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ISOLATION, STRUCTURE AND SYNTHESIS OF MAESANIN, A HOST DEFENSE STIMULANT FROM AN AFRICAN MEDICINAL PLANT MAESA LANCEOLATA

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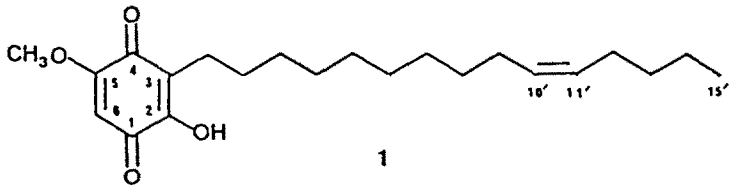
Abstract: The isolation, characterization and an efficient synthesis of maesanin 1*, a host defense stimulant isolated from an African medicinal plant Maesa lanceolata, is reported.*

The fruits of *Maesa lanceolata* (Myrsinaceae) were collected in East Africa on the basis of information provided by "Bwana Mganga", the local medicine man,[1] according to whom the hot water extract of the fruits is drunk to prevent cholera infection. In our preliminary test the methanol extract of the fresh fruits showed antimicrobial activity.[2] Subsequently, this crude extract was separated into hexane, ether, ethyl acetate and water-soluble portions. Monitoring of the separated portions with an antimicrobial assay indicated the hexane portion to be the active fraction. Flash chromatography of the bioactive hexane extract using a hexane-ethyl acetate mixture gave pale yellow needles, maesanin, in 0.35% yield. A more detailed bioassay with the pure compound indicated that maesanin invoked a non-specific host defense reaction in that mice treated with a single low dose (5mg/kg) were significantly protected from normally lethal *Escherichia coli* infection. Maesanin also inhibited 5-lipoxygenase, at IC_{90} 3×10^{-6}(M).



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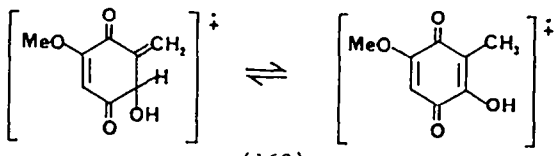
The structure of maesanin was determined by spectroscopic analysis. The UV spectrum showed absorption at 289 nm (log ε 4.48) and 425 nm (log ε 2.80), which suggested an dioxy-substituted benzoquinone. The IR spectrum showed characteristic bands at 3350, 1640 and 1600 cm^{-1}, attributable to a hydroxyl group, quinoid carbonyl and an olefinic bond, respectively. The 300 MHz ^{1}H-NMR spectrum revealed some typical signals at 5.86 (s, 1H, 6-H), 5.45 (m, 2H, -CH=CH-), 3.86 (s, 3H,

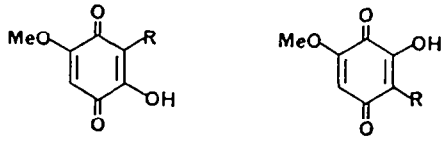
5-OCH_3), 2.45 (t, 2H, Ar-CH_2-), 1.98 (m, 4H, C=C-CH_2-), 1.3 (m, 18H, CH_2) and 0.92 ppm (t, 3H, CH_3). The ^{13}C-NMR spectrum showed signals at 182.8 (C-4, s), 181.6 (C-1, s), 161.2 (C-2, s), 151.5 (C-5, s), 119.3 (C-3, s) 102.2 (C-6, d) indicative of a *p*-benzoquinoid, at 129.9 and 130.0 (C-10', C-11', d) for the double bond, at 56.7 (-OCH_3, q) and signals ranging from 32.0-13.9 ppm (13 carbons) for the obtained side chain. These data suggested that maesanin is a *p*-benzoquinoid having three substituents, -OH, -OCH_3 and long side chain in the ring. It was also supported by MS spectrum showing a base peak (168) due to fragment ion as follows[3] (Fig-1).



