Diterpenes, Sesquiterpenes, and a Sesquiterpene−Coumarin Conjugate from *Jatropha integerrima*

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Five new compounds, 2α-hydroxyjatropholone (**1**), 2*β*-hydroxyjatropholone (**2**), 1,5-dioxo-2,3-dihydroxyrhamnofola-4(10),6,11(18),15-tetraene (**3**), 2-keto-5-hydroxyguai-3,11-diene (**4**), and a sesquiterpene−coumarin conjugate, jatrophadioxan (**5**), and nine known compounds have been isolated from the roots of *Jatropha integerrima*. The structures were established from spectroscopic data, and the relative configuration of **1** was confirmed by X-ray crystallography. Six diterpenes were evaluated for their antiplasmodial, antituberculosis, and cytotoxic activities.

In continuation of our recent studies of biologically active compounds from *Jatropha integerrima* Jacq. (Euphorbiaceae),[1,2] we herein report the isolation of five new compounds (**1**−**5**), three diterpenes, one sesquiterpene, and a sesquiterpene-coumarin conjugate. Nine known compounds, 1*β*-hydroxy-10*β*H-guaia-4,11-dien-3-one,[3] 4-hydroxy-10-epirotundone,[4] citlalitrione,[5] stigmast-4-en-6*β*-ol-3-one,[6] jatropholone A (**6**),[7] jatropholone B (**7**),[7] caniojane,[8] and 1,11-bisepi-caniojane,[8] were also isolated from a hexane extract of the roots.

Compound **1** was obtained as pale yellow plates with mp 208−210 °C. The HRESIMS spectrum gave an $[M + H]^+$ ion at *m/z* 313.1719, corresponding to the molecular formula $C_{20}H_{24}O_3$. The FTIR spectrum had absorption maxima indicating OH (3225 cm^{-1}), carbonyl (1693 cm^{-1}), and aromatic (1595 cm^{-1}) groups. The presence of an exocyclic methylene group was revealed by methylene proton signals at *δ* 5.17 and 4.63 (1H each) and ^{13}C NMR signals at *δ* 115.1 (CH_2) and 135.3 (qC). The ^{13}C NMR signals at *δ* 150.3 (qC), 146.0 (qC), 138.1 (qC), 134.3 (qC), 132.1 (qC), and 129.7 (qC) as well as signals of a methyl group at δ_H 2.25 (s) and δ_C 13.3 (CH_3) indicated a fully substituted aromatic ring with one OH and one methyl substituent group. Two mutually coupled methine proton signals [*δ* 1.55 (1H, d, $J = 8.1$ Hz) and 0.94] both showed HMBC correlations to the carbon resonances of two quaternary methyl groups [*δ* 28.1 (C-18) and 16.1 (C-19)] and to the aromatic carbon resonance at *δ* 138.1 (C-12), indicating connectivity between a cyclopropane moiety and an aromatic nucleus as found in jatropholones A (**6**) and B (**7**),[7] also isolated in the present study. The differences were a methyl proton singlet at δ_H 1.40 instead of a doublet at approximately δ_H 1.27, as well as two sets of AB doublets (benzylic methylene protons) at δ_H 3.10 and 2.99 (both with $J = 16.3$ Hz) instead of two sets of doublets of doublets at ca. δ_H 3.25 and 2.50, as reported for **6** and **7**, indicating the presence of an additional OH group at C-2. Long-range ^1H, ^{13}C correlations were observed from δ_H 3.10 (H-1) and 1.40 (H-16) to δ_C 207.1 (C-3). Thus, compound **1** was identified as 2-hydroxyjatropholone. Full assignments of the ^1H and ^{13}C NMR resonances (see Experimental Section) were based on $^1H-^1H$ COSY, HMQC, and HMBC experiments. The relative configuration of **1** was established from an X-ray single-crystal analysis (Figure 1), indicating an α-oriented 2-OH group.

