Lipoxygenase Inhibitory Constituents of the Fruits of Noni (*Morinda citrifolia*) Collected in Tahiti

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A phytochemical study of the fruits of noni (*Morinda citrifolia*) collected in Tahiti led to the isolation of two new lignans, (+)-3,4,3′,4′-tetrahydroxy-9,7′α-epoxylignano-7α,9′-lactone (**1**) and (+)-3,3′-bisdemethyltanegool (**2**), as well as seven known compounds, (−)-pinoresinol (**3**), (−)-3,3′-bisdemethylpinoresinol (**4**), quercetin (**5**), kaempferol (**6**), scopoletin (**7**), isoscopoletin (**8**), and vanillin. The structures of **1** and **2** were determined by spectroscopic techniques. Compounds **3**, **6**, and **8** were isolated for the first time from noni fruit. Compounds **1**−**8** were shown to inhibit 5- and/or 15-lipoxygenase, with IC_{50} values ranging from 0.43 to 16.5 μM. Compound **5** exhibited weak inhibitory activity toward cyclooxygenase-2.

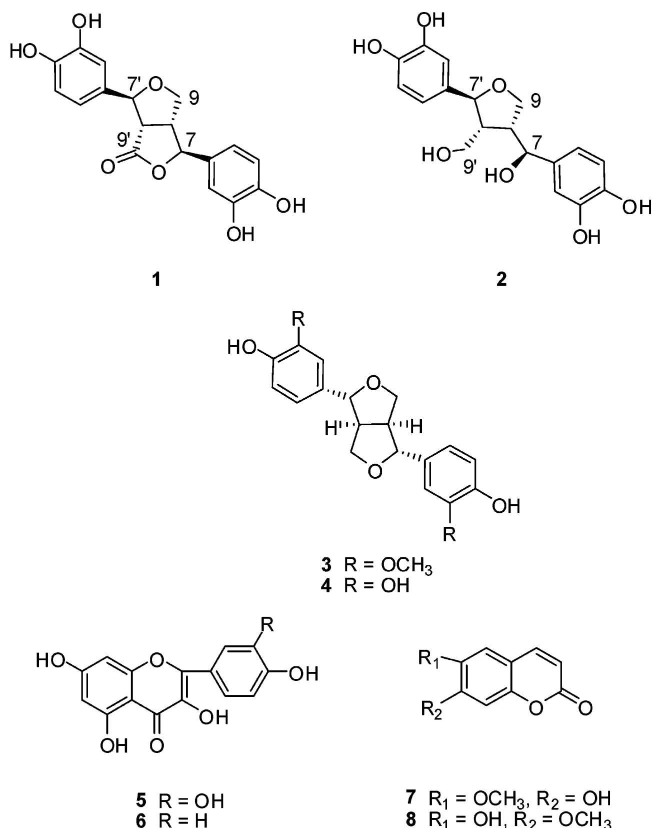
Morinda citrifolia L. (Rubiaceae) is a small tropical evergreen shrub or tree indigenous to the Pacific Islands, Southeast Asia, and other tropical and semitropical areas. Commonly called Indian Mulberry, or noni, the fruits have been used as folk medicine for thousands of years for the alleviation of many diseases including cancer, colds, diabetes, flu, hypertension, and pain.[1] In recent years, noni fruit juice has increased greatly in worldwide popularity as a dietary supplement or food.

Several classes of compound have been isolated from noni fruits, including amino acids, anthraquinones, coumarins, fatty acids, flavonoids, iridoids, lignans, polysaccharides, sterols, sugars, sulfur-containing compounds, and terpenoids.[2−9] Some of the isolates exhibited antioxidant activity, quinone reductase induction, and inhibitory effects on copper-induced LDL oxidation.[6,8,9]

Many natural constituents from fruits and vegetables have been identified in vitro as inhibitors of cyclooxygenase-2 (COX-2) and 5- and 15-lipooxygenase (5-LO and 15-LO) enzymatic activities, thus exhibiting potential anti-inflammatory effects. Such compounds have been suggested as possible aids in the prevention of inflammatory disorders.[10−13] This paper reports the phytochemical investigation of potential anti-inflammatory constituents from the fruits of *M. citrifolia* in terms of their lipoxygenase inhibition.

