Labdane Diterpenes of *Leonurus sibiricus*

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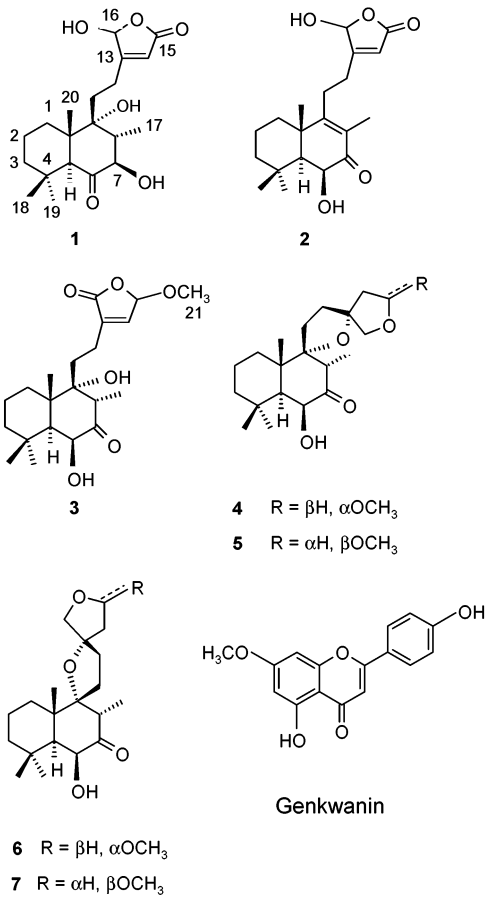
Seven new labdane diterpenes, sibiricinones A−E (**1**−**4**, **6**) and 15-*epi*-sibiricinones D and E (**5** and **7**), and the flavone genkwanin were isolated from the aerial parts of *Leonurus sibiricus*. Sibiricinone D (**4**) and 15-*epi*-sibiricinone D (**5**), and sibiricinone E (**6**) and 15-*epi*-sibiricinone E (**7**), respectively, were isolated as C-15 epimeric pairs. These secondary metabolites were identified on the basis of 1D and 2D NMR including ^{1}H−^{1}H COSY, HSQC, and HMBC spectroscopic techniques. The stereochemical configurations of compounds **4**−**7** were assigned through 2D T-ROESY and selective NOE experiments.

The genus *Leonurus* is a widely distributed, medicinally important member of the Lamiaceae, consisting of approximately 20 species.[1] Preparations of some plants of the genus have been utilized in the treatment of cardiovascular diseases and for sedative as well as uterotonic effects in Europe and mainland China.[1,2] Secondary metabolites reported from *Leonurus* include alkaloids,[1−4] flavonoids,[1,2] iridoids,[1,2] and phenylpropanoid glycosides.[1] Furthermore, several labdane diterpenes have been reported from *Leonurus*, some of which exhibit anti-platelet aggregation activity.[1,5,6] *L. sibiricus* L. is commonly referred to as "motherwort" in the West Indies, where it is utilized as a cough syrup and antipyretic for malaria. The juice of the fresh plant is used to treat hemoptysis, edema, gout, and arthritis.[7−10] There has been one prior report of three labdane diterpenes from *L. sibiricus* in 1982.[11] In the present paper, we describe the isolation of seven additional labdane diterpenes (**1**−**7**) and the flavone genkwanin from a CH_2Cl_2 extract of *L. sibiricus*.



