Antiviral and Anti-inflammatory Metabolites from the Soft Coral *Sinularia capillosa*

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Chemical investigations of the soft coral *Sinularia capillosa* resulted in the isolation of one new tetraprenylbenzoquinone, capilloquinone (**1**), two new furanobenzosesquiterpenoids, capillobenzopyranol (**2**) and capillobenzofuranol (**3**), one new furanosesquiterpenoid, capillofuranocarboxylate (**4**), and five previously characterized metabolites, comprising (*E*)-5-(2,6-dimethylocta-5,7-dienyl)furan-3-carboxylic acid (**5**), 2-[(2*E*,6*E*)-3,7-dimethyl-8-(4-methylfuran-2-yl)octa-2,6-dienyl]-5-methylcyclohexa-2,5-diene-1,4-dione (**6**), 2-[(2*E*,6*E*)-3,7-dimethyl-8-(4-methylfuran-2-yl)octa-2,6-dienyl]-5-methylbenzene-1,4-diol (**7**), (−)-loliolide (**8**), and 3,4,11-trimethyl-7-methylenebicyclo[6.3.0]undec-2-en-11α-ol (**9**). The structures of **1**−**4** were elucidated through extensive spectroscopic analysis. The cytotoxicity, anti-HCMV (human cytomegalovirus) activity, antibacterial activity, and anti-inflammatory effects of **1**−**9** were evaluated in vitro.

Soft corals of the genus *Sinularia* (Alcyoniidae) have been well recognized as a rich source of sesquiterpenes, diterpenes, polyhydroxylated steroids, and polyamine metabolites.[1,2] Previous bioassay results of these metabolites have revealed in vitro cytotoxicity against various cancer cell lines, anti-inflammatory properties, and antimicrobial activities.[2] Several furanosesquiterpenes, including methylfurans, furan methyl esters, and furan carboxylic acids, were isolated from the Australian soft coral *Sinularia capillosa* by Coll's group.[3] Capilloloid and three cytotoxic cembranolides were reported from the same organism by Zeng's group.[4] In addition, we have previously obtained a novel sesquiterpenoid, capillosanol, from *S. capillosa* collected by hand using scuba along the coast of the Dongsha Atoll off Taiwan.[5]

Our continuing chemical examinations on the bioactive metabolites of *S. capillosa* have resulted in the purification of one new tetraprenylbenzoquinone, capilloquinone (**1**), two new furanobenzosesquiterpenoids, capillobenzopyranol (**2**) and capillobenzofuranol (**3**), one new furanosesquiterpenoid, capillofuranocarboxylate (**4**), and five previously characterized metabolites, comprising (*E*)-5-(2,6-dimethylocta-5,7-dienyl)furan-3-carboxylic acid (**5**),[3] 2-[(2*E*,6*E*)-3,7-dimethyl-8-(4-methylfuran-2-yl)octa-2,6-dienyl]-5-methylcyclohexa-2,5-diene-1,4-dione (**6**),[3] 2-[(2*E*,6*E*)-3,7-dimethyl-8-(4-methylfuran-2-yl)octa-2,6-dienyl]-5-methylbenzene-1,4-diol (**7**),[3] (−)-loliolide (**8**),[6] and 3,4,11-trimethyl-7-methylenebicyclo[6.3.0]undec-2-en-11α-ol (**9**),[7] which were identified by comparison of their NMR spectroscopic data with those of authentic samples. The details of the isolation and structure elucidation of these isolated metabolites are discussed. Metabolites **1**−**9** were evaluated for cytotoxicity against three selected cancer cell lines, antiviral activity against HCMV (human cytomegalovirus), anti-inflammatory activity using RAW 264.7 macrophages, and antibacterial activity against five selected bacterial strains.

