Cytotoxic and Antimicrobial Benzophenones from the Leaves of *Tovomita longifolia*[#]

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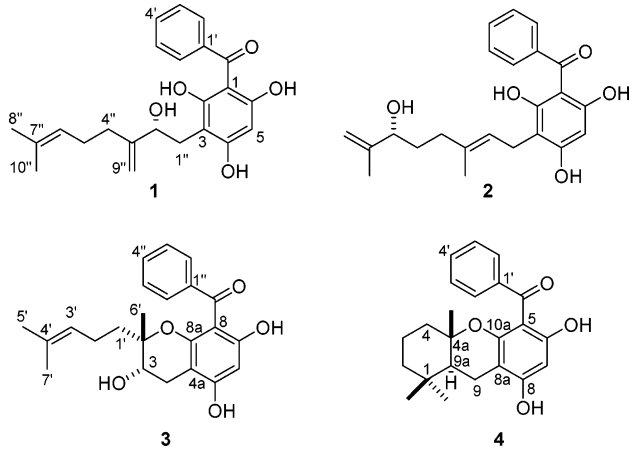
Bioassay-guided fractionation of the chloroform and ethanol extracts of *Tovomita longifolia* leaves using cytotoxic and antimicrobial assays resulted in the isolation of four new benzophenones, (*E*)-3-(2-hydroxy-7-methyl-3-methyleneoct-6-enyl)-2,4,6-trihydroxybenzophenone (**1**), (*E*)-3-(6-hydroxy-3,7-dimethylocta-2,7-dienyl)-2,4,6-trihydroxybenzophenone (**2**), 8-benzoyl-2-(4-methylpenten-3-yl)chromane-3,5,7-triol (**3**), and 5-benzoyl-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene-6,8-diol (**4**), and two known benzophenones, 4-geranyloxy-2,6-dihydroxybenzophenone (**5**) and 3-geranyl-2,4,6-trihydroxybenzophenone (**6**). The structures of **1**−**4** were established by spectroscopic means and by molecular modeling calculations. Compounds **1** and **3**−**5** demonstrated cytotoxic activities against breast (MCF-7), central nervous system (SF-268), and lung (H-460) human cancer cell lines, while compounds **3**−**6** showed antimicrobial activity against *Klebsiella pneumoniae*, *Mycobacterium smegmatis*, *Pseudomonas aeruginosa*, *Salmonella gallinarum*, and S*taphylococcus aureus*.

Within the framework of a multinational research project of the Organization of American States (OAS) and the Executive Secretariat of Andres Bello Agreement (SECAB) aimed at exploring Panamanian flora, the chloroform and ethanol extracts of the leaves of *Tovomita longifolia* (Rich.) Hochr. were found to possess cytotoxic activity against breast (MCF-7), central nervous system (SF-268), and lung (H-460) human cancer cell lines and antimicrobial activity against *Candida albicans*, *Escherichia coli*, *Klebsiella pneumoniae*, *Mycobacterium smegmatis*, *Pseudomonas aeruginosa*, *Salmonella gallinarum*, and *Staphylococcus aureus*. *T. longifolia* belongs to the Clusiaceae and occurs from Costa Rica to Brazil and Peru.[1] No ethnomedical, phytochemical, or biological reports on *T. longifolia* were found in the literature. However, the infusions of flowers of *T. brasiliensis* and *T. laurina* are used in Brazil and Colombia for the treatment of diarrhea,[2] while a *Tovomita* sp. in Peru has been reported to produce a hallucinogenic effect.[3]

Tovomita species have been reported to contain triterpenoids,[5,6] sterols,[7,8] coumarins,[9] xanthones,[10] and benzophenones.[11] The chloroform extract from roots of *T. brevistaminea* exhibited significant cytotoxicity against the KB cell line,[11] and the ethanol extract of *T. krukovii* inhibited the aspartic protease secreted by *Candida albicans*,[12] while the ethanol extract of *T. laurina* was active against P-388 leukemia, colon carcinoma, and melanoma B-16 cell lines.[13]

