

Supporting Information for
Total Synthesis of Giffonin H by Fluoride-Catalyzed Macrocyclization

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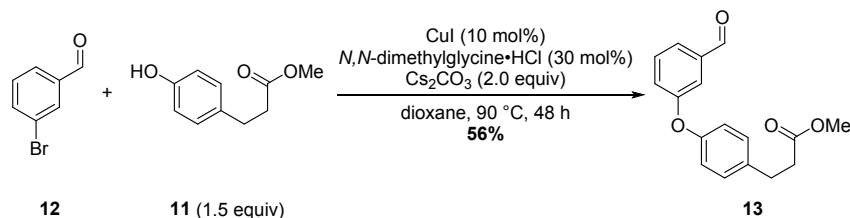
1. General Information

All reagents were purchased from chemical sources like Sigma Aldrich, Tokyo Chemical Industry (TCI), Alfa Aesar unless otherwise noted and they were used as received. Reactions were conducted under nitrogen atmosphere in solvents purchased from Sigma Aldrich and Alfa Aesar. Only THF was distilled over sodium and benzophenone. Thin layer chromatography (TLC) was carried out using Merck TLC glass plate coated with fluorescent indicator F254 (60 Å porosity). Purifications were carried out using ZEOCHEM ZEOprep 60 silica gel (60Å, 40-63 µm). NMR spectra were recorded on Bruker AV-600 spectrometer operating respectively at 600 MHz for ^1H NMR and 151 MHz for ^{13}C NMR. Chemical shifts are reported as δ in parts per million (ppm) downfield from tetramethylsilane, using the residual protiosolvent or tetramethylsilane as reference ($\delta_{\text{H}} = 7.26$ ppm, $\delta_{\text{C}} = 77.16$ ppm for CDCl_3 ; $\delta_{\text{H}} = 3.31$ ppm, $\delta_{\text{C}} = 49.00$ ppm for CD_3OD). Coupling constants (J) are reported in hertz (Hz). Spin multiplicities were reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; dddd, doublet of doublet of doublet of doublets; m, multiplet. Melting points were recorded by using Optimelt melting point apparatus. High-resolution mass spectra (HRMS) were obtained by the Q-TOF mass spectrometry. IR spectra were obtained from a Bruker Tensor 27 FT-IR spectrometer with a diamond ATR module.

2. Experimental procedures

2.1. Model System for Fluoride-Mediated Cyclization Reaction

Synthesis of methyl 3-(4-(3-formylphenoxy)phenyl)propanoate **13**



3-Bromobenzaldehyde **12** (3.5 mL, 30 mmol), phenol **11** (8.1 g, 45 mmol), copper (I) iodide (571 mg, 3.0 mmol), *N,N*-dimethylglycine hydrochloride (1.3 g, 9.0 mmol), and cesium carbonate (19.6 g, 60 mmol) were added into oven-dried flask and the flask was evacuated and back-filled with nitrogen three times. Dry 1,4-dioxane (120 mL) was then added to the flask and the resulting mixture was stirred at 90 °C for 48 h. The reaction was cooled down to room temperature and filtered through a pad of celite and the filtrate was concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:6, v/v)) to afford product **13** (4.78 g, 56%) as a colorless liquid. *R*_f = 0.43, ethyl acetate/hexane (1:3, v/v).

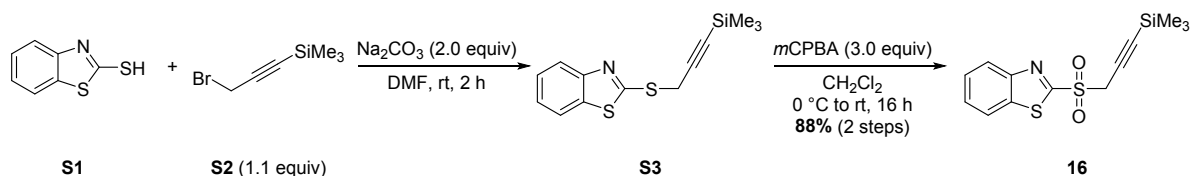
¹H NMR (600 MHz, Chloroform-*d*) δ 9.95 (s, 1H), 7.59 (dt, *J* = 7.5, 1.3 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 2.5, 1.4 Hz, 1H), 7.27 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H), 7.22 – 7.19 (m, 2H), 6.98 – 6.95 (m, 2H), 3.69 (s, 3H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H)

¹³C NMR (150 MHz, Chloroform-*d*) δ 191.6, 173.2, 158.6, 154.5, 138.0, 136.5, 130.4, 129.9, 124.6, 124.4, 119.7, 117.8, 51.7, 35.7, 30.2

HRMS-ESI *m/z* calculated for C₁₇H₁₆O₄Na [M+Na]⁺ 307.0941, found 307.0936

IR 3034, 2951, 2843, 2732, 1734, 1698, 1585, 1506, 1481, 1448, 1247, 1212, 1168, 1103, 1017, 943, 841, 792, 736, 683 cm⁻¹

Synthesis of BT-sulfone **16**



To a stirred solution of thiol **S1** (14.0 g, 83.5 mmol) in DMF (200 mL) was added sodium carbonate (17.7 g, 167 mmol) at room temperature. Propargyl bromide **S2** (15 mL, 91.8 mmol) was then added to the flask and the resulting mixture was stirred at room temperature for 2 h. The reaction was diluted with distilled water (1 L), extracted with ethyl acetate (twice). The organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated on a rotary evaporator and on a high vacuum. The crude material was used for the next step without further purification.

To a stirred solution of sulfide **S3** (23.2 g, 83.5 mmol) in dichloromethane (500 mL) was added *meta*-chloroperoxybenzoic acid (61.7 g, 250 mmol) at 0 °C. The reaction was allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was washed successively with saturated sodium thiosulfate solution (2 x 400 mL), saturated sodium bicarbonate solution (2 x 400 mL), and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:8, v/v)) to afford product **16** (22.7 g, 88%) as an amorphous white solid. *R*_f = 0.4, ethyl acetate/hexane (1:5, v/v).

mp: 118-120 °C

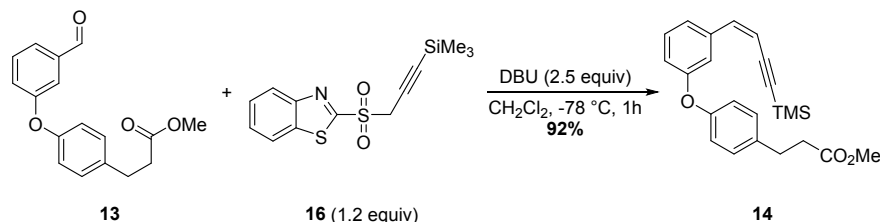
^1H NMR (600 MHz, Chloroform-*d*) δ 8.26 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H), 8.04 (ddd, J = 8.0, 1.4, 0.7 Hz, 1H), 7.66 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.62 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 4.40 (s, 2H), 0.03 (s, 9H)

^{13}C NMR (150 MHz, CDCl_3) δ 163.9, 152.5, 137.2, 128.3, 127.7, 125.7, 122.2, 95.7, 90.6, 48.5, -0.6

HRMS-ESI m/z calculated for $\text{C}_{13}\text{H}_{16}\text{NO}_2\text{S}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 310.0386, found 310.0374

IR 3067, 2960, 2903, 2186, 1554, 1471, 1421, 1388, 1343, 1317, 1251, 1165, 1141, 1086, 1043, 1026, 845, 762, 746, 730, 705, 692, 652, 611 cm^{-1}

Synthesis of methyl (Z)-3-(4-(3-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenoxy)phenyl)propanoate **14**



Starting aldehyde **13** (76 mg, 0.267 mmol) and BT-sulfone **16** (99.2 mg, 0.320 mmol) were added to oven-dried flask and dry dichloromethane (3 mL) was added. The resulting mixture was cooled down to $-78\text{ }^\circ\text{C}$ and DBU (92.0 μL , 0.668 mmol) was added to the reaction mixture. The reaction was stirred at $-78\text{ }^\circ\text{C}$ for 1 h and was allowed to warm up to room temperature. 1N HCl (3 mL) was added and the biphasic mixture was extracted with dichloromethane (twice). The combined organic extracts were washed with water and brine and dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:10, v/v)) to afford product **14** (93 mg, 92%) as a yellow liquid. R_f = 0.5, ethyl acetate/hexane (1:6, v/v).

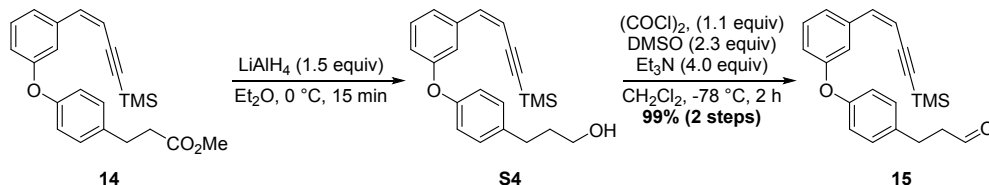
^1H NMR (600 MHz, Chloroform-*d*) δ 7.68 (t, J = 2.1 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.17 – 7.12 (m, 2H), 6.95 – 6.89 (m, 3H), 6.60 (d, J = 12.1 Hz, 1H), 5.71 (d, J = 12.1 Hz, 1H), 3.68 (s, 3H), 2.92 (t, J = 7.8 Hz, 2H), 2.62 (t, J = 7.8 Hz, 2H), 0.18 (s, 9H)

^{13}C NMR (150 MHz, Chloroform-*d*) δ 173.4, 157.0, 156.0, 139.1, 138.2, 135.2, 129.6, 129.5, 124.2, 119.5, 119.4, 118.6, 108.2, 103.4, 103.2, 51.7, 36.0, 30.3, -0.3

HRMS-ESI m/z calculated for $\text{C}_{23}\text{H}_{26}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 401.1543, found 401.1536

IR 3031, 2956, 2140, 1738, 1600, 1573, 1506, 1487, 1439, 1364, 1250, 1169, 1104, 1026, 934, 844, 798, 761, 688 cm^{-1}

Synthesis of (Z)-3-(4-(3-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenoxy)phenyl)propanal **15**



Starting ester **14** (3.1 g, 8.19 mmol) was dissolved in dry ether (50 mL) and the solution was cooled down to $0\text{ }^\circ\text{C}$ with ice bath. Lithium aluminium hydride (466 mg, 12.3 mmol) was added to the flask in one portion. The resulting mixture was stirred at $0\text{ }^\circ\text{C}$ for 15 min and quenched with sodium sulfate decahydrate at $0\text{ }^\circ\text{C}$ and stirred for 30 min. The slurry was filtered and washed with diethyl ether three times. The filtrate was concentrated on a rotary evaporator and on a high vacuum. The residue was used for the next step without further purification.

Oxalyl chloride (773 μL , 9.01 mmol) diluted in dry dichloromethane (15 mL) was cooled down to $-78\text{ }^\circ\text{C}$ and

dimethyl sulfoxide (1.34 mL, 18.8 mmol) in dry dichloromethane (19 mL) was added dropwise to the flask. The resulting mixture was stirred at -78 °C for 30 min. The crude alcohol in dry dichloromethane (9 mL) was added dropwise to the flask and the resulting mixture was stirred at -78 °C for 30 min. Triethylamine (4.57 mL, 32.76 mmol) was added to the reaction mixture and the reaction was stirred at -78 °C for 30 min and at room temperature for 30 min. The reaction was diluted with dichloromethane and washed with 1N HCl, saturated sodium bicarbonate solution, water, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:6, v/v)) to afford product **15** (2.83 g, 99%) as a colorless liquid. R_f = 0.5, ethyl acetate/hexane (1:3, v/v).

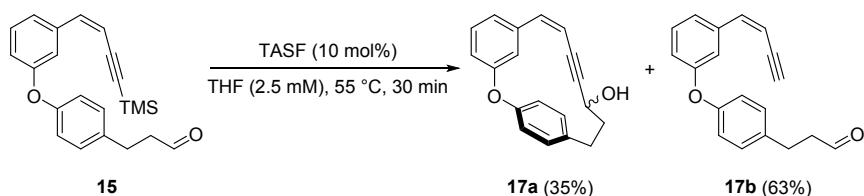
^1H NMR (600 MHz, Chloroform-*d*) δ 9.79 (t, J = 1.5 Hz, 1H), 7.70 (t, J = 2.0 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.14 – 7.10 (m, 2H), 6.93 – 6.89 (m, 3H), 6.59 (d, J = 12.1 Hz, 1H), 5.70 (d, J = 12.1 Hz, 1H), 2.91 (t, J = 7.5 Hz, 2H), 2.74 (t, J = 7.5 Hz, 2H), 0.17 (s, 9H)

^{13}C NMR (150 MHz, Chloroform-*d*) δ 201.5, 156.9, 156.0, 139.1, 138.2, 135.0, 129.6, 129.5, 124.3, 119.5, 119.4, 118.6, 108.2, 103.4, 103.2, 45.4, 27.4, -0.3

HRMS-ESI m/z calculated for $\text{C}_{22}\text{H}_{25}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 349.1618, found 349.1631

IR 3032, 2958, 2898, 2822, 2723, 2139, 1724, 1600, 1572, 1506, 1487, 1439, 1408, 1249, 1169, 1140, 1106, 1023, 933, 841, 799, 760, 687 cm^{-1}

Synthesis of cyclic product **17a**



Starting cyclic precursor **15** (17.5 mg, 52 μmol) was dissolved in dry tetrahydrofuran (21 mL, 2.5 mM) and the resulting solution was allowed to warm up to 55 °C. TASF (1.4 mg, 5.2 μmol) dissolved in dry DMF (0.1 mL) was added to the reaction mixture quickly. The resulting mixture was stirred at 55 °C for 30 min and cooled down to room temperature. The reaction was quenched with 1N HCl (1 mL) and stirred at room temperature for 10 min. The reaction mixture was diluted with water and extracted with ethyl acetate (twice). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (gradient, ethyl acetate/hexane (1:5, v/v)) to ethyl acetate/hexane (1:3, v/v) to afford product **17a** (5 mg, 35%) as a white solid and **17b** (9 mg, 63%) as a yellow liquid. R_f (**17a**) = 0.3, R_f (**17b**) = 0.48, ethyl acetate/hexane (1:3, v/v).

