Oblongifolins A−D, Polyprenylated Benzoylphloroglucinol Derivatives from *Garcinia oblongifolia*

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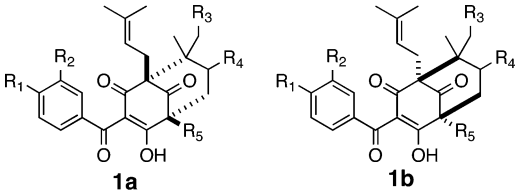
Oblongifolins A−D (**2**−**5**), four new polyprenylated 3,4-dihydroxybenzoylphloroglucinol compounds, were isolated from the bark of *Garcinia oblongifolia* collected in Vietnam. The bark was also found to contain the known compounds camboginol and guttiferone B. Extraction of the leaves gave **2** and camboginol. Details of the structure elucidation of **2**−**5** and stereochemical comparisons with known natural derivatives of general formula **1a**,**b** are presented. The biological activity of these compounds concerning interactions with tubulin was investigated.

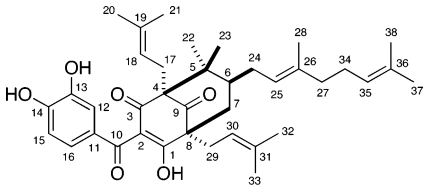
A number of polyprenylated benzoylphloroglucinol derivatives, corresponding to the general structure **1a** or **1b**, have been isolated from tropical plants belonging to the family Clusiaceae, and notably to the genera *Garcinia* and *Clusia*.[1] Compounds **1a** and **1b** are substituted derivatives with enantiomeric enolized bicyclo[3.3.1]-nonane-2,4,9-trione cores. A particular feature of this class of natural products, and also of related compounds, is the high diversity of isoprenoid units found as substituents R_3, R_4, and R_5.[1] Two recent reviews, concerning natural benzophenones including polyprenylated derivatives with the bicyclo[3.3.1]nonane skeleton, concern in particular structural elucidation.[1] As the absolute configuration of most of them is not known, except for xanthochymol,[2] guttiferone E,[3] and camboginol (garcinol),[3] these could have either structure **1a** or **1b**.



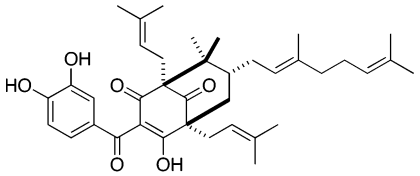
These compounds display a set of biological activities including antibacterial, anti-HIV, and cytotoxic effects. Our interest in this field originated in particular from the discovery that xanthochymol[4] was nearly as active as paclitaxel in a tubulin assembly inhibition test.[5] In the search for new derivatives of general structure **1**, we report herein a study concerning two extracts of *Garcinia oblongifolia* collected in Vietnam. As a result, four new natural products, related to **1a** or **1b** and named oblongifolins A (**2**), B (**3**), C (**4**), and D (**5**), were isolated, and their structures determined by spectroscopy. In addition, the known compounds camboginol[6] and guttiferone B[3] were also obtained.

Results and Discussion

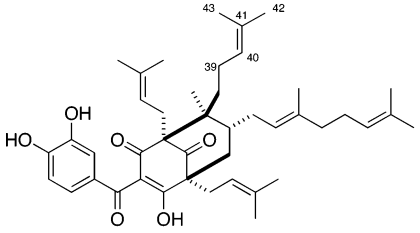
Extraction of the leaves of *G. oblongifolia* with ethyl acetate, followed by chromatography, allowed the isolation of two compounds, known as camboginol[6] and a new derivative, named oblongifolin A (**2**). The same procedure, applied to the bark, afforded again camboginol and oblongifolin A (**2**) along with guttiferone B[3] and three new compounds, oblongifolins B (**3**), C (**4**), and D (**5**).



