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A Novel Construction of Dibenzofuran-1,4-diones by Oxidative Cyclization of Quinone-arenols

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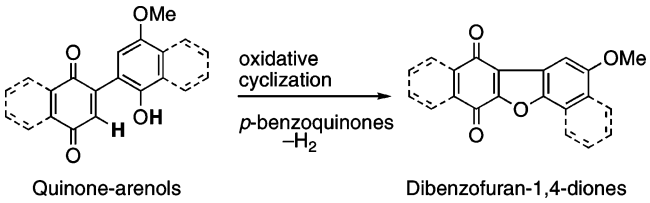
ABSTRACT



A novel oxidative cyclization of quinone-arenols 5 leading to products 6 with a dibenzofuran-1,4-dione structure, which forms the core of several natural products, has been developed and applied to the synthesis of violet-quinone (4).

Heterocyclic ring-fused quinone systems are found in many biologically and pharmacologically active compounds.[1] Among them, the dibenzofuran-1,4-dione core **1** is found in several natural products of biological importance, such as cytotoxic popolohuanone E (**2**),[2] antipruritic balsaminone A (**3**),[3] violet-quinone (**4**),[4] and other natural quinones.[5] (Figure 1). The biological activities of corresponding synthetic compounds have also been examined.[6] Several methods have been reported for the construction of the structure **1** by cyclization of 2,2′-biquinones,[7] coupling reaction of dichloroquinones with phenols,[6,8] transition metal-mediated cyclization,[9] and lithiation-mediated cyclization.[10] In addition, much effort has been directed to the synthesis of cytotoxic popolohuanone E (**2**),[7c,8b,c] and the 8-*O*-methyl derivative of **2** was synthesized by Katoh et al.[8c] However, synthesis of **2** itself has not yet been accomplished.

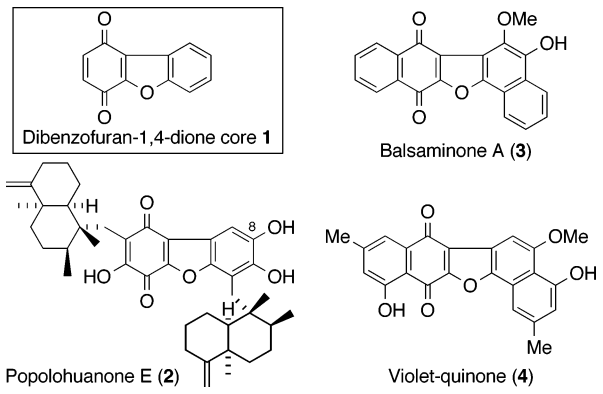


Figure 1. Natural products having a dibenzofuran-1,4-dione core.

† Deceased, June 19, 2006.

(1) Cheng, C. C. *Progress of Medicinal Chemistry*; Ellia, G. P., West, G. B., Eds.; Elsevier: Amsterdam, The Netherlands, 1988; Vol. 25, pp 35−83.
(2) Carney, J. R.; Scheuer, P. J. *Tetrahedron Lett.* **1993**, *34*, 3727−3730.
(3) Ishiguro, K.; Ohira, Y.; Oku, H. *J. Nat. Prod.* **1998**, *61*, 1126−1129.
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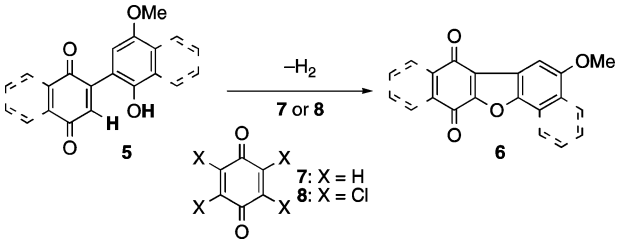
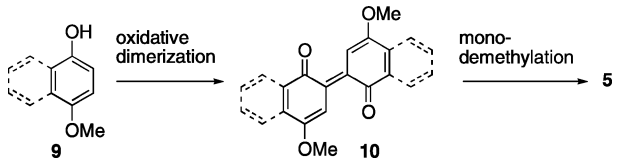
In the course of our research aimed at synthesizing **2**−**4**, we sought an efficient method for the construction of the core structure **1**. Herein, we report a novel oxidative cyclization of quinone-arenols **5** with benzo-1,4-quinone (**7**) or chloranil (**8**) in the presence of molecular oxygen (O_2), leading to cyclization products **6** having the dibenzofuran-1,4-dione core structure **1** (Scheme 1). This cyclization reaction was also applied to an efficient synthesis of **4**.

