Supplementary Information

Ruthenium-catalyzed C–H oxygenation of quinones by weak *O*-coordination for potent trypanocidal agents

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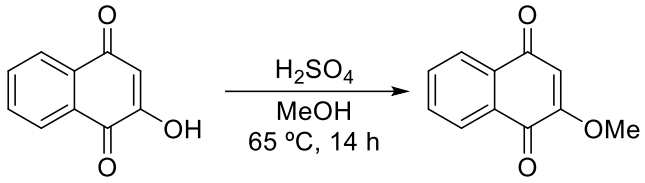
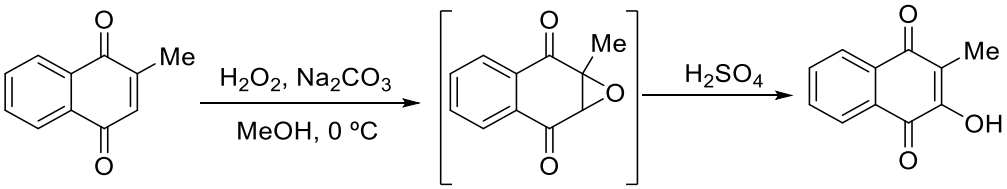
General Remarks

All catalytic reactions were carried out under air using pre-dried 25 mL Schlenk- or pressure tubes. 1,4-Naphthoquinone (**1a**) was purified *via* reduced pressure sublimation using a cold finger sublimation apparatus (50 °C, 0.9 mbar) and stored in a glovebox to prevent contact with moisture. Other chemicals were obtained from commercial sources and used without further purification. Yields refer to isolated compounds, estimated to be > 95% pure as determined by ^{1}H NMR and GC. TLC: Merck, TLC Silica gel 60 F_{254}, detection at 254 nm. Chromatographic separations were carried out on Merck Geduran SI-60 (0.040–0.063 mm). IR spectra were recorded on a Bruker ATR FT-IR Alpha device. MS: EI-MS: Jeol AccuTOF at 70 eV; ESI-MS: Bruker maXis and MicrOTOF. High resolution mass spectrometry (HRMS): Bruker maXis, Bruker MicrOTOF and Jeol AccuTOF. Melting points (M.p.): Büchi 540 capillary melting point apparatus, values are uncorrected. NMR spectra were recorded on Varian Mercury VX 300, Inova-500, Inova-600 and Bruker Avance 300, Avance III 300, Avance III HD 400, Avance III 400, Avance III HD 500 instruments, if not otherwise specified, chemical shifts (δ) are provided in ppm.

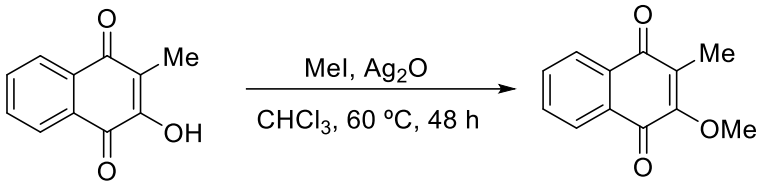
Synthesis of Substrates 1



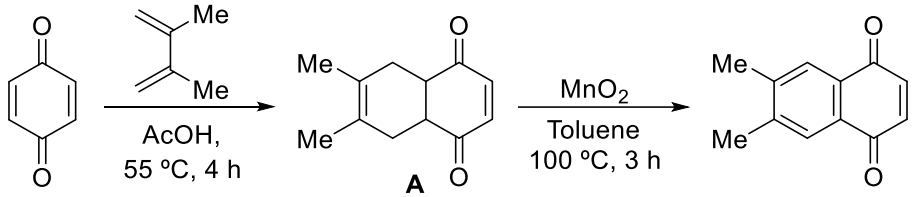
2-Methoxy-1,4-naphthoquinone (1c): 2-Hydroxy-1,4-naphthoquinone (**1a**) (1.04 g, 6.00 mmol) and concentrated sulfuric acid (0.4 mL) were added to MeOH (150 mL). The mixture was heated to 65 °C for 14 h and cooled to 25 ºC, then the solid was filtered and washed with MeOH (50 mL) and H_2O (100 mL) to provide 2-methoxy-1,4-naphthoquinone (**1c**) (1.03 g, 91%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.09–8.02 (m, 2H), 7.70–7.68 (m, 2H), 6.13 (s, 1H), 3.87 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 184.6, 179.9, 160.3, 134.2, 133.2, 131.9, 130.9, 126.6, 126.1, 109.8, 56.4; **m.p. (°C)** = 186-188. The data are consistent with those reported in the literature.[1]



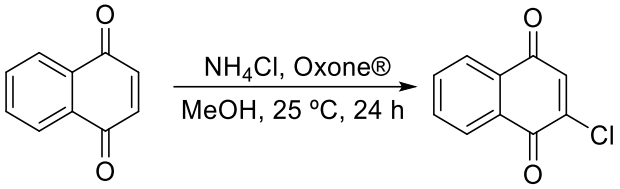
2-Hydroxy-3-methyl-1,4-naphthoquinone: 2-Methyl-1,4-naphthoquinone (**1f**), (1.0 g, 5.8 mmol) was dissolved in methanol (10 mL) at 0 ºC. Then, a solution of Na_2CO_3 (0.2 g in 1 mL of water) and H_2O_2 (1 mL of H_2O_2 30 % in 5 mL of water) were added slowly. Water (100 mL) was added and 2-methyl-1,4-naphthoquinone oxide precipitated as a white solid, which was filtered off. Concentrated H_2SO_4 (5 mL) was added and the mixture was kept in rest for 10 min. Addition of water (20 mL) provided a yellow solid, which was filtered and purified by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) to provide 2-hydroxy-3-methyl-1,4-naphthoquinone (808 mg, 74%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.10 (dd, J = 6.0, 1.5 Hz, 1H), 8.04 (dd, J = 6.0, 1.5 Hz, 1H), 7.71 (dd, J = 6.0, 1.5 Hz, 1H), 7.64 (dd, J = 6.0, 1.5 Hz, 1H), 7.30 (s, 1H), 2.08 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 185.0, 181.1, 153.1, 134.8, 132.8, 132.9, 129.4, 126.7, 126.1, 120.5, 8.7; **m.p. (°C)** = 173-174. The data are consistent with those reported in the literature.[2]



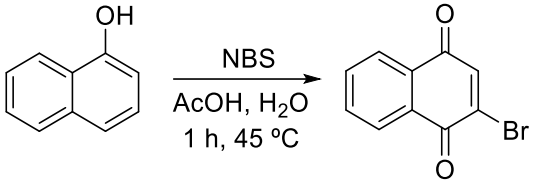
2-Methoxy-3-methyl-1,4-naphthoquinone (1e): 2-Hydroxy-3-methyl-1,4-naphthoquinone (376 mg, 2.00 mmol), Ag_2O (0.7 g, 3.0 mmol) and MeI (250 µL, 4.00 mmol,) were dissolved in $CHCl_3$ (50 mL) and heated to 60 °C for 48 h. After cooling to 25 ºC, the solids were removed through filtration through a Celite pad. The solvent was evaporated under reduced pressure. After purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) the 2-methoxy-3-methyl-1,4-naphthoquinone (**1e**) (287 mg, 71%) was obtained as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.05–8.00 (m, 2H), 7.67–7.64 (m, 2H), 4.09 (s, 3H), 2.07 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 185.6, 181.1, 157.7, 133.6, 133.1, 131.9, 131.7, 131.4, 126.1, 126.0, 61.0, 9.4; **m.p. (°C) =** 101-102. The data are consistent with those reported in the literature.[2]



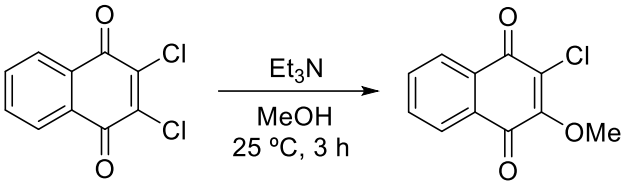
6,7-Dimethyl-1,4-naphthoquinone (1g): 2,3-Dimethyl-1,3-butadiene (1.2 mL, 10.2 mmol) and *p*-benzoquinone (1.03 g, 9.50 mmol,) were dissolved in HOAc (10 mL) and the solution was heated to 55 °C for 4 h. After cooling to 25 ºC, HOAc was evaporated under reduced pressure and EtOH (20 mL) was added. The solid was filtered off and washed with H_2O (100 mL), EtOH (50 mL) and Et_2O (50 mL) to provide a white solid. Without further purification, the white solid, 6,7-dimethyl-4a,5,8,8a-tetrahydronaphthalene-1,4-dione **A**, was dissolved in PhMe (100 mL) and heated to 100 °C. MnO_2 (13.0 g, 87.0 mmol) was added slowly over a period of 10 min and the solution was heated to 100 °C for 3 h. The solution was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The crude product was recrystallized from EtOH to afford 6,7-dimethyl-1,4-naphthoquinone (**1g**) (2.0 g, 80%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.77 (s, 2H), 6.86 (s, 2H), 2.36 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 185.1, 143.6, 138.4, 129.8, 127.3, 20.2; **m.p. (°C) =** 115-117. The data are consistent with those reported in the literature.[3]



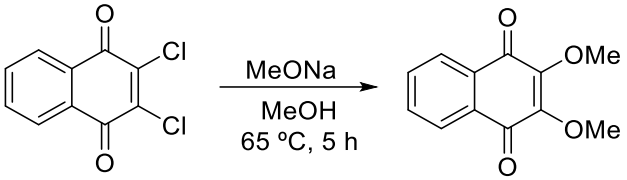
2-Chloro-1,4-naphthoquinone (1h): 1,4-Naphthoquinone (158 mg, 1.00 mmol,) and NH_4Cl (60 mg, 1.1 mmol) were added to MeOH (5 mL) under vigorous stirring. Oxone® (338 mg, 1.1 mmol,) was slowly added and the solution was allowed to stir at 25 ºC for 24 hours. H_2O was added (5 mL), the organic phase was extracted with EtOAc (10 mL) and dried over Na_2SO_4. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 25:1) yielded 2-chloro-1,4-naphthoquinone (**1h**) (102 mg, 53%), as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.15–8.13 (m, 1H), 8.07–8.05 (m, 1H), 7.76–7.74 (m, 2H), 7.19 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 182.9, 178.2, 146.6, 136.1, 134.7, 134.4, 132.0, 131.5, 127.7, 127.0; **m.p. (°C) =** 113-114. The data are consistent with those reported in the literature.[4,5,18]



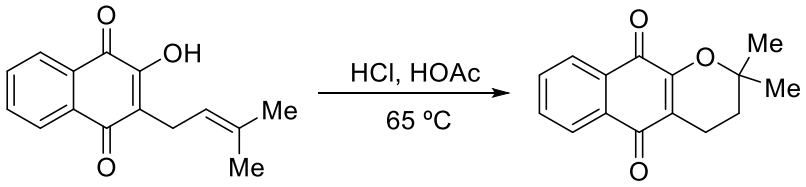
2-Bromo-1,4-naphthoquinone (1i): 1-Naphthol (1.0 g, 7.0 mmol) was dissolved in HOAc (70 mL) and added dropwise to solution of *N*-bromosuccinimide (4.5 g, 26 mmol in 70 mL HOAc/70 mL H_2O) at 45 ºC. After 1 h the mixture was cooled to 25 ºC and H_2O (70 mL) was added. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with sat. aq. $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed and the crude product purified by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) to yield 2-bromo-1,4-naphthoquinone (**1i**) (78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.15–8.12 (m, 1H), 8.06–8.04 (m, 1H), 7.77–7.71 (m, 2H), 7.48 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 182.4, 177.8, 140.3, 140.1, 134.4, 134.1, 131.7, 130.9, 127.8, 126.8; **m.p. (°C) =** 130-132. The data are consistent with those reported in the literature.[6]



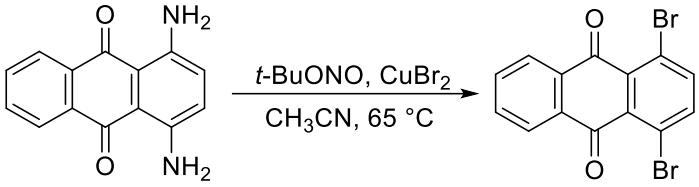
2-Chloro-3-methoxy-1,4-naphthoquinone (1j): 2,3-Dichloro-1,4-naphthoquinone (0.91 g, 4.00 mmol) and NEt_3 (0.61 mL, 4.40 mmol) were dissolved in MeOH (35 mL) at 25 ºC. After 3 h, the solid was filtered off and washed with cold H_2O (50 mL) to afford 2-cloro-3-methoxy-1,4-naphthoquinone (**1j**) (705 mg, 79%) as a green solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.12–8.03 (m, 2H), 7.73–7.70 (m, 2H), 4.28 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 179.5, 178.4, 156.6, 134.2, 133.8, 131.0, 128.2, 127.7, 126.9, 126.8, 61.8; **m.p. (°C) =** 143-145. The data are consistent with those reported in the literature.[7]



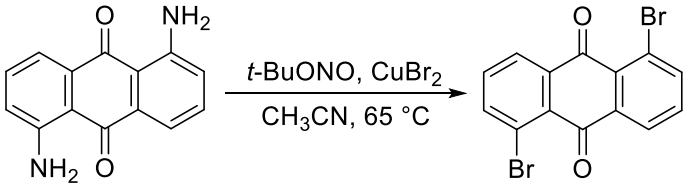
2,3-Dimethoxy-1,4-naphthoquinone (1k): 2,3-Dichloro-1,4-naphthoquinone (1.09 g, 5.00 mmol) and NaOMe (0.81 g, 15.0 mmol) were dissolved in MeOH (25 mL) and heated to 65 °C for 5 h. Then, a second portion of NaOMe (0.81 g, 15.0 mmol) was added and the mixture was heated to 65 °C for 1 h. The solvent was evaporated and H_2O (20 mL) was added. The solid was filtered off and washed with H_2O (100 mL) to provide 2,3-methoxy-1,4-naphthoquinone (**1k**) (810 mg, 74%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 7.97 (dd, J = 3.3, 2.4 Hz, 2H), 7.62 (dd, J = 3.3, 2.4 Hz, 2H), 4.04 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 181.6, 147.3, 133.5, 130.6, 126.0, 61.3; **m.p. (°C) =** 112-114. The data are consistent with those reported in the literature.[8]



α-Lapachone (1l): Lapachol (0.97 g, 4.00 mmol) was dissolved in HCl (40 mL) and HOAc (15 mL) at 25 ºC. Then, the mixture was heated to 65 ºC for 1 h. After cooling to 25 ºC, cold H_2O (250 mL) was added and the solid was filtered off. Recrystallization from EtOH provided α-lapachone (**1l**) (0.61 g, 63%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.06–8.02 (m, 2H), 7.69–7.59 (m, 2H), 2.59 (t, J = 6.6 Hz, 2H), 1.79 (t, J = 6.6 Hz, 2H), 1.40 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 184.2, 179.8, 154.5, 133.7, 132.8, 132.0, 131.1, 126.2, 125.9, 120.1, 78.1, 31.5, 26.6, 16.8; **m.p. (°C)** = 113-115. The data are consistent with those reported in the literature.[9]



1,4-Dibromo-9,10-anthraquinone (3a): 1,4-Diamino-9,10-anthraquinone (2.00 g, 8.39 mmol), $CuBr_2$ (4.23 g, 18.9 mmol) and *t*-BuONO (1.95 g, 18.9 mmol) were added to MeCN (15 mL). The mixture was heated to 65 ºC for 5 h and then cooled to 25 ºC. A aq. solution of HCl (1M, 100 mL) was added and the solution was extracted with CH_2Cl_2 (4 x 20 mL). Subsequently, the organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Then, the product was purified by column chromatography (PhMe) to yield 1,4-dibromo-9,10-anthraquinone (**3a**) (2.58 g, 84%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.14 (dd, J = 2.7, 3.3 Hz, 2H), 7.76 (s, 2H), 7.75–7.73 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 181.4, 140.5, 134.1, 133.4, 133.3, 126.8, 122.0; **m.p. (°C)** = 220-221. The data are consistent with those reported in the literature.[10]

