19-Nor- and 18,20-Epoxy-cardenolides from the Leaves of *Calotropis gigantea*

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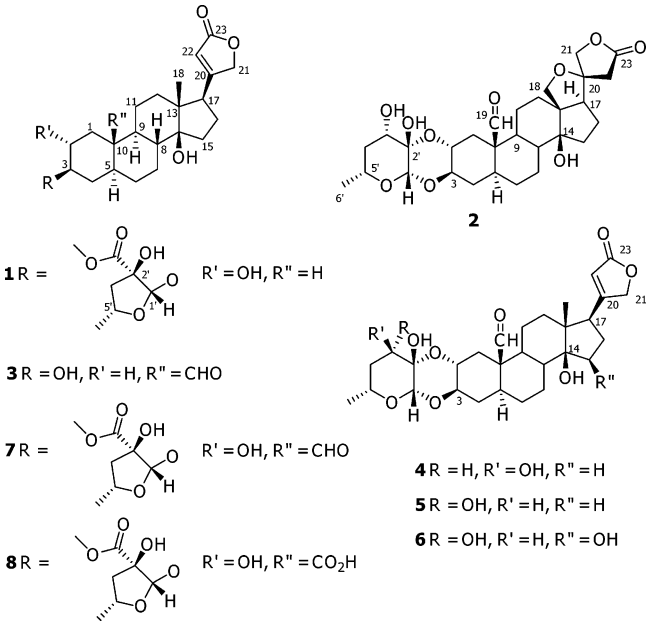
Two new cardenolides (**1** and **2**) along with 12 known compounds were isolated from the dichloromethane extract of the leaves of *Calotropis gigantea*. The structural elucidation was accomplished by spectroscopic methods. Some of the isolates were evaluated for cytotoxic activity against KB, BC, and NCI-H187 cancer cell lines, and all cardenolides tested were found to possess strong inhibitory effects. The presence of a deoxysugar at C-3, a formyl group at C-10, and an α,β-unsaturated γ-lactone was crucial for cytotoxic activity.

The genus *Calotropis* has been the target of numerous chemical investigations, leading to the isolation of many cardenolides,[1−6] flavonoids,[7] terpenes,[8,9] and a nonprotein amino acid.[10] *Calotropis gigantea* (Linn) (Asclepiadaceae), which is called "Rak" in Thailand, is a medium-sized shrub, growing from 2 to 3 m in height. The plant has purgative, alexipharmic, and anthelmintic properties and is used as a treatment for leprosy, leucoderma, ulcers, tumors, piles, and diseases of the spleen, liver, and abdomen. The juice is used as an anthelmintic, as a laxative, and to treat piles.[11] Although previous chemical studies on *C. gigantea* have been reported,[5−8,10] our present study was focused on a CH_2Cl_2 extract of the leaves of this plant, which caused 100% death of the brine shrimp nauplii at 250 ppm concentration and led to the isolation of two new cardenolides (**1** and **2**) in addition to 12 known compounds, taraxasteryl acetate,[12] pinoresinol,[13] medioresinol,[14] uzarigenin,[15] calotropin,[16] calactin,[17] calactinic acid methyl ester,[18] 19-carboxy-lcalactinic acid methyl ester,[18] drummondol,[19] 15β-hydroxycalotropin,[20] a C_{11} bicyclic lactone norisopenoid, loliolide,[21] and a rare dephenyl furofuran lignan, salicifoliol.[22] This paper deals with the characterization of the new compounds (**1** and **2**) and biological activity of some of the isolated compounds.



