Prenylated Benzophenone Derivatives from *Clusia havetiodes* var. *stenocarpa*

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Extracts of the fruit of *Clusia havetiodes* var. *stenocarpa* have yielded three new prenylated benzophenone derivatives, 28,29-epoxyplukenetione A (**1**), 33-hydroperoxyisoplukenetione C (**2**), and 15,16-dihydro-16-hydroperoxyplukenetione F (**3**), as well as four which have been previously described, plukenetiones C, F, and G and sampsonione G.

There is current widespread interest in the compounds from Guttiferae. Reasons for this include the recent entry of the chromeno-coumarin calanolide A, originally isolated from a Sarawak guttiferous species,[1a] into clinical trials as a nonnucleoside inhibitor of HIV-1 reverse transcriptase[1b] and the occurrence in the family of the structurally complex and generally bioactive polycyclic prenylated acyl phloroglucinol derivatives.[2] In continuation of our phytochemical survey of the Caribbean Guttiferae,[3] we have examined extracts of the aerial parts of *Clusia havetiodes* var. *stenocarpa*. *C. havetiodes* is a complex of endemic forms[4a] for which three varieties have been recognized.[4b]

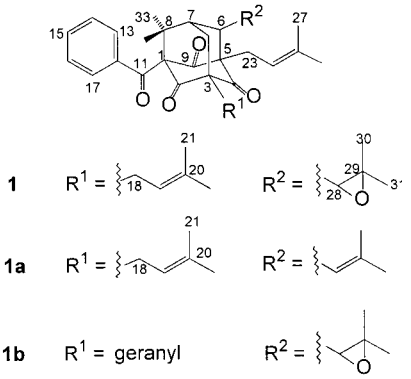
Results and Discussion

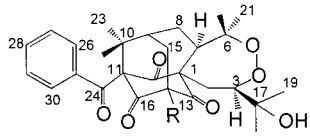
The air-dried fruits of *C. havetiodes* var. *stenocarpa* were extracted with hexane and acetone and the extract subjected to repeated column chromatography. This led to the isolation of seven prenylated benzophenone derivatives of which three (**1**−**3**) are new.

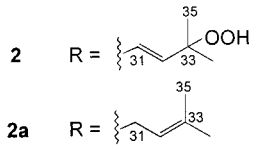
Compound **1**, a colorless oil, 0.009% of dried plant material, was assigned the molecular formula $C_{33}H_{40}O_5$ on the basis of HREIMS. Analysis of the NMR data revealed that **1** was closely related to the adamantane derivative plukenetione A (**1a**), a metabolite of *C. plukenetii* of Barbados.[3a] Thus, **1** contained a phenyl ketone, a *gem*-dimethyl, and two 2-methylbut-2-enyl groups. Tracing the connectivities from the *gem*-dimethyl group led to the formulation of a tricyclo[3.3.1.1^{3,7}]decane-2,4,9-trione system with the benzoyl, *gem*-dimethyl, and two prenyl groups attached to positions 1, 8, 3, and 5, respectively. Plukenetione A (**1a**) bears a 2-methylprop-2-enyl group at position 6. Signals for this residue are replaced in the NMR spectra of **1** by an oxymethine group (δ_C 61.36, δ_H 2.69) linked to a quaternary carbon bearing oxygen (δ_C 60.91) and to two methyl groups with relatively shielded protons (δ_H 1.32, 1.26). The chemical shifts of the oxygen-linked carbons and the molecular formula of **1** indicate that this is the 28,29-epoxy derivative of plukenetione A (**1a**). Compound **1** appears to be the lower homologue of the recently described sampsonione J (**1b**),[5] and there is close correspondence between the proton and carbon chemical shifts of the adamantane cages of **1** and **1b**.

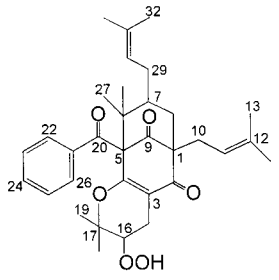
Compound **2** was isolated as a colorless oil (0.0006% of dried plant material) with a molecular formula of $C_{33}H_{42}O_9$ obtained from HREIMS. The most notable feature in the ^{1}H NMR spectrum of **2** was a pair of trans-coupled vinyl doublets at δ 6.16 and 5.72. This, considered with the molecular formula and the close coincidence of the other NMR data for **2** with those of plukenetione C (**2a**), led to the conclusion that **2** is the 33-hydroperoxy derivative of **2a** in which the double bond has migrated to C-31. Plukenetione C (**2a**) is a constituent of C. *plukenetii*[3c] and was also isolated in this study of *C. havetioides* var. *stenocarpa*. Compound **2** is derivable from **2a** via an ene reaction of singlet oxygen with the isopentenyl group.