(168)

Fig-1

The detremination of the methoxy position was accomplished by ^{1}H-^{1}H-NOE measurements using differential spectra. Irradiation of the methyl protons at 3.82 ppm gave n.O.e. on the proton at 5.81 ppm (15%), indicating that the OCH_3 group should be located on C-5. The position of the other substituents, i.e., the OH and side chain, on the *p*-benzoquinone ring were determined as on C-2 (hydroxyl) and C-3 (side-chain) based on the observation of small differences (1.2 ppm) in chemical shift between the C-1 and C-4 carbonyl shift (structure A in Fig-2). They could not be assigned to positions given in structure B, as shift differences observed for two carbonyl would be more than 10 ppm.[4]



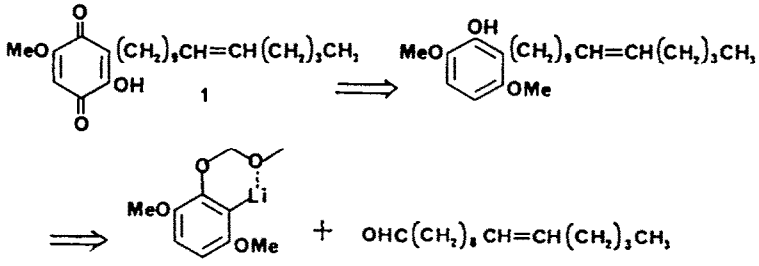
(A) (B)

Fig-2

The location of a double bond in the side chain was assigned to C-10' and 11' by an ozonization technique, and for the stereochemistry on the double bond, the lack of the IR absorption around 960 cm^{-1}, which is characteristic for *trans* double bond,[5] suggested to be *cis*. In order to confirm this point, the heteronuclear (^{1}H-^{13}C) chemical shift correlation spectrum (COSY) was obtained. According to the COSY contour plot, the signals at 26.9 and 27.1 ppm in the long side chain were clearly assigned to the allylic carbons of C-9' and C-12'. Comparison of their chemical shifts to a model compound, in which the chemical shift of *cis* carbons is 27.5 ppm and *trans* is 33 ppm,[6] permitted us to determine that the double bond in maesanin is *cis*.

These spectral data established maesanin is 3-[(z)-10'-pentadecenyl]-2-hydroxy-5-methoxy-1,4-benzoquinone.

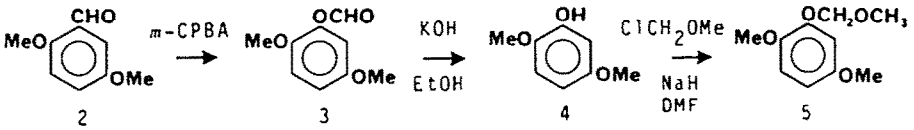
This simple chemical structure with unique biological activity is of primary synthetic interest. The general synthetic strategy envisaged for the preparation of maesanin (1) is dipicted in Scheme I.



Scheme I

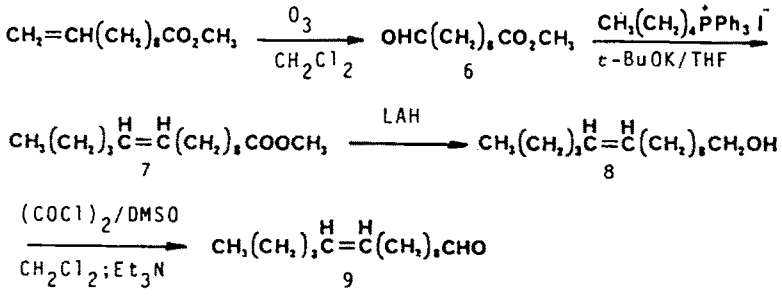
Our approach relies on the well-documented directed metallation[7] followed by trapping with electrophiles. The methoxymethyl ether group as a directive group is our choice and this protected phenol would also serve as a latent quinone grouping in the later step of the synthesis.

