

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

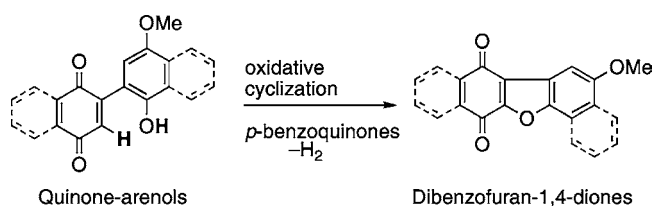
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ABSTRACT



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.

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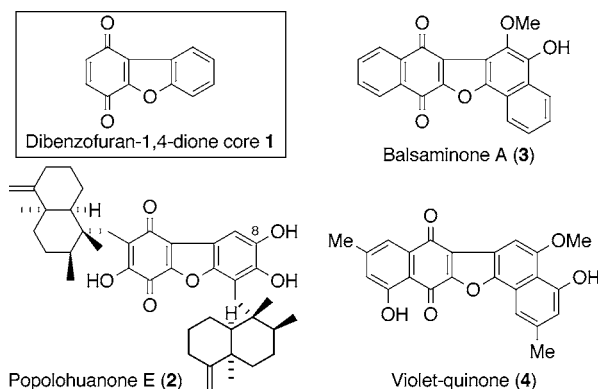
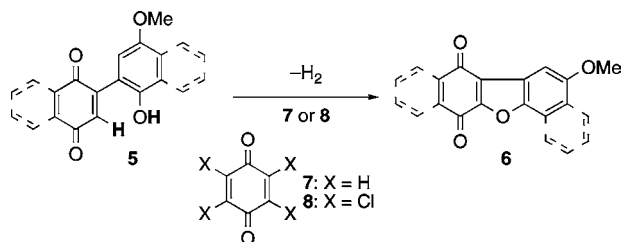


Figure 1. Natural products having a dibenzofuran-1,4-dione core.

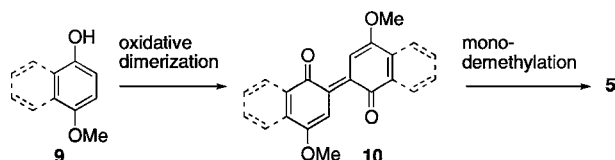
In the course of our research aimed at synthesizing **2–4**, we sought an efficient method for the construction of the core structure **1**. Herein, we report a novel oxidative cyclization of quinone-arenols **5** with benzo-1,4-quinone (**7**) or chloranil (**8**) in the presence of molecular oxygen (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 chloranil (**8**), respectively,

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

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

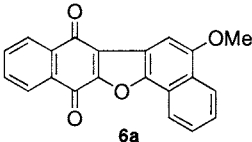
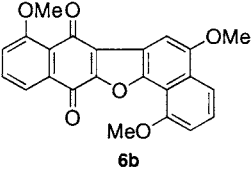
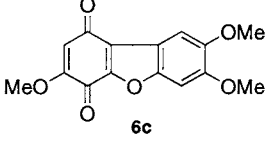
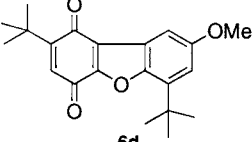
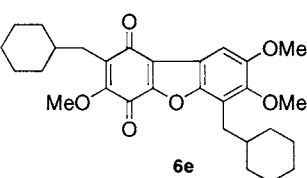
followed by *O*-monodemethylation of the [2,2']binaphthalenylidene-1,1'-diones **10a** and **10b** with SnO_2 (entries 1 and 2). Similarly, [2,2']biphenyl-1,4-diones **5c–e** were also prepared from the corresponding phenols **9c–e** (entries 3–5) (see Supporting Information).¹³

With the substrates **5a–e** in hand, we next examined the key oxidative cyclization of **5** using benzoquinone (**7**) or chloranil (**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

(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**.

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Table 2. Oxidative Cyclization of Quinone-areneols **5a–e** Leading to Dibenzofuranquinones **6a–e**^a

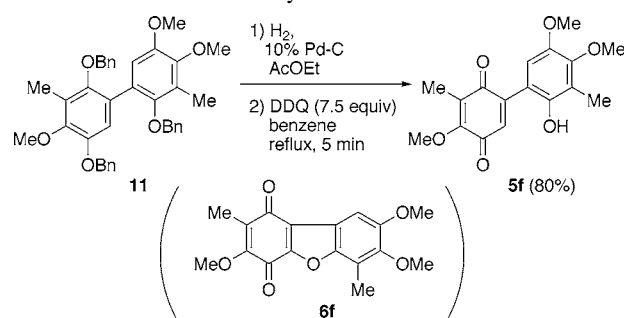
Entry	Conditions	Yield (%)	Product
1	5a , 7 , 3 h ^b	76	 6a
2	5a , 7 , 3 h	84	
3	5a , 8 , 2 h	54	
4	5b , 7 , 2.5 days	60 ^c	 6b
5	5b , 8 , 2.5 days	97	
6	5c , 7 , 4 days	56 ^d	 6c
7	5c , 8 , 5 days	80	
8	5d , 7 , 20 h	77	 6d
9	5d , 8 , 20 h	91	
10	5e , 7 , 5 days	68	 6e
11	5e , 8 , 4 days	94	
12	5e , 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 O₂-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 O₂. The use of O₂ 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 Ac₂O. Although the exact role of O₂ remains unclear, O₂ 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 debenzoylation 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. Debzoylation 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 $E^{\text{ox}} = +0.9$ V). In contrast, **8** (−0.08 V)^{11b} having a higher redox potential is a more suitable acceptor for the reaction of **5b**

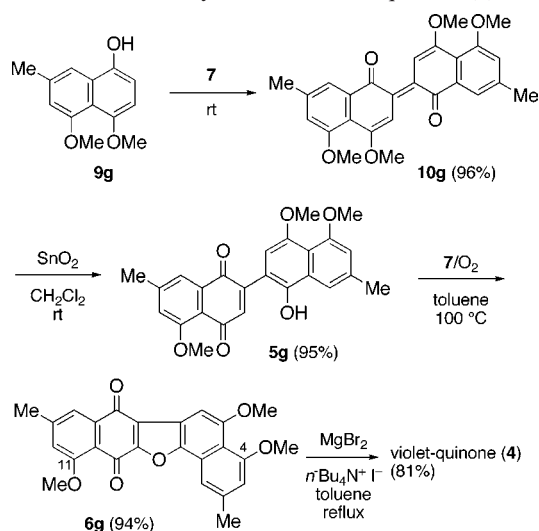
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(16) Potentials (V) are versus Ag/AgCl; all substrates were measured in the range of about 0.0–2.0 V. The oxidation potentials of anodic current (E) were obtained by cyclic voltammetry of 0.1 mM solutions of the substrates in an argon-saturated solvent (CH₂Cl₂) containing 0.1 M *n*-Bu₄NClO₄ 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 $E^{\text{ox}} = +0.9$ 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-

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



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 mono-demethylation with SnO_2 . On the basis of the above information, oxidative cyclization of **5g** ($E^{\text{ox}} = +0.82$ V) was carried out by using **7** ($E^{\text{red}} = -0.59$ 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}

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**.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5a–e**, **5g**, **6a–e**, **6g**, **10a–d'**, **10g**, and **4**; ^1H 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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