Electronic Supplementary Material (ESI) for Chemical Communications

Total Synthesis of Kottamide E

Thomas B. Parsons, Neil Spencer, Chi W. Tsang and Richard S. Grainger*

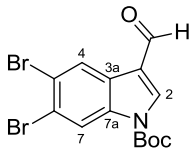
School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.

r.s.grainger@bham.ac.uk

Supplementary Electronic Information

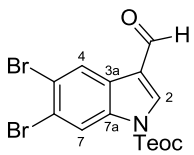
Contents

tert-Butyl 5,6-dibromo-3-formyl-1*H*-indole-1-carboxylate, 6a



5,6-Dibromo-1*H*-indole-3-carbaldehyde **5**[1] (298 mg, 0.984 mmol) was dissolved in THF (6 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (59 mg of a 60% dispersion in mineral oil, 1.48 mmol) was added in one portion and the mixture stirred for 20 min. After this time a solution of di-*tert*-butyl dicarbonate (236 mg, 1.08 mmol) in THF (3 mL) was added dropwise and the reaction mixture stirred for a further 90 min whilst warming to rt. After this time, t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.0) and formation of a single product (R_f 0.60). The reaction was quenched by the careful addition of water (3 mL) and the mixture diluted with diethyl ether (10 mL). The organic fraction was washed with water (3 x 10 mL) and the combined water fractions extracted with diethyl ether (2 x 10 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 3:1) to afford **6a** (375 mg, 95%) as a white solid, m.p. 135-136 °C; ν_{max} (solid state) 1760, 1677, 1545, 1445, 1357, 1338, 1242 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.71 (9H, s, $C(CH_3)_3$), 8.19 (1H, s, H-2), 8.50 (1H, s, H-7), 8.57 (1H, s, H-4), 10.05 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$), 28.2 (q, $C(CH_3)_3$), 86.8 (s, $C(CH_3)_3$), 120.3 (d, C-7), 120.5 (s, C-3), 120.9 (s, C-5/6), 122.2 (s, C-5/6), 126.6 (d, C-4), 126.6 (s, C-3a), 135.5 (s, C-7a), 137.1 (d, C-2), 148.2 (s, C(O)O^{t}Bu), 185.2 (CHO); *m/z* (ES^+) 458 ($M.MeOH.Na^+$, 52), 426 (MNa^+, 100), 402 (M^+, 10%); HRMS (ES^+) calculated for $C_{14}H_{13}{}^{79}Br_2NNaO_3$ (MNa^+) 423.9160, found 423.9165.

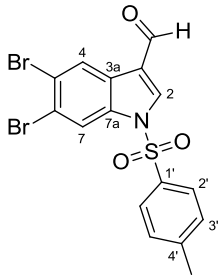
2-(Trimethylsilyl)ethyl 5,6-dibromo-3-formyl-1*H*-indole-1-carboxylate 6b



5,6-Dibromo-1*H*-indole-3-carbaldehyde **5**[1] (300 mg, 0.991 mmol) was dissolved in THF (10 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (48 mg of a 60% dispersion in mineral oil, 1.19 mmol) was added in one portion and the mixture

stirred for 20 min. After this time 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate (309 mg, 1.09 mmol) was added in one portion and the reaction mixture stirred for a further 16 hs whilst warming to rt. After this time, t.l.c. analysis (hexanes-ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.0) and formation of a single product (Rf (0.40). The reaction mixture was filtered, the filter cake washed with ethyl acetate (4 x 10 mL) and the combined filtrate subsequently washed with brine (20 mL), dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 9:1) to afford **6b** (443 mg, 95%) as a white solid, m.p. 118-119 °C; ν_{max} (solid state) 2954, 1746, 1676, 1442, 1337, 1248, 1224 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 0.13 (9H, s, $Si(CH_3)_3$), 1.23-1.29 (2H, m, $SiCH_2$), 4.57-4.63 (2H, m, OCH_2), 8.22 (1H, s, H-2), 8.48 (1H, s, H-7), 8.56 (1H, s, H-4), 10.04 (1H, s CHO); δ_C (100 MHz, $CDCl_3$), -1.4 (q, $Si(CH_3)_3$), 18.0 (t, $SiCH_2$), 68.0 (t, OCH_2), 120.2 (d, C-7), 121.0 (s, C-3), 121.1 (s, C-5/6), 122.4 (s, C-5/6), 126.6 (s, C-3a), 126.6 (d, C-4), 135.4 (s, C-7a), 136.8 (d, C-2), 149.9 (s, C(O)O^{t}Bu), 185.1 (d, CHO); *m/z* (EI^+) 447 (M^+, 24%); HRMS (EI^+) calculated for $C_{15}H_{17}{}^{79}Br_2NO_3Si$ (M^+) 444.9344, found 444.9341.

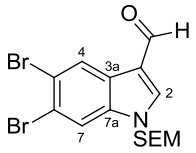
5,6-Dibromo-1-tosyl-1*H*-indole-3-carbaldehyde 6c



5,6-Dibromo-1*H*-indole-3-carbaldehyde **5**[1] (85 mg, 0.281 mmol) was dissolved in THF (4 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (17 mg of a 60% dispersion in mineral oil, 0.421 mmol) was added in one portion and the mixture stirred for 20 min. After this time *para*-toluenesulfonyl chloride (70 mg, 0.365 mmol) was added in one portion and the reaction mixture stirred for a further 40 min whilst warming to rt. After this time, t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.0) and formation of a single product (R_f 0.45). The reaction was quenched by the careful addition of ammonium chloride (2 mL of a saturated aqueous solution) and the mixture diluted with diethyl ether (10 mL). The organic fraction was

washed with water (3 x 5 mL) and the combined water fractions extracted with diethyl ether (2 x 5 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 3:1) to afford **6c** (104 mg, 81%) as a pale yellow solid, m.p. 208-210 °C; ν_{max} (solid state) 3103, 2819, 1672, 1595, 1536, 1439, 1405, 1375, 1171, 1144, 1114 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 2.41 (3H, s, CH_3), 7.34 (2H, d, *J* 8.3 Hz, H-3'), 7.83 (2H, d, *J* 8.3 Hz, H-2'), 8.19 (1H, s, H-2), 8.25 (1H, s, H-7), 8.54 (1H, s, H-4), 10.03 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$), 21.9 (q, CH_3), 118.2 (d, C-7), 121.3 (s, C-3), 121.7 (s, C-5/6), 122.5 (s, C-5/6), 126.8 (s, C-3a), 127.1 (d, C-4), 127.4 (d, C-2'), 130.7 (d, C-3'), 134.1 (s, C-7a), 134.7 (s, C-1'), 137.0 (d, C-2), 146.9 (s, C-4'), 184.7 (d, CHO); *m/z* (EI^+) 457 (M^+, 60%); HRMS (ES^+) calculated for $C_{16}H_{11}{}^{79}Br_2NO_3S$ (M^+) 454.8826, found 454.8839.

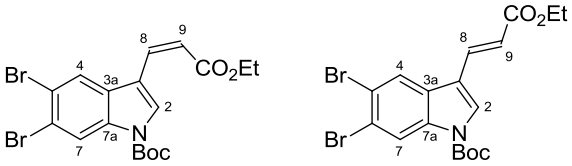
5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-3-carbaldehyde 6d



5,6-Dibromo-1*H*-indole-3-carbaldehyde **5**[1] (402 mg, 1.33 mmol) was dissolved in THF (20 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (80 mg of a 60% dispersion in mineral oil, 1.99 mmol) was added in one portion and the mixture stirred for 15 min. After this time 2-(trimethylsilyl)ethoxymethyl chloride (282 μL, 1.59 mmol) was added dropwise and the reaction mixture stirred for a further 1 h whilst warming to rt. After this time, t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.0) and formation of a single product (R_f 0.22). The reaction was quenched by the careful addition of ammonium chloride (5 mL of a saturated aqueous solution) and the mixture diluted with diethyl ether (20 mL). The organic fraction was washed with water (3 x 20 mL) and the combined water fractions extracted with diethyl ether (2 x 20 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 7:3) to afford **6d** (544 mg, 95%) as a pale orange solid, m.p. 79-80 °C; ν_{max} (solid state) 3112, 3052, 2950, 1655, 1540, 1454, 1394, 1374, 1250 cm^{-1}; δ_H (400 MHz, $CDCl_3$), -0.03 (9H, s, $Si(CH_3)_3$), 0.92 (2H, t, *J* 8.1 Hz, CH_2Si), 3.50 (2H, t, *J* 8.1 Hz, CH_2O), 5.48 (2H, s, OCH_2N), 7.77 (1H, s, H-2), 7.83 (1H, s, H-7), 8.61 (1H, s, H-4), 10.00 (1H, s, CHO); δ_C

(100 MHz, $CDCl_3$), -1.3 (q, $SiMe_3$), 17.8 (t, CH_2Si), 67.1 (t, CH_2O), 77.0 (t, OCH_2N), 115.8 (d, C-7), 118.2 (s, C-3), 119.4 (s, C-5/6), 120.2 (s, C-5/6), 126.1 (s, C-3a), 126.6 (d, C-4), 136.8 (s, C-7a), 139.1 (d, C-2), 184.6 (d, CHO); *m/z* (ES^+) 488 ($M.MeOH.Na^+$, 44), 456 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{15}H_{19}{}^{79}Br_2NNaO_2Si$ (MNa^+) 453.9449, found 453.9439.

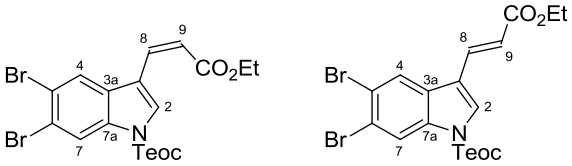
(*Z*)-*tert*-Butyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate 7a and (*E*)-*tert*-butyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate (*E*)-7a



Ethyl 2-(diphenoxyphosphoryl)acetate (65 µL, 0.242 mmol) was dissolved in THF (2 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (11 mg of a 60% dispersion in mineral oil, 0.279 mmol) was added in one portion and the mixture stirred for 15 min. In a fresh flask, *tert*-butyl 5,6-dibromo-3-formyl-1*H*-indole-1-carboxylate **6a** (75 mg, 0.186 mmol) was dissolved in THF (2 mL) and the solution cooled to -78 °C under an atmosphere of argon. The solution of the phosphoryl anion was added to this dropwise and the reaction mixture stirred for a further 90 min whilst maintaining the temperature at -78 °C. After this time, t.l.c. analysis (hexanes-ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.44) and formation of two products (R_f 0.63, 0.56). The reaction was quenched by the careful addition of ammonium chloride (5 mL of a saturated aqueous solution) and the mixture diluted with diethyl ether (15 mL). The organic fraction was washed with water (2 x 3 mL) and the combined water fractions extracted with diethyl ether (2 x 5 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 11:1) to afford first **7a** (71 mg, 81%) as a white solid, m.p. 117-118 °C; ν_{max} (solid state) 3174, 2973, 1738, 1712, 1619, 1452, 1435, 1366, 1263, 1171, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.32 (3H, t, *J* 7.1 Hz, CH_3), 1.69 (9H, s, $C(CH_3)_3$), 4.24 (2H, q, *J* 7.1 Hz, CH_2CH_3), 5.99 (1H, d, $J_{8,9}$ 12.6 Hz, H-9), 6.96 (1H, dd, $J_{2,8}$ <1 Hz, $J_{8,9}$ 12.6 Hz, H-8), 7.87 (1H, s, H-4), 8.52 (1H, s, H-7), 8.78 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), 14.5 (q, CH_3), 28.2 (q, $C(CH_3)_3$), 60.4 (t, OCH_2CH_3), 85.4 (s, $C(CH_3)_3$), 113.7 (s, C-3), 118.6 (d, C-9), 119.0 (s, C-5/6), 120.4

(s, C-5/6), 120.5 (d, C-7), 122.8 (d, C-4), 131.2 (s, C-3a), 131.6 (d, C-2), 131.6 (d, C-8), 134.5 (s, C-7a), 149.0 (s, NC(O)O), 166.4 (s, C-10); *m/z* (ES^+) 496 (MNa^+, 76), 440 ([M-^{t}Bu]Na^+, 100%); HRMS (ES^+) calculated for $C_{18}H_{19}{}^{79}Br_2NNaO_4$ (MNa^+) 493.9579, found 493.9583. Continued elution gave **(*E*)-7a** (11 mg, 13%) as a white solid, m.p. 124-126 °C; ν_{max} (solid state) 3128, 2986, 1747, 1717, 1619, 1529, 1436, 1365, 1325, 1279, 1263, 1221, 1170, 1144 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.36 (3H, t, *J* 7.1 Hz, CH_3), 1.68 (9H, s, $C(CH_3)_3$), 4.29 (2H, q, *J* 7.1 Hz, CH_2CH_3), 6.45 (1H, d, $J_{8,9}$ 16.2 Hz, H-9), 7.72 (1H, d, $J_{8,9}$ 16.2 Hz, H-8), 7.81 (1H, s, H-4), 8.08 (1H, s, H-7), 8.54 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), 14.5 (q, CH_3), 28.2 (q, $C(CH_3)_3$), 60.8 (t, OCH_2CH_3), 85.8 (s, $C(CH_3)_3$), 116.0 (s, C-3), 118.6 (d, C-9), 119.6 (s, C-5/6), 120.6 (d, C-7), 121.2 (s, C-5/6), 124.6 (d, C-4), 128.6 (s, C-3a), 129.6 (d, C-2), 135.2 (d, C-8), 135.8 (s, C-7a), 148.6 (s, NC(O)O), 167.1 (s, C-10); *m/z* (ES^+) 528 (M.MeOH.Na^+, 75), 496 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{18}H_{19}{}^{79}Br_2NNaO_4$ (MNa^+) 493.9579, found 493.9570.

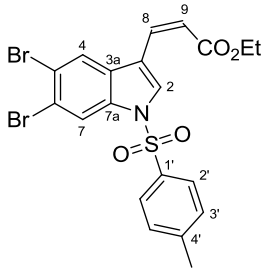
(*Z*)-2-(Trimethylsilyl)ethyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate 7b and (*E*)-2-(trimethylsilyl)ethyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate (*E*)-7b



Ethyl 2-(diphenoxyphosphoryl)acetate (45 µL, 0.166 mmol) was dissolved in THF (1.5 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (7.6 mg of a 60% dispersion in mineral oil, 0.191 mmol) was added in one portion and the mixture stirred for 15 min. In a fresh flask, 2-(trimethylsilyl)ethyl 5,6-dibromo-3-formyl-1*H*-indole-1-carboxylate **6b** (57 mg, 0.127 mmol) was dissolved in THF (1.5 mL) and the solution cooled to -78 °C under an atmosphere of argon. The solution of the phosphoryl anion was added to this dropwise and the reaction mixture stirred for a further 2 h whilst maintaining the temperature at -78 °C. After this time, t.l.c. analysis (hexanes-ethyl acetate, 9:1) indicated complete consumption of starting material (R_f 0.16) and formation of two products (R_f 0.53, 0.32). The reaction was quenched by the careful addition of ammonium chloride (2 mL of a saturated aqueous solution) and the mixture diluted with diethyl ether (5 mL). The organic fraction was washed with water (2 x 3 mL) and the combined water fractions extracted with

diethyl ether (2 x 5 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 19:1) to afford first **7b** (52 mg, 81%) as a white solid, m.p. 86-88 °C; ν_{max} (solid state) 3166, 2957, 1743, 1710, 1628, 1452, 1431, 1386, 1356, 1272, 1240, 1218, 1165 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 0.12 (9H, s, $Si(CH_3)_3$), 1.23-1.27 (2H, m, $SiCH_2$), 1.33 (3H, t, *J* 7.1 Hz, CH_3), 4.24 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.54-4.58 (2H, m, OCH_2CH_2), 5.99 (1H, d, $J_{8,9}$ 12.7 Hz, H-9), 6.94 (1H, d, $J_{8,9}$ 12.7 Hz, H-8), 7.85 (1H, s, H-4), 8.55 (1H, s, H-7), 8.91 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), -1.3 (q, $Si(CH_3)_3$), 14.5 (q, CH_3), 18.0 (t, $SiCH_2$), 60.5 (t, OCH_2CH_3), 67.0 (t, OCH_2CH_2), 112.1 (s, C-3), 118.8 (d, C-9), 119.3 (s, C-5/6), 120.4 (d, C-7), 120.7 (s, C-5/6), 122.9 (d, C-4), 131.2 (s, C-3a), 131.3 (d, C-2), 131.5 (d, C-8), 134.5 (s, C-7a), 151.9 (s, NC(O)O), 166.4 (s, C-10); *m/z* (ES^+) 540 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{19}H_{23}{}^{79}Br_2NNaO_4Si$ (MNa^+) 537.9661, found 537.9669. Continued elution gave **(*E*)-7b** (8 mg, 13%) as a white solid, m.p. 92-94 °C; ν_{max} (solid state) 3139, 2956, 2924, 1747, 1699, 1629, 1448, 1390, 1353, 1228, 1166 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 0.11 (9H, s, $Si(CH_3)_3$), 1.21-1.25 (2H, m, $SiCH_2$), 1.36 (3H, t, *J* 7.1 Hz, CH_3), 4.29 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.53-4.57 (2H, m, OCH_2CH_2), 6.46 (1H, d, $J_{8,9}$ 16.2 Hz, H-9), 7.71 (1H, d, $J_{8,9}$ 16.2 Hz, H-8), 7.84 (1H, s, H-4), 8.08 (1H, s, H-7), 8.55 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), -1.4 (q, $Si(CH_3)_3$), 14.5 (q, CH_3), 17.9 (t, $SiCH_2$), 60.8 (t, OCH_2CH_3), 67.2 (t, OCH_2CH_2), 116.5 (s, C-3), 118.9 (d, C-9), 119.9 (s, C-5/6), 120.6 (d, C-7), 121.4 (s, C-5/6), 124.7 (d, C-4), 128.5 (s, C-3a), 129.2 (d, C-2), 135.1 (d, C-8), 135.7 (s, C-7a), 150.1 (s, NC(O)O), 167.0 (s, C-10); *m/z* (ES^+) 572 ($M.MeOH.Na^+$, 54), 540 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{19}H_{23}{}^{79}Br^{81}BrNNaO_4Si$ (MNa^+) 539.9640, found 539.9638.

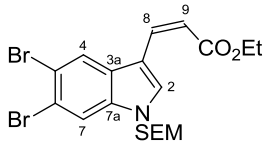
(*Z*)-Ethyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate 7c

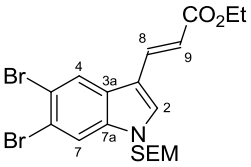


Ethyl 2-(diphenoxyphosphoryl)acetate (230 µL, 0.853 mmol) was dissolved in THF (5 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (39 mg of a 60% dispersion in mineral oil, 0.984 mmol) was added in one portion and the mixture stirred

for 15 min. In a fresh flask, 5,6-dibromo-1-tosyl-1*H*-indole-3-carbaldehyde **6c** (300 mg, 0.656 mmol) was dissolved in THF (5 mL) and the solution cooled to -40 °C under an atmosphere of argon. The solution of the phosphoryl anion was added to this dropwise and the reaction mixture stirred for a further 2 h whilst maintaining the temperature at between -50 °C and -30 °C. After this time, t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.45) and formation of a major products (R_f 0.70). The reaction was quenched by the careful addition of ammonium chloride (5 mL of a saturated aqueous solution) and the mixture diluted with diethyl ether (10 mL). The organic fraction was washed with water (2 x 5 mL) and the combined water fractions extracted with diethyl ether (2 x 5 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 9:1) to afford **7c** (276 mg, 80%) as a pale orange solid, m.p. 130-132 °C; ν_{max} (solid state) 3162, 3104, 2989, 1714, 1632, 1593, 1430, 1372, 1239, 1165, 1130, 1090, 1026 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.33 (3H, t, *J* 7.1 Hz, CH_3), 2.37 (3H, s, CH_3), 4.25 (2H, q, *J* 7.1 Hz, CH_2CH_3), 6.01 (1H, d, $J_{8,9}$ 12.6 Hz, H-9), 6.88 (1H, d, $J_{8,9}$ 12.6 Hz, H-8), 7.28 (2H, d, $J_{2',3'}$ 8.1 Hz, 2 x H-3'), 7.83 (2H, d, $J_{2',3'}$ 8.1 Hz, 2 x H-2'), 7.83 (1H, s, H-4), 8.30 (1H, s, H-7), 8.93 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), 14.4 (q, CH_2CH_3), 21.8 (q, CH_3), 60.1 (t, OCH_2CH_3), 114.9 (s, C-3), 118.5 (d, C-7), 119.4 (d, C-9), 119.8 (s, C-5/6), 120.7 (s, C-5/6), 123.3 (d, C-4), 127.2 (d, C-2'), 130.4 (d, C-3'), 130.8 (d, C-2), 131.4 (s, C-3a), 131.9 (d, C-8), 133.8 (s, C-7a), 134.8 (s, C-1'), 145.9 (s, C-4'), 166.1 (s, C-10); *m/z* (ES^+) 550 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{20}H_{17}{}^{79}Br_2NNaO_4S$ (MNa^+) 547.9143, found 547.9159.

(*Z*)-Ethyl 3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acrylate 7d and (*E*)-ethyl 3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acrylate 15

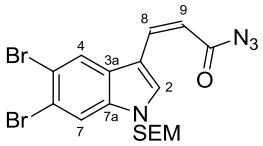




Ethyl 2-(diphenoxyphosphoryl)acetate (412 µL, 1.53 mmol) was dissolved in THF (15 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (71 mg of a 60% dispersion in mineral oil, 1.77 mmol) was added in one portion and the mixture stirred for 15 min. In a fresh flask, 5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-3-

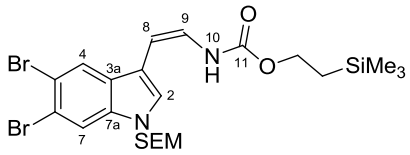
carbaldehyde **6d** (510 mg, 1.18 mmol) was dissolved in THF (15 mL) and the solution cooled to -40 °C under an atmosphere of argon. The solution of the phosphoryl anion was added to this dropwise and the reaction mixture stirred for a further 5 h whilst maintaining the temperature at between -50 °C and -30 °C. After this time, t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.22) and formation of two products (R_f 0.76, 0.58). The reaction was quenched by the careful addition of ammonium chloride (10 mL of a saturated aqueous solution) and the mixture diluted with diethyl ether (30 mL). The organic fraction was washed with water (2 x 10 mL) and the combined water fractions extracted with diethyl ether (2 x 10 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 9:1) to afford first **7d** (403 mg, 68%) as a white solid, m.p. 102-104 °C; ν_{max} (solid state) 2922, 1695, 1614, 1519, 1467, 1435, 1368, 1182 cm^{-1}; δ_H (400 MHz, $CDCl_3$), -0.05 (9H, s, $Si(CH_3)_3$), 0.89 (2H, t, *J* 8.1 Hz, $SiCH_2$), 1.33 (3H, t, *J* 7.1 Hz, CH_3), 3.48 (2H, t, *J* 8.1 Hz, OCH_2), 4.22 (2H, q, *J* 7.1 Hz, CH_2CH_3), 5.47 (2H, s, OCH_2N), 5.85 (1H, d, $J_{8,9}$ 12.6 Hz, H-9), 7.07 (1H, d, $J_{8,9}$ 12.6 Hz, H-8), 7.83 (1H, s, H-4), 7.98 (1H, s, H-7), 8.82 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), -1.3 (q, $Si(CH_3)_3$), 14.5 (q, CH_3), 17.8 (t, $SiCH_2$), 60.1 (t, OCH_2CH_3), 66.5 (t, OCH_2), 76.8 (t, OCH_2N), 110.5 (s, C-3), 114.0 (d, C-9), 115.9 (d, C-7), 117.1 (s, C-5/6), 118.2 (s, C-5/6), 122.8 (d, C-4), 130.5 (s, C-3a), 133.3 (d, C-2), 135.5 (s, C-7a), 135.6 (d, C-8), 167.2 (s, C-10); *m/z* (ES^+) 526 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{19}H_{25}{}^{79}Br_2NNaO_3Si$ (MNa^+) 523.9868, found 523.9875. Continued elution gave **15** (186 mg, 31%) as a white solid, m.p. 156-158 °C; ν_{max} (solid state) 2953, 1703, 1631, 1532, 1452, 1366, 1352, 1302, 1246, 1159 cm^{-1}; δ_H (400 MHz, $CDCl_3$), -0.05 (9H, s, $Si(CH_3)_3$), 0.89 (2H, t, *J* 8.1 Hz, $SiCH_2$), 1.36 (3H, t, *J* 7.1 Hz, CH_3), 3.46 (2H, t, *J* 8.1 Hz, OCH_2), 4.27 (2H, q, *J* 7.1 Hz, CH_2CH_3), 5.41 (2H, s, OCH_2N), 6.36 (1H, d, $J_{8,9}$ 16.1 Hz, H-9), 7.41 (1H, s, H-4), 7.77 (1H, d, $J_{8,9}$ 16.1 Hz, H-8), 7.80 (1H, s, H-7), 8.15 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), -1.3 (q, $Si(CH_3)_3$), 14.6 (q, CH_3), 17.8 (t, $SiCH_2$), 60.5 (t, OCH_2CH_3), 66.7 (t, OCH_2), 76.4 (t, OCH_2N), 112.7 (s, C-3), 115.3 (d, C-9), 115.9 (d, C-7), 117.7 (s, C-5/6), 119.1 (s, C-5/6), 125.0 (d, C-4), 127.3 (s, C-3a), 132.9 (d, C-2), 136.5 (d, C-8), 137.1 (s, C-7a), 167.7 (s, C-10); *m/z* (ES^+) 558 ($M.MeOH.Na^+$, 100), 526 (MNa^+, 44), 503 (M^+, 3%); HRMS (ES^+) calculated for $C_{19}H_{25}{}^{79}Br_2NNaO_3Si$ (MNa^+) 523.9868, found 523.9880.

