Synthesis of Mansonone F Based on the Regioselective Hydrolysis of a Hydroquinone Diacetate

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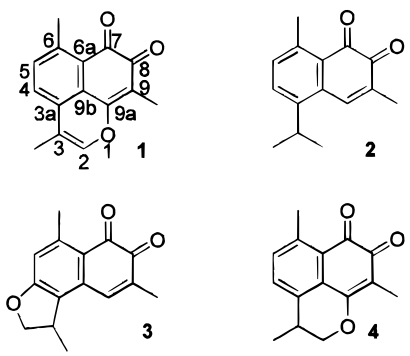
The synthesis of mansonone F (**1**), an antimicrobial sesquiterpenequinone, is described. Starting from 2,5-dimethyl-1,4-naphthoquinone (**5**), the corresponding selectively protected hydroquinone **9** was prepared in four steps. Alkylation of **9** using chloroacetone, cyclization, and oxidation to the *o*-quinone completed the reaction sequence in 7.5% overall yield. The regioselectivity for the basic hydrolysis of hydroquinone diacetate **6** was discussed on the basis of MO calculations.

An intensely violet compound, later called mansonone F (**1**),[1] was isolated from the heartwood of a West African tree, *Mansonia altíssima* Chev. (Sterculiaceae). The sawdust of this tree is responsible for heart problems and irritation in workers involved in the regional furniture industry,[2] and its bark extracts are used by natives for poisoning darts.[3] Several related compounds, mansonones A, B, C (**2**), D (**3**), and E (**4**),[2] were also identified, but only compound **1** has the rare 1-oxaphenalene-*o*-quinone structure found previously in the diterpene biflorine.[4]



Compounds **1** and **4** can also be classified as phytoalexins due to their formation in *Ulmus hollandica*[5,6] and *Ulmus glabra*,[7] in response to infection caused by the fungus *Ceratocystis ulmi*. Mansonone F was isolated also as constituent from *Ulmus laciniata*,[8,9] *Thespesia populnea*,[10] *Ulmus davidiana*,[11] and *Hibiscus tibiaceus*.[12] Compound **1** showed greater antifungal activity than **4**,[5] except against *Coriolus versicolor* and *Chondrostereum purpureum*.[7]

Detailed studies of the pharmacological properties and possible therapeutic application of **1** have, to our knowledge, not been performed due to its scarcity in nature. Furthermore, synthesis of such an orthoquinone represented an exciting synthetic challenge.

Results and Discussion

Syntheses of mansonones C (**2**),[13,14] D (**3**),[15] and E (**4**)[16] have been reported. The last procedure could be applied to the preparation of **1**, but was not used because of its complexity. Our synthetic approach followed the general strategy outlined by Prelog for the elucidation of the oxaphenalenequinone chromophore of biflorine.[17] Instead of menadione, our starting material was 2,5-dimethyl-1,4-naphthoquinone (**5**), obtained by direct oxidation of the corresponding naphthalene[18,19] or by BF_3-catalyzed Diels−Alder cycloaddition.[20] Compound **5** was transformed into the diacetate **6** by reductive acetylation (Scheme 1).[21]

The next step, hydrolysis of one of the acetate groups, was not expected to be regioselective for steric reasons. However, careful basic hydrolysis under very mild conditions occurred with high selectivity, producing the monoacetate **7** and its 4-substituted isomer in a ratio of 78:22. The substitution pattern of **7** was deduced by comparison of the ^{1}H NMR spectrum with the analogous compound obtained from menadione.[21]

The selectivity observed in the mild basic hydrolysis of **6** can be explained by steric effects in the tetrahedral anionic intermediate[22] resulting from attack of a hydroxyl ion to one of the acetate groups. In fact, AM1 (Austin Model 1)[23] calculations on these intermediates show that their dissociation to the corresponding phenolate anion and acetic acid should be the rate-determining step. Furthermore, when solvent effects are included via discrete model, hydrolysis of the acetate in position 4 has an activation energy about 3 kcal/mol lower than that in position 1. A more detailed presentation of these theoretical calculations is presented elsewhere.[24]

