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Swietemahalactone, a rearranged phragmalin-type limonoid with anti-bacterial effect, from *Swietenia mahagoni*†

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Swietemahalactone (1), a novel rearranged phragmalin-type limonoid, was isolated from *Swietenia mahagoni*. The structure of 1 was established on the basis of extensive spectroscopic and X-ray crystallographic methods. Swietemahalactone exhibited antibacterial activity using the agar diffusion method. The key biogenetic pathway of 1 is the semipinacol rearrangement.

Swietenia mahagoni (Linn.) Jacq. (Meliaceae), a large, deciduous, and economically important timber tree native to the West Indies, is mainly cultivated in tropical areas, such as southern China, Malaysia, and India.[1] Traditionally, various parts of this plant have been used in the treatment of fever, diabetes, malaria, hypertension and tuberculosis, and as an abortifacient, antiseptic, astringent, depurative, purgative, and tonic.[2] Modern pharmacological studies have implied that genus *Swietenia* had anti-diabetes, anti-bacterial, and cytotoxic activities.[3]

The diversified structures and significant biological activities of limonoids from the Meliaceae plant have prompted continuous studies on this kind of metabolite.[4] Previous chemical investigations of this genus led to the isolation of more than 60 limonoids.[5] Some of the limonoids from this genus showed anti-inflammatory, antifungal, antioxidant, and antifeeding effects.[6]

To further discover structurally diverse and biologically significant compounds from *S. mahagoni*, we examined its leaves and branches, which led to the isolation of swietemahalactone (**1**), a novel rearranged phragmalin-type limonoid. The structure of **1** was confirmed by the 1D and 2D NMR of triacetylate (**1a**) and the X-ray crystallographic analysis of the *p*-bromobenzoate derivative (**1b**) (Fig. 1). Herein we describe the structure elucidation and propose a biosynthetic route of **1**. Swietemahalactone selectively exhibited significant antibacterial activity against Gram-negative bacteria *Escherichia coli* (minimal inhibitory concentration (MIC) 0.01 μM).

The air-dried powder of leaves and branches of *S. mahagoni* (dry weight 5 kg) was extracted with MeOH by refluxing and concentrated *in vacuo* to give a crude extract (500 g), which was then partitioned in succession with H_2O, *n*-hexane, EtOAc, and then *n*-BuOH. The EtOAc fraction (100 g) was repeatedly chromatographed on silica gel, RP-18 and Sephadex LH-20 (MeOH) to yield swietemahalactone (**1**, 250 mg) and 1-*O*-deacetyl-2α-hydroxykhayanolide E (**2**, 100 mg) (for details see the ESI†).

Compound **1** was assigned a molecular formula of $C_{27}H_{30}O_{10}$, which was confirmed by high resolution electronspray ionization mass spectroscopy (HRESIMS, *m*/*z* $[M + H]^+$ 515.1910, calcd. for $C_{27}H_{31}O_{10}$, 515.1917) and NMR data (Table 1). Its IR spectrum showed the presence of a hydroxyl group (3444 cm^{-1}), carboxylate (1728 cm^{-1}) and α,β-unsaturated lactone (1643 cm^{-1}).

Its ^1H NMR spectrum (Table 1) showed three tertiary methyl signals at δ_H 1.90 (s), 1.64 (s) and 1.25 (s), one methoxyl signal at δ_H 2.86 (s), and four sp^2 methine signals at δ_H 6.17, 6.54, 7.68 and 7.75. The ^{13}C NMR-DEPT spectra (Table 1) displayed 27 carbon signals, including five methyl groups (one methoxyl group at δ_C 52.4), three methylene groups, nine methine groups (two oxygenated methines at δ_C 83.0 and 71.8, and four sp^2 methines

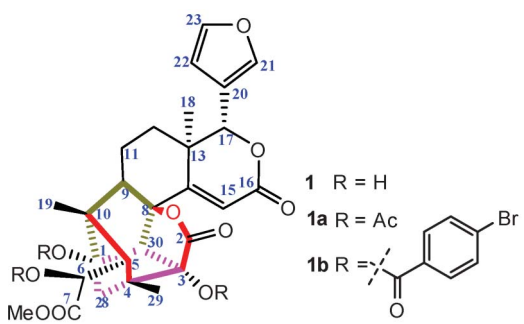

Fig. 1 The structures of **1**, **1a**, and **1b**.

