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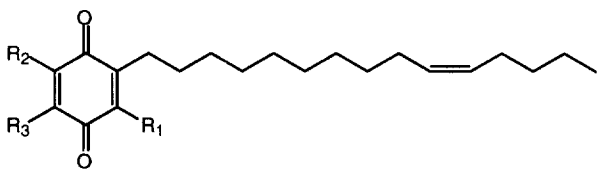
Synthesis of Cytotoxic Maesaquinone Bearing a 2,5-Dihydroxy-6-Methyl-1,4-Benzoquinone Nucleus

Yoshiyasu Fukuyama,* Hideyuki Yaso, Yuuko Kiriyama, Hironobu Takahashi and Hiroyuki Minami
Institute of Pharmacognosy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan

Tadao Kamikawa
Department of Chemistry, Faculty of Science and Technology, Kinki University, Kowakae, Higashi-Osaka, Osaka 577, Japan

Abstract: A synthesis of maesaquinone [2,5-dihydroxy-3-(*Z*)-10'-pentadecenyl-6-methyl-1,4-benzoquinone] has been achieved in nine steps starting from 1,4,5-trimethoxymethyloxy-2-methoxybenzene which can be readily obtained by successive deprotection and MOM protection of one methoxyl group of 2,5-dimethoxy-1,4-benzoquinone. © 1997 Elsevier Science Ltd.

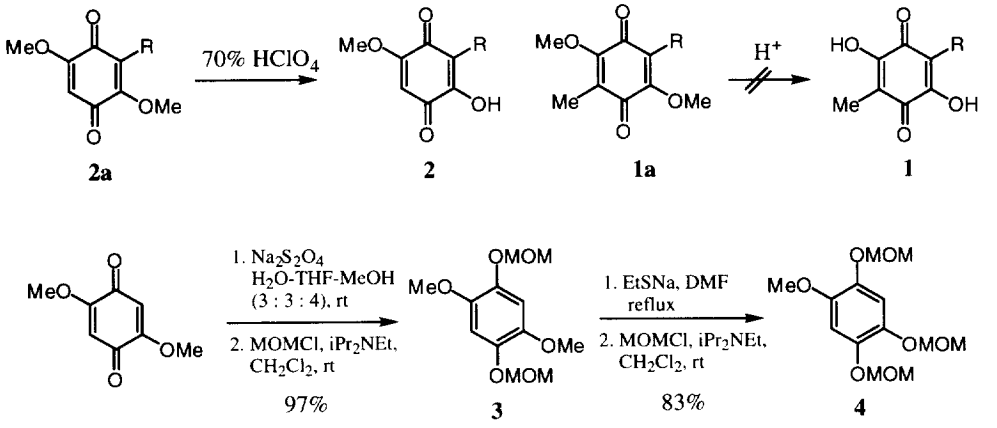
Maesanin (**2**),[1] isolated from the fruit of East African medicinal plant *Maesa lanceolate*, is a naturally occurring 1,4-benzoquinone which exhibits diverse biological activities, e.g., non-specific host defensive stimulant,[2] 5-lipoxygenase inhibitory activity,[3,4] mitochodorial oxidative phosphorylation,[5] cytotoxicity against several solid tumor cells,[6] and aldose reductase inhibitory activity.[6] These biological activities have stimulated synthetic studies on maesanin.[7-9] In 1994, Kubo[6] reported the isolation of fully substituted another 1,4-benzoquinone, maesaquinone (**1**), from the same plant, and indicated the profile of cytotoxicity different from maesanin.



