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Limonoids of the Phragmalin Type from *Swietenia macrophylla* and Their Chemotaxonomic Significance

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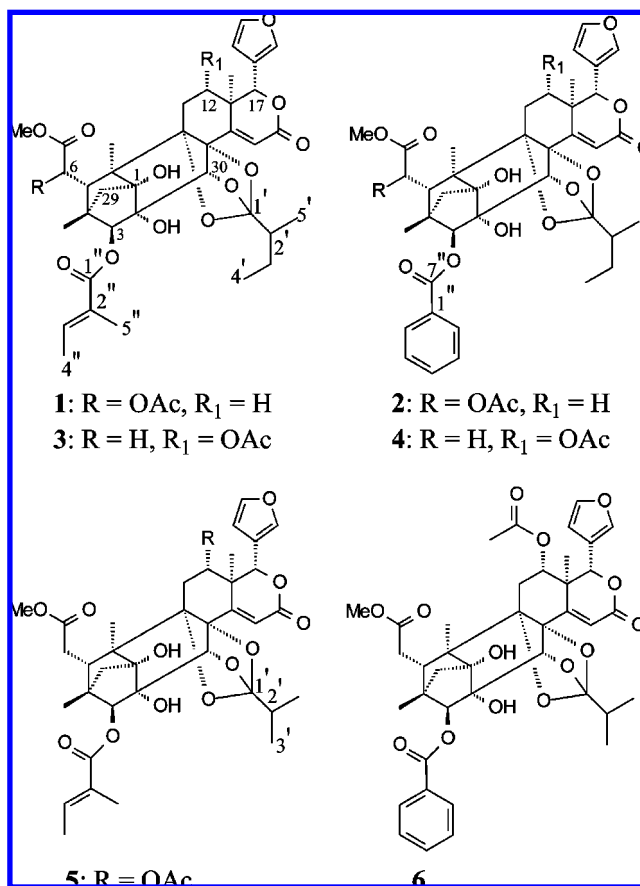
Species of *Swietenia* elaborate limonoid chemistry along only one route, which leads to the mexicanolide type in most species and the phragmalin type in *S. mahogani*. A hexane extract from leaves of *S. macrophylla* afforded six new phragmalins with a 8,9,30-ortho-ester unit, namely, 6-*O*-acetylswietephragmin E (**1**), 3 β -*O*-destigloyl-3 β -*O*-benzoyl-6-*O*-acetylswietephragmin E (**2**), 12 α -acetoxyswietephragmin C (**3**), 3 β -*O*-destigloyl-3 β -*O*-benzoyl-12 α -acetoxyswietephragmin C (**4**), 12 α -acetoxyswietephragmin D (**5**), and 3 β -*O*-destigloyl-3 β -*O*-benzoyl-12 α -acetoxyswietephragmin D (**6**). This appears to be the first record of phragmalins from *S. macrophylla*, and this study shows the potential of tricyclic [3.3.1^{2,10}.1^{1,4}]-decane limonoids as taxonomically useful chemical markers in the Meliaceae.

The family Meliaceae, comprising about 50 genera, provides valuable timber, such as mahogany (*Swietenia*) and cedar (*Cedrela*). The name “mahogany” refers to the red-brown wood of the species *Swietenia mahogani*, known as West Indian mahogany. Closely related to this is *S. macrophylla*, known as South American mahogany, which is also a highly valued timber species. This genus consists of three species, *S. mahogani* Jacq., *S. macrophylla* King, and *S. humilis* Zucc., and two natural hybrids. One is a product of a cross between *S. macrophylla* and *S. humilis* and is found in the areas of the distribution range in which these two species overlap. The second is a cross between *S. macrophylla* and *S. mahogani*, named *S. x aubrevilleana*.¹

Pennington and Styles classified the Meliaceae genera into four subfamilies, the Swietenioideae, Melioideae, Quivisianthoideae, and Capuronianthoideae.¹ Chemically, the family Meliaceae is distinguished by the frequent occurrence of characteristic limonoids, which are derived from tirucallol (20 α H) or euphol (20 β H) precursors, by oxidative opening either of rings D (**1.1**), B (**1.2**), or C (**1.3**), or both rings B/D (**1.1.1**) or A/B (**1.2.1**), as shown in Figure S1, Supporting Information.^{2–5} Genera of the Melioideae subfamily are the most prolific in the production of A,B-*seco* limonoids (**1.2.1**) but relatively deficient in the mexicanolide type (**1.1.1.1**). The C-*seco* limonoids (**1.3**) have so far been recorded only in genera of the Melioideae. In contrast, genera of the Swietenioideae contain mainly limonoids of the mexicanolide (**1.1.1.1**) and phragmalin groups (**1.1.1.1.1**).^{2–5} Quivisianthoideae and Capuronianthoideae are related phytochemically to normal members of the Swietenioideae, which also accumulate limonoids of the mexicanolide group (**1.1.1.1**).^{6,7}