Compound **1** was obtained as a colorless solid. The FTIR spectrum showed an OH band at ν_{max} 3446 cm^{-1}. Absorption bands at 1741, 1252, and 1073 cm^{-1} indicated the presence of an α,β-unsaturated γ-lactone. The molecular formula of $C_{29}H_{42}O_9$ was deduced from the HRESIMS spectrum. The ^{13}C NMR spectrum contained 29 signals assigned to three methyls, 10 methylenes, 10 methines, and six quaternary carbons including one olefinic (δ_C 174.4) and two carbonyl carbons (δ_C 174.4 and 172.9), respectively. The existence of an α,β-unsaturated γ-lactone subunit was evident from the ^1H and ^{13}C NMR signals at δ_H 5.89 (br s, H-22), δ_C 117.7 (CH, C-22), 174.4 (qC, C-20), 174.4 (qC, C-23), and δ_H 4.95 and 4.78 (both as dd, J = 18.1, 1.7 Hz, H_2-21), δ_C 73.4 (CH_2, C-21). Connectivity of C-20 to C-17 and a hydroxyl group to the quaternary C-14 was observed from the long-range HMBC correlations of H-17 (δ_H 2.75)/C-14 (δ_C 84.9, qC), C-20, C-21, and C-22. The relationship between the 2- and 3-oxymethine groups was revealed from not only the $^1H-^1H$ COSY cross-peak between H-2 (δ_H 3.35)/H-1 (δ_H 2.16, 0.84) and H-3 (δ_H 3.24) but also the $^1H-^{13}C$ long-range correlations between H-2/C-3 (δ_C 85.4, CH). The dideoxyfuranosyl subunit was detected from the $^1H-^1H$ COSY spectrum showing cross-peaks between H-5′ (δ_H 4.47)/H-4′ (δ_H 2.32, 2.12), H-6′ (δ_H 1.38, d, J = 6.2 Hz) and the long-range $^1H-^{13}C$ correlations of H-1′ (δ_H 4.88, s)/C-2′ (δ_C 84.4), C-4′ (δ_C 40.1, CH_2), and C-5′ (δ_C 76.3, CH). The HMBC cross-peak between H-1′ and C-3 further indicated connectivity of the C-3 oxygen atom to C-1′. The carbomethoxy group (δ_H 3.78, s, COO*CH*$_3$; δ_C 52.8, CH_3 and δ_C 172.9, qC, C-3′) connected to C-2′ was proposed from the key HMBC correlation between one of the H_2-4′ signals (δ_H 2.32) and C-3′. The spectroscopic data of compound **1** were similar to those of calactinic acid methyl ester obtained recently from *Asclepias curassavica*[18] and also from this study, except for the absence of aldehyde group signals at ~δ_H 9.88 and δ_C 207.6 (CH), with the presence of an extra methine signal at δ_H 1.16 (H-10) and δ_C 47.4 (CH, C-10), which exhibited the HMBC cross-peak of H-10/C-6 (δ_C 26.3, CH_2) and C-11 (δ_C 25.9, CH_2), demonstrating that the C-19 was not present. Compound **1** was therefore proposed to be 19-nor-10-hydrocalactinic acid methyl ester. The NOESY spectrum revealed NOE interactions of H-17/H-21, H-22, and of H_3-18/H-21, H-22 and indicated the stereochemistry of ring D to be as found in calactin and calotropin. Stereochemistry of ring A in a boat conformation was deduced from the NOE effect of H-2/H-3, with no NOE cross-peaks of H-2/H-10 and H-5/H-10, in addition to observation of H-10 at δ_H 1.16 as a double triplet (J = 10.8 and 2.3 Hz). The use of molecular model indicated dihedral angles between H-10 and H_2-1 to be around 30° and 90°, giving rise to $^3J_{1\beta,10\beta} \approx 2-3$ Hz and $^3J_{1\alpha,10} \approx 0$ Hz, respectively.