1 $R_1 = R_2 = OH$, $R_3 = Me$
2 $R_1 = OH$, $R_2 = OMe$, $R_3 = H$

Figure 1

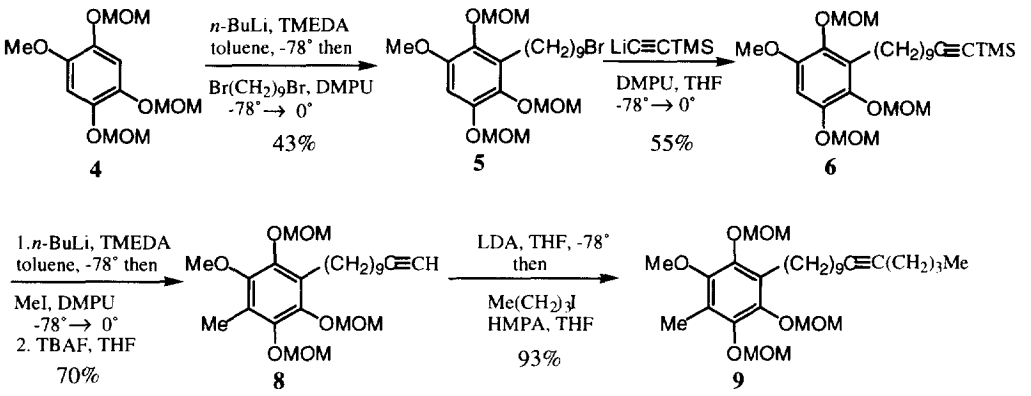
As a part of our studies on naturally occurring 5-lipoxygenase inhibitors,[10, 11] we have decided to synthesize maesaquinone (**1**) to supply amount enough to make out the property of its biological activity. Our synthetic strategy essentially follows the similar convergent procedure used for a practical synthesis of ardisiaquinone A.[12] Through the synthetic efforts of ardisiaquinone A, [12] we have observed that sterically hindered inside methoxy group on maesanin-type **2a** can be cleanly hydrolyzed with acid, but acid treatment of maesaquinone-type **1a** gives a complex mixture. Therefore, in synthesis of **1**, the inside methoxyl group of **1a** must be replaced by more labile one than methyl ether. To this end, we have chosen compound **4** as a starting material in order to accomplish the selective deprotection of the methoxy group on fully substituted 1,4-benzoquinone nucleus **1a** at the latter stage.



Scheme 1

A commercial available 2,5-dimethoxyquinone was reduced quantitatively to the hydroquinone, the two phenolic hydroxy groups of which were protected as MOM ethers giving rise to **3**. Fortunately, one of the methoxyl groups in **3** was cleanly deprotected with EtSH-NaH in DMF[13] to supply the requisite compound **4**, the hydroxy group of which was again protected as a MOM ether (Scheme 1). Thus, the inside MOM group can be discriminated from the outside methoxyl group on acid treatment in the last stage.

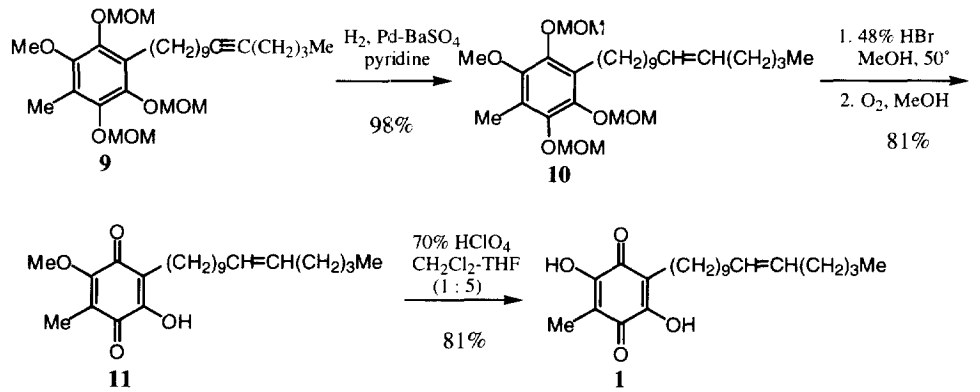
Tri-MOM **4** was lithiated at -78°C with *n*-BuLi in the presence of TMEDA followed by alkylation with 1,9-dibromononane to give **5** in 43% yield[14] according to the same procedure used for the synthesis of ardisiaquinone A.[12] Compound **6** was prepared in 55% yield by displacement of the bromide in **5** with lithium trimethylsilylacetylide.[15] Introduction of the extra methyl group onto the benzene ring was realized by directed lithiation with *n*-BuLi followed by the addition of MeI, and then desilylation gave the fully substituted benzene unit **8** in 70% yield. Alkylation of *n*-butyl iodide with the lithium acetylide *in stiu* prepared at -78°C from **8** with LDA smoothly proceeded to give the coupling product **9** in 93% yield (Scheme 2).



Scheme 2

Catalytic hydrogenation of the triple bond in **9** under the presence of Pd-$BaSO_4$ catalyst yielded the *Z* olefin **10** as a sole product. Next, all of the four MOM groups could be simultaneously removed on treatment of **10** with 48% HBr[16] in MeOH at 50°C to produce unstable phenol, which was directly exposed to bubble through the stream of oxygen giving rise to a monohydroxy 1,4-benzoquinone **11** in 81 % yield. Finally, treatment of **11** with a few drops of 70% $HClO_4$ hydrolyzed the remaining methoxy group to yield maesaquinone (**1**) in 81% yield, which was identical with natural one in all respects (IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra).

