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A novel polyprenylated phloroglucinol, garcinialone, from the roots of *Garcinia multiflora*

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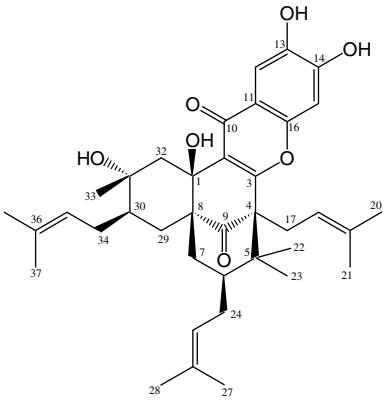
ABSTRACT

A novel polyprenylated phloroglucinol garcinialone (**1**) along with a known compound isoxanthochymol (**2**) have been isolated from the roots of *Garcinia multiflora*. The structures of **1** and **2** were elucidated spectroscopically, by 1D and 2D NMR and mass spectrometry.

Garcinia multiflora is an evergreen tree, belonging to the family Guttiferae. The genus *Garcinia* numbers over 200 species, though only three species occur in Taiwan, namely *G. subelliptica*, *G. multiflora*, and *G. linii*.[1] *G. multiflora* is a dioecious tree, about 3–10 m tall, distributed in southern mainland China, Hong Kong, and the southern part of Taiwan.[1] It is used in furniture manufacture and as a dye.

Previous phytochemical studies by Konoshima et al.[2] on the bark of *G. multiflora* led to the identification of 7 biflavonoids, and studies by Chen et al.[3,4] on the heartwood of this plant identified 11 flavonoids and xanthones. Several new xanthone derivatives and new benzophenone derivatives were isolated from the stems of *G. multiflora* and exhibited cytotoxic and antioxidative activity.[5] The twigs and leaves of this species were found to inhibit



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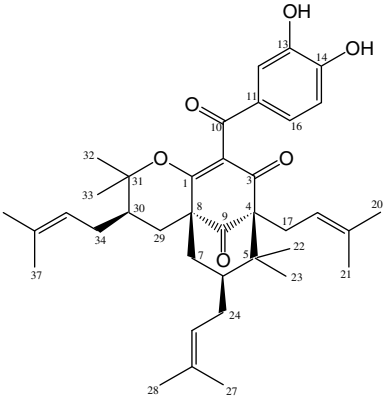

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strongly the polymerase of HIV-1 RT.[6] The roots of *G. multiflora* have not yet been analyzed, and we therefore resolved to research the chemical principals of this part.

The methanol extract of roots of *G. multiflora* exhibited good free radical scavenger activity, trapping superoxide, reducing power, and metal chelating activity (unpublished data). The MeOH extract was partitioned with EtOAc and H_2O, and the organic layer afforded a black syrup. This black syrup was repeatedly chromatographed on SiO_2 columns and by HPLC to give a novel polyprenylated phloroglucinol garcinialone (**1**) along with the known compound isoxanthochymol (**2**).[7,8] The structure of **2** had previously been determined from an X-ray crystallographic analysis of its di-*p*-bromobenzenesulfonate,[8] whereas the structure of **1** was deduced from that of **2** by a comparison of the physical and chemical data for **1** and **2**.

Garcinialone (**1**),[9] $[\alpha]_D^{25}$ −2.0 (*c* 0.02, MeOH), was obtained as a pale yellow plate. Its HRESIMS exhibited a molecular ion peak at *m/z* 618.3558, $[M]^+$ (calcd 618.3557) corresponding to $C_{38}H_{50}O_7$ with 14 degrees of unsaturation. IR absorption bands at 3410, 1726, 1627, 1587, and 1474 cm^{-1} implied the existence of hydroxyl, carbonyl, and phenyl groups. In the UV spectrum of **1**, absorption maxima were observed at 221, 249, 282 nm revealing the presence of the conjugated system.[10]

