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Articles

A Biomimetic Approach to Dihydrobenzofuran Synthesis

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A method for an acid-catalyzed construction of dihydrobenzofuran heterocycles (**14**) from 2-(2′-hydroxyethyl)quinone precursors **10** is presented. The putative oxonium ion intermediate **17** formed by an intramolecular hydroxyl cyclization followed by dehydration is reduced in situ by an added dihydroquinone source. Good to excellent yields of cyclized products are realized in all cases except for highly electron deficient systems, and these suffer reduction prior to oxonium ion formation. All products are monomeric and derived from a two-electron transfer except for **10g**, which affords the dimeric dihydrobenzofuran. The amount of cyclization or reduction product is governed by the HOMO/LUMO gap between the quinone substrate and the dihydroquinone additive, and the product distribution can be adjusted by modifying the electronic properties of the added reducing agent.

Introduction

The neolignans are a diverse family of biologically active plant metabolites that contain the dihydrobenzofuran moiety as a key structural element (Figure 1).[2] A common thread in synthetic approaches to these systems has involved a biomimetic coupling of a quinone and a phenylpropenyl moiety where either the quinone or a redox-derivative is induced to react with the styrene partner. Successful syntheses have used Lewis acid catalysis,[3] chemical or electrochemical oxidations,[4] and the cyclization of quinoneketals with Brønsted acids[5] to assemble the heterocycle. Dihydrobenzofuran systems have also been formed from functionalized aromatic precursors using a variety of conditions including radical,[6] transition metal,[7] benzyne,[8] electrocyclic,[9] anionic,[10] and dehydrative techniques.[11] While the above methods provide the desired heterocycles, few are truly general in scope and several produce a variety of side products.

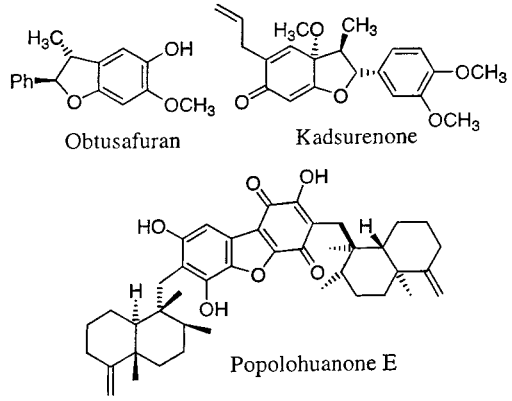

Figure 1. Representative neolignans and the antitumor agent Popolohuanone E.

Our studies toward the topoisomerase inhibitor Popolohuanone E showed that the products from the cyclization

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(2) Ward, R. S. *Nat. Prod. Rep.* **1995**, 183−205.

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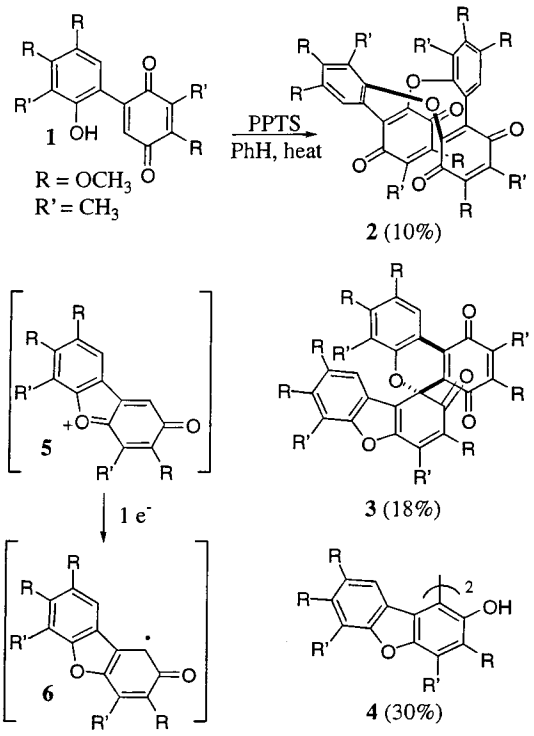
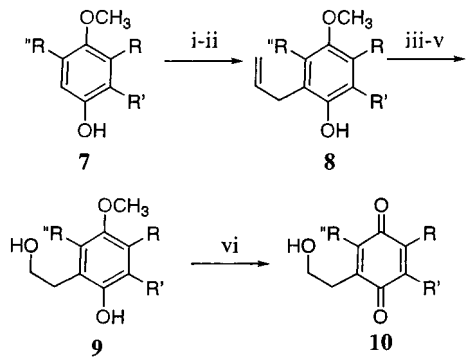


Figure 2. Proposed intermediates and product distribution from the acid-catalyzed cyclization of 2-(2′-hydroxyphenyl)-quinone **1**.[12]

of 2-(2′-hydroxyphenyl)quinone **1** arose from a series of electron-transfer reactions.[12] The oxonium ion **5** suffered single electron reduction from the dihydroquinone produced in situ to afford the key radical intermediate **6**, a common precursor to products **3** and **4** (Figure 2).

Scheme 1[a]



[a] (i) $H_2C{=}CHCH_2Br$, NaH, THF, 0 °C or K_2CO_3, $H_2C{=}CHCH_2Br$, *n*-Bu_4NI, acetone, heat; (ii) $PhNEt_2$, heat; (iii) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (iv) OsO_4 (cat), $NaIO_4$, acetone/Et_2O/H_2O; then $NaBH_4$, CH_3OH, 0 °C; (v) TBAF, THF, 0 °C; (vi) CAN, CH_3CN/H_2O.

Incorporation of dihydro-1,4-benzoquinone (DHQ) into the reaction led to monomeric products via a two electron reductive pathway. The electrochemical properties of hydroxyquinone systems have been studied[13] and, with respect to α-tocopherol model systems, it has been shown that hydroxychromanones undergo electrochemical oxidation to provide the ring-opened hydroxyalkylquinones.[14] These studies support oxonium ions as viable intermediates en route to hemi-ketal systems, a fundamental principle in the mode-of-action of vitamin E. Enabling the reverse of this system by using dihydroquinones as mediators for the reductive cyclizations of 2-(2′-hydroxyethyl)quinones would not only provide a general approach to dihydrobenzofuran synthesis but it would be an ideal biomimetic model: quinone-containing systems (ubiquinones, plastoquinone) provide electron transport that is essential to plant metabolism.[15] Herein we report the realization of this method.

Results and Discussion

The general utility of the intramolecular cyclization reaction of 2-(2′-hydroxyethyl)quinones to dihydrobenzofurans was determined by a systematic study of the electronic effects of different substituents. The study also included the effects of the stoichiometric amounts of the acid catalyst (PPTS) and dihydrobenzoquinone (DHQ) on the cyclization. A series of unsymmetrical β-hydroxyethylquinone systems (**10a**−**j**) were synthesized efficiently using a regioselective Claisen rearrangement of allyl phenyl ethers (Scheme 1, Table 1). The appropriate

(3) (a) Engler, T. A. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B. V.: New York, 1995; vol. 16, pp 547−569. (b) Engler, T. A.; Lynch, K. O., Jr.; Chai, W.; Meduna, S. P. *Tetrahedron Lett.* **1995**, *36*, 2713−2716. (c) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, K. O., Jr.; Ray, J. E. *J. Org. Chem.* **1994**, *59*, 6567−6587. (d) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem.* **1994**, *59*, 6588−6599. (e) Engler, T. A.; Chai, W.; La Tessa, K. O. *J. Org. Chem.* **1996**, *61*, 9297−9308. (f) Engler, T. A.; Combrink, K. D.; Ray, J. E.; *J. Am. Chem. Soc.* **1988**, *110*, 7931−7933.

