New Sesquiterpenoids from the Root of *Guatteria multivenia*

Zhizhen Zhang,† Hala N. ElSohly,*,† Melissa R. Jacob,† David S. Pasco,†,‡ Larry A. Walker,†,§ and Alice M. Clark*,†,‡

National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, Department of Pharmacognosy, and Department of Pharmacology, School of Pharmacy, The University of Mississippi, University, Mississippi 38677

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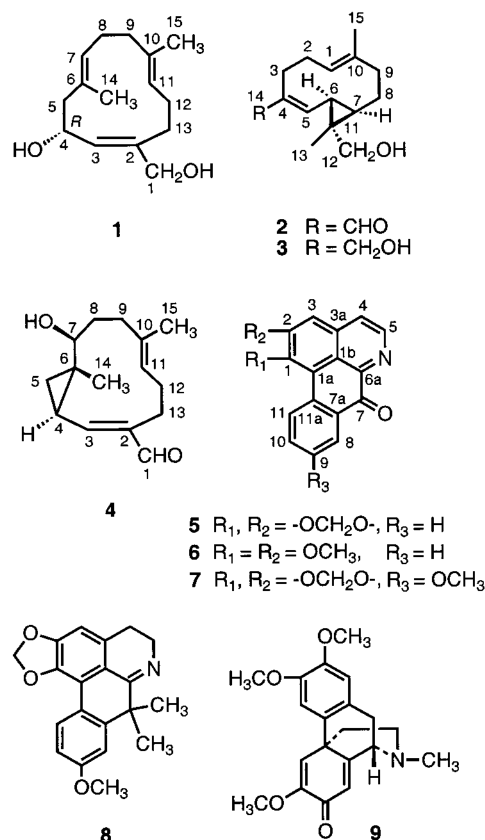
A phytochemical investigation of the $CHCl_3$ fraction of an ethanol extract of the root of *Guatteria multivenia* furnished nine compounds, of which four are sesquiterpenes (**1**−**4**) and five are alkaloids (**5**−**9**). Of the four sesquiterpenes, two are new (**1**, **3**), named guatterin A (**1**) and dihydromadolin-K (**3**), and two are known (**2**, **4**), identified as madolin-K (**2**) and madolin-W (**4**). The five known alkaloids were identified as liriodenine (**5**), lysicamine (**6**), lanuginosine (**7**), guadiscine (**8**), and *O*-methylpallidine (**9**). All the known compounds were isolated from this species for the first time. Structures of the new compounds were determined by extensive NMR studies, including DEPT, COSY, HMQC, HMBC, and NOESY. Compound **7** showed weak inhibitory effect against *Candida albicans* secreted aspartic proteases (SAP) with IC_{50} of 45 μg/mL. Compound **5** was found to have antimicrobial activity against *C. albicans, Cryptococcus neoformans, Staphylococcus aureus*, and methicillin-resistant *S. aureus* (MRS) with IC_{50}/MIC values of 3.5/6.25, 2.0/12.5, 2.0/3.13, and 2.0/3.13 μg/mL, respectively.

The genus *Guatteria*, comprising about 250 species, is the largest in the family Annonaceae. Only about 25 species seem to have been studied phytochemically, resulting in the isolation of over 140 different alkaloids.[1−8] *Guatteria multivenia* Diels. is a tall tree, known for the use of its wood for house and deck construction.[9] To our knowledge, there has been no report on the chemical constituents, nor a recorded traditional use of this plant. In the course of our screening program searching for *Candida albicans* secreted aspartic proteases (SAP) inhibitors from higher plants,[10,11] an ethanol extract of the root of *G. multivenia* was found to be active. Phytochemical investigation of the $CHCl_3$ fraction from this active extract led to the isolation and identification of four sesquiterpenoids, two new (**1**, **3**) and two known (**2**, **4**). The new sesquiterpenoids were named guatterin A (**1**) and dihydromadolin-K (**3**), while the known sesquiterpenoids were identified as madolin-K (**2**) and madolin-W (**4**). The five known alkaloids were identified as liriodenine (**5**), lysicamine (**6**), lanuginosine (**7**), guadiscine (**8**), and *O*-methylpallidine (**9**). In this study we report on the isolation and characterization of compounds **1**−**4** and some biological activities of **1**−**9**.



