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Flavanone Glycosides from *Miconia trailii*

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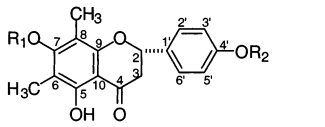
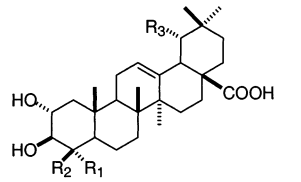
Assay-guided fractionation of the ethanol extract of the twigs and leaves of *Miconia trailii* yielded two new flavanone glycosides, matteucinol 7-*O*-α-L-arabinopyranosyl(1→6)-*β*-D-glucopyranoside (miconioside A, **1**) and farrerol 7-*O*-*β*-D-apiofuranosyl(1→6)-*β*-D-glucopyranoside (miconioside B, **2**), along with the known compounds matteucinol 7-*O*-*β*-D-apiofuranosyl(1→6)-*β*-D-glucopyranoside (**3**), matteucinol (**4**), 2α,3*β*,19α-trihydroxyolean-12-ene-24,28-dioic acid (bartogenic acid, **5**), 2α,3*β*,23-trihydroxyolean-12-ene-28-oic acid (arjunolic acid, **6**), 2α,3α,19α, 23-tetrahydroxyurs-12-ene-28-oic acid (myrianthic acid, **7**), and stigmast-4-ene-3,6-dione (**8**). The structures of **1**−**8** were elucidated by spectroscopic methods, including 2D NMR.

In the course of our screening program searching for fatty acid synthase inhibitors from higher plants,[1] an ethanol extract of a mixture of twigs and leaves of *Miconia trailii* Cogn. (Melastomataceae) was found to be active. *Miconia* is a large genus of 700 species of trees and shrubs native to tropical America and West Indies.[2] Previous phytochemical investigations of *Miconia* species have resulted in the isolation of triterpenes,[3,4] flavanones,[5,6] a quinone, and quinol compounds.[7] To our knowledge, no phytochemical work was reported on *M. trailii*.

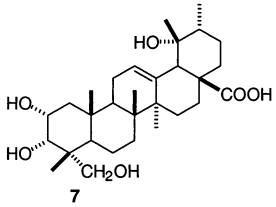
Bioactivity-guided fractionation of the active ethanol extract of *M. trailii* yielded two new flavanone glycosides (**1**, **2**) and six known compounds (**3**−**8**). We report herein the structure elucidation of the new flavanones and the biological evaluation of compounds **1**−**8**.



1 R_1 = α-L-Ara(1→6)-β-D-Glc, R_2 = CH_3
2 R_1 = β-D-Api(1→6)-β-D-Glc, R_2 = H
3 R_1 = β-D-Api(1→6)-β-D-Glc, R_2 = CH_3
4 R_1 = H, R_2 = H



5 R_1 = CH_3, R_2 = COOH, R_3 = OH
6 R_1 = CH_2OH, R_2 = CH_3, R_3 = H



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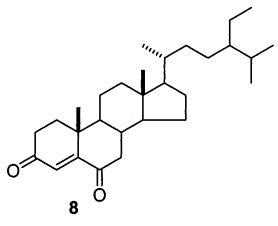

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Results and Discussion

Six known compounds were identified as matteucinol 7-*O*-*β*-D-apiofuranosyl(1 → 6)-*β*-D-glucopyranoside (**3**),[8] matteucinol (**4**),[9,10] 2α,3*β*,19α-trihydroxyolean-12-ene-24,28-dioic acid (bartogenic acid, **5**),[11,12] 2α,3*β*,23-trihydroxyolean-12-ene-28-oic acid (arjunolic acid, **6**),[13] 2α,3α,19α,23-tetrahydroxyurs-12-ene-28-oic acid (myrianthic acid, **7**),[14] and stigmast-4-ene-3,6-dione (**8**),[15,16] respectively, by comparison of their spectral data with published values. The ^{13}C NMR data for **5** are reported for the first time, although the ^{13}C NMR data for its dimethyl ester and diacetyl derivative were previously reported.[11,12]

Table 1. ^{13}C NMR Data (*δ*) for Compounds **1** and **2** (in CD_3OD)[a]

