Naturally Occurring 5-Lipoxygenase Inhibitors. VI.[1] Structures of Ardisiaquinones D, E, and F from *Ardisia sieboldii*

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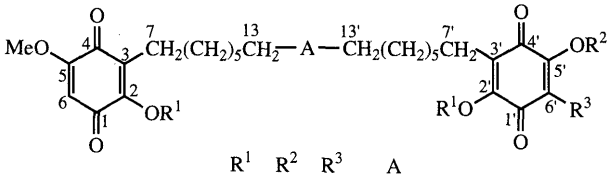
New 1,4-benzoquinone derivatives, ardisiaquinones D (2), E (4), and F (5) along with the known ardisiaquinones A (1) and B (3) have been isolated from the leaves of *Ardisia sieboldii* (Myrsinaceae) and shown to be 5-lipoxygenase inhibitors. Their structures have been elucidated by spectroscopic analysis and chemical degradation. The degree of inhibition of 5-lipoxygenase activity by the ardisiaquinones and some derivatives of ardisiaquinone A is reported.

Key words *Ardisia sieboldii*; 1,4-benzoquinone; 5-lipoxygenase inhibitor; ardisiaquinone D; ardisiaquinone E; ardisiaquinone F

In the arachidonic acid cascade of prostaglandin biosynthesis, 5-lipoxygenase is an important enzyme catalyzing the oxygenation of arachidonic acid specifically at C-5, the initial step in the biosynthesis of the slow-reacting substances of anaphylaxis which are now known to be leukotrienes C4, D4, and E4. A group of leukotrienes is regarded as one of the chemical mediators of bronchial asthma.[2] Hence, from a medicinal point of view it is important to search for a specific inhibitor of 5-lipoxygenase in natural products. We have already reported that some alkenyl-1,4-benzoquinones, ardisianones A and B,[3] and alkenylphenol, belamcandol A,[4] isolated from *Ardisia japonica* and *Belamcanda chinensis*, respectively, exhibit 5-lipoxygenase inhibitory activity. Previous results suggest that naturally occurring 1,4-benzoquinones could be candidates for evaluation of their 5-lipoxygenase inhibitory activity. Extensive study of the distribution of benzoquinone derivatives among Myrsinaceae plants by Natori *et al.*,[5] indicated the *Ardisia* species to be a rich source of benzoquinone derivatives. In fact, we have already reported that ardisiaquinone A (**1**), the main component of *Ardisia sieboldii*, is a potent 5-lipoxygenase inhibitor.[1] These results encouraged us to reinvestigate the chemical constituents of *Ardisia sieboldii* collected on the island of Ishigaki during our search for analogs of ardisiaquinone A for structure function studies. Repeated chromatography of the methanol extract of its leaves resulted in the isolation of new 1,4-benzoquinones, **2**, **4**, and **5**, designated as ardisiaquinones D, E, and F along with the known ardisiaquinones A (**1**) and B (**3**).[6,7] As expected, these benzoquinones strongly inhibited 5-lipoxygenase activity in the cytosol of guinea pig polymorphonuclear leukocytes. In this paper, we report the structures of these three new benzoquinones **2**, **4**, and **5**, and their 5-lipoxygenase inhibitory activity.

Ardisiaquinone D (**2**), mp 88—90 °C, has the molecular formula $C_{31}H_{42}O_8$ [*m/z* 542.2878 (M^+); Calcd 542.2879] suggesting the addition of an extra methyl group to ardisiaquinone A (**1**). The ultraviolet (UV) spectrum showed a dioxygenated benzoquinone chromophore at 284 and 420 nm.[8] The infrared (IR) spectrum revealed absorptions at 3370, 1660, and 1630 cm^{-1} attributable to hydroxy groups and the benzoquinone moiety, respectively, and the presence of the two hydroxy groups was also supported by the detection of temperature-variable proton signals, observed at δ_H 7.14 and 7.24 at 27 °C, in the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum. The ^{1}H-NMR spectrum of **2** contained singlet methyl and methoxy signals at δ_H 1.93 and 4.09, in addition to a series of signals, being made up of a methoxy at δ_H 3.86 (3H, s), olefinic protons at δ_H 5.33 (2H, t, J=4.8 Hz) and 5.84 (1H, s), and methylenes integrated with 28H (δ_H 1.30—1.44 and 2.00—2.43), which were very similar to those of **1**.[1] Additionally, the ^{13}C-nuclear magnetic resonance (^{13}C-NMR) data (Table 1) of **2** in combination with the distortionless enhancement by polarization transfer



