Oxabicyclo[3.2.1]octane Derivatives as Highly Reactive Dienophiles: Synthesis of Bicyclo[5.n.0] Systems

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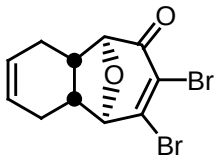
Supporting Information

General. The ^{1}H and ^{13}C spectra were recorded at 500 and 125 MHz respectively. All melting points are uncorrected. High-resolution mass spectrometry was provided by the University of Illinois Urbana-Champaigne Mass Spectrometry laboratory. All reagents were used directly from commercial sources unless otherwise stated. All reported yields are the average of at least two independent runs.

Preparation of starting materials. Compound **1** was prepared by using literature procedures.[1] Cyclopentadiene was freshly distilled.

Preparation of Diels-Alder adduct 2.

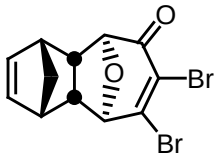


2

To a sealed tube was added 3,4-dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (1.0 g, 3.6 mmol). Toluene (1.5 mL) was added and the reaction stirred until all starting material was in solution. Sulfolene (1.27 g, 10.7 mmol) was added and the tube sealed. The tube was heated in an oil bath at 135 ºC for 30 h. The tube was removed from the oil bath and the solution allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2; 100 g) using 5% ethyl acetate in hexanes as the eluent to afford **2** as a white solid (955 mg, 80%): R_f= .47 (95:5 Hex:EtOAc); mp= 69-71 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00-5.93 (m, 2H), 4.68 (s, 1H), 4.45 (s, 1H), 2.59-2.44 (m, 3H),

2.32 (dd, J= 8.5, 7.6 Hz, 1H), 2.01-1.92 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.0, 151.6, 129.2, 128.9, 123.8, 88.7, 43.9, 40.6, 28.1, 27.8; IR (NaCl, cm^{-1}) 3040.3, 2939.3, 2838.9, 1703.4, 1571.4, 1233.8, 1188.9, 1079.2, 1038.4; HRMS m/z 331.9044 (calculated $C_{11}H_{10}Br_2O_2$, 331.9048).

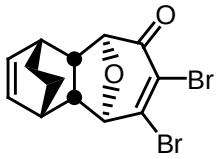
Preparation of Diels-Alder adduct 3.



3

To a 10 mL round bottom flask was added 3,4-dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (1.0 g, 3.6 mmol). Dichloromethane (1.5 mL) was added followed by cyclopentadiene (0.710 mL, 10.7 mmol). The flask was capped and stirred at 25 ºC for 24 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2; 100 g) using 5% ethyl acetate in hexanes as the eluent to afford **3** as a white solid (1.20 g, 97%): R_f= .45 (95:5 Hex:EtOAc); mp= 117-119 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (dd, J= 5.6, 2.9 Hz, 1H), 6.13 (dd, J= 5.6, 2.9 Hz, 1H), 4.55 (s, 1H), 4.34 (s, 1H), 3.07-3.04 (m, 2H), 2.99 (dd, J= 7.8, 3.9 Hz, 1H), 2.76 (dd, J= 7.8, 4.2 Hz, 1H), 1.60 (dt, J= 8.5, 1.7 Hz, 1H), 1.53-1.50 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.8, 152.8, 134.4, 134.2, 124.0, 83.9, 82.6, 53.5, 52.0, 47.6, 45.6, 45.4; IR (NaCl, cm^{-1}) 2973.1, 2890.2, 1710.7, 1361.8, 1223.2; Anal. Calcd. For $C_{12}H_{10}Br_2O_2$: C, 41.65; H, 2.91. Found: C, 41.99; H, 2.90.

Preparation of Diels-Alder adduct 4.

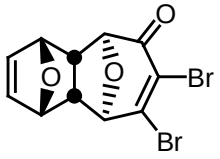


4

To a sealed tube was added 3,4-dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (1.0 g, 3.6 mmol). Toluene (1.5 mL) was added and the reaction stirred until all starting material was in solution. Cyclohexadiene (1.01 mL, 10.7 mmol) was added and the tube sealed. The tube was heated in an oil bath at 130 ºC for 30 h. The tube was removed from the oil bath and the solution allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2; 100 g) using 5% ethyl acetate in hexanes as the eluent to afford **4**

as a white solid (1.22 g, 95%): R_f= .47 (95:5 Hex:EtOAc); mp= 130-132 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25-6.22 (m, 2H), 4.67 (s, 1H), 4.45 (s, 1H), 2.92-2.87 (m, 1H), 2.84-2.81 (m, 1H), 2.46 (dd, J=8.2, 2.7 Hz, 1H), 2.28 (dd, J=8.2, 2.7 Hz, 1H), 1.59-1.45 (m, 2H), 1.30-1.23 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.8, 152.4, 132.7, 131.8, 124.6, 87.3, 86.2, 48.4, 44.9, 33.9, 33.7, 24.7, 23.8; IR (NaCl, cm^{-1}) 3046.3, 2938.2, 2866.4, 1703.7, 1566.0, 1227.8, 1051.4; Anal. Calcd. For $C_{13}H_{12}Br_2O_2$: C, 43.37; H, 3.36. Found: C, 43.45; H, 3.33.

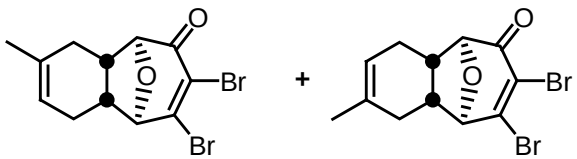
Preparation of Diels-Alder adduct 5.



5

To a sealed tube was added 3,4-dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (1.0 g, 3.6 mmol). Benzene (1.5 mL) was added and the reaction stirred until all starting material was in solution. Furan (0.779 mL, 10.7 mmol) was added and the tube sealed. The tube was heated in an oil bath at 100 ºC for 5 d. The tube was removed from the oil bath and the solution allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2; 100 g) using 33% ethyl acetate in hexanes as the eluent to afford **5** as a white solid (746 mg, 60%): R_f= .26 (2:1 Hex:EtOAc); mp= 161-163 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (dd, J= 5.9, 1.7 Hz, 1H), 6.43 (dd, J= 5.9, 1.7 Hz, 1H), 5.04 (dd, J=10.7, 4.9 Hz, 2H), 4.50 (s, 1H), 4.27 (s, 1H), 3.19 (dd, J= 7.8, 4.9 Hz, 1H), 2.98 (dd, J= 7.8, 4.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ185.9, 151.8, 134.5, 134.4, 124.2, 81.6, 80.3, 79.6, 79.4, 51.8, 47.6; IR (NaCl, cm^{-1}) 3005.0, 2955.6, 1711.5, 1362.1, 1223.0; Anal. Calcd. For $C_{11}H_8Br_2O_3$: C, 37.97; H, 2.32. Found: C, 38.14; H, 2.32.

Preparation of Diels-Alder adduct 6.