Sibiricinone A (**1**) was obtained as a colorless oil, and the molecular formula, $C_{20}H_{30}O_6$, was determined by HREIMS. The IR spectrum had absorptions characteristic of hydroxy (3450 cm^{-1}) and γ-lactone (1756 cm^{-1}) functionalities. The ^{1}H NMR spectrum (Table 1) showed resonances due to four methyl groups at δ 1.28 (3H, s, H_3-18), 1.24 (3H, d, J = 6.5 Hz, H_3-17), 0.99 (3H, s, H_3-19), and 0.90 (3H, s, H_3-20). From the ^{1}H−^{1}H COSY spectrum, key correlations were seen between H-12a/b and H-14 and H-16 of the γ-lactone. The ^{13}C NMR spectrum (Table 2) exhibited resonances for 20 carbons, including a free keto carbonyl at δ 211.3 (C-6, s) and an ester carbonyl δ 170.6 (C-15, s). The presence of the γ-hydroxy-α,β-unsaturated-γ-lactone moiety was confirmed by the HMBC data, as the lactone carbonyl at C-15 showed correlations to H-16 (δ_H 6.03, d) and H-14 (δ_H 5.89, d). It was observed that H-5 appeared at δ 2.93 (1H, s), suggesting that the keto group is attached to C-6.[6] The methyl group at C-8 was assigned as equatorial, as its coupling constant with H-8 was 6.5 Hz; an axial methyl group would exhibit a larger J value ($J \approx 8.0$ Hz).[5,6] A relatively large coupling constant of J = 12.0 Hz was observed between the H-7 and H-8 protons, which confirmed their axial−axial *trans* relationship and permitted the assignment of the C-7 hydroxy group as equatorial. This was confirmed by a NOESY experiment, in which cross-peaks were observed between the oxymethine proton at δ 3.88 (H-7) and the C-8 methyl group at δ 1.24. This information led to the characterization of compound **1** as 7β,9α,16ξ-trihydroxy-6,15,-dioxolabd-13-en-13,16-olide, for which the trivial name sibiricinone A is suggested.

Sibericinone B (**2**) was assigned the molecular formula $C_{20}H_{28}O_5$, which indicated seven degrees of unsaturation, one more than in **1**, and this was explained by the second set of sp^2 carbons at δ 129.0 (C-8, s) and 167.6 (C-9, s). The IR spectrum had absorptions at 3500 (hydroxy), 1753 (γ-lactone), and 1678 (α,β-unsaturated ketone) cm^{-1}. The presence of the α,β-unsaturated ketone chromophore was supported by a UV λ_{max} at 250 nm (log ϵ 4.11). The ^{1}H NMR spectrum exhibited signals at δ 5.96 (1H, s, H-14) and 6.04 (1H, s, H-16), which were indicative of a γ-hydroxybuteno-

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Table 1. ^{1}H NMR Spectral Data for Compounds **1**−**7**

position	**1**[a]	**2**[a]	**3**[a]	**4**/**5**[b]	**6**/**7**[b]
1	1.65 (m)	1.89 (m)	⟨1.46⟩[c] (m)	⟨1.38⟩[c] (m) × 2	⟨1.38⟩[c] (m)/1.31 (m)
	1.49 (m)	1.29 (m)			1.24 (m)
2	1.62 (m)	⟨1.58⟩[c] (m)	1.70 (m)	1.74 (m)/1.72 (m)	1.73 (m)/1.72 (m)
	1.58 (m)		1.54 (m)	1.55 (m)/1.52 (m)	1.54 (m)/1.52 (m)
3	1.34 (m)	1.44 (m)	1.36 (m)	1.36 (m)/1.35 (m)	1.35 (m) × 2
	1.10 (m)	1.21 (m)	1.20 (m)	1.18 (m) × 2	1.19 (m)/1.18 (m)
5	2.93 (s)	1.56 (d, 2.8)	1.78 (d, 2.8)	1.64 (d, 2.8)/1.68 (d, 2.8)	1.64 (d, 2.8) × 2
6		4.34 (d, 2.8)	4.36 (d, 2.8)	4.34 (m) × 2	4.35 (m) × 2
7	3.88 (d, 10.7)				
8	1.88 (m)		3.52 (d, 5.9)	3.52 (d, 5.0)/3.46 (d, 5.0)	3.53 (d, 5.0)/3.51 (d, 5.0)
11	1.99 (m)	⟨1.90⟩[c] (t, 4.8)	⟨1.90⟩[c] (t, 4.0)	2.27 (m)/2.22 (m)	2.16 (m)/2.20 (m)
	1.82 (m)			1.86 (m)/1.91 (m)	1.89 (m)/1.86 (m)
12	2.62 (m)	⟨2.55⟩[c] (t, 4.8)	⟨2.43⟩[c] (t, 4.0)	2.18 (m)/2.08 (m)	2.17 (m)/2.08 (m)
	2.41 (m)			2.12 (m)/1.91 (m)	2.05 (m)/1.91 (m)
14	5.89 (brs)	5.96 (s)	6.79 (brs)	2.28 (m)/2.16 (m)	2.39 (m)/⟨2.20⟩[c] (m)
				1.88 (m)/2.09 (m)	1.93 (m)
15			5.73 (brs)	5.02 (d, 2.8)/4.94 (d, 2.8)	5.01 (d, 2.8)/4.93 (d, 2.8)
16	6.03 (brs)	6.04 (brs)		3.97 (m)/3.86 (m)	3.89 (m)/3.72 (m)
				3.81 (m)/3.54 (m)	3.66 (m)/3.43 (m)
17	1.24 (d, 6.5)	1.84 (s)	1.12 (d, 5.9)	0.99 (d, 5.0) × 2	1.06 (d, 5.0)/1.04 (d, 5.0)
18	1.28 (s)	1.31 (s)	1.28 (s)	1.27 (s) × 2	1.27 (s)/1.26 (s)
19	0.99 (s)	1.06 (s)	1.02 (s)	1.02 (s)/1.01 (s)	1.01 (s) × 2
20	0.90 (s)	1.41 (s)	1.43 (s)	1.43 (s) × 2	1.42 (s) × 2
21			3.58 (s)	3.30 (s)/3.36 (s)	3.32 (s)/3.35 (s)