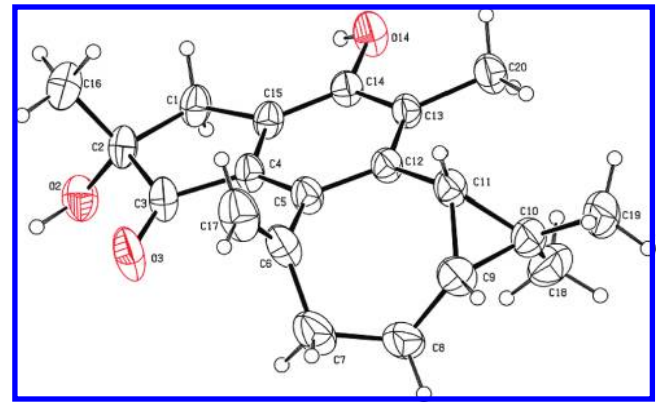
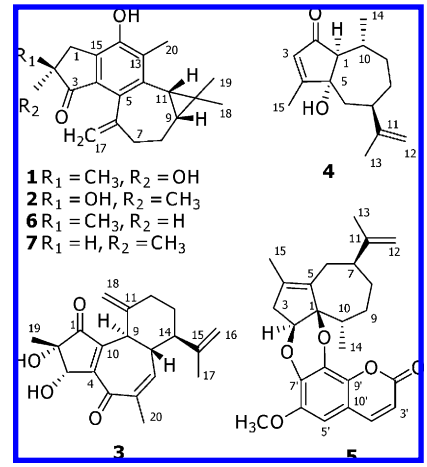


Figure 1. ORTEP drawing of **1**.



Compound **2** was a colorless oil having the molecular formula $C_{20}H_{24}O_3$ (HRESIMS). The FTIR and ^1H and ^{13}C NMR spectra of **2** were similar to those of compound **1**. The difference in the ^1H NMR spectrum of **2** was the two benzylic methylene protons (H_2-1) found as an obscured triplet at δ_H 3.07 with a coupling constant of 17.1 Hz instead of AB doublets (δ_H 3.10 and 2.99) as found in **1**. Full assignments of ^1H and ^{13}C NMR resonances are given in the Experimental Section. Compound **2** was thus 2*β*-hydroxyjatropholone, the C-2-epimer of **1**.

Compound **3** was isolated as a colorless solid, mp 144−146 °C, with molecular formula $C_{20}H_{24}O_4$ (HRESIMS). The FTIR spectrum

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indicated absorption maxima for OH (3434 cm^{-1}) and conjugated carbonyl (1732 and 1651 cm^{-1}) groups. The ^{13}C NMR spectrum showed 20 signals indicating three methyl, four methylene, five methine, and eight quaternary carbons including two keto carbons (see Experimental Section). The $^1H-^1H$ COSY spectrum indicated connectivity from H-7 (δ 5.82) to H-9 (δ 3.19) and from H-8 (δ 2.60) to H-12 (δ 2.40 and 2.24). Two exocyclic double bonds were evident from ^1H NMR signals at δ 4.75 and 4.14 and ^{13}C NMR signals at δ 148.1 (qC) and 108.3 (CH_2), in conjunction with the ^1H NMR chemical shifts at δ 4.84 and 4.80 and the ^{13}C NMR resonances at δ 146.5 (qC) and 113.3 (CH_2). HMBC correlations of H-3/C-1, C-4, C-10, and C-19 and of H-7/C-5, C-14, and C-20, in combination with the HMBC correlations between H-9/C-4, C-8, C-10, and C-18, led to the establishment of a rhamnofolane skeleton with double bonds at C-4(10), C-6(7), C-15(16), and C-11(18), together with keto groups at C-1 and C-5 and OH groups at C-2 and C-3. Relative configurations at C-8, C-9, and C-14 were deduced from coupling constants and were consistent with those reported for curcusones A−D.[9] The 3-OH group had an α-orientation due to the presence of homoallylic coupling between H-3 and H-9 (J = 1.6 Hz), as found in 2-epijatrogrossidione.[8] The NOESY spectrum showed a cross-peak between H-3/H_3-19, implying that both H-3 and H_3-19 were β-oriented. Compound **3** was thus proposed to be 1,5-dioxo-2,3-dihydroxyrhamnofola-4(10),6,11(18),15-tetraene.

