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A New Method for the Synthesis of 2-Hydroxy-3-nitro-1,4-naphthoquinones: Application to Regiospecific Preparation of Unsymmetrical Nitrobiquinones

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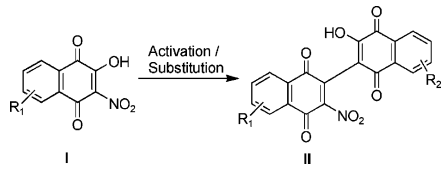
Received April 19, 2006



Novel 2-hydroxy-3-nitro-1,4-naphthoquinones were synthesized by an improved method utilizing nitronium tetrafluoroborate in high yields. A subsequent conversion to 2-chloro-3-nitro-1,4-naphthoquinones and a substitution of the chlorine by hydroxyquinone anions yielded 3-nitro-2,2′-binaphthoquinones with a complete regiocontrol.

Biquinones and higher quinone oligomers, which contain two or more quinone units linked together at the quinone double bond, are a unique group of natural products. Their diverse biological activities, including anti-HIV activity,[1,2] and synthetically challenging structures have stimulated interest in the design of efficient and regiocontrolled methods for the construction of bi- and triquinones. An original biomimetic route to biquinones is based on oxidative dimerization of phenols to form the key quinone−quinone bond.[3−5] Palladium-catalyzed coupling approaches involving 2-quinonylstannanes[6−8] and 2-quinonylboronic esters[9] have also been developed allowing for a regiocontrolled preparation of biquinones. Elegant strategies for the assembly of triquinones relying on transition metal-mediated annulations of cobalt complexes[10] or chromium Fisher carbenes[11] have been reported. The substitution of a halogen atom on a quinone core represents an attractive method for the formation of the quinone−quinone linkage since, in contrast to the biomimetic coupling,[3] no further oxidation of the resulting adducts is required, and the preparation of haloquinones is usually less challenging than the synthesis of stannyl- or boronylquinones, or the transition metal complexes. Investigations by Smith[12] and others[13] revealed that 2,3-dihaloquinones could undergo stepwise substitutions by two different active methylene anions. Although a wide variety of active methylene nucleophiles have been used, reactions with hydroxyquinone anions and their synthetic equivalents remain rare,[13] and the problematic regiocontrol in the substitution on unsymmetrical biselectrophilic quinone cores has not been satisfactorily addressed. As a part of our program aimed at the preparation of biologically active natural and unnatural biquinones and triquinones related to the anti-HIV active natural product conocurvone **1**,[1] we have been pursuing the design of biselectrophilic quinone synthons, which would allow us to control the regiochemistry of coupling reactions of quinone nucleophiles with unsymmetrically substituted quinone cores (Figure 1). We have demonstrated an efficient assembly of trimeric quinones via addition−elimination reactions of a hydroxyquinone anion to a symmetrical 2,3-dihaloquinone affording a good yield of a chlorohydroxybiquinone, which could be methylated and subjected to a second addition−elimination reaction to yield trimeric quinones.[14] Although this method permitted the stepwise attachment of two different hydroxyquinone units to a symmetrical quinone core, regiocontrolled coupling to an unsymmetrical (e.g., unsymmetrically substituted in the fused aryl ring) naphthoquinone core with a complete regiocontrol was not permitted. A regioselective substitution of the 2-trifluoromethanesulfonyl-3-iodo-6-methoxy-1,4-naphthoquinone providing 3′-hydroxy-3-iodo-6-methoxy-2,2′-binaphthoquinone exclusively proved to be an exception, arising due to the electronic effect exerted by the 6-methoxy substitutent.[15] Attempted stepwise substitution reactions in other doubly activated unsymmetrical quinone cores bearing two different halogens, or a halogen and the trifluoromethanesulfonyl activating groups (e.g., 2-chloro-3-bromo-6-methoxy-1,4-naphthoquinone, 2-trifluoromethanesulfonyl-3-chloro(or 3-iodo)-7-methoxy-1,4-naphthoquinone), with 2-hydoxynaphthoquinone anions revealed that mixtures of hydroxybiquinones with compositions ranging from 65:35 to 90:10 were obtained.[15]

Herein, we describe a solution to the problem of regiocontrol in the substitution of unsymmetrical doubly activated quinone