Limonoids with an intact carbon skeleton (**1**), B,D-*seco* (**1.1.1**; Figures S1 and S2, Supporting Information) and mexicanolides (**1.1.1.1**, Figures S1 and S3, Supporting Information) have been reported from *Swietenia* species, but the phragmalin type (**1.1.1.1.1**, Figures S1 and S4, Supporting Information) appears to be present only in *S. mahogani* (Table S1, Supporting Information). However, phragmalins have been found only in the leaves and stem bark of *S. mahogani*, which were not studied in other species (Table S1). We describe herein the isolation and structural elucidation of six

new limonoids, **1–6**, possessing an ortho-ester group at the 8,9,30 positions, similar to swietephragmins C–E,⁸ from the leaves of *S. macrophylla*.



Results and Discussion

The hexane extract from leaves of *S. macrophylla* after repetitive chromatographic separation afforded six new limonoids, **1–6**.

Limonoid **1** gave a molecular formula of C₃₉H₄₈O₁₄ as determined from the pseudomolecular ion peak at *m/z* 763.6 [M + Na]⁺ in the positive ESIMS and by elemental analysis. The ¹H NMR spectrum (Table 1) indicated the presence of three tertiary methyl groups (δ_H 1.31, 1.27, 0.98), a methyl group of

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Table 1. ^1H NMR Chemical Shifts of Compounds **1–6**^a

| position | 1 | 2 | 3 | 4 | 5 | 6 |
|--------------------|----------------------|----------------------|----------------------|----------------------------------|----------------------|----------------------------------|
| 3 | 4.78 s | 5.00 s | 4.83 s | 5.03 s | 4.83 s | 5.04 s |
| 5 | 2.81 brs | 2.97 brs | 2.41 brs | 2.58 d (12) | 2.42 d (12.2) | 2.58 dd (12) |
| 6 | 5.48 brs | 5.55 s | 3.19 d 2.36 d (15.8) | 3.25 d (16.5) 2.41 dd (16.5, 12) | 3.19 d (15.6) 2.37 m | 3.26 d (16.7) 2.41 dd (16.7, 12) |
| 11 | | 2.17 m | 2.21 m 1.90 m | | 2.18 m | 2.23 dd (13.4, 4.0) 1.90 m |
| 12 | 1.19 m 1.68 m | 1.75 m 1.21 m | 4.79 dd (13.5, 4.0) | 4.79 dd (13.2, 4.2) | 4.79 dd (13.2, 3.9) | 4.84 dd (13.4, 4.0) |
| 15 | 5.94 s | 5.75 s | 6.01 s | 6.02 s | 6.02 s | 5.83 s |
| 17 | 5.64 s | 5.74 s | 5.82 s | 5.83 s | 5.83 s | 5.91 s |
| Me-18 | 1.31 s | 1.24 s | 1.51 s | 1.51 s | 1.51 s | 1.43 s |
| Me-19 | 1.27 s | 1.31 s | 1.31 s | 1.31 s | 1.31 s | 1.35 s |
| 21 | 7.50 brs | 7.52 brs | 7.46 d (1.0) | 7.52 brs | 7.41 t (1.7) | 7.49 brs |
| 22 | 6.45 d (1.0) | 6.43 d (1.1) | 6.55 d (1.1) | 6.42 brs | 6.55 d (1.2) | 6.50 d (1.3) |
| 23 | 7.43 t (1.5) | 7.44 m | 7.41 t (1.7) | 7.44 m | 7.46 brs | 7.40 t (1.6) |
| Me-28 | 0.98 s | 1.07 s | 0.82 s | 0.82 s | 0.82 s | 0.92 s |
| 29 | 2.08 d (10.8) 1.79 m | 2.16 d 1.89 d (11.1) | 2.43 d 1.78 d (11.3) | 1.89 m | 1.85 m | 1.93 d 1.85 d (10.1) |
| 30 | 4.47 s | 4.52 s | 4.48 s | 4.52 s | 4.49 s | 4.54 s |
| CH ₃ CO | 2.22 s | 2.25 s | 1.53 s | 1.52 s | 1.53 s | 1.53 s |
| 2' | 1.92 m | 1.88 m | 1.92 m | 1.92 m | 2.19 m | 2.18 m |
| 3' | 1.70 m | 1.69 m | 1.70 m 1.22 m | | 1.04 d (6.6) | 1.04 d (6.8) |
| 4' | 0.92 t (7.5) | 0.91 t (7.4) | 0.93 t (7.5) | 0.93 t (7.8) | 1.04 d (6.6) | 1.04 d (6.8) |
| 5' | 1.01 d (6.6) | 1.01 d (6.8) | 1.02 d (6.9) | 1.01 d (6.9) | | |
| 2'' | | 7.99 dd (7.5, 1.8) | | 8.08 dd (8.5, 1.5) | | 8.08 dd (8.5, 1.3) |
| 3'' | 6.76 dq (7.2, 1.1) | 7.44 m | 6.93 qq (7.0, 1.4) | 7.45 m | 6.94 qq (7.0, 1.5) | 7.44 t (7.9) |
| 4'' | 1.73 dd (7.2, 1.1) | 7.59 t (7.5) | 1.72 dd (7.0, 1.1) | 7.45 m | 1.73 dd (7.0, 1.1) | 7.57 t (7.9) |
| 5'' | 1.83 t (1.1) | 7.44 m | 1.84 dd (1.4, 1.1) | 7.45 m | 1.84 brs | 7.44 t (7.9) |
| 6'' | | 7.99 dd (7.5, 1.8) | | 8.08 dd (8.5, 1.5) | | 8.08 dd (8.5, 1.3) |
| 1-OH | 3.51 s | 3.56 s | 3.40 s | 3.72 s | 3.41 s | 3.44 s |
| 2-OH | 3.54 s | 3.62 s | 3.56 s | 3.44 s | 3.58 s | 3.58 s |
| OCH ₃ | 3.75 s | 3.82 s | 3.74 s | 3.79 s | 3.74 s | 3.80 s |