	R^1	R^2	R^3	A
1	H	Me	H	
1a	Me	Me	H	
1b	H	Me	H	CH_2CH_2
1c	H	Me	H	
2	H	Me	Me	
2a	Me	Me	Me	
2b	Me	Me	Me	
3	H	H	Me	

4 R = H

5 R = Me

Fig. 1

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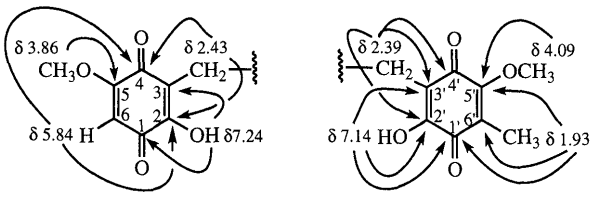
(DEPT) indicated the presence of fourteen sp^2 carbon signals assignable to one disubstituted double-bond (δ_C 129.9) and two kinds of 1,4-benzoquinone units, half the signals of which were identical with those of the 1,4-benzoquinone ring in **1**, whereas the remaining six quaternary signals at δ_C 118.7, 122.7, 150.8, 157.2, 183.7, and 184.2 could be allocated to the carbons of a fully substituted 1,4-benzoquinone by the ^{1}H-detected multiple-bond heteronuclear multiple quantum coherence (HMBC) spectrum as shown in Fig. 2. Thus, the olefinic methyl proton signal at δ_H 1.93 correlated with C-1′, C-6′, and C-5′, whereas the hydroxy proton signal at δ_H 7.14 showed clear cross peaks with C-1′, C-2′, and C-3′, the latter two carbons in turn showed correlations with the methylene signals observed at δ_H 2.39. Additionally, it was evident that the two methoxy groups, which resonated at δ_H 3.86 and 4.09, were attached to C-5 and C-5′, not only by HMBC (Fig. 2) but also by observation of the nuclear Overhauser effect (NOE) between the high-field methoxy signal and the singlet olefinic proton signal at δ_H 5.84. Furthermore, additional evidence supporting the presence of two types of *p*-benzoquinones was obtained from the prominent fragment ion peaks at *m/z* 168, 169, and 183 in the electron impact-mass spectrometry (EI-MS)[7] as shown in Fig. 3. The above spectral data showed that the two 1,4-benzoquinone rings present in **2** were the same as **1** and 3-alkenyl-2-hydroxy-5-methoxy-6-methyl-1,4-benzoquinone. Thus, taking the molecular formula into consideration, the two *p*-benzoquinone units were linked to the terminal positions of the C_{16} long chain having one double-bond like ardisiaquinone A (**1**). Compound **2** was converted to the methoxy derivative **2a** by diazomethane. The sole double-bond on the C_{16} linker in **2a** was oxidized with *m*-chloroperbenzoic acid followed by HIO_4 to give the two degraded products **2c** and **2d**, the spectral data of which showed equivalent structures and, thereby, the location of the double-bond must be at C-14 and 14′. The stereochemistry of the double-bond was assigned to *Z* from the diagnostic chemical shift of the allylic methylene carbon at δ 27.2.[9] Thus, these data corroborated that the structure of ardisiaquinone D (**2**) was (*Z*)-1-(3′,6′-dioxo-2′-hydroxyl-5′-methoxylcyclohexa-1′,4′-dienyl)-16-(3′,6′-dioxo-2′-hydroxyl-5′-methoxyl-4′-methylcyclohexa-1′,4′-dienyl)-8-hexadecene.

