The 2- or 6-(α-Hydroxyalkyl- and α-Oxoalkyl)-5,8-dimethoxy-1,4-naphthoquinones from the Oxidative Demethylation of 2-(α-Hydroxyalkyl- and α-Oxoalkyl)-1,4,5,8-tetramethoxynaphthalenes with Cerium(IV) Ammonium Nitrate, and the Further Demethylations to Naphthazarins[1)]

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(Received October 28, 1987)

Oxidative demethylation of 2-(α-hydroxyalkyl- and α-oxoalkyl)-1,4,5,8-tetramethoxynaphthalene with $(NH_4)_2Ce(NO_3)_6$ gave two isomeric dimethoxynaphthoquinones: 2-substituted and 6-substituted 5,8-dimethoxy-1,4-naphthoquinones. Further demethylations of the former isomers to the corresponding dihydroxynaphthoquinones required an AgO-40%HNO_3 reagent, while the latter isomers needed $AlCl_3$ as the demethylation reagent. Some comments regarding the mechanism of these oxidative demethylations with $(NH_4)_2Ce(NO_3)_6$ are given.

Naphthoquinones occur widely in nature among microorganisms and fungi,[2)] and have been studied regarding their colors and structures[3)] by many investigators. These days, many people are placing their hopes on such physiological activities[4)] as antitumor and antibiotic actions. Recently, Isayama et al.[5)] have applied for many patents for 5,8-dihydroxy-1,4-naphthoquinones as drugs for thrombosis, delayed hypersensitivity, and the healing of wounds.

Since our synthetic studies of naphthoquinone derivatives started, many problems have often occurred concerning the demethylation process of polymethoxynaphthalenes to hydroxynaphthoquinones. Therefore, the purpose of the present investigation was to search for a suitable reagent for a complete methoxyl cleavage of polymethoxynaphthalene intermediates. Although many reports[6)] have already appeared concerning demethylation, for example, on simple methyl ethers such as anisole, *p*-dimethoxybenzene, and monomethoxynaphthalene, no information in the literature has been found concerning the tetramethoxynaphthalenes, which we will report here.

It has been found by us that the demethylation of 1,4,5,8-tetramethoxynaphthalene with boron tribromide easily give naphthazarin.[7)] However, the treatment of the 2-substituted 1,4,5,8-tetramethoxynaphthalenes with boron tribromide or trimethylsilyl iodide gave no any desirable product, but, rather, only unidentified polymeric colored materials.

Demethylations of them with cerium(IV) ammonium nitrate[8)] (CAN) were successful and gave two isomeric dimethoxynaphthoquinones.

Further demethylation of them to the corresponding naphthazarins required AgO-40%HNO_3 or $AlCl_3$.

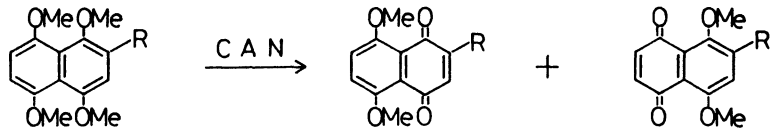
Fusarubin,[9)] Erythrostominone,[9)] Purpuromycin,[10)] and Fredericamycin A[11)] are new series of naphthazarin antibiotics.

Knowledge and information concerning demethylation, and the products obtained here, will generally be applicable for the synthesis of the above-mentioned naphthazarin antibiotics.[12)]

Results and Discussion

The demethylation of 2-substituted 1,4,5,8-tetramethoxynaphthalene (**1—9**) with 2.5 equiv of CAN usually gave two isomeric products, 2-substituted and 6-substituted 5,8-dimethoxy-1,4-naphthoquinones (former is named as type A and latter as type B) (Scheme 1, Table 1). The product mixture of A and B could be separated by silica gel or alumina column chromatography, and eluted by chloroform in the order of B and A.

Identifications of these naphthoquinone isomers were easy by ^1H NMR. The signals of their quinone ring protons were always observed more upfield than those of the benzene ring protons (Chart 1).[3a)] For example, in 5,8-dimethoxy-1,4-naphthoquinone (**1a**), the proton signals due to the quinone ring were observed at δ 6.77 (lit,[3a)] 6.75) and the benzene ring protons were at δ 7.32 (lit,[3a)] 7.31). A quinone ring proton of type A showed an allylic coupling with the



1 - 9 Type A 1a - 9a Type B 2b - 9b

Scheme 1.

protons at the α-positions of the side chain. For instance, the C_3-proton in 2-hydroxymethyl-5,8-dimethoxy-1,4-naphthoquinone (**2a**) showed a sharp triplet (J=1.6 Hz), clearly showing a coupling with two methylene protons of the hydroxymethyl side chain (Chart 2).

