# Vismiaphenones D−G, New Prenylated Benzophenones from *Vismia cayennensis*†

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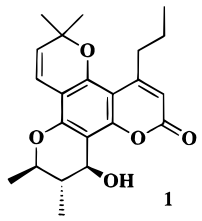
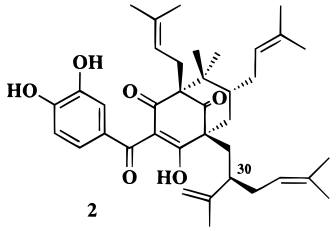
Following anti-HIV bioassay-guided fractionation, four new prenylated benzophenones, vismiaphenones D−G (**7**−**10**), were isolated from extracts of leaves of *Vismia cayennensis*. The structures were elucidated by spectral analyses. Only vismiaphenone D (**7**) exhibited HIV-inhibitory activity in the NCI primary screen.

The plant family Guttiferae (Clusiaceae) has proved to be a valuable source of leads to HIV-inhibitory natural products. (+)-Calanolide A (**1**), a specific inhibitor of HIV-1 reverse transcriptase, was isolated from *Calophyllum langiferum* var. *austrocoriaceum*[2−4] and is now in phase I clinical trials. Anti-HIV guttiferones (e.g., **2**),[5] new analogues of the camboginol class of polyprenylated benzophenones,[6] were found in species of the genera *Garcinia*, *Clusia*, and *Symphonia*.




**1**



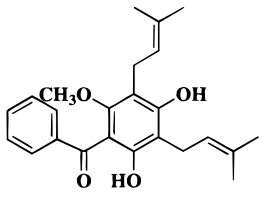

**2**

Among the consequences of these discoveries were the needs to dereplicate other extracts from this family for the presence of the guttiferone/camboginol chemotype[7] and to search for better sources of the calanolides or new, more potent members of that class.[8,9] The former has already led to extension of the known range of the guttiferones/camboginols to the genus *Allanblackia*[1] and has suggested other possible sources in the family.[7] Herein we report an investigation of one of those leads, *Vismia cayennensis* (Jacq) Pers.

There have been numerous chemical studies of the genus *Vismia* and at least one report on the chemistry of *V. cayennensis*.[10] Most relevant to this work are reports on vismiaphenones A−C and isovismiaphenone B (**3** − **6**, respectively)[11,12] and seemingly derived xanthones.[13] Other compound types found in the genus include anthracenones,[14] anthrones,[15] anthraquinones,[16,17] and lignans.[18]

## Results and Discussion

In chemotaxonomic screening,[7] one of three HIV-inhibitory *Vismia* extracts gave a TLC profile suggestive of, but not conclusive for, the presence of guttiferones. That extract, the organic extract of leaves of *V. cayennensis*, was separated by solvent−solvent partitioning, gel permeation chromatography, and normal-phase HPLC on a cyano-bonded phase to give four new compounds, vismiaphenones D−G (**7**−**10**).

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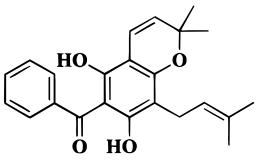


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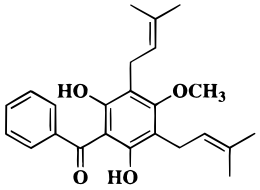


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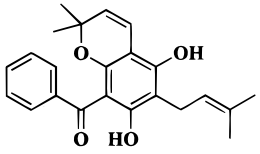


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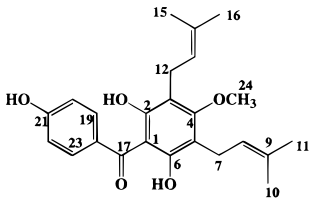


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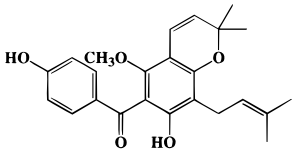


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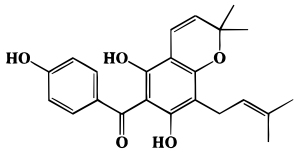
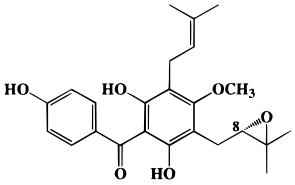



