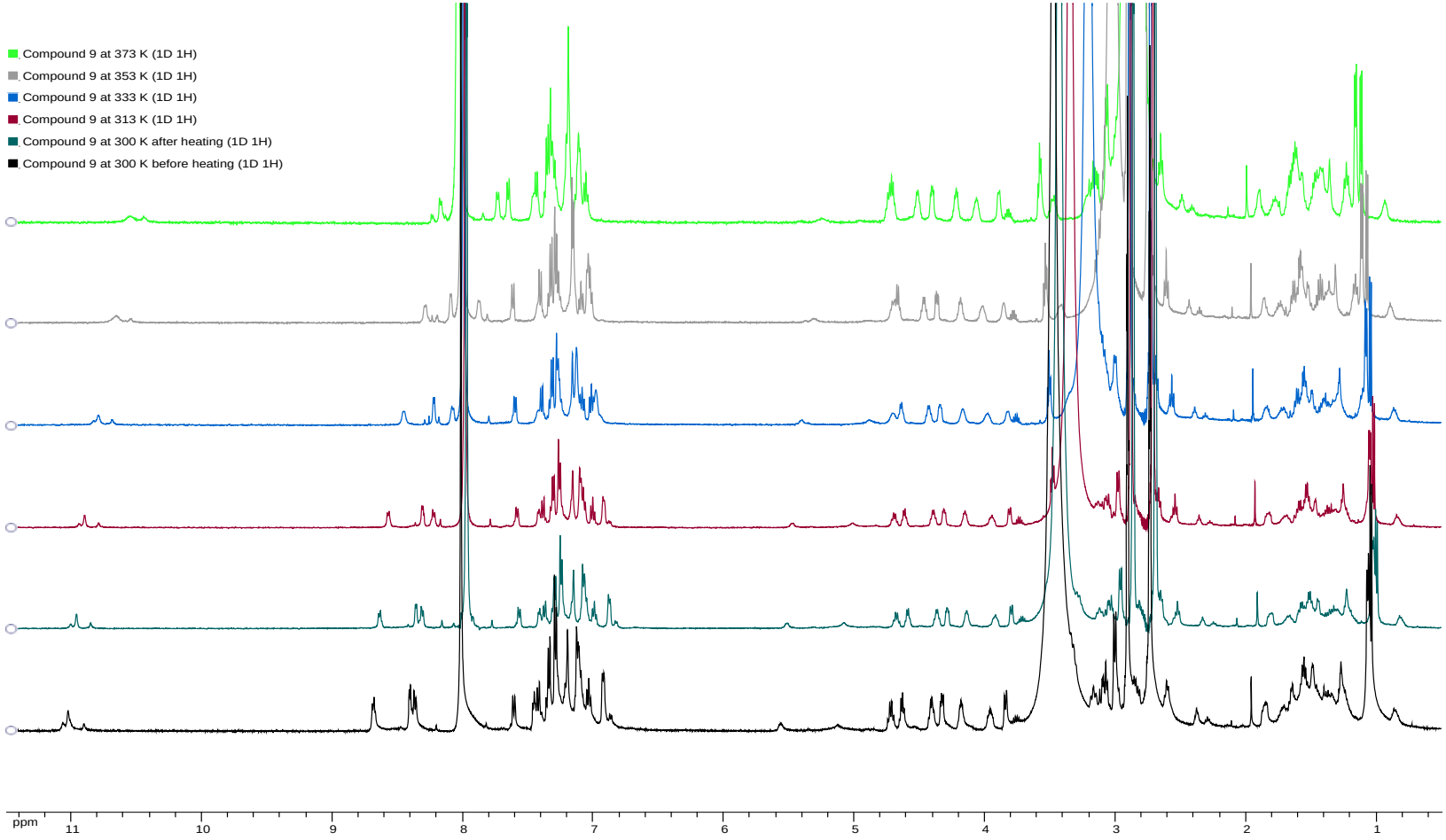
L-363,301 (**9**, LCMS analysis, top; UV spectrum, bottom; TIC)



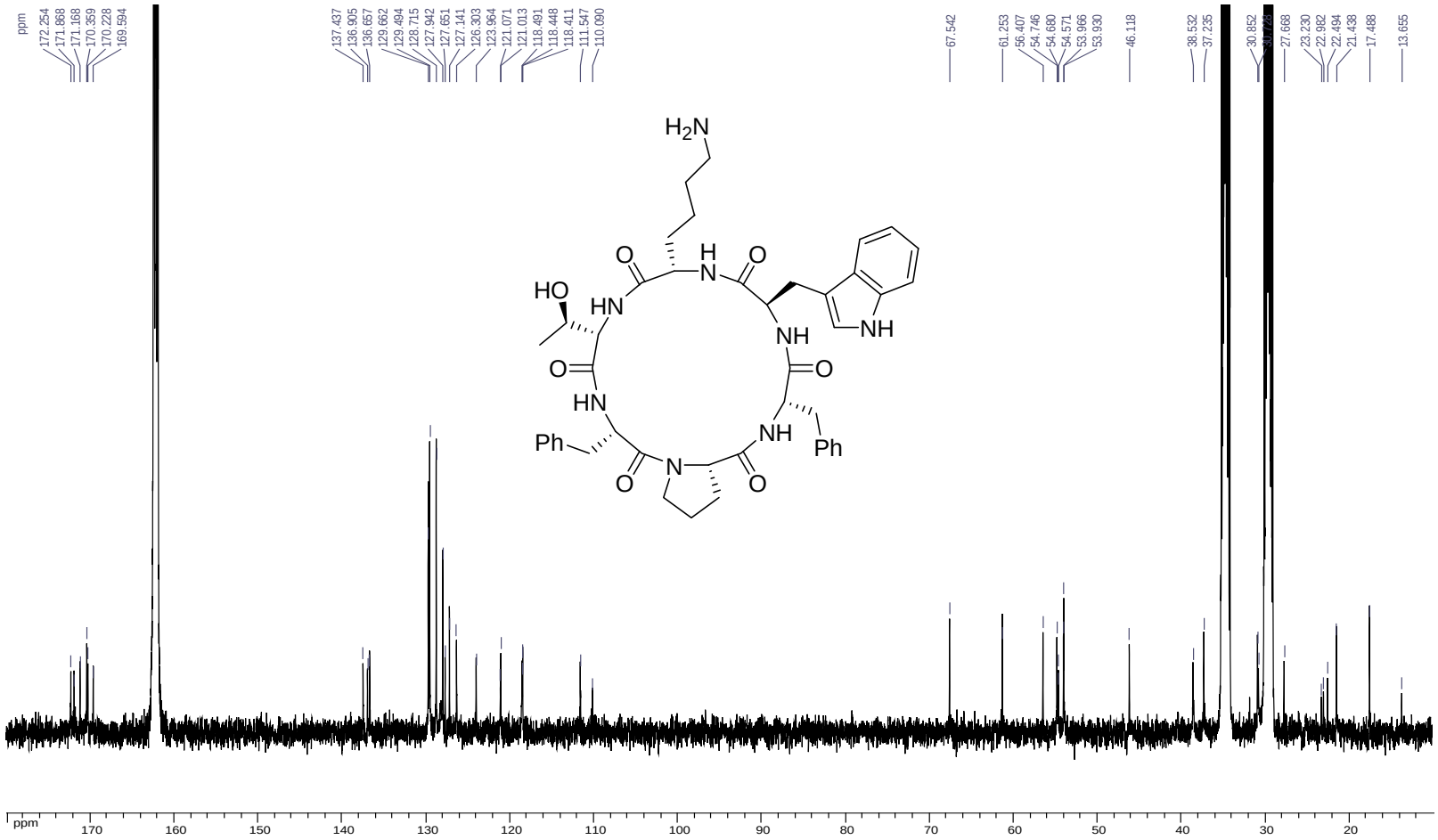
L-363,301 (**9**) ^{1}H NMR (500 MHz, DMF-d_7)



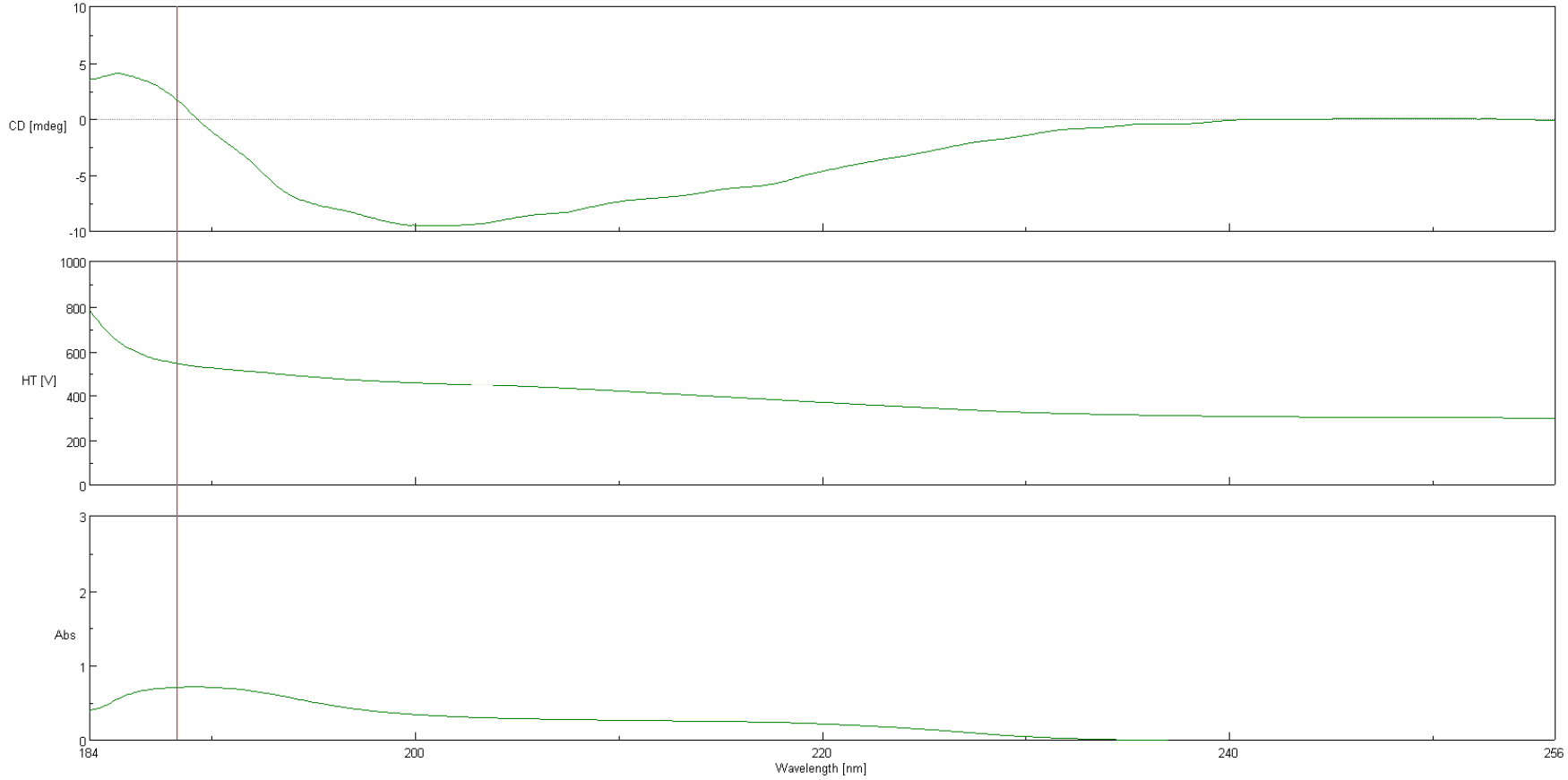
L-363,301 (**9**) ^{1}H NMR at various temperature (500 MHz, DMF-d_7)



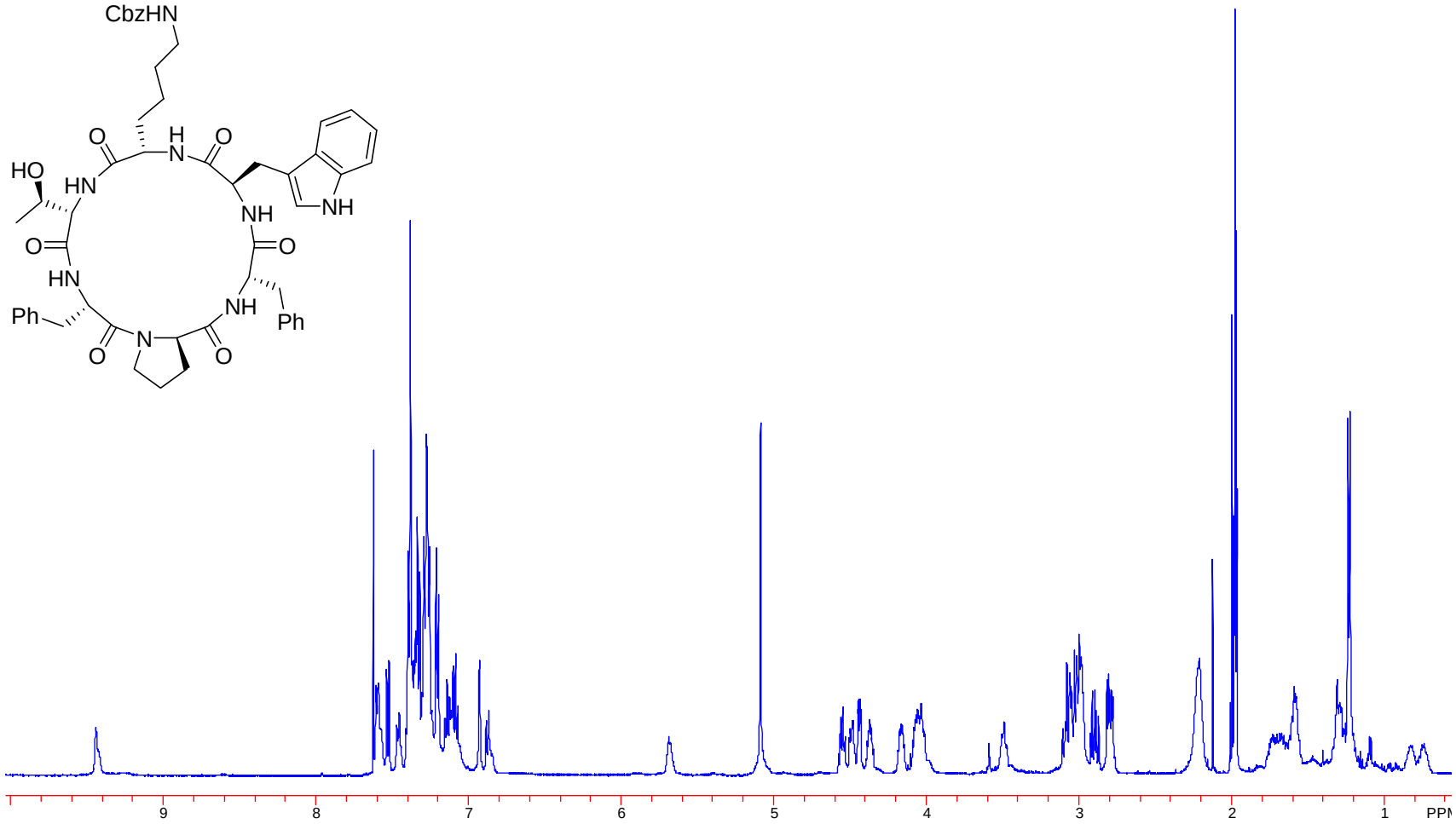
L-363,301 (**9**) ^{13}C NMR (500 MHz, DMF-d_7)



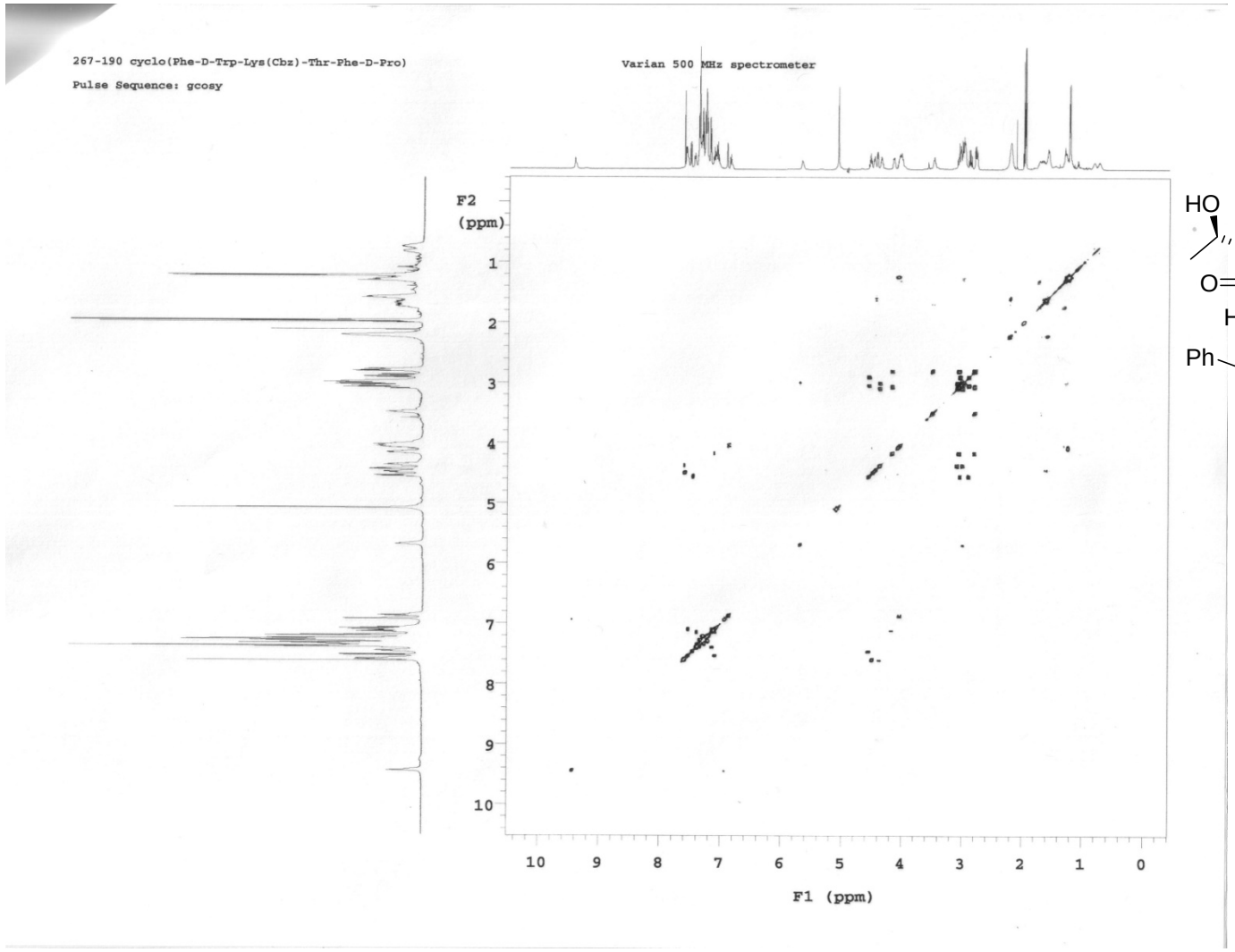
L-363,301 (**9**) CD spectrum pH 7.4 phosphate buffer.

