1,4-Naphthoquinone Cations as Antiplasmodial Agents: Hydroxy-, Acyloxy-, and Alkoxy-Substituted Analogues

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SUPPORTING INFORMATION

Chemistry

Chemicals were obtained from commercial sources and used without further purification. Reaction products were purified by flash chromatography on silica gel (60-100 mesh) and visualized under UV on TLC plates (silica gel 60 F_{254}). Melting points were determined with a melting point apparatus and are uncorrected. Exact mass measurements of final compounds were performed by electrospray ionization on a Thermo Scientific Orbitrap Elite spectrometer. NMR spectra were recorded on a Varian Inova 500 MHz spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane or residual solvent as an internal standard.

Preparation of 2-alkyl 1,4-naphthoquinone 4 via radical decarboxylation; general procedure. 1,4-Naphthoquinone (374 mg, 2.36 mmol), $AgNO_3$ (197 mg, 1.18 mmol), and the corresponding n-bromoalkyl carboxylic acid (1.18 mmol) were combined in a round bottom flask containing 7.5 mL of MeCN. Ammonium persulfate (270 mg, 1.18 mmol) in 7.5 mL of H_2O was then added and the mixture was refluxed with stirring for 6-18 h. After cooling to rt, the dark solution was extracted with EtOAc (3 x 15 mL). The combined organic layers was washed with brine (1 x 15 mL), dried over $MgSO_4$, filtered, and evaporated. Final purification of quinone **4** was achieved by silica gel chromatography using a gradient of 9-17% EtOAc in hexanes.

2-(5-Bromopentyl)naphthalene-1,4-dione 4a. Yield: 11%; yellow solid, mp 56-58 ºC; TLC (SiO_2) R_f 0.50 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.03 (m, 2H), 7.95-7.70 (m, 2H), 6.79 (s, 1H), 3.45-3.41 (m, 2H), 2.64-2.57 (m, 2H), 1.95-1.89 (m, 2H), 1.70-1.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 185.1, 151.4, 134.8, 133.7, 133.6, 132.2, 132.0, 126.6, 126.0, 35.5, 32.3, 29.4, 27.8, 27.2; MS (EI, 80 eV): *m/z* (%) = 306 (M, 20%), 199 (100), 172 (63), 157 (20), 144 (35), 128 (35).

2-(10-Bromodecyl)naphthalene-1,4-dione 4b. Yield: 75%; yellow solid, mp 43-45 ºC; TLC (SiO_2) R_f 0.36 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.07 (m, 1H), 8.05-8.03 (m, 1H), 7.74-7.71 (m, 2H), 6.78 (s, 1H), 3.40 (t, 2H, *J* = 7.0 Hz), 2.56 (t, 2H, *J* = 7.5 Hz), 1.84 (qnt, 2H, *J* = 7.0 Hz), 1.58 (qnt, 2H, *J* = 7.5 Hz), 1.43-1.29 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 185.1, 151.9, 134.7, 133.6, 132.3, 132.1, 126.6, 126.0, 34.0, 32.8, 29.6, 29.4, 29.4, 29.3, 28.7, 28.2, 27.1; MS (EI, 80 eV): *m/z* (%) = 376 (M, 14%), 199 (27), 173 (100).

Epoxidation of of 2-alkyl 1,4-naphthoquinone; general procedure. A solution of 30% H_2O_2 (1.5 mL), Na_2CO_3 (60 mg, 0.57 mmol) and H_2O (0.6 mL) was added to a suspension of quinone **4** (4.4 mmol) in 3 mL EtOH. The mixture was stirred at rt for 1-3 h until the reaction was complete. Water (3 mL) was then added and the product was extracted with DCM (3 x 5 mL). The combined organic layers was dried over $MgSO_4$, filtered, and concentrated to provide epoxide **5** which was used without further purification.

1α-(10-Bromodecyl)naphtho[2,3-β]oxirene-2,7(1α*H*,7α*H*)-dione 5b. Yield: 82%; white semi-solid; TLC (SiO_2) R_f 0.48 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03-8.01 (m, 1H), 7.96-7.94 (m, 1H), 7.78 (m, 2H), 3.87 (s, 1H), 3.41 (t, 2H, *J* = 6.5 Hz), 2.31-2.05 (m, 1H), 1.91-1.82 (m, 3H), 1.52-1.47 (m, 2H), 1.42-1.38 (m, 4H), 1.29 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2, 191.9, 134.7, 134.5, 132.6, 132.0, 127.6, 126.9. 64.2, 60.4, 34.3, 32.9, 29.8, 29.6, 29.5, 29.4, 28.9, 28.4, 28.3, 24.7; MS (EI, 80 eV): *m*/*z* (%) = 392 (M, 29%), 188 (100), 160 (17).

Cleavage of epoxide 5; general procedure. Sulfuric acid (1.4 mL) and epoxide **5** (1.3 mmol) were combined in 50 mL beaker and stirred at rt for 15 mins. Ice water (30 mL) was then added and the resulting mixture was then extracted with DCM (2 x 10 mL). The combined DCM layers was dried over $MgSO_4$, filtered and concentrated. Final purification of product **6** was achieved by silica gel chromatography using a gradient of 9-25% EtOAc in hexanes.

2-(5-Bromopentyl)-3-hydroxynaphthalene-1,4-dione 6a. Yield: 20%; yellow solid mp 109-110 ºC; TLC (SiO_2) R_f 0.36 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 7.5 Hz), 8.07 (d, 1H, *J* = 7.0 Hz), 7.75 (t, 1H, *J* = 7.5 Hz), 7.67 (t, 1H, *J* = 7.5 Hz), 7.42 (s, 1H), 3.42 (t, 2H, *J* = 7.0 Hz), 2.62 (t, 2H, *J* = 7.0 Hz), 1.92 (qnt, 2H, *J* = 7.0 Hz), 1.60-1.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 181.4, 153.1, 134.9, 132.9, 132.8, 129.4, 126.7, 126.1, 124.2, 33.7, 32.5, 28.1, 27.3, 23.0; MS (EI, 70 eV): *m*/*z* (%) = 322 (M, 48%), 242 (15), 213 (15), 188 (100), 160 (28).

2-(Bromodecyl)-3-hydroxynaphthalene-1,4-dione 6b. Yield 65%; yellow solid; TLC (SiO_2) R_f 0.43 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 1H, *J* = 7.5 Hz), 8.06 (d, 1H, *J* = 7.5Hz), 7.76-7.73 (m, 1H), 7.69-7.65 (m, 1H), 7.38 (s, 1H), 3.41-3.38 (t, 2H, *J* = 7.0 Hz), 2.61 (t, 2H, *J* = 7.5 Hz), 1.84 (qnt, 2H, *J* = 7.0 Hz), 1.55 (qnt, 2H, *J* = 7.0 Hz), 1.40-1.25 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 181.6, 153.2, 134.9, 134.7, 134.5, 133.1, 133.0, 132.6, 129.6, 127.6, 126.93, 126.91, 126.2, 124.9, 34.3, 33.0, 29.9, 29.7, 29.6, 29.5, 28.9, 28.4, 28.3, 23.5; MS (EI, 80 eV): *m*/*z* (%) = 392 (M, 15%), 312 (21), 207 (30), 188 (100), 160 (20).

