An Approach to Dibenzofuran Heterocycles. 1. Electron-Transfer Processes en Route to Dibenzofuran-1,4-diones

John W. Benbow,* Bonnie L. Martinez, and William R. Anderson

Department of Chemistry, Lehigh University, 6 East Packer Avenue, Bethlehem, Pennsylvania 18015-3172

Received July 1, 1997

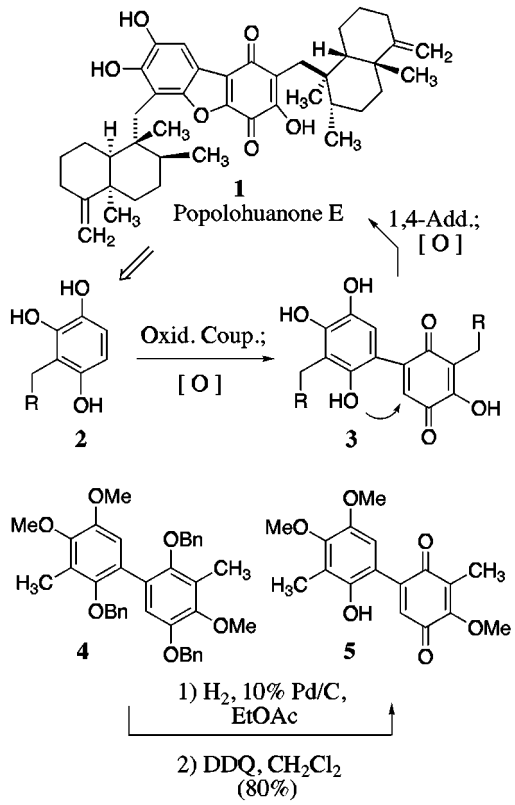
Introduction

The unusual dibenzofuran-1,4-dione heterocycle is the central architectural feature of popolohuanone E, a marine natural product that inhibits topoisomerase-II (IC_{50} = 400 nM) and shows good selectivity toward A549 human lung cancer (IC_{50} = 2.5 mg/mL), a nonsmall cell tumor line that is particularly resistant to medical treatment.[1] An approach to this heterocycle could involve biaryl formation via the oxidative dimerization of two arenol "monomers" **2** followed by a selective oxidation to form hydroxyquinone **3** (Scheme 1). A subsequent intramolecular phenol cyclization would afford a dihydroquinone that would generate the title heterocycle upon oxidation. Enzymatic oxidative coupling processes frequently provide biaryl bonds in natural systems,[2] and biomimetic oxidation sequences have been utilized in the total synthesis of several natural products.[3] The recent report[4] of a popolohuanone E model system prompts the disclosure of our approach to this target, an effort that has uncovered a complex series of redox processes.

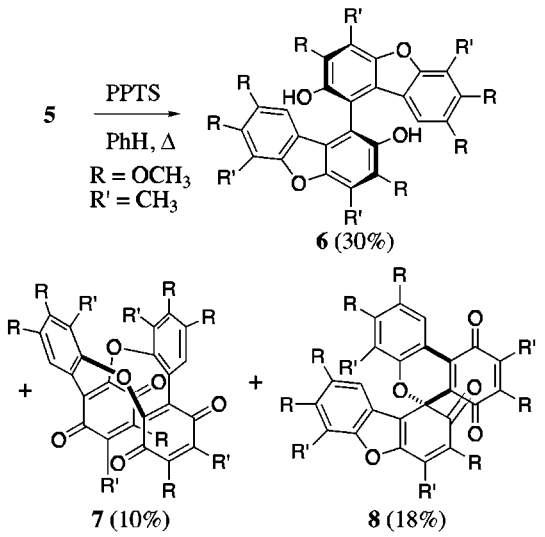
Results and Discussion

We envisioned the dimerization of permethylated or perbenzylated derivatives of 2,3,6-trihydroxytoluene followed by cleavage of the ether linkages to afford **3**, and our studies regarding the Suzuki protocol for the formation of biaryl systems[5] afforded ample quantities of the symmetrically protected biaryls (Scheme 1). While neither of these compounds could be suitably deprotected, a differentially protected biaryl (**4**) circumvented this problem. This compound cleanly underwent hydrogenolysis to afford the triol and furnished hydroxyquinone **5** upon oxidation with dichlorodicyanoquinone (DDQ). A spontaneous ring closure to form the central furan did not occur, nor was any cyclization induced from treatment of this material with a series of bases (Et_3N, NaH, KH). However, refluxing a benzene solution of **5** for 48 h in the presence of a mild acid catalyst (PPTS) afforded three new products, **6** (30%), **7** (10%), and **8** (18%), and a fourth fraction that was a mixture of three dimeric products (7%) (Scheme 2).