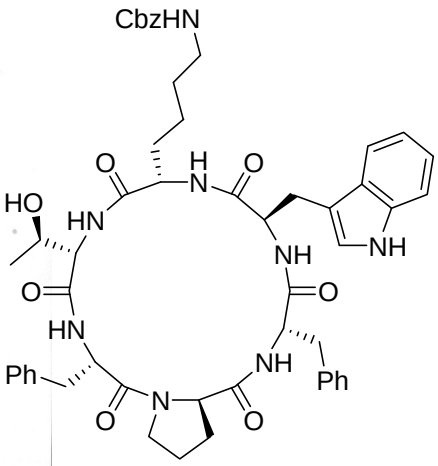


***cyclo*-(L-phenylalanyl-D-tryptophanyl-*N*$^{\varepsilon}$-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**10**, ^{1}H NMR, 500 MHz, CD_3CN)

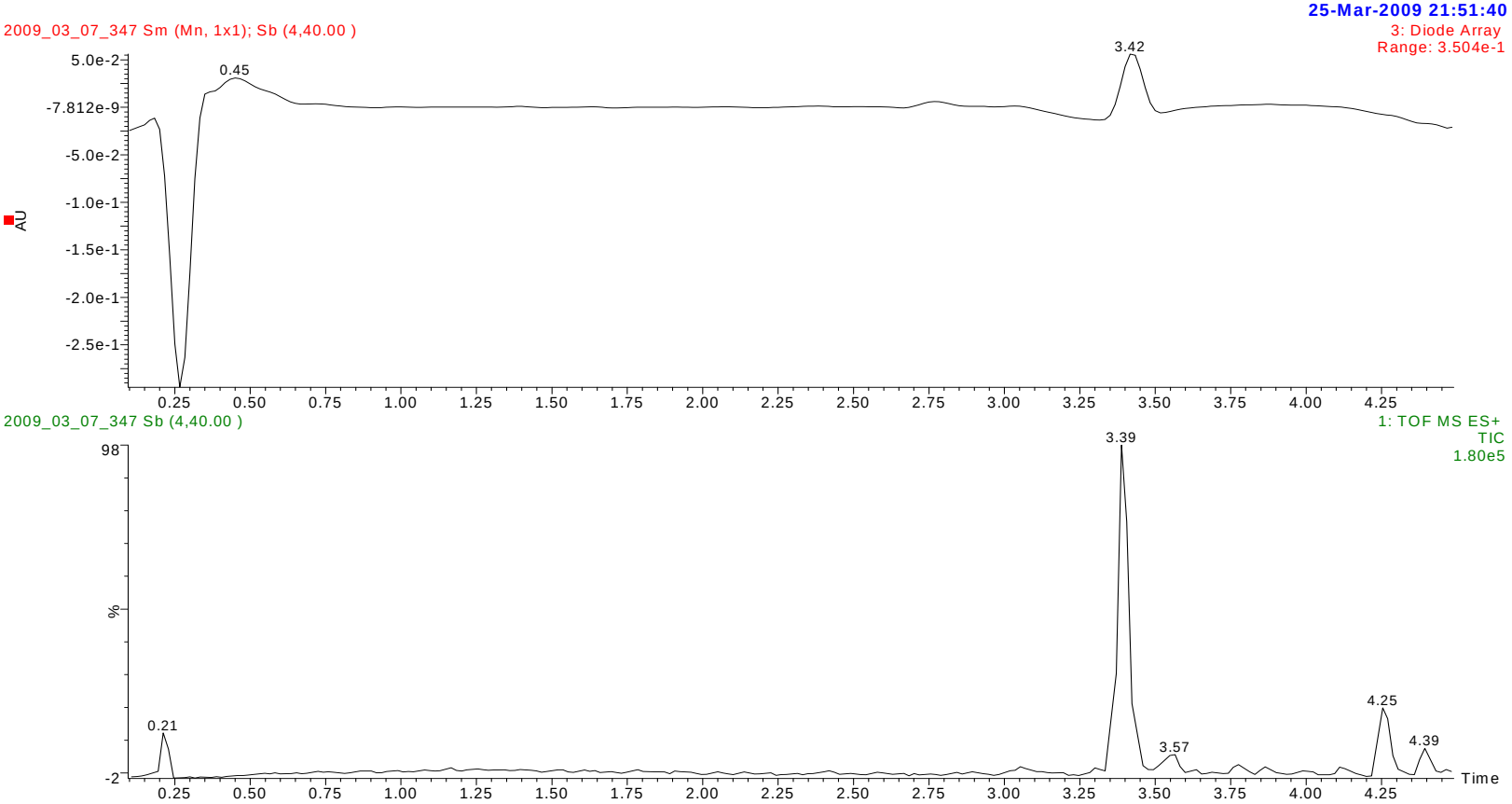


***cyclo*-(L-phenylalanyl-D-tryptophanyl-*N*$^{\varepsilon}$-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**10**, ^{1}H-^{1}H cosy, 500 MHz, CD_3CN)

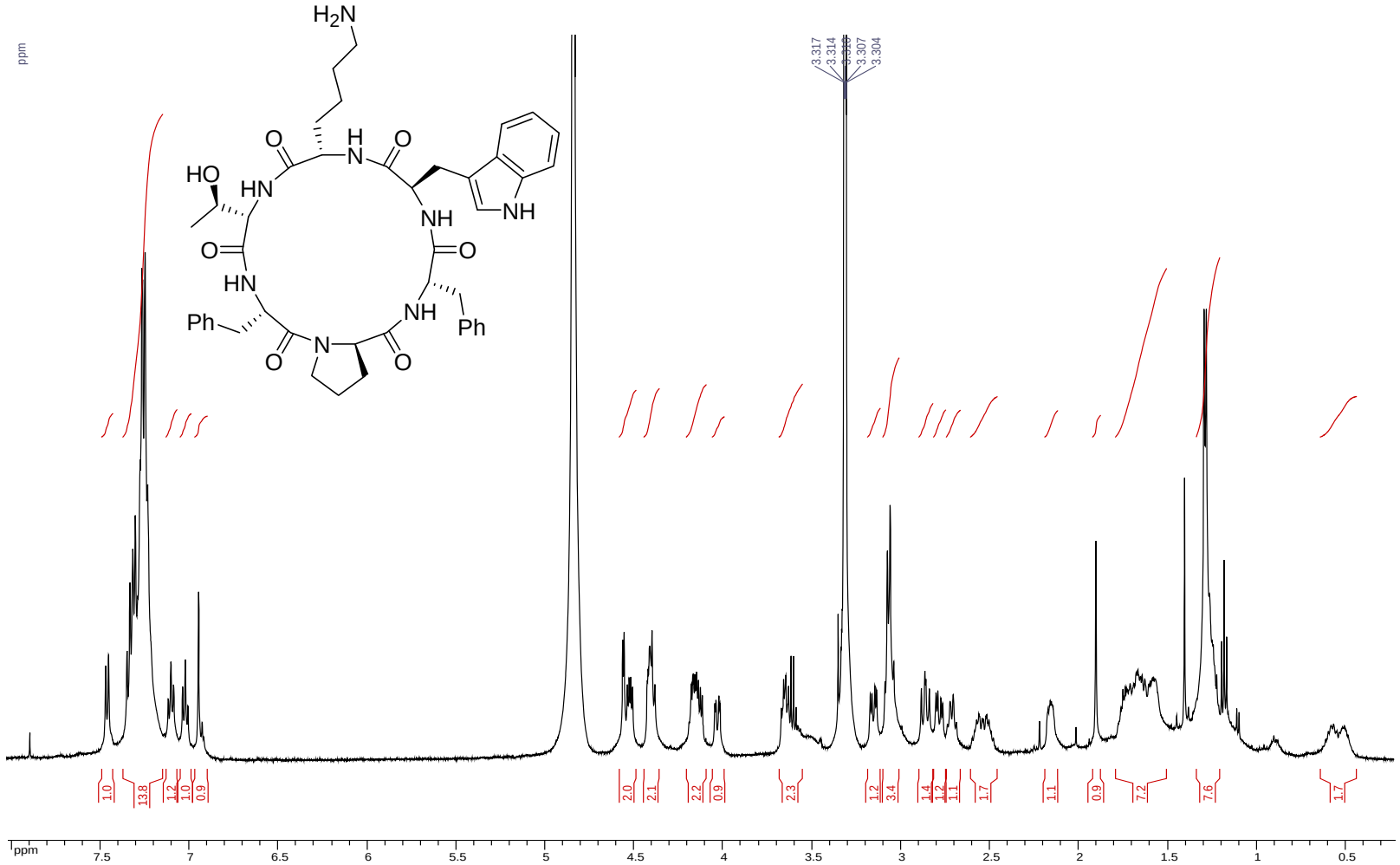




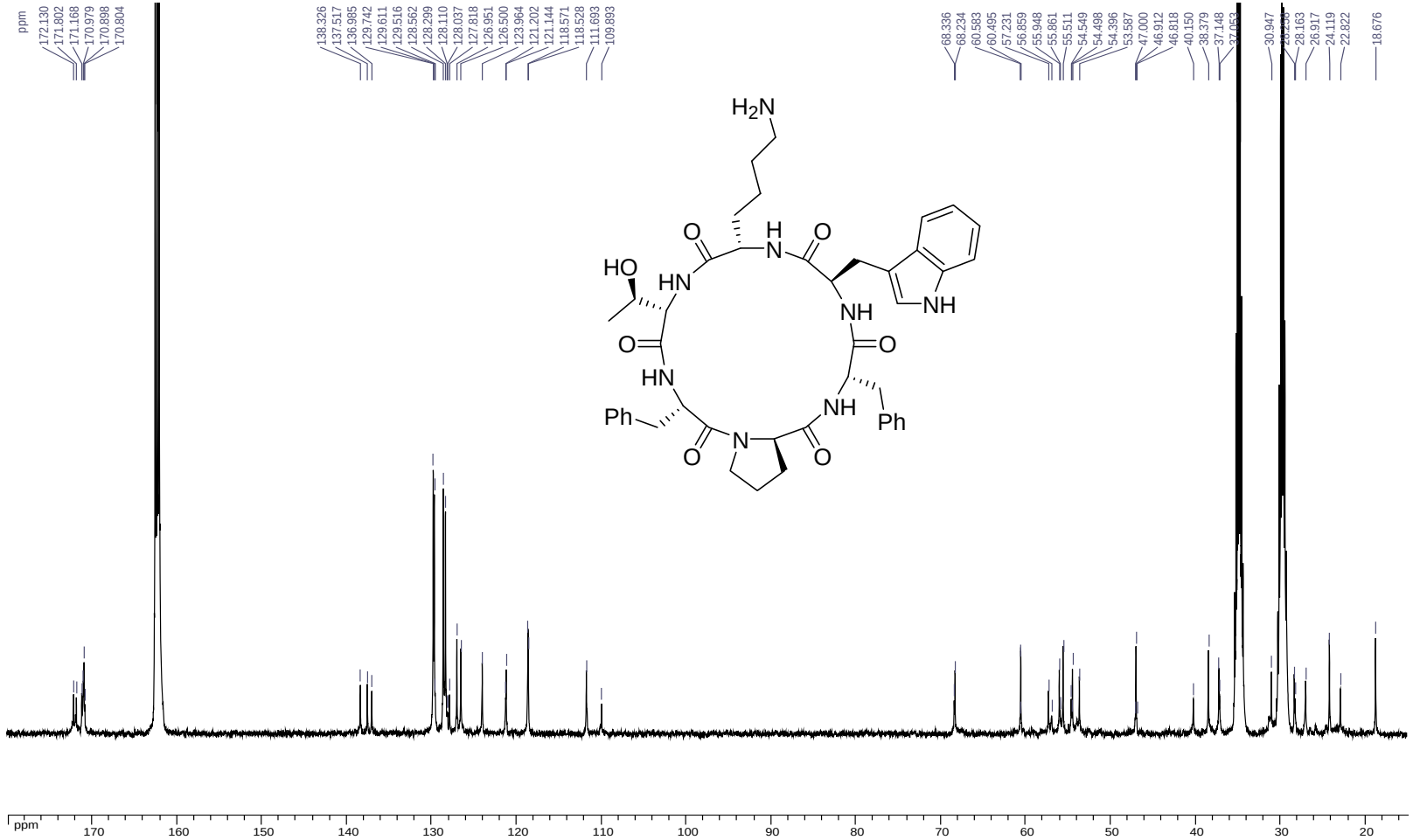
***cyclo*-(L-phenylalanyl-D-tryptophanyl-*N*$^{\varepsilon}$-benzyloxycarbonyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**10**, LCMS analysis, top; UV spectrum, bottom; TIC)



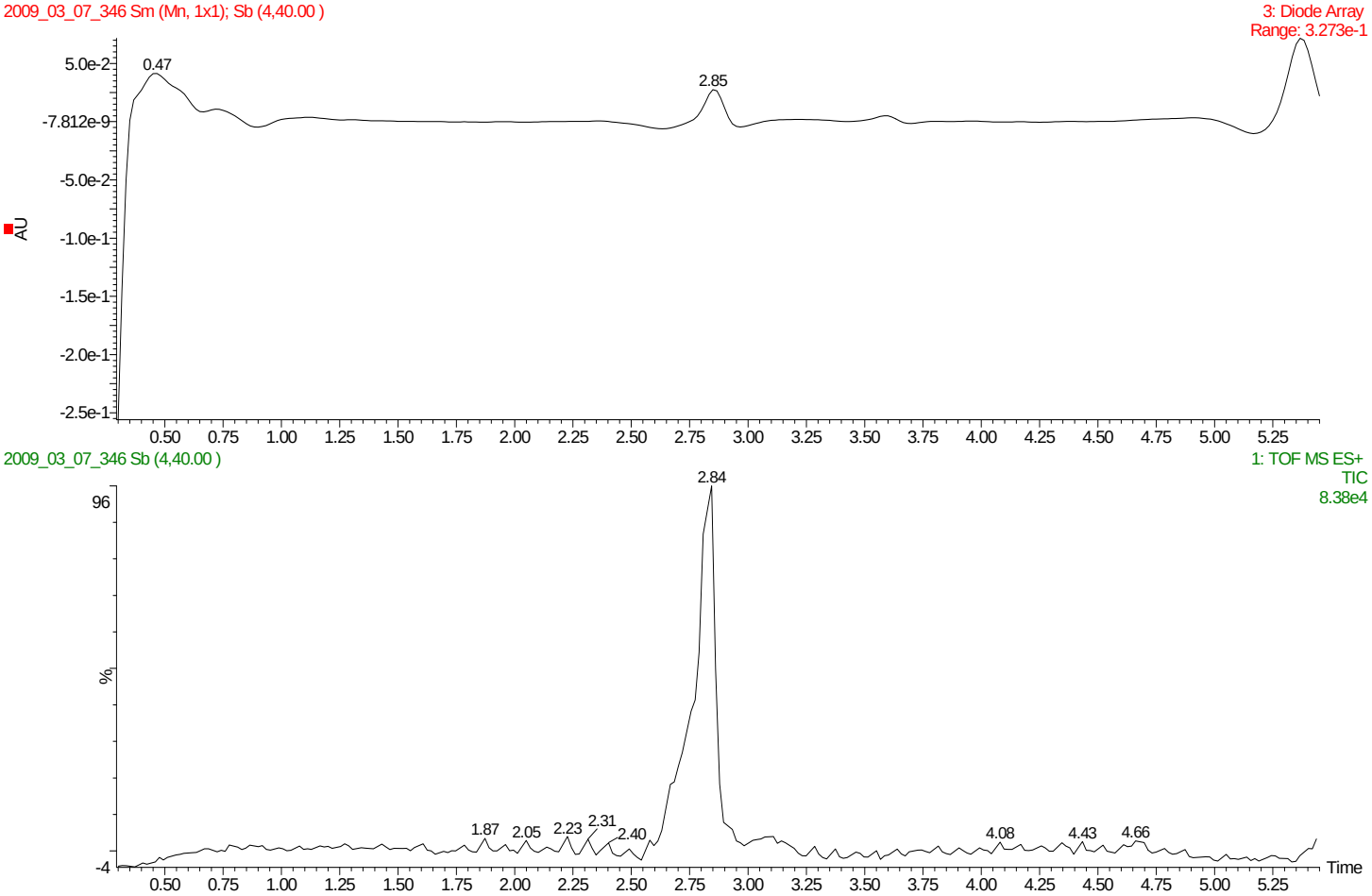
***cyclo*-(L-phenylalanyl-D-tryptophanyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**11**) ^{1}H NMR (500 MHz, CD_3OD)