The screening of LO/COX-2 inhibitors from the active EtOAc partition of *M. citrifolia* fruits was carried out by a series of chromatographic techniques and led to the isolation of two new lignans, (+)-3,4,3′,4′-tetrahydroxy-9,7′α-epoxylignano-7α,9′-lactone (**1**) and (+)-3,3′-bisdemethyltanegool (**2**), as well as seven known compounds. The structures of **1** and **2** were elucidated by 1D and 2D NMR spectroscopy and HRESIMS.

Compound **1**, isolated as a light brown resinous semisolid, showed a protonated ion at *m/z* 345.0954 in the positive-ion HRESIMS, corresponding to the empirical molecular formula $C_{18}H_{16}O_7$. The ^{1}H NMR spectrum exhibited an oxygenated methylene signal at δ 4.26 (1H, dd, J = 9.4, 7.0 Hz) and 3.98 (1H, dd, J = 9.4, 4.2 Hz), two oxygenated methine signals at δ 5.31 (1H, d, J = 3.6 Hz) and 5.16 (1H, d, J = 3.4 Hz), and two methane resonances at δ 3.26 (1H, m) and 3.58 (1H, dd, J = 9.0, 3.4 Hz). In addition, the presence of two 1,3,4-trisubstituted phenyl units (ABX systems) was indicated by signals at δ 6.77 (1H, d, J = 7.9 Hz), 6.69 (1H, dd, J = 7.9, 2.0 Hz), and 6.76 (1H, d, J = 2.0 Hz), as well as at δ 6.82 (1H, d, J = 1.8 Hz), 6.74 (1H, d, J = 7.8 Hz), and 6.72 (1H, dd, J = 7.8, 1.8 Hz). The COSY spectrum of compound **1** revealed the presence of the moiety $-CH_2-CH(CH)-CH-CH-$, which corresponds to positions C-7, -8, -9, -7′, and -8′ in a dioxabicyclo[3.3.0]octane skeleton. Its ^{13}C and DEPT NMR spectra indicated the presence of 18 carbons, including an ester carbonyl group (δ 179.9), two oxygenated methine groups (δ 87.2 and 85.2), two non-oxygenated methine groups (δ 52.0 and 54.5), and 12 aromatic carbons in the range δ 114.0 to 147.0. The ^{1}H and ^{13}C NMR spectroscopic data of compound **1** (Table 1) resembled those of graminone A.[14]



In the HMBC spectrum of **1**, the following key correlations were observed: H-7 → C-2, C-6, C-9, C-8′, and C-9′; H-8 → C-1, C-7′, and C-9′; H-9 → C-7 and C-8′; H-7′ → C-8, C-9, C-2′, C-6′, and C-9′; H-8′ → C-7, C-9, and C-1′ (Table 1). The relative configuration of compound **1** was established by the analysis of coupling constants in the ^{1}H NMR spectrum and from the NOESY spectroscopic data. The coupling constants of H-7 (J = 3.6 Hz) and H-7′ (J = 3.4 Hz) suggested that axial protons were present at

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Table 1. ^{1}H and ^{13}C NMR Spectroscopic Data (500 Mz, CD_3OD) for Isolates **1** and **2**[a]