Capilloquinone (**1**) was obtained as a yellow, viscous oil. The positive HRESIMS of **1** showed a pseudomolecular ion peak at *m*/*z* 451.2821 $[M + Na]^+$ and established a molecular formula of $C_{27}H_{40}O_4$. The ^{13}C NMR and DEPT spectra (Table 2) showed the presence of six methyls, seven methylenes, five methines, one oxygenated methine, five quaternary olefinic carbons, one oxygenated quaternary carbon, and two carbonyl carbons. The presence of a 5-methyl-1,4-benzoquinone moiety was revealed by the NMR features (Tables 1 and 2) [δ_H 6.50 (1H, s) and 6.59 (1H, d, $J = 1.6$ Hz); δ_C 185.9 (C), 186.4 (C), 147.2 (C), 144.4 (C), 132.5 (CH), 131.3 (CH), and 16.6 (CH_3)], as well as from the UV λ_{max} absorptions at 250, 297, and 342 nm and the IR absorption at 1654 cm^{-1} (conjugated carbonyl group). Moreover, the $^1H-^1H$ COSY correlation (Figure 1) between H-6′ and H_3-7′, together with the HMBC correlations (Figure 1) from H-3′ to C-5′ and C-1′, from H-6′ to C-4′ and C-7′, and from H_3-7′ to C-4′, C-5′, and C-6′, confirmed the presence of the 2-alkyl-5-methyl-1,4-benzoquinone moiety.

The other partial structural fragment was determined by 2D NMR data, including COSY, HSQC, and HMBC experiments. From the COSY spectrum of **1**, it was possible to establish the proton sequence from H_2-1 to H-2; H_2-4 to H-6 through H_2-5; H_2-8 to H-10 through H_2-9; and H_2-12 to H-14 through H_2-13. The methyl groups attached at C-3, C-7, and C-11 were determined on the basis of the key HMBC correlations from H_3-18 to C-10, C-11, and C-12; H_3-19 to C-6, C-7, and C-8; and H_3-20 to C-2, C-3, and C-4. The above HMBC correlations also confirmed the linkages established by the COSY experiment. Moreover, the location of the 1,2-diol was positioned at C-14 and C-15 by the crucial HMBC correlations from H_3-16/17 to C-15 and C-14, respectively. Eventually, the connectivity of the above two fragments was elucidated by the key HMBC correlations from H_2-1 to C-1′, C-2′, and C-3′. The *E*-geometry of the three double bonds at C-2, C-6, and C-10 was identified by the NOESY correlations between H-2/H-4, H-6/H-8, H-10/H-12, H-1/H_3-20, H-5/H_3-19, and H-9/H_3-18. We were unsuccessful in preparing Mosher's esters of **1**. The absolute configuration of **1** was proposed on the basis of comparison of its specific rotation ($[\alpha]^{25}_D$ −15) with that of the isomeric tetraprenylquinone diol from the brown alga *Sargassum micracanthum*, (+)-2-[(14*R*,2*E*,6*E*,10*E*)-14,15-dihydroxy-3,7,11,15-tetramethylhexadeca-2,6,10-trienyl]-6-methylcyclohexa-2,5-diene-1,4-dione ($[\alpha]^{25}_D$ +11.3),[8] whose absolute configuration has been unambiguously determined, indicating the 14*S* configuration for **1**. Hence, the structure of **1** was established.

The HRFABMS of capillobenzopyranol (**2**) exhibited a pseudomolecular ion peak at *m*/*z* 339.1962 $[M + H]^+$, consistent with the molecular formula $C_{22}H_{26}O_3$, requiring 10 degrees of unsaturation. The NMR features (Tables 1 and 2) of **2** were analogous to those of **7**[3] with the exception that the resonances for the 2*H*-chromen-6-ol[8−10] ring in **2** were replaced by those of a 5-methyl-1,4-benzoquinol moiety in **7**. The UV λ_{max} absorptions at 226, 269, and 332 nm, the IR absorption at 3406 cm^{-1} (hydroxy group), and the NMR