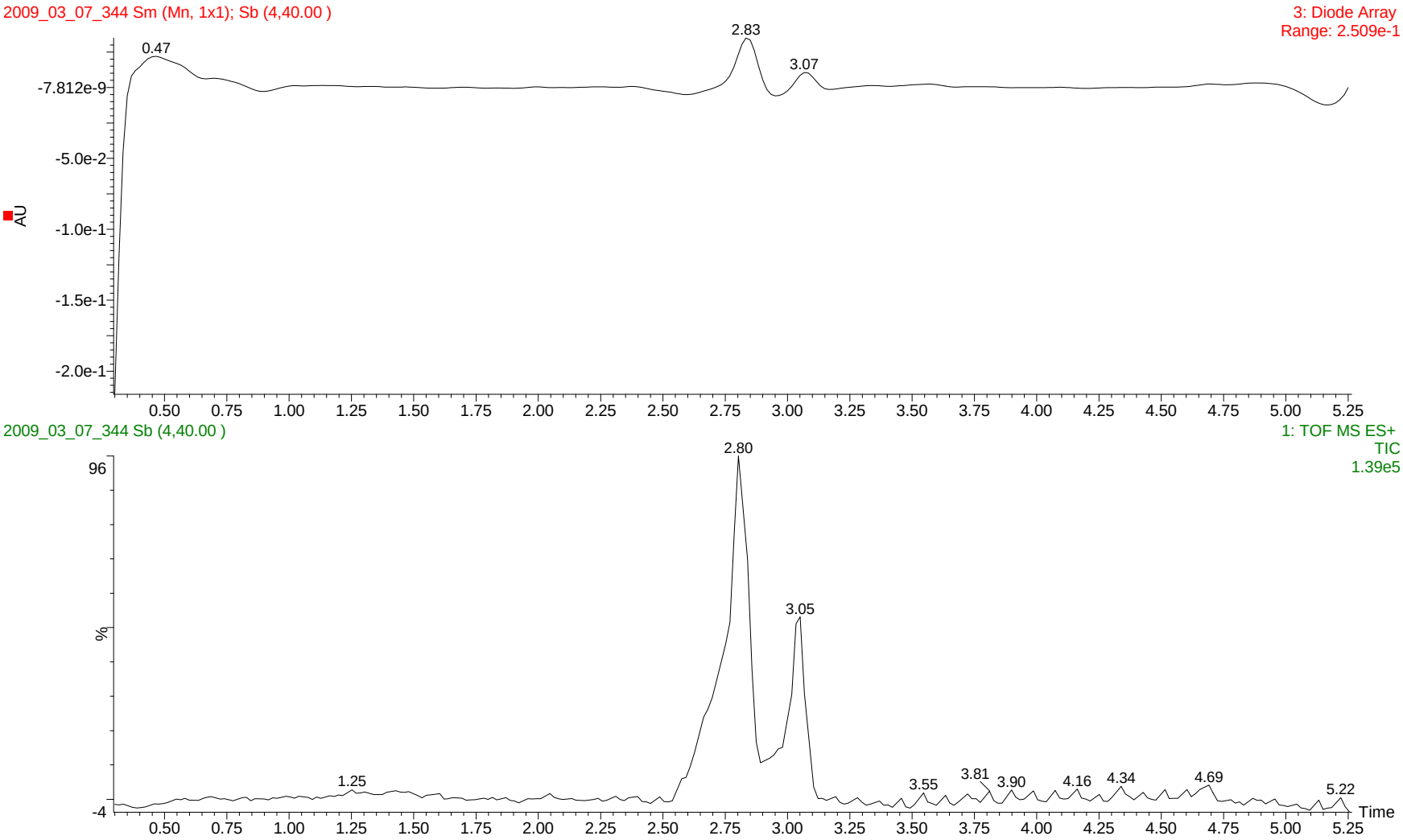
***cyclo*-(L-phenylalanyl-D-tryptophanyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**11**) ^{13}C NMR (500 MHz, DMF-d_7)



***cyclo*-(L-phenylalanyl-D-tryptophanyl-L-lysyl-L-threonyl-L-phenylalanyl-D-proline)** (**11**, LCMS analysis, top; UV spectrum, bottom; TIC)

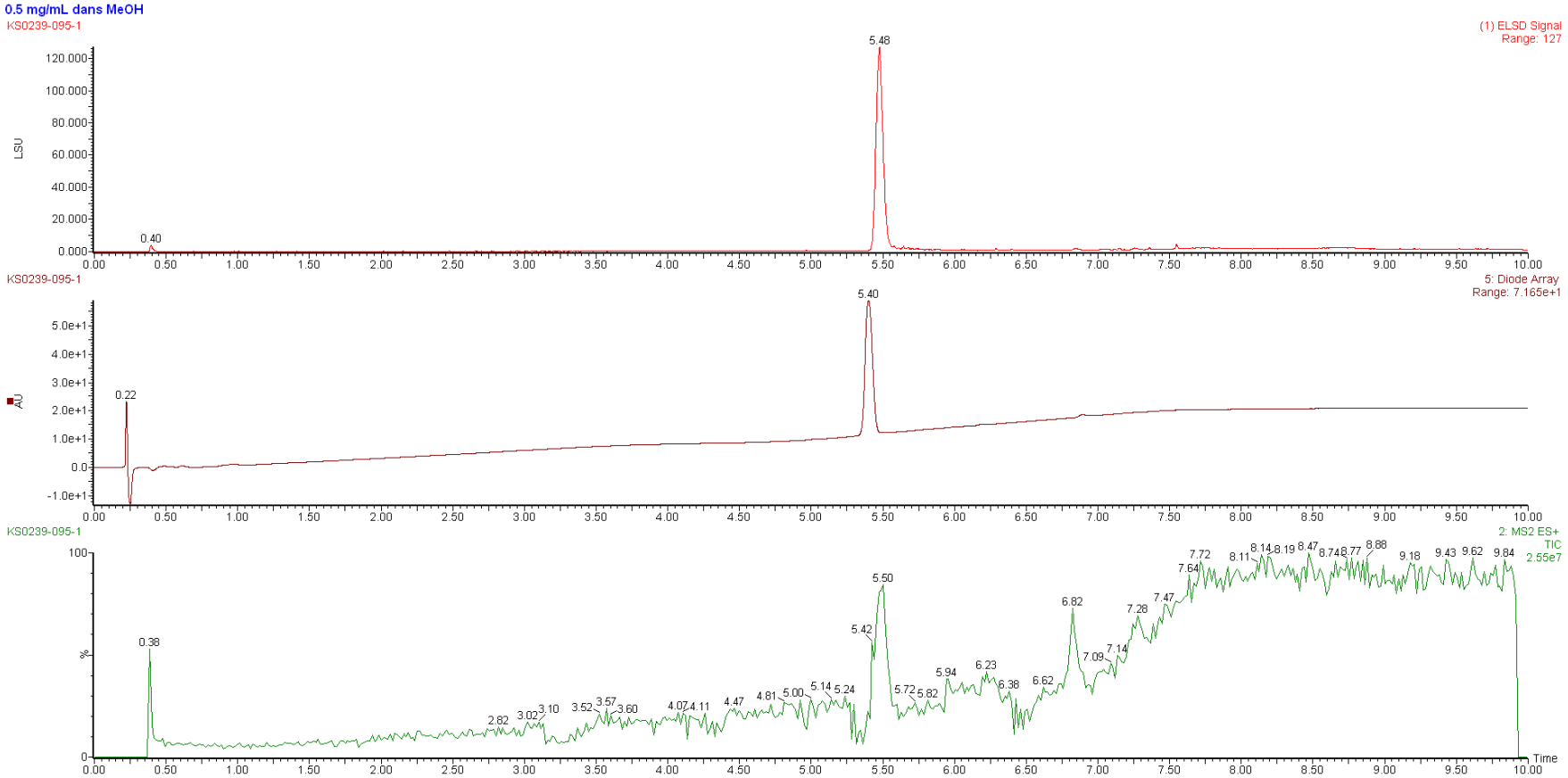


Mixture of L-363,301 (9) and *cyclo*-(Phe-D-Trp-Lys-Thr-Phe-D-Pro) (11) (LCMS analysis, top; UV spectrum, bottom; TIC)



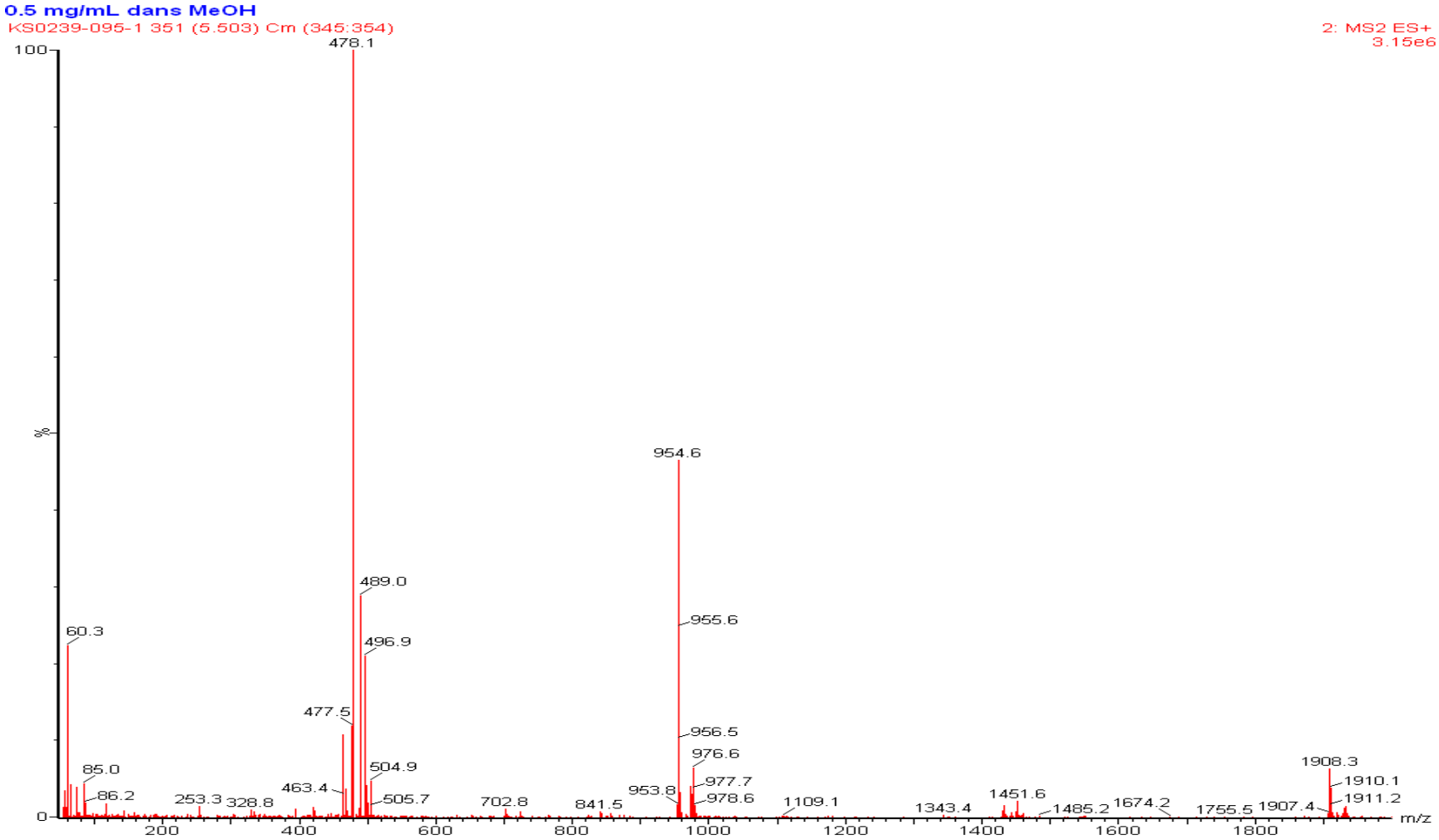
***cyclo*-[N^{ω}-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**).

(LCMS analysis, top; ELSD spectrum, mid; UV spectrum, bottom; TIC)

