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TOTAL SYNTHESIS OF THE HOST DEFENSE STIMULANT MAESANIN

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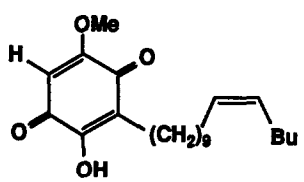
Summary: An efficient total synthesis of the host defense stimulant maesanin has been achieved by a route featuring a photochemical aromatic annulation as a key step.

In East Africa the *Bwana Mganga* tribal medicine men prescribe an extract of the berries of the *Maesa lanceolata* bush as a drug for protection against cholera infection. Kubo and coworkers have identified maesanin as the active "host defense stimulant" compound in this drug, and in recent studies they have elucidated the structure of maesanin and confirmed the assignment by synthesis.[1] Maesanin is an inhibitor of KDO transferase and exhibits activity against gram negative bacteria; it also blocks 5-lipoxygenase and is under investigation as an antiasthmatic drug.[1,2]



Maesanin

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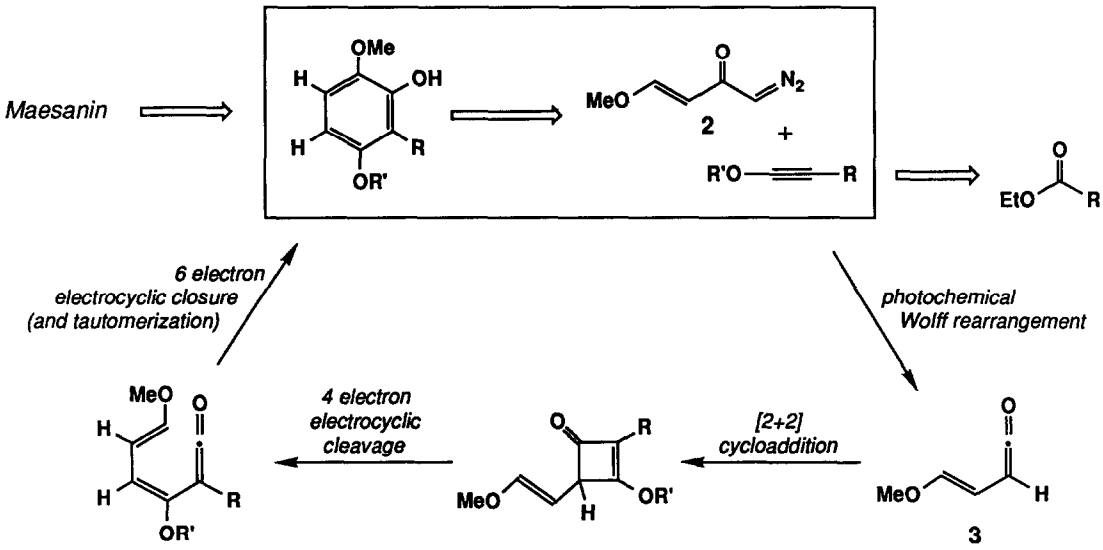
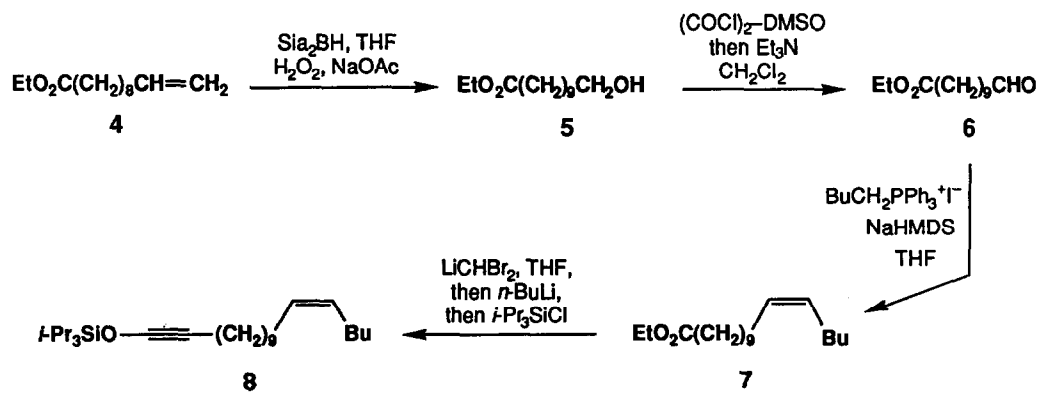
The previous synthesis of maesanin by Kubo and coworkers employed a classical *linear substitution strategy* in which the requisite fifteen-carbon appendage was introduced via the reaction of 10-pentadecenal with an aryllithium compound generated by directed metalation of a differentially protected 1,2,4-trihydroxybenzene derivative. As detailed below, our synthetic approach involves the application of a *convergent annulation strategy* in which the six-membered aromatic ring is assembled from acyclic precursors in a single step with the pentadecenyl substituent already in place. Previously we have shown that the addition of vinylketenes to acetylenes provides an efficient annulation route to highly substituted aromatic systems.[3] Our strategy for the synthesis of maesanin is based on a recently developed "second-generation" version of this aromatic annulation method[4] in which irradiation of the α,β-unsaturated α'-diazo ketone **2** triggers a photochemical Wolff rearrangement which produces the vinylketene **3**, and thereby initiates a cascade of pericyclic transformations ending with the formation of the desired substituted phenol. Oxidation then furnishes maesanin.