Results and Discussion

Compound **1** was isolated as a colorless solid. Its molecular formula of $C_{15}H_{24}O_2$ was determined by HRESIMS and indicated four degrees of unsaturation. There was evidence of hydroxyl absorption in the IR spectrum at 3241 cm^{-1}. The ^{13}C NMR (Table 1) for **1** displayed 15 carbons including two methyls, five methylenes, one oxymethylene, one oxymethine, and three quaternary carbons, assigned by DEPT experiment. The ^{1}H NMR spectrum of **1** displayed three signals of olefinic protons at δ 5.33 (1 H, d, J = 10 Hz), 4.85 (1H, t, J = 7.3 Hz), and 4.74 (1H, t, J = 7.3 Hz). The ^{13}C NMR of **1** also showed six signals of olefinic carbons (Table 1). The two methyl signals at δ 1.43 and 1.52 were vinylic and showed a correlation in the COSY spectrum with olefinic protons at δ 4.85 and 4.74. The COSY and HMQC spectra helped establish three structural fragments: $-CH_2-CHOH-CH=C-CH_2OH$ (**a**), $-C=CH-CH_2-CH_2-$ (**b**), and $-CH_2-CH_2-CH=C-$ (**c**). The skeleton was elucidated from the HMBC experiment (Figure 1). The ^2J and ^3J correlations between CH_3-15 at δ 1.43 and the carbons at δ 133.2 (C-10), 125.5 (C-11), and 38.7 (C-9) established the connectivity of fragments **b** and **c** and a methyl at C-10.

Other significant correlations in the HMBC spectrum of **1** observed from δ 15.2(CH_3-14) to δ 127.5 (C-7), 131.2

* To whom correspondence should be addressed. Tel: 662-915-7610. Fax: 662-915-7989. E-mail: helsohly@olemiss.edu. Tel: 662-915-1005. Fax: 662-915-1006. E-mail: pgclark@olemiss.edu.
† National Center for Natural Products Research.
‡ Department of Pharmacognosy.
§ Department of Pharmacology.

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Table 1. ^{13}C NMR Data of **1**, **3**, and **5**−**7** (100 or 125 MHz in $CDCl_3$)[a]

C	**1**	**3**	C	**5**[b]	**6**	**7**
1	65.4	123.8	1	148.6	152.2	147.8
2	140.7	27.5	1a	108.1	120.0	108.7
3	129.8	27.9	1b	123.5	122.3	123.2
4	68.3	139.8	2	152.3	157.0	152.2
5	47.5	124.9	3	103.5	106.6	102.9
6	131.2	24.4	3a	145.1	145.4	145.8
7	127.5	30.0	4	124.9	123.8	124.6
8	25.1	23.1	5	144.6	145.2	145.3
9	38.7	40.4	6a	136.3	135.7	136.2
10	133.2	134.6	7	182.8	182.9	183.0
11	125.5	24.5	7a	131.3	132.2	126.6
12	24.5	73.5	8	128.8	129.0	110.8
13	27.6	11.7	9	128.9	129.1	160.2
14	18.3	67.4	10	134.4	134.6	123.0
15	15.4	17.2	11	127.7	128.6	129.5
			11a	133.2	134.5	133.3
			$-CH_2-$	103.0		102.7
			OCH_3		56.4, 60.8	56.2

[a] Assignment was based on the DEPT, COSY, HMQC, HMBC, and NOESY experiments. [b] The data were recorded in $CDCl_3$/CD_3OD (3:1).

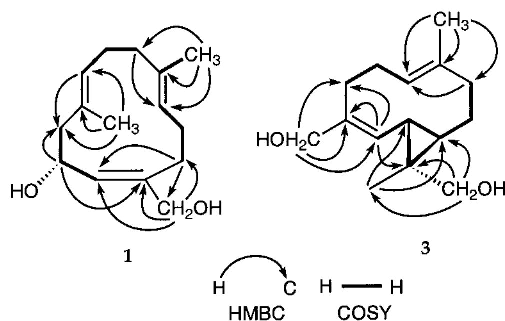

Figure 1. Key HMBC and COSY correlations for **1** and **3**.

