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Tetrahedron Letters

Tetrahedron Letters 48 (2007) 7480–7484

Swiemahogins A and B, two novel limonoids from *Swietenia mahogani*

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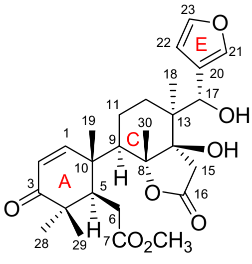
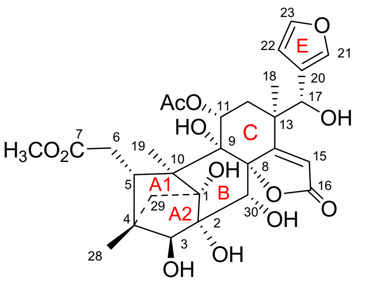
Received 20 June 2007; revised 16 August 2007; accepted 17 August 2007
Available online 22 August 2007

Abstract—Two novel limonoids, swiemahogins A (**1**) and B (**2**) isolated from the twigs and leaves of *Swietenia mahogany*, are the first examples of andirobin and phragmalin types of limonoids, of which the D-ring δ-lactone is demolished and a rare γ-lactone is fused to the C-ring at C-8 and C-14. Their structures were elucidated by extensive spectroscopic means, and that of **1** was confirmed by single-crystal X-ray diffraction.

The diversified structures and significant biological activities of limonoids from plants of the Meliaceae family have prompted continuous studies on this kind of metabolite.[1] *Swietenia mahagoni* (Linn.) Jacq. (Meliaceae), a large, deciduous, and economically important timber tree native to the west Indies, is mainly cultivated at tropical zone, such as India, Malaysia, and southern China.[1b,2] Its seeds have been applied as a folk medicine for the treatment of hypertension, diabetes, and malaria, while the decoction of its bark has been used as a febrifuge.[1b,3] Previous chemical investigations on this species from some countries such as India, Indonesia, and Egypt have led to the isolation of more than 40 limonoids belonging to the structural types of gendunin, mexicanolide, and phragmalin.[1b,4] However, the plants cultivated in China have not been chemically studied. In our present research, swiemahogins A (**1**) and B (**2**) that are the first examples of andirobin and phragmalin types of limonoids with a rare γ-lactone ring fused to the C-ring at C-8 and C-14 instead of the usual D- ring δ-lactone have been isolated from the twigs and leaves of *S. mahogany* collected from Hainan Island of China. We report herein the isolation and structural elucidation of swiemahogins A (**1**) and B (**2**).



1



2

The air-dried powder of the plant material (5.0 kg) was percolated with 95% EtOH (3 L × 3) to give 800 g of a crude extract, which was dissolved in 2.5 L of aqueous methanol (30%, v/v) to give a suspension, which was extracted successively with petroleum ether and $CHCl_3$. The $CHCl_3$ soluble extract (130 g) was subjected to a silica gel column eluted with petroleum ether and acetone in gradients (25:1 to 1:1) to afford eight fractions (Fr. 1–8) according to the TLC monitoring. Fr. 6 (22 g) was extensively chromatographed over columns of MCI gel, silica gel, and reversed-phase C_{18} silica gel to give a mixture containing two major compounds, which was further purified by semi-preparative HPLC using CH_3CN/H_2O (50:50, 3 mL/min) as mobile phase to afford swiemahogins A (**1**, 50 mg) and B (**2**, 5 mg).

Swiemahogin A (**1**),[5] a colorless crystal, showed the molecular formula of $C_{27}H_{36}O_8$ as determined by HREIMS at *m/z* 470.2296 $[M-H_2O]^+$ (calcd for $C_{27}H_{34}O_7$,

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Keywords: *Swietenia mahogani*; Meliaceae; Swiemahogins A and B; Limonoid; Single-crystal X-ray diffraction.

