Substitution of a Haloquinone by Phenols under Pyridine-Free Conditions: Synthetic, Mechanistic, and Solid-State Considerations Involving 2,3-Dicholoro-1,4-naphthoquione

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Supporting Information

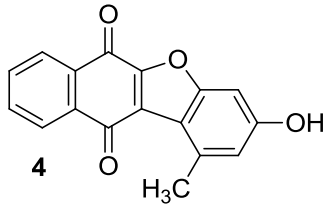
Experimental

General. Unless otherwise noted, all starting materials were obtained from commercial suppliers and were used without further purification. Anhydrous grade Cs_2CO_3 and DMSO were purchased from Aldrich. Analytical thin-layer chromatography was performed with EM Reagents 0.25 mm silica gel 60-F TLC plates. Flash column chromatography was carried out with silica gel (230-400 mesh) from Silicycle. High resolution mass spectrometry (ESI) was obtained from the University of Iowa Mass Spectrometry Facility.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 spectrometer. Chemical shifts are expressed in parts per million (δ) using tetramethylsilane (TMS, δ 0 ppm) or DMSO-d_5 (δ 2.50 ppm or 39.43 ppm) as the internal standard. Coupling constants, *J*, are reported in Hertz (Hz), and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). All potentially ambiguous signals were further characterized and assigned based on COSY, HMQC, HMBC and/or NOESY spectroscopy. The ^{1}H and ^{13}C NMR spectra of each compound synthesized are displayed in the Supplemental Figures section.

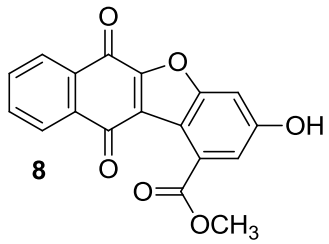
To determine % conversion (eq S1) for the entries in Table 1 a small sample was removed from the crude reaction mixture after HCl quench. The sample was dissolved in $CDCl_3$:DMSO-d_6 (50:1) and a ^{1}H NMR was obtained. To determine conversion the integrations of the entire aromatic naphthoquinone region (assumed to be unchanged over the course of the reaction (denominator eq S1) were compared to the two distinct orcinol-derived hydrogen peaks of **4** (numerator eq S1). The ^{1}H NMR sample was returned to the remainder of the reaction mixture and the solvent was removed *in vacuo* prior to chromatographic purification.

$$\text{(S1)} \qquad \% \text{ Conversion} = \frac{\text{int}(\ 7.10\text{-}6.90 \text{ ppm}) + \text{int}(6.85\text{-}6.80 \text{ ppm})}{((\text{int}(\ 8.30\text{-}8.10 \text{ ppm}) + \text{int}(7.90\text{-}7.70 \text{ ppm}))\ /\ 2)} \times 100$$



4

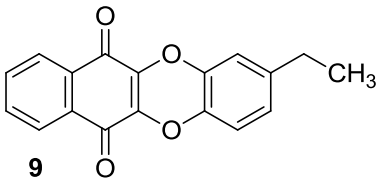
3-Hydroxy-1-methylbenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (4). In a 20 mL reaction vial orcinol (123.7 mg, 1.00 mmol), DMSO (10 mL), and then 2,3-dichloronaphthoquinone (226.7, 1.00 mmol) were combined. Upon reaching solution homogeneity anhydrous Cs_2CO_3 (10 eq) was added and the reaction was vigorously stirred at 100 °C for 2 h then quenched with 1 M HCl. The product was extracted with EtOAc (3 × 50 mL) and washed with 50 mL of brine. The combined organic layers were then dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification by flash chromatography[1] (hexanes→30% EtOAc in hexanes) afforded the title compound **4**[2] (92.1 mg, 0.331 mmol, 33.1%) as a red powder. R_f = 0.48 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6:$CDCl_3$ (50:1)): δ 10.39 (s, 1H), 8.12 (m, 2H), 7.89 (m, 2H), 6.99 (m, 1H), 6.81 (m, 1H), 2.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6:$CDCl_3$ (50:1)): δ 180.2, 174.1, 159.9, 158.2, 152.3, 136.0, 133.8, 133.5, 133.1, 131.5, 126.7, 125.6, 117.4, 114.2, 95.4, 22.2; HRMS (ESI): calcd for $C_{17}H_{11}O_4$ [M + H]: 279.0657; found: 279.0659.



8

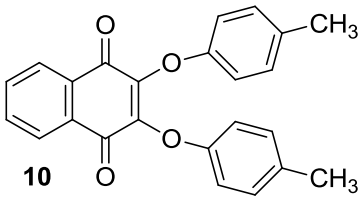
Methyl 3-hydroxy-6,11-dioxo-6,11-dihydrobenzo[*b*]naphtho[2,3-*d*]furan-1-carboxylate (8). In a 20 mL reaction vial 3,5-dihydroxybenzoate (169.0 mg, 1.01 mmol), DMSO (10 mL), and then 2,3-dichloronaphthoquinone (225.3, 0.99 mmol) were combined. Upon reaching solution homogeneity anhydrous Cs_2CO_3 (10 eq) was added and the reaction was vigorously stirred at 100 °C for 2 h then quenched with 1 M HCl. The product was extracted with CH_2Cl_2 (5 × 50 mL) and washed with 50 mL of brine. The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes→30% EtOAc in hexanes) afforded the title compound **8**

(91.4 mg, 0.2853 mmol, 29%) as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6:$CHCl_3$ (100:1)): δ 10.90 (s, 1H), 8.10 (m, 2H), 7.89 (m, 2H), 7.35 (s, 1H), 7.13 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6:$CHCl_3$ (100:1)): δ 180.0, 174.2, 167.4, 159.5, 157.4, 153.3, 134.3, 134.1, 132.9, 131.8, 129.8, 126.4, 126.1, 123.5, 115.0, 110.8, 100.4, 52.5; HRMS (ESI): calcd for $C_{18}H_{10}O_6Na$ [M + Na]: 345.0375; found: 345.0368.