The preparation of the protected phenol 5 was achieved as indicated in Scheme II. Baeyer-Villiger oxidation of 2,5-dimethoxybenzaldehyde (2) with *m*-chloroperbenzoic acid gave 2-formyloxy-1,4-dimethoxybenzene (3), which was easily hydrolyzed with potassium hydroxide to give 2,5-dimethoxyphenol (4).[8] Etherification of 4 with sodium hydride and methoxymethyl chloride in DMF gave the desired protected phenol 5 in 47% yield from 2.



Scheme II

For a suitable equivalent to the side chain, we chose (z)-10-pentadecenal (9), which could be prepared from methyl 9-formylnonanoate (6)[9] by Wittig olefination, reduction and oxidation (Scheme III). Ozonolysis of methyl 10-undecylenate followed by reductive work-up gave the aldehyde 6 in 88% yield. Wittig olefination of 6 with *n*-pentylidene triphenylphosphorane gave (z)-olefinic ester 7.[9] The ester 7 was reduced with lithium aluminum hydride to give the alcohol 8, which was then oxidized by Swern's procedure[10] to give the desired aldehyde 9 in 55% yield from methyl 10-undecylenate. GLC analysis showed more than 98% of 9 was the *cis* isomer.

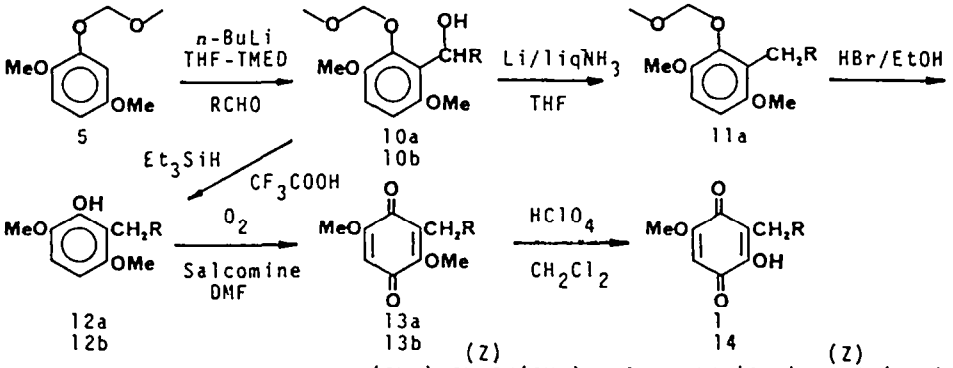


Scheme III

Attachment of the side chain to the aromatic ring was achieved by hetreoatom-facilitated directive lithiation[7] (Scheme IV). Metallation of 5 with *n*-butyllithium in the presence of tetramethylethylenediamine at 0°C for 30 minutes followed by addition of the aldehyde 9 gave the benzyl alcohol 10a in 77% yield. The ^{1}H-NMR spectrum of 10a showed the presence of a carbinol proton at 4.92 ppm (broad multiplet) and of the non-equivalent methylene protons of the methoxymethyl ether group (AB type quartet, J=6 Hz). Hydrogenolysis of the benzylic alcohol using lithium (3 eq) in liquid ammonia and THF at -30°C followed by quenching with ammonium chloride after 5 minutes afforded the deoxy compound 11a in 65% yield. The amount of lithium was crucial for the hydrogenolysis. If larger amount of lithium was used, to our astonishment, the methoxymethyloxy group was also reduced to give 1-(2,5-dimethoxyphenyl)-10-pentadecene as a by-product. Removal of the MOM group of 11a by Fujita's procedure[11] gave the phenol 12a in 93% yield. The phenol 12a was also obtained directly from 10a by ionic hydrogenation procedure[12] using triethylsilane and trifluoroacetic acid with concomitant acid hydrolysis of the protected group in 73% yield.