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doi:10.1016/j.tetlet.2007.08.066

470.2305), implying ten degrees of unsaturation. This assignment was supported by the pseudo molecular ion peaks at m/z 489 $[M+H]^+$ and 511 $[M+Na]^+$ in the positive mode of ESIMS. The IR absorption bands at 3361, 1761, 1726, and 1691 cm^{-1} implied the presence of hydroxyl(s), five-membered γ-lactone, ester carbonyl, and α,β-unsaturated ketone groups, respectively. The ^{13}C NMR and DEPT spectra displayed 27 carbon resonances comprising six methyls (one methoxyl), four methylenes, three sp^3 methines (one oxygenated), five sp^3 quaternary carbons (two oxygenated), three double bonds, and three carbonyl groups. Furthermore, the ^{1}H and ^{13}C NMR spectral data (Table 1) revealed the presence of five tertiary methyls, a β-substituted furyl ring, an α,β-unsaturated ketone, and one methoxyl group. Three double bonds and three carbonyl groups accounted for six out of the ten degrees of unsaturation, the remaining four degrees of unsaturation therefore indicated compound **1** being tetracyclic. The aforementioned data suggested that swiemahogin A possessed limonoid features.

Table 1. ^{1}H and ^{13}C NMR data of **1** and **2**[a]

Position	**1**		**2**	
	δ_C	δ_H (multi, J in Hz)	δ_C	δ_H (multi, J in Hz)
1	153.3	6.86 (d, 10.7)	84.3	
2	124.8	5.92 (d, 10.7)	76.8	
3	203.7		86.1	3.64 (s)[b]
4	46.0		43.8	
5	44.7	2.44 (m)[b]	39.8	2.89 (t like, 6.0)
6	32.2	a 2.24 (dd, 18.9, 5.4) b 2.47 (m)[b]	33.5	2.32 (d, 6.0, 2H)
7	174.9		172.7	
8	93.1		95.4	
9	51.4	1.64 (d, 10.7)	79.3	
10	43.9		53.1	
11α	21.5	1.46 (m)[b]	73.3	
11β		1.16 (m)[b]		5.56 (dd, 3.4, 11.6)
12α	33.3	1.19 (m)[b]	35.3	1.56 (dd, 11.6,13.1)
12β		1.48 (m)[b]		2.15 (dd, 3.9, 13.1)
13	41.9		44.9	
14	86.5		175.2	
15	42.2	α 2.30 (d, 17.0) β 2.80 (d, 17.0)	119.6	6.05 (s)
16	174.8		170.6	
17	70.6	5.19 (s)	67.7	5.45 (s)
18	17.0	0.96 (s, 3H)[b]	20.8	1.10 (s, 3H)
19	19.3	1.33 (s, 3H)	15.4	1.23 (s, 3H)
20	125.4		123.2	
21	140.6	7.34 (br s)[b]	141.1	7.73 (br s)
22	109.9	6.30 (br s)	110.0	6.65 (br s)
23	142.8	7.26 (br s)[b]	142.6	7.42 (br s)
28	23.0	1.00 (s, 3H)[b]	14.9	0.92 (s, 3H)
29	22.7	1.05 (s, 3H)	41.9	*pro-R* 1.61 (d, 11.2) *pro-S* 1.99 (d, 11.2)
30	16.0	1.77 (s, 3H)	65.0	4.90 (d, 5.6)
7-OMe	52.2	3.62 (s, 3H)	52.0	3.70 (s, 3H)
11-OAc			169.1	
			29.7	2.05 (s, 3H)
-OH		4.69 (br s, 14-OH) 6.66 (br s, 17-OH)		4.30 (br s, 1-OH) 2.80 (br s, 2-OH) 4.60 (br s, 3-OH) 3.40 (br s, 9-OH) 3.65 (br s, 17-OH)[b] 4.08 (br s, 30-OH)

[a] Data were recorded in $CDCl_3$ at 400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively.

[b] Proton signals were overlapped.