Compound **4** was obtained as colorless needles ($C_{15}H_{22}O_2$). The IR spectrum showed absorption maxima for OH (3435 cm^{-1}) and α,β-unsaturated carbonyl (1688 and 1622 cm^{-1}) groups. The ^{13}C NMR spectrum indicated the presence of three methyl, four methylene, four methine, and four quaternary carbons including one carbonyl, two olefinic, and an oxygenated quaternary carbon. The $^1H-^1H$ COSY spectrum indicated cross-peaks between H-3/H-15 and between H-12 and H-13/H-7 and sequential connectivities from H-1 to H-6. A guaiane sesquiterpene skeleton with a keto group at C-2, an OH at C-5, and double bonds at C-3(4) and C-11(12) was indicated on the basis of HMBC correlations of H-3/C-1, C-2, C-5, and C-15 and of H-7/C-5, C-11, C-12, and C-13. Compound **4** was proposed to be 2-keto-5-hydroxyguai-3,11-diene. Relative configurations at C-1, C-10, and C-7 were deduced from NOE effects and coupling constants between related protons. The NOESY spectrum showed a cross-peak between H-1 and H_3-14. The $J_{1,10}$ and $J_{6,7}$ values of ca. 10 and 12 Hz, respectively, indicated that H-1 and H-10 were both α-oriented and that the isopropenyl group was β-oriented.[10] The ^1H and ^{13}C NMR assignments are as given in the Experimental Section.

Compound **5** was isolated as a yellow solid. The HRESIMS indicated a molecular formula of $C_{25}H_{28}O_5$, and the FTIR spectrum showed absorption maxima consistent with conjugated carbonyl (1732 cm^{-1}) and olefinic (1614 and 983 cm^{-1}) groups. The ^1H NMR spectrum exhibited signals indicating an α,β-unsaturated carbonyl moiety as two sets of doublets at δ 7.54 and 6.22, both with coupling constants of 9.4 Hz, as well as ^{13}C NMR signals at δ 160.9 (qC), 144.9 (qC), 143.7 (CH), 140.6 (qC), 140.0 (qC), 129.1 (qC), 113.2 (CH), 110.6 (qC), and 100.4 (CH) that indicated the presence of a coumarin nucleus (see Experimental Section). NOE interactions between H-3′/H-4′, H-4′/H-5′, and 6′-OCH_3/H-5′ were detected in the NOESY spectrum. The guaiane sesquiterpene skeleton was established from the $^1H-^1H$ COSY spectrum, which indicated connectivity of an oxymethine proton (H-2, δ 4.96) to H-3 and sequentially from H-6 to H_3-14, in combination with the long-range ^1H, ^{13}C correlations between H-6/C-1, C-4, C-8, and C-11, as well as between H-14/C-1 and C-9 and H-12/C-7, C-11, and C-13 in its HMBC spectrum. The key long-range $^1H-^{13}C$ correlations between H-2/C-3, C-10, and C-7′ required an ether linkage between C-2 and C-7′. An NOE effect between H-2/H_3-14 indicated the C-10 methyl group and H-2 to be in close proximity. The relative configuration at C-7, although it could not be obtained from the NOESY spectrum, was deduced from the $J_{6,7}$ value of ca. 13 Hz, which revealed that the dihedral angle between one of the H_2-6 protons and H-7 was close to 180°, thus indicating a β-oriented isopropenyl group.[10] The presence of an additional ether linkage between C-1 and C-8′ was expected from the molecular formula. Accordingly, the structure of **5** was assigned as shown, and this compound has been given the name jatrophadioxan.