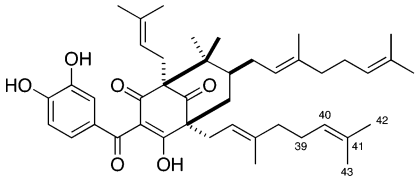
(+)-oblongifolin A (**2**)



(+)-oblongifolin B (**3**)



(+)-oblongifolin C (**4**)



(+)-oblongifolin D (**5**)

Derivatives **2**−**5** exhibited similar UV spectra, typical for benzoylphloroglucinol **1a** or **1b** (see Experimental Section and Supporting Information). In particular, the bathochromic shift of their λ_{max} in alkaline solution[4] was in agreement with the presence of phenolic and enolic systems. The IR data were also close to those described for derivatives of this class of compounds, indicating characteristic bands for hydroxy and carbonyl groups (one isolated and two conjugated). The ^{13}C NMR spectra of **2**−**5** also showed the presence of a bicyclo[3.3.1]nonane-2,4,9-trione moiety,[3] with

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Table 1. ^{13}C and ^{1}H NMR Data (150 and 600 MHz, CD_3OD + 0.1% TFA-*d*) for Compounds **2**−**5**

	oblongifolin A (**2**)		oblongifolin B (**3**)		oblongifolin C (**4**)		oblongifolin D (**5**)	
position	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)
1	196.3		196.5		194.7		195.2	
2	117.9		118.9		119.6		118.0	
3	195.9		195.9		191.4		194.6	
4	68.8		69.7		69.5		68.2	
5	48.4		49.0		51.6		49.2	
6	47.8	1.53, m	44.2	1.60, m	42.0	1.78, m	48.0	1.53, m
7	40.8	eq. 2.16, m	43.3	eq. 2.05, m	43.2	eq. 2.07, m	40.7	eq. 2.20, m
		ax. 2.08, m		ax. 1.47, t (13.0)		ax. 1.46, t (12.8)		ax. 2.11, m
8	61.8		64.3		64.2		66.5	
9	209.8		209.1		209.1		209.8	
10	195.8		195.5		196.6		195.9	
11	129.5		130.0		130.3		129.7	
12	117.4	7.17, d (2.1)	117.4	7.20, d (2.1)	117.5	7.20, d (2.1)	117.5	7.20, d (2.1)
13	146.2		146.1		146.4		146.3	
14	152.5		152.4		152.6		152.7	
15	115.2	6.70, d (8.3)	115.2	6.70, d (8.3)	115.2	6.70, d (8.3)	115.3	6.68, d (8.3)
16	125.1	6.97, dd (8.3, 2.1)	125.1	6.95, dd (8.3, 2.1)	125.3	6.96, dd (8.3, 2.1)	125.6	6.98, dd (8.3, 2.1)
17	27.0	2.71, dd (9.0, 13.0)	27.4	2.71, dd (9.0, 13.0)	26.7	2.74, dd (9.0, 13.0)	27.3	2.73, dd (9.0, 13.0)
		2.58, m		2.61, m		2.66, m		2.58, m
18	120.7	4.94, m	121.1	4.90, m	121.4	4.87, m	121.0	4.94, m
19	135.5		135.5		135.1		135.9	
20	26.3	1.71, s	26.5	1.71, s	26.4	1.62, s	26.5	1.65, s
21	18.3	1.67, s	18.5	1.67, s	18.5	1.69, s	18.4	1.68, s
22	27.4	1.01, s	16.5	0.79, s	16.4	0.82, s	27.5	1.02, s
23	23.3	1.24, s	24.0	1.17, s	37.6	1.68, m	23.4	1.23, s
24	30.1	2.15, m	29.2	2.13, m	30.1	2.10, m	30.2	2.15, m
		2.06, m		1.74, m		1.77, m		2.07, m
25	125.6	4.90, m	123.9	4.98, m	123.9	5.00, m	125.8	4.87, m
26	137.3		138.0		138.2		137.5	
27	40.8	1.96, m	40.8	1.96, m	40.9	1.98, m	41.0	1.98, m
28	16.4	1.47, s	16.6	1.54, s	16.6	1.56, s	16.6	1.48, s
29	32.0	2.52, dd (8.0, 14.0)	31.5	2.52, dd (8.0, 14.0)	31.7	2.54, dd (8.0, 14.0)	32.0	2.52, m
		2.47, m		2.47, m		2.46, m		
30	120.7	5.16, m	120.9	5.14, m	121.0	5.12, m	120.7	5.16, m
31	135.7		135.4		135.6		139.3	
32	26.3	1.69, s	26.1	1.64, s	26.4	1.71, s	41.1	1.98, m
33	18.3	1.67, s	18.4	1.66, s	18.4	1.66, s	17.0	1.69, s
34	27.5	2.06, m	27.6	2.06, m	27.6	2.06, m	27.8	2.05, m
35	125.1	5.06, m	125.2	5.04, m	125.0	5.05, m	125.4	5.06, m
36	132.1		132.3		132.4		132.2	
37	26.0	1.65, s	26.0	1.65, s	26.1	1.64, s	26.0	1.58, s
38	17.8	1.56, s	18.0	1.58, s	18.0	1.57, s	17.9	1.53, s
39					25.3	1.98, m	27.7	2.05, m
40					125.6	5.05, m	125.4	5.06, m
41					132.6		132.3	
42					26.0	1.67, s	26.1	1.65, s
43					18.0	1.60, s	17.9	1.59, s