[a] Measured in $CDCl_3$ at 100 mHz. [b] Measured in $CDCl_3$ at 125 mHz. [c] Average value for an incompletely resolved CH_2 group.

Table 2. ^{13}C NMR Spectral Data for Compounds **1**−**7**

carbon	**1**[a]	**2**[a]	**3**[a]	**4**/**5**[b,c]	**6**/**7**[b,c]
1	31.6 t	37.4 t	33.8 t	34.1/34.3 t	34.0/33.5 t
2	18.1 t	18.4 t	18.7 t	18.9/18.8 t	18.8 × 2 t
3	41.9 t	43.4 t	43.4 t	43.9/43.8 t	43.8/43.7 t
4	32.2 s	34.0 s	34.9 s	35.0/34.8 s	35.0 × 2 s
5	55.9 d	54.4 d	49.4 d	50.1/49.5 d	50.0/50.1 d
6	211.3 s	71.0 d	75.9 d	76.0/75.8 d	76.1/76.0 d
7	77.1 d	199.0 s	211.1 s	210.1/210.0 s	210.1/209.8 s
8	47.5 d	129.0 s	46.1 d	45.6/45.3 d	45.5/45.7 d
9	77.2 s	167.6 s	81.7 s	96.6/96.1 s	96.7/96.1 s
10	49.0 s	41.0 s	44.0 s	43.1/43.2 s	43.1 × 2 s
11	30.9 t	32.7 t	31.6 t	29.9/29.2 t	29.8 × 2 t
12	21.5 t	26.9 t	21.7 t	38.7/39.6 t	37.5/39.6 t
13	169.1 s	168.1 s	138.7 s	90.6/89.8 s	90.4/90.0 s
14	117.8 d	118.1 d	142.0 d	47.4/46.6 t	47.0/46.2 t
15	170.6 s	170.4 s	102.7 d	105.6/104.9 d	105.0/104.4 d
16	98.6 d	98.2 d	171.6 s	77.9/75.1 t	77.1/74.4 t
17	12.4 q	11.6 q	8.5 q	9.3/8.9 q	9.3/9.2 q
18	22.2 q	24.0 q	24.6 q	24.7 × 2 q	24.7 × 2 q
19	32.6 q	32.4 q	33.3 q	32.7/32.8 q	32.7 × 2 q
20	18.2 q	22.1 q	18.9 q	20.1/20.0 q	20.1/19.9 q
21			57.2 q	54.7/55.1 q	54.9 × 2 q