Scheme 1



Scheme 2



The identities of these singular materials were determined from detailed spectroscopic analysis. The mass spectral data supported a dimeric structure for **6** (*m/e* = 602) and indicated that a dehydration had taken place in its formation. A kinetically favored intramolecular 5-*exo*-trig cyclization[6] provides a hemiketal (Scheme 3) that, after oxonium formation (−H_2O) and reduction via single electron transfer, produces the ketone-stabilized radical **10**; internal electron transfers are common processes in quinone cyclization reactions.[7] Dimerization through C-5 and subsequent tautomerization furnishes **6**.

(1) Carney, J. R.; Scheuer, P. J. *Tetrahedron Lett.* **1993**, *34*, 3727−3730.

(2) (a) Wildman, W. C.; Pursey, B. A. *The Alkaloids*, Vol. 9; Manke, R. H. F., Ed.; Academic Press: New York, 1968; pp 407−457 and references therein. (b) Kupchan, S. M.; Kim, C.-K.; Lynn, J. T. *J. Chem. Soc., Chem. Commun.* **1976**, 86.

(3) (a) Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K. *J. Org. Chem.* **1978**, *43*, 4076−4081. (b) Kende, A. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 267−268. (c) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 1162−1163. (d) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 1742−1745.

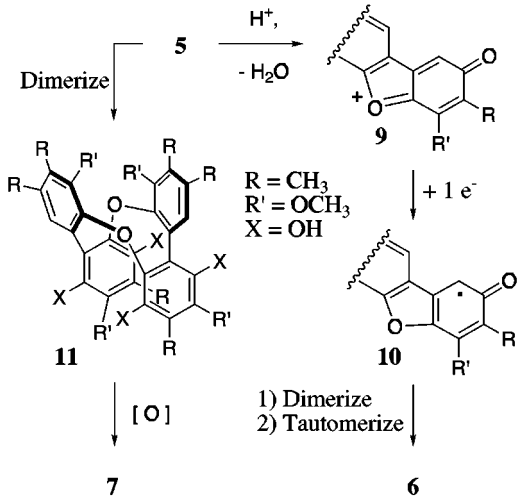
(4) Ueki, Y.; Itoh, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 5719−5722.

(5) Benbow, J. W.; Martinez, B. L. *Tetrahedron Lett.* **1996**, *37*, 8829−8832.

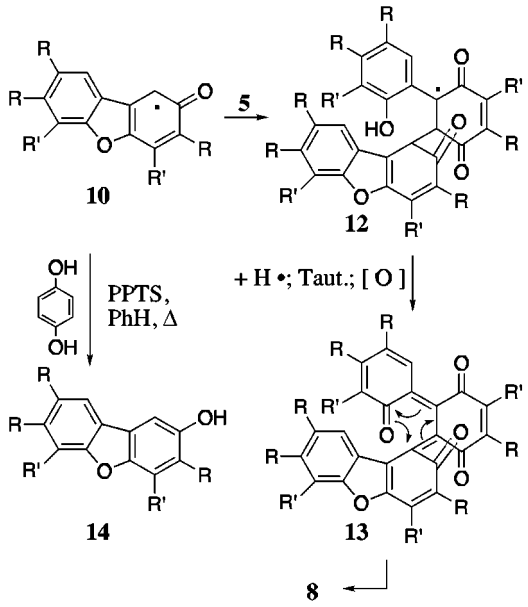
(6) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736−738.

S0022-3263(97)01196-1 CCC: $14.00

Scheme 3



Scheme 4



The mass spectral data for **7** and **8** also identified these compounds as dimers (*m/e* = 632 and 616, respectively) and provided some indication as to their mode of formation. The mass for compound **7** suggested an oxidative dimerization pathway, while that for **8** indicated an oxidation and dehydration process. Compound **7** arises by an intermolecular hydroxyquinone cyclization followed by a second intramolecular addition to provide the bis-dihydroquinone dimer **11**. The four-electron oxidation to **7** can occur either through an intermolecular electron-transfer process or by reaction with adventitious O_2. The lowest energy conformer[8] of **7** is the saddle, and this contains a C_2 axis that explains the simplified ^{1}H and the ^{13}C spectra.