Thus, we have accomplished the first synthesis of maesaquinone (**1**).[17] This essentially same procedure developed for practical synthesis of ardisiaquinone A turned out to be useful for the preparation of 2,5-dihydroxy-6-methyl substituted 1,4-benzoquinone derivatives such as maesaquinone (**1**) and ardisiaquinone B.[18]



Scheme 3

EXPERIMENTAL

General Melting point were determined on a Yanagimoto micro melting point apparatus without correction. IR spectra were recorded on a JASCO 5300 FTIR spectrometer. ^{1}H-NMR spectra were taken on Varian unity-200 or JEOL GX-400 spectrometer. Chemical shifts are expressed in δ units (part per million downfield from Me_4Si). Mass spectra (MS) were recorded on a JEOL AX-500. Air- and moisture-sensitive reagents were transferred via syringe or cannula, and reactions involving these materials were carried out in oven-dried flasks under a positive pressure of argon. Silica gel (Wako, C-300) was used for column chromatography. Analytical thin-layer chromatographies (TLC) were performed with Merck precoated TLC plates (Kiselgel 60 F_{254}, 0.25 mm), and spots were visualized with ultraviolet light and 40% $CeSO_4$-H_2SO_4.

1,4-Dimethoxy-2,5-dimethoxymethyloxybenzene **(3)** To a solution of 2,5-dimethoxyquinone (1g, 5.92 mmol) in MeOH (15 ml), THF (15 ml) and water (20 ml) was added $Na_2S_2O_4$ (4.12 g). The mixture was stirred at room temperature for 3h. The solid was filtered and well washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give a residue, which was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was dissolved in CH_2Cl_2(10 ml). To the resultant solution was added diisopropylethylamine (3.11 ml, 17.9 mmol), and chloromethyl methyl ether (1.35 ml, 17.9 mmol). The mixture was stirred at room temperature for 18 h. The mixture was diluted with CH_2Cl_2, washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacua.* Purification by column chromatography [benzene-ethyl acetate (94 : 1)] afforded **3** (1.5 g, 97 %) as colorless plates, mp 59-60.5°C (*n*-hexane). IR (KBr) 1510 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.83 (2H, s), 5.14 (4H, s), 3.82 (6H, s), 3.53 (6H, s); EIMS *m/z* (rel. int.) 258 (M^+, 50), 183 (26), 213 (34): Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.84; H, 7.03. Found: C, 55.75; H, 7.09.

1-Methoxy-2,4,5-trimethoxymethyloxybenzene **(4)** To a suspension of 50% oil dispersion NaH (69.8 mg, 1.7 mmol) in DMF (5 ml) was added dropwise methylmercaptane (0.14 ml, 1.82 mmol). The mixture was stirred at room temperature for 5 min. A solution of **3** (100 mg, 0.39 mmol) in DMF (5 ml) was added and then the mixture was refluxed for 30 min. After being cooled to room temperature, the reaction mixture was acidified with 2 M HCl solution and extracted with ether (3 times). The combined organic layer was washed with water and saturated aqueous NaCl , dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel [hexane-ethyl acetate (2 : 1)] to afford 2,5-dimethoxymethyloxy-4-methoxyphenol (75 mg, 79%) as an oil. IR (film) 3408, 1664, 1512 cm^{-1}; ^{1}H- NMR ($CDCl_3$, 200 MHz) δ 3.51 (3H, s), 3.56 (3H, s), 3.81 (3H, s), 5.12 (2H, s), 5.15 (2H, s), 5.92 (1H, s), 6.74 (1H, s), 6.84 (1H, s); EIMS *m/z* (rel. int.) 244 (M^+, 23), 214 (19), 199 (12), 169 (32); HREIMS calcd 244.0947 for $C_{11}H_{16}O_6$, found 244.0950. To a solution of 2,5-dimethoxymethyloxy-4-methoxyphenol (70 mg, 0.28 mmol) in methylene chloride (4 ml) was added successively diisopropylethylamine (0.08 ml, 0.46 mmol) and chloromethyl methyl ether (0.04 ml, 0.47 mmol). The mixture was stirred at room temperature for 16 h,

diluted with ether, and washed with saturated aqueous NaCl. The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel [hexane-ethyl acetate (2 : 1)] to afford **4** (78.3 mg, 95% as an oil. IR (film) 1512 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.54 (6H, s), 3.55 (3H, s), 3.84 (3H, s), 5.12 (2H, s), 5.25 (2H, s), 5.17 (2H, s), 6.81 (1H, s), 7.04 (1H, s); EIMS *m/z* (rel. int.) 288 (M^+, 19), 258 (12), 213 (20), 167 (18); HREIMS calcd 288.1209 for $C_{13}H_{20}O_7$, found 288.1216.