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(1) Decosterd, L. A.; Parsons, I. C.; Gustafson, K. R.; Cardellina, J. H., II; McMahon, J. B.; Gragg, G. M.; Murata, Y.; Pannell, L. K.; Steiner, J. R.; Boyd, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 6673−6679.
(2) Thomson, R. H. *Naturally Occurring Quinones IV. Recent Advances*; Chapman & Hall: London, Great Britain, 1997.
(3) Laatsch, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 423−424.
(4) Okamoto, I.; Dio, H.; Kotani, E.; Takeya, T. *Tetrahedron Lett.* **2001**, *42*, 2987−2989.
(5) Ogata, T.; Okamoto, I.; Dio, H.; Kotani, E.; Takeya, T. *Tetrahedron Lett.* **2003**, *44*, 2041−2044.
(6) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048−9055.
(7) Liebeskind, L. S.; Riesinger, S. W. *Tetrahedron Lett.* **1991**, *32*, 5681−5682.
(8) Bringmann, G.; Gotz, R.; Keller, P. A.; Walter, R.; Boyd, M. R.; Lang, F.; Garcia, A.; Walsh, J. J.; Tellitu, I.; Bhaskar, K. V.; Kelly, T. R. *J. Org. Chem.* **1988**, *63*, 1090−1097.
(9) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *J. Org. Chem.* **2001**, *66*, 3525−3532.
(10) Yin, J.; Liebeskind, L. S. *J. Org. Chem.* **1998**, *63*, 5726−5727.
(11) Jiang, M. X.; Rawat, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 5970−5971.
(12) Smith, L. I.; Austin, F. L. *J. Am. Chem. Soc.* **1942**, *64*, 528−533.
(13) Finley, K. T. *The Chemistry of the Functional Groups. The Chemistry of the Quinonoid Compounds*; John Wiley & Sons: New York, 1974; Vol. 2, pp 1047−1072.
(14) Emadi, A.; Harwood, J. S.; Kohanim, S.; Stagliano, K. W. *Org. Lett.* **2002**, *4*, 521−525.
(15) Stagliano, K. W.; Emadi, A.; Lu, Z.; Malinakova, H. C.; Twenter, B.; Yu, M.; Holland, L. E.; Rom, A. M.; Harwood, J. S.; Amin, R.; Johnson, A. A.; Pommier, Y. *Bioorg. Med. Chem. Lett.* **2006**, *14*, 5651−5665.

10.1021/jo060825c CCC: $33.50
Published on Web 07/27/2006

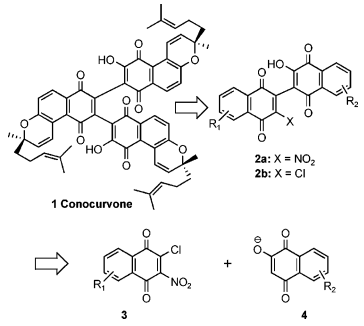
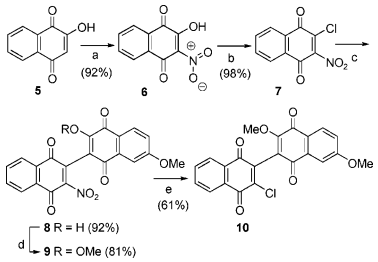


FIGURE 1. Stepwise substitution approach to trimeric quinones.

SCHEME 1. Synthesis of Simple 3-Nitro-2,2′-biquinones[a]



[a] Reagents and conditions: (a) Method A: conc HNO_3, $CHCl_3$, rt, 1 h (65%). Method B: NO_2BF_4 (1.2 equiv), MeCN, rt, 30 min (92%). (b) $(COCl)_2$ (2 equiv), cat. DMF, CH_2Cl_2, rt, 15 min (98%). (c) 2-Hydroxy-6-methoxy-1,4-naphthoquinone, Cs_2CO_3 (2 equiv), MeCN, rt, 3 days (92%). (d) $(CH_3)_3OBF_4$, $((CH_3)_2CH)_2NC_2H_5$, CH_2Cl_2, rt, 6 h (81%). (e) $(COCl)_2$ (10 equiv), cat. DMF, CH_2Cl_2, rt, 24 h (61%).