(*Z*)-3-(5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acryloyl azide 8



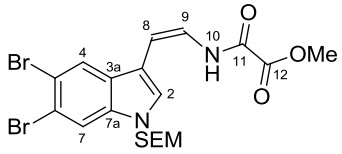
(*Z*)-Ethyl 3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acrylate **7d** (238 mg, 10.473 mmol) was dissolved in methanol (5 mL) and THF (5 mL). Sodium hydroxide (2.36 mL of a 1 M aqueous solution, 2.36 mmol) was added and the reaction mixture heated to 65 °C. After 90 min t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.72) and formation of a single product (R_f 0.20). The reaction was cooled to 0 °C, diluted with diethyl ether (10 mL) and acidified to pH 2. The mixture was separated and the aqueous fraction extracted with diethyl ether (3 x 10 mL). The organic fractions were combined, washed with water (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (10 mL) and cooled to 0 °C under an atmosphere of argon. Sodium hydride (28 mg, 0.709 mmol) was added and the mixture stirred for 20 min. After this time DPPA (153 µL, 0.709 mmol) was added dropwise. The reaction mixture was stirred for 90 min whilst gradually warming to rt. After this time t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of the carboxylic acid intermediate (Rf (0.20) and formation of a major product (Rf (0.80). The reaction mixture was diluted with diethyl ether (10 mL), washed with water (2 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 47:3) to afford **8** (215 mg, 91%) as a yellow solid, m.p. 99-100 °C (decomposes); ν_{max} (solid state) 2953, 2917, 2136, 1681, 1585, 1510, 1431, 1378, 1251, 1169 cm^{-1}; δ_H (400 MHz, $CDCl_3$), -0.03 (9H, s, $Si(CH_3)_3$), 0.90 (2H, t, *J* 8.1 Hz, $SiCH_2$), 3.50 (2H, t, *J* 8.1 Hz, OCH_2), 5.48 (2H, s, OCH_2N), 5.76 (1H, d, $J_{8,9}$ 12.4 Hz, H-9), 7.15 (1H, d, $J_{8,9}$ 12.4 Hz, H-8), 7.84 (1H, s, H-4), 7.97 (1H, s, H-7), 8.96 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), -1.5 (q, $Si(CH_3)_3$), 17.6 (t, $SiCH_2$), 66.5 (t, OCH_2), 76.7 (t, OCH_2N), 110.9 (s, C-3), 113.3 (d, C-9), 116.0 (d, C-7), 117.6 (s, C-5/6), 118.6 (s, C-5/6), 122.6 (d, C-4), 130.2 (s, C-3a), 135.5 (s, C-7a), 136.3 (d, C-8), 136.5 (d, C-2), 171.6 (s, C-10); *m/z* (ES^-) 535 ($M.Cl^-$, 86), 499 (M^-, 8%); HRMS (ES^-) calculated for $C_{17}H_{20}{}^{79}Br_2N_4O_2Si$ (M^-) 496.9644, found 496.9640.

(*Z*)-2-(Trimethylsilyl)ethyl (2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)carbamate 9



(*Z*)-3-(5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acryloyl azide **8** (241 mg, 0.486 mmol) and 2-(trimethylsilyl)ethanol (207 µL, 1.45 mmol) were dissolved in toluene (5 mL). The yellow solution was heated to reflux with stirring under an atmosphere of argon in the absence of light. After 30 min t.l.c. analysis (hexanes-ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.75) and formation of a major product (R_f 0.55). The bright blue reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 9:1) to afford **9** (220 mg, 77%) as a clear oil; ν_{max} (neat) 2953, 1723, 1661, 1540, 1486, 1248, 1211 cm^{-1}; δ_H (400 MHz, $CDCl_3$), -0.03 (9H, s, $Si(CH_3)_3$), 0.05 (9H, s, $Si(CH_3)_3$), 0.91 (2H, t, *J* 8.1 Hz, $SiCH_2$), 1.02 (2H, br d, *J* 7.7 Hz, $SiCH_2$), 3.48 (2H, t, *J* 8.1 Hz, OCH_2), 4.24 (2H, br d, *J* 7.7 Hz, OCH_2), 5.40 (2H, s, OCH_2N), 5.63 (1H, br d, $J_{8,9}$ 8.6 Hz, H-8), 6.56 (1H, br d, $J_{9,10}$ 9.4 Hz, H-10), 6.77 (1H, br t, *J* 9.3 Hz, H-9), 7.14 (1H, s, H-4), 7.77 (1H, s, H-7), 7.83 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), -1.5 (q, $Si(CH_3)_3$), -1.4 (q, $Si(CH_3)_3$), 17.7 (t, $SiCH_2$), 17.8 (t, $SiCH_2$), 64.0 (t, OCH_2), 66.4 (t, OCH_2), 75.9 (t, OCH_2N), 98.0 (d, C-8), 110.9 (s, C-3), 115.1 (d, C-7), 116.0 (s, C-5/6), 118.4 (s, C-5/6), 123.8 (d, C-4), 123.9 (d, C-9), 126.6 (d, C-2), 128.5 (s, C-3a), 136.0 (s, C-7a), 153.8 (s, C-11); *m/z* (ES^+) 613 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{22}H_{34}{}^{79}Br_2N_2NaO_3Si_2$ (MNa^+) 611.0372, found 611.0377.

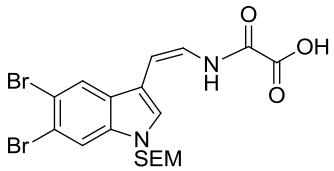
(*Z*)-Methyl 2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl) amino)-2-oxoacetate 11



(*Z*)-2-(Trimethylsilyl)ethyl (2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)carbamate **9** (49 mg, 0.083 mmol) was dissolved in THF (1 mL) and cooled to 0 °C under an atmosphere of argon. Sodium bis(trimethylsilyl)amide (166 µL of a 1 M solution in

THF, 0.166 mmol) was added dropwise and the mixture stirred for 10 min. After this time methyl oxalyl chloride (38 µL, 0.415 mmol) was added dropwise. The reaction mixture was stirred for 90 min, quenched with water (1 mL) and extracted into diethyl ether (2 x 3 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (1 mL) and cooled to 0 °C under an atmosphere of argon. TBAF (108 µL of a 1 M solution in THF, 0.108 mmol) was added and the reaction mixture stirred for 70 min whilst warming to rt. After this time t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of enecarbamate intermediate **10** (R_f 0.74) and formation of a major product (R_f 0.26). The reaction mixture was quenched with water (1 mL) and extracted into diethyl ether (2 x 3 mL). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 4:1 then 3:2) to afford **11** (29 mg, 66%) as a bright yellow oil; ν_{max} (neat) 3386, 2953, 1706, 1538, 1496, 1439, 1289, 1230, 1075 cm^{-1}; δ_H (400 MHz, $CDCl_3$), -0.04 (9H, s, $Si(CH_3)_3$), 0.92 (2H, t, *J* 8.1 Hz, $SiCH_2$), 3.50 (2H, t, *J* 8.1 Hz, OCH_2), 3.93 (3H, s, OCH_3), 5.45 (2H, s, OCH_2N), 6.03 (1H, d, $J_{8,9}$ 9.1 Hz, H-8), 6.94 (1H, dd, $J_{8,9}$ 9.1 Hz, $J_{9,10}$ 11.3 Hz, H-9), 7.25 (1H, s, H-2), 7.81 (1H, s, H-7), 7.86 (1H, s, H-4), 9.01 (1H, d, $J_{9,10}$ 11.3 Hz, H-10); δ_C (100 MHz, $CDCl_3$), -1.5 (q, $Si(CH_3)_3$), 17.8 (t, $SiCH_2$), 54.0 (q, OCH_3), 66.5 (t, OCH_2), 76.1 (t, OCH_2N), 105.0 (d, C-8), 110.2 (s, C-3), 115.3 (d, C-7), 116.4 (s, C-5/6), 118.8 (s, C-5/6), 120.0 (d, C-9), 123.8 (d, C-4), 127.2 (d, C-2), 128.3 (s, C-3a), 136.0 (s, C-7a), 153.1 (s, C-11), 160.9 (s, C-12); *m/z* (ES^+) 555 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{19}H_{24}{}^{79}Br_2N_2NaO_4Si$ (MNa^+) 552.9783, found 552.9770.

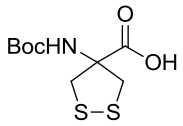
(*Z*)-2-((2-(5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetic acid 12



(*Z*)-Methyl 2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl) amino) -2-oxoacetate **11** (30.5 mg, 0.0573 mmol) was dissolved in THF (0.5 mL) and MeOH (0.5 mL). Sodium hydroxide (0.29 mL of a 1 M aqueous solution, 0.29 mmol) was added and the reaction mixture was stirred at rt for 1 h. After this time t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.27) and formation of a

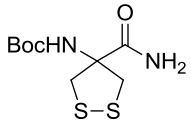
single product (R_f 0.0). The reaction mixture was cooled to 0 °C, diluted with diethyl ether (3 mL) and acidified to pH 2 using hydrochloric acid (1M aqueous solution). Water (2 mL) was added and the mixture separated. The organic fraction was washed with water (3 x 1 mL) and the aqueous fraction re-extracted with diethyl ether (2 x 2 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford **12** (29.6 mg, 100%) as a yellow oil which was used immediately without further purification.

4-((*tert*-Butoxycarbonyl)amino)-1,2-dithiolane-4-carboxylic acid



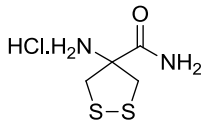
Methyl 4-((*tert*-butoxycarbonyl)amino)-1,2-dithiolane-4-carboxylate[2,3] **13** (156 mg, 0.558 mmol) was dissolved in THF (2 mL) and methanol (2 mL). Sodium hydroxide (2.79 mL of a 1 M aqueous solution, 2.79 mmol) was added and the reaction mixture was stirred at rt for 90 min. After this time t.l.c. analysis (hexanes-ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.33) and formation of a single product (R_f 0.0). The reaction mixture was cooled to 0 °C, diluted with diethyl ether (10 mL) and acidified to pH 2 using hydrochloric acid (1M aqueous solution). Water (5 mL) was added and the mixture separated. The organic fraction was washed with water (3 x 3 mL) and the aqueous re-extracted with diethyl ether (3 x 5 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford 4-((*tert*-butoxycarbonyl)amino)-1,2-dithiolane-4-carboxylic acid (146 mg, 99%) as a very pale yellow foam, m. p. 159-161 °C (decarboxylates); ν_{max} (solid state) 3392, 2986, 1741, 1656, 1521, 1364, 1287, 1217, 1161; δ_H (300 MHz, acetone-D_6), 1.39 (9H, s, $C(CH_3)_3$), 3.59 (2H, d, *J* 12.3 Hz, SCH_2), 3.63 (2H, d, *J* 12.3 Hz, SCH_2), 6.74 (1H, br s, NH), 11.48 (1H, br s, OH); δ_C (100 MHz, acetone-D_6), 28.4 (q, $C(CH_3)_3$), 49.4 (t, SCH_2); *m/z* (ES^-) 264 ([M-H^+], 42%); HRMS (ES^-) calculated for $C_9H_{14}NO_4S_2$ ([M-H^+]) 264.0364, found 264.0374.

tert-Butyl (4-carbamoyl-1,2-dithiolan-4-yl)carbamate



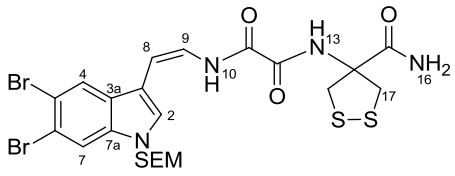
4-((*tert*-Butoxycarbonyl)amino)-1,2-dithiolane-4-carboxylic acid (128 mg, 0.482 mmol) was dissolved in THF (2 mL) and cooled to 0 °C under an atmosphere of argon. Triethylamine (202 µL, 1.45 mmol) was added and the mixture was stirred for 10 min. *iso*-Butyl chloroformate (188 µL, 1.45 mmol) was added dropwise and the mixture stirred for a further 30 min at 0 °C. After this time the reaction mixture was cooled to -20 °C and ammonia (689 µL of a 7 M solution in MeOH, 4.82 mmol) was added rapidly dropwise. After 20 min t.l.c. analysis (hexanes-ethyl acetate, 2:3) indicated complete consumption of mixed anhydride intermediate (R_f 0.90) and formation of a single product (R_f 0.25). The reaction mixture was diluted with diethyl ether (5 mL) and quenched by addition of water (2 mL). The mixture was separated, the organic fraction was washed with water (3 mL) and the aqueous re-extracted with diethyl ether (3 x 5 mL). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 1:1 then 2:3) to afford *tert*-butyl (4-carbamoyl-1,2-dithiolan-4-yl)carbamate (114 mg, 89%) as a white solid, m. p. 153-156 °C (decomposes); ν_{max} (solid state) 3403, 3301, 2974, 1686, 1655, 1522, 1392, 1367, 1288, 1251, 1157; δ_H (300 MHz, acetone-D_6), 1.40 (9H, s, $C(CH_3)_3$), 3.57 (2H, d, *J* 12.1 Hz, SCH_2), 3.61 (2H, d, *J* 12.1 Hz, SCH_2), 6.51 (1H, br s, NH), 6.66 (1H, br s, NH), 7.19 (1H, br s, NH); δ_H (400 MHz, DMSO-D_6), 1.37 (9H, s, $C(CH_3)_3$), 3.45 (4H, ABq, *J* 12.1 Hz, 2 x SCH_2), 7.24 (3H, br s, 3 x NH); δ_C (100 MHz, DMSO-D_6), 28.1 (q, $C(CH_3)_3$), 47.9 (t, SCH_2), 71.5 (s, $C(CH_3)_3$), 78.7 (s, C-α), 154.4 (s, NHC(O)O^{t}Bu), 172.2 (s, $C(O)NH_2$); *m/z* (ES^+) 287 (MNa^+, 96), 243 ([M-$CONH_2$]Na^+, 33%); HRMS (ES^+) calculated for $C_9H_{16}N_2NaO_3S_2$ (MNa^+) 287.0500, found 287.0511.

4-Amino-1,2-dithiolane-4-carboxamide hydrochloride 3



tert-Butyl (4-carbamoyl-1,2-dithiolan-4-yl)carbamate (103 mg, 0.390 mmol) was dissolved in MeOH (3 mL) and cooled to 0 °C under an atmosphere of argon. Thionyl chloride (28.4 µL, 0.390 mmol) was added dropwise and the mixture warmed to 50 °C. After 1 h t.l.c. analysis (hexanes-ethyl acetate, 2:3) indicated complete consumption of starting material (R_f 0.25) and formation of a single product (R_f 0.0). The reaction mixture was cooled and the solvent removed *in vacuo* to afford **3** (78 mg, quant.) as a white solid which was used without further purification.

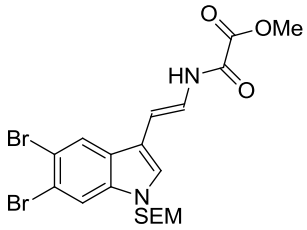
(*Z*)-N^1-(4-Carbamoyl-1,2-dithiolan-4-yl)-N^2-(2-(5,6-dibromo-1-((2-trimethylsilyl)ethoxy) methyl)-1*H*-indol-3-yl)vinyl)oxalamide ***or*** **SEM-protected kottamide E 14**



(*Z*)-2-((2-(5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetic acid **12** (29.0 mg, 0.0560 mmol) was dissolved in DMF (2 mL) under an atmosphere of argon. *O*-Benzotriazole-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (29.7 mg, 0.0783 mmol) was added and the mixture stirred at rt for 30 min. In a fresh flask 4-amino-1,2-dithiolane-4-carboxamide hydrochloride **3** (18.0 mg, 0.0895 mmol) was suspended in DMF (1 mL) and triethylamine (15.6 µL, 0.112 mmol) added. The mixture was stirred for 15 min over which time the suspension dissolved. The resulting solution was added dropwise to the solution of activated carboxylic acid and the reaction mixture heated to 50 °C for 3 days. After this time t.l.c. analysis (hexanes-ethyl acetate, 3:7) indicated consumption of acid **12** (R_f 0.0) and formation of a major product (R_f 0.33). The reaction mixture was cooled, diluted with diethyl ether (5 mL) and quenched with water (2 mL). The mixture was separated, the aqueous fraction was extracted with diethyl ether (3 x 3 mL) the combined organics washed with water (3 x 2 mL). The combined organics were dried ($MgSO_4$),

concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 2:3) to afford **14** (23.0 mg, 66%) as a bright yellow solid, m. p. 118-140 °C (decomposes); ν_{max} (solid state) 3329, 2952, 1666, 1531, 1482, 1363, 1247, 1075; δ_H (400 MHz, $CDCl_3$), -0.04 (9H, s, $Si(CH_3)_3$), 0.91 (2H, t, *J* 8.1 Hz, $SiCH_2$), 3.49 (2H, t, *J* 8.1 Hz, OCH_2), 3.63, (2H, d, *J* 12.4 Hz, SCH_2), 3.67 (2H, d, *J* 12.4 Hz, SCH_2), 5.43 (2H, s, OCH_2N), 5.88 (1H, br s, H-16), 6.04 (1H, d, $J_{8,9}$ 9.1 Hz, H-8), 6.64 (1H, br s, H-16'), 6.84 (1H, dd, $J_{8,9}$ 9.1 Hz, $J_{9,10}$ 11.6 Hz, H-9), 7.26 (1H, s, H-2), 7.79 (1H, s, H-7), 7.83 (1H, s, H-4), 8.32 (1H, s, H-13), 9.30 (1H, d, $J_{9,10}$ 11.6 Hz, H-10); δ_C (100 MHz, $CDCl_3$), -1.4 (q, $Si(CH_3)_3$), 17.8 (t, $SiCH_2$), 46.6 (t, SCH_2), 66.5 (t, OCH_2), 71.7 (s, C-14), 76.2 (t, OCH_2N), 105.6 (d, C-8), 110.0 (s, C-3), 115.4 (d, C-7), 116.4 (s, C-5/6), 118.8 (s, C-5/6), 119.2 (d, C-9), 123.7 (d, C-4), 127.3 (d, C-2), 128.4 (s, C-3a), 136.0 (s, C-7a), 155.9 (s, C-11), 159.5 (s, C-12), 170.9 (s, C-15); *m/z* (ES^+) 687 (MNa^+, 19%); HRMS (ES^+) calculated for $C_{22}H_{28}{}^{79}Br_2N_4NaO_4S_2Si$ (MNa^+) 684.9586, found 684.9595.

(*E*)-Methyl 2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl) amino)-2-oxoacetate 16

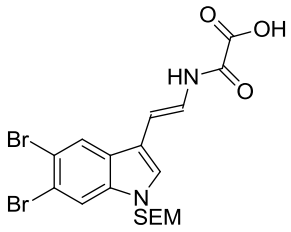


(*E*)-Ethyl 3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acrylate **15** (550 mg, 1.09 mmol) was dissolved in methanol (10 mL) and THF (10 mL). Sodium hydroxide (5.46 mL of a 1 M aqueous solution, 5.46 mmol) was added and the reaction mixture heated to 65 °C. After 2 h t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.58) and formation of a single product (R_f 0.0). The reaction was cooled to 0 °C, diluted with diethyl ether (20 mL) and acidified to pH 2. The mixture was separated and the aqueous fraction extracted with diethyl ether (3 x 10 mL). The organic fractions were combined, washed with water (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the corresponding carboxylic acid (515 mg, 99%) as a pale yellow solid. The acid was dissolved in THF (20 mL) and cooled to 0 °C under an atmosphere of argon. Sodium hydride (65 mg, 1.63 mmol) was added and the mixture stirred

for 20 min. After this time DPPA (328 µL, 1.63 mmol) was added dropwise. The reaction mixture was stirred for 3 h whilst gradually warming to rt. After this time t.l.c. analysis (hexanes-ethyl acetate, 4:1) indicated complete consumption of the carboxylic acid intermediate (R_f 0.0) and formation of a major product (R_f 0.29). The reaction mixture was diluted with diethyl ether (20 mL), washed with water (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (hexanes-ethyl acetate, 17:3) to afford (*E*)-3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acryloyl azide **(*E*)-8** (650 mg, ~120% contaminated with DPPA-derived material) as a pale yellow solid. A fraction of this material (542 mg) was dissolved in toluene (10 mL) and 2-(trimethylsilyl)ethanol (394 µL, 2.75 mmol) was added. The yellow solution was heated to reflux with stirring under an atmosphere of argon in the absence of light. After 2 h the deep red reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 9:1) to afford (*E*)-2-(trimethylsilyl)ethyl (2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)carbamate **(*E*)-9** (552 mg) as a pale yellow oil. A fraction of this product (212 mg) was dissolved in THF (5 mL) and cooled to 0 °C under an atmosphere of argon. Sodium bis(trimethylsilyl)amide (718 µL of a 1 M solution in THF, 0.718 mmol) was added dropwise and the mixture stirred for 10 min. After this time methyl oxalyl chloride (165 µL, 1.80 mmol) was added dropwise. The reaction mixture was stirred for 16 h, quenched with water (3 mL) and extracted into diethyl ether (2 x 5 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (7 mL) and cooled to 0 °C under an atmosphere of argon. TBAF (467 µL of a 1 M solution in THF, 0.467 mmol) was added and the reaction mixture stirred for 90 min whilst warming to rt before the addition of further TBAF (233 µL, 0.233 mmol). After 1 h a final portion of TBAF (233 µL, 0.233 mmol) was added and the reaction mixture stirred for a further 1 h. After this time, t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of enecarbamate intermediate (R_f 0.58) and formation of a major product (R_f 0.16). The reaction mixture was quenched with water (3 mL) and extracted into diethyl ether (2 x 5 mL). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 4:1 then 3:2) to afford **16** (86 mg, 47% over 4 steps) as a bright yellow solid, m. p. 144-146 °C; ν_{max} (solid state) 3335, 1727, 1685, 1545, 1288, 1270, 1208, 1077; δ_H (400 MHz, $CDCl_3$), -0.04 (9H, s, $Si(CH_3)_3$), 0.89 (2H, t, *J* 8.1 Hz, $SiCH_2$), 3.46 (2H, t, *J* 8.1 Hz, OCH_2), 3.97 (3H,

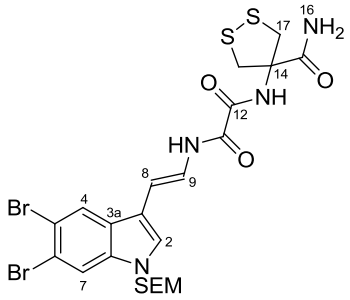
s, OCH_3), 5.38 (2H, s, OCH_2N), 6.47 (1H, d, $J_{8,9}$ 14.7 Hz, H-8), 7.22 (1H, s, H-2), 7.31 (1H, dd, $J_{8,9}$ 14.7 Hz, $J_{9,10}$ 10.8 Hz, H-9), 7.76 (1H, s, H-7), 7.97 (1H, s, H-4), 8.82 (1H, d, $J_{9,10}$ 10.8 Hz, H-10); δ_C (100 MHz, $CDCl_3$), -1.5 (q, $Si(CH_3)_3$), 17.7 (t, $SiCH_2$), 53.9 (q, OCH_3), 66.3 (t, OCH_2), 76.0 (t, OCH_2N), 108.6 (d, C-8), 111.7 (s, C-3), 115.3 (d, C-7), 116.3 (s, C-5/6), 118.2 (s, C-5/6), 119.4 (d, C-9), 124.0 (d, C-4), 127.3 (s, C-3a), 127.4 (d, C-2), 136.5 (s, C-7a), 152.7 (s, C-11), 160.9 (s, C-12); *m/z* (ES^+) 555 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{19}H_{24}{}^{79}Br_2N_2NaO_4Si$ (MNa^+) 552.9770, found 552.9762.