Table 1. ^{13}C-NMR Data (100 MHz, $CDCl_3$) for Compounds **1**—**5**

Carbon	1	2	3	4	5
1	182.8	182.8	182.9	182.9	182.8
2	151.5	151.5	151.6	151.7	151.6
3	119.2	119.2	119.3	119.3	119.2
4	181.7	181.7	181.7	182.0	181.7
5	161.1	161.1	161.2	161.1	161.1
6	102.2	102.2	102.2	102.2	102.2
7	29.7	29.6	29.5	31.0	31.2
13	27.1	27.2	27.2	27.1	27.2
14	130.0	129.9	129.9	130.0	130.0
1′	182.8	184.2	181.7	156.7	154.6
2′	151.5	150.8	151.6	107.9	107.7
3′	119.2	118.7	116.1	146.0	142.0
4′	181.7	183.7	182.9	107.9	107.7
5′	161.1	157.2	161.1	156.7	154.6
6′	102.2	122.7	111.6	100.2	107.7
7′	29.7	29.7	29.7	35.8	35.5
13′	27.1	27.2	27.2	27.1	27.2
14′	130.0	129.9	129.9	130.0	130.0
C_5-OMe	56.8	56.7	56.8	56.8	56.8
$C_{5'}$-OMe	56.8	61.5	—	—	—
$C_{6'}$-Me	—	8.0	8.5	—	7.6

The carbon signals assignable for C-8—C-12 and C-8′—C-12′. **1**: δ 22.6, 28.0, 29.2, 29.3, 29.5; **2**: δ 22.6, 28.0, 28.3, 29.2, 29.3, 29.4, 29.5; **3**: δ 22.4, 22.6, 28.0, 29.3, 29.4; **4**: δ 22.6, 28.0, 29.0, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7; **5**: δ 22.6, 28.2, 28.3, 29.2, 29.3, 29.4, 29.5.



Left 1,4-Benzoquinone Ring Right 1,4-Benzoquinone Ring

Fig. 2. Long Range C–H Correlations for the Left and Right 1,4-Benzoquinone Rings of **2** Based on HMBC (J_{C-H}=8.1 Hz)

Ardisiaquinone E (**4**), isolated as a viscous yellow oil, has the molecular formula $C_{29}H_{40}O_6$ determined by high resolution (HR) EI-MS. The UV and IR spectra of **4** showed the presence of hydroxy groups and a *p*-benzoquinone at 280 nm, and 3390, 1642 and 1610 cm^{-1}. The ^{1}H- and ^{13}C-NMR spectra of **4** revealed signals [δ_H 3.84 (3H, s, OCH_3), 5.83 (1H, s); δ_C: see Table 1] typical of a 3-alkenyl-2-hydroxy-5-methoxy-1,4-benzoquinone which is the common structural unit in **1** and **2**, and signals assignable to a symmetrical resorcinol-type benzene ring at δ_H 6.20 (1H, t, J=2.2 Hz) and 6.25 (2H, d, J=2.2 Hz), and δ_C 100.2 (C-6′), 107.9 (C-2′, 4′), 146.0 (C-3′), and 156.7 (C-1′, 5′), as well as signals due to the C_{16} alkenyl linker at δ_H 1.29—1.55 (20H, m), 2.19 (4H, m), 2.44 (2H, t, J=7.7 Hz), and 2.47 (2H, t, J=7.7 Hz). These spectral data imply that ardisiaquinone E consists of a *p*-benzoquinone unit identical with that in **1** and the resorcinol part, both of which are presumably linked *via* the C_{16} alkenyl chain containing one double-bond. This was supported by the detection of characteristic fragment ion peaks at *m/z* 168, 169, and *m/z* 123 and 124 in the EI-MS[4] as shown in Fig. 3, accounting for the rupture of the benzylic bonds of the alkenyl group, and by ob-