**8**




**10**

HREIMS established a molecular formula of $C_{24}H_{28}O_5$ for vismiaphenone D (**7**). Cursory inspection of the NMR spectra indicated that there had to be some element(s) of symmetry in the molecule. Two aromatic ring systems were present, one fully substituted, the other *p*-disubstituted; integration of the $^1$H NMR spectrum revealed that both

† HIV-Inhibitory Natural Products. 50. For part 49, see Fuller et al.[1]

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**Table 1.** $^{1}H$ and $^{13}C$ NMR Assignments of Vismiaphenones D−G (**7** − **10**)[a]

| | **7** | | **8** | | **9** | | **10** | |
|---|---|---|---|---|---|---|---|---|
| carbon | $^{13}C$ | $^{1}H$[b] | $^{13}C$ | $^{1}H$[b] | $^{13}C$ | $^{1}H$[b] | $^{13}C$ | $^{1}H$[b] |
| 1 | 111.6 | | 104.0 | | 108.3 | | 110.9 | |
| 2 | 156.2 | | 158.3 | | 159.9 | | 158.5 | |
| 3 | 115.8 | | 110.7 | | 114.0 | | 115.7 | |
| 4 | 162.8 | | 156.7 | | 157.3 | | 152.8 | |
| 5 | 115.8 | | 107.4 | | 114.1 | | 106.1 | |
| 6 | 156.2 | | 150.0 | | 155.6 | | 162.2 | |
| 7 | 23.6 | 3.28 (2H, d, 7) | 22.2 | 3.22 (2H, d, 7) | 22.7 | 3.27 (2H, d, 7) | 26.9 | 2.60 (1H, dd, 17, 5.3)<br>2.92 (1H, dd, 17, 7) |
| 8 | 124.7 | 5.19 (1H, br t, 7) | 124.1 | 5.17 (1H, br t, 7) | 123.5 | 5.18 (1H, br t, 7) | 69.6 | 3.60 (1H, dd, 7, 5.3) |
| 9 | 131.8 | | 131.2 | | 128.8 | | 78.5 | |
| 10 | 17.1 | 1.75 (3H, s) | 17.9 | 1.76 (3H, s) | 17.8 | 1.78 | 25.3 | 1.04 (3H, s) |
| 11 | 26.1 | 1.67 (3H, s) | 25.1 | 1.65 (3H, s) | 25.6 | 1.66 | 20.5 | 1.01 (3H, s) |
| 12 | 23.6 | 3.28 (2H, d, 7) | 117.5 | 6.56 (1H, d, 10) | 117.4 | 6.49 (1H, d, 10) | 22.7 | 3.29 (2H, d, 7) |
| 13 | 124.7 | 5.19 (1H, br t, 7) | 126.7 | 5.52 (1H, d, 10) | 128.7 | 5.62 (1H, d, 10) | 124.4 | 5.19 (1H, br t, 7) |
| 14 | 131.8 | | 78.1 | | 78.2 | | 131.6 | |
| 15 | 17.1 | 1.75 (3H, s) | 28.2 | 1.49 (6H, s) | 28.0 | 1.43 (3H, s) | 17.8 | 1.77 (3H, s) |
| 16 | 26.1 | 1.67 (3H, s) | 28.2 | 1.49 (6H, s) | 28.0 | 1.43 (3H, s) | 25.7 | 1.67 (3H, s) |
| 17 | 198.8 | | 198.3 | | 198.6 | | 199.7 | |
| 18 | 131.9 | | 132.2 | | 133.5 | | 133.2 | |
| 19 | 133.5 | 7.64 (2H, d, 9) | 133.0 | 7.58 (2H, d, 8.5) | 133.0 | 7.62 (2H, d, 9) | 132.6 | 7.54 (2H, d, 8.5) |
| 20 | 115.7 | 6.79 (2H, d, 9) | 115.5 | 6.78 (2H, d, 8.5) | 115.3 | 6.79 (2H, d, 9) | 115.3 | 6.78 (2H, d, 8.5) |
| 21 | 163.9 | | 162.2 | | 163.3 | | 162.7 | |
| 22 | 115.7 | 6.79 (2H, d, 9) | 115.5 | 6.78 (2H, d, 8.5) | 115.3 | 6.79 (2H, d, 9) | 115.3 | 6.78 (2H, d, 8.5) |
| 23 | 133.5 | 7.64 (2H, d, 9) | 133.0 | 7.58 (2H, d, 8.5) | 133.0 | 7.62 (2H, d, 9) | 132.6 | 7.54 (2H, d, 8.5) |
| 24 | 61.9 | 3.71 (3H, s) | | | 63.0 | 3.32 (3H, s) | 60.9 | 3.76 (3H, s) |