The spectroscopic data for **8** reveals an unsymmetrical molecule with only three C=O's in the ^{13}C NMR spectrum. This structure, a hybrid of **6** and **7**, arises from dibenzofuran radical **10** addition to hydroxyquinone **5** to provide the dihydroquinone **12** after hydrogen atom abstraction and tautomerization. A possible mechanism for the formation of **8** involves four-electron oxidation to the oxaquinodimethane **13** followed by an electrocyclic ring closure to generate **8** (Scheme 4); several stepwise two electron transfers are also viable pathways to **13**.

The formation of products **6** and **8** is dependent upon the formation of **10**, which in turn relies on the dihydroquinone reductant **11**; without a reducing agent, the intermediate hemiketal would return to the hydroxyquinone. While several electron-transfer scenarios can be envisioned, the exact intermediate(s) responsible for the transfer are difficult to discern. A model describing the potential electron-transfer possibilities based on the present data would not be complete because the mass balance for the reaction is moderate (66%) and no consideration has been made of the hydroxyquinone **5** as a partner in a redox couple.

These results suggest that the inclusion of an external reducing agent should decouple the formation of the intermolecular dimer **6** from the intramolecular systems **7** and **8**. Indeed, treatment of the hydroxyquinone **5** with PPTS in the presence of 1,4-dihydroquinone produced the monomeric dibenzofuran **14** (Scheme 4). Apparently the lifetime of semiquinone radical **10** is short under these conditions. This result may be attributed to 1,4-dihydroquinone being a smaller, more efficient reducing agent than more sterically hindered dihydroquinones such as **11** and/or that reduction of the semiquinone ketal occurs faster than the coupling to form **7** or **8**. More importantly, no **6** was produced, showing that the intramolecular 1,2-addition pathway can be made the major reaction route.

Our biomimetic sequence to access dibenzofuran-1,4-dione heterocycles has uncovered a complex system of electron transfer pathways. The structures of these materials and a fundamental understanding of the processes involved in their formation have been presented. We are currently pursuing a series of experiments to determine the electron-transport intermediates in order to optimize the formation of each of these products; the dimeric dibenzofurandiol **6** has potential as an additive in catalytic processes and the saddle dimer **7** is an excellent substrate from which to examine quinone photochemistry. These studies are currently in progress, and the results will be reported in due course.

Experimental Section

General Procedure. All reactions were run in flame-dried glassware under a nitrogen atmosphere unless otherwise noted. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl prior to use. Benzene (PhH), toluene ($PhCH_3$), and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. The pyridinium *p*-toluenesulfonate was recrystallized from EtOH. All other chemicals were purchased from Aldrich Chemical Co. and were used as received. Reaction progress was monitored by TLC using E. Merck silica gel 60 F-254, and preparative TLC was performed with these plates (10 × 20 × 0.25 cm). Solvents were removed on a Büchi rotary evaporator at reduced pressure (15−20 Torr).

3-Methyl-2-methoxy-5-(4′,5′-dimethoxy-2′-benzyloxy-3′-methylphenyl)-1,4-dihydroquinone Bis(benzyl ether) 4. A solution of 50.0 mg (0.133 mmol) of 3,6-bis(benzyloxy)-4-iodo-2-methylanisole in THF (1.0 mL) was cooled to −78 °C, and a solution of *sec*-BuLi (0.306 mmol of a 1.2 M solution in hexanes) was added in a dropwise fashion. After the solution was stirred for 40 min, 75.2 mg of $B(O\text{-}i\text{-}Pr)_3$ was added and the contents were allowed to warm to room temperature over 2 h. The resulting dispersion was dissolved by the addition of 10% HCl

(7) (a) Hewgill, F. R.; Kennedy, B. R. *J. Chem. Soc. C* **1966**, 362−366. (b) Hoegberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2517−2520. (c) Brockmann, H. *Liebigs Ann. Chem.* **1988**, 1−8.