Having constructed the requisite frame-work, we then carried out the necessary functional transformations. After many unsuccessful attempts, oxidation of 12a into quinone 13a was performed by using molecular oxygen catalyzed by salcomine[13] in 83% yield. The two methoxy groups were easily distinguished from each other by their NMR spectrum. The methoxy group at C-5 (3.73 ppm) was somewhat broad due to the long-range coupling with C-6. This assignment was also supported by the n.O.e. enhancement of the quinone proton (20%) when the spectrum was irradiated at 3.73 ppm. Direct comparison of 13a was made with the sample obtained by the methylation of natural maesanin with dimethylsulfate. The two samples were identical in IR, TLC, GLC and NMR. In a previous communication,[14] we have reported selective demethylation of 13a using boron trichloride in methylene chloride at -70 to -40°C to give maesanin although the yield was poor (26%). Eventually it was found that simple acid hydrolysis[15] extrudes the more hindered methoxy group to give maesanin in good yield (77%). Our synthetic 1 was identical in all respects (IR, NMR, TLC, GLC and HPLC) with natural maesanin.

By using essentially the same method, we obtained dihydromaesanin (14). This methodology is also applicable to many functional derivatives of maesanin and to homologues of plumbagin[16] and to 3-(ω-phenylalkyl)catechols.[17]



Scheme IV

EXPERIMENTAL

Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride was distilled from P_2O_5. Triethylamine, tetramethylethylene diamine and DMF were distilled from CaH_2. All reactions were monitored by thin-layer chromatography carried out on 0,25mm E. Merck silica gel plates (60F-254). UV light or 7% phosphomolybdic acid-ethanol and heat was used as developing agent. E. Merck silica gel (60, particle size 0.040-0.063 mm) and Fuji silica gel (KC-2, 100-200 mesh) were used for column chromatography. Melting and boiling points were uncorrected. UV spectrum was recorded on Hitachi 100-80 spectrophotometer. IR spectra were recorded on a Nippon Bunko IRA-1 IR spectrometer. Low-resolution electron-impact mass spectra were obtained using a Shimadzu KLB-900 GC-MS spectrometer. High-resolution electron-impact mass spectra were obtained on a JEOL JMS-HX 100 spectrometer. 300 MHz ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Nicolet QE 300 spectrometer. Elemental analysis were performed by Mr. Goda, Osaka City University.

Maesanin 1. The methanol extract of fresh fruits (1.5 kg) of *Maesa lanceolata* (Myrsinaceae), which were collected in East Africa, was evaporated to dryness, water was added, and the aqueous solution was partitioned with hexane, chloroform and ethyl acetate. The bioactive portion was chromatographed on a silica gel column using a hexane-ethyl acetate solvent system to give 5 g of maesanin as yellow needles, mp 77°. UV(EtOH); 289 (logε 4.48), 425 nm (logε 2.80). IR($CHCl_3$); 3420, 1690, 1650, 1620, 1470, 1450, 1405, 1250 and 850 cm^{-1}. ^{1}H-NMR($CDCl_3$); 0.92 (t, J=6 Hz, 3H), 1.3 (m, 18H), 1.98 (m, 4H), 2.45 (t, J=6 Hz, 2H), 3.86 (s, 3H), 5.45 (m, 2H) and 5.86 (s, 1H). ^{13}C-NMR($CDCl_3$); 13.9 (q, CH_3), 22.3 (t, C-14'), 22.6 (t, C-1'), 26.9 (t, C-9'), 27.1 (t, C-12'), 28.0-29.7 (7 carbons), 32.0 (t, C-13'), 56.7 (q, OCH_3), 102.2 (d, C-6), 119.3 (s, C-3), 129.9 130.0 (d, C-10', C-11'), 151.5 (s, C-5), 161.2 (s, C-2), 181.6 (s, C-1) and 182.8 (s, C-4).