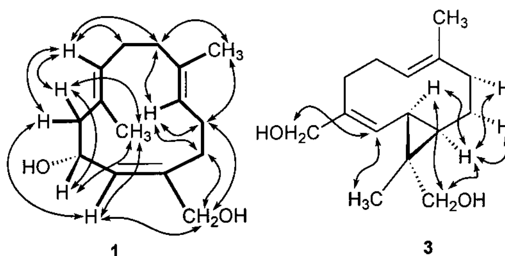

Figure 2. Selective NOE correlations for **1** and **3**.

(C-6), and 47.5 (C-5) suggested linkages between fragments **a** and **b** and another methyl group at C-6. The linkage between fragments **a** and **c** was confirmed by the HMBC correlations between δ 27.6 (C-13) and 5.33 (H-3). The oxymethine appeared at δ_C 68.3 and δ_H 4.23 (1H, ddd $J =$ 10.0, 10.0, 3.3 Hz) and was placed on C-4 on the basis of HMBC correlations of δ 4.23 (H-4) with C-2 (δ 140.7) and C-5 (δ 47.5). Similarly, in the HMBC the methylene protons at H-1 (δ 3.91, 4.03, each 1H, d, $J =$ 13.1 Hz) showed three cross-peaks with C-2 (δ 140.7), C-3 (δ 129.8), and C-13 (δ 27.6), thus establishing the oxymethylene position at C-1. Therefore, the structure of **1** was deduced as a humulane-type sesquiterpene.[12] The NOESY experiment of **1** (Figure 2) showed that all of the $\Delta^{2,3}$, $\Delta^{6,7}$, and $\Delta^{10,11}$ double bonds had *E* configuration.[13,14] The stereochemistry of the hydroxyl group at C-4 was determined to be *R* based on its negative optical rotation.[13,14] The ^1H and ^{13}C NMR signals (Experimental Section) (Table 1) of **1**, a new sesquiterpene named guatterin A (4α(*R*)-hydroxyl-6,10-dimethyl-2(*E*),6(*E*),-10(*E*)-cyclododecatriene-1-hydroxymethyl), were unambiguously assigned using HMQC and HMBC NMR correlations (Figure 1). Guatterin A is closely related to madolin-L[14] and the sesquiterpene portion of aristoloterpenate-III and -IV,[13] previously isolated from *Aristolochia heterophylla*.

Compound **2** was obtained as a colorless oil. Its molecular formula of $C_{15}H_{22}O_2$ was determined by HRESIMS. Careful examination of its spectroscopic data indicated that **2** is the known bicyclic sesquiterpenoid madolin-K, previously isolated[14] from *Aristolochia heterophylla* Hemsl.

Compound **3** was also obtained as a colorless oil. Its molecular formula of $C_{15}H_{24}O_2$ was determined by HRESIMS and indicated that it is 2 mass units higher than **2**. Comparison of the NMR data of **3** with **2** indicated that they are related. The signal of the aldehyde group in **2** (δ_H 9.23 and δ_C 194.9)[14] was replaced in **3** by ^1H NMR signals at δ 3.92 and 4.05 (each 1H, d, $J =$ 12.5 Hz) and by a ^{13}C NMR signal at δ 67.4, indicating an oxymethylene group. The ^{13}C NMR of **3** displayed 15 carbons, including two oxymethylenes, two methyls, four methines, four methylenes, and three quaternary carbons assigned from the DEPT spectrum. The ^1H NMR spectrum of **3** showed two methyls at δ 1.12 (3H, s, CH_3-13) and 1.35 (3H, s, CH_3-15), two olefinic protons at δ 5.06 (1H, br s, H-1) and 5.22 (1H, d, $J =$ 9.0 Hz, H-5), and two oxymethylenes at δ 3.27 and 3.41 (each 1H, d, $J =$ 10.9 Hz, H-12) and δ 3.92 and 4.05 (each 1H, d, $J =$ 12.5 Hz, H-14). The assigned positions for the two methyls and the two oxymethylenes were established by HMBC correlations (Figure 1). The methine protons at δ 1.29 (H-6, d, $J =$ 9.0 Hz) and 0.60 (H-7) correlated in the HMQC spectrum with C-6 (δ 24.4) and C-7 (δ 30.0). The 9.0 Hz coupling constant and nuclear Overhauser effect (NOE) between H-6 and H-7 indicated a *cis* configuration of a cyclopropane moiety.[14] On the other hand, the configuration of the C-12 oxymethylene group was determined as α due to cross-peaks between H-12 (δ 3.41) and H-6 (δ 1.29) and H-7 (δ 0.60) in the NOESY experiment (Figure 2). The ^1H and ^{13}C NMR signals (Experimental Section) (Table 1) of **3**, a new bicyclic sesquiterpenoid named dihydromadolin-K, were unambiguously assigned using HMQC and HMBC NMR correlations (Figure 1).