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Chart 1

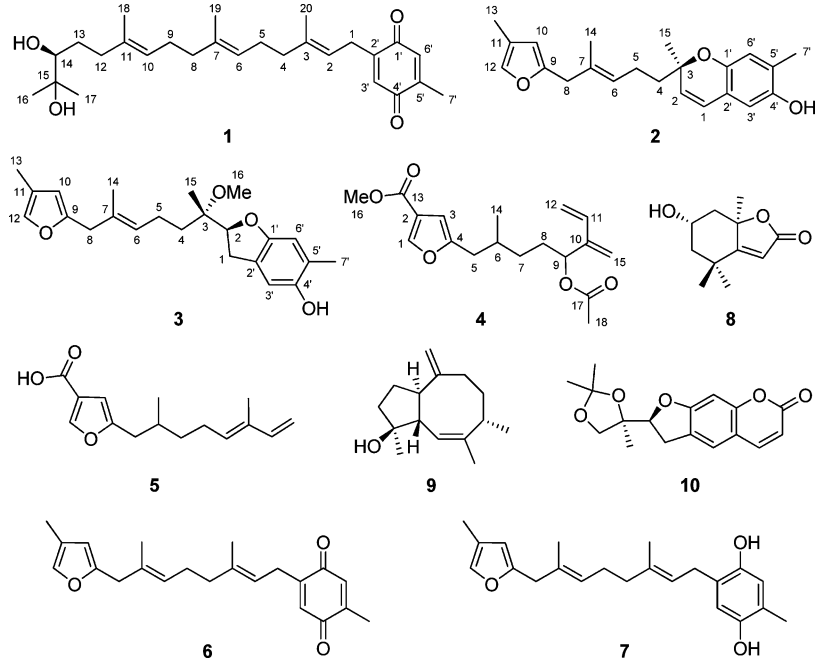

Table 1. ^{1}H NMR Spectroscopic Data (400 MHz) of **1**−**4**[a] in $CDCl_3$

position	**1**, δ_H (*J* in Hz)	**2**, δ_H (*J* in Hz)	**3**, δ_H (*J* in Hz)	**4**, δ_H (*J* in Hz)
1	3.11, d (7.2)	6.25, d (9.6)	3.07, d (9.6)	7.88, s
2	5.15, m	5.53, d (9.6)	4.74, t (9.6)	
3				6.34, s
4	2.11, m	1.68, m	1.64, t (4.4)	
5	2.11, m	a: 2.15, m	2.09, m	a: 2.59, dd (15.2, 7.6)
		b: 2.12, m		b: 2.12, dd (15.2, 7.6)
6	5.01, t (4.4)	5.21, td (7.2, 1.2)	5.24, td (7.2, 1.2)	1.80, m
7				a: 1.38, m; b: 1.17, m
8	2.08, m	3.20, s	3.24, s	1.72, m
9	2.11, m			5.44, t (5.2)
10	5.19, m	5.86, s	5.88, s	
11				6.30, dd (18.0, 10.4)
12	a: 2.23, m	7.06, d (1.2)	7.07, d (0.8)	a: 5.36, d (18.0)
	b: 2.00, m			b: 5.13, d (10.4)
13	a: 1.58, m; b: 1.43, m	1.98, d (1.2)	1.98, d (0.8)	
14	3.36, d (10.8)	1.58, s	1.62, s	0.89, d (6.8)
15		1.36, s	1.15, s	a: 5.16, s
				b: 5.15, s
16	1.16, s		3.28, s	3.82, s
17	1.20, s			
18	1.60, s			2.07, s
19	1.59, s			
20	1.62, s			
3′	6.50, s	6.42, s	6.63, s	
6′	6.59, d (1.6)	6.56, s	6.56, s	
7′	2.04, d (1.6)	2.18, s	2.18, s	

[a] Assigned by COSY, HSQC, NOESY, and HMBC experiments.

features (Tables 1 and 2) [δ_H 6.42 (1H, s) and 6.56 (1H, s); δ_C 146.7 (C), 119.6 (C), 112.4 (CH), 147.4 (C), 124.4 (C), 118.1 (CH), 15.8 (CH_3), 122.4 (CH), 129.7 (CH), and 77.9 (C)] suggested that **2** possessed a 2*H*-chromen-6-ol ring moiety,[8,10] which was identified by the ^{1}H−^{1}H COSY correlations between H-6′/H_3-7′ and H-1/H-2, along with the HMBC correlations from H_3-7′ to C-4′, C-5′, and C-6′; H-3′ to C-1′ and C-5′; H-6′ to C-2′ and C-4′; H-1 to C-1′ and C-3′; and H-2 to C-2′. Although there were no direct HMBC correlations available, the remaining unsaturation and the NOESY correlation from H-6′ (δ_H 6.56) to H_3-15 indicated that the position of the ether linkage was at C-3 and C-1′, resulting in the formation of a 2*H*-chromen-6-ol. The geometry of double bond at C-1 was assigned as *Z* on the basis of the coupling constant (J = 10.0 Hz) and a NOESY correlation between H-1 and H-2. The CD spectrum of **2** exhibited a negative Cotton effect around λ_{max} ($\Delta\varepsilon$) 261 (−0.49) and 275 (−0.31) nm due to the styrene chromophore. The absolute configuration of C-3 was determined to be *R* by comparison with the reported CD data of sargatriol, a related chiral chromenol.[11] Thus, the structure of **2** was determined.

