Naturally Occurring 5-Lipoxygenase Inhibitor. II.[1] Structures and Syntheses of Ardisianones A and B, and Maesanin, Alkenyl-1,4-benzoquinones from the Rhizome of *Ardisia japonica*

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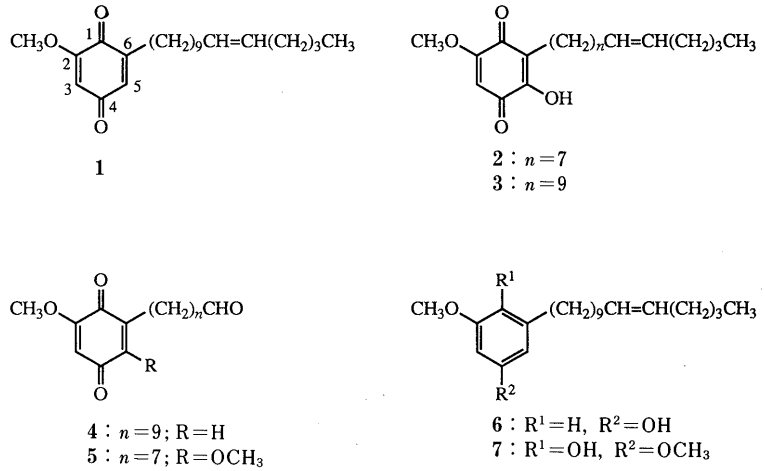
New alkenyl-1,4-benzoquinones, ardisianones A (1) and B (2), and the known maesanin (3) as 5-lipoxygenase inhibitors have been isolated from the rhizome of *Ardisia japonica*. Their structures have been elucidated as 2-methoxy-6-[(*Z*)-10′-pentadecenyl]-1,4-benzoquinone and 5-hydroxy-2-methoxy-6-[(*Z*)-8′-tridecenyl]-1,4-benzoquinone, respectively, on the basis of spectroscopic data and chemical degradation. Ardisianone A (1), maesanin (3) and belamcandol A (7) have been synthesized starting from belamcandol B (6), readily prepared by Wittig reaction between 9-(2-tetrahydropyranyloxy)nonanal and 3,5-dimethoxybenzyltriphenylphsophonium bromide followed by selective demethylation with sodium thioethoxide.

Keywords ardisianone A; ardisianone B; maesanin; belamcandol A; belamcandol B; 1,4-benzoquinone

Ardisia japonica (Myrsinaceae) has been used in Chinese traditional medicine as an antitussive, diuretic, and alexipharmic agent, and elaborates phenols such as bergenin and ardisinol,[2] and 1,4-benzoquinones like rapanone and embelin[3] along with a mixture of several alkyl and alkenyl benzoquinones.[4] Among the constituents, only bergenin was identified as an antitussive principle in this plant.[5] In the course of our investigation on prostaglandin biosynthesis regulators in natural products,[1,6] we found that the *n*-hexane extract of *A. japonica* could inhibit specifically 5-lipoxygenase in the cytosol of guinea pig polymorphonuclear leukocytes. Hence, extensive fractionation monitored by inhibitory activity against 5-lipoxygenase resulted in the isolation of two new 1,4-benzoquinones **1** and **2**, named ardisianones A and B, respectively, along with maesanin (**3**), previously isolated as a host defense stimulant from the African medicinal plant *Maesa lanceolata*.[7,8] Synthesis of ardisianone A (**1**), maesanin (**3**), and belamcandol A (**7**)[1] were also attempted from a common biosynthetic precursor, belamcandol B (**6**),[1] because of the similarity of their structures and intriguing biological property. In this paper, we deal with the structural elucidation of new benzoquinones **1** and **2**, and a degree of 5-lipoxygenase inhibitory activity for all the benzoquinones isolated in this study, as well as with convergent synthesis of compounds **1**, **3**, **6**, and **7**.

Isolation and Structures of Ardisianones A (1)[9] and B (2) The methanol extract of the dried rhizomes of *A. japonica* was partitioned between *n*-hexane and a mixture of methanol and water (1 : 4). From *n*-hexane-soluble portion active against 5-lipoxygenase, ardisianones A (**1**) and B (**2**), and measanin (**3**) were isolated as active substances by a combination of silica gel chromatography and HPLC.

