Polyprenylated Benzophenone Derivatives from Cuban Propolis

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Three new polyprenylated benzophenone derivatives, propolones B−D (**5**−**7**), together with garcinielliptone I (**8**) and hyperibone B (**9**), were isolated from Cuban propolis. All the structures, including relative configurations, were elucidated by spectroscopic methods and computer-generated molecular modeling.

Propolis is a resinous substance collected by honeybees from various plant sources. It contains mostly sticky plant substances, beeswax, and other bee secretions. Propolis has been reported to possess various biological activities, e.g., anticancer, antioxidant, antiinflammatory, antibiotic, and antifungal.[1,2] The chemical composition of propolis depends on the vegetation of the area from which it was collected.[1−3] For example, propolis from temperate zones, especially European propolis, contains phenolic compounds, predominantly flavonoids,[4,5] while propolis from tropical zones contains different classes of natural products, among them polyprenylated benzophenones.[6−9] Previously we isolated four of these compounds, propolone A (**1**), nemorosone (**2**), guttiferone E (**3**), and xanthochymol (**4**), from Cuban propolis[8,9] (Figure 1). In this investigation three new polyprenylated benzophenone derivatives, named propolones B−D (**5**−**7**), together with garcinielliptone I (**8**) and hyperibone B (**9**), were isolated from a Cuban propolis sample collected in Guantánamo Province (Cuba).

Propolis sample was extracted with methanol. Part of the extract was fractionated on Sephadex LH-20 and silica gel and purified by RP-HPLC to give five polyprenylated benzophenone derivatives (**5**−**9**). Except garcinielliptone I (**8**) and hyperibone B (**9**), isolated recently from *Garcinia subelliptica*[10] and *Hypericum scabrum*,[11] respectively, compounds **5**−**7** were new natural products, identified on the basis of the evidence outlined below (Figure 2).

The molecular formula of compound **5** was determined to be $C_{33}H_{44}O_7$ by MS, ^{13}C NMR, and ^{13}C DEPT NMR analyses. The ESIMS of **5** showed an $[M + H]^+$ ion at *m/z* 553 and an $[M + H - H_2O]^+$ ion at *m/z* 535 in the MS/MS spectrum. The IR spectrum showed a strong broad hydroxyl band (3500 cm^{-1}) and both nonconjugated (1726 cm^{-1}) and conjugated (1690 and 1702 cm^{-1}) carbonyl groups. Additional evidence for the three carbonyl groups was the presence of resonances corresponding to an unconjugated (δ 210.3) and two conjugated carbonyls (δ 193.1 and 194.1) in the ^{13}C NMR spectrum. Comparison of the NMR spectra with those of propolone[8] (**1**) suggested similar bicylo[3.3.1]-nonane moieties, the skeleton most frequently encountered among polyprenylated benzophenone derivatives isolated from Clusiaceae. ^{13}C chemical shifts at δ 72.3 (C-1), 166.3 (C-2), 111.1 (C-3), 194.1 (C-4), 63.9 (C-5), 43.0 (C-6), 42.7 (C-7), 48.0 (C-8), and 210.3 (C-9) supported the presence of the bicylo[3.3.1]nonane moiety. The ^1H NMR spectrum exhibited only one set of signals, suggesting the absence of a tautomeric equilibrium. NMR data also permitted identification of the presence of three C_5 units and an unsubstituted benzoyl moiety. The ^1H NMR spectrum also exhibited signals for one vinylic proton (δ 4.95), two vinylic methyl groups (δ 1.55, 1.67), and two allylic protons (δ 1.70, 2.14), indicating the presence of only one isopent-2-enyl group in the molecule. This isoprenoid unit was identified from the NMR data as a 2-methylbut-2-enyl group (C-27 to C-31) attached to a methine carbon, δ_C 42.7 (C-7). The absence of further signals for sp^2 carbons suggested that the two remaining C_5 units were modified 2-methylbut-2-

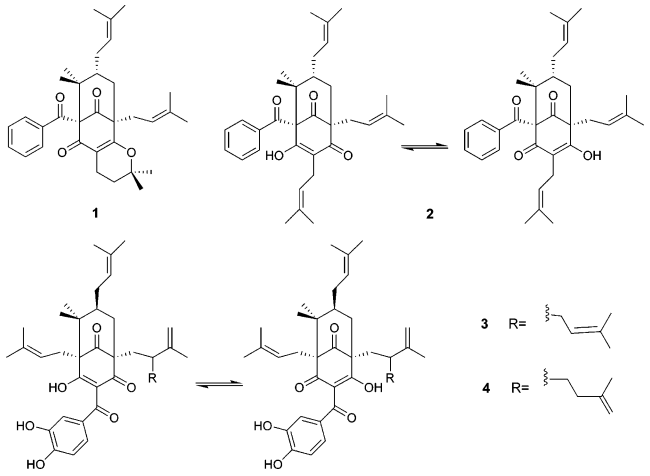

Figure 1. Propolone A (**1**), nemorosone (**2**), guttiferone E (**3**), and xanthochymol (**4**).