Capillobenzofuranol (**3**) was isolated as a yellow, viscous oil. The HRESIMS of **3** exhibited a $[M + Na]^+$ peak at *m*/*z* 393.2038 and established a molecular formula of $C_{23}H_{30}O_4$, implying nine degrees of unsaturation. Comparison of the NMR spectroscopic data (Tables 1 and 2) with those obtained for **2** showed that **3** was also a furanobenzosesquiterpenoid analogue of **2**. This significant difference could be explained by the formation of a 2,3-dihydrobenzofuran-5-ol ring[10,12,13] in **3** instead of the 2*H*-chromen-6-ol ring in **2**. This explanation was further supported by the COSY correlation between H_2-1 and H-2 and the HMBC correlations from H_3-15 to C-2, C-3, and C-4. In addition, the methoxy group attached

Table 2. ^{13}C NMR Spectroscopic Data of **1**−**4**[a]

C#	**1**, δ_C, mult.	**2**, δ_C, mult.	**3**, δ_C, mult.	**4**, δ_C, mult.
1	28.0, CH_2	122.4, CH	31.9, CH_2	146.2, CH
2	117.1, CH	129.7, CH	87.1, CH	119.5, C
3	138.7, C	77.9, C	77.7, C	106.0, CH
4	40.2, CH_2	40.7, CH_2	34.0, CH_2	156.6, C
5	27.2, CH_2	22.8, CH_2	22.6, CH_2	34.9, CH_2
6	123.1, CH	126.4, CH	125.6, CH	32.2, CH
7	133.8, C	132.0, C	131.3, C	32.0, CH_2
8	40.3, CH_2	38.4, CH_2	39.0, CH_2	31.3, CH_2
9	27.4, CH_2	154.3, C	153.3, C	73.6, CH
10	124.2, CH	108.8, CH	108.4, CH	145.1, C
11	134.2, C	120.5, C	119.8, C	135.6, CH
12	37.5, CH_2	137.7, CH	136.8, CH	114.8, CH_2
13	30.4, CH_2	9.8, CH_3	10.9, CH_3	163.9, C
14	78.2, CH	15.9, CH_3	16.8, CH_3	19.4, CH_3
15	73.0, C	26.1, CH_3	19.7, CH_3	115.4, CH_2
16	24.2, CH_3		50.7, CH_3	51.5, CH_3
17	27.3, CH_3			170.3, C
18	17.2, CH_3			21.2, CH_3
19	17.0, CH_3			
20	17.1, CH_3			
1′	185.9, C	146.7, C	152.4, C	
2′	147.2, C	119.6, C	124.1, C	
3′	132.5, CH	112.4, CH	111.5, CH	
4′	186.4, C	147.4, C	146.3, C	
5′	144.4, C	124.4, C	122.4, C	
6′	131.3, CH	118.1, CH	110.4, CH	
7′	16.6, CH_3	15.8, CH_3	17.1, CH_3	

[a] Spectra recorded at 100 MHz in $CDCl_3$.

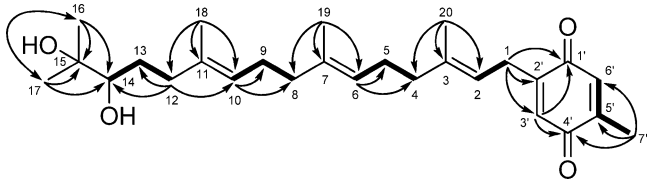

Figure 1. Selected COSY (—) and HMBC (→) correlations of **1**.

at C-3 was confirmed on the basis of the HMBC correlation from H_3-16 to C-3. The absolute configurations of C-2 and C-3 were proposed as 2*S* and 3*S* on the basis of the negative specific rotation and CD data, which are in good agreement with the reported data of (2*S*,1′*S*)-2,3-dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-7*H*-furo[3,2-*g*][1]benzopyran-7-one (**10**).[14] Consequently, the structure of **3** was deduced.