(*E*)-2-((2-(5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetic acid (*E*)-12



(*E*)-Methyl 2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl) amino) -2-oxoacetate (41.1 mg, 0.0772 mmol) was dissolved in THF (1 mL) and MeOH (1 mL). Sodium hydroxide (0.39 mL of a 1 M aqueous solution, 0.39 mmol) was added and the reaction mixture was stirred at rt for 1 h. After this time t.l.c. analysis (hexanes-ethyl acetate, 7:3) indicated complete consumption of starting material (R_f 0.16) and formation of a single product (R_f 0.0). The reaction mixture was cooled to 0 °C, diluted with diethyl ether (5 mL) and acidified to pH 2 using hydrochloric acid (1M aqueous solution). Water (2 mL) was added and the mixture separated. The organic fraction was washed with water (3 x 1 mL) and the aqueous re-extracted with diethyl ether (2 x 2 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford (*E*)-2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetic acid **(*E*)-12** (40.0 mg, 100%) as a bright yellow solid which was used immediately without further purification.

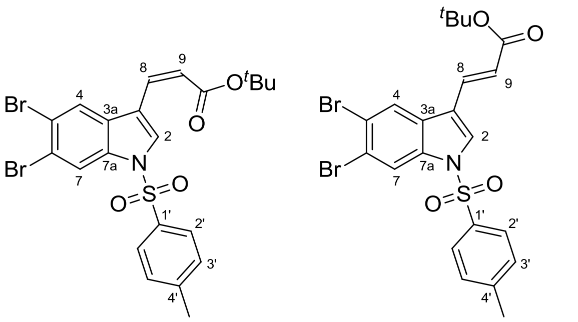
(*E*)-N^1-(4-Carbamoyl-1,2-dithiolan-4-yl)-N^2-(2-(5,6-dibromo-1-((2-trimethylsilyl)ethoxy) methyl)-1*H*-indol-3-yl)vinyl)oxalamide *or* **SEM-protected (*E*)-kottamide E (*E*)-14**



(*E*)-2-((2-(5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetic acid **(*E*)-12** (41.4 mg, 0.0799 mmol) was dissolved in DMF (2 mL) under an atmosphere of argon. *O*-Benzotriazole-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (42.4 mg, 0.119 mmol) was added and the mixture stirred at rt for 30 min. In a fresh flask 4-amino-1,2-dithiolane-4-carboxamide hydrochloride **3** (25.7 mg, 0.128 mmol) was suspended in DMF (1 mL) and triethylamine (22.3 µL, 0.160 mmol) added. The mixture was stirred for 15 min over which time the suspension dissolved. The resulting solution was added dropwise to the solution of activated carboxylic acid and the reaction mixture heated to 50 °C for 3 days. After this time t.l.c. analysis (hexanes-ethyl acetate, 3:7) indicated consumption of acid **(*E*)-12** (R_f 0.0) and formation of a major product (R_f 0.65). The reaction mixture was cooled, diluted with diethyl ether (5 mL) and quenched with water (2 mL). The mixture was separated, the aqueous fraction was extracted with diethyl ether (3 x 3 mL) the combined organics washed with water (3 x 2 mL). The combined organics were dried ($MgSO_4$) concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 2:3) to afford **(*E*)-14** (35.2 mg, 66%) as a bright yellow solid, m. p. 188-191 °C; ν_{max} (solid state) 3333, 2954, 1692, 1653, 1489, 1351, 1245, 1069; δ_H (300 MHz, acetone-D_6), -0.08 (9H, s, $Si(CH_3)_3$), 0.87 (2H, t, *J* 8.0 Hz, $SiCH_2$), 3.54 (2H, t, *J* 8.0 Hz, OCH_2), 3.73 (2H, d, *J* 12.2 Hz, SCH_2), 3.81 (2H, d, *J* 12.2 Hz, SCH_2), 5.57 (2H, s, OCH_2N), 6.81 (1H, br s, H-16), 6.90 (1H, d, $J_{8,9}$ 14.8 Hz, H-8), 7.32 (1H, dd, $J_{9,10}$ 10.4 Hz, $J_{8,9}$ 14.8 Hz, H-9), 7.46 (1H, br s, H-16'), 7.66 (1H, s, H-2), 7.94 (1H, s, H-7), 8.00 (1H, s, H-4), 8.41 (1H, br s, H-13), 10.05 (1H, d, $J_{9,10}$ 10.4 Hz, H-10); δ_C (100 MHz, acetone-D_6), -1.3 (q, $Si(CH_3)_3$), 18.2 (t, $SiCH_2$), 48.3 (t, SCH_2), 66.6 (t, OCH_2), 72.9 (s, C-14), 76.5 (t, OCH_2N), 109.2 (d, C-8), 112.9 (s, C-3), 115.9 (s, C-5/6), 116.7 (d, C-7), 117.7 (s, C-5/6), 121.0 (d, C-9), 124.5 (d, C-4), 128.5 (s, C-3a), 129.6 (d, C-2), 137.7 (s, C-7a), 157.4 (s, C-

11), 160.3 (s, C-12), 171.3 (s, C-15); *m/z* (ES^+) 685 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{22}H_{28}{}^{79}Br_2N_4NaO_4S_2Si$ (MNa^+) 684.9586, found 684.9600.

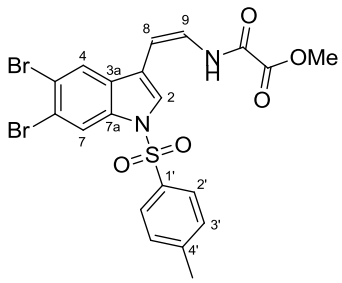
(*Z*)-*tert*-Butyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate 17 and (*E*)-*tert*-butyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate (*E*)-17



tert-Butyl 2-(diphenoxyphosphoryl)acetate (168 µL, 0.592 mmol) was dissolved in THF (4 mL) and the solution cooled to 0 °C under an atmosphere of argon. Sodium hydride (29 mg of a 60% dispersion in mineral oil, 0.728 mmol) was added in one portion and the mixture stirred for 15 min. In a fresh flask, 5,6-dibromo-1-tosyl-1*H*-indole-3-carbaldehyde **6c** (208 mg, 0.455 mmol) was dissolved in THF (4 mL) and the solution cooled to -78 °C under an atmosphere of argon. The solution of the phosphoryl anion was added to this dropwise and the reaction mixture stirred for a further 90 min whilst maintaining the temperature at -78 °C. After this time, t.l.c. analysis (hexanes-ethyl acetate, 4:1) indicated complete consumption of starting material (Rf (0.20) and formation of two products (R_f 0.55, 0.45). The reaction was quenched by the careful addition of ammonium chloride (5 mL of a saturated aqueous solution) and the mixture diluted with diethyl ether (15 mL). The organic fraction was washed with water (2 x 5 mL) and the combined water fractions extracted with diethyl ether (2 x 10 mL). The combined organic fractions were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 19:1 then 93:7 then 4:1) to afford first **17** (196 mg, 78%) as a white foam; ν_{max} (neat) 2977, 2926, 1705, 1429, 1377, 1130 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.25 (9H, s, $C(CH_3)_3$), 2.37 (CH_3), 5.95 (2H, d, $J_{8,9}$ 12.6 Hz, H-9), 6.78 (2H, d, $J_{8,9}$ 12.6 Hz, H-8), 7.27 (2H, d, $J_{2',3'}$ 8.3 Hz, 2 x H-3'), 7.80 (1H, s, H-4), 7.82 (2H, d, $J_{2',3'}$ 8.3 Hz, 2 x H-2'), 8.30 (1H, s, H-7), 8.79 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), 21.8 (q, CH_3), 28.3 (q, $C(CH_3)_3$), 81.0 (s, $C(CH_3)_3$), 115.3 (s, C-3), 118.6 (d, C-9), 119.7 (s, C-5/6), 120.6 (s, C-5/6), 122.1 (d, C-7), 123.5 (d, C-4), 127.2 (d, C-2'), 129.5 (d, C-2), 130.3 (d, C-3'), 131.3 (d, C-8), 131.4 (s, C-3a), 133.9 (s,

C-7a), 134.9 (s, C-1'), 145.8 (s, C-4'), 165.5 (s, C-10); *m/z* (ES^+) 610 ($M.MeOH.Na^+$, 98), 578 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{22}H_{21}{}^{79}Br_2NNaO_4S$ (MNa^+) 575.9456, found 575.9479. Continued elution gave **(*E*)-17** (12 mg, 5%) as a colourless solid, m.p. 157-160 °C; ν_{max} (solid state) 2928, 2926, 1715, 1643, 1596, 1433, 1380, 1324, 1168, 1137 cm^{-1}; δ_H (300 MHz, $CDCl_3$), 1.54 (9H, s, $C(CH_3)_3$), 2.38 (CH_3), 6.35 (2H, d, $J_{8,9}$ 16.1 Hz, H-9), 7.29 (2H, d, *J* 8.2 Hz, 2 x H-3'), 7.57 (2H, d, $J_{8,9}$ 16.1 Hz, H-8), 7.76 (2H, d, *J* 8.2 Hz, 2 x H-2'), 7.76 (1H, s, H-4), 8.03 (1H, s, H-7), 8.30 (1H, s, H-2); δ_C (100 MHz, $CDCl_3$), 21.8 (q, CH_3), 28.4 (q, $C(CH_3)_3$), 81.1 (s, $C(CH_3)_3$), 117.6 (s, C-3), 118.7 (d, C-9), 120.4 (s, C-5/6), 121.5 (s, C-5/6), 121.5 (d, C-7), 125.1 (d, C-4), 127.1 (d, C-2'), 128.9 (s, C-3a), 129.1 (d, C-2), 130.5 (d, C-3'), 133.3 (d, C-8), 134.5 (s, C-7a), 135.2 (s, C-1'), 146.2 (s, C-4'), 166.1 (s, C-10); *m/z* (ES^+) 578 (MNa^+, 100%); HRMS (ES^+) calculated for $C_{22}H_{21}{}^{79}Br_2NNaO_4S$ (MNa^+) 575.9456, found 575.9453.

(*Z*)-Methyl 2-((2-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetate 20

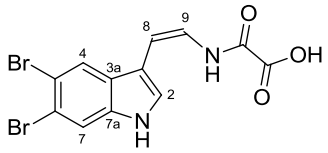


(*Z*)-*tert*-Butyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate **17** (1.36 g, 2.46 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. TFA (7 mL) was added and the reaction mixture stirred for 1 h. After this time t.l.c. analysis (hexanes-ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.55) and formation of a single product (R_f 0.0). The reaction mixture was concentrated *in vacuo* to afford the corresponding carboxylic acid (1.24 g, quant.) as a white solid. NMR analysis indicated that no isomerisation of the alkene double bond had occurred. A portion of this product (540 mg, 1.08 mmol) was dissolved in THF (20 mL) and cooled to 0 °C under an atmosphere of argon. Sodium hydride (69 mg, 1.73 mmol) was added and the mixture stirred for 20 min. After this time DPPA (303 µL, 1.41 mmol) was added dropwise. The reaction mixture was stirred for 3 h whilst gradually warming to rt. After this time, t.l.c. analysis (hexanes-ethyl acetate, 1:1) indicated complete consumption of the carboxylic acid intermediate (R_f 0.12) and formation of a major

product (R_f 0.80). The reaction mixture was diluted with diethyl ether (20 mL), washed with water (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (hexanes-ethyl acetate, 9:1) to afford a mixture of *Z* and *E* α,β-unsaturated acyl azides **18** (577 mg, 3.2:1, ~95% pure, contaminated with DPPA-derived material) as a white solid. A fraction of this material (480 mg, ~0.870 mmol) was dissolved in toluene (12 mL) and 2-(trimethylsilyl)ethanol (394 µL, 2.75 mmol) was added. The yellow solution was heated to reflux with stirring under an atmosphere of argon in the absence of light. After 1 h the deep blue reaction mixture was concentrated *in vacuo* and the residue was purified twice by flash column chromatography on silica gel (hexanes-ethyl acetate, 9:1) to afford enecarbamate **19** (428 mg) as a pale yellow oil. A fraction of this product (36 mg) was dissolved in THF (1 mL) and cooled to 0 °C under an atmosphere of argon. Sodium bis(trimethylsilyl)amide (146 µL of a 1 M solution in THF, 0.146 mmol) was added dropwise and the mixture stirred for 10 min. After this time methyl oxalyl chloride (27 µL, 0.293 mmol) was added dropwise. The reaction mixture was stirred for 1 h, quenched with water (2 mL) and extracted into diethyl ether (2 x 3 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (2 mL) and cooled to 0 °C under an atmosphere of argon. TBAF (76 µL of a 1 M solution in THF, 0.076 mmol) was added and the reaction mixture stirred for 1 h whilst warming to rt before the addition of further TBAF (76 µL, 0.076 mmol). Two further portions of TBAF (76 µL, 0.076 mmol) were added at 20 min intervals and the reaction mixture stirred for 20 min further. After this time t.l.c. analysis (hexanes-ethyl acetate, 3:2) indicated complete consumption of enecarbamate intermediate (R_f 0.64) and formation of a major product (R_f 0.21). The reaction mixture was quenched with water (3 mL) and extracted into diethyl ether (2 x 5 mL). The combined organics were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (hexanes-ethyl acetate, 9:1 then 3:2) to afford **20** (13.2 mg, 32% over 5 steps) as a pale yellow foam, ν_{max} (solid state) 3386, 2956, 2924, 2853, 1712, 1651, 1542, 1494, 1436, 1378, 1289, 1169, 1140, 1088; δ_H (400 MHz, $CDCl_3$), 2.38 (3H, s, CH_3), 3.99 (3H, s, OCH_3), 5.87 (1H, d, $J_{8,9}$ 9.2 Hz, H-8), 7.04 (1H, dd, $J_{8,9}$ 9.2 Hz, $J_{9,10}$ 11.5 Hz, H-9), 7.31 (2H, d, $J_{2',3'}$ 8.2 Hz, H-3'), 7.62 (1H, s, H-2), 7.75 (1H, s, H-4), 7.83 (2H, d, $J_{2',3'}$ 8.2 Hz, H-2'), 8.33 (1H, s, H-7), 8.97 (1H, d, $J_{9,10}$ 11.5 Hz, H-10); δ_C (100 MHz, $CDCl_3$), 21.8 (q, CH_3), 54.3 (q, OCH_3), 102.8 (d, C-8), 116.0 (s, C-3), 118.7 (d, C-7), 120.0 (s, C-5/6), 121.7 (s, C-5/6), 123.0 (d, C-9), 124.3 (d, C-4), 124.7 (d, C-2), 127.0 (s, C-1'), 127.1 (d, C-2'), 130.4 (s, C-3a), 130.5 (d, C-3'), 134.5 (s, C-7a), 146.0 (s, C-4'), 153.4 (s, C-

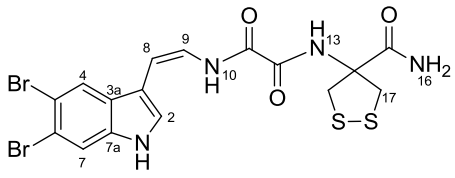
11), 160.8 (s, C-12); *m/z* (ES^-) 555 ([M-H^+], 11%); HRMS (ES^-) calculated for $C_{20}H_{15}{}^{79}Br^{81}BrN_2O_5S$ ([M-H^+]) 554.9048, found 554.9047.

(*Z*)-2-((2-(5,6-Dibromo-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetic acid 21



(*Z*)-Methyl 2-((2-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetate **20** (9.6 mg, 0.0173 mmol) was dissolved in THF (0.3 mL) and MeOH (0.3 mL). Sodium hydroxide (0.17 mL of a 1 M aqueous solution, 0.173 mmol) was added and the reaction mixture was stirred at rt for 2 h. After this time, t.l.c. analysis (dichloromethane-methanol, 9:1) indicated complete consumption of starting material and formation of a single product (R_f 0.0). The reaction mixture was cooled to 0 °C, diluted with diethyl ether (3 mL) and acidified to pH 2 using hydrochloric acid (1M aqueous solution). Water (2 mL) was added and the mixture separated. The organic fraction was washed with water (3 x 1 mL) and the aqueous re-extracted with diethyl ether (5 x 2 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford **21** (6.5 mg, 97%) as a brown oil which was used immediately without further purification.

(*Z*)-*N*1-(4-carbamoyl-1,2-dithiolan-4-yl)-*N*2-(2-(5,6-dibromo-1*H*-indol-3-yl)vinyl)oxalamide kottamide E 1



(*Z*)-2-((2-(5,6-Dibromo-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetic acid **21** (7.3 mg, 0.0188 mmol) was dissolved in DMF (0.3 mL) under an atmosphere of argon. *O*-Benzotriazole-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (7.1 mg, 0.0188 mmol) was added and the mixture stirred at rt for 30 min. In a fresh flask 4-amino-1,2-dithiolane-4-carboxamide hydrochloride **3** (2.9 mg, 0.0145 mmol) was suspended in DMF (0.3 mL) and triethylamine

(4.0 µL, 0.0289 mmol) added. The mixture was stirred for 10 min during which time the suspension dissolved. The resulting solution was added dropwise to the solution of activated carboxylic acid and the reaction mixture stirred at rt for 24 h. After this time analytical HPLC (Shimadzu Prominence instrument using Chromeleon software (version 6.80, build 2673 (161349)) connected to a Shimadzu SPD-20A detector at wavelengths of 239 nm and 305 nm; a Phenomenex Luna 5 µ 100 Å C-18 column, 250 x 4.6 mm, was used) indicated complete consumption of the activated carboxylic acid. The reaction mixture was diluted with MeCN-H_2O (3.5 mL, 1:1), filtered through a syringe filter (45 µm pore size) and subjected to HPLC purification in three 0.9 mL batches using a Dionex P580 instrument using Chromeleon software (version 6.11, build 490) connected to a Dionex UVD 170S detector with an analytical flow cell for increased sensitivity, at wavelengths of 239 nm, 254 nm, 280 nm and 305 nm. A semi-preparative HPLC (Phenomenex Luna 10 µ 100 Å C-18(2) column, 250 x 10 mm) was used. The column was eluted with a linear gradient of 0-100% MeCN over 40 min followed by a 100% MeCN wash for 10 min and reequilibration with H_2O for 10 min, all at a flow rate of 3 mL min^{-1}. The product eluted with a retention time of 32.5 min; kottamide E (3.0 mg, 38%), yellow powder, approximately 80% pure; m.p. 236-238 °C (decomposes); ν_{max} (solid state) 3369, 3272, 1682, 1663, 1524, 1486, 1408, 1381, 1230; δ_H (600 MHz, DMSO-D_6), 3.72 (2H, d, *J* 12.0 Hz, SCH_2), 3.74 (2H, d, *J* 12.0 Hz, SCH_2), 6.21 (1H, d, $J_{8,9}$ 8.9 Hz, H-8), 6.69 (1H, at, *J* 10.0 Hz, H-9), 7.32 (1H, br s, H-16), 7.57 (1H, br s, H-16'), 7.61 (1H, s, H-2), 7.83 (1H, s, H-7), 8.01 (1H, s, H-4), 8.96 (1H, br s, H-13), 9.42 (1H, d, $J_{9,10}$ 11.0 Hz, H-10), 11.68 (1H, br s, H-1); δ_C (151 MHz, DMSO-D_6), 47.9 (t, SCH_2), 71.8 (s, C-14), 105.8 (d, C-8), 109.5 (s, C-3), 113.9 (s, C-5/6), 116.3 (s, C-5/6), 116.6 (d, C-7), 118.2 (d, C-9), 123.2 (d, C-4), 126.1 (d, C-2), 127.5 (s, C-3a), 135.6 (s, C-7a), 156.7 (s, C-11/12), 159.6 (s, C-11/12), 170.8 (s, C-15); *m/z* (ES^-) 533 ([M-H^+], 73%); HRMS (ES^-) calculated for $C_{16}H_{13}{}^{79}Br^{81}BrN_4O_3S_2$ ([M-H^+]) 532.8775, found 532.8771. A portion of this material (1.5 mg, 1 mg mL^{-1} in MeCN-H_2O, 1:1) was subjected to a second round of purification in 100 µL batches using a Shimadzu Prominence instrument using Chromeleon software (version 6.80, build 2673 (161349)) connected to either a Shimadzu SPD-20A detector at wavelengths of 239 nm and 305 nm or a Shimadzu SPD-M20A diode array detector at wavelengths of 239 nm, 254 nm, 280 nm and 305 nm.. An analytical HPLC (Phenomenex Luna 5 µ 100 Å C-18 column, 250 x 4.6 mm) was used. The column was eluted with 45% MeCN-H_2O for 40 min followed by a 100% MeCN wash for 10 min and reequilibration with H_2O for 10 min, all at a flow rate of 1 mL min^{-1}. The product eluted with

a retention time of 31 min; kottamide E (1.0 mg, 68%), white foam, approximately 85% pure. Analytical data obtained was in agreement with those reported previously.[4]

SEM deprotection conditions tested

DMF, TBAF, ethylene diamine[5]

PPTS, MeOH[6]

CsF, DMF, heat[7]

CSA, THF, rt[8]

$BF_3{\cdot}OEt_2$, DCM, 0 °C then base (triton B), reflux[9]

TBAF at high vacuum[10]

HCl in EtOH[11]

HCl in THF[12,13]

TAS-F in THF[14]

$MgBr_2$[15]

TBAF, molecular sieves, THF[16]

$LiBF_4$, MeCN, H_2O[17]

$LiBF_4$, TFA, 1,2-dimercaptoethane[18]

TFA[20]

References

(1) Parsons, T. B.; Ghellamallah, C.; Male, L.; Spencer, N.; Grainger, R. S. *Org. Biomol. Chem.* **2011**, *9*, 5021.

(2) Morera, E.; Nalli, M.; Pinnen, F.; Rossi, D.; Lucente, G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1585.

(3) Morera, E.; Lucente, G.; Ortar, G.; Nalli, M.; Mazza, F.; Gavuzzo, E.; Spisani, S. *Bioorg. Med. Chem.* **2002**, *10*, 147.

(4) Appleton, D. R.; Copp, B. R. *Tetrahedron Lett.* **2003**, *44*, 8963.

(5) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203.

(6) Phillips, J. G.; Fadnis, L.; Williams, D. R. *Tetrahedron Lett.* **1997**, *38*, 7835.

(7) Bobko, M. A.; Evans, K. A.; Kaura, A. C.; Shuster, L. E.; Su, D.-S. *Tetrahedron Lett.* **2012**, *53*, 200.

(8) Hirao, S.; Yoshinaga, Y.; Iwao, M.; Ishibashi, F. *Tetrahedron Lett.* **2010**, *51*, 533.

(9) Bennasar, M. L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597.

(10) Moreno, O. A.; Kishi, Y. *Bioorg. Med. Chem.* **1998**, *6*, 1243.

(11) Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 2615.

(12) Busacca, C. A.; Eriksson, M. C.; Dong, Y.; Prokopowicz, A. S.; Salvagno, A. M.; Tschantz, M. A. *J. Org. Chem.* **1999**, *64*, 4564.

(13) Laronze, M.; Boisbrun, M.; Léonce, S.; Pfeiffer, B.; Renard, P.; Lozach, O.; Meijer, L.; Lansiaux, A.; Bailly, C.; Sapi, J.; Laronze, J. Y. *Bioorg. Med. Chem.* **2005**, *13*, 2263.

(14) Bartlett, S.; Nelson, A. *Org. Biomol. Chem.* **2004**, *2*, 2874.

(15) Eils, S.; Winterfeldt, E. *Synthesis* **1999**, *1999*, 275.

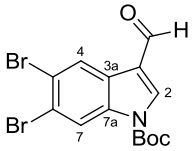
(16) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343.