The 2D NMR spectra including HSQC and HMBC revealed that compound **1** had the same A-ring as that of turrapubesins A and B.[6] In the HMBC, the correlations of H-5/C-6 and C-7, H$_2$-6/C-5 and C-7, and OMe/C-7 indicated the attachment of a methyl acetate group to C-5, which featured the *seco*-B limonoid with cleavage of the C-7–C-8 bond. A proton signal at δ_H 5.19 (s) showing HMBC correlations with C-20, C-21, and C-22 was assignable to H-17, while a singlet proton resonance at δ_H 6.66 distinguished as an exchangeable proton by HSQC was assigned to OH-17 based on its HMBC correlation to C-13. Both the proton and carbon resonances of CH-17 (δ_C 70.6) in compound **1** were obviously upfield shifted as compared to those in the andirobin-type limonoids bearing a D-ring of six membered lactone.[7] The above data indicated that the δ-lactone of D-ring was hydrolyzed, and this deduction was further supported by the absence of HMBC correlation between H-17 and C-16, which is not necessary but definitely sufficient for the existence of δ-lactone in the D-ring. The HMBC correlations of H$_3$-18/C-12, C-13, C-14, and C-17; H$_3$-30/C-8, C-9, and C-14; H-9/C-11; H-11/C-10; and H-12α/C-11 furnished the C-ring embodying two oxygenated quaternary carbons C-8 (δ_C 93.1) and C-14 (δ_C 86.5). Furthermore, the other exchangeable proton signal at δ_H 4.69 (br s) as distinguished by the HSQC spectrum was assigned to 14-OH by its pronounced HMBC correlation with C-15. Besides the A, C, and E-rings, the presence of one more ring was required to meet the tetracyclic feature of compound **1**. The severely downfield shifted quaternary carbon C-8 tentatively indicated the linkage between C-8 and C-16 via an oxygen atom to form the γ-lactone. The planar structure of **1** was thus established.

The relative configuration and the conformation of **1** were mainly determined by the ROESY experiment (Fig. 1). The correlations from H-9 to H-12α and H-15α indicated that H-9, H-12α, and CH$_2$-15 were co-facial and each occupied an axial bond of the chair-alike C-ring, and were arbitrarily fixed as α-oriented. In consequence, Me-18 was in α-orientation from the ROESY cross peaks of H$_3$–18/H$_2$-15 and H-17/H-11β. Me-30 was β-oriented based on the correlation between H$_3$-30 and H-17. Therefore, the newly formed five-membered γ-lactone ring was cis-fused to the C-ring. Furthermore, ROESY correlations of H-1/H-11β and H$_3$-30, H-5/H-11α and H-9, and H-9/H$_3$-19 suggested that the torsion angle between two planes of A-ring and C-ring along the C-9–C-10 bond was about 90° to keep the least steric strain (or lowest energy) in the molecule.

Finally, a qualified single crystal was obtained in the mixed solvent of MeOH containing a small amount of $CHCl_3$. The structure of **1** was unequivocally confirmed by single-crystal X-ray crystallographic analysis (Fig. 2).[8] The conformation of **1** in the solution as

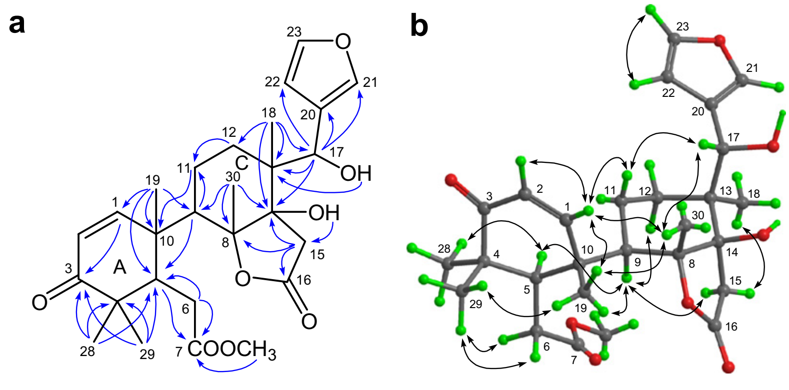

Figure 1. Key HMBC (**a**, H→C) and ROESY (**b**, H↔H) correlations of **1**.

furnished by ROESY experiment was well matched with that of **1** in solid state as obtained by X-ray crystallographic study.