[a] Measured in $CDCl_3$ at 100 mHz. [b] Measured in $CDCl_3$ at 125 mHz. [c] Signal pairs are separated by "/".

lide ring. The methyl group at δ 1.84 (H_3-17) showed HMBC cross-peaks to C-7, C-8, and C-9, enabling the placement of the double bond between C-8 and C-9. The COSY spectrum had cross-peaks between H-5 and H-6, which indicated that **2** has a C-6 hydroxy, C-7 keto arrangement. NOESY cross-peaks were also observed between H-5 and H-6, and this confirmed that the C-6 hydroxy group was β-oriented.[12] Compound **2** was thus identified as 6β,16ξ-dihydroxy-7-oxolabda-8,13-dien-13,16-olide.

Sibiricinone C (**3**) gave the molecular formula $C_{21}H_{32}O_6$, and this indicated that there was one more carbon present when compared to **1** and **2**. In the ^{1}H NMR spectrum, a methoxy group was apparent at δ 3.58 (3H, s, H_3-21), and it showed a HMBC correlation with C-15. A butenolide ring, in which the carbonyl group was at C-16, was evident from signals at δ 6.79 (bs, H-14) and 5.73 (bs, H-15), which showed COSY cross-peaks to each other. The ^{13}C NMR data (Table 2) confirmed the presence of the α,β-unsaturated γ-lactone, with signals at δ_C 102.7 (C-15), 138.7 (C-14), 142.0 (C-13), and 171.6 (C-16). In addition, C-9 correlated with protons at H-8, H-11a,b, H-17, and H-20. In the NOESY spectrum, cross-peaks were observed between the H-6 oxymethine proton at δ 4.36 (1H, d, J = 3.4 Hz) and the protons at δ 1.78 (1H, d, J = 2.8 Hz, H-5) and 1.02 (3H, s, H-19), revealing that the C-6 hydroxy group was β-oriented. Compound **3** was therefore characterized as 6β,9α-dihydroxy-15-methoxy-7,16-dioxolabd-13-en-13,16-olide.

Sibiricinone D (**4**) and 15-*epi*-sibiricinone D (**5**) were isolated as an epimeric mixture (3:1) of two isomers, with the molecular formula $C_{21}H_{34}O_5$. The ^{1}H NMR spectrum (Table 1) had resonances due to methyl groups between δ 0.99 and 1.43 (H_3-17−H_3-20). Additionally, an oxymethine proton at δ 4.34 (H-6) was apparent and showed a COSY cross-peak with the H-5 proton. The HMBC spectrum revealed that the hydroxy group at C-6 was flanked by a neighboring keto group (C-7), as in sibiricinones B (**2**) and C (**3**). Resonances for the H-15 oxymethine protons were present at δ 5.02 (**4**) and 4.94 (**5**), which suggested that these compounds have the opposite stereochemistry at C-15. They exhibited NOESY cross-peaks between the C-16 protons and the methyl protons on C-8, which indicated that in these two compounds C-16 lies to the right of the structure (Figure 1) and therefore has a 13*R* stereochemistry, as in other compounds in this series.[11] Compounds **4**/**5** are therefore the C-15α- and β-methoxy epimers, respectively, of (13*R*)-9α,13α;15,16-diepoxy-6β-hydroxy-15-methoxylabd-7-one.

Compounds **6**/**7** were assigned the molecular formula $C_{21}H_{34}O_5$, which indicated that they are stereoisomeric with compounds **4**/**5**. The ^{1}H NMR spectrum revealed that they occurred as a (2:1) epimeric mixture. Resonances characteristic of the H-15 oxymethine protons at δ 5.01 (**6**) and 4.93 (**7**) again suggested the opposite stereochemistry at C-15 for these compounds.[12,13] On the basis of the largest chemical shift differences (C-14−C-16), it was postulated that compounds **6**/**7** differed from compounds **4**/**5** in the stereochemistry of the uppermost spirocyclic ring, and this was confirmed by T-ROESY and selective NOE spectral data (Figure 1). However, a NOE was observed between