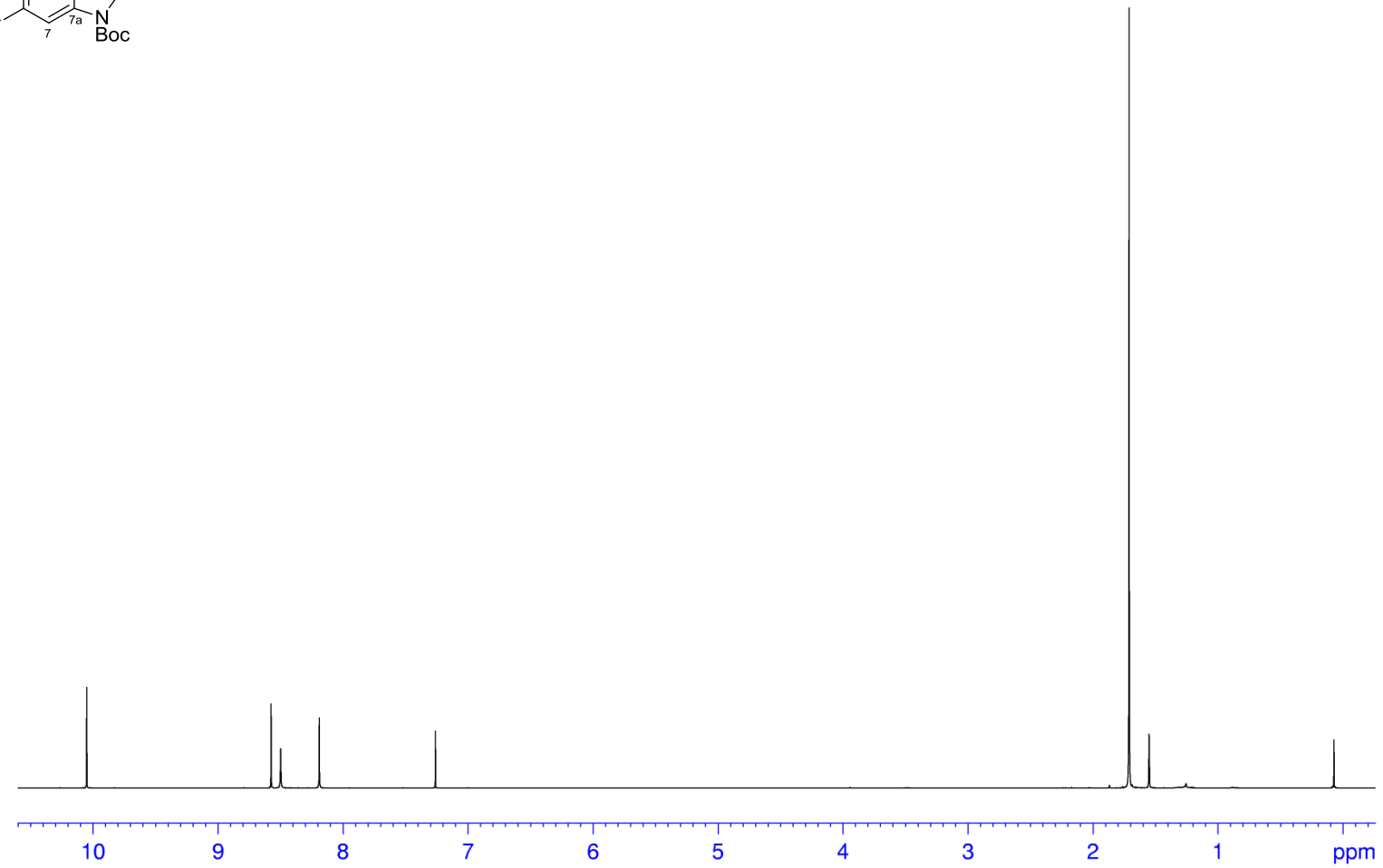
(17) Piers, E.; Britton, R.; Andersen, R. J. *J. Org. Chem.* **2000**, *65*, 530.

(18) Witty, D. R.; Walker, G.; Bateson, J. H.; O'Hanlon, P. J.; Cassels, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1375.

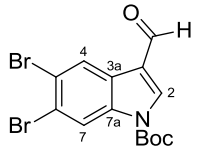
(20) Patent: EP1935890 A1, 2008; location in patent: page 41; column 42.

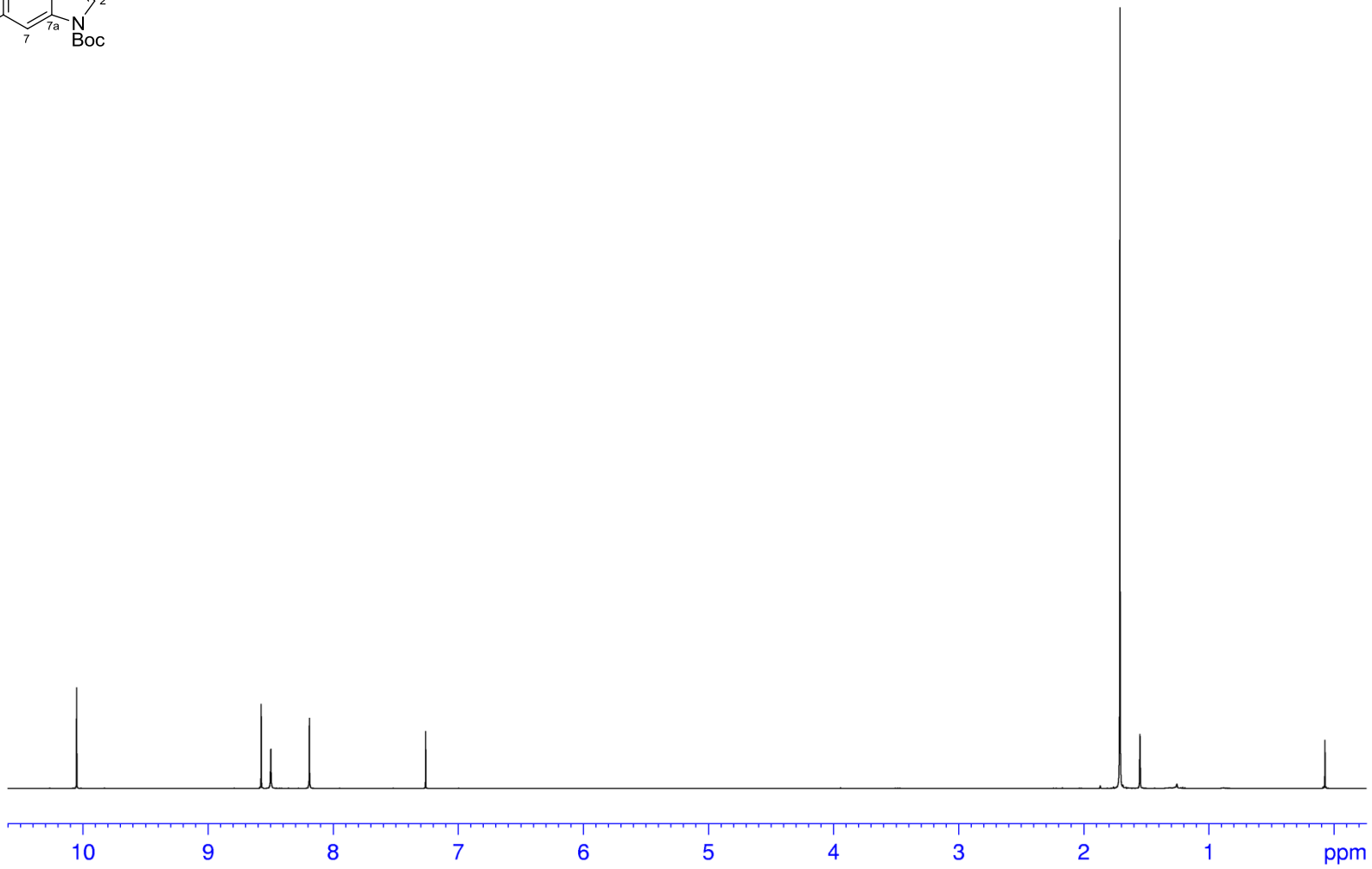
tert-Butyl 5,6-dibromo-3-formyl-1*H*-indole-1-carboxylate **6a**; 400 MHz, $CDCl_3$



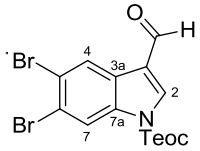


tert-Butyl 5,6-dibromo-3-formyl-1*H*-indole-1-carboxylate **6a**; 100 MHz, $CDCl_3$

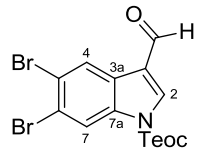


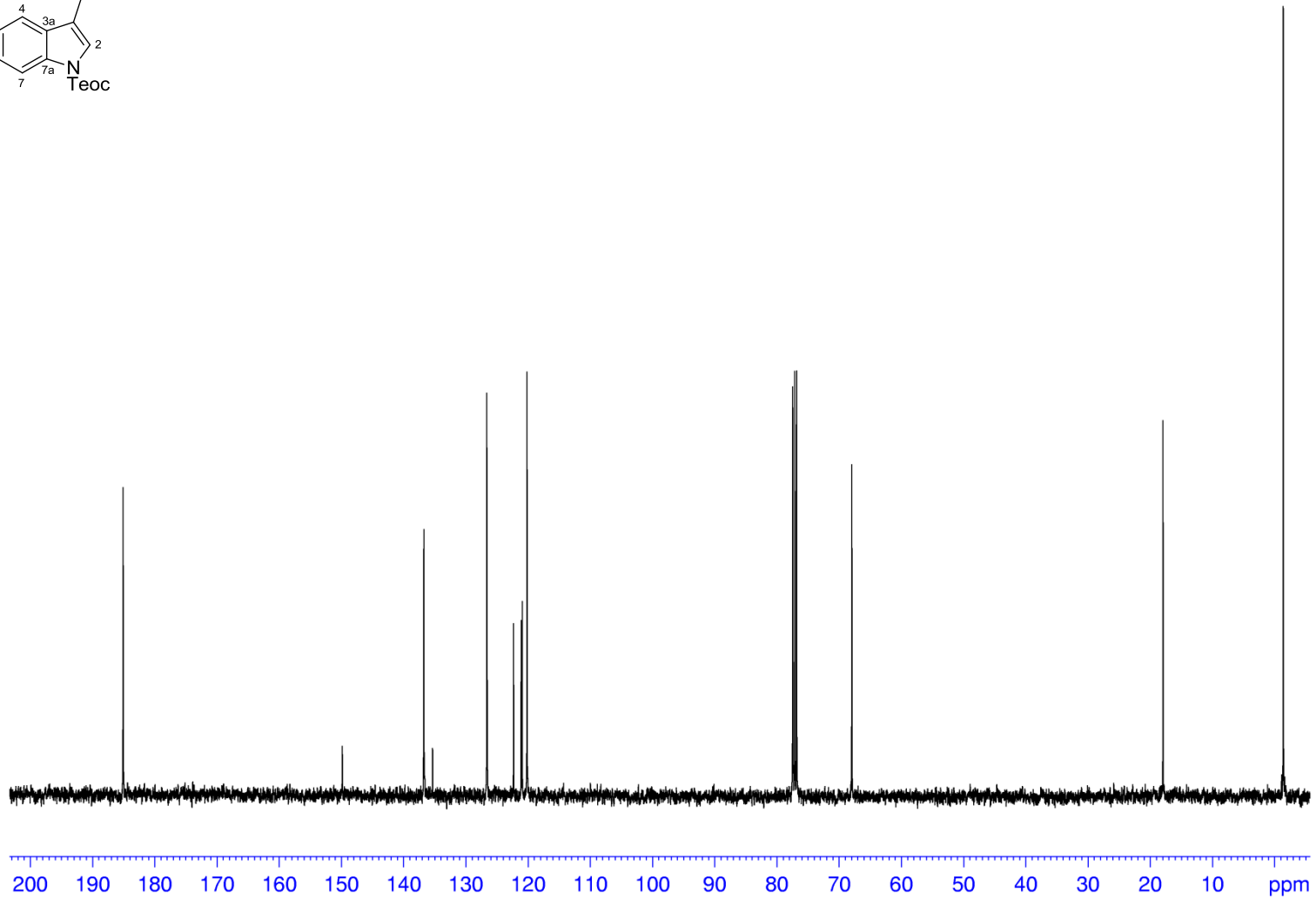


2-(Trimethylsilyl)ethyl 5,6-dibromo-3-formyl-1*H*-indole-1-carboxylate **6b**; 300 MHz, $CDCl_3$

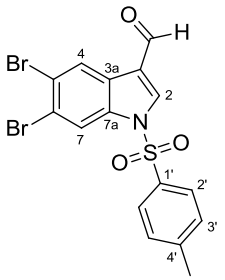


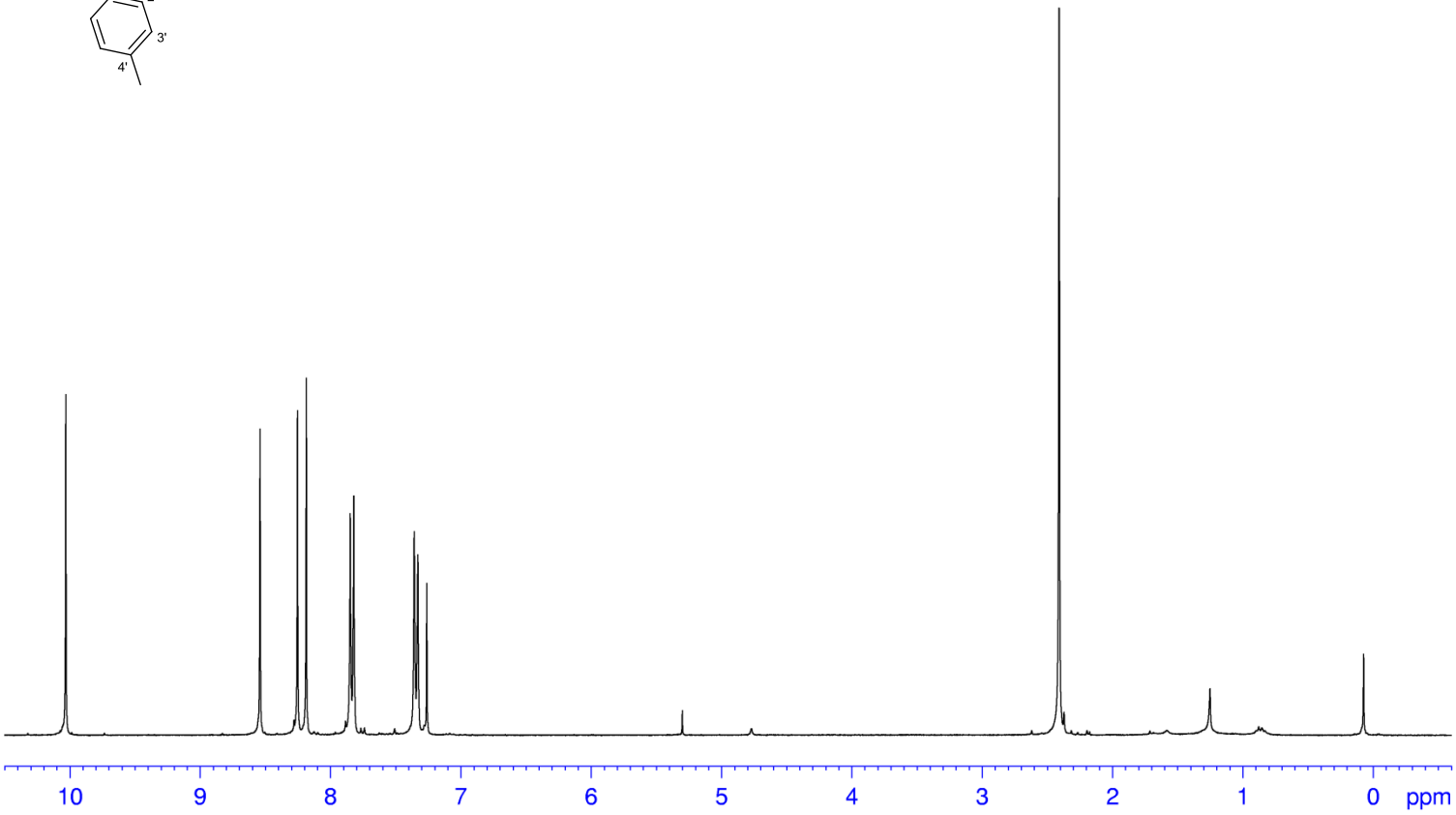
2-(Trimethylsilyl)ethyl 5,6-dibromo-3-formyl-1*H*-indole-1-carboxylate **6b**; 100 MHz, $CDCl_3$



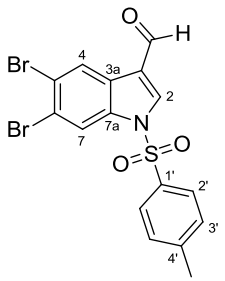


5,6-Dibromo-1-tosyl-1*H*-indole-3-carbaldehyde **6c**; 300 MHz, $CDCl_3$

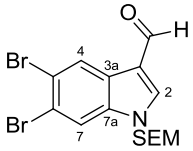




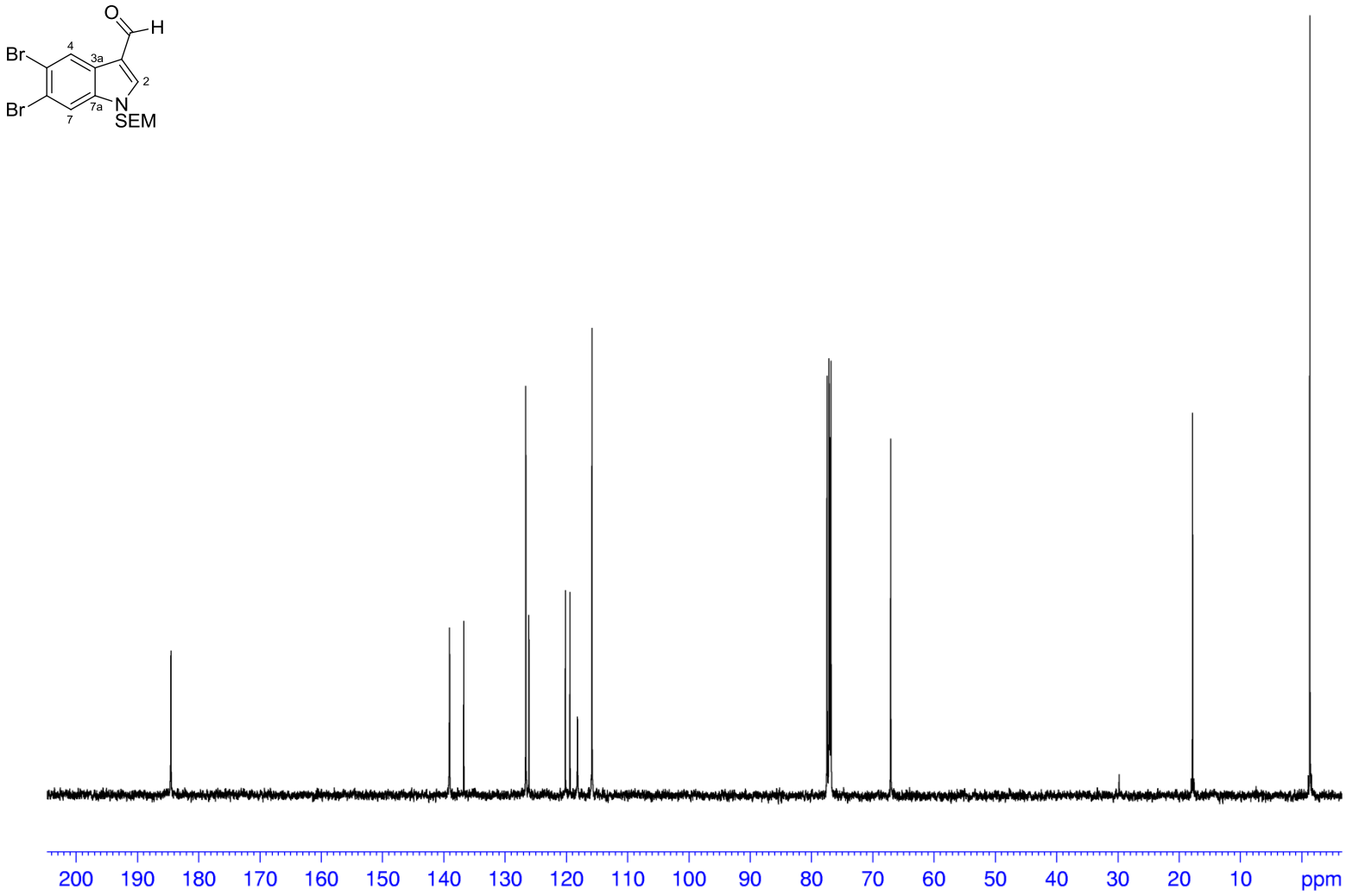
5,6-Dibromo-1-tosyl-1*H*-indole-3-carbaldehyde **6c**; 100 MHz, $CDCl_3$



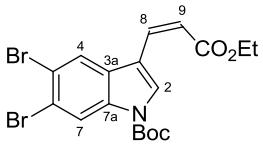
5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-3-carbaldehyde **6d**; 400 MHz, $CDCl_3$

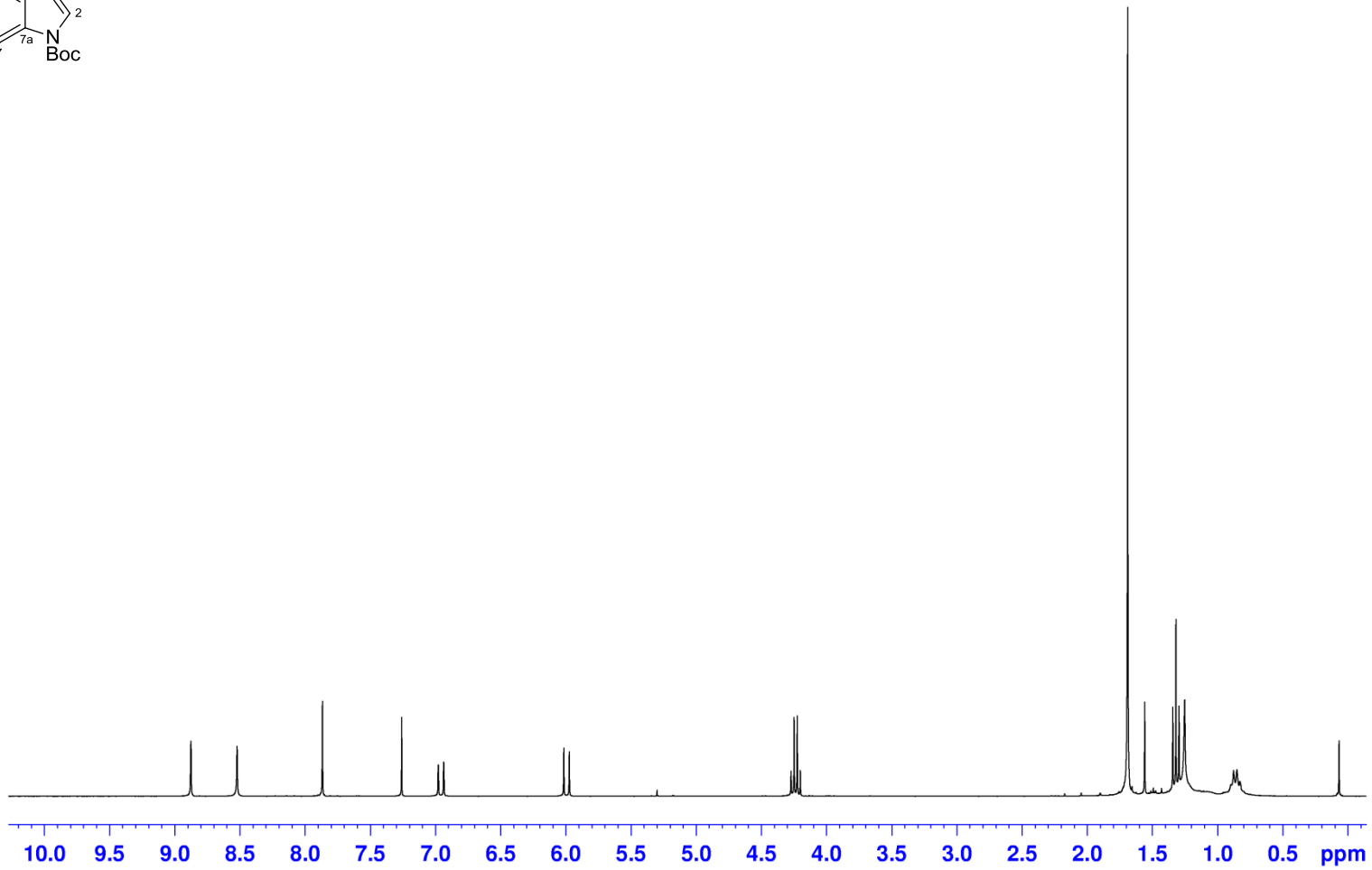


5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole-3-carbaldehyde **6d**; 100 MHz, $CDCl_3$