Bioassay-guided fractionation of the chloroform and ethanol extracts of the leaves of *T. longifolia*, using MCF-7, H-460, and SF-268 human cancer cell lines, and antimicrobial assays against *C. albicans* (*C.a*), *Escherichia coli (E.c)*, *Klebsiella pneumoniae (K.p)*, *Mycobacterium smegmatis* (*M.s*), *Pseudomonas aeruginosa* (*P.a*), *Salmonella gallinarum* (*S.g*), and *Staphylococcus aureus* (*S.a*) resulted in the isolation of four new benzophenones (**1**−**4**) and two known compounds, **5**[14a] and **6**.[12,14b] However, compound **5** was isolated only from the ethanol extract of *T. longifolia* leaves, while compounds **1**−**4** and **6** were isolated from the chloroform extract of *T. longifolia* leaves. The structural determination of the four new natural products **1**−**4** and the cytotoxic and antimicrobial activities of compounds **1**−**6** are discussed herein.



Chloroform and ethanol extracts of the leaves of *T. longifolia* showed activity against human cancer cell lines ($CHCl_3$ extract GI_{50}: MCF-7, 3.2; H-460, 5.5; and SF-268, 7.7 μg/mL; EtOH extract GI_{50}: MCF-7, 26; H-460 and SF-268, 17 μg/mL, respectively) and antimicrobial activity ($CHCl_3$ extract MIC (minimum inhibitory concentration): *S.a*, 50 μg/mL and *M.s*, 25 μg/mL; EtOH extract: *S.a*, 50 μg/mL and *M.s*, 50 μg/mL). The fractionation was carried out using both liquid−liquid partition and column chromatography as indicated in the Experimental Section. A preliminary analysis of the ^{13}C NMR spectra of the six isolated compounds (**1**−**6**) revealed the presence of a series of aromatic signals and one carbonyl group, which were readily associated with the presence of a benzophenone system in all of the compounds.[11]

Compound **1** was isolated as a yellow amorphous powder. HRESIMS of **1** showed a pseudomolecular ion at *m*/*z* 383.1847 [M + H$^+$], corresponding to the molecular formula $C_{23}H_{26}O_5$. The IR spectrum showed the presence of hydroxyl (3320 cm^{-1}) and carbonyl (1600 cm^{-1}) groups. The ^1H NMR spectrum showed one singlet at 6.00 ppm (H-5), one olefinic proton doublet at 5.14 ppm (H-6″), and two singlets at 1.62 and 1.93 ppm, corresponding to two methyl groups; it also showed two singlets at 5.10 and 4.92

[#] Dedicated to Dr. Norman R. Farnsworth of the University of Illinois at Chicago for his pioneering work on bioactive natural products.

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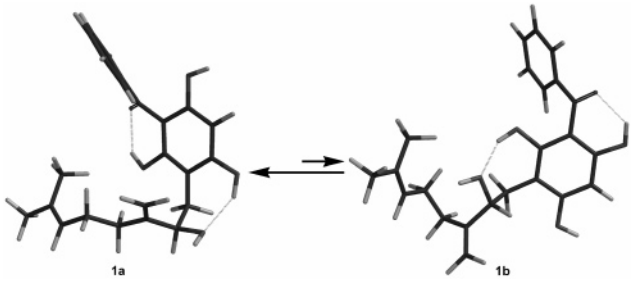

Figure 1. Low-energy conformers **1a** and **1b** of compound **1** showing alternative hydrogen bonds.