From Table 1, it can be seen that upon the demethylation of 2-substituted 1,4,5,8-tetramethoxynaphthalenes with CAN, substrates having electron-donating α-hydroxyalkyls gave, principally, type-A quinones; the minors were type-B. On the other hand, a substrate having electron-withdrawing an acetyl or a formyl group resulted in the formation of type-B, preferentially. These results suggested that CAN chose its target and attacked at the carbon atom having the highest electron density among the C_1, C_4, C_5, and C_8 (Table 2).

The ^{13}C chemical shifts of the ring carbon atoms of 2-substituted 1,4,5,8-tetramethoxynaphthalenes (**2—7**)

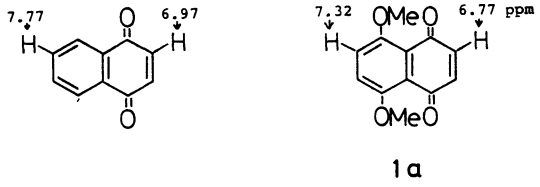


Chart 1.

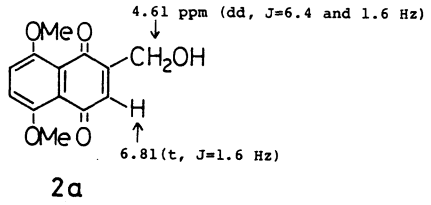
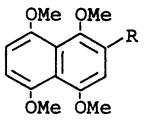
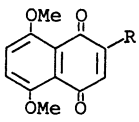
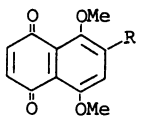


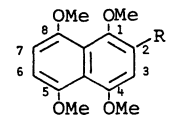
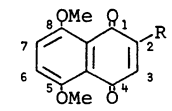
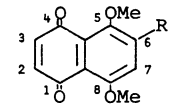
Chart 2.

Table 1. Demethylation of 2-Substituted 1,4,5,8-Tetramethoxynaphthalene with CAN

Substrate	Product (yield %)	
		
R	Type A	Type B
1:[a] H	**1a** (70)	—
2: CH_2OH	**2a** (75)	**2b** (13)
3: $CH(OH)CH_3$	**3a** (61)	**3b** (13)
4: $CH(OH)(CH_2)_3CH_3$	**4a** (42)	**4b** (16)
5:[a] $CH(OH)(CH_2)_2CH(CH_3)_2$	**5a**[a] (52)	**5b**[a] (17)
6:[a] $CH(OH)(CH_2)_2C(OH)(CH_3)_2$	**6a**[a] (70)	**6b**[a] (15)
7:[a] $CH(OH)(CH_2)_2COCH_3$	**7a** (33)	**7b** (33)
8: $COCH_3$	**8a** (3)	**8b** (77)
9:[a] CHO	**9a** (0)	**9b**[b] (85)

a) See Ref. 7. b) See Ref. 12.

Table 2. ^{13}C NMR Chemical Shifts (ppm) of the Ring Carbon Atoms of 2-Substituted 1,4,5,8-Tetramethoxynaphthalene and 2-Substituted or 6-Substituted 5,8-Dimethoxy-1,4-naphthoquinone

Substrate  R	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
1: H	151.27	108.84	108.84	151.27	151.27	108.84	108.84	151.27
2: CH_2OH	146.82	131.17	107.45	153.03	151.12	107.61	108.05	150.00
3: $CH(OH)CH_3$	145.84	135.58	105.51	153.27	151.22	107.61	108.25	150.10
4: $CH(OH)(CH_2)_3CH_3$	146.09	134.69	105.95	153.13	151.18	107.61	108.20	150.10
5: $CH(OH)(CH_2)_2CH(CH_3)_2$	146.23	134.65	106.00	153.18	151.22	107.71	108.30	150.14
6: $CH(OH)(CH_2)_2C(OH)(CH_3)_2$	145.70	134.75	106.05	153.03	151.03	107.37	108.15	149.95
7: $CH(OH)(CH_2)_2COCH_3$	145.96	134.02	105.71	153.11	151.09	107.59	108.24	149.99
8: $COCH_3$	153.11	129.66	105.71	151.22	151.22	111.16	108.11	151.48
9: CHO	156.81	125.84	101.29	151.29	151.29	112.72	108.37	153.43
								
1a: H	184.59	138.17	138.17	184.59	153.56	120.38	120.38	153.56
2a: CH_2OH	184.92	148.36	133.69	185.44	153.95	120.25	120.77	153.76
								
9b: CHO	183.81	138.88	137.96	183.81	156.09	135.12	116.88	155.83

are shown in Table 2. In the compounds **2—7** of the electron-donating groups, the C_1s were shielded to an extent of about 5 ppm; inversely in **8** and **9** of the electron-withdrawing groups, the C_1s were deshielded to 1.8 and 5.5 ppm, respectively.