cores, exploiting the reactivity of 2-chloro-3-nitronaphthoquinones **3** (Figure 1). A new methodology for the conversion of 2-hydroxynaphthoquinones into 2-chloro-3-nitronaphthoquinones[16] under exceedingly mild conditions has been developed, and the 2-chloro-3-nitronaphthoquinones **3** were used in a regiocontrolled substitution of the 2-chloro substituent with hydroxyquinone anions **4** to afford nitrohydroxybiquinones **2a** ($X = NO_2$). An unprecedented conversion of 2-nitrobiquinone into 2-chlorobiquinones was discovered, providing chlorobiquinone synthons **2b** ($X = Cl$), which were previously converted to trimeric quinones.[14] This study opens up new synthetic applications of previously unexplored nitroquinones, and delineates a strategy for a future stepwise assembly of trimeric quinones featuring unsymmetrical center cores.

We became intrigued with the possibility of using 2-chloro-3-nitronaphthoquinone **7** as a doubly activated quinone equivalent for the synthesis of trimeric quinones via a stepwise substitution (Scheme 1). The method for the preparation of 2-hydroxy-3-nitronaphthoquinone **6** previously reported by Buckle[16] utilized highly acidic conditions, and would not be useful for functionalization of acid-sensitive derivatives of naturally occurring pyranylquinones.[1,2] After much experimentation, we discovered that the treatment of 2-hydroxynaphthoquinone **5** with commercially available nitronium tetrafluoroborate[17,18] (1.2 equiv) in dry acetonitrile for 30 min at room temperature afforded the nitrohydroxynaphthoquinone **6** as a bright yellow solid in 92% yield (Scheme 1, Method B). Notably, the transformation proceeds under virtually neutral conditions. The MS and IR data confirmed the presence of the nitro group (C−NO_2),[19] and the ^1H and ^{13}C NMR analyses indicated that the nitration occurred exclusively at the C-3 position on hydroxyquinone **5**.

Seeking a protocol for the conversion of the hydroxy group in quinone **6** into a leaving group, quinone **6** was subjected to the conditions previously used by us for the synthesis of dihalogenated quinones ($(COCl)_2$ (10 equiv), cat. DMF, rt, 20 h).[14] However, we were surprised to note that both the hydroxy and nitro groups were replaced with chlorine, providing 2,3-dichloronaphthoquinone. Careful experimentation revealed that the rate of substitution of the hydroxy group in quinone **6** with chlorine was faster than the substitution of the nitro group (chlorination of the hydroxy group was completed within 15 min with only a trace of dichloro product present), and we reasoned that a pure 2-chloro-3-nitronaphthoquinone **7** would be accessible after limiting the amount of oxalyl chloride and the reaction time. Under the optimized conditions employing oxalyl chloride (1.5−2.0 equiv), anhydrous CH_2Cl_2 with 10% DMF for 15 min at room temperature, 2-chloro-3-nitronaphthoquinone **7** was isolated as a bright yellow solid in an excellent yield (98%) (Scheme 1).

Anticipating that the nitro group would direct a regiospecific substitution of the chlorine atom at C-2 with hydroxyquinone anions regardless of the potential presence of substituents in the aromatic ring of the naphthoquinone skeleton, a model reaction of 2-chloro-3-nitronaphthoquinone **7** with 2-hydroxy-6-methoxynaphthoquinone in the presence of cesium carbonate (2 equiv) in dry acetonitrile[14] was investigated. As expected, the substitution provided 3-nitro-2,2′-biquinone **8** in 92% yield (Scheme 1). The ^1H and ^{13}C NMR spectra indicated that a single regioisomer **8** was formed, and the presence of the nitro group in biquinone **8** was unequivocally established by IR spectroscopy.[20] The hydroxy group in biquinone **8** was then methylated with trimethyloxonium tetrafluoroborate providing nitromethoxybiquinone **9** in an excellent yield (81%).

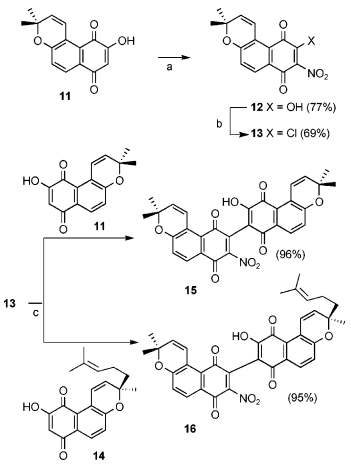
Taking advantage of our earlier observation, optimum conditions for the conversion of the nitro group in biquinone **9** to chlorine were sought. The treatment of biquinone **9** with oxalyl chloride (10 equiv) under catalysis with DMF in CH_2Cl_2 at room temperature afforded chloromethoxybiquinone **10** in a good yield (61%) (Scheme 1).