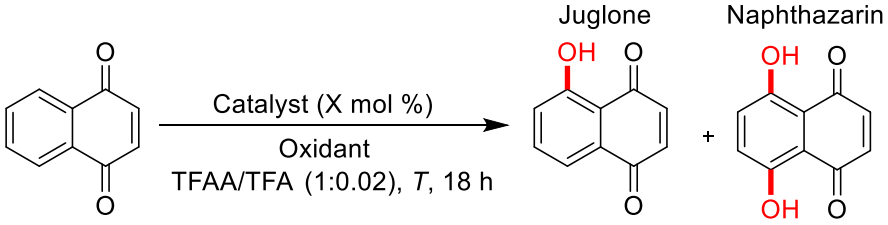


1,5-Dibromine-9,10-anthraquinone (3b): 1,5-Diamino-9,10-anthraquinone (2.00 g, 8.39 mmol), $CuBr_2$ (4.23 g, 18.9 mmol) and *t*-BuONO (1.95 g, 18.9 mmol) were added to MeCN (15 mL). The mixture was heated to 65 ºC for 5 h and then cooled to 25 ºC. A

aq. solution of HCl (1M, 100 mL) was added and the solution was extracted with CH_2Cl_2 (4 x 20 mL). Subsequently, the organic extract was dried over Na_2SO_4 and solvent was evaporated under reduced pressure. Then, the product was purified by column chromatography (PhMe) to yield 1,5-dibromine-9,10-anthraquinone (**3b**) (2.58 g, 84%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 8.29 (dd, J = 6.6, 1.2 Hz, 1H), 7.99 (dd, J = 6.6, 1.2 Hz, 1H), 7.60–7.54 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 181.0, 140.8, 137.1, 134.1, 130.2, 127.7, 122.0; **m.p. (°C)** = 294-296. The data are consistent with those reported in the literature.[10]

C–H Oxygenation reactions

Table S1: Optimization studies for the ruthenium(II)-catalyzed oxygenation of 1,4-naphthoquinone

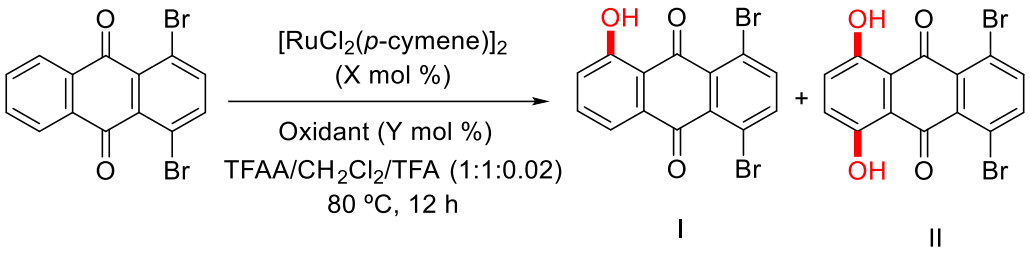


Entry	Catalyst	Oxidant	*T* / ºC	Juglone	Naphthazarin
1	$[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %)	PIFA (2 equiv.) / Ag_2CO_3 (1 equiv.)	110	52%	32%
2	$[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %)	PIFA (2 equiv.)	110	53%	42%
3	$[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %)	PIFA (1.2 equiv.)	80	87%	5%
4	$[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %)	PIDA (1.2 equiv.)	80	71%	Trace
5[a]	**$[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %)**	**PIFA (1.2 equiv.)**	**80**	**92%**	**3%**
6	-	PIFA (1.2 equiv.)	80	NR	NR
7	$[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %)	$NH_4S_2O_8$ (1.2 equiv.)	80	NR	NR
8	$RuCl_3{\cdot}nH_2O$ (5.0 mol %)	PIFA (1.2 equiv.)	80	NR	NR
9	$[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %)	PIFA (1.2 equiv.)	80	79%	13%

10	$Pd(OAc)_2$ (5.0 mol %)	PIFA (1.2 equiv.)	80	NR	NR
11	$[RuCl_2(p\text{-cymene})]_2$ (1.5 mol %)	PIFA (1.2 equiv.)	80	79%	11%
12	$[RuCl_2(p\text{-cymene})]_2$ (1.0 mol %)	PIFA (1.2 equiv.)	80	71%	7%
13	$CoCp^*(CO)I_2$ (10 mol %)	PIFA (1.2 equiv.)	80	NR	NR
14	$[RhCp^*Cl_2]_2$ (5.0 mol %)	PIFA (1.2 equiv.)	80	NR	NR
15	$[Ru(OAc)_2(p\text{-cymene})]$ (5.0 mol %)	PIFA (1.2 equiv.)	80	86%	7%
16	$MnBr(CO)_5$ (10 mol %)	PIFA (1.2 equiv.)	80	NR	NR

Reactions conditions: 1,4-naphthoquinone (63 mg, 0.4 mmol), TFAA (1 mL) and TFA (0.02 mL). Entries 1-4, 12 hours of reaction. Entry 5-16, 18 hours of reaction.

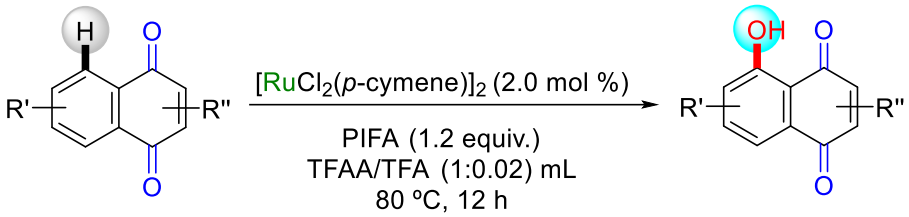
Table S2: Optimization studies for the ruthenium(II)-catalyzed oxygenation of 1,4-dibromo-anthraquinone



I II

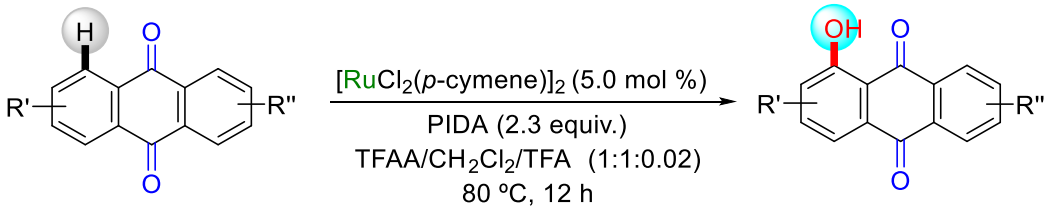
Entry	Catalyst	Oxidant	I	II	SM
1	$[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %)	PIFA (1.2 equiv.)	17%	-	65%
2	$[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %)	PIFA (1.2 equiv.)	15%	8%	51%
3	$[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %)	PIFA (2 equiv.)	52%	10%	31%
4	$[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %)	PIDA (2.3 equiv.)	70%	10%	6%

Reaction conditions: 1,4-dibromoanthraquinone (73 mg, 0.2 mmol), TFAA (1 mL), CH_2Cl_2 (1 mL), TFA (0.02 mL), 80 °C, 12 h.



General Procedure A:

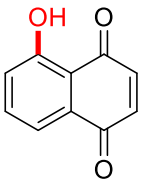
The corresponding naphthoquinone (0.4 mmol), [bis(trifluoroacetoxy)iodo]benzene (PIFA) (215 mg, 0.50 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (5 mg, 2.0 mol %) were added to a pressure tube. Trifluoroacetic anhydride (TFAA) (1 mL) and trifluoroacetic acid (0.02 mL) was subsequently added. The tube was sealed and the mixture was stirred at 80 ºC for 12 h and then cooled to 25 ºC. The mixture was transferred to a 25 mL flask and under vigorous magnetic stirring CH_2Cl_2 (1 mL), H_2O (1 mL) and a aq. solution of HCl (1M, 0.2 mL) were added dropwise. After 5 min, the solution was extracted with CH_2Cl_2 (3 x 10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).



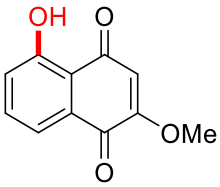
General procedure B:

The corresponding 9,10-anthraquinone (0.3 mmol), (diacetoxyiodo)benzene (PIDA) (0.7 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (9 mg, 5.0 mol %) was added to a pressure and trifluoroacetic anhydride (TFAA) (1 mL), trifluoroacetic acid (0.02 mL) and CH_2Cl_2 (1 mL) were added. The mixture was stirred at 80 ºC for 12 h. Then, the mixture was cooled to 25 ºC and transferred to a 25 mL flask. CH_2Cl_2 (1 mL), H_2O (1 mL) and a aq. solution of HCl (1M, 0.1 mL) were added dropwise. After 5 min, the solution was extracted with CH_2Cl_2 (3 x 10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (PhMe).

Characterization Data of Products 2 and 4

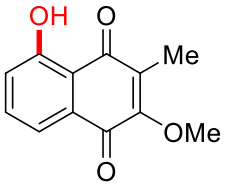


5-Hydroxy-1,4-naphthoquinone (2a): The general procedure A was followed by using 1,4-naphthoquinone as starting material (64 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 50:1) yielded **2a** (64 mg, 92%) as an orange solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 11.85 (s, 1H), 7.60–7.57 (m, 2H), 7.23 (dd, J = 5.4, 1.8 Hz, 1H), 6.90 (s, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 190.0 (C_q), 184.0 (C_q), 161.3 (CH), 139.4 (CH), 138.5 (C_q), 136.4 (C_q), 131.6 (C_q), 124.4 (CH), 119.0 (CH), 114.9 (CH); **IR** (ATR): $\tilde{\nu}$ = 1678, 1625, 1597, 1444, 1219, 1075, 769 cm^{-1}; **m.p. (°C) =** 160-162; **HRMS** (EI): Calcd for $C_{10}H_6O_3$ $[M]^+$ 174.0317, found 174.0309. The data are consistent with those reported in the literature.[11,12] 5,8-Dihydroxy-1,4-naphthoquinone (**2b**) was also isolated in 3% yield and The data are consistent with those reported in the literature.[13]

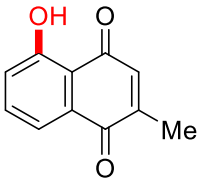


5-Hydroxy-2-methoxy-1,4-naphthoquinone (2b): The general procedure A was followed by using 2-methoxy-1,4-naphthoquinone as starting material (75 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10:1) yielded **2b** (62 mg, 76%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 12.13 (s, 1H), 7.58 (dd, J = 6.3, 1.2 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.19 (dd, J = 7.5, 1.2 Hz, 1H), 6.02 (s, 1H), 3.85 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 190.5 (C_q), 179.1 (C_q), 160.9 (C_q), 160.9 (C_q), 135.3 (CH), 130.9 (C_q), 125.1 (CH), 119.4 (CH), 114.1 (C_q), 109.4 (CH), 56.6 (CH_3); **IR** (ATR): $\tilde{\nu}$ = 1678, 1625, 1597, 1444, 1219, 1075, 769 cm^{-1}; **m.p. (°C) =** 162-163; **HRMS** (EI): Calcd for $C_{11}H_8O_4$ $[M]^+$ 204.0423, found 204.0415. The data are consistent with those reported in the literature.[14] *The structure of the product was also confirmed by X-ray diffraction* (CCDC number = 1859289). 5,8-Dihydroxy-2-methoxy-1,4-naphthoquinone (**2d**) was also isolated in 3% yield and the

structure was solved by *X-ray diffraction* (CCDC number = 1859290) and The data are consistent with those reported in the literature.[15]

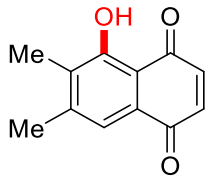


5-Hydroxy-2-methoxy-3-methyl-1,4-naphthoquinone (2e): The general procedure A was followed by using 2-methoxy-3-methyl-1,4-naphthoquinone as starting material (81 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 50:1) yielded **2e** (47 mg, 54%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 12.21 (s, 1H), 7.52–7.49 (m, 2H), 7.17 (dd, J = 4.5, 2.7 Hz, 1H), 4.11 (s, 3H), 2.03 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 191.0 (C_q), 180.4 (C_q), 160.7 (C_q), 158.2 (C_q), 135.2 (CH), 131.4 (C_q), 130.7 (C_q), 124.4 (CH), 118.8 (CH), 114.3 (C_q), 61.1 (CH_3), 8.7 (CH_3); **IR** (ATR): $\tilde{\nu}$ = 1666, 1608, 1454, 1258, 1158, 763, 686 cm^{-1}; **m.p. (°C) =** 130-131; **HRMS** (ESI): Calcd for $C_{12}H_{11}O_4$ $[M+H]^+$ 219.0652, found 219.0644; $C_{12}H_{10}NaO_4$ $[M+Na]^+$ 241.0471, found 241.0468. The data are consistent with those reported in the literature.[16] *The structure of the product was also confirmed by X-ray diffraction* (CCDC number = 1859454).

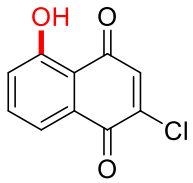


5-Hydroxy-2-methyl-1,4-naphthoquinone (2f): The general procedure A was followed by using 2-methyl-1,4-naphthoquinone as starting material (69 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 50:1) yielded **2f** (46 mg, 61%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 11.92 (s, 1H), 7.58–7.55 (m, 2H), 7.21 (dd, J = 2.1, 5.4 Hz, 1H), 6.75 (q, J = 1.5 Hz, 1H), 2.15 (d, J = 1.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 190.0 (C_q), 184.6 (C_q), 161.0 (C_q), 149.5 (C_q), 136.0 (CH), 135.3 (CH), 132.0 (C_q), 124.1 (CH), 119.2 (CH), 115.1 (C_q), 16.6 (CH_3); **IR** (ATR): $\tilde{\nu}$ = 1661, 1641, 1603, 1451, 1228, 833, 745 cm^{-1}; **m.p. (°C) =** 77-78;

HRMS (EI): Calcd for $C_{11}H_8O_3$ $[M]^+$ 188.0473, found 188.0478. The data are consistent with those reported in the literature.[17] *The structure of the product was also confirmed by X-ray diffraction* (CCDC number = 1859288).

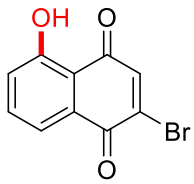


5-Hydroxy-6,7-dimethyl-1,4-naphthoquinone (2g): The general procedure A was followed by using 6,7-dimethyl-1,4-naphthoquinone as starting material (75 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 100:3) yielded **2g** (48 mg, 59%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 12.27 (s, 1H), 7.39 (s, 1H), 6.85 (s, 1H), 6.85 (s, 1H), 2.35 (s, 3H), 2.23 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 189.9 (C_q), 184.4 (C_q), 159.8 (C_q), 146.1 (C_q), 139.2 (CH), 138.5 (CH), 133.0 (C_q), 128.5 (C_q), 120.8 (CH), 112.4 (C_q), 20.9 (CH_3), 11.8 (CH_3); **IR** (ATR): $\tilde{\nu}$ = 2924, 1668, 1598, 1392, 1308, 1143, 1057 cm^{-1}; **m.p. (°C) =** 132-134; **HRMS** (EI): Cald. for $C_{12}H_{10}O_3$ $[M]^+$ 202.0630, found 202.0633.

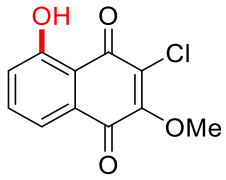


2-Chloro-5-hydroxy-1,4-naphthoquinone (2h): The general procedure A was followed by using 2-choro-1,4-naphthoquinone as starting material (77 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 100:3) yielded **2h** (60 mg, 72%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 11.76 (s, 1H), 7.69 (dd, J = 6.3, 1.2 Hz, 1H), 7.61 (dd, J = 7.8, 0.3 Hz, 1H), 7.28 (dd, J =7.2, 1.2 Hz, 1H), 7.16 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 187.7 (C_q), 177.1 (C_q), 161.5 (C_q), 147.0 (C_q), 136.4 (CH), 135.7 (CH), 131.0 (C_q), 125.2 (CH), 120.6 (CH), 114.5 (C_q); **IR** (ATR): $\tilde{\nu}$ = 1674, 1637, 1589, 1240, 891, 746 cm^{-1}; **m.p. (°C) =** 107-108; **HRMS** (EI): Calcd for $C_{10}H_5{}^{35}ClO_3$ [M, $^{35}Cl]^+$ 207.9927, found 207.9927; calcd for $C_{10}H_5{}^{37}ClO_3$ [M, $^{37}Cl]^+$ 209.9898, found 209.9910. The data are consistent with those reported in the

literature.[18] *The structure of the product was also confirmed by X-ray diffraction* (CCDC number = 1859455).

