JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

New Constituents from Noni (*Morinda citrifolia*) Fruit Juice

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Morinda citrifolia L. (Rubiaceae), known as noni, has a long history of traditional use in the Hawaiian and Tahitian islands. More recently, an array of commercial noni fruit juice products are gaining popularity as dietary supplements, with claims of anticancer and immunostimulant activities. The biologically active principles of noni are not fully known. In continuation of work on the isolation of markers from dietary supplements, this paper reports the isolation of three new markers, namely, 1-*O*-(3′-methylbut-3′-enyl)-β-D-glucopyranose (**1**), 1-*n*-butyl-4-(5′-formyl-2′-furanyl)methyl succinate (**2**), and 4-*epi*-borreriagenin (**3**), together with the known iridoid glycosides asperulosidic acid (**4**) and deacetylasperulosidic acid (**5**) and a mixture of 1-*n*-butyl-4-methyl-2-hydroxysuccinate (**6a**) and 1-*n*-butyl-4-methyl-3-hydroxysuccinate (**6b**), as well as a mixture of α- and β-glucopyranose from noni fruit juice obtained from Puerto Rico. The structures of compounds were based on ^{1}H and ^{13}C NMR, mainly 2D NMR COSY, HMQC, HMBC, and NOESY experiments, and HRMS. Furthermore, samples from fresh-squeezed noni fruit juice from Japan revealed the presence of scopoletin (**7**), in addition to compounds **1**−**6**, indicating no significant differences in the marker constituents of noni collected from Atlantic and Pacific regions.

KEYWORDS: Noni; *Morinda citrifolia*; Rubiaceae; fruit juice; glycoside; iridoid; succinyl esters

INTRODUCTION

The genus *Morinda* (Rubiaceae) consists of about 80 species, mostly of Old World origin. The most well-known species of this genus is *Morinda citrifolia* L., commonly known as noni. Other common names include Indian mulberry, ba ji tian, nono or nonu, cheese fruit, and nhau in various cultures throughout the world. The noni plant is a small evergreen tree found growing in open coastal regions at sea level and in forest areas up to about 1300 feet above sea level. The fruit can grow in size up to 12 cm or more and has a lumpy surface covered by polygonal-shaped sections.

M. citrifolia fruit has a long history of use as a food in tropical regions of the world (*1*, *2*). The roots, stems, bark, leaves, flowers, and fruits of noni are all used in various combinations in almost 40 known and recorded herbal remedies for different diseases. The fruit juice is in high demand as an alternative medicine for various illnesses such as arthritis, diabetes, high blood pressure, muscle pains, menstrual difficulties, headaches, heart disease, AIDS, cancers, gastric ulcers, sprains, mental depression, senility, poor digestion, atherosclerosis, blood vessel problems, and drug addiction (*3*). However, scientific evidence of the benefits of the noni fruit juice is limited. The juice of noni fruits has been shown to prolong the life span of mice implanted with Lewis lung carcinoma (*4*). It was reported that the fruits of noni suppress the growth of tumors by stimulating the immune system (*5*). Currently, a freeze-dried noni fruit extract is in phase I clinical trials at the Cancer Research Center of Hawaii, University of Hawaii. [For details see http://www.crch.org/CenStudyNoni.htm (date 06/07/2006).]

The increasing use of noni products as dietary supplements suggested an urgent need to isolate and identify marker compounds from noni fruit juice for quality control purposes. Therefore, the current study involves the isolation and characterization of chemical markers from commercially available noni fruit juice. To date, several chemical and biological investigations on noni fruit extracts have been reported, but the chemical studies on noni fruit juice are very limited compared to its biological investigations. The isolation and identification of constituents **1**−**7** now allow us to develop an HPLC analytical method for quality control of noni fruit juice. Furthermore, we choose two major commercial samples of noni fruit juices, which are representative of the two main regions (namely, Pacific and Atlantic), where noni is commercially cultivated. The constituents/markers isolated in the current study will be

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10.1021/jf060672u CCC: $33.50
Published on Web 07/21/2006