Ardisianone A (**1**), mp 39.5—41.5 °C, had the molecular formula $C_{22}H_{34}O_3$ (*m/z* 346.2497 (M^+); Calcd 346.2507). The ultraviolet (UV) and the infrared (IR) spectra showed the absorptions at 266 and 362 nm, and at 1680, 1650, 1625, and 1605 cm^{-1}, respectively, which suggested the presence of an oxygenated *p*-benzoquinone moiety.[11] The 400 MHz, ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectrum of **1** revealed the *meta* coupled signals at δ 5.88 and 6.48, one of which displayed a long-range coupling of 1.4 Hz with a signal at δ 2.43 (2H, td, J=7.8, 1.4 Hz), and a signal due to a methoxyl group at δ 3.82, as well as signals typical of



1

2 : n=7
3 : n=9

4 : n=9; R=H
5 : n=7; R=OCH_3

6 : R^1=H, R^2=OH
7 : R^1=OH, R^2=OCH_3

Fig. 1

a long alkenyl side chain at δ 0.93 (3H, t, J=7.3 Hz), 1.20—1.40 (18H, m), 2.01 (4H, m), and 5.35 (2H, t, J=4.5 Hz). The ^{13}C nuclear magnetic resonance (^{13}C-NMR) spectrum showed the signals indicative of a methoxylated 1,4-benzoquinone, at δ 187.5 (s, C-4), 182.2 (s, C-1), 158.9 (s, C-2), 147.9 (s, C-6), 133.1 (d, C-5), 107.3 (d, C-3), and 56.2 (q, OCH_3), and signals at δ 130.0 (d, C-10′,11′) for the double bond, and at δ 13.9—32.0 (13 carbons) for the long side chain. These spectral data disclosed that ardisianone A was a 1,4-benzoquinone substituted at C-2 and 6 with a methoxy group and a long side chain. This was also supported by detection of a base ion peak at m/z 154 in the mass spectrum (MS) accounting for rupture of the benzylic bond of the alkenyl group, and by observation of nuclear Overhauser effects (NOEs) for the H-3 signal at δ 5.88 and the H-5 signal at δ 6.48 upon irradiation of the methoxy proton signal and the H-1′ signal at δ 2.43, respectively. The double bond in the side chain was determined to be placed at C-10′ and 11′ by the identification of the aldehyde **4** (m/z, 292.1665 (M^+); Calcd 292.1675 for $C_{17}H_{24}O_4$), obtained by epoxidation of **1** followed by HIO_4 oxidation,[1] and its stereochemistry was assigned as Z on the basis of the chemical shift values (δ 27.0 and 27.3)[10] of the two allylic methylene carbons. These results established ardisianone A (**1**) to be 2-methoxy-6-[(*Z*)-10′-pentadecenyl]-1,4-benzoquinone.

Ardisianone B (**2**), mp 62—64 °C, had the molecular formula $C_{20}H_{30}O_4$ established by the high resolution electron impact mass spectrum (HREIMS). The UV spectrum showed a dioxygenated benzoquinone chromophore at 287 and 420 nm,[11] whereas the IR spectrum displayed the absorptions at 3360 cm^{-1} and 1660, 1635, and 1600 cm^{-1} attributable to a hydroxy group and a benzoquinone moiety, respectively. The ^{1}H-NMR spectrum contained a singlet signal at δ 5.83 which showed NOE interaction with the methoxy proton signal at δ 3.85, and a series of signals assignable to a tridecenyl group. These spectral data suggest that **2** is closely related to maesanin (**3**). In fact, the ^{13}C-NMR data for the 1,4-benzoquinone ring in **2** were almost identical with those of maesanin; **2** (maesanin): δ 181.6 (181.6, C-1), 161.2 (161.2, C-2), 102.2 (102.2, C-3), 182.8 (182.5, C-4), 151.5 (151.8, C-5), 119.3 (119.6, C-6). On the other hand, the mass spectra showed a slight difference between these compounds, indicating a variant in the position of the double bond in the long side chain. Hence, according to essentially the same procedures used for **1**, the position and geometry of the double bond in the tridecenyl group was established to be at C-8′ and to be *Z* by oxidative degradation of *O*-methyl derivative, giving rise to an aldehyde **5** (m/z 294) and the ^{13}C-NMR shift values (δ 26.9, 27.2) for allylic methylene carbons, respectively. Accordingly, ardisianone B (**2**) was assigned as 5-hydroxy-2-methoxy-6-[(*Z*)-8′-tridecenyl]-1,4-benzoquinone.

Inhibitory activity against 5-lipoxygenase in the cytosol of guinea pig polymorphonuclear leukocytes[12] by the 1,4-benzoquinones isolated in the present study are summarized in Table I. The degree of inhibition caused by each compound was about ten times weaker than AA-861,[13] a reference 1,4-benzoquinone.

Syntheses of Ardisianone A (1), Maesanin (3), and Belamcandols A (7) and B (6) Several synthetic challenges for this type of 1,4-benzoquinones having alkyl chains of various length have been achieved in the past because of their interesting biological activities.[14] Most synthetic routes have been focused on elaboration of the side chain on the aromatic ring[8,15-18] except for Danheiser's unique

Table I. Inhibition of 5-Lipoxygenase in the Cytosol of Guinea Pig Polymorphonuclear Leukocytes by Compounds **1**—**3**

Compound	Concentration (μM)	Inhibition (%)
1	0.1	0
	1	10
	3	13
	10	81
2	0.1	10
	1	40
	3	59
	10	87
3	0.1	0
	1	16
	3	40
	10	80
AA-861[a]	0.1	0
	1	96

a) IC_{50} 0.18 μM.