6

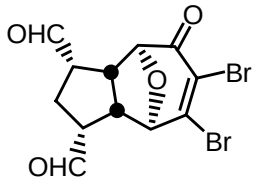
To a sealed tube was added 3,4-dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (1.0 g, 3.6 mmol). Toluene (1.5 mL) was added and the reaction stirred until all starting material was in solution. Isoprene (1.22 mL,

10.7 mmol) was added and the tube sealed. The tube was heated in an oil bath at 110 ºC for 5 d. The tube was removed from the oil bath and the solution allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2; 100 g) using 5% ethyl acetate in hexanes as the eluent to afford a mixture of regioisomers **6** as a white solid (746 mg, 60%): R_f= .55 (95:5 Hex:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60-5.57 (m, 2H), 4.67 (s, 1H), 4.43 (s, 1H), 2.51-2.25 (m, 8H), 2.05-1.87 (m, 4H), 1.75 (d, J= 7.3 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.14, 187.12, 151.9, 151.7, 137.6, 137.2, 123.8, 123.7, 121.7, 121.4, 88.8, 88.7, 88.3, 88.2, 44.1, 44.0, 40.8, 40.6, 33.6, 33.2, 28.5, 28.2, 23.07, 23.06; IR (NaCl, cm^{-1}) 2931.0, 2839.2, 1703.9, 1571.1, 1234.5, 1192.5; HRMS m/z 345.9204 (calculated $C_{12}H_{12}Br_2O_2$, 345.9204).

Procedure for Diels-Alder Competition Studies.

3,4-dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (1.0 eq) and a bridged dienophile **8-12** (1.0 eq) were dissolved in methylene chloride (3.6 M). Cyclopentadiene (1.0 eq) was added and the reaction was stirred at 25 ºC for 24 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2; 10g) using 5% ethyl acetate in hexanes as the eluent. The compounds isolated were **3** (95%) and **8-12**.

Preparation of Dialdehyde 13.



13 To a 10 mL round bottom flask was added THF (3.0 mL) and *t*BuOH (1.0 mL). 4-methylmorpholine-N-oxide (51.0 mg, 0.434 mmol) was added and the mixture was stirred at 25 ºC. Osmium tetraoxide, 4 wt.% in water, (0.092 mL, 0.0145 mmol) was added followed by **2** (100 mg, 0.289 mmol). The solution was stirred at 25 ºC for 2 h. Sat. sodium bisulfite (0.500 mL) was added and the solution stirred for 30 min. The layers were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organics were dried over sodium sulfate and concentrated to give the crude diol as a white solid (112 mg, 102%). The diol was dissolved in THF (3.0 mL)

and water (1.0 mL). Sodium periodate (93 mg, 0.434 mmol) was added and the solution was stirred at 25 ºC for 10 min. The white precipitate was filtered off and washed with EtOAc (3x10 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give **13** as a white solid (96 mg, 88%): R_f= 0.20 (1:2 Hex:EtOAc); mp= decomposed above 95 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.94 (d, J= 0.98 Hz, 1H), 5.13 (s, 1H), 4.70 (s, 1H), 3.30 (dd, J= 6.8, 2.2 Hz, 1H), 3.15-3.00 (m, 3H), 2.26-2.21 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.5, 199.7, 185.6, 124.6, 84.1, 83.2, 53.6, 52.6, 48.6, 45.6, 27.3; IR (NaCl, cm^{-1}) 3054.9, 2977.8, 1707.8, 1263.3; HRMS m/z 375.8950 (calculated $C_{12}H_{10}Br_2O_4$, 375.8946).

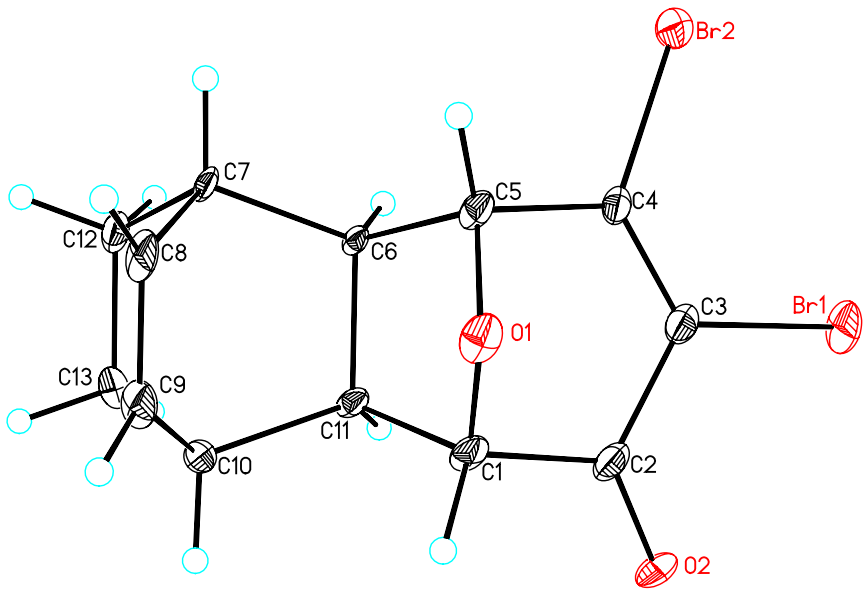


Figure 1: X-ray structure of compound **4.**

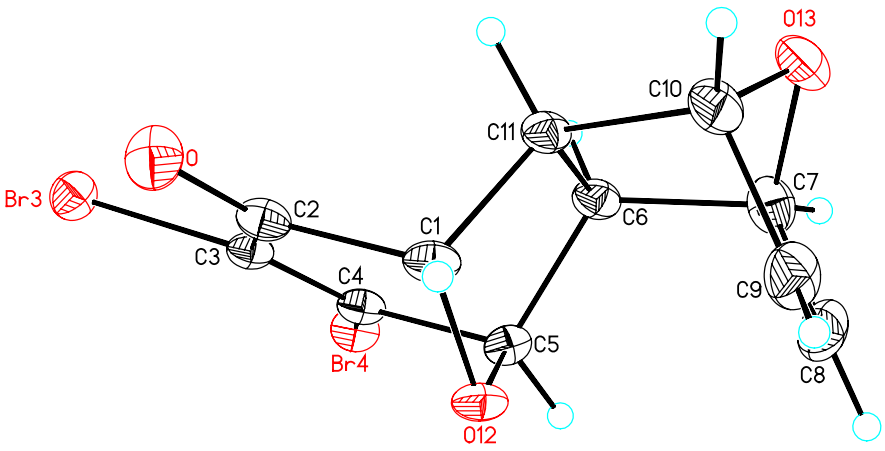
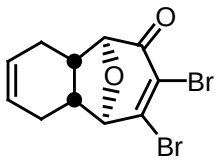


Figure 2: X-ray structure of compound **5**.