(4) Chemical: (a) Bolzacchini, E.; Brunow, G.; Meinardi, S.; Orlandi, M.; Rindone, B.; Rummakko, P.; Setala, H. *Tetrahedron Lett.* **1998**, *39*, 3291−3294. (b) Snider, B. B.; Han, L.; Xie, C. *J. Org. Chem.*, **1997**, *62*, 6978−6984. (c) Kerns, M. L.; Conroy, S. M.; Swenton, J. S. *Tetrahedron Lett.* **1994**, *35*, 7529−7532. (d) Callinan, A.; Chen, Y.; Morrow, G. W.; Swenton, J. S. *Tetrahedron Lett.* **1990**, *31*, 4551−4552. Electrochemical: (e) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135−2143. (f) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem.* **1991**, *56*, 1979−1981. (g) Shizuri, Y.; Yamamuri, S. *Tetrahedron Lett.* **1983**, *24*, 5011−5012. (h) Shizuri, Y.; Nakamura, K.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1985**, 530−531.

(5) (a) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717−3719. (b) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073−8075.

(6) (a) Jiménez, M. C.; Miranda, M. A.; Tormas, R. *J. Org. Chem.* **1998**, *63*, 1323−1326. (b) Meijs, G. F.; Beckwith, A. L. J. *J. Am. Chem. Soc.* **1986**, *108*, 5890−5893.

(7) Larock, R. C.; Yang, H.; Pace, P., Narayanan, K.; Russell, C. E.; Cacchi, S.; Fabrizi, G. *Tetrahedron* **1998**, *54*, 7473−7356.

(8) Birkett, M. A.; Knight, D. W.; Mitchell, M. B. *Tetrahedron Lett.* **1993**, *34*, 6939−6940.

(9) Ponpipom, M. M.; Yue, B. Z.; Bugianesi, R. L.; Brooker, D. R.; Chang, M. N.; Shen, T. Y. *Tetrahedron Lett.* **1986**, *27*, 309−312.

(10) Solladié, G.; Boeffel, D.; Maignan, J. *Tetrahedron* **1995**, *51*, 9559−9568.

(11) (a) Stafford, J. A.; Valvano, N. L. *J. Org. Chem.* **1994**, *59*, 4346−4349. (b) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. *Tetrahedron Lett.* **1993**, *34*, 7483−7486.

(12) Benbow, J. W.; Martinez, B. L.; Anderson, W. R. *J. Org. Chem.* **1997**, *62*, 9345−9347.

(13) (a) Burton, G. W.; Doba, T.; Gabe, E. J.; Highes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053−7065. (b) Hughes, L.; Burton, G. W.; Ingold, K. U.; Slaby, M.; Foster, D. O. *Custom Design of Better In Vivo Antioxidants Structurally Related to Vitamin E*; ACS Symposium Series 507 (Phenolic Compounds in Food and Their Effects on Health II − Antioxidants & Cancer Prevention); American Chemical Society: Washington, DC, 1992; pp 184−199.

(14) (a) Smith, L. I.; Kolthoff, I. M.; Wawzonek, S.; Ruoff, P. M. *J. Am. Chem. Soc.* **1941**, *63*, 1018−1024. (b) Parker, V. D. *J. Am. Chem. Soc.* **1969**, *91*, 5380−5381. (c) Marcus, M. F.; Hawley, M. D. *J. Org. Chem.* **1970**, *35*, 5, 2185−2190. (d) Svanholm, U.; Bechgaard, K.; Parker, V. D. *J. Am. Chem. Soc.* **1974**, *96*, 2409−2413.

(15) (a) Kröger, A.; Klingenberg, M. *Curr. Top. Bioenerg.* **1967**, *2*, 151−193. (b) Moore, A. L.; Day, D. A.; Dry, I. B.; Wiskich, J. T. In *Highlights of Ubiquinone Research: Proceedings of the International Symposium "Biochemisrtry, Bioenergetics, and Clinical Applications of Ubiquinone*; Lenaz, G., Ed.; Taylor and Francis: London, 1990; pp 170−173. (c) Masayo, I.; Shigeru, I. *Adv. Chem. Ser.* **1991**, *228 (Electron-Transfer Inorg., Org., Biol. Syst.)*, 163−178.

Table 1. Synthesis of Substituted 2-(2′-Hydroxyethyl)quinones from *p*-Hydroxyanisoles 7

7	R	R′	R″	8 (%)	9 (%)	10 (%)
a	H	H	H	92	52	96
b	OCH_3		H	93	72	98
c	OCH_3	H	H	84[a]	51	99
d	CH_3	H	H	85[a]	51	98
e	Br	H	H	84[a]	74	98
f	CO_2CH_3	H	H	89[a]	61	64
g	H	OCH_3	H	93	49	97
h	H	CH_3	H	86	49	88
i	H	OCH_3	OCH_3	61	49	89
j	H	Cl	H	62	70	98

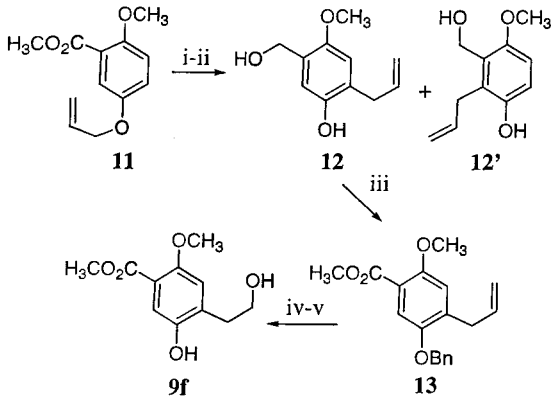
[a] The ratio of regioisomeric *ortho*-products: **8c**/**8c′** (13:1); **8d**/**8d′** (5:2); **8e**/**8e′** (5:6); **8f**/**8f′** (2:5).

p-hydroxyanisoles **7** were converted into the allyl ethers and then rearranged by heating in freshly distilled *N*,*N*-diethylaniline to provide the *o*-allylphenols **8** in excellent yield. The regioselectivity of the rearrangement is dictated by the electronic properties of the substituent *meta* to the allyl ether. As previously reported by Bruce,[16] electron-releasing substituents provide allylation *para* to the substituent whereas electron-withdrawing substituents provide mainly *ortho* substitution, an observation that was explained using hydrogen bonding phenomena. While our selectivities do correlate with that study, the inability of substrates derived from **7** to hydrogen bond suggests that the selectivity is electronically derived, with hydrogen bonding serving to enhance the inherent bias in Bruce's substrates.

Protection of the phenol **8** (TBSOTf, CH_2Cl_2) was necessary prior to the oxidative cleavage of the allylic double bond to the 2-hydroxyethyl side chain (OsO_4, $NaIO_4$/$NaBH_4$); however, this multistep protocol consistently afforded **9** in satisfactory overall yield (49−74%). Oxidation of the phenolic ethers to the quinones (CAN, CH_3CN/H_2O) generated the desired cyclization precursors **10** as oils that discolored rapidly, even upon storage under an inert atmosphere in the cold.[17] Consequently, the materials in this sequence were best stored at the phenolic stage (**9**), and the hydroxyquinones **10** were cyclized immediately after their formation.

The *ortho*-selectivity of the electron poor substrates *meta* to the allyl ether in the Claisen rearrangement made this sequence inefficient for the preparation of compounds such as **10f**. This was remedied by first reducing the ester to the electron-releasing hydroxymethyl group. Thus, reduction of the carbomethoxy allyl ether **11**[18] with $LiAlH_4$/THF (Scheme 2) and rearrangement of the resultant benzylic alcohol provided a separable mixture of the *para* and *ortho* allyl derivatives **12** and **12′** (Scheme 2) in a 3:1 ratio.[19] Selective protection of the phenol **12** as the benzyl ether and oxidation using the Corey protocol (MnO_2, NaCN, CH_3OH)[20] allowed reintroduction of the ester moiety in excellent overall yield. Subjection of **13** to the standard oxidative cleavage/reduction sequence followed by hydrogenolysis afforded adequate quantities of the 2-hydroxyethyl phenol **9f** for the cyclization study.