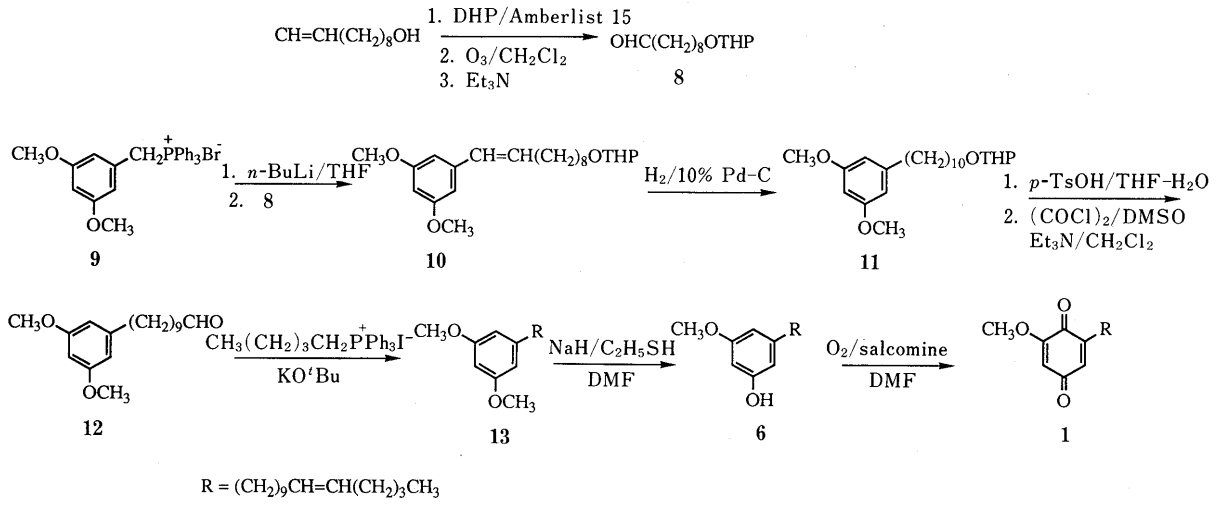


Fig. 2. Synthetic Scheme for Ardisianone A (**1**)

method.[19] We envisioned that belamcandol B (**6**) would function as a common intermediate for our target benzoquinones bearing a (*Z*)-8-pentadecenyl side chain because related compounds **1**, **3**, and **7** could presumably be biosynthesized *via* oxidation from belamcandol B (**6**).[1] Therefore, first of all, a practical method for the synthesis of belamcandol B (**6**) has been explored starting from the known phosphonium salt **9**.[20]

The phosphonium salt **9** was converted into its ylide and then allowed to react with 9-(2-tetrahydropyranyloxy)-nonanal (**8**) which, in turn, was prepared from 9-decen-1-ol by ozonolysis of the double bond after protection of the hydroxy group. The double bond in **10** was reduced by catalytic hydrogenation to give compound **11**, the tetrahydropyranyl ether of which was deprotected with aqueous acid hydrolysis followed by Swern oxidation to afford the aldehyde **12** in good yield. Wittig olefination of **12** with *n*-pentyltriphenylphosphonium iodide gave (*Z*)-olefin **13** in 93% yield. Selective demethylation of the symmetrical *O*-methyl groups in **13** was realized with C_2H_5SNa in *N*,*N*-dimethylformamide (DMF),[21] thus giving belamcandol B (**6**) in 91% yield.

Compound **6** was easily oxidized into a 1,4-benzoquinone, ardisianone A (**1**) by a power of molecular oxygen catalyzed by salcomine[22] in 63% yield. The synthetic ardisianone A thereby obtained was superimposable with the natural one in all the spectra data (IR, MS, and ^{1}H- and ^{13}C-NMR).

Next, our attention was given to the synthesis of maesanin (**3**) from the common intermediate **6**, which requires selective oxygenation at C-5 to achieve our goal. To this end, selective bromination at the C-5 position should be appropriate because it is regarded as equivalent to a requisite hydroxy group. We employed a *N*-bormosuccinimide (NBS) DMF reagent[23] for the selective bromination on the aromatic ring without concomitant bromination of the double bond in the side chain. In spite of a good conversion yield, selectivity (**14**/**15**=36/55) was not satisfactory. After several attempts, carbon tetrachloride (CCl_4) was found to be a suitable solvent to increase selectivity. Bromination of **6** with NBS in CCl_4 at room temperature afforded **14** (63%) and **15** (13%), which were readily separable by chromatography on silica gel. The brominated phenol **14** was subjected to the salcomine-catalyzed oxidation, thus furnishing the benzoquinone **16** in 31% yield (75%, based on the reacted **14**). Subsequent oxygenation at the C-5 position was realized by CH_3OH–Na_2CO_3 in the presence of a catalytic amount of Pd(0) to give the dimethoxybenzoquinone **17** in quantitative yield. It should be noted that the substitution of the bromine with methanol did not proceed in the absence of Pd(0). Finally, a more hindered methoxy group in **17** was selectively hydrolyzed with 70% $HClO_4$ to give maesanin (**3**) in high yeild, which was identical in all respects to the natural one.