C	**1**	**2**	C	**1**	**2**
aglycone			6-CH_3	9.3	9.2
2	80.2	80.3	8-CH_3	10.0	9.9
3	44.4	44.4	4′-OCH_3	55.9	
4	199.9	199.8	Glc		
5	159.9	160.0	1″	105.1	105.4
6	113.2	113.1	2″	75.8	75.9
7	162.8	162.8	3″	78.3	78.2
8	112.1	112.2	4″	71.8	71.9
9	159.4	159.5	5″	77.9	77.2
10	106.6	106.6	6″	69.3	68.8
1′	132.6	131.5	Ara/Api		
2′	129.0	129.1	1‴	104.7	111.1
3′	115.2	116.5	2‴	72.4	78.1
4′	161.5	159.1	3‴	74.2	80.6
5′	115.2	116.5	4‴	69.6	75.1
6′	129.0	129.1	5‴	66.8	66.1

[a] The assignments were based upon DEPT, COSY, HMQC, and HMBC experiments.

Compound **1** was isolated as an optically active yellowish solid. HRESIMS analysis established its molecular formula as $C_{29}H_{36}O_{14}$, which is the same as **3**. It showed IR (3411 and 1633 cm^{-1}) and UV absorptions (230 and 282 nm) characteristic of a flavanone. The ^1H NMR spectrum of **1** showed signals due to two aromatic methyl groups at *δ* 2.12 (3H, s) and 2.11 (3H, s), a 4′-methoxyphenyl moiety at *δ* 3.81 (3H, s), 6.94 (2H, d, *J* = 8.6 Hz), and 7.42 (2H, d, *J* = 8.6 Hz), and an ABX-system [*δ* 2.78 (1H, dd, *J* = 2.5, 17.7 Hz), 3.12 (1H, dd, *J* = 13.0, 17.7 Hz), and 5.37 (1H, dd, *J* = 2.5, 13.0 Hz)] corresponding to a C-ring of a flavanone. These data indicated that the flavanone moiety was matteucinol (**4**).[6,8−10] The ^{13}C NMR and DEPT-135 spectra showed 29 carbon signals (Table 1); 18 of these signals were identical to those reported for matteucinol (**4**).[6,8−10] The remaining 11 signals were indicative of the presence of one hexose and one pentose. ^1H and ^{13}C NMR analyses suggested that **1** differed from **3** only in the sugar moiety.[8]

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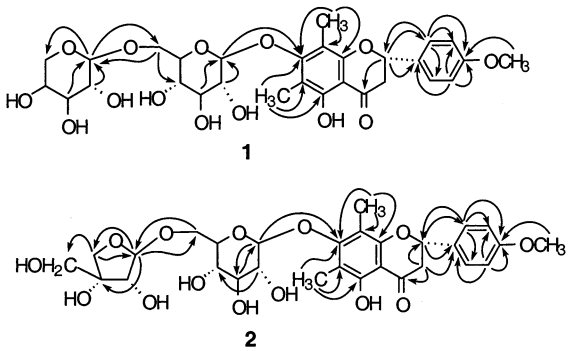

Figure 1. HMBC correlations of **1** and **2**.

Acid hydrolysis of **1** furnished matteucinol (**4**), glucose, and arabinose detected by co-TLC comparison with the authentic samples. The configuration of the anomeric carbons was defined as β for glucose and α for arabinose from their coupling constants of 7.6 and 6.7 Hz, respectively.[17] As observed in the HMBC spectrum (Figure 1), the long-range correlations of H-6″ (δ 3.70, 3.92) of glucose with C-1‴ (δ 104.7) of arabinose and H-1‴ (δ 4.12) of arabinose with C-6″ (δ 69.3) of glucose established the linked position between the two sugar moieties as α-L-arabinopyranosyl-(1 → 6)-β-D-glucopyranose. The glycosidation position was unambiguously determined by a three-bond correlation between the glucosyl anomeric proton H-1″ (δ 4.72) and ring A C-7 (δ 162.8) using HMBC. The absolute configuration at C-2 of the aglycone was determined to be *S* on the basis of the strong negative Cotton effect at 289 nm observed in the CD spectrum of **1**.[18] On the basis of the above evidence, the structure of **1** was established as matteucinol 7-*O*-α-L-arabinopyranosyl(1 → 6)-β-D-glucopyranoside, a new flavanone glycoside named miconioside A.