- data for **17a**:

mp: 164-166 °C

^1H NMR (600 MHz, Chloroform-*d*) δ 7.37 (dd, J = 8.2, 2.2 Hz, 1H), 7.29 (dd, J = 8.1, 2.2 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.13 – 7.08 (m, 2H), 7.07 (dd, J = 8.1, 2.5 Hz, 1H), 6.96 (dd, J = 2.6, 1.6 Hz, 1H), 6.72 (dt, J = 7.5, 1.4 Hz, 1H), 6.28 (d, J = 12.3 Hz, 1H), 5.58 (dd, J = 12.3, 1.9 Hz, 1H), 4.52 (d, J = 8.3 Hz, 1H), 3.06 (dt, J = 13.4, 4.5 Hz, 1H), 2.71 (ddd, J = 13.3, 11.1, 4.8 Hz, 1H), 2.22 – 2.11 (m, 2H)

^{13}C NMR (150 MHz, Chloroform-*d*) δ 161.5, 154.0, 138.2, 136.7, 135.6, 130.8, 130.4, 129.3, 124.3, 123.4, 123.2, 117.2, 111.8, 106.2, 100.7, 83.3, 63.6, 39.3, 33.2

HRMS-ESI m/z calculated for $\text{C}_{19}\text{H}_{16}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 299.1103, found 299.1096

IR 3351, 3055, 2927, 2858, 1594, 1575, 1575, 1505, 1484, 1440, 1413, 1328, 1299, 1265, 1235, 1210, 1165, 1154, 1101, 1035, 998, 972, 943, 926, 876, 850, 831, 795, 740, 689 cm^{-1}

- data for **17b**

^1H NMR (600 MHz, Chloroform-*d*) δ 9.83 (t, J = 1.4 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.18 – 7.14 (m, 2H), 6.99 – 6.94 (m, 3H), 6.66 (d, J = 12.0 Hz, 1H), 5.67 (dd, J = 12.0, 2.7 Hz, 1H), 3.24 (dd, J = 2.7, 1.0 Hz, 1H), 2.95 (t, J = 7.5 Hz, 2H), 2.80 – 2.76 (m, 2H)

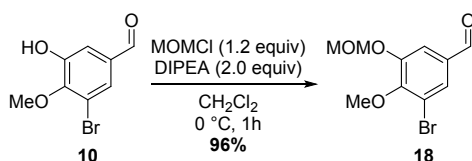
^{13}C NMR (150 MHz, Chloroform-*d*) δ 201.5, 157.5, 155.3, 139.9, 137.7, 135.4, 129.6, 129.5, 123.8, 119.5, 119.0, 118.0, 107.0, 84.8, 81.6, 45.4, 27.4

HRMS-ESI m/z calculated for $\text{C}_{19}\text{H}_{17}\text{O}_2$ $[\text{M}+\text{H}]^+$ 277.1223, found 277.1194.

IR 3286, 3032, 2925, 2853, 2727, 2090, 1722, 1600, 1573, 1506, 1486, 1441, 1407, 1389, 1248, 1168, 1141, 1105, 1058, 1016, 986, 920, 883, 832, 798, 739, 688 cm^{-1}

2.2 Total Synthesis of Giffonin H

Synthesis of 3-bromo-4-methoxy-5-(methoxymethoxy)benzaldehyde **18**



3-Bromo-5-hydroxy-4-methoxybenzaldehyde **10** (10.7 g, 46.3 mmol) and dry dichloromethane (110 mL) were added to the oven-dried flask and *N,N*-diisopropylethylamine (16.1 mL, 92.6 mmol) was then added. The resulting yellow mixture was cooled down to $0\text{ }^\circ\text{C}$ and chloromethyl methyl ether (4.22 mL, 55.6 mmol) was added dropwise to the reaction and the resulting mixture was stirred at $0\text{ }^\circ\text{C}$ for 1 h. The reaction was diluted with dichloromethane and washed with 1N HCl, saturated sodium bicarbonate solution, water, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:6, v/v)) to afford product **18** (12.2 g, 96%) as a colorless liquid. R_f = 0.55, ethyl acetate/hexane (1:3, v/v).

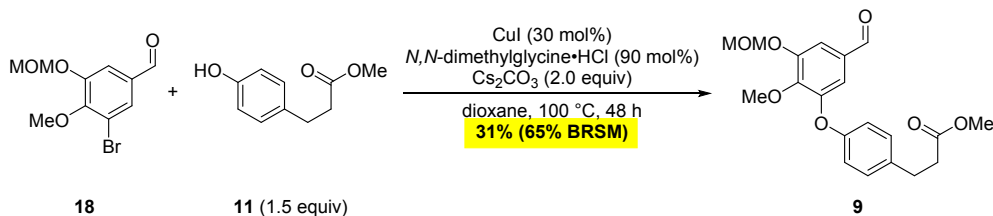
^1H NMR (600 MHz, Chloroform-*d*) δ 9.84 (s, 1H), 7.73 (d, J = 1.9 Hz, 1H), 7.61 (d, J = 1.9 Hz, 1H), 5.29 (s, 2H), 3.97 (s, 3H), 3.53 (s, 3H)

^{13}C NMR (150 MHz, Chloroform-*d*) δ 189.7, 152.3, 151.6, 133.1, 128.6, 118.3, 115.5, 95.2, 61.0, 56.6

HRMS-ESI m/z calculated for $\text{C}_{10}\text{H}_{12}\text{BrO}_4$ $[\text{M}+\text{H}]^+$ 274.9913, found 274.9911

IR 2940, 2831, 2729, 2595, 1698, 1589, 1566, 1483, 1429, 1378, 1277, 1234, 1205, 1156, 1129, 1084, 1012, 951, 925, 860, 839, 817, 786, 747, 665 cm^{-1}

Synthesis of methyl 3-(4-(5-formyl-2-methoxy-3-(methoxymethoxy)phenoxy)phenyl)propanoate **9**



Starting aryl bromide **18** (10.7 g, 38.9 mmol), phenol **11** (10.5 g, 58.3 mmol), copper (I) iodide (2.22 g, 11.7 mmol), *N,N*-dimethylglycine hydrochloride (4.89 g, 35.0 mmol), and cesium carbonate (25.6 g, 77.8 mmol) were added into oven-dried flask and the flask was evacuated and back-filled with nitrogen (three times). Dry dioxane (160 mL) was then added to the flask and the resulting mixture was stirred at $100\text{ }^\circ\text{C}$ for 48 h. The reaction was cooled down to room temperature and filtered through a pad of celite and the filtrate was concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:3, v/v)) to afford

product **9** (4.5 g, 31% (65%, BRSM)) as a colorless liquid with recovered starting material (7.4 g, 26.9 mmol). R_f = 0.23, ethyl acetate/hexane (1:3, v/v).

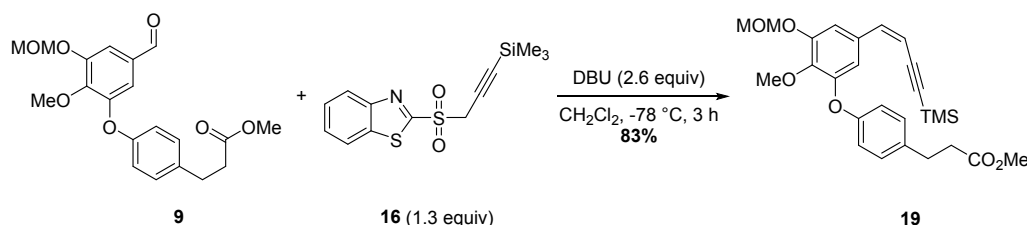
^1H NMR (600 MHz, Chloroform- d) δ 9.77 (s, 1H), 7.47 (d, J = 1.9 Hz, 1H), 7.20 – 7.16 (m, 2H), 7.14 (d, J = 1.9 Hz, 1H), 6.95 – 6.91 (m, 2H), 5.31 (s, 2H), 3.96 (s, 3H), 3.67 (s, 3H), 3.54 (s, 3H), 2.94 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H)

^{13}C NMR (150 MHz, Chloroform- d) δ 190.4, 173.2, 155.3, 151.7, 150.6, 146.9, 135.9, 131.8, 129.7, 118.2, 115.5, 112.4, 95.3, 61.3, 56.5, 51.6, 35.7, 30.2

HRMS-ESI m/z calculated for $\text{C}_{20}\text{H}_{22}\text{O}_7\text{Na}$ $[\text{M}+\text{Na}]^+$ 397.1254, found 397.1246

IR 2950, 2832, 2732, 2634, 1735, 1695, 1582, 1506, 1436, 1406, 1383, 1323, 1214, 1154, 1128, 1097, 1045, 999, 924, 843, 736, 648 cm^{-1}

Synthesis of methyl (Z)-3-(4-(2-methoxy-3-(methoxymethoxy)-5-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenoxy)phenyl)propanoate **19**



Starting aldehyde **9** (2.3 g, 6.14 mmol) and BT-sulfone **16** (2.47 g, 7.99 mmol) were added to oven-dried flask and dry dichloromethane (60 mL) was added. The resulting mixture was cooled down to -78°C and DBU (2.39 mL, 16.0 mmol) was added to the reaction mixture. The reaction was stirred at -78°C for 3 h and was allowed to warm up to room temperature. 1N HCl solution was added and the biphasic mixture was extracted with dichloromethane (twice). Organic phase was washed with water and brine and dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:8, v/v)) to afford **19** (2.39 g, 83%) product as a yellow liquid. R_f = 0.45, ethyl acetate/hexane (1:3, v/v).

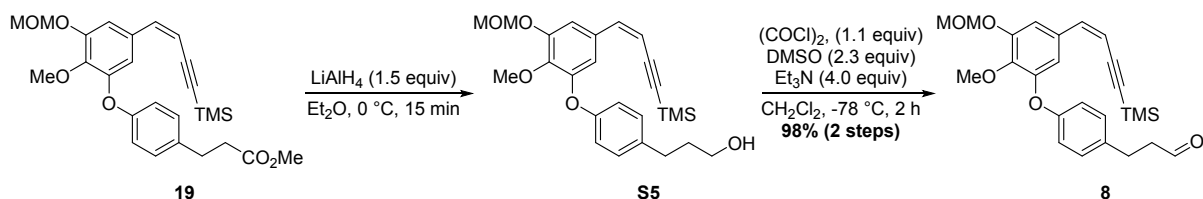
^1H NMR (600 MHz, Chloroform- d) δ 7.55 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.13 – 7.10 (m, 2H), 6.89 – 6.87 (m, 2H), 6.46 (d, J = 12.1 Hz, 1H), 5.64 (d, J = 12.1 Hz, 1H), 5.25 (s, 2H), 3.84 (s, 3H), 3.65 (s, 3H), 3.53 (s, 3H), 2.90 (t, J = 7.8 Hz, 2H), 2.60 (td, J = 8.4, 7.3 Hz, 2H), 0.14 (s, 9H)

^{13}C NMR (150 MHz, Chloroform- d) δ 173.3, 156.6, 151.0, 148.9, 142.8, 138.4, 134.6, 132.3, 129.5, 116.9, 116.3, 113.2, 107.1, 103.2, 103.1, 95.5, 61.2, 56.5, 51.6, 35.9, 30.2

HRMS-ESI m/z calculated for $\text{C}_{26}\text{H}_{33}\text{O}_6\text{Si}$ $[\text{M}+\text{H}]^+$ 469.2041, found 469.2018

IR 2955, 2830, 2138, 1738, 1602, 1570, 1506, 1434, 1403, 1323, 1250, 1217, 1157, 1100, 1049, 1004, 975, 927, 845, 761, 739, 702, 640 cm^{-1}

Synthesis of (Z)-3-(4-(2-methoxy-3-(methoxymethoxy)-5-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenoxy)-phenyl)propanal **8**



Starting ester **9** (1.73g, 3.69 mmol) was dissolved in dry ether (20 mL) and the solution was cooled down to 0 °C with ice bath. Lithium aluminium hydride (210 mg, 5.53 mmol) was added to the flask in one portion. The resulting mixture was stirred at 0 °C for 15 min and quenched with sodium sulfate decahydrate at 0 °C and stirred for 30 min. The slurry was filtered and washed with diethyl ether three times. The filtrate was concentrated on a rotary evaporator and on a high vacuum. The residue was used for the next step without further purification.

Oxalyl chloride (348 µL, 4.06 mmol) diluted in dry dichloromethane (8 mL) was cooled down to -78 °C and dimethyl sulfoxide (602 µL, 8.48 mmol) in dry dichloromethane (9 mL) was added dropwise to the flask. The resulting mixture was stirred at -78 °C for 30 min. The crude alcohol in dry dichloromethane (4 mL) was added dropwise to the flask and the resulting mixture was stirred at -78 °C for 30 min. Triethylamine (2.06 mL, 14.8 mmol) was added to the reaction mixture and the reaction was stirred at -78 °C for 30 min and at room temperature for 30 min. The reaction was diluted with dichloromethane and washed with 1N HCl, saturated sodium bicarbonate solution, water, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:4, v/v)) to afford product **8** (1.59 g, 98%) as a colorless liquid. R_f = 0.5, ethyl acetate/hexane (1:2, v/v).

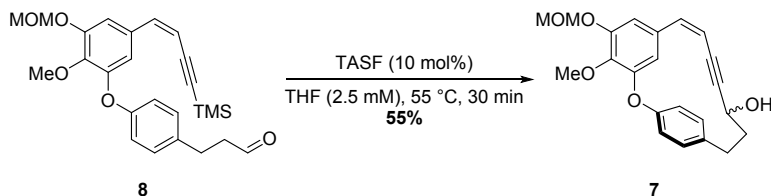
^1H NMR (600 MHz, Chloroform-*d*) δ 9.80 (t, J = 1.4 Hz, 1H), 7.54 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.12 – 7.09 (m, 2H), 6.90 – 6.87 (m, 2H), 6.46 (d, J = 12.1 Hz, 1H), 5.65 (d, J = 12.1 Hz, 1H), 5.25 (s, 2H), 3.84 (s, 3H), 3.53 (s, 3H), 2.91 (t, J = 7.5 Hz, 2H), 2.75 (td, J = 7.6, 1.5 Hz, 2H), 0.14 (s, 9H)

^{13}C NMR (150 MHz, Chloroform-*d*) δ 201.6, 156.6, 151.0, 148.8, 142.8, 138.4, 134.4, 132.3, 129.5, 117.0, 116.2, 113.2, 107.2, 103.2, 95.5, 61.3, 56.5, 45.5, 27.4, -0.3

HRMS-ESI m/z calculated for $\text{C}_{25}\text{H}_{31}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^+$ 439.1936, found 439.1942

IR 2967, 2901, 2829, 2725, 2138, 1724, 1601, 1569, 1505, 1432, 1402, 1322, 1249, 1216, 1157, 1136, 1099, 1048, 1004, 974, 926, 844, 761, 702, 640 cm^{-1}

Synthesis of cyclic product **7**



Starting cyclic precursor **8** (11.5 mg, 26 µmol) was dissolved in dry tetrahydrofuran (10.5 mL, 2.5 mM) and the resulting solution was allowed to warm up to 55 °C. TASf (0.7 mg, 2.6 µmol) dissolved in dry DMF (50 µL) was added to the reaction mixture quickly. The resulting mixture was stirred at 55 °C for 30 min and cooled down to room temperature. The reaction was quenched with 1N HCl (1 mL) and stirred at room temperature for 10 min. The reaction mixture was diluted with water and extracted with ethyl acetate (twice). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:3, v/v)) to afford product **7** (5.3 mg, 55%) as a white solid. R_f = 0.2, ethyl acetate/hexane (2:5, v/v).

mp: 123-125 °C

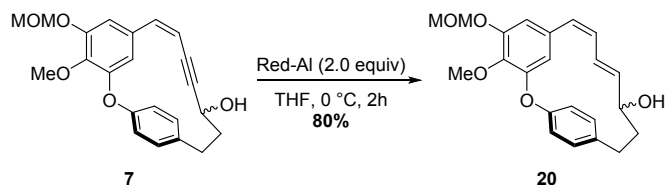
^1H NMR (600 MHz, Chloroform-*d*) δ 7.36 (dd, J = 8.2, 2.2 Hz, 1H), 7.28 (dd, J = 8.1, 2.3 Hz, 1H), 7.11 (dd, J = 8.2, 2.4 Hz, 1H), 7.08 (dd, J = 8.1, 2.5 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.16 (d, J = 12.3 Hz, 1H), 5.51 (dd, J = 12.3, 1.9 Hz, 1H), 5.21 (s, 2H), 4.53 – 4.49 (m, 1H), 4.06 (s, 3H), 3.52 (s, 3H), 3.06 (dt, J = 13.4, 4.5 Hz, 1H), 2.70 (ddd, J = 13.4, 11.0, 4.9 Hz, 1H), 2.21 – 2.11 (m, 2H), 1.92 (d, J = 4.1 Hz, 1H)