Scheme 2[a]



[a] (i) $LiAlH_4$, THF, 0 °C; (ii) $PhNEt_2$, heat (80% from **11**); (iii) BnCl, KOH, *n*-Bu_4NI, DMF; MnO_2, CH_2Cl_2; NaCN, CH_3OH, CH_3CO_2H, MnO_2 (83%); (iv) OsO_4, $NaIO_4$, acetone/Et_2O/H_2O; $NaBH_4$, CH_3OH, 0 °C; (v) H_2, Pd/C, EtOH (66% from **13**).

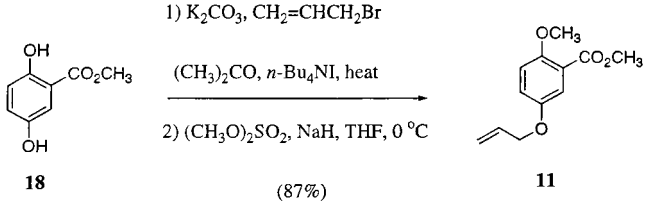
We were pleased to find that a 0.05 M solution of the 2-(2′-hydroxyethyl)quinone **10b** was smoothly cyclized to the corresponding dihydrobenzofuran **14b** upon treatment with a catalytic amount of PPTS (20 mol %) in the presence of DHQ (Table 2). The electron rich derivatives **10c** and **10d** generated dihydrobenzofurans **14c** and **14d**, respectively, though the cyclization of the 3-methoxy system was considerably faster (compare entries 3 and 4). The bromide **10e** and chloride **10j** afforded a mixture of the desired heterocycle and the 1,4-dihydroquinone (DH) from reduction (DH**10e** and DH**10j**, respectively) whereas the carbomethoxyquinone **10f** afforded only the reduction product DH**10f**. In some instances scrupulous exclusion of O_2 could eliminate this side reaction (entries 7 and 18).

Interestingly, the 2-methoxyquinone **10g** decomposed under the standard conditions (toluene, PPTS, DHQ, heat), but the use of dioxane solvent resulted in a sluggish reaction that eventually produced two products, the desired heterocycle **14g** and the dimer **15g**. This cyclization could be facilitated by increasing the amount of PPTS (1.2 equiv), though further increases in the acid concentration or deoxygenation did not affect the reaction distribution (compare entries 8−11). The 2-methyl compound, **10h**, behaved similarly but produced a cleaner reaction with no dimer formation. Highly electron rich systems such as the 2,5-dimethoxy derivative **10i** were difficult to manipulate, producing some dihydrobenzofuran materials while the majority of the sample was rapidly converted into intractable polar materials. In an

(16) (a) Bruce, J. M.; Roshan-Ali, Y. *J. Chem. Soc., Perkins Trans. 1* **1981**, 2677−2679. (b) White, W. N.; Slater, C. D. *J. Org. Chem.* **1961**, *26*, 3631−3638. (c) Marvel, C. S.; Higgins, N. A. *J. Am. Chem. Soc.* **1948**, *70*, 2218−2219.

(17) In practice, the hydroxyquinones were generated and cyclized on the same day to avoid material loss due to decomposition.

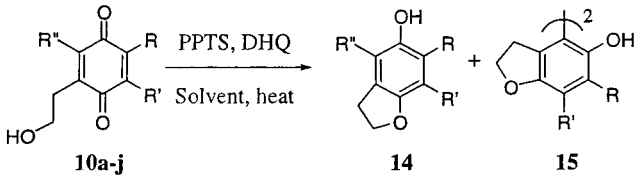
(18) Compound **11** was prepared from methyl 2,5-dihydroxybenzoate using a modification of the Harwood procedure (Harwood: L. M. *J. Chem. Soc., Chem. Commun.* **1983**, 530−532):



(19) The identity of the benzylic alcohol in rearrangement precursor effected the outcome of the Claisen reaction; the methoxymethyl (MOM) ether and the acetate ester afforded a 1.5:1 and 2:1 ratio of *para*:*ortho* products, respectively, indicating that even small electronic perturbations affect this ratio.

(20) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616−5617.

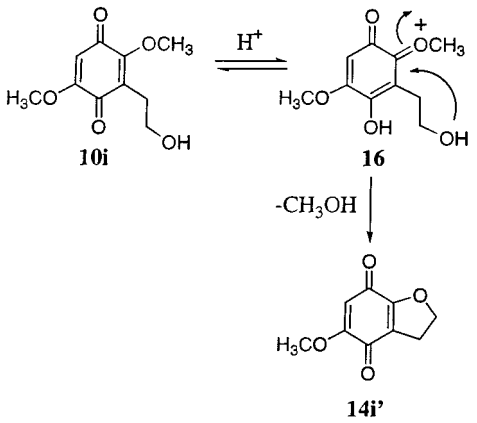
Table 2. Cyclization of Substituted 2-(2′-Hydroxyethyl)quinones under Acid Catalysis in the Presence of Dihydroquinone (DHQ)



10a-j **14** **15**

entry	subst	PPTS (equiv)	solvent	*t* (h)	**10** (%)	**14** (%)	**15** (%)
1	**10a**	0.2	$PhCH_3$	3	-	76	-
2	**10b**	0.2	$PhCH_3$	3	-	79	-
3	**10c**	0.2	$PhCH_3$	3	-	76	-
4	**10d**	0.2	$PhCH_3$	8	-	75	-
5	**10e**	0.2		6	20[a]	26	-
6	**10e**	1.2		6	-[b]	59	-
7	**10e**	1.2	$PhCH_3$[c]	2	-	73	-
8	**10g**	0.2		6	24	9	27
9	**10g**	1.2		3	-	12	49
10	**10g**	2.2		3	-	11	47
11	**10g**	2.2		3	-	11	35
12	**10h**	0.2		5	35	32	-
13	**10h**	1.2		5	4	70	-
14	**10h**	2.2		2.5	-	71	-
15	**10j**	0.2	$PhCH_3$	5	15[d]	5	-
16	**10j**	1.2	$PhCH_3$[c]	2	21[e]	17	-
17	**10j**	0.2	$PhCH_3$[c]	5	21[f]	52	-
18	**10j**	1.2	$PhCH_3$	2	-	57	-

[a] The reduction product, 2-bromo-5-(2′-hydroxy)ethyl-1,4-dihydroquinone (DH**10e**) was also isolated (30%). [b] DH**10e** was isolated (23%). [c] The solvent was degassed with N_2 prior to the reaction. [d] DH**10j** was also isolated (70%). [e] DH**10j** was also isolated (56%). [f] DH**10j** was also isolated (19%).



10i **16** **14i'**

Figure 3. Proposed reaction pathway for the cyclization of 2-(2′-hydroxyethyl)quinone **10i**.

effort to retard the decomposition, the reaction was run under deoxygenated conditions that provided the dihydrofuranoquinone **14i′** (42%) and a small quantity of impure **14i** (<2%). The cyclized quinone product arises from the protonated compound **16** by hydroxyl addition and loss of methanol (Figure 3).

The electronic properties of the 2-(2′-hydroxyethyl)-quinone substrates establish the HOMO/LUMO gap between the DHQ and control the resonance activation of the C-1 carbonyl, thereby determining the course of the cyclization reaction. Electron-donating groups at C-3 raise the ground-state energy of the LUMO (**10c** and **10d**), thus making the DHQ_{HOMO}/$\mathbf{10}_{LUMO}$ gap insurmountable. However, resonance activation of C-1 with intramolecular cyclization and formation of the oxonium ion **19** leads to an intermediate with a lower energy LUMO[21]