The molecular formula of compound **3** was determined









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to be $C_{33}H_{42}O_6$ by HREIMS, requiring 13 degrees of unsaturation. The NMR data indicated the presence of a benzoyl group; two additional carbonyls, one of which was part of an enone system; and two isopentenyl groups. There were no other sp^2 hybridized centers; therefore, the molecule contained three additional rings. Comparison of the spectra of **3** with those of plukenetiones F and G[3c] revealed that **3** contained a similarly substituted bicyclo[3.3.1]-nonane moiety. Completion of the structure required addition of an oxidized 2,2-dimethyl-2H-dihydropyran ring inferred from the NMR data and satisfying the final degree of unsaturation. The position of this oxygen heterocycle was determined from the HMBC data. The position of the C-2 conjugated carbonyl group was established by cross-peaks between this signal and those for the H-8 and H-10 protons, while the quaternary carbon C-4 (δ 173.2), ascribed to an enol ether, showed connectivity to the H-15 proton.

The proton and carbon shifts at position 16 (δ_C 93.5, δ_H 4.66) were deshielded relative to those of a secondary alcohol and, when considered with the molecular formula, suggested that a hydroperoxy group was present at this position.[6] Compound **3** was therefore formulated as the 15,16-dihydro-16-hydroperoxy derivative of plukenetione F.[3c] Compound **3** gave a positive peroxide reaction with FeSCN,[7] as did the hydroperoxide (**2**), but attempts to reduce **3** with triphenylphosphine were unsuccessful.

In compound **3**, the six-membered ring composed of carbons 1, 9, 5, 6, 7, and 8 appears to have adopted a boat conformation, as described for *O*-methyl-7-*epi*-nemorosone and *O*-acetylplukenetiones D and E;[9] there is close coincidence of the carbon shifts of the *gem*-dimethyl group and proton shifts of the C-8 methylene group of **3** (and $\Delta\delta$ values) with those of the corresponding groups in the aforementioned compounds. Additionally, the *J* values observed for the C-16 peroxymethine hydrogen indicate that it is pseudoaxial.

Plukenetiones F and G, a slowly interconverting regioisomeric pair,[3c] and sampsonione G[8a] were also isolated from the fruit extract of *C. havetiodes* var. *stenocarpa*. Plukenetiones C (**2a**), F, and G were previously reported from *C. plukenetii* of Barbados.[3c] There is also a recent report of the isolation of the 17,18-dihydro derivative of plukenetione G from Cuban propolis collected in areas in which the main species foraged by the bees are *C. minor* and *C. rosea*.[8b] Sampsonione G was originally isolated from *Hypericum sampsonii* of Singapore[8a] and has been established as being epimeric at C-3 and C-5 to plukenetione B,[9a] also known from *C. plukenetii*.[3c] *C. havetiodes* var. *stenocarpa* therefore accumulates prenylated benzophenone derivatives that are closely related or identical to those of *C. plukenetii*.

Fractionation of the hexane extract of the leaves and twigs of *C. havetiodes* var. *stenocarpa* afforded the triterpenoids friedelin, 3β-friedelinol, betulinic acid, oleanolic acid, oleanolic aldehyde, and an inseparable mixture of α-amyrin, β-amyrin, and lupeol. These were identified from their spectral data and by comparison of these and physical constants with literature values.[10−15]

Experimental Section

General Experimental Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. IR spectra were recorded on a FT-IR SPECTRUM 1000 spectrometer with KBr pellets for solids or NaCl disks for oils. UV spectra were recorded in EtOH on a Perkin-Elmer UV/vis/NIR Lambda 19 spectrometer. NMR spectra were obtained on Varian GEMINI-200 and UNITY-500 spectrometers with $CDCl_3$ as solvent, unless otherwise stated, and TMS as internal standard. All MS were obtained on a Micromass VG 70−250S mass spectrometer; EIMS were obtained at 70 eV and FABMS with Xe atoms accelerated to 8 keV using *m*-nitrobenzyl alcohol as a matrix. Adsorption column chromatography was performed with Si gel 60 (230−400 mesh). TLC analysis was performed with Whatman precoated Si gel 60 F_{254} plates. Spots were visualized under UV and by spraying with 4% phosphomolybdic acid in 5% H_2SO_4 followed by heating.