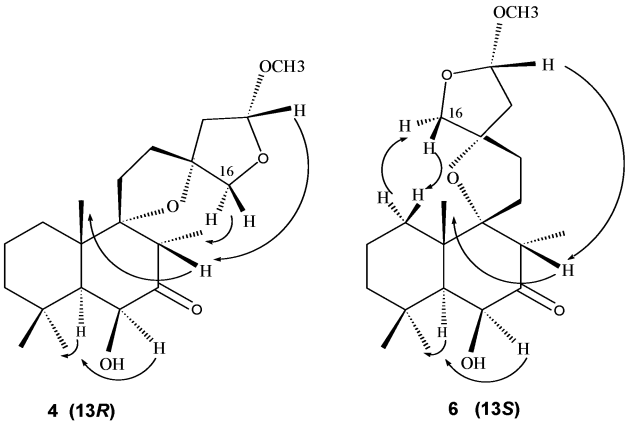

Figure 1. Selected key NOE correlations for sibiricinones D and E (**4** and **6**).

the protons of C-16 and the methylene protons of C-1 in compounds **6/7**, which indicated that C-16 occurs to the left in the structure (Figure 1) and therefore has 13*S* stereochemistry.[1,12−14] Compounds **6/7** were thus characterized as the (13*S*)-stereoisomers of compounds **4/5**, respectively. Due to lack of definitive NOEs, the stereochemistry of the C-15 methoxy group was assigned as α-substituted in sibiricinones D (**4**) and E (**6**) and as *β*-substituted in 15-*epi*-sibiricinones D (**5**) and E (**7**), by comparison to leopersin N.[13]

Finally genkwanin (=apigenin 7-*O*-methyl ether) was identified on the basis of comparison to spectral and physical data reported in the literature; it is considered a chemotaxonomic marker of the genus *Leonurus*.[13,15,16] This work further highlights the rich variety of labdane diterpenes found within the genus *Leonurus*.[1,5,6,11−14] It establishes *L. sibiricus* as a source of α,*β*-butenolide and C-15 epimeric spirocyclic labdanes. We have also identified further C-15 methoxy-substituted labdanes; leopersin N was the first and only such metabolite reported from the genus *Leonurus* to date.[13] The previously reported leosibiricin of *L. sibiricus* was at the time tentatively proposed as a 13*S*-labdane (due to lack of NOE experiments).[11] The 13*S*-stereoisomers reported in this paper present the possibility that these compounds may be of significance as taxonomic markers of *L. sibiricus*.

Experimental Section

General Experimental Procedures. Optical rotations were measured at 20 °C in $CHCl_3$ on a Perkin-Elmer 341 polarimeter with the Na 589 line. UV spectra were recorded on a HP8452A diode array spectrophotometer in MeOH solution. IR spectra were recorded on a Nicolet Nexus spectrophotometer as thin films. NMR data were acquired on a Varian UNITY 500 MHz spectrometer or on a Bruker Avance DRX 400 MHz spectrometer in $CDCl_3$ as solvent, using TMS as internal standard. The high- and low-resolution EIMS were recorded on a Micromass 70-250S mass spectrometer at an ionizing voltage of 70 eV. High-performance liquid chromatography (HPLC) was performed utilizing a Supelcosil LC-18 (25 cm × 21.2 mm, 5 μm) column fitted on a Beckman HPLC instrument with a PDA detector. Flash column chromatography was performed using Merck silica gel (grade 9385, 230−400 mesh, 60 Å). Analytical TLC was done using Aldrich aluminum-backed plates coated with silica gel with 254 nm fluorescent indicator. Chromatograms were first viewed under UV light and then visualized by staining with Ehrlich's reagent (1 g of 4-dimethylaminobenzaldehyde in a mixture of 25 mL of 36% HCl and 75 mL of MeOH).

Plant Material. The plant material was collected in St. Joseph, Barbados, in September 2001. It was identified by Dr. C. Durant of the Tanaud Research Unit, Shire Biochem, Inc., St. Michael, Barbados, as an authentic sample of *Leonurus sibiricus*. A voucher specimen is deposited in the National Herbarium (DMB #3) located on Cave Hill Campus, University of the West Indies, Bridgetown, Barbados.