Compound **2** was obtained as a yellowish amorphous solid. Its UV, IR, and CD spectral data (Experimental Section) were similar to those of **3**. HRESIMS of **2** displayed an ion at *m/z* 617.1879 $[M + Na]^+$, corresponding to a molecular formula of $C_{28}H_{34}O_{14}$, 14 mass units less than **3**. Comparison of the ^1H and ^{13}C NMR data (Tables 1 and 2) of **2** with **3** indicated the absence of the methoxyl group (δ 3.81, 3H, s) in **3**. The sugar moieties were determined to be glucose and apiose from ^1H and ^{13}C NMR data. A β-D-apiofuranosyl moiety was recognized by the NMR signals of C-1‴ (δ_C 111.1) and H-1‴ (δ_H 4.93, d, J = 1.4 Hz), along with one oxyquaternary carbon at δ 80.6 (C-3‴), two oxymethylenes at C-4‴ (δ_C 75.1, δ_H 3.71 and 3.78, each 1H, d, J = 10.0 Hz) and C-5‴ (δ_C 66.1, δ_H 3.53, 2H, s), and one oxymethine at C-2‴ (δ_C 78.1, δ_H 3.85, 1H, d, J = 1.4 Hz) (Tables 1 and 2). These data were in agreement with the reported values.[19] HMQC and HMBC correlations (Figure 1) allowed for the complete assignments of the proton and carbon signals of **2**. Thus, the structure of **2** was established as farrerol 7-*O*-β-D-apiofuranosyl(1→6)-β-D-glucopyranoside, a new flavananone glycoside named miconioside B.

Compounds **1**−**8** were evaluated against fatty acid synthase (FAS) inhibition.[1] The results showed that only **1** had a weak inhibitory effect against FAS with an IC_{50} value of >50 μg/mL. Cerulenin was used as a positive control (IC_{50} of 0.19 μg/mL). We concluded that the observed activity in the crude ethanol extract (IC_{50} of 90 μg/mL) was probably attributable to the contribution of the nonselective inhibitory effects of unknown polyphenols or other compounds present.

Experimental Section

General Experimental Procedures. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Optical rotations were determined on a Jasco DIP-370 digital polarimeter. CD spectra were recorded on a Jasco J 715 spectropolarimeter. UV spectra were recorded on a Hewlett-Packard 8435 spectrometer. IR spectra were obtained on an ATI Mattson Genesis Series FTIR spectrometer. The NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C. 2D NMR spectra were measured on a Bruker Avance DRX-500 operating at 500 MHz using 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. Silica gel (40 μm, J. T. Baker) and RP silica 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 (4:1, solvent A), toluene/EtOAc/MeOH (4:1:1, solvent B), and $CHCl_3$/EtOAc (6:1, solvent C) or reversed-phase KC_{18} F Si gel 60 (Whatman) using MeOH/H_2O (70:30, solvent D). The detailed procedures for the bioassays are described in a previous paper.[1]

Table 2. ^1H NMR Data (δ) for Compounds **1** and **2** (in CD_3OD)

H	1	2
aglycone		
2	5.37 (1H,dd, 2.5, 13.0 Hz)	5.40 (1H, m)
3	2.78 (1H, dd, 17.7/2.5 Hz),	2.81 (1H, dd,17.2/2.5 Hz)
	3.12 (1H, dd, 17.7/13.0 Hz)	3.19 (1H, dd, 17.2/12.8 Hz)
2′	7.42 (1H, d, 8.6 Hz)	7.40 (1H, d, 8.4 Hz)
3′	6.94 (1H, d, 8.6 Hz)	6.87 (1H, d, 8.4 Hz)
5′	6.94 (1H, d, 8.6 Hz)	6.87 (1H, d, 8.4 Hz)
6′	7.42 (1H, d, 8.6 Hz)	7.40 (1H, d, 8.4 Hz)
6-CH_3	2.12 (3H, s)	2.19 (3H, s)
8-CH_3	2.11 (3H, s)	2.17 (3H, s)
4′-OCH_3	3.81 (3H, s)	
Glc		
1″	4.72 (1H, d, 7.6 Hz)	4.72 (1H, d, 7.7 Hz)
2″	3.51(1H, m)	3.56 (1H, m)
3″	3.43 (1H, m)	3.44.(1H, m)
4″	3.36 (1H, m)	3.37 (1H, m)
5″	3.34 (1H, m)	3.35 (1H, m)
6″	3.70 (1H, d, 11.8 Hz)	3.63
	3.92 (1H, d, 11.8 Hz)	3.91
Ara/Api		
1‴	4.12 (1H, d, 6.7 Hz)	4.93 (1H, d, 1.4 Hz)
2‴	3.45 (1H, m)	3.85 (1H, d, 1.4 Hz)
3‴	3.32 (1H, m)	
4‴	3.70 (1H, m)	3.71 (1H, d, 10.0 Hz),
		3.78 (1H, d, 10.0 Hz)
5‴	3.45 (1H, m)	3.53 (2H, s)
	3.80 (1H, m)	