Plant Material. Leaves and twigs of *C. havetiodes* var. *stenocarpa* were collected at Ecclesdown, Portland, Jamaica, in June 1994, and fruit was harvested at the same locale in March 1998. Voucher specimens from both collections (nos. 33 597 and 34 544) are held in the herbarium, Department of Life Sciences, University of the West Indies, Mona, Jamaica.

Extraction and Isolation. Air-dried fruits (350 g) were initially blended with hexane (1.5 L), and, after filtration, the plant material was repeatedly extracted with hexane. The hexane extract was taken to dryness under reduced pressure to yield a brown gum (43 g). A portion of this extract (13.6 g) was chromatographed over Si gel and eluted with 0−100% EtOAc−hexane mixtures. The residue from the 5% EtOAc−hexane fraction (4.32 g) was rechromatographed, eluting with 5−15% EtOAc−hexane. Three major fractions were obtained: fraction A, 5% EtOAc−hexane (75 mg); fraction B, 10% EtOAc−hexane (151 mg); fraction C, 15% EtOAc−hexane (674 mg). Fraction A (75 mg) was chromatographed in a gradient system of 0−1% Me_2CO−hexane to provide 28,29-epoxyplukenetione A (**1**) (10 mg) from the 1% Me_2CO−hexane fractions. Fraction B (151 mg) was chromatographed in a gradient of 0−10% Me_2CO−hexane to afford sampsonione G[8a] (7 mg) from the 5% Me_2CO−hexane fractions. Fraction C (674 mg) was further chromatographed in a gradient system of 0−100% Me_2CO−hexane. The residue from the 7% Me_2CO−hexane fraction consisted of plukenetione C (**2a**) (22 mg) and the residues of two groups of fractions were subjected to further purification: fraction D (8 mg) eluted with 8% Me_2CO−hexane; fraction E (60 mg) eluted with neat Me_2CO. 15,16-Dihydro-16-hydroperoxyplukenetione F (**3**) (3 mg) was obtained from fraction D after chromatography in 1% Me_2CO−CH_2Cl_2. 33-Hydroperoxyisoplukenetione C (**2**) (5 mg) was isolated from fraction E after chromatography in Me_2CO−CH_2Cl_2−$CHCl_3$ (1:39:60).

The Me_2CO extract (13.9 g) of the marc after hexane extraction was dissolved in 10% EtOH−H_2O, and this solution was extracted with CH_2Cl_2. The residue from evaporation of the CH_2Cl_2 extract (9.12 g) was subjected to three stages of chromatography with mixtures of EtOAc−hexane (10%, 6%, 4%) to provide a tautomeric mixture of plukenetiones F and G[3c] (47 mg), which could be separated for a brief period, as previously described,[3c] after which each tautomer reequilibrated to the mixture.

28,29-Epoxyplukenetione A (1): colorless oil; $[\alpha]_D$ −4.4° (*c* 0.98, $CHCl_3$); UV λ_{max} (log ϵ) 248 (3.46) nm; IR ν_{max} 1738, 1704, 1686 cm^{-1}; ^1H NMR [$(CD_3)_2CO$, compound dec. in $CDCl_3$, 500 MHz] δ 7.51 (1H, tt, J = 8.3, 0.8, H-15), 7.36 (2H, t, J = 8.3, H-14, H-16), 7.20 (2H, dd, J = 8.3, 0.8, H-13, H-17), 5.21 (1H, tm, J = 7.1, 1.7, H-19), 5.08, (1H, br t, J = 7.1, H-24), 2.74 (1H, ddd, J = 9.1, 2.6, 1.7, H-6), 2.69 (1H, d, J = 9.1, H-28), 2.67 (2H, m, H-10), 2.53 (2H, d, J = 7.1, H-18), 2.51 (1H, dd, J = 15.1, 6.4, H-23a), 2.45 (1H, dd, J = 15.1, 7.6, H-23b), 1.94 (1H, dd, J = 5.6, 2.6, H-7), 1.66 (9H, s, H-21, H-22, H-27), 1.63 (3H, s, H-26), 1.47 (3H, s, H-32), 1.42 (3H, s, H-33), 1.32 (3H, s, H-30), 1.26 (3H, s, H-31); ^{13}C NMR [$(CD_3)_2CO$, 125 MHz] δ 203.0 (C-4), 202.9 (C-2), 202.1 (C-9), 193.8 (C-11), 135.8 (C-12), 135.1 (C-20), 134.6 (C-25), 133.3 (C-15), 129.9 (C-13, C-17), 128.8 (C-14, C-16), 119.8 (C-24), 119.7 (C-19), 82.8 (C-1), 71.5 (C-5), 69.8 (C-3), 61.4 (C-28), 60.9 (C-29), 56.3 (C-8), 51.9 (C-6), 45.1 (C-7), 41.3 (C-10), 28.4 (C-18), 26.9 (C-23), 26.1 (C-22, C-26), 24.4 (C-30), 23.4 (C-32), 22.8 (C-33), 19.7 (C-31), 18.2 (C-27), 18.1 (C-21); HMBC (C/H) 1/7, 32, 33, 3/10, 18, 4/6, 10, 23, 5/6, 7, 23, 6/10, 28, 7/6, 10, 28, 32, 33, 8/10, 32, 33, 9/23, 10/6, 18, 11/13, 17, 12/14, 16, 13,17/15, 17,