Extraction and Isolation. The aerial parts of *L. sibiricus* (3.4 kg) were air-dried, cut into smaller pieces, and then blended in MeOH (3 × 14.0 L) and allowed to stand for one week. The combined methanolic extracts were concentrated in vacuo, resuspended in MeOH−H_2O (2:1), and extracted with CH_2Cl_2 (2 × 250 mL). The crude CH_2Cl_2 extract (21.9 g) was subjected to flash column chromatography, utilizing gradient elution with Me_2CO−hexane systems (5−100%). Forty-nine 500 mL fractions were obtained and pooled on the basis of TLC monitoring, to give 12 major fractions, designated A−L. Column chromatography of fraction E (6.4 g) yielded two subfractions, E1 (189 mg) and E2 (147 mg). Preparative HPLC was performed on subfraction E1 (189 mg) in 67:33 MeOH−H_2O, to give compounds **1** (7.6 mg), **2** (8.8 mg), and **3** (19.0 mg), as colorless oils. Column chromatography of subfraction E2 (147 mg) afforded genkwanin (25 mg) as a yellow amorphous solid. Column chromatography was performed on fraction C (0.6 g), followed by preparative HPLC in 60:40 MeOH−H_2O, to give compounds **4/5** (12.2 mg) and compounds **6/7** (23.1 mg), as transparent oils. The spectral and physical data of genkwanin were identical to those published in the literature.[15,16]

Sibiricinone A (1): colorless oil; $[\alpha]^{20}_D$ +18.4° (*c* 0.64, $CHCl_3$); IR (film) ν_{max} 3450, 1756, 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$), see Table 2; EIMS *m/z* 366 $[M]^+$ (31), 349 (39), 333 (24), 213 (91), 193 (42), 151 (60), 123 (61), 109 (91), 96 (37), 81 (60), 69 (100); HREIMS *m/z* 366.2036, $[M]^+$ (calcd for $C_{20}H_{30}O_6$, 366.2042).

Sibiricinone B (2): colorless oil; $[\alpha]^{20}_D$ +4.4° (*c* 0.18, $CHCl_3$); UV (MeOH) λ_{max} 250 nm (log ϵ 4.11); IR (film) ν_{max} 3500, 1753, 1678, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$), see Table 2; EIMS *m/z* 348 $[M]^+$ (5), 333 (4), 213 (62), 123 (38), 109 (52), 95 (43), 83 (50), 69 (72), 57 (100); HREIMS *m/z* 348.1924, $[M]^+$ (calcd for $C_{20}H_{28}O_5$, 348.1937).

Sibiricinone C (3): colorless oil; $[\alpha]^{20}_D$ +4.7° (*c* 1.58, $CHCl_3$); IR (film) ν_{max} 3440, 1760, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$), see Table 2; EIMS *m/z* 380 $[M]^+$ (8), 363 (30), 345 (17), 213 (53), 181 (49), 109 (100), 95 (70), 81 (66), 69 (98), 57 (71); HREIMS *m/z* 380.2188, $[M]^+$ (calcd for $C_{21}H_{32}O_6$, 380.2199).

Sibiricinone D and 15-*epi*-sibiricinone D (4/5): colorless oil; IR (film) ν_{max} 3500, 1713, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$), see Table 2; EIMS *m/z* 366 $[M]^+$ (3), 334 (4), 305 (4), 277 (5), 213 (65), 109 (100), 95 (50); HREIMS *m/z* 366.2404, $[M]^+$ (calcd for $C_{21}H_{34}O_5$, 366.2406).

Sibiricinone E and 15-*epi*-sibiricinone E (6/7): colorless oil; IR (film) ν_{max} 3450, 1712, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$), see Table 2; EIMS *m/z* 366 $[M]^+$ (3), 334 (4), 305 (4), 277 (5), 213 (65), 109 (100), 95 (50); HREIMS *m/z* 366.2399, $[M]^+$ (calcd for $C_{21}H_{34}O_5$, 366.2406).

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