	1			**2**		
position	δ_C	δ_H (J in Hz)	HMBC[b]	δ_C	δ_H (J in Hz)	HMBC[b]
1	132.7		5, 7, 8	130.2		5, 7, 8
2	114.0	1H, 6.76, d (2.0)	6, 7	112.9	1H, 6.82, d (1.8)	6, 7
3	147.1		5	145.0		5
4	146.7		2, 6	144.1		2, 6
5	116.6	1H, 6.77, d (7.9)		115.0	1H, 6.74, d (8.1)	
6	118.7	1H, 6.69, dd (7.9, 2.0)	2, 7	116.9	1H, 6.68, dd (8.1, 1.8)	2
7	87.2	1H, 5.31, d (3.6)	2, 6, 9, 8′	82.3	1H, 4.80, d (6.0)	2, 9, 9′
8	52.0	1H, 3.26, m	7, 9, 7′, 8′	50.1	1H, 3.34, m	9′
9	73.9	Ha: 4.26, dd (9.4, 7.0); Hb: 3.98, dd (9.4, 4.2)	7, 7′, 8′	69.4	Ha: 3.77, dd (8.3, 8.3); Hb: 3.29, dd (8.3, 8.3)	7
1′	133.5		5′, 7′, 8′	132.6		5′, 7′, 8′
2′	114.2	1H, 6.82, d (1.8)	7′	113.3	1H, 6.80, d (1.8)	7′
3′	147.0		5′	145.0		5′
4′	146.4		2′, 6′	144.6		2′, 6′
5′	116.4	1H, 6.74, d (7.8)		114.9	1H, 6.73, d (7.8)	
6′	118.4	1H, 6.72, dd (7.8, 1.8)	2′, 7′	117.8	1H, 6.69, dd (7.8, 1.8)	2′, 7′
7′	85.2	1H, 5.16, d (3.4)	8, 9, 2′, 6′	88.2	1H, 4.33, d (6.7)	2′, 9′
8′	54.5	1H, 3.58, dd (9.0, 3.4)	7, 8, 9, 7′	54.0	1H, 2.89, ddd (8.2, 6.7, 6.7)	9
9′	179.9		7, 8, 7′, 8′	70.7	Ha: 4.05, d (9.4); Hb: 3.82, dd (9.4, 6.7)	7, 7′

[a] Chemical shifts are shown in δ values (ppm) relative to TMS. Assignments and determination of multiplicities were aided by 2D NMR (COSY, HMQC, and HMBC). [b] HMBC correlations are from proton(s) to the indicated carbons.

these positions. The NOESY spectrum of compound **1** exhibited correlations between H-8 and H-8′, H-7 and H-9b, and H-8 and H-9a, which indicated that these protons are on the same face of the molecule and confirmed the relative configuration proposed (Figure S1, Supporting Information). On the basis of the above-mentioned data, compound **1** was identified as a previously unreported lignan, (+)-3,4,3′,4′-tetrahydroxy-9,7′α-epoxylignano-7α,9′-lactone.[15]

Compound **2** was obtained as a greenish-brown resinous semisolid. Its spectroscopic data (UV, IR, ^{1}H and ^{13}C NMR) were very similar to those of compound **1**, suggesting it was another lignan. Its molecular formula of $C_{18}H_{20}O_7$ was established on the basis of the observation of the protonated molecular ion peak at m/z 349.1265 in the HRESIMS (calcd for $C_{18}H_{21}O_7$, 349.1281). By comparing the ^{1}H NMR spectra of compounds **1** and **2**, the addition of two more oxygenated methylene proton signals at H-9′ [δ 4.05 (1H, d, $J = 9.4$ Hz) and 3.82 (1H, dd, $J = 9.4, 6.7$ Hz)] was evident in **2**. Further comparison of the ^{13}C NMR spectra of **1** and **2** indicated the absence of a carbonyl signal in **2**. The COSY spectrum suggested the presence of $-CH_2-CH(CH)-CH(CH)-CH_2-$ as a partial structure in the molecule of compound **2**. The gross structure of this isolate was fully elucidated by the HMBC spectrum, from the key correlations between H-7 and C-2, C-6, C-9, C-8′, and C-9′; H-7′ and C-2′, C-6′, and C-9′; and H-9′ and C-8 (Table 1). The relative configuration of **2** was revealed by the correlations between H-8 and H-8′, H-8 and H-9a, and H-7′ and H-9b, observed in the NOESY spectrum (Figure S1, Supporting Information). Its structure was also confirmed by comparison with (+)-tanegool, a 3,3′-dimethoxylated derivative of **2**, reported previously.[16] Accordingly, compound **2** was elucidated as a new compound, 9,7′-epoxylignan-3,4,7,3′,4′,9′-hexaol, also named 3,3′-bisdemethyltanegool.