13, 14,16/16, 14, 15/13, 17, 18/10, 19/18, 21, 22, 20/18, 21, 22, 21/19, 22, 22/19, 22, 24/23, 26, 27, 25/23, 26/24, 27, 27/24, 26, 28/31, 29/6, 30, 31, 30/28, 31, 31/30, 32/33, 33/32; EIMS *m/z* 516 $[M]^+$ (5), 501 (6), 488 (19), 417 (11), 403 (8), 364 (8), 349 (14), 309 (13), 283 (13), 229 (11), 187 (18), 173 (9), 149 (7), 105 (100), 83 (10), 77 (33), 69 (34), 58 (15), 55 (13); HREIMS *m/z* 516.2859 (calcd for $C_{33}H_{40}O_5$ 516.2876).

33-Hydroperoxyisoplukenetione C (2): colorless oil; $[\alpha]_D$ −3.9° (*c* 0.23, $CHCl_3$); UV λ_{max} (log ϵ) 245 (4.05), 273 (sh) (3.80) nm; IR ν_{max} 3632, 1732, 1704, 1685 cm^{-1}; ^1H NMR (500 MHz) δ 8.02 (1H, s, OO*H*), 7.44 (1H, t, *J* = 7.8, H-28), 7.32 (2H, td, *J* = 7.8, 0.9, H-27, H-29), 7.18 (2H, dd, *J* = 7.8, 0.9, H-26, H-30), 6.16 (1H, d, *J* = 16.6, H-31), 5.72 (1H, d, *J* = 16.6, H-32), 4.59 (1H, dd, *J* = 11.7, 3.0, H-3), 3.52 (1H, dd, *J* = 14.9, 11.6, H-2a), 2.84 (1H, dd, *J* = 11.2, 8.2, H-7), 2.84 (1H, m, H-15a), 2.48 (1H, m, H-8a), 2.18 (1H, m, H-9), 2.10 (1H, m, H-15b), 1.58 (1H, m, H-2b), 1.56 (1H, m, H-8b), 1.51 (3H, s, H-23), 1.43 (3H, s, H-35), 1.42 (3H, s, H-34), 1.39 (3H, s, H-22), 1.30 (3H, s, H-21), 1.13 (3H, s, H-19), 1.07 (3H, s, H-18), 1.06 (3H, s, H-20);^{13}C NMR (125 MHz) δ 207.2 (C-12), 204.2 (C-13), 203.1 (C-16), 191.5 (C-24), 137.1 (C-32), 134.5 (C-25), 132.6 (C-28), 128.7 (C-26, C-30), 128.2 (C-27, C-29), 126.8 (C-31), 88.7 (C-3), 88.4 (C-6), 82.0 (C-33), 81.6 (C-11), 73.0 (C-17), 69.1 (C-14), 66.9 (C-1), 50.3 (C-10), 44.4 (C-9), 42.4 (C-7), 39.4 (C-15), 31.4 (C-2, C-8), 28.2 (C-21), 25.9 (C-18), 25.0 (C-23), 24.8 (C-19), 24.6 (C-34), 24.1 (C-35), 22.7 (C-22); HMBC (C/H) 1/2, 7, 2/3, 3/2, 18, 19, 6/7, 8, 20, 21, 7/2, 20, 21, 8/7, 15, 9/7, 15, 22, 23, 10/15, 22, 23, 11/22, 23, 12/2, 7, 13/2, 7, 15, 14/15, 32, 16/15, 17/18, 19, 18/19, 19/18, 20/7, 21, 21/20, 22/23, 23/22, 24/26, 30, 25/27, 29, 26,30/28, 30, 26, 27,29/29, 27, 28/26, 30, 31/15, 32/34, 35, 33/31, 32, 34, 35, 35/32, 34; FABMS *m/z* 582 $[M]^+$ (1), 552 (4), 534 (5), 500 (3), 327 (4), 267 (3), 187 (5), 149 (9), 129 (3), 105 (100); HREIMS *m/z* 582.2846 (calcd for $C_{33}H_{42}O_9$ 582.2829).