To test the utility of the described methodology in the synthesis of pyranylated biquinones structurally related to the naturally occurring anti-HIV active conocurvone,[1] an unsymmetrically substituted hydroxyquinone **11** accessible by condensation of naphthalene-2,7-diol and 3-methylbut-2-enal followed by oxidation[21,22] was converted into pyranylated 2-hydroxy-3-nitronaphthoquinone **12** in 77% yield using the nitration with NO_2BF_4 (Method B) (Scheme 2). Treatment of nitrohydroxy-

(16) Buckle, D. R.; Cantello, B. C. C.; Smith, H.; Smith, R. J.; Spicer, B. A. *J. Med. Chem.* **1977**, *20*, 1059−1064.
(17) Kuhn, S. J.; Olah, G. A. *J. Am. Chem. Soc.* **1958**, *80*, 6541−6545.
(18) Kuhn, S. J.; Olah, G. A. *J. Am. Chem. Soc.* **1961**, *83*, 4564−4571.

(19) HRMS (FAB) calculated for $C_{10}H_6NO_5$ $(M + H)^+$ 220.0246, found 220.0239. The fragment mass (174) in the MS(FAB) spectrum indicated the fragmentation of the C−N bond in nitrohydroxyquinone **6**. The two absorptions (1535 (s), 1334 (m) cm^{-1}) in the IR spectrum confirmed the presence of a nitro group, the signal at 1535 cm^{-1} corresponding to the asymmetrical stretch of the N−O bond and the signal at 1334 cm^{-1} corresponding to the symmetrical stretch of the N−O bond.
(20) The two peaks (1547 cm^{-1}, asymmetrical stretch of the N−O bond; and 1334 cm^{-1}, symmetrical stretch of the N−O bond) in the IR spectrum confirmed the presence of a nitro group in nitrobiquinone **8**.
(21) Cannon, J. R.; Josshi, K. R.; McDonald, I. A.; Retallack, R. W.; Sierakowski, A. F.; Wong, L. C. H. *Tetrahedron Lett.* **1975**, *32*, 2795−2798.
(22) Jacobsen, E. N.; Vander Velde, S. L. *J. Org. Chem.* **1995**, *60*, 5380−5381.

SCHEME 2. Regiospecific Synthesis of Pyranylated 3-Nitro-2,2′-biquinones[a]



[a] Reagents and conditions: (a) NO_2BF_4 (1.2 equiv), $MeCN/CH_2Cl_2$, 0 °C, (77%). (b) $(COCl)_2$ (2 equiv), cat. DMF, CH_2Cl_2, rt, 15 min (69%). (c) Cs_2CO_3 (2 equiv), MeCN, rt, 3 days, quinones **11** or **14**.

naphthoquinone **12** under the established chlorination conditions afforded the pyranylated 2-chloro-3-nitronaphthoquinone **13** as a deep red solid in 69% yield. Both the pyranylated nitroquinones **12** and **13** could be purified by flash column chromatography; however, a careful selection of the adsorbent and the elution system was necessary. Best results were obtained with silica instead of Florisil and eluting quinone **12** with 80% EtOAc and 5% AcOH in hexanes, and quinone **13** with 10% EtOAc in hexanes.

The tolerance of the acid-sensitive pyran ring of hydroxyquinone **11** to the novel nitration conditions is notable and significant from the standpoint of the synthesis of complex naturally occurring quinones.