Compound **2** was obtained as a white solid. The FTIR spectrum indicated hydroxyl and carbonyl functions at ν_{max} 3445 and 1779 cm^{-1}, respectively. The molecular formula $C_{29}H_{40}O_{10}$ was deduced from the HRESIMS. The ^{13}C NMR spectrum exhibited 29 signals comprising one methyl, 12 methylenes, 10 methines, and six quaternary carbons including one carbonyl (δ_C 175.7) and one dioxygenated carbon (δ_C 91.1). The ^1H NMR spectrum showed no

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Table 1. Cytotoxicity of Compounds **2**−**9**[a]

compound	KB	BC	NCI-H187
2	1.29×10^{-3}	2.21×10^{-3}	3.64×10^{-3}
3	9.61×10^{-3}	8.95×10^{-3}	9.77×10^{-3}
4	4.13×10^{-5}	2.07×10^{-5}	3.45×10^{-4}
5	6.20×10^{-5}	4.13×10^{-5}	4.71×10^{-4}
6	6.02×10^{-4}	5.47×10^{-4}	3.33×10^{-3}
7	3.73×10^{-3}	5.65×10^{-3}	1.44×10^{-2}
8	inactive	inactive	inactive
9	inactive	inactive	inactive
doxorubicin[b]	2.19×10^{-4}	2.88×10^{-4}	4.05×10^{-5}
ellipticine[b]	8.12×10^{-4}	6.82×10^{-4}	2.23×10^{-3}

[a] Values indicated are the IC_{50} values in mM, inactive at 20 μg/mL. [b] Positive control.

signals typical of an α,β-unsaturated γ-lactone moiety as found in **1**. Two sets of double doublets corresponding to two nonequivalent oxymethylene groups were observed instead at δ_H 3.35, 4.04 (both as d, $J = 9.9$ Hz, H-18, δ_C 71.2, CH_2, C-18) and δ_H 3.96, 4.27 (both as d, $J = 9.9$ Hz, H_2-21, δ_C 76.0, CH_2, C-21), as well as an AB doublet signal corresponding to a *CH*$_2$-CO group at δ_H 2.62 and 2.55 (both as d, $J = 17.7$ Hz). The aldehyde proton resonated as a singlet at δ_H 9.92 (s). The presence of a 4,6-dideoxypyranosyl moiety was disclosed from observation of an anomeric proton (δ_H 4.47, H-1′) and from the $^1H-^1H$ COSY cross-peaks between H_3-6′ (δ_H 1.21)/H-5′ (δ_H 3.57), H-5′/H-4′ (δ_H 1.72 and 1.46), and H-4′/H-3′ (δ_H 3.56). Attachment of C-1′ to the C-3 oxygen atom was indicated from the $^3J(^1H-^{13}C)$ correlation between H-1′/C-3 (δ_C 71.7). Although direct HMBC correlation of H-2/C-2′ was not observed in our HMBC spectrum, possibly due to inadequate acquisition time, the mass spectrum implied a C-2′−O−C-2 ether linkage. The arrangement of H-3′ as β was assumed from the *J*-value of the signal at δ_H 3.61 (d, $J = 11.7$, 4.7 Hz), which is in accordance with the coupling constant of the β-H-3′ reported for calotropin.[16] The formyl group attached to C-10 was detected from the long-range $^1H-^{13}C$ correlations of H-19 (δ_H 9.92, s)/C-1 (δ_C 35.9, CH_2) and also of H-5 (δ_H 1.14)/C-19 (δ_C 207.4, CH). The 2D experiments led to assignment of all ^1H and ^{13}C resonances of compound **2**. Compound **2** was concluded to be 18,20-epoxycalotropin. The NOESY spectrum showing a NOE effect between H-17/H-21 indicated the C-20 configuration as *S*, which is similar to those previously documented in the (20*S*)-epimer of 18,20-oxido-20,22-dihydrodigitoxigenin[23] and (20*S*)-18,20-epoxy-digitoxigenin α-L-thevetoside.[23]