9-Bromo-1-(5-methoxy-2,3,6-trimethoxymethyloxyphenyl)nonane (**5**) To a solution of **4** (500 mg, 1.74 mmol) and TMEDA (0.17 ml, 2.09 mmol) in THF (2 ml) was added dropwise *n*-BuLi (1.22 ml, 1.6 M hexane sol., 2.09 mmol) at -78°C under an argon atmosphere . After being stirred for 30 min at -78°C, a solution of 1,9-dibromononane (593.4 mg, 2.09 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone [DMPU (0.26 ml, 2.09 mmol)] in THF (1 ml) was added. The mixture was stirred for 30 min and then at room temperature overnight. The reaction was terminated by the addition of saturated NH_4Cl solution and the mixture was extracted with ether (3 times). The combined organic layer was washed with water and saturated aqueous NaCl dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel [hexane-ethyl acetate (4 : 1)] to afford **5** (275.6 mg, 32.2 %) and the starting material **4** (126.3 mg, 25 %) as an oil, respectively. IR (film) 1595, 1487, 1232, 1157, 1047, 845, 760, 698, 640 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.32 (12H, m), 1.85 (2H, m), 2.71 (2H, dd, J = 7.8, 8.2), 3.40 (2H, t, J = 6.7), 3.51 (3H, s), 3.58 (3H, s), 3.59 (3H, s), 3.79 (3H, s), 5.02 (2H, s), 5.03 (2H, s), 5.14 (2H, s), 6.64 (1H, s); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 18.4, 25.5, 28.5, 28.8, 29.1, 29.5, 29.5, 30.1, 32.8, 34.0, 56.1, 56.2, 57.4, 99.1, 99.3, 99.9, 131.8, 138.8, 139.2, 146.3, 148.7; EIMS *m/z* (rel.int) 494 (M^+, 8), 492 (M+, 8), 418 (15), 416 (14), 373 (17), 371 (17), 181 (18); HREIMS calcd 492.1723 for $C_{22}H_{37}O_7{}^{79}Br$, found 492.1714.

11-trimethylsilyl-1-(5-methoxy-2,3,6-trimethoxymethyloxyphenyl)undecan-10-yne (**6**) To a solution of trimethylacetylene (0.12 ml, 0.84 mmol) and DMPU (0.1 ml, 0.84 mmol) in THF (2 ml) was added dropwise *n*-BuLi (0.49 ml, 1.6 M hexane sol., 0.84 mmol) at -78°C under an argon atmosphere. After being stirred for 1h at -78°C, a solution of **5** (200 mg, 0.41 mmol) in THF (1 ml) was added and the mixture was stirred for 30 min and then at room temperature overnight. Saturated NH_4Cl solution was added and the mixture was extracted with ether (4 times). The combined organic layer was washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-ethyl acetate (5 : 1) to afford **6** (115.6 mg, 55 %) as an oil. IR (film) 3287, 1595, 1487, 1398, 1342, 1232, 1049, 843, 638 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.14 (9H, s), 1.29 (14H, m), 2.20 (2H, t, J = 7.0), 2.71 (2H, dd, J = 7.7, 8.1), 3.51 (3H, s), 3.58 (3H, s), 3.59 (3H, s), 3.80 (3H, s), 5.02 (2H, s), 5.03 (2H, s), 5.14 (2H, s), 6.64 (1H, s); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 0.2, 19.9, 25.5, 28.7, 28.9, 29.1, 29.5, 29.6, 30.0, 30.2, 56.1, 56.2, 57.4, 84.2, 85.7, 99.1, 99.3, 99.9, 107.8, 131.8, 138.8, 139.2, 146.3, 148.7; EIMS *m/z* (rel. int.) 510 (M^+, 27), 434 (50), 416 (14), 402 (13), 241 (10), 181 (12), 73 (26), 45 (100); HREIMS calcd 510.3013 for $C_{27}H_{46}O_7Si$, found 510.3007.