^a Spectra of **1–6** were run in CDCl₃ and coupling constants are in Hz.

an acetate function (δ_{H} 2.22), a methoxyl singlet (δ_{H} 3.75 s), two signals for vinylic methyls (δ_{H} 1.83 t, $J = 1.1$ Hz; 1.73 dd, $J = 7.0$ and 1.1 Hz), three downfield shifted signals attributable to a β -substituted furan ring (δ_{H} 7.50, 7.43, 6.45), four signals characteristic of protons attached to a carbon adjacent to an oxygen atom (δ_{H} 5.64 s; 4.78 s; 5.48 brs; 4.47 s), two olefinic protons (δ_{H} 5.94 s; 6.76 dq, $J = 7.2$ and 1.1 Hz), an AB-type methylene (δ_{H} 2.08 d, $J = 10.8$ Hz; 1.79 m), and four signals characteristic of a 2-substituted-butyl group (δ_{H} 1.01 d, $J = 6.6$ Hz; 1.92 m; 1.70 m; 0.92 t, $J = 7.5$ Hz). The ^{13}C NMR spectrum revealed 39 carbon signals, which were assigned by DEPT and HETCOR experiments (Table 2). The HMBC spectrum of **1** showed correlation characteristics of a furan ring at C-17 of a D-ring α,β -unsaturated δ -lactone limonoid. The principal correlations observed were between H-17 (δ_{H} 5.64, δ_{C} 79.8)/C-21 (δ_{C} 141.8); H₃-18 (δ_{H} 1.31, δ_{C} 19.7)/C-17, C-12 (δ_{C} 29.3), C-13 (37.8), and C-14 (δ_{C} 152.7); and H-15 (δ_{H} 5.94)/C-16 (δ_{C} 162.8). Moreover, the correlations observed between H-15/C-8 (δ_{C} 83.6) and 2H-12 (δ_{H} 1.19 and 1.68)/C-9 (δ_{C} 86.8) indicated a tertiary hydroxyl or ether substituent at C-8 and C-9. The oxymethine proton at δ_{H} 4.47 showed a one-bond correlation with the ^{13}C NMR signals at δ_{C} 77.7 and cross-peaks with δ_{C} 122.5 and C-8, thus indicating the presence of an ether function at C-30 and permitting the assignment of the signals at δ_{H} 4.47 to H-30, δ_{C} 77.7 to C-30, and δ_{C} 122.5 to an ortho-carbon. The HMBC spectrum suggested the presence of an isolated structural unit, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ (δ_{H} 1.01 d, 3H, $J = 6.6$ Hz; 1.92 m, 1H; 1.70 m, 2H; 0.92 t, 3H, $J = 7.5$ Hz). The methyl signal at δ_{H} 1.01 showed a cross-peak with the ^{13}C NMR signal at δ_{C} 122.5, characteristic of an ortho-carbon, identified as a 2-methylbutanoate group, which was located at the positions C-8, C-9, and C-30.