ppm, corresponding to a methylidene. Finally, a multiplet appeared between 7.4 and 7.7 ppm for five aromatic protons (H-2′−H-6′). The ^{13}C NMR spectrum showed signals of a trisubstituted double bond (δ 123.7, CH, C-6″; 132.0, C, C-7″) and of one methylidene (δ 109.3, C-9″). Additionally, there was a characteristic signal for an oxygenated methine (δ 77.0, C-2″) and a group of signals between 127.8 and 140.3 ppm assigned to a phenyl group. In the HMBC spectrum, the methylidene protons, at 4.92 (H-9b″) and 5.10 (H-9a″) ppm, correlated with the methine at δ 77.0 (C-2″; H-2″, δ 4.37 ppm d, J = 7.8 Hz), supporting a hydroxyl group and connected to the methylene at 29.1 ppm, (H-1a″, δ 3.11, d; H-1b″ δ 2.73, dd). This multiplicity pattern indicated the existence of a conformational restriction of the side chain, caused by a hydrogen bond between the aliphatic hydroxyl group and one phenolic hydroxyl. Molecular modeling studies for this compound (Figure 1), using a force field MM2 system, revealed that all of the low-energy conformers showed two intramolecular hydrogen bonds. Conformer **1a** displays a hydrogen bond between the carbonyl and the OH-2 groups and a second one between the aliphatic hydroxyl and the OH-6 phenol groups (Figure 1a). In conformer **1b**, the hydrogen bonds are formed between the carbonyl and the OH-6 phenol group and the second one between the side-chain hydroxyl and the OH-2 phenolic hydroxyl (Figure 1b). In both cases, hydrogen bonding would restrict the side-chain rotational freedom, affecting particularly the H-1a″ and H-1b″ benzylic methylene protons. The energy differences between conformers are very small. However, the calculated theoretical J values for conformer **1a** are in fair agreement with the experimental data. Ab initio calculations at the Hartree−Fock level of theory with the 3-21G* basis set[15] confirmed the greater stability (1.5 kcal/mol) of **1a**. These data were corroborated in the ^{1}H NMR spectrum, which showed two low-field signals of labile protons at 10.93 (sharp singlet of the phenol associated with the carbonyl) and 8.80 ppm (broad signal associated with the alcohol−phenol interaction). In the HMBC spectrum, the signal at 10.93 ppm showed correlations with the oxygenated aromatic carbon at 161.9 ppm (C-2) and with another nonprotonated carbon at 104.5 ppm. As a result, the signal at 10.93 ppm corresponded to the phenolic OH-2 proton, while that at 8.80 ppm corresponded to that of the OH-6 group. Other heteronuclear correlations permitted us to assign the rest of the structure and to establish the structure of compound **1** as (*E*)-3-(2-hydroxy-7-methyl-3-methyleneoct-6-enyl)-2,4,6-trihydroxybenzophenone.

Compound **2** was isolated as an optically active yellow amorphous solid. The HRFABMS showed a molecular ion at *m*/*z* 383.1847 [M + H$^+$], corresponding to molecular formula $C_{23}H_{26}O_5$. Its IR (3282 and 1624 cm^{-1}) and NMR spectra were closely related to those of compound **1**. The ^{13}C NMR spectrum showed signals that correlated easily with those of the benzoylphloroglucinol moiety of compound **1**. The number and types of the ^{1}H and ^{13}C NMR signals associated with the side chain were essentially the same as those of compound **1**, with only small differences in their chemical shifts. The complete analysis of the correlations observed in the HMBC spectrum permitted us to assign all the spectral signals and to propose the structure of (*E*)-3-(6-hydroxy-3,7-dimethylocta-2,7-dienyl)-2,4,6-trihydroxybenzophenone for compound **2**. The NMR data for labile protons and their respectively correlated carbons revealed a higher rotational freedom for the side chain of this compound, due to the absence of hydrogen bonding between the aliphatic and the phenolic hydroxyls.