Table 1. Antiplasmodial, Antituberculosis, and Cytotoxic Activities of the Isolates

compound	antiplasmodial[a]	anti-TB[b]	cytotoxicity[a]
compound **1**	4.1 ± 0.2	inactive[d]	noncytotoxic[f]
compound **2**	inactive[c]	inactive[d]	49.4
caniojane	3.3 ± 0.6	25	12.9
1,11-bisepi-caniojane	7.9	nd[e]	nd[e]
jatropholone A (**6**)	5.4 ± 1.7	inactive[d]	noncytotoxic[f]
jatropholone B (**7**)	inactive[c]	inactive[d]	noncytotoxic[f]
dihydroartemisinine[g]	(4.0 nM)		
isoniazide[g]		0.1	
kanamycin[g]		2.5	
ellipticine[g]			0.7 ± 0.2

[a] IC_{50} in μg/mL. [b] MIC in μg/mL. [c] Inactive at 10 μg/mL. [d] Inactive at 200 μg/mL. [e] nd = not determined. [f] Noncytotoxic at 50 μg/mL. [g] Positive control substance.

Compounds **1**, **2**, **6**, **7**, caniojane, and 1,11-bisepi-caniojane were evaluated for their *in vitro* activity against *Plasmodium falciparum*, K-1 strain. Caniojane exhibited the greatest inhibitory activity, with an IC_{50} value of 3.3 ± 0.6 μg/mL. Compounds **1** and **6** showed weaker activity, with IC_{50} values 4.1 ± 0.2 and 5.4 ± 1.7 μg/mL, respectively (Table 1). Compound **2**, the C-2 epimer of **1**, and compound **7** were not active at 10 μg/mL. Only caniojane showed moderate inhibitory activity against *Mycobacterium tuberculosis* H37Ra with an MIC value of 25 μg/mL. Compound **2** and caniojane showed mild to marginal cytotoxicity against Vero cells, whereas compounds **1**, **6**, and **7** were noncytotoxic at 50 μg/mL.

Experimental Section

General Experimental Procedures. Melting points were measured using an Electrothermal melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP 1020 polarimeter. IR spectra were obtained on a Perkin-Elmer 1760x FTIR spectrophotometer. The ^1H and ^{13}C spectra were recorded with a Bruker AVANCE 400 MHz spectrometer. Chemical shifts are referenced to the residual solvent signals ($CDCl_3$: δ_H 7.24 and δ_C 77.0 ppm). The HRESIMS was recorded on a Bruker Daltonics microTOF instrument.

Plant Material. Roots of *J. integerrima* were collected from plants growing within the Ramkhamhaeng University area during May 2004. Botanical identification was achieved by morphological comparison with a voucher specimem (Nos. SN 239681−239682) kept in the herbarium collections of the Sirindhorn Museum (Bangkok Herbarium), Botanical Section, Department of Agriculture, Ministry of Agriculture and Cooperatives. A voucher specimen (SSJI 1/04) is kept at the Department of Chemistry, Ramkhamhaeng University, Bangkok, Thailand.

Extraction and Isolation. Dried pulverized roots (5 kg) were extracted successively using hexane, CH_2Cl_2, and MeOH using Soxhlet apparatus to obtain hexane (38.6 g), CH_2Cl_2 (29.8 g), and MeOH (155.0 g) extracts, respectively.