Swiemahogin B (**2**),[9] a white amorphous solid, possessed a molecular formula of $C_{29}H_{36}O_{13}$ with 12 double bond equivalents as established by HRESIMS at *m*/*z* 615.2031 $[M+Na]^+$ (calcd 615.2054). The IR absorption bands at 3435 and 1745 cm^{-1} implied the presence of hydroxyl and carbonyl groups. The ^{1}H and ^{13}C NMR (with DEPT) spectra (Table 1) revealed the existence of three tertiary methyls, one methoxyl, one acetyl, and a typical β-furyl ring. In addition, the remaining 19 carbon resonances in the ^{13}C NMR were distinguished as three methylenes, five sp^3 methines (three oxygenated), seven sp^3 quaternary carbons (four oxygenated), one trisubstituted double bond, and two ester carbonyl groups. The data mentioned above thus characterized a hexacyclic feature of limonoid for **2**.

Comprehensive analysis of the ^{1}H and ^{13}C NMR data (Table 1) and 2D NMR spectra of **2**, especially HMBC (Fig. 3) outlined the A1, A2, B, C, E rings and the C-6–C-7 unit, which are the typical features of a phragmalin-type limonoid.[1b] However, the 1D and 2D NMR spectra of **2** revealed that the most characteristic D-ring comprising the typical δ-lactone of a limonoid was absent, while, an α,β-unsaturated γ-lactone ring was incorporated in the C-ring. This could be rationalized as hydrolysis of the six-membered lactone in the ring-D of a typical limonoid, and followed by the formation of the unique α,β-unsaturated five-membered lactone ring between C-8 and C-16 in **2**. And this was verified by the severely upfield shifted H-17 (δ_H 5.45) and C-17 (δ_C 67.7), and the obviously downfield shifted C-8 (δ_C 95.4). Six exchangeable proton signals at δ_H 2.80, 3.40, 3.68, 4.08, 4.30, and 4.60 (s, each ca. 1H) in the ^{1}H NMR as distinguished by the HMQC were assignable to six hydroxyls, four of which were readily placed at C-1 and C-3 by the HMBC correlations of O*H*-1/C-1 and O*H*-3/C-3; and C-17 and C-30 by the ^{1}H–^{1}H COSY correlations of O*H*-17/H-17 and O*H*-30/H-30 (Fig. 3), respectively. The downfield shifted proton resonance of H-11 at δ_H 5.56 (dd, $J = 11.6$, 3.4 Hz) clearly indicated the attachment of an acetoxyl moiety at C-11.[4a,10] With the settlement of all the other oxygenated carbons, the remaining two hydroxyls at δ_H 2.80 and 3.40 were tentatively distributed at the remaining two oxygenated quaternary carbons C-2 (δ 76.8) and C-9 (δ 79.3), and this assignment was supported by the mutual HMBC correlations of C-2/H-3, $H_{pro\text{-}S}$-29, and H-30; and C-9/H-12α and H-19, respectively. The planar structure of **2** was thus figured out.

The relative stereochemistry of **2** was established on the basis of ROESY spectra (Fig. 3). The ROESY correlation from H-3 to $H_{pro\text{-}R}$-29 helped to establish the 3α-H and the corresponding 3β-OH (Fig. 3). Similarly, ROESY interactions of H-30/H-5, H-17 and H-11, H-11/H-12β, H-17 and H-5, and $H_{pro\text{-}S}$-29/Me-19 indicated that the B/C rings were cis-fused and 11-OAc, 30-OH, and Me-19 were α-oriented. The C-ring adopted a chair-like conformation on the basis of the large coupling constant ($J = 11.6$ Hz) between H-11 and H-12α.