Compound **4** was obtained as colorless oil. Its molecular formula of $C_{15}H_{22}O_2$ was determined by HRESIMS. Careful examination of its spectroscopic data indicated that **4** is the known 4,6-cyclohumulane-type sesquiterpene madolin-W, previously isolated from *Aristolochia mollissima*.[15]

The five known alkaloids were identified as liriodenine (**5**), lysicamine (**6**), lanuginolide (**7**), guadiscine (**8**), and *O*-methylpallidine (**9**) by comparison of the spectral data with the reported values.[16−19] The ^{13}C NMR data of compounds **5**−**7** are listed in Table 1 since these data are not available in the literature.

All the isolated compounds were evaluated in the *C. albicans* secreted aspartic proteases (SAP) assay;[10] only compound **7** showed a weak activity against SAP with a IC_{50} of 45 μg/mL. In addition, compound **5** was found to be active against *C. albicans, Cryptococcus neoformans, Staphylococcus aureus,* and methicillin-resistant *S. aureus* (MRS) with IC_{50}/MIC values of 3.5/6.25, 2.0/12.5, 2.0/3.13, and 2.0/3.13 μg/mL, respectively.

The crude EtOH extract was tested in the SAP assay and found to have marginal activity, with IC_{50} of 15 μg/mL. Pepstatin was used as a positive control with IC_{50} of 0.006 μg/mL. Solvent partitioning resulted in four fractions: hexane, $CHCl_3$, EtOAc, and MeOH/H_2O. The activity resided in the MeOH/H_2O fraction with IC_{50} of 6 μg/mL. Tannins in this active fraction were removed by passage

over a polyamide column and then washing with MeOH. The MeOH wash (tannin-free) was inactive, indicating that activity was concentrated in the tannin-rich fraction. Therefore, the MeOH/H_2O fraction was not further investigated.

Experimental Section

General Experimental Procedures. Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. UV spectra were recorded on a Hewlett-Packard 8435 spectrometer. IR spectra were obtained on a ATI Mattson Genesis Series FTIR spectrometer. The NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DRX-400 or DRX 500 spectrometer. Proton and carbon chemical shifts are relative to the internal standard TMS. 2D NMR were measured with standard pulse programs and acquisition parameters. HRESIMS were measured on a Bruker-Magnex BioAPEX 30es ion cyclotron high-resolution HPLC-FT spectrometer by direct injection into an electrospray interface. Si gel (40 μm, J. T. Baker) and RP Si gel (RP-18, 40 μm, J. T. Baker) were used for low-pressure chromatography. HPLC was performed using an ODS column (Phenomenex Prodigy ODS prep, 21.2 mm i.d. × 250 mm, 10 μm). TLC was performed on Si gel 60 F_{254} (EM Science) using $CHCl_3$/MeOH (9:1, solvent A), CH_2Cl_2/EtOAc/MeOH (35:15:3, solvent B), and $CHCl_3$ (solvent C) or reversed-phase KC_{18} F Si gel 60A (Whatman) using MeOH/H_2O (80:20, solvent D).

Plant Material. *Guatteria multivenia* Diels. (root) was collected in Peru on April 6, 1998, and identified by Sidney McDaniel. A voucher specimen is on deposit at the National Center for Natural Products Research, The University of Mississippi (IBE # 12150).