Column chromatograpic fractionation of the hexane extract (16.2 g) using a gradient of hexane−CH_2Cl_2 (100:0) to CH_2Cl_2−MeOH (90:10) gave seven fractions. Fraction 3 (2.52 g) was chromatographed (silica gel, hexane−EtOAc, 97:3 to 90:10) to give five subfractions (3.1−3.5). Subfraction 3.2 was further purified using column chromatography (CC) (silica gel, hexane−EtOAc, 97:3 to 90:10) to give compounds **6** (176 mg) and **7** (223 mg). Subfraction 3.3 after CC (silica gel, hexane−CH_2Cl_2, 50:50 to 0:100) gave four fractions (3.3.1−3.3.4). Subfraction 3.3.2, after separation using reversed-phase CC (C_{18}, H_2O−MeOH, 50:50 to 0:100), gave compound **5** (6 mg) and citlalitrione (10.5 mg), respectively. Fraction 4 (1.22 g) was fractionated using CC (silica gel, hexane−EtOAc, 94:6 to 92:8) to give four subfractions (4.1−4.4). Subfraction 4.3 was chromatograhed (silica gel, hexane−EtOAc, 97:3 to 90:10) to give four subfractions (4.3.1−4.3.4), and subfraction 4.3.3 (32 mg) after purification using silica gel CC (hexane−CH_2Cl_2,

75:25 to 0:100) gave compound **4** (2 mg). Subfraction 4.3.4 after further CC (2×, silica gel, hexane−CH_2Cl_2, 30:70 to 0:100, then hexane−EtOAc, 93:7) yielded 1,11-bisepi-caniojane (2.6 mg) and caniojane (2.5 mg). Subfraction 4.4 (122 mg) yielded additional **4** (17 mg) after repeated CC (silica gel, hexane−EtOAc, 93:7 to 90:10) followed by reversed-phase CC (C_{18}, H_2O−MeOH, 50:50 to 0:100). Fraction 5 (6.31 g) was subjected to CC (silica gel, hexane−EtOAc, 75:25 to 0:100) and gave four subfractions (5.1−5.4). Subfraction 5.2 (2.86 g) was further purified using silica gel CC (hexane−EtOAc, 90:10 to 85:15) to give six subfractions (5.2.1−5.2.6). Subfraction 5.2.3 yielded 1β-hydroxy-10βH-guaia-4,11-dien-3-one (5.1 mg), and subfraction 5.2.4 (133 mg) gave 4-hydroxy-10-epirotundone (17.2 mg) and stigmast-4-en-6β-ol-3-one (6.5 mg) after CC (silica gel, hexane−EtOAc, 9:91). Subfraction 5.3 was chromatographed (silica gel, CH_2Cl_2−MeOH, 100:0 to 85:15) to give four subfractions. Subfraction 5.3.3 (345 mg) after reversed-phase CC (C_{18}, H_2O−MeOH, 20:80 to 0:100) gave five subfractions. Subfraction 5.3.3.3 yielded compounds **1** (9.4 mg) and **2** (10.6 mg) after further CC (silica gel, hexane−EtOAc, 88:12 to 87:13). Fraction 6 (3.25 g) was purified using silica gel CC (hexane−EtOAc, 88:12 to 85:15) to obtain three subfractions. Subfraction 6.2 (178.5 mg) was fractionated using CC (reversed-phase C_{18}, H_2O−MeOH, 20:80 to 0:100, then silica gel, CH_2Cl_2−MeOH, 99:1) to obtain compound **3** (3.0 mg).

