Dimerization of 2,5-Dihydroxybenzoquinones in Water

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2,5-Dihydroxybenzoquinones, when heated in water, react to form different types of compounds through dimerization. The features of this unique reaction were clarified using a model compound, 2,5-dihydroxy-3-methylbenzoquinone. The structures of the products were established by X-ray analysis and spectroscopic means.

Key words 2,5-dihyroxybenzoquinone; dimerization; furanylidene benzofuranone; 1,4-dibenzofurandione; X-ray analysis

In a previous paper, we showed that 2,5-dihydroxy-3-undecyl-*p*-benzoquinone, embelin (**1b**), was transformed into different types of compounds when heated in boiling water (Chart 1). The dimeric structures **2b** and **3b** were assigned to the products, though rigorous proof was not available.[2)] Since such a transformation seemed to be reasonable for any 2,5-dihydroxybenzoquinone, we carried out the reaction with a synthetic model compound, 2,5-dihydroxy-3-methyl-*p*-benzoquinone (**1a**), in order to clarify the structure determination of the products. This paper deals, in detail, with the structure determinations of the dimeric products obtained on heating **1a** in boiling water.

Results and Discussion

2,5-Dihydroxy-3-methyl-*p*-benzoquinone (**1a**), when heated in boiling water gave, as in the case of embelin (**1b**), several products (Fig. 1), from which two compounds, A (**2a**) and B (**3a**), were isolated in 12% and 37% yields, respectively.

Compound A (**2a**) gave orange-red needles of mp 273—278 °C. Compound B (**3a**) gave fine dark-red crystals of mp 250—252 °C. They were dimers of **1a** ($C_{14}H_{10}O_7$ and $C_{14}H_{10}O_6$, respectively, being revealed by MS and elementary analyses), and shared spectral similarities (Tables 1—3) with those of **2b** and **3b**, respectively, prepared from embelin (**1b**),[2)] indicating that they were formed by the same transformation as **2b** and **3b**.

Structure of Compound A (2a) Compound A (**2a**) exhibited two singlet *C*-methyls at δ 1.81 and 2.08, and a singlet aromatic proton (δ 7.05). No other information was available from the ^{1}H-NMR spectrum, except for three hydroxyl signals at δ 9.54, 9.76 and 11.78 (each br s), all of which disappeared on addition of D_2O. On usual acetylation, compound A gave a tri-*O*-acetate **4a**, mp 191—194 °C, and on *p*-bromobenzoylation, it gave a tri-*O*-*p*-bromobenzoate **4b**, mp 159—162 °C, confirming the presence of three OH groups in **2a**.

The ^{13}C-NMR spectrum (Table 2) indicated the presence of the following groups: two methyls at δ 6.4 and 8.6, one =CH at δ 107.4, four olefinic carbons which do not bear any oxygen atom at δ 102—115, four olefinic carbons which bear an oxygen atom at δ 140—150, and three C=O or its equivalents at δ 160—175. Its IR spectrum exhibited four intense peaks at 1769, 1724, 1651, and 1626 cm^{-1} in the carbonyl region suggesting the presence of a γ-lactone moiety in the molecule.

The C–H correlation spectroscopy (COSY) spectrum correlated the methyls at δ_H 1.81 and 2.08 with δ_C 6.4 and 8.6, respectively, and =CH at δ_H 7.05 with δ_C 107.4. The correlation spectroscopy *via* long-range coupling (COLOC) spectrum (J=8 Hz) showed the following correlation peaks: the Me at δ 1.81 with the carbons at δ 102.3, 161.4, 167.6; the Me at δ 2.08 with the carbons at δ 108.7, 146.8, 147.8; the =C–H at δ 7.05 with carbons at δ 146.8 and 147.8. Thus, the partial structures **a** and **b** were elucidated (Fig. 2), which were integrated into the structure **2a** for compound A (or its geometrical isomer).

Compounds of analogous structure have been reported by Steglich *et al.*[3)] who prepared **2c** and **2d** (bovilactone-4,4) by heating 2,5-dihydroxybenzoquinone and 2,5-dihydroxy-3-geranylgeranylbenzoquinone with acetylated

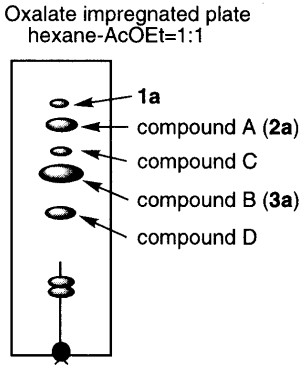
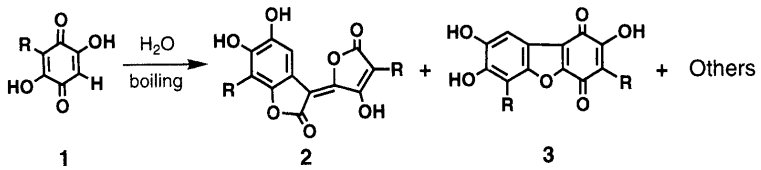


Fig. 1. TLC of Reaction Products



a: R=Me; **b**: R=$(CH_2)_{10}CH_3$

Chart 1

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Table 1a. Spectral Characteristics of Furanylidene Benzofuranones (**2**)[a]

	UV (λ_{max}, nm)	IR (KBr, cm^{-1})
2a	275, 381, 466	1769, 1724, 1651, 1626
2b	275, 381, 466	1763, 1721, 1651, 1626
2c[b]	272, 290, 360, 450	1785, 1745, 1650, 1629
2d[c]	275, 382, 460	1795, 1760, 1730, 1645, 1620[d]

Table 1b. Spectral Characteristics of 1,4-Dibenzofurandiones (**3**)[a]

	UV (λ_{max}, nm)	IR (KBr, cm^{-1})
3a	210, 257, 290, 351, 536	1678, 1636, 1622
3b	214, 259, 290, 356, 551	1661, 1639, 1618

a) Structures see Chart 1, **a**: R=Me; **b**: R=$(CH_2)_{10}CH_3$; **c**: R=H; **d**: R=geranylgeranyl. *b*) See reference 3*a*. *c*) See reference 3*b*. *d*) In CCl_4.