Extraction and Isolation. The powdered material (650 g) was percolated with 95% EtOH (3000 mL × 5), and the alcoholic extracts were combined and evaporated to dryness (38.0 g, IC_{50} 15 μg/mL). Part of the ethanolic extract (36.0 g) was suspended in MeOH/H_2O (7:3) (500 mL), then partitioned successively with hexane (400 mL × 3), $CHCl_3$ (400 mL × 3), and EtOAc (400 mL × 3) to give a hexane (3.0 g), $CHCl_3$ (12.0 g), EtOAc (4.0 g), and MeOH/H_2O fractions (16.5 g, IC_{50} 6 μg/mL). Part of the $CHCl_3$ fraction (8.0 g) was chromatographed over a Si gel column (400 g) using mixtures of $CHCl_3$/EtOAc of increasing polarity (1:1, 2:1, 3:2, each 1000 mL) and then MeOH (1000 mL) to give 14 fractions: A (1−200 mL, 100 mg), B (200−400 mL, 150 mg), C (400−600 mL, 100 mg), D (600−800 mL, 500 mg), E (800−1000 mL, 500 mg), F (1000−2000 mL, 560 mg), G (2000−2200 mL, 180 mg), H (2200−2400 mL, 300 mg), I (2400−2600 mL, 310 mg), J (2600−2700 mL, 1.3 g), K (2700−2800 mL, 1.0 g), L (2800−2900 mL, 0.8 g), M (2900−3000 mL, 1.0 g), and N (3000−4000 mL, 1.2 g). Part of fraction F (500 mg) was rechromatographed over a Si gel column (100 g) using $CHCl_3$/MeOH (9:1, 1500 mL) to afford five fractions: F_1 (1−300 mL, 100 mg), F_2 (300−600 mL, 148 mg), F_3 (600−900 mL, 100 mg), F_4 (900−1200 mL, 120 mg), and F_5 (1200−1500 mL, 30 mg). Fraction F_2 was applied onto a low-pressure ODS column (60 g) and washed with MeOH/H_2O (60:40, 500 mL) to give eight fractions, of which fraction 4 (180−240 mL, 30 mg) was purified by preparative TLC (Si gel 60 F_{254}, $CHCl_3$/MeOH, 9:1) to yield **8** (1.1 mg), and fraction 5 (240−300 mL, 10 mg) was purified by HPLC (MeOH/H_2O, 80:20, UV 268 nm) to yield **5** (2.0 mg, t_R 34.5 min) and a mixture of **6** and **7**. This mixture was further separated by preparative TLC (Si gel 60 F_{254}, toluene/EtOAc, 1:4) to give **6** (1.0 mg) and **7** (1.1 mg). F_4 and F_5 were pooled to give fraction P (150 mg). Chromatography of fraction P using a low-pressure ODS column (60 g) and washing with MeOH/H_2O (50:50, 80:20, 100:0, each 200 mL) afforded four fractions: P_1 (1−200 mL, 10 mg), P_2 (200−250 mL, 20 mg), P_3 (250−400 mL, 60 mg), and P_4 (400−600 mL, 60 mg). Fraction P_2 was purified by preparative TLC (Si gel 60 F_{254}, $CHCl_3$/MeOH, 9:1) to give P_{2A} (5 mg) and P_{2B} (15 mg). P_{2A} was purified by HPLC (MeOH/H_2O, 65:35, UV 268 nm) to yield **9** (1.0 mg, t_R 37.0 min). P_{2B} was further purified by preparative TLC (Si gel 60 F254, toluene/EtOAc, 1:1) to yield **3** (5 mg). Fraction P_3 was repeatedly separated by preparative TLC (Si gel 60 F_{254}, toluene/EtOAc, 2:3) to yield **1** (10 mg).

Part of fraction D (300 mg) was chromatographed over a Si gel column (100 g) using $CHCl_3$/EtOAc (5:1, 600 mL) to afford 15 fractions. Of these, fractions 12−15 (440−600 mL, 30 mg) were combined and then separated by preparative TLC (Si gel 60 F_{254}, toluene/EtOAc, 1:1) to furnish **2** (10 mg) and **4** (12 mg).