The pyranylated hydroxyquinone **11** and naturally occurring Teretifolione B **14**,[21] which was prepared by published procedures,[22] were treated with 2-chloro-3-nitronaphthoquinone **13** in the presence of a mild base (Cs_2CO_3) to afford biquinones **15** and **16** as single regioisomers in quantitative yields with a complete control of the substitution patterns (Scheme 2). Quinones **15** (96%) and **16** (95%) were obtained as pure red solids after chromatographic purification. Our previously published work indicated the compatibility of pyranylquinones with the O-methylation, and demonstrated the conversion of biquinone **10** into a trimeric quinone via substitution.[14]

In conclusion, a novel method for the preparation of 2-hydroxy-3-nitronaphthoquinones and 2-chloro-3-nitronaphthoquinones under mild conditions was described. The chloronitronaphthoquinones were successfully used in a regiospecific synthesis of 3-nitro-3′-hydroxy-2,2′-biquinones. Feasibility of the conversion of 3-nitro-3′-methoxy-2,2′-biquinones into 3-chloro-3′-methoxy-2,2′-biquinones was established, providing an access to unique activated biquinone synthons poised for a future conversion to trimeric quinones.

In conjunction with our prior studies, this protocol opens up for the first time a pathway to a stepwise regiocontrolled elaboration of unsymmetrical biselectrophilic quinone cores via a stepwise double substitution.

Experimental Section

2-Hydroxy-3-nitronaphthalene-1,4-dione (6) (Method B). To a vigorously stirred suspension of the 2-hydroxynaphthoquinone (0.174 g, 1.000 mmol) in dry acetonitrile (15 mL) under nitrogen at room temperature was added nitronium tetrafluoroborate (0.152 g, 1.150 mmol). The resulting reaction mixture was stirred for 30 min during which the light yellow suspension turned into a transparent yellow solution. The solvent (acetonitrile) was evaporated followed by the addition of 4 N HCl (50 mL). The resulting aqueous suspension was extracted with ethyl ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to yield nitrohydroxynaphthoquinone **6** (0.201 g, 92%) as a yellow solid: mp 154−156 °C (lit.[16] mp 162−163 °C); R_f 0.23 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.96 (m, 2 H), 8.19−8.26 (m, 2 H), 8.68 (s, br, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 126.3, 131.0, 132.3, 133.4, 135.0, 135.4, 136.7, 161.9, 172.0, 184.0; FT-IR (KBr) 3317 (s and br), 1688, 1651, 1607, 1536, 1334, 779, 722 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 220 [(M + H)$^+$, 48], 195 (37), 171 (15), 154 (100), 136 (96), 124 (18), 107 (34); HRMS (FAB) calcd for $C_{10}H_6NO_5$ (M + 1)$^+$ 220.0246, found 220.0239.

2-Hydroxy-3-nitronaphthalene-1,4-dione (**6**) was also prepared using fuming HNO_3 in $CHCl_3$ (method A) as previously described.[16]

2-Chloro-3-nitronaphthalene-1,4-dione (7). To a suspension of 2-hydroxy-3-nitronaphthoquinone **6** (0.300 g, 1.37 mmol) in dry CH_2Cl_2 (30 mL) was added oxalyl chloride (0.239 mL, 2.74 mmol) and DMF (0.011 mL, 0.14 mmol). The reaction mixture was stirred for 15 min at room temperature during which a transparent yellow solution formed. The solution was poured into cold H_2O (100 mL) and stirred for 10 min to quench the excess oxalyl chloride. The mixture was extracted with CH_2Cl_2 (1 × 50 mL). The combined organic layers were washed with H_2O (4 × 70 mL), dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by flash chromatography on silica eluting with 10% EtOAc in hexanes to yield 0.317 g (98%) of the chloronitronaphthoquinone **7** as a bright yellow solid: mp 155 °C; R_f 0.29 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.84 (m, 2 H), 8.19−8.24 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.6 (2 C), 128.1, 129.6, 130.4, 135.4, 135.6, 151.1, 173.5, 176.2; FT-IR (KBr) 1689, 1677, 1550, 1369, 789, 715, 691 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 238.9 [(M + 2H)$^+$, 22], 236.9 (M$^+$, 63), 190.9 (100), 162.9 (40), 134.9 (58); HRMS (FAB) calcd for $C_{10}H_6NO_4Cl$ (M + 2H)$^+$ 238.9985, found 238.9964.