Belamcandol A (**7**) could routinely be derived from ardisianone A (**1**) by reduction followed by selective methylation[24] as shown in Fig. 4.

In conclusion, we synthesized 5-lipoxygenase inhibitors, ardisianone A (**1**), maesanin (**3**), and belamcandol A (**7**) from a common biogenetic intermediate, phenol **6**, and thus our preparative method of synthesis should allow the ready preparation of analogues such as ardisianone B (**2**), irisquinone,[25] rapanone, and irisoquin,[26] which differ primarily in the presence of a hydroxy goup at the C-5 position and in the type of side chain attached at the C-6 ring position on the 1,4-benzoquinone nucleus.

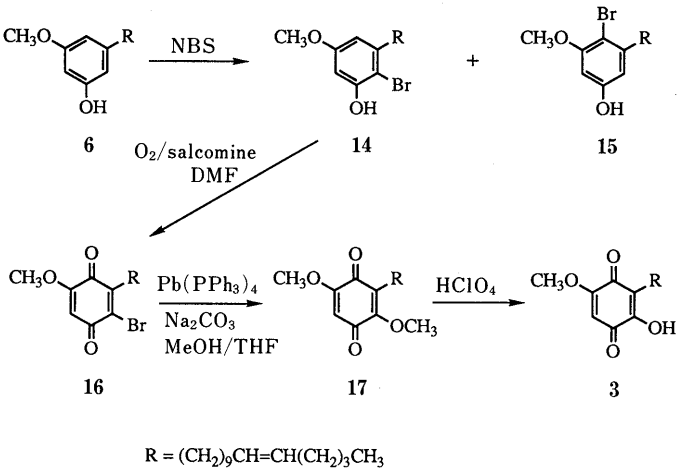


Fig. 3. Synthetic Scheme for Maesanine (**3**)

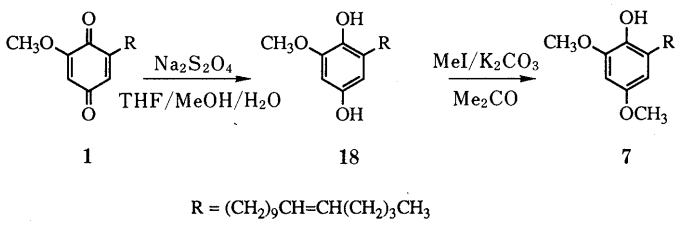


Fig. 4. Synthetic Scheme for Belamcandol A (**7**)

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 with a Jasco A-202 spectrophotometer. ^{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 a Brucker WH 400 and a Varian Unity 200. Chemical shift values were expressed in ppm downfield from tetramethylsilane as an internal standard. The MS were recorded on a Varian MAT 200 and a JEOL JMS SX-102. Silica gel (Wako, C-300) and Sephadex (Pharmacia Fine Chemicals, LH-20) were used for column chromatography. High performance liquid chromatography (HPLC) was performed using a Waters 6000 A and a Jasco UVDEC-100-II UV detector. Both silica gel F_{254} and RP-8 F_{254} (Merck) were used for analytical thin layer chromatography, and spots were visualized by UV (254 nm) illumination and by spraying 40% $CeSO_4$–H_2SO_4 followed by heating.

Extraction and Purification Dried and powdered rhizomes (2.19 kg) of *Ardisia japonica* collected in Ooasa, Tokushima prefecture, were immersed three times in methanol at room temperature for 3 d. Combined methanol extracts were evaporated *in vacuo* to give a gummy extract, which was partitioned between *n*-hexane and water–methanol (4:1). The *n*-hexane soluble portion (9.3 g) was chromatographed over silica gel eluting with $CHCl_3$ and $CHCl_3$–CH_3OH (20:1). The fraction eluted with $CHCl_3$ was rechromatographed on silica gel with $CHCl_3$ and then purified by HPLC [column: 20% $AgNO_2$–SiO_2, i.d. 8×300 mm; solvent; *n*-hexane–EtOAc (17:3), 3.5 ml/min] to give ardisianone A (**1**) (58 mg). The fraction eluted with $CHCl_3$–CH_3OH (20:1) was rechromatographed on silica gel ($CHCl_3$) and then purified by HPLC [column: Lichrosorb RP-2, i.d. 8×300 mm; solvent: CH_3OH–water–AcOH (75:25:0.6), 4 ml/min] to give ardisianone B (**2**) (98 mg) and maesanin (**3**) (98 mg).