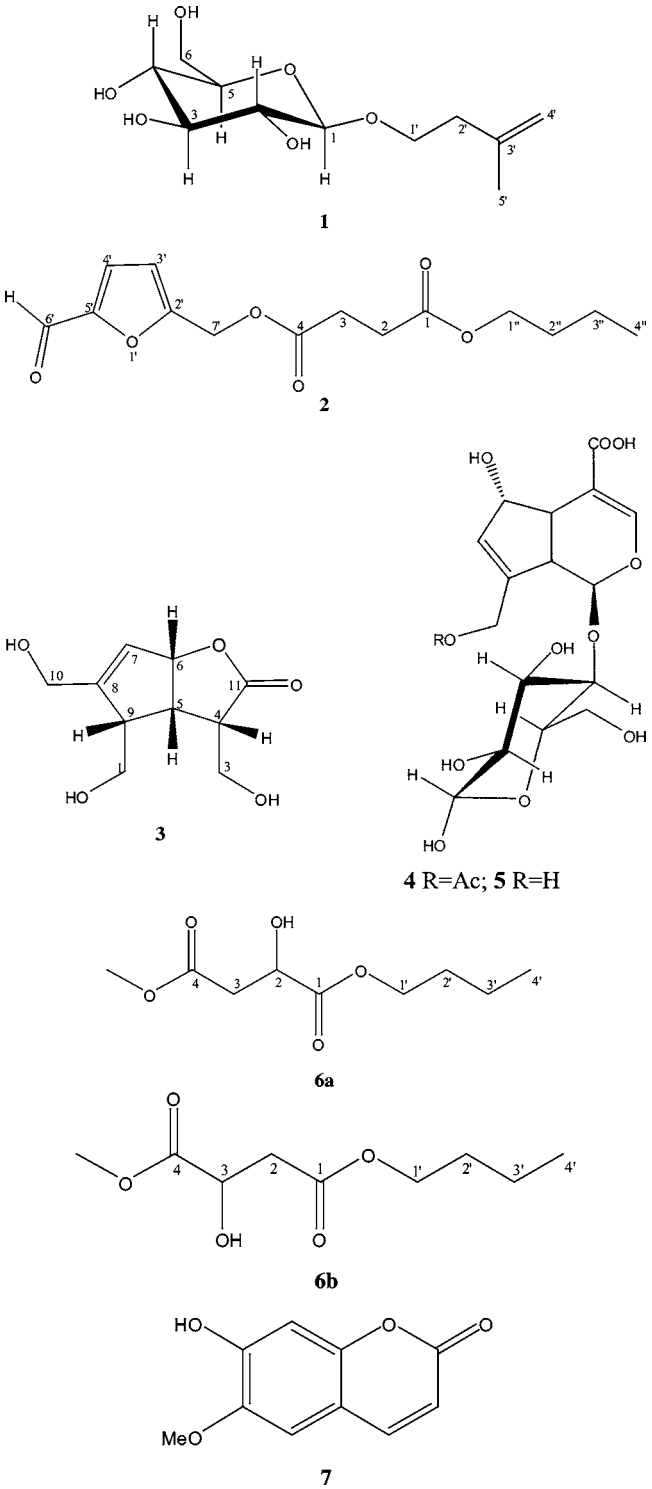

Figure 1. Structures of compounds isolated from noni juice.

useful for the quality control of almost any commercially available noni fruit juice.