In this study, anti-inflammatory activities of isolates from noni fruit were evaluated against a panel of key enzymes relating to inflammation, including COX-2, 5-LO, and 15-LO in in vitro assays, as summarized in Table 2. In the 15-LO assay, compounds **1**, **2**, **4**, and **5** were shown to be inhibitors, with IC_{50} values less than 1 μM. In the 5-LO assay, compounds **1**−**6** were found to inhibit the 5-LO enzyme with IC_{50} values ranging from 0.79 to 13.8 μM. In addition, compound **5** showed an inhibitory effect against the COX-2 enzyme activity with an IC_{50} value of 28.6 μM. These findings may contribute to the anti-inflammatory effects of noni fruit.

Table 2. Inhibitory Activities against the 5-LO, 15-LO, and COX-2 Enzymes of Isolates **1**−**8** from the Fruits of *M. citrifolia*

	IC_{50}[a] (μM)		
compound	5-LO	15-LO	COX-2
1	5.6	0.52	90.2
2	9.2	0.76	73.9
3	13.8	3.5	>100
4	5.9	0.52	>100
5	0.79	0.43	28.6
6	2.7	2.2	>100
7	>100	16.5	>100
8	>100	15.1	>100
nordihydroguaiaretic acid[b]	0.13		
PD-146176[b]		1.12	
rofecoxib[b]			0.12

[a] IC_{50} values represent concentration (μM) of samples to inhibit enzyme activities by 50%. Data represent average ± SD of triplicate determinations; [b] Positive controls.

In previous biological studies, quercetin (**5**) and kaempferol (**6**) were found to interfere with many stages in ecosanoid metabolism. They were reported to be inhibitors of COX-2 promotion, expression, or transcription in lipopolysaccharide-stimulated macrophages and other cell models, with IC_{50} values of less than 50 μM.[17,18] In addition, quercetin (**5**) was also found to inhibit COX-2 enzyme activities at a micromolar level and to be a potent 5-LO inhibitor ($IC_{50} = 0.8$ μM).[19,20] Two methylated metabolites of quercetin (**5**), isorhamnetin and tamarixetin, exhibited more potent inhibitory activity against prostaglandin E_2 production, suggesting quercetin (**5**) may exert its pharmacological effects via its metabolites.[21] Two recent studies on COX-1 inhibition by quercetin (**5**) produced different results ($IC_{50} = 8$ μM vs 44% inhibition at 200 μM).[19,22] In the present work, no significant inhibitory effects were observed for the COX-1 enzyme by quercetin (**5**) or on the COX-1 and -2 enzymes by kaempferol (**6**) ($IC_{50} > 100$ μM).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 °C. UV data were recorded on a Varian Cary 1C UV/vis spectrophotometer, and IR spectra were taken on a Thermo Nicolet Avatar 360 FT-IR spectrometer. All ^{1}H NMR and ^{13}C NMR data were recorded on a Varian INOVA-500 spectrometer using $CDCl_3$ or CD_3OD as solvents and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are expressed in ppm with reference to the TMS signal. The ^{1}H−^{1}H COSY, HSQC,