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† Electronic supplementary information (ESI) available: Experimental procedures; 1D and 2D NMR spectra of swietemahalactone (**1**) and 1,3,6-*O*-triacetyl-swietemahalactone (**1a**); X-ray data of 1,3,6-tris(4-bromobenzoyl) swietemahalactone (**1b**). CCDC 900980. See DOI: 10.1039/c3ra23401k

Table 1 ^{1}H and ^{13}C NMR-DEPT data for **1** (600 Hz and 150 Hz, respectively, in pyridine-d_5)

No.	δ_C multi	δ_H (multi; J in Hz)	No.	δ_C multi	δ_H (multi; J in Hz)
1	91.9 s		15	115.4 d	6.17 (s)
2	177.2 s		16	165.1 s	
3	87.7 s		17	83.0 d	5.22 (s)
4	51.3 s		18	20.9 q	1.25 (s)
5	46.3 d	2.84 (d; 1.7)	19	15.9 q	1.64 (s)
6	71.8 d	4.93 (d; 3.3)	20	121.3 s	
7	176.6 s		21	142.5 d	7.75 (s)
8	91.0 s		22	111.1 d	6.54 (d; 1.2)
9	48.6 d	2.76 (dd; 12.1, 8.2)	23	144.1 d	7.68 (t; 1.6)
10	54.0 s		28	45.3 t	3.30 (d; 9.4); 2.86 (dd; 9.3, 1.3)
11	16.7 t	2.28 (dt; 12.7, 12.4, 9.8); 1.81–1.85 (m)	29	12.7 q	1.90 (s)
12	27.2 t	1.94–1.97 (m); 1.26–1.28 (m)	30	62.7 d	3.69 (s)
13	40.1 s		OMe	52.4 q	3.86 (s)
14	164.8 s				

at δ_C 144.1, 142.5, 115.4 and 111.1), and nine quaternary carbons (three oxygenated quaternary carbons at δ_C 91.9, 91.0 and 87.7, one sp^2 quaternary carbon at δ_C 164.8 and three carboxylate groups at δ_C 177.2 (s), 176.6 (s) and 165.1 (s)).

The above data show that the structure of **1** is similar to khayanolide C.[7] The A1, B, C, D and furan-ring fragments were deduced as those of khayanolide C by comparing the ^{13}C NMR data of **1** with khayanolide C, together with the analysis of the HMQC, HMBC, and ^{1}H–^{1}H COSY data of **1** (Fig. 2).

However, the ^{13}C NMR spectrum of **1** showed an ester carbonyl signal at δ_C 177.2 and a quaternary-carbon signal at δ_C 87.6 instead of one carboxyl signal (C-2) and one oxygenated methine signal (C-3) as in khayanolide C. In the HMBC spectrum, the correlations from δ_C 87.7 to H_3-29, H_2-28, H-5, and H-30 determined that the signal of δ_C 87.7 belonged to C-3. Furthermore, the correlations between H-30 and δ_C 177.2, C-3, C-8, C-9, and C-10 in the HMBC spectrum indicated that the signal of δ_C 177.2 pertained to C-2. Thus, the lactone in **1** may be located at C-2/C-8 or C-2/C-1. But it was difficult to determine whether it was 2,8-lacone or 2,1-lactone in **1** only by the 1D and 2D NMR spectra. Consequently, a triacetyl product, 1,3,6-triacetyl swietemahalactone (**1a**), was obtained by acetylation of **1** (for details see the ESI†).

The signals of H_3-18, H_3-19, and H_3-29 at δ_H 1.22, 1.07 and 1.13, respectively, were assigned by the HMQC and HMBC spectra of **1a** (for its 1D and 2D NMR data see the ESI†). Following that, H_3-18, H_3-19 and H_3-29 were found to be correlated with δ_C 82.3, 93.9 and 88.5 in the HMBC spectrum, respectively, which indicated that the above carbon signals belonged to C-17, C-1, and C-3, respectively. Finally, in the HMBC spectrum, two of the acetyl methyl signals were correlated with C-6 and C-3, and the other one was correlated with C-1. Therefore, three acetyl groups were assumed to be attached to OH-1, OH-3 and OH-6, respectively. Thus, compound **1** was a 2,8-lactone and the planar structure of **1** was deduced.

The relative configuration of **1** was determined on the basis of a ROESY experiment of **1a** (Fig. 3). H-9α showed remarkable correlations with H-11, H_3-18α, and H_3-19α, and H-5β exhibited correlation with H-11β. However, it was hard to determine the absolute configuration of C-6 and the relative configurations of O-8 and OH-3 in **1** by a ROESY experiment.

None but the single-crystal X-ray would be helpful to confirm the stereochemistry of **1**. However, compounds **1** and **1a** were not easy to crystallize in most kinds of organic solvents. Fortunately, the *p*-bromoxybenzoylation of **1** afforded 1,3,6-tris(4-bromobenzoyl) swietemahalactone (**1b**) which crystallized in the CH_3OH–

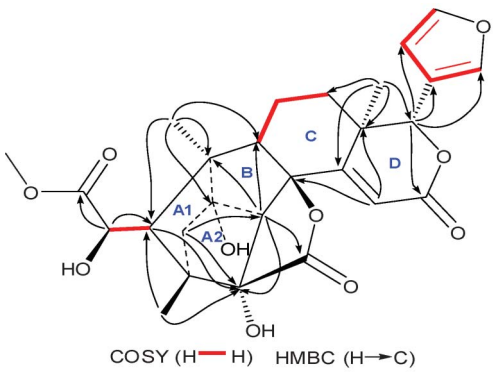


Fig. 2 Key COSY and key HMBC correlations of **1**.