[a] Recorded in $CD_3OD$. [b] $\delta$ (H, multiplicity, $J$ in Hz).

rings were symmetrically substituted. The substituents on the *p*-disubstituted ring were determined to be hydroxyl and carbonyl, from chemical shift arguments and mass spectral fragmentation (*m*/*z* 93, 121). The substituents on the other ring were one methoxyl, one carbonyl, two hydroxyl, and two 3,3-dimethylallyl (prenyl) groups. The hydroxyls were placed ortho to the carbonyl to account for the hydrogen-bonding indicated in the IR (1607 $cm^{-1}$) and NOEs observed between the methoxyl group and the olefinic and methylene protons of the prenyl groups. Thus, vismiaphenone D has structure **7**; it is the 21-hydroxy derivative of vismiaphenone C.[11]

Vismiaphenone E, $C_{23}H_{24}O_5$ by HREIMS, lacked both a methoxyl substituent and the symmetry element in the fully substituted phenyl ring. The additional site of unsaturation, relative to **7**, and the changes in chemical shifts for the protons and carbons of one of the prenyl groups indicated cyclization to a pyran ring. Its structure was assigned as **8** on the basis of comparison of its $^{1}H$ NMR spectrum with those of vismiaphenone B (**4**) and isovismiaphenone B (**6**)[11,12] and related compounds.[19,20]

Vismiaphenone F (**9**), $C_{24}H_{26}O_5$, was a monomethoxylated analogue of **8**. The regiochemistry of the cyclized prenyl group (chromene ring) was assigned as in **4**, **6** and **8**, based on similar chemical shift patterns. The methoxyl group was placed ortho to the chromene ring and para to the normal prenyl group on the basis of modest NOE correlations to the chromene ring olefinic proton. The anomalous chemical shift of the aryl methoxyl group ($\delta$ 3.32) is likely due to anisotropic shielding by the *p*-hydroxyphenyl ring, which would be orthogonal to the hydrogen-bonded aryl carbonyl chromophore.

Vismiaphenone G (**10**) contained one more oxygen atom than vismiaphenone D ($C_{24}H_{28}O_6$ by HREIMS). Asymmetrical substitution of the fully substituted ring was again obvious from the NMR spectra. The methoxyl group was placed para to the carbonyl substituent because of its chemical shift ($\delta$ 3.76) and weak NOEs to the methylenes of both prenyl groups (H-7, H-12). One prenyl group was present as the typical 3,3-dimethylallyl substituent, while the other had undergone epoxidation of the olefinic bond (ABX spin system at $\delta$ 3.60, 2.92, 2.60, each signal a 1H doublet of doublets; see Table 1). Thus, structure **10** was determined for vismiaphenone G. Vismiaphenone G was optically active, $[\alpha]_D$ −8°; the absolute configuration at C-8 could be proposed as *S* on the basis of analogy to several known epoxides of prenyl groups.[21,22]

Of the four new compounds, only vismiaphenone D (**7**) exhibited any consistent activity in the primary anti-HIV screen ($EC_{50}$ ca. 11 $\mu$g/mL).[23,24] However, much like the guttiferones,[5,10] complete cytoprotection was not achieved, and **7** was rather cytotoxic to the CEM-SS host cells ($IC_{50}$ ca. 30 $\mu$g/mL). The vismiaphenones might be viewed as biosynthetic relatives of, and possibly precursors to, the guttiferones. Additional prenylation and subsequent carbocyclization would lead to guttiferone analogues.