The AB-type methylene protons at δ_{H} 2.08 and 1.79 were attributed to H₂-29 by their correlation with the C-1 signal at δ_{C} 84.6 and suggested that **1** is a phragmalin-type limonoid. The methyl proton signal at δ_{H} 0.98 and the H₂-29 signals showed cross-peaks with the ^{13}C NMR signal at δ_{C} 86.9, which exhibited a one-bond correlation with the ^1H NMR signal at δ_{H} 4.78 and a long-range correlation to the ^{13}C NMR signal at δ_{C} 167.6, thus indicating that

an ester substituent occurred at C-3 and leading to their assignments as H₃-28, C-3, and H-3, respectively. The HMBC correlations between H-3'' (δ_{H} 6.76, δ_{C} 139.5)/C-1'' (δ_{C} 167.6), C-2'' (δ_{C} 129.9); H₃-5'' (δ_{H} 1.83)/C-1''; and H₃-4'' (δ_{H} 1.73, δ_{C} 12.4)/C-3'' (δ_{C} 139.5), C-2'' suggested a tigloyl ester at C-3. A hydroxyl must be connected to C-2 due to the observed correlation between the H-3 signal and ^{13}C NMR quaternary signal at δ_{C} 75.6.

The oxymethine proton at δ_{H} 5.48 showed a one-bond correlation with the ^{13}C NMR signal at δ_{C} 71.4 and long-range correlation with the signal for C-5 and the ^{13}C NMR signals at δ_{C} 169.8 and 171.0. The methoxyl singlet at δ_{H} 3.75 showed a cross-peak with the ^{13}C NMR signal at δ_{C} 171.0, and a methyl signal at δ_{H} 2.22 correlated to δ_{C} 169.8, indicating the presence of a carbomethoxy group at C-7 and an acetoxyl substituent at C-6.

The structural assignment was also supported by comparison of the ^{13}C NMR spectrum of **1** (Table 2) with that of swietephragmin E.⁸ The stereochemistry suggested for **1** was based on the biosynthesis of limonoids.³ However, for H-3 and H-30 the configurations were assigned by g-NOESY 1-D experiments, which showed a NOE between H-30 (δ_{H} 4.47) and H-15 (δ_{H} 5.94), requiring H-30 to be on the β -side of the molecule. Inspection of a model for **1** showed that when H-30 is on the β -side of the molecule, the formation of a less strained 8,9,30-*ortho*-2-methylbutanoate group is allowed only on the α -side. In addition, irradiation of the H-3 signal at δ_{H} 4.78 showed a NOE with the H-29 signal at δ_{H} 1.79, showing that H-3 is thus on the α -side of the molecule. The new natural product was, therefore, assigned as 6-*O*-acetylswietephragmin E (**1**).

Limonoid **2** showed spectroscopic characteristics similar to those of **1**. The principal changes observed in the ^1H and ^{13}C NMR spectra (Tables 1 and 2) of **2** were due to the replacement of the resonances for a tigloyl ester by signals for a benzoate group (δ_{H} 7.99 dd, $J = 7.5$ and 1.8 Hz, 2H; 7.44 m, 2H; 7.59 t, $J = 7.5$ Hz; 166.5, 139.4; 129.7, 2C; 129.0, 2C; 134.2). An HMBC experiment, in addition to showing correlations similar to those of **1**, revealed a cross-peak of the ^1H NMR signal at δ_{H} 5.00, assigned to H-3, with the ^{13}C NMR signal at δ_{C} 166.5, aiding the location of the benzoate group at C-3. This conclusion was supported by the observed correlation between the aromatic ^1H NMR signals and ^{13}C NMR