Table 2. ^{13}C-NMR Data of Compound **2** and Derivatives in $CDCl_3$

No.	**2a**[a]	**2b**	**5**[b]	**6**	**8a**	**8b**	**9a**
2	172.5	173.3	—	164.3	163.6	163.6	164.0
3 or 3a	110.7	112.0	—	117.0	117.7	117.8	117.6
3a or 3	107.4	107.9[c]	—	107.7	106.5	106.5	115.1
4	107.4	108.4	109.9	107.1	118.1	118.1	117.6
5	142.7	140.7	—	150.0	140.3	140.3	139.8
6	146.8	146.8	—	150.8	153.0	153.1	152.5
7	108.7	114.3	—	115.6	115.9	116.0	116.2
7a	147.8	148.1	—	147.1	150.2	150.3	151.2
2′	148.2	149.4	—	149.1	150.4	150.5	149.5
3′	161.4	162.4	—	163.2	163.0	163.0	162.2
4′	102.3	108.1[c]	—	105.8	106.0	106.0	105.7
5′	167.6	169.4	—	168.5	168.3	168.2	168.2
7-Me	8.6	—[d]	9.3	9.0	9.2	9.28	9.3
4′-Me	6.4	—[d]	9.3	9.3	9.3	9.30	9.5
5-OMe			—	60.8	—	—	—
6-OMe			60.0	56.6	59.9	60.0	59.5
3′-OMe			61.2	60.0	61.1	61.3	61.1
Others		—[d]			20.7	127.9, 129.2, 131.8, 132.2	20.9
					169.3	164.3	169.2

a) In DMSO-d_6. *b*) Only the signals listed were identified because of poor signal to noise ratio of the spectrum. *c*) These assignments may be interchanged. *d*) Side chain signals are omitted.

polyamide or polyamide in AcOEt, respectively (Table 1a). Although the spectral data reported for **2c** and **2d** had good similarity with those of **2a** and **2b**, no experimental details for structure determination or details of spectral data (such as ^{13}C-NMR) except those in Table 1a have been published.[4] We therefore determined the structure of **2a** independently.

Treatment of **2a** with diazomethane for a short period (in methanol at 0 °C for 5 min)[5] gave a mixture of di-*O*-methyl and tri-*O*-methyl derivatives, **5** and **6**, which were separated by chromatography on silica gel in the yields of 49% and 38%, respectively (Chart 2). The COLOC, heteronuclear multiple bond connectivity (HMBC), and nuclear Overhauser enhancement spectroscopy (NOESY) spectra of **6** confirmed the structure suggested above (Fig. 2). Particularly, the NOE enhancements observed between the aromatic proton at δ 7.34 and the OMe group at δ 3.90, between the *C*-Me group at δ 2.22 and the OMe group at δ 3.87, and between the *C*-Me group at δ 2.21 and the OMe group at δ 4.25, enabled the assignments of the OMe groups and phenolic carbons. Alkaline degradation of **6** gave a compound of mp 121—122 °C, though in very low yield, whose spectral