three quaternary carbons, one methine, one methylene, a nonconjugated ketone (ca. δ 209), and an enolized 1,3-diketone (two signals (C) at ca. δ 195 and one at ca. δ 118). Substitution by a dihydroxylated benzoyl group could also be deduced from the chemical shifts of the aromatic carbons and of the conjugated carbonyl (ca. δ 196).[3] Several isoprenyl appendages, as shown by ^{1}H NMR (vide infra), were included to complete the structural elements of **2**−**5**. This information, associated with data for known compounds in these series and with a knowledge of the known phytochemistry of the genus *Garcinia*,[1] suggested that **2**−**5** are guttiferone-type structures[3] with prenyl and geranyl chains. The A-type of cyclization (benzoyl group substituting one of the bridgehead carbons)[1a,7] could be excluded because the C-17 methylene is not bis-allylic but on a sp^3 carbon (^{1}H NMR spectrum).

The positive-ion HRESIMS, with the ions $[M + Na]^+$ at *m*/*z* 625 (**2** and **3**) and *m*/*z* 693 (**4** and **5**), showed that these isolates can be considered as two pairs of isomers: **2** and **3** ($C_{38}H_{50}O_6$), on one hand, and **4** and **5** ($C_{43}H_{58}O_6$), on the other hand.

The ^{1}H and ^{13}C NMR spectra of **2**−**5** (Table 1) were recorded in CD_3OD + 0.1% TFA-*d*, to enhance the rate of the keto−enol interconversion of the β-hydroxy-α,β-unsaturated ketone[3] and to simplify the analysis[8] (the spectra in $CDCl_3$ showed tautomeric pairs).[9] The data obtained demonstrated the presence of isoprene units, with one of them being an integral part of the bicyclo[3.3.1]-nonane-2,4,9-trione skeleton, and of a 3,4-dihydroxybenzoyl function (typical chemical shifts and coupling constants for this AMX system).[3] Whereas two methyl groups on the sp^3 carbon are present in **2**, **3**, and **5** (δ_H for positions 22 and 23, Table 1), there is only one in **4**. The number of olefinic protons and uncyclized isoprene units is four in **2** and **3**, with seven methyls on sp^2 carbons, and five in **4** and **5**, with, respectively, nine and eight vinylic methyl groups. HMBC and NOE NMR data (see Supporting Information) were used to establish the type of substitution, the distribution, and the location of the side chains. These experiments showed that a *gem*-dimethyl substitution at C-5 (correlations with C-22 and C-23) is present in **2**, **3**, and **5**, whereas one of these methyl groups is substituted by a prenyl in **4** (correlations for the isopent-2-enyl with C-23). The four compounds (**2**−**5**) all possess a prenyl at the bridgehead position C-4, next to the tetrasubstituted carbon (correlations with C-22 and C-23), and a geranyl at C-6 (correlations for a two-isoprene unit with the methine C-6 or the methylene C-7). The other bridgehead C-8 is substituted by a prenyl in **2**−**4** and by a geranyl in **5** (correlations with the methylene C-7). The *E* configuration of the double bond in the geranyl side chains was