Table 2. ^{13}C NMR Chemical Shifts of Compounds **1–6**^a

| carbon | 1 | 2 | 3 | 4 | 5 | 6 |
|--------------------|-------|-------|-------|-------|-------|-------|
| 1 | 84.6 | 84.6 | 84.5 | 84.5 | 84.4 | 84.5 |
| 2 | 75.6 | 75.6 | 75.7 | 75.7 | 75.7 | 75.7 |
| 3 | 86.9 | 87.4 | 86.6 | 87.1 | 86.5 | 86.4 |
| 4 | 43.6 | 43.7 | 43.8 | 43.9 | 43.8 | 43.9 |
| 5 | 44.8 | 44.9 | 40.7 | 40.8 | 40.6 | 40.8 |
| 6 | 71.4 | 71.5 | 32.9 | 33.0 | 32.9 | 33.0 |
| 7 | 171.0 | 171.2 | 174.6 | 174.7 | 174.5 | 174.7 |
| 8 | 83.6 | 83.7 | 83.3 | 83.4 | 83.4 | 83.6 |
| 9 | 86.8 | 86.8 | 86.3 | 86.3 | 86.3 | 87.2 |
| 10 | 48.4 | 48.4 | 47.3 | 47.4 | 47.3 | 47.4 |
| 11 | 25.6 | 25.6 | 32.0 | 32.1 | 32.0 | 32.1 |
| 12 | 29.3 | 29.3 | 68.6 | 68.6 | 68.6 | 68.6 |
| 13 | 37.8 | 38.0 | 42.7 | 42.8 | 42.7 | 42.9 |
| 14 | 152.7 | 152.7 | 151.3 | 151.3 | 151.2 | 151.3 |
| 15 | 122.4 | 122.2 | 123.9 | 123.6 | 123.9 | 123.7 |
| 16 | 162.8 | 161.8 | 162.4 | 161.3 | 162.4 | 161.3 |
| 17 | 79.8 | 79.7 | 78.2 | 78.1 | 78.2 | 78.0 |
| Me-18 | 19.7 | 19.5 | 14.5 | 14.4 | 14.4 | 14.3 |
| Me-19 | 16.3 | 16.4 | 15.5 | 15.5 | 15.5 | 15.5 |
| 20 | 119.5 | 119.6 | 121.3 | 121.4 | 121.2 | 121.4 |
| 21 | 141.8 | 141.7 | 141.9 | 141.8 | 143.1 | 141.8 |
| 22 | 110.0 | 110.0 | 110.3 | 110.3 | 110.2 | 110.3 |
| 23 | 143.1 | 143.0 | 143.0 | 143.0 | 143.1 | 143.0 |
| Me-28 | 15.5 | 15.5 | 14.4 | 14.3 | 14.3 | 14.4 |
| 29 | 39.8 | 39.8 | 38.9 | 38.9 | 38.9 | 39.8 |
| 30 | 77.7 | 77.6 | 78.1 | 78.0 | 78.1 | 78.2 |
| CH ₃ CO | 21.0 | 21.1 | 19.8 | 19.8 | 19.8 | 19.8 |
| CH ₃ CO | 169.8 | 169.7 | 170.4 | 170.5 | 170.4 | 170.4 |
| 1'' | 167.6 | 139.4 | 167.8 | 129.6 | 167.8 | 129.7 |
| 2'' | 129.9 | 129.7 | 130.0 | 129.7 | 130.0 | 129.8 |
| 3'' | 139.5 | 129.0 | 139.8 | 129.1 | 139.8 | 129.0 |
| 4'' | 12.4 | 134.2 | 12.4 | 134.1 | 12.4 | 134.1 |
| 5'' | 14.3 | 129.0 | 14.6 | 129.1 | 14.5 | 129.0 |
| 6'' | | 129.7 | | 129.7 | | 129.8 |
| 7'' | | 166.5 | | 166.7 | | 166.7 |
| 1' | 122.5 | 122.4 | 122.7 | 122.7 | 122.7 | 122.7 |
| 2' | 35.5 | 35.5 | 35.5 | 35.5 | 28.9 | 29.0 |
| 3' | 23.7 | 23.7 | 23.7 | 23.7 | 16.7 | 16.6 |
| 4' | 11.6 | 11.6 | 11.6 | 11.6 | 16.8 | 16.7 |
| 5' | 13.3 | 13.5 | 13.3 | 13.3 | | |
| CH ₃ O | 53.2 | 53.4 | 52.1 | 52.2 | 52.1 | 52.2 |
| CH ₃ CO | | | | | | |
| CH ₃ CO | | | | | | |

^a The spectra of **1–10** were run in CDCl₃. Assignments are based on HETCOR, HSQC, and HMBC experiments.

signal at δ_{C} 166.5. In a g-NOESY 1D experiment, NOE interactions of H-30 at δ_{H} 4.52 with H-15 (δ_{H} 5.75) and H-5 (δ_{H} 2.97; weak) required H-30 to be on the β -side of the molecule. This implied that the 8,9,30-*ortho*-2-methylbutanoate group is thus in the α -orientation. In the same way, a NOE interaction of H-29 at δ_{H} 1.89 with H-3 at δ_{H} 5.00 showed that H-3 is thus on the α -side of the molecule. Elemental analysis and ESIMS confirmed the molecular formula as C₄₁H₄₆O₁₄. The structure of the new natural product **2** was thus established as 3 β -*O*-destigloyl-3 β -*O*-benzoyl-6-*O*-acetylswietephragmin E.