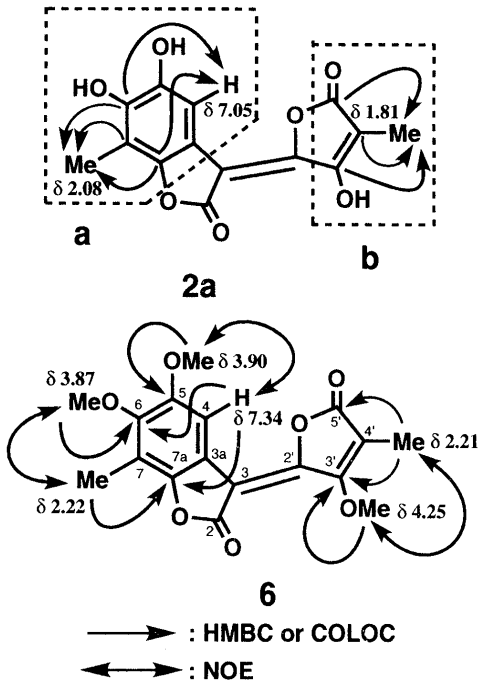

Fig. 2. C H Correlations and NOE of **2a** and **6**

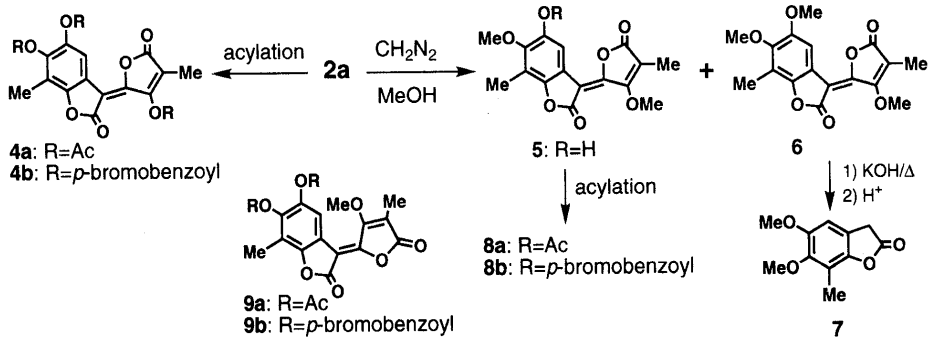

Chart 2

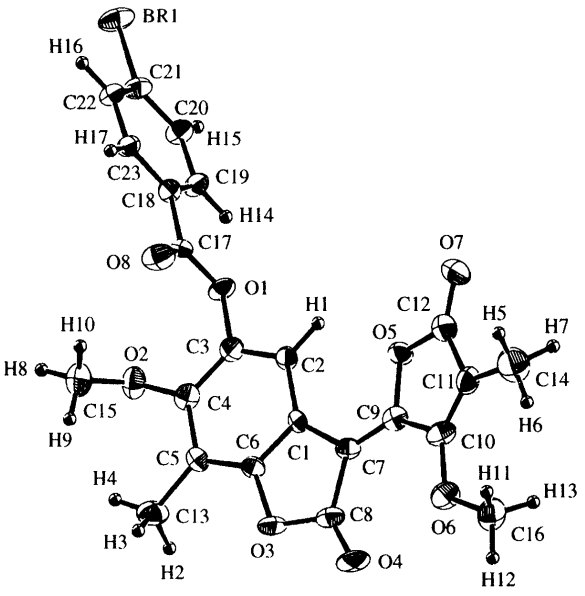

Fig. 3. ORTEP Drawing of **8b**

The crystal contained two molecules per unit cell. Only one molecule is indicated here.

Table 3. ^{13}C-NMR Data of Compound **3** and Derivatives

No.	**3a** (DMSO-d_6)	**3b** (CD_3OD)	**10b** ($CDCl_3$)
1	179.1	180.5	179.8
2	154.0	155.1	156.3
3	114.8	120.6	128.2
4	177.1	178.9	177.5
4a	151.3	152.9	152.1
5a	150.0	152.0	151.0
6	108.3	114.1	117.3
7	145.5	146.4[a]	149.2
8	145.9	147.2[a]	152.9
9	101.9	103.2	100.5
9a	112.3	114.5	120.6
9b	118.7	120.2	117.2
3-Me	7.8	—[b]	8.7
6-Me	8.7	—[b]	9.1
2-OMe			61.3
7-OMe			56.2
8-OMe			60.9

a) These assignments may be interchanged. *b*) Side chain signals are omitted.

data were compatible with the expected dimethoxy-γ-lactone structure **7**.

The di-*O*-methyl derivative **5** gave a monoacetate **8a** on acetylation and a mono-*p*-bromobenzoate **8b** on *p*-bromobenzoylation. Isomers **9a** and **9b** (structure assignments tentative) were also obtained in these acylations, respectively.[6] Compound **8b** formed yellow prisms, which were suitable for X-ray crystal analysis. A single crystal having approximate dimensions of 0.2 × 0.1 × 0.3 mm was submitted for analysis and the results finally established the structure of **8b** and thus of compound A (**2a**) including the stereochemistry of the tetronic acid moiety. The ORTEP drawing of the structure is shown in Fig. 3.

Structure of Compound B (3a) Compound B showed two *C*-methyl groups (δ 1.83 and 2.29) and an aromatic

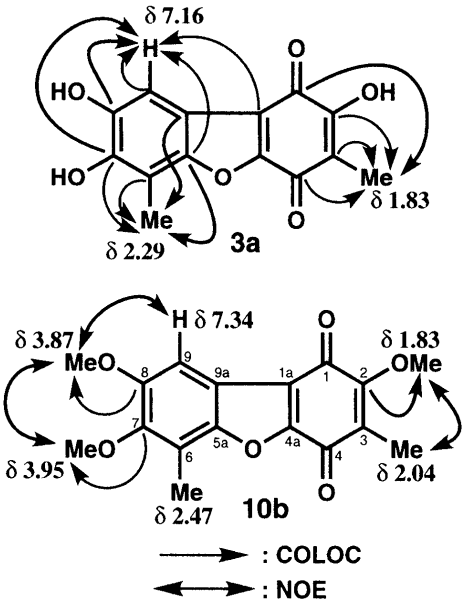

Fig. 4. C–H Correlations and NOE of **3a** and **10b**

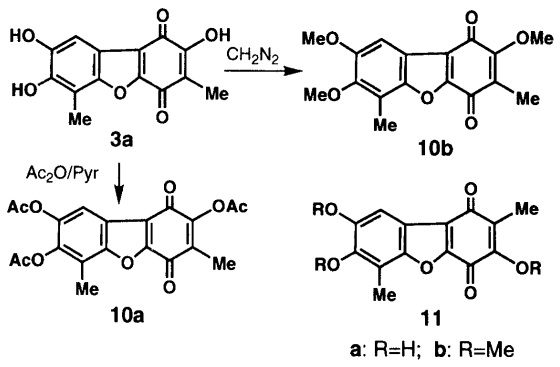

Chart 3

proton (δ 7.16) in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum (Table 3) exhibited, in addition to two Me signals (δ 7.8 and 8.7), 12 carbons, of which the signal at δ 101.9 was correlated with δ_H 7.16 by the C–H COSY spectrum. Among the other signals, four were assignable to C=C (δ 108.3, 112.3, 114.8, 118.7), five to =C–O (δ 145.5, 145.9, 150.0, 151.3, 154.0), and two to C=O (δ 177.1, 179.1). Detailed analysis of the COLOC spectra (J=4, 8 Hz) of compound B revealed the correlations shown in Fig. 4. From the above data, a 1,4-dibenzofurandione structure **3a** or its isomer **11a** was proposed for compound B (Chart 3). Compound B gave a tri-*O*-acetate **10a** on acetylation, and a tri-*O*-methyl ether **10b** on methylation with diazomethane in methanol, revealing the presence of three phenolic OH groups. The results of COLOC and NOE analysis of **10b** were compatible with the above 1,4-dibenzofurandione structures.