^{13}C NMR (150 MHz, Chloroform-*d*) δ 154.9, 154.0, 150.5, 139.0, 138.2, 135.2, 131.1, 130.7, 130.3, 124.3, 123.2, 112.0, 107.8, 105.6, 100.4, 95.5, 83.2, 63.6, 61.3, 56.3, 39.2, 33.2

HRMS-ESI m/z calculated for $\text{C}_{22}\text{H}_{23}\text{O}_5$ $[\text{M}+\text{H}]^+$ 367.1540, found 367.1542

IR 3450, 2931, 1602, 1575, 1506, 1434, 1404, 1327, 1299, 1265, 1213, 1158, 1098, 1046, 1002, 924, 869, 830, 738, 704, 642 cm^{-1}

Synthesis of (7E,9Z)-16-methoxy-15-(methoxymethoxy)-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-7,9-dien-6-ol **20**



Starting propargyl alcohol **7** (10 mg, 27 μmol) was dissolved in dry tetrahydrofuran (1 mL) and the resulting solution was cooled down to 0 $^\circ\text{C}$. Red-Al (60% in PhMe) (17.8 μL , 55 μmol) was added dropwise to the flask. The reaction was stirred at 0 $^\circ\text{C}$ for 2 h. The reaction was quenched with sodium sulfate decahydrate at 0 $^\circ\text{C}$ and stirred for 30 min. The slurry was filtered and washed with diethyl ether three times. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:2, v/v)) to afford product **20** (8 mg, 80%) as a white solid. R_f = 0.3, ethyl acetate/hexane (2:3, v/v).

mp: 128-130 $^\circ\text{C}$

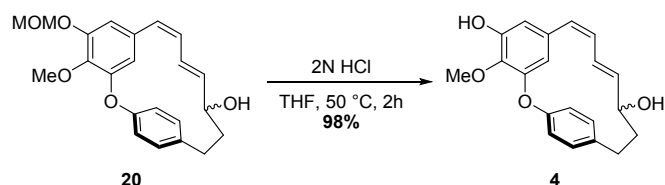
^1H NMR (600 MHz, Methanol- d_4) δ 7.41 (dd, J = 8.2, 2.2 Hz, 1H), 7.33 (dd, J = 8.3, 2.3 Hz, 1H), 7.17 (dd, J = 8.3, 2.6 Hz, 1H), 7.00 (dd, J = 8.2, 2.5 Hz, 1H), 6.56 (d, J = 2.0 Hz, 1H), 6.11 (d, J = 11.4 Hz, 1H), 5.97 – 5.93 (m, 1H), 5.69 (d, J = 2.0 Hz, 1H), 5.64 (d, J = 1.1 Hz, 1H), 5.63 – 5.61 (m, 1H), 5.19 (s, 2H), 4.05 (dtd, J = 6.9, 3.4, 1.3 Hz, 1H), 3.99 (s, 3H), 3.50 (s, 3H), 3.02 (dt, J = 12.9, 3.6 Hz, 1H), 2.69 (td, J = 13.2, 3.3 Hz, 1H), 2.05 – 2.01 (m, 1H), 1.64 (ddt, J = 14.6, 13.4, 3.3 Hz, 1H)

^{13}C NMR (150 MHz, Methanol- d_4) δ 156.6, 156.0, 152.2, 141.5, 140.6, 139.5, 133.7, 133.4, 131.1, 129.9, 129.3, 126.7, 126.3, 123.1, 113.6, 111.9, 96.7, 73.6, 61.8, 56.6, 42.6, 34.9

HRMS-ESI m/z calculated for $\text{C}_{22}\text{H}_{28}\text{NO}_5$ $[\text{M}+\text{NH}_4]^+$ 386.1962, found 386.1957

IR 3405, 2934, 2829, 1724, 1572, 1503, 1431, 1402, 1324, 1296, 1232, 1205, 1157, 1096, 1041, 924, 881, 863, 830, 764, 737, 717, 703, 630 cm^{-1}

Synthesis of giffonin H **4**



MOM-protected giffonin H **20** (2.0 mg, 5.4 μmol) was dissolved in THF (1 mL) and 2N HCl (1 mL) was then added to the flask. The resulting mixture was allowed to warm up to 50 $^\circ\text{C}$ and stirred for 2 h. The reaction was cooled down to room temperature and extracted with ethyl acetate (twice). The organic phase was dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:2, v/v)) to afford giffonin H **4** (1.73 mg, 98%) as an amorphous white solid. R_f = 0.25, ethyl acetate/hexane (1:2, v/v).

mp: thermal decomposition accelerated around 150 $^\circ\text{C}$

^1H NMR (600 MHz, Methanol- d_4) δ 7.40 (dd, J = 8.2, 2.3 Hz, 1H), 7.32 (dd, J = 8.3, 2.3 Hz, 1H), 7.16 (dd, J = 8.3, 2.6 Hz, 1H), 7.00 (dd, J = 8.1, 2.5 Hz, 1H), 6.26 (dd, J = 2.1, 0.6 Hz, 1H), 6.06 (d, J = 11.3 Hz, 1H), 5.91 (dd, J = 11.3, 9.9 Hz, 1H), 5.65 (ddd, J = 15.3, 9.9, 1.1 Hz, 1H), 5.59 (dd, J = 15.4, 8.6 Hz, 1H), 5.48 (d, J = 2.1 Hz,

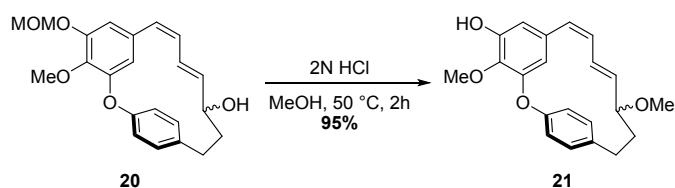
1H), 4.05 (dt, $J = 8.5, 3.3$ Hz, 1H), 3.99 (s, 3H), 3.01 (dt, $J = 12.9, 3.7$ Hz, 1H), 2.68 (td, $J = 13.1, 3.3$ Hz, 1H), 2.02 (dq, $J = 14.6, 3.5$ Hz, 1H), 1.63 (ddt, $J = 14.5, 13.4, 3.2$ Hz, 1H)

^{13}C NMR (150 MHz, Methanol- d_4) δ 156.7, 155.8, 151.9, 141.5, 140.2, 137.0, 133.8, 133.3, 131.0, 130.2, 129.0, 127.0, 126.3, 123.2, 111.1, 111.0, 73.7, 61.6, 42.7, 34.9

HRMS-ESI m/z calculated for $\text{C}_{20}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^+$ 325.1435, found 325.1438

IR 3526, 3338, 2925, 2855, 1739, 1593, 1570, 1501, 1449, 1431, 1408, 1378, 1344, 1264, 1237, 1205, 1186, 1163, 1137, 1075, 1039, 1027, 981, 946, 920, 879, 860, 847, 833, 818, 788, 741, 711, 629 cm^{-1}

Synthesis of giffonin H methyl ether **21**



MOM-protected giffonin H **20** (2.0 mg, 5.4 μmol) was dissolved in MeOH (1 mL) and 2N HCl (1 mL) was then added to the flask. The resulting mixture was allowed to warm up to 50 $^\circ\text{C}$ and stirred for 2 h. The reaction was cooled down to room temperature and extracted with ethyl acetate (twice). The organic phase was dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:4, v/v)) to afford giffonin H methyl ether **21** (1.75 mg, 95%) as an amorphous white solid. $R_f = 0.45$, ethyl acetate/hexane (1:2, v/v).

mp: thermal decomposition accelerated around 150 $^\circ\text{C}$

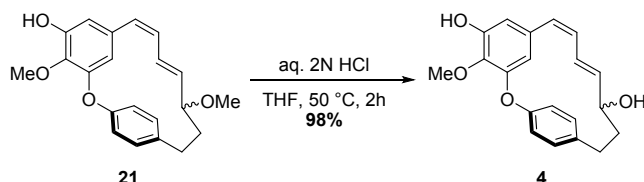
^1H NMR (600 MHz, Methanol- d_4) δ 7.42 (dd, $J = 8.2, 2.3$ Hz, 1H), 7.32 (dd, $J = 8.3, 2.3$ Hz, 1H), 7.16 (dd, $J = 8.3, 2.6$ Hz, 1H), 7.01 (dd, $J = 8.2, 2.6$ Hz, 1H), 6.28 (d, $J = 2.0$ Hz, 1H), 6.10 (d, $J = 11.3$ Hz, 1H), 5.95 (t, $J = 10.9$ Hz, 1H), 5.75 (dd, $J = 15.4, 10.4$ Hz, 1H), 5.50 – 5.43 (m, 2H), 4.00 (s, 3H), 3.60 (dt, $J = 9.3, 3.3$ Hz, 1H), 3.18 (s, 3H), 3.02 (dt, $J = 12.9, 3.7$ Hz, 1H), 2.63 (td, $J = 13.2, 3.4$ Hz, 1H), 2.06 (dq, $J = 14.8, 3.7$ Hz, 1H), 1.60 – 1.53 (m, 1H)

^{13}C NMR (150 MHz, Methanol- d_4) δ 156.6, 155.8, 152.0, 141.3, 138.0, 137.1, 133.7, 133.5, 131.0, 130.5, 129.9, 128.5, 126.3, 123.3, 111.1, 111.0, 83.7, 61.5, 56.7, 40.9, 35.0

HRMS-ESI m/z calculated for $\text{C}_{21}\text{H}_{23}\text{O}_4$ $[\text{M}+\text{H}]^+$ 339.1591, found 339.1594

IR 3373, 2932, 2856, 1725, 1593, 1573, 1505, 1449, 1431, 1406, 1352, 1306, 1266, 1245, 1206, 1164, 1136, 1098, 1081, 1038, 994, 904, 874, 864, 830, 739, 713, 629 cm^{-1}

Synthesis of giffonin H **4** from giffonin H methyl ether **21**



Giffonin H methyl ether **21** (1.75 mg, 5.2 μmol) was dissolved in THF (1 mL) and 2N HCl (1 mL) was then added to the flask. The resulting mixture was allowed to warm up to 50 $^\circ\text{C}$ and stirred for 2 h. The reaction was cooled down to room temperature and extracted with ethyl acetate (twice). The organic phase was dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (ethyl acetate/hexane (1:2, v/v)) to afford giffonin H **4** (1.64 mg, 98%) as an amorphous white

solid. $R_f = 0.25$, ethyl acetate/hexane (1:2, v/v).

mp: thermal decomposition accelerated around 150 °C

^1H NMR (600 MHz, Methanol- d_4) δ 7.40 (dd, $J = 8.2, 2.3$ Hz, 1H), 7.32 (dd, $J = 8.3, 2.3$ Hz, 1H), 7.16 (dd, $J = 8.3, 2.6$ Hz, 1H), 7.00 (dd, $J = 8.1, 2.5$ Hz, 1H), 6.26 (dd, $J = 2.1, 0.6$ Hz, 1H), 6.06 (d, $J = 11.3$ Hz, 1H), 5.91 (dd, $J = 11.3, 9.9$ Hz, 1H), 5.65 (ddd, $J = 15.3, 9.9, 1.1$ Hz, 1H), 5.59 (dd, $J = 15.4, 8.6$ Hz, 1H), 5.48 (d, $J = 2.1$ Hz, 1H), 4.05 (dt, $J = 8.5, 3.3$ Hz, 1H), 3.99 (s, 3H), 3.01 (dt, $J = 12.9, 3.7$ Hz, 1H), 2.68 (td, $J = 13.1, 3.3$ Hz, 1H), 2.02 (dq, $J = 14.6, 3.5$ Hz, 1H), 1.63 (ddt, $J = 14.5, 13.4, 3.2$ Hz, 1H)

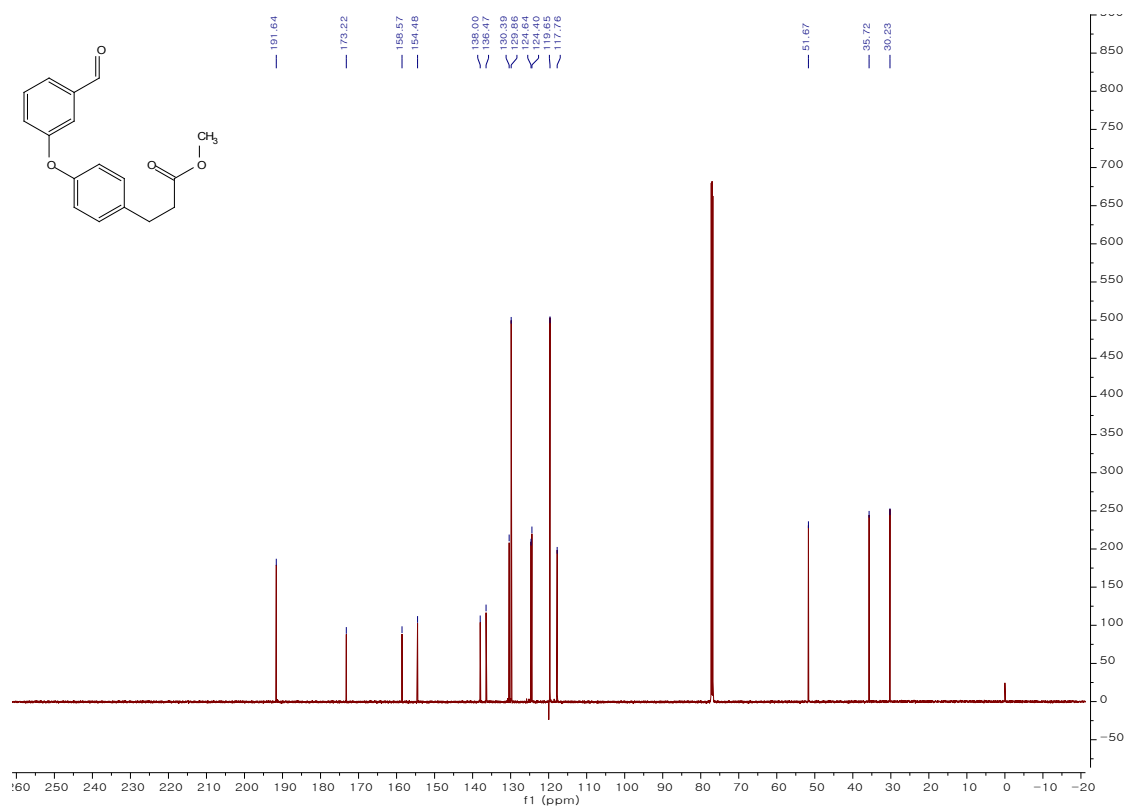
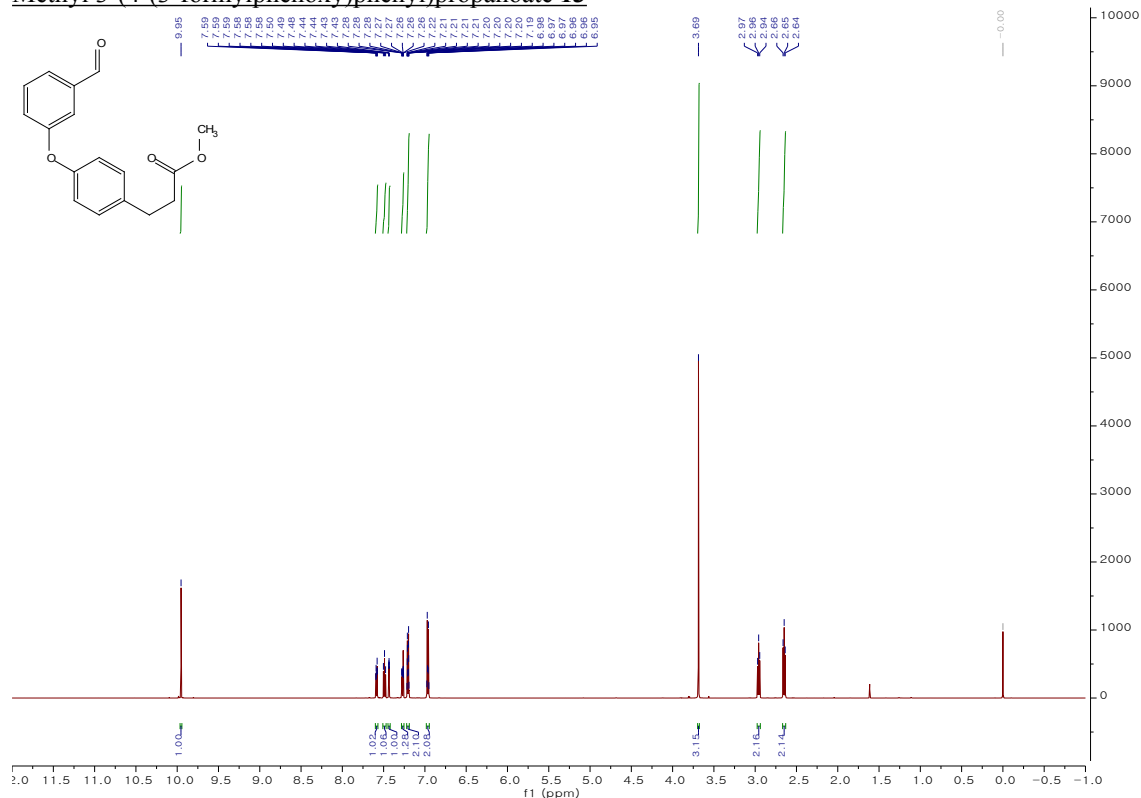
^{13}C NMR (150 MHz, Methanol- d_4) δ 156.7, 155.8, 151.9, 141.5, 140.2, 137.0, 133.8, 133.3, 131.0, 130.2, 129.0, 127.0, 126.3, 123.2, 111.1, 111.0, 73.7, 61.6, 42.7, 34.9