2α-Hydroxyjatropholone (1): pale yellow plates; mp 208−210 °C; $[\alpha]^{27}_D$ +37.2 (*c* 0.47, $CHCl_3$); FTIR (KBr) ν_{max} 3563, 3225, 3082, 2946, 2921, 2857, 1693, 1635, 1595, 1573, 1455, 1420, 1403, 1340, 1308, 1288, 1220, 1167, 1110, 1087, 965, 893, 867, 784, 760, 677, 646, 523 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.17 (1H, t, J = 1.8 Hz, H-17), 4.63 (1H, t, J = 2.1 Hz, H-17), 3.10 (1H, d, J = 16.3 Hz, H-1), 2.99 (1H, d, J = 16.3 Hz, H-1), 2.71 (1H, ddd, J = 15.0, 6.3, 2.3 Hz, H-7), 2.62 (1H, ddd, J = 15.0, 7.0, 5.0 Hz, H-7), 2.25 (3H, s, H_3-20), 1.82 (1H, m, H-8), 1.55 (1H, d, J = 8.1 Hz, H-11), 1.40 (3H, s, H_3-16), 1.22 (3H, s, H_3-18), 0.94 (1H, ddd, J = 12.5, 8.1, 5.5 Hz, H-9), 0.80 (3H, s, H_3-19); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 207.1 (C, C-3), 150.3 (C, C-14), 146.0 (C, C-6), 138.1 (C, C-12), 135.3 (C, C-5), 134.3 (C, C-4), 132.1 (C, C-13), 129.7 (C, C-15), 115.1 (CH_2, C-17), 77.7 (C, C-2), 37.6 (CH_2, C-1), 33.3 (CH_2, C-7), 28.3 (CH, C-11), 28.1 (CH_3, H-18), 26.1 (CH_3, C-16), 26.0 (CH, C-9), 21.4 (CH_2, C-8), 19.6 (C, C-10), 16.1 (CH_3, C-19), 13.3 (CH_3, C-20); EIMS *m/z* (%) 312 (M^+, 69), 294 (63), 284 (26), 279 (47), 252 (100), 251 (63), 238 (49), 213 (40), 209 (78), 199 (38), 195 (49), 185 (62), 181 (51); HRESIMS $[M + H]^+$ *m/z* 313.1791 (calcd for $C_{20}H_{25}O_3$, 313.1803).

2β-Hydroxyjatropholone (2): yellow gum; $[\alpha]^{27}_D$ +119.5 (*c* 0.53, $CHCl_3$); FTIR (KBr) ν_{max} 3391, 3079, 2925, 2862, 2735, 1705, 1636, 1577, 1456, 1404, 1376, 1355, 1338, 1310, 1286, 1218, 1166, 1125, 1104, 1082, 1034, 986, 969, 894, 865, 799, 756, 668, 628, 522, 465 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.27 (1H, d, J = 1.4 Hz, H-17), 4.73 (1H, brs, H-17), 3.07 (1H, t, J = 17.1 Hz, H-1), 2.60 (2H, obs dd, J = 10.4, 4.7 Hz, H-7), 2.26 (3H, s, H-20), 1.81 (1H, ddd, J = 10.0, 7.9, 3.5 Hz, H-8), 1.56 (1H, d, J = 8.3 Hz, H-11), 1.37 (3H, s, H_3-16), 1.22 (3H, s, H_3-18), 0.93 (1H, ddd, J = 11.1, 8.6, 3.9 Hz, H-9), 0.87 (1H, m, H-8), 0.81 (3H, s, H_3-19); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 206.1 (C, C-3), 150.1 (C, C-14), 144.4 (C, C-6), 137.9 (C, C-12), 135.7 (C, C-5), 134.6 (C, C-4), 132.4 (C, C-13), 128.7 (C, C-15), 116.2 (CH_2, C-17), 77.5 (C, C-2), 37.2 (CH_2, C-1), 33.4 (CH_2, C-7), 28.3 (CH, C-11), 28.1 (CH_3, H-18), 25.9 (CH, C-9), 25.7 (CH_3, C-16), 21.4 (CH_2, C-8), 19.6 (C, C-10), 16.2 (CH_3, C-19), 13.4 (CH_3, C-20); EIMS *m/z* (%) 312 (M^+, 21), 294 (29), 279 (26), 269 (40), 256 (65), 252 (87), 251 (76), 241 (63), 239 (46), 238 (89), 237 (59), 227 (44), 226 (32), 225 (34), 223 (61), 213 (48), 211 (43), 210 (44), 209 (100), 199 (62), 197 (40), 195 (60), 185 (99), 181 (48), 171 (31), 165 (23); HRESIMS $[M + H]^+$ *m/z* 313.1791 (calcd for $C_{20}H_{25}O_3$, 313.1803).