3′-Nitro-3-hydroxy-7-methoxy-2,2′-binaphthalenyl-1,4,1′,4′-tetraone (8). The mixture of 2-chloro-3-nitronaphthoquinone **7** (0.150 g, 0.63 mmol), 2-hydroxy-6-methoxynaphthoquinone[23] (0.129 g, 0.63 mmol), and cesium carbonate (0.411 g, 1.26 mmol) was stirred in anhydrous CH_3CN (7 mL) at room temperature for 3 days during which the color changed from deep red to dark purple. The mixture was acidified with concentrated HCl to pH 2 (litmus) forming a yellow precipitate. The suspension was poured into water (100 mL) and stirred for 30 min to dissolve remaining traces of cesium carbonate. The precipitate was filtered and the product air-dried for 3 days at room temperature to yield the nitrohydroxybiquinone **8** (0.234 g, 92%) as a yellow solid: mp 214−216 °C; R_f 0.38 ($CHCl_3$ and 3 drops of MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.93 (s, 3 H), 7.34 (dd, J = 8.7 Hz, 2.7 Hz, 1 H), 7.40 (d, J = 2.7 Hz, 1 H), 7.98−8.00 (m, 2 H), 8.02 (d, J = 8.7 Hz, 1 H), 8.07−8.10 (m, 1 H), 8.13−8.16 (m, 1 H);[24] ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.5, 110.6, 111.2, 119.9, 123.7, 127.2, 127.3, 129.7, 130.2, 131.6, 134.5, 134.6, 135.8, 136.0, 151.7, 160.2, 165.0, 175.2, 179.1, 180.9, 181.8; FT-IR (KBr) 3321 (s and br), 1679, 1664, 1590, 1547, 1334, 785, 762 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 407 [(M + 2H)$^+$, 4], 391 (5), 371 (2), 307 (66), 286 (56), 220 (27), 205 (12), 154 (100), 136 (96). Repeated attempts to detect a molecular ion in the high-resolution mass spectra were unsuccessful. The use of **8** in subsequent reactions yielded the expected product **9**, which was fully characterized.

(23) Kasturi, T. R.; Arunachalam, T. *Can. J. Chem.* **1966**, *44*, 1086−1089.

(24) The signal for the H−O in quinone **8** and **12** was not detected in ^{1}H NMR spectra due to significant broadening.

3′-Nitro-3,7-methoxy-2,2′-binaphthalenyl-1,4,1′,4′-tetraone (9). To a solution of nitrohydroxybiquinone **8** (0.304 g, 0.75 mmol) and trimethyloxonium tetrafluoroborate (0.133 g, 0.90 mmol) in dry methylene chloride (20 mL) was added *N*,*N*′-diisopropylethylamine (0.116 g, 0.90 mmol). The resulting dark purple solution was stirred under nitrogen for 6 h at room temperature during which the reaction mixture turned a brown-yellow color. The solution was diluted with CH_2Cl_2 (50 mL) and successively washed with water containing 3 drops of HCl (3 × 100 mL) and 10% $NaHCO_3$ (3 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated yielding the nitromethoxybiquinone **9** (0.255 g, 81%) as a yellow solid: mp 230−232 °C; R_f 0.25 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3 H), 4.24 (s, 3 H), 7.22 (dd, J = 8.7 Hz, 2.7 Hz, 1 H), 7.51 (d, J = 2.7 Hz, 1 H), 7.87−7.91 (m, 2 H), 8.06 (d, J = 8.7 Hz, 1 H), 8.17−8.20 (m, 1 H), 8.23−8.26 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 56.1, 109.9, 118.7, 120.5, 124.6, 127.3 (2C), 127.6, 129.2, 129.5, 130.1, 131.4, 133.1, 133.4, 135.1, 158.5, 164.8, 174.9, 179.0, 181.3, 181.6; FT-IR (KBr) 1678, 1591, 1545, 1329, 760, 742 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 420 [(M + H)$^+$, 8], 391(4), 360 (4), 359 (3), 307 (27), 285 (13), 220 (14), 205 (7), 179 (6), 154 (100), 136 (84), 107 (26); HRMS (FAB) calcd for $C_{22}H_{14}NO_8$ (M + H)$^+$ 420.0719, found 420.0703.