HRMS-ESI m/z calculated for $\text{C}_{20}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^+$ 325.1435, found 325.1438

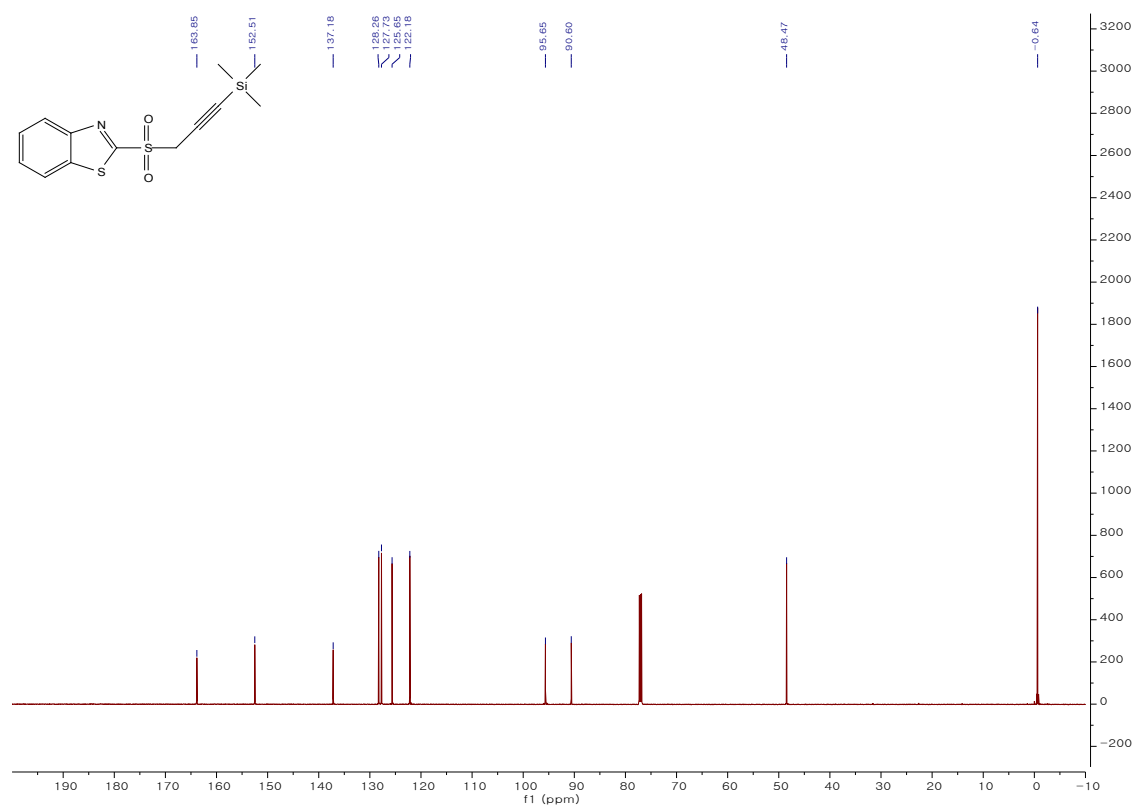
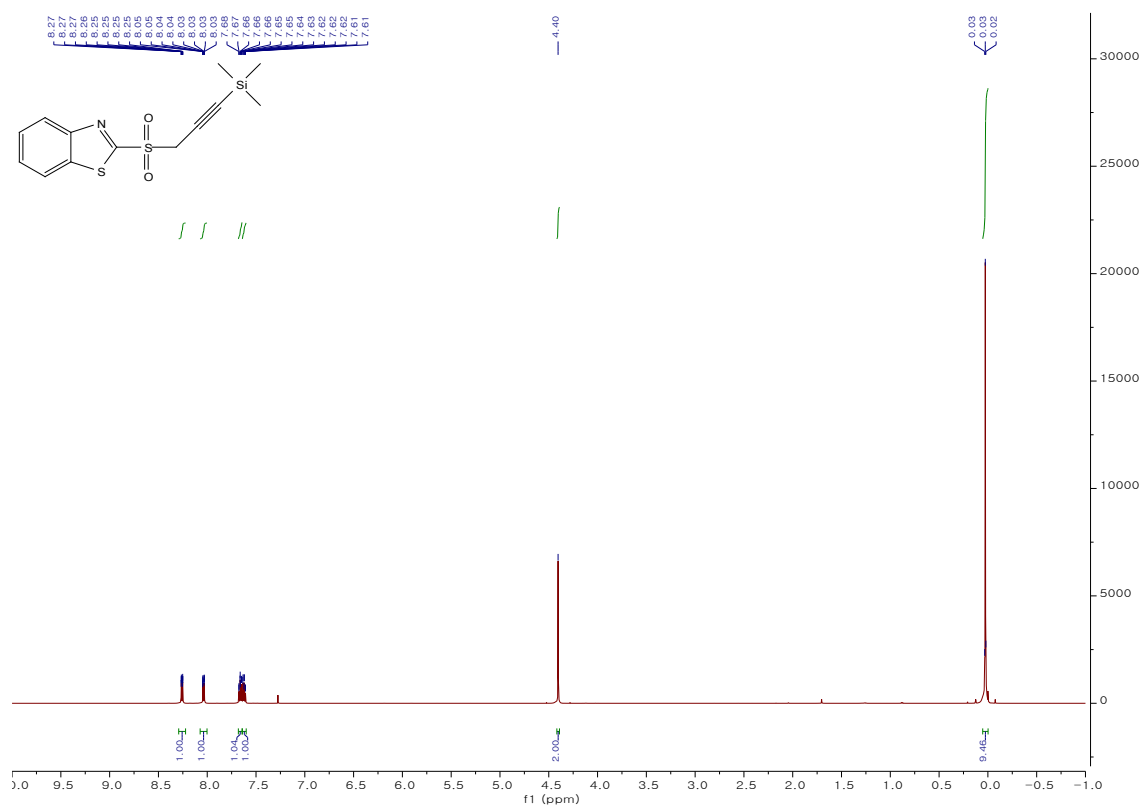
IR 3526, 3338, 2925, 2855, 1739, 1593, 1570, 1501, 1449, 1431, 1408, 1378, 1344, 1264, 1237, 1205, 1186, 1163, 1137, 1075, 1039, 1027, 981, 946, 920, 879, 860, 847, 833, 818, 788, 741, 711, 629 cm^{-1}

3. ^1H NMR and ^{13}C NMR spectra

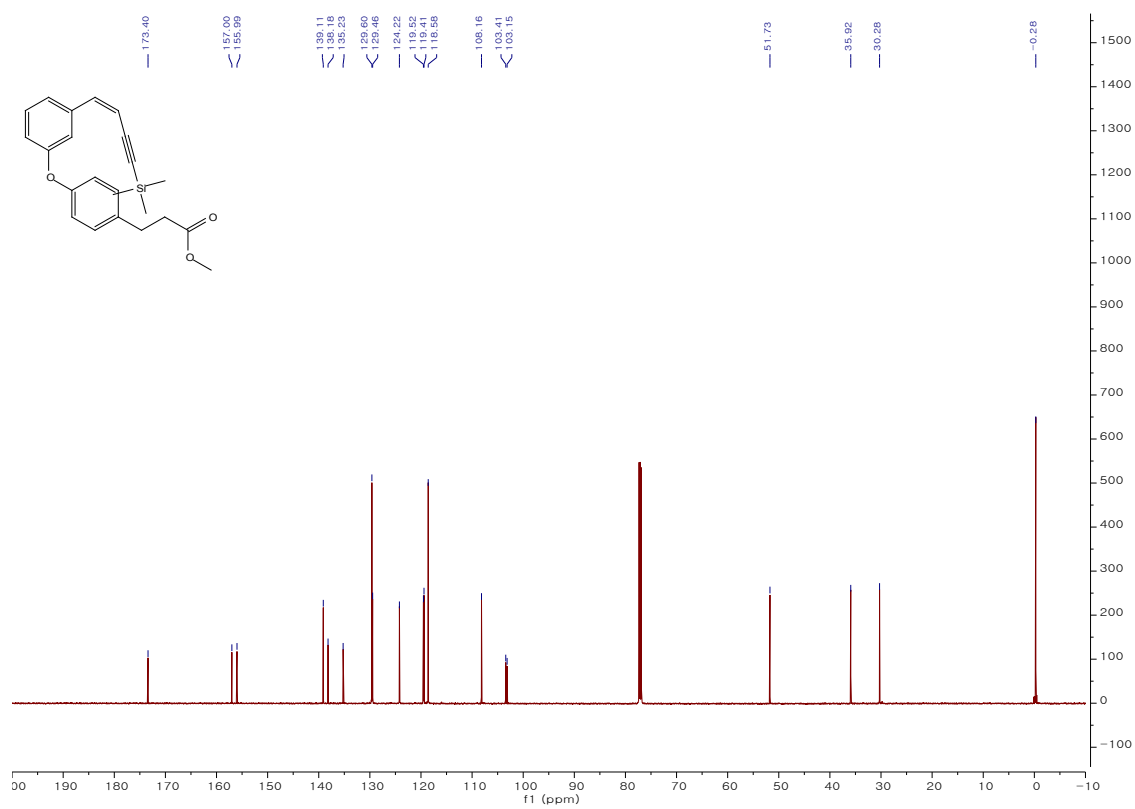
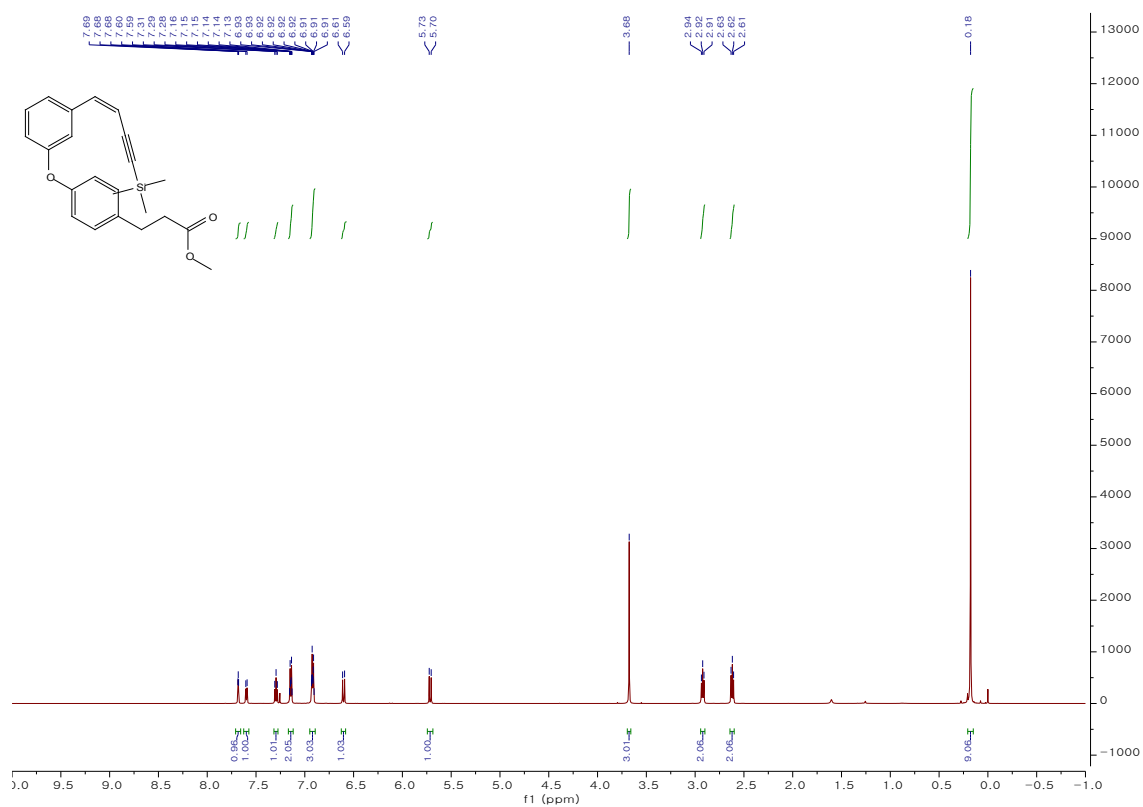
Methyl 3-(4-(3-formylphenoxy)phenyl)propanoate **13**