HMQC, NOESY, and HMBC experiments were performed using standard pulse sequences. High-resolution mass spectra (HRMS) were obtained on an Agilent 1100 series liquid chromatograph/mass selective detector (LC/MSD) time-of-flight (TOF) mass spectrometer (Agilent Technologies, Inc., Palo Alto, CA), equipped with an electrospray ion source (ESI). The spectrometer was operated in the positive-ion mode. Vacuum-liquid chromatography (VLC) was carried out on Merck silica gel 60 (200−400 mesh). Preparative HPLC was performed with a Waters Alliance 2690 separations module coupled to a Waters 2996 photodiode array (PDA) detector, utilizing a Waters XTerra preparative MS C_{18} OBD column (10 μm, 19 × 300 mm, Wexford, Ireland) at a flow rate of 5−6 mL/min. Analytical thin-layer chromatography (TLC) was carried out on Merck TLC plates (250 μm thickness; KGF Si gel 60 and KGF RP-18 Si gel 60), and compounds were visualized by spraying the dried plates with *p*-anisaldehyde−H_2SO_4−EtOH (1:1:48), followed by heating at 110 °C.

Plant Material. The fruits of *Morinda citrifolia* were collected from the Mataiea farm in the Tahitian Islands in June 2004 and identified by the Quality Control Department of Tahitian Noni International Inc. The fresh juice of *M. citrifolia* was dried using a lyophilizer. A reference sample of freeze-dried powder of fruits was deposited in TNI R&D lab (lot #52410). A fingerprint of the MeOH extract of the fruit powder was determined for reproducibility and quality control purposes (Figure S2, Supporting Information).

Extraction and Isolation. The freeze-dried powder of *M. citrifolia* fruits (2 kg) was percolated with 20 L of methanol. After evaporation of solvent, the MeOH extract was added to 3 L of H_2O, then partitioned sequentially against petroleum ether (3000 mL × 4), EtOAc (3000 mL × 3), and *n*-BuOH (2000 mL × 3) to afford petroleum ether (41.7 g), EtOAc (47.7 g), and *n*-BuOH (168.1 g) partitions. The residue was lyophilized to afford a dried aqueous partition. At a concentration of 100 μg/mL, the MeOH extract exhibited inhibitory activity against the COX-2 and LO enzymes (COX-2: 43%, COX-1: 15%, 5-LO: 27%, 15-LO: 80%). Among these partitions, bioactivity was concentrated in the EtOAc partition (COX-2: 85%, COX-1: 0%, 5-LO: 39%, 15-LO: 89%). The petroleum ether layer showed nonselective inhibition toward COX-2 (83%) and COX-1 (88%) enzymes. Both the *n*-BuOH and H_2O layers displayed less than 50% inhibition in these assays.

The EtOAc partition (30 g) was subjected to flash column chromatography (1 kg of silica gel, 200−400 mesh), eluting with a stepwise gradient solvent system of CH_2Cl_2−MeOH (98:2 → 0:100), to afford 13 pooled fractions (F1−F13). Fraction F9 (920 mg) was chromatographed over Sephadex LH-20 (180 g), eluting with isocratic MeOH to give six secondary fractions (F9-1 to F9-6). Fraction F9-5 (41 mg) was further separated by reversed-phase preparative HPLC, eluting with an isocratic solvent system of MeCN−MeOH−H_2O (15:15:70) at a flow rate of 6 mL/min, yielding compounds **1** (5.5 mg, t_R = 26.5 min), **2** (4.0 mg, t_R = 31.0 min), and **3** (6.4 mg, t_R = 36.0 min). Fraction F2 (500 mg) was fractionated over Sephadex LH-20 (180 g) to give four further secondary fractions, F2-1 to F2-4. Purification of fraction F2-3 (180 mg) was accomplished by reversed-phase preparative HPLC (isocratic 55% MeOH in H_2O, 5 mL/min), resulting in the isolation of compounds **4** (3.5 mg, t_R = 18.2 min), **7** (5.6 mg, t_R = 10 min), **8** (26.6 mg, t_R = 14.8 min), and **9** (4.0 mg, t_R = 20.1 min). Compound **5** (77 mg) was precipitated from fraction F8 at room temperature. Compound **6** (9.4 mg) was obtained from fraction F4 after purification over Sephadex LH-20 (180 g), eluted with MeOH.