The HRESIMS of **4** exhibited a $[M + Na]^+$ peak at *m*/*z* 343.1519, which suggested a molecular formula of $C_{18}H_{24}O_5$. The NMR features (Tables 1 and 2) [δ_H 7.88 (1H, s), 6.34 (1H, s), and 3.82 (3H, s); δ_C 146.2 (CH), 119.5 (C), 106.0 (CH), 156.6 (C), 163.9 (C), and 51.5 (CH_3)] indicated the presence of an 1-alkyl-3-carbomethoxyfuran,[3] which was further supported by the COSY correlations between H-1 and H-3 and the HMBC correlations from H-1 to C-2, C-3, and C-4, from H-3 to C-2 and C-4, and from H-1/H-3 to C-13. Interpretation of the $^1H-^1H$ COSY spectrum from H_2-5 to H-9 through H-6, H_2-7, and H_2-8 and from H-12 to H_2-15 led to two partial structures. The connectivity of the two partial structures was further established by the HMBC correlations from H_2-15 to C-9, C-10, and C-11. Moreover, the crucial HMBC correlation from H-5 to C-4 led to the assignment of the long chain at C-4. The location of the acetyl group at C-9 was clarified by analysis of the HMBC correlation from H-9 to C-17. The relative configuration of C-6 and C-9 for **4** was not determined. Therefore, the structure of capillofuranocarboxylate (**4**) was determined.

The cytotoxic results showed that **1** and **2** exhibited weak cytotoxicty against P-388 (mouse lymphocytic leukemia) with ED_{50} values of 9.8 and 12.7 μM, respectively. The other tested metabolites were not cytotoxic to P-388, A549 (human lung carcinoma), and HT-29 (human colon adenocarcinoma) cell lines. The anticancer agent mithramycin was used as the positive control and exhibited ED_{50}'s of 0.06, 0.07, and 0.07 μM against P-388, HT-29, and A549 cells, respectively. The results for inhibition of HCMV activity revealed that **3**, **6**, and **7** exhibited antiviral activity with IC_{50}'s of 13.5, 5.9, and 15.0 μM, respectively. In addition, the results for inhibition of antibacterial activity assay against *Enterobacter aerogenes* (ATCC13048), *Salmonella enteritidis* (ATCC13076), *Serratia marcescens* (ATCC25419), *Shigella sonnei* (ATCC11060), and *Yersinia enterocolitica* (ATCC23715) are all negative at a concentration of 100 μg/mL.

As shown in Figure 2, the in vitro anti-inflammatory activity of **1**−**9** was tested using LPS-stimulated cells. Stimulation of RAW 264.7 cells with LPS resulted in up-regulation of the pro-inflammatory iNOS and COX-2 proteins. At a concentration of 10 μM, **6** significantly reduced the levels of the iNOS (0.32 ± 0.0%) and COX-2 (48.7 ± 11.4%) proteins compared with the control cells stimulated with LPS alone group. Under the same concentration, **1**, **2**, and **7** did not inhibit the COX-2 protein expression, but significantly inhibited iNOS protein (39.6 ± 8.8%, 36.7 ± 10.0%, and 39.5 ± 9.2%, respectively) expression by LPS stimulation. Metabolites **3**−**5**, **8**, and **9** did not inhibit both iNOS and COX-2 protein expression at the same concentration. None of these isolated compounds affected β-actin protein expression at a 10 μM concentration. Under the same experimental conditions, 10 μM CAPE (caffeic acid phenylethyl ester) reduced the levels of iNOS and COX-2 proteins to 1.5 ± 2.1% and 70.2 ± 11.5%, respectively, relative to the control cells stimulated with LPS.

Numerous farnesyl quinones and quinols have been obtained from other marine organisms, including sponges,[15] algae,[16] and ascidians.[17] Many of these mixed $C_{15} + C_6$ analogues are of considerable interest from the standpoint of bioactivities such as cytotoxicity, anti-HIV-1 reverse transcriptase, and antimicrobial activities.[15−17] The primary biological results of **1**−**7** suggested that furanobenzosesquiterpenoid **6** had the best anti-HCMV and anti-inflammatory activities. Previously, (−)-loliolide (**8**) has been identified in higher plant species and a marine alga,[6a−d] and its chemical synthesis has also been achieved.[6e,f] Metabolite **9** has previously been isolated only from the Argentina liverwort *Du-*