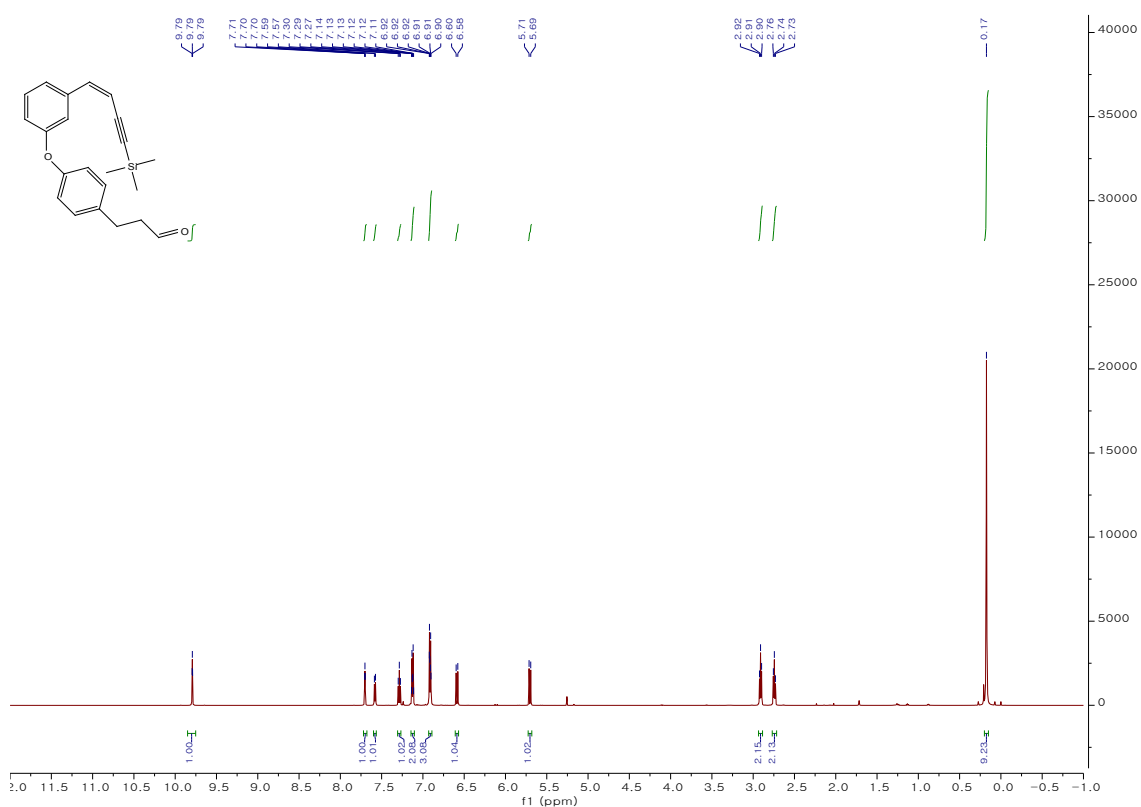
2-((3-(trimethylsilyl)prop-2-yn-1-yl)sulfonyl)benzo[d]thiazole 16



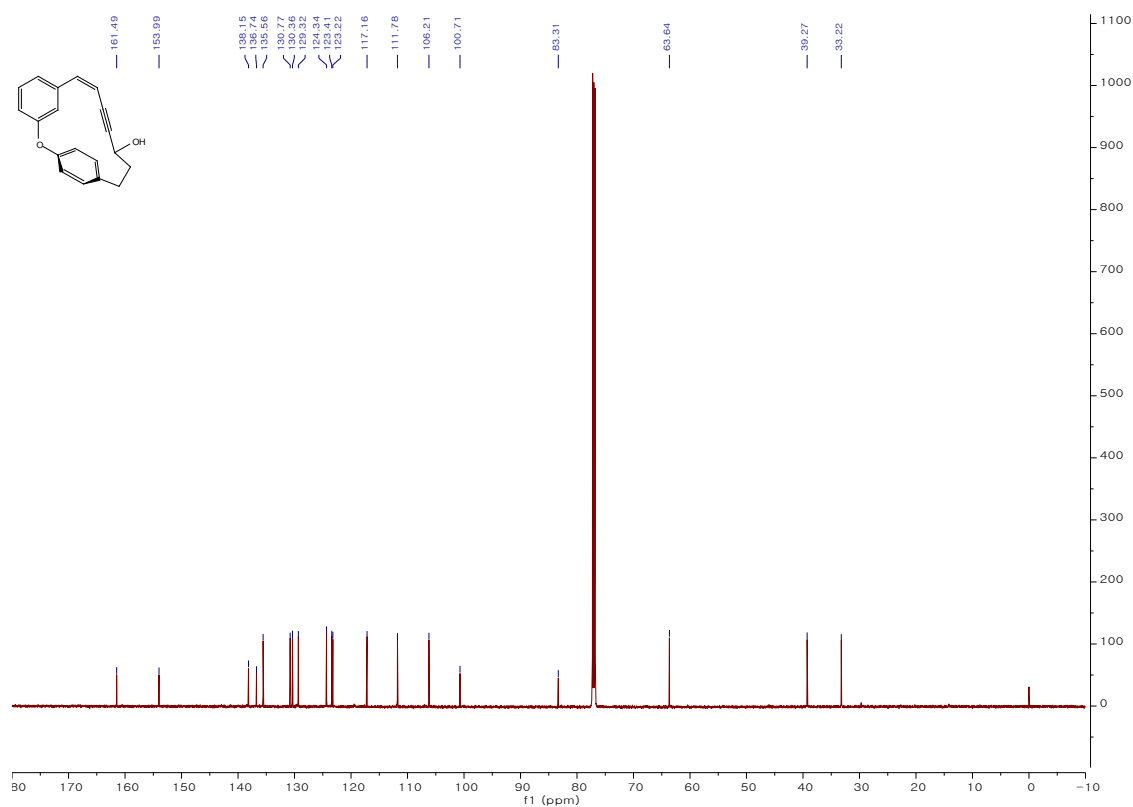
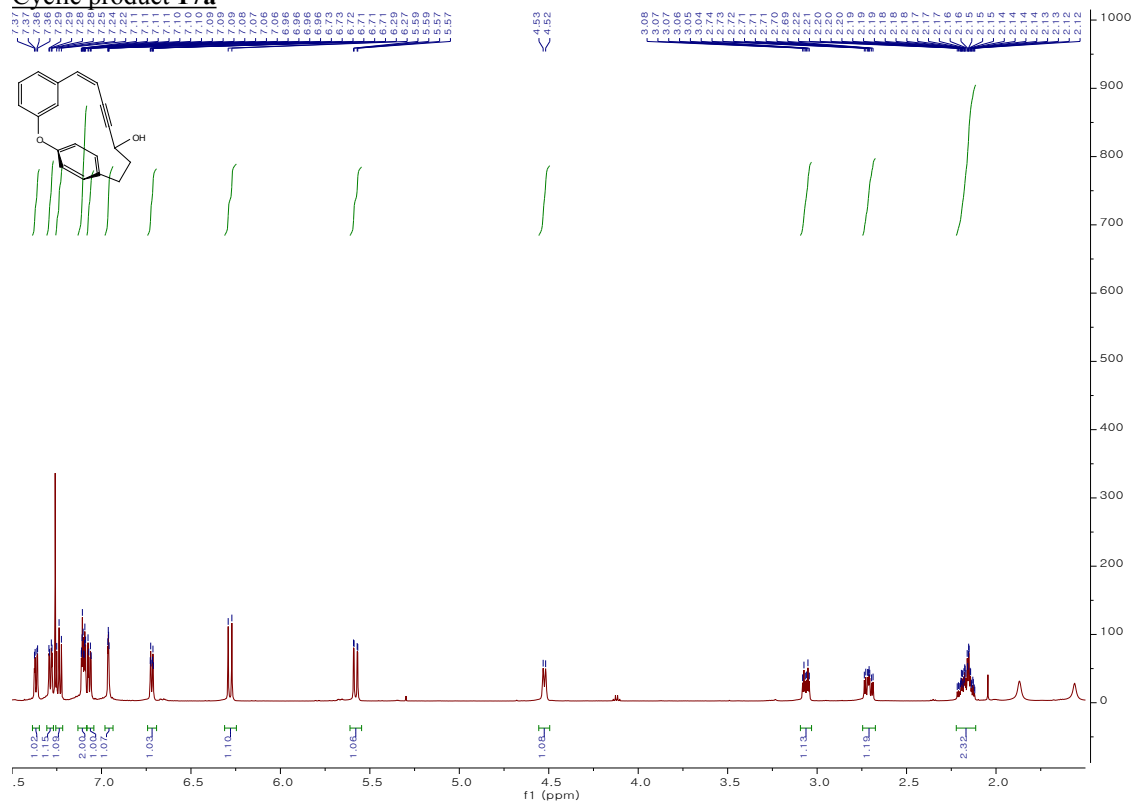
Methyl (Z)-3-(4-(3-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenoxy)phenyl)propanoate **14**



(Z)-3-(4-(3-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenoxy)phenyl)propanal 15



Cyclic product 17a

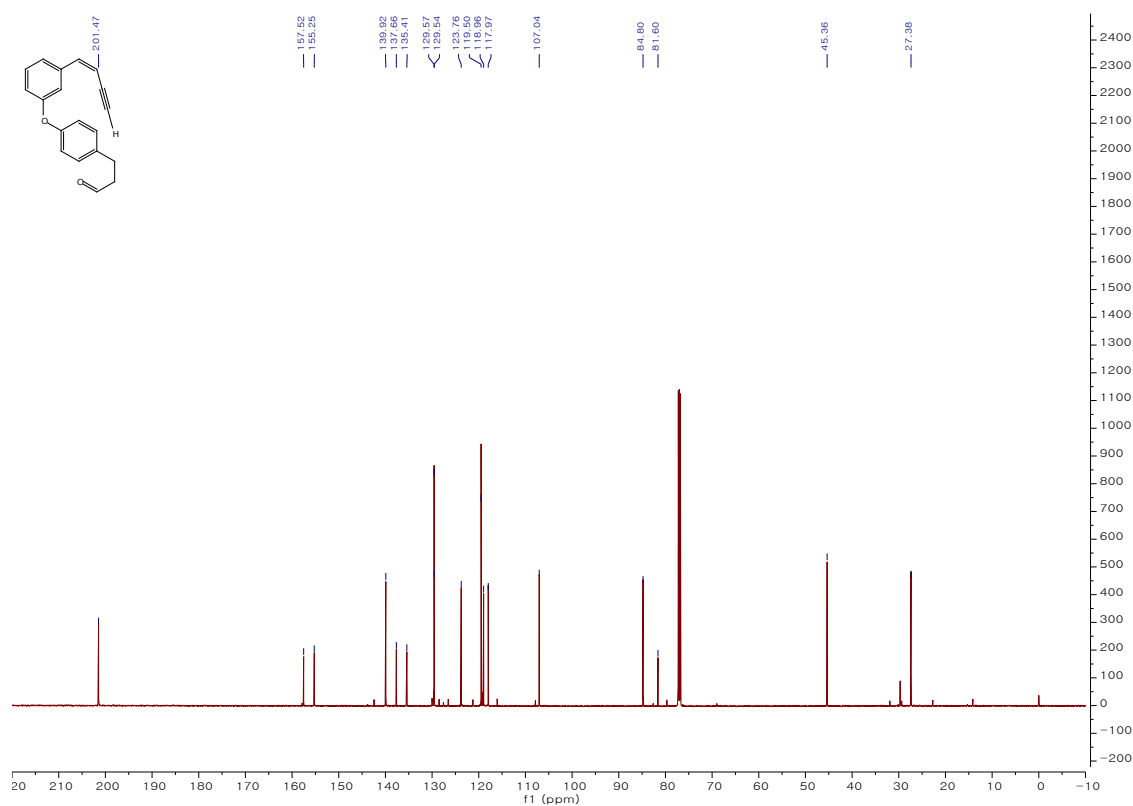


Chemical structure of compound 10: O=C1CCc2ccc(OCC#Cc3ccccc3)cc2

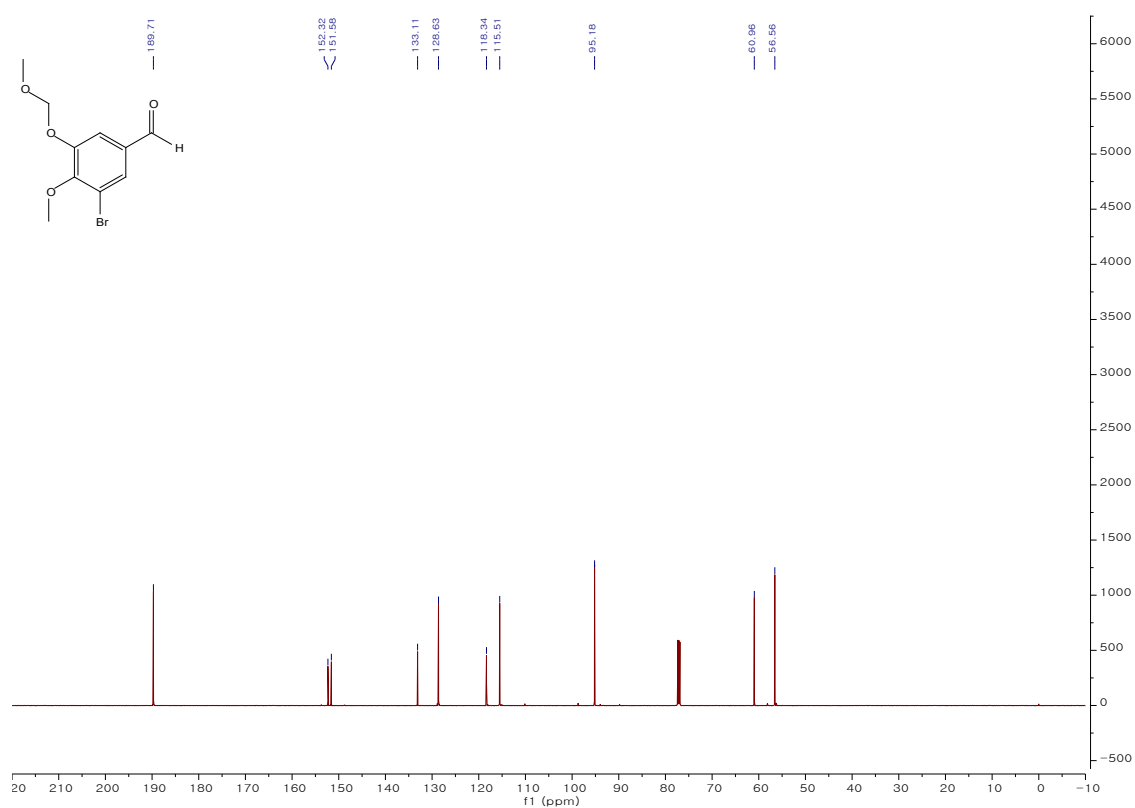
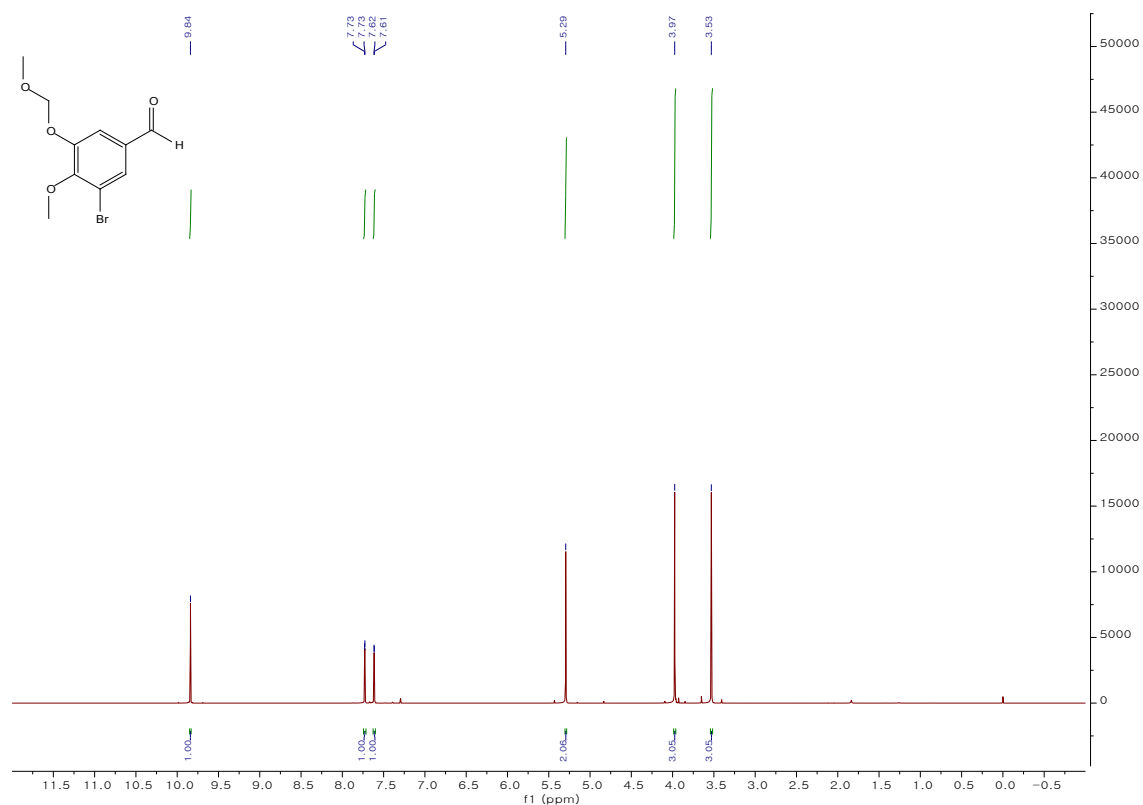
¹H NMR spectrum (CDCl₃) of compound 10. The x-axis represents the chemical shift in ppm (f1), ranging from 12.0 to -1.0. The y-axis represents the intensity in arbitrary units, ranging from -500 to 6500. The spectrum shows several peaks, with integration values indicated below the baseline.