Scheme 1. Oxidative Cyclization of Quinone-arenols **5**



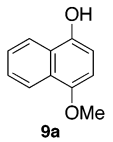
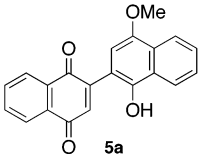
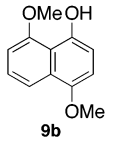
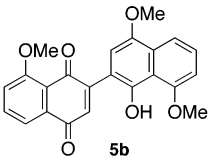
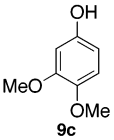
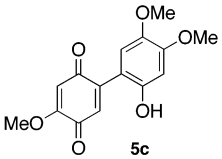
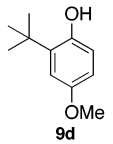
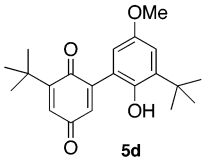
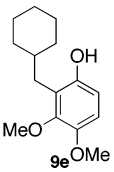
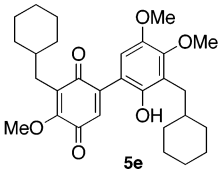
Our research began with preparation of the starting 2,2′-quinonearenols **5** via a two-step sequence involving oxidative dimerization of hydroquinone monomethyl ethers **9** and monodemethylation of the resulting [2,2′]arenylidene-1,1′-diones **10** (Scheme 2, Table 1).[7b,11,12] Thus, the 2,2′-

Scheme 2. Preparation of Quinone-arenols **5**



quinonenaphthols **5a** and **5b** were readily prepared by oxidative dimerization of the corresponding 1-naphthols **9a** and **9b** with benzoquinone (**7**) and chloranyl (**8**), respectively,

Table 1. Preparation of Quinone-arenols **5** from Hydroquinone Monomethylethers **9**

entry	hydroquinone monomethyl ether **9**	conditions	quinone-arenol **5**
1	 **9a**	1) **7** (99%) 2) SnO_2 (96%)	 **5a**
2	 **9b**	1) **8** 2) SnO_2 (84%, 2 steps)	 **5b**
3	 **9c**	1) $K_3[Fe(CN)_6]$ Na_2CO_3 (40%) 2) SnO_2 (97%)	 **5c**
4	 **9d**	1) Ag_2O Et_3N SiO_2 (95%) 2) *hν* (96%)	 **5d**
5	 **9e**	1) Ag_2O Et_3N 2) SnO_2 (55%, 2 steps)	 **5e**

followed by *O*-monodemethylation of the [2,2′]binaphthalenylidene-1,1′-diones **10a** and **10b** with SnO_2 (entries 1 and 2). Similarly, [2,2′]biphenyl-1,4-diones **5c**−**e** were also prepared from the corresponding phenols **9c**−**e** (entries 3−5) (see Supporting Information).[13]