9

2-Ethylbenzo[*b*]naphtho[2,3-*e*][1,4]dioxine-6,11-dione (9). In a 20 mL reaction vial ethylcatechol (140.0 mg, 1.01 mmol), DMSO (10 mL), and then 2,3-dichloronapthoquinone (229.2 mg, 1.01 mmol) were combined. Upon reaching solution homogeneity anhydrous Cs_2CO_3 (10 eq) was added and the reaction was vigorously stirred for 1 h. The reaction was quenched with 1 M HCl. The product was filtered with a Büchner funnel and dried to yield 263.5 mg (0.90 mmol, 89%) of **9** as a pink solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (m, 2H), 7.74 (m, 2H), 6.86 (m, 3H), 2.55 (q, J = 7.5 Hz, 2H), 1.20 (t, J = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.6, 177.5, 161.8, 142.6, 140.3, 139.8, 139.6, 138.4, 134.1, 134.1, 129.9, 126.4, 126.4, 124.9, 117.0, 116.7, 28.1, 15.1; HRMS (ESI) [M + H]: calcd for $C_{18}H_{13}O_4$, 293.0814; found, 293.0800.



10

2,3-Bis-(*p*-tolyloxy)-1,4-naphthoquinone (10). To a 20 mL vial *p*-cresol (2.03 mmol, 219.5 mg, 2.01 equiv), anhydrous DMSO (10 mL), and then 2,3-dichloronaphthoquinone (1.01 mmol, 229.3 mg, 1 equiv) were combined. Upon reaching solution homogeneity anhydrous Cs_2CO_3 (2 g, 6 equiv) was added and the reaction was vigorously stirred for 30 min. The reaction was quenched by the addition of 1 M HCl and extracted into CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with 50%

aqueous brine solution (100 mL), dried over sodium sulfate, filtered, and the solvent was removed *in vacuo*. Purification by silica gel flash chromatography (hexanes → ethyl acetate:hexanes, 2:5) afforded 306.6 mg of the product (0.828 mmol, 82.0%) as a red solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (dd, 2H, *J* = 3.3 Hz, *J* = 5.7 Hz), 7.74 (dd, 2H, *J* = 3.3 Hz, *J* = 5.7 Hz), 7.03 (d, 4H, *J* = 8.3 Hz), 6.81 (d, 4H, *J* = 8.5 Hz), 2.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6, 154.6, 146.4, 134.2, 133.0, 130.8, 129.9, 126.7, 116.4, 20.6; TLC R_f = 0.29 (Et_3N:hexanes, 3:17); HRMS (ESI) [M + H]: calcd for $C_{24}H_{19}O_4$ 371.1283, found 371.1285.

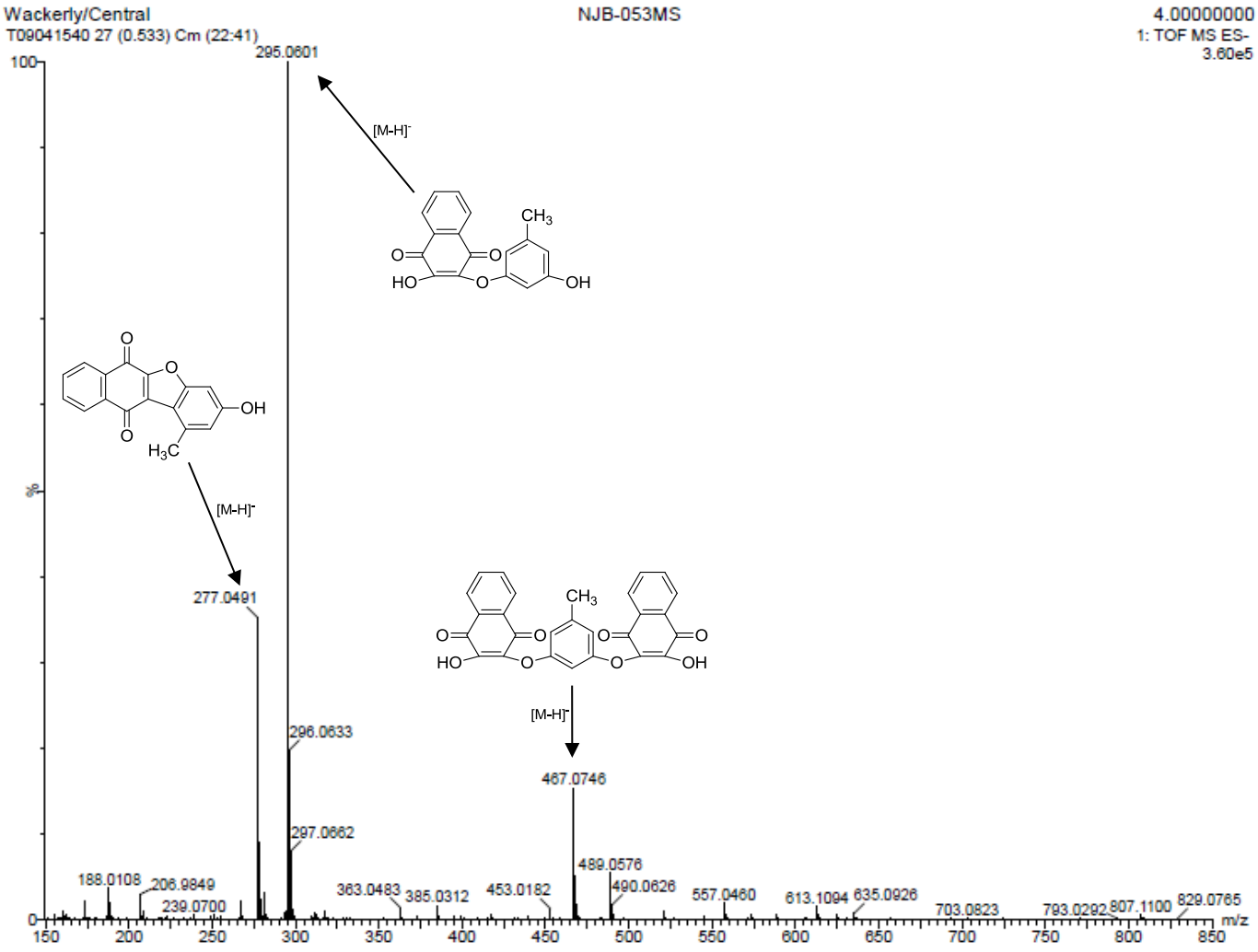


Figure S1. Electrospray ionization mass spectrum in negative ion mode for the crude, hydrolyzed sample of **4** + oligomers.