Eight compounds comprising compound **2**, uzarigenin (**3**), calactin (**4**), calotropin (**5**), 15β-hydroxycalotropin (**6**), calactinic acid methyl ester (**7**), 19-carboxylcalactinic acid methyl ester (**8**), and taraxasteryl acetate (**9**) were evaluated for their cytotoxicity against human oral epidermal carcinoma (KB), breast cancer (BC), and human small cell lung cancer (NCI-H187) cell lines (Table 1). Calactin (**4**) was the most potent, whereas its 3′-epimer, calotropin (**5**), was less potent, indicating the importance of the stereochemistry at C-3′ of the deoxy sugar residue. Uzarigenin (**3**), which possesses no sugar unit and with only a hydroxyl group at C-3, was at least 100 times less active than calotropin (**5**). Among the cardenolides with a similar sugar residue, **2**, **5**, and **6**, the order of cytotoxic activity was found to be **5** > **6** > **2**, implying that an α,β-unsaturated γ-lactone unit is crucial for cytotoxic activity. The steric effect exerted by the β-OH-15 group in **6** caused, in part, the reduction of cytotoxicity. When comparing **5** and calactinic acid methyl ester (**7**), which possess six- and five-membered-ring sugar moieties, respectively, compound **5** was more cytotoxic than **7**. The presence of a formyl group at C-10 gave enhanced cytotoxic effect, since the 19-carboxylcalactinic acid methyl ester (**8**) exhibited no inhibition in any of the cell lines tested. Compounds **3**, **4**, **5**, and **9** were inactive in antituberculosus and antimalarial assays.

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a Jasco DIP 1020 polarimeter. The IR spectra were obtained on a Perkin-Elmer 1760x FT-IR spectrophotometer. EIMS and HRFABMS spectra were recorded on a Finnigan MAT 90, and HRESIMS were recorded on a Bruker Daltonics microTOF instrument. ^1H and ^{13}C spectra were obtained with a Bruker AVANCE 400 MHz spectrometer with the solvent signal as internal reference.

Plant Material. The leaves of *Calotropis gigantea* (Linn) (Asclepiadaceae) were collected from the Suwinthawong Road area, Minburi District, Bangkok, in June 2002. Botanical identification was achieved through comparison with a voucher specimen, No. 11 SN 227321, BK 15951, kept in the herbarium collection of the Sirindhorn Museum (Bangkok Herbarium), Botanical Section, Botany and Weed Section, Department of Agriculture, Ministry of Agriculture and Cooperatives. Voucher specimen SSCG/2002 is deposited at the Department of Chemistry, Faculty of Science, Ramkhamhaeng University.