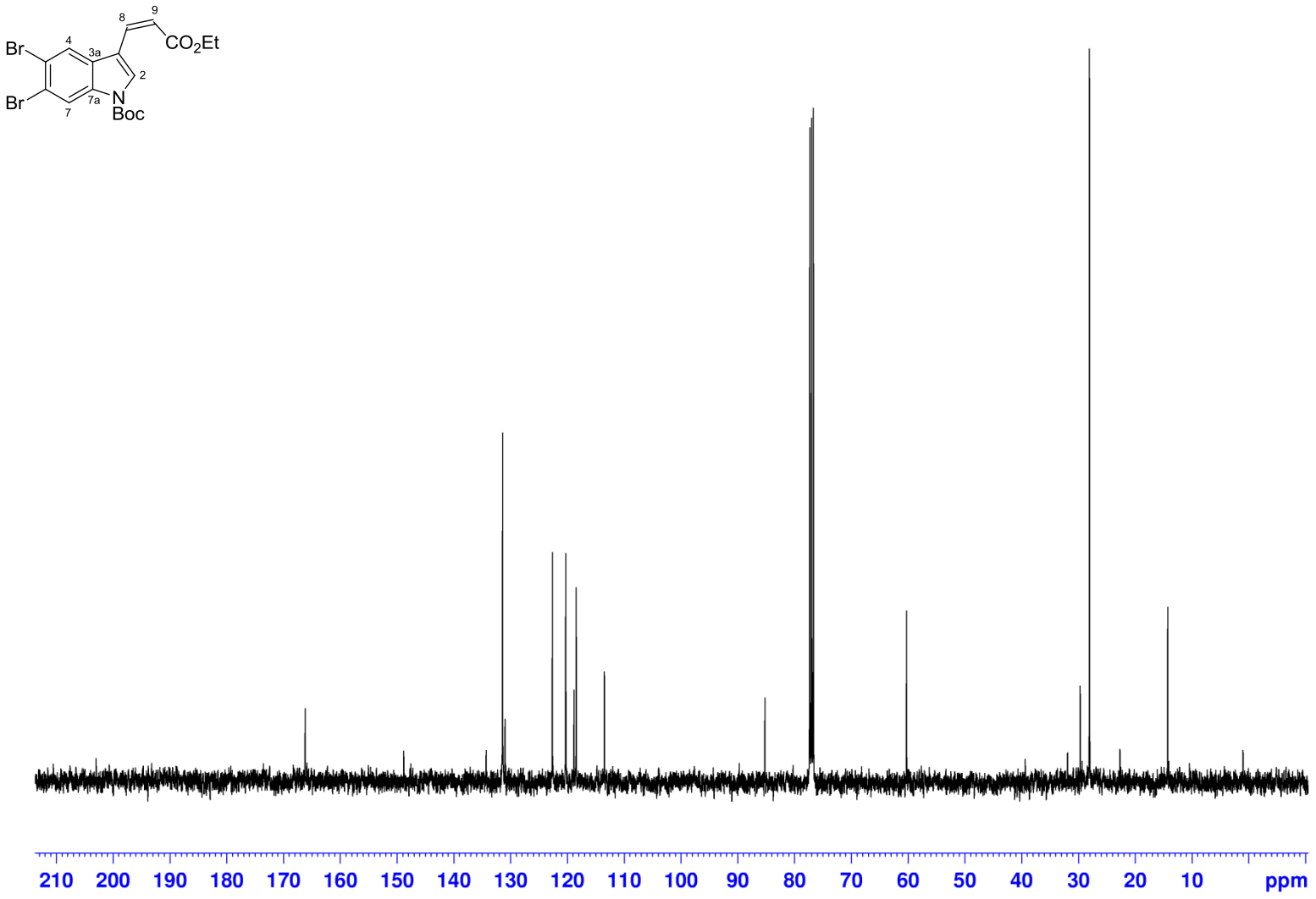


(*Z*)-*tert*-Butyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate **7a**; 300 MHz, $CDCl_3$

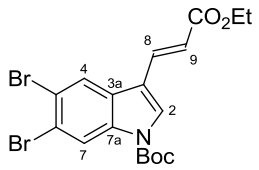


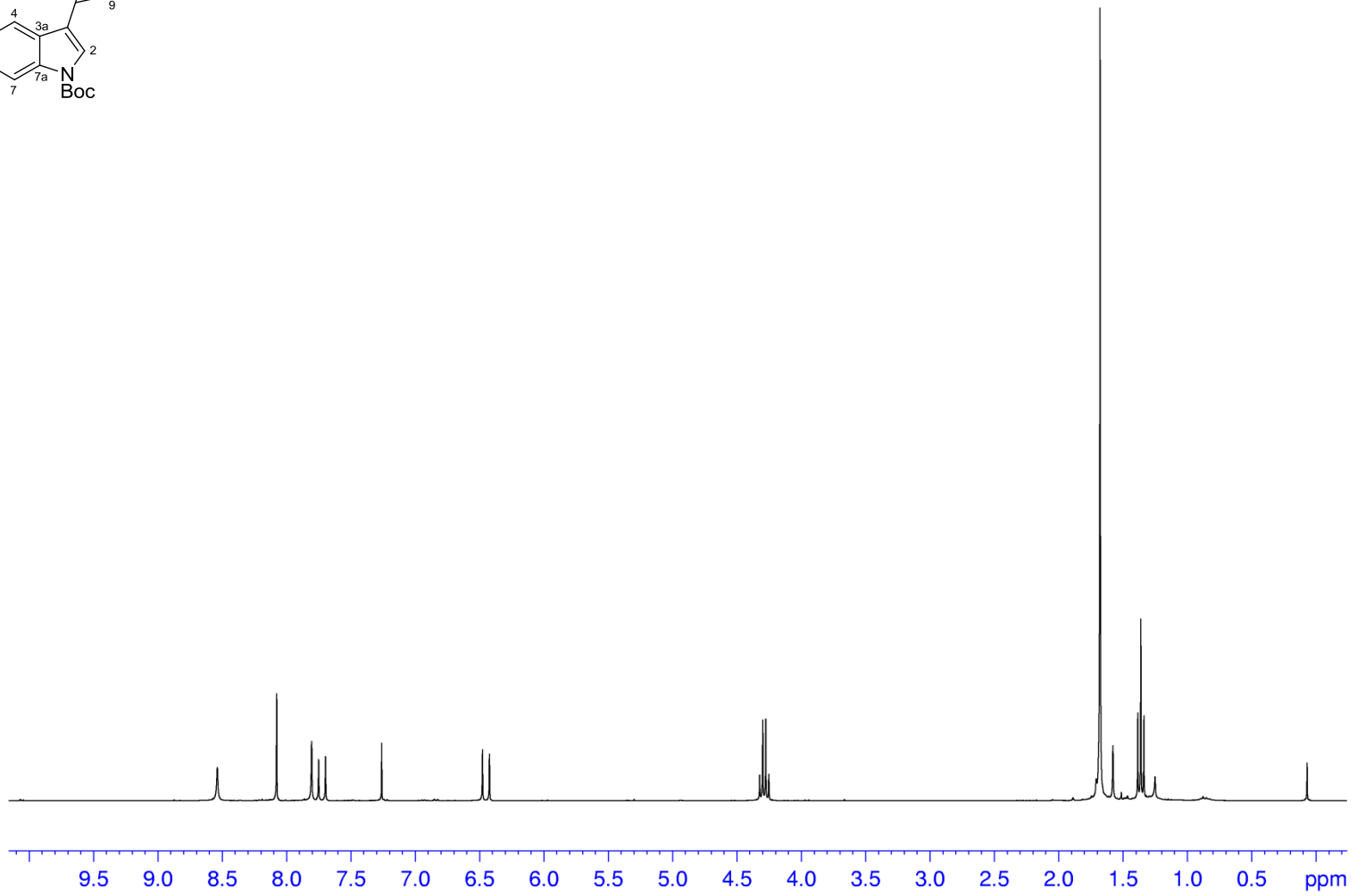


(*Z*)-*tert*-Butyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate **7a**; 100 MHz, $CDCl_3$

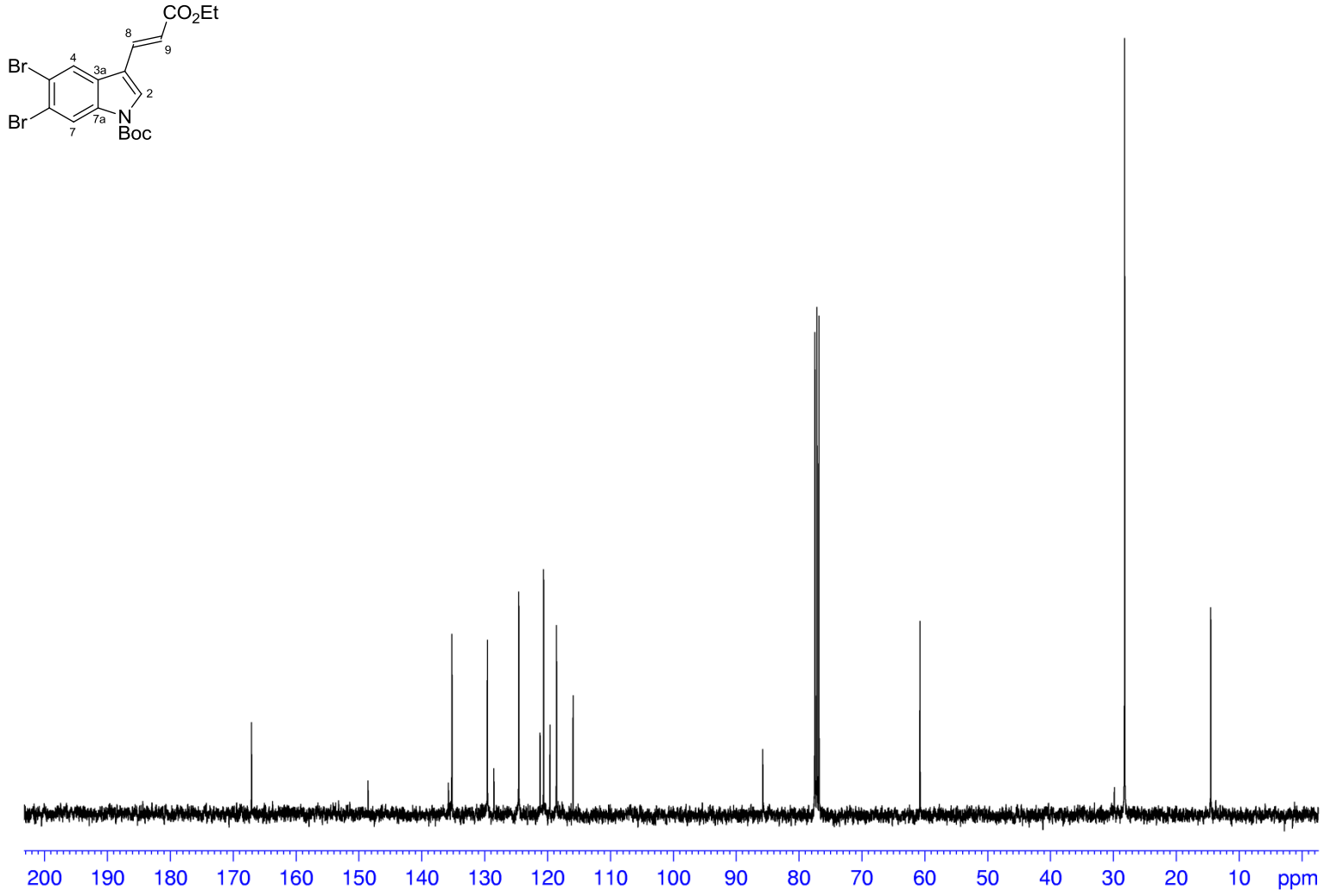


(*E*)-*tert*-Butyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate **(*E*)-7a**; 300 MHz, $CDCl_3$

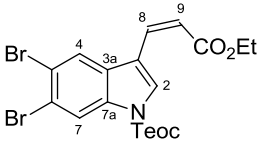




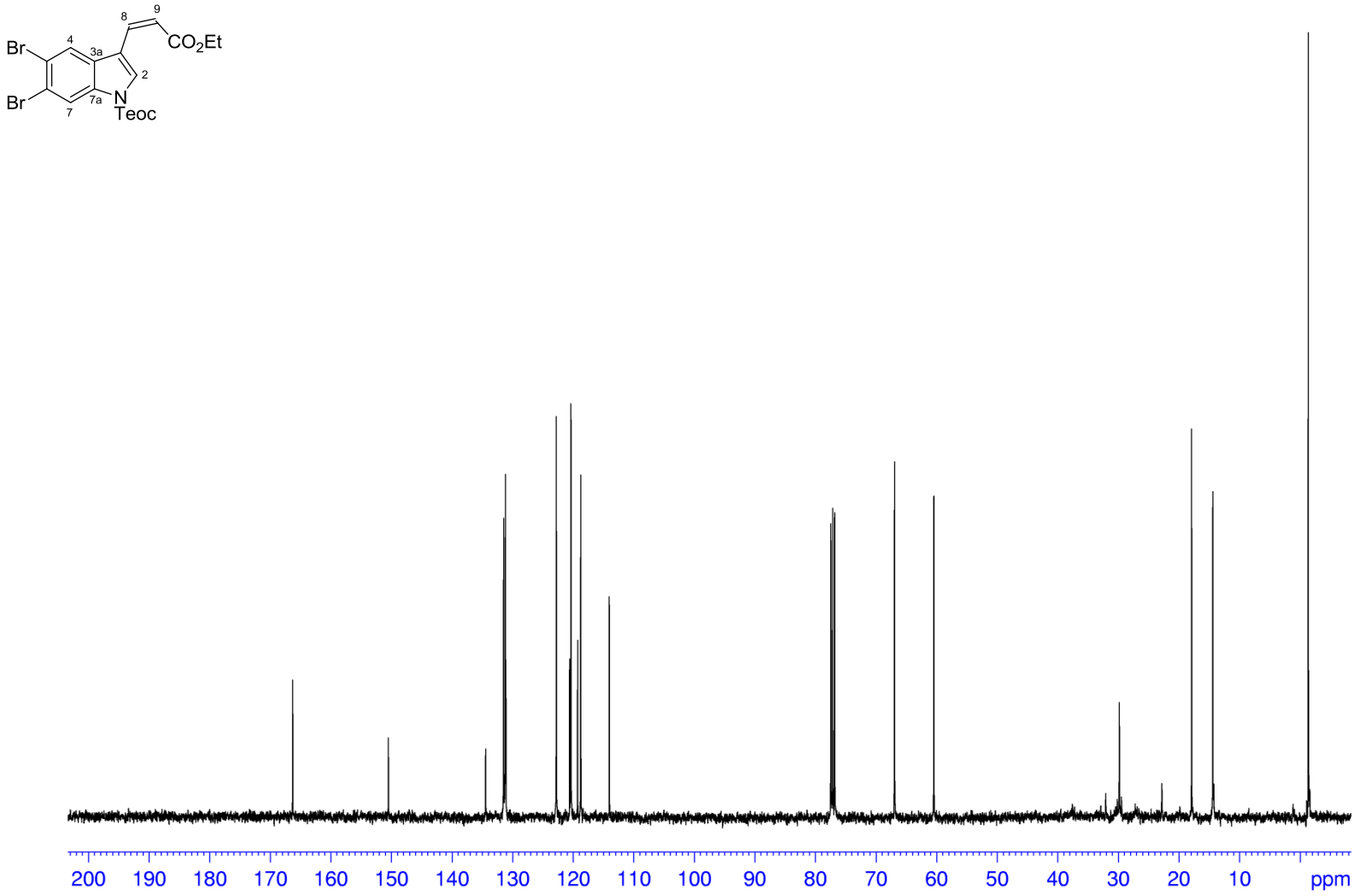
(*E*)-*tert*-Butyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate **(*E*)-7a**; 100 MHz, $CDCl_3$



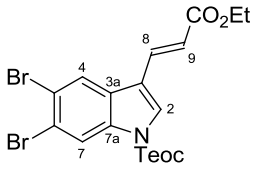
(Z)-2-(Trimethylsilyl)ethyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate **7b**; 400 MHz, $CDCl_3$



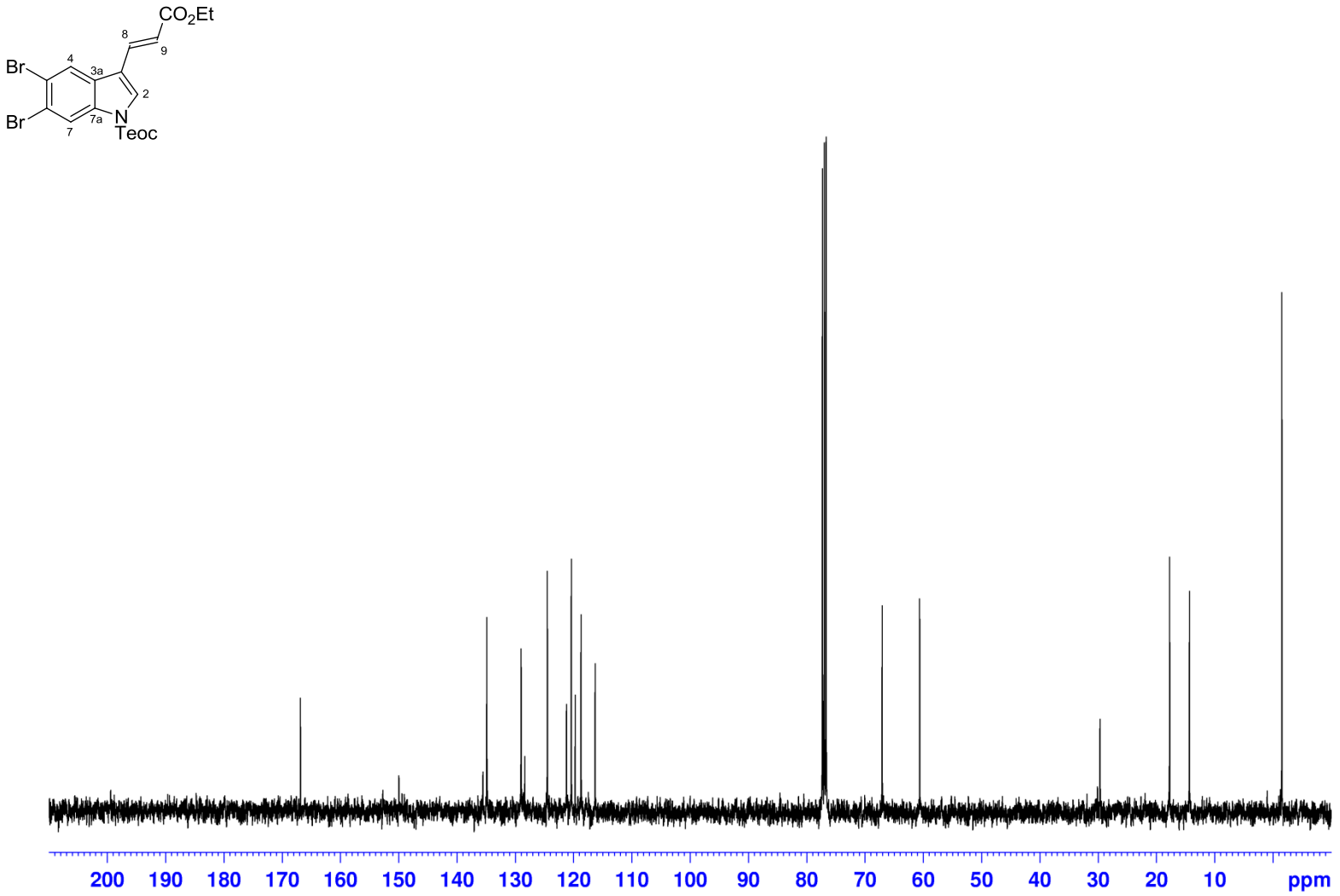
(*Z*)-2-(Trimethylsilyl)ethyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate **7b**; 100 MHz, $CDCl_3$



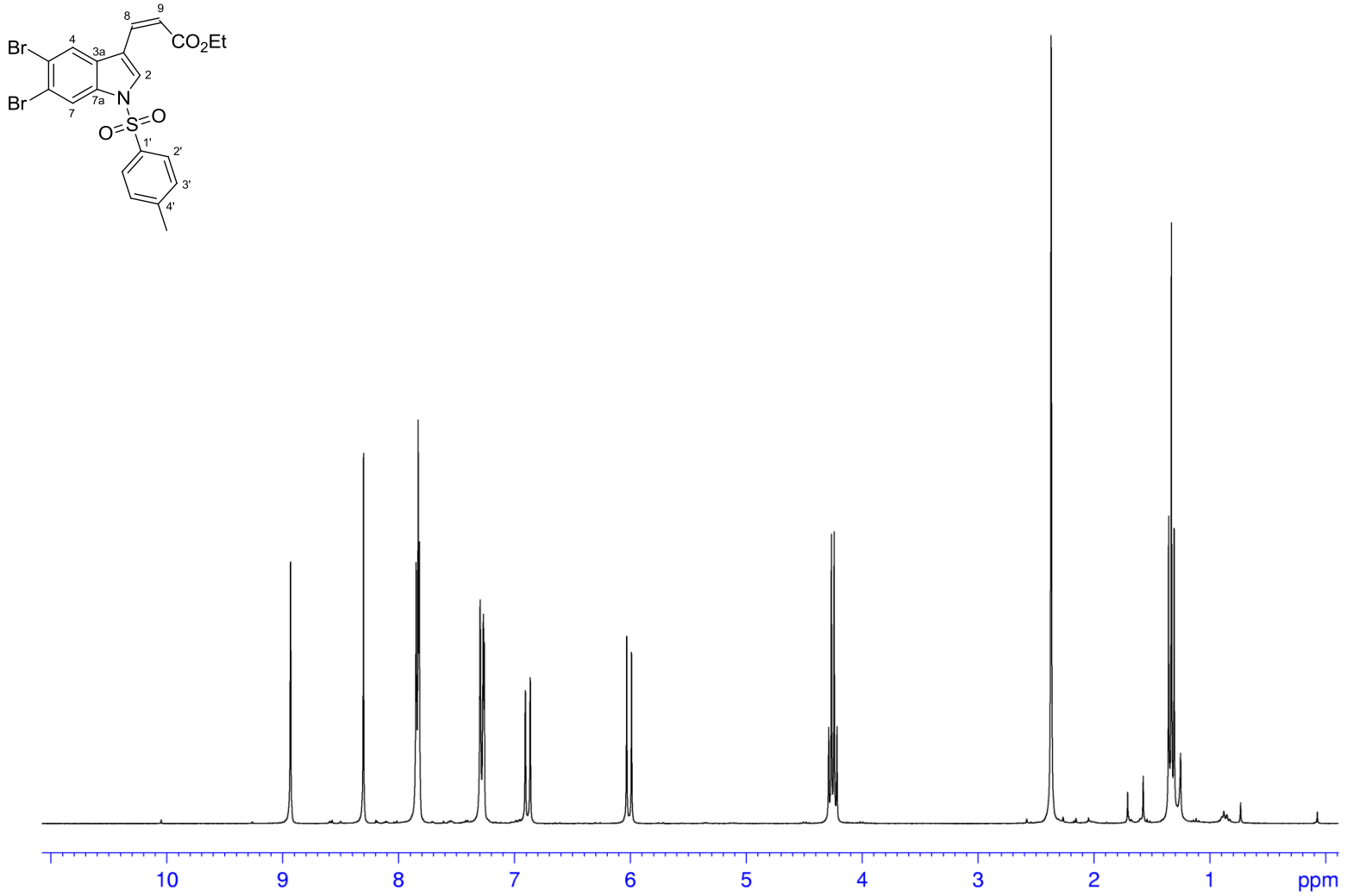
(*E*)-2-(Trimethylsilyl)ethyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate **(*E*)-7b**; 400 MHz, $CDCl_3$



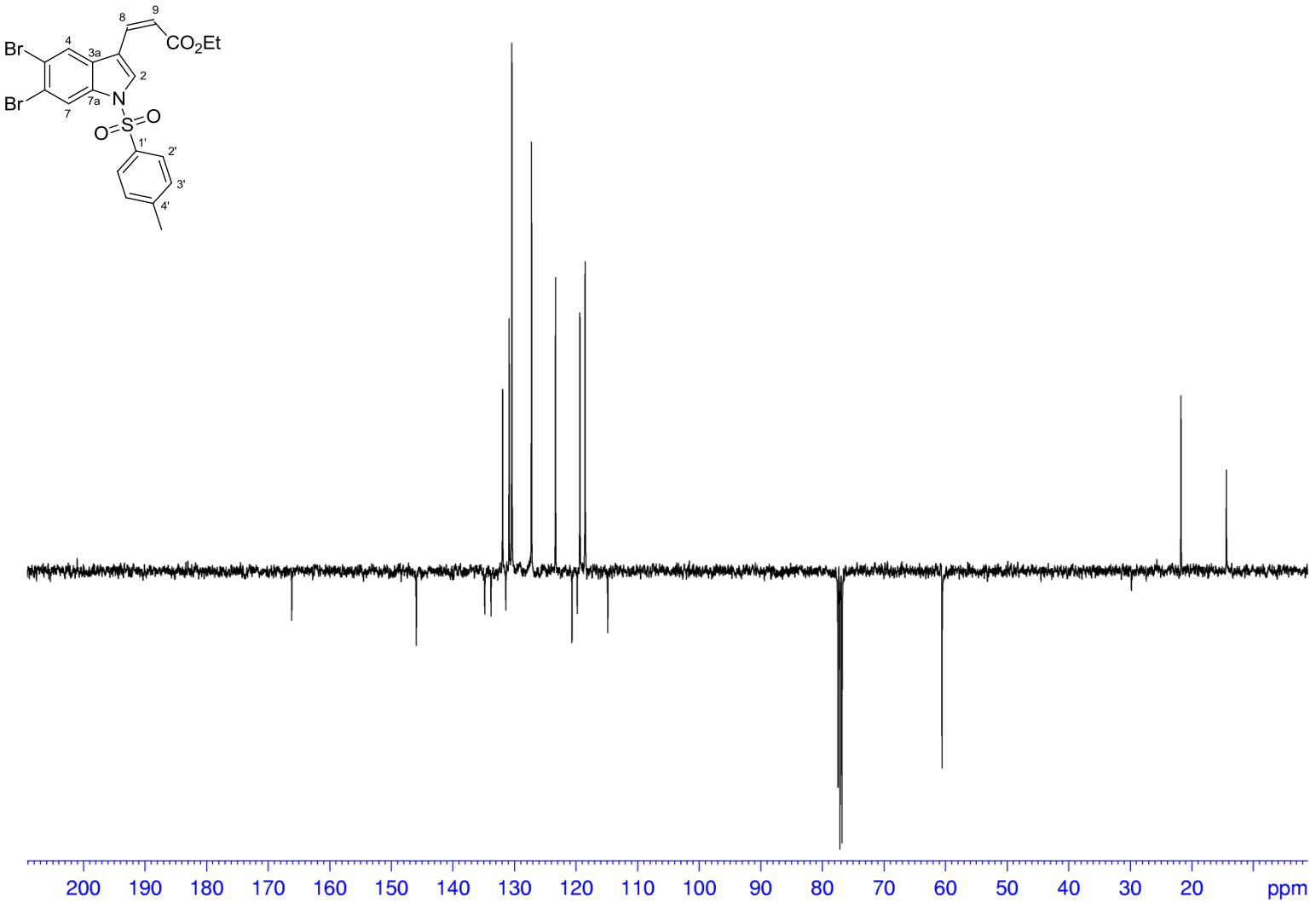
(*E*)-2-(Trimethylsilyl)ethyl 5,6-dibromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate **(*E*)-7b**; 100 MHz, $CDCl_3$