Plant Material. *Miconia trailii* (twig, leaf) used in this study was collected by Manuel Rimachi in Loreto, Peru, in June of 1999 and identified by Sydney McDaniel. A voucher specimen is on deposit at the Herbarium of Mississippi State University (voucher #IBE 12272).

Extraction and Isolation. The dried powdered plant material (370 g) was extracted by percolation with 95% EtOH (3000 mL × 3). The extracts were combined and concentrated in vacuo to dryness (10.1 g, IC_{50} 90 μg/mL). Part of the ethanolic extract (9.05 g) was chromatographed over a silica gel column (360 g) and eluting with $CHCl_3$/MeOH (9:1, 4:1, 2:1, and 0:1, each 1000 mL) to afford six fractions: A (0.1 g, 0−400 mL), B (2.8 g, 400−800 mL), C (0.62 g, 800−1600 mL), D (0.8 g, 1600−2000 mL, IC_{50} 120 μg/mL), E (1.96 g, 2000−2400 mL, IC_{50} 40 μg/mL), and F (2.80 g, 2400−4000 mL). Part of the most active fraction, E (1.07 g), was rechromatographed over a silica gel column (60 g) eluting with $CHCl_3$/MeOH (4:1, 2:1, and 0:1, each 500 mL) to give E_1 (26.6 mg, 0−135 mL), E_2 (191.0 mg, 135−300 mL), E_3 (60.0 mg, 300−465 mL), and E_4 (792.0 mg, 465−1500 mL). Further fractionation of fraction E_3 using a low-pressure ODS column (15 g) and washing with MeOH/H_2O (60:40, 150 mL) afforded **2** (1.2 mg, 50−100 mL)

and a mixture (33 mg, 100−150 mL). The mixture was further purified by silica PTLC using $CHCl_3$/MeOH (4:1) to yield **1** (25 mg) and **3** (3.3 mg).

Part of fraction D (635 mg) was further purified on a silica gel column (60 g) and eluting with $CHCl_3$/MeOH (9:1, 4:1, 0:1, each 500 mL) to afford D_1 (150 mg, 0−425 mL), D_2 (137 mg, 425−525 mL), **1** (30 mg, 525−625 mL), and D_3 (340 mg, 625−1500 mL). Part of fraction D_2 (100 mg) was rechromatographed using a low-pressure ODS column (30 g) and eluting with MeOH/H_2O (50:50, 80:20, 0:100, each 200 mL) to give D_4 (58 mg, 200−400 mL). Fraction D_4 was further purified by a low-pressure ODS column (20 g) and washing with MeOH/H_2O (60:40, 120 mL) to afford **5** (2 mg, 10−20 mL), **6** (5 mg, 70−80 mL), and **7** (7.5 mg, 40−50 mL).

Part of the less polar fraction B (1.0 g) was chromatographed on a silica gel column (50 g) eluting with $CHCl_3$/MeOH (1:0, 1:1, 0:1, each 350 mL) to give fraction B_1 (80 mg, 175−315 mL). Refractionation of B_1 using a low-pressure ODS column (15 g) and washing with MeOH/H_2O (95:5, 100:0, each 120 mL) afforded B_2 (20 mg, 40−200 mL) and B_3 (7 mg, 200−240 mL). Compound **4** (20 mg) was crystallized from fraction B_2, and **8** (3 mg) was obtained from fraction B_3 by preparative TLC (Si gel, toluene/EtOAc, 9:1).

The structures of the known compounds (**3**−**8**) were identified by comparison of their spectral data with literature values.