Our study on the correlation between Tables 1 and 2 resulted in the following conclusions. The carbon atom having the highest electron density among the C_1, C_4, C_5, and C_8 (namely, the carbon atom which was observed[13] at the most upfield), will receive the CAN-attack, and the para positional methoxyl group will immediately suffer the next oxidative demethylation to form dimethoxynaphthoquinones. The obtained dimethoxynaphthoquinones should not be affected by CAN any more because of their two carbonyls (as described later in this text). This conclusion will be supported by the fact that the demethylation of tetramethoxynaphthalene to dimethoxynaphthoquinone required 2 molar equiv of CAN (Table 3), and the use of any excess amount of CAN resulted only in the formation of dimethoxynaphthoquinone, with no other possible product such as mono-, tri-, and tetrahydroxylated naphthalenes.

Castagnoli et al.[8] studied the demethylation of 1,4-dimethoxy-2,3,5,6-tetramethylbenzene (**10**) with CAN in $H_2{}^{18}O$ and proved the fact that the product, quinone **12**, received two heavy oxygen atoms in their carbonyls from the heavy water medium. They proposed a demethylation mechanism (Scheme 2) in which a pathway through intermediate **11** is shown. However, they did not discuss the more detailed reaction mechanism.

In our case, we also suppose two kinds of intermediates: one is **16** when the substituent R is electron-donating, and the other is **20** when R is electron-withdrawing (Chart 3).

The mechanism of the side-chain oxidation of alkylated aromatic hydrocarbons with CAN has been well established by Baciocchi et al.[14] There is no doubt that the first step of the reactions on toluene, for example, is a formation of the radical cation:

$$ArCH_3 + Ce^{IV}NO_3 \rightarrow ArCH_3{}^{\dagger} + Ce^{III}NO_3$$

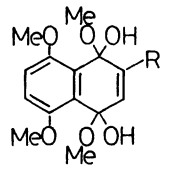
By analogy with their result, we supposed that the compounds **2—7** will form a radical cation intermediate **13**, which will be attacked by water to form the next radical **14**. Accordingly, as CAN in an aqueous solution is dissociated into $[Ce(NO_3)_6]^{2-}$ and $NH_4{}^+$ ions,[15] one-electron oxidation in the case of **2—7** with $[Ce(NO_3)_6]^{2-}$ gives a radical cation[16] **13** and an electron-donating group R will help in its formation and stabilization. Next, water attacks **13** to form radical **14** and the subsequent oxidation of the para positional methoxyl by another $[Ce(NO_3)_6]^{2-}$ ion affords **16** and the final products **2a—7a**, through **15**.

On the other hand, when R is an electron-withdrawing group, substrates **8** and **9** gave **8b** and **9b**,

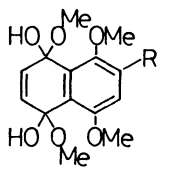
Table 3. Demethylation of 2-Formyl-1,4,5,8-tetramethoxynaphthalene **9** with Various Amounts of CAN

CAN(molar equiv. amount)	Yield of **9b** (%)
1.0	38+47[a]
1.5	68+16[a]
2.0	81
2.5	85
3.0	80
5.0	79
10.0	73

a) The recovery of **9**.