Acetylation of 3-hydroxy naphthoquinone 6; general procedure. To a solution of quinone **6** (0.375 mmol) in DCM (8 mL) was added acetyl chloride (54 μl, 0.75 mmol) and 2,6-lutidine (70 μL, 0.68 mmol). The mixture was then stirred for 1.5 h at rt and reaction was quenched with 0.5 M HCl (10 mL). The product was extracted with DCM (2 x 10 mL) and the combined organic layers was washed with brine (2 x 10 mL) and dried over $MgSO_4$. Evaporation of the solvent provided acetylated product **7** which was used without further purification.

3-(5-Bromopentyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl acetate 7a. Yield: 93%; yellow solid, mp 46-47 °C ; TLC (SiO_2) R_f 0.25 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.10 (m, 2H), 7.77-7.70 (m, 2H), 3.41 (t, 2H, *J* = 6.5 Hz), 2.58 (t, 2H, *J* = 6.5 Hz), 2.43 (s, 3H), 1.90 (t, 2H, *J* = 6.0 Hz), 1.55-1.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 178.1, 168.1, 151.3, 139.2, 134.1, 133.9, 132.1, 130.9, 126.8, 126.7, 33.5, 32.3, 28.2, 27.6, 24.1, 20.5; MS (EI, 80 eV): *m*/*z* (%) = 322 (M – 42, 69%), 244 (18), 207 (32), 189 (34), 159 (36), 131 (15).

3-(10-Bromodecyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl acetate 7b. Yield: 98%; yellow solid, mp 52-54 °C; TLC (SiO_2) R_f 0.48 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.09 (m, 2H), 7.75-7.73 (m, 2H), 3.04 (t, 2H, *J* = 6.5 Hz), 2.55 (t, 2H, *J* = 8.0 Hz), 2.41 (s, 3H), 1.85 (qnt, 2H, *J* = 7.0 Hz), 1.51 (t, 2H, *J* = 7.0 Hz), 1.42-1.29 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 178.3, 168.2, 151.3, 140.0, 134.3, 134.0, 132.3, 131.1, 126.9, 126.8, 34.3, 33.0, 29.9, 29.6, 29.4, 28.9, 28.7, 28.3, 24.5, 20.6; MS (EI, 80 eV): *m*/*z* (%) = 392 (M – 42, 41%), 312 (15), 207 (23), 188 (100), 160 (20).

Synthesis of phosphonium bromide salt 8; general procedure. Naphthoquinone **7** (13 μmol) and the corresponding tertiary phosphine (26 μmol) were combined in a 5 mL conical-shaped tube containing 3:1 ^{i}PrOH:PhMe (3 mL). The tube was sealed with a crimp-top cap and heated to 100 °C. After 18-72 h, the dark solution was evaporated and the crude residue was purified by flash chromatography on silica gel using acetone to elute nonpolar impurities followed by 5-10% MeOH in DCM to isolate the phosphonium salt **8**.

(10-(3-Acetoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)decyl)triphenylphosphonium bromide 8a: Yield: 30%; pale yellow oil; TLC (SiO_2) R_f 0.27 (10:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09-8.06 (m, 2H), 7.85-7.73 (m, 17H), 3.68 (s, 2H), 2.53 (t, 2H, *J* = 7.5 Hz), 2.40 (s, 3H), 2.17 (s, 2H), 1.62 (s, 4H), 1.48-1.45 (m, 2H), 1.32-1.21 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 184.6, 178.1, 168.1, 151.1, 139.8, 135.1, 134.1, 133.9, 133.7, 133.6, 132.0, 130.8, 130.6, 130.5, 126.7, 126.6, 118.6, 117.5, 30.5, 30.4, 29.6, 29.3, 29.2, 29.1, 28.5, 24.3, 22.9, 22.6, 20.5; HRMS (ESI): *m*/*z* = calcd for $C_{32}H_{52}O_3P^+$ $[M]^+$ 617.31791, found 617.31783.

(4-(3-Acetoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentyl)triphenylphosphonium bromide 8b. Yield: 4%; yellow oil; TLC (SiO_2) R_f 0.40 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08-8.05 (m, 2H), 7.87-7.69 (m, 17H), 3.87-3.82 (m, 2H), 2.52 (t, 2H, *J* = 7.5 Hz), 2.44 (s, 3H), 1.78-1.77 (m, 2H), 1.67-1.64 (m, 2H), 1.50-1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7, 177.9, 168.4, 151.4, 139.1, 135.0, 134.1, 133.9, 133.7, 131.9, 130.8, 130.6, 130.5, 126.6, 118.7, 117.9, 30.3, 30.2, 27.9, 23.9, 22.4, 20.8; HRMS (ESI): *m*/*z* = calcd for $C_{35}H_{32}O_3P^+$ $[M]^+$ 547.20327, found 547.20385.

Deacetylation of naphthoquinone 8; general procedure. 3-Acetoxy phosphonium bromide **8** was dissolved in a 50% solution of 5 M HCl in ^{i}PrOH (10 mL) and stirred at 65 °C for 12-28 h. After the reaction was complete, the mixture was evaporated, and the product **9** was purified by silica gel chromatography using a gradient of 5-10% MeOH in DCM.

(5-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentyl)triphenylphosphonium bromide 9a. Yield: 22%; red oil; TLC (SiO_2) R_f 0.46 (9:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.85-7.76 (m, 17H), 3.72 (m, 2H), 2.50 (m, 2H), 1.71 (m, 4H), 1.54 (m, 2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 185.4, 184.7, 150.0, 135.04, 135.02, 134.4, 133.7, 133.7, 133.1, 132.6, 130.6, 130.5, 129.9, 126.4, 126.1, 123.5, 118.7, 118.0, 29.6, 27.2, 22.8, 22.2, 21.9; HRMS (ESI): *m*/*z* = calcd for $C_{33}H_{30}O_3P^+$ $[M]^+$ 505.19271, found 505.19268.

(10-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)decyl)tributylphosphonium bromide 9b. Yield: 14%; orange red oil; TLC (SiO_2) R_f 0.23 (9:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, 1H, *J* = 7.5 Hz), 8.07 (d, 1H, *J* = 7.5 Hz), 7.75 (t, 1H, *J* = 7.5 Hz), 7.67 (t, 1H, *J* = 7.5 Hz), 2.59 (t, 2H, *J* = 8.0 Hz), 2.44-2.33 (m, 10H), 1.53-1.35 (m, 22H), 1.27-1.19 (m, 18H), 0.97-0.93 (12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 150.0, 134.8, 133.0, 132.9, 129.6, 126.7, 126.1, 124.7, 32.2, 30.8, 30.7, 29. 7, 29.29, 29.27, 29.22, 28.9, 28.2, 26.4, 24.1, 24.0, 23.9, 23.8, 23.4, 22.0, 19.6, 19.4, 19.2, 19.0, 14.2, 13.5; HRMS (ESI): *m*/*z* = calcd for $C_{32}H_{52}O_3P^+$ $[M]^+$ 515.36486, found 515.36481.

(10-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)decyl)tribenzylphosphonium bromide 9c. Yield: 15%; orange red oil; TLC (SiO_2) R_f 0.22 (9:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, 2H, *J* = 7.0 Hz), 8.07 (d, 2H, *J* = 7.0 Hz), 7.35-7.27 (m, 15H), 4.18 (d, 6H, *J* = 15.0 Hz), 2.61-2.58 (m, 2H), 1.99-1.95 (m, 2H), 1.55-1.51 (m, 2H), 1.37-1.31 (m, 2H), 1.28-1.21 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4, 185.3, 165.5, 161.8, 134.9, 132.9, 130.3, 129.6, 128.6, 128.0, 127.9, 126.7, 126.1, 124.7, 103.3, 30.8, 29.6, 29.2, 29.0, 28.7, 28.2, 26.5, 23.3, 21.6; HRMS (ESI): *m*/*z* = calcd for $C_{41}H_{46}O_3P^+$ $[M]^+$ 617.31791, found 617.31783.