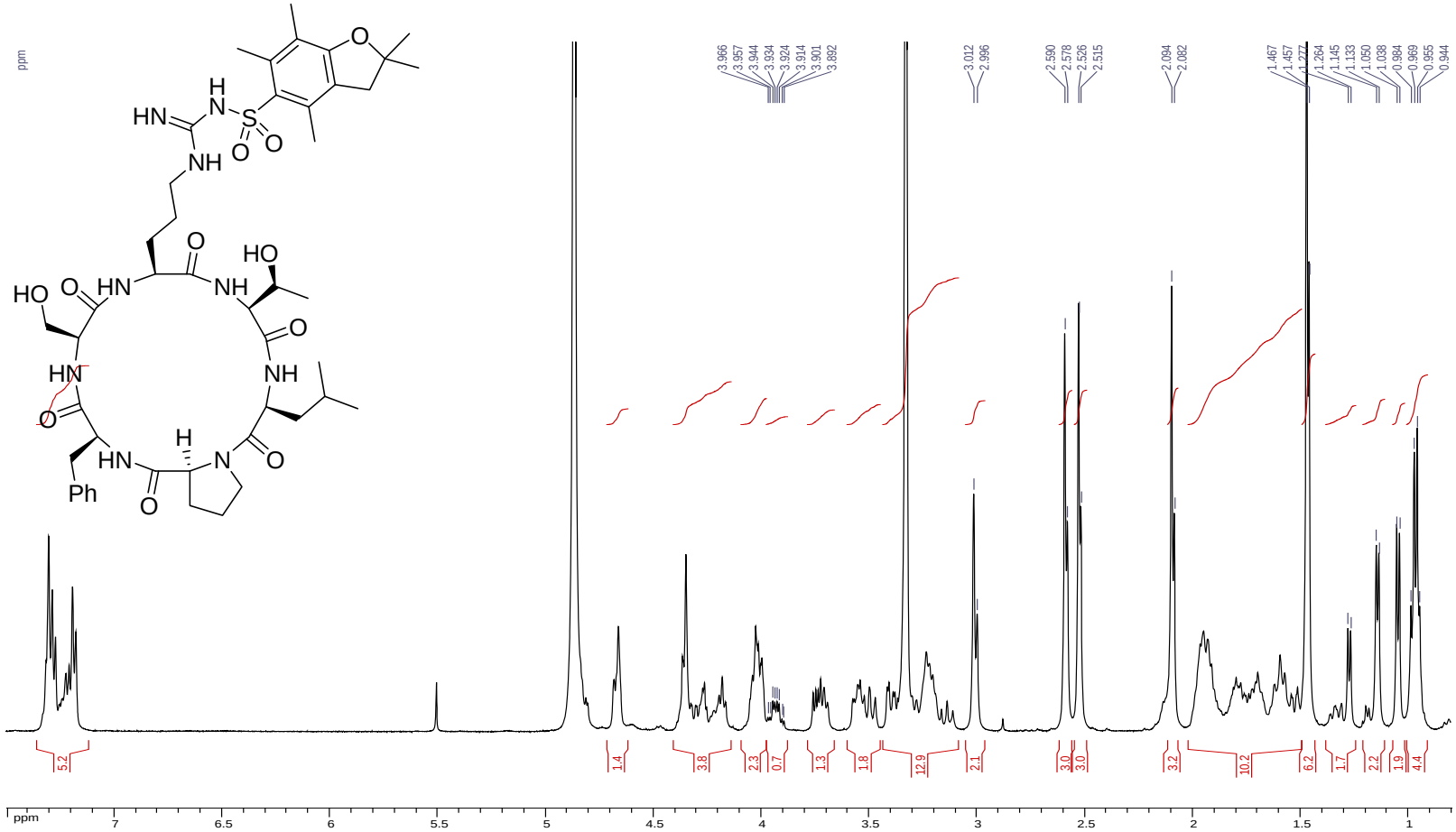


***cyclo*-[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**).

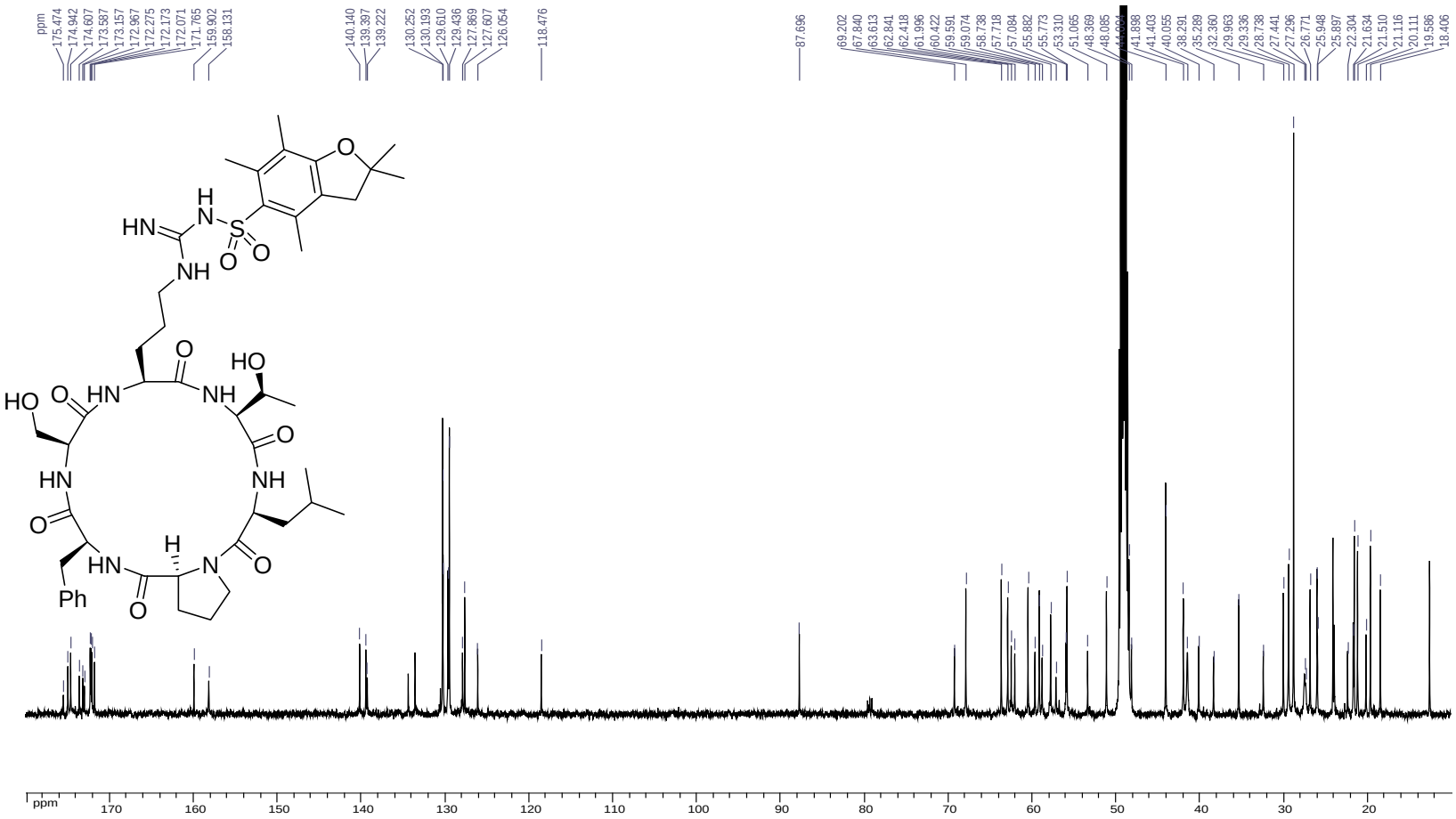
(LRMS at 5.50 min.)



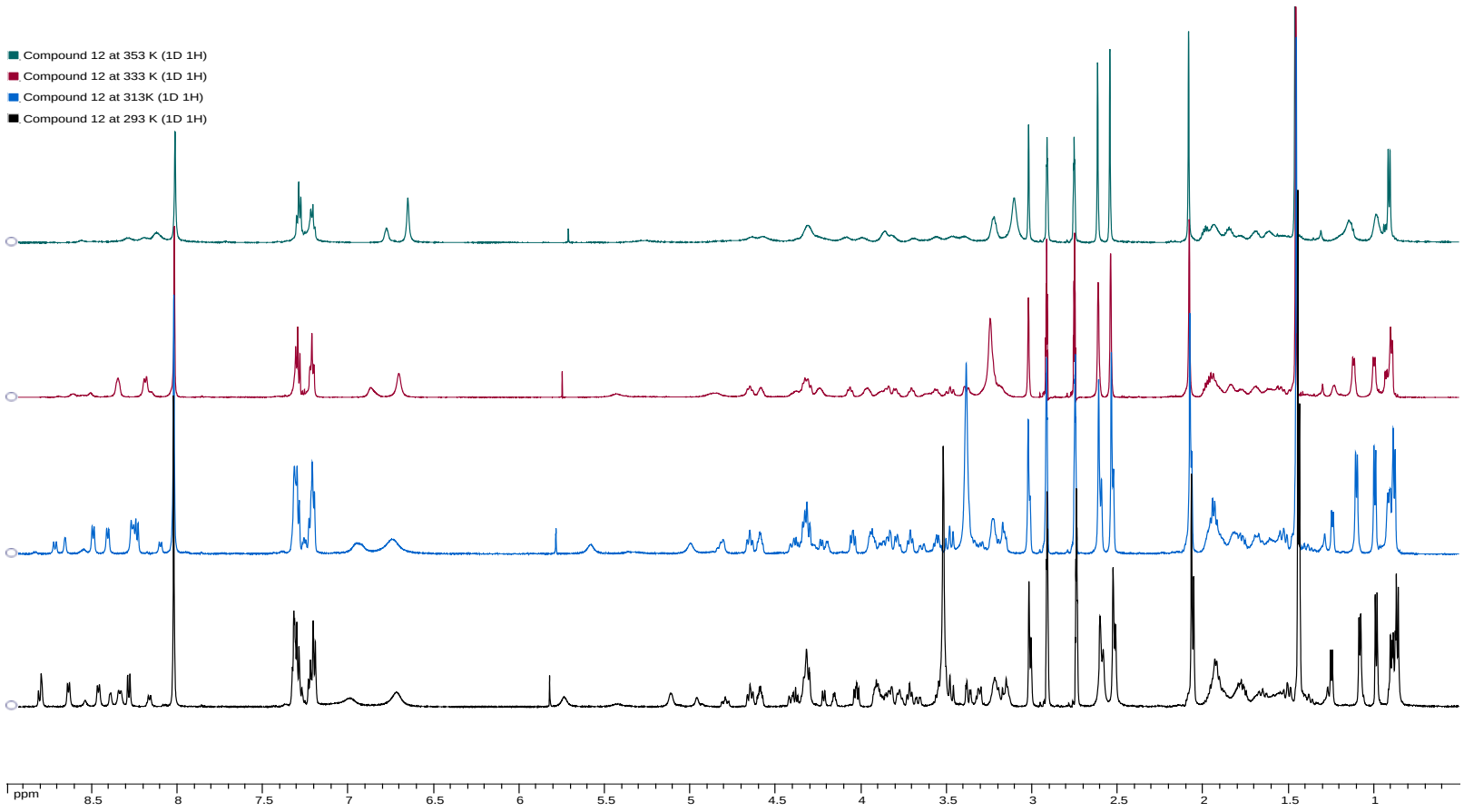
***cyclo*-[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**). ^{1}H NMR (500 MHz, CD_3OD at 25 ^{o}C)



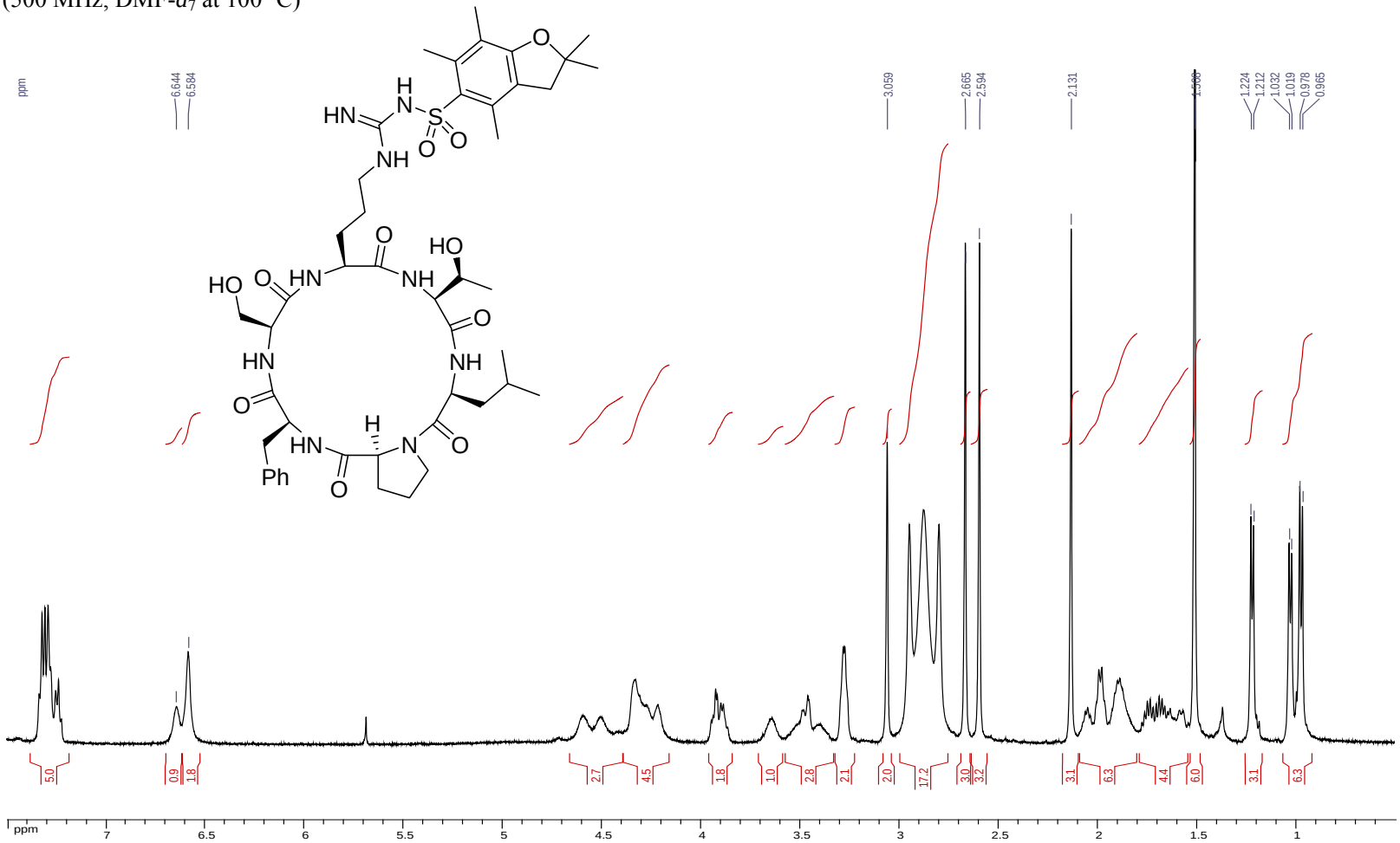
***cyclo*-[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**). ^{13}C NMR (125 MHz, CD_3OD at 25 ^{o}C)



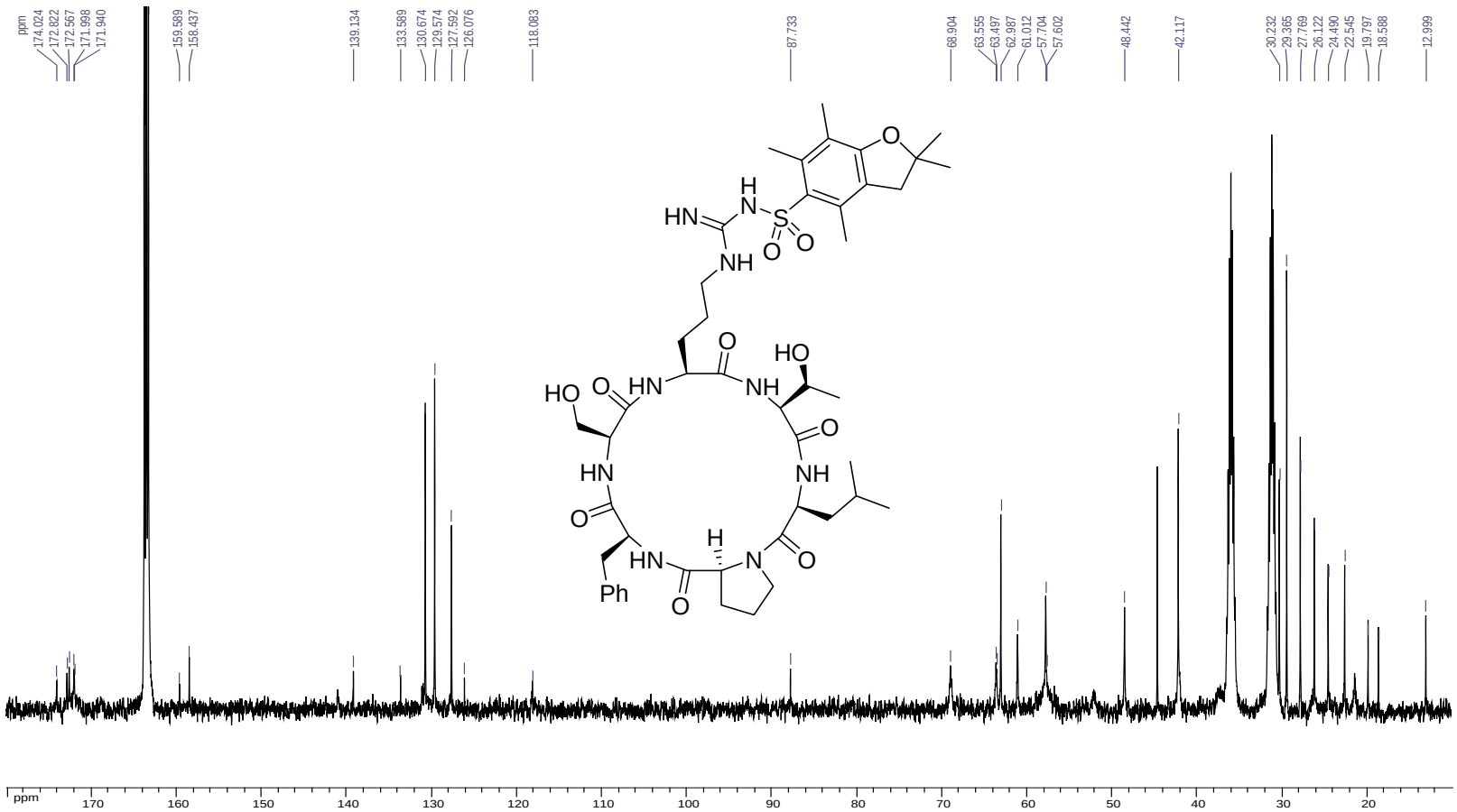
***cyclo*-[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**). ^{1}H NMR (600 MHz, DMF-d_7 at various temperatures)