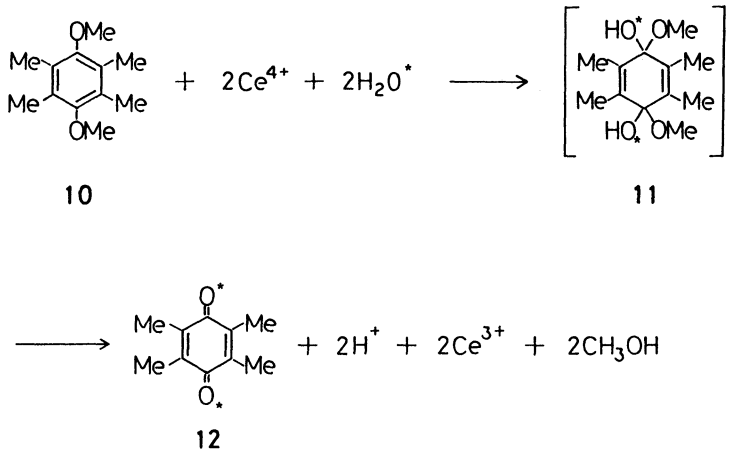


16



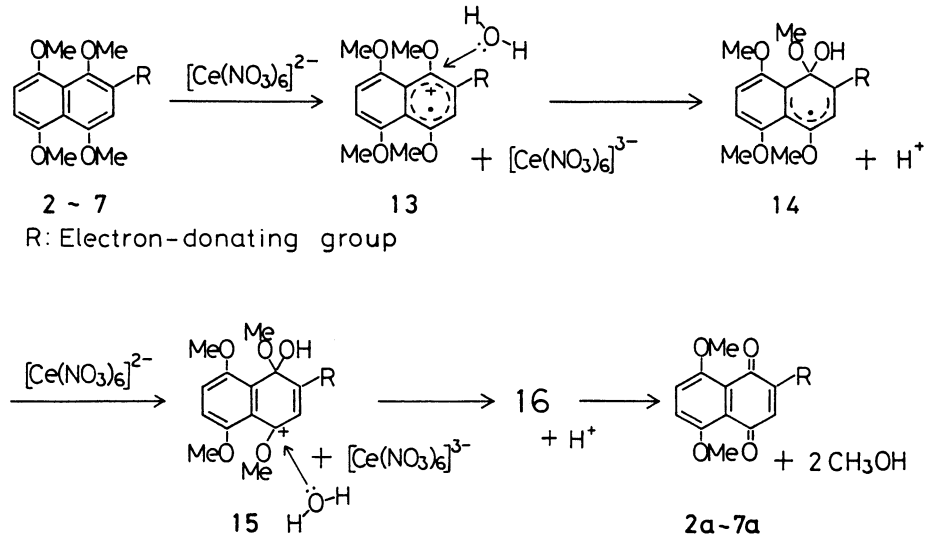
20

Chart 3.

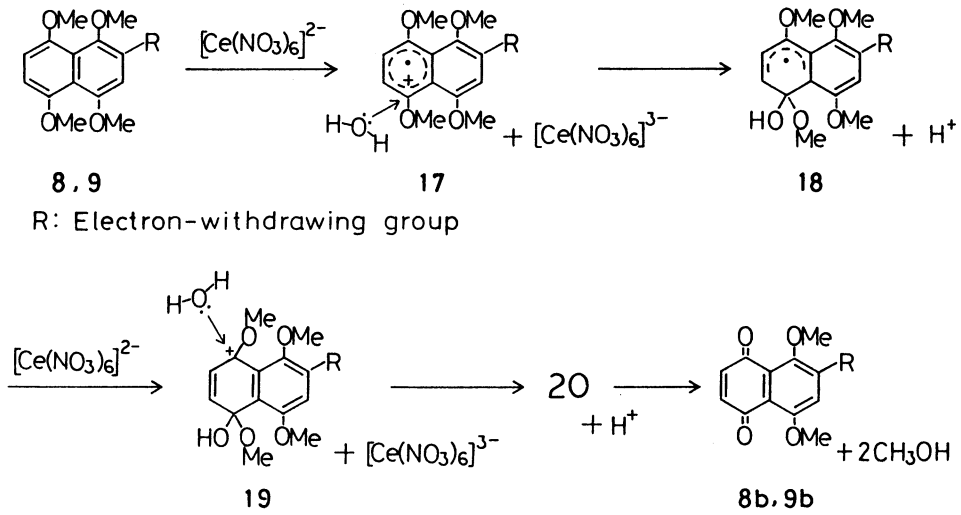


10 **11** **12**

Scheme 2.



Scheme 3.



Scheme 4.

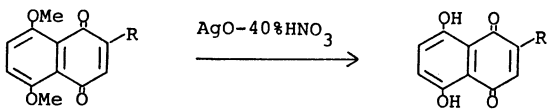
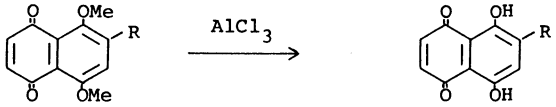
respectively, via intermediates **17**, **18**, **19**, and **20**.

A further treatment of these dimethoxynaphthoquinones **1a—6a**, **8a**, and **9b** with CAN resulted in no reaction; only the starting materials were recovered.

The ^{13}C chemical shifts of the ring carbon atoms of **1a**, **2a**, and **9b** are shown in Table 2, where the C_5 and C_8 carbons are more deshielded than those of **1**, **2**, and **9** within a range of 2—5 ppm. These downfield shifts are attributable to a decrease in the electron density of the carbon atoms (C_5 and C_8 of **1a**, **2a**, and **9b**) by near $C_{1,4}$-quinone-dicarbonyls. The decrease of the electron density at C_5 or C_8 prohibits a further CAN-attack either at C_5 or C_8.