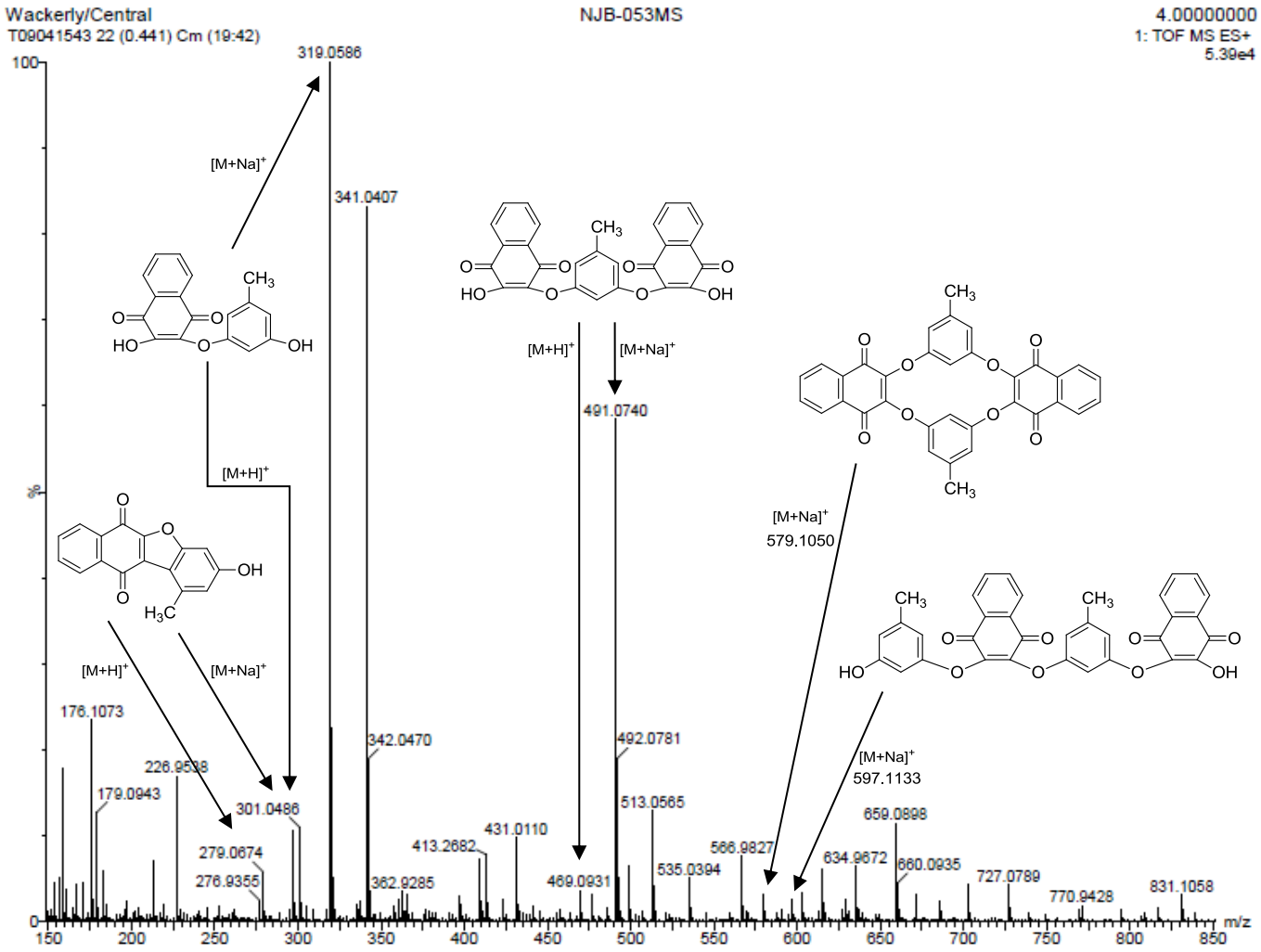


Figure S2. Electrospray ionization mass spectrum in positive ion mode for the crude, hydrolyzed sample of **4** + oligomers.

Table S1. Measured and calculated masses for the $[M+Na]^+$ ions from the sample shown in Figure S2.

Formula	Measured	Calculated
$C_{17}H_{10}NaO_4^+$	301.0486	301.0471
$C_{17}H_{12}NaO_5^+$	319.0586	319.0577
$C_{27}H_{16}NaO_8^+$	491.0740	491.0737
$C_{34}H_{20}NaO_8^+$	579.1050	579.1050
$C_{34}H_{22}NaO_9^+$	597.1133	597.1156