Integration values (from left to right): 0.93, 1.00, 1.00, 1.00, 3.13, 1.07, 1.00, 0.87, 2.21, 2.10.

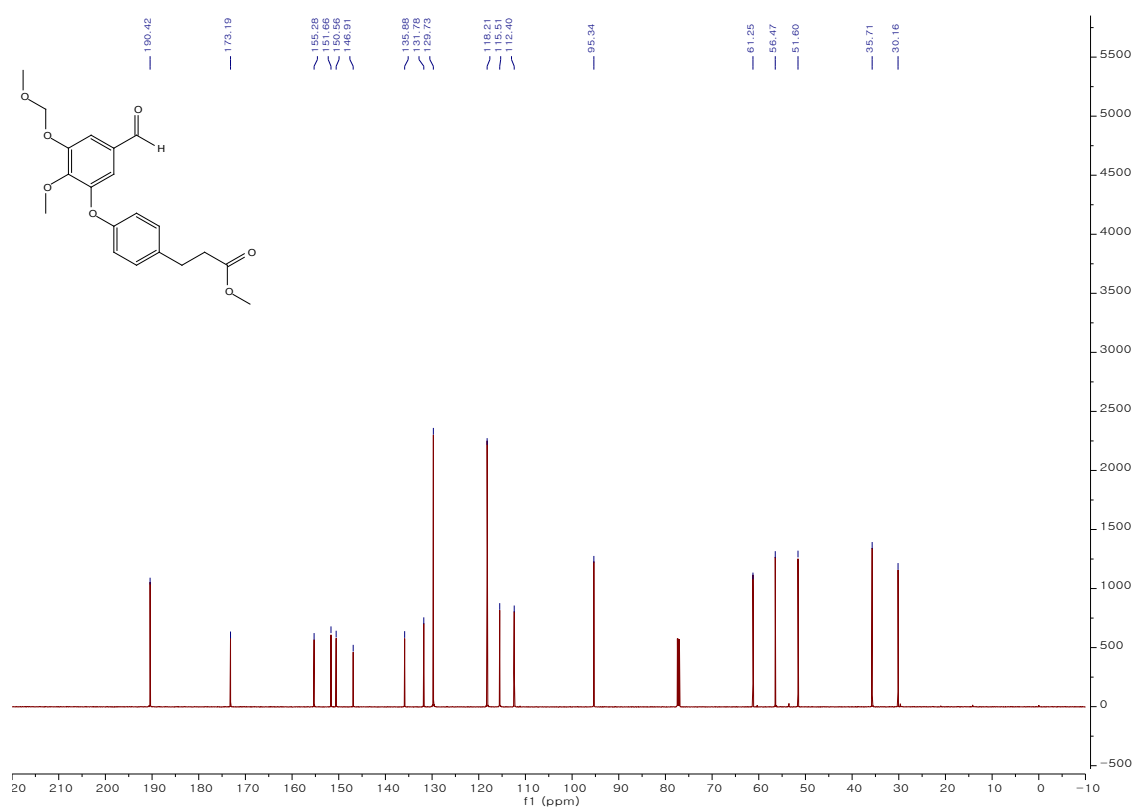
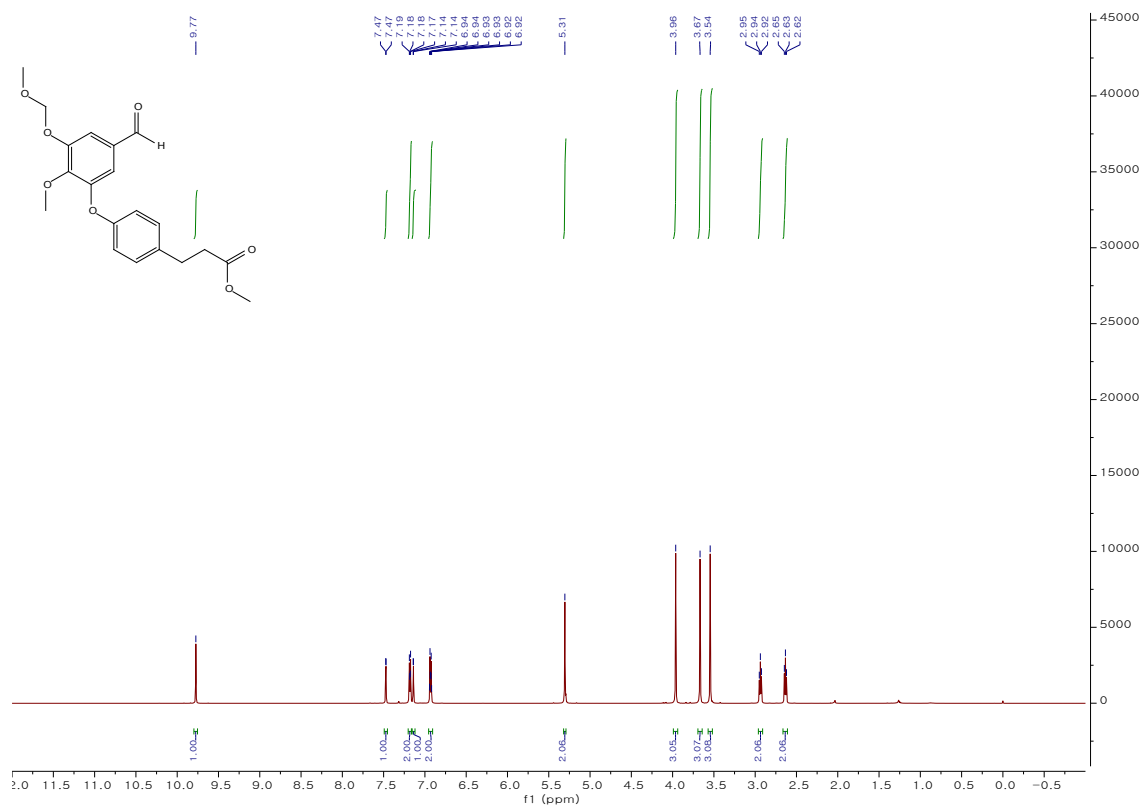
Chemical shift values (ppm) labeled above the peaks (from left to right): 9.83, 9.82, 7.81, 7.61, 7.59, 7.48, 7.32, 7.31, 7.22, 7.17, 7.16, 7.15, 6.98, 6.97, 6.96, 6.95, 6.94, 6.67, 6.65, 5.68, 5.67, 5.65, 3.25, 3.24, 3.24, 3.24, 2.95, 2.95, 2.93, 2.80, 2.79, 2.78, 2.77, 2.77, 2.77.



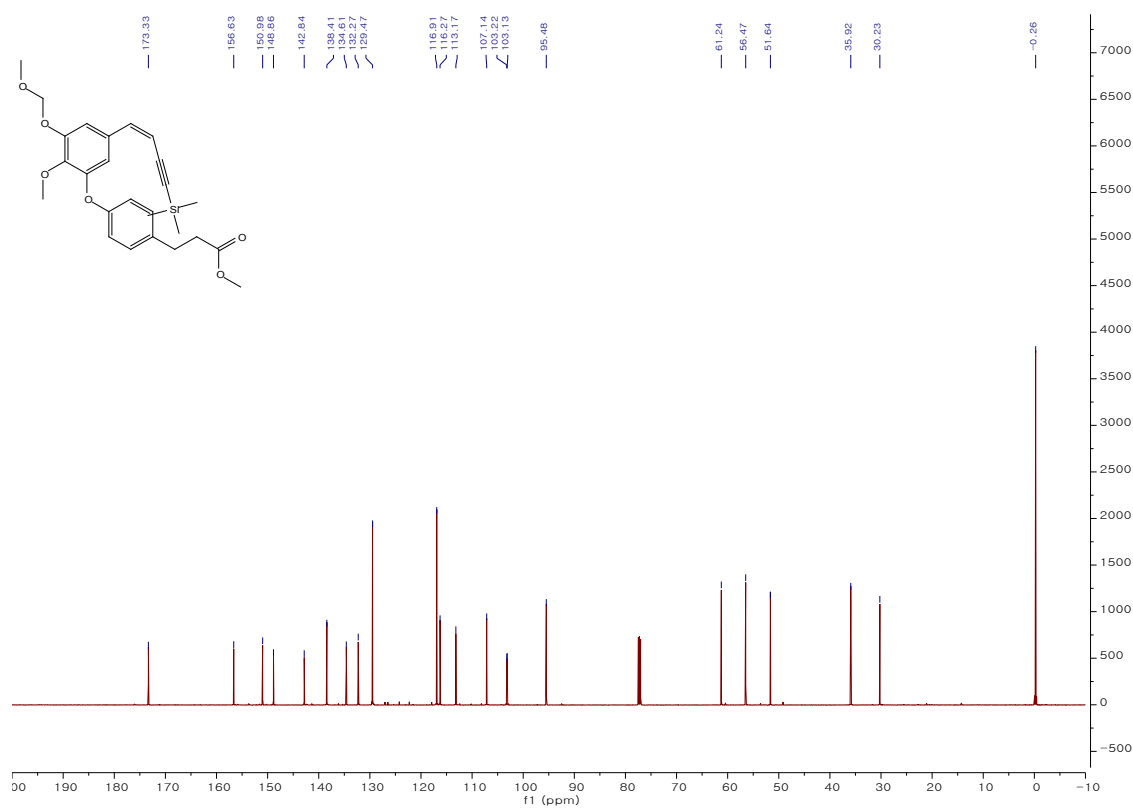
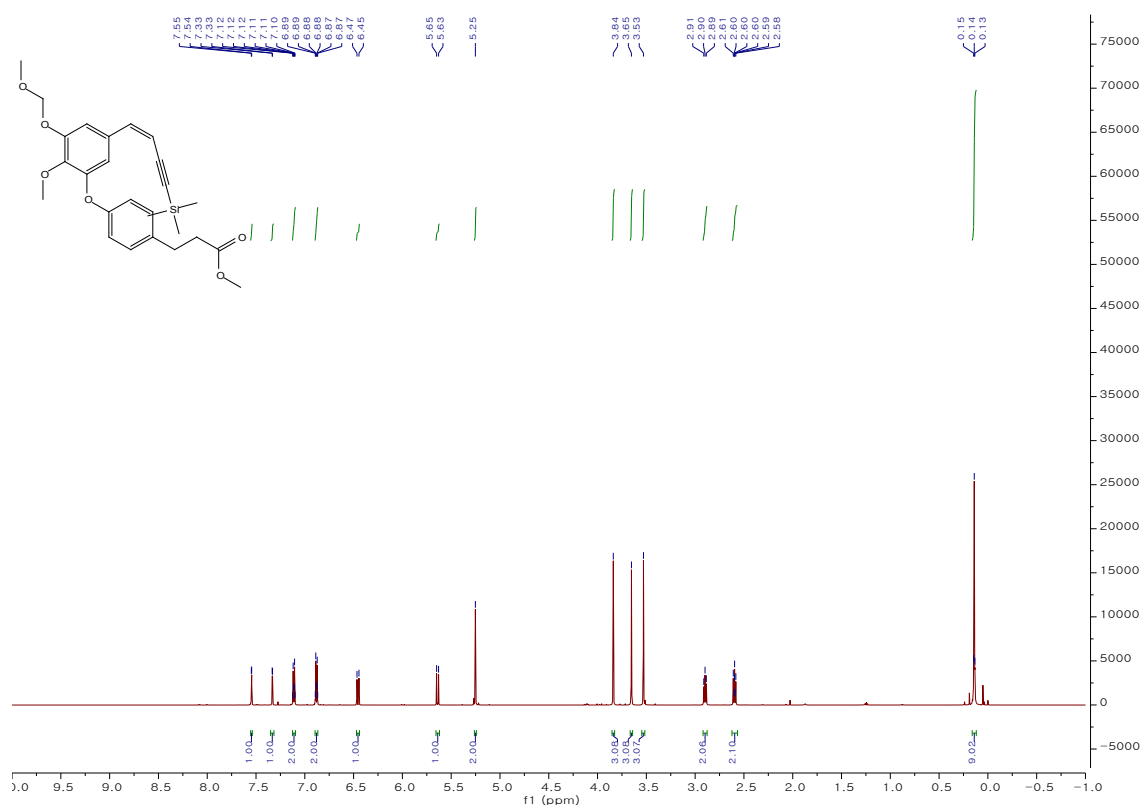
3-Bromo-4-methoxy-5-(methoxymethoxy)benzaldehyde **18**