Compound **7** was then protected by the benzyl group, which is rather stable under strongly basic conditions and easily cleaved by hydrogenolysis or strong acids, producing compound **8**. The next step was the basic hydrolysis of the acetate group to produce compound **9**. Due to its instability in oxygen, crude **9** was immediately alkylated with chloroacetone and anhydrous K_2CO_3, producing crystalline **10**. Cyclization of **10**, following the polyphosphoric acid procedure,[17] produced only traces of the expected oxaphenalene **11**, easily recognized by its bright blue fluorescence, and several unidentified decomposition products. Use of concentrated H_2SO_4 produced exclusively **11**, but only in 10% yield. Clean cyclization of **10** was achieved in good yield using tetrafluoroboric acid in ether. However, crude **11** is easily oxidized to **1** and to other decomposition products when standing in air. For this reason **11** was immediately oxidized to **1** using SeO_2, a well-known reagent for the synthesis of 1,2-diketones that has been used successfully in a similar oxidation in the synthesis of **3**.[15] This method proved to be very clean and high yielding, much superior to the oxidation by Fe^{3+} or Fremy's salt reported in the literature.[16,17]

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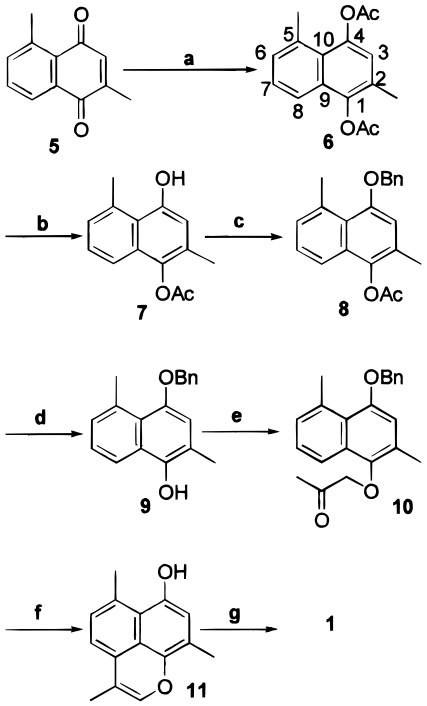
Scheme 1



(a) Ac_2O, NaOAC, Zn; (b) K_2CO_3, $Na_2S_2O_4$, $MeOH/H_2O$, rt.; (c) $BrCH_2C_6H_5$, CH_3COCH_3, K_2CO_3, rt.; (d) NaOH, $Na_2S_2O_4$, $MeOH/H_2O$, rt.; (e) CH_3COCH_2Cl, CH_3COCH_3, K_2CO_3; (f) HBF_4/Et_2O, CH_2Cl_2, 0 °C; (g) SeO_2, $CHCl_3$, rt.

Starting from 2,5-dimethyl-1,4-naphthoquinone (**5**), the described sequence of seven steps produced mansonone F (**1**) in 7.5% overall yield; chromatographic purification was necessary only in the last step. Physical and spectroscopic properties (NMR and MS) of **1** were in agreement with data published for the natural product.[11]

Experimental Section

General Experimental Procedures. Melting points were determined on an Electrothermal 9100 instrument and are uncorrected. ^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were obtained on a Varian Unity plus spectrometer. UV spectra were recorded on a Perkin−Elmer Lambda 6 spectrometer. IR spectra were obtained on a Fourier transform spectrometer Bruker IFS66. MS were performed on a Finnigan Mat GCQ spectrometer, equipped with a 30-m DB5 capillary column. Direct insertion was used for mass analysis of compounds **1** and **10**. HREIMS was performed on a VG Autospec spectrometer.