With the substrates **5a**−**e** in hand, we next examined the key oxidative cyclization of **5** using benzoquinone (**7**) or chloranyl (**8**) as an oxidant (Scheme 1, Table 2). After screening various solvents and temperatures for cyclization of **5a**, the best result was obtained by heating in toluene with **7**. Thus, the quinone-naphthol **5a**, on heating with **7** (1.1 equiv) in toluene at 100 °C under argon, underwent oxidative cyclization with consumption of **7** to give **6a** in 76% yield along with some polymeric precipitates (entry 1). To clarify hydroquinone formation from benzoquinone (**7**) during the reaction, the reaction mixture was treated with acetic anhydride (Ac_2O) in the presence of $Mg(ClO_4)_2$[14] to furnish hydroquinone diacetate in 80% yield from **7**. This result shows that **7** acts as an oxidant, accepting two hydrogen

(7) (a) Buchan, R.; Musgrave, O. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 90−92. (b) Ogata, T.; Okamoto, I.; Kotani, E.; Takeya, T. *Tetrahedron* **2004**, *60*, 3941−3948. (c) Anderson, J. C.; Denton, R. M.; Wilson, C. *Org. Lett.* **2005**, *7*, 123−125.

(8) (a) Shand, A. J.; Thomson, R. H. *Tetrahedron* **1963**, *19*, 1919−1937. (b) Ueki, Y.; Itoh, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 5719−5722. (c) Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. *Org. Lett.* **2001**, *3*, 2701−2704.

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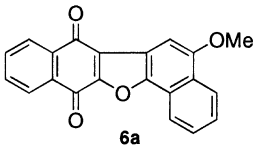
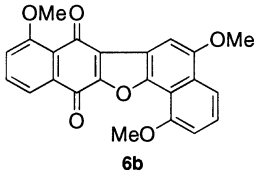
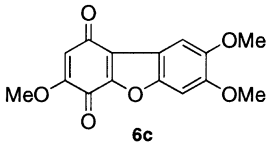
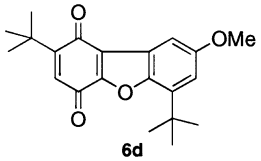
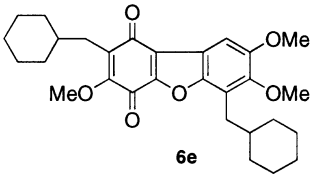
(11) (a) Takeya, T.; Otsuka, T.; Okamoto, I.; Kotani, E. *Tetrahedron* **2004**, *60*, 10681−10693. (b) Takeya, T.; Kondo, H.; Otsuka, T.; Doi, H.; Okamoto, I.; Kotani, E. *Chem. Pharm. Bull.* **2005**, *53*, 199−206.

(12) Hewgill, F. R.; Greca, B. L.; Legge, F.; Roga, P. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 131−134.

(13) The intermediate **10c** for the preparation of **5c** was obtained in only 40% yield by oxidative dimerization, crystallization, and collection by filtration. The low yield may be due to low crystallinity of **10c**.

(14) Chakraborti, A. K.; Sharma, L.; Gulhane, R.; Shivani, S. *Tetrahedron* **2003**, *59*, 7661−7668.

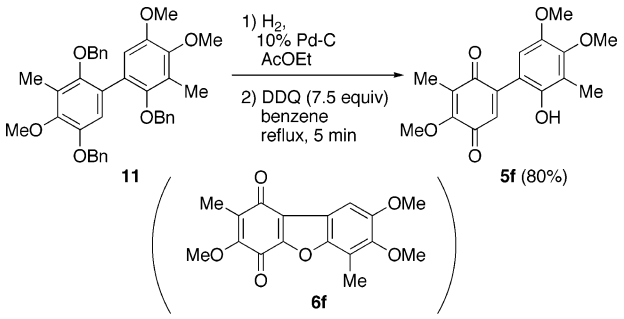
Table 2. Oxidative Cyclization of Quinone-arenols **5a**−**e** Leading to Dibenzofuranquinones **6a**−**e**[a]