(10-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)decyl)triphenylphosphonium bromide 9d. Yield: 18%; red oil; TLC (SiO_2) R_f 0.14 (10:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, 1H, *J* = 7.5 Hz), 8.02 (d, 1H, *J* = 7.5 Hz), 7.84-7.77 (m, 9H), 7.72-7.67 (m, 7H), 7.62 (t, 1H, *J* = 7.5 Hz), 3.74-3.70 (m, 2H), 2.55 (t, 2H, *J* = 7.5 Hz), 1.62-1.58 (m, 4H), 1.50-1.46 (m, 2H), 1.31-1.19 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 181.4, 153.2, 135.0, 134.8, 133.8, 133.7, 133.0, 132.9, 130.67, 130.5, 129.6, 126.7, 126.1, 124.8 118.8, 118.2, 30.4, 30.3, 29.6, 29.3, 29.2, 29.1, 28.2, 23.3, 22.6; HRMS (ESI): *m*/*z* = calcd for $C_{38}H_{40}O_3P^+$ $[M]^+$ 575.27096, found 575.27096.

1,4-Dioxo-3-(phenyliodonio)-1,4-dihydronaphthalen-2-olate 11. To a stirring suspension of lawsone **10** (800 mg, 2.08 mmol) in $CHCl_3$ (25 mL) at 0 °C was added (diacetoxyiodo)benzene (540 mg, 2.08 mmol). After 1 h, the ice bath was removed and the mixture was stirred at rt for 8 h. The product was then vacuum filtered, washed with $CHCl_3$, aired dried, and used in subsequent reactions without further purification.

Synthesis of bromoalkoxyadehyde 13. The preparation of 4-(3-bromopropoxy)benzaldehyde, 4-(4-bromobutoxy)benzaldehyde, and 4-((10-bromodecyl)oxy)benzaldehyde was performed as under acetone reflux in the presence of K_2CO_3 (1.1 equiv.) and 2-fold excess of corresponding dibromoalkane.

Arylation of phenyliodonium ylide 11; general procedure. Aldehyde **13** (1.65 mmol), ylide **11** (419 mg, 1.72 mmol), and BF_3OEt_2 (210 μL, 1.65 mmol) were combined in 10 mL of $CHCl_3$. The mixture was heated to reflux and the progress of the reaction was monitored by TLC. Upon completion, the dark solution was evaporated and the quinone **14** was purified by flash chromatography on silica gel using a gradient of 7-25% EtOAc in hexanes.

2-(4-(4-Bromobutoxy)phenyl)-3-hydroxynaphthalene-1,4-dione 14a. Yield: 43%; red solid, mp 120-121 °C; TLC (SiO_2) R_f 0.22 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, 1H, *J* = 7.5 Hz), 8.14 (d, 1H, *J* = 7.5 Hz), 7.80 (t, 1H, *J* = 8.0 Hz), 7.73 (t, 1H, *J* = 8.0 Hz), 7.51 (d, 2H, *J* = 9.0 Hz), 6.98 (d, 2H, *J* = 9.0 Hz), 4.06 (t, 2H, *J* = 6.0 Hz), 3.51 (t, 2H, *J* = 6.5 Hz), 2.07 (qnt, 2H, *J* = 7.0 Hz), 1.98 (qnt, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 181.8, 159.1, 151.9, 135.1, 133.1, 132.9, 132.3, 129.4, 127.2, 126.0, 122.2, 121.9, 113.9, 66.8, 33.4, 29.4, 27.9; MS (EI, 80 eV): *m*/*z* (%) = 320 (M – 80, 100%), 266 (86), 238 (34), 221(28), 207 (41), 165 (33), 152 (33).

2-(4-(10-Bromodecyloxy)phenyl)-3-hydroxynaphthalene-1,4-dione 14b. Yield: 38%; red solid, mp 110-112 °C; TLC (SiO_2) R_f 0.35 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, 1H, *J* = 8.0 Hz), 8.11 (d, 1H, *J* = 7.0 Hz), 7.78 (t, 1H, *J* = 7.5 Hz), 7.71 (t, 1H, *J* = 7.5 Hz), 7.49 (t, 2H, *J* = 8.5 Hz), 6.98 (t, 2H, *J* = 8.5 Hz), 3.99 (t, 2H, *J* = 6.5 Hz), 3.41 (t, 2H, *J* = 6.5 Hz), 1.85 (qnt, 2H, *J* = 7.0 Hz), 1.79 (qnt, 2H, *J* = 7.0 Hz), 1.46-1.25 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9, 181.8, 159.4, 151.8, 135.1, 133.0, 132.2, 129.4, 127.2, 125.9, 121.9, 113.9, 67.9, 33.9, 32.8, 29.3, 28.7, 28.1, 25.9.

Acetylation of naphthoquinone 14. The reaction procedure was performed as previously described for compound **7** using acetyl chloride and 2,6-lutidine.

2-(4-(4-Bromobutoxy)phenyl)-1,4-dihydro-1,4-dioxonaphthalen-3-yl acetate 15a. Yield: 76%; yellow solid, mp 58-60 ºC; TLC (SiO_2) R_f 0.52 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18-8.14 (m, 2H), 7.84-7.77 (m, 2H), 7.33 (d, 2H, *J* = 8.5 Hz), 6.97 (d, 2H, *J* = 8.5 Hz), 4.09-4.04 (m, 2H), 3.52-3.49 (m, 2H), 2.27 (s, 3H), 2.11-2.04 (m, 2H), 2.00-1.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 179.6, 168.3, 159.9, 149.7, 137.0, 134.3, 134.0, 132.1, 132.0, 131.6, 130.9, 127.1, 126.5, 121.2, 114.1, 66.9, 33.2, 29.5, 27.9, 20.5; MS (EI, 80 eV): *m*/*z* (%) = 320 (M – 122, 100%), 304 (40), 281 (28), 266 (84), 249 (57), 238 (31), 222 (48), 207 (100), 181 (25), 165 (51), 135 (28).

2-(4-(10-Bromodecyloxy)phenyl)-1,4-dihydro-1,4-dioxonaphthalen-3-yl acetate 15b. Yield: 92%; yellow solid, mp 75-76 ºC; TLC (SiO_2) R_f 0.29 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17-8.15 (m, 2H), 7.78-7.77 (m, 2H), 7.33 (d, 2H, *J* = 8.0 Hz), 6.97 (d, 2H, *J* = 8.0 Hz), 4.00 (t, 2H, *J* = 6.5 Hz), 3.41 (t, 2H, *J* = 6.5 Hz), 2.27 (s, 3H), 1.89-1.79 (m, 4H), 1.47-1.26 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 178.6, 168.3, 160.2, 149.6, 137.0, 134.2, 133.9, 132.0, 131.6, 130.9, 127.1, 126.5, 120.9, 114.1, 68.0, 34.0, 32.8, 29.4, 29.3, 29.2, 28.7, 28.1, 26.0, 20.5; MS (EI, 80 eV): *m*/*z* (%) = 279 (M -248, 11%), 207 (10), 167 (30), 149 (100).