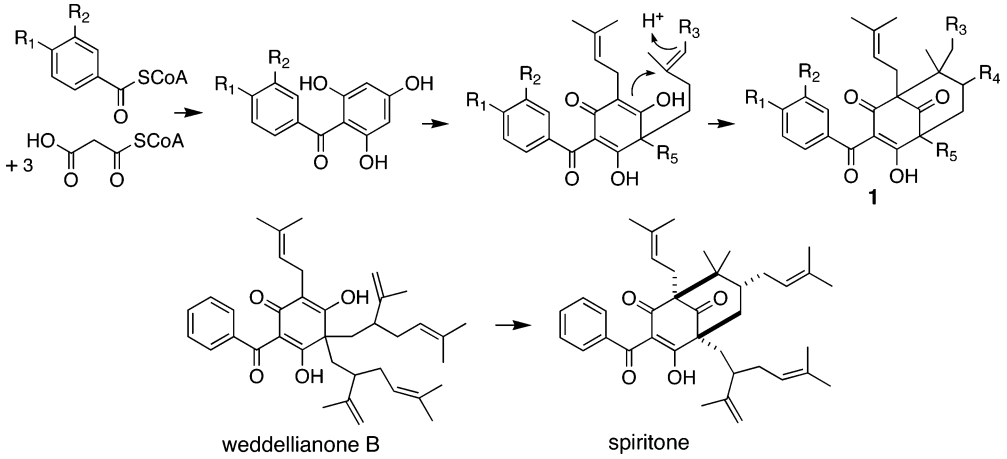

Figure 1. Biogenetic scheme for the formation of **1**.

assigned in the ^{13}C NMR spectrum, with δ_C ca. 17 for the methyls C-28 (**2**−**5**) and C-33 (**5**), *cis* to respectively C-24 and C-29, and δ_C ca. 41 for the methylenes C-27 (**2**−**5**) and C-32 (**5**), *trans* to the same positions.[1a]