Entry	Conditions	Yield (%)	Product
1	**5a**, **7**, 3 h[b]	76	 **6a**
2	**5a**, **7**, 3 h	84	
3	**5a**, **8**, 2 h	54	
4	**5b**, **7**, 2.5 days	60[c]	 **6b**
5	**5b**, **8**, 2.5 days	97	
6	**5c**, **7**, 4 days	56[d]	 **6c**
7	**5c**, **8**, 5 days	80	
8	**5d**, **7**, 20 h	77	 **6d**
9	**5d**, **8**, 20 h	91	
10	**5e**, **7**, 5 days	68	 **6e**
11	**5e**, **8**, 4 days	94	
12	**5e**, DDQ, 1 h	34	

[a] Unless otherwise noted, all reactions were carried out by using substrate (1 mmol), benzoquinone (**7**), or chloranil (**8**) (1.1 equiv) in O_2-saturated toluene at 100 °C in a sealed tube. [b] The reaction was conducted under an argon atmosphere. [c] The starting material **5b** (40%) was recovered. [d] The starting material **5c** (32%) was recovered.

atoms from **5a**. Next, a similar reaction was conducted in the presence of O_2. The use of O_2 resulted in an improvement of the yield of **6a** (84%) and prevented the formation of undesired polymeric precipitates (entry 2). In addition, hydroquinone diacetate (62%) was again obtained by exposure of the reaction mixture to Ac_2O. Although the exact role of O_2 remains unclear, O_2 might partially act for recycling benzoquinone (**7**) and for preventing the undesired polymerization of **5a**. The reaction of **5a** with chloranil (**8**) was less clean, giving **6a** in 54% yield (entry 3). Cyclization of **5b** was examined under similar conditions (entries 4 and 5). Although the cyclization of **5b** required a prolonged reaction time, reaction with **8** afforded an excellent yield (97%) of **6b** (entry 5). We next applied our method to **5c**−**e** as shown in entries 6−11. In all cases, the cyclizations proceeded to afford the corresponding dibenzofuranquinones **6a**−**c** in good to high yields. In addition, entries 6−11 show that the use of **8** gave better results than in the case of **7** (entries 7, 9, and 11 versus entries 6, 8, and 10). It should be noted that **6e** has a substituent pattern similar to that of popolohuanone E (**2**).[8b] In contrast to the high-yield formation of **6e**, it was reported that debenzylation of **11** followed by oxidation with a large excess of 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) in a short time gave the quinone-phenol **5f** instead of the dibenzofuranquinone derivative **6f** (Scheme 3).[15] Indeed, reaction of **5e** with DDQ gave only 34% yield

Scheme 3. Debenzylation and Oxidation of **11**



of the cyclization product **6e** along with unidentified byproducts probably due to overreaction, although the reaction time (1 h) was much shorter than that with **7** or **8** (Table 2, entry 12).

These facts implied that selection of the oxidant might be very important for efficient cyclization of **5** without an undesired side reaction, and prompted us to employ cyclic voltammetry of **5** to examine this point. The measurements suggested a correlation of the oxidation potentials (E^{ox}) of **5** as donors with the reduction potentials (E^{red}) of benzoquinone (**7**) and chloranil (**8**) as acceptors for efficient cyclization (Table 3, see also Table 2). For example, **7** (−0.59 V)[11b]

Table 3. Oxidation Potentials (E^{ox}) of **5a**−**e** and Reduction Potentials (E^{red}) of **7** and **8**

5 (E^{ox}, V)[a]	**7** and **8** (E^{red}, V)[a]
5a (+0.85)	**7** (−0.59)
5b (+0.93)	**8** (−0.08)
5c (+1.04)	
5d (+0.92)	
5e (+1.14)	

[a] See ref 16.

with a lower redox potential is a more suitable acceptor in the reaction of **5a** (+0.85 V) (observed below $E^{ox} = +0.9$ V). In contrast, **8** (−0.08 V)[11b] having a higher redox potential is a more suitable acceptor for the reaction of **5b**