(4-(10-(3-Acetoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl) phenyl)bromodecyloxy)triphenylphosphonium bromide 16a. The reaction procedure was performed at 100 °C in 3:1 ^{i}PrOH:PhMe as previously described for compound **8**. Yield: 10%; orange red oil; TLC (SiO_2) R_f 0.18 (9:1 $CHCl_3$:MeOH);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17-8.13 (m, 2H), 7.86-7.78 (m, 10H), 7.72-7.70 (m, 7H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.96 (d, 2H, *J* = 8.0 Hz), 3.98 (t, 2H, *J* = 6.0 Hz), 3.79-3.75 (m, 2H), 2.27 (s, 3H), 1.77 (qnt, 2H, *J* = 6.5 Hz), 1.41 (qnt, 2H, *J* = 6.5 Hz), 1.29-1.24 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 178.6, 168.4, 160.3, 149.6, 137.1, 135.0, 134.3, 134.0, 133.8, 133.7, 132.1, 131.6, 130.9, 130.6, 130.5, 127.1, 126.5, 120.9, 118.8, 118.1, 114.2, 68.1, 29.4, 29.3, 29.2, 29.1, 26.0, 22.7, 20.5; HRMS (ESI): *m*/*z* = calcd for $C_{46}H_{46}O_5P^+$ $[M]^+$ 709.30774, found 709.30776.

(4-(10-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-phenyl)decyloxy)triphenylphosphonium bromide 17b. The reaction procedure was performed as previously described for compound **9.** Yield: 13%; orange red oil; TLC (SiO_2) R_f 0.12 (9:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, 1H, *J* = 7.5 Hz), 8.13 (d, 1H, *J* = 7.5 Hz), 7.87-7.73 (m, 16H), 7.48 (d, 2H, *J* = 8.0 Hz), 6.96 (d, 2H, *J* = 8.0 Hz), 3.99 (t, 2H, *J* = 5.5 Hz), 1.79-1.75 (m, 2H), 1.69-1.65 (m, 4H), 1.45-1.40 (m, 2H), 1.31-1.23 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 181.8, 159.5, 151.9, 150.0, 135.2, 134.3, 134.2, 133.1, 132.9, 132.3, 130.9, 130.8, 129.4, 127.3, 126.1, 122 .0, 121.9, 118.9, 118.2, 114.1, 68.0, 32.6, 31.0, 29.5, 29.4, 29.3, 29.2, 26.0, 22.9; HRMS (ESI): *m*/*z* = calcd for $C_{44}H_{44}O_4P^+$ $[M]^+$ 667.29717, found 667.29722.

Acylation of phthiocol; general procedure. To a stirring solution of phthiocol (**24**, 0.56 mmol) and n-bromoacyl chloride (0.62 mmol) in DCM (10 mL) was added 2,6-lutidine (0.62 mmol) at 0 °C. The reaction was warmed to rt and monitored by TLC until it was complete. The solution was then washed twice with 5% citric acid, dried over $MgSO_4$, filtered, and evaporated. Final purification of product **25** was achieved by silica gel chromatography using a gradient of 10-15% EtOAc in hexanes.

1,4-Dihydro-2-methyl-1,4-dioxonaphthalen-3-yl 4-bromobutanoate 25a. Yield: 69%; brown solid, mp 58-60 ºC; TLC (SiO_2) R_f 0.45 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07-8.02 (m, 2H), 7.71-7.10 (m, 2H), 3.61 (t, 2H, *J* = 6.5 Hz), 2.89 (t, 2H, *J* = 7.0 Hz), 2.33 (qnt, 2H, *J* = 6.5 Hz), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 177.7, 169.6, 150.9, 136.1, 134.1, 133.8, 131.9, 130.7, 126.7, 126.5, 32,4, 32.0, 27.6, 9.9; MS (EI, 80 eV): *m*/*z* (%) = 338 (M + 1, 1%), 310 (4), 188 (24), 160 (22), 149 (100), 131 (11).

1,4-Dihydro-2-methyl-1,4-dioxonaphthalen-3-yl 11-bromoundecanoate 25b. Yield: 75%; yellow solid, mp 67-68 ºC; TLC (SiO_2) R_f 0.55 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09-8.05 (m, 2H), 7.73-7.69 (m, 2H), 3.04 (t, 2H, *J* = 6.5 Hz), 2.67 (t, 2H, *J* = 8.0 Hz), 2.08 (s, 3H), 1.85 (qnt, 2H, *J* = 7.0 Hz), 1.78 (qnt, 2H, *J* = 7.0 Hz), 1.48-1.28 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 177.9, 170.6, 151.1, 135.9, 133.9, 133.7, 131.9, 130.8, 126.6, 126.5, 34.0, 33.7, 32.8, 29.3, 29.2, 29.1, 28.9, 28.7, 28.1, 24.8, 9.8; MS (EI, 80 eV): *m*/*z* (%) = 436 (M + 1, 1%), 247 (100), 190 (20), 149 (26), 131 (12).

Synthesis of triphenylphosphonium bromide salt 26. The reaction procedure was performed at 100 °C in 3:1 ^{i}PrOH:PhMe as previously described for compound **8**.

4-(1,4-Dihydro-2-methyl-1,4-dioxonaphthalen-3-yl) butanoate triphenylphosphonium bromide 26a. Yield: 11%; red oil; TLC (SiO_2) R_f 0.65 (9:1 DCM: MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, 2H, *J* = 7.0 Hz), 8.02 (d, 1H, *J* = 7.0 Hz), 8.01-7.89 (m, 6H), 7.86-7.80 (m, 3H), 7.80-7.70 (m, 8H), 4.15-4.09 (m, 2H), 3.33 (s, 2H), 2.14-2.11 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7, 178.1, 170.5, 151.0, 136.7, 135.24, 135.22, 134.3, 133.9, 133.8, 132.1, 130.8, 130.7, 130.6, 126.9, 126.6, 118.5, 117.8, 33.4, 21.9, 18.5, 10.3; HRMS (ESI): *m*/*z* = calcd for $C_{33}H_{28}O_4P^+$ $[M]^+$ 519.17197, found 519.17192.

11-(1,4-Dihydro-2-methyl-1,4-dioxonaphthalen-3-yl)undecanoate triphenylphosphonium bromide 26b. Yield: 9%; red oil; TLC (SiO_2) R_f 0.60 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.10 (m, 1H), 8.08-8.07 (m, 1H), 7.86-7.79 (m, 9H), 7.75-7.70 (m, 8H), 3.75 (s, 2H), 2.65 (t, 2H, *J* = 7.5 Hz), 2.09 (s, 3H), 1.76 (qnt, 2H, *J* = 7.5 Hz), 1.64 (s, 4H), 1.41 (qnt, 2H, *J* = 7.0 Hz), 1.26-1.21 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 178.2, 170.8, 151.3, 136.1, 135.2, 135.1, 134.1, 133.9,

133.8, 133.7, 132.1, 130.9, 130.7, 130.6, 126.8, 126.7, 118.8, 118.1, 33.9, 30.6, 30.4, 29.8, 29.3, 29.27, 29.21, 29.0, 24.9, 22.8, 10.0; HRMS (ESI): *m/z* = calcd for $C_{40}H_{42}O_4P^+$ $[M]^+$ 617.28152, found 617.28165.

O-Alkylation of 2-hydroxy 1,4-naphthoquinones; general procedure. Quinone (1.5 mmol), dibromoalkane (3.3 mmol), K_2CO_3 powder (235 mg, 1.7 mmol), and TBAI (74 mg, 0.2 mmol) were combined in 10 mL of dry THF. The solution was stirred at 70 °C for 15 mins then 18-crown-6 (43 μL, 0.2 mmol) was added. After 16-22 h, the mixture was concentrated, redissolved in EtOAc (15 mL) and washed 5% Na_2CO_3 (2 x 10 mL). The aqueous layer was extracted once more with EtOAc then the combined organic layers was dried over $MgSO_4$, filtered, and evaporated. Final purification of product **27** was achieved by silica gel chromatography using a gradient of 0-15% EtOAc in hexanes.