Limonoid **3** also showed spectroscopic characteristics of an 8,9,30-*ortho*-2-methylbutanoate of 1,2-dihydroxy-3 β -*O*-tigloylphragmalin. Elemental analysis and ESIMS indicated the molecular formula to be C₃₉H₄₈O₁₄, which strongly suggested this compound to be an isomer of **1**. However, the methyl proton at δ_{H} 1.51 showed long-range correlations with the C-17 signal (δ_{C} 78.2) and the ^{13}C NMR signals at δ_{C} 68.6 (CH, by HETCOR and DEPT 135°), 42.7 (quaternary), and 151.3, thus indicating a double bond at C-14 and a secondary hydroxyl or ester substituent at C-12 and leading to their assignments as H₃-18, C-12, C-13, and C-14, respectively. The C-12 signal at δ_{C} 68.6 showed one-bond correlations with the ^1H NMR signals at δ_{H} 4.79 (dd, J = 13.5 and 4.0 Hz), which was coupled to the ^1H NMR signals at δ_{H} 2.21 and 1.90 (m), permitting their assignment to 2H-11. The ^1H NMR signals at δ_{H} 4.79 and a methyl signal at δ_{H} 1.53 showed a long-range correlation with the

^{13}C NMR signals at δ_{C} 170.4, indicating an acetoxyl group at C-12. The ^1H NMR and HMBC experiments suggested the presence of the structural unit $-\text{CH}_2\text{COOMe}$ (δ_{H} 3.19, d; 2.36 d, J = 15.8 Hz; 2H-6; 3.74, s) for C-6 and C-7. The NOESY experiments showed correlations between H-12 and H-17 (δ_{H} 5.82), H-5 (δ_{H} 2.41), and H β -6 (δ_{H} 3.19), indicating a β -orientation for these four hydrogens. In addition, the signal of H-29 (δ_{H} 1.78) showed cross-peaks with the signals of H-3, thereby requiring H-3 to be on the α -side of the molecule. The structural assignment was also supported by comparison of the ^{13}C NMR spectrum (Table 2) with that of swietephragmin C.⁸ Thus, the structure of compound **3** was proposed as 12 α -acetoxyswietephragmin C.

Limonoid **4** exhibited similar NMR spectra to those of an 8,9,30-*ortho*-2-methylbutanoate of 1,2-dihydroxy-3 β -*O*-benzoylphragmalin. Elemental analysis and ESIMS indicated the molecular formula to be C₄₁H₄₆O₁₄, which suggested it to be an isomer of **2**. However, a long-range correlation observed between the methyl proton signal at δ_{H} 1.51 and the C-17 signal (δ_{C} 78.1) and the ^{13}C NMR signals at δ_{C} 68.6 (CH, by HETCOR and DEPT 135°) thus indicated a secondary acetoxyl substituent now affixed to C-12, similar to **3**. The coupling constants for H-12 (δ_{H} 4.79 dd, J = 13.2 and 4.2 Hz) were in agreement with a pseudoaxial orientation as in **3** and in xylocensin Q (δ_{H} 4.80 dd, J = 4.0, 13.5 Hz). The structural assignment was also supported by comparison of the ^{13}C NMR spectrum (Table 3) with those of **2**, **3**, and xylocensin Q.⁹ In the

g-NOESY experiments, the observed NOE interactions were similar to those found for **3**. The new natural product **4** was proposed as 3 β -*O*-destigloyl-3 β -*O*-benzoyl-12 α -acetoxyswietenephragmin C.

Limonoid **5** showed spectroscopic characteristics similar to those of **3**. The principal changes observed in the ^1H and ^{13}C NMR spectra (Tables 1 and 2) of **5** were the replacement of resonances for an *ortho*-2-methylbutanoate group by signals for an *ortho*-isobutylate (δ_{H} 2.19 m; 1.04 d, 6H, $J = 6.6$ Hz; δ_{C} 122.7; 28.9; 16.7; 16.8). The HMBC experiments, in addition to showing correlations similar to those for **3**, revealed a cross-peak of the ^1H NMR signal at δ_{H} 4.49, assigned to H-30, with the ^{13}C NMR signal at δ_{C} 122.7. The methyl signal (6H) resonating at δ_{H} 1.04 showed a cross-peak with the ^{13}C NMR signal at δ_{C} 122.7, characteristic of an *ortho*-carbon, identified as an isobutylate group, which was located at positions C-8, C-9, and C-30. In a g-NOESY 1D experiment, the NOE interaction of H-30 at δ_{H} 4.49 with H-15 (δ_{H} 6.02) and H-5 (δ_{H} 2.42; weak) required H-30 to be on the β -side of the molecule. This implied that the 8,9,30-*ortho*-isobutylate group is thus in an α -orientation. A NOE interaction of the H-12 signal at δ_{H} 4.79, coming from H-17 at δ_{H} 5.83 and H-5 at δ_{H} 2.42, showed that H-12 was thus on the β -side of the molecule. Elemental analysis and ESIMS confirmed the molecular formula as $\text{C}_{38}\text{H}_{46}\text{O}_{14}$. The structural assignment was also supported by comparison of the ^{13}C NMR spectrum (Table 3) with that of swietenephragmin D.⁸ Thus, the structure of the new natural product **5** was thus established as 12 α -acetoxyswietenephragmin D.