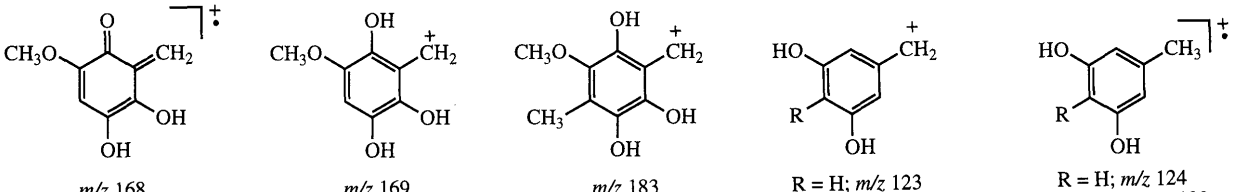


Fig. 3

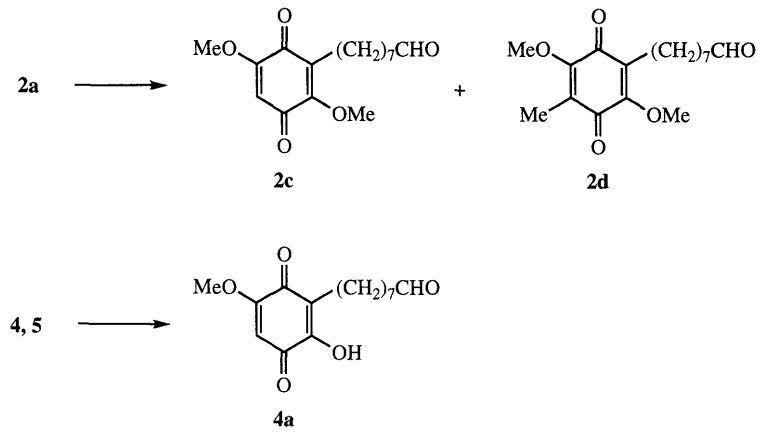


Chart 1. Degradation Products Obtained from **2a**, **4**, and **5** by Oxidative Cleavage of the Internal Olefin

servation of NOEs for the H-6 at δ_H 5.83, and the H-2′ and 4′ at δ_H 6.25 upon irradiation of the methoxy signal at δ_H 3.84 and the benzylic proton signal at δ_H 2.44, respectively. The location of the double-bond in the C_{16} linker was found to be at C-14 and 14′ by identification of the aldehyde **4a** [*m/z* 280 (M^+); δ_H 9.76 (1H, t, J= 2.2 Hz)], obtained from oxidative degradation of **4** by the same procedure as for **2**; its stereochemistry was also assigned as *Z* on the basis of the chemical shifts (δ_C 27.1) for the allylic methylene carbon. Accordingly, the structure of ardisiaquinone E (**4**) was assigned as (*Z*)-1-(3′,6′-dioxo-2′-hydroxyl-5′-methoxylcyclohexa-1′,4′-dienyl)-16-(3′,5′-dihydroxylphenyl)-8-hexadecene.

Ardisiaquinone F (**5**), mp 85—87 °C, has the molecular formula $C_{30}H_{42}O_6$ (*m/z* 498.2972, Calcd 498.2981), and its UV and IR spectra indicated the presence of hydroxy groups and a 1,4-benzoquinone moiety. The ^{1}H-NMR spectrum of **5** was closely related to that of ardisiaquinone E (**4**) except for an olefinic methyl at δ_H 2.10 (3H, s) and a 2H singlet aromatic proton signal at δ_H 6.25, indicating that there was one methyl group at δ_C 7.6 (q) at the C-6′ position on the resorcinol ring in **4**. This gross structure was consistent with the other spectral data as follows; ^{13}C-NMR (Table 1), EI-MS [*m/z* 168, 169, 137, 138 (base)], and NOE [δ_H 5.83/3.85 (OCH_3), δ_H 6.25/2.44 (benzylic H)]. The stereochemistry and position of the internal double-bond in the C_{16} alkenyl chain linking both rings was determined as *Z* (δ_C 27.2 for C-13 and 13′) and located at C-14 and 14′ by identification of **4a** degraded from **5** according to the same oxidative procedure as for **4** (Chart 1). Thus, the structure of ardisiaquinone F (**5**) was represented as (*Z*)-1-(3′,6′-dioxo-2′-hydroxyl-5′-methoxylcyclohexa-1′,4′-dienyl)-16-(3′,5′-dihydroxyl-4′-methylphenyl)-8-hexadecene.