3,4,3′,4′-Tetrahydroxy-9,7′α-epoxylignano-7α,9′-lactone (1): light brown, resinous semisolid; $[\alpha]_D^{25}$ +7.5 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ϵ) 230 (4.11), 282 (3.71) nm; IR ν_{max} (CH_2Cl_2) 3400 (OH), 2920, 1750 (CO_2R), 1675, 1520 (Ar), 1420, 1162, 1030, 830 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HRESIMS *m/z* 345.0954 $[M + H]^+$ (calcd for $C_{18}H_{17}O_7$, 345.0968).

3,3′-Bisdemethyltanegool (2): greenish-brown, resinous semisolid; $[\alpha]_D^{25}$+5.6 (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ϵ) 227 (4.08), 279 (3.53) nm; IR ν_{max} (CH_2Cl_2) 3404, 2922, 1675, 1580, 1435, 1270, 1171 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HRESIMS *m/z* 349.1265 $[M + H]^+$ (calcd for $C_{18}H_{21}O_7$, 349.1281).

The known compounds were identified by comparing their spectroscopic data with the published literature and/or with those of authentic samples as (−)-pinoresinol (**3**),[23,24] (−)-3,3′-bisdemethylpinoresinol (**4**),[6] quercetin (**5**), kaempferol (**6**),[25] scopoletin (**7**), isoscopoletin (**8**),[26] and vanillin. Isoscopoletin, kaempferol, and pinoresinol were isolated for the first time from noni fruits.

5- and 15-Lipoxygenase Inhibition Assays. Human peripheral blood mononuclear cells (PBMC) and rabbit reticulocytes were used in the 5-lipoxygenase (5-LO) and 15-lipoxygenase (15-LO) inhibition bioassays. The assays were conducted according to the protocols reported previously, with either linoleic acid or arachidonic acid as substrate.[27,28] LO activity was measured by quantifying immunodetectable leukotriene B4 (LTB_4) specifically with enzyme immunoassay (EIA) in the 5-LO assay or monitoring 13-hydroperoxy-9,11-octadecadienoic acid (13-HPODE) spectrophotometrically in the 15-LO assay. Nordihydroguaiaretic acid (NDGA) and PD-146176 were used as positive controls in the 5-LO and 15-LO assays, respectively. The results were expressed as either percentage inhibition or IC_{50} for test samples. The data represent the average ± SD of triplicate determinations.

Cyclooxygenase-1 and 2 Inhibition Assays. Both inhibition assays were performed by the methods described previously with minor modifications.[29,30] The cyclooxygenase (COX)-2 enzyme was purchased from Sigma (St. Louis, MO; cat. no. C-0858), the COX-1 enzyme was obtained from Taipei Blood Center in Taiwan, and the PGE_2 EIA kit was obtained from Amersham (cat. no. RPN 220). Human recombinant COX-2, expressed in insect Sf21 cells, and COX-1 from human platelets were used in their respective assays. The extract and partitions were dissolved in DMSO (Sigma) and tested at 100 μg/mL (final concentration). The pure compounds were initially tested at 30 μM. The IC_{50} values were determined if their activities were over 50% in the preliminary experiments. Test samples were preincubated with 0.12 μg/mL enzyme in modified Tris-HCl buffer at pH 7.7 (COX-2) and with cells (5 × 10^7/mL) in modified HEPES buffer pH 7.4 (COX-1) for 15 min at 37 °C. The reactions were initiated by addition of 0.3 μM arachidonic acid (COX-2) and 100 μM arachidonic acid (COX-1), respectively, for another 5 min incubation period, then terminated by further addition of 1 N HCl. An aliquot was then combined with the EIA kit for spectrophotometric determination of the quantity of PGE_2 formed. Rofecoxib and indomethacin were used as positive controls for the COX-2 and -1 assay, with IC_{50} values of 0.12 and 0.036 μM, respectively.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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