MATERIALS AND METHODS

General Apparatus and Chemical. Optical rotations were measured using an AUTOPOL IV instrument at room temperature; UV spectra were recorded by a Hewlett-Packard 8452A UV−vis spectrometer; IR spectra were obtained using a Bruker Tensor 27 instrument; ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 instrument at 500 MHz (^{1}H) and 125 MHz (^{13}C), using the residual solvent signal as internal standard; multiplicity determinations (DEPT 135) and 2D NMR spectra (COSY, NOSEY, HMQC, and HMBC) were acquired using standard Bruker pulse programs; HRMS were obtained by direct injection using a Bruker Bioapex-FTMS with electrospray ionization (ESI) source. TLC was performed with silica gel 60 GF_{254} plates (EM Science) and $CHCl_3$/MeOH (7:3 and 1:1) as solvent. Column chromatography was performed with flash silica gel (J. T. Baker, 40 μM flash), and centrifugal preparative TLC (CPTLC; using a Chromatotron instrument, Harrison Research Inc. model 8924) was carried out on 1 mm Si gel GF coated rotors with F_{254} indicator (Analtech, Inc.), with the solvent system MeOH/$CHCl_3$ (0:1 to 1:1). The isolated compounds were visualized using short-wave UV light (254 nm), followed by spraying with 1% vanillin−H_2SO_4 reagent. Fraction collection was carried out by means of a CF-1 fraction collector. Solvents were eliminated by means of a Savant Speed Vac Plus SC210A concentrator (evaporator).

Sample. *M. citrifolia* (Rubiaceae) (noni) was cultivated by Antonio Mendez under the auspices of his company, RICONONI, in Puerto Rico**.** A voucher specimen is deposited at the Collection of Tropical Plants, Department of Biology, University of Puerto Rico at Rio Piedras. The juice is processed without the addition of sugar, adjuvant, or other blended juices. The processed juice was stored in sealed plastic bottles and kept in a refrigerator until the bottles were opened for analysis. Fruits weighing roughly 1 lb each were used for the preparation of juices. The fruit and fresh juice of *M. citrifolia* (RICONONI) were obtained by Professor James Rushing, Clemson University, in May 2003 under USDA-APHIS permit. A sample of noni juice from Okinawa, Japan (manufacturer, Ryukyu Bio-Resource Development Co., Ltd.), was kindly provided by Professor David Gangemi in July 2004.

Rapid Isolation of Markers by Centrifugal Preparative TLC. Noni juice (RICONONI, 900 mL) was partitioned successively with *n*-hexane, EtOAC, and *n*-BuOH (each 3 × 400 mL) to afford 5, 7, and 15 g of a solid residue, respectively. The *n*-BuOH fraction (11.0 g) was subjected to flash CC over silica gel (600 g) and eluted with $CHCl_3$ and then with $CHCl_3$ containing increasing amounts of CH_3OH (1:0 to 1:1), and fractions (1−200) were pooled by TLC. The pooled fractions were purified by CPTLC (1 or 2 mm Si gel GF disk, solvent 10% MeOH/$CHCl_3$, flow rate = 3 mL/min) connected to a fraction collector. Fractions 149−169 (200 mg) were eluted with 10% MeOH/$CHCl_3$, followed by 15 and 20% MeOH/$CHCl_3$. Separation of two weak fluorescent bands was monitored under UV light, and the collected fractions (50) were dried using a Speed Vac. Samples of the first 10 test tubes (in MeOD) were manually injected to the tubeless NMR probe, and the ^{1}H NMR spectrum at 500 MHz of each sample was recorded. Fractions 7 and 9 were scanned for UV/HRMS with Agilent MSD TOF, which exhibited $[M - H]^-$ at *m*/*z* 179.0553 and 389.1080, respectively. On the basis of the NMR and HRMS data, fractions 2−7 (103 mg, mixture of α- and β-glucose) and 9−10 (60 mg, **5**) contained two different compounds, whereas fraction 8 was a mixture. Using a similar procedure, compounds **1** (43 mg, $[M - H]^-$ at *m*/*z* 247.1193) and **3** (15 mg) were purified from fraction 72−73 (76 mg), and compounds **2** (17 mg) and **6** (33 mg) were isolated from fractions 28−35 (63 mg) and 7−23 (160 mg), respectively; compound **4** (18 mg, $[M - H]^-$ at *m*/*z* 431.1186) was obtained from fractions 96−107 (256 mg). A sample from Okinawa, Japan, was subjected to the above isolation procedure, which yielded compounds **1**−**6** and scopoletin (**7**). The structures of **4**, **5**, and **7** were established by comparing their physical and spectral data with those published in the literature (*6*, *7*).