However, initial observation of the ^{13}C NMR and DEPT spectra of **1** only found 38 signals, assigned as two carbonyl groups (one isolated and one conjugated), six phenyl carbons, eight olefinic carbons, nine CH_3 groups, six sp^3 CH_2, two oxygenated sp^3 C, three sp^3 C, and two sp^3 CH. Characteristic ^{13}C NMR resonances, including those for three tertiary oxygenated aromatic carbon signals appeared at δ_C 142.7, 151.6, and 150.8, together with one sp^2 C (δ_C 115.8) and two sp^2 CH signals (δ_C 102.2, δ_H 6.82, s; δ_C 107.4, δ_H 7.52, s) indicated the presence of a 1,2,4-trioxygenated benzene ring. Two of them link to hydroxyl groups disclosing from two phenolic signals at δ_H 5.70 and 9.10 (exchangeable with D_2O). The lower shift of the aromatic proton at δ 7.52 disclosed that it was *ortho* to a carbonyl group, which was assigned as a γ-pyrone functionality due to its IR absorption (ν_{max} 1627 cm^{-1}) and ^{13}C data (δ_C 177.5). Resonances for a six-membered ring consisting of an isolated ketone (δ_C 209.2, ν_{max} 1726 cm^{-1}) flanked by two quaternary carbons (δ_C 61.2, 54.4) and an enolized 1,3-dioxygenated carbon (δ_C 76.2, 122.0, 164.0) were also observed. Support for this assignment was provided by ^{13}C NMR signals (signals are similar to compound **2**) for quaternary (δ_C 49.6, C-5), methine (δ_C 44.0, C-6), and methylene (δ_C 38.8, C-7) carbons which are part of the bicyclo[3.3.1]nonane ring system. The ^1H NMR spectrum indicated three trisubstituted olefinic protons [δ_H 5.32 (1H, m), 4.91 (1H, br s), and 4.37 (1H, br s)], and nine quaternary methyl groups including six methyl groups attached to olefines (δ_H 1.73, 1.65 × 2, 1.51, 1.48, 1.12), one methyl group attached to a carbon bearing a hydroxyl group (δ_H 1.46), and two geminal methyl groups (δ_H1.01 and 0.97) attached to a sp^3 carbon. H-18 (δ_H 4.37) and H_3-20 (δ_H 1.12) were shifted to higher field by shielding from the Δ^2 double bond and an oxygen atom. On account of seven oxygen atoms in compound **1**, the remaining two oxygens are present as two hydroxyl groups which are revealed from the ^{13}C NMR data (two oxygenated sp^3 C: δ_C 76.2, C-1; δ_C 74.0, C-31).

This partial structure was further refined by HMBC (see Fig. 1) and NOESY spectra (see Fig. 2). In analysis of the HMBC spectrum of **1**, the correlations H_3-33 (δ_H 1.46)/C-30, C-31, C-32; H-32 (δ_H 1.17)/C-31 were observed. Several further correlations H-29 (δ_H 1.28)/C-7, C-8, C-9, and C-31; H-34 (δ_H 1.83)/C-30, C-35, C-36 suggested that compound **1** has a cyclohexyl ring and an isoprenyl group attached to the C-30, which led to the establishment of partial structure **1a** (Fig. 1). In addition, the HMBC spectrum of **1** also shows correlations from CH_3-22 (δ_H 1.01, s) to C-4, C-5, and C-6, from CH_3-23 (δ_H 0.97, s) to C-4, C-5, and C-6, from H-17 (δ_H 2.57, m) to C-9, C-18, and C-19, and from H-24 (δ_H 1.54, m) to C-6 and C-25. These observed HMBC correlations showed that **1** has a bicyclo[3.3.1]nonane ring system, and two isoprenyl groups attached to the C-4 and C-6, respectively, and gave rise to another partial structure **1b** (Fig. 1). A further HMBC correlation of H-7 (δ_H 2.34, m) to C-1, C-6, C-8, and C-9 permitted fragment **1a** and **1b** to be joined together as shown in fragment **1c** (Fig. 1).

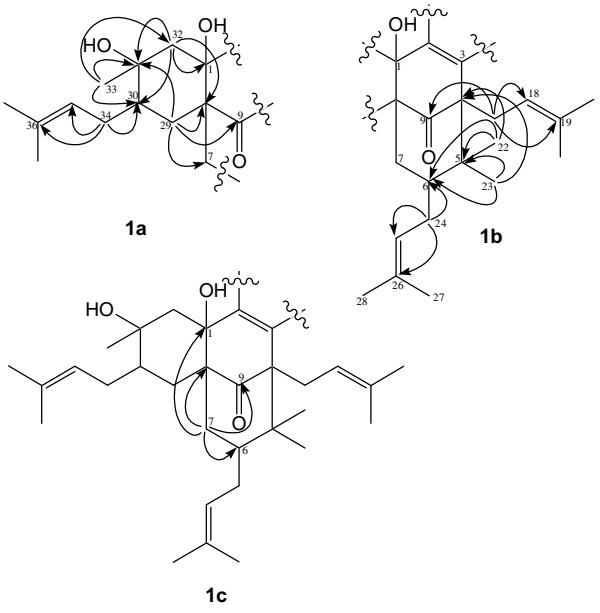

Figure 1. Structural fragments and HMBC correlations of **1**.