1,5-Dioxo-2,3-dihydroxyrhamnofola-4(10),6,11(18),15-tetraene (3): colorless needles; mp 144−146 °C; $[\alpha]^{26}_D$ −312.5 (*c* 0.13, $CHCl_3$); FTIR (KBr) ν_{max} 3434, 2929, 2857, 1732, 1651, 1447, 1374, 1187, 1149, 1119, 1046, 893, 836, 801, 605, 544, 499 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.82 (1H, dq, J = 5.2, 1.6 Hz, H-7), 4.84 (1H, brs, H-16), 4.83 (1H, t, J = 1.6 Hz, H-3). 4.80 (1H, brs, H-16), 4.75 (1H, brs, H-18), 4.14 (1H, brs, H-18), 3.19 (1H, brd, J = 12.3 Hz, H-9), 2.60 (1H, tdd, J = 12.3, 5.2, 1.5 Hz, H-8), 2.40 (1H, ddd, J = 12.6, 4.4, 2.7 Hz, H-12), 2.32 (1H, dt, J = 11.9, 4.1 Hz, H-14), 2.24 (1H, brdt, J = 12.6, 4.5 Hz, H-12), 1.89 (1H, m, H-13), 1.84 (3H, t, J = 1.6 Hz, H-20), 1.57 (3H, s, H-17), 1.45 (1H, dt, J = 12.9, 4.4 Hz, H-13), 1.43 (3H, s, H-19); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 209.5 (C, C-1), 198.2 (C, C-5), 157.9 (C, C-4), 148.1 (C, C-11), 146.8 (C, C-10), 146.5 (C, C-15), 142.0 (C, C-6), 136.0 (CH, C-7), 113.3 (CH_2, C-16), 108.3 (CH_2, C-18), 74.0 (C, C-2), 51.9 (CH, C-14), 45.0 (CH, C-9), 43.6 (CH, C-8), 36.5 (CH_2, C-12), 34.3 (CH_2, C-13), 24.0 (CH_3, H-19), 18.7 (CH_3, C-20), 18.6 (CH_3, C-17); HRESIMS found $[M + Na]^+$ ion at *m/z* 351.1575 (calcd for $C_{20}H_{24}O_4Na$, 351.1566).

2-Keto-5-hydroxyguai-3,11-diene (4): colorless needles, mp 92−94 °C; $[\alpha]^{28}_D$ +9.5 (*c* 0.90, $CHCl_3$); FTIR (KBr) ν_{max} 3435, 2921, 2852, 1688, 1622, 1447, 1374, 1312, 1246, 1218, 1154, 1072, 936, 892, 849, 782, 674, 618, 550, 500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 5.80 (1H, s, H-3), 4.67 (1H, brs, H-12), 4.65 (1H, brs, H-12). 2.53 (1H, dt, J = 11.9, 2.7 Hz, H-7), 2.16 (1H, d, J = 10.1 Hz, H-1), 2.01 (3H, s, H-15), 1.92 (1H, brd, J = 14.1 Hz, H-6), 1.86 (1H, m, H-8), 1.76 (1H, obs ddq, J = 10.3, 6.4, 1.7 Hz, H-10), 1.68 (3H, s, H-13), 1.63 (1H, tt, J = 12.1, 2.0 Hz, H-9), 1.56 (1H, obs ddt, J = 12.5, 5.8, 1.7 Hz, H-9), 1.37 (1H, dd, J = 14.1, 11.8 Hz, H-6), 1.04 (3H, d, J = 6.4 Hz, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 205.8 (C, C-2), 177.6 (C, C-4), 150.8 (C, C-11), 128.7 (CH, C-3), 109.1 (CH_2, C-12), 82.5 (C, C-5), 67.2 (CH, C-1), 41.1 (CH, C-7), 40.7 (CH_2, C-6), 36.3 (CH_2, C-8), 35.2 (CH_2, C-9), 34.3 (CH, C-10), 23.8 (CH_3, C-14), 20.6 (CH_3, C-13), 12.8 (CH_3, C-15); HRESIMS found $[M + Na]^+$ ion at *m/z* 257.1541 (calcd for $C_{15}H_{22}O_2Na$, 257.1512).