11-trimethylsilyl-1-(4-methyl-5-methoxy-2,3,6-trimethoxymethyloxyphenyl)undecan-10-yne (**7**) To a mixture of **6** (266 mg, 0.51 mmol) and TMEDA (0.08 ml, 0.66 mmol) in toluene (1 ml) was added dropwise *n*- BuLi (0.45 ml, 1.6 M hexane sol., 0.72 mmol) at -78°C under an argon atmosphere. After the mixture was stirred for 1h, a solution of iodomethane (0.04 ml, 0.66 mmol) and DMPU (0.08 ml, 0.66 mmol) in toluene (1 ml) was added. The mixture was stirred at -78°C for 30 min and then at room temperature for 4 h. Saturated NH_4Cl solution was added and the mixture was extracted with ether (3 times). The combined organic layer was washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel [hexane-ethyl acetate (4 : 1)] to afford **7** (187.4 mg, 70.4 %) as an oil. IR (film) 3320, 1609, 1466, 1294, 1125, 1063, 764, 710, 598 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.14 (9H, s), 1.31 (14H, m), 2.19 (2H, m), 2.20 (3H, d, J = 1.3), 2.67 (2H, m), 3.58 (3H, s), 3.59 (3H, s), 3.60 (3H, s), 3.74 (3H, s), 5.03 (4H, s), 5.06 (2H, s); EIMS *m/z* (rel. int.) 524 (M^+, 10), 448 (99), 388 (35), 194 (21), 73 (34), 45 (100); HREIMS calcd 524.3170 for $C_{28}H_{48}O_7Si$, found 524.3181.

1-(4-methyl-5-methoxy-2,3,6-trimethoxymethyloxyphenyl)undecan-10-yne (**8**) To a stirred solution of **7** (187.4 mg, 0.36 mmol) in THF (2 ml) was added TBAF (0.26 ml, 0.82 mmol) at room temperature, and stirring was continued for 1h under an argon atmosphere. The reaction mixture was extracted with ether, washed with water, saturated NaCl solution, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane-ethyl acetate (9 : 1) to afford **8** (145.4 mg, 90 %) as an oil. IR (film) 3291, 1458, 1391, 1159, 970, 635 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.31 (14H, m), 1.93 (2H, t, J = 2.6), 2.15 (2H, m), 2.20 (3H, s), 2.67 (2H, m), 3.57 (3H, s), 3.58 (6H, s), 3.73 (3H, s), 5.02 (4H, s), 5.06 (2H, s); EIMS *m/z* (rel. int.) 452 (M^+, 20), 376 (100), 331 (57), 258 (16), 183 (24), 111 (58), 45 (100); HREIMS calcd for 452.2810 for $C_{25}H_{40}O_7$, found 452.2792.

1-(4-methyl-5-methoxy-2,3,6-trimethoxymethyloxyphenyl)pentadecan-10-yne (**9**) A solution of *n*-BuLi (0.25 ml, 1.6 M hexane sol., 0.39 mmol) was added to a solution of diisopropylamine (0.06 ml, 0.49 mmol) in THF (1.5 ml) at -78°C under an argon atmosphere, and the mixture was stirred for 30 min at -78°C. A solution of **8** (145.4 mg, 0.32 mmol) in THF (1 ml) containing HMPA (0.19 ml, 0.94 mmol) was added to the LDA solution and the mixture was stirred for 1.5 h at -78°C. To this solution was added dropwise a solution of 1-iodobutane (72.1 mg, 0.94 mmol) in THF (1 ml) was added. The reaction mixture was stirred for 30 min at -78°C and then at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution, and then extracted with ether. The organic layer was washed with water, saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent left the residue, which was chromatographed on silica gel [hexane-ethyl acetate (9 : 1)] to give **9** (151.1 mg, 93%) as an oil. IR (film) 1454, 1391, 1159, 1038, 972 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.90 (3H, t, J = 7.0 Hz), 1.30 (18H, m), 2.13 (4H, m), 2.19 (3H, s), 2.67 (2H, m), 3.57 (3H, s), 3.58 (8H, s), 3.74 (3H, s), 5.02 (2H, s), 5.02 (2H, s), 5.06 (2H, s). EIMS *m/z* (rel. int.) 508 (M^+, 19), 432 (82), 400 (100), 387 (48), 183 (45), 45 (95); HREIMS calcd 508.3400 for $C_{29}H_{48}O_7$, found 508.3421.