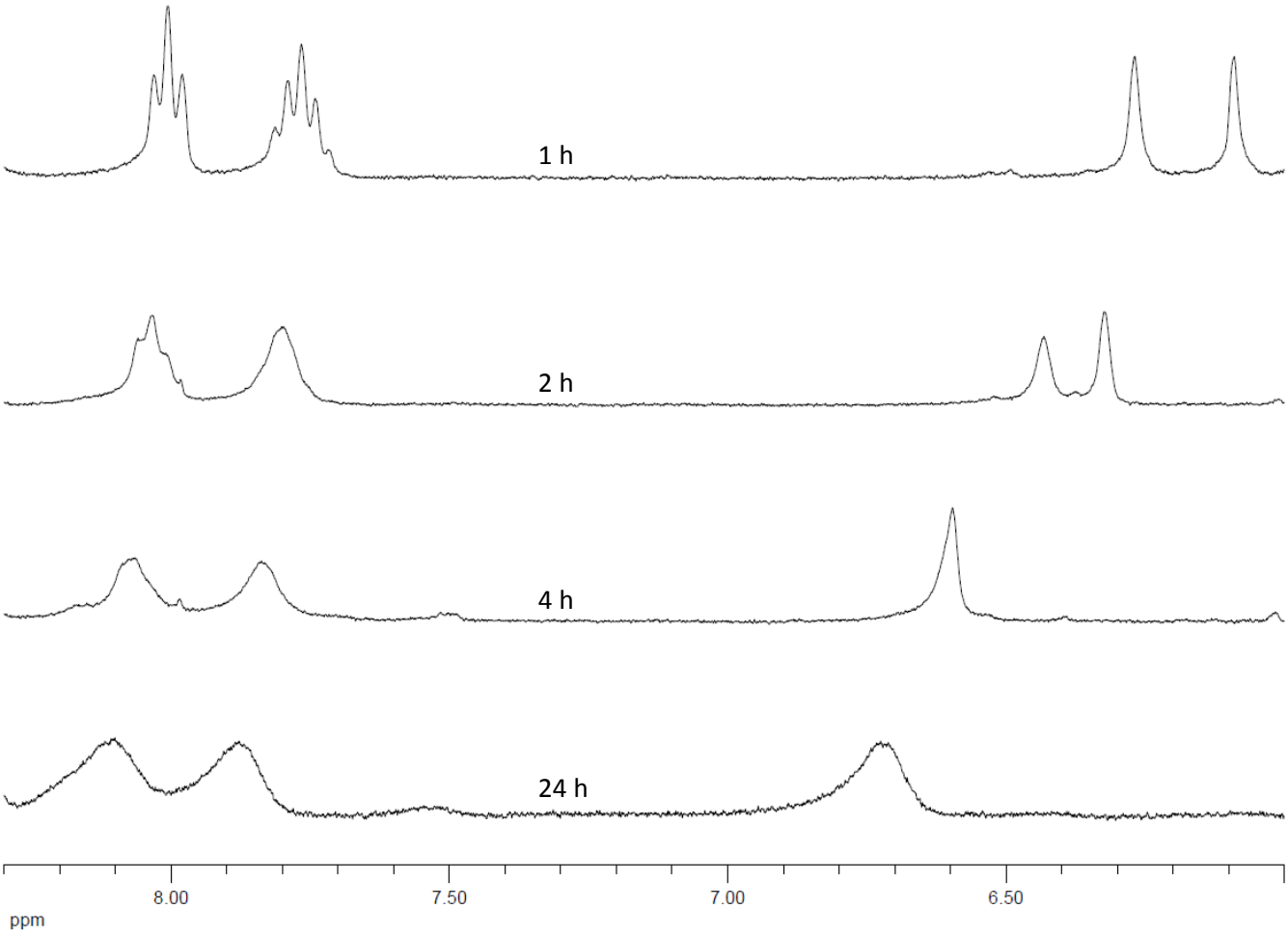
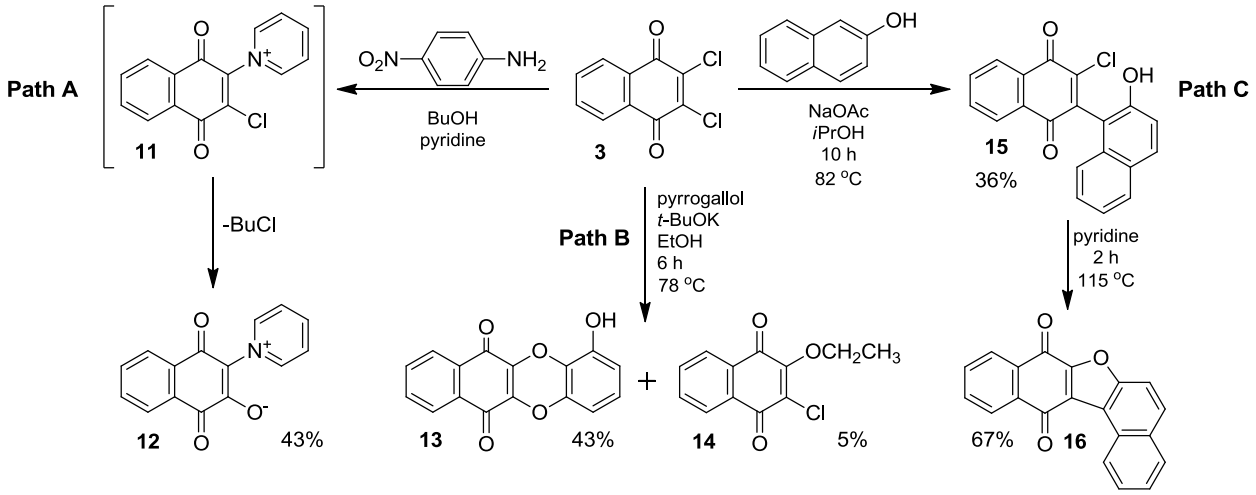
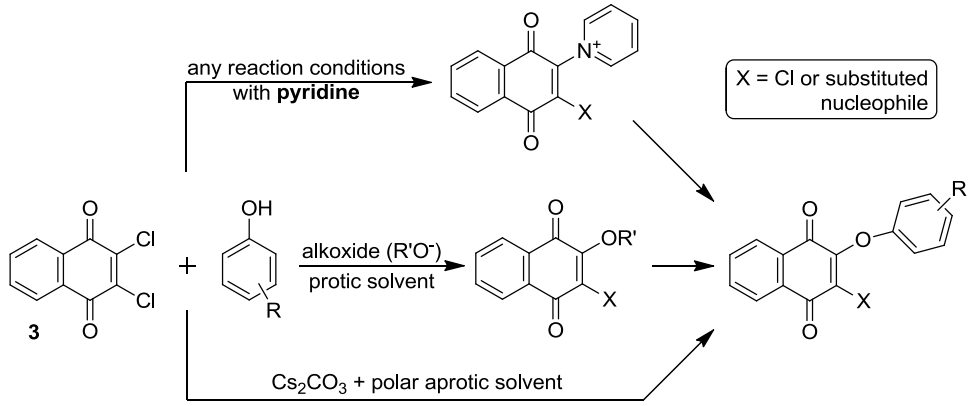


Figure S3. ^{1}H NMR spectra of the aromatic region after re-subjection of **4** to the reaction conditions (DMSO, Cs_2CO_3, 100 °C) at various times.