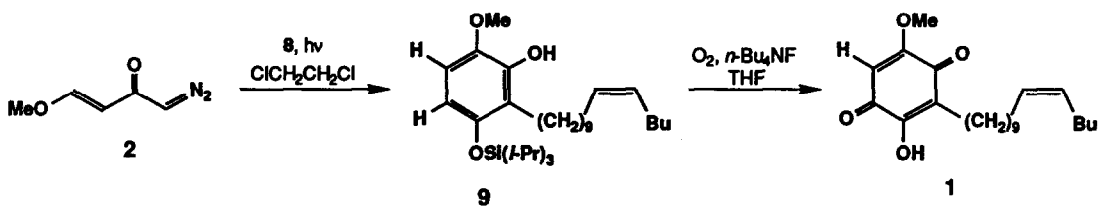
The siloxyalkyne **8** was selected as the acetylene component for the pivotal aromatic annulation step. Siloxyalkynes can be conveniently prepared from carboxylic esters using the Kowalski reaction[5] and function as outstanding ketenophiles in our aromatic annulation reaction.[3c,4,6] (Z)-Ethyl 11-hexadecenoate (**7**), the immediate precursor to **8**, was easily prepared in three steps from inexpensive ethyl 11-undecenoate (**4**) as outlined below. Hydroboration of **4** with 2 equiv of disiamylborane in THF (0 °C, 3 h) followed by oxidation with 6.6 equiv of 30% hydrogen peroxide and 3 equiv of sodium acetate (rt, 15 h) furnished ethyl 11-hydroxyundecanoate (**5**)[7] in 78-82% yield after chromatographic purification.[8] Swern oxidation[9] then provided the aldehyde **6**[10] (86-92% yield), which was treated with pentylidenetriphenylphosphorane under Bestmann conditions[11] (THF, -70 °C, 2 h, then 0 °C, 15 min) to produce the requisite unsaturated ester **7**[12] in 88-94% yield (greater than 98:2 ratio of Z : E olefin isomers). Sequential treatment of **7** with 2.2 equiv of dibromomethyllithium (from the metalation of dibromomethane with LiTMP; -78 °C, 10 min), 5.0 equiv of *n*-butyllithium (-78 °C, 10 min, then rt, 45 min), and finally 5.0 equiv of triisopropylsilyl chloride (-78 °C, 2 h, then rt, 16 h) gave the



siloxyacetylene **8**[13] in 52-54% yield after purification by column chromatography on silica gel.

The diazo ketone **2** required for the key aromatic annulation reaction was prepared employing the improved "detrifluoroacetylative" diazo transfer method recently developed in our laboratory.[14] Exposure of 4-methoxy-3-butenone to 1.05 equiv of LiHMDS in THF at -78 °C for 30 min furnished the corresponding lithium enolate, which was trifluoroacetylated by treatment with 2.1 equiv of $CF_3CO_2CH_2CF_3$ (-78 °C, 15 min). At this point the cooling bath was removed, and a solution of 3 equiv of methanesulfonyl azide, 1.5 equiv of triethylamine, and 2 equiv of water in acetonitrile was added to the reaction mixture. After 16 h at room temperature, the reaction was worked up, and the crude product was purified by column chromatography on silica gel to afford the α-diazo ketone **2**[15] as an unstable orange oil in 39% yield. It should be noted that none of the desired diazo ketone was obtained when standard "deformylative" diazo transfer procedures[16] were employed for this reaction.

The key aromatic annulation step was accomplished by irradiating a degassed 0.5 M solution of the siloxyacetylene **8** and the diazo ketone **2** in 1,2-dichloroethane in a vycor tube using a low-pressure mercury lamp (254 nm). After 4 h, a second equivalent of **2** was added and irradiation was continued for 4.5 h. Concentration and chromatographic purification provided the phenol **9**[17] in 53-54% yield. Cleavage of the silyl



ether protective group and oxidation to produce maesanin was then achieved in a single operation (67% yield) by exposure of **9** to the action of 1.1 equiv of tetra-*n*-butylammonium fluoride in THF (-78 °C to rt, 30 min) in the presence of oxygen. Column chromatography on silica gel furnished maesanin as yellow needles, mp 69-69.5 °C [lit.[1] mp 69-70 °C], with spectral properties indistinguishable from those of an authentic sample of the natural product.[18]