1-O-(3′-Methylbut-3′-enyl)-β-D-glucopyranose (1): colorless powder; $[\alpha]^{28}_D$ −17.3° (*c* 0.15, MeOH); UV (MeOH) λ_{max}, nm, 198, 230; IR (film) ν_{max}, cm^{-1}, 3374 (OH), 2930 (CH), 2886 (CH), 1650 (C═C), 1077 (C−O), 1034 (C−O), 893 (═CH_2); ^{1}H NMR and ^{13}C NMR data, see **Table 1**; HRMS (ESI), *m*/*z* 247.1193 ([M − H]$^-$) (calcd for $C_{11}H_{19}O_6$ $[M - H]^-$, 247.1182).

1-n-Butyl-4-(5′-formyl-2′-furyl)methyl succinate (2): gum; UV (MeOH) λ_{max}, nm, 195, 227, 282; IR (film) ν_{max}, cm^{-1}, 2961 (CH), 2873 (CH), 1731 (C═O), 1675 (C═O), 1583 (C═C), 1192 (C−O); ^{1}H NMR and ^{13}C NMR data, see **Table 1**; HRMS (ESI), *m*/*z* 305.0989 ([M + Na]$^+$) (calcd for $C_{14}H_{18}O_6Na$ $[M + Na]^+$, 305.1001).

4-epi-Borreriagenin (3): white powder; $[\alpha]^{27}_D$ −5° (*c* 0.2, MeOH); UV (MeOH) λ_{max}, nm, 197, 242; IR (film) ν_{max}, cm^{-1}, 3354 (OH), 2927 (CH), 2887 (CH), 1742 (C═O), 1187 (C−O), 1046 (C−O); ^{1}H NMR and ^{13}C NMR data, see **Table 1**; HRMS (ESI), *m*/*z* 237.0726

Table 1. ^{1}H and ^{13}C NMR Spectral Data (in Parts per Million, *J* Values in Hertz, in Parenthesis) for **1**–**3**[a]

	1		**2**		**3**	
H/C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	4.03 dd (7.7, 17.0) 3.69 m	68.1 t		172.3 s	3.69 dd (6.7, 11.5) 3.72 dd (4.4, 11.5)	59.4 t
2	2.38 t (7.1)	37.6 t	2.62 m	29.2 t		
3		142.4 s	2.65 m	29.4 t	3.83 dd (3.6, 10.8) 3.90 dd (4.6, 10.8)	61.5 t
4	4.77 s, 4.78 s	110.7 t		176.1 s	2.95 ddd (9.1, 4.6, 3.6)	44.5 d
5	1.78 s	22.0 q			3.30 m	42.6 d
6					5.40 d (7.5)	86.9 d
7					5.84 s	127.7 d
8						152.0 s
9					3.10 br d (8.0)	48.6 d
10					4.15 d (15.2), 4.22 d (15.2)	59.2 t
11						179.6 s
1′	4.30 d (7.7)	102.9 d				
2′	3.20 dd (8.8, 8.6)	73.8 d		160.7 s		
3′	3.38 dd (8.8, 8.5)	76.8 d	6.51 d (3.3)	110.0 d		
4′	3.31 m	70.4 d	7.22 d (3.3)	123.1 d		
5′	3.31 m	76.6 d		152.0 s		
6′	3.89 d (12.0), 3.69 m	61.6 t	9.54 s	177.5 d		
7′			4.70 s	57.6 t		
1″			4.08 t (7.0)	64.9 t		
2″			1.60 tt (7.0, 6.6)	30.9 t		
3″			1.36 tq (7.0, 6.6)	19.4 t		
4″			0.91 t (7.0)	14.0 q		

[a] NMR spectra were recorded in CD_3OD for **1** and **3** and in $CDCl_3$ for **2**.