1,4-Dimethoxy-3-methoxymethyleneoxybenzene 5. To an ice cold solution of 2,5-dimethoxybenzaldehyde (6.64g, 0.04mol) in CH_2Cl_2 (100mL) was added *m*-chloroperbenzoic acid (12.9g, 0.074mol). After the initial exothermic reaction, the mixture was stirred at room temperature for 5 hr and the resulting precipitates were filtered. The filtrate was washed with aq $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated to give 3 as a colorless oil (6.57g). ^{1}H-NMR($CDCl_3$); 3.76 (s, 3H), 3.80 (s, 3H), 6.68 (t, J=2 Hz, 1H), 6.74 (d-d, J=3, 8 Hz, 1H), 6.92 (d-d, J=2, 8 Hz, 1H) and 8.20 (s, 1H). IR(neat); 2840, 1750, 1620, 1590, 1280, 1150, 1090, 1020, 890, 795 and 750 cm^{-1}.

The formate 3 was hydrolysed with 10% KOH (40mL) and ethanol (20mL) at 50°C for 10 mon. The mixture was extracted with ether and the aqueous layer was acidified with dil. HCl and was extracted with ether. The organic phase was washed with brine, dried and evaporated to give 4 (4.39g) as an oil, which, without purification, was subjected to etherification.

The phenol 4 (4.39g, 0.0285mol) in 12mL of DMF was added to a slurry of NaH (1.37g of 60% oil dispersion, 0.034mol) in 15mL of DMF at 0°C under argon atmosphere. The solution was stirred for 15 min at 0°C before methoxymethyl chloride (7.72g, 0.0428mol) was added and the resulting solution was allowed to warm to room temperature. After 3 hours stirring at room temperature, the mixture was treated with ice water and extracted with CH_2Cl_2. The organic phase was washed with dil HCl and brine, dried ($MgSO_4$) and concentrated in vacuo. Vaccum distillation afforded 4.14g (52% from 2) of 5 as a colorless oil; bp 110-114°/2Torr. IR(neat); 1610, 1590, 1515, 1460, 1230, 1155, 1130, 1080, 1050, 1000, 920, 840 and 790 cm^{-1}. ^{1}H-NMR(CCl_4); 3.52 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 5.12 (s, 2H), 6.40 (d-d, J=2, 8 Hz, 1H), 6.68 (d, J=2 Hz, 1H) and 6.74 (d, J=8 Hz, 1H). Anal. calcd. for $C_{10}H_{14}O_4$: C, 60.56; H, 7.12. Found: C, 60.56; H, 7.19.

Methyl 9-formylnonanoate 6. A current of ozonised oxygen was passed through a solution of methyl 10-undecylenate (2g) in CH_2Cl_2 (25mL) at -78°C until an excess of ozone was present. The solution was then flushed with nitrogen and Et_3N (2.8mL) was added after which the solution was allowed to warm to room temperature. The solvent was evaporated and the mixture was chromatographed (SiO_2, 95:5 C_6H_6-AcOEt as eluent) to afford 6 (1.79g, 89%) as an oil. IR(neat); 2720, 1740, 1200,

and 1180 cm^{-1}. ^{1}H-NMR(CCl_4); 1.1-1.8 (m, 12H), 2.25 (t, J=6 Hz, 2H), 2,36 (d-t, J=2, 6 Hz, 2H), 2.56 (s, 3H) and 9,58 (t, J=2 Hz, 1H),

10-Pentadecenol 8. To a suspension of *n*-pentyltriphenylphosphonium iodide (4.89g, 10.7mmol) in 20mL of dry THF at room temperature under an argon atmosphere was added a solution of *tert*-BuOK (sublimed under reduced pressure, 1.31g, 10.7mmol) in 10mL of THF. After the mixture had been stirred for 30 min, 1.79g (7.87mmol) of the aldehyde ester 6 in 5mL of THF was added. After 1 hr, 2.5mL of water was added and the mixture was partitioned between hexane and brine. The organic layer was concentrated in vacuo and the residue again extracted with hexane. The hexane soluble portion of the product was purified by chromatography (SiO_2, 9:1 C_6H_6-AcOEt as eluent) to afford an oil (1.87g, 82%). The NMR spectrum of the oil showed that it was the mixture of the methyl ester 7 and the corresponding *tert*-butylester. The mixture was used in the next step without further purification. MS; Calcd. for $C_{16}H_{30}O_2$: 254.2292. Found: 254.2269.