Compound **3** was isolated as a yellow amorphous solid and was optically active. The HRESIMS showed a molecular ion at *m*/*z* 383.1863 [M + H$^+$], corresponding to $C_{23}H_{26}O_5$. The IR spectrum exhibited bands of hydroxyl (3300 cm^{-1}) and carbonyl (1620 cm^{-1}) groups. The presence of only one isolated double bond, in combination with the molecular weight, indicated the presence of an additional ring as part of a chromane skeleton, as confirmed by the following spectral analysis. In the ^{1}H NMR spectrum, a singlet at 12.10 ppm denoted the presence of a phenolic group in *ortho* position to the benzophenone carbonyl. In the HMBC spectrum this OH signal correlated with the aromatic methine at 95.8 ppm (C-6) and with two nonprotonated aromatic carbons at 105.7 and 163.9 ppm, assigned respectively to C-8 and C-7. The relative deshielding of C-7, of approximately 4 ppm with respect to compounds **1** and **2**, is due to the fact that the carbonyl can form a hydrogen bond only with the OH-7 group. The H-6 signal showed correlations with the nonprotonated carbons at 105.7 (C-8), 98.5 (C-4a), and 161.0 (C-5) ppm. The proton signals at 2.84 and 2.79 ppm, attached to C-4 (25.3 ppm) in the HMQC spectrum, connected with the *ortho*-oxygenated carbons at 155.4 (C-8a) and 161.0 (C-5) ppm and with the nonprotonated carbon at 98.5 (C-4a) ppm. The doublet of doublets patterns of the H-4a,b signals and their comparison with those of the other benzophenones reported here confirmed the existence of the chromane system. Furthermore, H-4a,b correlated with a nonprotonated oxygenated carbon at 79.9 ppm (C-2), to which, in turn, was connected the methyl signal at 0.91 ppm (δ 17.6, C-6′). Finally, both the nonprotonated carbons and the methyl group correlated with an oxygenated methine at 3.74/67.1 ppm (C-3). All the correlations observed in the HMBC and COSY spectra were in agreement with the structure 8-benzoyl-2-(4-methylpenten-3-yl)chromane-3,5,7-triol, proposed for compound **3**. In the NOESY spectrum of **3**, strong NOEs were observed between the 6′ methyl at 0.91 ppm and the protons at H-3 (3.74, dd) and H-4b (2.79, dd). H-3, in turn, showed a NOE with both H-4a,b methylene protons. The combination of these NMR results with those of molecular modeling calculations for the 2,3 stereoisomers (Figure 2) led to the conclusion that the only compatible 3D-structure was that displaying the C-6′ methyl and the hydroxyl group at C-3 in a *trans*-diaxial arrangement (Figure 2a). This *cis*-stereoisomer, with the axially oriented side chain (Figure 2b), is not compatible with the NOEs experimentally observed. Chemical shifts found for compound **3** are in agreement with those reported for similar structural arrangements present in catechins.[16]

Compound **4** was isolated as a yellow amorphous solid. It showed a pseudomolecular ion at *m*/*z* 367.1904 [M + H$^+$] in the HRESIMS, in agreement with a molecular formula of $C_{23}H_{26}O_4$. The IR spectrum showed hydroxyl (3300 cm^{-1}) and carbonyl (1620 cm^{-1}) bands. The ^{13}C NMR spectrum showed one carbonyl signal at 200.4 ppm (C-7′) along with those associated with the two aromatic rings of a benzophenone, also supported by several HMBC correlations. The ^{1}H NMR spectrum showed a singlet at 12.39 ppm of a phenolic OH···OC group. In its HMBC spectrum, this signal was connected with resonances for three aromatic carbons, a methine at 95.1 ppm (C-7), a nonprotonated carbon at 105.7 ppm (C-5), and an oxygenated carbon at 163.7 ppm (C-6). The aromatic methine at 6.04 ppm (H-7) was connected with two nonprotonated carbons, C-8a (δ 101.4) and C-5, as well as with two other oxygenated carbons, C-6 and C-4 (160.7 ppm). The two double doublets centered at 2.1 and 2.6 ppm (H-9α, H-9β) showed correlations with C-8a (101.4 ppm), C-10a (156.1 ppm), and C-8, of the aromatic region, and with the oxygenated aliphatic C-4a (78.6 ppm), which is connected to the methyl group at 1.04/20.6 ppm. All these data

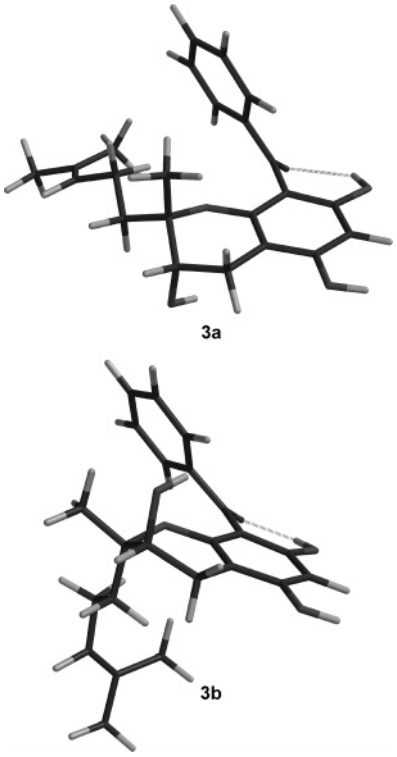

Figure 2. Epimers of compound **3** at position 8 (**3a** and **3b**).

revealed some similarity with compound **3**, but compound **4** was assigned an additional ring, as deduced from the formula and from the set of additional correlations in the HMBC spectrum. Thus, the methine signal assigned to C-9a (47.2 ppm) was connected with the methyl singlets at 0.98 (Me-1α) and 0.85 (Me-1*β*), confirming the existence of a bond between C-1 and C-9a, forming a cyclohexane-fused ring. The *trans* fusion of the resulting hexahydroxanthene structure was established through the analysis of the NOESY spectrum, notably the correlation between the pseudoaxial H-9a and only one of the H-9 protons. As a result, compound **4** was identified as *trans*-5-benzoyl-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene-6,8-diol.