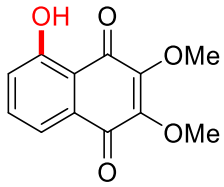


2-Bromo-5-hydroxy-1,4-naphthoquinone (2i): The general procedure A was followed by using 2-bromo-1,4-naphthoquinone as starting material (95 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 100:3) yielded **2i** (90 mg, 89%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 11.73 (s, 1H), 7.70 (dd, J = 6.3, 1.2 Hz, 1H), 7.64–7.58 (m, 1H), 7.46 (s, 1H), 7.28 (dd, J = 7.2, 1.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 187.3 (C_q), 177.0 (C_q), 161.6 (C_q), 140.8 (C_q), 140.2 (CH), 136.3 (CH), 130.6 (C_q), 125.0 (CH), 120.9 (CH), 114.6 (C_q). **IR** (ATR): $\tilde{\nu}$ = 1675, 1633, 1586, 1451, 1196, 893, 745 cm^{-1}; **m.p. (°C) =** 138-139; **HRMS** (EI): Calcd for $C_{10}H_5{}^{79}BrO_3$ [M, $^{79}Br]^+$ 251.9422, found 251.9427. Calcd for $C_{10}H_5{}^{81}BrO_3$ [M, $^{81}Br]^+$ 253.9402, found 253.9390. The data are consistent with those reported in the literature.[19] *The structure of the product was also confirmed by X-ray diffraction* (CCDC number = 1859287).

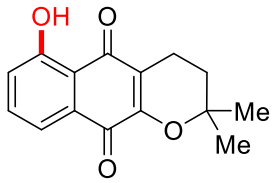


3-Chloro-5-hydroxy-2-methoxy-1,4-naphthoquinone (2j): The general A procedure was followed by using 2-chloro-3-methyl-1,4-naphthoquinone as starting material (90 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **2j** (50 mg, 52%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 11.82 (s, 1H), 7.56–7.54 (m, 2H), 7.22 (dd, J = 3.6, 3.0 Hz, 1H), 4.30 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 183.6 (C_q), 178.7 (C_q), 161.1 (C_q), 157.1 (C_q), 135.8 (CH), 130.7 (C_q), 126.8 (CH), 125.1 (C_q), 119.9 (CH), 113.3 (C_q), 62.0 (CH_3); **IR** (ATR): $\tilde{\nu}$ = 3440, 1630, 1671, 1245, 747 cm^{-1}; **m.p. (°C) =** 140-142; **HRMS** (ESI): calcd for $C_{11}H_7{}^{35}ClNaO_4$

[M+Na, $^{35}Cl]^+$ 260.9931, found 260.9925 and calcd for $C_{11}H_7{}^{37}ClNaO_4$ $[M+Na^{37}Cl]^+$ 262.9901, found 262.9896. The data are consistent with those reported in the literature.[20] *The structure of the product was also confirmed by X-ray diffraction* (CCDC number = 1859453).

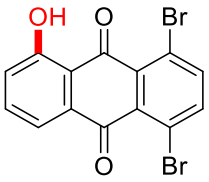


5-Hydroxy-2,3-dimethoxy-1,4-naphthoquinone (2k): The general procedure A was followed by using 2,3-dimethoxy-1,4-naphthoquinone as starting material (87 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10:1) yielded **2k** (23 mg, 25%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 11.87 (s, 1H), 7.57–7.50 (m, 2H), 7.18 (dd, J = 4.2, 0.6 Hz, 1H), 4.09 (s, 3H), 4.06 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 187.2 (C_q), 181.2 (C_q), 161.2 (C_q), 148.1 (C_q), 146.6 (C_q), 136.0 (CH), 130.8 (C_q), 124.5 (CH), 119.1 (CH) 113.3 (C_q), 61.7 (CH_3), 61.4 (CH_3); **IR** (ATR): $\tilde{\nu}$ = 1670, 1640, 1441,1303, 1069, 758 cm^{-1}; **m.p. (°C) =** 88-89; **HRMS** (ESI): Calcd for $C_{12}H_{11}O_5$ $[M+H]^+$ 235.0606, found 235.0597. The data are consistent with those reported in the literature.[21]

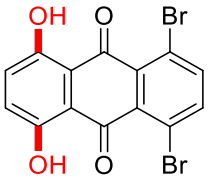


6-Hydroxy-α-lapachone (2l): The general procedure A was followed by using α-lapachone as starting material (97 mg, 0.4 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20:1) yielded **2l** (53 mg, 51%) as a yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 12.31 (s, 1H), 7.57 (dd, J = 6.0, 1.5 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.16 (dd, J = 1.2, 7.2 Hz, 1H), 2.55 (t, J = 6.6 Hz, 2H), 1.79 (t, J = 6.6 Hz, 2H), 1.40 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 189.8 (C_q), 179.0 (C_q), 160.7 (C_q), 155.2 (C_q), 134.9 (CH), 131.0 (C_q), 124.6 (CH), 119.4 (C_q), 119.0 (CH), 114.0 (C_q), 78.6 (C_q), 31.3 (CH_3), 26.6 (CH_3), 16.2 (CH_2); **IR** (ATR): $\tilde{\nu}$ = 1680, 1628,

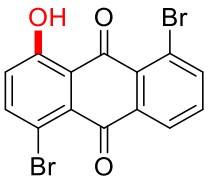
1601, 1258, 1158, 831, 769 cm^{-1}; **m.p. (°C) =** 176-177; **HRMS** (ESI): Calcd for $C_{15}H_{14}NaO_4$ $[M+Na]^+$ 281.0790, found 281.0784. The data are consistent with those reported in the literature.[22]



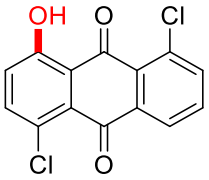
1,4-Dibromo-5-hydroxy-9,10-anthraquinone (4a): The general procedure B was followed by using 1,4-dibromo-9,10-anthraquinone as starting material (110 mg, 0.30 mmol). Purification by column chromatography on silica gel (PhMe) yielded **4a** (80 mg, 70%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 12.09 (s, 1H), 7.80 (s, 2H), 7.72 (dd, J = 7.6, 1.4 Hz, 1H), 7.65 (dd, J = 8.1, 0.4 Hz, 1H), 7.28 (dd, J = 8.1, 1.4 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 185.9 (C_q), 180.7 (C_q), 161.8 (C_q), 141.1 (CH), 141.0 (CH) 136.9 (CH), 133.7 (C_q), 133.4 (C_q), 132.6 (C_q), 124.1 (C_q), 124.0 (C_q), 122.5 (CH), 119.3 (C_q), 116.0 (CH); **IR** (KBr): $\tilde{\nu}$ = 2923, 1711, 1671,1454, 1301, 1235, 717 cm^{-1}; **m.p. (°C) =** 129-131; **HRMS** (EI): Calcd for $C_{14}H_6O_3{}^{79}Br_2$ [M, ^{79}Br]$^+$ 379.8684, found 379.8690; Compound **4a'** was isolated in 10% yield.



1,4-Dibromo-5,8-hydroxy-9,10-anthraquinone (4a'): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.57 (s, 2H), 7.83 (s, 2H), 7.30 (s, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 184.3 (C_q), 157.3 (C_q), 141.4 (C_q), 132.9 (CH), 129.3 (C_q), 122.8 (C_q), 112.6 (CH). **IR** (KBr): $\tilde{\nu}$ = 2924, 1668, 1635, 1538, 1454, 1302, 1236, 769 cm^{-1}; **m.p. (°C) =** 155-157; **HRMS** (EI): Calcd. for $C_{14}H_6O_4{}^{79}Br_2$ [M, ^{79}Br]$^+$ 395.8633, found 395.8634.



1,5-Dibromo-4-hydroxy-9,10-anthraquinone (4b): The general procedure B was followed by using 1,5-dibromo-9,10-anthraquinone as starting material (73 mg, 0.2 mmol). Purification by column chromatography on silica gel (PhMe) yielded **4b** (42 mg, 55%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 12.97 (s, 1H), 8.30 (dd, J = 3.6, 1.2 Hz, 1H), 8.02 (dd, J = 8.7, 1.2 Hz, 1H), 7.84 (dd, J = 8.7, 0.3 Hz, 1H), 7.61–7.56 (m, 1H), 7.14 (d, J = 8.7 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 186.5 (C_q), 180.3 (C_q), 162.6 (C_q), 143.4 (CH), 141.3 (CH), 136.8 (C_q), 134.5 (CH), 129.6 (CH), 129.4 (CH), 127.8 (C_q), 125.4 (C_q), 122.3 (C_q), 118.2 (C_q), 112.6 (C_q); **IR** (ATR): $\tilde{\nu}$ = 1634, 1411, 1328, 1266, 1219, 1158, 1123, 789, 745, 441 cm^{-1}; **m.p. (°C) =** 218-219; **HRMS** (EI): Calcd for $C_{14}H_6O_3{}^{79}Br_2$ [M, ^{79}Br]$^+$ 379.8684, found 379.8675.



1,5-Dichloro-4-hydroxy-9,10-anthraquinone (4c): The general procedure B was followed by using 1,5-dichloro-9,10-anthraquinone as starting material (68 mg, 0.3 mmol). Purification by column chromatography on silica gel (PhMe) yielded **4c** (49 mg, 57%) as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 13.01 (s, 1H), 8.26 (dd, J = 7.7, 1.5 Hz, 1H), 7.79 (dd, J = 8.0, 1.4 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.24 (d, J = 4.0 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 186.8 (C_q), 180.3 (C_q), 162.0 (C_q), 140.1 (CH), 137.6 (CH), 136.8 (C_q), 135.1 (C_q), 134.5 (CH), 128.2 (C_q), 128.1 (C_q), 127.1 (CH), 125.9 (C_q), 125.5 (CH), 117.8 (C_q); **IR** (ATR): $\tilde{\nu}$ = 1627, 1574, 1443, 1413, 1332, 1261, 1216, 1126, 769, 751 cm^{-1}; **m.p. (°C) =** 250-251; **HRMS** (EI): Calcd for $C_{14}H_6O_3{}^{35}Cl_2$ [M, ^{35}Cl]$^+$ 291.9694, found 291.9698.

Trypanocidal Assays

Stock solutions of the compounds were prepared in dimethylsulfoxide (DMSO), with the final concentration of the latter in the experiments never exceeding 0.1%. Preliminary experiments showed that concentrations up to 0.5%, DMSO have no deleterious effect on the parasites. Bloodstream trypomastigotes of the Y strain were obtained at the peak of parasitaemia from infected albino mice, isolated by differential centrifugation and resuspended in Dulbecco's modified Eagle medium (DME) to a parasite concentration of 10^7 cells/mL in the presence of 10% of mouse blood. This suspension (100 µL) was added in the same volume of each compound previously prepared at twice the desired final concentrations. Cell counts were performed in Neubauer chamber and the trypanocidal activity was expressed as IC_{50}, corresponding to the concentration that leads to lysis of 50% of the parasites.

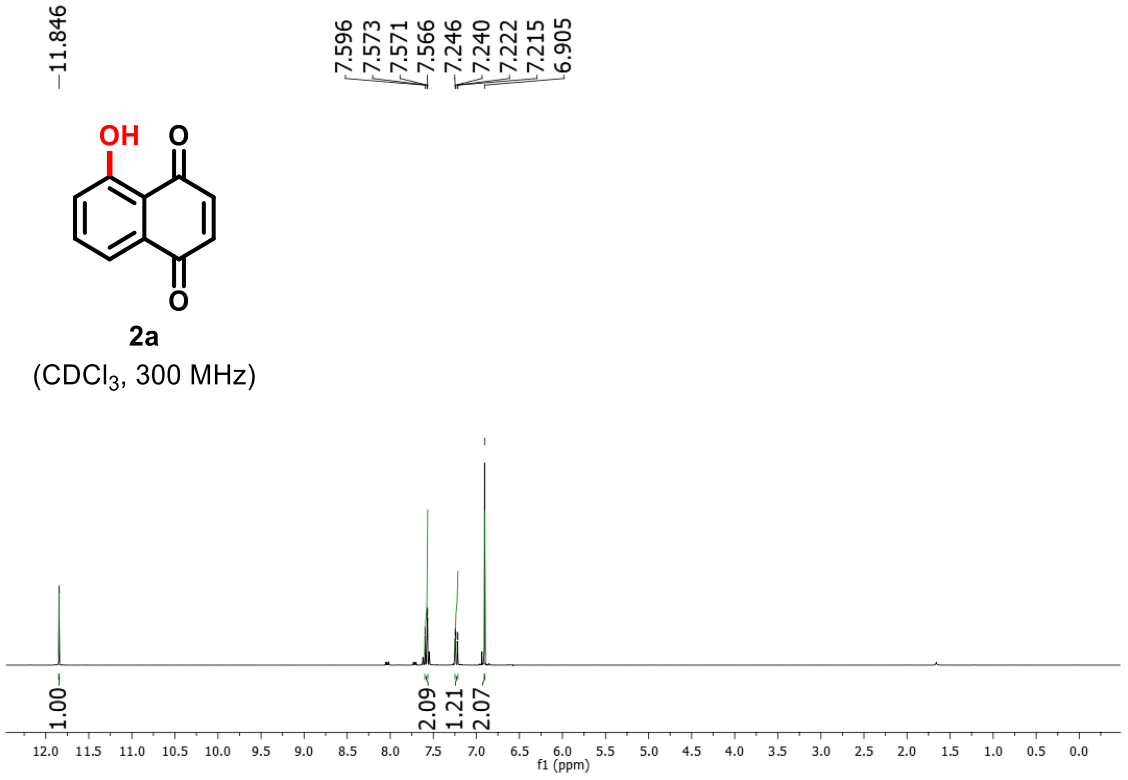
Table S3. Activity of napththoquinones on trypomastigote forms of *T. cruzi*.