To a suspension of LAH (0.25g, 6.7mmol) in 30mL of dry ether was added a solution of the esters (1.69g) in 10mL of ether. The mixture was stirred at room temperature for 4 hr, and quenched by successive dropwise addition of water and 2N HCl. The solution was extracted with ether, and the ether layer was washed with sat. $NaHCO_3$ solution and brine and then dried ($MgSO_4$). Removal of the solvent in vacuo gave 1.36g of the alcohol 8 as an oil. IR(neat); 3320 and 1060 cm^{-1}. ^{1}H-NMR(CCl_4); 0.92 (t, J=6 Hz, 3H), 1.67 (s, 1H, exchangeable with D_2O), 3.54 (t, J=6 Hz, 2H) and 5.27 (t, J=5 Hz, 2H). MS; m/z 208 (M^+-18). Calcd for $C_{15}H_{30}O$: 226.2336. Found: 226.2316.

10-Pentadecenal 9. To a solution of $(COCl)_2$ (0.84g, 6.6mmol) in 20mL of CH_2Cl_2 was added DMSO (0.94mL) dissolved in 3mL of CH_2Cl_2 at -70°C. The mixture was stirred for 5 min and the alcohol 8 (1.36g, 6.0mmol), dissolved in 12mL of CH_2Cl_2, was added within 5 min. The stirring was continued for an additional 15 imn. Triethylamine (4.2mL) was added and the mixture was stirred for 5 min and then allowed to warm to room temperature. Water was then added and the aqueous layer was re-extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried and evaporated. The crude product was purified by chromatography (SiO_2, 9:1 hexane-ether as eluent) to afford 0.951g (76%) of 9, GLC analysis showed more than 98% was the *cis* isomer. IR(neat); 2700, 1730, 1460 and 965 cm^{-1}. ^{1}H-NMR(CCl_4); 0.92 (t, J=6 Hz, 3H), 2.34 (t, J=7 Hz, 2H), 5.24 (t, J=5 Hz, 2H) and 9.59 (t, J=1.5 Hz, 1H). MS; Calcd. for $C_{15}H_{28}O$: 224.2072. Found: 224.2106.

1-[(3,6-Dimethoxy-2-methoxymethyleneoxy)phenyl]-10-pentadecen-1-ol 10a. *n*-Butyllithium (3.4mL, 5.1mmol, 1.49M hexane solution) was added to a solution of 5 (0.84g, 4.24mmol) in the mixture of THF (20mL) and tetramethylethylenediamine (4mL) cooled to 0°C under argon atmosphere. After the solution had been stirred at room temperature for 30 min, the solution of 10-pentadecenal (0.951g, 4.24mmol) in 5mL of THF was added dropwise with continued stirring at room temperature for 1 hr. The reaction was quenched by addition of sat. NH_4Cl solution and ether. The aqueous phase was extracted with ether. The organic layers were combined, washed with 1N HCl and then dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography (SiO_2, 9:1 C_6H_6-AcOEt as eluent) to afford 1.38g (77%) of 10a as a colorless oil. IR(neat); 3560, 1600, 1490, 1260, 1160, 1070, 980 and 790 cm^{-1}. ^{1}H-NMR(CCl_4); 0.92 (t, J=6 Hz, 3H), 3.11 (t, J=11 Hz, 1H), 3.54 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 4.92 (m, 1H), 5.07 (q, J=6 Hz, 2H), 5.30 (t, J=5 Hz, 2H), 6.43 (d, J=8 Hz, 1H) and 6.59 (d, J=8 Hz, 1H). Anal. calcd. for $C_{25}H_{42}O_5$; C, 71.05; H, 10.02. Found; C, 71.06; H, 10.12.