Due to the very small amounts of pure compounds obtained, which were mainly used for evaluating their biological activities, no attempt was made to establish chemically the absolute configuration of the new benzophenone derivatives.

Compounds **5** and **6** were identified as the known 4-geranyloxy-2,6-dihydroxybenzophenone (**5**) and 3-geranyl-2,4,6-trihydroxybenzophenone (**6**) by comparison of their NMR and MS data with those reported in the literature. ^{13}C NMR data for compound **5** are included in the Experimental Section.

The original extracts and their successive fractions, as well as all the purified compounds (**1**−**6**), were evaluated in anticancer and antimicrobial assays according to established protocols.[17,18] Compound **4** was the most active against the MCF-7 (1.8 *μ*g/mL), H-460 (2.1 *μ*g/mL), and SF-268 (1.7 *μ*g/mL) cancer cell lines and against *M.s* (6.25 *μ*g/mL), *K.p* (6.25 *μ*g/mL), *S.g* (12.5 *μ*g/mL), and *P.a* (12.5 *μ*g/mL). Compound **1** was active against MCF-7 (6.7 *μ*g/mL), H-460 (7.8 *μ*g/mL), and SF-268 (6.5 *μ*g/mL) cells. Compound **3** showed activity against cell lines MCF-7 (6.8 *μ*g/mL), H-460 (6.5 *μ*g/mL), and SF-265 (5.6 *μ*g/mL) and antimicrobial activity against *M.s* (25 *μ*g/mL) and *K.p* (25 *μ*g/mL). Compound **1** did not show either cytotoxic or antimicrobial activity. Compound **5** showed cytotoxicity in the human cancer cell lines MCF-7 (4.8 *μ*g/mL), H-460 (4.4 *μ*g/mL), and SF-268 (2.0 *μ*g/mL) and antimicrobial activity against *S.a* (12.5 *μ*g/mL) and *M.s* (12.5 *μ*g/mL). Finally, compound **6** was active only against *M.s* (50 *μ*g/mL).

Experimental Section

General Experimental Procedures. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured in an Autopol III automatic polarimeter (Rudolph Research Analytical) at 25 °C. UV spectra were recorded on a Perkin-Elmer UV/vis Lambda 2S. IR spectra were recorded (KBr 1%) on a Perkin-Elmer 1310 spectrophotometer. ^{1}H, ^{13}C NMR, HMBC, HSQC, COSY, and NOESY NMR spectra were recorded using a Brüker Avance 300 spectrometer in $CDCl_3$ at 300 MHz for ^{1}H and 75 MHz for ^{13}C NMR. For HRFABMS analysis, a VG-TS250 mass spectrometer was used, and ESIMS were acquired on a Q-TOF2tm (Micromass Ltd, Manchester, UK) hybrid mass spectrometer operated in MS mode and acquiring data with a TOF analyzer. Silica gel [Merck, Kieselgel 60 (0.063−0.200 mm) and (0.015−0.040 mm)] and Sephadex LH-20 (Sigma, 25−100 mm) were used for column chromatography; precoated silica gel plates (Merck, Kieselgel 60 F_{254s}, 0.25 mm and 1 mm) were used for TLC and preparative TLC analysis.

Plant Material. The leaves of *Tovomita longifolia* were collected from Cerro Jefe, in the Province of Panama (09°12′ N, 079°22′ W), Republic of Panama, in September 2001. Its taxonomic identity was established by one of the authors (M.C.), at the National Herbarium of the University of Panama (PMA), where voucher specimens (Florpan 5328) are deposited.