Compounds	**IC_{50}/ 24 h[a] (µM)**
2a	105.0 (± 5.0)
2c	>1000.0
2e	>1000.0
2f	93.5 (± 8.3)
2g	101.6 (± 12.7)
2h	32.9 (± 4.3)
2i	29.5 (± 2.8)
2j	176.1 (± 39.9)
2k	>1000.0
2l	>1000.0
Benznidazole	103.6 ± 0.6[23]

References

1. F. Brommel, P. Zou, H. Finkelmann and A. Hoffmann, *Soft Matter*, 2013, **9**, 1674–1677.
2. G. A. M. Jardim, E. H. G. da Cruz, W. O. Valença, D. J. B. Lima, B. C. Cavalcanti, C. Pessoa, J. Rafique, A. L. Braga, C. Jacob and E. N. da Silva Júnior, *Molecules*, 2018, **23**, 83.
3. D. J. Sullivan, R. Clérac, M. Jennings, A. J. Lough and K. E. Preuss, *Chem. Commun.* 2012, **48**, 10963-10965.
4. S. Neufeind, N. Hülsken, J.-M. Neudörfl, N. Schlörer and H.-G. Schmalz, *Chem. Eur. J.* **2011**, *17*, 2633-2641.
5. P. Swamy, M. A. Kumar, M. M. Reddy, M. Naresh, K. Srujana and N. Narender, *RSC Adv.* 2014, **4**, 26288-26294.
6. P. Bachu, J. Sperry, M. A. Brimble, *Tetrahedron*, 2008, **64**, 4827-4834.
7. M. Delarmelina, R. D. Daltoé, M. F. Cerri, K. P. Madeira, L. B. A. Rangel, V. L. Júnior, W. Romão, A. G. Taranto and S. J. Greco, *J. Braz. Chem. Soc.* 2015, **26**, 1804-1816.
8. Y. Brandy, N. Brandy, E. Akinboye, M. Lewis, C. Mouamba, S.t Mack, R. J. Butcher, A. J. Anderson and O. Bakare, *Molecules* 2013, **18**, 1973-1984.
9. C. Salas, R. A. Tapia, K. Ciudad, V. Armstrong, M. Orellana, U. Kemmerling, J. Ferreira, J. D. Maya, A. Morello, *Bioorg. Med. Chem.* 2008, **16**, 668-674.
10. Brett VanVeller, Dale Robinson, and Timothy M. Swager, *Angew. Chem. Int. Ed.* 2012, **51**, 1182-1186.
11. K. T.de Oliveira, L. Z. Miller and D. T. McQuade, *RSC Advances* 2016, **6**, 12717-12725.
12. N. Bao, J. Ou, W. Shi, N. Li, L. Chen and J. Sun, *Eur. J. Org. Chem.*, 2018, 2254-2258.
13. J. Zhang, Y. Liu, D. Shi, G. Hu, B. Zhang, X. Li, R. Liu, X. Han, X. Yao and J. Fang, *Eur. J. Med. Chem.*, 2017, **140**, 435-447.
14. Y. Zhou, B. Yang, Y. Jiang, Z. Liu, Y. Liu, X. Wang and H. Kuang, *Molecules* 2015, **20**, 15572-15588.
15. E. Brötz, J. Herrmann, J. Wiese, H. Zinecker, A. Maier, G. Kelter, J. F. Imhoff, R. Müller and T. Paululat, *Eur. J. Org. Chem.*, 2014, 5318-5330