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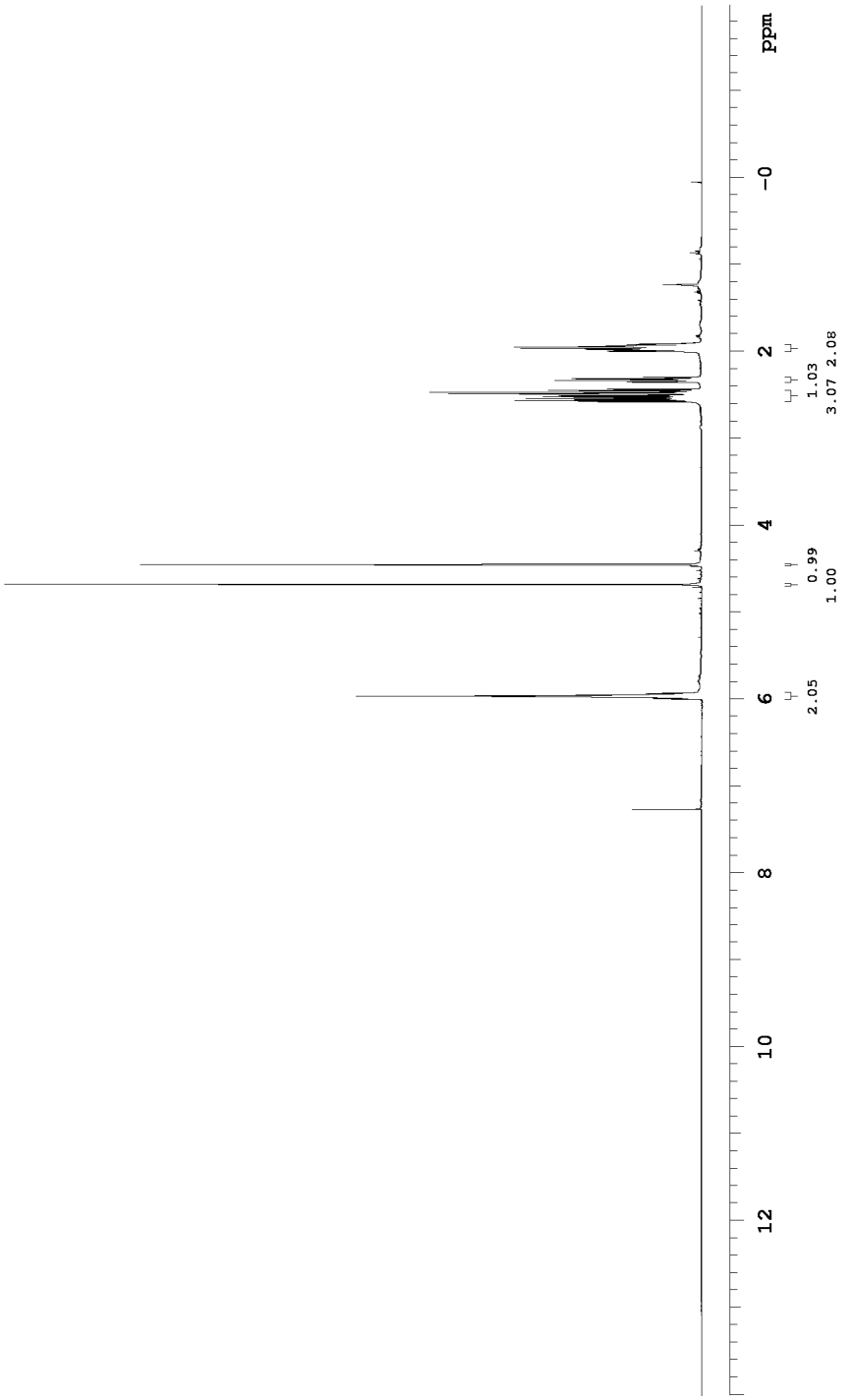

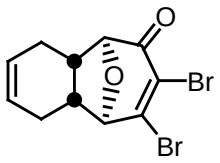

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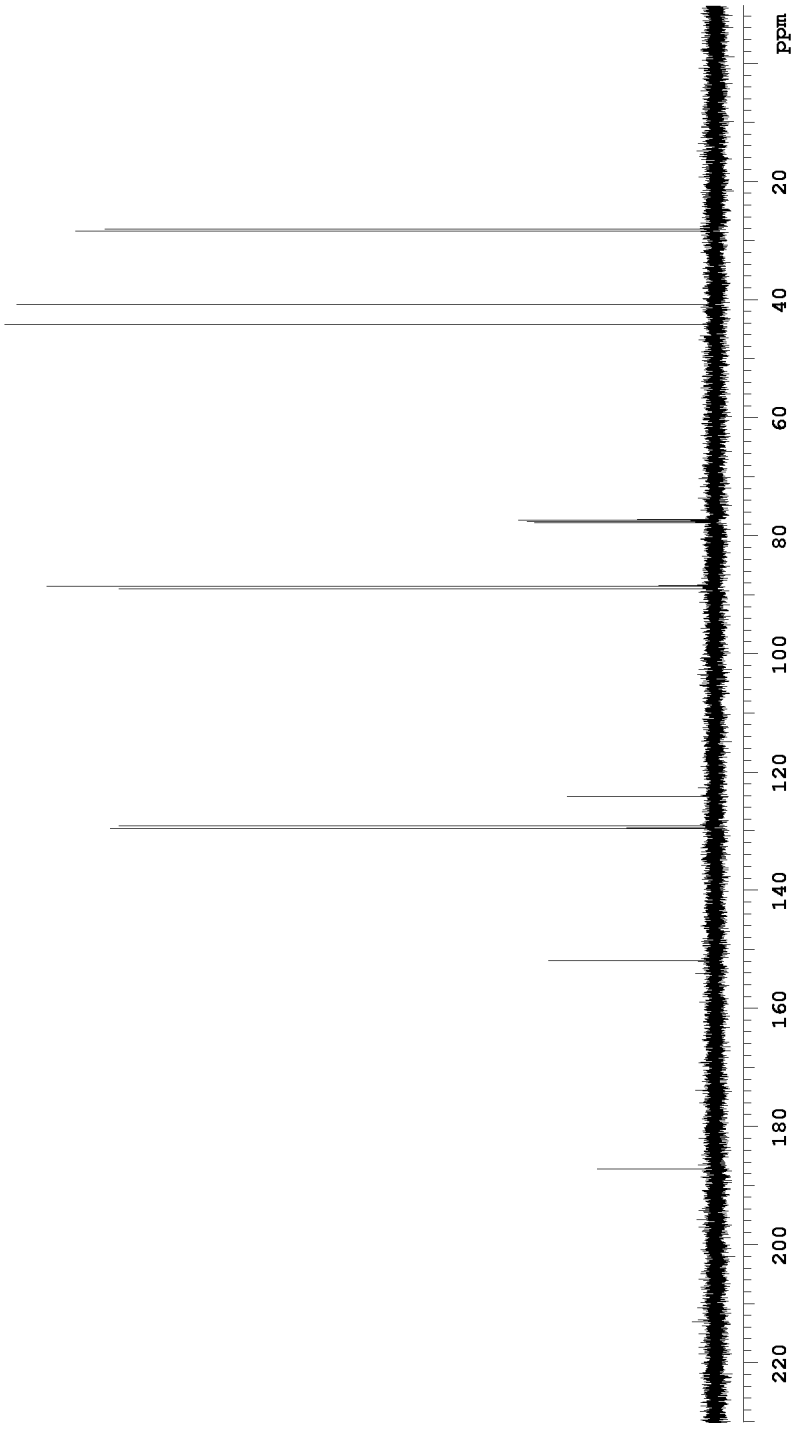

