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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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Summary: 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 fruit of *Maesa lanceolata* (Myrsinaceae) was 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 fruit is drunk to prevent cholera infection. In our preliminary test the methanol extract of the fresh fruit 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[2] indicated the hexane portion to be the active fraction. Flash chromatography[3] of the bioactive hexane extract using a hexane-ethyl acetate mixture gave a pure yellow needle, maesanin in 0.35% yield. More detailed bioassays with pure compound indicated that maesanin involked a non-specific host defence reaction in that mice treated with a single low dose (5 mg/kg) were significantly protected from normally lethal *Escherichia coli* infection.

Maesanin 1, m.p. 77 °C, $C_{22}H_{36}O_4$ (CI-MS with *iso*-butane and elemental analysis) contains 3-alkyl-2-hydroxy-5-methoxy-1,4-benzoquinone moiety as shown by the following spectral data; UV (EtOH) 289 and 425 nm (log ε 4.48 and 2.80), IR ($CHCl_3$) 3420 (OH), 1690 and 1650 cm^{-1} (quinoid CO), ^1H NMR ($CDCl_3$) 3.84 (s, 3H; OCH_3), 5.82 (s, 1H) and 7.26 ppm (s, 1H, OH), and ^{13}C NMR ($CDCl_3$), 182.9 and 181.7 (s, quinoid CO), 161.4 (d) 151.7 (s), 119.5 (s) and 56.9 ppm (s, OCH_3). This is also supported by the fairly strong peaks at m/z 168 and 169 of the corresponding hydroquinone fragments[4]. The position at the double bond in the side chain was established by ozonisation. The lack of the absorption around 960 cm^{-1} indicates that the double bond is *cis*[5]. This was also supported by the ^{13}C NMR signals attributable to the allylic carbons[6].

The combined spectral data established that maesanin possessed 3-(Z-10-pentadecenyl)-2-hydroxy-5-methoxy-1,4-benzoquinone 1.

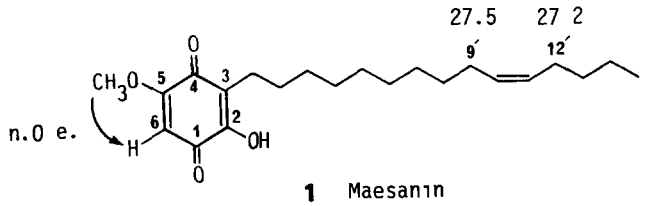
This simple chemical structure with unique biological activity is of primary synthetic interest. We now report a facile synthesis of this type of quinone by a short reaction which exploits the regioselective metalation of an appropriately substituted 1,2,4-trialkoxybenzene. Reaction of 2,5-dimethoxyphenol using 1 eq of $MeOCH_2Cl$ and 1.2 eq of NaH (DMF, room temp., 4 hrs) gave 79% of methoxymethyl ether 2. Heteroatom-facilitated lithiation[7] of ether 2 (1.5 eq n-BuLi, THF, 1 eq TMEDA, 0°-20°, 30 min), followed by addition of 1 eq of (Z)-10-pentadecenal 3[8] gave 75% of the benzyl alcohol 4 as a viscous oil [IR (neat) 3420 cm^{-1}, NMR (CCl_4) 0.92 (t, J=6 Hz, 3H), 3.11 (d, J=12 Hz, 1H), 3.54 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 4.92 (brm, 1H), 5.07 (q, J=6 Hz, 2H), 5.30 (t, J=5 Hz, 2H), 6.43 (d, J=8 Hz, 1H), 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]. Hydrogenolysis of the benzylic oxygen using Li (3 eq, THF-liq NH_3, -30°, 5 min) gave in 65% yield the deoxy compound 5 [IR (neat) 1590, 785, 710 cm^{-1}, NMR(CCl_4) 0.92 (t, J=6 Hz, 3H), 2.64 (t, J=7 Hz,2H), 3.51 (s, 3H), 3.76 (s, 3H), 4.98 (s, 2H), 5.28 (t, J=5 Hz, 2H), 6.32 (d, J=9 Hz, 1H), 6.48 (d, J=9 Hz, 1H), Anal Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41.Found: C, 73.83; H, 10.54]. Removal of the MOM group by treatment of 5 with 47% HBr in ethanol (65°, 15 min) yielded the dimethoxyphenol 6 [IR (neat) 3540, 1600, 750 cm^{-1}, NMR (CCl_4) 0.96 (t, J=6 Hz, 3H), 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), 6.37 (d, J=9 Hz, 1H)]. The phenol 6 was obtained directly from 4 by ionic hydrogenation[9] with concomitant removal of the MOM group (Et_3SiH, CF_3CO_2H, CH_2Cl_2, room temp., 30 min) in 55% yield.

Oxidation of 6 was carried out by passing a stream of oxygen into a solution of the phenol in DMF containing 10 mole % of salcomine[10]. This gave, in 78% overall yield from 5, the new quinone 7 as a yellow oil [IR (neat) 1660, 1600, 840 cm^{-1}, 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), 5.49 (s, 1H), MS Calcd for $C_{23}H_{36}O_4$: 376.2622, Found 376.2614]. Direct comparison of 7 was made with the sample obtained by methylation of natural maesanin 1 with Me_2SO_4 (K_2CO_3, acetone, reflux, 2 hrs). The two samples gave identical IR, TLC and NMR. The methoxy signal at δ 3.73 (C-5, OMe) in the NMR of 7 was somewhat broad compared to that of C-2 OMe at δ 3.98. This broadening is caused by long-range coupling of the OMe protons with the quinone ring proton, and this could be confirmed by NOE enhancement of quinone proton signal (20%) when the sample was irradiated at δ 3.73.