16. R. G. F. Giles and G. H. P. Roos, *J. Chem. Soc., Perkin Trans 1*, 1976, **19**, 2057-2060.
17. N. Bao, J. Ou, W. Shi, N. Li, L. Chen and J. Sun, *Eur. J. Org. Chem.*, 2018, **19**, 2254-2258.
18. L. Boisvert and P. Brassard, *J. Org. Chem.* 1988, **53**, 4052-4059.
19. R. C. Montenegro, A. J. Araújo, M. T. Molina, J. D. B. M. Filho, D. D. Rocha, E. Lopéz-Montero, M. O.F. Goulart, E.S. Bentc, A. P. N. N. Alves, C. Pessoa, M. O. de Moraes, L. V. Costa-Lotufo, *Chem-bio. Interact*. 2010, **184**, 439-448.
20. G. Wurm, H. Gurka and U. Geres, *Arch. Pharm.* 1986, **319**, 1106-1113.
21. H. Laatsch, *Liebigs Ann.*1983, **11**, 1886-1900.
22. C. Ríos-Luci, E. L. Bonifazi, L. G. León, J. C. Montero, G. Burton, A. Pandiella, R. I. Misico, J. M. Padrón, *Eur. J. Med. Chem*. 2012, **53**, 264-274.
23. E. N. da Silva Júnior, R. F. S. Menna-Barreto, M. C. F. R. Pinto, R. S. F. Silva, D. V. Teixeira, M. C. B. V. de Souza, C. A. de Simone, S. L. de Castro, V. F. Ferreira and A. V. Pinto, *Eur. J. Med. Chem.*, 2008, **43**, 1774.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O
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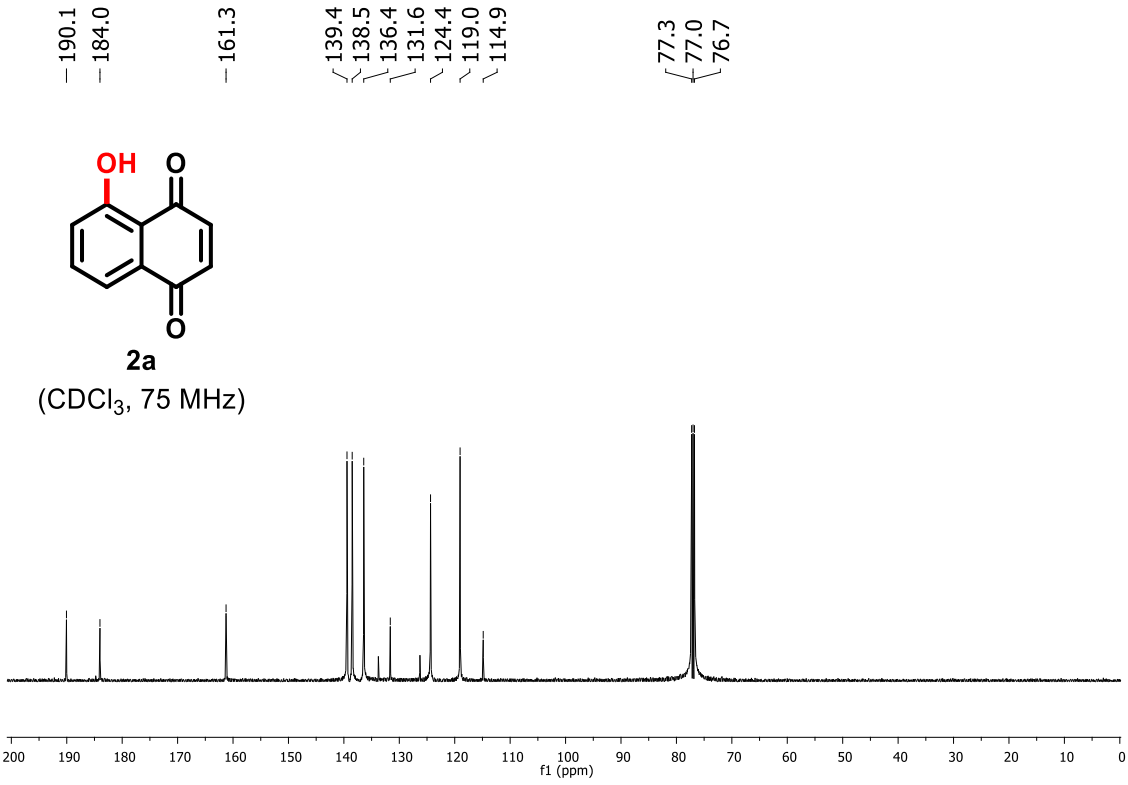
2.07
f1 (ppm)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O
2a
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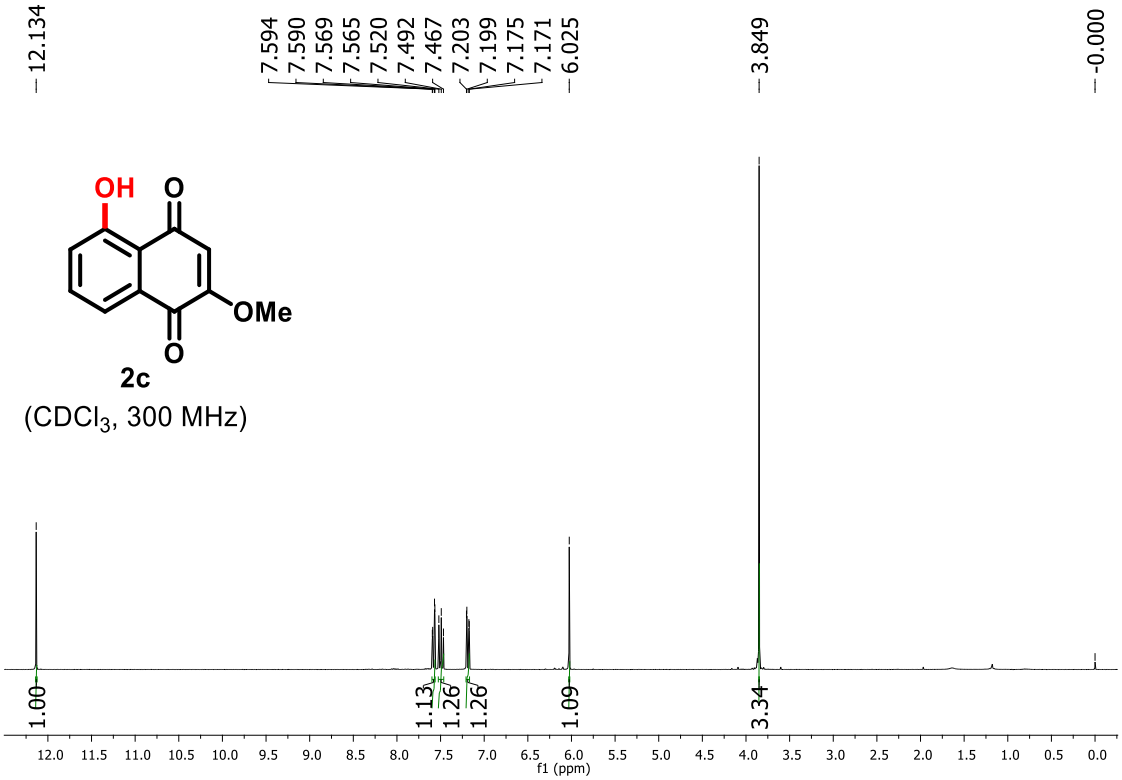
f1 (ppm)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3.849
-0.000
OH
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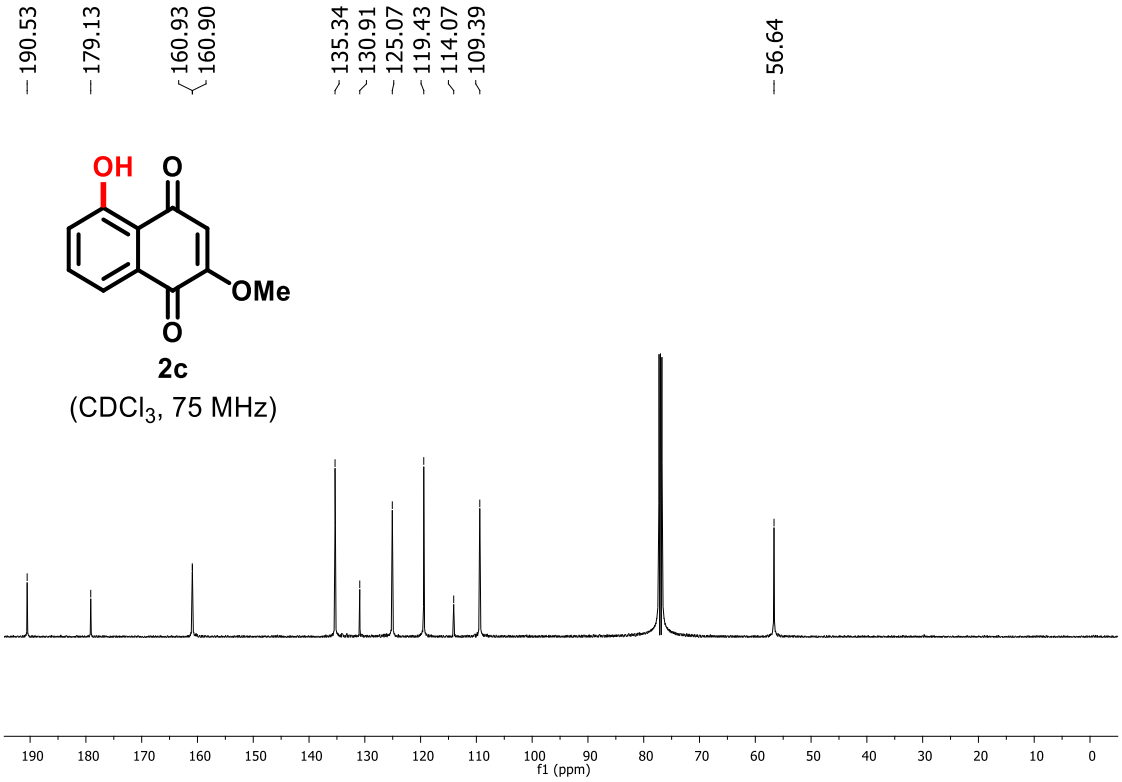
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O
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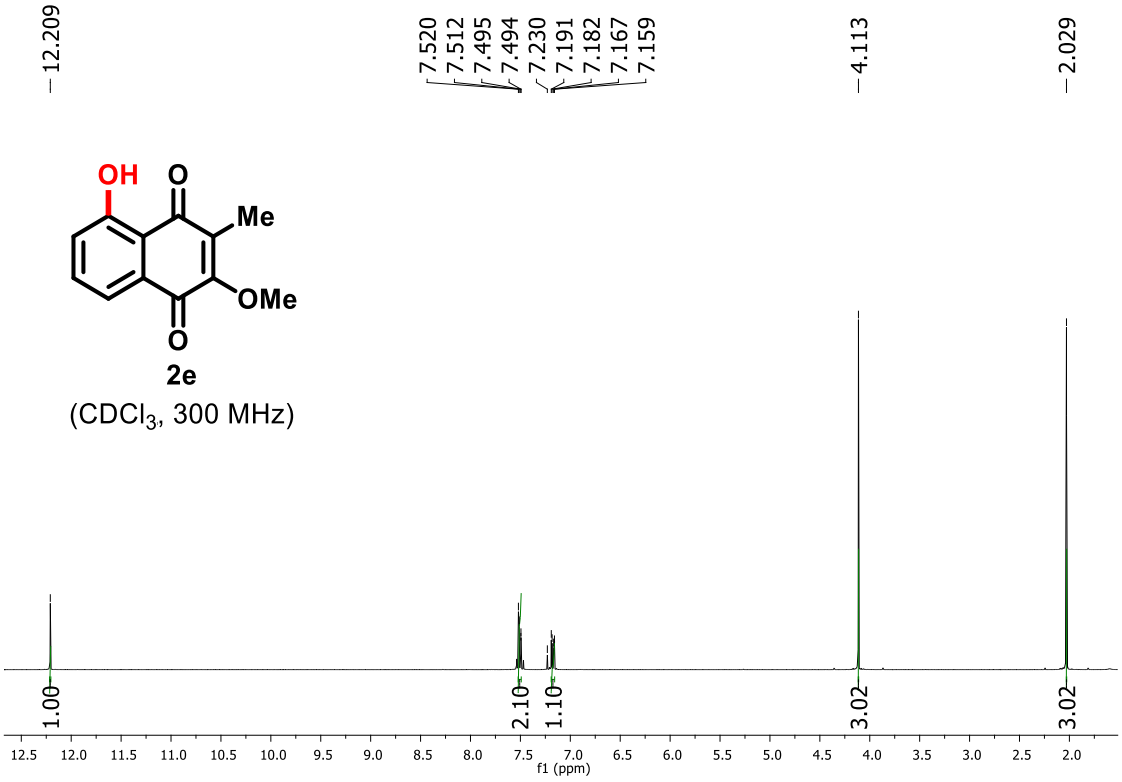
f1 (ppm)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7.167
7.159
4.113
2.029
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O
Me
OMe
O
2e
(CDCl3, 300 MHz)
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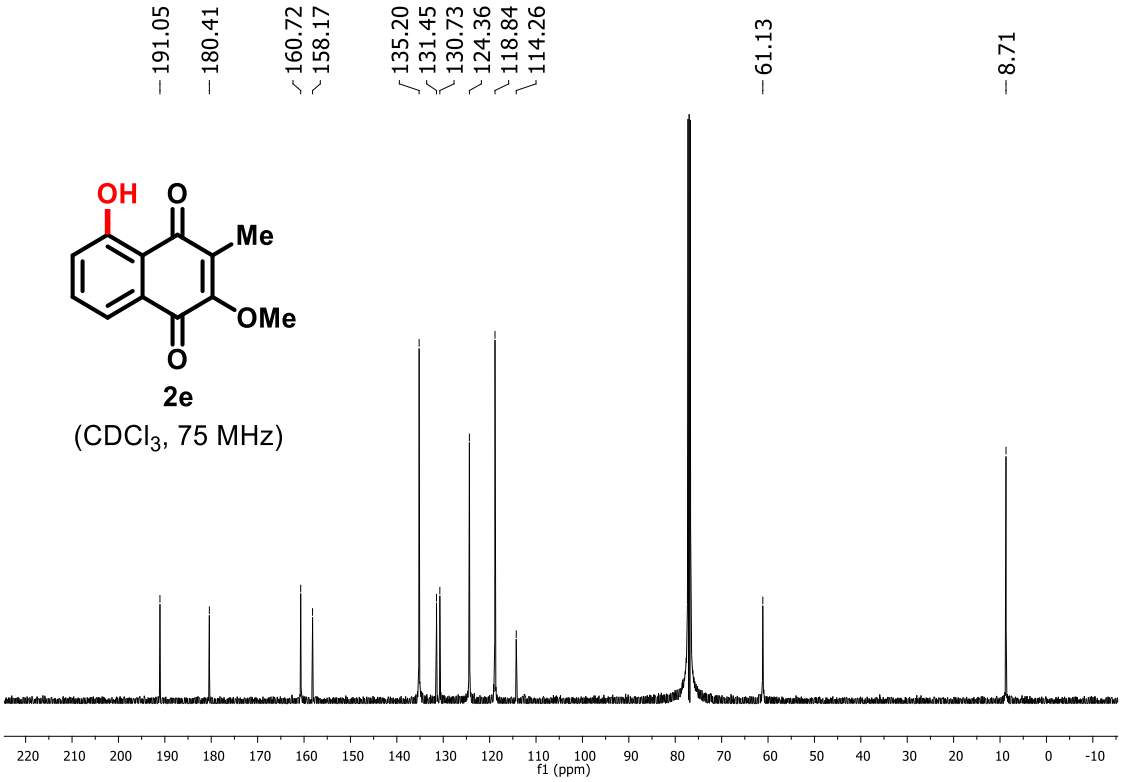
1.10
3.02
3.02
f1 (ppm)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Me
OMe
O
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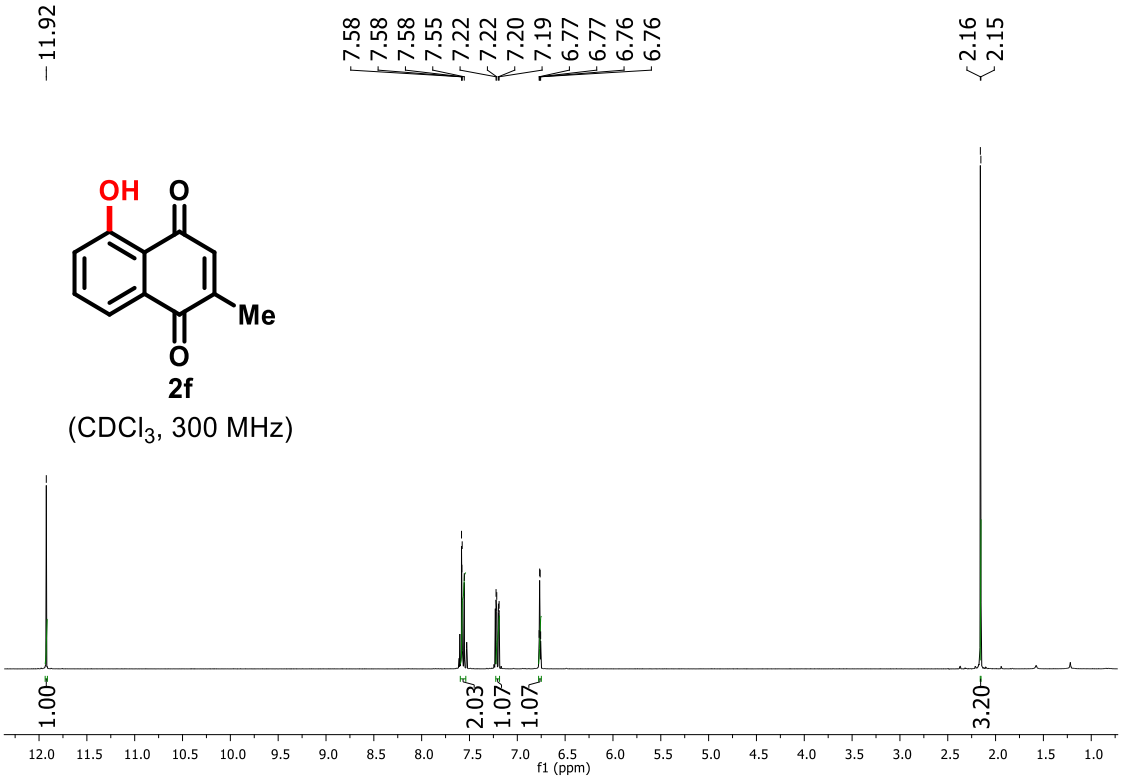
f1 (ppm)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O
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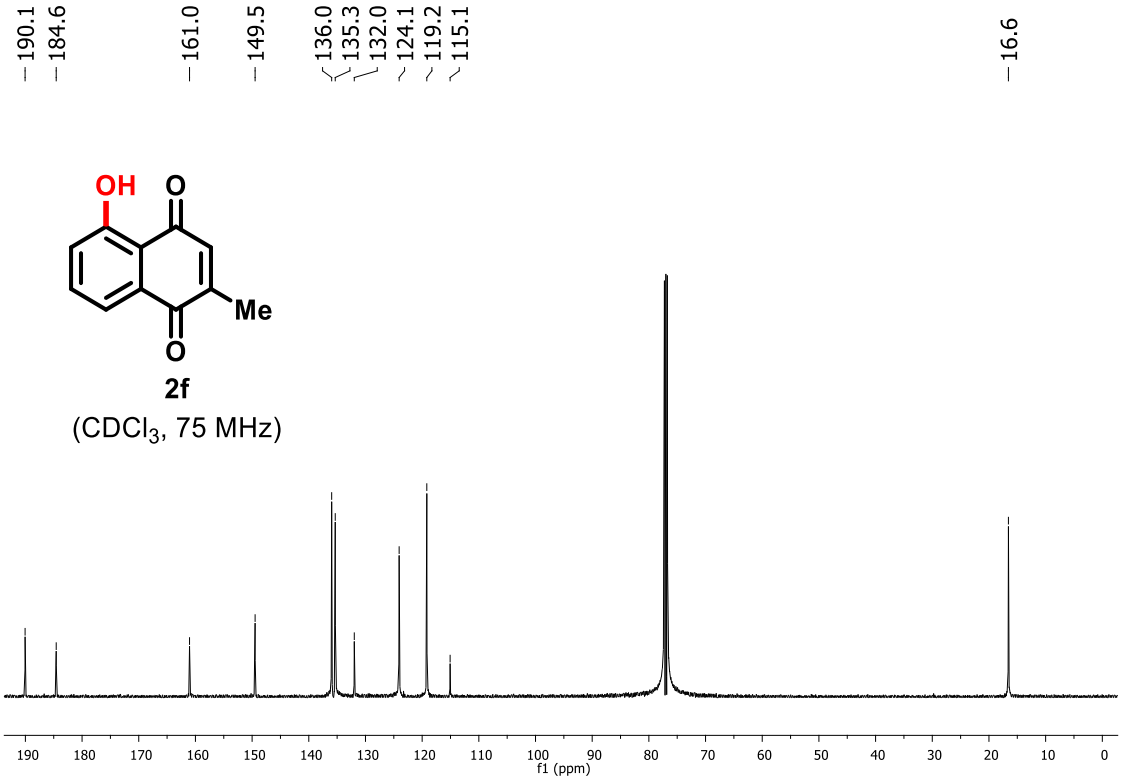
f1 (ppm)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O
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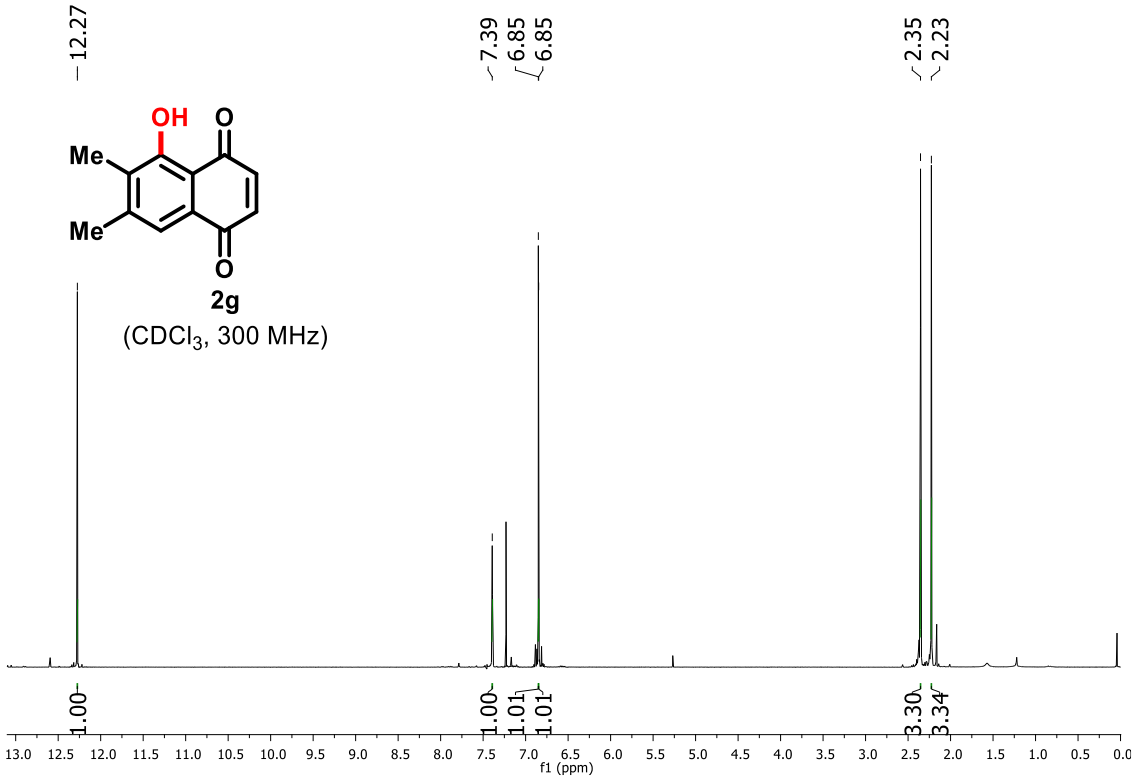
(CDCl3, 75 MHz)