Recently, Ueki *et al.*[7] reported 1,4-dibenzofurandiones **11a** and **11b**, which are isomeric to **3a** and **10b**, respectively. Although the spectral data of these compounds were not reported, their reported melting points are apparently different from those of compound B and its tri-*O*-methyl ether, indicating them to be **3a** and **10b**, respectively. The substitution pattern of the Me and OMe groups on the quinone ring was also supported by comparisons of the

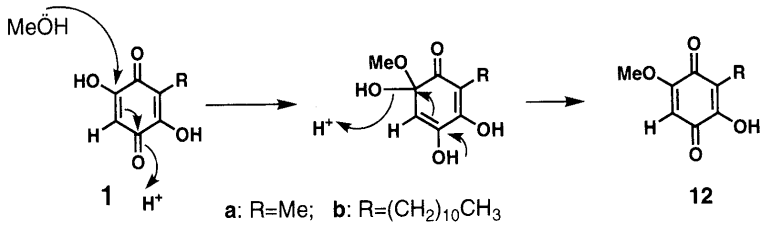

Chart 4

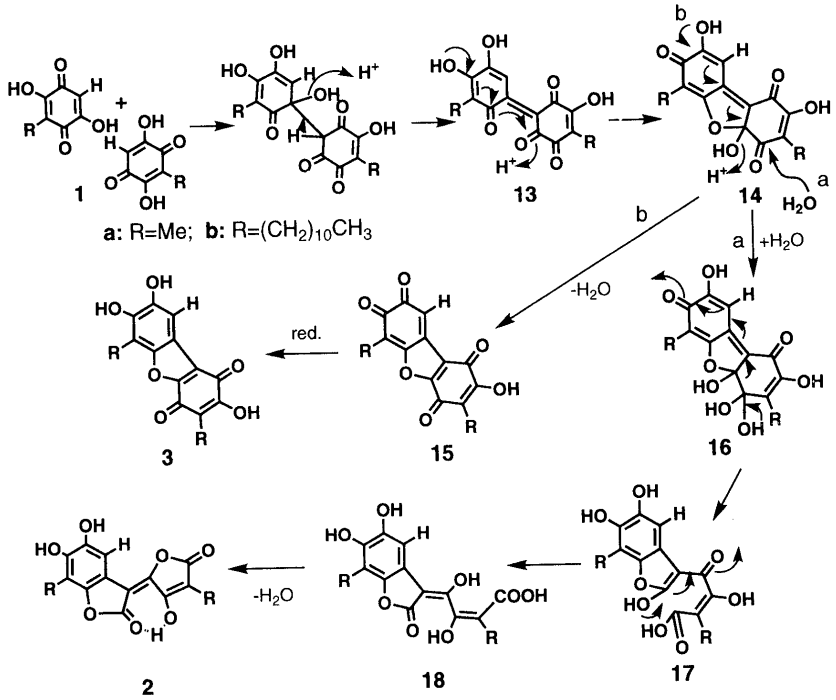

Chart 5

chemical shifts of the quinone carbonyl carbons with those of analogous compounds[8] and the reaction mechanism discussed below. Thus, the structure of compound B was elucidated as **3a**, and the compound obtained by a similar reaction of embelin (**1b**) should have the same skeletal structure (**3b**) as assigned previously.[2]

Reaction Mechanism 2,5-Dihyroxy-3-methylbenzoquinone (**1a**) behaves in boiling methanol as embelin does,[2] to give a 5-*O*-methyl ether **12a** in acceptable yield, as a result of the Michael addition of MeOH to the more reactive and less hindered enone system followed by dehydration (Chart 4). Thus, in the dimerization and dehydration of **1**, the initial steps of the formation of **2** and **3**, should proceed in a similar manner as shown in Chart 5. The resulting diquinone equivalent **13** would give an intramolecular hemiacetal **14** which would be dehydrated to an orthoquinone **15** (path b). A reductive step, though we could not identify the reducing species, will lead from **15** to the 1,4-dibenzofurandione **3**. On the other hand, hydration of **14** (path a) followed by retro-aldol reaction of the hydrate **16** would give the seco product **17**, which will form the stable γ-lactone rings to give **2**.[9]

Experimental

General Unless otherwise stated, the following procedures were adopted. Melting points were determined with a YANACO melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu IR-460 spectrometer using KBr disks and the data are given in cm^{-1}. UV spectra were measured with a Shimadzu UV-1600 in EtOH and are given by λ_{max} in nm ($\log\varepsilon$). ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GSX500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) spectrometer with tetramethylsilane as an internal standard and chemical shifts are given in δ. MS were recorded with a JEOL JSM-SX102 spectrometer and major peaks are given by *m/z* (%). Column chromatography was performed on acid-treated silica gel, which was prepared as follows: Wako gel C-200 was immersed in 0.5 N oxalic acid solution for 48 h, filtered, washed almost free from acid, and dried. TLC was done on Macherey–Nagel precoated plates. When acid-treated plates were necessary, the plates were dipped in 0.5 N oxalic acid solution and dried before use. Spots were developed by spraying with 10% H_2SO_4 and heating until colors developed.

2,5-Dihydroxy-3-methyl-*p*-benzoquinone (1a) This was prepared by the reported method.[10] Orange-red plates from benzene, mp 173—175 °C (dec.) (lit. 173—175 °C, dec.).[10] IR: 3310, 1619. ^{1}H-NMR ($CDCl_3$): 1.97 (3H, s), 6.01 (1H, s). 7.68 (2H, br s, OH). *Anal.* Calcd for $C_7H_6O_4$: C, 54.55; H, 3.92. Found: C, 54.34; H, 3.89.

Methylation of 1a 1) With Diazomethane: Compound **1a** (104 mg) in ether (5 ml) was treated with excess diazomethane for 10 min at room temperature to give a di-*O*-methyl ether (107 mg, 87.1%), as yellow needles from AcOEt–hexane, mp 115—119 °C. ^{1}H-NMR ($CDCl_3$): 1.95 (3H, s, Me), 3.81, 4.06 (each 3H, s, OMe), 5.74 (1H, s). MS: 182 (M^+, 43), 167 (39), 153 (76), 109 (91).