Limonoid **6** also showed spectroscopic characteristics of an 8,9,30-*ortho*-isobutylate of 1,2-dihydroxyphragmalin. The principal change observed in the ^1H and ^{13}C NMR spectra (Tables 1 and 2) of **6** when compared to compound **5** was the replacement of resonances for a tigloyl ester by signals for a benzoate group (δ_{H} 8.08 dd, $J = 8.5$ and 1.3 Hz, 2H; 7.44 t; $J = 7.9$ Hz, 2H; 7.57 t, $J = 7.9$ Hz; δ_{C} 166.7; 129.7; 129.8; 2C; 129.0, 2C; 134.1). The HMBC experiment, in addition to showing correlations similar to those for **5**, revealed a cross-peak of the ^1H NMR signal at δ_{H} 5.04, assigned to H-3, with the ^{13}C NMR signal at δ_{C} 166.7, helping to determine the position of the benzoate group at C-3. This conclusion was supported by the observed correlation between the aromatic ^1H NMR signals and the ^{13}C NMR signal at δ_{C} 166.7. In a g-NOESY 1D experiment, the observed NOE interactions were similar to those found for **5**. Elemental analysis and ESIMS confirmed the molecular formula as $\text{C}_{40}\text{H}_{44}\text{O}_{14}$. The structure of the new natural product **6** was thus established as 3 β -*O*-destigloyl-3 β -*O*-benzoyl-12 α -acetoxyswietenephragmin D.

Compounds **1–6** show significant chemotaxonomic evidence in favor of the link between the species *S. macrophylla* and *S. mahogany*. As discussed earlier, species of *Swietenia* elaborate limonoid chemistry along only one route, which leads to compounds of the mexicanolide group (1.1.1.1) in all species and of the phragmalin type (1.1.1.1) only in *S. mahogany*. The present study appears to be the first record of phragmalins from *S. macrophylla*. This study supports the use of phragmalins as taxonomically useful chemical markers in this species and clearly shows that the leaves, stems, and roots of *Swietenia* species are in need of further phytochemical work, particularly searching for limonoids with a tricyclic [3.3.1^{2,10},1⁴] decane ring system.

Experimental Section

General Experimental Procedures. Optical rotations were measured by using a Perkin-Elmer 241 spectropolarimeter. IR spectra were recorded on a Bomen-Ft/IR spectrometer. NMR spectra were recorded in CDCl_3 at room temperature on a Bruker DRX 400 and a Varian Mercury-300 NMR spectrometer, and the solvent resonance was used as internal shift reference (tetramethylsilane as standard). The 2D NMR spectra were recorded by using standard pulse sequence. ESIMS were recorded on a Micromass Quattro LC instrument, equipped with a "Z-spray" ion source. Elemental analyses were recorded on an EA 1108, CHNS-O (Fisons). HPLC was performed on a Shimadzu model SCL-10A.

Plant Material. *Swietenia macrophylla* was collected in Aurora do Pará, Pará State, Brazil, in April 2002, and was identified by Prof. Dr. Orlando Shigueo Ohashi from the Botany Department, Universidade Federal Rural da Amazônia, Brazil. A voucher specimen (no. 1320) was deposited at the Herbarium of the Museum Paraense Emílio Goeldi, Belém, Pará, Brazil.

Extraction and Isolation. Ground leaves (1.4 kg) from *S. macrophylla* were extracted with hexane, then CH_2Cl_2 , and finally MeOH, at room temperature, three times. The concentrated hexane extract (30 g) was subjected to column chromatography over silica gel (70–230 mesh) under vacuum. Elution with a hexane–EtOAc gradient yielded four fractions. Purification of fraction 4 was carried out by applying to an ODS (C_{18}) SPE cartridge. The solvent was removed from the cartridge under vacuum. The eluent was evaporated and resuspended in MeOH and subjected to rp-HPLC (H_2O –MeOH, 28:72; detection, UV 217 nm, flow rate, 4.7 mL min^{-1} , Phenomenex Gemini C_{18} column, 250 \times 10 mm i.d.), yielding compounds **1** (42 min; 13.6 mg), **2** (31 min; 24.8 mg), **3** (44 min; 26.1 mg), **4** (35 min; 10.5 mg), **5** (47 min; 15.4 mg), and **6** (38 min; 13.7 mg).