Ardisianone A (1) Yellow needles [from C_2H_5OH–water (1:4)], mp 39.5—41.5 °C. HREIMS *m/z*: 346.2497 (M^+), Calcd 346.2507 for $C_{22}H_{34}O_3$. EIMS *m/z* (rel. int.): 346 (25, M^+), 154 (100). UV λ_{max}^{EtOH} nm (ε): 266 (11000), 362 (750). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 2875, 1680, 1650, 1625, 1605. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz, H_3-15′), 1.20—1.40 (18H, m), 2.01 (4H, m, H_2-9′, 12′), 2.43 (2H, td, J=7.8, 1.4 Hz,

H-1′), 3.82 (3H, s, OCH_3), 5.35 (2H, t, J=4.5 Hz, H-10′, 11′), 5.88 (1H, d, J=2.2 Hz, H-3), 6.48 (1H, dt, J=2.2, 1.4 Hz, H-5). ^{13}C-NMR ($CDCl_3$) δ: 13.9 (q, C-15′), 22.4 (t, C-14′), 27.0 (t, C-12′), 27.3 (t, C-9′), 28.0—29.8 (8×C), 32.0 (t, C-1′), 56.2 (q, OCH_3), 107.3 (d, C-3), 130.0 (d, C-10′, 11′), 133.1 (d, C-5), 147.9 (s, C-6), 158.9 (s, C-2), 182.2 (s, C-1), 187.5 (s, C-4).

Ardisianone B (2) Yellow-orange plates [from C_2H_5OH–water (4 : 1)], mp 62—64 °C. HREIMS m/z: 334.2128 (M^+), Calcd 334.2143 for $C_{20}H_{30}O_4$. EIMS m/z (rel. int.): 334 (20, M^+), 168 (100). UV λ_{max}^{EtOH} nm (ε): 287 (17700), 420 (500). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360 (OH), 2940, 2860, 1660, 1635, 1600. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz, H-13′), 1.2—1.40 (12H, m), 1.45 (2H, m, H-12′), 2.01 (4H, m, H-7′, 10′), 2.43 (2H, t, J=7.5 Hz, H-1′), 3.85 (3H, s, OCH_3), 5.34 (2H, t, J=4.5 Hz, H-8′, 9′), 5.83 (1H, s, H-3), 7.22 (1H, s, OH). ^{13}C-NMR ($CDCl_3$) δ: 13.9 (q, C-13′), 22.3 (t, C-12′), 22.6 (t, C-11′), 26.9 (t, C-10′), 27.2 (t, C-7′), 28.0—29.7 (5×C), 31.9 (t, C-1′), 56.6 (q, OCH_3), 102.2 (d, C-3), 119.3 (s, C-6), 129.8 (d, C-8′, 9′), 151.5 (s, C-5), 161.2 (s, C-2), 181.6 (s, C-1), 182.8 (C-4).

Oxidative Cleavage of the Double Bond in 1 A mixture of **1** (20 mg, 0.058 mmol), *m*-chloroperbenzoic acid (9 mg), and CH_2Cl_2 (3 ml) 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 with sat. NaCl sol. After being dried over $MgSO_4$, the organic layer was evaporated *in vacuo* to leave a residue, which was purified by column chromatography on silica gel eluting with CH_2Cl_2–EtOAc (9 : 1) to afford an epoxide (12.8 mg). To a solution of the epoxide obtained in THF–water (1 ml, 4 : 1) was added HIO_4 (9.3 mg) and the reaction mixture was stirred at room temperature for 12 h. Ether was added and 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 leave a residue, which was purified by Sephadex LH-20 eluting with CH_3OH–CH_2Cl_2 (1 : 1) to yield the aldehyde **4** (3 mg) as an oil. HREIMS m/z: 292.1665 (M^+), Calcd 292.1675 for $C_{17}H_{24}O_4$. EIMS m/z: 292 (M^+), 154 (M^+-138). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.42 (2H, t, J=5.7 Hz, H-1′), 3.81 (3H, OCH_3), 5.87 (1H, d, J=2.2 Hz, H-5), 6.48 (1H, d, J=2.2 Hz, H-3), 9.77 (1H, t, J=1.8 Hz, CHO).

Oxidative Cleavage of the Double Bond in 2 Ardisianone B (**2**) (7 mg) was methylated with CH_2N_2 and then its double bond was cleaved by the same procedure as for **1**, yielding the aldehyde **5** (1.5 mg) as an oil. EIMS m/z: 294 (M^+), 183, 167.

9-(2-Tetrahydropyranyloxy)nonanal (8) A mixture of 9-decen-1-ol (15 g, 0.096 mol), 3,4-dihydropyran (8.08 g, 0.096 mol), Amberlist 15 (10 mg), and CH_2Cl_2 (150 ml) was stirred at room temperature for 6 h. After filtering the resin off, the solution was evaporated to leave an oil, which was chromatographed on silica gel (*n*-hexane–EtOAc, 10 : 1) to give a pyranyl ether (21.8 g, 95%). A current of ozonized oxygen was passed through a solution of the resulting pyranyl ether (10.3 g, 0.043 mol) in CH_2Cl_2 (100 ml) at −78 °C until the solution became blue. The solution was flushed with argon, and Et_3N (12 ml) was added, and the mixture was allowed to warm to room temperature. Ice water was added and the mixture was extracted with EtOAc. The organic layer was washed with water and with sat. NaCl sol, dried over $MgSO_4$, and evaporated to give a crude product, which was chromatographed on silica gel (*n*-hexane–EtOAc, 10 : 1) to afford **8** (7.2 g, 71%) as an oil. HREIMS m/z: 242.1862 (M^+), Calcd 242.1882 for $C_{14}H_{26}O_3$. IR ν_{max}^{film} cm^{-1}: 2720, 1725. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.2—1.8 (18H, m), 2.38 (2H, td, J=7.2, 1.5 Hz), 3.2—3.8 (4H, m), 4.56 (1H, t, J=3.1 Hz), 9.71 (1H, t, J=1.5 Hz).