2) With MeOH: A mixture of **1a** (117 mg) and *p*-TsOH (26 mg) in MeOH (5 ml) was stirred for 5.5 h at 70 °C. Evaporation of the solvent and chromatography of the residue gave the mono-*O*-methyl ether **12a** (98 mg, 76.8%) with recovery of **1a** (14 mg). It formed orange plates from AcOEt–hexane, mp 130—135 °C. IR: 3540, 3460, 1640, 1592. ^{1}H-NMR ($CDCl_3$): 1.95 (3H, s, Me), 3.87 (3H, s, OMe), 5.85 (1H, s), 7.31 (1H, s, OH). ^{13}C-NMR ($CDCl_3$): 7.8, 56.7, 102.2, 114.8, 151.6, 161.2, 181.9, 182.6. MS: 168 (M^+, 100), 153 (18), 125 (33). *Anal.* Calcd

Table 4. Positional Parameters and B_{eq} for Compound **8b**

Atom	x	y	z	B_{eq}	Atom	x	y	z	B_{eq}
Br(1)	0.5820 (1)	0.1300 (1)	0.08258 (7)	5.92 (8)	C(59)	0.4161 (7)	0.2717 (7)	−0.1384 (6)	3.6 (6)
Br(2)	0.5356 (1)	0.3597 (1)	0.57045 (7)	6.32 (8)	C(60)	0.3729 (7)	0.2226 (7)	−0.2061 (6)	3.5 (6)
O(1)	0.5703 (5)	0.0966 (5)	−0.3200 (4)	3.9 (4)	C(61)	0.3261 (7)	0.1593 (8)	−0.1814 (7)	4.5 (7)
O(2)	0.7136 (5)	0.0158 (5)	−0.3503 (5)	4.9 (4)	C(62)	0.3368 (8)	0.170 (1)	−0.0930 (7)	5.1 (8)
O(3)	0.6089 (5)	0.0446 (5)	−0.6349 (4)	4.2 (4)	C(63)	0.6836 (7)	0.5386 (7)	−0.0338 (7)	4.8 (7)
O(4)	0.5289 (5)	0.0841 (5)	−0.7497 (4)	5.6 (5)	C(64)	0.2753 (9)	0.092 (1)	−0.2230 (8)	7.2 (8)
O(5)	0.3925 (5)	0.2124 (5)	−0.5681 (4)	3.9 (4)	C(65)	0.751 (1)	0.480 (1)	0.1465 (8)	7.0 (9)
O(6)	0.4006 (5)	0.1989 (5)	−0.7756 (4)	5.6 (4)	C(66)	0.3455 (8)	0.2055 (9)	−0.3487 (7)	5.9 (7)
O(7)	0.3029 (5)	0.3163 (5)	−0.5480 (5)	5.9 (5)	C(67)	0.5996 (8)	0.3471 (7)	0.2194 (7)	3.7 (6)
O(8)	0.6633 (5)	0.2063 (5)	−0.3006 (5)	5.2 (5)	C(68)	0.5795 (7)	0.3498 (7)	0.3037 (6)	3.4 (6)
O(11)	0.5411 (5)	0.3903 (5)	0.1681 (4)	4.2 (4)	C(69)	0.5207 (8)	0.4059 (7)	0.3269 (7)	4.3 (6)
O(12)	0.6617 (6)	0.4981 (5)	0.1318 (5)	5.2 (5)	C(70)	0.5061 (8)	0.4094 (8)	0.4058 (7)	4.6 (7)
O(13)	0.5710 (5)	0.4356 (5)	−0.1481 (4)	4.4 (4)	C(71)	0.5519 (8)	0.3555 (8)	0.4607 (6)	4.4 (6)
O(14)	0.4964 (5)	0.3807 (6)	−0.2596 (4)	6.5 (5)	C(72)	0.6117 (8)	0.2996 (8)	0.4393 (6)	4.4 (6)
O(15)	0.3905 (5)	0.2365 (5)	−0.0708 (4)	4.3 (4)	C(73)	0.6258 (7)	0.2968 (7)	0.3601 (7)	4.2 (6)
O(16)	0.3888 (5)	0.2471 (5)	−0.2793 (4)	5.4 (4)	H(1)	0.4725	0.1508	−0.4487	4.0
O(17)	0.3064 (5)	0.1285 (6)	−0.0447 (5)	7.0 (5)	H(2)	0.7281	−0.0750	−0.5426	6.2
O(18)	0.6581 (5)	0.3081 (6)	0.1991 (5)	5.6 (5)	H(3)	0.7798	0.0072	−0.5458	6.2
C(1)	0.5362 (6)	0.1003 (6)	−0.5399 (6)	2.5 (5)	H(4)	0.7836	−0.0409	−0.4651	6.2
C(2)	0.5237 (6)	0.1183 (7)	−0.4596 (6)	3.2 (5)	H(5)	0.2986	0.4118	−0.7048	7.7
C(3)	0.5848 (8)	0.0881 (7)	−0.4003 (6)	3.5 (6)	H(6)	0.2831	0.3581	−0.7827	7.7
C(4)	0.6576 (8)	0.0457 (7)	−0.4148 (6)	3.6 (6)	H(7)	0.2197	0.3525	−0.7206	7.7
C(5)	0.6701 (7)	0.0253 (7)	−0.4935 (6)	3.4 (6)	H(8)	0.8337	0.0346	−0.2910	6.8
C(6)	0.6075 (7)	0.0556 (7)	−0.5522 (6)	3.5 (6)	H(9)	0.8252	0.0531	−0.3826	6.8
C(7)	0.4894 (7)	0.1269 (7)	−0.6193 (5)	3.1 (5)	H(10)	0.7899	0.1164	−0.3258	6.8
C(8)	0.5375 (8)	0.0848 (7)	−0.6785 (7)	3.9 (6)	H(11)	0.3668	0.2971	−0.8471	7.1
C(9)	0.4241 (7)	0.1791 (7)	−0.6336 (6)	3.2 (6)	H(12)	0.3731	0.2151	−0.8951	7.1
C(10)	0.3814 (8)	0.2255 (7)	−0.7049 (6)	4.1 (6)	H(13)	0.2948	0.2304	−0.8511	7.1
C(11)	0.3336 (8)	0.2859 (8)	−0.6816 (7)	4.4 (7)	H(14)	0.5188	0.0541	−0.2023	4.3
C(12)	0.3370 (8)	0.2772 (9)	−0.5943 (8)	4.7 (7)	H(15)	0.5095	0.0444	−0.0605	4.6
C(13)	0.7451 (8)	−0.0242 (7)	−0.5135 (7)	5.4 (7)	H(16)	0.6741	0.2373	−0.0141	5.3
C(14)	0.2811 (8)	0.353 (1)	−0.7233 (7)	6.8 (8)	H(17)	0.6833	0.2499	−0.1547	4.2
C(15)	0.7942 (9)	0.056 (1)	−0.3367 (7)	6.2 (8)	H(18)	0.4646	0.3088	0.0439	4.2
C(16)	0.3573 (8)	0.236 (1)	−0.8469 (6)	6.1 (7)	H(19)	0.7161	0.5656	0.0115	5.4
C(17)	0.6165 (8)	0.1579 (8)	−0.2758 (6)	3.5 (6)	H(20)	0.7235	0.5161	−0.0666	5.4
C(18)	0.6030 (7)	0.1527 (7)	−0.1889 (6)	3.1 (5)	H(21)	0.6517	0.5825	−0.0664	5.4
C(19)	0.5508 (7)	0.0921 (7)	−0.1637 (6)	3.8 (6)	H(22)	0.2156	0.0906	−0.2146	8.1
C(20)	0.5455 (7)	0.0874 (7)	−0.0808 (6)	3.9 (6)	H(23)	0.2735	0.0911	−0.2815	8.1
C(21)	0.5911 (7)	0.1408 (8)	−0.0275 (6)	4.0 (6)	H(24)	0.2975	0.0354	−0.2058	8.1
C(22)	0.6422 (7)	0.2009 (8)	−0.0539 (6)	4.3 (6)	H(25)	0.7645	0.4191	0.1601	7.8
C(23)	0.6474 (7)	0.2067 (7)	−0.1351 (6)	3.5 (6)	H(26)	0.7831	0.4900	0.1022	7.8
C(51)	0.5136 (7)	0.3673 (7)	−0.0493 (6)	3.3 (5)	H(27)	0.7845	0.5087	0.1931	7.8
C(52)	0.5063 (6)	0.3520 (7)	0.0305 (6)	3.7 (6)	H(28)	0.2838	0.2072	−0.3519	6.8
C(53)	0.5561 (8)	0.3973 (7)	0.0880 (6)	3.4 (6)	H(29)	0.3600	0.2253	−0.3979	6.8
C(54)	0.6165 (8)	0.4554 (8)	0.0692 (7)	3.9 (6)	H(30)	0.3598	0.1448	−0.3464	6.8
C(55)	0.6240 (8)	0.4712 (7)	−0.0094 (7)	4.0 (6)	H(31)	0.4893	0.4425	0.2861	4.8
C(56)	0.5724 (8)	0.4272 (7)	−0.0663 (6)	3.5 (6)	H(32)	0.4641	0.4505	0.4221	5.3
C(57)	0.4736 (7)	0.3332 (7)	−0.1260 (6)	3.0 (5)	H(33)	0.6426	0.2641	0.4808	4.9
C(58)	0.5101 (8)	0.3829 (8)	−0.1886 (6)	4.1 (6)	H(34)	0.6679	0.2586	0.3433	5.1