Our subsequent studies concerning further demethylation of the 5,8-dimethoxy-1,4-naphthoquinones have yielded some other interesting results, as follows. The demethylation of the dimethoxynaphthoquinones (**1a—6a**) having electron-donating substituents with AgO-40% HNO_3[17] reagent gave 5,8-dihydroxy-1,4-naphthoquinones (**1c—6c**) (Table 4).

Table 4. Demethylation of 2-Substituted or 6-Substituted 5,8-Dimethoxy-1,4-naphthoquinone

Substrate	Product (%)
	
R	
1a: H	**1c** (53)
2a: CH_2OH	**2c** (52)
3a: $CH(OH)CH_3$	**3c** (22)
4a: $CH(OH)(CH_2)_3CH_3$	**4c** (22)
5a: $CH(OH)(CH_2)_2CH(CH_3)_2$	**5c** (28)
6a: $CH(OH)(CH_2)_2C(OH)(CH_3)_2$	**6c** (27)
	
8b: $COCH_3$	**8c** (71)
9b: CHO	**9c** (43)

However, the demethylation of the dimethoxynaphthoquinones **8b** and **9b**, having electron-withdrawing substitutents, required $AlCl_3$ instead of the above AgO-40%HNO_3 as the demethylation agent (Table 4). The AgO-40%HNO_3 system was quite unsuitable in these cases because of no reaction.

Experimental

^1H and ^{13}C NMR spectra were taken on a JEOL JNM-60 in $CDCl_3$ using Me_4Si and $CDCl_3$ as internal standards, respectively. Mass spectra and IR spectra were obtained with a JEOL DX-300 spectrometer, and a Hitachi 260-30 spectrometer, respectively. Column chromatography was carried out on silica gel (Wakogel C-200) or on alumina (Sumitomo, KCG-30) eluting with chloroform. Melting points were determined with a Yanagimoto micromelting point apparatus and were uncorrected.

2-Hydroxymethyl-1,4,5,8-tetramethoxynaphthalene (2). A sample of 2-formyl-1,4,5,8-tetramethoxynaphthalene (**9**)[7] (2.0 g, 7.24 mmol) in THF (40 ml) was reduced with $LiAlH_4$ (1.37 g, 36 mmol) under ice cooling. After stirring at room temperature for 3 h, the reaction mixture was decomposed by an addition of 1M HCl (1M=1 mol dm^{-3}), and extracted with chloroform (100 ml×3). The chloroform solution was washed with brine, dried over Na_2SO_4, and the solvent was evaporated. The crude product was chromatographed on silica gel to give 1.92 g (99%) of a sample of **2**, mp 99—100 °C. IR (KBr) 3520 (OH) and 1060 cm^{-1} (OCH_3, OH); ^1H NMR δ=2.42 (s, 1H, OH), 3.76, 3.88, 3.90, 3.92 (each s, 3H, OCH_3), 4.84 (s, 2H, CH_2), 6.80 (s, 2H, ArH), and 6.91 (s, 1H, ArH); MS, m/z 278 (M^+), 263, and 245. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52%. Found: C, 64.39; H, 6.57%.

2-(1-Hydroxyethyl)-1,4,5,8-tetramethoxynaphthalene (3). The aldehyde **9** (2.76 g, 10 mmol) in THF (40 ml) was added to methylmagnesium iodide (30 mmol) in ether (30 ml), and the mixture was stirred at room temperature for 1 h, decomposed with aq. NH_4Cl, and extracted with chloroform (100 ml×3). The usual work up and purification of the crude product by alumina chromatography gave 2.9 g (99%) of a sample of **3**. Recrystallization from hexane gave an analytical sample, mp 84—85 °C. IR (KBr) 3450 (OH), 1600, and 1070 cm^{-1}; ^1H NMR δ=1.50 (d, J=6.5 Hz, 3H, CH_3), 2.23 (broad, 1H, OH), 3.76, 3.89 (each s, 3H, OCH_3), 3.93 (s, 6H, OCH_3), 5.43 (q, J=6.5 Hz, 1H, CH), 6.81 (s, 2H, ArH), and 7.00 (s, 1H, ArH); MS, m/z 292 (M^+), 274 (M^+-H_2O), and 220. Calcd for $C_{16}H_{20}O_5$: C, 65.73; H, 6.91%. Found: C, 65.62; H, 7.00%.