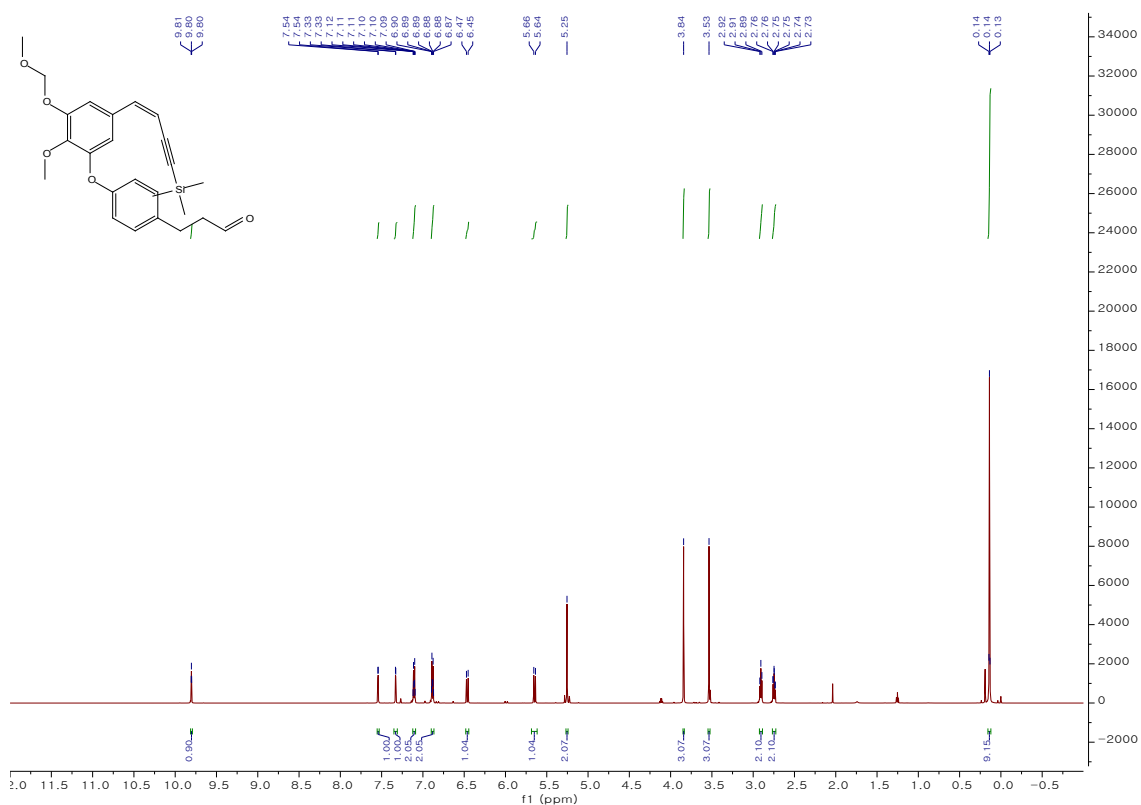
Methyl 3-(4-(5-formyl-2-methoxy-3-(methoxymethoxy)phenoxy)phenyl)propanoate **9**



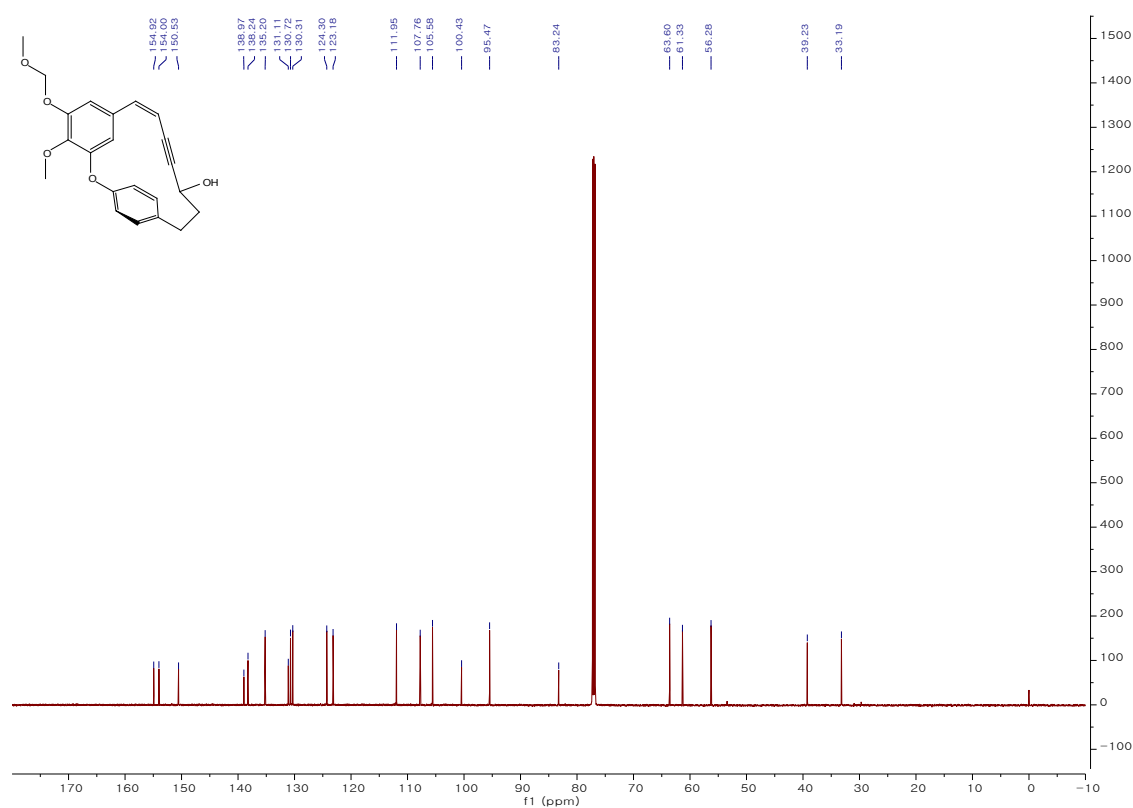
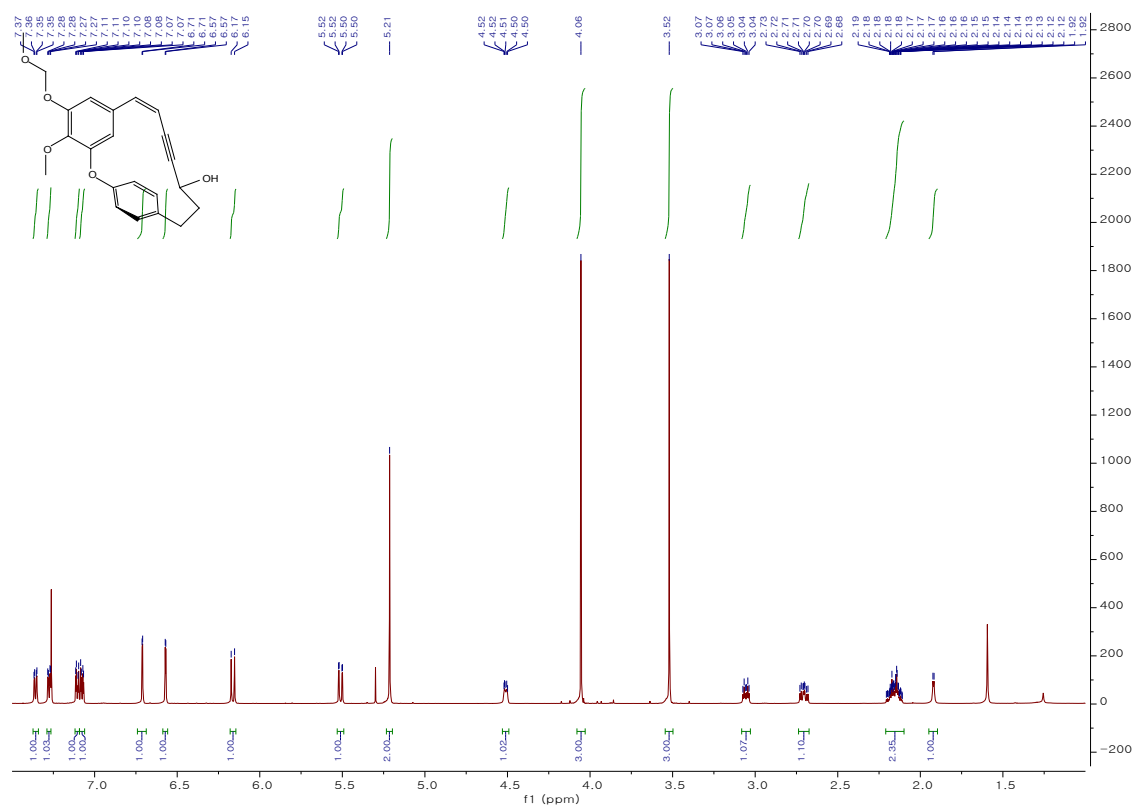
Methyl (Z)-3-(4-(2-methoxy-3-(methoxymethoxy)-5-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenoxy)phenyl)propanoate **19**



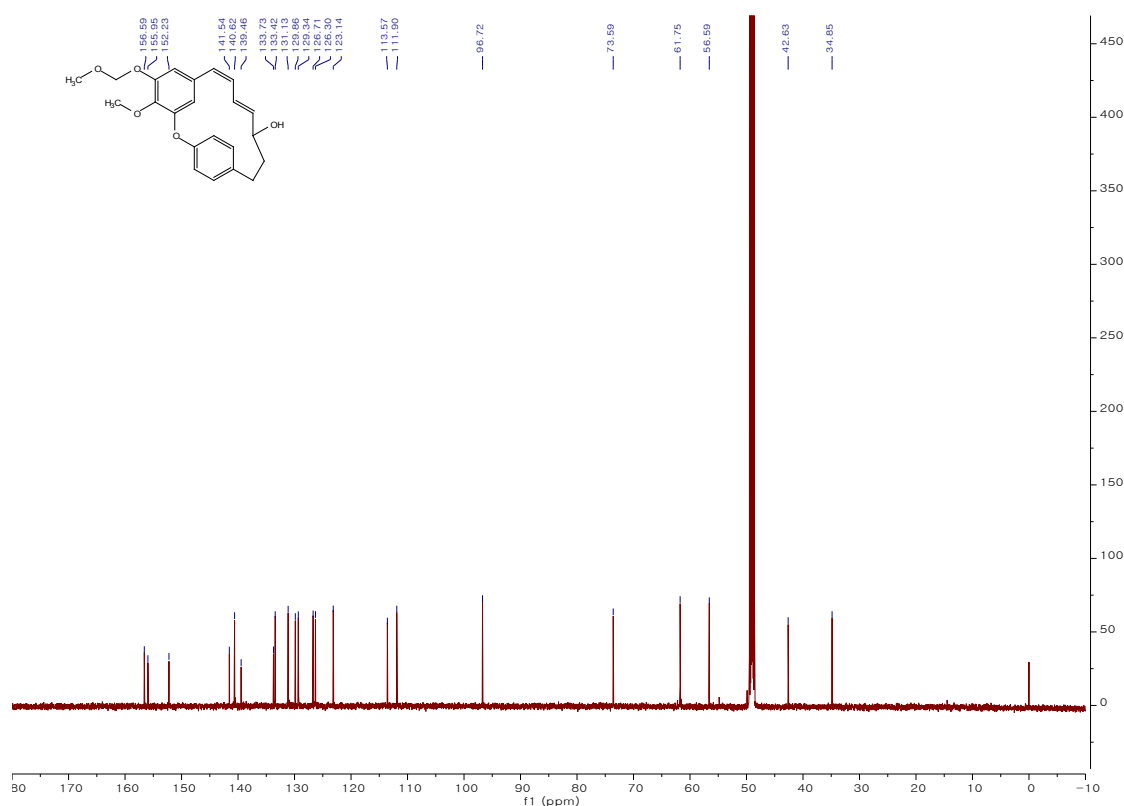
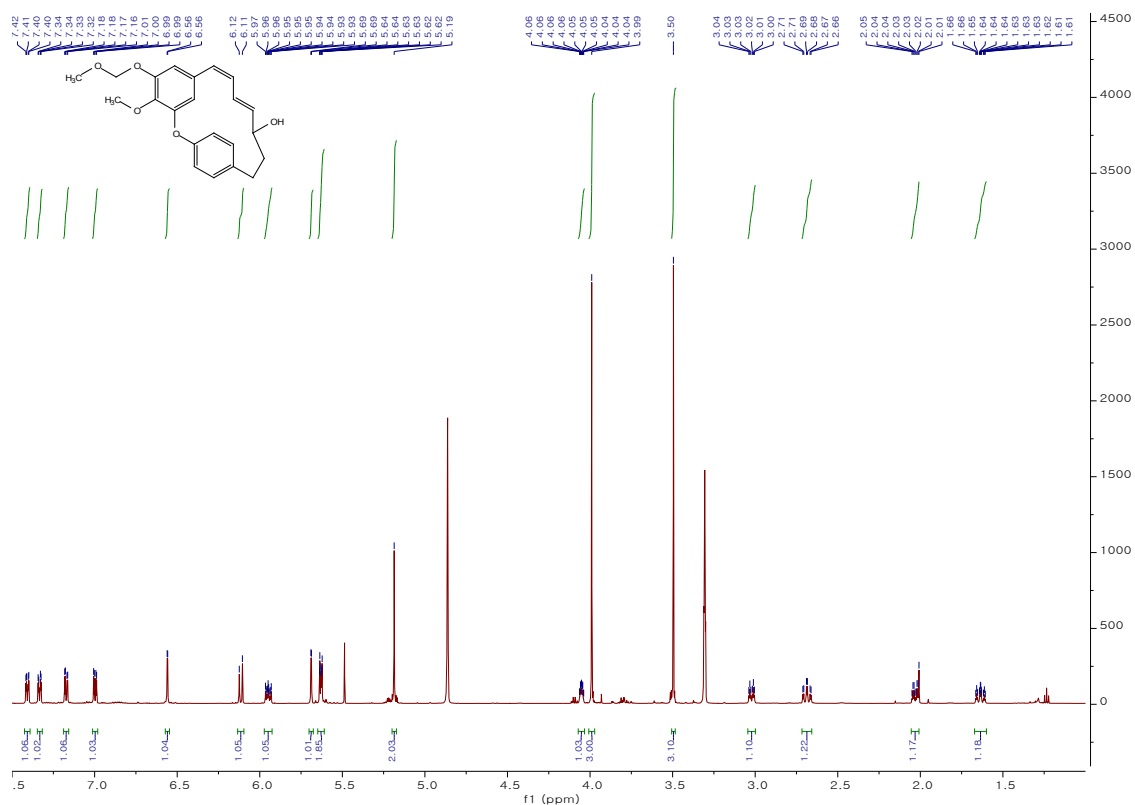
(Z)-3-(4-(2-methoxy-3-(methoxymethoxy)-5-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)phenoxy)phenyl)propanal 8