Guatterin A (1): colorless solid; mp 156−157 °C (MeOH); $[\alpha]_D^{26}$ −51.0° (*c* 0.10, MeOH); IR (KBr) ν_{max} 3241, 2952, 2920, 2901, 2850, 1435, 1378, 1284, 1032, 1015, 941, 863, 832, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (3H, s, CH_3-15), 1.52 (3H, s, CH_3-14), 1.95 (2H, m, H-9), 2.02 (1H, m, H-5), 2.05 (2H, m, H-8), 2.09 (2H, m, H-12), 2.19 (2H, m, H-13), 2.37 (1H, dd, *J* = 10.0, 3.3 Hz, H-5), 3.91 (1H, d, *J* = 13.1 Hz, H-1), 4.03 (1H, d, *J* = 13.1 Hz, H-1), 4.23 (1H, ddd, *J* = 10.0, 10.0, 3.3 Hz, H-4), 4.74 (1H, t, *J* = 7.3 Hz, H-11), 4.85 (1H, t, *J* = 7.3 Hz, H-7), 5.33 (1H, d, *J* = 10.0 Hz, H-3); ^{13}C NMR data (Table 1); HRESIMS *m/z* 219.1748 $[M - OH]^+$, 259.1651 $[M + Na]^+$, 275.1418 $[M + K]^+$, 495.3449 $[dimer + Na]^+$ (calcd for $C_{15}H_{24}O_2$, 219.1743 $[M - OH]^+$, 259.1668 $[M + Na]^+$, 275.1408 $[M + K]^+$, 495.3444 $[dimer + Na]^+$); R_f 0.33 and 0.57 (Si gel, solvents A and B, respectively), 0.53 (reversed-phase KC_{18} F, solvent D).

Dihydromadolin-K (3): colorless oil; $[\alpha]_D^{26}$ +52.0° (*c* 0.05, MeOH); IR (KBr) ν_{max} 3239, 2953, 2920, 2901, 2850, 1435, 1379, 1284, 1032, 1015, 941, 862, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60 (1H, m, H-7), 0.80 (1H, m, H-8β), 1.12 (3H, s, CH_3-13), 1.29 (1H, t, *J* = 9.0 Hz, H-6), 1.35 (3H, s, CH_3-15), 1.68 (1H, m, H-8α), 1.99 (1H, m, H-9α), 2.11 (H, m, H-9β), 2.15 (4H, m, H-2, 3), 3.27 (1H, d, *J* = 10.9 Hz, H-12a), 3.41 (1H, d, *J* = 10.9 Hz, H-12b), 3.92 (1H, d, *J* = 12.5 Hz, H-14a), 4.05 (1H, d, *J* = 12.5 Hz, H-14b), 5.06 (1H, br s, H-1), 5.22 (1H, d, *J* = 9.0 Hz, H-5); ^{13}C NMR data (Table 1); HRESIMS *m/z* 219.1743 $[M - OH]^+$, 254.2114 $[M + NH_4]^+$, 259.1703 $[M + Na]^+$, 275.1408 $[M + K]^+$ (cal. for $C_{15}H_{24}O_2$, 219.1743 $[M - OH]^+$, 254.2114 $[M + NH_4]^+$, 259.1668 $[M + Na]^+$, 275.1408 $[M + K]^+$); R_f 0.38 and 0.73 (Si gel, solvents A and B, respectively), 0.63 (reversed-phase KC_{18} F, solvent D).

Biological Testing. The SAP and antimicrobial assays were conducted as previously described.[10] Pepstatin A was used as a positive control (IC_{50} 0.006 μg/mL) for SAP assays. For antimicrobial assays, amphotericin B, the positive control for *C. albicans* and *C. neoformans,* had IC_{50}/MIC values of 0.06/0.31 and 0.30/0.63 μg/mL, respectively. Ciprofloxacin was used as a positive control for *S. aureus* and methicillin-resistant *S. aureus* (MRS) with IC_{50}/MIC values of 0.07/0.39 and 0.10/3.13 μg/mL, respectively.

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