For the relative configuration of these compounds, it should be noted that the bridged bicyclic system requires that the side chains at C-4 and C-8 are equatorial. Then, it was necessary to determine the *cis*−*trans* relationship of the geranyl group at C-6 with the bridgehead substituents (for **2**−**5**) and with the homoprenyl at C-5 (for **4**). For **3** and **4**, the coupling constant between H-6 and H-7ax (ca. 13 Hz) showed that these protons are diaxial, and thus the geranyl group at C-6 is equatorial (*cis* to the C-4 and C-8 prenyls). In the case of **2**, $J_{H-6,H-7ax}$ (ca. 6 Hz, measured after irradiation of H-6) was in favor of the axial position for the geranyl side chain at C-6; this compound is thus the epimer of **3** at C-6. The configuration of the C-6 substituent, for the *gem*-dimethyl compounds, could also be deduced from the value of δ_C of the axial methyl C-22 (27.4 for **2** and 27.5 for **5**, with the axial geranyl, and 16.5 for **3**, with the equatorial group), as generally observed for compounds **1a** or **1b** in such a situation.[1a] This is due, in part, to the γ-gauche interaction shielding of the axial methyl by the C-6 substituent when this group is equatorial. For **4**, with only one methyl at C-5, the NOE interaction of H-7ax with H-22 (axial Me) was in agreement with the presence of the equatorial homoprenyl chain at C-5. The *cis* relationship of the methyl at C-5 with the geranyl chain at C-6 was corroborated by the value of δ_C for C-22 (16.4), as seen with **3**. Compound **4** has the same substitution pattern and relative configuration as those reported for guttiferone G,[10] and the ^1H and ^{13}C NMR data of **4** were run in pyridine-d_5 as solvent, to make comparisons, and were the same as those of guttiferone G. As the signs for the optical rotation of the two compounds are opposite, it is proposed that these are enantiomers. Moreover, the data published for guttiferone I by Singh et al.,[11] while the present study was ongoing, and concerning the ^1H and ^{13}C NMR spectra also recorded in pyridine-d_5, were almost identical with those of guttiferone G. The authors, who noted this similarity, suggested another relative configuration, due to differences of the absolute values of $[\alpha]_D$ between the two compounds (see Supporting Information) and a twisted boat conformation for the cyclohexanone ring of guttiferone I. If this were the case, δ_C and δ_H for positions 5, 6, 7, 22, 23, and 24 should be different for compounds with chair and boat conformations, but these are identical for guttiferones G and I, and also for **4**. Guttiferone I and oblongifolin C (**4**) could be the same compound, with the differences in optical rotations (+8.7 and +14.5, respectively, in chloroform) resulting perhaps from variations of the tautomeric ratio with the solution concentration (*c* 1.5 and 0.21, respectively). In such a case, oblongifolin C (**4**) should not be a new natural product, but guttiferone I could better be depicted by structure **4**. The absolute configurations for **2**−**5**, with a positive optical rotation, can be regarded only as tentative, if it is considered that the geometry of the bridged bicyclic system is responsible for the bulk of the chiroptical properties (same sign of $[\alpha]_D$ as for xanthochymol and guttiferone E; see Supporting Information).

Table 2. Activity of **2**−**5**, Camboginol, and Guttiferone B in the Tubulin-Microtubule System

compound	microtubule disassembly inhibition IC_{50} (μmol/L)	tubulin assembly inhibition IC_{50} (μmol/L)
2	inactive	(41%)[a]
3	(7%)[a]	69
4	inactive	53
5	inactive	92
camboginol	(46%)[a]	97
guttiferone B	inactive	53
paclitaxel	0.5[b]	inactive

[a] A percentage inhibition at 10 mg/mL concentration is given whenever the IC_{50} could not be calculated. [b] Reference compound.[5]

A plausible biosynthetic pathway for explaining the formation of benzoylphloroglucinol derivatives of general structure **1** and of **2**−**5** can be proposed (see Figure 1). By analogy with recent findings concerning hyperforin biosynthesis,[12] the logical precursors are likely to be polyketides, which, by reaction with isoprene units, could give trialkylated intermediates cyclizing to **1**. The recent isolation[13] in *Clusia* floral resins of both spiritone and its possible precursor weddellianone B supports this view.

The biological activity of **2**−**5**, camboginol, and guttiferone B in terms of interaction with tubulin[5] was evaluated and compared with that of paclitaxel.[5] The results are presented in Table 2. While xanthochymol is a potent inhibitor of microtubule disassembly,[4] compounds **2**−**5** were only very weak inhibitors of tubulin assembly. The recent discovery that camboginol (garcinol) is a natural histone acetyltransferase inhibitor, which represses chromatin transcription and alters global gene expression,[14] suggests that additional laboratory work will have to be done in order to determine the cellular targets for **2**−**5**.

The isolation from the bark and leaves of *G. oblongifolia* of four new derivatives, oblongifolins A−D (**2**−**5**), constituted a further example showing the remarkable structural variety of natural acylphloroglucinol derivatives, of general structure **1**, extracted from plants. A general biogenetic process is likely to explain the formation of this interesting class of natural products. In this process, diversity would be generated by the variation of the phenyl ring substitution, as well as by the introduction of a large array of isoprene units. A third element of diversity is the selective production of the stereoisomeric and enantiomeric forms **1a** and **1b**. As far as this last aspect is concerned, if the structures of these

natural products can be assigned now with certainty using spectroscopic methods, the attribution of their absolute configuration remains to be confirmed for most of these substances. Another very important goal in the future will also be further studies concerning the biological activities of these derivatives, which appear to be promising and are apparently very sensitive to structural variations.