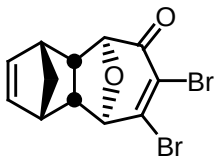

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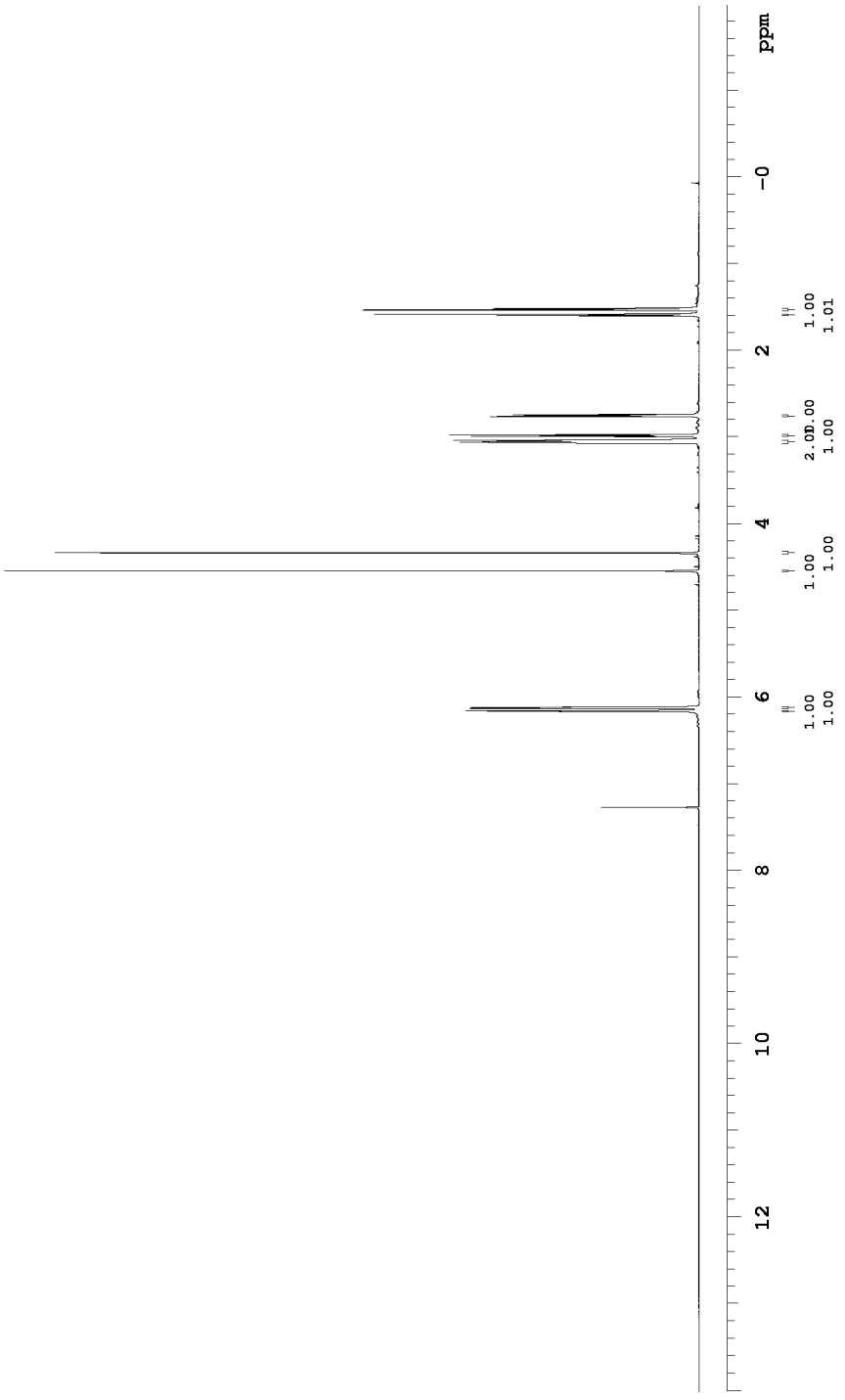

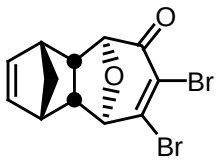

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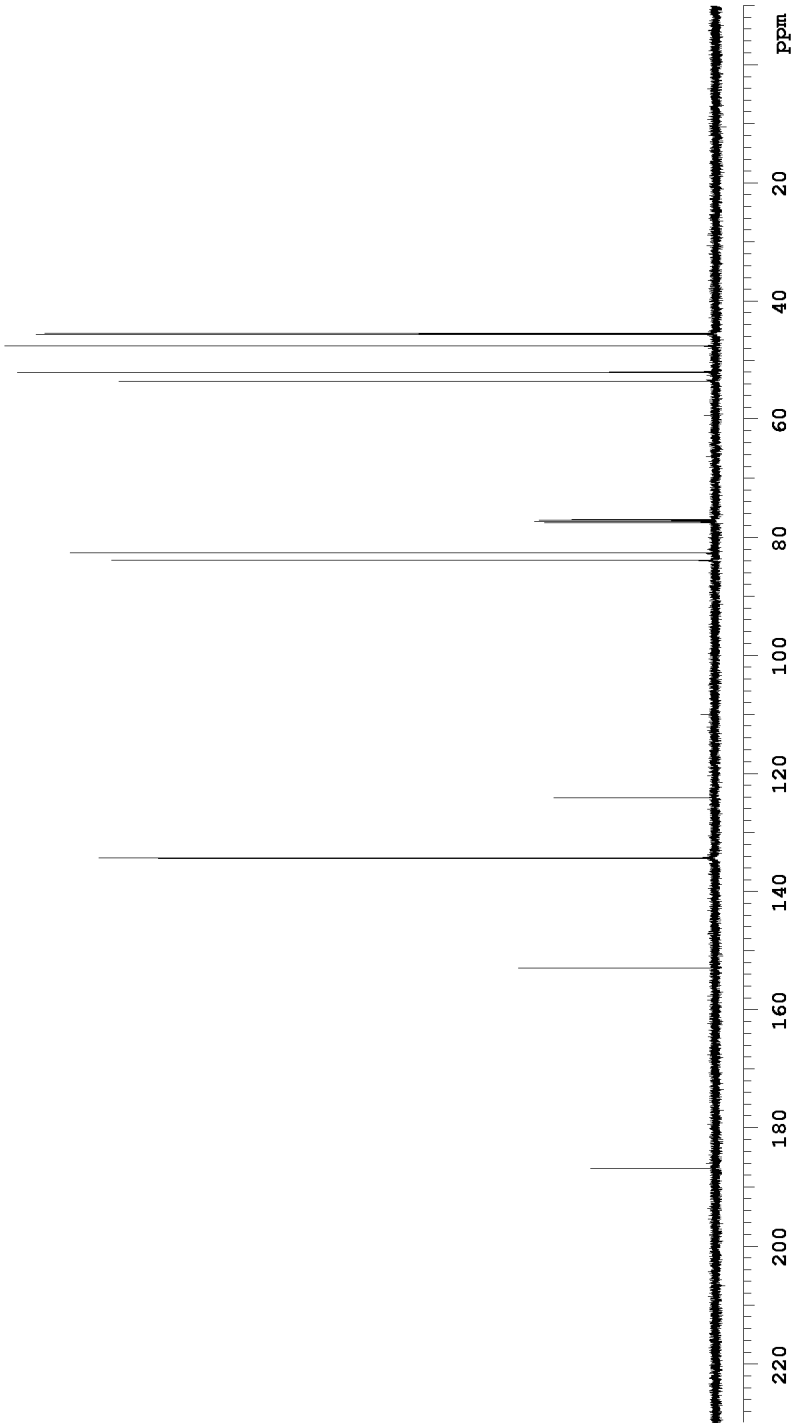