(8) Spartan Semiempirical Program: IBM Release 4.1a4, Wavefunction, Inc. Geometry optimization with Model RHF/AM1. The saddle conformation was 69 kcal/mol more stable than the "planar" conformer using these calculations.

solution (40 μL) followed by extraction with Et_2O (10 mL). The organic layer was washed with a 10% HCl solution (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a yellow oil. Purification by SiO_2 chromatography (10% THF/hexanes) provided 38.2 mg (97%) of the boronic acid as an off-white solid: mp 99−100 °C; R_f = 0.16 (20% EtOAc/hexanes); IR (thin film) ν 3494, 2930, 1588, 1374, 1340, 1220, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.29 (m, 11H), 6.38 (s, 2H), 5.03 (s, 2H), 4.72 (s, 2H), 3.81 (s, 3H), 2.21 (s, 3H) ppm. A solution of 38.2 mg (0.130 mmol) of this boronic acid, 48.9 mg (0.130 mmol) of 2-benzyloxy-4,5-dimethoxy-3-methyliodobenzene, 4.6 mg (3.94 μmol) of tetrakis(triphenylphosphine)-palladium, and 49.4 mg (0.325 mmol) of CsF in benzene (0.65 mL) was heated to reflux and maintained for 12 h. The resulting suspension was transferred to a separatory funnel with EtOAc (10 mL) and washed with H_2O (2 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo, and the residue was purified by SiO_2 chromatography (10% EtOAc/hexanes) to provide 66.6 mg (86%) of **4** as a colorless oil: R_f = 0.41 (20% EtOAc/hexanes); IR (neat) ν 3037, 2932, 2867, 1088, 1003 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (m, 15H), 7.00 (s, 1H), 6.89 (s, 1H), 4.97 (s, 2H), 4.53 (s, 2H), 4.49 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 3.75 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 149.1, 148.7, 148.6, 147.9, 147.7, 147.0, 137.3, 137.2, 137.1, 128.4, 128.2, 128.1, 127.8, 127.7, 127.3, 127.0, 126.9, 126.1, 126.0, 114.3, 112.2, 74.7, 74.6, 70.8, 60.4, 60.3, 55.8, 10.0, 9.90 ppm. Anal. Calcd for $C_{38}H_{38}O_6$: C, 77.27; H, 6.48. Found: C, 77.11; H, 6.71.

3-Methyl-2-methoxy-5-(4′,5′-dimethoxy-2′-hydroxy-3′-methylphenyl)-1,4-benzoquinone (5). To a solution of 119 mg (0.202 mmol) of biaryl **4** in EtOAc (1.0 mL) was added 12 mg of 10% Pd on activated charcoal. The contents were stirred under an atmosphere of H_2 for 12 h at which point the catalyst was removed by filtration through a Celite pad and the solids were washed thoroughly with CH_2Cl_2. The solvent was removed in vacuo, and the triol was isolated in quantitative yield as a clear oil that was used directly without further purification. Partial characterization for the triol: R_f = 0.11 (30% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 6.71 (s, 1H), 6.60 (s, 1H), 5.31 (s, 1H), 5.06 (s, 1H), 4.99 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H). A solution of 0.487 g (1.52 mmol) of the triol in dry benzene (7.60 mL) was stirred at 0 °C while 0.346 g (1.52 mmol) of DDQ was added. After 5 min, the solvents were concentrated in vacuo and the remaining solid was purified by SiO_2 chromatography (10% EtOAc/hexanes) to provide 0.388 g (80%) of **5** as a dark brown solid: mp = 57−58 °C; R_f = 0.37 (30% EtOAc/hexanes); UV/vis (λ_{max} (ϵ)) 354 (3180), 280 (7730), 242 (11540); IR (thin film) ν 3408, 1653, 1601, 1089, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (s, 1H), 6.58 (s, 1H), 6.51 (s, 1H), 4.12 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 2.20 (s, 3H), 2.00 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 190.4, 183.2, 155.7, 150.7, 147.2, 147.1, 146.9, 133.0, 128.5, 122.3, 116.7, 111.5, 61.1, 60.4, 56.3, 9.54, 9.11 ppm. Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.05; H, 5.75.

Acid-Catalyzed Cyclization of Hydroxyquinone. A solution of 100 mg (0.314 mmol) of **5** and 3.0 mg (0.012 mmol) of PPTS in benzene (2.0 mL) was heated and maintained at a gentle reflux in air for 36 h. The solvent was removed in vacuo, and the residue was purified by SiO_2 chromatography (10% EtOAc/hexanes) to provide the intramolecular dibenzofuran dimer **6** (29.6 mg, 30%), the intermolecular dimer **7** (10.1 mg, 10%), and the spiro-dibenzofuran **8** (17.7 mg, 18%).