2-(10-Bromodecyloxy)-3-methylnaphthalene-1,4-dione 27a. Yield: 48%; yellow oil; TLC (SiO_2) R_f 0.62 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.04 (m, 1H), 8.00-7.98 (m, 1H), 7.71-7.65 (m, 2H), 5.10 (s, 2H), 4.35 (t, 2H, *J* = 6.5 Hz), 3.48 (t, 2H, *J* = 6.5 Hz), 2.22 (qnt, 2H, *J* = 6.5 Hz), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.8, 181.3, 157.6, 133.7, 133.2, 132.0, 131.9, 131.5, 126.1, 73.7, 34.0, 32.8, 30.5, 29.4, 29.3, 28.7, 28.2, 25.8, 9.4; MS (EI, 80 eV): *m/z* (%) = 406 (M – 16, 4%), 207 (23), 201 (30), 188 (100), 172 (34), 160 (29).

2-(6-Bromohexyloxy)-3-methylnaphthalene-1,4-dione 27b. Yield: 57%; yellow solid, mp 35-36 °C; TLC (SiO_2) R_f 0.43 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03-7.99 (m, 2H), 7.69-7.64 (m, 2H), 4.33 (t, 2H, *J* = 6.5 Hz), 3.42 (t, 2H, *J* = 6.0 Hz), 2.08 (s, 3H), 1.88 (qnt, 2H, *J* = 7.0 Hz), 1.79 (qnt, 2H, *J* = 7.0 Hz), 1.52-1.47 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 181.3, 157.4, 133.7, 133.2, 132.0, 131.9, 131.5, 126.1, 73.4, 33.8, 32.7, 30.4, 27.9, 25.1, 9.5; MS (EI, 80 eV): *m/z* (%) = 352 (M – 14, 4%), 201 (44), 188 (100), 172 (43), 160 (45), 132 (28).

2-(3-Bromopropoxy)-3-methylnaphthalene-1,4-dione 27c. Yield: 67%; yellow oil; TLC (SiO_2) R_f 0.71 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.02 (m, 2H), 7.71-7.68 (m, 2H), 4.47 (dt, 2H, *J* = 7.0, 1.5 Hz), 3.65 (dt, 2H, *J* = 7.0, 1.5 Hz), 2.34 (qnt, 2H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 181.3, 157.1, 133.9, 133.4, 132.3, 132.1, 131.5, 126.3, 126.3, 70.9, 33.5, 29.8, 9.5; MS (EI, 70 eV): *m/z* (%) = 310 (M +1, 4%), 229 (18), 201 (91), 188 (27), 172 (100), 160 (41), 132 (40).

2-(3-Bromopropoxy)naphthalene-1,4-dione 27d. Yield: 12%; yellow solid, mp 102-104 °C; TLC (SiO_2) R_f 0.22 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 7.0 Hz), 8.08 (d, 1H, *J* = 7.0 Hz), 7.77-7.72 (m, 2H), 4.17 (t, 2H, *J* = 5.0 Hz), 3.63 (t, *J* = 5.5 Hz), 2.49-2.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.0, 180.6, 159.6, 134.5, 133.5, 132.1, 131.3, 126.8, 126.4, 110.7, 110.6, 66.9, 31.4, 29.5; MS (EI, 80 eV): *m/z* (%) = 294 (M + 1, 5%), 215 (30), 197 (21), 187 (61), 158 (100), 146 (31), 130 (30)

2-(6-Bromohexyloxy)naphthalene-1,4-dione 27e. Yield: 20%; yellow oil; TLC (SiO_2) R_f 0.60 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 7.0 Hz), 8.07 (d, 1H, *J* = 7.0 Hz), 7.74-7.71 (m, 2H), 4.01 (t, 2H, *J* = 6.5 Hz), 3.44-3.42 (m, 2H), 1.92-1.91 (m, 4H), 1.53 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 180.3, 159.9, 134.4, 133.5, 132.2, 131.3, 126.8, 126.3, 110.4, 69.6, 33.8, 32.7, 28.3, 27.9, 25.3; MS (EI, 80 eV): *m/z* (%) = 336 (M + 1, 9%), 281 (26), 207 (78), 187 (52), 175 (100), 158 (74), 146 (79), 130 (30), 123 (25).

Synthesis of triphenylphosphonium bromide salt 28. The reaction procedure was performed at 100 °C in 3:1 ^{i}PrOH:PhMe as previously described for compound **8**.

10-(2-Oxy-3-methylnaphthalene-1,4-dione)decyl triphenylphosphonium bromide 28a. Yield: 30%; orange oil; TLC (SiO_2) R_f 0.30 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.04 (m, 2H), 7.86-7.71 (m, 17H), 4.33-4.31 (m, 2H), 3.74 (m, 2H), 2.09 (s, 3H), 1.82-1.22 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 185.5, 181.6, 157.7, 150.6, 135.2, 133.9, 133.8, 133.4, 132.1, 131.7, 130.7, 130.6, 126.3, 118.9, 118.3, 81.5, 73.9, 48.7, 34.3, 30.6, 29.6, 29.4, 29.3, 28.8, 28.2, 25.9, 22.8, 9.6; HRMS (ESI): *m/z* = calcd for $C_{39}H_{42}O_3P^+$ $[M]^+$ 589.28661, found 589.28652.

6-(2-Oxy-3-methylnaphthalene-1,4-dione)hexyl triphenylphosphonium bromide 28b. Yield: 36%; red oil; TLC (SiO_2) R_f 0.57 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-8.04 (m, 1H), 8.00-7.99 (m, 1H), 7.87-7.81 (m, 8H), 7.72-7.67 (m, 9H), 4.25 (m, 2H), 3.79 (m, 2H), 2.05 (s, 3H), 1.74-1.68 (m, 6H), 1.49 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.9, 131.4, 157.6, 135.2, 133.8, 133.4, 132.2, 132.1, 131.5, 130.7, 130.6, 126.2, 113.8, 118.1, 73.5, 30.2, 30.1, 25.5, 22.7, 9.6; HRMS (ESI): *m/z* = calcd for $C_{35}H_{34}O_3P^+$ $[M]^+$ 533.22401, found 533.22411.

3-(2-Oxy-3-methylnaphthalene-1,4-dione)propyl triphenylphosphonium bromide 28c. Yield: 24%; yellow oil; TLC (SiO_2) R_f 0.33 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02-8.01 (m, 1H), 7.96 (dd, 1H, *J* = 5.0, 2.0 Hz), 7.89 (dd, 6H, *J* = 12.0, 8.0 Hz), 7.82-7.81 (m, 2H), 7.74-7.67 (m, 9H), 4.56 (m, 2H), 4.10 (t, 2H, *J* = 14.0 Hz), 2.25 (m, 2H), 2.06 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6, 181.0, 156.9, 135.2, 133.7, 133.6, 133.4, 132.7, 131.9, 131.2, 130.6, 130.5, 126.2, 118.4, 117.7, 72.3, 23.9, 23.2, 9.8; HRMS (ESI): *m/z* = calcd for $C_{31}H_{26}O_3P^+$ $[M]^+$ 491.17706, found 491.17695.