For the D-*seco* limonoids, they are usually furnished with a six-membered δ-lactone in the D-ring, such as in the gendunin, andirobin, mexicanolide, and phragmalin types.[1b] Only in the rare cases, the δ-lactone in the

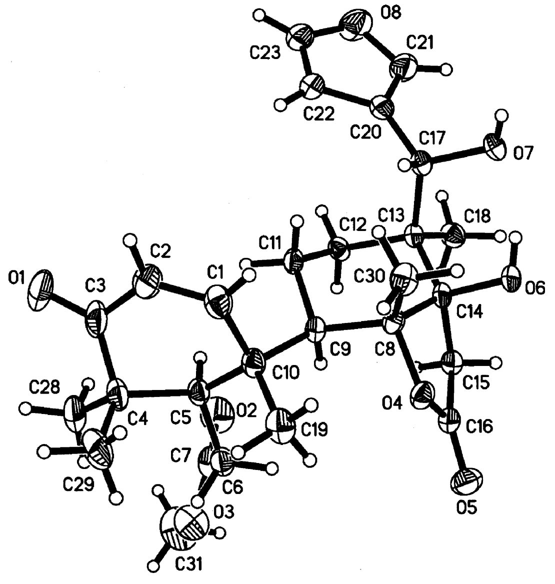

Figure 2. X-ray structure of swiemahogin A (**1**).

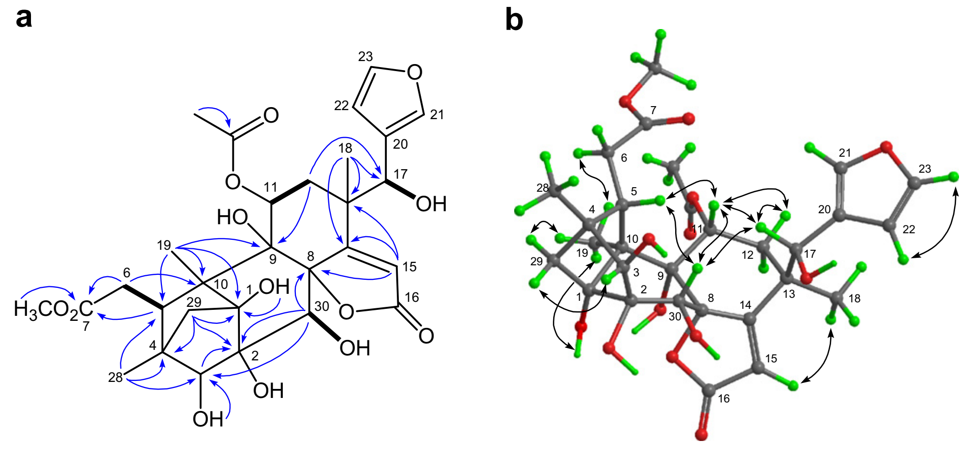

Figure 3. ^1H–^1H COSY (**a**, ▬), key HMBC (**a**, H→C) and key ROESY (**b**, H↔H) correlations of **2**.

ring-D was opened via a possible hydrolysis.[4a,11] Swiemahogins A (**1**) and B (**2**) represent, respectively, the first examples of andirobin and phragmaline-types of limonoids incorporating a rare five-membered γ-lactone fused to the C-ring at C-8 and C-14 where the six-membered δ-lactone in the D-ring demolished. Both swiemahogins A and B, which were monitored by TLC to exist in the crude extract or subfractions obtained from the mild processes, are genuine natural products of this plant.

Acknowledgments

Financial support of the Key Project of National Natural Science Foundation (Grant No. 30630072) and the Shanghai Municipal Scientific Foundation (Grant No. 06DZ22028) of the People's Republic of China is gratefully acknowledged. We thank Professor S.-M. Huang, Department of Biology, Hainan University for the collection and identification of the plant material.

Supplementary data

The MS, IR, and 1D and 2D NMR spectra of **1** and **2** are available in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.066.