Scheme S1. Summary of mechanistic results from the reaction of 2,3-dichloronaphthoquinone with nucleophiles. Path A) VanAllan and Reynolds[3] showed that when **3** was heated in 25:4 (v:v) mixture of 1-butanol:pyridine intermediate **11** was detected and a reasonable yield of **12** was obtained. Additionally, Lee and coworkers[4] found that when **3** was reacted with phenol in pyridine with K_2CO_3 **12** was the predominant product (48%). Path B) Abdel-Monem and coworkers,[5] among other researchers noted in the paper and SI, showed that hydroxyl oxygen atoms preferentially react as the nucleophile, even under strongly basic conditions. This mechanism contrasts with Path C[6] showing initial C-C bond formation. Thus the acetate in 2-propanol conditions are unique in that they are the only conditions we could find in our survey of the literature that exhibit carbon substitution over oxygen substitution.



Scheme S2. Three proposed mechanistic pathways for substitution of phenols on **3** based on our results and previously reported mechanistic studies.

Table S2. Literature survey of reactions of 2.0-2.2 equiv of a monophenol with quinone **3**.

Reference	Phenol	Additive(s)	Solvent	Temp.	Time	Yield
7	*m*-methoxyphenol	K_2CO_3	DMSO	50 °C	16 h	55%
8	*p*-cresol	H_3PO_4	pyridine	180 °C	3 h	43%
8	3,5-dimethylphenol	HCl, methanol	pyridine	rt	24 h	34%
9	phenol	Cs_2CO_3	THF	reflux	18 h	58%
10	2,4,5-trichlorophenol	Cs_2CO_3	THF	reflux	18 h	39%
9	*p*-nitrophenol	Cs_2CO_3	THF	reflux	18 h	75%
9	*m*-hydroxybenzaldehyde	Cs_2CO_3	THF	reflux	18 h	27%
9	*p*-hydroxybenzaldehyde	Cs_2CO_3	THF	reflux	18 h	34%
9	*o*-cyanophenol	Cs_2CO_3	THF	reflux	18 h	59%
9	*p*-trifluoromethoxyphenol	Cs_2CO_3	THF	reflux	18 h	72%
10	*p*-fluorophenol	NaH	THF	0 °C → rt	1 h	72%
11	phenol	LD[1], K_2CO_3	H_2O	90-100 °C	30 h	15%
11	phenol	SDS[2], K_2CO_3	H_2O	90-100 °C	30 h	16%
11	*p*-cresol	LD[1], K_2CO_3	H_2O	90-100 °C	24 h	50%
11	*p*-cresol	SDS[2], K_2CO_3	H_2O	90-100 °C	24 h	48%
11	*p*-methoxyphenol	LD[1], K_2CO_3	H_2O	90-100 °C	40 h	35%
11	*p*-methoxyphenol	SDS[2], K_2CO_3	H_2O	90-100 °C	40 h	35%
11	3,5-dimethylphenol	LD[1], K_2CO_3	H_2O	90-100 °C	40 h	15%
11	3,5-dimethylphenol	SDS[2], K_2CO_3	H_2O	90-100 °C	40 h	15%
11	*p*-chlorophenol	LD[1], K_2CO_3	H_2O	90-100 °C	40 h	26%
11	*p*-chlorophenol	SDS[2], K_2CO_3	H_2O	90-100 °C	40 h	27%
12	2,6-dimethylphenol	K_2CO_3	DMSO	rt	24 h	60%
13	7-hydroxy-4-methyl-2*H*-chromen-2-one	Na_2CO_3	DMSO	rt	6 h	12%
13	7-hydroxy-2*H*-chromen-2-one	Na_2CO_3	DMSO	rt	6 h	20%
14[3]	phenol	K_2CO_3	phenol	100 °C	1 h	96%[3]

[1]Laundry Detergent. [2]Sodium dodecyl sulfate. [3]This reaction does not fit the conditions since it utilizes phenol as the solvent but is shown as an example illustrating that higher yields are achievable. This large excess of phenol may be impractical for reactions with some phenols

Single crystal X-ray diffraction

Single-crystal XRD was measured on a Nonius Kappa CCD single-crystal X-ray diffractometer using MoK_α radiation (λ =0.7107 Å). Structure solution and refinement were accomplished using SHELXS-97 and SHELXL-97, respectively or SHELXL-2014.[15,16] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms associated with carbon atoms were refined in geometrically constrained positions.