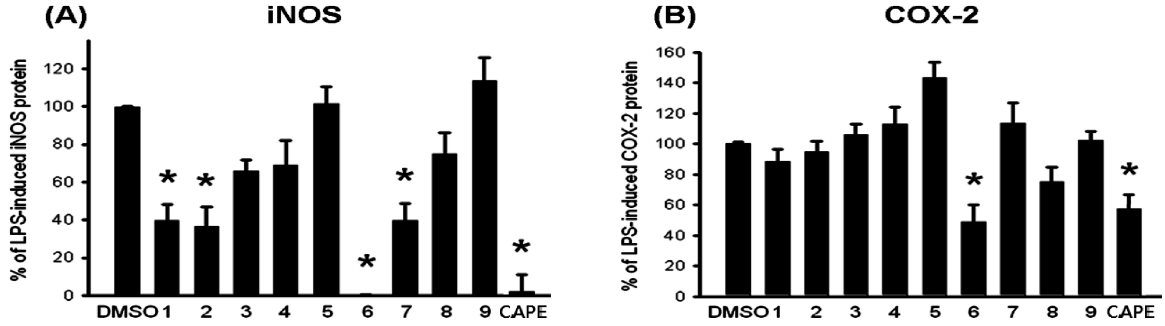

Figure 2. Effect of metabolites **1**−**9** at 10 μM on the LPS-induced pro-inflammatory iNOS and on COX-2 protein expression of RAW 264.7 macrophage cells by immunoblot analysis. (A) Immunoblot of iNOS. (B) Immunoblot of COX-2. A and B values are mean ± SEM ($n = 5$). The relative intensity of the LPS alone stimulated group was taken as 100%. *Significantly different from LPS-stimulated (control) group (*$P < 0.05$). Caffeic acid phenylethyl ester (CAPE) was used as the positive control substance.

mortiera hirsuta[7] and, therefore, is reported from a marine organism for the first time.

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a JASCO P1020 polarimeter. UV, CD, and IR spectra were measured on JASCO V-650, JASCO J-815, and JASCO FT/IR-4100 spectrophotometers, respectively. The NMR spectra were recorded on a Varian 400 MR NMR spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively. Chemical shifts are expressed in δ (ppm) referring to the solvent peaks δ_H 7.27 and δ_C 77.0 for $CDCl_3$, respectively, and coupling constants are expressed in Hz. FABMS were obtained with a VG Quattro GC/MS spectrometer. ESIMS were recorded by ESI FT-MS on a Bruker APEX II mass spectrometer. Silica gel 60 (Merck, 230−400 mesh) was used for column chromatography; precoated Si gel plates (Merck, Kieselgel 60 F_{254}, 0.25 mm) were used for TLC analysis. C_{18} reversed-phase silica gel (230−400 mesh, Merck) was also used for column chromatography. High-performance liquid chromatography (HPLC) was performed on a Hitachi L-7100 pump equipped with a Hitachi L-7400 UV detector at 220 nm and a ODS column (Merck, Hibar Purospher RP-18e, 5 μm, 250 × 10 mm).

Animal Material. The soft coral *Sinularia capillosa* was collected by hand using scuba at the Dongsha Atoll off Taiwan in April 2007, at a depth of 7 m, and was stored in a freezer for two months until extraction. This soft coral was identified by one of the authors (C.-F.D.). A voucher specimen (TS-06) was deposited in the Department of Marine Biotechnology and Resources, National Sun Yat-sen University.

Extraction and Isolation. The frozen soft coral (1.5 kg) was chopped into small pieces and extracted exhaustively by maceration with fresh acetone for 24 h at room temperature. The acetone extract was filtered and concentrated under vacuum to yield a brownish, oily residue, which was subsequently partitioned between EtOAc and H_2O. The resulting EtOAc-soluble residue (60 g) was subjected to column chromatography on silica gel using *n*-hexane and *n*-hexane−EtOAc of increasing polarity to give 25 fractions. Fraction 9 was further separated by RP-18 HPLC eluted with MeOH−H_2O (9:1) to obtain **3** (2 mg), **6** (105 mg), and **7** (2 mg). Fraction 14 was further separated by RP-18 HPLC eluted with MeOH−H_2O (17:1) to obtain **2** (4 mg), **4** (2 mg), and **9** (3 mg). Fraction 16 was subjected to column chromatography on silica gel using *n*-hexane and *n*-hexane−EtOAc of increasing polarity to give **5** (156 mg). Fraction 18 was fractioned by column chromatography on silica gel column eluting with *n*-hexane and *n*-hexane−EtOAc of increasing polarity to afford seven subfractions. The subfraction 18-1 was applied to column chromatography on a RP-18 gel column eluted with MeOH to provide **1** (2 mg). Similarly, metabolite **8** (3 mg) was purified by RP-18 HPLC of the subfraction 18-3 (48 mg) eluted with MeOH−H_2O (4:1).