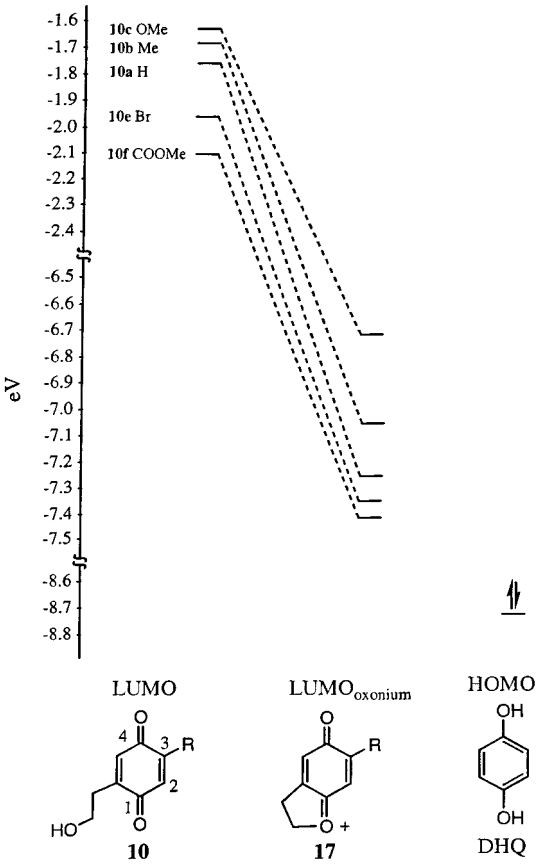


Figure 4. The lowering of the quionone LUMO upon oxonium formation. Data was generated from semiempirical calculations using a Spartan 5 program.

that enables electron transfer from the DHQ_{HOMO} (Figure 4). In contrast, the LUMO of haloquinones **10e** and **10j** is at a lower energy and enjoys a more favorable interaction with the DHQ_{HOMO} leading to the production of DH-**10e** and DH-**10j** (entries 5 and 15). The inductive activation of these systems is similar to **10g**, such that adding more than 1 equiv of acid allows protonation of C-1 and cyclization to **14e** and **14j** is observed (entries 6 and 16). Deoxygenated conditions greatly suppress the competitive reduction pathway, allowing good isolated yields of cyclized products to be realized (entries 7 and 18); it is possible that dissolved oxygen may function as a single electron-transfer agent that facilitates the reduction process. In the case of **10f**, the LUMO is substantially lower than the other systems such that rapid reduction to DH**10f** is observed under all of the aforementioned conditions.

Theoretically the competitive reduction of **10** to the dihydroquinone (entries 5, 6 and 15) could be eliminated if the energy of the $HOMO_{DHQ}$ was lowered. Using 2-chloro-1,4-dihydroquinone (DHCQ) in place of DHQ for the cyclization of **10e** afforded a complex reaction mixture from which the dihydrobenzofuran **14e** (30%) was isolated, but more importantly no DH**10e** was produced. The use of the more deactivated 2,5-dihydroxyacetophenone (DHAP) provided dihydrobenzofuran **14e** (42%) in a much cleaner but more sluggish reaction. After 6 h, a considerable amount of starting material (20%) remained, and

(21) All calculations used semiempirical level geometry optimizations with an AM1 model system and were run with a Spartan 5 program on a SGI workstation.

while longer reaction times failed to provide a significant increase in the yield of **10e**, no DH**10e** was observed. Application of DHAP to the cyclization of ester **10f** was not successful in producing the dihydrobenzofuran product. No reaction was observed at room temperature and heating in either toluene or dioxane led to rapid decomposition of the ester with no change in DHAP; the lack of activation at the C-1 carbonyl in **10f** may prohibit the formation of a reactive oxonium ion intermediate.

The dimeric product from the cyclization of **10g** is intriguing especially in light of our earlier work; all dimer formation from radical **6** was suppressed upon the addition of DHQ. The formation of **15g** must be kinetically favored and may be linked to the lifetime of the radical intermediate resulting from electron transfer to the oxonium ion. Compared to the vinylogous ketone systems (**10b** and **10h**), the C-4 carbonyl in **10g** should provide a higher energy α-radical because of its vinylogous ester nature. A slower addition of the second electron into the higher lying "ester" SOMO would prolong the lifetime of this intermediate and favor dimerization. This theory was tested using the 2-chloro substrate **10j**. The chloro substituent should increase the C-4 $C{=}O_{LUMO}$ energy and lessen the stabilization by the C-4 carbonyl even further than in **10g**, thereby favoring products derived from radical coupling.

Cyclization of **10j** provided several important results. After 5 h under standard conditions (0.2 equiv of PPTS, $PhCH_3$, Δ), the main pathway resulted from reduction to DH**10j** (65−70%). Very little cyclized product was observed, and starting material was recovered, even when the amount of PPTS was increased to 1.2 equiv. However, if the system was deoxygenated prior to heating, the cyclized material was produced as the major product (52%) and the amount of DH**10j** produced decreased substantially (19%). Increasing the amount of PPTS (1.2 equiv) provided essentially the same results (57%, **14j**) but the reaction time was halved (entry 18). Interestingly, no dimeric products were isolated in any of these reactions. This suggests that in electron deficient systems (**10e** and **10j**) adventitious O_2 may serve as a redox carrier between the quinone substrate **10** and the dihydroquinone additive. It also demonstrates that the formation of dimeric materials in the cyclization of **10g** is not solely determined by the nature of the substituent at C-2. More studies will be necessary to completely understand this phenomenon.

We have demonstrated a novel synthesis of dihydrobenzofuran products from readily available precursors using a reagent-based electrochemical transformation. We have also shown that by assessment of the reduction potentials of the hydroxyquinone and the added reducing agent, one can select for either cyclization or reduction over a range of potentials. While many systems can be cyclized under atmospheric conditions, the exclusion of oxygen can facilitate the cyclization of substrates with lower reduction potentials. The main advantage of this reagent-based system is the use of organic media as opposed to an aqueous system with added electrolyte. The utility of this method is limited by the availability of the dihydroquinone additive as well as by the substitution on the 2-(2′-hydroxyethyl)quinone; substrates such as **10f** failed under all conditions. This "biomimetic" route to dihydrobenzofuran heterocycles is well suited for neolignan natural product synthesis, and the results of these endeavors 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 ($PhCH_3$), methylene chloride (CH_2Cl_2), and diethylaniline (Et_2NPh) were distilled from calcium hydride. Dioxane was purified by percolation through an activated alumina column followed by refluxing with $NaBH_4$ and subsequent distillation. The pyridinium *p*-toluenesulfonate was recrystallized from EtOH. All other chemicals were purchased from Aldrich Chemical Company and were used as received except for allyl bromide that was distilled. Reaction progress was monitored by TLC using E. Merck silica gel 60 F-254. Solvents were removed on a Büchi rotary evaporator at reduced pressure (15−20 Torr).

The following compounds have been synthesized previously but were prepared according to our protocols for this publication; all analytical data correlated with that found in the literature references: **8a**,[22] **8c**,[23] **8c′**,[24] **8d** and **8d′**,[25] **8e** and **8e′**,[26] **8g**,[27] **9a**,[28] **10a**,[29] **10d**.[30]

General Procedure for Phenolic *O*-Allylation and Claisen Rearrangement: **Procedure A**. To a suspension of 0.17 g (4.20 mmol) of 60% NaH in THF (8.0 mL) at 0 °C was added a solution of 0.50 g (3.00 mmol) of phenol **7b** in THF (15.0 mL). The mixture was stirred for 30 min prior to the addition of 4.46 g (3.20 mmol) of allyl bromide. The mixture was allowed to warm to room temperature and, after 12 h, the reaction was quenched by the addition of sat. NH_4Cl solution. This mixture was extracted with Et_2O, and the organic phases were combined and washed with sat. brine. The organic solution was dried over Na_2SO_4, filtered, and concentrated in vacuo to leave a residue that was purified by SiO_2 chromatography (15% EtOAc/hexanes) to provide the allyl phenyl ether as an oil. **Procedure B**. To a solution of 1.0 g (8.06 mmol) of phenol **7a** in acetone (40 mL) was added 2.23 g (16.1 mmol) of solid K_2CO_3 and 0.60 g (1.61 mmol) of tetra-*n*-butylammonium iodide. This suspension was stirred as 1.46 g (12.1 mmol) of allyl bromide was added and the mixture was heated at reflux. After 12 h the mixture was cooled to room temperature and poured into H_2O. Extraction of this mixture with Et_2O, combination of the organic phases, and washing with sat. brine provided an organic solution that was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by SiO_2 chromatography (20% EtOAc/hexanes) to provide the allyl phenyl ether as an oil. **Claisen Rearrangement**. An 0.4 M solution of 1.0 g (4.80 mmol) of the allyl phenyl ether (from procedure A) in Et_2NPh was heated under a nitrogen atmosphere until the starting material had been consumed (3−4 h). The solution was diluted with Et_2O and then washed with 10% HCl solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to leave a residue that was purified over SiO_2 (20% EtOAc/hexanes) to provide the *o*-allyl phenol as an oil.