1-(4-methyl-5-methoxy-2,3,6-trimethoxymethyloxyphenyl)-10-(Z)-pentadecene (**10**) A suspension of **9** (100 mg, 0.2 mmol) and palladium on barium sulfate (10 mg) in pyridine (2 ml) was stirred under a hydrogen

atmosphere for 36 h. After filtering the catalyst, the filtrate was evaporated to leave the residue, which was chromatographed on silica gel [hexane-ethyl acetate (2 : 1)] to afford **10** (100.6 mg, 98.6 %) as an oil. IR (film) 1458, 1391, 1159, 974 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.89 (3H, t, J = 7.0 Hz), 1.28 (18H, m), 2.04 (4H, m), 2.19 (3H, s), 2.66 (2H, m), 3.57 (9H, s), 3.73 (3H, s), 5.02 (4H, s), 5.06 (2H, s), 5.35 (2H, t, J = 4.5 Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 9.9, 14.0, 22.4, 25.3, 26.9, 27.2, 29.3, 29.6, 29.7, 29.8, 30.4, 30.4, 32.0, 57.4, 57.5, 57.7, 60.1, 99.2, 99.4, 99.4, 123.8, 128.9, 129.9, 129.9, 144.6, 145.0, 145.1, 147.6; EIMS *m/z* (rel. int.) 510 (M^+, 20), 434 (100), 402 (42), 389 (62), 195 (25), 45 (55); HREIMS calcd for 510.3557 for $C_{29}H_{50}O_7$; 510.3552.

5-methoxy-2-methoxymethyloxy-6-methyl-3-(Z)-10'-pentadecenyl-1,4-benzoquinone (**11**) A solution of **10** (130.8 mg, 0.25 mmol) in MeOH (3 ml) was added one drop of 48% hydrobromic acid and the mixture was stirred at 50°C for 10 min. After removal of the solvent, the crude mixture was dissolved in MeOH (4 ml) and stirred under an oxygen atmosphere overnight. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica gel [hexane-EtOAc (9 : 1)] to yield **11** (77.0 mg, 81 %) as an oil. IR (film) 3366, 1645, 1454, 1304, 1128, 989 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.90 (3H, t, J = 7.2 Hz), 1.27 (18H, m), 1.93 (3H, s), 2.00 (4H, m), 2.40 (2H, t, J = 7.4 Hz), 4.09 (3H, s), 5.35 (2H, t, J = 4.6 Hz), 7.10 (1H, s). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 8.1, 14.0, 22.4, 22.6, 26.9, 27.2, 28.3, 29.3, 29.4, 29.6, 29.7, 29.8, 32.0, 61.5, 118.7, 122.7, 129.8, 129.9,150.7, 157.2, 183.6, 184.1; EIMS *m/z* (rel. int.) 376 (M^+, 100), 183 (44), 167 (13). HREIMS calcd 376.2614 for $C_{23}H_{36}O_4$, found 376.2617.

Maesaquinone (**1**) To a solution of **11** (57 mg, 0.15 mmol) in THF and methylene chloride (5 : 1, 3.0 ml) was added three drops of 70% perchloric acid, and the mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with ethyl acetate and washed with water, saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by Sephadex LH-20 eluted with MeOH-$CHCl_3$ (11 : 9) to afford maesaquinone (**1**) (43.9 mg, 80.1 %) as orange crystals. mp 126-128°C (lit; 124-125°C); IR (film) 3318, 2918, 2851, 1609, 1460, 1366, 1294, 1123, 1061, 764, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.89 (3H, t, J = 6.6 Hz), 1.26 (16H, m), 1.46 (2H, m), 1.94 (3H, s), 2.01 (4H, m), 2.42 (2H, t, J = 7.7 Hz), 5.35 (2H, t, J = 4.8), 7.62 (2H, br s). ^{13}C-NMR ($CDCl_3$, 100 MHz,) δ 7.4, 14.0, 22.3, 22.4, 26.9, 27.2, 28.0, 29.3, 29.4, 29.5, 29.8, 32.0, 111.6, 116.1, 129.8, 129.9. EIMS *m/z* (rel. int.): 362 (M^+, 100), 182 (11), 168 (63); HREIMS calcd 362.2457 for $C_{22}H_{34}O_4$, found 362.2444. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found C, 72.70; H, 9.60%.

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