Extraction and Isolation. The fresh leaves of *C. gigantea* (24.5 kg) were ground and extracted successively with hexane, CH_2Cl_2, and MeOH to obtain hexane (125 g), CH_2Cl_2 (76 g), and MeOH (385 g) extracts. The CH_2Cl_2 extract was subjected to gradient column chromatography (CC) (silica gel, hexane−CH_2Cl_2, 95:5, to CH_2Cl_2−MeOH, 1:9) to yield 10 fractions. The nonpolar fraction 2 was purified using column chromatography (silica gel, hexane−CH_2Cl_2, 95:5, to CH_2Cl_2−MeOH, 3:2) to yield taraxasteryl acetate (**9**, 394 mg). A mixture of β-sitosterol and stigmasterol (298 mg) was obtained from fraction 7. Fraction 8 was column chromatographed (silica gel, hexane−CH_2Cl_2, 1:4, to CH_2Cl_2−MeOH, 1:9) and gave four subfractions (8.1−8.4). Subfraction 8.2 was chromatographed (silica gel, hexane−CH_2Cl_2, 1:4, to CH_2Cl_2−MeOH, 2:3) to give four subfractions (8.2.1−8.2.4). Subfraction 8.2.3 was purified using reversed-phase CC (C_{18}, MeOH−H_2O, 1:1, to 100% MeOH) to yield three subfractions (8.2.3.1−8.2.3.3). The most polar subfraction was further chromatographed (silica gel, hexane−EtOAc, 9:1) to give five subfractions (8.2.3.1.1−8.2.3.1.5). Subfraction 8.2.3.1.2 gave loliolide (5 mg) after additional CC. Subfraction 8.2.3.1.4 yielded pinoresinol (10.8 mg). Reversed-phase CC (C_{18}, MeOH−H_2O, 1:1 to 7:3) of subfraction 8.2.3.1.3 gave salicifoliol (2.9 mg). Subfraction 8.2.3.1.5 was further purified (C_{18}, MeOH−H_2O, 2:3, to 100% MeOH) and yielded medioresinol (6.4 mg). Subfraction 8.3.1 was chromatographed (silica gel, CH_2Cl_2−MeOH, 99:1 to 2:3) to obtain four subfractions (8.3.1.1−8.3.1.4). Subfraction 8.3.1.2 gave uzarigenin (**3**, 12.1 mg) after reversed-phase CC (C_{18}, MeOH−H_2O, 3:2 to 7:3) and further purification using silica gel CC (CH_2Cl_2−MeOH, 99:1). Subfraction 8.3.1.3 was fractionated (reversed-phase CC, C_{18}, MeOH−H_2O, 1:1, to 100% MeOH) to give three subfractions (8.3.1.3.1−8.3.1.3.3). 19-Carboxylcalactic acid methyl ester (**8**, 8.1 mg) was obtained from the most polar subfraction (8.3.1.3.1) after purification using HPLC (C_{18}, MeOH−1% THF in H_2O, 3:2). The moderately polar subfraction 8.3.1.3.2 yielded **7** (28 mg) and 19-nor-10-hydrocalactic acid methyl ester (**1**, 2.6 mg) after HPLC (C_{18}, MeOH−1% THF in H_2O, 3:2). Subfraction 8.3.1.4 was chromatographed (silica gel, hexane−EtOAc, 3:1, to 100% EtOAc) to give four subfractions (8.3.1.4.1−8.3.1.4.4). Calotropin (**5**, 102 mg) and calactin (**4**, 8.6 mg) were obtained after subfraction 8.3.1.4.3 was purified using HPLC (C_{18}, MeOH−H_2O, 11:9). Subfraction 8.3.1.4.4 (silica gel, CH_2Cl_2−MeOH, 98:2 to 17:3) yielded three subfractions. The nonpolar subfraction (8.3.1.4.4.1) yielded **2** (7.8 mg) after reversed-phase CC (C_{18}, MeOH−H_2O, 2:3, to 100% MeOH), and the moderately polar subfraction 8.3.1.4.4.2 yielded 15β-hydroxycalotropin (**6**, 63.6 mg) after reversed-phase CC (C_{18}, MeOH−H_2O, 1:1, to 100% MeOH). Subfraction 8.3.1.4.2 gave drummondol (11 mg) after repeated CC (silica gel, CH_2Cl_2−MeOH, 98:2, to 3:1), then reversed-phase C_{18} (MeOH−H_2O, 7:3 to 4:1).

19-Nor-10-hydrocalactinic acid methyl ester (1): colorless solid; $[\alpha]_D^{23.7}$ −23.1 (*c* 0.130, MeOH); IR (KBr) ν_{max} 3446, 1741, 1252, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, br s, H-22), 4.95 (1H, dd, $J = 18.1$, 1.7 Hz, H-21), 4.88 (1H, s, H-1′), 4.78 (1H, dd, $J = 18.1$, 1.7 Hz, H-21), 4.47 (1H, dq, $J = 10.0$, 6.0 Hz, H-5′), 3.78 (3H, s, O*CH*$_3$), 3.35 (1H, ddd, $J = 10.9$, 8.6, 4.5 Hz, H-2), 3.24 (1H, obsc ddd, $J = 11.0$, 8.6, 4.5 Hz, H-3), 2.75 (1H, dd, $J = 9.6$, 5.5 Hz, H-17), 2.32 (1H, dd, $J = 13.3$, 10.2 Hz, H-4′a), 2.13 (1H, m, H-15a), 2.12 (2H, overlapped m, H-15b, H-4′b), 2.16 (1H, ddd, $J = 12.5$, 8.7, 2.9 Hz, H-1a), 2.02 (1H, dt, $J = 13.3$, 9.7 Hz, H-16a), 1.92 (1H, m, H-6a), 1.84 (1H, m, H-16b), 1.74 (1H, m, H-11a), 1.64 (1H, ddd, $J = 12.6$,