3,4-Dimethoxy-2-methyl-6-(2-propenyl)phenol (8b): R_f = 0.40 (30% EtOAc/hexanes). IR (neat) ν 3463 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.52 (s, 1H), 5.98 (dt, J = 18.0, 10.4, 6.5 Hz, 1H), 5.16 (br d, J = 18.0 Hz, 1H), 5.15 (br d, J = 10.8 Hz, 1H), 4.69 (s, 1H, exchanges with D_2O), 3.79 (s, 3H), 3.76 (s, 3H), 3.34

(22) Darling, S. D.; Willis, K. D. *J. Org. Chem.* **1967**, *32*, 2794−2796.
(23) Büchi, G.; Chu, P.-S. *J. Am. Chem. Soc.* **1981**, *103*, 2718−2721.
(24) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717−3719.
(25) Falshaw, C. P.; Lane, S. A.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1973**, 491−2.
(26) Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422−33.
(27) Royer, R.; Demerseman, P.; Rossignol, J. F.; Cheutin, A. *Bull. Soc. Chim. Fr.* **1971**, *6*, 2072−83.
(28) Lal, K.; Ghosh, S.; Salomon, R. G. *J. Org. Chem.* **1987**, *52*, 1072−78.
(29) Bruce, J. M.; Creed, D.; Dawes, K. *J. Chem. Soc. C* **1971**, 3749−56.
(30) Nakao, H.; Fukushima, M.; Torizuka, T. *Sankyo Kenkyusho Nempo* **1970**, *22*, 90−102.

(br d, J = 6.5 Hz, 2H), 2.15 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 146.6, 146.5, 136.5, 119.6, 119.2, 116.5, 111.5, 60.4, 56.3, 35.6, 9.0 ppm. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.88; H, 7.77.

Methyl 5-Hydroxy-2-methoxy-4-(2-propenyl)benzoate (8f): R_f = 0.25 (25% Et_2O/hexanes). IR (neat) ν 3421 br, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 6.72 (s, 1H), 6.03−5.92 (m, 1H), 5.48 (s, 1H, exchanges with D_2O), 5.15−5.08 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.42 (d, J = 6.1 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.6, 153.6, 147.3, 135.4, 132.3, 118.5, 118.0, 116.9, 114.6, 56.7, 52.1, 35.0 ppm. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.79; H, 6.27.

Methyl 3-Hydroxy-6-methoxy-2-(2-propenyl)benzoate (8*f′*): R_f = 0.35 (25% Et_2O/hexanes). IR (neat) ν 3421 br, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.68 ($AB_{quartet}$, J_{AB} = 9.0 Hz, 2H), 5.93−5.82 (m, 2H, 1H exchanges with D_2O), 5.05−4.99 (m, 2H), 3.86 (s, 3H), 3.69 (s, 3H), 3.29 (d, J = 6.1 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 169.0, 150.1, 148.2, 135.5, 124.5, 117.4, 116.0, 110.5, 56.4, 52.4, 32.1 ppm. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.76; H, 6.32.

2-Methyl-4-methoxy-6-(2-propenyl)phenol (8h): R_f = 0.30 (25% EtOAc/hexanes). IR (neat) ν 3464 br cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.59 (d, J = 3.0 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 6.04−5.93 (m, 1H), 5.15 (br d, J = 17.4 Hz, 1H), 5.14 (br d, J = 9.7 Hz, 1H), 4.69 (s, 1H), 3.73 (s, 3H), 3.36 (br d, J = 6.5 Hz, 2H), 2.21 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 153.2, 146.4, 136.4, 125.9, 125.4, 116.5, 114.5, 113.1, 55.6, 35.7, 16.3 ppm. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.95; H, 7.72.

2,4,5-Trimethoxy-6-(2-propenyl)phenol (8i): R_f = 0.32 (25% EtOAc/hexanes). IR (neat) ν 3447 br cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.42 (s, 1H), 6.05−5.94 (m, 1H), 5.58 (s, 1H, exchanges with D_2O), 5.02 (d, J = 17.1 Hz, 1H), 4.96 (d, J = 10.1 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.44 (d, J = 6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 145.4, 142.0, 141.5, 137.6, 136.4, 120.3, 114.3, 96.7, 60.7, 56.3, 56.0, 28.0 ppm. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.12; H, 6.98.

General Procedure for the Formation of β-Hydroxyethyl Phenols 9. To a solution of 0.250 g (1.20 mmol) of allyl phenyl ether **8a** in CH_2Cl_2 (6.0 mL) at 0 °C was added 0.182 g (1.80 mmol) of Et_3N followed by 0.38 g (1.44 mmol) of *tert*-butyldimethylsilyl triflate. The solution was allowed to warm to room temperature and after 2 h was diluted with Et_2O and washed with sat. brine. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by SiO_2 chromatography (10% EtOAc/hexanes) to yield a pale yellow oil. To a solution of 0.39 g (1.20 mmol) of the silyl ether in Et_2O (24 mL) was added 4.80 mL (0.24 mmol) of a 0.05 M solution of OsO_4 in acetone. The resulting dark brown solution was stirred for 10 min prior to the addition of H_2O (24 mL), and 2.57 g (12.0 mmol) of finely powdered $NaIO_4$ was added in 5 portions over a 5 h period. The tan slurry was stirred an additional 3 h and was then diluted with Et_2O followed by separation of the layers. The organic phase was washed with sat. brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product mixture was dissolved in CH_3OH (6.0 mL), cooled to 0 °C and treated with 0.14 g (3.60 mmol) of $NaBH_4$. After 30 min the excess hydride was quenched by the addition of 10% HCl, and the resultant mixture was extracted with Et_2O. The combined organic extracts were washed with sat. brine, dried (Na_2SO_4), filtered through a plug of SiO_2 (1.0 in.) over a pad of Celite, and concentrated in vacuo. This residue was dissolved in CH_2Cl_2 (6.0 mL), cooled to 0 °C, and 1.44 mL (1.44 mmol) of an 1.0 M solution of tetra-*n*-butylammonium fluoride in THF was added dropwise. This solution was warmed to room temperature for 1 h and then poured into sat. NH_4Cl solution. This mixture was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo to leave an oil that was purified by SiO_2 chromatography (50% EtOAc/hexanes) to provide 0.183 g of the β-hydroxyethyl phenol **9a** as a pale white solid.

3,4-Dimethoxy-6-(2′-hydroxy)ethyl-2-methylphenol (9b): mp = 74−76 °C; R_f = 0.30 (50% EtOAc/hexanes); IR (neat) ν 3401 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.49 (s, 1H), 5.20−4.30 (br s, 2H, exchanges with D_2O), 3.97 (t, J = 5.2 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.83 (t, J = 5.2 Hz, 2H), 2.19 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 147.5, 146.3, 145.9, 121.6, 120.3, 111.8, 64.3, 60.2, 56.1, 34.6, 9.2 ppm. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.24; H,7.61.

3,4-Dimethoxy-6- (2′-hydroxy)ethylphenol (9c): R_f = 0.13 (50% EtOAc/hexanes). IR (neat) ν 3170 br cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.57 (s, 1H), 6.53 (s, 1H), 3.96 (t, J = 5.0 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 2.82 (t, J = 5.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 149.4, 148.7, 142.5, 117.2, 114.5, 101.9, 65.0, 56.6, 55.9, 34.1 ppm. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.47; H, 7.07.