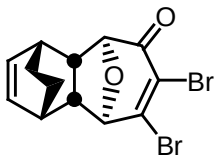

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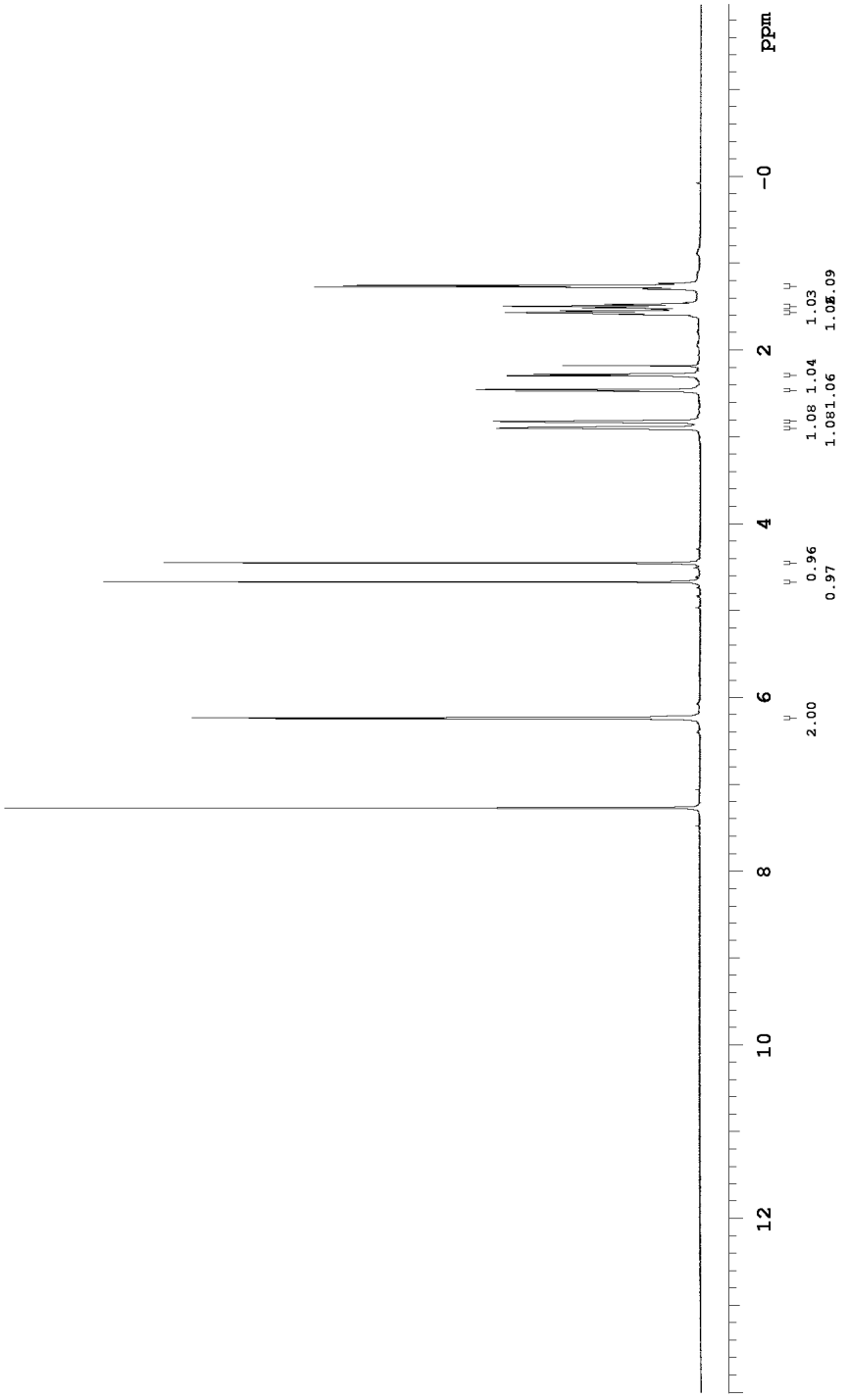

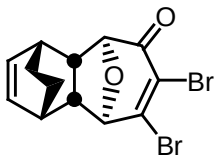

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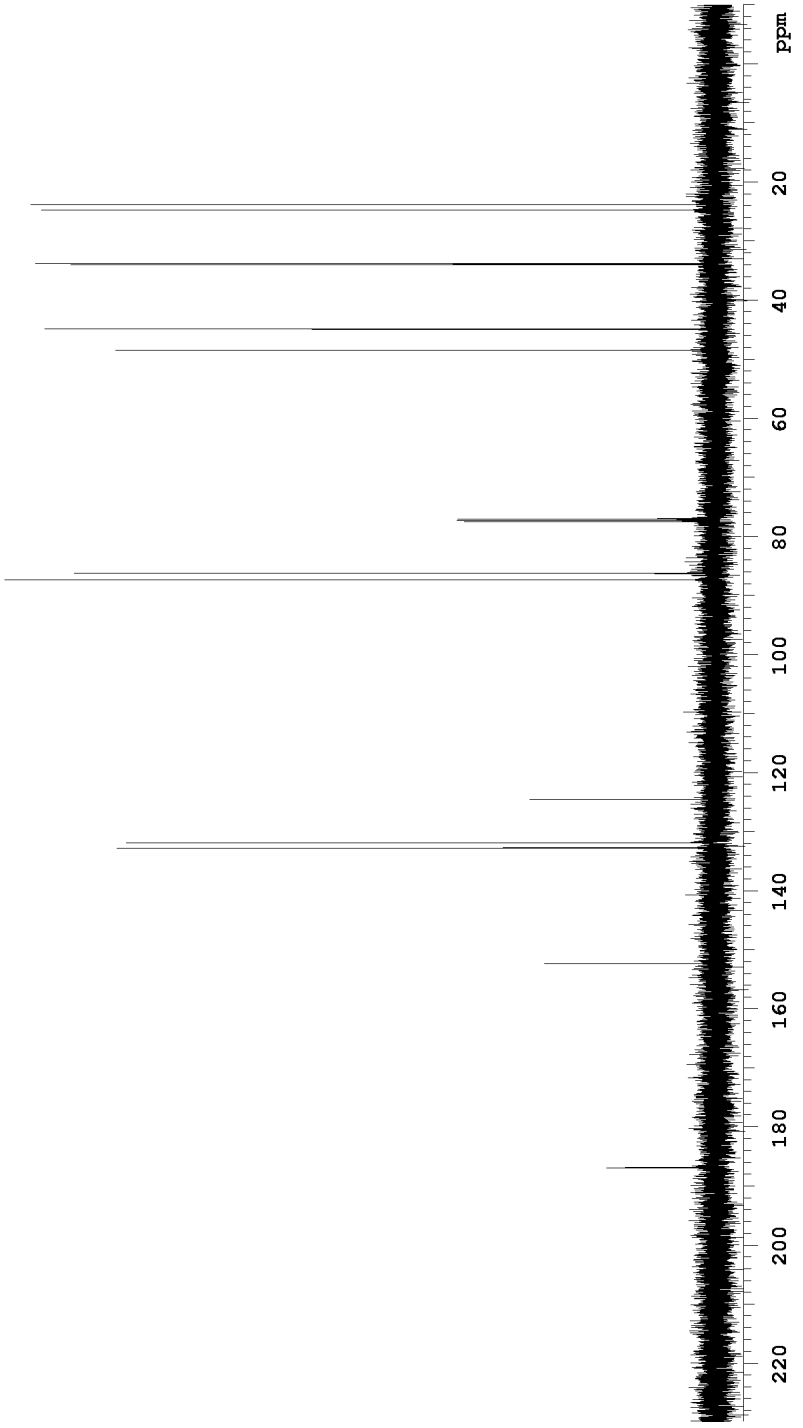