Extraction and Isolation. The dried, powdered leaves of *T. longifolia* (958 g) were extracted with chloroform (2.5 L) at room temperature for 2 days and subsequently extracted with 95% ethanol (2.0 L) at room temperature for 3 days. Evaporation of the solvent yielded a chloroform extract (28.5 g) and an ethanol extract (98.0 g). Ten grams of each extract was subjected to solvent partitioning as described by Hussein et al.[19] Four partitions were obtained from each extract (hexane, 90% methanol, ethyl acetate, and water). The activities were retained in the 90% MeOH partitions of both extracts, and the bioassay-guided fractionation was monitored using cytotoxicity and antimicrobial assays.

The 90% MeOH fraction (3.58 g) from chloroform extract was chromatographed on a silica gel column with a gradient elution using $CHCl_3$−EtOAc (0−50% EtOAc) and EtOAc−MeOH (0−100% MeOH). Fractions (100 mL) were combined on the basis of their TLC profiles, and the solvent was removed in vacuo to give fractions A−C. On the basis of bioactivity data, fraction B was subsequently chromatographed on silica gel columns using $CHCl_3$−hexane (7:3), $CHCl_3$−EtOAc (0−50% EtOAc), and EtOAc−MeOH (0−100% MeOH), leading to the isolation of **1** (6.4 mg, 0.00067%) and **6** (3.8 mg, 0.00039%).

The second 90% MeOH fraction (10 g) from the chloroform extract was chromatographed on a silica gel column using gradient mixtures of $CHCl_3$−hexane (7:3), $CHCl_3$−EtOAc (0−100% EtOAc), and EtOAc−MeOH (0−100% MeOH) to afford fractions D−F. Workup of fraction E by repeated column chromatography using a gradient of $CHCl_3$−toluene−EtOAc yielded **2** (4.9 mg 0.00051%), **3** (10 mg 0.00104%), and **4** (18 mg 0.00188%).

The 90% MeOH fraction (978.5 mg) from the ethanol extract was purified on a silica gel column with gradient elution using $CHCl_3$−hexane (7:3), $CHCl_3$−EtOAc (0−50% EtOAc), and EtOAc−MeOH (0−100% MeOH), to afford compound **5** (17.4 mg 0.00182%).

(*E*)-3-(2-Hydroxy-7-methyl-3-methyleneoct-6-enyl)-2,4,6-trihydroxybenzophenone (1): yellow amorphous powder; mp 100 °C; $[\alpha]^{25}_D$ −0.10 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 307 (4.49) nm; IR (KBr) ν_{max} 3320, 2940, 1600, 1320, 1240, 1160 cm^{-1}; ^{1}H NMR δ 10.93 (1H, s, OH-2), 8.80 (1H, bs, OH-6), 7.64 (2H, d, J = 7.4 Hz, H-2′, H-6′), 7.56 (1H, m, H-4′), 7.50 (2H, m, H-3′, H-5), 6.0 (1H, s, H-5), 5.14 (1H, d, J = 6.7 Hz, H-6″), 5.10 (1H, s, H-9a″), 4.92 (1H, s, H-9b″), 4.37 (1H, d, J = 7.8 Hz, H-2″), 3.11 (1H, dd, J = 7.8, 15.0 Hz, H-1a″), 2.73 (1H, dd, J = 7.8, 15.0 Hz, H-1b″), 2.19 (2H, m, H-4″), 2.19 (2H, m, H-5″), 1.93 (3H, s, H-8″), 1.62 (3H, s, H-10″); ^{13}C NMR δ 197.8 (CO), 164.2 (C, C-4), 161.9 (C, C-2), 159.8 (C, C-6), 151.0 (C, C-3″), 140.3 (C, C-1′), 132.3 (CH, C-4′), 132.0 (C, C-7″), 129.0 (2CH, C-3′, C-5′), 127.8 (2CH, C-2′, C-6′), 123.7 (CH, C-6″), 109.3 (CH_2, C-9″), 105.8 (C, C-3), 104.5 (C, C-1), 97.1 (CH, C-5), 77.0 (CH, C-2″), 32.2 (CH_2, C-4″), 29.1 (CH_2, C-1″), 26.5 (CH_2, C-5″), 25.7 (CH_3, C-8″), 17.7 (CH_3, C-10″); HRESIMS *m*/*z* 383.1847 [M + H$^+$] (calcd for $C_{23}H_{27}O_5$, 383.1858).