Capilloquinone (1): yellow, viscous oil; $[\alpha]^{25}_D$ −15 (*c* 0.1, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 250 (3.67), 297 (3.24), 342 (2.95) nm; IR (KBr) ν_{max} 3450, 2958, 2923, 2858, 1654, 1616, 1446, 1385 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 451 [M + Na]$^+$; HRESIMS *m/z* 451.2821 [M + Na]$^+$ (calcd for $C_{27}H_{40}O_4Na$, 451.2824).

Capillobenzopyranol (2): yellow, viscous oil; $[\alpha]^{25}_D$ +48 (*c* 0.1, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 226 (4.06), 269 (3.28), 332 (3.35) nm; CD (1.48 × 10^{-4} M, MeOH) λ_{max} ($\Delta\varepsilon$) 250 (−0.14), 261 (−0.49), 275 (−0.31), 330 (−0.54) nm; IR (KBr) ν_{max} 3406, 3038, 2973, 2928, 1619, 1498, 1456, 1422, 1373, 1187 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2; FABMS *m/z* 339 [M + H]$^+$; HRESIMS *m/z* 339.1962 [M + H]$^+$ (calcd for $C_{22}H_{27}O_3$, 339.1960).

Capillobenzofuranol (3): yellow, viscous oil; $[\alpha]^{25}_D$ −22 (*c* 0.1, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 220 (3.72), 301 (3.26) nm; CD (1.35 × 10^{-4} M, MeOH) λ_{max} ($\Delta\varepsilon$) 223 (+0.15), 250 (−0.14), 271 (+0.08), 328 (−0.09) nm; IR (KBr) ν_{max} 3381, 3042, 2970, 2925, 1623, 1498, 1457, 1418, 1369, 1191, 1115 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 393 [M + Na]$^+$; HRESIMS *m/z* 393.2038 [M + Na]$^+$ (calcd for $C_{23}H_{30}O_4Na$, 393.2042).

Capillofuranocarboxylate (4): white, amorphous powder; $[\alpha]^{25}_D$ −90 (*c* 0.1, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 218 (3.58), 230 (3.43) nm; IR (KBr) ν_{max} 2956, 1714, 1689, 1440, 1378, 1216 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 343 [M + Na]$^+$; HRESIMS *m/z* 343.1519 [M + Na]$^+$ (calcd for $C_{18}H_{24}O_5Na$, 343.1521).

(*E*)-5-(2,6-Dimethylocta-5,7-dienyl)furan-3-carboxylic acid (5): $[\alpha]^{25}_D$ −28 (*c* 0.1, CH_2Cl_2).

(−)-Loliolide (8): $[\alpha]^{25}_D$ −120 (*c* 0.1, CH_2Cl_2); lit. $[\alpha]_D$ −92 (*c* 1.1, $CHCl_3$),[6a] and $[\alpha]^{25}_D$ −100 (*c* 0.07, $CHCl_3$).[6b]

3,4,11-Trimethyl-7-methylenebicyclo[6.3.0]unde-2-en-11α-ol (9): $[\alpha]^{25}_D$ +110 (*c* 0.1, CH_2Cl_2).

Biological Assays. The in vitro cytotoxicity, anti-inflammatory activity, HCMV activity, and antibacterial assays were carried out according to the procedures described previously.[18−21]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2009**, *26*, 170–244, and literature cited in previous reviews.
(2) Lakshmi, V.; Kumar, R. *Nat. Prod. Res.* **2009**, *23*, 801–850, and references therein.
(3) Bowden, B. F.; Coll, J. C.; de Silva, E. D.; de Costa, M. S. L.; Djiura, P. J.; Mahendran, M.; Tapiolas, D. M. *Aust. J. Chem.* **1983**, *36*, 371–376.
(4) Su, J.; Yang, R.; Kuang, Y.; Zeng, L. *J. Nat. Prod.* **2000**, *63*, 1543–1545.
(5) Cheng, S.-Y.; Huang, K.-J.; Wang, S.-K.; Wen, Z.-H.; Hsu, C.-H.; Dai, C.-F.; Duh, C.-Y. *Org. Lett.* **2009**, *11*, 4830–4833.
(6) (a) Hodges, R.; Porte, A. L. *Tetrahedron* **1964**, *20*, 1463–1467. (b) Pettit, G. R.; Herald, C. L.; Ode, R. H.; Brown, P.; Gust, D. J.; Michel, C. *J. Nat. Prod.* **1980**, *43*, 752–755. (c) Okunade, A. L.; Wiemer, D. F. *J. Nat. Prod.* **1985**, *48*, 472–473. (d) Valdes, L. J., III. *J. Nat. Prod.* **1986**, *49*, 171. (e) Rouessac, F.; Zamarlik, H.; Gnonlonfoun, N. *Tetrahedron Lett.* **1983**, *24*, 2247–2250. (f) Zamarlik, H.; Gnonlonfoun, N.; Rouessac, F. *Can. J. Chem.* **1984**, *62*, 2326–2329.
(7) Toyota, M.; Bardón, A.; Kamiya, N.; Takaoka, S.; Asakawa, Y. *Chem. Pharm. Bull.* **1997**, *45*, 2119–2121.