1,3-Dimethoxy-5-[10-(2-tetrahydropyranyloxy)-1-decenyl]benzene (10) To a solution of 3,5-dimethoxybenzyltriphenylphosphonium bromide (7.55 g, 15 mmol) in tetrahydrofuran (THF, 96 ml) was added dropwise *n*-BuLi (9.7 ml, 1.6 M hexane sol.) at room temperature under argon. After being stirred for 15 min, a solution of **8** (3 g, 12 mmol) in THF (16 ml) was added dropwise and the reaction mixture was stirred for another 18 h. Ice water was added and the mixture was extracted with EtOAc. The organic layer was washed with water and with sat. NaCl sol., dried over $MgSO_4$, and evaporated to give a crude product, which was purified by chromatography on silica gel (*n*-hexane–EtOAc, 10 : 1) to afford **10** (4.04 g, 87%) as an oil. HREIMS m/z 376.2601 (M^+), Calcd 376.2614 for $C_{23}H_{36}O_4$. EIMS m/z (rel. int.): 376 (33, M^+), 300 (47), 292 (73), 191 (61), 152 (100). IR ν_{max}^{film} cm^{-1}: 1600, 1480. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.79 (6H, s), 4.56 (1H, t, J=6.5 Hz), 6.28 (1H, d, J=18.0 Hz), 6.35 (1H, dt, J=18.0, 6.5 Hz), 6.42 (1H, t, J=2.2 Hz), 6.71 (2H, d, J=2.2 Hz).

1,3-Dimethoxy-5-[10-(2-tetrahydroxypyranyloxy)decanyl]benzene (11) A solution of **10** (3.6 g, 9.5 mmol) in C_2H_5OH (300 ml) was hydrogenated over 10% Pd–C (400 mg) under an ordinary hydrogen pressure for 12 h. After filtering off the catalyst, the filtrate was evaporated to give **11** (3.27 g, 91%) as an oil. HREIMS m/z: 378.2790 (M^+), Calcd 378.2770 for $C_{23}H_{38}O_4$. EIMS m/z (rel. int.): 378 (4, M^+), 294 (23), 152 (100). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.54 (2H, t, J=7.6 Hz), 3.78 (6H, s), 4.58 (1H, t, J=7.0 Hz), 6.29 (1H, t, J=2.4 Hz), 6.34 (2H, d, J=2.4 Hz).

10-(3,5-Dimethoxyphenyl)decanal (12) A solution of **11** (3.4 g, 9 mmol) and *p*-toluenesulfonic acid (100 mg) in THF–water (40 ml, 3 : 1) was stirred at room temperature for 18 h. The reaction mixture was poured into ice water and then extracted with EtOAc. The organic layer was washed successively with sat. $NaHCO_3$ sol., water, and sat. NaCl sol. After being dried over $MgSO_4$, the extract was evaporated to give an alcohol (2.49 g, 94%). Dimethylsulfoxide (1.79 ml) was added dropwise to a solution of oxalyl chloride (1.46 ml, 16.3 mmol) in CH_2Cl_2 at −78 °C and the mixture was stirred for 10 min. To this solution was added dropwise at −78 °C a solution of the alcohol (2.4 g, 8.2 mmol) obtained above in CH_2Cl_2 (100 ml). After being stirred for 1 h, Et_3N (8.74 ml) was added and the mixture was allowed to warm to 0 °C. Stirring was continued for 20 min, then sat. NaCl sol. was added and the mixture was extracted with EtOAc. The organic layer was washed with sat. NaCl sol. and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a crude product, which was purified by chromatography on silica gel (*n*-hexane–EtOAc, 5 : 1) to yield **12** (1.85 g, 78%) as an oil. HREIMS m/z: 292.2019 (M^+), Calcd 292.2038 for $C_{18}H_{28}O_3$. IR ν_{max}^{film} cm^{-1}: 1715, 1590. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.41 (2H, td, J=6.0, 1.8 Hz), 2.54 (2H, t, J=7.6 Hz), 3.78 (6H, s), 6.29 (1H, t, J=2.2 Hz), 6.34 (2H, d, J=2.2 Hz), 9.76 (1H, t, J=1.8 Hz).