***cyclo*-[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**). ^{1}H NMR (500 MHz, DMF-d_7 at 100 ^{o}C)

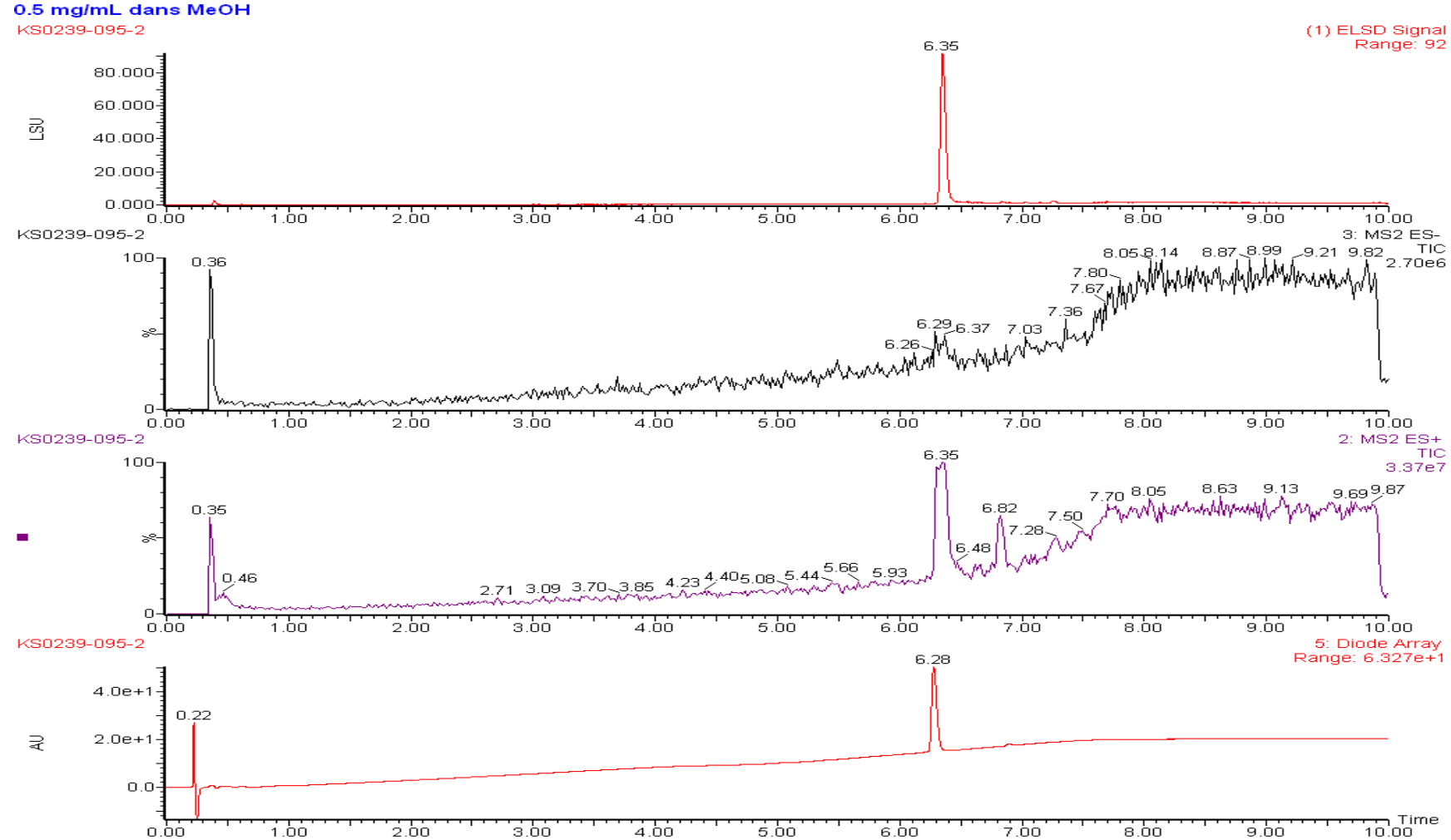


***cyclo*-[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**12**). ^{13}C NMR (500 MHz, DMF-d_7 at 100 ^{o}C)



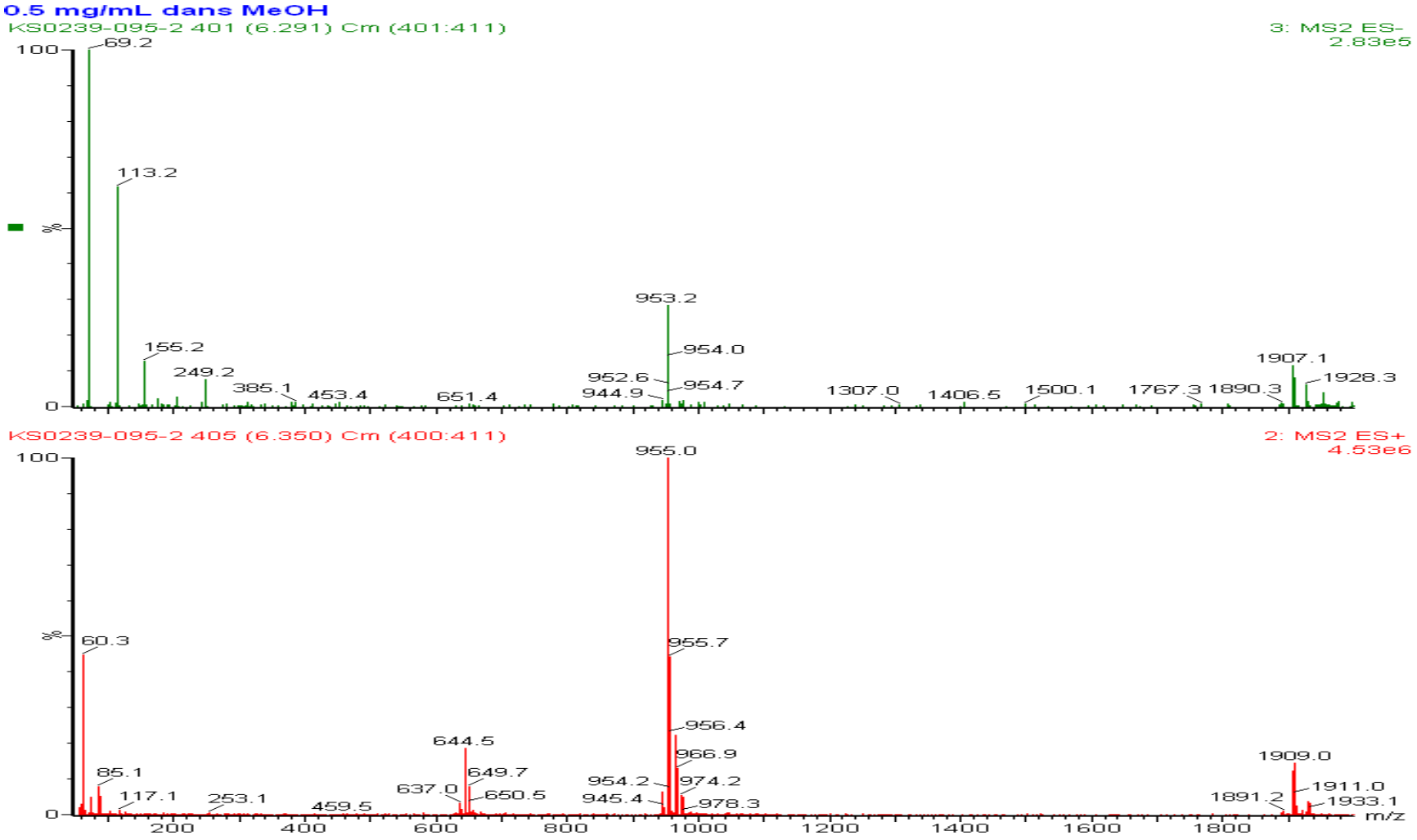
***cyclo*-bis[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**13**).

(LCMS analysis, top; ELSD spectrum, mid-two; TICs, bottom; UV spectrum)

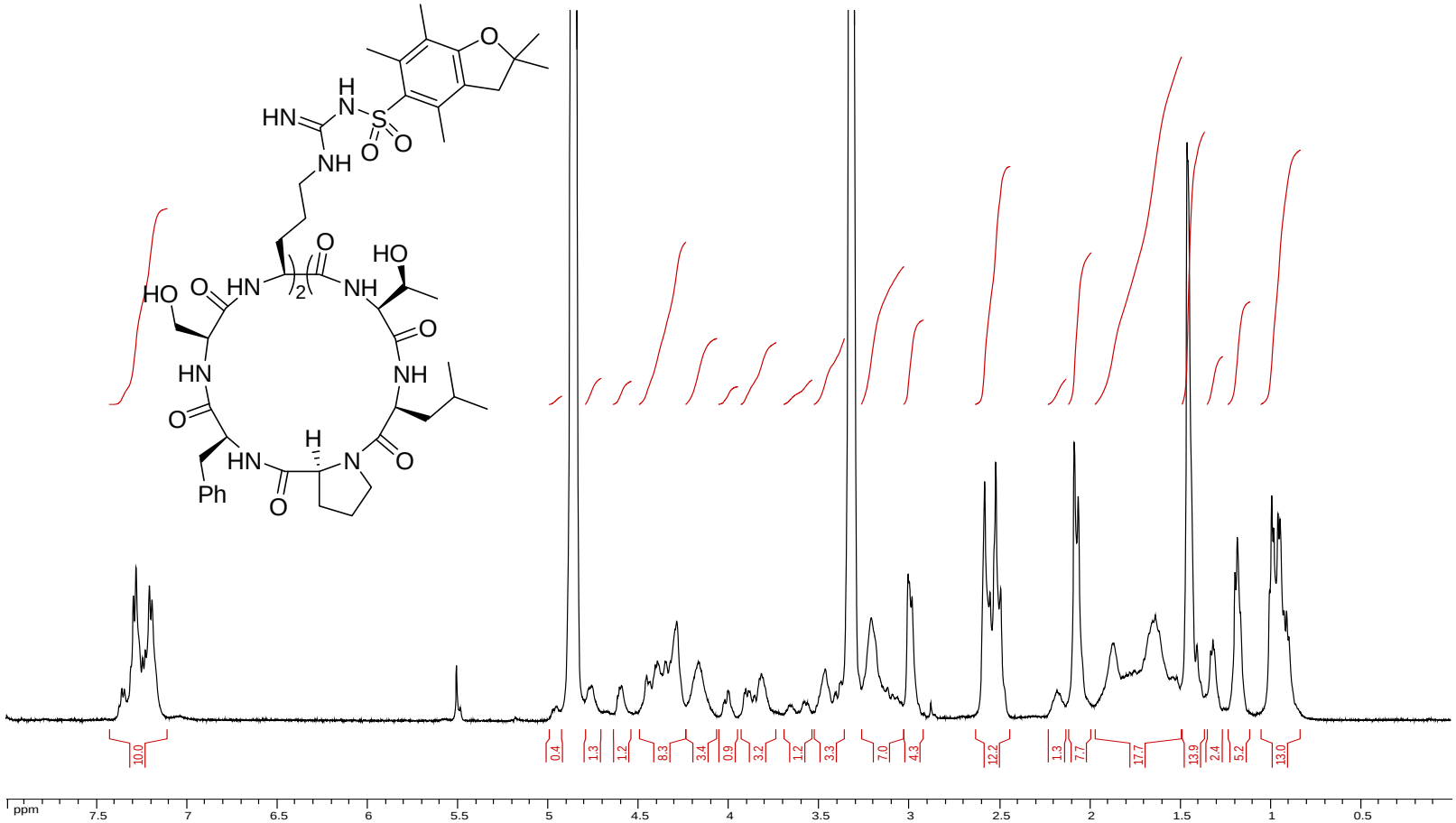


***cyclo*-bis[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**13**).

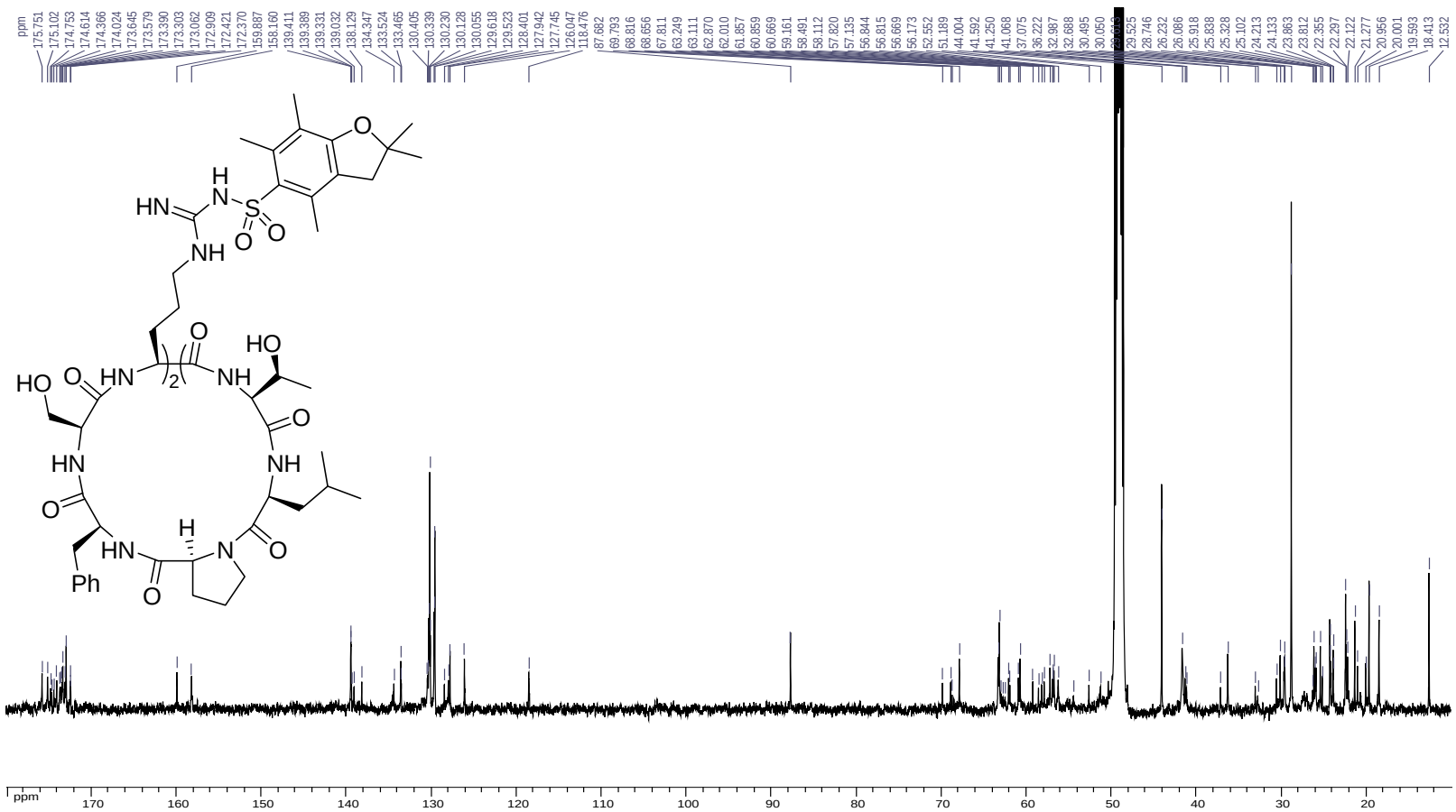
(LRMS, top; negative, bottom; positive at 6.92 min.)



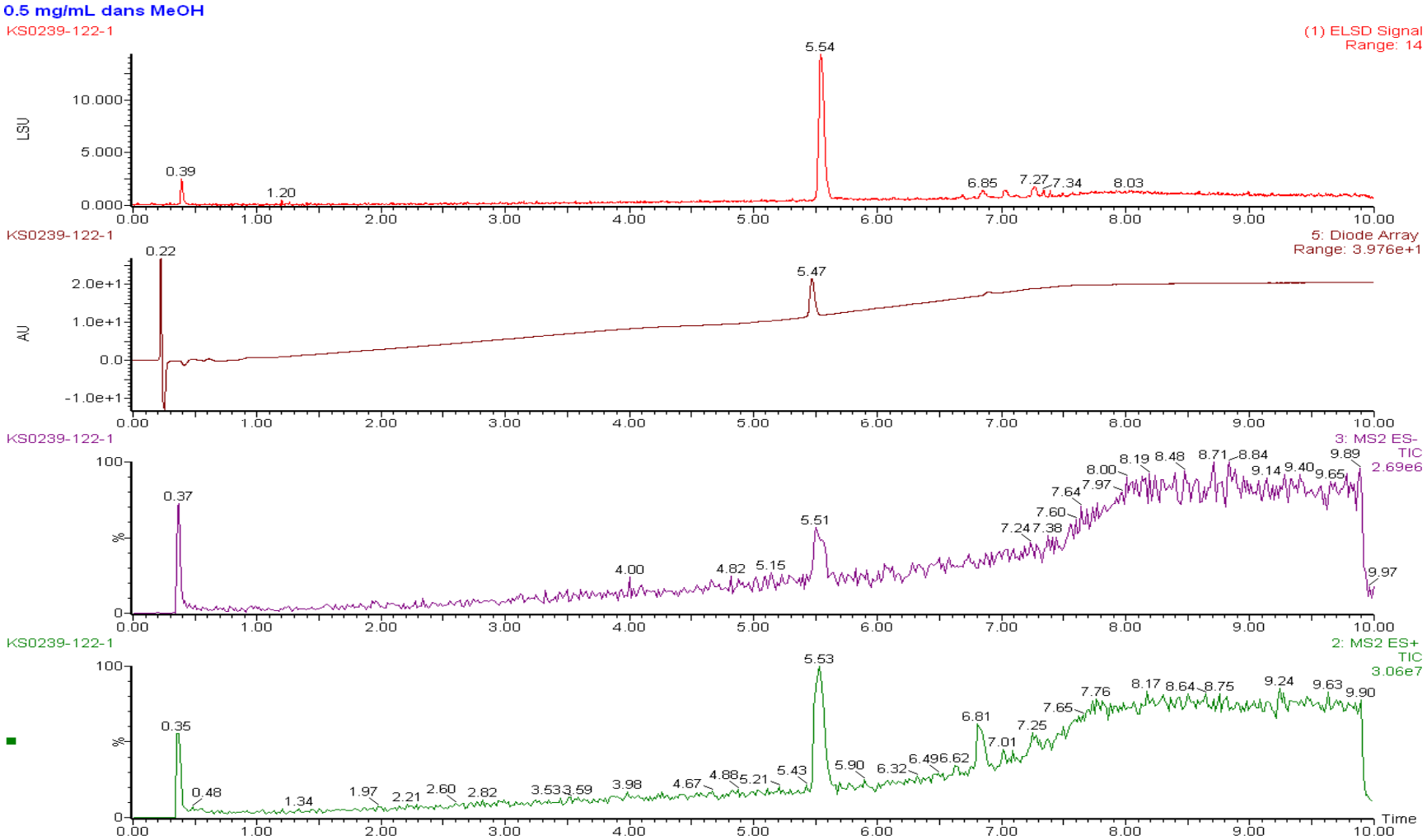
***cyclo*-bis[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**13**). ^{1}H NMR (500 MHz, CD_3OD)