for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.09; H, 4.69.

Reaction of 2,5-Dihydroxy-3-methylbenzoquinone (1a) in Boiling Water Compound **1a** (1 g) in distilled water (100 ml) was heated under reflux for 2 h. The cooled mixture was filtered to separate precipitates (410 mg). The filtrate was extracted with AcOEt to give an extract (480 mg). The precipitates showed spots, **2a** and **3a**, and the filtrate showed several additional spots on TLC. They were separately chromatographed on acid-treated silica gel with hexane–AcOEt (3 : 1 to 0 : 1). Fractions of the same *Rf* were combined and subjected to further purification to afford compounds A (**2a**) (109 mg, 12%), B (**3a**) (333 mg, 37%), C (15 mg), and D (48 mg).

Compound A (**2a**): Orange-red needles from AcOEt–hexane, mp 273—278 °C. UV: 275 (4.35), 381 (4.14), 466 (4.08). IR: 3535, 3375, 1769, 1724, 1651, 1626. ^{1}H-NMR (DMSO-d_6): 1.81 (3H, s, 4′-Me), 2.08 (3H, s, 7-Me), 7.05 (1H, s, H-4), 9.54, 9.76, 11.78 (each 1H, br s, OH). ^{13}C-NMR: Table 2. MS: 290 (M^+, 100), 206 (99). FAB-MS (positive): 291 ($M+H^+$, 39), 290 (M^+, 50). FAB-MS (negative): 289 ($M-H^-$, 100). *Anal.* Calcd for $C_{14}H_{10}O_7$: C, 57.94; H, 3.47. Found: C, 57.68; H, 3.41.

Compound B (**3a**): Fine dark-red crystals from AcOEt, mp 250—252 °C. UV: 210 (4.52), 257 (4.44), 290 (4.07), 351 (3.80), 536 (3.40). IR: 3455, 3305, 3250, 1678, 1636, 1622. ^{1}H-NMR (DMSO-d_6): 1.83 (3H, s, 3-Me), 2.29 (3H, s, 6-Me), 7.16 (1H, s, H-9), 9.12, 9.96, 10.74 (each 1H, br s, OH). ^{13}C-NMR: Table 3. MS: 274 (M^+, 100), 246 (45). *Anal.* Calcd for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68. Found: C, 61.04; H, 3.60.