The 5-lipoxygenase inhibitory activity of the new compounds isolated during the present study and the previously known 1,4-benzoquinone derivatives was evaluated using enzyme from guinea pig peritoneal polymorphonuclear leukocytes according to the method of Yamamoto *et al.*[10] The degree of inhibition (%) of 5-lipoxygenase by ardisiaquinone A (**1**) and its derivatives **1a**—**c**, and ardisiaquinones D (**2**), B (**3**), E (**4**), F (**5**), and some alkenyl 1,4-benzoquinones **6**—**8**[3,11] is listed in Table 2. Ardisiaquinone A (**1**), which exhibited 43% inhibition of 5-lipoxygenase activity at 0.1 μM was the most potent inhibitor of all the dimeric ardisiaquinones. The derivative **1c** containing an epoxide ring exhibited the strongest inhibitory activity of all the analogs of **1**. The methylated and dihydrogenated derivatives, **1a** and **1b**, however, exhibited decreased inhibitory activity, presumably due to a slight loss of hydrophilicity and free movement of both *p*-benzoquinone units spatially oriented in the same direction by the internal *Z* olefin. On the other hand, in comparison with the simple alkenyl 1,4-benzoquinones **6**—**8**, they were much less potent inhibitors than the dimeric 1,4-benzoquinones **1**—**5** except for maesanin (**7**).[11] The structural variation among these eight natural products and the three analogs of **1** allowed us to propose preliminary structure–activity relationships. It appears that one of the two dioxygenated 1,4-benzoquinone rings in ardisiaquinone A is essential, the hydroxy group at C-2 is somewhat less critical, and the nature of the other ring at the terminal position and the length of the linker are open to considerable variation.

Ardisiaquinone A[1] is a potent inhibitor of 5-lipoxygenase and exhibit almost identical activity to that of the clinically useful AAA-861.[12] Hence, synthesis of derivatives of ardisiaquinones may lead to compounds with increased potency.[13]

Table 2. Inhibition (%) of 5-Lipoxygenase in the Cytosol of Guinea Pig Polymorphonuclear Leukocytes by Ardisiaquinones and Their Derivatives

Compound	Inhibition (%)			
	Concentration (μM)			
	0.1	0.3	1.0	3.0
1	43	63	94	96
1a	7	54	88	91
1b	17	41	88	97
1c	66	92	96	96
2	4	44	86	—
3	21	—	89	89
4	24	28	70	80
5	7	29	58	—
6	0	0	16	—
7	10	22	67	—
8	0	0	10	13
NDGA[a]	0	24	—	—

a) Nor-dihydroguaiaretic acid.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were recorded on a Hitachi 340 spectrophotometer. IR spectra were measured on a Jasco A-2-2 spectrophtometer. ^{1}H- and ^{13}C-NMR spectra were obtained at 400 or 200 MHz (^{1}H-NMR) and 100.16 MHz (^{13}C-NMR) using JEOL GX-400 and Varian Unity 200 instruments. Chemical shift values were expressed in ppm downfield from tetramethylsilane as an internal standard. The MS were recorded on a JEOL AX-500 instrument. Silica-gel (Wako, C-300) was used for column chromatography. Silica-gel F_{254} (Merck) was used for analytical (0.25 mm) and preparative (0.5 mm) thin-layer chromatographies, and spots were visualized under UV (254 nm) light and by spraying with 40% $CeSO_4$–H_2SO_4 followed by heating.