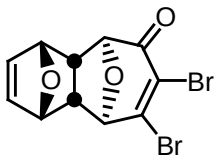

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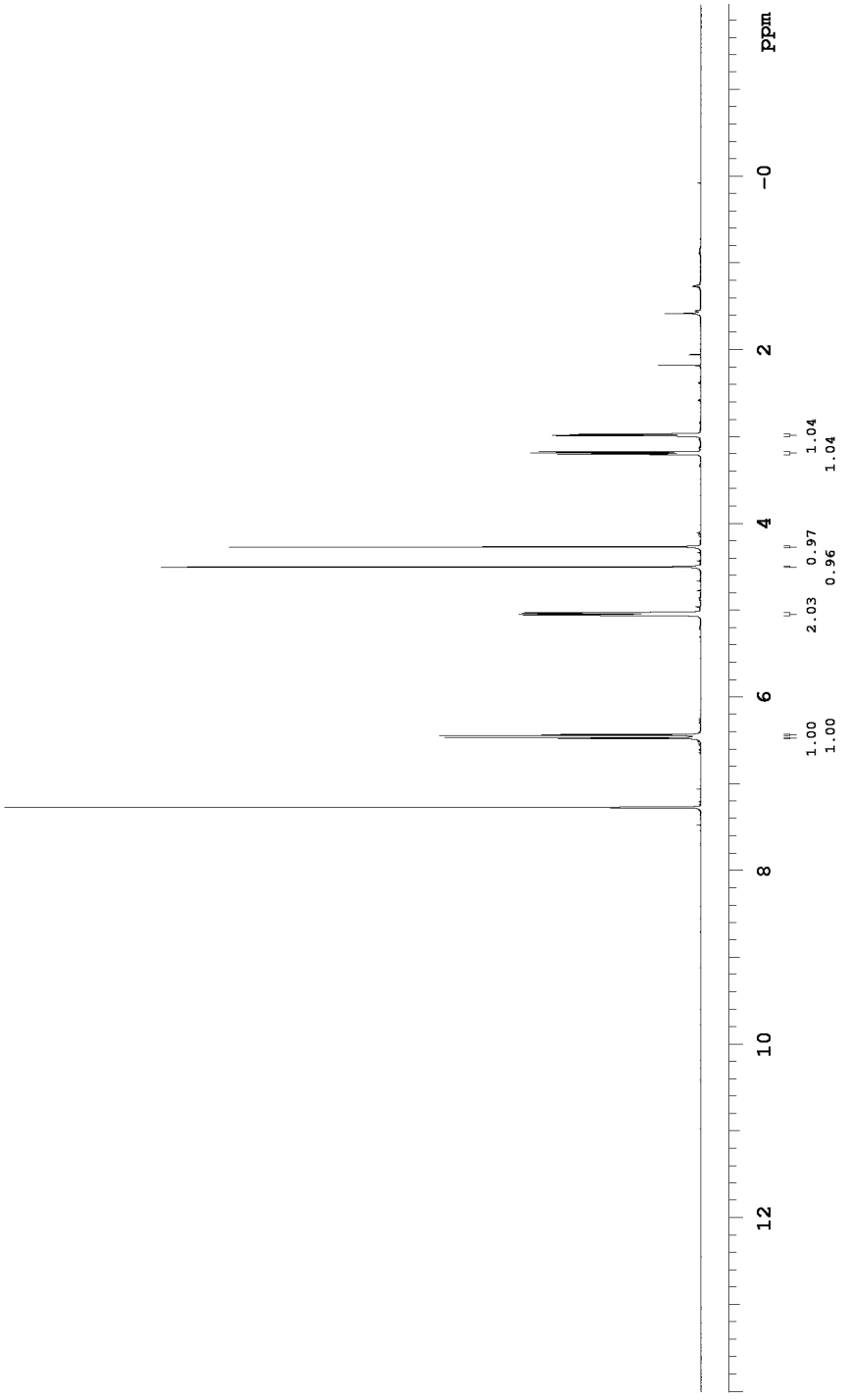

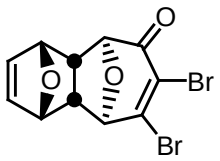

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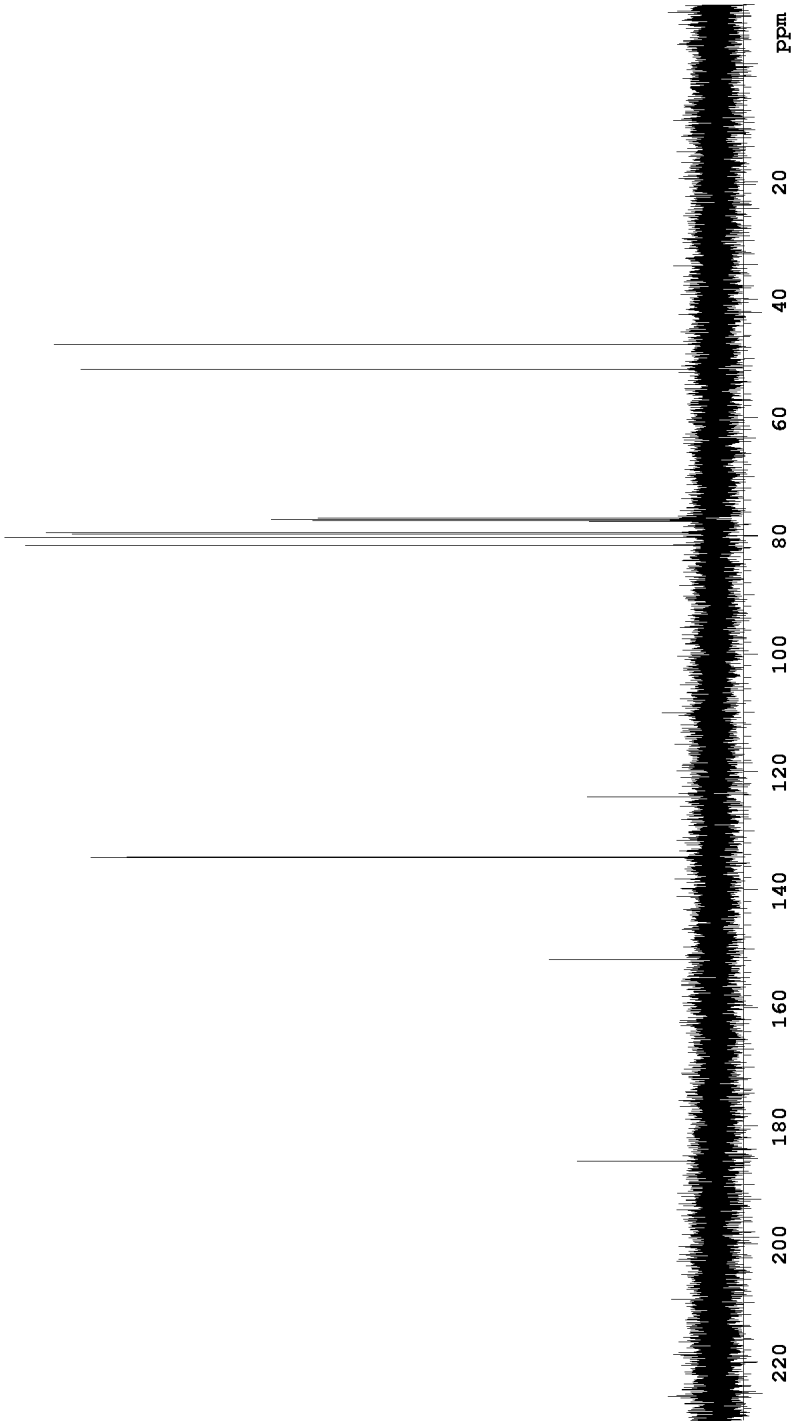