Compound C: Fine orange crystals from AcOEt, mp >290 °C. UV: 294. ^{1}H-NMR (acetone-d_6): 2.09 (3H, s), 2.15 (3H, d, J=7.3 Hz), 6.40 (1H, q, J=7.3 Hz). ^{13}C-NMR (acetone-d_6): 8.0, 16.4, 113.8, 116.1, 125.0, 144.95, 144.98, 145.01, 167.4. MS: 318 (4), 303 (11), 290 (10), 238 (25), 194 (100), 164 (48).

Compound D: Dark-brown needles from AcOEt, mp >290 °C. UV: 260, 292, 345. ^{1}H-NMR (acetone-d_6): 1.88, 1.97, 2.41 (each 3H, s). ^{13}C-NMR (acetone-d_6): 8.2, 8.3, 9.4, 108.3, 109.8, 112.2, 113.3, 115.3, 115.8, 120.6, 144.2, 147.3, 151.6, 154.4, 154.8, 172.1, 178.6, 179.5. FAB-MS (negative): 425 (100).

Acetylation of 2a Compound **2a** (9.8 mg) was treated with pyridine (0.5 ml) and acetic anhydride (0.5 ml) for 22 h at room temperature. The reaction mixture was diluted with water and extracted with ether. The

extract was washed with 1 N HCl, saturated $NaHCO_3$, and brine, and concentrated. Chromatography of the product on silica gel (hexane–AcOEt = 2 : 1) gave the tri-*O*-acetate **4a** (12 mg, 85.4%), mp 191—194 °C, as yellow needles from MeOH. IR: 1777, 1641. ^{1}H-NMR ($CDCl_3$): 2.02, 2.16 (each 3H, s, Me), 2.31, 2.34, 2.47 (each 3H, s, OAc), 7.62 (1H, s). MS: 416 (M^+, 7), 374 (14), 332 (52), 290 (100). *Anal.* Calcd for $C_{20}H_{16}O_{10}$: C, 57.70; H, 3.87. Found: C, 57.45; H, 3.84.

***p*-Brompbenzoylation of 2a** A mixture of **2a** (18 mg) and *p*-bromobenzoyl chloride (120 mg) in pyridine (1 ml) was kept for 10 min at room temperature. The mixture was poured into water and extracted with $CHCl_3$. The extract was chromatographed on silica gel to yield tri-*O*-*p*-bromobenzoate **4b** (6 mg), mp 159-162 °C, as yellow needles from AcOEt. ^{1}H-NMR ($CDCl_3$): 2.07, 2.18 (each 3H, s, Me), 7.81 (1H, s), 7.53, 7.55, 7.91, 8.08 (each 2H, d, J = 8.8 Hz, Ar-H), 7.71, 7.88 (each 2H, d, J = 8.3 Hz, Ar-H). FAB-MS (negative): 842 (2.0), 841 (2.1), 840 (4.5), 839 (2.7), 838 (4.1), 837 (1.1), 836 (1.2).

***O*-Methylation of 2a** Compound **2a** (103 mg) in MeOH (2 ml) was treated with an excess of ethereal diazomethane at 0 °C for 5 min. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane–AcOEt = 2 : 1) to yield di-*O*-methyl ether **5** (55.3 mg, 49%) and tri-*O*-methyl ether **6** (45 mg, 37.9%).

Di-*O*-methyl Ether **5**: Fine red needles from AcOEt–hexane, double mp 218—221 °C and 255—257 °C. UV: 276 (4.05), 365 (4.13), 445 (3.79), 630 (1.72). IR: 3380, 1794, 1753, 1621. ^{1}H-NMR ($CDCl_3$): 2.20, 2.27 (each 3H, s, Me), 3.85, 4.24 (each 3H, s, OMe), 5.48 (1H, s, OH), 7.45 (1H, s, Ar-H). MS: 318 (M^+, 100), 303 (34). *Anal.* Calcd for $C_{16}H_{14}O_7$: C, 60.38; H, 4.43. Found: C, 60.16; H, 4.44.

Tri-*O*-methyl Ether **6**: Fine red needles from AcOEt–hexane, mp 185—188 °C. IR: 1783, 1760, 1614. ^{1}H-NMR ($CDCl_3$): 2.21 (3H, s, 4-Me), 2.22 (3H, s, 7-Me), 3.87 (3H, s, 6-OMe), 3.90 (3H, s, 5-OMe), 4.25 (3H, s, 3′-OMe), 7.34 (1H, s, H-4). ^{13}C-NMR: Table 2. MS: 332 (M^+, 100), 317 (34). *Anal.* Calcd for $C_{17}H_{16}O_7$: C, 61.44; H, 4.85. Found: C, 61.16; H, 4.79.

Alkaline Degradation of 6 The tri-*O*-methyl ether **6** (11 mg) was heated with 30% NaOH (1 ml) at 80 °C for 0.5 h. The mixture was acidified with HCl and extracted with AcOEt. Chromatography of the product gave **7** (1.6 mg) as a UV positive compound. Colorless needles from hexane, mp 121—122 °C. IR ($CHCl_3$): 1796 (w), 1712. ^{1}H-NMR ($CDCl_3$): 2.24 (3H, s, Me), 3.70 (2H, s, CH_2), 3.81, 3.84 (each 3H, s, OMe), 6.72 (1H, s). ^{13}C-NMR ($CDCl_3$): 9.2, 33.9, 56.5, 60.6, 106.2, 116.4, 116.8, 147.6, 147.9, 149.9, 174.7. MS: 208 (M^+, 100), 193 (28), 180 (70), 165 (69), 137 (61), 120 (65).

Acetylation of 5 The di-*O*-methyl ether **5** (20 mg) was acetylated with acetic anhydride (0.5 ml) and pyridine (0.5 ml) and worked up as usual to give the acetate **8a** (10 mg, 54%) and its isomer **9a** (8 mg, 46%).