8.9, 4.2 Hz, H-7a), 1.49 (1H, dt, J = 10.5, 3.2 Hz, H-12a), 1.38 (3H, d, J = 6.2 Hz, H_3-6′), 1.36 (1H, m, H-12b), 1.16 (1H, obsc dt, J = 10.8, 2.3 Hz, H-10), 1.05 (1H, m, H-11b), 0.99 (1H, m, H-8), 0.98 (4H, overlapped m, H_2-4, H-6b, H-7b), 0.93 (1H, m, H-9), 0.86 (3H, s, H_3-18), 0.84 (1H, obsc t, J = 12.3 Hz, H-1b) 0.75 (1H, br m, $w_{1/2}$ = 23 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (2×, qC, C-20, C-23), 172.9 (qC, C-3′), 117.7 (CH, C-22), 109.7 (CH, C-1′), 85.4 (CH, C-3), 84.9 (qC, C-14), 84.4 (qC, C-2′), 76.3 (CH, C-5′),73.4 (CH_2, C-21), 73.4 (CH, C-2), 52.8 (CH_3, OCH_3), 50.7 (CH, C-17), 49.5 (qC, C-13), 47.4 (CH, C-10), 45.2 (CH, C-5), 43.5 (CH, C-9), 40.3 (CH, C-8),40.1 (CH_2, C-4′), 39.8 (CH_2, C-12), 37.7 (CH_2, C-7), 35.5 (CH_2, C-1), 33.0 (CH_2, C-4), 32.8 (CH_2, C-16), 27.0 (CH_2, C-15), 26.3 (CH_2, C-6), 25.9 (CH_2, C-11), 21.9 (CH_3, C-6′), 15.7 (CH_3, C-18); HMBC correlations H-1/C-2, C-3, C-5, C-9; H-2/C-3; H-6/C-8, C-9; H-7/C-5; H-8/C-11; H-9/C-8; H-10/C-6, C-11; H-11/C-8; H-12/C-9, C-11, C-18; H-15/C-8, C-16; H-16/C-13, C-14, C-15, C-17, C-20, C-21, C-23; H-17/C-12, C-14, C-15, C-20, C-21, C-22, C-23; H-18/C-12, C-13, C-14, C-17; H-21/C-20, C-22, C-23; H-22/C-17, C-20, C-21, C-23;H-1′/C-3, C-2′, C-4′, C-5′; H-4′/C-1′, C-2′, C-3′, C-5′, C-6′; H-6′/C-4′, C-5′; O*CH*$_3$/C-3′; ESIMS m/z 557.2713 $[M + Na]^+$ (calcd for $C_{29}H_{42}NaO_9$, 557.2721).