(*E*)-3-(6-Hydroxy-3,7-dimethylocta-2,7-dienyl)-2,4,6-trihydroxybenzophenone (2): yellow amorphous solid; $[\alpha]^{25}_D$ −0.13 (*c* 0.1,

$CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 305 (5.01) nm; IR (KBr) ν_{max} 3282, 2920, 2852, 2282, 1624, 1378, 1260, 1176, 1120 cm^{-1}; ^1H NMR δ 10.34 (1H, s, OH-2), 7.40 (2H, m, H-2′, H-6′), 7.40 (2H, m, H-3′, H-5′), 7.40 (1H, m, H-4′), 6.25 (1H, bs, OH-4), 5.90 (1H, s, H-5), 5.30 (1H, t, J = 3.5 Hz, H-2″), 4.83 (1H, s, H-8a″), 4.92 (1H, s, H-8b″), 4.05 (1H, m, H-6″), 3.36 (2H, d, J = 7.1 Hz, H-1″), 2.09 (2H, m, H-5″), 1.81 (3H, s, H-9″), 1.71 (3H, s, H-10″), 1.70 (2H, m, H-4″); ^{13}C NMR δ 197.8 (CO), 162.5 (C, C-4), 160.9 (C, C-2), 159.5 (C, C-6), 147.3 (C, C-7″), 140.1 (C, C-1′), 138.3 (CH, C-3″), 132.3 (CH, C-4′), 129.2 (2CH, C-3′, C-5′), 127.9 (2CH, C-2′, C-6′), 122.2 (CH, C-2″), 111.2 (CH_2, C-8″), 106.7 (C, C-3), 104.7 (C, C-1), 95.2 (CH, C-5), 75.7 (CH, C-6″), 35.8 (CH_2, C-4″), 32.9 (CH_2, C-5″), 21.7 (CH_2, C-1″), 17.8 (CH_3, C-10″), 16.2 (CH_3, C-9″); HRFABMS m/z 383.1847 [M + H^+] (calcd for $C_{23}H_{27}O_5$, 383.1853).

8-Benzoyl-2-(4-methylpenten-3-yl)-chromane-3,5,7-triol (3): yellow amorphous solid; $[\alpha]^{25}_D$ −0.05 (c 0.07, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 306 (4.48) nm; IR (KBr) ν_{max} 3300, 2940, 1620, 1420, 1260, 1100 cm^{-1}; ^1H NMR δ 12.10 (1H, s, OH-7), 7.49 (2H, d, J = 7.4 Hz, H-2″, H-6″), 7.40 (2H, m, H-3″, H-5″), 7.36 (1H, m, H-4″), 6.53 (1H, s, OH-5), 6.04 (1H, s, H-6), 4.85 (1H, t, J = 7.0 Hz, H-3′), 3.74 (1H, t, J = 6.2 Hz, H-3), 2.84 (1H, dd, J = 5.4, 15.9 Hz, H-4a), 2.79 (1H, dd, J = 5.4, 15.9 Hz, H-4b), 1.63 (3H, s, H-5′), 1.56 (2H, m, H-2′), 1.49 (3H, s, H-7′), 1.30 (2H, m, H-1′), 0.91 (3H, s, H-6′); ^{13}C NMR δ 200.0 (CO), 163.9 (C, C-7), 161.0 (C, C-5), 155.4 (C, C-8a), 142.5 (C, C-1″), 131.9 (C, C-4′), 130.5 (CH, C-4″), 127.7 (2CH, C-2″, C-6″), 127.4 (2CH, C-3″, C-5″), 123.8 (CH, C-3′), 105.7 (C, C-8), 98.5 (C, C-4a), 95.8 (CH, C-6), 79.9 (C, C-2), 67.1 (CH, C-3), 37.2 (CH_2, C-1′), 25.6 (CH_3, C-5′), 25.3 (CH_2, C-4), 21.2 (CH_2, C-2′), 17.7 (CH_3, C-7′), 17.6 (CH_3, C-6′); HRESIMS m/z 383.1863 [M + H^+] (calcd for $C_{23}H_{27}O_5$, 383.1858).