Experimental Section

General Experimental Procedures. Optical rotations were measured at 20 °C on a Perkin-Elmer 241 polarimeter. UV spectra were recorded on a Varian Cary 100 UV−vis spectrophotometer and IR spectra on a Perkin-Elmer Spectrum BX FT-IR instrument. The NMR spectra were recorded on Bruker AC-600 and AM-400 spectrometers, using TMS as internal standard. The NMR assignments were based on 2D COSY, HMQC, HMBC, and ROESY experiments. EIMS were obtained on a Micromass Zabspec/T and ESI and HRMS on a Waters-Micromass LCT mass spectrometers.

Plant Material. Leaves and stem bark of *Garcinia oblongifolia* were collected in April 1996 at Nhu Xuân, Thanh Hoa, Vietnam, by Vincent Dumontet. The voucher specimens (respective batch numbers VN0098 and VN0082) are deposited at the herbarium of the Institute of Ecology (NCST-Hanoi).

Extraction and Isolation. The ground dried leaves of *G. oblongifolia* (1.0 kg) were extracted by ethyl acetate (3 × 5 L) by successive overnight soaking with stirring. The combined extracts were evaporated under reduced pressure to give a brown gum (31.7 g), which was subjected to silica gel column chromatography and successively eluted with heptane−ethyl acetate (95:5 to 50:50) to give 12 fractions (100 mL). Fraction VI was subsequently chromatographed on a small silica gel column and eluted with heptane−ethyl acetate (90:10 to 75:25) to give a yellow oil (610 mg), which was rechromatographed on a silica gel column and eluted with heptane−ethyl acetate (95:5 to 50:50) to give 10 fractions (25 mL). Three fractions were pooled (130 mg) and were chromatographed on a small silica gel column, eluted with heptane−ethyl acetate (90:10 to 75:25), to give oblongifolin A (**2**) as a yellow oil (75 mg). Fraction VII (350 mg) was rechromatographed on a silica gel column and eluted with heptane−acetone (95:5 to 50:50) to give camboginol as a yellow oil (83 mg).

The ground, dried bark of *G. oblongifolia* (500 g) was extracted with ethyl acetate (3 × 1.5 L) by successive overnight soaking with stirring. The combined extracts were evaporated under reduced pressure to give a brown gum (15.2 g), which was subjected to silica gel column chromatography and successively eluted with heptane−ethyl acetate (95:5 to 50:50) to give five fractions. Fraction III (4.1 g) was chromatographed on a silica gel column and eluted with heptane−ethyl acetate (90:10 to 75:25) to give three fractions, of which one was evaporated under reduced pressure. The residue (1.32 g) was purified by HPLC on a symmetry C18 column, eluting with H_2O−CH_3CN (5:95) + 0.1% formic acid to give oblongifolins A (**2**, 62 mg), B (**3**, 19 mg), C (**4**, 110 mg), and D (**5**, 35 mg), camboginol (41 mg), and guttiferone B (20 mg).

Oblongifolin A (2): yellow oil; $[\alpha]^{20}_D$ +23 (*c* 0.35, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 230 (sh), 279.5 (3.80), 357 (sh) nm; + 3 drops 0.1 N NaOH λ_{max} (log ϵ) 252.5 (3.57), 286.5 (3.72), 347.5 (3.67) nm; IR ($CHCl_3$) ν_{max} 3400, 2928, 1727, 1663, 1600, 1444, 1377, 1291, 1215, 1122 cm^{-1}; ^1H NMR (CD_3OD + 0.1% TFA-*d*, 600 MHz) and ^{13}C NMR (CD_3OD + 0.1% TFA-*d*, 150 MHz) (see Table 1); EIMS *m*/*z* $[M]^+$ 602, 533 $[M - C_5H_9]^+$, 137 $[C_6H_4(OH)_2CO]^+$, 110 $[C_6H_4(OH)_2]^+$, 109 $[C_6H_3(OH)_2]^+$, 69 $[C_5H_9]^+$; APCIMS *m*/*z* 603 $[MH]^+$, 535 $[MH - C_5H_8]^+$, 479 $[MH - C_9H_{16}]^+$, 343 $[MH - 2\ C_5H_8 - C_9H_{16}]^+$; APCIMS (−) *m*/*z* 601 $[M - H]^-$, 109 $[C_6H_3(OH)_2]^-$; HRESIMS (+) *m*/*z* 625.3538 $[M + Na]^+$ (calcd for $C_{38}H_{50}O_6Na$ 625.3505).