Jatrophadioxan (5): pale yellow solid; $[\alpha]^{27}_D$ +437.1 (*c* 0.30, $CHCl_3$); FTIR (KBr) ν_{max} 3442, 2922, 2852, 1732, 1614, 1574, 1499, 1446, 1417, 1377, 1303, 1195, 1138, 1072, 983, 915, 840, 748, 606, 563 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.54 (1H, d, J = 9.4 Hz, H-4′), 6.44 (1H, s, H-5′), 6.22 (1H, d, J = 9.4 Hz, H-3′), 4.96 (1H, t, J = 7.6 Hz, H-2), 4.71 (1H, brs, H-12), 4.68 (1H, brs, H-12), 2.50 (2H, brd, J = 7.6 Hz, H-3), 2.45 (1H, brd, J = 13.4 Hz, H-6), 2.33 (1H, obs dq, J = 9.2, 7.3 Hz, H-10), 2.18 (1H, t, J = 12.7 Hz, H-6), 1.82 (2H, m, H-7 and H-8), 1.73 (3H, s, H-13), 1.64 (3H, s, H-15), 1.46 (2H, m, H-8, H-9), 1.35 (1H, dd, J = 12.9, 9.7 Hz, H-9), 1.04 (3H, d, J = 7.2 Hz, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 160.9 (C, C-2′), 150.4 (C, C-11), 144.9 (C, C-6′), 140.6 (C, C-8′), 140.0 (C, C-9′), 137.4 (C, C-6), 136.3 (C, C-4), 129.1 (C, C-7′), 113.2 (CH, C-3′), 110.6 (C, C-10′), 108.9 (CH_2, C-12), 100.4 (CH, C-5′), 90.8 (C, C-1), 73.7 (CH, C-2), 56.4 (CH_3, 6′-OCH_3), 49.6 (CH, C-7), 42.3 (CH, C-10), 39.4 (CH_2, C-3), 36.3 (CH_2, C-8), 32.5 (CH_2, C-9), 29.8 (CH_2, C-6), 20.4 (CH_3, C-13), 16.9 (CH_3, C-14), 14.1 (CH_3, C-15); HRESIMS $[M + H]^+$ ion *m/z* 409.2002 (calcd for $C_{25}H_{29}O_5$, 409.2010).

X-ray Crystallographic Data of Compound 1. Crystal data for compound **1** at 298(2) K: $C_{20}H_{24}O_3$, M_r = 312.41, tetragonal, space group $P4_12_12$ (No. 92) with a = 13.2026(3) Å, b = 13.2026(3) Å, c = 19.8568(5) Å, V = 3461.21(14) $Å^3$, Z = 8, D_{calc} = 1.199 Mg/m^3; F_{000} = 1344, μ = 0.079 mm^{-1}. Data collection and reduction: crystal size 0.10 × 0.15 × 0.20 mm, θ range 1.02−27.48°, 13 323 reflection collected, 3918 independent reflections (R_{int} = 0.020), final R indices ($I > 2\sigma(I)$: 0.0589, wR_2 = 0.1713 for 209 parameters, GOF = 1.053. Intensity data were measured on a Bruker-Nonius kappaCCD diffractometer. Crystallographic data for the structure **1** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-728465. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Bioassays. Antiplasmodial activity was evaluated against *Plasmodium falciparum* (K1 multidrug-resistant strain) cultured continuously according to Trager and Jensen.[11] Quantitative determination of activity *in vitro* was conducted by means of the microculture radioisotope technique based on the method of Desjardins et al.[11] The antimycobacterial activity (anti-TB) assay was performed against *Mycobacterium tuberculosis* H37Ra using an Alamar Blue microplate assay.[12] Cytotoxicity assay was determined using African green monkey kidney fibroblasts by the colorimetric method described by Skehan and coworkers.[13]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**−**5** (Figures S1−S10), HMBC correlations of **1**−**5**, and cif files of the X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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