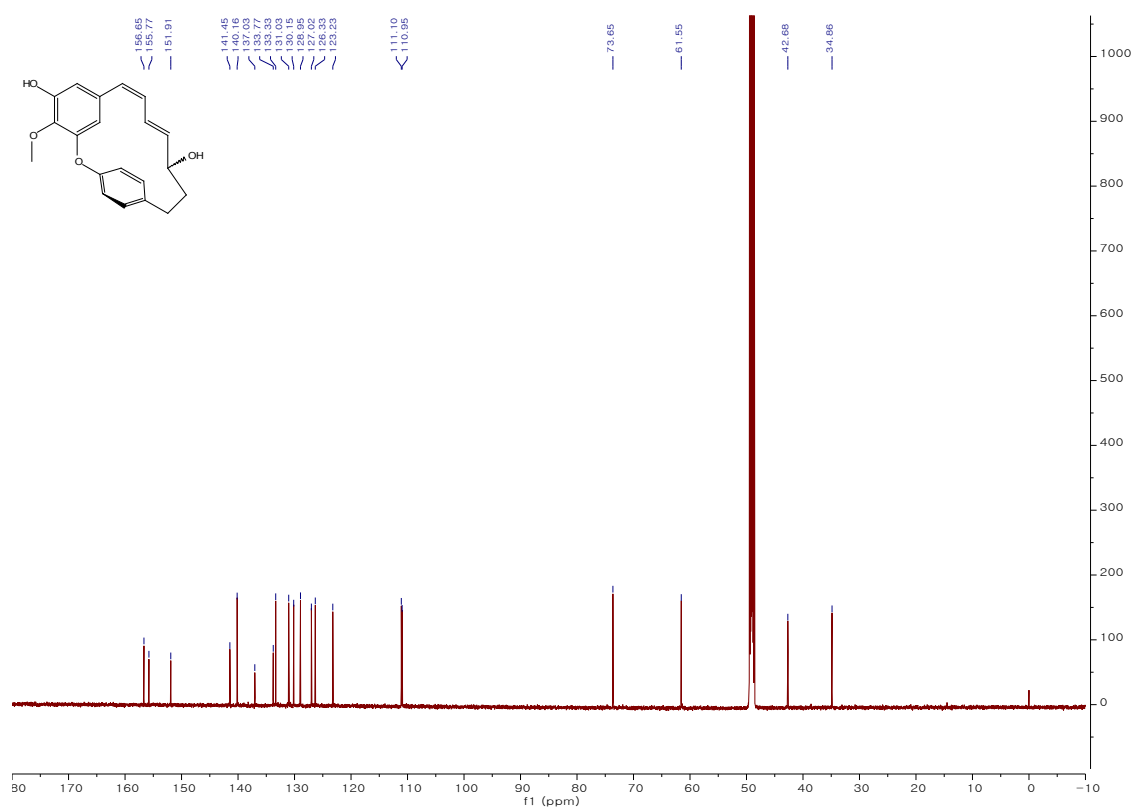
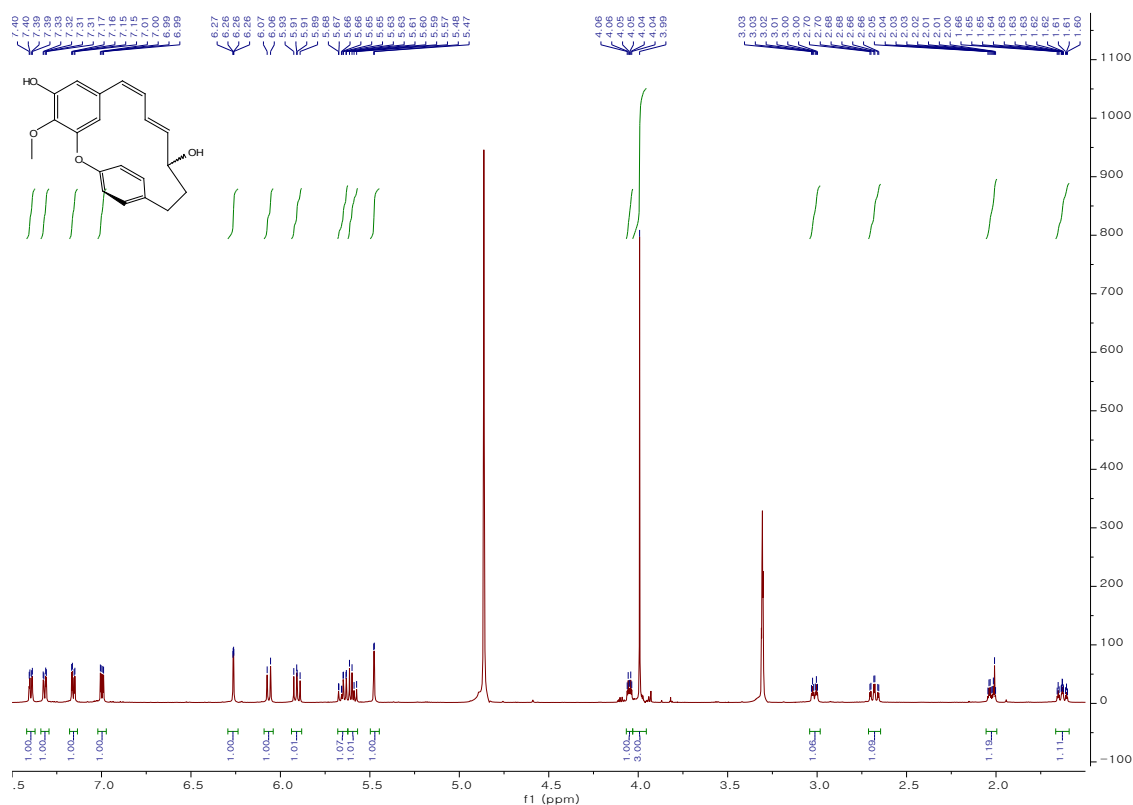
Cyclic product 7



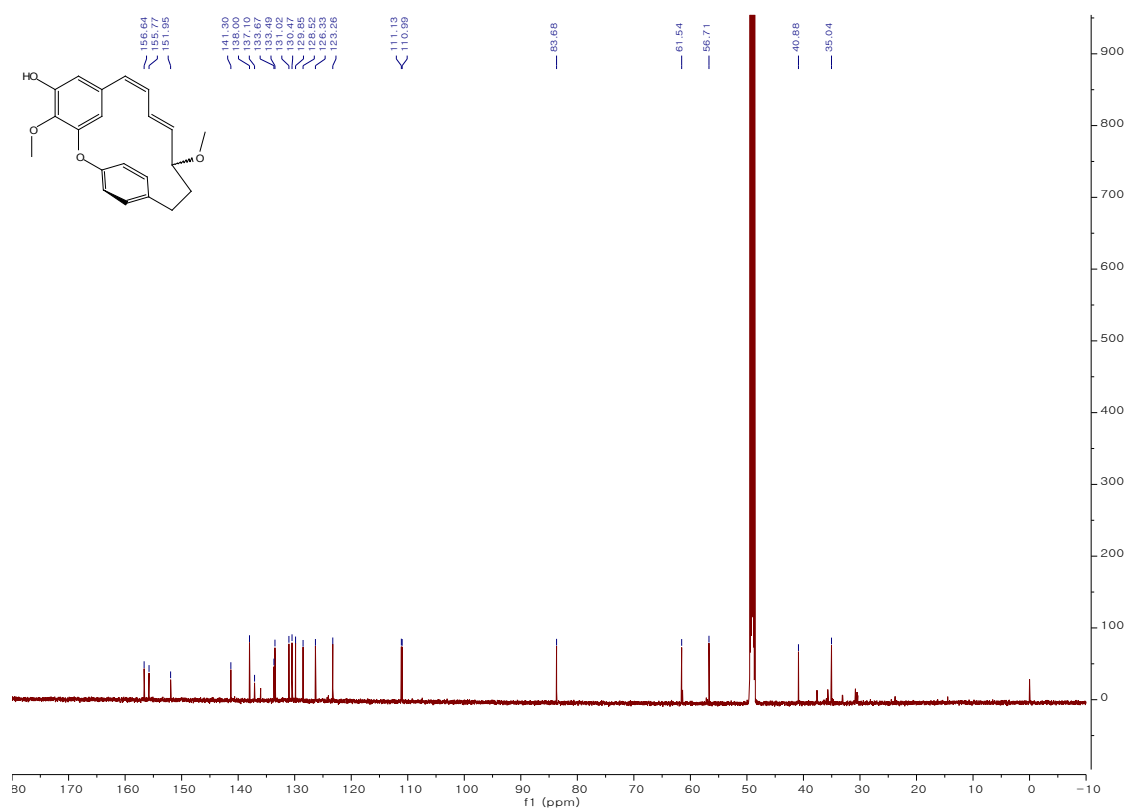
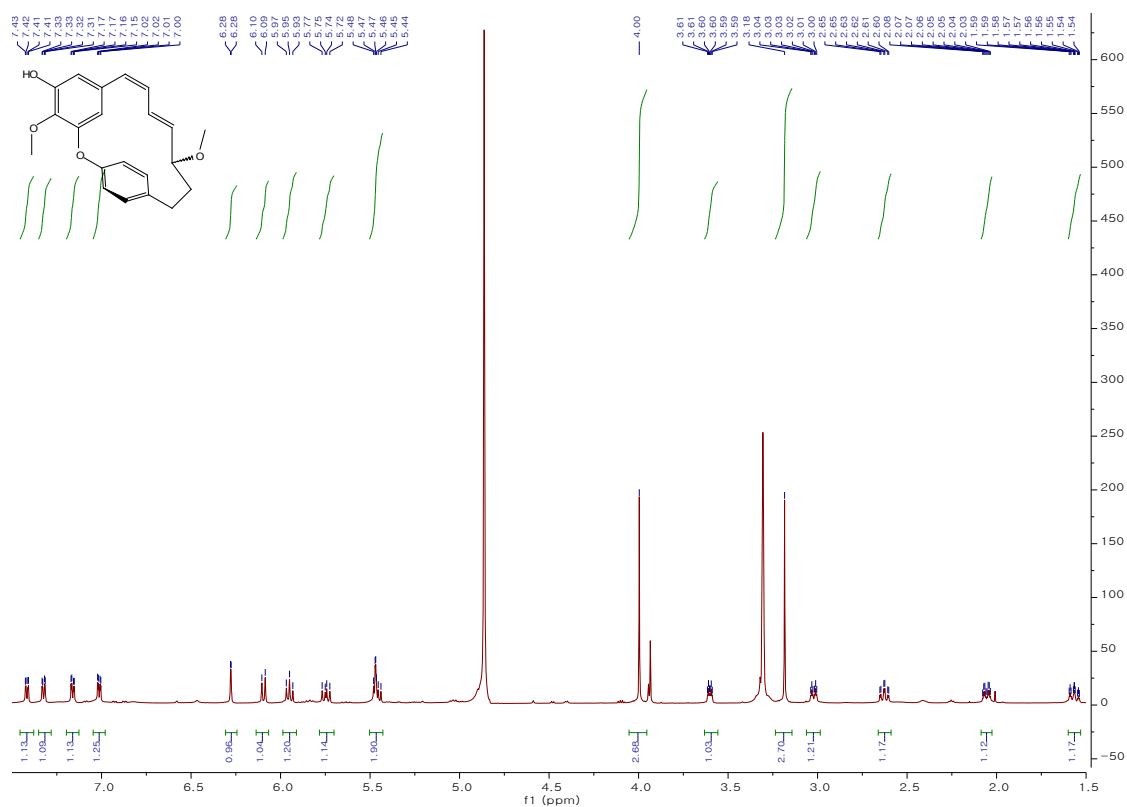
(7E,9Z)-16-methoxy-15-(methoxymethoxy)-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-7,9-dien-6-ol 20



Giffonin H 4



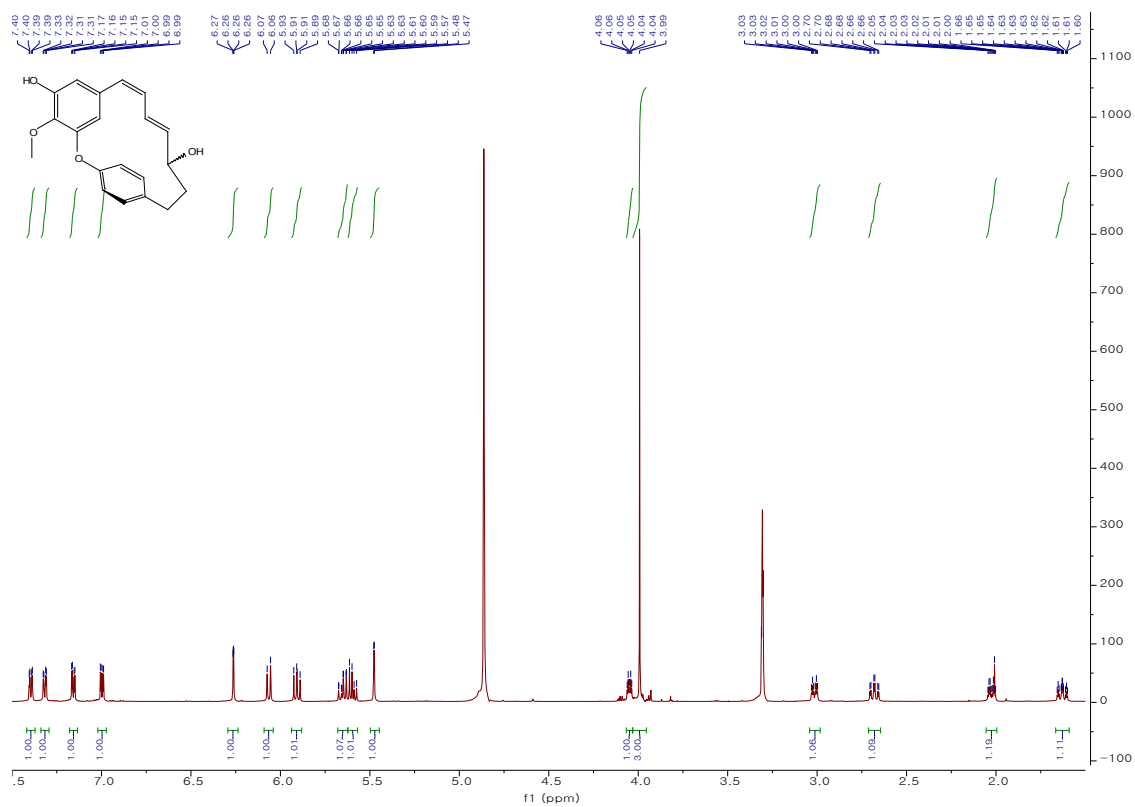
Giffonin H methyl ether **21**



A comparison of NMR spectra between synthetic giffonin H and natural giffonin H¹(600 MHz, δ ppm, in Metahnol-*d*₄)

Synthetic giffonin H δ_{H} (<i>J</i> in Hz)	Natural giffonin H δ_{H} (<i>J</i> in Hz)	Synthetic giffonin H δ_{C}	Natural giffonin H δ_{C}	$\Delta \delta_{\text{C}}$ ($\delta_{\text{Natural}} - \delta_{\text{Synthetic}}$)
		156.7	156.7	0
		155.8	155.6	-0.2
		151.9	151.7	-0.2
		141.5	140.9	-0.6
5.59, dd (15.4, 8.6)	5.63, dd (15.4, 8.6)	140.2	140.1	-0.1
		137.0	136.9	-0.1
		133.8	133.5	-0.3
7.32, dd (8.3, 2.3)	7.36, dd (8.3, 1.9)	133.3	133.2	-0.1
7.40, dd (8.2, 2.3)	7.44, dd (8.3, 1.9)	131.0	130.7	-0.3
6.06, d (11.3)	6.09, d (11.2)	130.2	129.9	-0.3
5.91, dd (11.3, 9.9)	5.94, t (11.2)	129.0	128.8	-0.2
5.65, ddd (15.3, 9.9, 1.1)	5.68, dd (15.4, 11.2)	127.0	126.8	-0.2
7.00, dd (8.1, 2.5)	7.03, dd (8.3, 1.9)	126.3	126.3	-0.2
7.16, dd (8.3, 2.6)	7.19, dd (8.3, 1.9)	123.2	123.0	-0.2
6.26, dd (2.1, 0.6)	6.30, d (1.7)	111.1	110.8	-0.3
5.48, d (2.1)	5.51, d (1.7)	111.0	109.6	-1.4
4.05, dt (8.5, 3.3)	4.09, dt (8.6, 3.4)	73.7	73.2	-0.5
3.99, s	4.03, s	61.6	60.0	-1.6
2.02, dq (14.6, 3.5); 1.63, ddt (14.5, 13.4, 3.2)	2.05, dq (14.2, 3.4); 1.67, tt (14.2, 3.4)	42.7	42.5	-0.2
3.01, dt (12.9, 3.7); 2.68, td (13.1, 3.3)	3.04, dt (13.0, 3.3); 2.72, td (13.0, 3.3)	34.9	34.6	-0.3

¹H NMR spectrum of synthetic giffonin H



1. Masullo, M.; Cerulli, A.; Olas, B.; Pizza, C.; Piacente, S., *J. Nat. Prod.* **2015**, 78, 17-25.