Extraction and Purification Dried and powdered leaves (1.23 kg) of *Ardisia sieboldii* collected on Ishigaki island were immersed three times in methanol at room temperature for 3 d. Combined extracts were evaporated *in vacuo* to give a gummy extract (138 g), which was partitioned between *n*-hexane and water–methanol (4 : 1). The resultant water–methanol phase was extracted three times with benzene. The benzene soluble portion (37.8 g) was chromatographed over silica-gel eluting with benzene–EtOAc (8 : 1) and benzene–EtOAc (4 : 1). The fraction eluted with benzene–EtOAc (8 : 1) was rechromatographed on silica-gel with $CHCl_3$ to give ardisiaquinone D (**2**) (172 mg) as crystals. The precipitate which was formed from the fraction eluted with benzene–EtOAc (4 : 1) was recrystallized from C_2H_5OH–benzene to give ardisiaquinone A (**1**) (2.5 g) and the filtrate was chromatographed on silica-gel using a stepwise gradient [$CHCl_3$, $CHCl_3$–CH_3OH (50 : 1), and $CHCl_3$–CH_3OH (10 : 1)] to give ardisiaquinone B (**3**) (148 mg), ardisiaquinone E (**4**) (140 mg), and ardisiaquinone F (**5**) (135 mg).

Ardisiaquinone D (2) Yellow-orange powder (from benzene–*n*-hexane), mp 88—90 °C. EI-MS *m/z* (rel. int.): 542 (M^+, 78), 514 (23), 360 (14), 183 (100), 169 (95), 168 (96). UV λ_{max}^{EtOH} nm: 284 (ε 34900), 420 (ε 800). IR ν_{max}^{KBr} cm^{-1}: 3370 (OH), 1660, 1630. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (16H, m), 1.44 (4H, m), 1.93 (3H, s, $C_{6'}$-Me), 2.01 (4H, m, H-13, 13′), 2.39 (2H, t, J=7.8 Hz, H-7′), 2.43 (2H, t, J=7.7 Hz, H-7), 3.86 (3H, s, C_5-OMe), 4.09 (3H, s, $C_{5'}$-OMe), 5.33 (2H, t, J=4.8 Hz, H-14, 14′), 5.84 (1H, s, H-6), 7.14 (1H, s, $C_{2'}$-OH), 7.24 (1H, s, C_2-OH). ^{13}C-NMR: see Table 1. HR EI-MS *m/z*: 542.2878 (M^+), Calcd 542.2879 for $C_{31}H_{42}O_8$.

Oxidative Cleavage of the Double Bond in 2 Ardisiaquinone (**2**) (9 mg) was methylated with diazomethane to give the methylated derivative **2a** (9.2 mg), which was dissolved in CH_2Cl_2 (3 ml). To this solution was added *m*-chloroperoxybenzoic acid (4 mg) and then the reaction mixture was left standing at room temperature for 4 h. Ether was added to the reaction mixture and then the organic layer was washed with sat. $NaHCO_3$ sol. and sat. NaCl sol. After being dried over $MgSO_4$, the organic layer was evaporated *in vacuo* to give a residue, which was purified by prep. TLC ($CHCl_3$) giving rise to an epoxide **2b** (3.3 mg). To a solution of this epoxide in THF–water (2 ml, 1 : 1) was added HIO_4 (2.5 mg) and the reaction mixture was stirred at 45 °C for 2 h. Ether was added and the organic layer was washed with sat. $NaHCO_3$ sol. and sat. NaCl sol. After drying over $MgSO_4$, the organic layer was evaporated *in vacuo* to leave a residue, which was purified by prep. TLC ($CHCl_3$) to yield the aldehydes **2c** (0.5 mg) and **2d** (0.6 mg). **2c**: EI-MS *m/z*: 294, 279, 167, 153. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.25—1.55 (m), 2.41 (2H, m), 3.85 (3H, s), 4.05 (3H, s), 9.75 (1H, t, J=2.2 Hz). **2d**: EI-MS *m/z*: 308, 293, 280, 197, 181, 167, 153. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.20—1.55 (m), 1.98 (3H, s), 2.44 (2H, m), 4.04. (3H, s), 4.08 (3H, s), 9.76 (1H, t, J=1.8 Hz).