1,4-Diacetoxy-2,5-dimethylnaphthalene (6). A mixture of 10 mmol (1.8 g) of 2,5-dimethylnaphthoquinone (**5**), 12 mL of Ac_2O, 22 mmol (1.8 g) of anhydrous NaOAc, and 23 mmol (1.5 g) of zinc dust was heated under reflux until complete disappearance of the yellow color of the quinone (about 15 min). Then, 20 mL of HOAc were added, heating continued for 2 min, and the mixture poured over 100 g of ice. After standing for 12 h in the refrigerator, the crystalline product was filtered, washed with water, and dried. Yield: 2.58 g (95%). Crystallization from HOAc−H_2O gave pure **6** as colorless needles. Yield: 2.37 g (87%); mp 139−140 °C; UV (MeOH) λ_{max} (log ϵ) 226 (3.47), 290 (2.56) nm; IR (KBr) ν_{max} 1749, 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (3H, s, 2-CH_3), 2.38 (3H, s, 1-OAc), 2.46 (3H, s, 4-OAc), 2.74 (3H, s, 5-CH_3), 7.01 (1H, s, H-3), 7.22 (1H, d, J = 7.2 Hz, H-6), 7.35 (1H, dd, J = 8.4 and 7.2 Hz, H-7), 7.62 (1H, d, J = 8.4 Hz, H-8) ppm; ^{13}C NMR ($CDCl_3$) δ 170.6 (s, 1-C═O), 169.5 (s, 4-C═O), 145.6 (s, C-4), 143.3 (s, C-1), 133.5 (s, C-5), 131.0 (s, C-2), 129.8 (s, C-7), 127.3 (d, C-6), 126.9 (s), 126.5 (s), 122.9 (d, C-8), 120.2 (d, C-3), 24.0 (q, 5-CH_3), 22.3 (q, 4-CH_3), 21.3 (q, 1-CH_3), 16.9 (q, 2-CH_3) ppm; MS (EI, 70 eV) *m/z* (%) 272 [M^+] (12), 230 (33), 188 (100); *anal.* C 70.24, H 5.98; calcd for $C_{16}H_{16}O_4$, C 70.60, H 5.92.

1-Acetoxy-2,5-dimethyl-4-hydroxynaphthalene (7). Diacetate **6** (2 mmol; 0.54 g) was dissolved in 5 mL of MeOH and, at 0 °C, a solution of 1 mmol (0.13 g) of K_2CO_3 and 1 mmol (0.174 g) of $Na_2S_2O_4$ in 5 mL of H_2O was added. The flask was tightly closed and stirred at 29 °C. After 4 days, the mixture was poured over 50 g of ice and acidified with HOAc to pH 6. Extraction with EtOAc, drying over Na_2SO_4 and evaporation of the solvent gave a crystalline mass whose ^1H NMR analysis indicated a ratio 1-Ac:4-Ac of 78:22. Crude yield: 0.39 g (84%). Crystallization from CCl_4−CH_2Cl_2 gave colorless crystals of **7**. Yield: 0.30 g (64%); mp 184−185 °C; UV (MeOH) λ_{max} (log ϵ) 227 (2.61), 306 (2.36) nm; IR (KBr) ν_{max} 3409, 1731, 1395, 1226 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 2.16 (3H, s, 2-CH_3), 2.40 (3H, s, 1-OAc), 2.89 (3H, s, 5-CH_3), 6.75 (1H, s, H-3), 7.12 (1H, d, J = 7.2 Hz, H-6), 7.28 (1H, dd, J = 8.4, 7.2 Hz, H-7), 7.56 (1H, d, J = 8.4 Hz, H-8), 8.84 (1H, s, OH) ppm; ^{13}C NMR ($CDCl_3$) δ 170.4 (s, 1-C═O), 154.6 (s, C-4), 139.0 (s, C-1), 137.1 (s, C-5), 131.1 (s, C-2), 130.5 (s, C-9), 128.7 (s, C-6), 127.8 (d, C-7), 124.8 (d, C-10), 120.4 (s, C-8), 112.8 (d, C-3), 25.5 (q, 5-CH_3), 21.2 (q, 1-CH_3), 16.9 (q, 2-CH_3) ppm; EIMS (70 eV) *m/z* (%) 230 [$M]^+$ (29), 188 (100), 173 (25), 145 (37); *anal.* C 72.89, H 6.21; calcd for $C_{14}H_{14}O_3$, C 73.02, H 6.13.