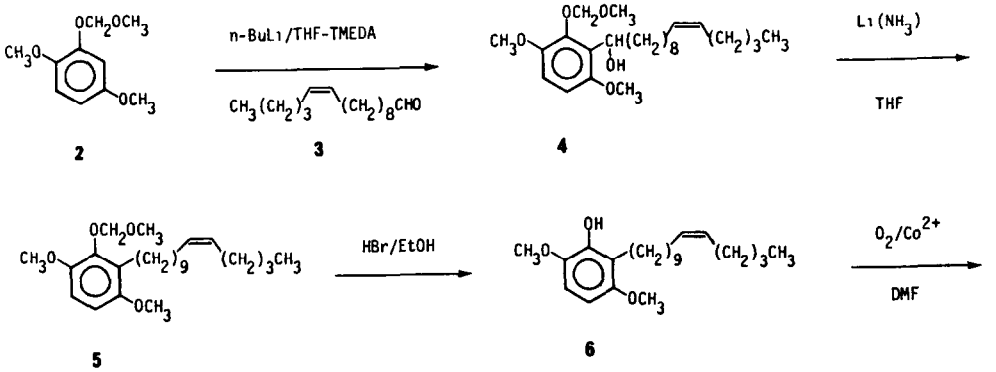
Selective demethylation of 7 was achieved using BCl_3 (3 eq, -78° to -40°, 30 min) following the analogy of Jung[11]. This afforded 26% of 1 (mp 76.5° to 77.5° from hexane, mixed mp with maesanin 77°) and 57% of recovered

7, readily separated with silica gel pre-packed columns using $CHCl_3$-MeOH, 99:1) as an eluent. Under more vigorous conditions (at 0°C), BCl_3 treatment led to chlorination of the alkenyl side chain. Our synthetic 1 was identical in all respects (IR, NMR, HPLC, TLC) with natural maesanin.

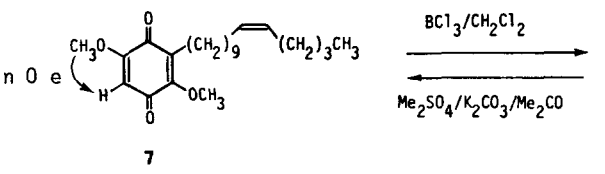
An alternative metalation route to maesanin involving the tetraalkoxybenzene 8[12] was also investigated. In this series, the lithiation and aldehyde



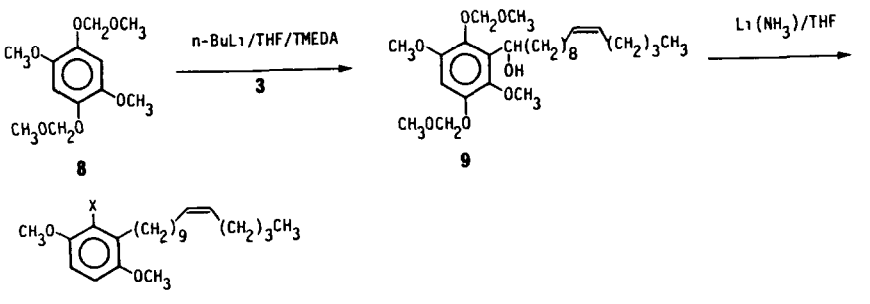
1 Maesanin



2 3 4 5 6



1 7



3 8 9

10 X=H

11 X=OCH_2OCH_3

quench to give 9, proceeded in only 27% yield, with substantial recovery of 8. More surprisingly, the Birch reduction of carbinol 9 led to the alkenylbenzene derivatives 10 [NMR (CCl_4) 0.90 (t, J=6 Hz, 3H), 2.51 (t, J=7 Hz, 2H), 3.68 (s, 3H), 3.73 (s, 3H), 5.26 (t, J=5 Hz, 2H), 6.51 (m, 3H)] and 11 [NMR (CCl_4) 0.90 (t, J=6 Hz, 3H), 2.62 (t, J=6 Hz, 2H), 3.50 (s, 3H), 3.75 (s, 6H), 4.99 (s, 3H), 5.30 (t, J=5 Hz, 2H), 6.41 (d, J=8 Hz, 1H), 6.59 (d, J=8 Hz, 1H)], in yields of 39% and 8%, respectively.

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8. Aldehyde 3 [NMR (CCl_4) 0.92 (t, J=6 Hz, 3H), 2.34 (t, J=7 Hz, 2H), 5.24 (t, J=5 Hz, 2H), 9.59 (t, J=1.5 Hz, 1H)] was prepared from methylundecylenate by a four step sequence involving ozonization at -78°, Wittig olefination (n-pentylphosphonium iodide, n-BuLi, THF, -30° to room temp., 4 hrs), reduction (3.6 eq $LiAlH_4$, Et_2O, room temp, 2 hrs) and Swern oxidation [1.1 eq $(COCl)_2$, 2.2 eq DMSO, CH_2Cl_2, -78°, 15 min then 5 eq Et_3N] in 28% overall yield.
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12. Compound 8 was prepared from 2,5-dimethoxybenzoquinone by reduction (4 eq $Na_2S_2O_4$, 1:1 THF-H_2O, room temp., 1 hr), followed by etherification of the hydroquinone (2.4 eq $MeOCH_2Cl$, 2.4 eq $(i\text{-}Pr)_2NEt$, CH_2Cl_2, room temp., 4 hrs) in 41% overall yield.

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