3′-Chloro-3,7-methoxy-2,2′-binaphthalenyl-1,4,1′,4′-tetraone (10). The reaction of the nitromethoxybiquinone **9** (0.045 g, 0.11 mmol), oxalyl chloride (0.094 mL, 1.07 mmol), and DMF (1 drop), according to the general procedure described above for the preparation of **7**, yielded chlorobiquinone **10** (0.027 g, 61%) as a dark yellow solid: mp 290−292 °C. Compound **10** was also prepared by the published procedures.[14]

9-Hydroxy-8-nitro-3,3-dimethyl-3*H*-benzo[*f*]chromene-7,10-dione (12). To a vigorously stirred solution of the pyranylated hydroxynaphthoquinone **11** (0.256 g, 1.00 mmol) in dry CH_2Cl_2 (30 mL) under nitrogen at 0 °C was added a solution of nitronium tetrafluoroborate (0.159 g, 1.20 mmol) in dry acetonitrile (10 mL) dropwise over 20 min. The resulting reaction mixture was warmed to room temperature and stirred for an additional 10 min. The solvents (acetonitrile and CH_2Cl_2) were evaporated under reduced pressure at room temperature. The crude product was quenched with water (100 mL) followed by the addition of concentrated HCl to pH 2 (litmus). The resulting aqueous suspension was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by flash chromatography on silica eluting with 80% EtOAc and 5% AcOH in hexanes to yield the pyranylated nitrohydroxynaphthoquinone **12** (0.230 g, 77%) as a red solid: mp 165−166 °C; R_f 0.26 (EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (s, 6 H), 6.06 (d, J = 10.2 Hz, 1 H), 7.14 (d, J = 8.4 Hz, 1 H), 7.48 (d, J = 10.5 Hz, 1 H), 7.85 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (200 MHz, DMSO-d_6) δ 27.6 (2 C), 76.3, 119.8, 120.2, 121.6, 125.9, 127.6, 127.8, 134.1, 135.0, 155.9, 163.1, 171.3, 186.8; FT-IR (KBr) 3321 (s and br), 1665, 1655, 1536, 1334, 756, 749 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 302 [(M + H)$^+$, 37], 286 (17), 255 (22), 231 (35), 213 (46), 187 (17), 165 (22), 154 (77), 136 (73), 115 (39), 107 (36); HRMS (FAB) calcd for $C_{15}H_{12}NO_6$ (M + H)$^+$ 302.0665, found 302.0688.

9-Chloro-8-nitro-3,3-dimethyl-3*H*-benzo[*f*]chromene-7,10-dione (13). Reaction of nitrohydroxynaphthoquinone **12** (0.230 g, 0.77 mmol) with oxalyl chloride (0.067 mL, 0.77 mmol) in the presence of DMF (0.006 mL, 0.08 mmol) for 15 min, as described above for the preparation of **7**, yielded pyranylated 2-chloro-3-nitronaphthoquinone **13** (0.168 g, 69%) (after purification by flash chromatography on silica eluting with 10% EtOAc in hexanes) as a red solid: mp 149−151 °C; R_f 0.28 (10% EtOAc in Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 6 H), 6.07 (d, J = 10.5 Hz, 1 H), 7.17 (d, J = 8.1 Hz, 1 H), 7.65 (d, J = 10.5 Hz, 1 H), 8.02 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1 (2 C), 77.9, 119.1, 122.8, 123.6, 124.9, 130.0, 130.8, 135.3, 137.2, 150.1, 160.4, 172.7, 178.2; FT-IR (KBr) 1676, 1664, 1553, 1368, 770, 743 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 320 [(M + H)$^+$, 27], 306 (22), 289 (12), 239 (4), 213 (10), 179 (8), 167 (20), 154 (100), 136 (91), 107 (37); HRMS (FAB) calcd for $C_{15}H_{11}ClNO_5$ (M + H)$^+$ 320.0326, found 320.0321.