15,16-Dihydro-16-hydroperoxyplukenetione F (3): colorless oil; $[\alpha]_D$ +24.7° (*c* 0.3, $CHCl_3$); UV λ_{max} (log ϵ) 245 (sh) (4.05), 273 (sh) (3.80) nm; IR ν_{max} 3628, 1730, 1705, 1699, 1688 cm^{-1}; ^1H NMR (500 MHz) δ 7.58 (2H, dd, *J* = 7.9, 1.1, H-22, H-26), 7.50 (1H, t, *J* = 7.9, H-24), 7.36 (2H, tt, *J* = 7.9, 1.1, H-23, H-25), 5.09 (1H, tq, *J* = 7.1, H-11), 4.90 (1H, t, *J* = 5.8, H-30), 4.66 (1H, dd, *J* = 11.7, 7.9, H-16), 2.96 (1H, dd, *J* = 15.0, 8.8, H-15a), 2.81 (1H, dd, *J* = 15.0, 10.8, H-15b), 2.61 (1H, dd, *J* = 14.1, 6.4, H-10a), 2.50 (1H, dd, *J* = 14.1, 7.8, H-10b), 2.25 (1H, br d, *J* = 15.3, H-29a), 2.18 (1H, dd, *J* = 14.3, 7.2, H-8a), 2.11 (1H, br d, *J* = 13.2, H-8b), 2.00 (1H, dt, *J* = 15.3, 8.8, H-29b), 1.72 (3H, s, H-13), 1.69 (3H, s, H-33), 1.67 (3H, s, H-14), 1.56 (3H, s, H-32), 1.50 (1H, m, H-7), 1.48 (3H, s, H-28), 1.43 (3H, s, H-27), 0.91 (3H, s, H-18), 0.90 (3H, s, H-19), −0.1 (1H, s, EXSY cross-peak w. H_2O, OO*H*); ^{13}C NMR (125 MHz) δ 207.7 (C-9), 193.1 (C-20), 190.7 (C-2), 173.2 (C-4), 137.1 (C-21), 134.8 (C-12), 132.8 (C-24, C-31), 128.5 (C-23, C-25), 128.2 (C-22, C-26), 124.6 (C-30), 119.3 (C-11), 118.6 (C-3), 93.5 (C-16), 70.8 (C-17), 68.5 (C-5), 63.5 (C-1), 48.9 (C-6), 48.5 (C-7), 40.7 (C-8), 29.8 (C-10), 29.7 (C-29), 27.0 (C-15), 26.8 (C-27), 26.4 (C-18), 26.1 (C-33), 25.8 (C-14), 23.7 (C-19), 23.6 (C-28), 18.2 (C-13), 18.0 (C-32); HMBC (C/H) 1/8, 10, 2/8, 10, 3/15, 4/15, 5/27, 28, 6/8, 27, 28, 7/8, 29, 8/10, 29, 9/8, 10, 11/10, 13, 14, 12/10, 13, 14, 14/11, 13, 16/15, 18, 19, 17/15, 18, 19, 18/19, 19/18, 20/22, 26, 21/23, 25, 22,26/24, 26, 22, 23,25/25, 23, 24/22, 26, 27/28, 28/27, 29/8, 30/29, 32, 33, 31/29, 32, 33, 32/30, 33; EIMS *m/z* 534 $[M]^+$ (1), 518 (25), 503 (6), 465 (6), 449 (19), 435 (18), 393 (12), 381 (43), 363 (13), 327 (52), 309 (13), 268 (26), 231 (12), 189 (16), 177 (12), 149 (45), 135 (14), 123 (18), 109 (21), 105 (100), 99 (22), 95 (31), 93 (21), 81 (30), 69 (76); HREIMS *m/z* 534.2957 (calcd for $C_{33}H_{42}O_6$ 534.2981).

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Supporting Information Available: Structures and spectroscopic data for plukenetiones C (**2a**), F (**4**), and G (**5**) and sampsonione G (**6**). This material is available free of charge via the Internet at http://pubs.acs.org.

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