([M + Na]$^+$) (calcd for $C_{10}H_{14}O_5Na$ [M + Na]$^+$, 237.0739); *m*/*z* 197.0809 ([M + H]$^+$ − H_2O) (calcd for $C_{10}H_{13}O_4$ [M + H]$^+$ − H_2O, 197.0814); *m*/*z* 179.0708 ([M + H]$^+$ − 2H_2O) (calcd for $C_{10}H_{11}O_3$ [M + H]$^+$ − 2H_2O, 179.0708).

*1-n-Butyl-4-methyl-2-hydroxysuccinate (**6a**) and 1-n-butyl-4-methyl-3-hydroxysuccinate (**6b**) mixture:* oil; UV (MeOH) λ_{max}, nm, 199, 228; IR (film) ν_{max}, cm^{-1}, 3354 (OH), 2927 (CH), 2887 (CH), 1742 (C═O), 1187 (C—O), 1046 (C—O); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.48 (1H, dd, *J* = 10.4, 4.4 Hz, H-2/H-3), 4.19 (1H, m) and 4.09 (1H, t, *J* = 6.6 Hz) (H-1′), 3.78 and 3.69 (each 3H, s, COOMe), 2.80 (2H, m, H-3/H-2), 1.60 (2H, m, H-2′), 1.36 (2H, m, H-3′), 0.92 (3H, t, *J* = 7.5 Hz, H-4′); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 173.5 and 173.1 (s, C-4), 170.6 and 170.3 (s, C-1), 67.45 and 67.41 (d, C-2/C-3), 66.0 and 65.0 (t, C-1′), 52.9 and 52.1 (q, OMe), 38.94 and 38.85 (t, C-3/C-2), 30.82 and 30.76 (t, C-2′), 19.39 and 19.32 (t, C-3′), 14.00 and 13.96 (q, C-4′); HRMS (ESI) *m*/*z* 227.0880 ([M + Na]$^+$) (calcd for $C_9H_{16}O_5Na$ [M + Na]$^+$, 227.0895).

RESULTS AND DISCUSSION

The *n*-butanol partition of the fruit juice of *M. citrifolia*, obtained from Puerto Rico, was fractionated by flash chromatography over silica gel, and the column fractions were purified by centrifugal preparative TLC followed by analysis using tubeless NMR and UV-HRMS of isolated pure compounds in different fractions, which yielded compounds **1**−**6** (**Figure 1**). Among these compounds, **4**, **5** (*6*), and a mixture of α- and *β*-glucose were obtained as major marker constituents.

Compound **1** was obtained as a colorless powder, and its molecular formula was determined as $C_{11}H_{20}O_6$ by ESI-HRMS (*m*/*z* 247.1193 ([M − H]$^-$). The ^{1}H NMR spectrum (see **Table 1**) demonstrated two terminal methylene protons at δ 4.77 and 4.78 (each 1H, s; δ_{C-4} 110.7, t, and δ_{C-3} 142.4, s), one methyl group (δ 1.78, 3H, s; δ_{C-5} 22.0), oxymethylene protons at δ 4.03 (1H, dd, *J* = 7.7, 17.0 Hz) and δ 3.69 (1H, m; δ_{C-1} 68.1), and methylene protons at δ 2.38 (2H, t, *J* = 7.7 Hz; δ_{C-2} 37.6), attributed to the *O*-(3′-methylbut-3′-enyl) unit of **1**. In addition, the ^{1}H NMR spectrum showed an anomeric proton at δ 4.30 (1H, d, *J* = 7.7 Hz, H-1′) and six oxygenated protons between δ 3.20 and 3.90, attributed to a *β*-D-glucopyranose unit, which was supported by the ^{13}C NMR signals at δ_C 102.6, 73.8, 76.8, 70.4, 76.6, and 61.6, assigned to C-1′−C-6′, respectively (*8*). The gross structure of the glycoside was assigned as **1**, which was confirmed by the detailed 2D NMR COSY, HMQC, and HMBC experiments. The COSY spectrum confirmed the spin correlations for glucose protons, whereas the HMBC spectrum demonstrated ^3J correlations between H-1′ (δ 4.30) and C-5′ (δ 76.6) and C-1 (δ 68.1) and between H-5 (δ 1.78) and C-2 (δ 37.6) and C-4 (δ 110.7). On the basis of the above data, the structure of **1** was assigned as 1-*O*-(3′-methylbut-3′-enyl)-*β*-D-glucopyranose.