Miconioside A (1): yellowish amorphous solid; $[\alpha]^{22}_D$ −18.9° (*c* 0.33, MeOH); UV (MeOH) λ_{max} (log ϵ) 206 (3.33), 230 (3.31), 282 (3.06), 360 (2.44) nm; IR (KBr) ν_{max} 3411, 1633, 1513, 1479, 1344, 1249, 1170, 1122, 1058, 1033 cm^{-1}; CD (*c* 0.41 × 10^{-3} M, MeOH) $[\theta]_{251}$ + 2946 (max), $[\theta]_{289}$ − 20493 (max), $[\theta]_{353}$ + 6196 (max); ^{13}C and ^1H NMR data (Tables 1 and 2); HRESIMS *m*/*z* 631.2032 $[M + Na]^+$ (calcd for $C_{29}H_{36}O_{14}$Na, 631.1997); R_f 0.33 and 0.21 (Si gel, solvents A and B), 0.43 (reversed-phase KC18 F, solvent D).

Miconioside B (2): yellowish amorphous solid; $[\alpha]^{22}_D$ −23.2° (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ϵ) 206 (3.43), 230 (3.15), 282 (3.08), 362 (2.49) nm; IR (KBr) ν_{max} 3413, 1632, 1513, 1445, 1343, 1248, 1170, 1121, 1060, 1034 cm^{-1}; CD (*c* 0.42 × 10^{-3} M, MeOH) $[\theta]_{251}$ + 1091 (max), $[\theta]_{289}$ − 7703 (max), $[\theta]_{354}$ + 3521 (max); ^{13} C and ^{1}H NMR data (Tables 1 and 2); HRESIMS *m*/*z* 617.1879 $[M + Na]^+$ (calcd for $C_{28}H_{34}O_{14}$Na, 617.1846); R_f 0.17 and 0.13 (Si gel, solvents A and B), 0.62 (reversed-phase KC18 F, solvent D).

2α,3*β*,19α-Trihydroxyolean-12-ene-24, 28-dioic acid (5): colorless amorphous powder; mp 314−315 °C; $[\alpha]^{22}_D$ +58° (*c* 0.2 MeOH) (lit.[13] mp 318 °C; $[\alpha]^{22}_D$ + 118°); IR (KBr) ν_{max} 3413, 2933, 1692, 1459, 1384, 1269, 1045 cm^{-1}; ^1H NMR (CD_3-OD) δ 0.90 (3H, s, CH_3-26), 0.94 (3H, s, CH_3-29), 1.01 (3H, s, CH_3-30), 1.02 (3H, s, CH_3-25), 1.30 (3H, s, CH_3-27), 1.37 (3H, s, CH_3-23), 2.75 (1H, d, J = 9.5 Hz, H-3), 3.23 (1H, br s, H-18), 3.28 (1H, d, J = 3.7 Hz, H-19), 4.08 (1H, m, H-2), 5.33 (1H, br s, H-12); ^{13}CNMR (CD_3OD) δ 187.0 (C-28), 184.8 (C-24), 146.4 (C-13), 124.6 (C-12), 85.7 (C-3), 83.9 (C-19), 70.3 (C-2), 58.9 (C-5), 51.2 (C-4), 49.1 (C-9), 48.9 (C-1[a]), 48.2 (C-17), 46.7 (C-18), 43.2 (C-14), 41.1 (C-8), 40.2 (C-10), 36.5 (C-20), 35.1 (C-16[b]), 35.0 (C-7[b]), 30.6 (C-21), 30.2 (C-15), 29.7 (C-22), 29.4 (C-29), 26.4 (C-23), 26.0 (C-30), 25.5 (C-11), 25.4 (C-27), 22.3 (C-6), 18.6 (C-26), 16.1 (C-25); R_f 0.45 and 0.25 (Si gel, solvents A and B), 0.88 (reversed-phase KC18 F, solvent D). [a]Signal was overlapped by solvent, and [b]data may be interchangeable.

Acid Hydrolysis of 1. Compound **1** and the sugar authentic samples (glucose and arabinose) were spotted on a silica gel TLC plate and hydrolyzed in situ by exposure to HCl vapor at 70 °C for 25 min. The TLC plate was then developed with $CHCl_3$/MeOH/AcOH/H_2O (14:6:2:1) and sprayed with 10% H_2SO_4 for detection. Glucose and arabinose were detected with R_f values of 0.19 and 0.23, respectively, while matteucinol (**4**) was detected with an R_f value of 0.62.

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