***trans*-5-Benzoyl-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene-6,8-diol (4):** yellow amorphous solid; $[\alpha]^{25}_D$ −0.01 (c 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 306 (4.48) nm; IR (KBr) ν_{max} 3300, 2920, 1620, 1320, 1280, 1160 cm^{-1}; ^1H NMR δ 12.39 (1H, s, OH-6), 7.45 (2H, d, J = 7.2 Hz, H-2′, H-6′), 7.41 (1H, m, H-4′), 7.38 (2H, m, H-3′, H-5′), 6.35 (1H, s, OH-8), 6.04 (1H, s, H-7), 2.61 (1H, dd, J = 4.0, 11.4 Hz, H-9β), 2.19 (1H, dd, J = 2.6, 13.3 Hz, H-9α), 1.64 (2H, m, H-4), 1.40 (2H, m, H-3), 1.27 (2H, s, H-2), 1.04 (3H, s, Me-4), 0.98 (3H, s, Me-1α), 0.85 (3H, s, Me-1β); ^{13}C NMR δ 200.4 (CO), 163.7 (C, C-6), 160.7 (C, C-8), 156.1 (C, C-10a), 142.9 (C, C-1′), 129.9 (CH, C-4′), 127.6 (2CH, C-2′, C-6′), 127.2 (2CH, C-3′, C-5′), 105.7 (C, C-5), 101.4 (C, C-8a), 95.1 (CH, C-7), 78.6 (C, C-4a), 47.2 (CH, C-9a), 41.3 (CH_2, C-4), 38.3 (CH_2, C-2), 32.2 (CH_3, Me-1α), 26.4 (C, C-1), 20.9 (CH_3, Me-1β), 20.6 (CH_3, C-Me_{4a}), 19.4 (CH_2, C-3), 17.5 (CH_2, C-9); HRESIMS m/z 367.1904 [M + H^+] (calcd for $C_{23}H_{27}O_4$, 367.1909).

(*E*)-4-(3,7-Dimethylocta-2,6-dienyloxy)-2,6-dihydroxybenzophenone (5): ^{13}C NMR δ 197.2 (CO), 166.4 (C, C-4), 162.4 (C, C-6), 162.4 (C, C-2), 142.2 (C, C-1′), 139.8 (C, C-3″), 132.3 (CH, C-4′), 131.9 (C, C-7″), 129.2 (CH, C-3′), 129.2 (CH, C-5′), 127.7 (CH, C-6′), 127.7 (CH, C-2′), 123.6 (CH, C-6″), 118.4 (CH, C-2″), 104.4 (C, C-1), 95.6 (CH, C-3), 95.6 (CH, C-5), 65.3 (CH_2, C-1″), 39.5 (CH_2, C-4″), 26.2 (CH_2, C-5″), 25.6 (CH_3, C-8″), 17.7 (CH_3, C-10″), 16.7 (CH_3, C-9″).

Molecular Modeling. Calculations were performed on a Silicon Graphics Indigo computer. Compounds were built using Macromodel v.4.[20] Conformational analysis was performed by a Monte Carlo random search. All freely rotating bonds were searched with MM2[21] minimization to a gradient of less than 0.001 kcal/mol. Full geometry optimization of the two main conformers of each compound was performed using a molecular orbital ab initio method at the Hartree−Fock level of theory with the 3-21G** basis set.[15] The calculations were carried out using the SPARTAN ’04 Macintosh program distributed by Wavefunction, Inc.

Cytotoxicity Bioassays. The cytotoxicity assays were performed with breast (MFC-7), CNS (SF-268), and lung (H-460) human cancer cell lines, according to the method of Monks et al.[17] During the isolation process, the activity of all fractions and compounds was monitored using all three cell lines.

Antimicrobial Bioassay. The antimicrobial activity was assessed against *Candida albicans* (ATCC 10231), *Escherichia coli* (ATCC 9637), *Klebsiella pneumoniae* (ATCC 10031), *Mycobacterium smegmatis* (ATCC 607), *Pseudomonas aureuginosa* (ATCC 27853), *Salmonella gallinarum* (ATCC 9184), and *Staphylococcus aureu*s (ATCC 6538) according to Mitscher et al.[18] During the isolation process, the activity of all fractions and compounds was monitored using all microorganisms.

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Supporting Information Available: Cytotoxic and antimicrobial activities of the isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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