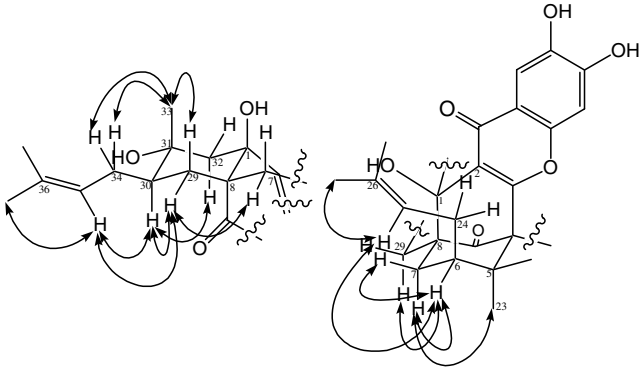

Figure 2. Structural fragments and key NOESY correlations of **1**.

The relative stereochemistry of **1** was constructed from the combination of the NOESY spectrum (see Fig. 2) and 1D NMR of **1**. The configuration of the hydroxyl group at C-31 was deduced to be the α-equatorial orientation from the NOESY correlation of H_3-33 with H_β-29 (δ_H 1.28, m), but the lack of NOESY correlation with H-30 suggested that H_3-33 was in the β-axial orientation. By further NOESY correlation of H-30 with H-35, H_α-29 (δ_H 2.05, dd, J = 13.2, 4.4 Hz), and H_α-32 (δ_H 1.17, d, J = 13.6 Hz), H-30 was deduced to be in the α-axial orientation. The following NOESY correlation: H-6/H_2-7, H-25, H_3-28; H_3-23/H_α-7 disclosed H-6 and H_3-23 to be in α-equatorial and α-axial orientations, respectively. Furthermore, the H_3-33 (δ_H 1.46, s) signal by the downfield shift indicated that the methyl group was in a 1,3-diaxial interaction with the hydroxyl group (attached to C-1). The H-18 and H_3-20 observed at higher field [(δ_H 4.37, br s) and (δ_H 1.12, s)] indicated that both of the two must be shielded by the anisotropic effect from the oxygen atom and double bond.