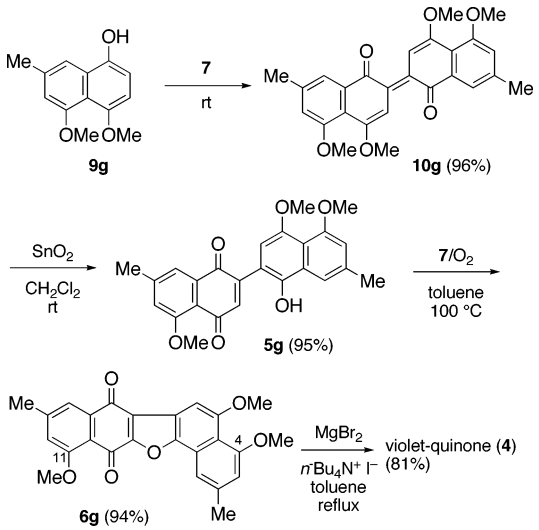
(15) Benbow, J. W.; Martinez, B. L.; Anderson, W. R. *J. Org. Chem.* **1997**, *62*, 9345−9347.

(16) Potentials (V) are versus Ag/AgCl; all substrates were measured in the range of about 0.0−2.0 V. The oxidation potentials of anodic current (E) were obtained by cyclic voltammetry of 0.1 mM solutions of the substrates in an argon-saturated solvent (CH_2Cl_2) containing 0.1 M n-Bu_4NClO_4 as a supporting electrolyte at a Pt electrode. The voltage scan rate in cyclic voltammetry was 100 mV s^{-1} at 23 °C. E^{ox} = the first half-wave oxidation potential.[11b]

(+0.93 V) (observed above $E^{ox} = +0.9$ V). This makes it possible to readily select an effective acceptor for future oxidative cyclizations of a wide variety of quinone-arenols **5**, leading to the corresponding dibenzofuranquinones **6**.

The present oxidative cyclization was applied to the synthesis of violet-quinone (**4**) (Scheme 4). The quinone-arenol **5g** was readily prepared from **9g** via a two-step sequence similar to that used for the preparation of **9a**: oxidative dimerization with **7** followed by selective monodemethylation with SnO_2. On the basis of the above information, oxidative cyclization of **5g** ($E^{ox} = +0.82$ V) was carried out by using **7** ($E^{red} = -0.59$ V) as an oxidant in the presence of O_2, affording **6g** in high yield. Finally, $MgBr_2$-iodide-mediated selective demethylation of the C4- and C11-OMe groups of **6g** afforded the natural product **4** in 81% yield and mp of 332−335 °C. All physical data of the synthetic compound **4** were identical with those of an authentic sample.[4,7b]

Scheme 4. Synthesis of Violet-quinone (**4**)



As mentioned above, we have developed a simple method for the synthesis of dibenzofuranquinones **6**, which is the core structure of the natural products **2**−**4**, utilizing a novel oxidative cyclization of the quinone-arenols **5**. As an application of this method to natural product synthesis, a facile synthesis of **4** was accomplished, confirming the synthetic utility of the present cyclization. Toward the synthesis of popolohuanone E (**2**), since it was reported that 8-*O*-methyl group could not be removed under the conditions compatible with exocyclic methylenes,[8c] examination of the protective group of C8-oxygen functionality should be indeed indispensable for the synthesis of **2**. The preparation method of cyclization-precursor for **2** should be also examined because the yield of precursor **5e** was moderate. Despite the considerations of above, the present oxidative cyclization would be very attractive as an option for the construction of the skeleton of **2**.

Acknowledgment. This research was supported by a Grant-in-aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5a**−**e**, **5g**, **6a**−**e**, **6g**, **10a**−**d′**, **10g**, and **4**; ^{1}H NMR spectra of compounds **5c**−**e** and **10c**,**d′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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