1,3-Dimethoxy-5-[(*Z*)-10′-pentadecenyl]benzene (13) To a suspension of *n*-pentyltriphenylphosphonium iodide (4.7 g, 11.4 mmol) in THF (20 ml) at room temperature under an argon atmosphere was added a solution of *tert*-BuOK (1.3 g, 11.4 mmol) in THF (10 ml). After being stirred for 30 min, a solution of **12** (2 g, 6.8 mmol) in THF (5 ml) was added and then the mixture was stirred for 1 h. Water was added and the mixture was extracted with ether. The organic layer was washed with water, sat. $NaHCO_3$ sol., dried over $MgSO_4$, and evaporated to leave a residue, which was chromatographed on silica gel (*n*-hexane–CH_2Cl_2, 5 : 1) to afford **13** (2.17 g, 93%) as an oil. HREIMS m/z: 346.2866 (M^+), Calcd 346.2872 for $C_{23}H_{38}O_2$. EIMS m/z (rel. int.): 346 (77, M^+), 194 (18), 165 (12), 152 (100). *Anal.* Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.74; H, 11.19. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=5.6 Hz), 2.54 (2H, t, J=7.7 Hz), 3.77 (6H, s), 5.34 (2H, t, J=4.6 Hz), 6.24 (1H, t, J=2.2 Hz), 6.34 (2H, d, J=2.2 Hz).

3-Methoxy-5-[(*Z*)-10′-pentadecenyl]phenol (Belamcandol B) (6) To a suspension of 50% NaH (2.25 g, 46.8 mmol) in DMF (50 ml) was added a solution of ethanethiol (3.6 ml, 47.1 mmol). After the mixture was stirred for 5 min, a solution of **13** (3.6 g, 10.4 mmol) in DMF (50 ml) was added and the mixture was refluxed for 3 h. After being cooled at room temperature, the solution was acidified with 2 N HCl and extracted with ether. The organic layer was washed with sat. NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The resulting residue was chromatographed on silica gel (*n*-hexane–CH_2Cl_2, 1 : 3) to give **6** (3.13 g, 91%). HREIMS m/z: 332.2711 (M^+), Calcd 332.2715 for $C_{22}H_{36}O_2$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7.1 Hz), 2.02 (4H, m), 2.51 (2H, t, J=7.7 Hz), 3.76 (3H, s), 5.29 (1H, s, OH), 5.35 (2H, t, J=4.6 Hz), 6.23 (1H, dd, J=2.3, 2.3 Hz), 6.26 (1H, dd, J=2.3, 2.3 Hz), 6.32 (1H, dd, J=2.3, 2.3 Hz).

2-Methoxy-6-[(*Z*)-10′-pentadecenyl]-1,4-benzoquinone (Ardisianone A) (1) Into a stirred mixture of **6** (0.1 g, 0.31 mmol) and salcomine (10 mg) in DMF (2 ml) was bubbled oxygen for 14 h. The mixture was poured onto ice water and was extracted with ether. The organic layer was washed with sat. NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The resulting residue was chromatographed on silica gel to afford **1** (67.3 mg, 62.7%) as yellow needles, mp 40—41 °C. Its spectral data (IR, MS, ^{1}H- and ^{13}C-NMR) were identical with those of ardisianone A (**1**).

Bromination of 6 with NBS A solution of **6** (100 mg, 0.31 mmol) and NBS (55.1 mg, 0.31) in CCl_4 (2 ml) was stirred at room temperature for 4 h. After filtering the precipitates formed, the filtrate was evaporated to dryness. The residue was chromatographed on silica gel (*n*-hexane–EtOAc, 10 : 1) to give **14** (80.7 mg, 62.4%) and **15** (10.5 mg, 12.9%). **14**: HREIMS m/z: 410.1788 (M^+), Calcd 410.1820 for $C_{22}H_{35}O_2{}^{79}Br$. EIMS m/z (rel. int.): 412 (42) and 410 (42, M^+), 331 (39), 218 (97), 216 (100). IR ν_{max}^{film} cm^{-1}: 3512 (OH). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7.1 Hz), 2.65 (2H, t, J=7.5 Hz), 3.76 (3H, s), 5.35 (2H, t, J=4.4 Hz), 6.39 (1H, d, J=2.9 Hz), 6.41 (1H, d, J=2.9 Hz). **15**: HREIMS m/z: 410.1844 (M^+), 410.1820 for $C_{22}H_{35}O_2{}^{79}Br$. EIMS m/z (rel. int.): 412 (40) and 410 (40, M^+), 331 (48), 218 (52), 216 (52), 137 (100). IR ν_{max}^{film} cm^{-1}: 3435, 1587, 1466. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz), 2.67 (2H, t, J=7.8 Hz), 3.84 (3H, s), 5.35 (2H, t, J=4.9 Hz), 6.30 (1H, d, J=2.4 Hz), 6.33 (1H, d, J=2.4 Hz).