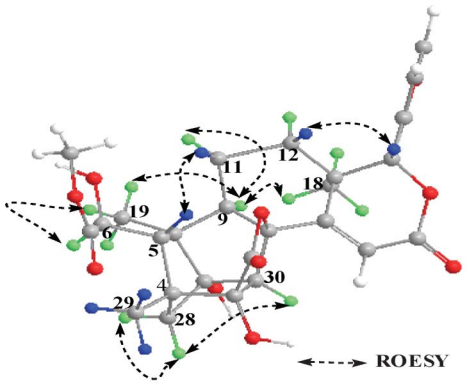


Fig. 3 Key ROESY correlations of **1a**.

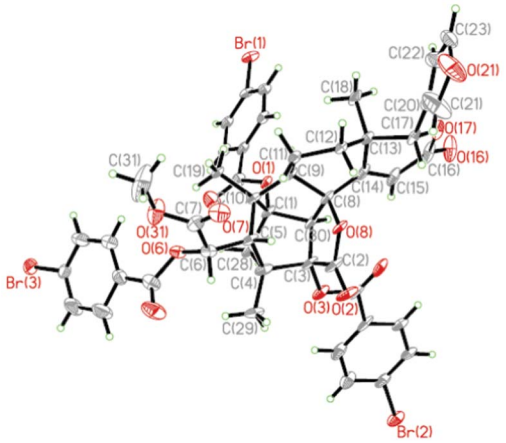
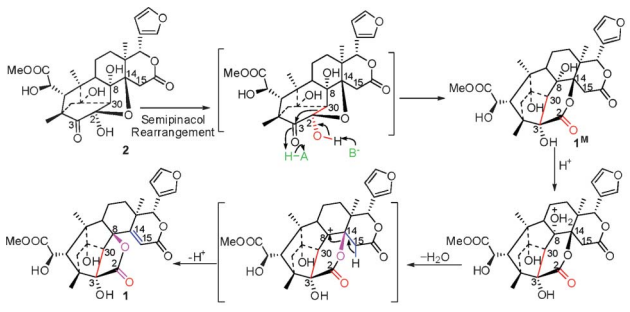


Fig. 4 Single-crystal X-ray structure of **1b**.

$CHCl_3$ (1 : 1) solvent.[8] Consequently, a single X-ray crystallographic diffraction of **1b** was conducted as shown in Fig. 4. Thus, the absolute configuration of C-6 was deduced as *S* and the relative configurations of OH-3 and O-8 were determined as α and β, respectively, by the standard anomalous scattering method. Finally, the structure of compound **1** was deduced and named as swietemahalactone.

Swietemahalactone (**1**) is a novel rearranged phragmalin-type limonoid. A plausible biosynthetic origin of **1** from 1-*O*-deacetyl-2α-hydroxykhayanolide E (**2**) was proposed (Scheme 1). **2** was found to be widely distributed in the leaves and branches of *S. mahagoni* and therefore considered to be a plausible biosynthetic precursor of **1**.

Semipinacol rearrangement, wildly used in natural product synthesis, is a special type of pinacol rearrangement in which an electrophilic carbon center is vicinal to an oxygen-containing carbon and can drive the 1,2-migration of a C–C or C–H bond to terminate the process, generating a carbonyl group.[9] This type of reaction was proposed to occur during the biosyntheses of various secondary metabolites, including aurachin B, aflatoxin B1, (+)-liphagal, (+)-asteltoxin, brevianamides, paraherquamide B, verscicolamide B, and notoamides.[10] Considering that C-3 in **2** is an electrophilic carbon center and C-2 in **2** is an oxygen-containing carbon, compound **2** could be transformed into $\mathbf{1^M}$ by the semipinacol rearrangement. Then, the $\mathbf{1^M}$ intermediate undergoes an acid catalyzed dehydration to produce **1**.



Scheme 1 Proposed biosynthetic pathway of **1**.

Table 2 Antimicrobial activities of compound **1**

	Zones of inhibition [mm]/MIC [μM]				
	E. coli	*S. aureus*	*P. aeruginosa*	*S. epidermidis*	*B. subtilis*
1	20/0.010	15/0.160	16/0.130	12/0.380	12/0.380
2[a]	30/0.0004	25/0.0031	24/0.0111	26/0.0045	22/0.0120

[a] Norfloxacin, as a positive control.

The insecticidal[11] and cytotoxic[12] activities of **1** were tested *in vitro*. However, **1** did not display cytotoxicity against HL-60, SMMC-7721, A-549, MCF-7, and SW480 cell lines (IC_{50} > 40 μM), and did not exhibit insecticidal activity using *Artemia salina* L (LD_{50} > 100 μg ml^{-1}).

Considering that some limonoids display anti-bacterial activity,[13] compound **1** was further evaluated for antimicrobial activity against Gram-positive and negative bacteria *via* a microdilution assay (for details see the ESI†). From the antimicrobial test results (Table 2), **1** selectively exhibited significant antibacterial activity against Gram-negative bacteria *Escherichia coli* (ATCC 25922).

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