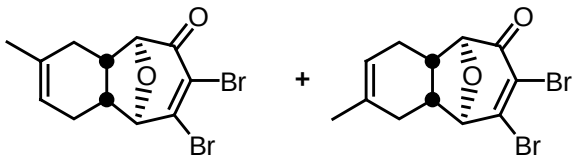

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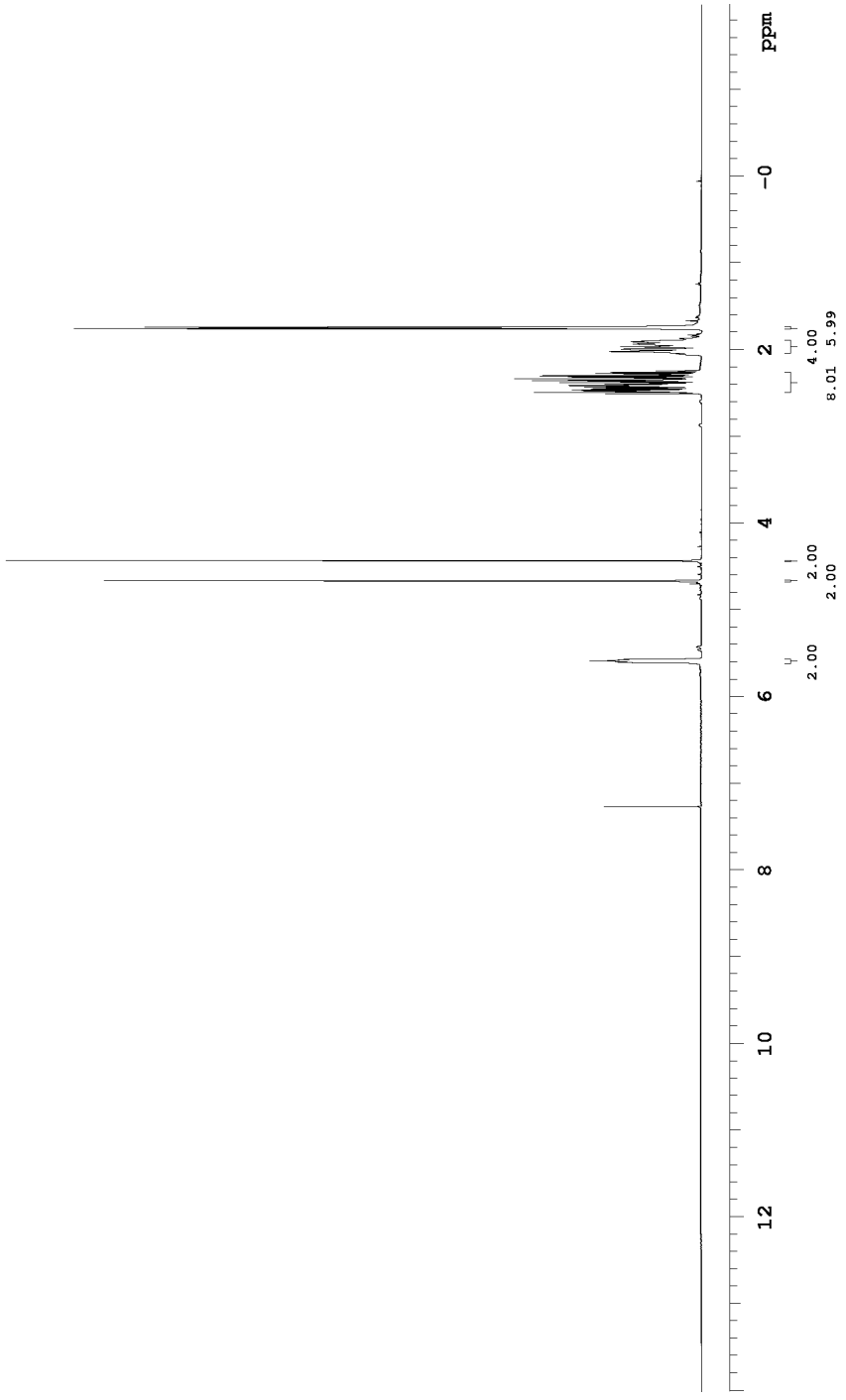

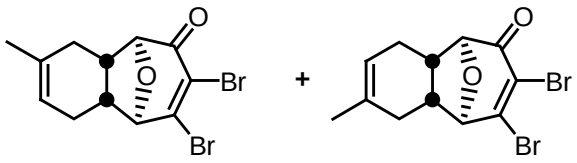

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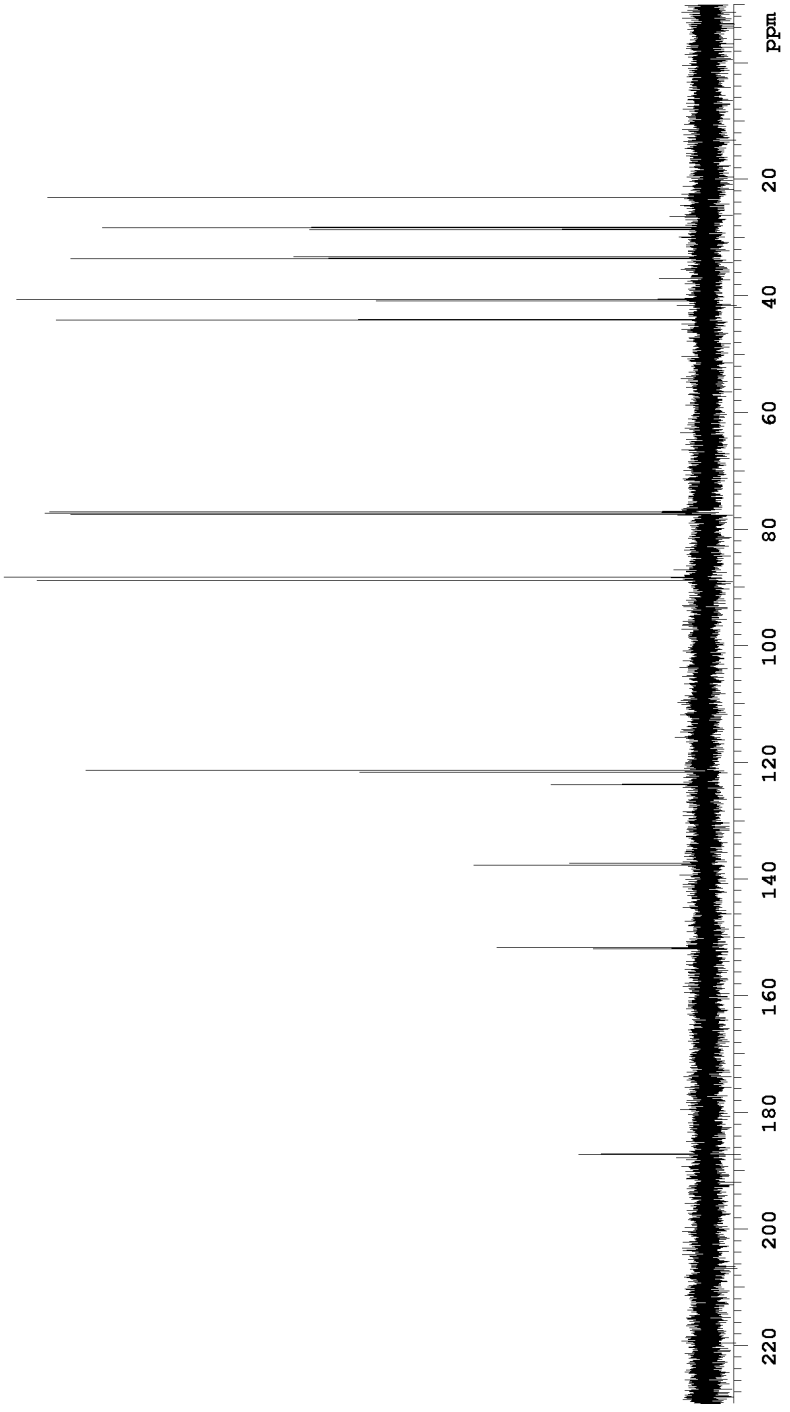