Table S2. Crystallographic parameters for **4** and **10**.

compound name	**4**	**10**
chemical formula	$C_{17}H_{10}O_4 \cdot C_2H_6OS$	$C_{24}H_{18}O_4$
formula mass	356.38	370.38
crystal system	monoclinic	orthorhombic
space group	C2/c	$Pmn2_1$
a/Å	37.702(4)	20.343(2)
b/Å	4.6294(5)	8.9785(9)
c/Å	19.640(2)	5.1800(5)
α/°	90	90
β/°	105.885(5)	90
γ/°	90	90
V/Å^3	3297.0(6)	946.1(2)
ρ_{calc} /g cm^{-3}	1.436	1.300
T/K	190(2)	293(2)
Z	8	2
radiation type	MoK_α	MoK_α
μ /mm^{-1}	0.224	0.088
no. of reflections measured	9865	4706
no. of independent reflections	2902	1631
no of reflection (I > 2σ(I))	2024	1298
R_{int}	0.0438	0.0273
R_1 (I > 2σ(I))	0.0490	0.0395
$wR(F^2)$ (I > 2σ(I))	0.1202	0.1057
R_1 (all data)	0.0802	0.0657
$wR(F^2)$ (all data)	0.1390	0.1460
CCDC deposition number	1429360	1429359

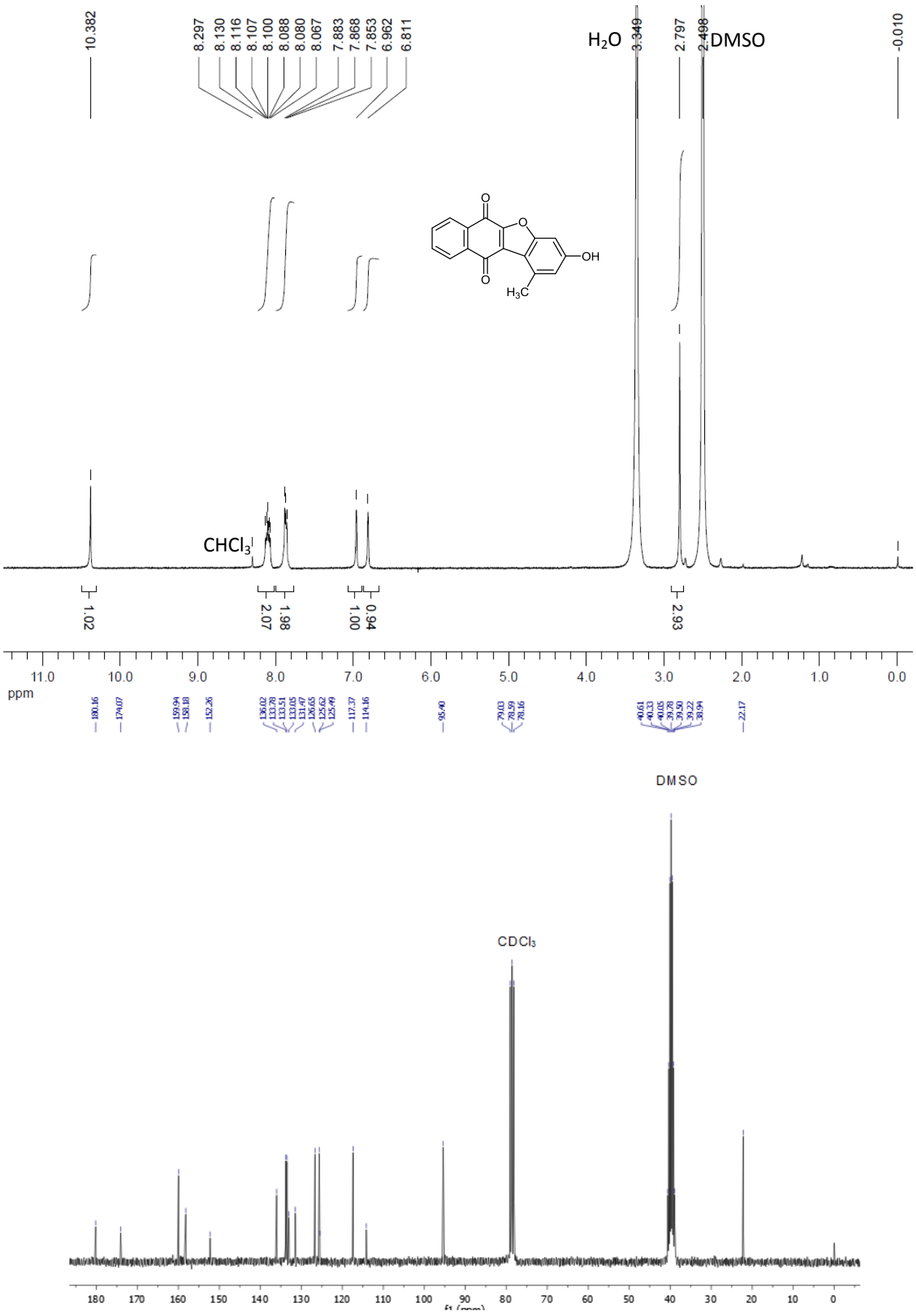


Figure S4. ^{1}H (top) and ^{13}C (bottom) NMRs of 3-hydroxy-1-methylbenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione **(4)**.