## Experimental Section

**General Experimental Procedures.** Gel permeation chromatography was carried out using Sephadex LH-20. HPLC utilized a Rainin SD-1 system equipped with a Dynamax-cyano column (4.1 × 30 cm), using a flow rate of 80 mL/min (hexane−$^{i}$PrOH, 17:3) and monitoring by UV at 290 nm. NMR spectra were recorded on a Varian VXR500 in $CD_3OD$ and $CDCl_3$ at 500 MHZ for $^{1}H$ and 125 MHZ for $^{13}C$. Other instrumentation included a Perkin−Elmer 241 polarimeter ($[\alpha]_D$), Perkin−Elmer spectrum 2000 (IR), and Beckman DU 64 (UV).

**Plant Material.** Leaves of *Vismia cayennensis* (Jacq) Pers were collected in the Pastaza Province of Ecuador by B. M. Boon, J. Rombold, and R. Doenges in December 1987. A voucher specimen (T-7858) is on deposit at the New York Botanical Garden. The dried leaves (872 g) were extracted by the NCI standard protocol as described elsewhere[25] to give 77.6 g of organic extract.

**Experimental.** The crude organic extract (10 g) was subjected to solvent−solvent partitioning, yielding hexane (1.35 g), MeOtBu (1.09 g), EtOAc (3.9 g), and $H_2O$ (2.99 g) fractions. The MeOtBu fraction was permeated through Sephadex LH-20 with $CH_2Cl_2$−MeOH (1:1), concentrating the activity in the second fraction (0.334 g). This active fraction was purified by HPLC on a normal-phase cyano column (hexane−

$^{i}$PrOH, 17:3) to give vismiaphenone D (**7**, 5 mg), vismiaphenone E (**8**, 136 mg), vismiaphenone F (**9**, 12 mg), and vismiaphenone G (**10**, 3 mg), all glasses.

**Vismiaphenone D (7):** UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 298 (4.04), 227 (4.32), 203 (4.52) nm); IR (film) $\nu_{max}$ 3368, 2976, 2928, 2857, 1607, 1513, 1440, 1376, 1282, 1216, 1166, 1099, 959, 891, 800 cm$^{-1}$; HREIMS *m/z* 396.1937 ($M^+$ calcd for $C_{24}H_{28}O_5$, 396.1936); LREIMS *m/z* 396, 353, 341, 325, 297, 285, 247, 231, 203, 127, 121, 93; for $^1$H and $^{13}$C NMR data, see Table 1.

**Vismiaphenone E (8):** UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 318 (3.9), 281 (4.01), 210 (4.30) nm; IR (film) $\nu_{max}$ 3308, 2925, 2857, 1603, 1510, 1440, 1376, 1321, 1282, 1167, 1129 cm$^{-1}$; HREIMS *m/z* 380.1601 ($M^+$, calcd for $C_{23}H_{24}O_5$, 380.1632); LREIMS *m/z* 380, 365, 309, 271, 231, 215, 189, 121, 93; for $^1$H and $^{13}$C NMR data, see Table 1.

**Vismiaphenone F (9):** UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 295 (3.4), 273 (4.0), 225 (4.2) nm; IR (film) $\nu_{max}$ 3303, 2925, 2856, 1600, 1459, 1376, 1284, 1164, 1127, 799 cm$^{-1}$; HREIMS *m/z* 394.1762 ($M^+$, calcd for $C_{24}H_{26}O_5$, 394.1780); LREIMS *m/z* 394, 379, 323, 285, 215, 135, 121, 93, 55.1; for $^1$H and $^{13}$C NMR data, see Table 1.

**Vismiaphenone G (10):** $[\alpha]_D$ −8° (*c* 0.08, $CHCl_3$); UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 291 (3.7), 227 (3.9), 210 (4.0) nm; IR (film) $\nu_{max}$ 3351, 2926, 1597, 1439, 1278, 1223, 1161, 1117 cm$^{-1}$; HRFABMS *m/z* 413.1948 ($MH^+$, calcd for $C_{24}H_{29}O_6$, 413.1964); LRFABMS *m/z* 413, 357, 341, 309, 247, 191, 119, 85; for $^1$H and $^{13}$C NMR data, see Table 1.

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