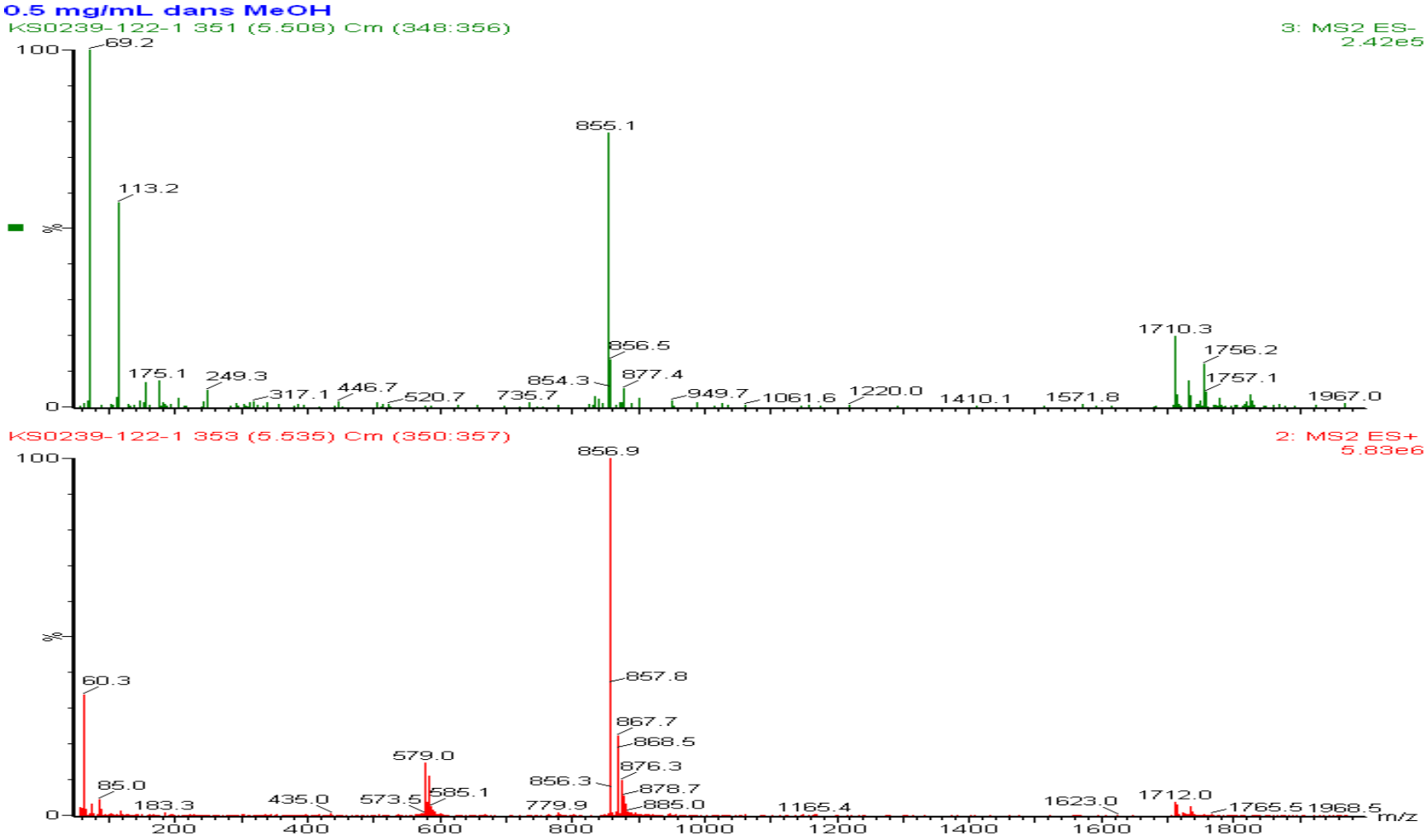
***cyclo*-bis[*N*$^{\omega}$-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-L-arginyl-L-threoninyl-L-leucinyl-L-prolinyl-L-phenylalaninyl-L-serine]** (**13**). ^{13}C NMR (125 MHz, CD_3OD)



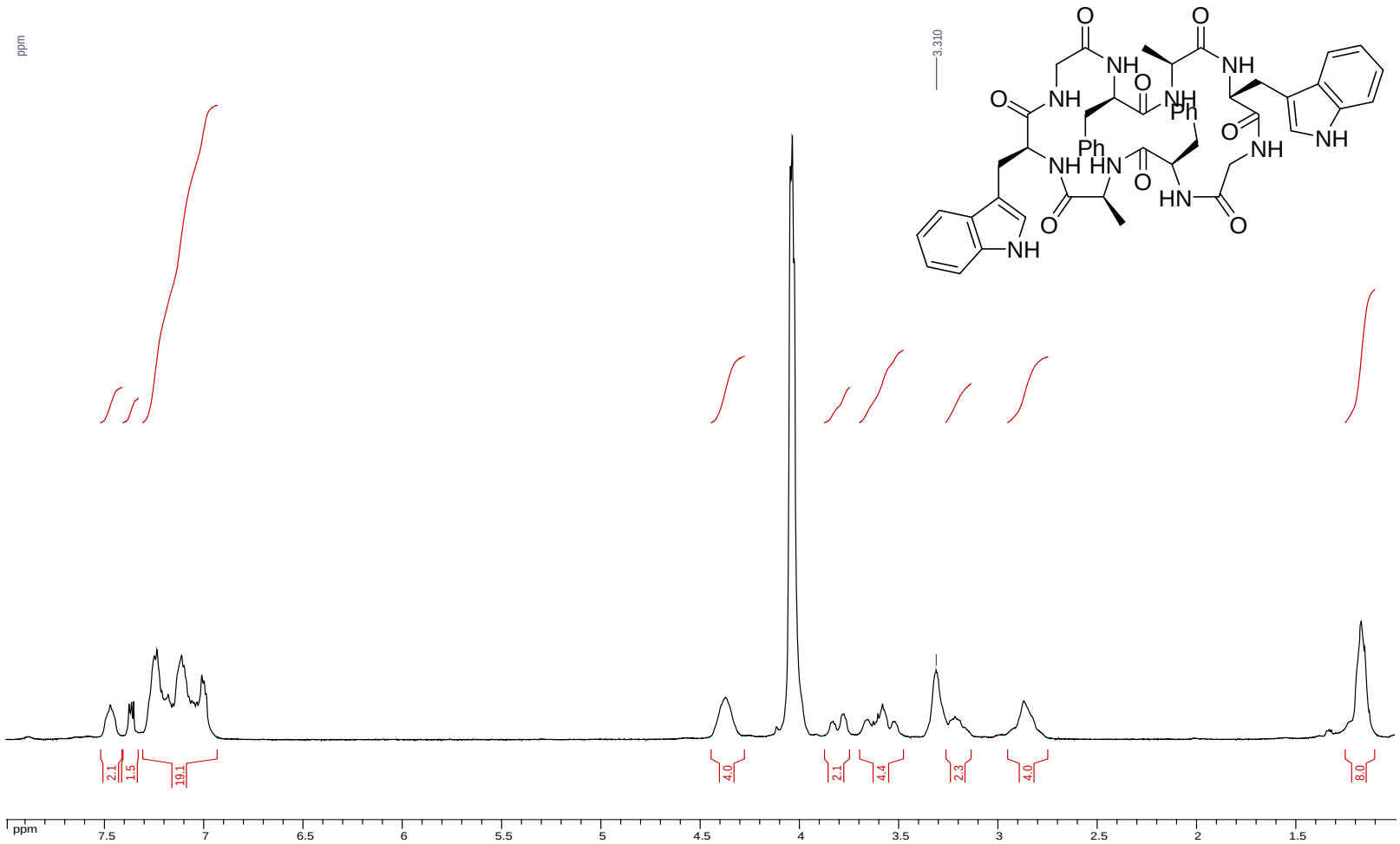
***cyclo*-(L-phenylalaninyl-L-serinyl-*N*$^{\omega}$-*p*-toluenesulfonyl-L-argininyl-L-threonyl-L-leucyl-L-proline)** (**14**). (LCMS analysis, top; ELSD spectrum, mid-two; TICs, bottom; UV spectrum)



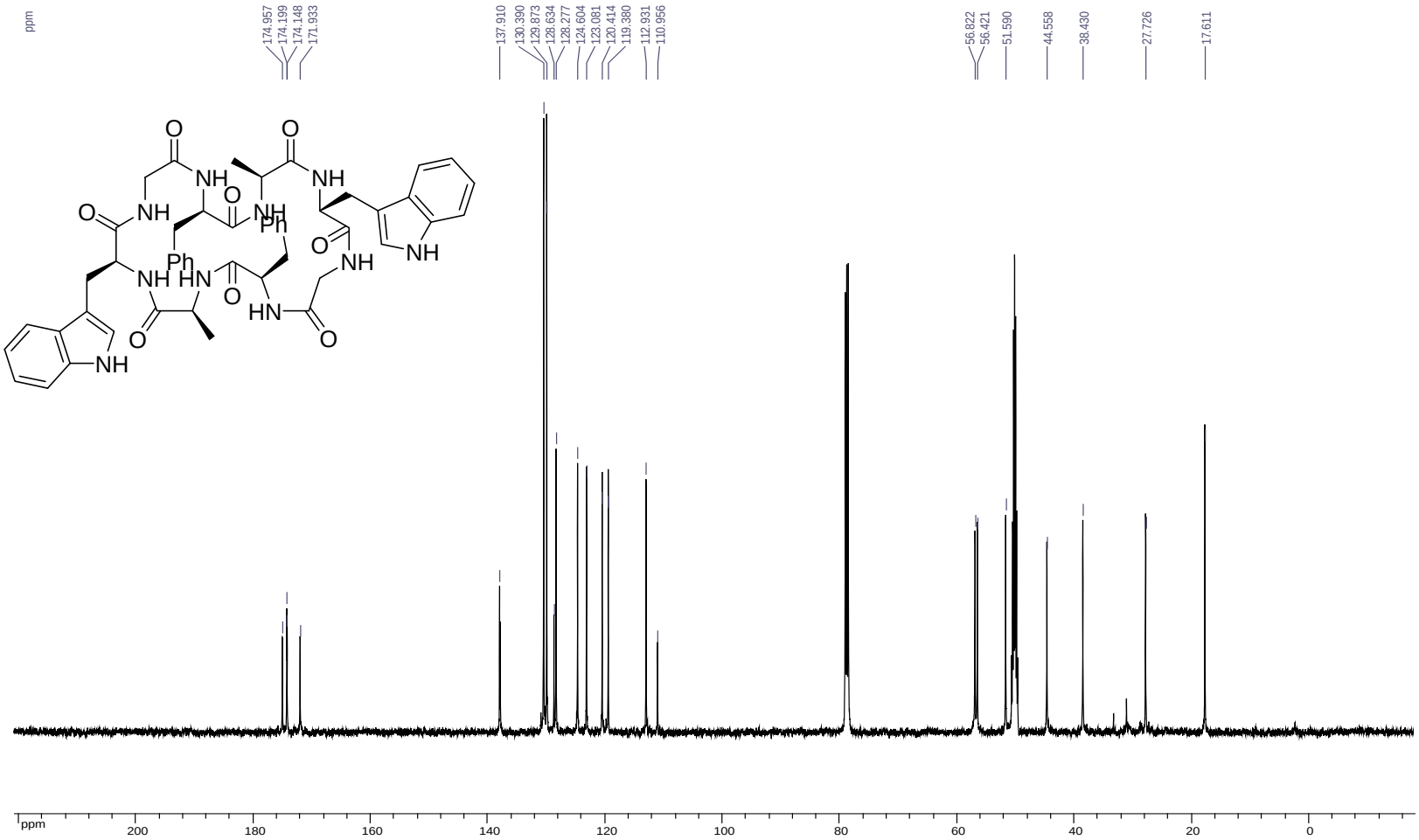
***cyclo*-(L-phenylalaninyl-L-serinyl-*N*$^{\omega}$-*p*-toluenesulfonyl-L-argininyl-L-threonyl-L-leucyl-L-proline)** (**14**). (LRMS, top; negative, bottom; positive at 5.51 min.)



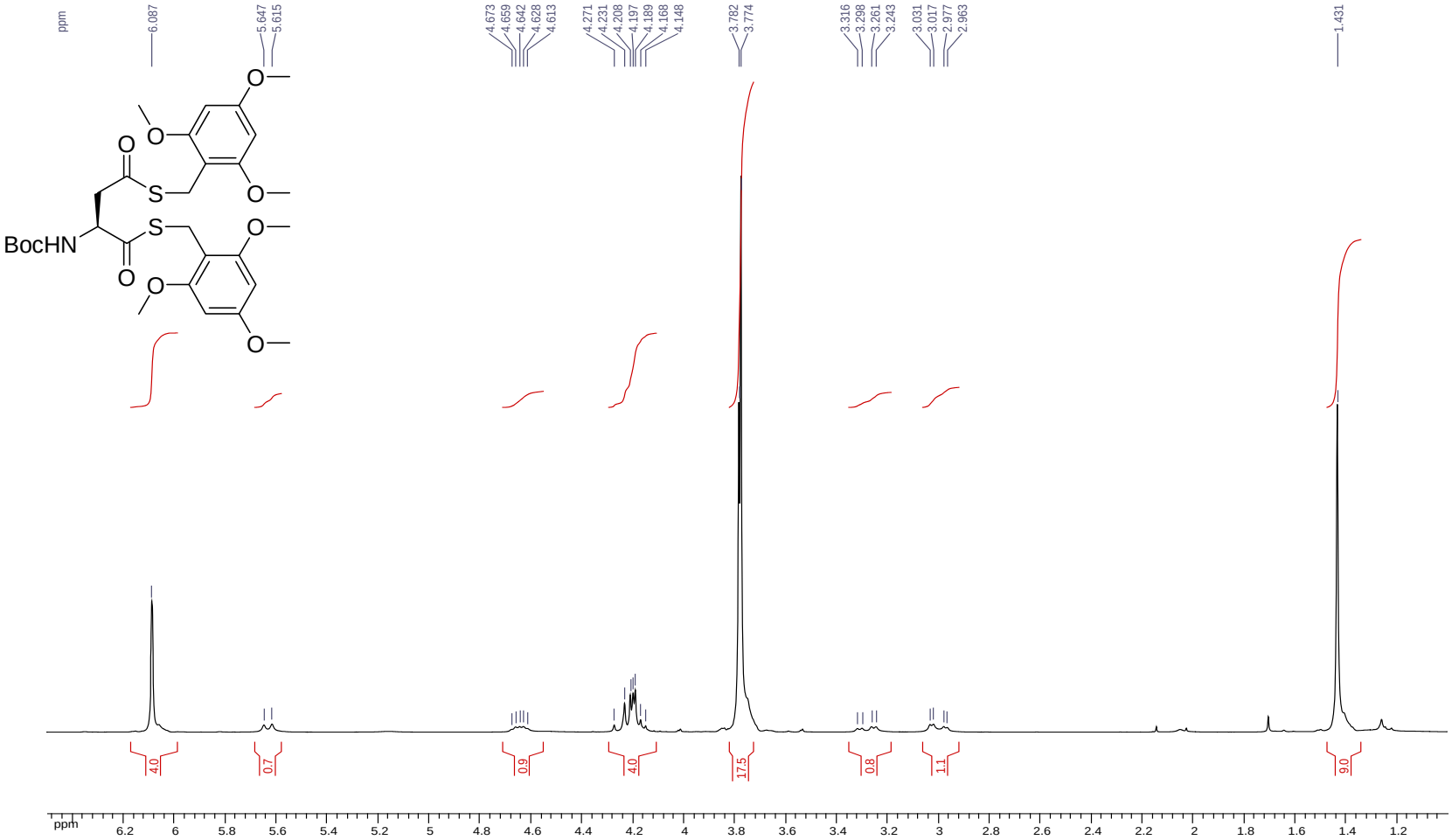
***cyclo*-bis(L-alaninyl-L-tryptophanyl-glycinyl-L-phenylalanine)** (**15**) ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ = 3/1)



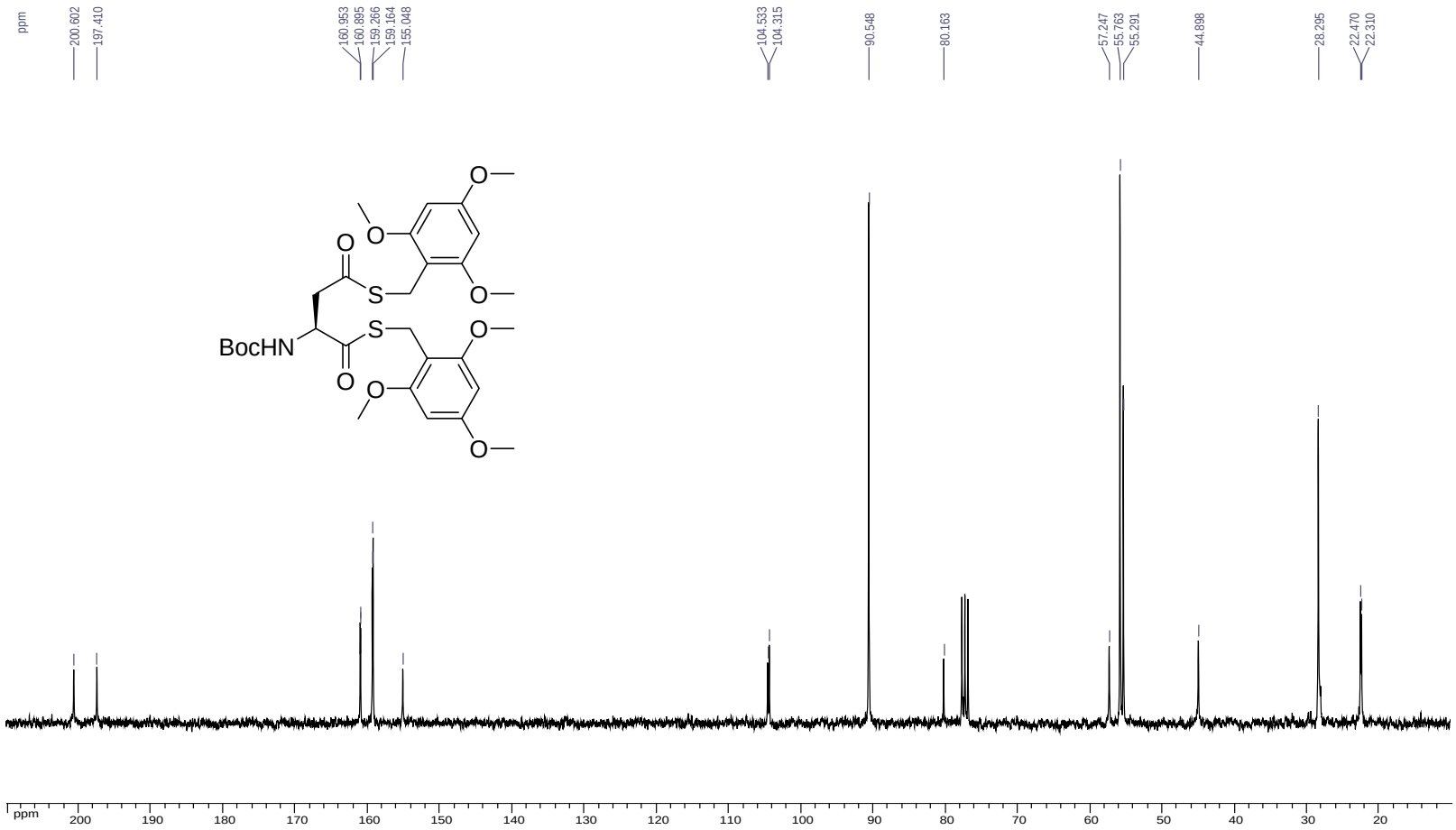
***cyclo*-bis(L-alaninyl-L-tryptophanyl-glycinyl-L-phenylalanine)** (**15**) ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 3/1)