f1 (ppm)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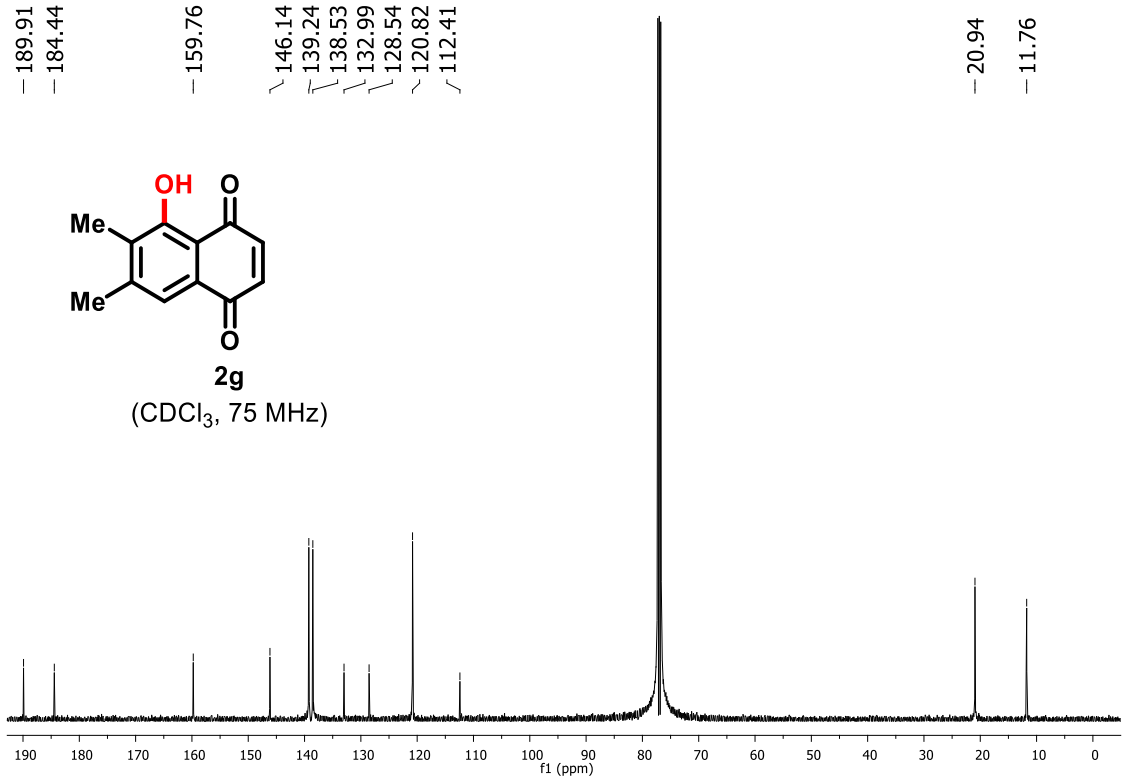
f1 (ppm)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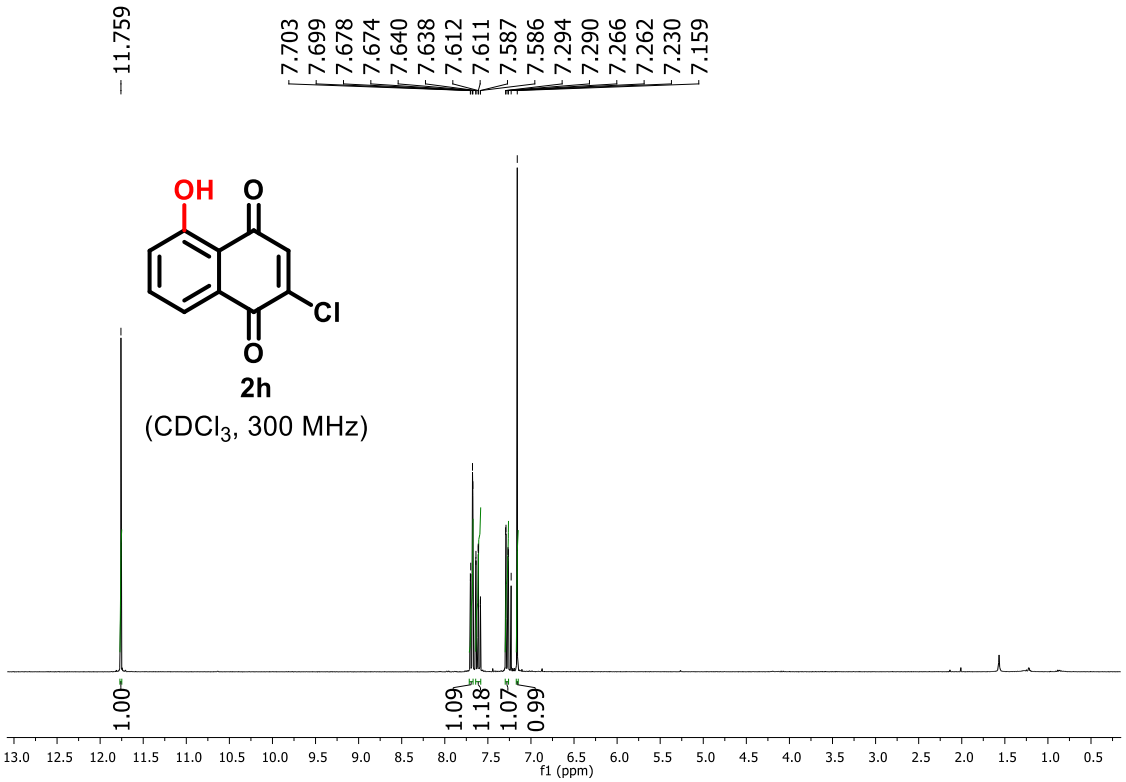
2g
(CDCl3, 75 MHz)
f1 (ppm)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7.262
7.230
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Cl
O
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(CDCl3, 300 MHz)
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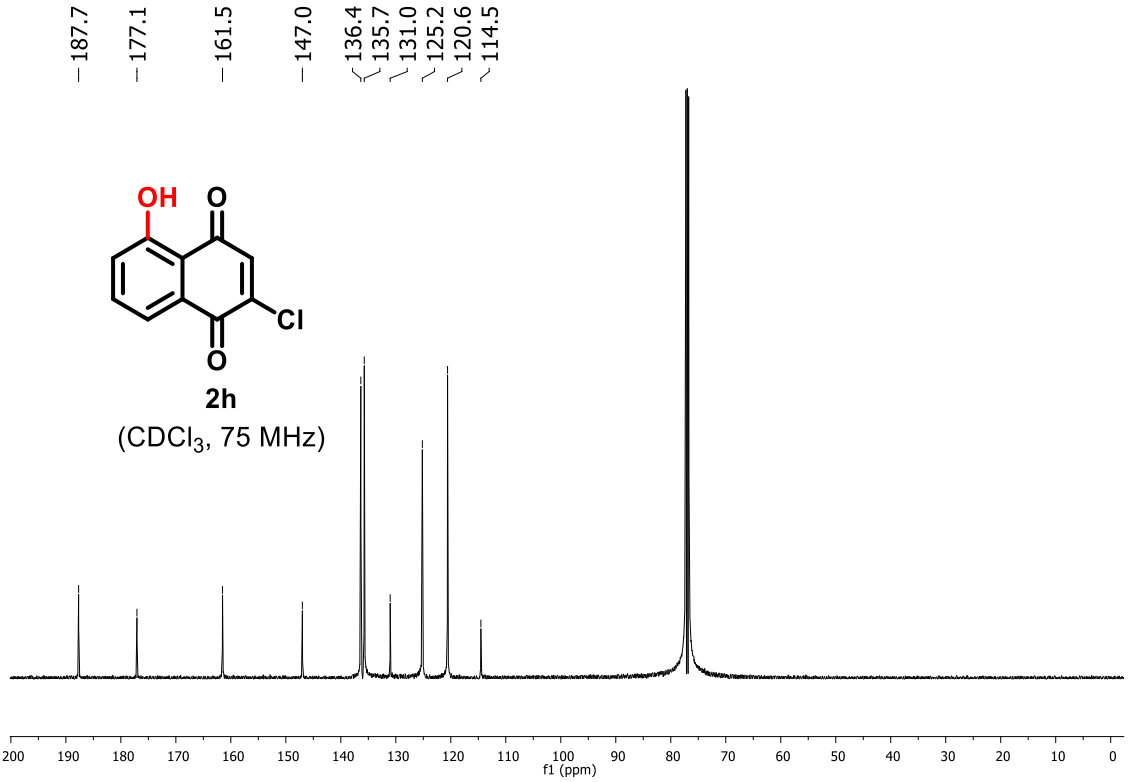
f1 (ppm)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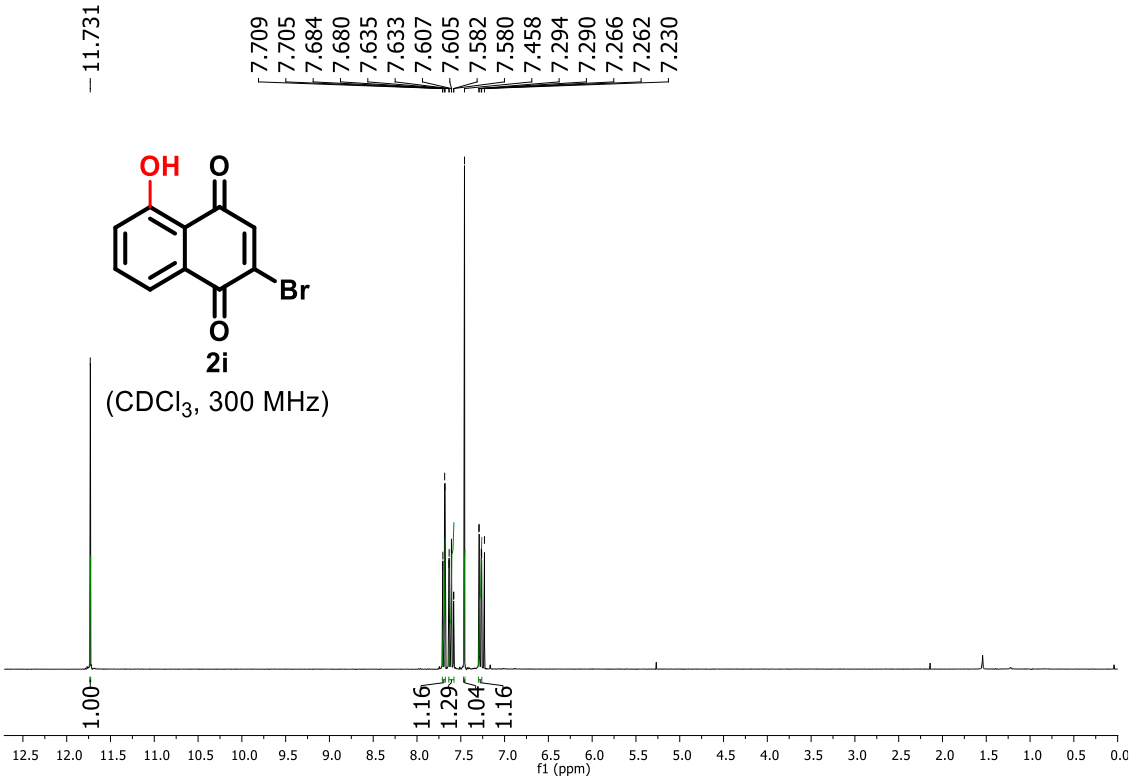
O
Cl
O
2h
(CDCl3, 75 MHz)
f1 (ppm)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7.294
7.290
7.266
7.262
7.230
OH
O
Br
O
2i
(CDCl3, 300 MHz)
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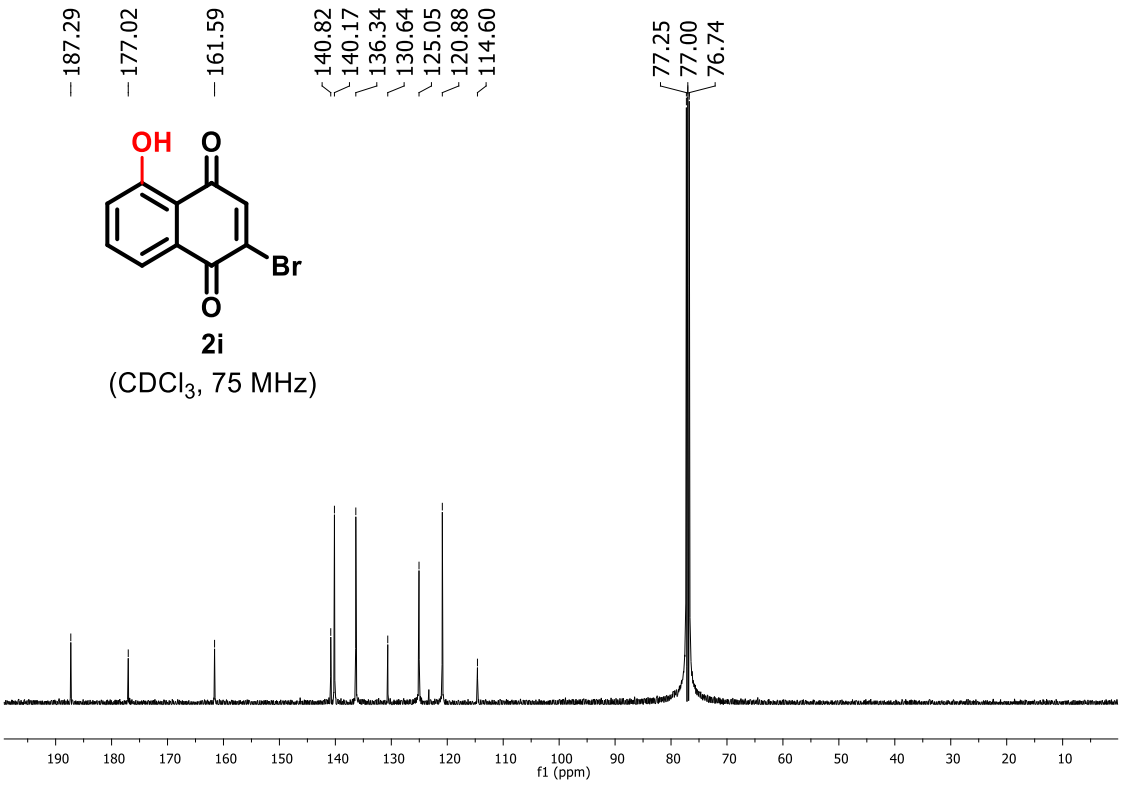
1.16
1.29
1.04
1.16
f1 (ppm)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136.34
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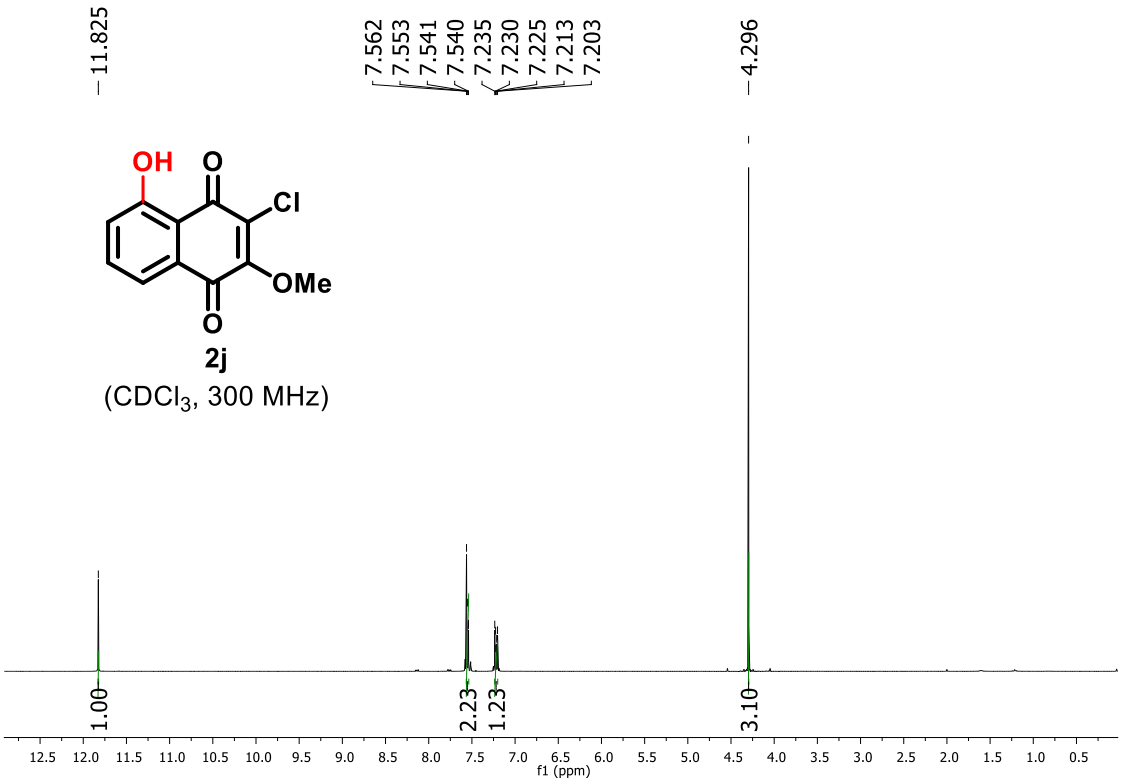
O
Br
O
2i
(CDCl3, 75 MHz)
f1 (ppm)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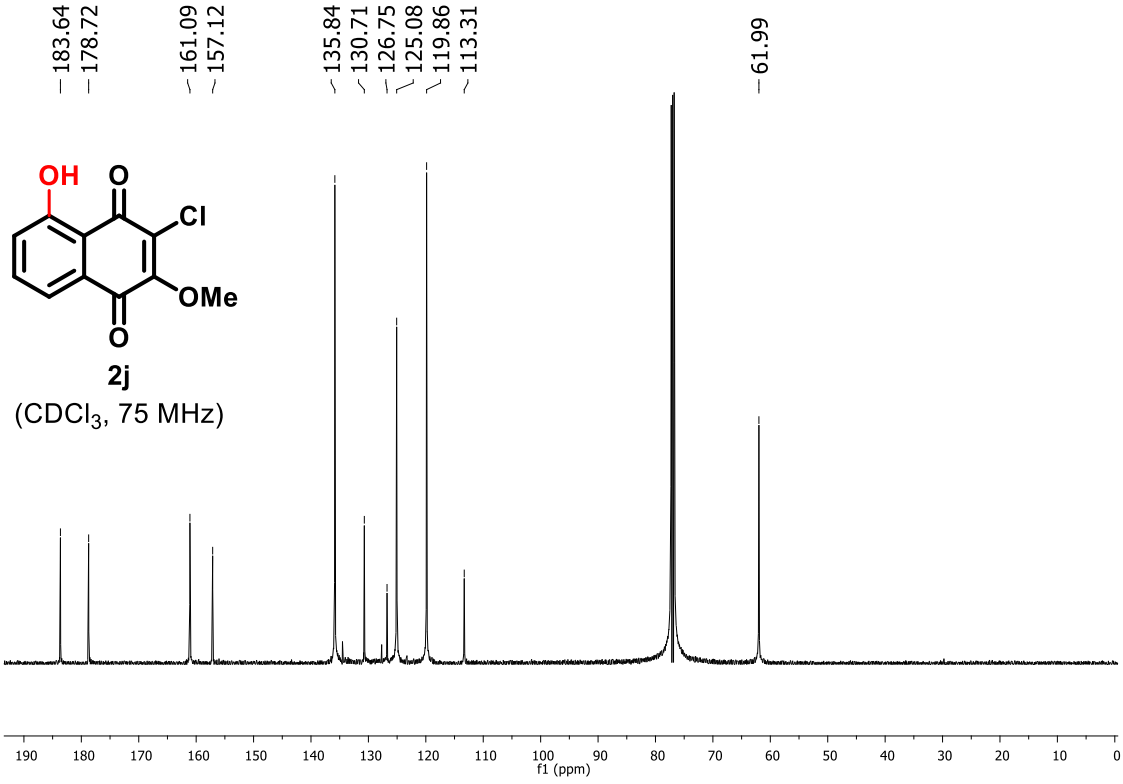
7.540
7.235
7.230
7.225
7.213
7.203
4.296
OH
O
Cl
OMe
O
2j
(CDCl3, 300 MHz)
1.00
2.23
1.23
3.10
f1 (ppm)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113.31
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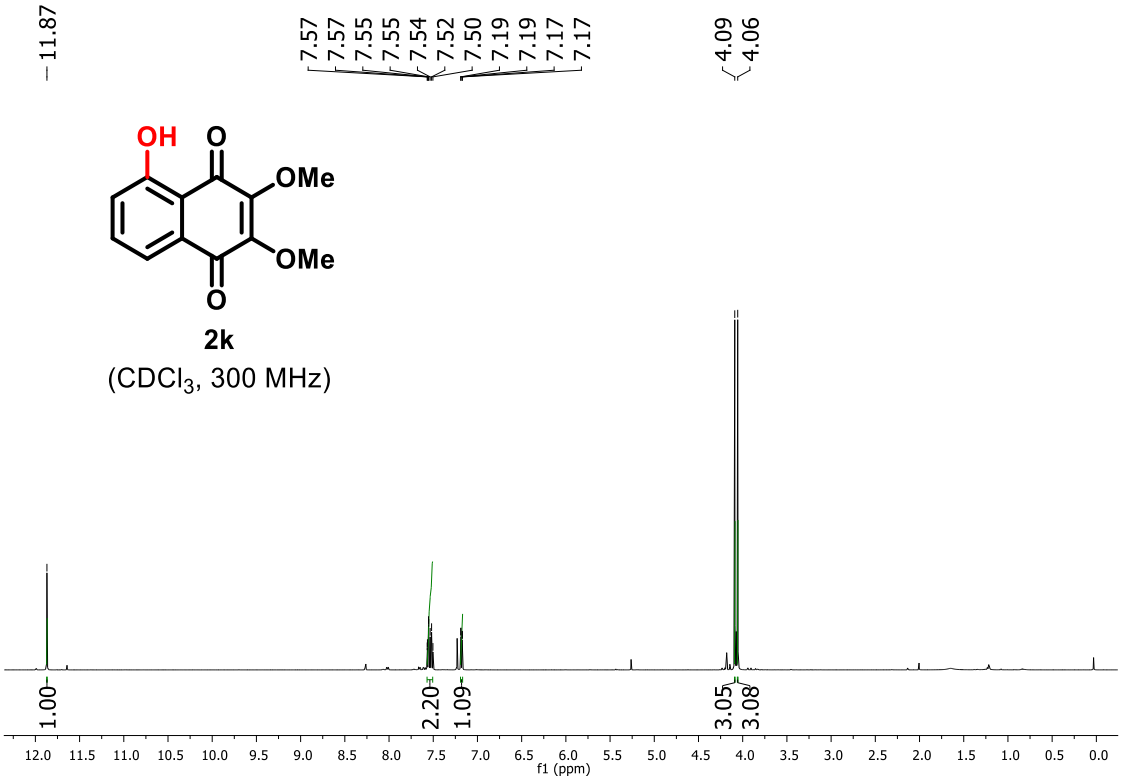
OH
O
Cl
OMe
O
2j
(CDCl3, 75 MHz)
f1 (ppm)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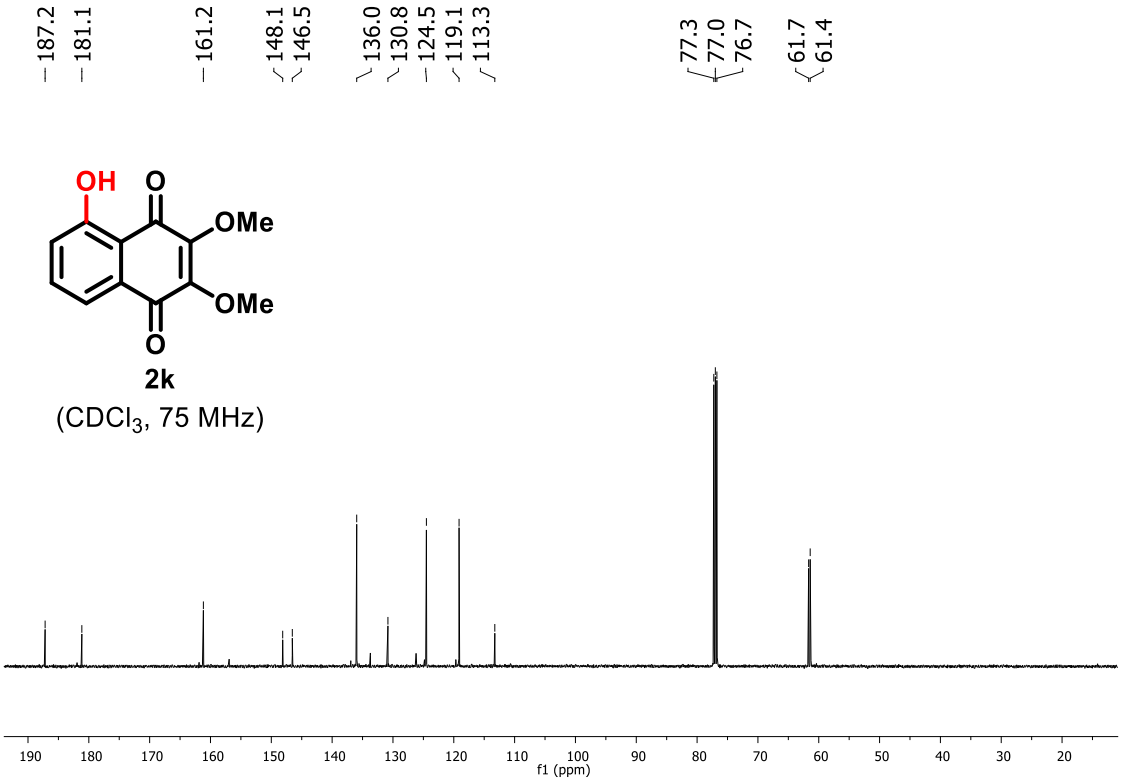
7.50
7.19
7.19
7.17
7.17
4.09
4.06
OH
O
OMe
OMe
O
2k
(CDCl3, 300 MHz)
1.00
2.20
1.09
3.05
3.08
f1 (ppm)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130.8
124.5
119.1
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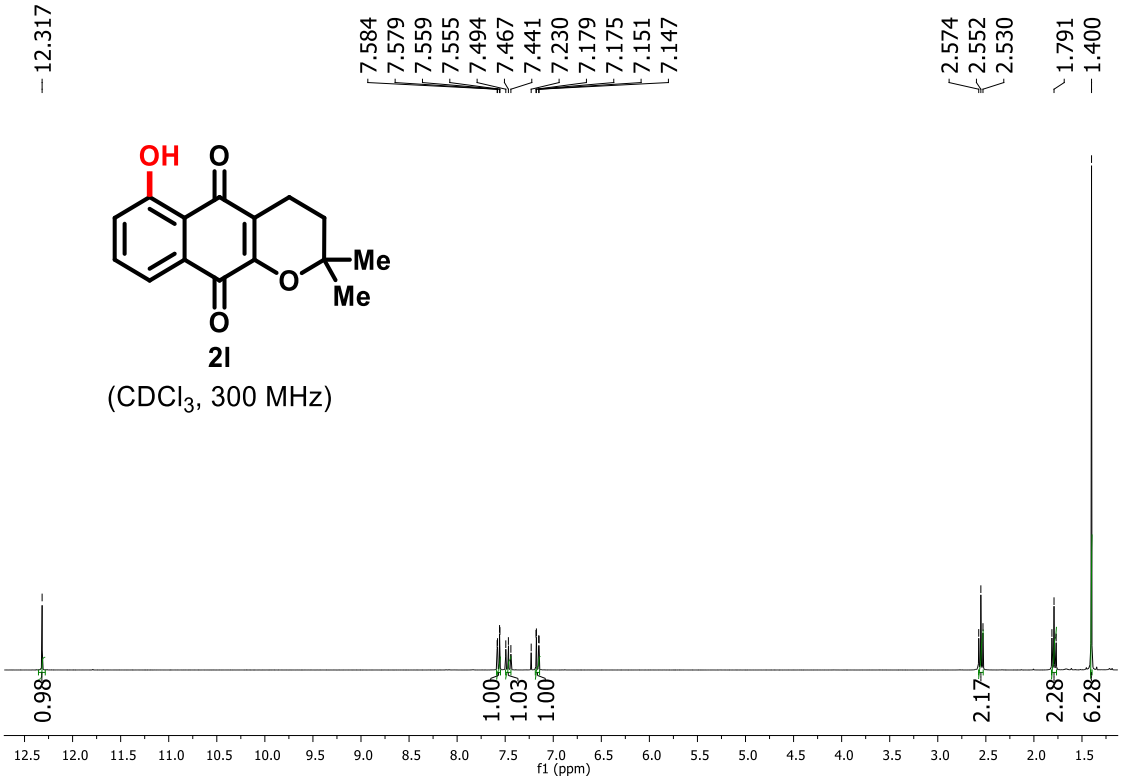
76.7
61.7
61.4
OH
O
OMe
OMe
O
2k
(CDCl3, 75 MHz)
f1 (ppm)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7.467
7.441
7.230
7.179
7.175
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7.147
2.574
2.552
2.530
1.791
1.400
OH
O
Me
Me
O
O
2l
(CDCl3, 300 MHz)
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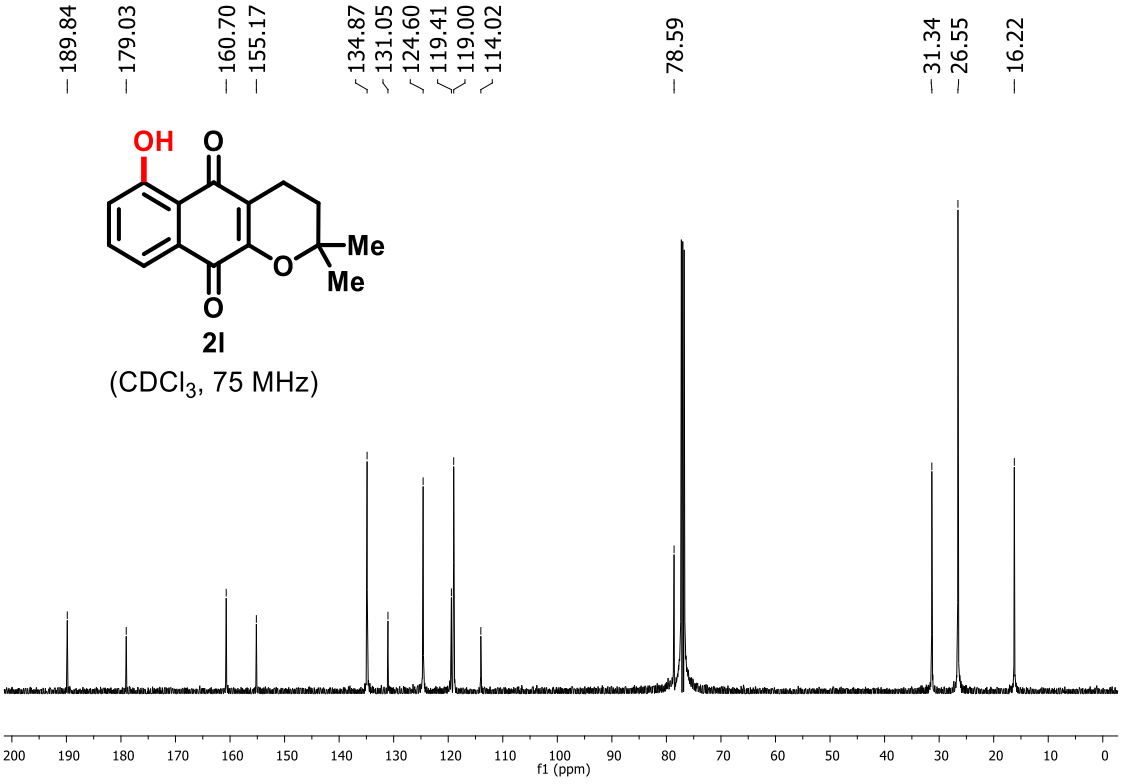
1.00
1.03
1.00
2.17
2.28
6.28
f1 (ppm)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114.02
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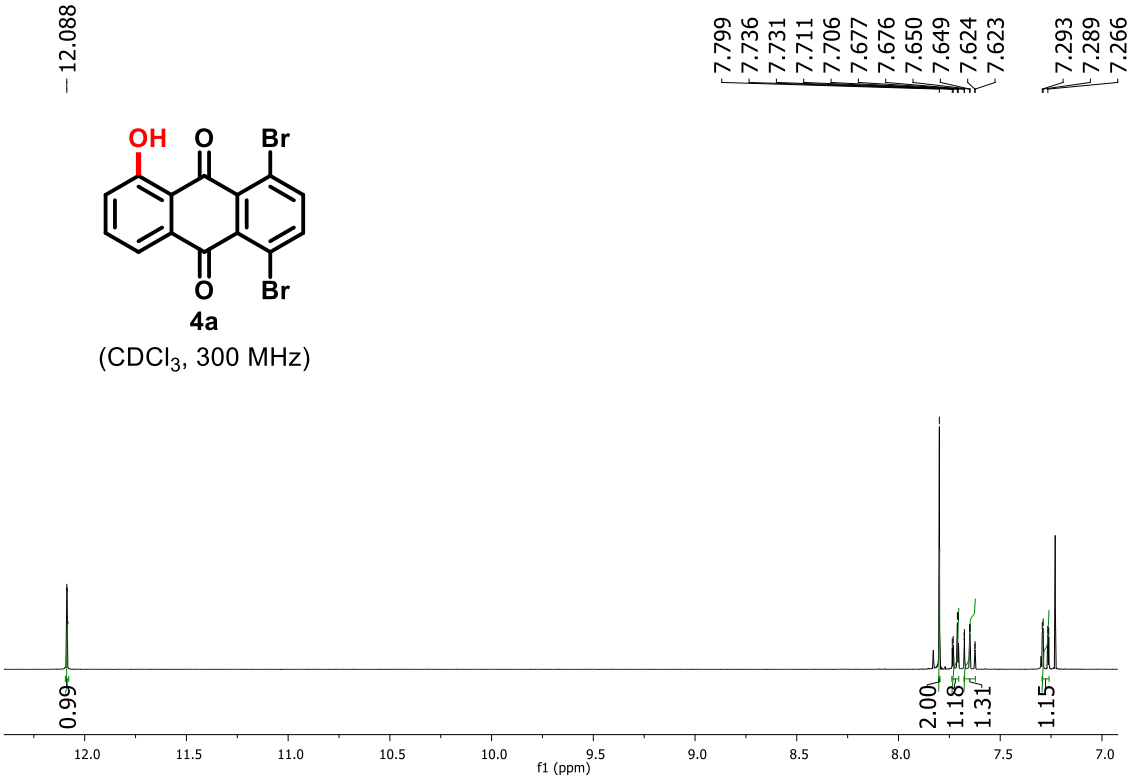
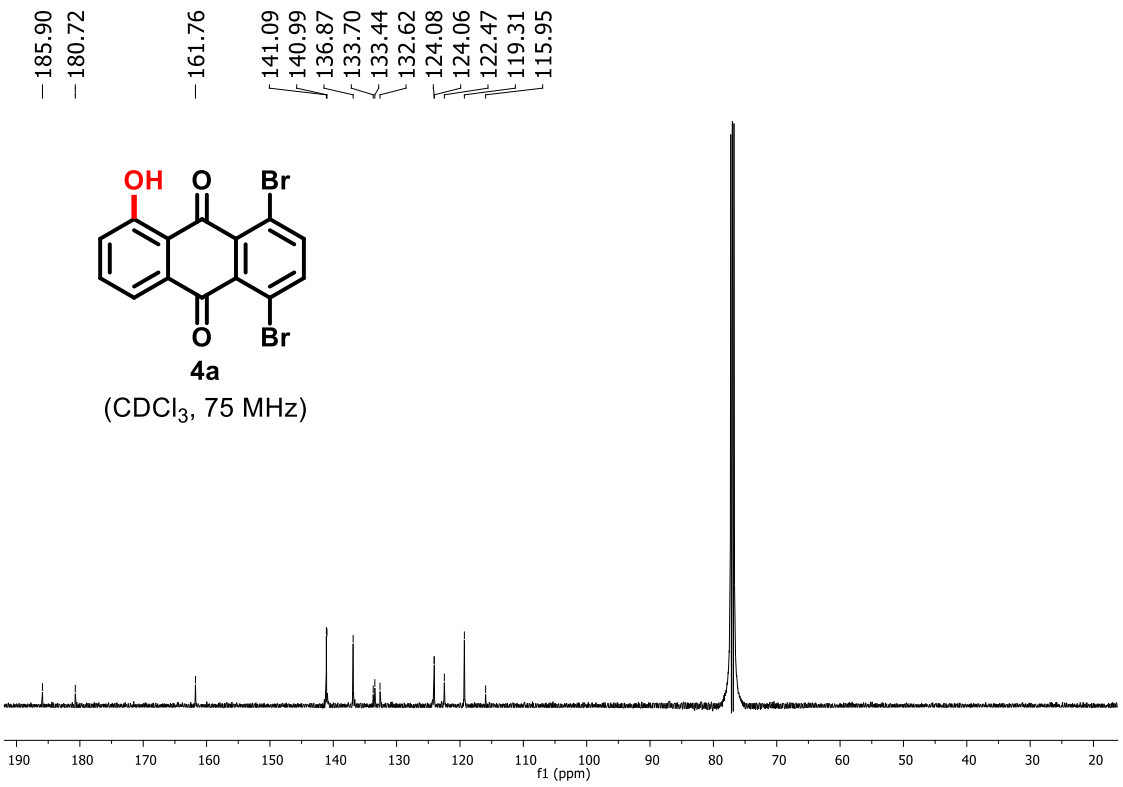
26.55
16.22
OH
O
Me
Me
O
O
2l
(CDCl3, 75 MHz)
f1 (ppm)