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5. Swiemahogin A (**1**). White crystals; mp 235–236 °C; $[\alpha]_{20}^{D}$ −40 (*c* 0.120, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 219 (4.50) nm; CD (CH_3OH) λ_{max} (Δε) 195.4 (−2.00), 226.6 (+0.046), 262.4 (−3.02), 326.8 (+10.68) nm; IR (KBr) ν_{max} 3361, 2975, 2949, 2879, 1761, 1726, 1691, 1468, 1385, 1292, 1256, 1175, 1095, 943, 827, 739, 604 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; EIMS *m/z* (rel int) 470 $[M-H_2O]^+$ (1), 374 (18), 261 (6), 210 (100), 165 (27), 149 (21), 137 (66), 121 (14), 97 (19), 95 (20); ESIMS (positive ion mode) *m/z* (rel int) 511 $[M+Na]^+$ (71), 489 $[M+H]^+$ (89), 471 $[M+H-H_2O]^+$ (87), 505 $[M+NH_3]^+$ (100); ESIMS (negative ion mode) *m/z* (rel int): 487 $[M-H]^-$ (40), 975 $[2M-H]^-$ (100); HREIMS *m/z* 470.2296 $[M-H_2O]^+$ (calcd for $C_{27}H_{34}O_7$, 470.2305).
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8. A crystal with dimensions of $0.495 \times 0.427 \times 0.387$ mm^3 growing from the mixed solvent of $MeOH/CHCl_3$ (30:1) was used for measurements on a Bruker SMART CCD detector employing graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) at 293 K and operating in the ϕ–ω scan mode. X-ray data of **1**: $C_{27}H_{36}O_8$, $M = 488.56$, orthorhombic, space group $P2_12_12_1$, $a = 8.1449(6)$ Å, $b = 14.8803(12)$ Å, $c = 21.1839(17)$ Å, $V = 2567.5(3)$ $Å^3$, $D_{calcd} = 1.264$ g cm^{-3}, $Z = 4$, $F(000) = 1048$, $\mu = 0.092$ mm^{-1}. A total number of 15135 reflections (3163 unique, $R_{int} = 0.1250$) were collected up to $\theta = 26.99°$. The structure was solved by direct methods SHELXS-97 and refined with full-matrix least-squares calculations on F^2 using SHELXL-97. All non-hydrogen atoms were given anisotropic thermal parameters. The hydrogen atom positions were geometrically idealized and allowed to ride on their parent atoms. The final stage converged to $R = 0.0495$ ($R_w = 0.1121$) for 2692 observed reflections [with $I \geqslant 2\sigma(I)$] and 338 variable parameters, $R = 0.0566$

($R_w = 0.1162$) and GOF = 1.009 for all unique reflections and $S = 1.009$. Crystallographic data for **1** have been deposited in the Cambridge Crystallographic Data Centre with the deposition numbers of CCDC 647896. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).

9. Swiemahogin B (**2**). White amorphous solid; $[\alpha]_{20}^{D}$ −33 (c 0.100, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 212 (2.51) nm; CD (CH_3OH) λ_{max} ($\Delta\varepsilon$) 203.5 (−0.352), 249.7 (+0.491) nm; IR (KBr) ν_{max} 3435, 2920, 1745, 1633, 1377, 1229, 1256, 1175, 1041, 962, 602 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS m/z (rel int) 496 (4), 460 (5), 418 (11), 400 (18), 283 (8), 237 (9), 225 (12), 182 (16), 164 (18), 123 (7), 95 (100),67 (9), 60 (14); ESIMS (positive ion mode) m/z (rel int) 609 $[M+NH_3]^+$ (44), 615 $[M+Na]^+$ (4), 1207 $[2M+Na]^+$ (100); ESIMS (negative ion mode) m/z (rel int): 591 $[M-H]^-$ (1), 637 $[M+HCOOH-H]^-$ (100), 1183 $[2M-H]^-$ (50); HRESIMS m/z 615.2031 $[M+Na]^+$ (calcd for $C_{29}H_{36}O_{13}Na$, 615.2054).
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