2,2′-Dihydroxy-3,3′,7,7′,8,8′-hexamethoxy-4,4′,6,6′-tetramethyl-1,1′-bidibenzofuran (6): colorless oil; R_f = 0.13 (30% EtOAc/hexanes); UV/vis (λ_{max} (ϵ)) 312 (38300), 242 (36400); IR (neat) ν 3434, 3005, 1099, 1001, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.14 (s, 2H), 5.58 (s, 2H, exchanges with D_2O), 3.96 (s, 6H), 3.73 (s, 6H), 3.40 (s, 6H), 2.64 (s, 6H), 2.45 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.7, 149.8, 149.2, 146.9, 144.7, 143.0, 119.1, 118.7, 115.7, 115.2, 110.4, 101.0, 61.5, 60.7, 55.7, 9.70, 9.13; HRMS *m/e* calcd for $C_{34}H_{34}O_{10}$ (M^+) 602.2181, found 602.2133.

3,7,8,12,16,17-Hexamethoxy-2,6,11,15-tetramethyl-1,4,-10,13-tetraoxotetrabenzo[*b*,*d*,*g*,*i*][5,14]dioxacyclodecene (7): orange solid; mp 162−163 °C; R_f = 0.51 (30% EtOAc/hexanes); UV/vis (λ_{max} (ϵ)) 462 (4800), 326 (7780), 252 (34300); IR (thin film) ν 1667, 1656, 1115, 1088, 671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (s, 2H), 4.06 (s, 6H), 3.93 (s, 6H), 3.85 (s, 6H), 2.45 (s, 6H), 2.03 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 184.2, 172.6, 155.8, 152.9, 151.5, 150.5, 149.6, 129.5, 122.6, 117.4, 117.2, 100.6, 61.3, 60.9, 56.1, 9.04, 8.84 ppm; HRMS *m/e* cacld for $C_{34}H_{33}O_{12}$ (MH^+) 633.1973, found 633.1972.

2,7-Dimethyl-3,8,9-trimethoxy-6-oxa-1,4-phenanthraquinone-5-spiro-1′-(4′,6′-dimethyl-3′,7′,8′-trimethoxy)dibenzofuran-2′(1′*H*)-one (8): brown oil; R_f = 0.45 (30% EtOAc/hexanes); UV/vis (λ_{max} (ϵ)) 552 (1540), 410 (6080), 356 (6110), 282 (9560), 242 (17300); IR (neat) ν 3001, 1681, 1649, 1115, 1091, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (s, 1H), 5.74 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.41 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H), 1.95 (s, 3H), 1.88 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 192.4, 187.5, 180.3, 154.8, 151.9, 150.5, 149.7, 149.6, 148.3, 147.4, 146.7, 145.6, 132.8, 132.7, 130.4, 128.6, 121.8, 120.4, 116.2, 116.0, 111.9, 109.0, 98.9, 76.3, 61.0, 60.8, 60.6, 60.2, 56.0, 55.6, 10.3, 9.00 ppm; HRMS *m/e* calcd for $C_{34}H_{33}O_{11}$ (MH^+) 617.2023, found 617.2029.

4,6-Dimethyl-2-hydroxy-3,7,8-trimethoxydibenzofuran (14): A solution of 20.0 mg (0.063 mmol) of **5**, 6.9 mg (0.063 mmol) of 1,4-dihydroquinone, and 1.0 mg (0.004 mmol) of PPTS in benzene (1.0 mL) was maintained at a gentle reflux in air for 2 h. The solvent was removed in vacuo, and the residue was purified by SiO_2 chromatography (10% EtOAc/hexanes) to provide 12.3 mg (65%) of **14** as an off-white solid: mp = 152−153 °C; R_f = 0.22 (30% EtOAc/hexanes); IR (neat) ν 3463, 2943, 1098, 1084, 754, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (s, 1H), 7.14 (s, 1H), 5.59 (s, 1H, exchanges with D_2O), 3.96 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.54 (s, 3H), 2.50 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.3, 149.8, 149.5, 146.8, 145.0, 144.3, 120.1, 118.8, 116.1, 114.8, 102.1, 99.8, 61.4, 60.8, 56.2, 9.55, 9.20 ppm. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.67; H, 5.79.

Acknowledgment. Financial support by the National Institutes of Health (Grant 1-R15-CA70990-01) is gratefully acknowledged. The authors are also indebted to Jack Stocker for his assistance in the nomenclature for compounds **6** and **8**.

Supporting Information Available: ^1H and ^{13}C spectra and full tabular listings of the 2D-NMR data are provided for compounds **6**, **7**, and **8** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971196X