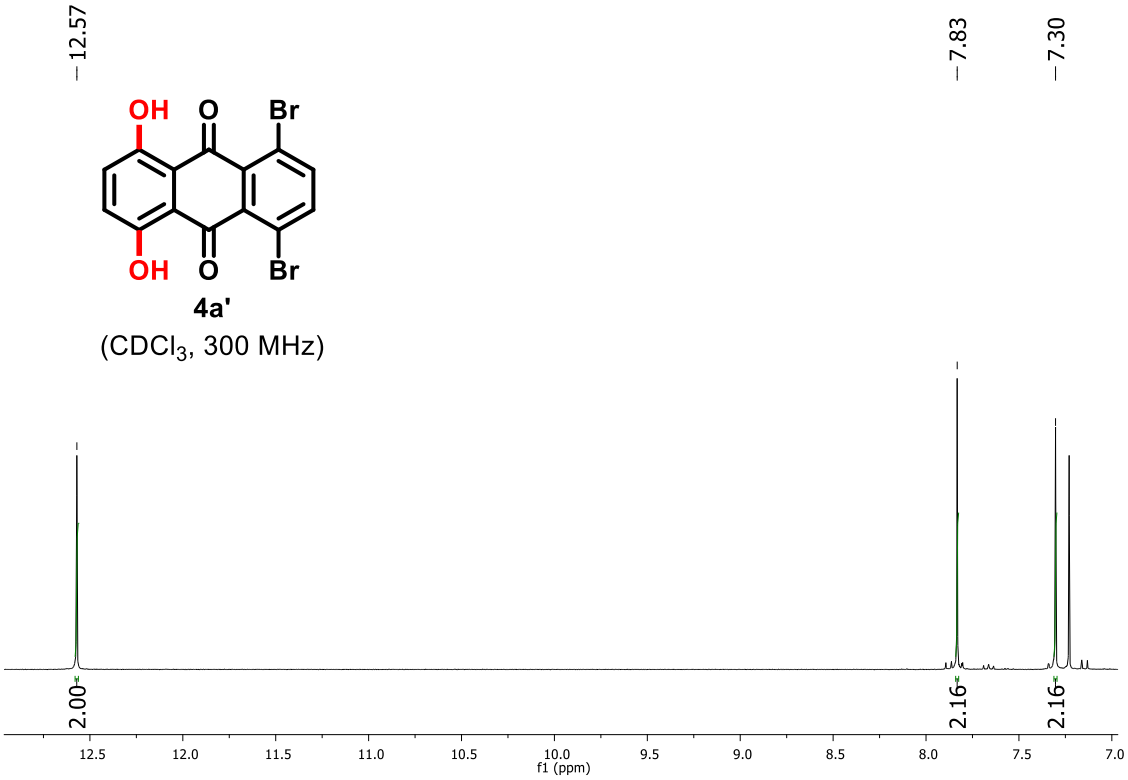
4a

($CDCl_3$, 300 MHz)