1-Acetoxy-4-benzyloxy-2,5-dimethylnaphthalene (8). To a solution of 2 mmol (0.46 g) of monoacetate **7** in 15 mL of Me_2CO, 5 mmol (0.7 g) of anhydrous K_2CO_3 and 2.2 mmol (0.25 mL) of benzyl bromide were added. The mixture was stirred with exclusion of oxygen over 6 h at 29 °C, filtered, and the solvent evaporated, yielding a crystalline mass: 0.54 g (85%). The solid residue was crystallized from heptane. Yield: 0.45 g (70%) of colorless crystals; mp 134−135 °C; UV (MeOH) λ_{max} (log ϵ) 224 (3.13), 301 (2.57), 331 (1.91) nm; IR (KBr) ν_{max} 1759, 1256, 1198, 1148, 1076 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (3H, s, 2-CH_3), 2.43 (3H, s, 1-CH_3), 2.81 (3H, s, 5-CH_3), 5.11 (2H, s, $CH_2C_6H_5$), 6.70 (1H, s, H-3), 7.14 (1H, d, J = 7.3 Hz, H-6), 7.32 (1H, dd, J = 7.0, 7.5 Hz, C_6H_5), 7.35 (1H, td, J = 7.0, 1.8 Hz, C_6H_5), 7.4 (1H, dd, J = 8.5, 7.3 Hz, H-7), 7.47 (1H, dd, J = 7.5, 1.8 Hz, C_6H_5), 7.53 (1H, d, J = 8.5 Hz, H-8) ppm; ^{13}C NMR ($CDCl_3$) δ 170.1 (s, C═O), 155.5 (s, C-4), 139.7 (s), 138.8 (s, C-1), 137.5 (s, C-5), 136.4 (s, C-9), 129.8 (s, C-2), 129.2 (d), 128.9 (d), 128.6 (d), 128.5 (d), 127.3 (d, C-7), 126.5 (d, C-6), 125.2 (s, C-10), 119.3 (d, C-8), 109.2 (d, C-3), 71.7 (t, CH_2), 26.2 (q, 5-CH_3), 21.3 (q, 1-CH_3), 17.3 (q, 2-CH_3) ppm; EIMS (70 eV) *m/z* (%) 320 [$M]^+$ (39), 278 (100), 200 (35), 187 (48); *anal.* C 78.88, H 6.44; calcd for $C_{21}H_{20}O_3$, C 78.72, H 6.29.

1-Hydroxy-4-benzyloxy-2,5-dimethylnaphthalene (9). To a solution of 2.5 mmol (0.1 g) of NaOH and 1 mmol (0.18 g) of $Na_2S_2O_4$ in 1 mL of H_2O−MeOH, 0.5 mmol (0.16 g) of product **8** was added. This mixture was stirred with exclusion of oxygen. After 24 h, 3 mL of 1N HOAc were added, and the mixture was extracted with ether. The extract was dried over Na_2SO_4 and evaporated. Yield: 0.12 g (80%) of crude **9** as a brownish solid. This product decomposed on standing in air or during attempted crystallization and, for this reason, was used immediately for the next step without purification.

1-(2-Oxopropoxy)-4-benzyloxy-2,5-dimethylnaphthalene (10). Crude **9** [0.35 mmol (0.1 g)] was dissolved in 10 mL of Me_2CO; 1.7 mmol (0.23 g) of anhydrous K_2CO_3 and 0.4 mmol (0.03 mL) of chloroacetone were added. After stirring for 12 h at 29 °C and under exclusion of oxygen, the solution was diluted with H_2O and extracted with ether. The extract was dried over Na_2SO_4. Evaporation of solvent resulted in an oily mass (0.08 g, 70%) that was crystallized from hexane containing some drops of diisopropyl ether. Yield: 0.09 g (60%) of colorless crystals: mp 107−109 °C; UV (MeOH) λ_{max} (log ϵ) 216 (3.33), 304 (2.57) nm; IR (KBr) ν_{max} 1727, 1254, 1235, 1176, 1073 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (3H, s, 2-CH_3), 2.30 (3H, s, 1-CH_3), 2.78 (3H, s, 5-CH_3), 4.20 (2H, s, CH_2), 4.97 (2H, s, CH_2- C_6H_5), 6.60 (1H, s, H-3), 7.20 (1H, d, J = 7.2 Hz, H-6), 7.32 (1H, dd, J = 7.0, 7.5 Hz, C_6H_5), 7.35 (1H, td, J = 7.0, 1.8 Hz, C_6H_5), 7.5 (1H, dd, J = 8.3, 7.2 Hz, H-7), 7.47 (1H, dd, J = 7.5, 1.8 Hz, C_6H_5), 7.55 (1H, d, J = 8.3 Hz, H-8) ppm; ^{13}C