Compound **2** was isolated as a gum, which was homogeneous on TLC and analyzed as $C_{14}H_{18}O_6$ by ESI-HRMS ([M + Na]$^+$ 305.0989). The ^{1}H NMR spectrum (**Table 1**) showed a deshielded proton at δ 9.54 (1H, s; $\delta_{C-6'}$ 177.5), two aromatic protons at δ 7.22 and 6.51 (each 1H, d, *J* = 3.3 Hz; $\delta_{C-4'}$ 123.1 and $\delta_{C-3'}$ 110.0, respectively), and an oxymethylene signal at δ 4.70 (2H, s; $\delta_{C-7'}$ 57.6), attributable to a hydroxymethyl furaldehyde base structure of **2**. In addition, the ^{1}H NMR spectrum exhibited a primary methyl group at δ 0.91 (3H, t, *J* = 7.0 Hz; $\delta_{C-4''}$ 14.0), two methylenes at δ 1.60 and 1.36 (each 2H; $\delta_{C-2''}$ 30.9 and $\delta_{C-3''}$ 19.4, respectively), and oxymethylene protons at δ 4.08 (2H, t, *J* = 7.0 Hz; $\delta_{C-1''}$ 64.9), assigned to the *n*-butyloxy side chain. The ^{1}H NMR spectrum also revealed four additional protons for two methylene groups centered at δ 2.65 and 2.62 (each 2H, m; δ_{C-3} 29.4 and δ_{C-2} 29.2, respectively), which were assigned to C-3 and C-2 by HMBC correlations (vide infra). The ^{13}C NMR spectrum showed four oxygenated quaternary carbons at δ_{C-4} 176.1, δ_{C-1} 172.3, $\delta_{C-2'}$ 160.7, and $\delta_{C-5'}$ 152.0; the first two were attributed to two ester carbonyls, whereas the latter two were assigned to the furaldehyde ring system. The 2D NMR COSY, HMQC, and HMBC spectra confirmed the structure of **2**. The COSY spectrum exhibited spin systems for 2-hydroxymethyl-5-formylfuran and *n*-butyloxy substructures. The HMBC spectrum showed key

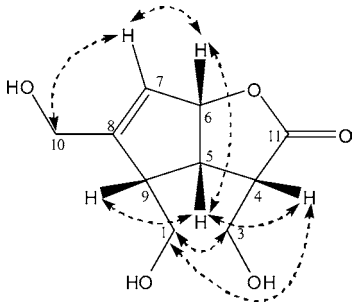

Figure 2. ^{1}H–^{1}H NOESY correlations of 4-*epi*-borreriagenin **3**.

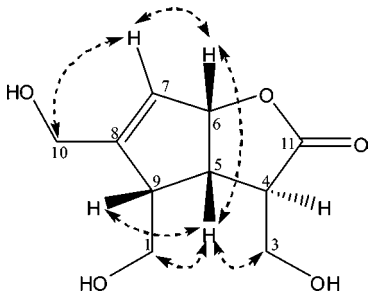

Figure 3. NOE correlations of borreriagenin by irradiation method (*9*).

correlations between H-3′ and C-2′, C-4′, and C-5′; between H-4′ and C-2′, C-3′, and C-5′; between H-7′ and C-2′ and C-3′; and between H-6′ (δ 9.54) and C-5′, confirming the attachments of the C-5′ formyl and C-2′ hydroxymethyl substituents of the furyl ring. In addition, HMBC also showed correlations between H-1″ and C-1, C-2″, and C-3″ and between H-3/H-2 and C-4 and C-1. On the basis of the above discussion, the structure of **2** was assigned as 1-*n*-butyl-4-(5′-formyl-2′-furyl)methyl succinate.