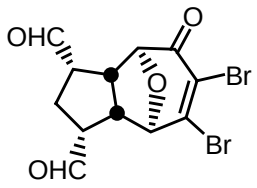

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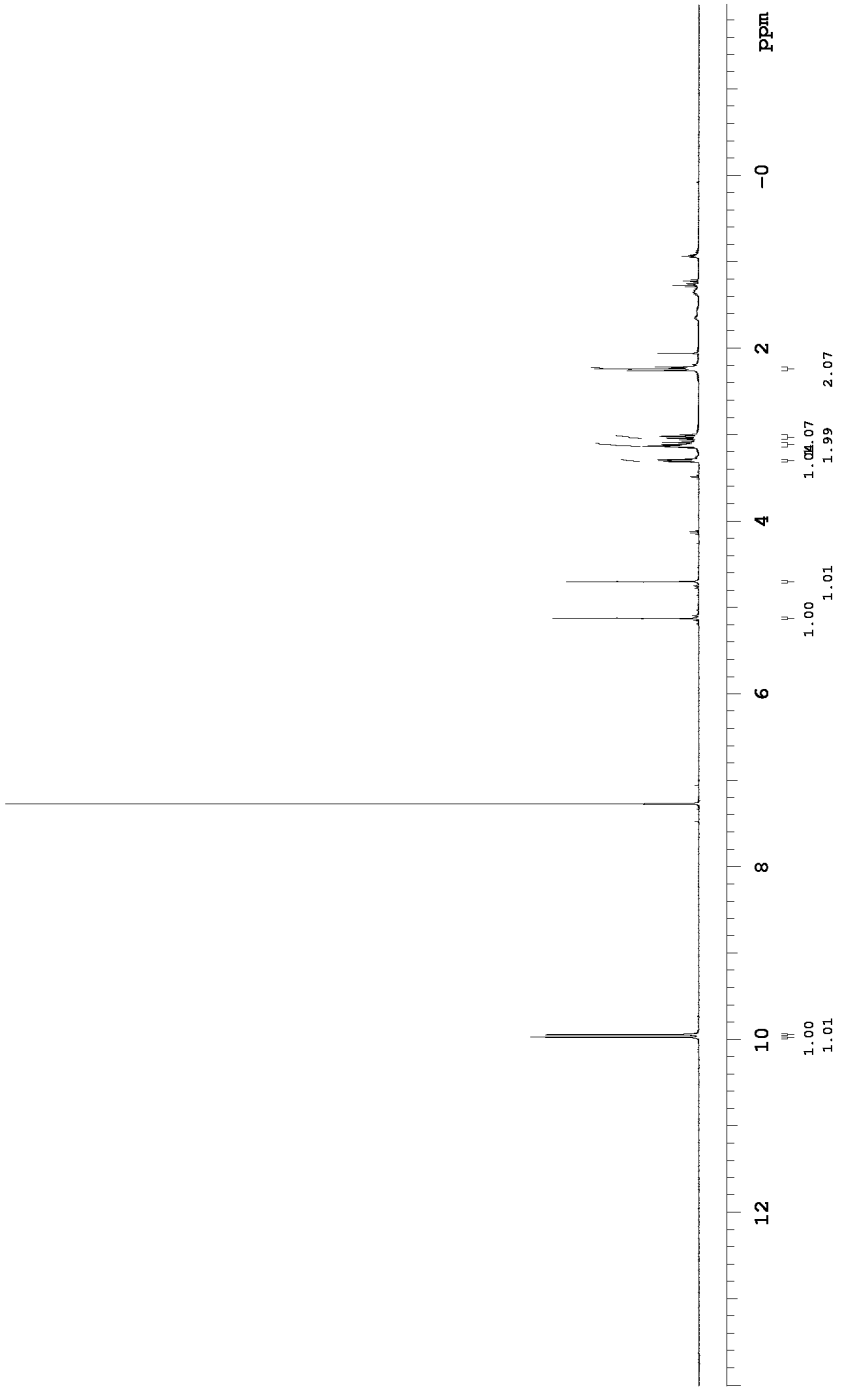

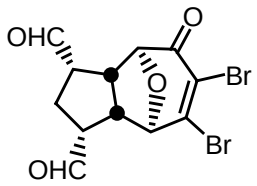

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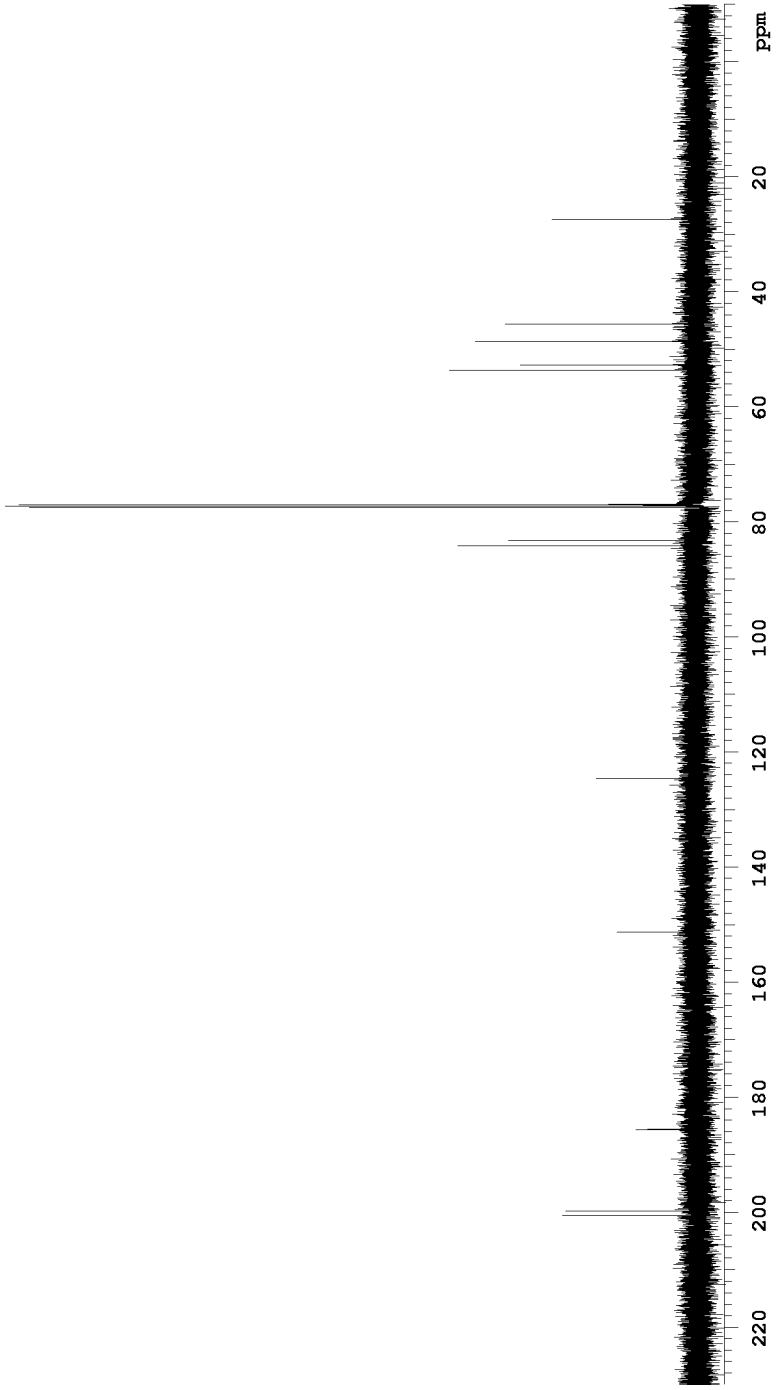

References:

1. Orugunty, R. S.; Wright, D. L.; Battiste, M. A.; Helmich, R. J.; Abboud, K. *J. Org. Chem.* **2004**, 69, 406-416.