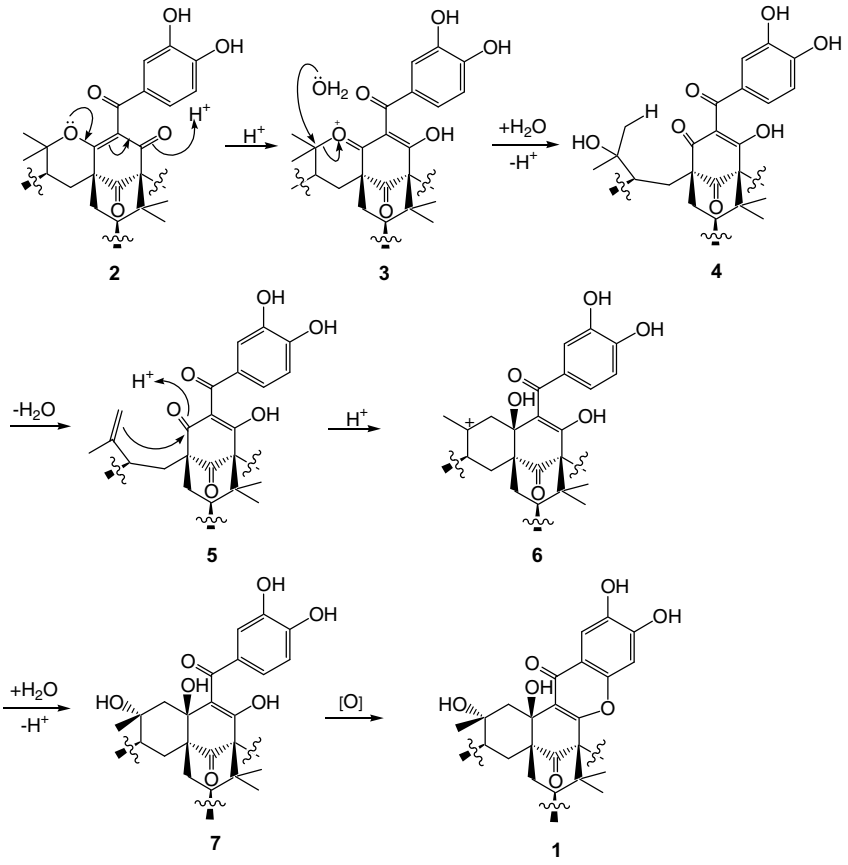

Figure 3. Possible biosynthetic pathway of **1**.

The absolute configuration **1** must be like **2** because the two compounds were isolated from the same plant, the biotransformations of **1** were proposed from **2**, and the pathway was sketched as in Figure 3. In acidic conditions, compound **2** was converted to the oxonium ion **3** which was subsequently hydrated to yield **4**. After dehydration, compound **5** was produced, which then underwent acidic catalysis to form the tertiary cation **6**. As the cyclization took place from the less hindered α-phase, the resulting β-axial hydroxyl group was formed. The hydration of cation **6** also occurred preferentially from the less hindered α-face to yield **7**. Intramolecular oxidative coupling between the enol and aromatic ring of compound **7** produced garcinialone (**1**).

Acknowledgment

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9. Garcinialone (**1**): Pale yellow plate, mp 252–253 °C; $[\alpha]_D^{25}$ −2.0 (*c* 0.02, MeOH); UV (MeOH) λ_{max} (log ε): 221 (3.90), 249 (4.06), 282 (3.85) nm; IR (KBr) ν_{max} 3410, 1726, 1627, 1587, 1474, 1381, 1288, 1176, 1149 cm^{-1}; positive ESIMS *m/z* (rel. int. %) 618 (M^+, 8), 599 (54), 479 (92), 285 (100); HRESIMS *m/z* 618.3558 (calcd for $C_{38}H_{50}O_7$, 618.3557). ^1H NMR ($CDCl_3$): δ 0.97 (3H, s, H-23), 1.01 (3H, s, H-22), 1.07 (1H, m, H-6), 1.12 (3H, s, H-20), 1.17 (1H, d, *J*=13.6, H-32α), 1.28 (1H, m, H-29β), 1.42 (1H, overlap, H-7α), 1.46 (3H, s, H-33), 1.48 (3H, s, H-27), 1.51 (3H, s, H-21), 1.54 (1H, m, H-24), 1.65 (3H, s, H-28), 1.65 (3H, s, H-37), 1.73 (3H, s, H-38), 1.83 (1H, dd, *J* = 14.8, 7.6, H-34), 1.92 (1H, m, H-24), 2.05 (1H, dd, *J* = 13.2, 4.4, H-29α), 2.23 (1H, m, H-30), 2.32 (1H, overlap, H-34), 2.34 (1H, overlap, H-7β), 2.57 (1H, m, H-17), 2.59 (1H, d, *J* = 13.6, H-32β), 2.76 (1H, br d, *J* = 13.6, H-17), 4.37 (1H, br s, H-18), 4.91 (1H, br s, H-25), 5.32 (1H, m, H-35), 5.70 (1H, br s, OH), 6.82 (1H, s, H-15), 7.52 (1H, s, H-12), 9.10 (1H, br s, OH); ^{13}C NMR ($CDCl_3$): δ 18.3 (C-27), 18.5 (C-21), 18.6 (C-37), 20.5 (C-23), 24.3 (C-33), 25.4 (C-22), 25.8 (C-20), 26.2 (C-28), 26.3 (C-38), 27.6 (C-17), 29.0 (C-24), 29.6 (C-34), 33.7 (C-29), 38.8 (C-7), 43.9 (C-30), 44.0 (C-6), 49.6 (C-5), 50.7 (C-32), 54.4 (C-8), 61.2 (C-4), 74.0 (C-31), 76.2 (C-1), 102.2 (C-15), 107.4 (C-12), 115.8 (C-11), 118.4 (C-18), 122.0 (C-2), 122.6 (C-25), 123.3 (C-35), 132.4 (C-26), 132.4 (C-36), 134.1 (C-19), 142.7 (C-13), 150.8 (C-16), 151.6 (C-14), 164.0 (C-3), 177.5 (C-10), 209.2 (C-9).
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