3-(2-Oxynaphthalene-1,4-dione)propyl triphenylphosphonium bromide 28d. Yield: 13%; yellow solid; TLC (SiO_2) R_f 0.61 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08-8.06 (m, 2H), 7.95-7.91 (m, 5H), 7.81-7.79 (m, 3H), 7.75-7.73 (m, 9H), 6.24 (s, 1H), 4.44 (m, 2H), 4.23 (m, 2H), 2.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 180.3, 159.1, 150.1, 135.3, 134.6, 134.2, 134.1, 133.4, 132.3, 131.2, 130.9, 130.8, 126.5, 118.7, 117.9, 68.8, 30.1, 22.9; HRMS (ESI): *m*/*z* = calcd for $C_{31}H_{26}O_3P^+$ $[M]^+$ 477.16141, found 477.16137.

6-(2-Oxynaphthalene-1,4-dione)hexyl triphenylphosphonium bromide 28e. Yield: 15%; orange oil; TLC (SiO_2) R_f 0.26 (19:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.87-7.80 (m, 10H), 7.72-7.71 (m, 7H), 6.14 (s, 1H), 3.39 (m, 2H), 3.79 (m, 2H), 1.86 (m, 2H), 1.78 (m, 2H), 1.69 (m, 2H), 1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 180.4, 159.9, 150.1, 135.2, 134.4, 133.9, 133.8, 133.4, 132.2, 131.2, 130.7, 130.6, 126.7, 126.3, 118.8, 118.1, 110.5, 110.4, 69.6, 31.1, 30.0, 29.8, 27.9, 25.6, 22.6; HRMS (ESI): *m*/*z* = calcd for $C_{34}H_{32}O_3P^+$ $[M]^+$ 519.20836, found 519.20827.

***tert*-Butyl 2-((3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)oxy)acetate 29.** The reaction procedure was performed as previously described for compound **27**. Yield: 62%; yellow solid, mp 62-64 °C; TLC (SiO_2) R_f 0.34 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J* = 7.0 Hz), 8.00 (d, 1H, *J* = 7.0 Hz), 7.68 (qnt, 2H, *J* = 7.0 Hz), 5.02 (s, 2H), 2.16 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.5, 181.7, 168.4, 155.7, 134.0, 133.3, 132.1, 131.5, 130.7, 126.3, 126.2, 82.6, 69.2, 28.2, 9.6; MS (EI, 70 eV): *m*/*z* (%) = 302 (M, 1%), 246 (18), 201 (100), 187 (22), 172 (19).

3-Bromopropyl 2-(1,4-dihydro-2-methyl-1,4-dioxonaphthalen-3-yloxy)acetate 30. The reaction procedure was performed as previously described for compound **27** using the carboxylic acid of quinone **29** obtained after stirring for 1 h in a 50% solution of TFA in DCM. Yield: 26%; yellow solid, mp 54-55 ºC; TLC (SiO_2) R_f 0.21 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.02 (m, 2H), 7.71-7.67 (m, 2H), 4.34 (t, 2H, *J* = 6.5 Hz), 3.40 (t, 2H, *J* = 6.5 Hz), 2.10 (s, 3H), 1.87-1.76 (m, 4H), 1.45-1.29 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 181.3, 155.1, 133.9, 133.2, 131.8, 131.1, 126.2, 68.5, 62.3, 31.6, 29.2, 9.5; MS (EI, 80 eV): *m*/*z* (%): 245 (M – 122, 12%), 230 (40), 207 (57), 201 (100), 188 (22), 172 (22), 160 (17), 144 (14), 131 (20).

3-(Propyl 2-(1,4-dihydro-2-methyl-1,4-dioxonaphthalen-3-yloxy)acetate)triphenylphosphonium bromide 31. The reaction procedure was performed as previously described for compound **8**. Yield: 7%; red oil; TLC (SiO_2) R_f 0.40 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, 1H, *J* = 7.0 Hz), 7.89-7.85 (m, 6H), 7.81-7.78 (m, 4H), 7.72-7.69 (m, 7H), 7.61 (t, 1H, *J* = 7.5 Hz), 5.05 (s, 2H), 4.55 (t, 2H, *J* = 6.0 Hz), 4.06-4.03 (m, 2H), 2.17-1.11 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 181.4, 168.9, 155.2, 135.2, 134.0, 133.8, 133.7, 133.2, 131.9, 131.3, 131.1, 130.6, 130.5, 126.3, 126.0, 118.4, 117.7, 68.8, 64.2, 29.7, 22.3, 9.6; HRMS (ESI): *m*/*z* = calcd for $C_{34}H_{30}O_5P^+$ $[M]^+$ 549.18254, found 549.18264.

2-Chloro-3-cyclohexylnaphthalene-1,4-dione 33c. The reaction procedure was performed as previously described for compound **4**. Yield: 13%; yellow solid, mp 139-140 ºC; TLC (SiO_2) R_f 0.37 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1H, *J* = 7.0 Hz), 8.05 (d, 1H, *J* = 7.0 Hz), 7.75-7.69 (m, 2H), 3.29-3.22 (m, 1H), 2.15-2.08 (m, 2H), 1.85 (m, 2H), 1.75 (m, 1H), 1.65 (m, 2H), 1.41-1.33 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 178.0, 150.9, 142.8, 134.1, 133.6, 132.3, 130.9, 127.0, 126.9, 41.7, 29.0, 26.7, 25.8; MS (EI, 80 eV): *m*/*z* (%) = 274 (M, 1%), 239 (63), 206 (100), 209 (35), 171 (35).

Methanolysis of 2-chloro naphthoquinone 34; general procedure. Quinone **33** (6.6 mmoL) was added to a stirring solution of KOH (3.7 g, 66 mmol) in MeOH:H_2O (3:1) and heated to 80 °C. After 2 h, the dark red solution was cooled to rt and acidified with 1 M HCl. The precipitated product **35** was then collected by vacuum filtration and allowed to dry overnight at rt.

2-(4-Chlorobenzyl)-3-hydroxynaphthalene-1,4-dione 34a. Yield: 65%; yellow solid, mp 159-160 ºC; TLC (SiO_2) R_f 0.42 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1H, *J* = 7.5 Hz), 8.05 (d, 1H, *J* = 8.0 Hz), 7.74 (t, 1H, *J* = 8.0 Hz), 7.67 (t, 1H, *J* = 7.5 Hz), 7.31 (d, 2H, *J* = 7.5 Hz), 7.20 (d, 2H, *J* = 7.0 Hz), 3.89 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3, 181.6, 153.1, 137.4, 135.1, 133.1, 132.7, 132.1, 132.1, 130.6, 129.4, 128.6, 126.2, 122.6, 28.5; MS (EI, 80 eV): *m*/*z* (%) = 298 (M, 100%), 281 (26), 263 (83), 235 (69), 217 (32), 207 (59), 189 (26), 178 (31), 131 (27), 125 (24).

2-Benzyl-3-hydroxynaphthalene-1,4-dione 34b. Yield: 47%; brown solid, mp 118-120 ºC; TLC (SiO_2) R_f 0.38 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 1H, *J* = 8.0 Hz), 8.05 (d, 1H, *J* = 8.0 Hz), 7.73 (t, 1H, *J* = 7.0 Hz), 7.66 (t, 1H, *J* = 7.0 Hz), 7.39 (d, 2H, *J* = 8.0 Hz), 7.26 (t, 2H, *J* = 6.5 Hz), 7.14 (t, 1H, *J* = 7.5 Hz), 3.95 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 181.9, 153.2, 139.1, 135.2, 133.2, 132.9, 129.6, 129.4, 128.6, 127.1, 126.5, 126.3, 123.3, 29.3; MS (EI, 80 eV): *m*/*z* (%) = 264 (M, 100%), 247 (21), 218 (16), 207 (14), 189 (16), 178 (14), 165 (11), 130 (13).