4a

($CDCl_3$, 75 MHz)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Br
OH
O
Br
4a'
(CDCl3, 300 MHz)
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2.16
2.16
12.5
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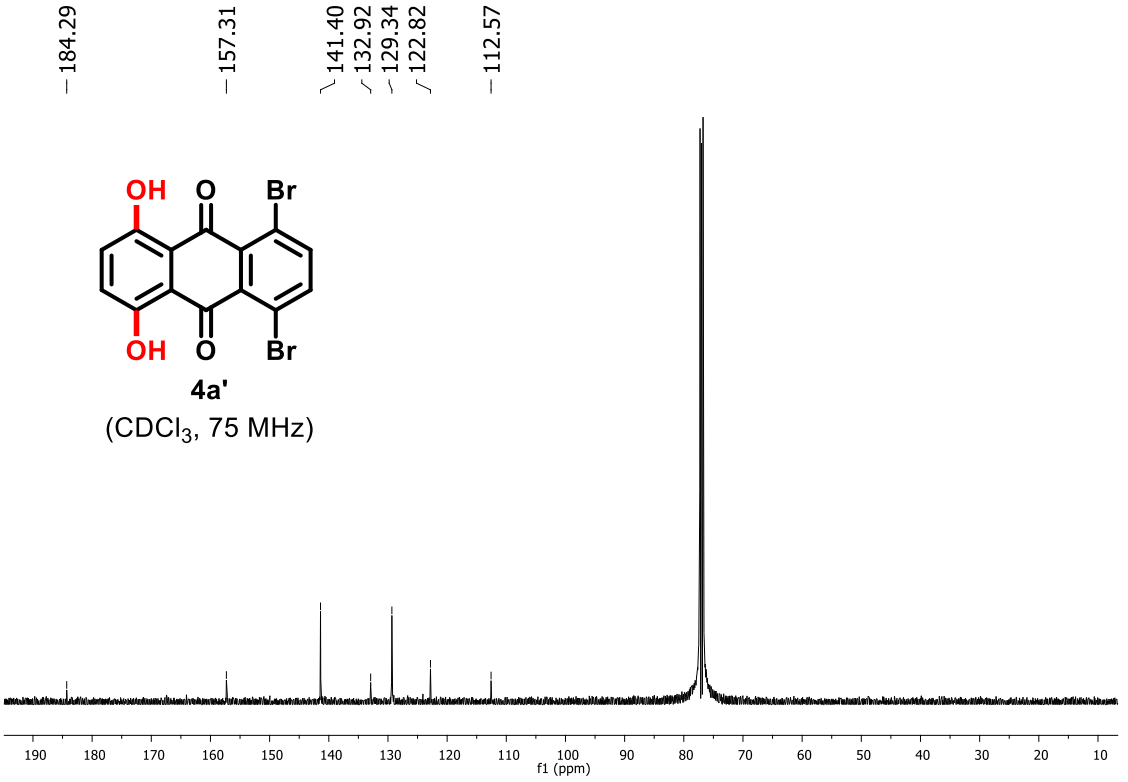
8.5
8.0
7.5
7.0
f1 (ppm)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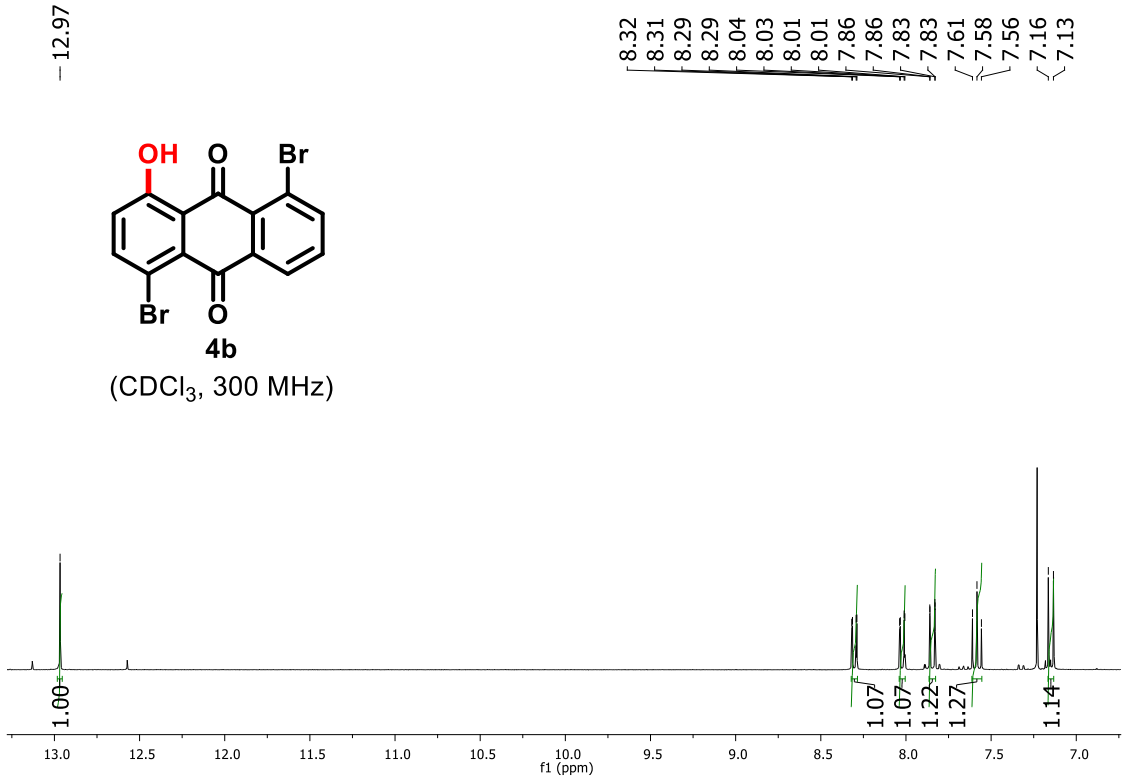
157.31
141.40
132.92
129.34
122.82
112.57
OH
O
Br
OH
O
Br
4a'
(CDCl3, 75 MHz)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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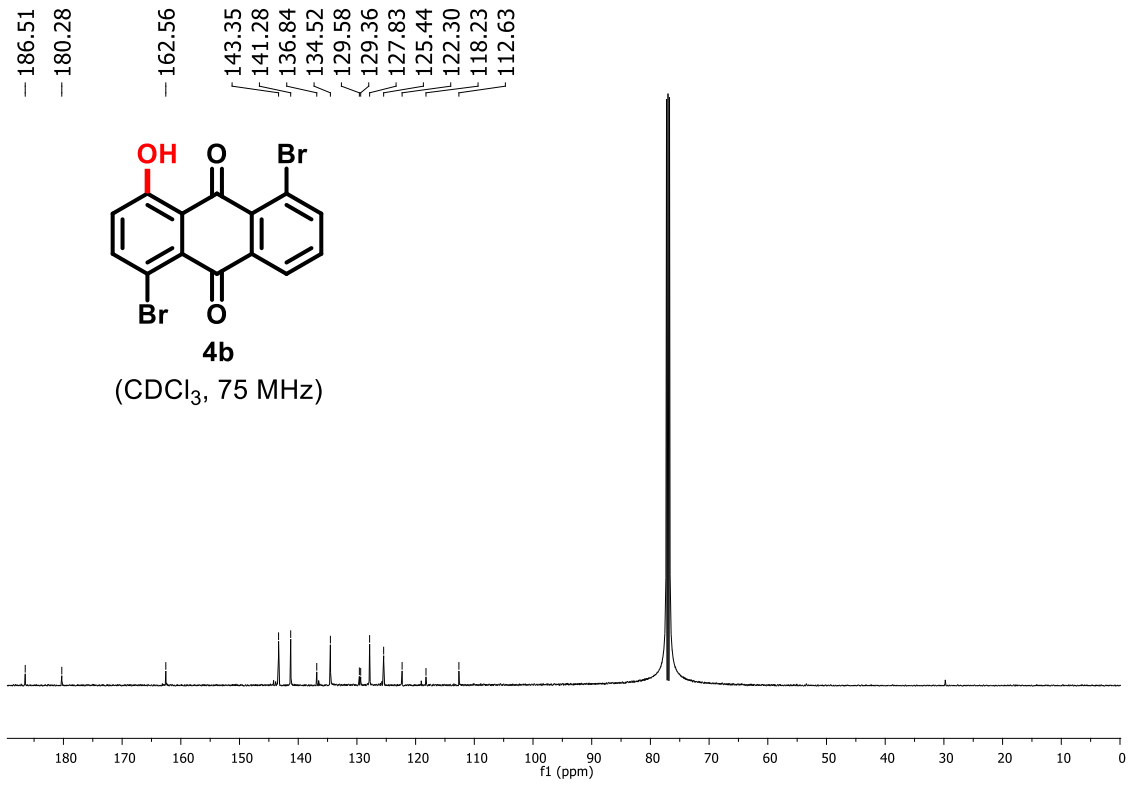
8.32
8.31
8.29
8.29
8.04
8.03
8.01
8.01
7.86
7.86
7.83
7.83
7.61
7.58
7.56
7.16
7.13
OH
O
Br
Br
O
4b
(CDCl3, 300 MHz)
1.00
1.07
1.07
1.22
1.27
1.14
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
f1 (ppm)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180.28
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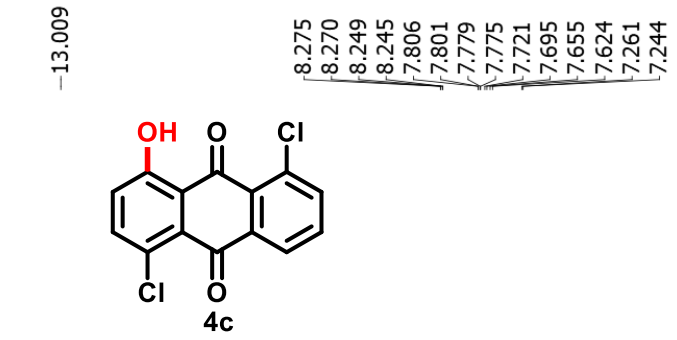
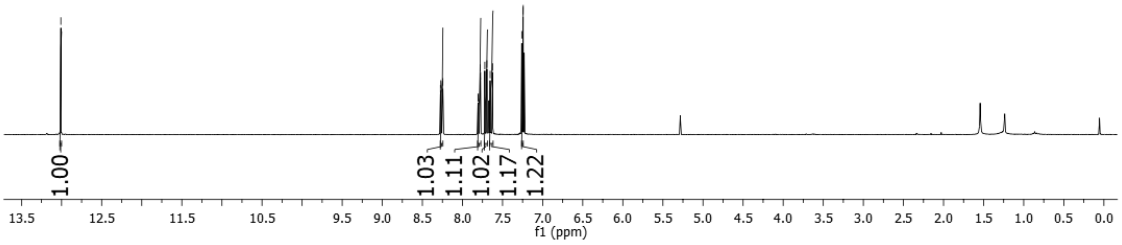
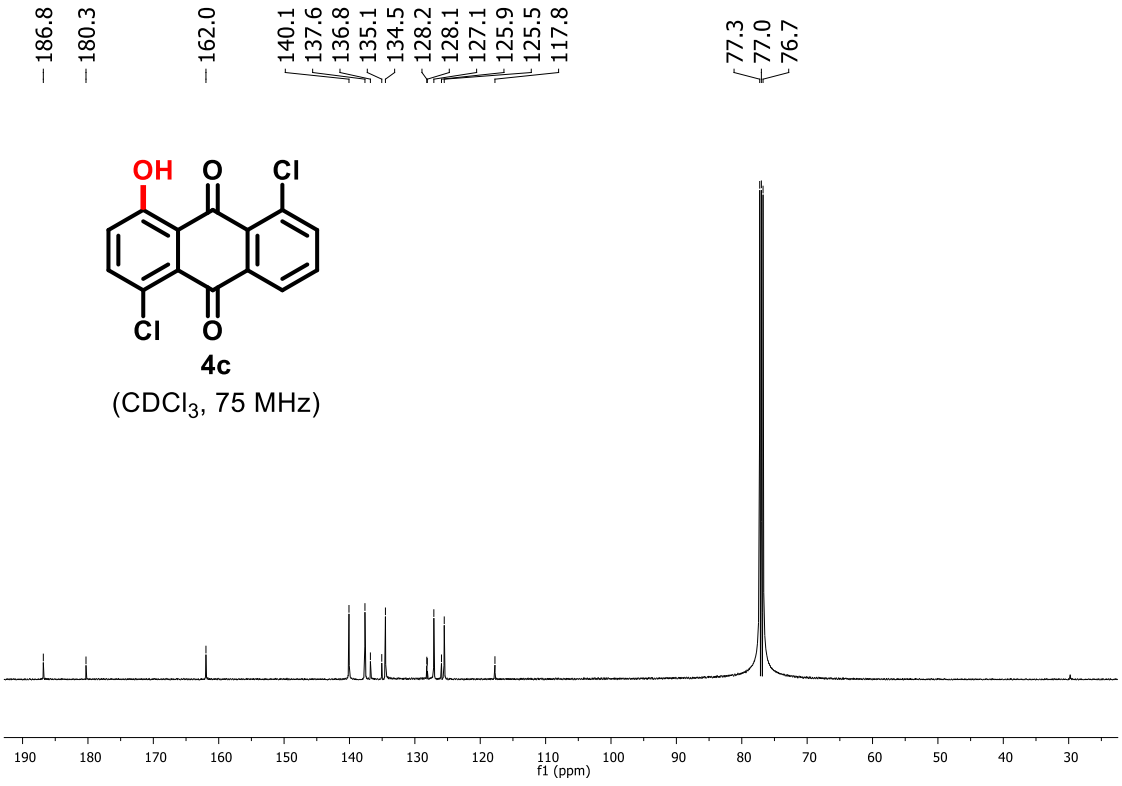
143.35
141.28
136.84
134.52
129.58
129.36
127.83
125.44
122.30
118.23
112.63
OH
O
Br
Br
O
4b
(CDCl3, 75 MHz)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



4c

($CDCl_3$, 300 MHz)





4c

($CDCl_3$, 75 MHz)