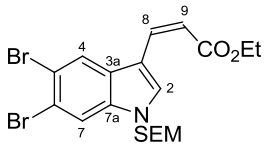
(*Z*)-Ethyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate **7c**; 300 MHz, $CDCl_3$

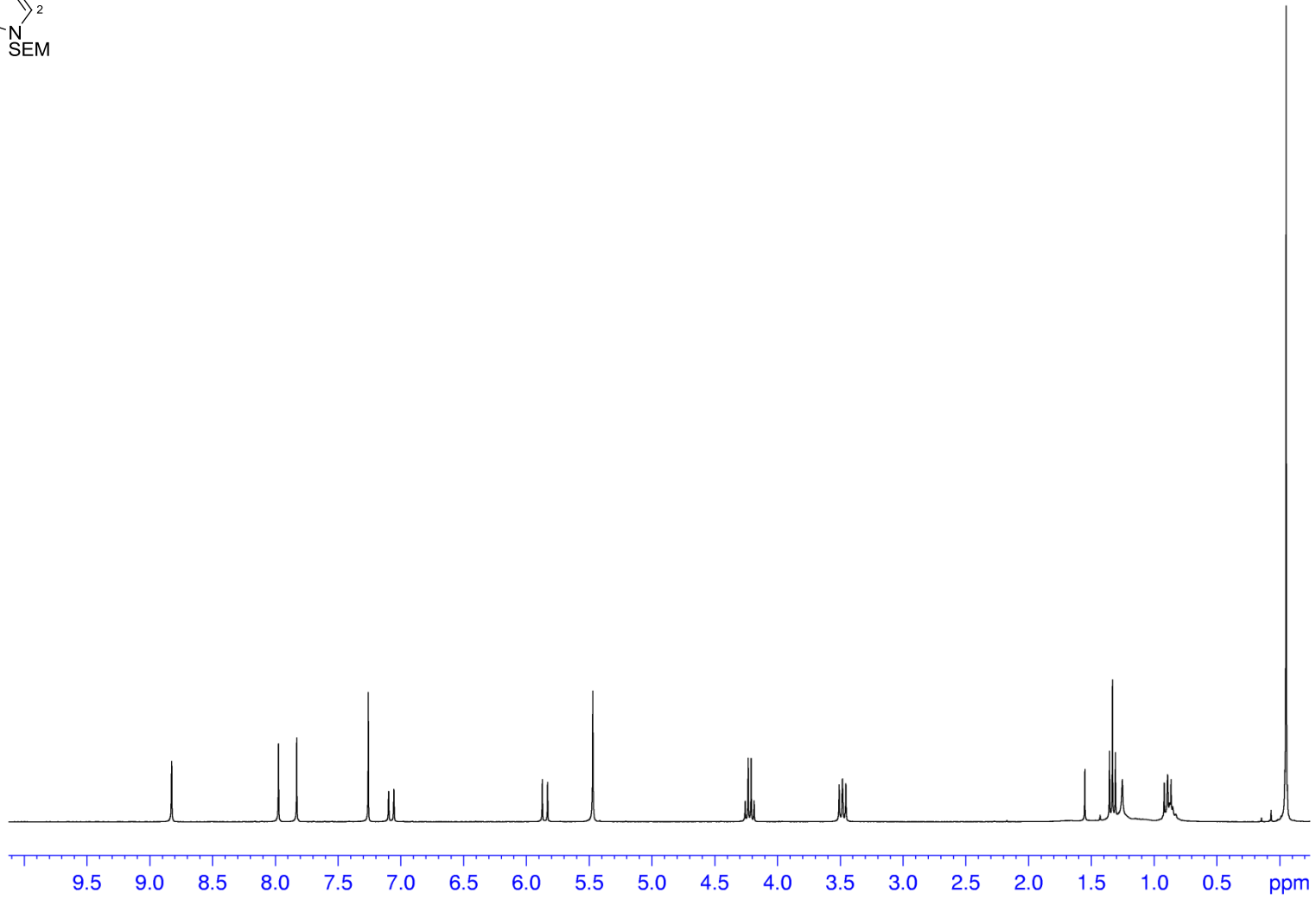


(*Z*)-Ethyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate **7c**; 100 MHz, $CDCl_3$

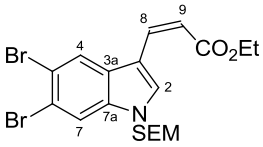


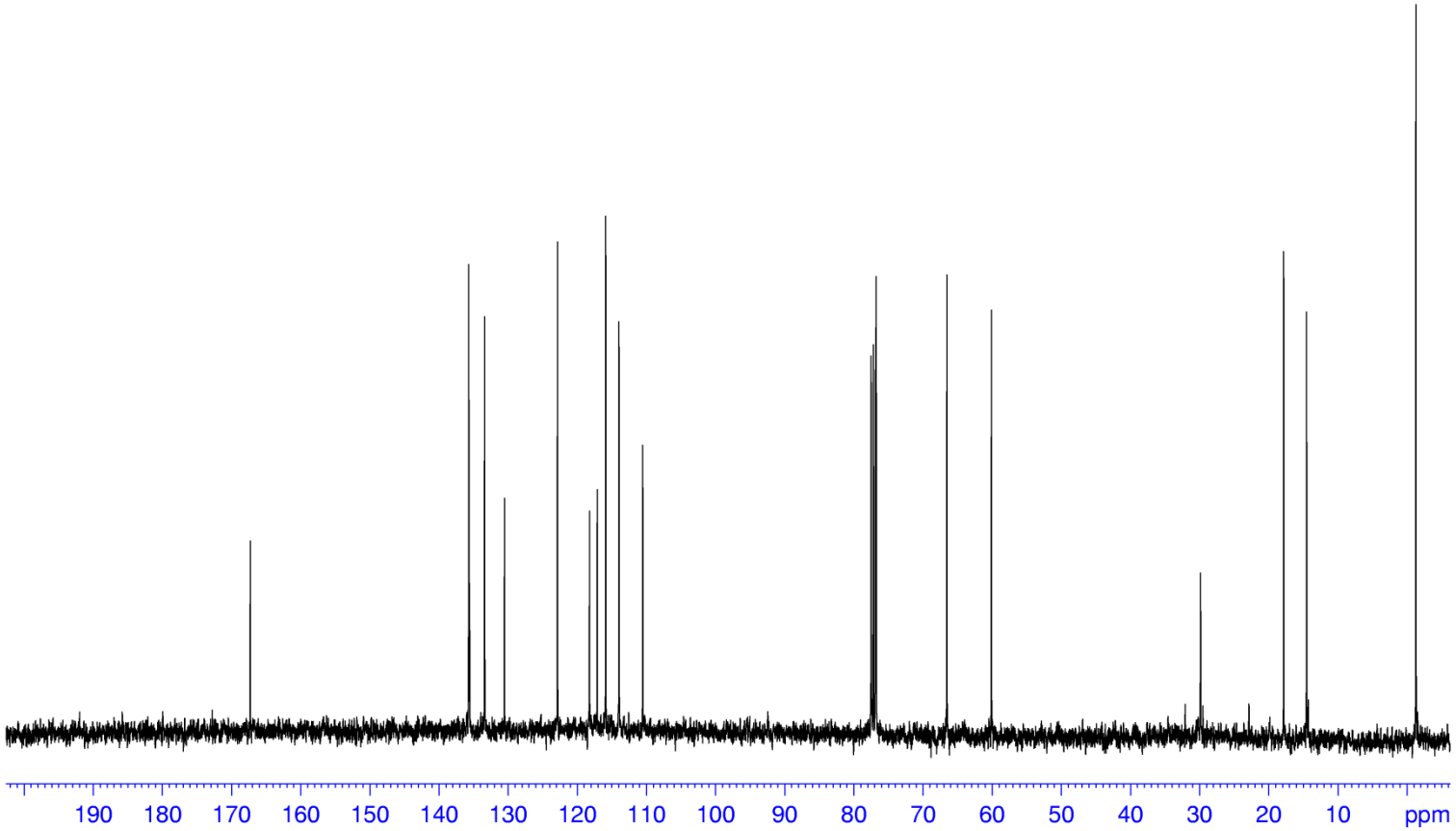
(*Z*)-Ethyl 3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acrylate **7d**; 400 MHz, $CDCl_3$



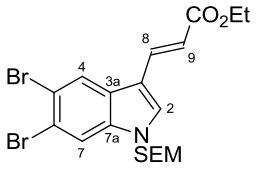


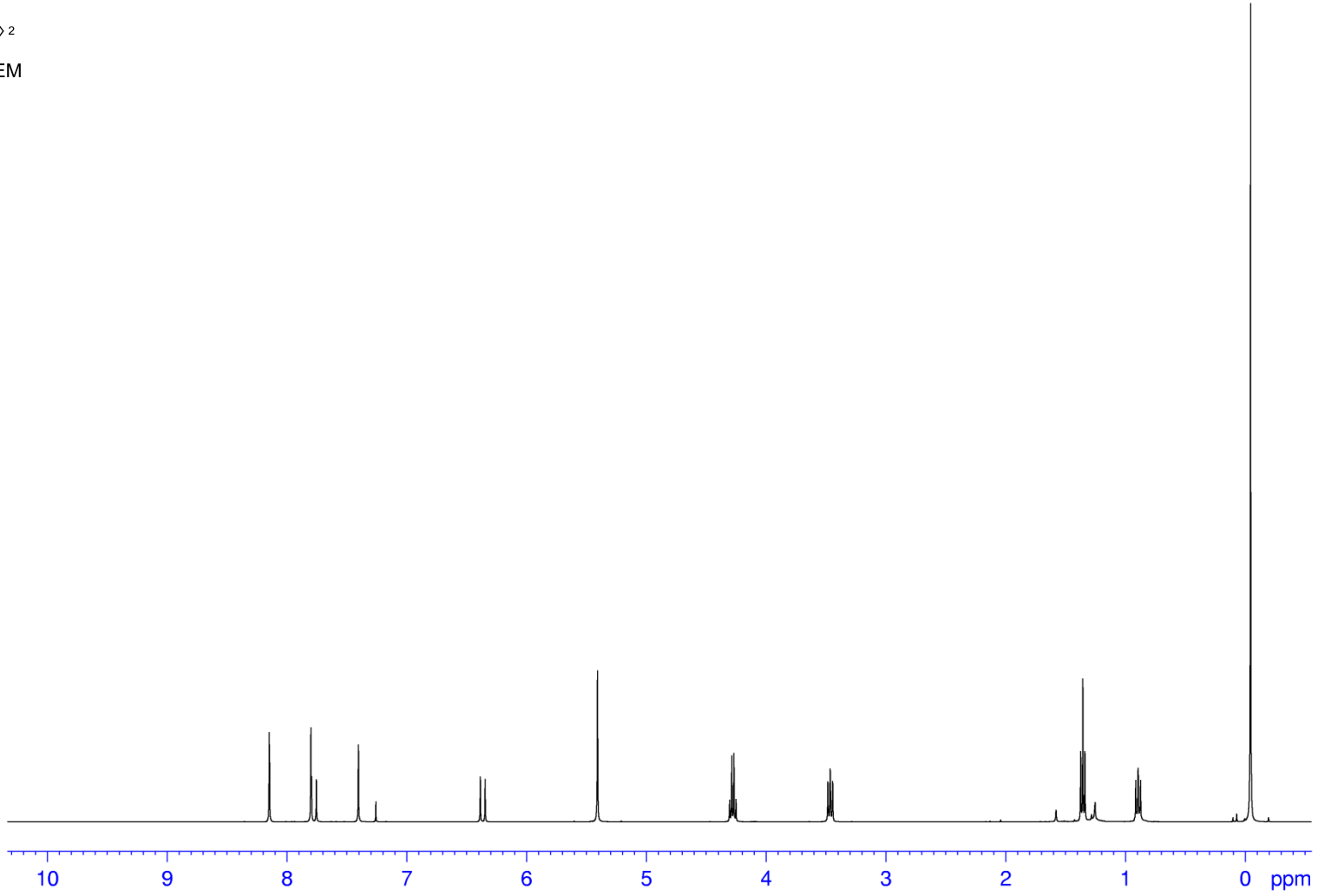
(*Z*)-Ethyl 3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acrylate **7d**; 100 MHz, $CDCl_3$



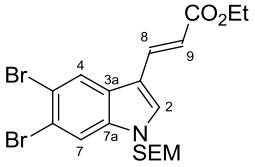


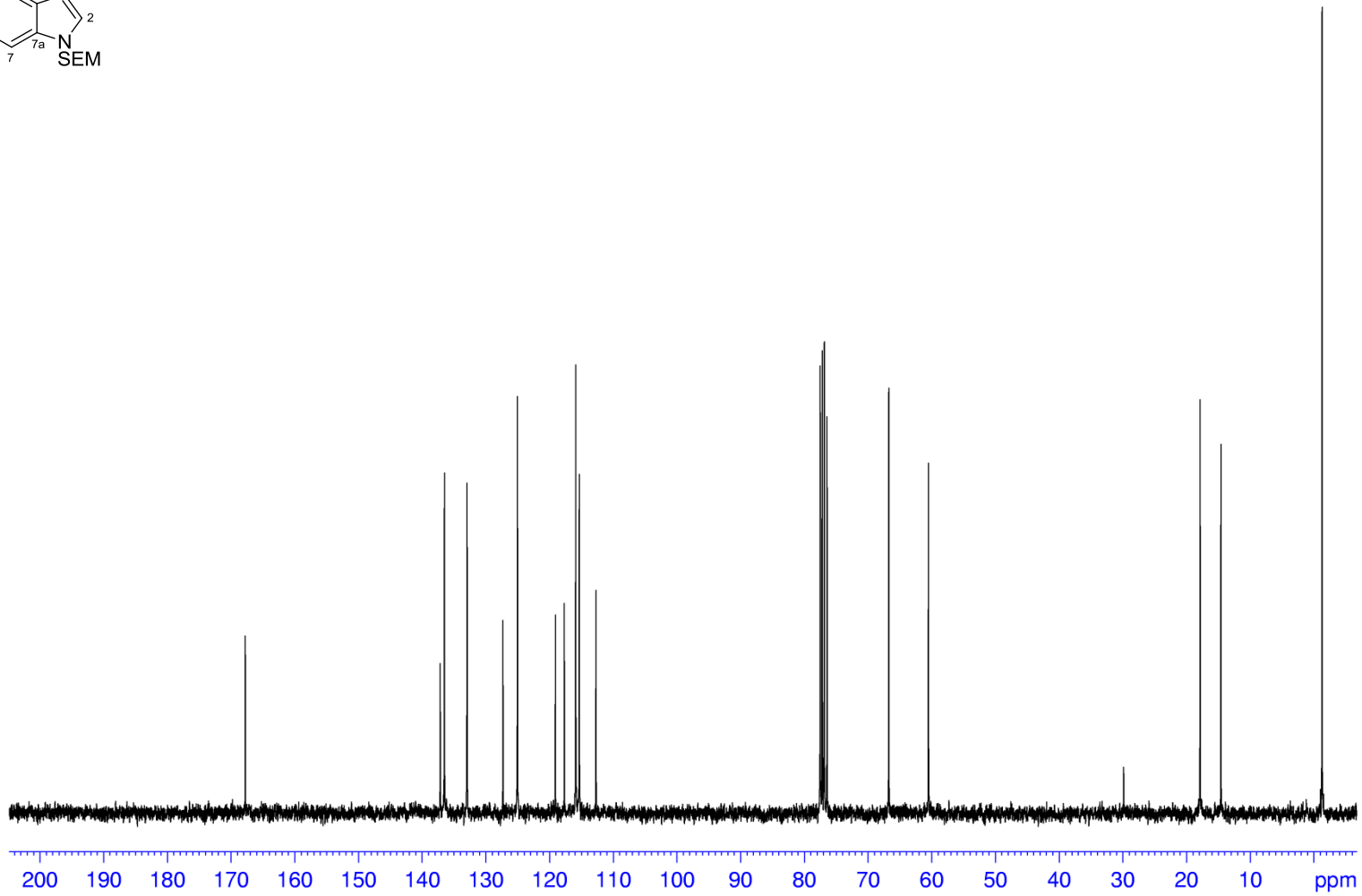
(*E*)-Ethyl 3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acrylate **15**; 400 MHz, $CDCl_3$



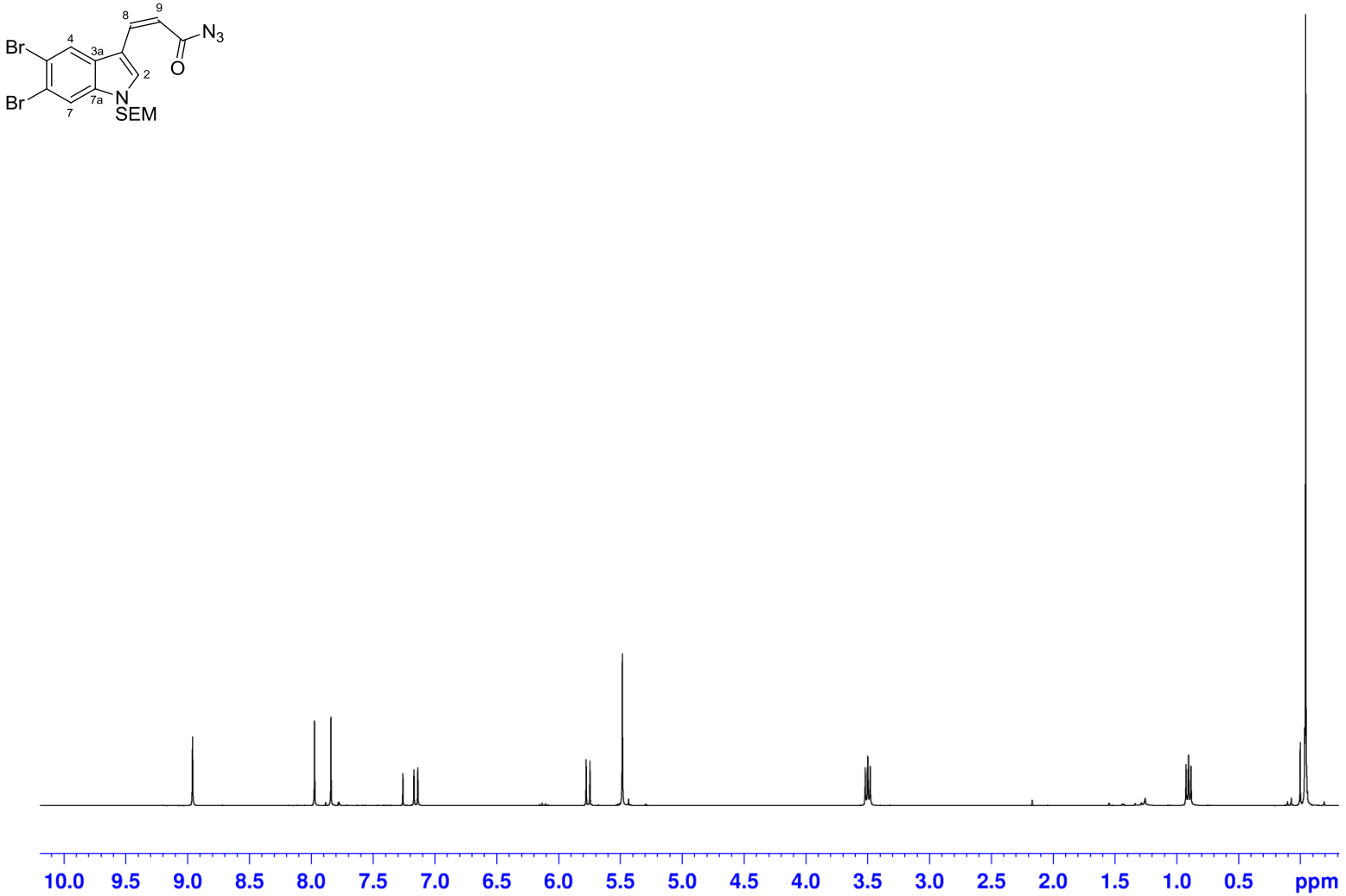


(*E*)-Ethyl 3-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acrylate **15**; 100 MHz, $CDCl_3$

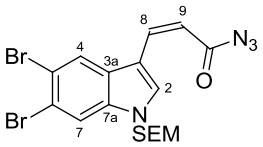




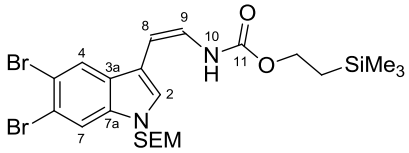
(*Z*)-3-(5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acryloyl azide **8**; 400 MHz, $CDCl_3$



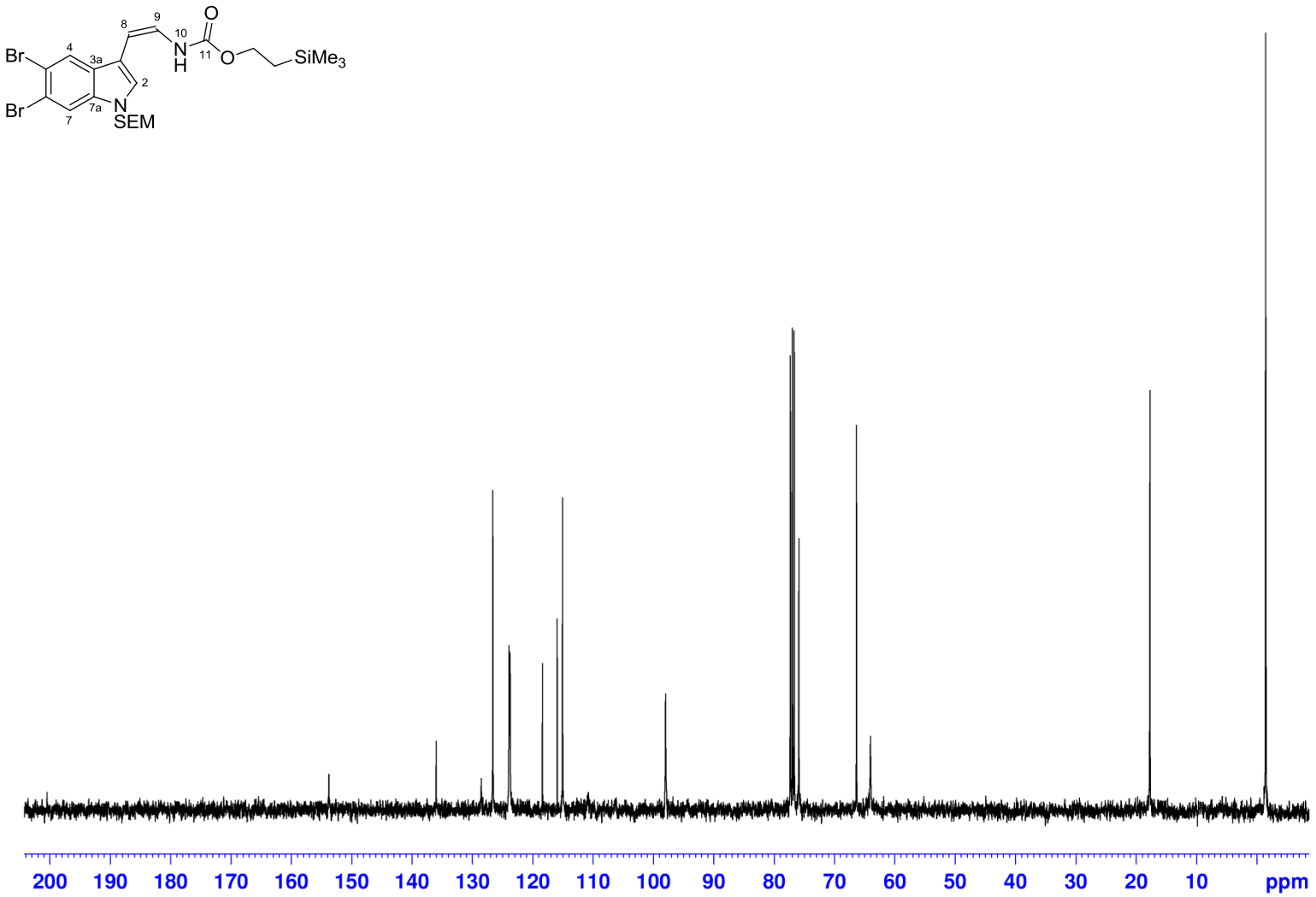
(Z)-3-(5,6-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acryloyl azide **8**; 100 MHz, $CDCl_3$