1-[(3,6-Dimethoxy-2-methoxymethyleneoxy)phenyl]-10-pentadecene 11a. The benzyl alcohol 10a (1.28g, 3.02mmol) was dissolved in 20mL of dry THF and ammonia (ca. 100mL), distilled from sodium, was condensed into the reaction flask and cooled to -30°C. Lithium metal (63mg, 9mmol) was added and the reaction mixture was stirred at -30°C. After 5 min the reaction mixture was quenched with NH_4Cl, the ammonia was allowed to evaporate, and water and ether were added. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give an oil (1.20g). The crude product was purified by chromatography (SiO_2, 95:5 C_6H_6-AcOEt as eluent) to afford 0.799g (65%) of 11a. An analytical sample was obtained by bulb to bulb distillation (oven temperature 180°/0.8Torr). IR(neat); 1590, 1480, 1250, 1065, 985, 785 and 710 cm^{-1}. ^{1}H-NMR(CCl_4); 0.92

(t, J=6 Hz, 3H), 2.64 (t, J=7 Hz, 2H), 3.51 (s, 3H), 3.78 (s, 3H), 4.98 (s, 2H), 5.28 (t, J=5 Hz, 2H), 6.32 (d, J=9 Hz, 1H) and 6.48 (d, J=9 Hz, 1H). MS; m/z 406 (base peak), 374, 362 and 167. Anal. calcd. for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.83; H, 10.55.

1-[(2-Hydroxy-3,6-dimethoxy)phenyl]-10-pentadecene 12a. (a) For the deprotection of the methoxy methyl ether the procedure of Fujita[11] was employed. To a solution of 11a (0.777g, 1.91mmol) in 10mL of ethanol was added few drops of 48% HBr and the mixture was heated at 65°C for 15 min. After the mixture had been diluted with ether, the solution was washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated to give 0.642g (93%) of 12a as an oil. IR(neat); 3540, 1600, 1490, 1250, 1120, 1090, 1060, 780 and 710 cm^{-1}. ^{1}H-NMR(CCl_4); 0.96 (t, J=6 Hz, 3H), 2.00 (m, 4H), 2.58 (t, J=7 Hz, 2H), 3.72 (s, 3H), 3.80 (s, 3H), 5.17 (t, J=5 Hz, 2H), 5.34 (s, 1H), 6.05 (d, J=9 Hz, 1H) and 6.37 (d, J=9 Hz, 1H). MS; m/z 362 (base peak), 167, 143 and 137.
(b) From the benzyl alcohol 10a the phenol was obtained directly by ionic hydrogenation.[12] To a solution of 10a (0.70g, 1.66mmol) and Et_3SiH (0.670g, 5.76mmol) in 10mL of CH_2Cl_2 was added CF_3COOH (2.2mL, 28.8mmol) at room temperature under argon. After stirring for 4 hr at room temperature, the mixture was poured onto sat. $NaHCO_3$ solution and CH_2Cl_2 followed by extraction with the same solvent. The combined organic layers were washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography (SiO_2, 95:5 C_6H_6-AcOEt as eluent) to afford 0.437g (73%) of 12a.

2,5-Dimethoxy-3-(10-pentadecenyl)-1,4-benzoquinone 13a. To a stirred mixture of 12a (0.642g, 1.77mmol) and salcomine[13] (64mg) in DMF (10mL) was bubbled oxygen for 3 hr at room temperature. The mixture was poured onto ice, and was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by chromatography (SiO_2, 9:1 C_6H_6-AcOEt as eluent) to give 0.541g (81%) of 13a as a yellow oil. IR(neat); 1660, 1600, 1210, 1050 and 840 cm^{-1}. ^{1}H-NMR(CCl_4); 0.91 (t, J=6 Hz, 3H), 2.33 (t, J=7 Hz, 2H), 3.73 (s, 3H), 3.98 (s, 3H), 5.19 (t, J=4 Hz, 2H) and 5.49 (s, 1H). MS; Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.04; H, 9.66.