Oblongifolin B (3): yellow oil; $[\alpha]^{20}_D$ +17.6 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 230 (sh), 279.5 (4.06), 355 (sh) nm; + 3 drops 0.1 N NaOH λ_{max} (log ϵ) 256 (3.85), 286.5 (3.89), 355.5 (3.83) nm; IR ($CHCl_3$) ν_{max} 3340, 2929, 1726, 1663, 1600, 1444, 1377, 1290, 1215, 1122 cm^{-1}; ^1H NMR (CD_3OD + 0.1% TFA-*d*, 600 MHz) and ^{13}C NMR (CD_3OD + 0.1% TFA-*d*, 150 MHz) (see Table 1); EIMS *m*/*z* $[M]^+$ 602; APCIMS *m*/*z* 603 $[MH]^+$, 535 $[MH - C_5H_8]^+$, 479 $[MH - C_9H_{16}]^+$, 343 $[MH - 2\ C_5H_8 - C_9H_{16}]^+$; APCIMS (−) *m*/*z* 601 $[M - H]^-$, 109 $[C_6H_3(OH)_2]^-$; HRESIMS (+) *m*/*z* 625.3532 $[M + Na]^+$ (calcd for $C_{38}H_{50}O_6Na$ 625.3505).

Oblongifolin C (4): yellow oil; $[\alpha]^{20}_D$ +14.5 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 230 (sh), 282 (3.93), 356 (sh) nm; + 3 drops 0.1 N NaOH λ_{max} (log ϵ) 256 (3.75), 286.5 (3.90), 351 (sh) nm; IR ($CHCl_3$) ν_{max} 3535, 3338, 2927, 1727, 1646, 1611, 1523, 1442, 1383, 1290, 1215, 1114 cm^{-1}; ^1H NMR (CD_3OD + 0.1% TFA-*d*, 600 MHz) and ^{13}C NMR (CD_3OD + 0.1% TFA-*d*, 150 MHz) (see Table 1); EIMS *m*/*z* $[M]^+$ 670; HRESIMS (+) *m*/*z* 693.4147 $[M + Na]^+$ (calcd for $C_{43}H_{58}O_6Na$ 693.4131).

Oblongifolin D (5): yellow oil; $[\alpha]^{20}_D$ +44.6 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 230 (sh), 279 (3.99), 353 (sh) nm; + 3 drops 0.1 N NaOH λ_{max} (log ϵ) 253 (3.84), 286.5 (3.96), 346 (3.93) nm; IR ($CHCl_3$) ν_{max} 3382, 2924, 1731, 1668, 1601, 1519, 1442, 1376, 1292, 1196, 1119 cm^{-1}; ^1H NMR (CD_3OD + 0.1% TFA-*d*, 600 MHz) and ^{13}C NMR (CD_3OD + 0.1% TFA-*d*, 150 MHz) (see Table 1); EIMS *m*/*z* $[M]^+$ 670; HRESIMS (+) *m*/*z* 693.4095 $[M + Na]^+$ (calcd for $C_{43}H_{58}O_6Na$ 693.4131).

Tubulin Binding Assays. Compounds were evaluated according to a published protocol.[5]

Supporting Information Available: Table of structures and optical rotations of compounds **1**, table of HMBC and NOE NMR data for compounds **2**−**5**, copies of ^1H and ^{13}C NMR spectra of **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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