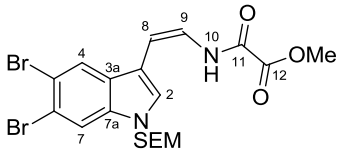
(*Z*)-2-(Trimethylsilyl)ethyl (2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)carbamate **9**; 400 MHz, $CDCl_3$



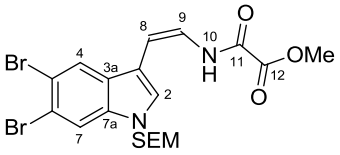
(*Z*)-2-(Trimethylsilyl)ethyl (2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)carbamate **9**; 100 MHz, $CDCl_3$



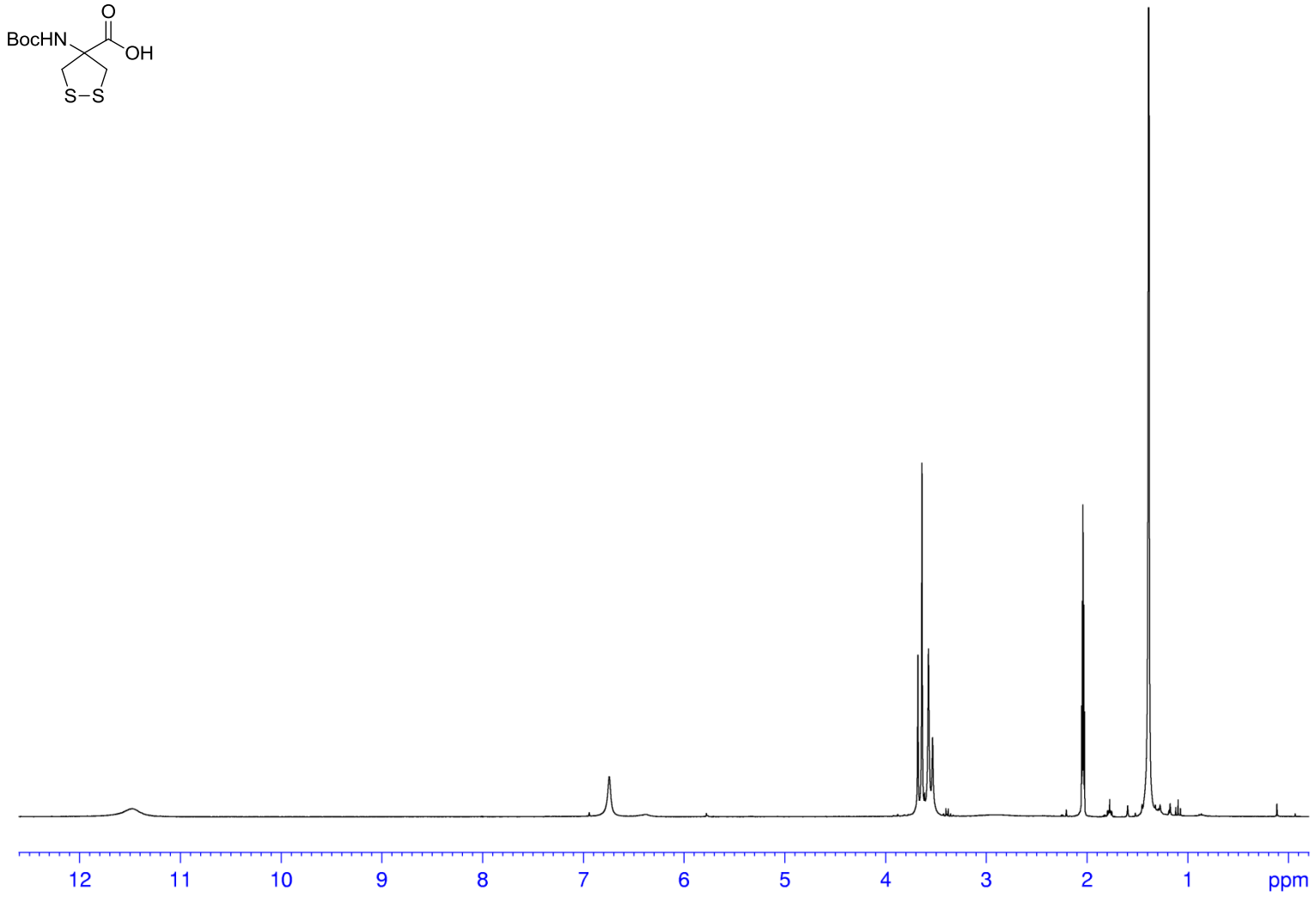
(*Z*)-Methyl 2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetate **11**; 400 MHz, $CDCl_3$



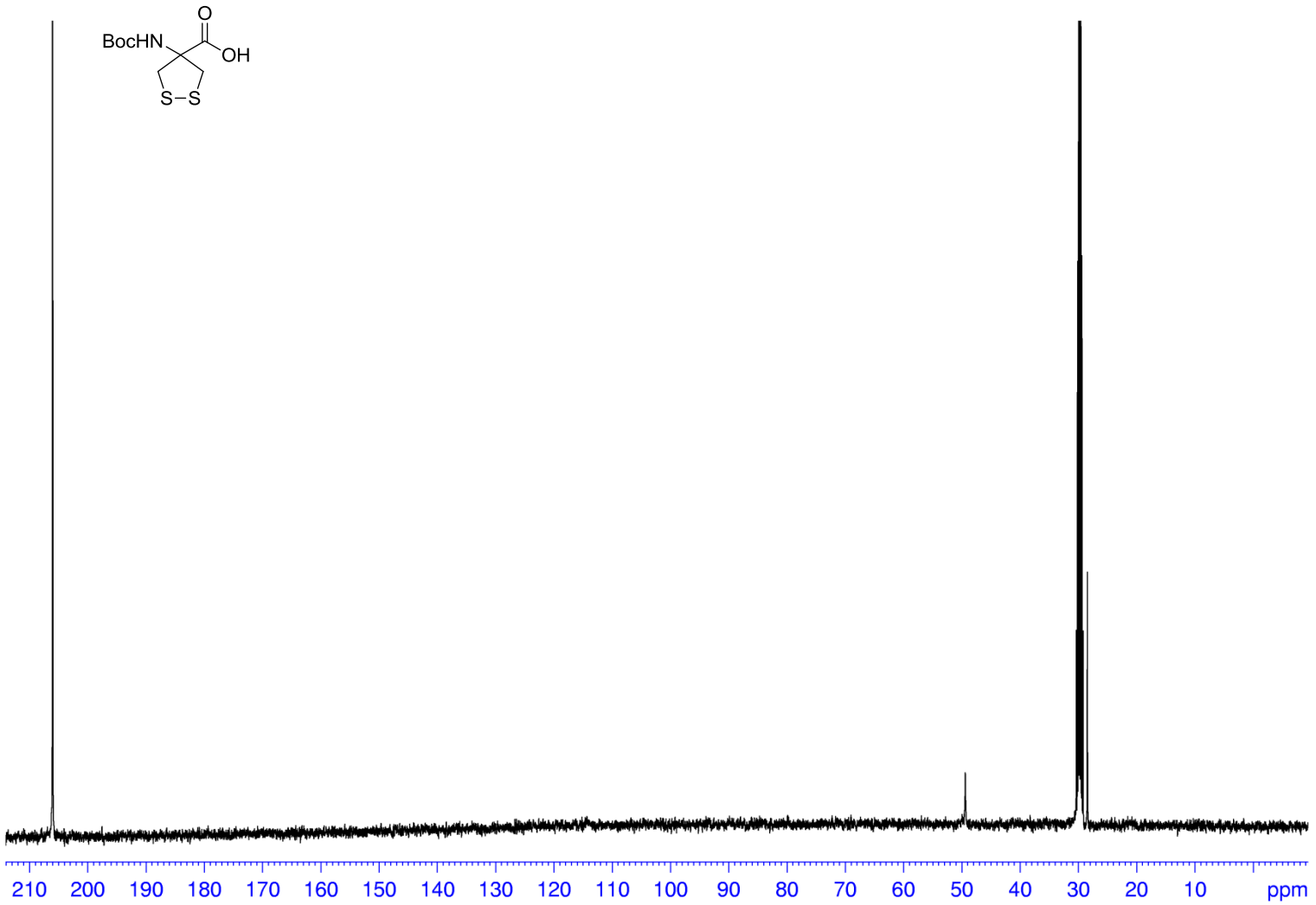
(*Z*)-Methyl 2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetate **11**; 100 MHz, $CDCl_3$



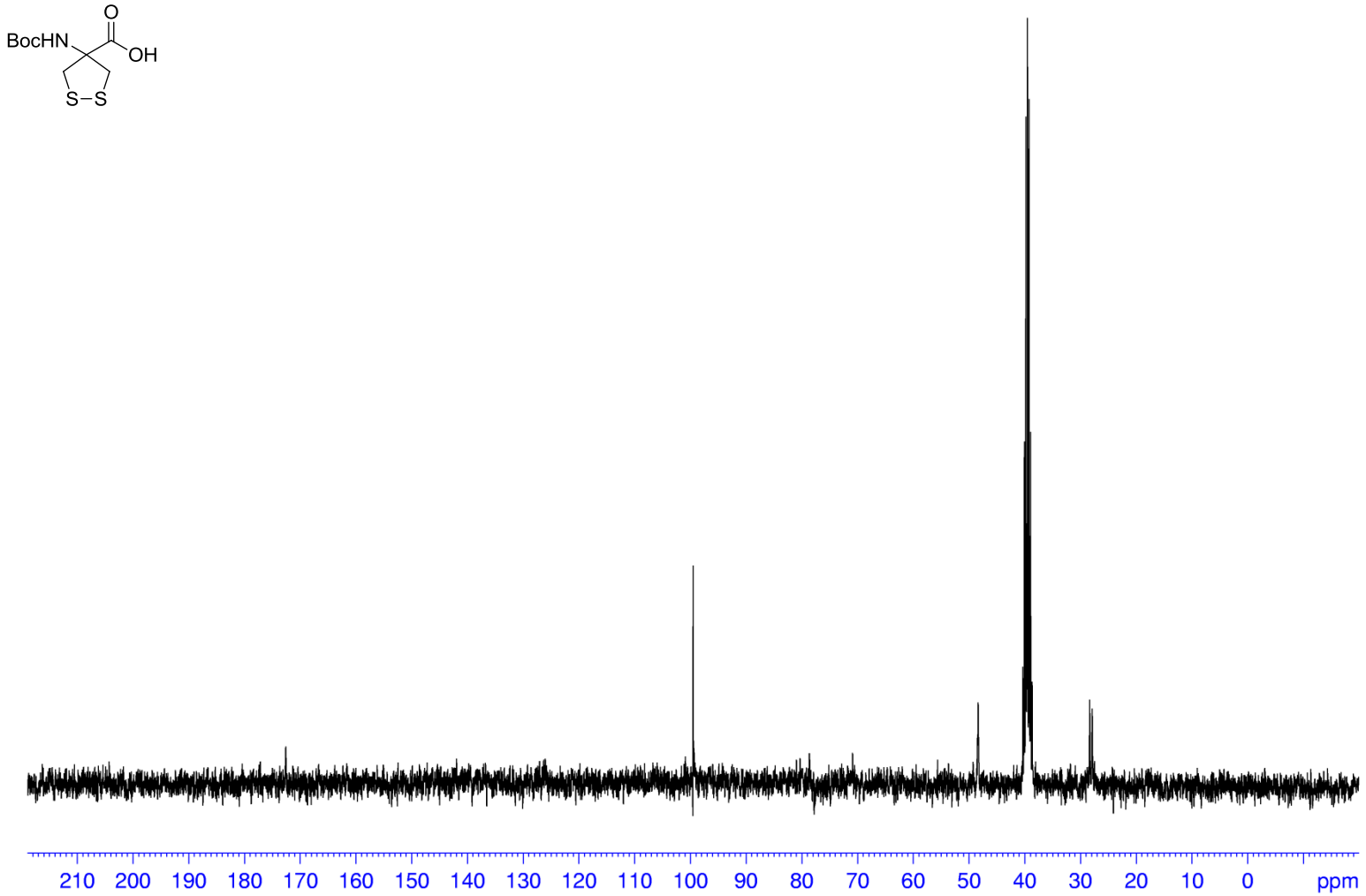
4-((*tert*-Butoxycarbonyl)amino)-1,2-dithiolane-4-carboxylic acid; 300 MHz, acetone-D_6



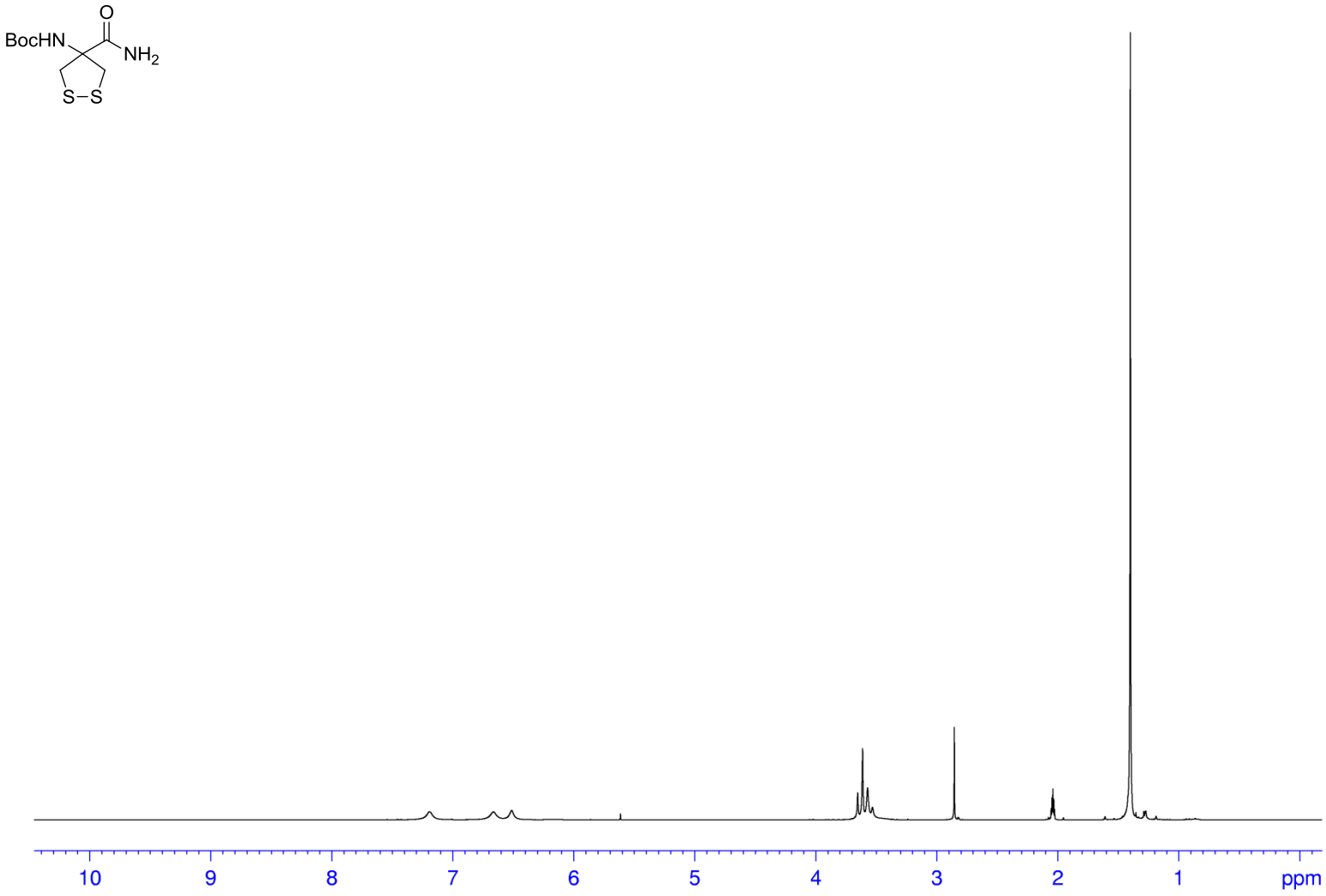
4-((*tert*-Butoxycarbonyl)amino)-1,2-dithiolane-4-carboxylic acid; 100 MHz, acetone-D_6



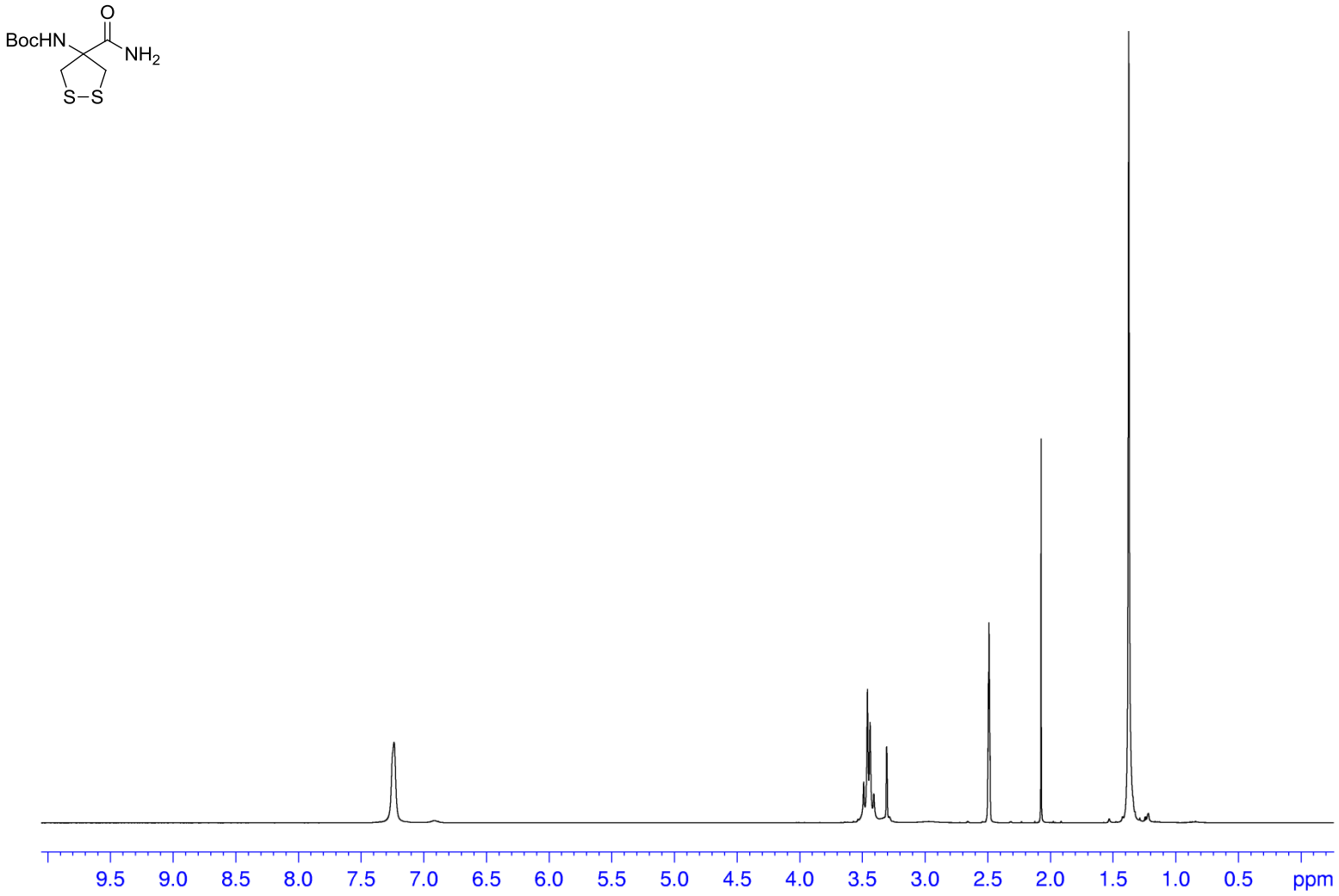
4-((*tert*-Butoxycarbonyl)amino)-1,2-dithiolane-4-carboxylic acid; 100 MHz, DMSO-D_6



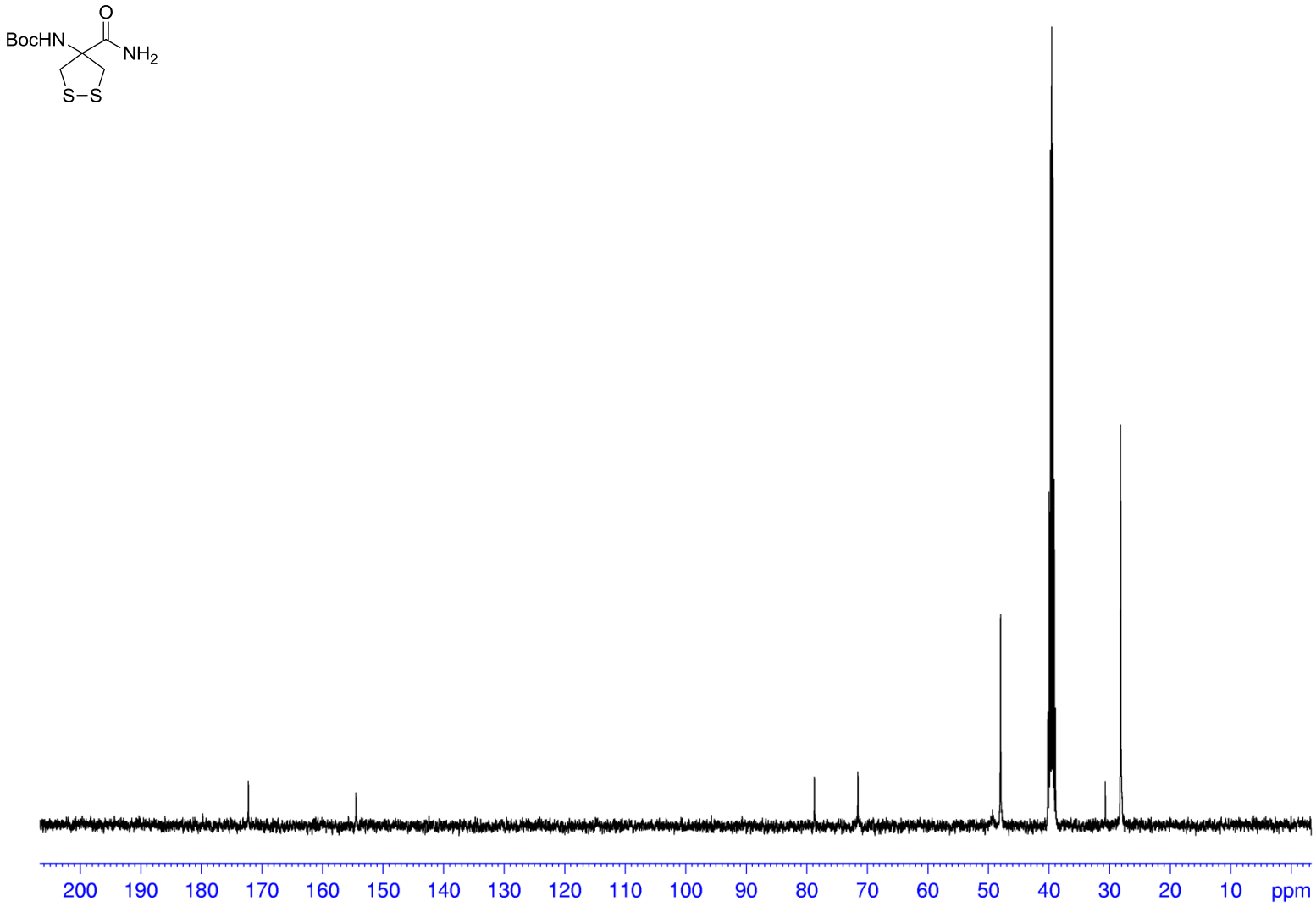
tert-Butyl (4-carbamoyl-1,2-dithiolan-4-yl)carbamate; 300 MHz, acetone-D_6