Compound **3** was isolated as a colorless solid. The ESI-HRMS of **3** exhibited ions for $[M + Na]^+$, together with $[M + H]^+ - H_2O$ and $[M + H]^+ - 2H_2O$ due to loss of one or two molecules of H_2O, respectively. Its ^{1}H and ^{13}C NMR spectral data (**Table 1**) were generally very similar to those reported for borreriagenin, isolated previously from *Borreria verticillata* (Rubiaceae) (*9*), except for the differences associated with the multiplicities of protons H-4, H-6, H-7, H-9, and H-10, as well as key NOESY correlations involving H-4 and H-5 (**Figure 2**). A complete analysis of 2D NMR COSY, HMQC, and HMBC spectra suggested its gross structure. The 2D NMR ^{1}H−^{1}H NOESY correlations of **3** appear to be different from those reported for borreriagenin by Vieira et al. (*9*). Thus, **3** showed NOESY correlations between protons H-5, H-4, H-6, and H-9, suggesting that these protons are *cis* to each other and on the β-face of the molecule, whereas borreriagenin (*9*) demonstrated NOE correlation (**Figure 3**), using an irradiation method, between protons H-5, H-6, and H-9, but no correlation between H-4 and H-5; thereby, H-4 was placed on the other side (α-face, 4*R*) of the molecule (*9*). Molecular modeling indicates that the NOESY correlations between H-4 and H-5 (2.3 Å) and between H-5 and H-9 (2.3 Å) are consistent with a 4*S*,5*S*,9*S* configuration as depicted in **3**. (Molecular modeling was done using CS Chem 3D Pro version 5.0 MM2 molecular dynamics minimization followed by MM2 steric minimization. The software was obtained from CambridgeSoft Corp., Cambridge, MA.) This was further substantiated by the coupling constant of $J = 9.1$ Hz between H-4 and H-5 protons, which was in agreement with the estimated J values of ~8.6 Hz, calculated from the dihedral angle ($\varphi = 15.1°$) of H-4 and H-5. In addition, **3** did not show any correlations between H-5 and H-3 (as observed for borreriagenin), whereas it exhibited correlations between H-1 and H-3 (suggesting their placement on the α-face) and between H-4 and H-1, due to their close spatial proximity according to the analysis of the molecular model. Thus, the structure of compound **3** was assigned as 4-*epi*-borreriagenin with 4*S*,5*S* configuration, which is a diastereoisomer of borreriagenin.

During the course of isolation of compounds **1**−**5**, a mixture of 1-*n*-butyl-4-methyl-2-hydroxysuccinate (**6a**) and 1-*n*-butyl-4-methyl-3-hydroxysuccinate (**6b**) (*10*) and mixture of α- and β-glucose were also isolated from noni fruit juice from Puerto Rico. It is quite possible that compounds **6a** and **6b** could be degradation products or precursors of **2**. Furthermore, an examination of noni fruit juice collected in Okinawa, Japan, also yielded markers **1**−**6** in addition to scopoletin (**7**), which was not isolated from samples collected in the Atlantic (Puerto Rico) region. Among the isolated markers, compounds **1**−**3** were isolated for the first time from a natural sources, although compound **1** and a debutylated derivative of **2** had previously been synthesized (*11*, *12*), whereas the epimer of **3**, borreriagenin, had originally been isolated from *Borreria verticillata* (Rubiaceae) (*9*) and latter reported from *M. citrifolia* (*13*). The difference in composition of markers of noni juice from the Atlantic (Puerto Rico) and Pacific (Japan) regions was not significant. Both juices contained compounds **1**−**6** as their major markers; scopoletin (**7**), however, was present only in the sample from Japan.

ACKNOWLEDGMENT

We thank Dr. David Gangemi, INR, Clemson University, for providing noni juice and dried tissues collected in Okinawa, Japan, and Dr. Erdal Bedir for recording some NMR spectra.

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Received for review March 9, 2006. Revised manuscript received June 9, 2006. Accepted June 18, 2006. This work is supported in part by U.S. Department of Agriculture ARS Specific Cooperative Agreement 58-6408-2-0009.

JF060672U