6-(2′-Hydroxy)ethyl-3-methyl-4-methoxyphenol (9d): R_f = 0.15 (30% EtOAc/hexanes); IR (neat) ν 3103 br cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.70 (s, 1H), 6.52 (s, 1H), 3.95 (t, J = 5.4 Hz, 2H), 3.75 (s, 3H), 2.83 (t, J = 5.4 Hz, 2H), 2.14 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) d 151.6, 148.6, 126.5, 123.8, 119.4, 113.0, 64.9, 56.0, 34.4, 15.8 ppm. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.74; H, 7.83.

3-Bromo-6-(2′-hydroxy)ethyl-4-methoxyphenol (9e): mp = 97−98 °C; R_f = 0.32 (70% EtOAc/hexanes); IR (neat) ν 3391 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10 (s, 1H), 6.60 (s, 1H), 3.97 (t, J = 5.4 Hz, 2H), 3.80 (s, 3H), 2.83 (t, J = 5.2 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 149.9, 149.8, 126.6, 121.9, 114.8, 110.1, 64.6, 57.0, 34.5 ppm. Anal. Calcd for $C_9H_{11}BrO_3$: C, 43.75; H, 4.49. Found: C, 43.59; H, 4.59.

2,4-Dimethoxy-6-(2′-hydroxy)ethylphenol (9g): R_f = 0.21 (50% EtOAc/hexanes). IR (neat) ν 3430 br cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.39 (d, J = 2.9 Hz, 1H), 6.28 (d, J = 2.9 Hz, 1H), 6.16 (br s, 1H), 3.85 (t, J = 6.1 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.88 (t, J = 6.1 Hz, 2H), 2.71 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 152.9, 147.5, 138.0, 125.2, 106.2, 97.7, 63.0, 55.9, 55.7, 34.1 ppm. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.55; H, 7.11.

6-(2′-Hydroxy)ethyl-2-methyl-4-methoxyphenol (9h): R_f = 0.34 (50% EtOAc/hexanes). IR (neat) ν 3392 br cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (br s, 1H, exchanges with D_2O), 6.59 (d, J = 3.0 Hz, 1H), 6.46 (d, J = 3.0 Hz, 1H), 3.94 (t, J = 5.0 Hz, 2H), 3.72 (s, 3H), 2.82 (t, J = 5.0 Hz, 2H), 2.52 (br s, 1H, exchanges with D_2O), 2.23 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 152.8, 147.4, 127.1, 126.7, 114.8, 113.6, 64.8, 55.7, 34.7, 16.6 ppm. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.64; H, 7.70.

6-(2′-Hydroxy)ethyl-2,4,5-trimethoxyphenol (9i): R_f = 0.18 (50% EtOAc/hexanes). IR (neat) ν 3434 br cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.56 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.66 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 149.2, 147.4, 145.5, 142.6, 123.2, 101.5, 65.2, 64.0, 59.8, 59.5, 31.2 ppm. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.88; H, 7.06.

General Procedure for the Formation of 2-(2′-Hydroxyethyl)-1,4-benzoquinones (10). To a solution of 0.47 mmol of phenol **9** in CH_3CN (4.7 mL) was added 1.03 mL (1.03 mmol) of a 1.0 M solution of ceric ammonium nitrate. After 5 min, the reaction mixture was diluted with Et_2O, the layers were separated, and the organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was immediately purified by SiO_2 chromatography (60% EtOAc/hexanes) to provide the labile 1,4-benzoquinones **10** as orange oils.

6-(2′-Hydroxyethyl)-3-methoxy-2-methyl-1,4-benzoquinone (10a): R_f = 0.39 (70% EtOAc/hexanes); IR (neat) ν 3471 br, 1650, 1610 cm^{-1}; ^{1}H NMR (CD_3OD) 6.50 (t, J = 1.4 Hz, 1H), 3.97 (s, 3H), 3.69 (t, J = 6.5 Hz, 2H), 2.61 (dt, J = 6.5, 1.4 Hz, 2H), 1.9 (s, 3H) ppm; ^{13}C NMR (CD_3OD) 189.4, 184.8, 156.9, 147.3, 133.4, 129.8, 61.2, 61.0, 33.5, 8.8 ppm.

2-(2′-Hydroxyethyl)-1,4-benzoquinone (10b): R_f = 0.35 (70% EtOAc/hexanes); IR (neat) ν 3247 br, 1694, 1655 cm^{-1}; ^{1}H NMR (CD_3OD) 6.80−6.66 (m, 3H), 3.71 (t, J = 6.1 Hz, 2H), 2.62 (dt, J = 6.5, 1.1 Hz, 2H) ppm; ^{13}C NMR (CD_3OD) 189.2, 188.7, 147.6, 138.0, 137.4, 135.0, 60.8, 33.4 ppm.

2-(2′-Hydroxyethyl)-5-methoxy-1,4-benzoquinone (10c): R_f = 0.22 (70% EtOAc/hexanes); IR (neat) ν 3334 br, 1666, 1642 cm^{-1}; ^{1}H NMR (CD_3OD) 6.60 (s, 1H), 6.02 (s, 1H), 3.81 (s, 3H), 3.70 (t, J = 6.5 Hz, 2H), 2.62 (br t, J = 6.5 Hz,

2H) ppm; ^{13}C NMR (CD_3OD) 188.9, 183.5, 160.3, 148.3, 133.2, 108.6, 61.0, 33.4 ppm.

2-(2′-Hydroxyethyl)-5-methyl-1,4-benzoquinone (10d): R_f = 0.22 (70% EtOAc/hexanes); IR (neat) ν 3483 br, 1652 cm^{-1}; ^{1}H NMR (CD_3OD) 6.64 (br s, 1H), 6.62 (br s, 1H), 3.70 (t, J = 6.5 Hz, 2H), 2.60 (dt, J = 6.5, 1.4 Hz, 2H), 2.00 (s, 3H) ppm.

5-Bromo-2-(2′-hydroxyethyl)-1,4-benzoquinone (10e): R_f = 0.24 (50% EtOAc/hexanes); IR (neat) ν 3525 br, 1654, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.26 (s, 1H), 6.85 (s, 1H), 3.81 (t, J = 6.0 Hz, 2H), 3.39 (br s, 1H, exchanges with D_2O), 2.66 (br t, J = 6.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) 185.1, 179.5, 146.7, 138.2, 137.4, 133.5, 60.5, 32.2 ppm.

2-(2′-Hydroxyethyl)-5-methylcarboxylate-1,4-benzoquinone (10f): R_f = 0.33 (70% EtOAc/hexanes); IR (neat) ν 3423 br, 1739, 1663 cm^{-1}; ^{1}H NMR (CD_3OD) 6.83 (s, 1H), 6.71 (s, 1H), 3.67 (t, J = 6.3 Hz, 2H), 3.34 (s, 3H), 2.55 (t, J = 6.5 Hz, 2H) ppm.

2-(2′-Hydroxyethyl)-6-methoxy-1,4-benzoquinone (10g): R_f = 0.24 (70% EtOAc/hexanes); IR (neat) ν 3493 br, 1676, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.63 (br s, 1H), 5.90 (d, J = 2.2 Hz, 1H), 3.83 (m, 5H), 2.71 (t, J = 6.1 Hz, 2H), 2.01 (br s, 1H, exchanges with D_2O) ppm; ^{13}C NMR ($CDCl_3$) 187.3, 182.2, 158.7, 144.0, 134.6, 107.6, 60.5, 32.2 ppm.

2-(2′-Hydroxyethyl)-6-methyl-1,4-benzoquinone (10h): R_f = 0.23 (50% EtOAc/hexanes); IR (neat) ν 3485 br, 1657, 1614 cm^{-1}; ^{1}H NMR (CD_3OD) 6.60−6.57 (m, 2H), 3.71 (t, J = 6.0 Hz, 2H), 2.63 (br t, J = 6.0 Hz, 2H), 2.03 (s, 3H) ppm; ^{13}C NMR (CD_3OD) 189.2, 188.8, 147.7, 147.6, 134.9, 133.9, 60.9, 33.6, 16.0 ppm.