(8) Iwashima, M.; Mori, J.; Ting, X.; Matsunaga, T.; Hayashi, K.; Shinoda, D.; Saito, H.; Sankawa, U.; Hayashi, T. *Biol. Pharm. Bull.* **2005**, *28*, 374–377.
(9) Moore, C. J.; Possner, S.; Hayes, P.; Paddon-Jones, G. C.; Kitching, W. *J. Org. Chem.* **1999**, *64*, 9742–9744.
(10) Seo, Y.; Park, K. E.; Kim, Y. A.; Lee, H.-J.; Yoo, J.-S.; Ahn, J.-W.; Lee, B.-J. *Chem. Pharm. Bull.* **2006**, *54*, 1730–1733.
(11) Tohru, K.; Yuji, M.; Toshio, Y.; Shozo, N; Hiroyuki, K.; Yoshiro, M.; Keisuke, K.; Kaoru, K. *Chem. Pharm. Bull.* **1983**, *31*, 106–113.
(12) Ahmed, A.-L.; Kïig, G. M.; Fisch, K. M.; Höller, U.; Jones, P. G.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 1605–1611.
(13) Tanaka, M.; Nara, F.; Yamasato, Y.; Ono, Y.; Ogita, T. *J. Antibiot.* **1999**, *52*, 827–830.
(14) Tovar-Miranda, R.; Cortés-García, R.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2002**, *13*, 1147–1152.
(15) (a) Schmitz, F. J.; Lakashmi, V.; Powell, D. R.; van der Helm, D. *J. Org. Chem.* **1984**, *49*, 241–244. (b) Venkateswarlu, Y.; Faulkner, D. J.; Steiner, J. L. R.; Corcoran, E.; Clardy, J. *J. Org. Chem.* **1991**, *56*, 6271–6274. (c) Rudi, A.; Benayahu, Y.; Kashman, Y. *Org. Lett.* **2004**, *6*, 4013–4016.
(16) (a) Talpir, R.; Rudi, A.; Kashman, Y. *Tetrahedron* **1994**, *50*, 4179–4184. (b) Rochfort, S. J.; Capon, R. J. *J. Nat. Prod.* **1994**, *57*, 849–851.
(17) (a) Fu, X.; Hossain, M. B.; Schmitz, F. J.; van der Helm, D. *J. Org. Chem.* **1997**, *62*, 3810–3819. (b) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **1999**, *62*, 1405–1409. (c) Issa, H. H.; Tanaka, J.; Rachmat, R.; Higa, T. *Tetrahedron Lett.* **2003**, *44*, 1243–1245.
(18) Hou, R.-S.; Duh, C.-Y.; Chiang, M. Y.; Lin, C.-N. *J. Nat. Prod.* **1995**, *58*, 1126–1130.
(19) Cheng, S.-Y.; Wen, Z.-H.; Chiou, S.-F.; Wang, S.-K.; Hsu, C.-H.; Dai, C.-F.; Chiang, M. Y.; Duh, C.-Y. *Tetrahedron* **2008**, *64*, 9698–9704.
(20) Cheng, S.-Y.; Wen, Z.-H.; Wang, S.-K.; Chiou, S.-F.; Hsu, C.-H.; Dai, C.-F.; Duh, C.-Y. *Bioorg. Med. Chem.* **2009**, *17*, 3763–3769.
(21) Stevens, M.; Balzarini, J.; Tabarrini, O.; Andrei, G.; Snoeck, R.; Cecchetti, V.; Fravolini, A.; De Clercq, E.; Pannecouque, C. *J. Antimicrob. Chemother.* **2005**, *56*, 847–855.

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