2-Bromo-5-methoxy-3-[(*Z*)-10′-pentadecenyl]-1,4-benzoquinone (16)

Into a stirred solution of **14** (318 mg) and salcomine (31 mg) in DMF (5 ml) was bubbled oxygen at room temperature for 20 h. Water was added and the mixture was extracted with ether. The organic layer was washed with sat. NaCl sol., dried over $MgSO_4$, and evaporated to give a crude product, which was chromatographed on silica gel (*n*-hexane–EtOAc, 7 : 1) to afford **16** (100.6 mg, 31%) and the recovered staring material **14** (188.4 mg, 60%). Yellow prisms (from EtOH), mp 89—91 °C. HREIMS *m/z*: 424.1631 (M^+), Calcd 424.1601 for $C_{22}H_{33}O_3{}^{79}Br$. *Anal.* Calcd for $C_{22}H_{33}BrO_3$: C, 62.11; H, 7.82. Found: C, 62.22; H, 7.99. EIMS *m/z* (rel. int.): 426 (52) and 424 (47, M^+), 345 (28), 233 (36), 231 (36), 193 (57), 179 (30), 153 (100). IR ν_{max}^{film} cm^{-1}: 1678, 1639, 1628, 1466, 1440. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7.1 Hz), 2.69 (2H, t, J=7.7 Hz), 3.84 (3H, s), 5.35 (2H, t, J=4.3 Hz), 6.67 (1H, s).

2,5-Dimethoxy-6-[(*Z*)-10′-pentadecenyl]-1,4-benzoquinone (17) To a stirred solution of **16** (11.0 mg, 0.025 mmol) and tetrakistriphenylphosphine palladium (0.5 mg) in CH_3OH–THF (10 ml, 1 : 1) under argon was added 2 N Na_2CO_3 sol. (0.05 ml). The mixture was stirred at 90 °C for 10 min. The solvent was evaporated to leave a residue, which was partitioned between EtOAc and water. The EtOAc layer was washed with sat. NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (*n*-hexane–EtOAc, 5 : 1) to give **17** (9.5 mg, 97%) as an oil. HREIMS *m/z*: 376.2594 (M^+), Calcd 376.2613 for $C_{23}H_{36}O_4$. EIMS *m/z* (rel. int.): 376 (100, M^+), 362 (4), 169 (22). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7.5 Hz), 2.43 (2H, t, J=7.3 Hz), 3.80 (3H, s), 4.05 (3H, s), 5.35 (2H, t, J=3.5 Hz), 5.72 (1H, s).

2-Hydroxy-5-methoxy-3-[(*Z*)-10′-pentadecenyl]-1,4-benzoquinone (Maesanin) (3) To a solution of **17** (100 mg) in CH_2Cl_2 (3 ml) was added two drops of 70% $HClO_4$ at room temperature under argon and the mixture was stirred for 2 h. The reaction mixture was washed with sat. $NaHCO_3$ sol. and sat. NaCl sol., dried over $MgSO_4$ and evaporated to give a crystalline solid (80 mg). Recrystallization from C_2H_5OH gave **3** as yellow needles, mp 69—70 °C (lit.[8] mp 70 °C), which was identical in the spectral data (IR, MS, and ^{1}H-NMR) with maesanin (**3**).

1,4-Dihydroxy-2-methoxy-6-[(*Z*)-10′-pentadecenyl]benzene (18) To a stirred solution of **1** (67.3 mg, 0.19 mmol) in THF–MeOH–H_2O (10 ml, 4 : 3 : 3) at room temperature under argon was added $Na_2S_2O_4$ (135.3 mg, 0.76 mmol) and stirring was continued for 20 h. The reaction solution was condensed *in vacuo* and extracted with EtOAc. The organic layer was washed with water and sat. NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (*n*-hexane–EtOAc, 5 : 1) to give **18** (40 mg, 61%). HREINS *m/z*: 348.2646 (M^+), Calcd 348.2665 for $C_{22}H_{36}O_3$. EIMS *m/z* (rel. int.): 348 (100, M^+), 154 (41). IR ν_{max}^{film} cm^{-1}: 3553, 3377, 1606, 1496, 1473, 1440. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.91 (3H, t, J=7.3 Hz), 2.55 (2H, t, J=7.3 Hz), 3.83 (3H, s), 5.35 (2H, t, J=4.5 Hz), 6.21 (1H, d, J=2.2 Hz), 6.32 (1H, d, J=2.2 Hz).

2,4-Dimethoxy-6-[(*Z*)-10′-pentadecenyl]phenol (Belamcandol A) (7) A mixture of **18** (13 mg, 0.037 mmol), methyl iodide (0.03 ml), K_2CO_3 (7.8 mg), and acetone (5 ml) was refluxed for 2 h. After being cooled to room temperature, water was added and the mixture was extracted with EtOAc. The organic layer was washed with water and sat. NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC (*n*-hexane–EtOAc, 4 : 1) to yield **7** (4 mg, 30%), which was identical in ^{1}H-NMR, IR, and MS spectrum with the natural specimen.

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References and Notes

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