2-Cyclohexyl-3-hydroxynaphthalene-1,4-dione 34c. Yield: 35%; yellow solid; TLC (SiO_2) R_f 0.40 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 8.0 Hz), 8.05 (d, 1H, *J* = 8.0 Hz), 7.75 (t, 1H, *J* = 7.0 Hz), 7.66 (t, 2H, *J* = 7.0 Hz), 3.08 (t, 1H, *J* = 12.5 Hz), 1.98 (q, 2H, *J* = 12.5 Hz), 1.82 (d, 2H, *J* = 12.5 Hz), 1.72 (d, 1H, *J* = 10.0 Hz), 1.61 (d, 2H, *J* = 12.0 Hz), 1.41-1.26 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 181.9, 152.9, 134.9, 133.2, 132.7, 129.2, 127.9, 126.9, 125.9, 35.2, 29.2, 26.8, 25.9.

O-Alkylation of naphthoquinone 34. The reaction procedure was performed as previously described for compound **27** using TBAI and 18-crown-6 as co-catalysts.

2-(4-Chlorobenzyl)-3-(6-bromohexyloxy)naphthalene-1,4-dione 35a. Yield: 29%; yellow oil; TLC (SiO_2) R_f 0.25 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, 1H, *J* = 6.5 Hz), 8.01 (d, 1H, *J* = 6.5 Hz), 7.70-7.65 (m, 2H), 7.25-7.20 (m, 4H), 4.41 (t, 2H, *J* = 6.0 Hz), 3.90 (s, 2H), 3.41 (t, 2H, *J* = 6.0 Hz), 1.88-1.84 (m, 2H), 1.78-1.75 (m, 2H), 1.49-1.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 181.9, 157.5, 137.8, 134.1, 133.5, 132.9, 132.1, 131.9, 131.6, 130.5, 128.6, 126.4, 126.3, 73.8, 33.9, 32.7, 30.5, 28.9, 27.9, 25.2; MS (EI, 80 eV): *m*/*z* (%) = 298 (M – 162, 100%), 281 (42), 263 (68), 235 (73), 207 (100), 189 (23), 178 (29).

2-Benzyl-3-((6-bromohexyl)oxy)naphthalene-1,4-dione 35b. Yield: 57%; yellow oil; TLC (SiO_2) R_f 0.47 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, 1H, *J* = 6.5 Hz), 8.02 (d, 1H, *J* = 6.5 Hz), 7.68-7.67 (m, 2H), 7.32-7.31 (m, 2H), 7.26-7.24 (m, 2H), 7.18-7.16 (m, 1H), 4.38 (t, 2H, *J* = 6.5 Hz), 3.95 (s, 2H), 3.41 (t, 2H, *J* = 6.5 Hz), 1.87 (t, 2H, *J* = 6.5 Hz), 1.77 (t, 2H, *J* = 6.5 Hz), 1.48 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 182.0, 157.6, 139.4, 134.0, 133.8, 133.4, 132.1, 131.7, 129.2, 128.6, 126.5, 126.3, 73.8, 33.9, 32.8, 30.5, 29.6, 28.0, 25.2; MS (EI, 70 eV): *m*/*z* (%) = 428 (M + 2, 4%), 426 (M, 4), 263 (40), 247 (10).

2-((6-Bromohexyl)oxy)-3-cyclohexylnaphthalene-1,4-dione 35c. Yield: 72%; yellow oil; TLC (SiO_2) R_f 0.34 (19:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, 1H, *J* = 7.0 Hz), 8.00 (d, 1H, *J* = 6.5 Hz), 7.69-7.66 (m, 2H), 4.28-4.27 (m, 2H), 3.45-3.43 (m, 2H), 3.12 (t, 1H, *J* = 12.5 Hz), 2.00-1.55 (m, 14H), 1.37-1.26 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 182.2, 158.0, 139.7, 133.9, 133.2, 132.6, 131.6, 126.5, 126.0, 73.8, 36.2, 34.0, 32.9, 30.3, 30.2, 28.1, 27.1, 26.3, 25.3; MS (*m*/z): 420 (M + 2, 13%), 418 (M, 13), 256 (100).

2-Benzyl-3-((3-bromopropyl)oxy)naphthalene-1,4-dione 35d. Yield: 36%; yellow oil; TLC (SiO_2) R_f 0.29 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, 1H, *J* = 5.5 Hz), 8.04 (d, 1H, *J* = 5.5 Hz), 7.69 (m, 2H), 7.30-7.17 (m, 5H), 4.51 (t, 2H, *J* = 5.5 Hz), 3.96 (s, 2H), 3.55 (t, 2H, *J* = 6.5 Hz), 2.29 (qnt, 2H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 185.1, 156.9, 149.9, 138.9, 133.9, 133.8, 133.3, 131.8, 128.9, 128.5, 126.4, 126.2, 71.1, 33.4, 29.4; MS (EI, 80 eV): *m*/*z* (%) = 386 (M + 1, 19%), 263 (100), 247 (73), 235 (40), 189 (33), 178 (30).

2-(3-Bromopropoxy)-3-cyclohexylnaphthalene-1,4-dione 35e. Yield: 82%; bright yellow oil; TLC (SiO_2) R_f 0.50 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.06 (d, 1H, *J* = 7.0 Hz), 8.02 (d, 1H, *J* = 7.5 Hz), 7.72-7.66 (m, 2H), 4.39 (t, 2H, *J* = 5.0 Hz), 3.68 (t, 2H, *J* = 5.5 Hz), 3.11 (t, 1H, *J* = 12.0 Hz), 2.39 (m, 2H), 1.98-1.91 (m, 2H), 1.84-1.82 (m, 2H), 1.62-1.60 (m, 2H), 1.41-1.25 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 181.9, 157.5, 140.3, 133.9, 133.3, 132.5, 131.5, 126.6, 126.1, 71.2, 36.3, 33.5, 30.3, 29.9, 27.1, 26.2; MS (EI, 80 eV): *m*/*z* (%) = 376 (M, 46%), 378 (48), 255 (100), 237 (20), 213 (17), 187 (49), 159 (18).

Synthesis of triphenylphosphonium bromide salt 36a-e. The reaction procedure was performed at 100 °C in 3:1 ^{i}PrOH:PhMe as previously described for compound **8**.

3-(2-Oxy-3-(4-chlorobenzyl)naphthalene-1,4-dione)hexyl triphenylphosphonium bromide 36a. Yield: 10%; green oil; TLC (SiO_2) R_f 0.32 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.02 (m, 1H), 7.97-7.96 (m, 1H), 7.80-7.70 (m, 17H), 7.18 (d, 2H, *J* = 5.5 Hz), 7.06 (d, 2H, *J* = 5.5 Hz), 4.01-3.62 (m, 7H), 2.20-1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 181.5, 157.0, 137.5, 135.2, 135.1, 134.1, 133.8, 133.7, 133.68, 133.65, 133.2, 131.9, 131.7, 131.4, 130.7, 130.6, 130.5, 130.2, 128.5, 126.4, 126.3, 118.6, 118.3, 117.9, 117.7, 71.9, 53.7, 53.6, 28.9, 23.9, 23.2, 22.8, 22.2; HRMS (ESI): *m*/*z* = calcd for $C_{41}H_{37}ClO_3P^+$ $[M]^+$ 643.21634, found 643.21639.