18,20-Epoxycalotropin (2): colorless solid; mp 219−222 °C; $[\alpha]_D^{23.5}$ −85.5 (c 0.150, MeOH); IR (KBr) ν_{max} 3445, 1779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (1H, s, H-19), 4.47 (1H, s, H-1′), 4.27 (1H, d, J = 9.9 Hz, H-21a), 4.04 (1H, d, J = 9.9 Hz, H-18a), 3.96 (1H, d, J = 9.9 Hz, H-21b), 3.89 (1H, dt, J = 10.9, 4.3 Hz, H-3), 3.80 (1H, dt, J = 11.8, 4.3 Hz, H-2), 3.57 (1H, m, H-5′), 3.56 (1H, dd, J = 11.9, 4.7 Hz, H-3′), 3.35 (1H, d, J = 9.9 Hz, H-18b), 2.62 (1H, d, J = 17.7 Hz, H-22a), 2.55 (1H, d, J = 17.7 Hz, H-22b), 2.39 (1H, dd, J = 12.4, 4.4 Hz, H-1a), 2.24 (1H, dq, J = 12.7, 2.8 Hz, H-11a), 2.08 (1H, dd, J = 9.3, 7.0 Hz, H-17), 1.92 (1H, m, H-16a), 1.78 (2H, m, H_2-15), 1.73 (1H, m, H-6a), 1.72 (1H, m, H-4′a), 1.68 (1H, m, H-12a), 1.67 (2H, m, H_2-7), 1.62 (1H, m, H-16b), 1.49 (1H, m, H-8), 1.48 (1H, m, H-9), 1.46 (1H, m, H-4′b), 1.38 (1H, m, H-12b), 1.33 (2H, m, H_2-4), 1.21 (3H, d, J = 6.2 Hz, H_3-6′), 1.18 (1H, m, H-11b), 1.14 (1H, m, H-5), 1.03 (1H, t, J = 12.2 Hz, H-1b), 0.79 (1H, t, J = 13.0 Hz, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4 (CH, C-19), 175.7 (qC, C-23), 95.6 (CH, C-1′), 91.1 (qC, C-2′), 88.5 (qC, C-20), 83.0 (qC, C-14), 76.0 (CH_2, C-21), 72.9 (CH, C-3′), 71.7 (CH, C-3), 71.2 (CH_2, C-18), 68.9 (CH, C-2), 68.1 (CH, C-5′), 58.8 (qC, C-13), 55.3 (CH, C-17), 52.7 (qC, C-10), 48.4 (CH, C-5), 44.4 (CH, C-8), 43.2 (CH, C-9), 38.3 (CH_2, C-4′), 37.1 (CH_2, C-22), 36.3 (CH_2, C-12), 35.9 (CH_2, C-1), 34.7 (CH_2, C-7), 33.1 (CH_2, C-4), 27.7 (CH_2, C-11), 27.5 (CH_2, C-16), 24.9 (CH_2, C-15), 24.3 (CH_2, C-6), 20.8 (CH_3, C-6′); HMBC correlations H-1/C-2,C-3, C-5, C-9, C-10, C-19; H-2/C-3; H-3/C-2; H-4/C-6, C-10; H-5/C-4, C-10, C-19; H-6/C-10; H-7/C-5, C-14; H-9/C-7, C-14; H-11/C-5, C-8; H-12/C-9, C-13, C-17; H-16/C-14, C-15, C-17, C-20; H-17/C-12, C-13, C-14, C-15, C-20, C-21, C-22; H-18/C-12, C-13, C-14, C-17, C-20; H-19/C-1; H-21/ C-17, C-20, C-22, C-23; H-22/C-17, C-20, C-21, C-23; H-1′/C-3, C-2′, C-5′; H-3′/C-1′, C-2′, C-4′, C-5′, C-6′; H-4′/C-3′, C-6′; H-5′/C-1′, C-2′, C-3′, C-4′, C-6′; H-6′/C-4′; ESIMS m/z 571.2521 $[M + Na]^+$ (calcd for $C_{29}H_{40}NaO_{10}$, 571.2514).

Bioassays. Antimalarial activity was evaluated against *Plasmodium falciparum* (K1 multidrug-resistant strain) cultured continuously according to Trager and Jensen.[24] Quantitative determination of antimalarial activity in vitro was achieved using the microculture radioisotope technique based on the Desjardin method.[25] Cytotoxicity assays were performed using the colorimetric method of Skehan and co-workers.[26]

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Supporting Information Available: ^{1}H, and ^{13}C NMR spectra of compounds **1** and **2** (Figures S1−S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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