3,6-Dimethoxy-2-(2′-hydroxyethyl)-1,4-benzoquinone (10i): R_f = 0.21 (70% EtOAc/hexanes); IR (neat) ν 3485 br, 1651, 1602 cm^{-1}; ^{1}H NMR (CD_3OD) 5.86 (s, 1H), 4.04 (s, 3H), 3.80 (s, 3H), 3.57 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 6.8, 2H) ppm; ^{13}C NMR (CD_3OD) 184.7, 183.9, 160.3, 158.4, 127.3, 106.6, 62.0, 61.1, 57.1, 27.6 ppm.

6-Chloro-2-(2′-hydroxyethyl)-1,4-benzoquinone (10j): R_f = 0.25 (50% EtOAc/hexanes); IR (neat) ν 3511 br, 1675, 1657 cm^{-1}; ^{1}H NMR (CD_3OD) 7.03 (br s, 1H), 6.70 (br s, 1H), 3.73 (t, J = 6.1 Hz, 2H), 2.68 (t, J = 6.1, 2H) ppm; ^{13}C NMR (CD_3OD) 186.5, 180.8, 147.7, 145.1, 135.2, 134.5, 60.6, 34.0 ppm.

General Procedure for the Formation of 2,3-Dihydrobenzofurans (14). To a solution of 98 mg (0.50 mmol) of hydroxyquinone **10a** in $PhCH_3$ (10.0 mL) was added 25 mg (0.10 mmol) of PPTS followed by 55 mg (0.50 mmol) of DHQ, and the reaction mixture was refluxed under a nitrogen atmosphere. The solution was concentrated and purified using flash chromatography (20 g of SiO_2, 15% EtOAc/hexanes) to provide 71 mg (79%) of the dihydrobenzofuran **14a** as a pale yellow oil.

2,3-Dihydro-5-hydroxybenzofuran (14a): mp = 106−107 °C; R_f = 0.51 (50% EtOAc/hexanes); IR (neat) ν 3334 br, 1605, 1489, 1128, 811 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.70 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 6.55 (dd, J = 8.5, 2.2, 1H), 5.09 (br s, 1H, exchanges with D_2O), 4.52 (t, J = 8.6 Hz, 2H), 3.14 (t, J = 8.6 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 153.9, 149.6, 128.1, 114.1, 112.4, 109.3, 71.3, 30.1 ppm. Anal. Calcd for $C_8H_8O_2$: C, 70.58; H, 5.92. Found: C, 70.60; H, 5.94.

2,3-Dihydro-5-hydroxy-6-methoxy-7-methylbenzofuran (14b): R_f = 0.54 (50% EtOAc/ Hexanes). IR (neat) ν 3426 br, 1474, 1240, 1092, 832 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.68 (s, 1H), 5.31 (s, 1H), 4.51 (t, J = 8.6, 2H), 3.76 (s, 3H), 3.14 (t, J = 8.6 Hz, 2H), 2.16 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 152.1, 144.6, 142.6, 121.3, 112.8, 108.4, 71.0, 60.9, 30.4, 9.40 ppm. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.55; H, 6.67.

2,3-Dihydro-5-hydroxy-6-methoxybenzofuran (14c): R_f = 0.46 (50% EtOAc/hexanes). IR (neat) ν 3402 br, 1502, 1461, 1320, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.76 (s, 1H), 6.40 (s, 1H), 5.22 (br s, 1H, exchanges with D_2O), 4.50 (t, J = 8.6 Hz, 2H), 3.81 (s, 3H), 3.10 (t, J = 8.6 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 153.3, 145.9, 139.5, 117.7, 110.6, 94.1, 71.5, 56.2, 29.9 ppm. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.93; H, 6.35.

2,3-Dihydro-5-hydroxy-6-methylbenzofuran (14d): R_f = 0.51 (50% EtOAc/hexanes). IR (neat) ν 3321 br, 2920, 1439, 1265, 1183, 1005, 868 cm^{-1}; ^{1}H NMR (CD_3OD) δ 6.61 (s, 1H), 6.44 (s, 1H), 4.41 (t, J = 8.6 Hz, 2H), 3.07 (t, J = 8.6 Hz, 2H), 2.10 (s, 3H) ppm; ^{13}C NMR (CD_3OD) δ 156.9, 152.6, 128.3, 127.1, 115.0, 114.1, 74.5, 33.5, 19.0 ppm. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.69; H, 6.58.

2,3-Dihydro-6-bromo-5-hydroxybenzofuran (14e): R_f = 0.47 (50% EtOAc/hexanes). IR (neat) ν 3297 br, 1531, 1491, 1235, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.86 (s, 1H), 6.85 (s, 1H), 5.10 (br s, 1H, exchanges with D_2O), 4.52 (t, J = 8.6 Hz, 2H), 3.12 (t, J = 8.6 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 154.2, 146.2, 128.4, 112.2, 111.7, 107.7, 71.7, 29.9 ppm. Anal. Calcd for $C_8H_7BrO_2$: C, 44.68; H, 3.28. Found: C, 44.93; H, 3.36.

Methyl 2,3-Dihydro-5-hydroxybenzofuran-6-yl carboxylate (14f): R_f = 0.42 (70% EtOAc/hexanes). IR (neat) ν 3419 br, 2956, 1674, 1625, 1443, 1225, 1053 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.19 (s, 1H), 6.73 (s, 1H), 3.90 (s, 3H), 3.76 (t, J = 6.8 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H) ppm; ^{13}C NMR (CD_3OD) δ 171.6, 156.0, 149.2, 137.3, 120.0, 115.0, 111.4, 62.4, 52.6, 35.3 ppm. Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.60; H, 5.54.

2,3-Dihydro-5-hydroxy-7-methoxybenzofuran (14g): R_f = 0.43 (50% EtOAc/hexanes). IR (neat) ν 3406 br, 2958, 1626, 1456, 1344, 1189, 1085 cm^{-1}; ^{1}H NMR (CD_3OD) d 6.28 (br s, 1H), 6.25 (br s, 1H), 4.47 (t, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.10 (t, J = 8.6 Hz, 2H) ppm; ^{13}C NMR (CD_3OD) d 155.6, 148.2, 145.2, 132.2, 107.2, 103.5, 74.8, 59.1, 34.1 ppm. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.31; H, 5.86.

2,3-Dihydro-5-hydroxy-7-methylbenzofuran (14h): R_f = 0.40 (50% EtOAc/hexanes). IR (neat) ν 3416 br, 1631, 1479, 1197, 935 cm^{-1}; ^{1}H NMR (CD_3OD) δ 6.47 (s, 1H), 6.34 (s, 1H), 4.43 (t, J = 8.6 Hz, 2H), 3.08 (t, J = 8.6 Hz, 2H), 2.07 (s, 3H) ppm; ^{13}C NMR (CD_3OD) δ 152.9, 152.0, 128.2, 120.4, 116.2, 110.3, 71.7, 31.4, 15.4 ppm. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.86; H, 6.97.

2,3-Dihydro-5-methoxy-benzofurano-4,7-quinone (14i′): R_f = 0.24 (70% EtOAc/hexanes). IR (neat) ν 1650, 1627, 1582, 1410, 1249, 1054 cm^{-1}; ^{1}H NMR (CD_3OD) δ 5.74 (s, 1H), 4.83 (t, J = 9.7 Hz, 2H), 3.90 (s, 3H), 2.98 (t, J = 9.7 Hz, 2H) ppm; ^{13}C NMR (CD_3OD) δ 183.2, 176.5, 167.8, 162.8, 116.4, 103.7, 76.8, 57.8 ppm. Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.29; H, 4.26.

3-Bromo-6-(2′-hydroxy)ethyl-1,4-dihydrobenzoquinone (DH10e): R_f = 0.13 (50% EtOAc/hexanes). IR (neat) ν 3321 br, 1501, 1433, 1194, 1032, 801 cm^{-1}; ^{1}H NMR (CD_3OD) δ 6.86 (s, 1H), 6.67 (s, 1H), 3.71 (t, J = 6.8 Hz, 2H), 2.72 (t, J = 6.8 Hz, 2H) ppm; ^{13}C NMR (CD_3OD) δ 150.2, 147.9, 127.5, 119.9, 108.0, 62.8, 34.8 ppm. Anal. Calcd for $C_8H_9BrO_3$: C, 41.23; H, 3.89. Found: C, 41.47; H, 3.84.