NMR ($CDCl_3$) δ 170.5 (s, C=O), 153.6 (s, C-4), 139.8 (s), 138.8 (s, C-1), 136.4 (s, C-5), 135.7 (s, C-9), 129.8 (s, C-2), 129.2 (d), 128.9 (d), 128.6 (d), 128.5 (d), 127.5 (d, C-7), 126.5 (d, C-6), 125.2 (d, C-10), 119.3 (s, C-8), 110.1 (d, C-3), 71.1 (t, CH_2), 69.8 (t, CH_2), 26.2 (q, 5-CH_3), 21.5 (q, 1-CH_3), 17.8 (q, 2-CH_3) ppm; EIMS (70 eV) *m/z* (%) 334 $[M]^+$ (40), 278 (100), 200 (18); *anal.* C 79.09, H 6.71; calcd for $C_{22}H_{22}O_3$, C 79.01, H 6.63.

Mansonone F (1). A solution of 0.2 mmol (0.07 g) of compound **10** in 1 mL of CH_2Cl_2 was added at once to 0.7 mL of ice-cold HBF_4−Et_2O (48%). After stirring for 2 min, H_2O was added. The mixture was extracted with $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated to a volume of approximately 3 mL. To this solution, 3 mmol (0.3 g) of SeO_2 was added and the mixture stirred for 12 h at room temperature. The violet solution was filtered and evaporated. The dark residue was purified on a Si gel column eluting with toluene−10% EtOAc. Dark brown crystals of metallic glitter were obtained from $CHCl_3$−cyclohexane. Yield: 0.026 g (40%); mp 213−214 °C; UV (MeOH) λ_{max} (log ϵ) 227 (4.90), 554 (3.78) nm; IR (KBr) ν_{max} 3089.6, 1682.7, 1626.6, 1599.9, 1576.0 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (3H, s, 9-CH_3), 2.13 (3H, d, J = 1.5 Hz, 3-CH_3), 2.72 (3H, s, 6-CH_3), 7.08 (1H, d, J = 1.5 Hz, H-2), 7.41 (1H, d, J = 8.1 Hz, H-5), 7.47 (1H, d, J = 8.1 Hz, H-4) ppm; ^{13}C NMR ($CDCl_3$) δ 181.9 (s, C-7), 177.9 (s, C-8), 161.7 (s, C-9a), 146.6 (s, C-6), 140.4 (d, C-2), 136.4 (d, C-5), 129.5 (s, C-3a), 128.4 (d, C-4), 126.2 (s, C-6a), 123.9 (s, C-9b), 113.4 (s, C-9), 112.2 (s, C-3), 23.1 (q, 6-CH_3), 12.9 (q, 3-CH_3), 7.7 (q, 9-CH_3) ppm; EIMS (70 eV) *m/z* (%) 240 $[M]^+$ (12), 212 (100), 211 (74), 195 (59), 169 (31); *anal.* C 74.78, H 5.19; calcd for $C_{15}H_{12}O_3$, C 74.99, H 5.03; HRMS (EI) *m/z* 240.0768 (calcd for $C_{15}H_{12}O_3$, 240.0786).

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Note Added in Proof: After conclusion of this work we took knowledge of a previous synthesis of mansonone F following the intramolecular Diels−Alder strategy[16] in 13 steps and 2% yield: Best, W. M.; Wege, D. *Aust. J. Chem.* **1986**, *39*, 647.

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