9-(9-Hydroxy-3,3-dimethyl-3*H*-benzo[*f*]chromen-8-yl)-3,3-dimethyl-8-nitro-3*H*-benzo[*f*]chromene-7,10-dione (15). Reaction of pyranylated 2-chloro-3-nitronaphthoquinone **13** (0.060 g, 0.19 mmol) with hydroxyquinone **11** (0.048 g, 0.19 mmol) in the presence of Cs_2CO_3 (0.122 g, 0.38 mmol) for 3 days, as described above for the preparation of **8**, yielded biquinone **15** (0.097 g, 96%) (after purification by flash chromatography on silica eluting with 35% EtOAc and 5% AcOH in hexanes) as a red solid: mp 129−132 °C; R_f 0.25 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 12 H), 5.97 (d, J = 10.5 Hz, 1 H), 6.04 (d, J = 10.5 Hz, 1 H), 7.14 (d, J = 7.8 Hz, 1 H), 7.17 (d, J = 8.4 Hz, 1 H), 7.58 (d, J = 10.2 Hz, 1 H), 7.73 (d, J = 10.5 Hz, 1 H), 8.00 (d, J = 8.4 Hz, 1 H), 7.90−8.00 (s, br, 1 H), 8.07 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (27.9), (28.0), 28.1 (2 C), 29.70 (2 C), 77.7 (2 C), 110.3, 119.3, 119.4, 121.8, 122.2, 122.4, 123.0, 123.1, 124.4, 126.2, 126.4, 129.5, 129.7, 132.3, 136.1, 136.9, 151.1, 153.9, 158.5, 160.2, 174.0, 180.6, 181.7, 183.5 (signals for the minor atropisomer arising from a hindered rotation about the quinone−quinone bond are given in parentheses); FT-IR (KBr) 3316 (s and br), 1671, 1664, 1642, 1554, 1356, 774, 731 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 540 [(M + H)$^+$, 10], 524 (12), 479 (18), 464 (11), 307 (8), 289 (8), 239 (7), 213 (46), 165 (16), 154 (100), 107 (38); HRMS (FAB) calcd for $C_{30}H_{21}NO_9$ (M)$^+$ 539.1216, found 539.1229.

9-(9-Hydroxy-3-methyl-3-(4-methylpent-3-enyl)-3*H*-benzo[*f*]-chromen-8-yl)-3,3-dimethyl-8-nitro-3*H*-benzo[*f*]chromene-7,10-dione (16). Reaction of pyranylated 2-chloro-3-nitronaphthoquinone **13** (0.060 g, 0.19 mmol) with hydroxyquinone **14** (0.061 g, 0.19 mmol) in the presence of Cs_2CO_3 (0.122 g, 0.38 mmol) for 3 days, as described above for the preparation of **8**, yielded biquinone **16** (0.108 g, 95%) (after purification by flash chromatography on silica eluting with 15% EtOAc and 5% AcOH in hexanes) as a red solid: mp 127−131 °C; R_f 0.25 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 3 H), 1.49 (s, 6 H), 1.57 (s, 3 H), 1.66 (s, 3 H), 1.71−1.79 (m, 2 H), 2.05−2.13 (m, 2 H), 5.08 (t, J = 2.0 Hz, 1 H), 5.97 (d, J = 11.1 Hz, 1 H), 6.00 (d, J = 10.2 Hz, 1 H), 7.13 (d, J = 8.4 Hz, 1 H), 7.17 (d, J = 8.7 Hz, 1 H), 7.58 (d, J = 10.5 Hz, 1 H), 7.81 (d, J = 10.2 Hz, 1 H), 7.90−8.00 (s, br, 1 H), 8.00 (d, J = 8.4 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 22.6, 25.7 (26.7) (2 C), 28.1 (29.7) (2 C), 41.4 (41.3), 77.7, 79.8, 110.3, 119.4, 119.8, 121.8, 122.1, 122.4, 122.5, 122.7, 123.0, 123.3 (123.4), 124.4, 126.2, 126.3, 129.6, 129.7, 132.3 (132.4), 136.1, 136.2, 151.1, 153.9, 158.8, 160.2, 174.0, 180.5, 181.7, 183.5 (signals for the minor atropisomer arising from a hindered rotation about the quinone−quinone bond are given in parentheses); FT-IR (KBr) 3317 (s and br), 1672, 1665, 1641, 1545, 1356, 772, 755 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 608 [(M + H)$^+$, 37], 562(32), 524 (43), 479 (44), 478 (18), 307 (18), 285 (10), 220 (21), 205 (10), 154 (100), 136 (73); HRMS (FAB) calcd for $C_{35}H_{30}NO_9$ (M)$^+$ 608.1921, found 608.1949.

Acknowledgment. We acknowledge the National Institutes of Health (Grant AI43687) to K.W.S. for support of this research, and thank the University of Notre Dame Mass Spectrometry Facility for assistance with low- and high-resolution mass spectra, and thank Mr. Chad D. Hopkins (University of Kansas) for assistance with recording the ^{13}C NMR spectra.

Supporting Information Available: General experimental details and ^{1}H and ^{13}C NMR spectra for **6**−**9**, **12**, **13**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060825C