2-Hydroxy-5-methoxy-3-(10-pentadecenyl)-1,4-benzoquinone (Maesanin) 1. To a stirred solution of 13a (0.405g, 1.08mmol) in CH_2Cl_2 (5mL) was added a few drops of $HClO_4$ (70%). After the mixture had been stirred for 1 hr at room temperature under argon, it was washed with sat. $NaHCO_3$ solution and brine, dried and evaporated to give the crystalline 1 (0.30g, 77%). An analytical sample was obtained by recrystallization from hexane followed by sublimation (bath temp. 150°/0.25Torr), mp 69-70°, yellow needles. IR($CHCl_3$); 3420, 1650, 1620, 1470, 1450, 1405, 1250 and 850 cm^{-1}. ^{1}H-NMR($CDCl_3$); 0.92 (t, J=6 Hz, 3H), 1.98 (m, 4H), 2.45 (t, J=6 Hz, 2H), 3.86 (s, 3H), 5.45 (t, J=4 Hz, 2H) and 5.86 (s, 1H). MS; Calcd. for $C_{22}H_{34}O_4$: 362.2523. Found: 362.2490.

1,4-Dimethoxy-2-methoxymethyleneoxy-3-pentadecylbenzene 10b was prepared as described for the benzyl alcohol 10a by using 786mg (3.98mmol) of 5, 4.78mmol of *n*-BuLi (1.4M hexane solution) and 0.9g of pentadecanal. Purification by chromatography gave 1.21g (77%) of 10b as a colorless oil. IR(neat); 3550, 1590, 1480, 1255, 1070, 980, 930, 790 and 720 cm^{-1}. ^{1}H-NMR(CCl_4); 0.85 (t, J=6 Hz, 3H), 3.48 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 4.8 (br, 1H), 5.02 (q, J=5 Hz, 2H), 6.43 (d, J=9 Hz, 1H) and 6.67 (d, J=9 Hz, 1H).

2-Hydroxy-1,4-dimethoxy-3-pentadecylbenzene 12b was prepared as described previously for the phenol 12a by using 1.21g (2.85mmol) of 10b, 663mg (5.7mmol) of Et_3SiH and 4.39mL (57mmol) of CF_3COOH in 10mL of CH_2Cl_2. Purification by chromatography gave 717mg (69%) of 12b as a colorless oil. IR(neat); 3550, 1600, 1490, 1245, 1125, 1090, 1060, 780 and 710 cm^{-1}. ^{1}H-NMR(CCl_4); 0.89 (t, J=6 Hz, 3H), 2.59 (t, J=7 Hz, 2H), 3.72 (s, 3H), 3.78 (s, 3H), 5.53 (s, 1H), 6.17 (d, J=9 Hz, 1H) and 6.52 (d, J=9 Hz, 1H).

2,5-Dimethoxy-3-pentadecyl-1,4-benzoquinone 13b was prepared as described for the quinone 13a by using 0.620g (1.70mmol) of 12b and salcomine (62mg) in 10mL of DMF. Purification by chromatography gave 0.523g (81%) of 13b as yellow prisms. An analytical sample was obtained by recrystallisation from hexane, mp 72-74°. IR($CHCl_3$); 1650, 1640, 1595, 1045 and 840 cm^{-1}. ^{1}H-NMR(CCl_4); 0.90 (t, J=6 Hz, 3H), 2.36 (br, 2H), 3.80 (s, 3H), 4.04 (s, 3H) and 5.62 (s, 1H). Anal. calcd.

for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.01; H, 10.16.

2-Hydroxy-5-methoxy-3-pentadecyl-1,4-benzoquinone (Dihydromaesanin) 14 was prepared as described previously for maesanin 1 by using 22mg of 13b and 1 drop of $HClO_4$ in 1mL of CH_2Cl_2 (yield: 18mg, 85%). An analytical sample was obtained by sublimation (bath temp. 130°/0.3Torr) which gave orange yellow prisms, mp 102-103°. IR($CHCl_3$); 3400, 1650, 1640, 1605 and 840 cm^{-1}. ^{1}H-NMR($CDCl_3$); 0.85 (t, J=6 Hz, 3H), 2.42 (t, J=7 Hz, 2H), 3.83 (s, 3H) and 5.80 (s, 1H). Anal. calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.46; H, 9.99.

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