Ardisiaquinone E (4) Yellow colored oil. EI-MS *m/z* (rel. int.): 484 (M^+, 100), 169 (28), 168 (38), 124 (39), 123 (28). UV λ_{max}^{EtOH} nm: 280 (ε 35800). IR ν_{max}^{film} cm^{-1}: 3390 (OH), 1642, 1610. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.29 (16H, m), 1.45 (2H, m), 1.55 (2H, m), 2.19 (4H, m, H-13, 13′), 2.44 (2H, t, J=7.7 Hz, H-7′), 2.47 (2H, t, J=7.7 Hz, H-7), 3.84 (3H, s, C_5-OMe), 5.34 (2H, t, J=4.6 Hz, H-14, 14′), 5.83 (1H, s, H-6), 6.20 (1H, t, J=2.2 Hz, H-6′), 6.25 (2H, d, J=2.2 Hz, H-2′, 4′). ^{13}C-NMR: see Table 1. HR EI-MS *m/z*: 484.2821 (M^+), Calcd 484.2825 for $C_{29}H_{40}O_6$.

Oxidative Cleavage of the Double Bond in 4 The double-bond of **4** (7 mg) was cleaved by the same procedure as for **2**, affording the aldehyde **4a** (1.7 mg) as an oil. EI-MS *m/z*: 280 (M^+). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.43 (2H, t, J=7.0 Hz), 3.85 (3H. s), 5.83 (1H, s), 9.76 (1H, t, J=2.2 Hz).

Ardisiaquinone F (5) Orange powder (from benzene–EtOAc), mp 85—87 °C. EI-MS *m/z* (rel. int.): 498 (M^+, 70), 169 (50), 168 (78), 138 (100), 137 (97). UV λ_{max}^{EtOH} nm: 283 (ε 48900). IR ν_{max}^{KBr} cm^{-1}: 3375 (OH), 1642, 1618. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.29 (16H, m), 1.60 (2H, m), 1.90 (2H, m), 2.00 (4H, m, H-13, 13′), 2.10 (3H, s, $C_{6'}$-Me), 2.44 (2H, t, J=7.8 Hz, H-7′), 2.47 (2H, t, J=7.7 Hz, H-7), 3.85 (3H, s, C_5-OMe), 4.98 (2H, br s, OH), 5.33 (2H, t, J=6.5 Hz, H-14, 14′), 5.83 (1H, s, H-6), 6.25 (2H, s, H-2′, 4′). ^{13}C-NMR: see Table 1. HR EI-MS *m/z*: 498.2972 (M^+), Calcd 498.2981 for $C_{30}H_{42}O_6$.

Oxidative Cleavage of the Double Bond in 5 The double-bond of **5** (5 mg) was cleaved by the same procedure as for **4**, affording the aldehyde **4a** (0.7 mg) as an oil.

Methylation of Ardisiaquinone A (1) To a solution of **1** (10 mg) in CH_3OH–ether (3 ml, 2 : 1) was added an excess etheral solution of diazomethane at 0 °C. The mixture remained at room temperature overnight. Solvent was removed *in vacuo* to give on oil, which was purified using a short silica-gel column ($CHCl_3$) to afford **1a** (9.2 mg) as an oil. EI-MS *m/z* (rel. int.): 556 (M^+, 100), 183 (41), 153 (31). IR ν_{max}^{film} cm^{-1}: 1657, 1599. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (20H, m), 1.99 (4H, m), 2.43 (4H, t, J=7.4 Hz), 3.82 (6H, s), 4.05 (6H, s), 5.34 (2H, t, J=4.6 Hz), 5.73 (2H, s). HR EI-MS *m/z*: 556.3055 (M^+), Calcd 556.3036 for $C_{32}H_{44}O_8$.