5,5′-Dihydroxy-7,7′-dimethoxy-4,4′-bi-2,2′,3,3′-dihydrobenzofuran (15g): R_f = 0.23 (50% EtOAc/hexanes). IR (neat) ν 3450 br, 1625, 1214, 1090, 934 cm^{-1}; ^{1}H NMR (CD_3OD) δ 6.38 (s, 2H), 4.53−4.41 (m, 4H), 3.81 (s, 6H), 3.14−3.05 (m, 2H), 2,81−2.72 (m, 2H) ppm; ^{13}C NMR (CD_3OD) δ 150.1, 145.0, 142.3, 130.4, 113.8, 101.5, 72.5, 56.7, 31.4 ppm. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.46; H, 5.59.

3-Hydroxymethyl-4-methoxy-6-(2-propenyl)phenol (12). To a stirred, ice-cold suspension of 0.171 g (4.5 mmol) of $LiAlH_4$ in THF (9.0 mL) was added a solution of 0.50 g (2.25 mmol) of methyl benzoate **11** as a solution in THF (11.3 mL). This mixture was stirred for 1 h, and the reaction was quenched by dropwise addition of H_2O (3 mL), MeOH (9 mL), and H_2O (3 mL). The suspension was then slowly poured into excess ice-cold 10% HCl solution to dissolve the precipitated aluminum hydroxide and stirred for a period of 1 h. The organic layer was separated, dried (Na_2SO_4), and filtered through a Celite pad, and the removed solids were washed thoroughly with Et_2O. The filtrate was concentrated, and the residue was separated using flash chromatography (90 g of SiO_2, 25% EtOAc/hexanes) to provide 0.407 g (93%) of the benzylic alcohol as a clear liquid. This material was dissolved in diethylaniline (3.5 mL) and rearranged according to the protocol above to provide 0.263 g (65%) of phenol **12** and 0.087 g (21%) of the

regioisomeric phenol **12′** as oils. Phenol **12** (major): $R_f = 0.22$ (50% EtOAc/hexanes). IR (neat) ν 3353 br, 1509, 1413, 1206, 1038, 863 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.81 (s, 1H), 6.64 (s, 1H), 5.97 (m, 2H), 5.02 (br d, $J = 17.8$ Hz, 1H), 4.98 (br d, $J = 10.4$ Hz, 1H), 4.53 (s, 2H), 3.75 (s, 3H), 3.32 (d, $J = 6.8$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 151.6, 149.5, 138.4, 129.3, 127.1, 116.3, 115.3, 113.6, 60.2, 56.4, 35.2 ppm. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.96; H, 7.25. Phenol **12′** (minor): $R_f = 0.28$ (50% EtOAc/hexanes). IR (neat) ν 3339 br, 1490, 1440, 1272, 1218, 806 cm^{-1}; ^1H NMR (CD_3OD) δ 6.71 ($AB_{quartet}$, $J_{AB} = 8.6$ Hz, $\varnothing\nu = 15.1$ Hz, 2H), 5.96 (m, 1H), 4.93−4.86 (m, 2H), 4.63 (s, 2H), 3.75 (s, 3H), 3.52 (dt, $J = 5.9$, 1.8 Hz, 2H) ppm; ^{13}C NMR (CD_3OD) δ 153.1, 150.3, 138.5, 129.3, 128.2, 115.9, 114.7, 111.0, 56.7, 56.3, 31.1 ppm. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.99; H, 7.18.

Methyl 5-Benzyloxy-2-methoxy-4-(2-propenyl)benzoate (13). To a solution of 25 mg (0.129 mmol) of phenol **12** in DMF (0.64 mL) were added 15 mg (0.116 mmol) of BnCl, 10 mg (0.026 mmol) of Bu_4NI, and 0.039 mL of 3.0 N KOH solution. The suspension was stirred for a period of 18 h and then diluted with 5 mL of Et_2O and dried (Na_2SO_4). The solids were removed by filtration through a Celite pad and washed with copious amounts of Et_2O. The filtrate was concentrated and the residue purified using flash chromatography (7 g of SiO_2, 20% EtOAc/hexanes) to yield 34 mg (94%) of the benzylic alcohol as an oil. To a solution of 32 mg (0.113 mmol) of the benzylic alcohol in CH_2Cl_2 (1.1 mL) was added 196 mg (2.25 mmol) of activated MnO_2. The resulting suspension was stirred for 10 h, and the oxidant was removed by filtration through a Celite pad. The filtrate was concentrated in vacuo, the residue was dissolved in CH_3OH (2.8 mL), and the following reagents were added sequentially: 28 mg (0.563 mmol) of NaCN, 0.02 mL (16 mol %) of acetic acid, and 196 mg (2.25 mmol) of activated MnO_2. This mixture was stirred for 20 h and the solids were removed by filtration through a Celite pad. The filtrate was concentrated and the residue purified via flash chromatography (7 g of SiO_2, 20% EtOAc/hexanes) to yield 28 mg (88%) of the methyl benzoate **13** as an oil. $R_f = 0.31$ (25% EtOAc/hexanes). IR (neat) ν 3065 br, 1729, 1612, 1244, 1075, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45−7.26 (m, 6H), 6.84 (s, 1H), 6.06−5.94 (m, 1H), 5.13−5.08 (m, 2H), 5.05 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.47 (d, $J = 6.5$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.2, 153.7, 149.6, 136.5, 135.6, 135.3, 128.3, 127.6, 127.1, 117.4, 116.2, 114.6, 114.5, 70.5, 56.5, 51.7, 34.3 ppm. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.73; H, 6.43.

Methyl 4-(2′-Hydroxy)ethyl-5-hydroxy-2-methoxybenzoate (9f). To a solution of 200 mg (0.64 mmol) of the benzyl ether **13** in Et_2O (3.2 mL) was added 2.56 mL of 0.05 M OsO_4 solution in acetone. The resulting dark brown solution was stirred for 10 min prior to the addition of 3.2 mL of distilled H_2O and 1.37 g (6.4 mmol) of finely powdered $NaIO_4$ was added in 5 portions over a period of 5 h period. The temperature was maintained at 24−26 °C, and the tan slurry was stirred for an additional 5 h during which period the initially dark brown reaction mixture changed to pale yellow. The slurry was diluted with Et_2O, and the layers were separated. The organic phase was washed with brine, dried (Na_2SO_4), filtered through a pad of 1 in. silica gel over Celite, and finally concentrated in vacuo. The crude mixture was then dissolved in CH_3OH (3.2 mL), cooled to 0 °C, and treated with 73 mg (1.92 mmol) of $NaBH_4$. After 30 min the excess hydride was quenched by the addition of 10% HCl, and the resultant mixture was extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated. To a solution of the crude residue in EtOH (3.2 mL) was added 64 mg (64 mmol) of 10% Pd/C catalyst and then stirred over a hydrogen atmosphere for 16 h. The catalyst was filtered off using a Celite pad, and the filtrate was concentrated in vacuo and further purified using flash chromatography (30 g of SiO_2, 50% EtOAc/hexanes) to yield 96 mg (66% overall) of the phenol **9f** as an oil. $R_f = 0.16$ (50% EtOAc/hexanes). IR (neat) ν 3433 br, 1709, 1610, 1511, 1267, 1075, 1057, 889 cm^{-1}; ^1H NMR (CD_3OD) δ 7.19 (s, 1H), 6.89 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.77 (t, $J = 6.8$ Hz, 2H), 2.86 (t, $J = 6.8$ Hz, 2H) ppm; ^{13}C NMR (CD_3OD) δ 168.3, 154.1, 150.2, 133.7, 119.2, 118.3, 117.1, 62.6, 57.2, 52.3, 35.3 ppm. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.34; H, 6.13.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR and IR spectra are available free of charge via the Internet at http://pubs.acs.org.

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