6-(2-Oxy-3-benzylnaphthalene-1,4-dione)hexyl triphenylphosphonium bromide 36b. Yield: 62%; orange oil; TLC (SiO_2) R_f 0.31 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03-8.02 (m, 1H), 7.98-7.97 (m, 1H), 7.85-7.79 (m, 9H), 7.70 (m, 8H), 7.26 (m, 2H), 7.18 (m, 2H), 7.08 (m, 1H), 4.30 (m, 2H), 3.89 (s, 2H), 3.77 (m, 2H), 1.72-1.65 (m, 6H), 1.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 181.8, 157.4, 139.2, 135.1, 133.9, 133.7, 133.4, 131.8, 131.5, 130.6, 130.5, 129.0 ,128.4, 126.3, 126.2, 118.6, 117.9, 77.4, 73.6, 30.1, 30.0, 29.7, 29.4, 25.5, 22.7; HRMS (ESI): *m*/*z* = calcd for $C_{41}H_{38}O_3P^+$ $[M]^+$ 609.25531, found 609.25535.

6-(2-Oxy-3-cyclohexylnaphthalene-1,4-dione)hexyl triphenylphosphonium bromide 36c. Yield: 16%; red oil; TLC (SiO_2) R_f 0.42 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, 1H, *J* = 7.0 Hz), 7.97 (d, 1H, *J* = 7.0 Hz), 7.88-7.78 (m, 9H), 7.72-7.64 (m, 8H), 4.18 (t, 2H, *J* = 6.0 Hz), 3.89-3.83 (m, 2H), 3.05 (t, 1H, *J* = 12.5 Hz), 1.94-1.86 (m, 4H), 1.79-1.74 (m, 6H), 1.71-1.68 (m, 2H), 1.55-1.52 (m, 4H), 1.33-1.26 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 185.5, 185.4, 182.1, 166.0, 157.9, 150.1, 139.8, 135.2, 133.9, 133.8, 133.2, 132.5, 131.6, 130.7, 130.6, 126.5, 125.9, 118.9, 118.2, 110.1, 73.8, 36.2, 30.2, 30.0, 27.0, 26.2, 25.7, 22.9; HRMS (ESI): *m*/*z* = calcd for $C_{40}H_{42}O_3P^+$ $[M]^+$ 601.28661, found 601.28662.

3-(2-Oxy-3-benzylnaphthalene-1,4-dione)propyl triphenylphosphonium bromide 36d. Yield: 78%; yellow oil; TLC (SiO_2) R_f 0.32 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, 1H, *J* = 7.0 Hz), 7.96 (d, 1H, *J* = 7.0 Hz), 7.87-7.81 (m, 3H), 7.79-7.75 (m, 7H), 7.71-7.66 (m, 7H), 7.21 (d, 2H, *J* = 7.0 Hz), 7.09 (t, 2H, *J* = 7.0 Hz), 6.99 (t, 1H, *J* = 7.0 Hz), 4.69 (m, 2H), 4.08-4.05 (m, 2H), 3.93 (s, 2H), 1.19-1.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 181.7, 157.1, 146.7, 139.0, 135.2, 134.2, 133.9, 133.8, 133.7, 133.5, 131.9, 131.6, 130.7, 130.6, 128.8, 128.6, 126.6, 126.4, 118.6, 117.9, 72.5, 48.7, 29.6, 24.1, 23.4, 23.1; HRMS (ESI): *m*/*z* = calcd for $C_{38}H_{32}O_3P^+$ $[M]^+$ 567.20836, found 567.20831.

3-(2-Oxy-3-cyclohexylnaphthalene-1,4-dione)propyl triphenylphosphonium bromide 36e. Yield: 68%; yellow oil; LC (SiO_2) R_f 0.33 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, 1H, *J* = 7.0 Hz), 7.75 (d, 1H, *J* = 7.0 Hz), 7.92-7.87 (m, 5H), 7.82-7.80 (m, 4H), 7.74- 7.68 (m, 8H), 4.44 (m, 2H), 4.16-4.10 (m, 2H), 3.00 (t, 1H, *J* = 11.0 Hz), 2.33-2.32 (m, 2H), 1.85 (q, 2H, *J* = 12.5 Hz), 1.75 (d, 2H, *J* = 12.5 Hz), 1.67 (d, 1H, *J* = 12.0 Hz), 1.56 (m, 1H), 1.34-1.19 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6, 181.2, 157.3, 140.6, 135.3, 134.1, 134.0, 133.9, 133.8, 133.4, 132.5, 131.3, 130.8, 130.7, 126.5, 126.1, 118.7, 117.9, 72.9, 72.8, 36.5, 30.4, 26.9, 26.0, 24.0, 23.3, 22.9; HRMS (ESI): *m*/*z* = calcd for $C_{37}H_{36}O_3P^+$ $[M]^+$ 559.23966, found 559.23978.

2-Hydroxy-3-(4-methoxyphenyl)naphthalene-1,4-dione 38. The reaction procedure was performed as previously described for compound **14**. Yield: 57%; red solid, mp 153-154ºC; TLC (SiO_2) R_f 0.22 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, 1H, *J* = 7.5 Hz), 8.12 (d, 1H, *J* = 7.0 Hz), 7.78 (t, 1H, *J* = 7.5 Hz), 7.72 (t, 1H, *J* = 7.5 Hz), 7.64 (s, 1H), 7.52 (d, 2H, *J* = 8.0 Hz), 6.99 (d, 2H, *J* = 8.0 Hz), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 181.8, 165.6, 159.9, 151.9, 135.2, 133.1, 132.9, 132.3, 129.4, 127.3, 126.1, 122.2, 121.9, 113.5, 55.4; MS (EI, 80 eV): *m*/*z* (%) = 280 (M, 100%), 265 (29), 252 (18), 237 (20), 221 (13), 209 (28), 165 (15), 152 (30).

2-(3-Bromopropoxy)-3-(4-methoxyphenyl)naphthalene-1,4-dione 39. The reaction procedure was performed as previously described for compound **27**. Yield: 48%; red oil; TLC (SiO_2) R_f 0.48 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.09 (m, 2H), 7.76-7.72 (m, 2H), 7.34 (d, 2H, *J* = 7.5 Hz), 6.98 (d, 2H, *J* = 7.5 Hz), 4.24 (t, 2H, *J* = 5.0 Hz), 3.86 (s, 3H), 3.03 (t, 2H, *J* = 6.5 Hz), 2.08 (qnt, 2H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 181.9, 159.9, 156.1, 134.1, 133.5, 132.9, 132.0, 131.4, 126.7, 126.1, 122.5, 113.4, 71.3, 55.3, 33.1, 29.9.

3-(2-Oxy-3-(4-methoxyphenyl)naphthalene-1,4-dione)propyl triphenylphosphonium bromide 40. The reaction procedure was performed as previously described for compound **8**. Yield: 13%; red oil; TLC (SiO_2) R_f 0.31 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09-8.05 (m, 2H), 7.79-7.68 (m, 17H), 7.32 (d, 2H, *J* = 6.5 Hz), 6.81 (d, 2H, *J* = 6.5 Hz), 4.48 (s, 2H), 3.74 (s, 2H), 3.67 (s, 3H), 1.98 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 182.0, 159.8, 156.2, 135.2, 134.4, 134.2, 133.9, 133.8, 133.7, 133.6, 132.6, 132.3, 132.0, 131.5, 130.6, 130.5, 126.8, 126.3, 122.9, 118.5, 118.4, 117.9, 113.7, 72.9, 72.8, 55.4, 23.9; HRMS (ESI): *m*/*z* = calcd for $C_{38}H_{32}O_4P^+$ $[M]^+$ 583.20327, found 583.20299.