Compound **8a**: Yellow needles from MeOH, mp 181—184 °C. UV: 226 (4.04), 376 (4.07), 630 (1.56) IR: 1787, 1767, 1624. ^{1}H-NMR ($CDCl_3$): 2.21, 2.26 (each 3H, s, Me), 2.35 (3H, s, OAc), 3.82, 4.26 (3H, s, OMe), 7.52 (1H, s). ^{13}C-NMR: Table 2. MS: 360 (M^+, 23), 318 (100), 303 (56). *Anal.* Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 59.86; H, 4.48.

Compound **9a**: Yellow prisms from benzene, mp 172—176 °C. UV: 268 (3.96), 365 (4.06), 630 (1.60). IR: 1782, 1778, 1633. ^{1}H-NMR ($CDCl_3$): 2.25, 2.26 (each 3H, s, Me), 2.36 (3H, s, OAc), 3.83, 4.33 (3H, s, OMe), 7.53 (1H, s). ^{13}C-NMR: Table 2. MS: 360 (M^+, 28), 318 (100), 303 (67). *Anal.* Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 59.76; H, 4.51.

***p*-Bromobenzoylation of 5** A mixture of **5** (50 mg) and *p*-bromobenzoyl chloride (100 mg) in pyridine (1 ml) was stirred for 20 h at room temperature. The products were extracted with AcOEt and separated by silica gel column chromatography (hexane–AcOEt = 2 : 1) then purified by preparative TLC (benzene–acetone = 20 : 1) to yield the *p*-bromobenzoate **8b** (17 mg, 21%) and its isomer **9b** (3 mg, 4%).

Compound **8b**: Yellow prisms from MeOH, mp 221—223 °C. UV: 256 (4.14), 377 (3.86), 630 (1.75). IR: 1788, 1742, 1625. ^{1}H-NMR ($CDCl_3$): 2.21, 2.29 (each 3H, s, Me), 3.80, 4.26 (each 3H, s, OMe) , 7.63 (1H, s), 7.69, 8.08 (each 2H, d, J = 8.8 Hz, Ar-H). ^{13}C-NMR: Table 2. MS: 502 (42), 500 (42), 317 (7), 185 (100), 183 (100).

Compound **9b**: Yellow needles from MeOH, mp 232—234 °C. UV: 256 (4.02), 372 (3.75), 629 (1.70). IR: 1788, 1766, 1743, 1627. ^{1}H-NMR ($CDCl_3$): 2.25, 2.30 (each 3H, s, Me), 3.81, 4.30 (each 3H, s, OMe), 7.67 (1H, s), 7.70, 8.10 (each 2H, d, J = 8.8 Hz, Ar-H). MS: 502 (31), 500 (30), 185 (96), 183 (100).

X-Ray Analysis of the *p*-Bromobenzoate (8b) The reflection data were collected on a Rigaku AFC-5R four-circle diffractometer with graphite-monochromated CuK_α radiation using the ω–2θ scan technique to a maximum 2θ value of 120.2° at a speed of 32.0°/min. Of the 6733 reflections which were collected, 6471 were unique. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 2277 observed reflections ($I > 3\sigma(I)$) and converged with unweighted agreement factor of $R = 0.047$.[11] Positional parameters are given in Table 4. Crystal data: $C_{23}H_{17}BrO_8$, monoclinic, a = 15.743(7), b = 15.996(4), c = 16.789(2) Å, β = 98.84(2)°, V = 4178(2) Å^3, D_c = 1.594 g/cm^3. Space group $P2_1/a$, Z = 8.

Acetylation of 3a Compound **3a** (15 mg) was treated with pyridine (0.5 ml) and acetic anhydride (0.5 ml) at room temperature for 17 h and worked up as described above to give the tri-*O*-acetate **10a** (12 mg, 69.4%), mp 205—208 °C, as fine orange crystals from MeOH. IR: 1776, 1672. ^{1}H-NMR ($CDCl_3$): 2.00, 2.26 (each 3H, s, Me), 2.30, 2.34, 2.37 (each 3H, s, OAc), 7.69 (1H, s). MS: 400 (M^+, 6), 358 (22), 316 (39), 274 (100). *Anal.* Calcd for $C_{20}H_{16}O_9$: C, 60.00; H, 4.03. Found: C, 59.86; H, 3.91.

***O*-Methylation of 3a** Compound **3a** (108 mg) in MeOH (5 ml) was treated with an excess of ethereal diazomethane for 30 min at room temperature and worked up as described for **2a**. Chromatography of the product with $CHCl_3$ gave the tri-*O*-methyl ether **10b** (88 mg, 70.7%), mp 195—198 °C, as fine dark-red needles from AcOEt. IR: 1667, 1658. ^{1}H-NMR ($CDCl_3$): 2.04 (3H, s, 3-Me), 2.47 (3H, s, 6-Me), 3.87 (3H, s, 8-OMe), 3.95 (3H, s, 7-OMe), 4.11 (3H, s, 2-OMe), 7.34 (1H, s, H-9). ^{13}C-NMR: Table 3. MS: 316 (M^+, 100), 301 (34), 273 (17). *Anal.* Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.33; H, 5.07.

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References and Notes

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4) The authors thank Dr. A. Mühlbauer and Prof. W. Steglich for providing spectral data of bovilactone-4,4.
5) Longer treatment (30 min, room temperature) of **2a** gave, instead of **5** and **6**, three products, all of which had five OMe groups. Although spectral analyses of the products suggested *ortho*-ester structures, detailed structure determination will be the subject of a future publication.
6) Compounds **8a** and **8b** reversibly isomerized on silica gel plates, though only to a small extent, to **9a** and **9b**, respectively. However, **4a**, **5**, and **6** did not show such behavior on similar treatment. The reason for this isomerization is not clear at this moment.
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