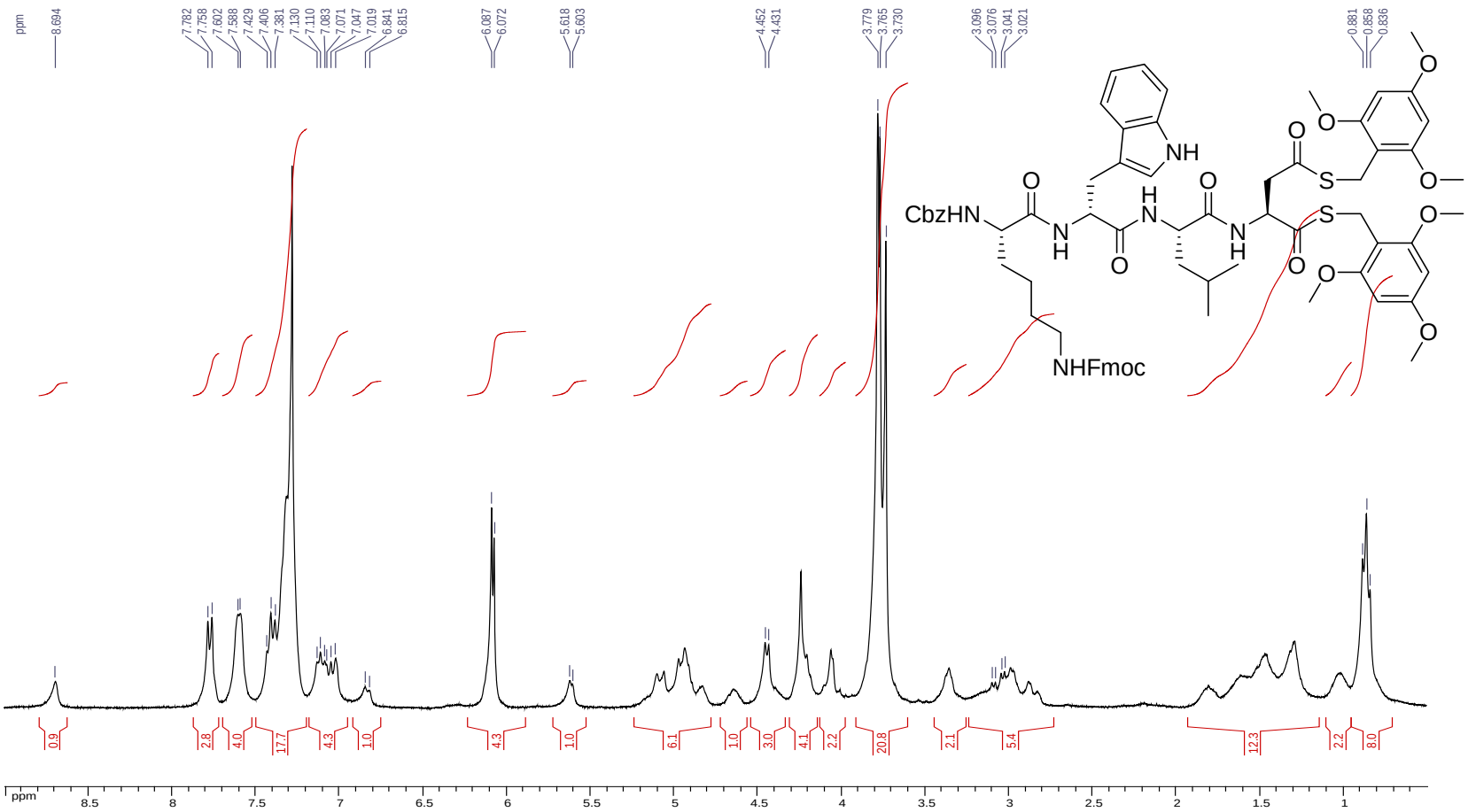
***S,S'*-Bis(2,4,6-trimethoxybenzyl) *N-tert*-butoxycarbonyl-L-dithioaspartate (16)** ^{1}H NMR (300 MHz, $CDCl_3$)



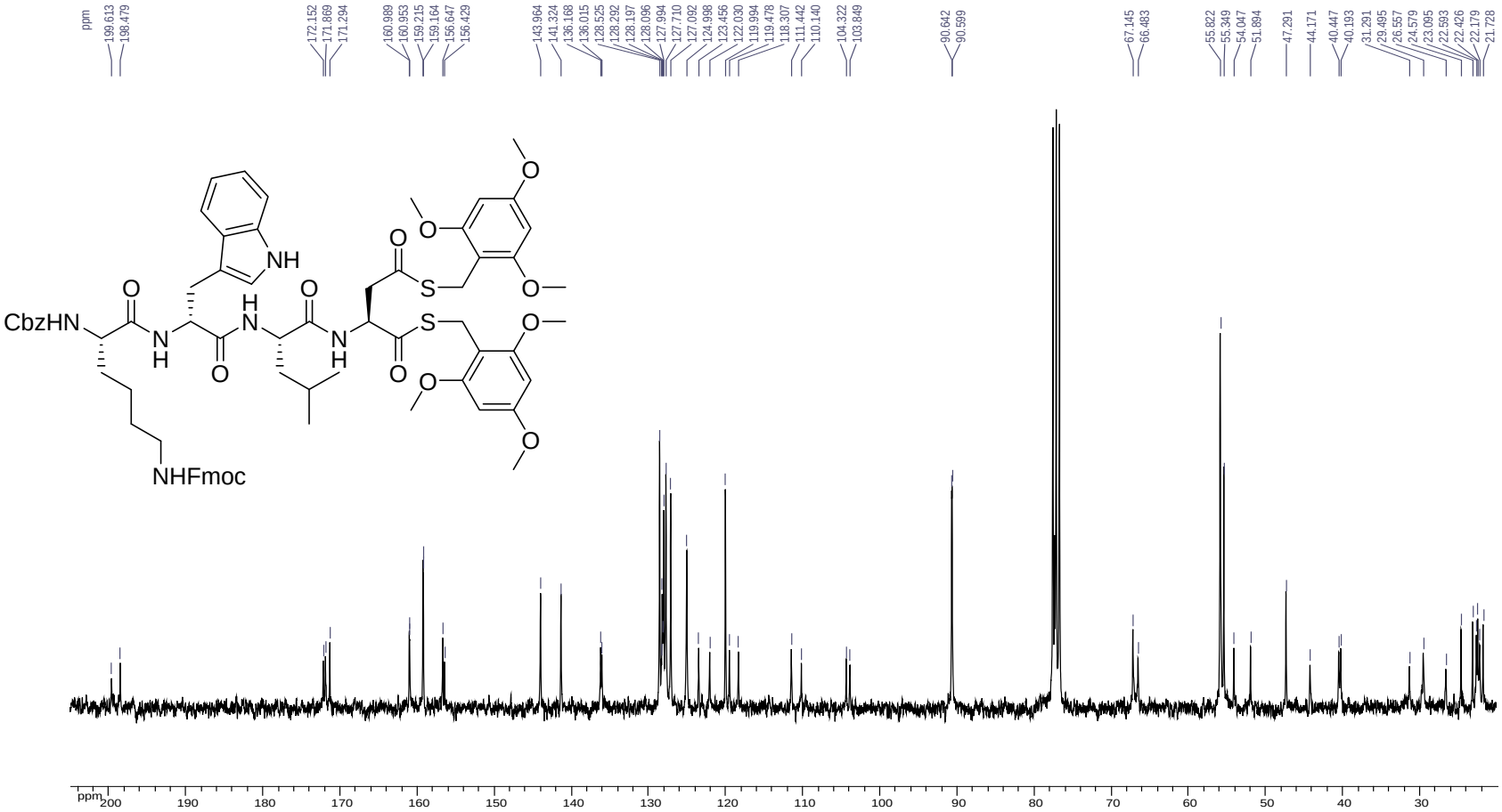
***S,S'*-Bis(2,4,6-trimethoxybenzyl) *N-tert*-butoxycarbonyl-L-dithioaspartate (16)** ^{13}C NMR (75 MHz, $CDCl_3$)



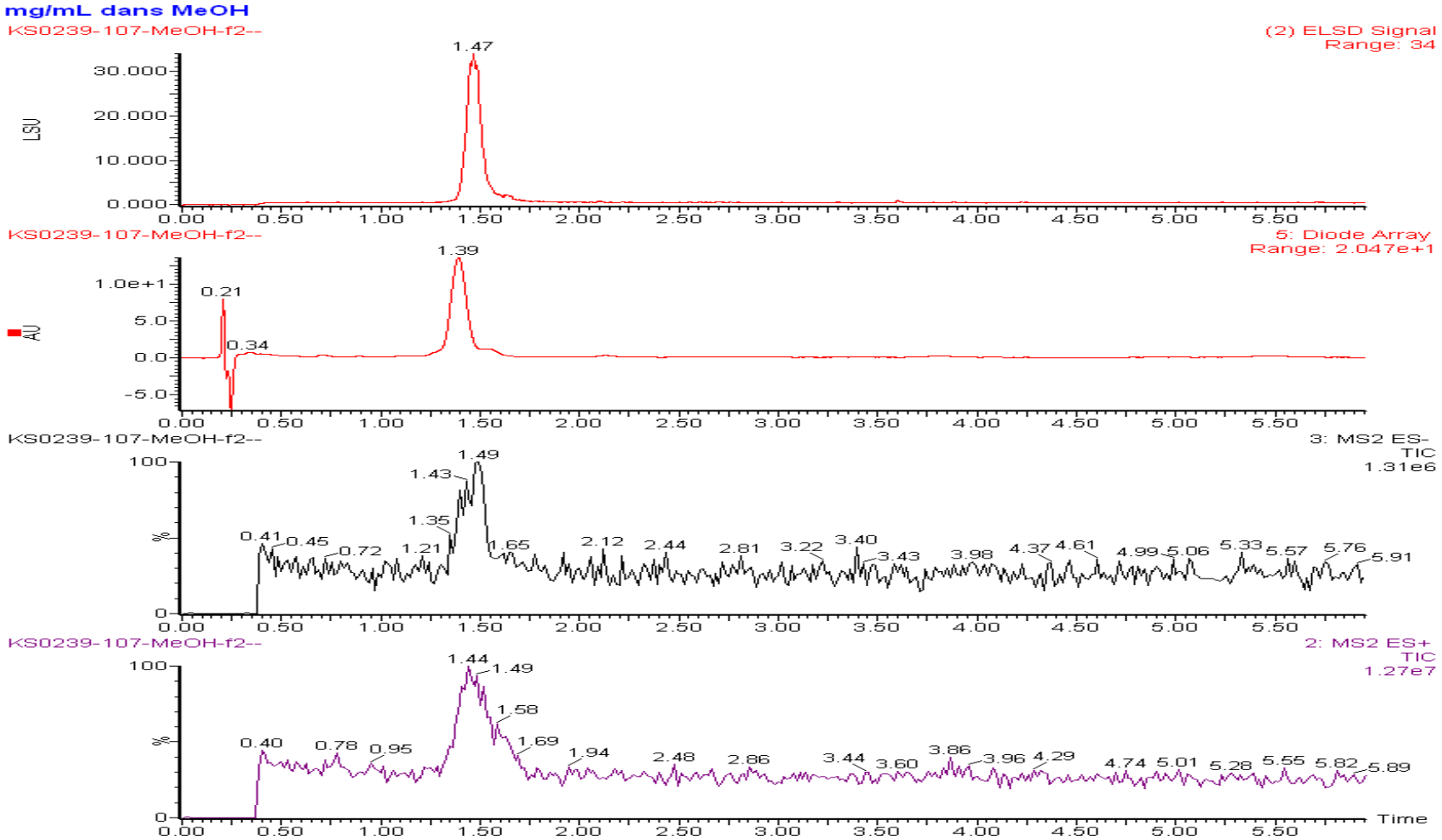
***S,S'*-Bis(2,4,6-trimethoxybenzyl) *N*$^{\alpha}$-benzyloxycarbonyl-*N*$^{\varepsilon}$-fluorenylmethoxycarbonyl-L-lysyl- D-tryptophanyl-L-leucyl-L-dithioaspartate (17)** ^{1}H NMR (300 MHz, $CDCl_3$)



***S,S'*-Bis(2,4,6-trimethoxybenzyl) *N*$^{\alpha}$-benzyloxycarbonyl-*N*$^{\varepsilon}$-fluorenylmethoxycarbonyl-L-lysyl- D-tryptophanyl-L-leucyl-L-dithioaspartate (17)** ^{13}C NMR (300 MHz, $CDCl_3$)

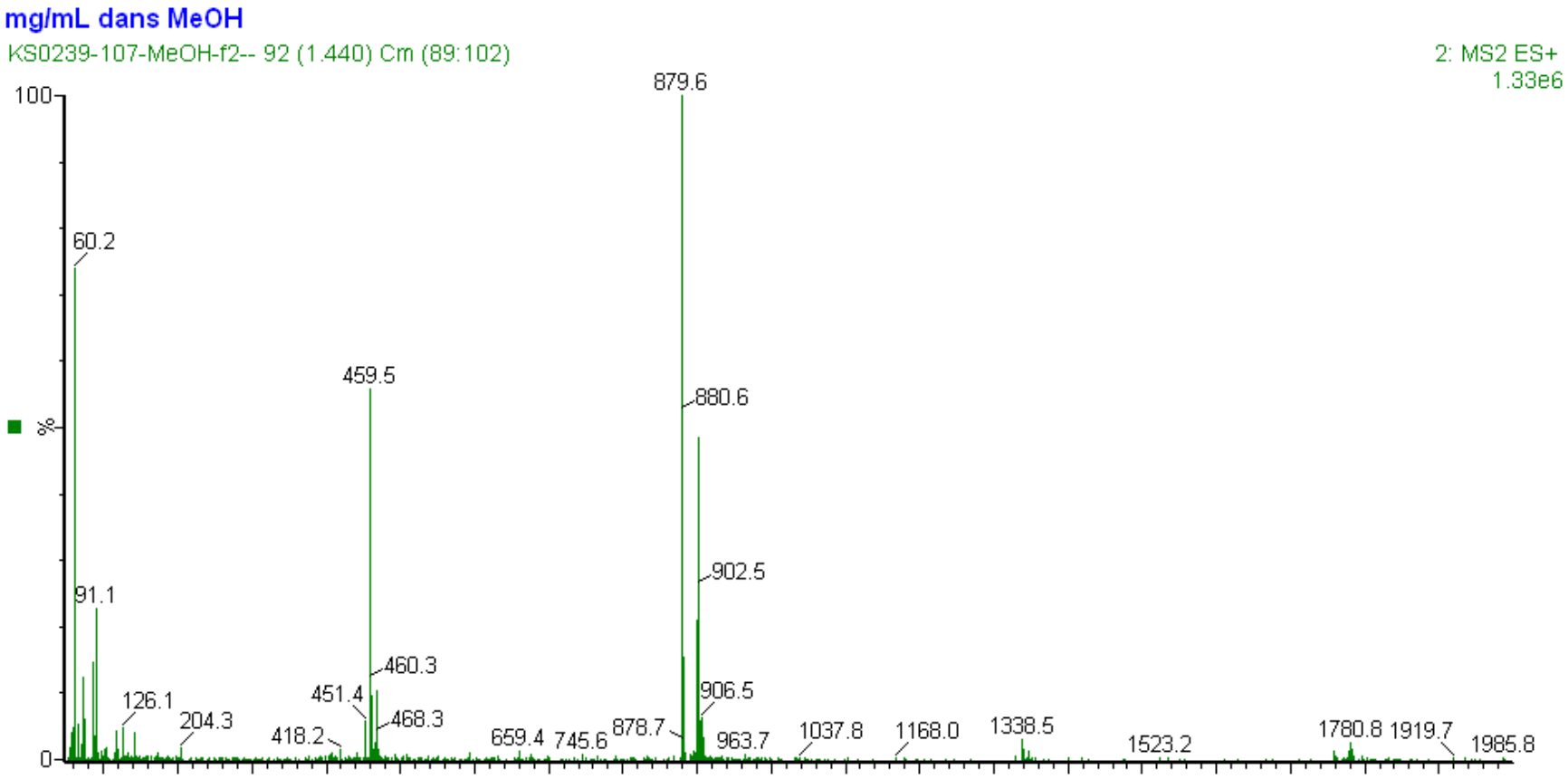


***cyclo*-[N^{α}-benzyloxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-N^{γ}-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine]** (**19**) (LCMS analysis, top; ELSD spectrum, mid-two; TICs, bottom; UV spectrum)