2-(1-Hydroxypentyl)-1,4,5,8-tetramethoxynaphthalene (4). Treatment of the aldehyde **9** (1.66 g, 6 mmol) with butylmagnesium bromide (18 mmol) gave a crude product. Chromatographic purification on silica gel gave 1.99 g (99%) of a sample of **4** as an oil. IR (neat) 3450 (OH), 1600, and 1070 cm^{-1}; ^1H NMR δ=0.89 (t, J=6.6 Hz, 3H, CH_3), 1.1—1.9 (m, 6H, CH_2), 2.42 (broad, 1H, OH), 3.74, 3.88 (each s, 3H, OCH_3), 3.92 (s, 6H, OCH_3), 5.22 (t, J=6.0 Hz, 1H, CH), 6.80 (s, 2H, ArH), and 6.97 (s, 1H, ArH); MS, m/z 334 (M^+), 316 (M^+-H_2O), 301, 270, 231, and 137; HRMS m/z Calcd for $C_{19}H_{26}O_5$ 334.1781. Found 334.1784.

2-Acetyl-1,4,5,8-tetramethoxynaphthalene (8). A mixture of the alcohol **3** (610 mg, 2.09 mmol) and an activated manganese dioxide[18] (6 g) in benzene (20 ml) was refluxed for 15 h. Filtration, concentration, and chromatography on silica gel gave 382 mg (63%) of a sample of **8**. Recrystallization from hexane gave yellow crystals, mp 68—68.5 °C. IR (KBr) 1665 (C=O), 1600, 1370, 1070, and 1050 cm^{-1}; ^1H NMR δ=2.77 (s, 1H, $COCH_3$), 3.79, 3.90, 3.96, 3.98 (each s, 3H, OCH_3), 6.92 (s, 2H, ArH), and 7.09 (s, 1H, ArH); MS, m/z 290 (M^+), 275 (M^+-CH_3), 260, 232, and 218. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25%. Found: C, 66.11; H, 6.30%.

General Procedure for Oxidative Demethylation of 2-Substituted 1,4,5,8-Tetramethoxynaphthalenes (1—9) with CAN. A solution of CAN (2.5—3 mmol, 2.5—3 equiv) in water (5 ml) was added dropwise to a solution of 2-substituted 1,4,5,8-tetramethoxynaphthalene (1 mmol) in acetonitrile (10 ml), or in a mixture of acetonitrile-chloroform (5 : 1 v/v), at room temperature for 30 min, the reaction mixture was diluted with water, extracted with chloroform, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel with chloroform as eluent and recrystallized.

1a: reddish-orange crystals from ligroine (bp 75—120 °C)-benzene; mp 160—161 °C (lit,[19] 157 °C); IR (KBr) 1650 (C=O), 1582, 1565, 1045, and 1020 cm^{-1}; ^1H NMR δ=3.96 (s, 6H, OCH_3), 6.77 (s, 2H, quinone ring H), and 7.32 (s, 2H, benzene ring H); MS, m/z 218 (M^+), 189, 172, 161, 131, and 76.

2a and 2b. 2b: the first fraction from silica gel chromatography; mp 135—136 °C; ^1H NMR δ=2.49 (t, J=6.1 Hz, 1H, OH), 3.83, 3.40 (each s, 3H, OCH_3), 4.87 (d, J=6.1 Hz, 2H, CH_2), 6.78 (s, 2H, quinone ring H), and 7.51 (s, 1H, benzene ring H). **2a:** the second fraction; orange crystals (from ethanol); mp 176—176.5 °C; IR (KBr) 3480, 3350, 1640 (C=O), 1585, 1565, 1075, 1045, and 965 cm^{-1}; ^1H NMR δ=2.41 (t, J=6.1 Hz, 1H, OH), 3.96 (s, 6H, OCH_3), 4.61 (dd, J=6.1 and 1.6 Hz, 2H, CH_2), 6.81 (t, 1H, J=1.6 Hz, quinone ring H), and 7.32 (s, 2H, benzene ring H); MS, m/z 248 (M^+), 233, 218, and 201. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87%. Found: C, 62.56; H, 4.88%.

3a and 3b. 3b: the first fraction from silica-gel chromatography; an orange semisolid; ^1H NMR δ=1.56 (d, J=6.5 Hz, 3H, CH_3), 2.2 (broad, 1H, OH), 3.83, 3.99 (each s, 3H, OCH_3), 5.30 (q, J=6.5 Hz, 1H, CH), 6.76 (s, 2H, quinone ring H), and 7.55 (s, 1H, benzene ring H). **3a:** the second fraction; orange crystals (from ligroine-benzene); mp 144—145 °C; IR (KBr) 3480 (OH), 1650 (C=O), 1050, and 1020 cm^{-1}; ^1H NMR δ=1.48 (J=6.6 Hz, 3H, CH_3), 2.70 (d, J=5.2 Hz, 1H, OH), 3.96, 3.97 (each s, 3H, OCH_3), 4.94 (m, 1H, CH), 6.78 (d, J=1.3 Hz, 1H, quinone ring H), and 7.32 (s, 2H, benzene ring H); MS, m/z 262 (M^+), 247 (M^+-CH_3), 231, 219, and 205. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38%. Found: C, 64.33; H, 5.43%.