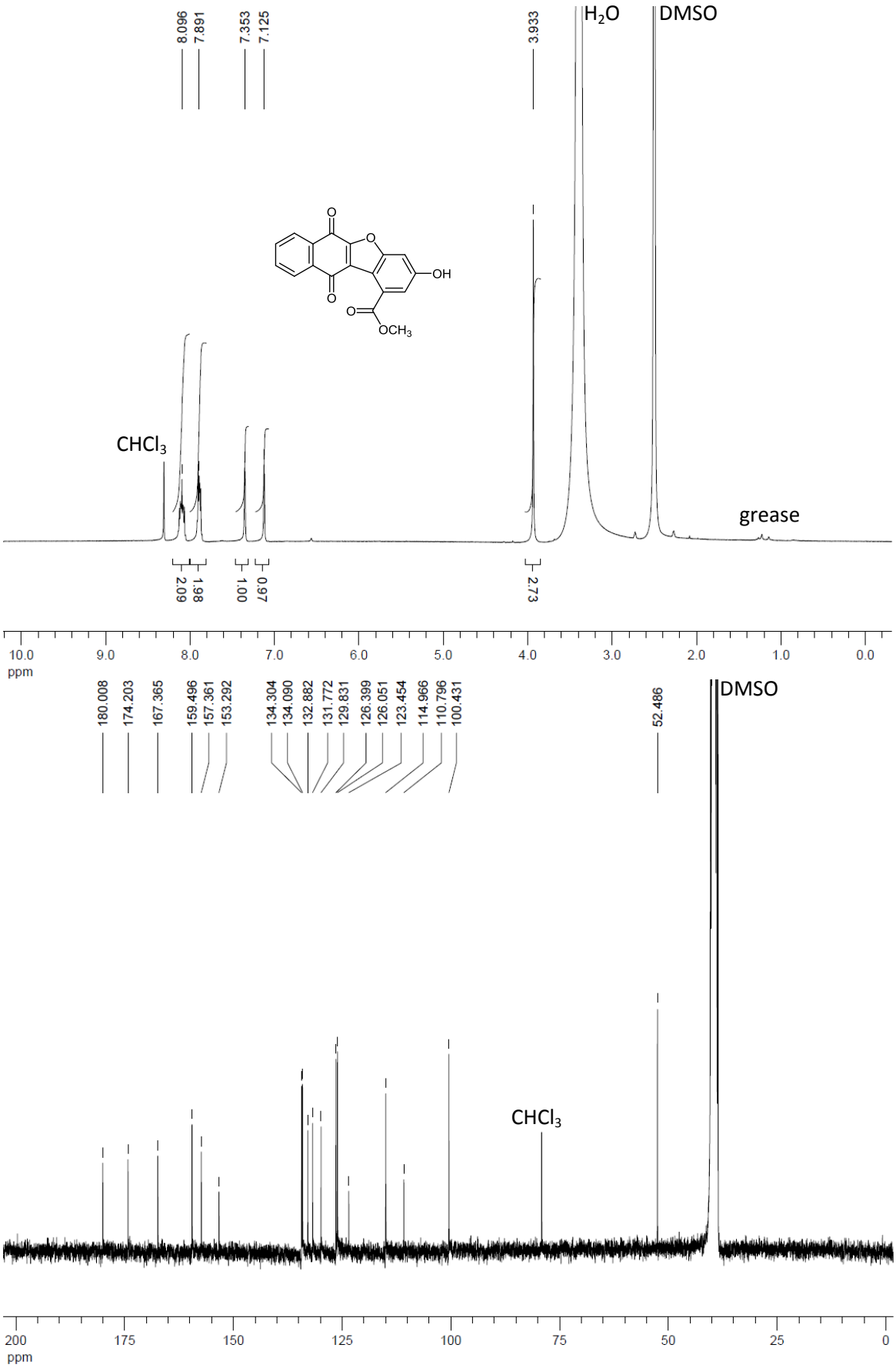


Figure S5. ^{1}H (top) and ^{13}C (bottom) NMRs of methyl 3-hydroxy-6,11-dioxo-6,11-dihydrobenzo[*b*]naphtho[2,3-*d*]benzofuran-1-carboxylate **(8)**.

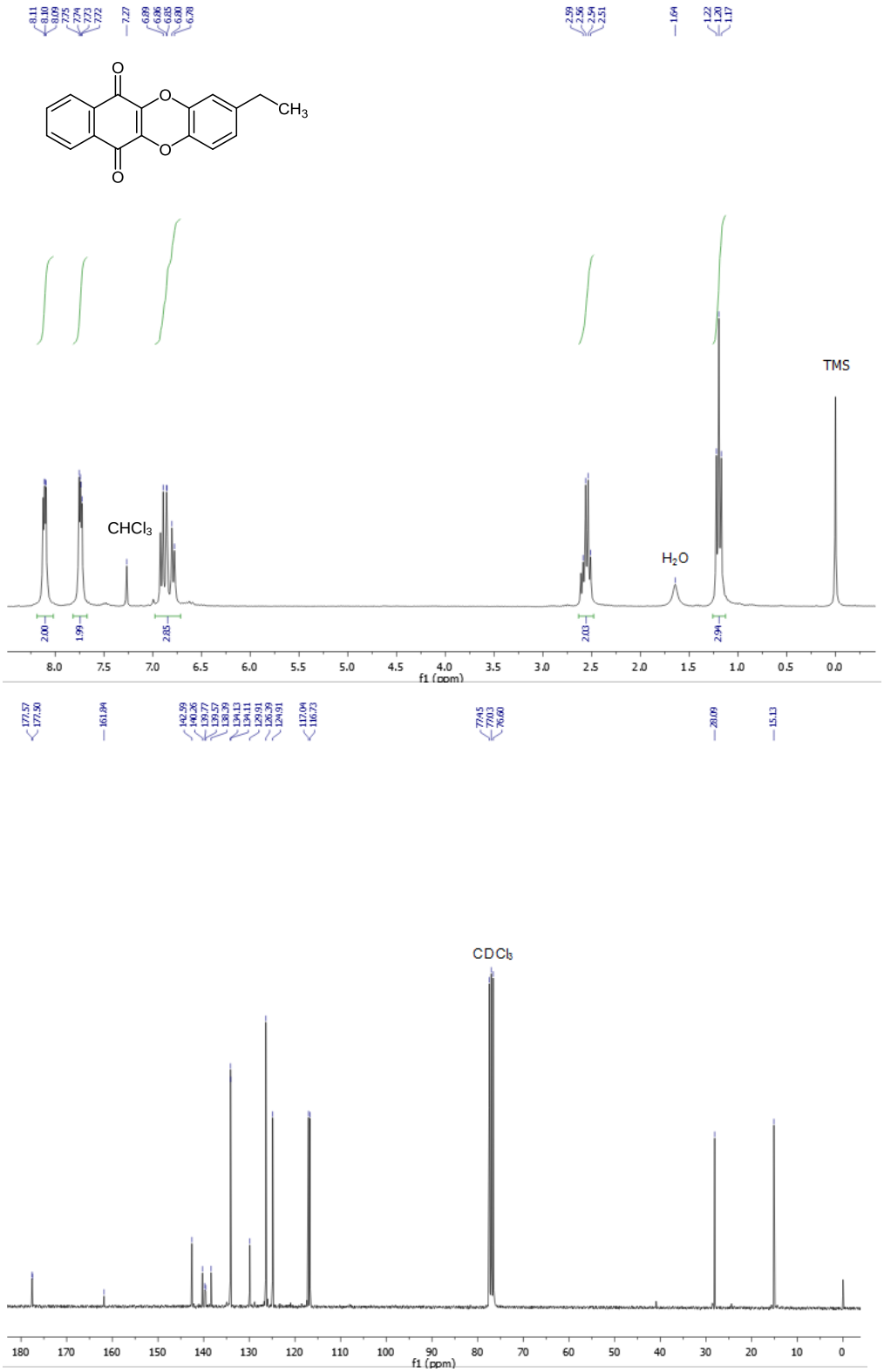


Figure S6. ^{1}H (top) and ^{13}C (bottom) NMRs of 2-ethylbenzo[*b*]naphtho[2,3-*e*][1,4]dioxine-6,11-dione **(9)**.