6-*O*-Acetylswietenephragmin E (1): amorphous, white solid; $[\alpha]_{\text{D}}^{25} -10.6$ (c 0.0012, CHCl_3); IR (film) ν_{max} 3520 (OH), 1730 (carboxyl group) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3), see Table 1; ^{13}C NMR (100 MHz, CDCl_3), see Table 2; ESIMS m/z 763.6 $[\text{M} + \text{Na}]^+$ (100); *anal.* found C 63.30%, H 6.43%, calcd for $\text{C}_{39}\text{H}_{48}\text{O}_{14}$, C 63.23%, H 6.53%, O 30.24%.

3 β -*O*-Destigloyl-3 β -*O*-benzoyl-6-*O*-acetylswietenephragmin E (2): amorphous, white solid; $[\alpha]_{\text{D}}^{25} -12.6$ (c 0.003, CHCl_3); IR (film) ν_{max} 3509 (OH), 1731 (carboxyl group) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3), see Table 1; ^{13}C NMR (100 MHz, CDCl_3), see Table 2; ESIMS m/z 785.3 $[\text{M} + \text{Na}]^+$ (100); *anal.* found C 64.40%, H 6.09%, calcd for $\text{C}_{41}\text{H}_{46}\text{O}_{14}$, C 64.56%, H 6.08%, O 29.36%.

12 α -Acetylswietenephragmin C (3): amorphous, white solid; $[\alpha]_{\text{D}}^{25} +54.0$ (c 0.003, CHCl_3); IR (film) ν_{max} 3507 (OH), 1730 (carboxyl group) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3), see Table 1; ^{13}C NMR (100 MHz, CDCl_3), see Table 2; ESIMS m/z 763.6 $[\text{M} + \text{Na}]^+$ (100); *anal.* found C 63.27%, H 6.50%, calcd for $\text{C}_{39}\text{H}_{48}\text{O}_{14}$, C 63.23%, H 6.53%, O 30.24%.

3 β -*O*-Destigloyl-3 β -*O*-benzoyl-12 α -acetoxyswietenephragmin C (4): amorphous, white solid; $[\alpha]_{\text{D}}^{25} +30.4$ (c 0.003, CHCl_3); IR (film) ν_{max} 3473 (OH), 1728 (carboxyl group) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3), see Table 1; ^{13}C NMR (100 MHz, CDCl_3), see Table 2; ESIMS m/z 785.3 $[\text{M} + \text{Na}]^+$ (100); *anal.* found C 64.50%, H 6.10%, calcd for $\text{C}_{41}\text{H}_{46}\text{O}_{14}$, C 64.56%, H 6.08%, O 29.36%.

12 α -Acetoxyswietenephragmin D (5): amorphous, white solid; $[\alpha]_{\text{D}}^{25} +23.4$ (c 0.003, CHCl_3); IR (film) ν_{max} 3473 (OH), 1728 (carboxyl group) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3), see Table 1; ^{13}C NMR (100 MHz, CDCl_3), see Table 2; ESIMS m/z 749.3 $[\text{M} + \text{Na}]^+$ (100); *anal.* found C 63.00%, H 6.25%, calcd for $\text{C}_{38}\text{H}_{46}\text{O}_{14}$, C 62.80%, H 6.38%, O 30.82%.

3 β -*O*-Destigloyl-3 β -*O*-benzoyl-12 α -acetoxyswietenephragmin D (6): amorphous, white solid; $[\alpha]_{\text{D}}^{25} -13.4$ (c 0.003, CHCl_3); IR (film) ν_{max} 3473 (OH), 1728 (carboxyl group) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3), see Table 1; ^{13}C NMR (100 MHz, CDCl_3), see Table 2; ESIMS m/z 749.3 $[\text{M} + \text{H}]^+$ (100); *anal.* found C, 64.10%, H 6.00%, calcd for $\text{C}_{40}\text{H}_{44}\text{O}_{14}$, C 64.16%, H 5.92%, O 29.91%.

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Supporting Information Available: Biogenetic pathway for limonoid types found in the family Meliaceae (Figure S1), occurrence of limonoids classified into structural types (Figures S2–S4) in *Swietenia* species (Table S1), and ^1H and ^{13}C NMR spectra of compounds **1–6** are available free of charge via the Internet at <http://pubs.acs.org>.

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