4a and 4b. 4b: the first fraction from alumina chromatography; an orange oil; ^1H NMR δ=0.90 (t, J=6.0 Hz, 3H, CH_3), 1.1—1.9 (m, 6H, CH_2), 2.55 (broad, 1H, OH), 3.83, 3.99 (each s, 3H, OCH_3), 5.12 (m, 1H, CH), 6.77 (s, 2H, quinone ring H), and 7.51 (s, 1H, benzene ring H). **4a:** the second fraction; an orange oil; IR (neat) 3480 (OH), 1655, 1590, 1570, and 1060 cm^{-1}; ^1H NMR δ=0.90 (t, J=6.0 Hz, 3H, CH_3), 1.1—1.9 (m, 6H, CH_2), 2.55 (broad, 1H, OH), 3.96 (s, 6H, OCH_3), 4.74 (m, 1H, CH), 6.76 (d, J=1.4 Hz, 1H, quinone ring H), and 7.31 (s, 2H, benzene ring H); MS, m/z 304 (M^+), 289 (M^+-CH_3), and 247; HRMS, m/z Calcd for $C_{17}H_{20}O_5$ 304.1311. Found 304.1314.

7a and 7b. 7b: the first fraction from silica-gel chromatography; an orange oil; ^1H NMR δ=2.18 (s, 3H, $COCH_3$), 1.5—

2.9 (m, 5H, CH_2 and OH), 3.81, 3.94 (each s, 3H, OCH_3), 5.10 (m, 1H, CH), 6.77 (s, 2H, quinone ring H), and 7.55 (s, 1H, benzene ring H). **7a:** the second fraction; an orange oil; IR (KBr) 3470 (OH), 1710 (ketone C=O), 1655 (quinone C=O), 1590, 1570, and 1055 cm^{-1}; ^1H NMR δ=2.18 (s, 3H, $COCH_3$), 1.5—2.9 (m, 5H, CH_2 and OH), 3.94 (s, 6H, OCH_3), 4.78 (m, 1H, CH), 6.83 (s, 1H, quinone ring H), and 7.30 (s, 2H, benzene ring H); MS, *m/z* 318 (M^+), 300, and 247; HRMS, *m/z* Calcd for $C_{17}H_{18}O_6$ 318.1104. Found 318.1129.

8a and 8b. 8b: the first fraction from silica-gel chromatography; orange crystals (from ligroine-benzene); mp 155—155.5 °C; IR (KBr) 1685 (ketone C=O), 1655 (quinone C=O), 1620, 1580, and 1040 cm^{-1}; ^1H NMR δ=2.69 (s, 3H, $COCH_3$), 3.85, 4.00 (each s, 3H, OCH_3), 6.84 (s, 2H, quinone ring H), and 7.48 (s, 1H, benzene ring H); MS, *m/z* 260 (M^+), 245 (M^+-CH_3), 231, and 131. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65%. Found: C, 64.17; H, 4.72%. **8a:** the second fraction; an orange semisolid; ^1H NMR δ=2.60 (s, 3H, OCH_3), 3.85, 3.97 (each s, 3H, OCH_3), 6.98 (s, 1H, quinone ring H), and 7.35 (s, 2H, benzene ring H).

General Procedure for Oxidative Demethylation of 2-Substituted 5,8-Dimethoxy-1,4-naphthoquinones (1a—6a) with AgO-40%HNO_3. 40% HNO_3 (12 ml) was added dropwise to a mixture of AgO (10 mmol, 10 equiv), acetone (24 ml), and 2-substituted 5,8-dimethoxy-1,4-naphthoquinone (1 mmol) at 15—25 °C for 5 min. After stirring at room temperature for 30 min, the mixture was diluted with water, extracted with dichloromethane (50 ml×3) washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica-gel chromatography and recrystallized.

1c: reddish brown crystals; mp 202—205 °C (lit,[20] 201—202 °C); IR (KBr) 1610 (C=O), 1565, and 1225 cm^{-1}; ^1H NMR δ=7.14 (s, 4H, ArH) and 12.39 (s, 2H, ArOH); MS, *m/z* 190 (M^+), 136, 134, and 108.