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References and Notes

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6. Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693.
7. Ethyl 11-hydroxyundecanoate (**5**) was obtained as a colorless oil: IR (film) 3400, 2925, 2855, 1735, 1465, 1375, 1180, 1100, 1055, and 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.01 (q, J = 7 Hz, 2 H), 3.61 (appar t, J = 6 Hz, 2 H), 2.26 (t, J = 8 Hz, 2 H), 1.55 (m, 4 H), 1.27 (m, 13 H), and 1.23 (t, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 66.7, 60.0, 34.2, 32.6, 29.4, 29.3, 29.2, 29.1, 29.0, 25.6, 24.8, and 14.1; Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.83; H, 11.17.
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10. Ethyl 11-oxoundecanoate (**6**) was obtained as a colorless oil: IR (film) 2930, 2860, 2720, 1730, 1465, 1375, 1185, 1100, and 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 2 Hz, 1 H), 4.10 (q, J = 7 Hz, 2 H), 2.39 (dt, J = 2 Hz, J = 7 Hz, 2 H), 2.26 (t, J = 8 Hz, 2 H), 1.59 (m, 4 H), 1.24 (m, 10 H), and 1.23 (t, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 173.6, 60.0, 43.7, 34.2, 29.1 (2 C), 29.0 (2 C), 28.9, 24.8, 21.9, and 14.1; Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.64; H, 10.88.
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12. Ethyl (Z)-11-hexadecenoate (**7**) was obtained as a colorless oil: IR (film) 2949, 2370, 1740, 1470, 1380, 1250, 1185, 1100, and 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (m, 2 H), 4.08 (q, J = 7 Hz, 2 H), 2.24 (t, J = 8 Hz, 2 H), 1.96 (m, 4 H), 1.57 (m, 2 H), 1.25 (m, 19 H), and 0.86 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 129.8 (2 C), 60.0, 34.3, 31.9, 29.7, 29.4 (2 C), 29.3, 29.2, 29.1, 27.1, 26.9, 24.9, 22.3, 14.2, and 13.9; Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.79; H, 12.42.
13. 1-(Triisopropylsiloxy)-(Z)-11-heptadecen-1-yne (**8**) was obtained as a colorless oil: IR (film) 3000, 2925, 2860, 2280, 1465, 1260, and 885 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (m, 2 H), 2.00 (m, 6 H), 1.27 (m, 21 H), 1.10 (d, J = 1 Hz, 18 H), and 0.87 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.9, 129.8, 86.7, 32.0, 30.5, 30.0, 29.8, 29.6, 29.5, 29.3, 29.2, 28.8, 27.2, 26.9, 22.3, 17.3, 17.2, 14.0, and 11.8; Anal. Calcd for $C_{26}H_{50}OSi$: C, 76.77; H, 12.39. Found: C, 76.90; H, 12.41.
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15. 1-Diazo-4-methoxy-3-buten-2-one (**2**) was obtained as an orange oil: IR (film) 3100, 2120, 1650, 1590, 1450, 1380, 1310, 1255, 1218, 1145, 1090, and 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 12 Hz, 1 H), 5.40 (d, J = 12 Hz, 1 H), 5.14 (s, 1 H) and 3.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 160.7, 102.4, 57.7 and 54.8; UV λ max (methanol) 258 (ε=7200) and 295 nm (ε=14000).
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17. 2-[(Z)-10-Pentadecenyl]-6-methoxy-3-(triisopropylsiloxy)phenol (**9**) was obtained as a yellow oil: IR (film) 3540, 2920, 2855, 1590, 1480, 1460, 1440, 1290, 1245, 1090, 1010, 885, 840, and 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (d, J = 9 Hz, 1 H), 6.25 (d, J = 9 Hz, 1 H), 5.61 (s, 1 H), 5.32 (m, 2 H), 3.80 (s, 3 H), 2.62 (m, 2 H), 2.00 (m, 4 H), 1.50 (m, 2 H), 1.30 (m, 19 H), 1.08 (d, J = 8 Hz, 18 H), and 0.87 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 148.8, 144.4, 140.7, 130.0, 129.8, 120.0, 107.8, 107.5, 56.2, 32.0, 30.0, 29.8, 29.7, 29.6 (2 C), 29.3, 29.2, 27.2, 26.9, 24.4, 22.3, 18.1, 14.0, and 13.1; Anal. Calcd for $C_{31}H_{56}O_3Si$: C, 73.75; H, 11.18. Found: C, 73.59; H, 11.23.
18. Maesanin (**1**) was obtained as yellow needles: mp 69-69.5 °C [lit.[1] 69-70 °C]; IR ($CHCl_3$) 3400, 3010, 2935, 2860, 1650, 1620, 1465, 1448, 1400, 1365, 1330, 1230, and 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (s, 1 H), 5.36 (m, 2 H); 3.82 (s, 3 H); 2.40 (t, J = 8 Hz, 2 H), 2.00 (m, 4 H), 1.30 (m, 19 H), and 0.87 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 182.8, 181.6, 161.0, 151.5, 129.8, 129.7, 119.2, 102.1, 56.7, 31.9, 29.7, 29.6, 29.5 (2 C), 29.4, 29.2, 28.0, 27.2, 26.9, 22.6, 22.3, and 14.0; UV λ max (EtOH) 288 (ε = 22000) and 421 nm (ε=610); Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.92; H, 9.20.

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