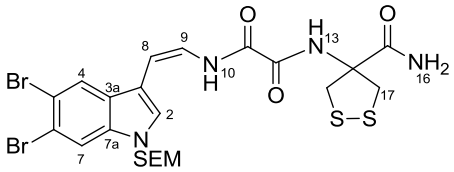
tert-Butyl (4-carbamoyl-1,2-dithiolan-4-yl)carbamate; 400 MHz, DMSO-D_6

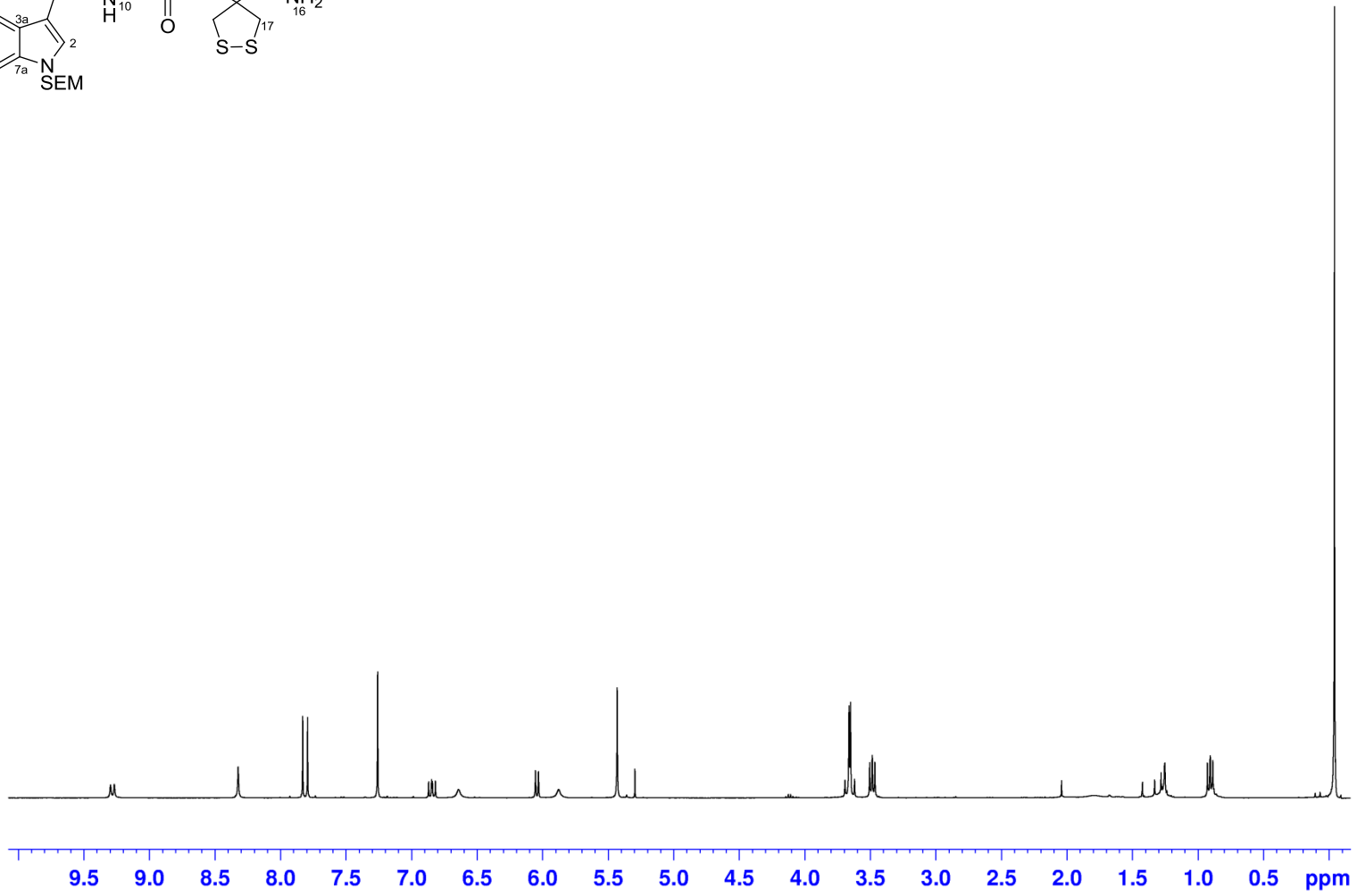


tert-Butyl (4-carbamoyl-1,2-dithiolan-4-yl)carbamate; 100 MHz, DMSO-D_6

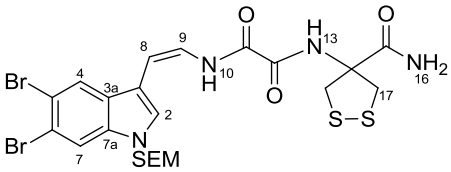


(*Z*)-N^1-(4-Carbamoyl-1,2-dithiolan-4-yl)-N^2-(2-(5,6-dibromo-1-((2-trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)oxalamide *or* SEM-protected kottamide E **14**; 400 MHz, $CDCl_3$

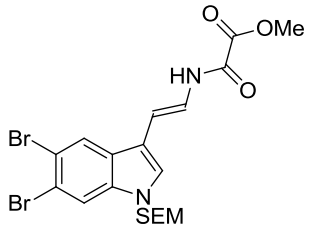


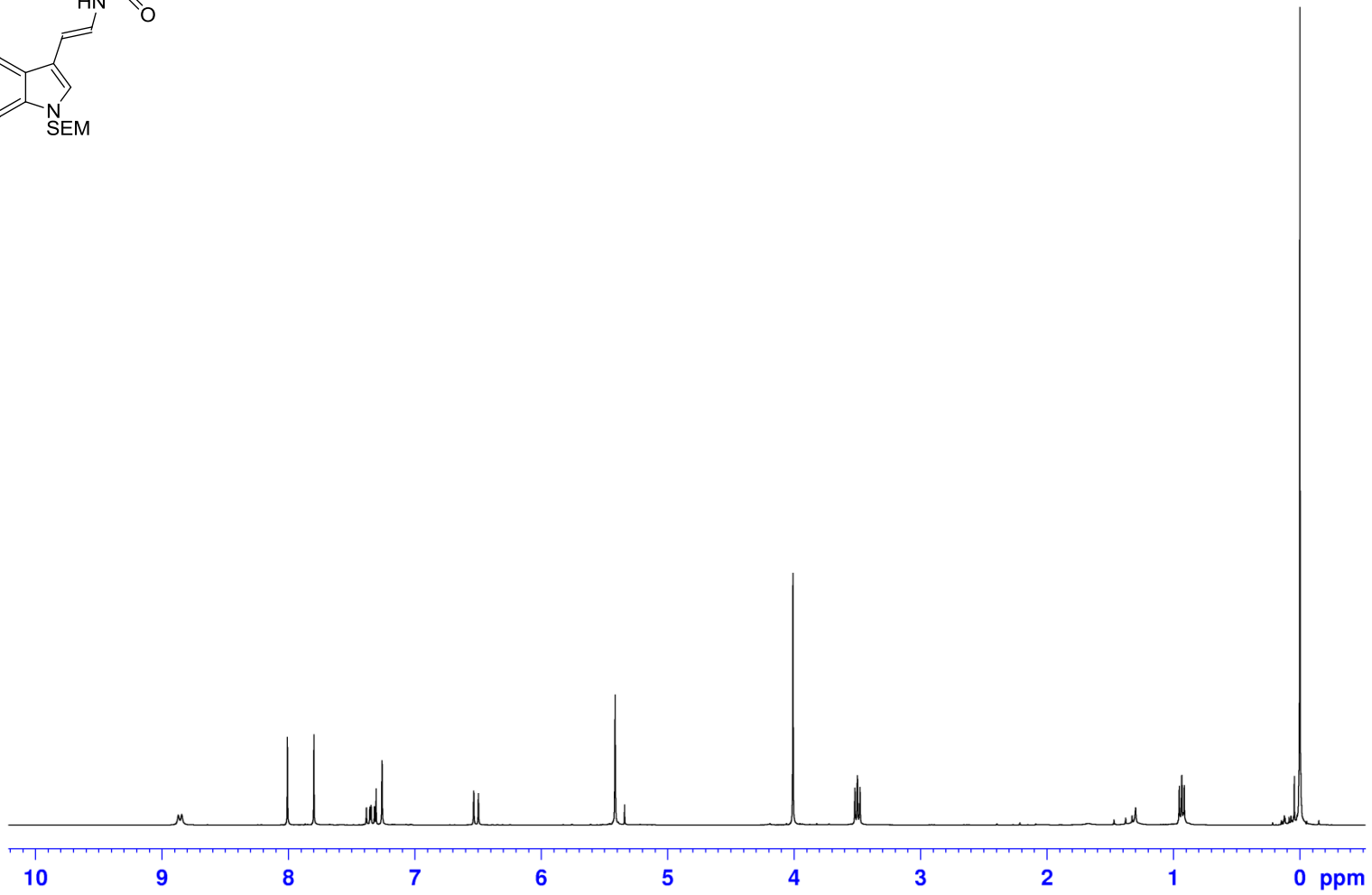


(*Z*)-N^1-(4-Carbamoyl-1,2-dithiolan-4-yl)-N^2-(2-(5,6-dibromo-1-((2-trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)oxalamide *or* SEM-protected kottamide E **14**; 100 MHz, $CDCl_3$

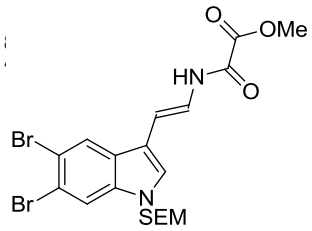


(*E*)-Methyl 2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl) amino)-2-oxoacetate **16**; 400 MHz, $CDCl_3$

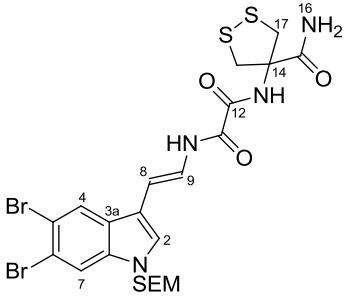




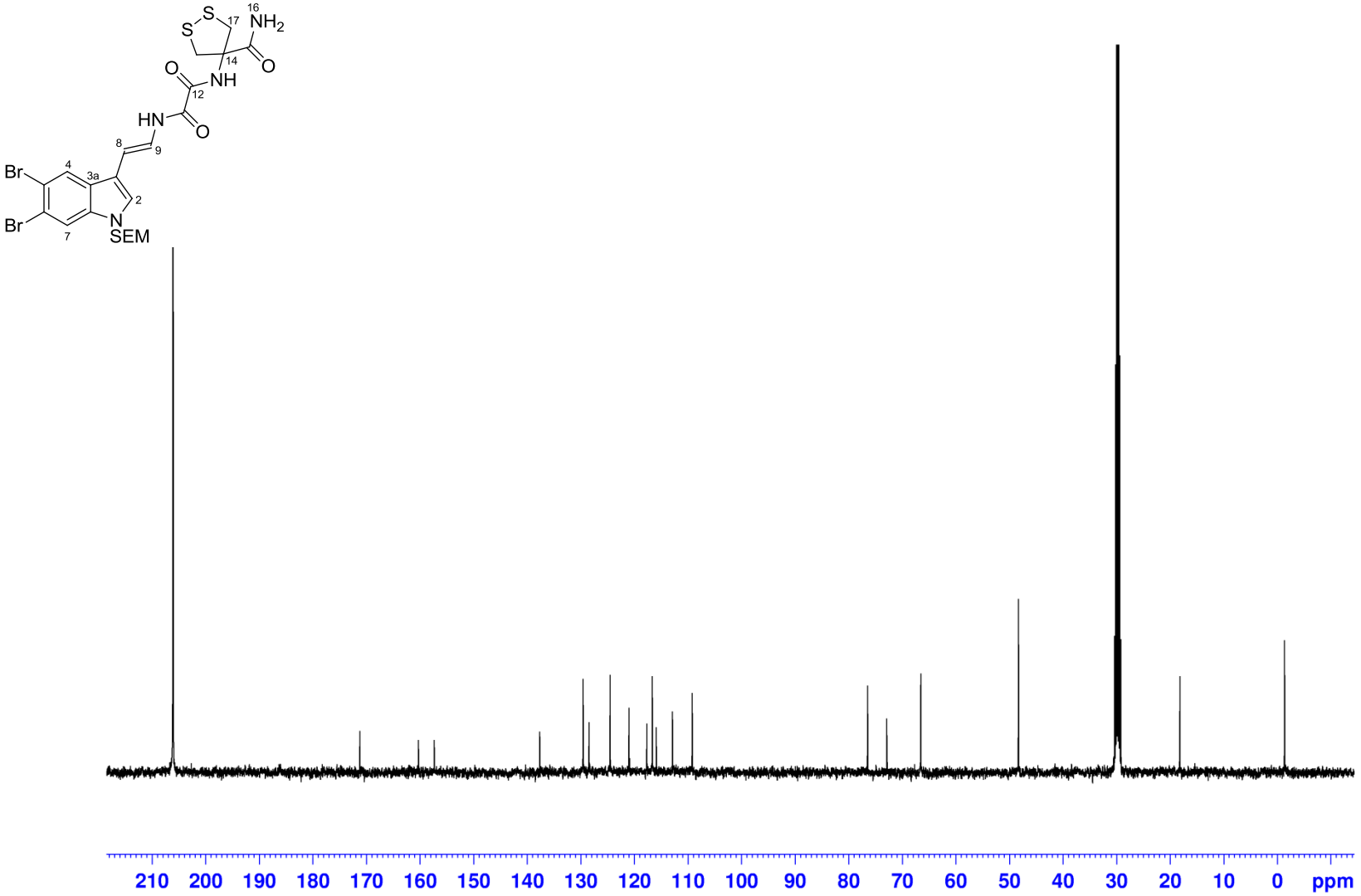
(*E*)-Methyl 2-((2-(5,6-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl) amino)-2-oxoacetate **16**; 100 MHz, $CDCl_3$



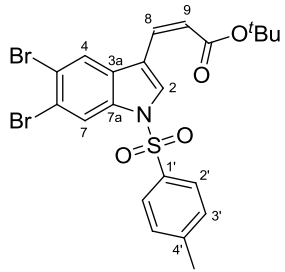
(*E*)-N^1-(4-Carbamoyl-1,2-dithiolan-4-yl)-N^2-(2-(5,6-dibromo-1-((2-trimethylsilyl)ethoxy) methyl)-1*H*-indol-3-yl)vinyl)oxalamide *or* SEM-protected (*E*)-kottamide E **(*E*)-14**; 300 MHz, acetone-D_6



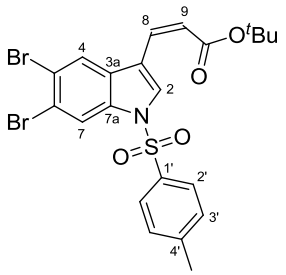
(*E*)-N^1-(4-Carbamoyl-1,2-dithiolan-4-yl)-N^2-(2-(5,6-dibromo-1-((2-trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)vinyl)oxalamide *or* SEM-protected (*E*)-kottamide E **(*E*)-14**; 100 MHz, acetone-D_6



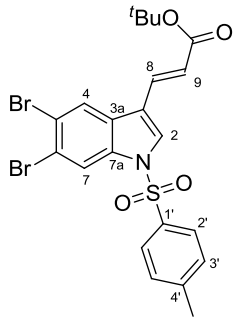
(*Z*)-*tert*-Butyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate **17**; 100 MHz, $CDCl_3$



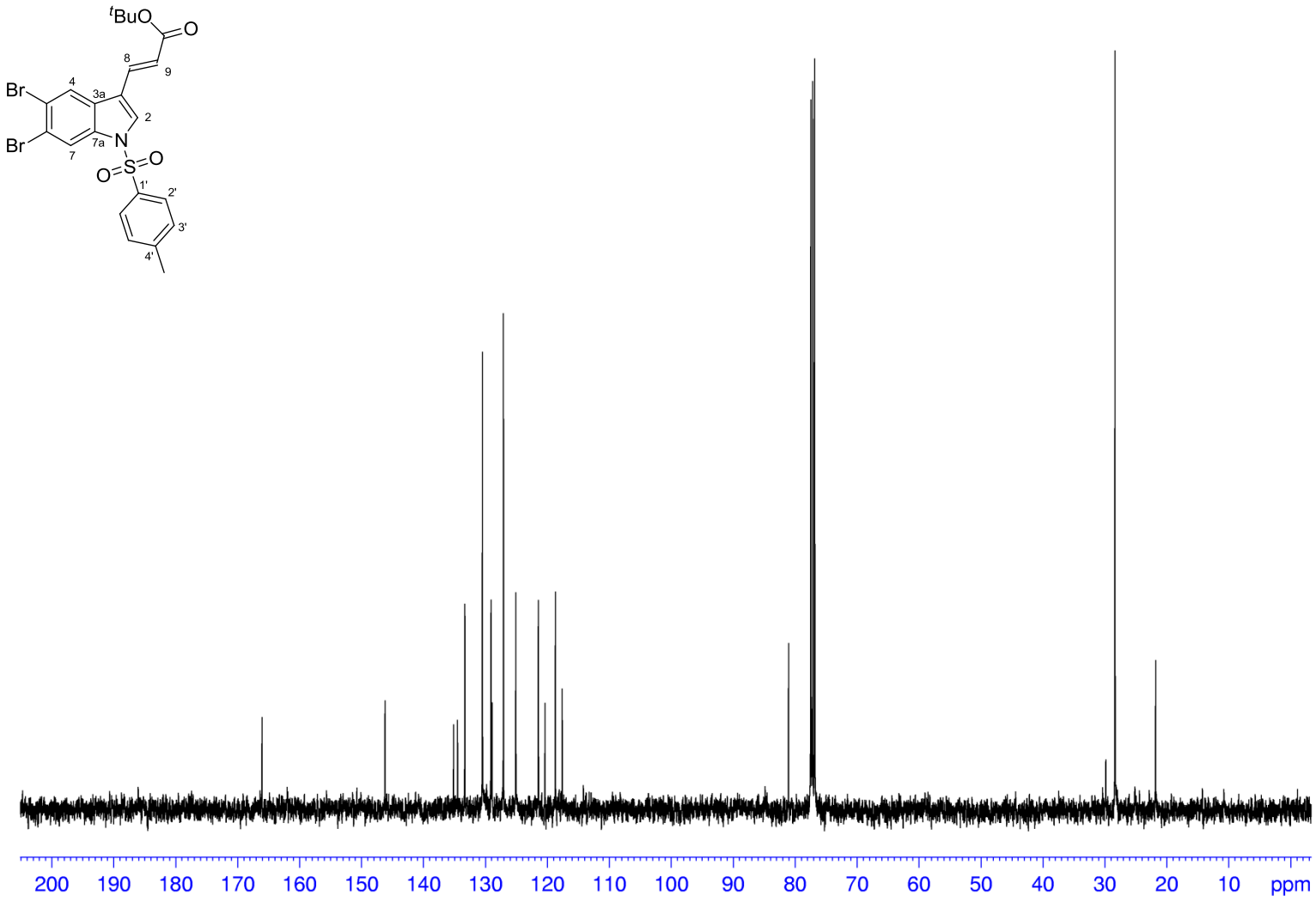
(*Z*)-*tert*-Butyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate **17**; 100 MHz, $CDCl_3$



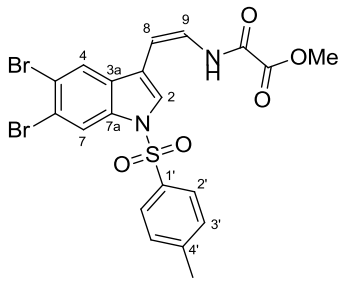
(*E*)-*tert*-Butyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate **(*E*)-17**; 300 MHz, $CDCl_3$



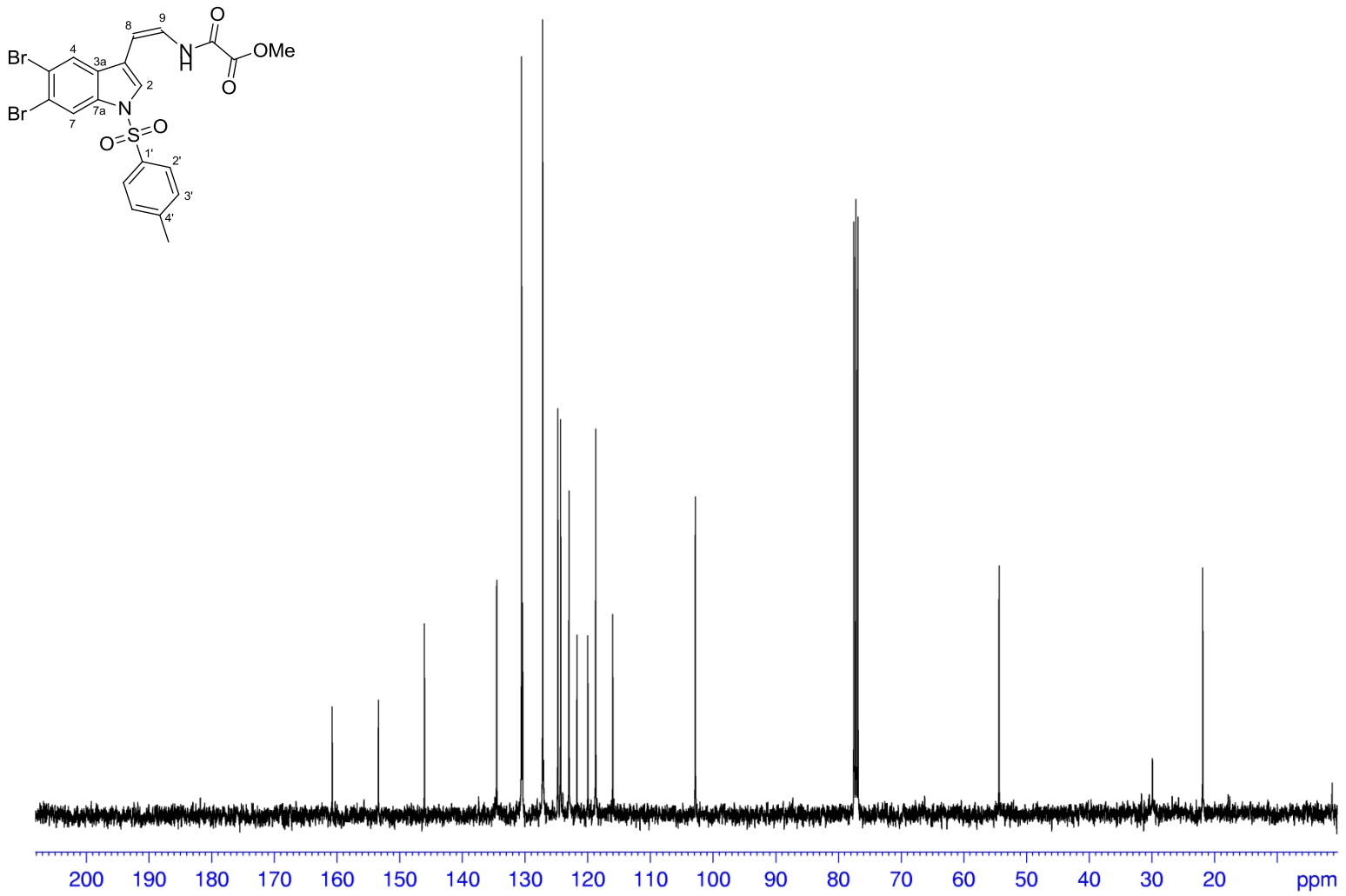
(*E*)-*tert*-Butyl 3-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)acrylate **(*E*)-17**; 100 MHz, $CDCl_3$



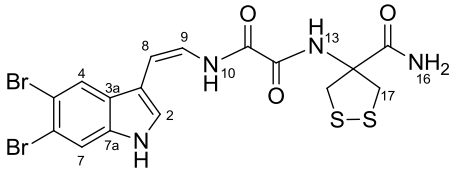
(*Z*)-Methyl 2-((2-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetate **20**; 400 MHz, $CDCl_3$



(*Z*)-Methyl 2-((2-(5,6-dibromo-1-tosyl-1*H*-indol-3-yl)vinyl)amino)-2-oxoacetate **20**; 100 MHz, $CDCl_3$



Kottamide E **1** after semi-preparative HPLC purification; 600 MHz, DMSO-D_6 [impurities indicated with *]



Kottamide E **1** after semi-preparative HPLC purification; 151 MHz, DMSO-D_6 [impurities indicated with *]