2c: brown crystals (from hexane-ethanol); mp 180—183 °C; IR (KBr) 3430 (sharp, OH), 1610 (C=O), 1560, 1205, and 1080 cm^{-1}; ^1H NMR δ=2.11 (t, *J*=6.1 Hz, 1H, OH), 4.76 (dd, *J*=6.1 and 1.7 Hz, 2H, CH_2), 7.16 (t, *J*=1.5 Hz, 1H, quinone ring H), 7.21 (s, 2H, benzene ring H), 12.46 and 12.48 (each s, 1H, ArOH); MS, *m/z* 220 (M^+), 202 (M^+-H_2O), 191, 174, and 149. Calcd for $C_{11}H_8O_5$: C, 60.01; H, 3.66%. Found: C, 59.98; H, 3.77%.

3c: brown crystals (from hexane); mp 128—129.5 °C; IR (KBr) 3350 (broad, OH), 1610, 1570, 1200, 1105, and 1045 cm^{-1}; ^1H NMR δ=1.54 (d, *J*=6.6 Hz, 3H, CH_3), 1.96 (broad, 1H, OH), 5.08 (qd, *J*=6.6 and 1.3 Hz, 1H, CH), 7.17 (d, *J*=1.3 Hz, quinone ring H), 7.21 (s, 2H, benzene ring H), 12.46 and 12.58 (each s, 1H, ArOH); MS, *m/z* 234 (M^+), 216 (M^+-H_2O), 168, and 139. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30%. Found: C, 60.80; H, 4.30%.

4c: brown crystals (from hexane-ethanol); mp 95.5—96.5 °C; IR (KBr) 3250 (broad, 1H, OH), 1615, 1575, 1200, 1115, and 1060 cm^{-1}; ^1H NMR δ=0.92 (t, *J*=5 Hz, 3H, CH_3), 1.1—1.9 (m, 6H, CH_2), 2.20 (broad, 1H, OH), 4.89 (td, *J*=5.1 and 1.0 Hz, 1H, CH), 7.12 (d, *J*=1.0 Hz, 1H, quinone ring H), 7.19 (s, 2H, benzene ring H), 12.46 and 12.58 (each s, 1H, ArOH); MS, *m/z* 276 (M^+), 258 (M^+-H_2O), 229, 220, and 219. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84%. Found: C, 64.45; H, 5.91%.

General Procedure for Demethylation of 6-Substituted 5,8-Dimethoxy-1,4-naphthoquinones (8b and 9b) with $AlCl_3$. $AlCl_3$ (10 mmol, 10 equiv) was added to a solution of 6-substituted 5,8-dimethoxy-1,4-naphthoquinone (1 mmol) in dichloromethane (10 ml) cooled in an ice bath. After stirring at room temperature for 2 h, the reaction mixture was decomposed with 5 wt% aqueous oxalic acid (100 ml), extracted with chloroform, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica-gel chromatography and recrystallized from hexane. **8c:** brown crystals; mp 120—121.5 °C; IR (KBr) 1678 (ketone C=O), 1610 (quinone C=O), 1550, and 1215 cm^{-1}; ^1H NMR δ=2.71 (s, 3H, CH_3), 7.11 (s, 2H, quinone ring H), 7.60 (s, 1H, benzene ring H), 12.13 and 13.08 (each s, 1H, ArOH); MS, *m/z* 232 (M^+), 217, 189, and 161. Calcd for $C_{12}H_8O_5$: C, 62.07; H, 3.47%. Found: C, 61.73; H, 3.51%.

9c: brown crystals; mp 172—174 °C (decomp); IR (KBr) 1690 (ketone C=O), 1610 (quinone C=O), 1555, and 1190 cm^{-1}; ^1H NMR δ=7.10 (s, 2H, quinone ring H), 7.79 (s, 1H, benzene ring H), 10.54 (s, 1H, CHO), 12.03 and 12.77 (each s, 1H, ArOH); MS, *m/z* 218 (M^+), 190 (M^+-CO), 172, and 134. Calcd for $C_{11}H_6O_5$: C, 60.56; H, 2.77%. Found: C, 60.42; H, 3.00%.

We are grateful to Professor Otohiko Tsuge of Kyushu University for valuable suggestions. We also thank Mr. Yoshiyuki Kitajima, Mr. Iwao Seto, Mr. Toshiyuki Tsuboi, and Mr. Takayuki Hayashida for their technical assistances, Mr. Yoshiharu Okada for the elemental analyses, Mrs. Eriko Furukawa for the NMR spectra, and Mrs. Keiko Yamaguchi for MS spectra.

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