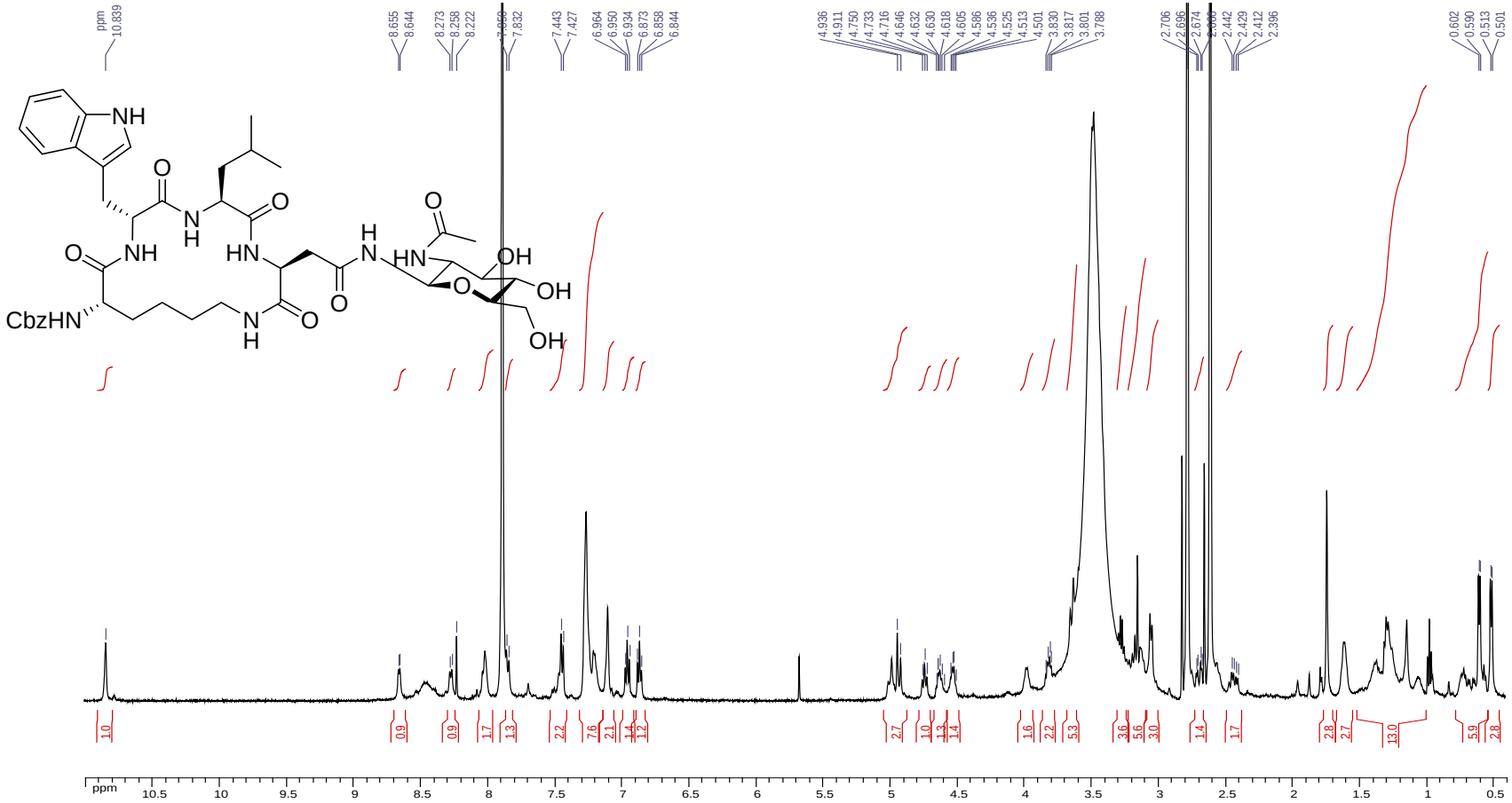
***cyclo*-[*N*$^{\alpha}$-benzyloxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-*N*$^{\gamma}$-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine]** (**19**)

(LRMS, top; positive, bottom; negative at 1.44 min.)

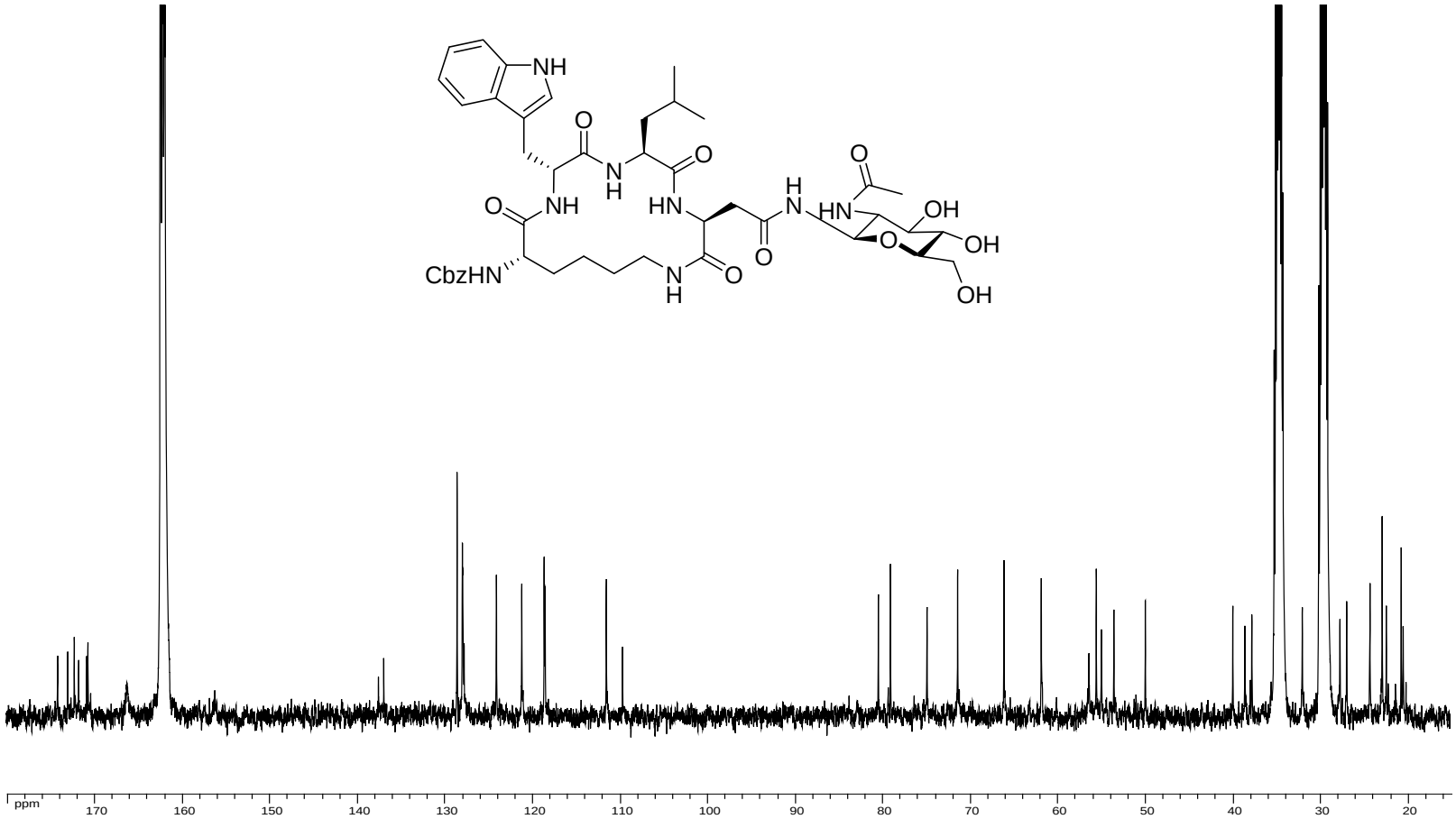


$[M+K+H]^{2+}$ $[M+H]^{+}$, $[M+Na]^{+}$

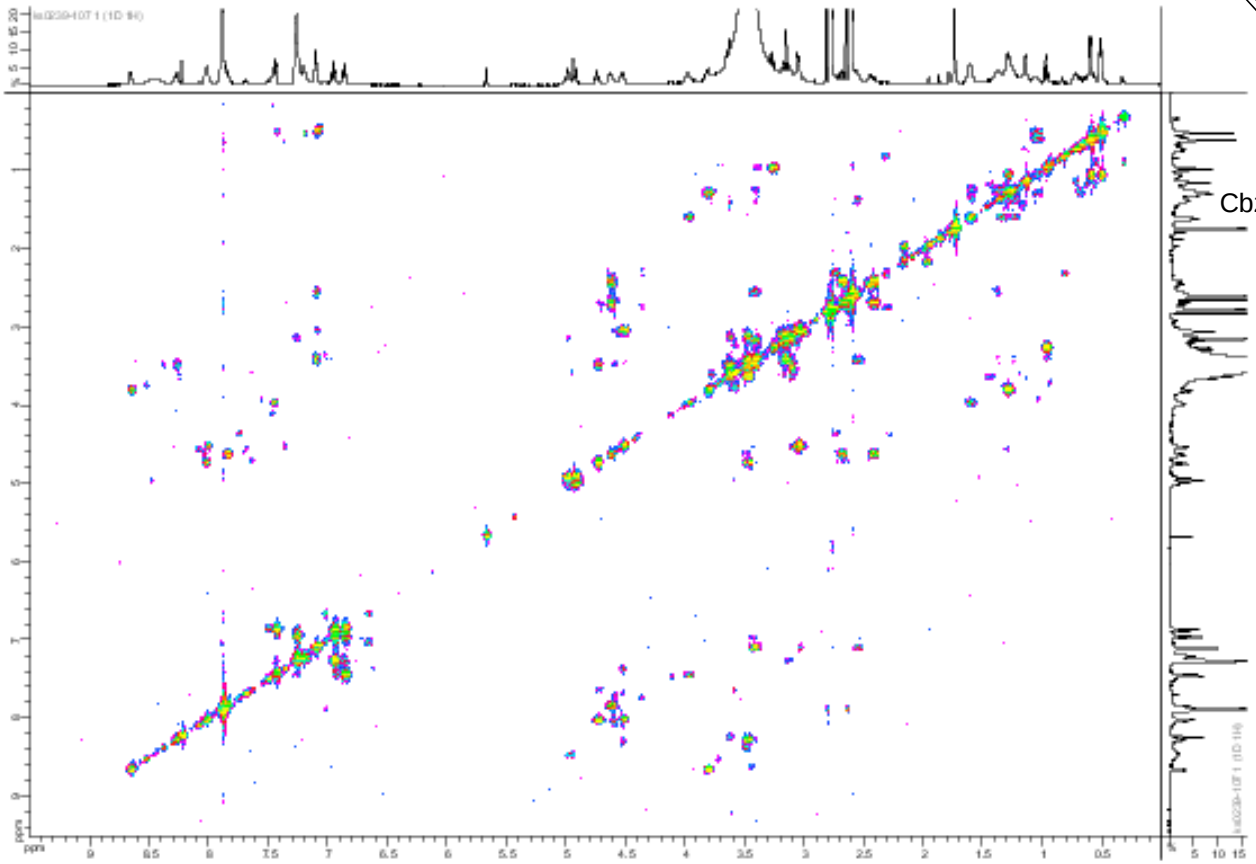
***cyclo*-[*N*$^{\alpha}$-benzyloxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-*N*$^{\gamma}$-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine]** (**19**) ^{1}H NMR (500 MHz, $CDCl_3$)

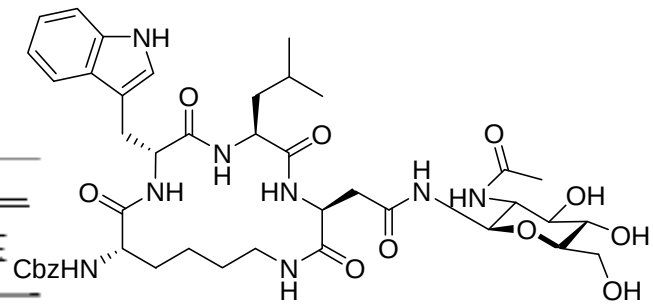


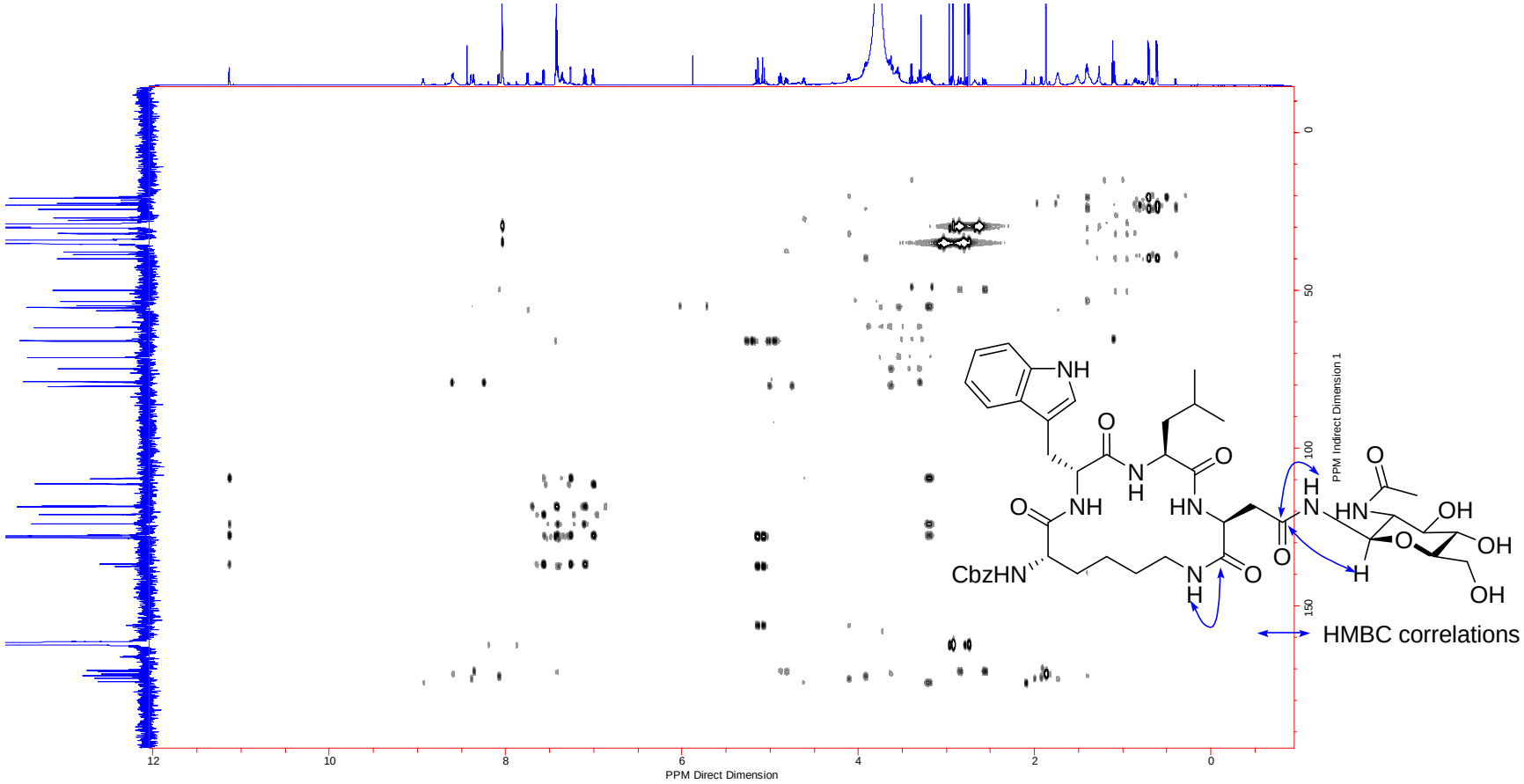
***cyclo*-[*N*$^{\alpha}$-benzyloxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-*N*$^{\gamma}$-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine]** (**19**) ^{13}C NMR (125 MHz, $CDCl_3$)



***cyclo*-[N^{α}-benzyloxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-N^{γ}-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine]** (**19**) ^{1}H-^{1}H COSY (500 MHz, DMF-d_7)





***cyclo*-[N^{α}-benzyloxycarbonyl-L-lysyl-D-tryptophanyl-L-leucyl-N^{γ}-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine] (19)**

HMBC (600 MHz, DMF-d_7, 0 °C)