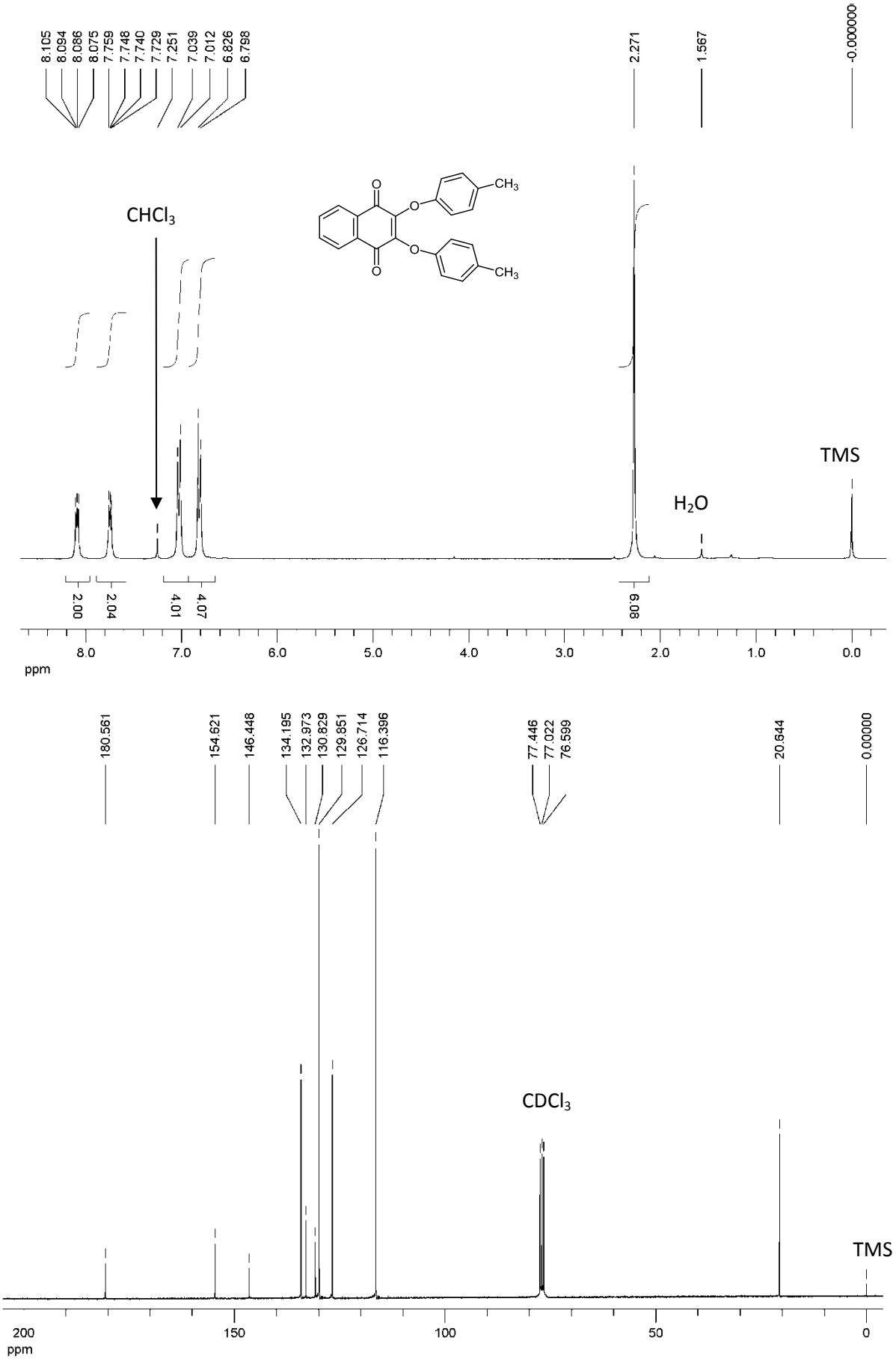


Figure S7. ^{1}H (top) and ^{13}C (bottom) NMRs of 2,3-bis(*p*-tolyloxy)-1,4-naphthoquinone (**10**).

References & Notes

1) Due to the poor solubility of the product in organic solvents chromatographic purification was conducted by "dry loading" the crude reaction mixture before separation. This technique, while consistent, seemed to give *ca.* 5% loss of the product on the column, compared to the conversion as determined by ^{1}H NMR.
2) The regioisomer of **4** (1-hydroxy-3-methylnaphtho[2,3-b]benzofuran-6,11-dione) could be formed in the mixture to some extent. However, we were not able to identify it by TLC, isolate it by chromatographic purification, or differentiate its structure from **4** by MS, and it has been reputed by others to not form in the reaction: (a) Finley, K. T. In *Quinoid Compounds*, Vol. 2; Patai, S., Ed.; John Wiley & Sons: Chichester, **2010**. (b) Finley, K. T. In *Supplement E: The Chemistry of Hydroxyl, Ether and Peroxide Groups*, Vol. 2; Patai, S., Ed.; John Wiley & Sons: Chichester, **2010**, 1027.
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