Catalytic Hydrogenation of 1 A solution of **1** (5 mg) in C_2H_5OH (1 ml) was hydrogenated over 10% Pd–C (1 mg) under hydrogen at normal pressure for 2 h. After filtering off the catalyst, the filtrate was evaporated to give **1b** (5.1 mg) as an oil. EI-MS *m/z* (rel. int.): 530 (M^+, 86), 502 (100), 169 (38). IR ν_{max}^{film} cm^{-1}: 3341 (OH), 1635, 1599. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31 (28H, m), 2.44 (4H, t, J=7.1 Hz), 3.86 (6H, s), 5.84 (2H, s). HR EI-MS *m/z*: 530.2864 (M^+), Calcd 530.2879 for $C_{30}H_{42}O_8$.

Epoxidation of 1 A mixture of **1** (20 mg), *m*-chloroperoxybenzoic acid (12 mg), and CH_2Cl_2 (3 ml) was left standing at room temperature for 2 h. Ether was added to the reaction mixture and then the organic layer was washed with sat. $NaHCO_3$ sol. and sat. NaCl sol. After drying over $MgSO_4$, the organic layer was evaporated *in vacuo* to yield an epoxide **1c** (22 mg) as an oil. EI-MS *m/z* (rel. int.): 544 (M^+, 27), 516 (26), 282 (35), 193 (26), 169 (100). IR ν_{max}^{film} cm^{-1}: 3331 (OH), 1645, 1608. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.48—2.14 (24H, m), 2.44 (4H, t, J=4.6 Hz), 2.91 (2H, m), 3.86 (6H, s), 5.84 (2H, s). HR EI-MS *m/z*: 544.2700 (M^+), Calcd 544.2673 for $C_{30}H_{40}O_9$.

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References and Notes

1) Part V: Fukuyama Y., Kiriyama Y., Kodama M., Iwaki H., Hosozawa S., Aki S., Matsui K., *Chem. Pharm. Bull.*, **42**, 2211 (1994).
2) Samuelsson B., *Angew. Chem.*, **22**, 805 (1983).
3) Fukuyama Y., Kiriyama Y., Okino J., Kodama M., Iwaki H., Hosozawa S., Matsui K., *Chem. Pharm. Bull.*, **41**, 561 (1993).
4) Fukuyama Y., Okino J., Kodama M., *Chem. Pharm. Bull.*, **39**, 1877 (1991).
5) Ogawa H., Natori S., *Phytochemistry*, **7**, 773 (1968).
6) Ogawa H., Sakai S., Koshihira K., Natori S., *Tetrahedron Lett.*, **1968**, 1387.
7) Ogawa H., Natori S., *Chem. Pharm. Bull.*, **16**, 1709 (1968).
8) Thomson R. H., "Naturally Occurring Quinones. III. Recent Advance," Chapman and Hall, New York, 1987, p. 11.
9) De Haan J. W., De Ven L. J., *Org. Magn. Resonance*, **5**, 147 (1979).
10) Ochi K., Yoshimoto T., Yamamoto S., *J. Biol. Chem.*, **258**, 5754 (1983).
11) Kubo I., Kim M., Ganjian I., Kamikawa T., Yamagiwa Y., *Tetrahedron*, **43**, 2653 (1987).
12) Yoshimoto T., Yokoyama C., Ochi K., Yamamoto S., Maki Y., Ashida Y., Terao S., Shiraishi M., *Biochim. Biophys. Acta*, **713**, 470 (1982).
13) Total syntheses of ardisiaquinones D (**2**), E (**4**), and F (**5**) have been already achieved by us. Their synthetic detail will be reported in due time.