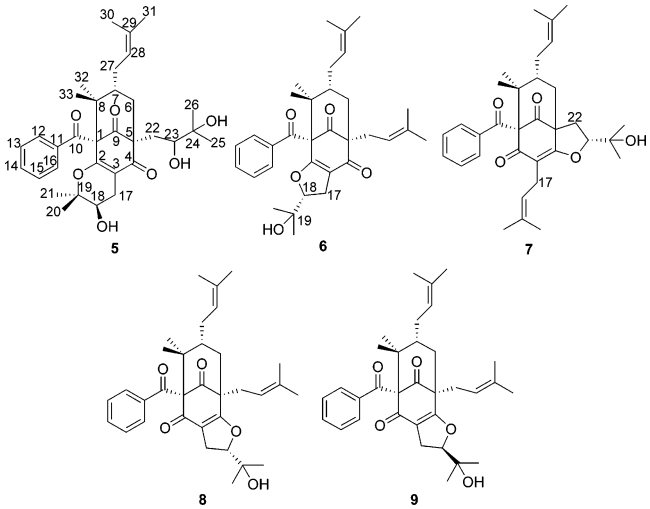

Figure 2. Polyprenylated benzophenones (**5**−**9**) from Cuban propolis.

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Table 1. NMR Data for Compounds **5** and **6** in $CDCl_3$[a]

	5			**6**		
position	δ ^{13}C	δ ^{1}H (J_{H-H} in Hz)	HMBC[b]	δ ^{13}C	δ ^{1}H (J_{H-H} in Hz)	HMBC[b]
1	72.3			70.6		
2	166.3			171.9		
3	111.1			118.3		
4	194.1			188.1		
5	63.9			65.3		
6ax	43.0	1.45 dd (13.4, 11)	4, 5, 7	41.8	1.46 overlapped	4, 5, 7, 8, 9
6eq		2.03 overlapped	4, 8, 9		2.00 dd (13.6, 4.4)	
7	42.7	1.82 m	27	43.2	1.67 overlapped	27
8	48.0			47.0		
9	210.3			206.9		
10	193.1			193.2		
11	137.1			137.2		
12,16	128.3	7.70 d (7.8)	10, 14	128.5	7.58 d (7.9)	10, 14
13,15	128.0	7.30 t (7.8)	11, 12, 16	128.2	7.35 t (7.9)	11, 12, 16
14	132.2	7.42 t (7.8)	13, 15	132.8	7.49 t (7.7)	13, 15
17	25.2	2.63 dd (17.1, 4.4)	3, 18, 19	26.5	2.96 d (9.9) (2H)	2, 3, 18, 19
		2.56 dd (17.1, 4.0)	2, 3			
18	67.6	3.60 bt		93.5	4.65, 2H, t (9.9)	19, 20, 21
19	82.1			70.6		
20	22.6	1.22 s	18, 19	23.7	0.90 s	18, 19, 21
21	23.5	0.52 s	18, 19, 20	26.4	0.90 s	18, 19, 20
22a	32.6	2.08 (2H) overlapped	9, 4, 23, 24	29.3	2.48 m	4, 5, 9, 23, 24
22b					2.57 m	
23	74.7	3.56 dd (9.6, 3.1)		119.5	5.06 m	
24	73.0			134.7		
25	24.1	1.21 s	23, 26	18.1	1.70 s	23, 24, 26
26	25.8	1.24 s	23, 24, 25	26.0	1.67 s	23, 24, 25
27	27.6	1.70 overlapped	7, 28	27.7	1.65 overlapped	
		2.14 overlapped			2.13 m	
28	122.3	4.95 m	30, 31	122.3	4.96 m	
29	133.6			133.5		
30	17.9	1.55 s	28, 29, 31	17.9	1.56 s	28, 29, 31
31	25.8	1.67 s	28, 29, 30	25.9	1.67 s	28, 29, 30
32ax	16.3	1.21 s	7, 8, 33	15.7	1.24 s	1, 7, 8, 33
33eq	24.1	1.39 s	1, 7, 8, 32	24.1	1.34 s	1, 7, 8, 32

[a] Chemical shift values are in ppm from TMS, and values in Hz are presented in parentheses. All signals were assigned by DQF-COSY, HSQC, and HMBC experiments. [b] Carbons that correlate with the proton resonance.

enyl groups. HMBC connectivities enabled differentiation between the isoprenoid groups at C-3 and C-5. Carbon C-2 (δ 166.3) showed correlations to the C-17 protons, indicating the presence of one five-carbon unit at C-3. HSQC, COSY, and HMBC data indicated involvement of $C_{17}-C_{21}$ in a 2,2-dimethyl-2*H*-dihydropyran ring (Table 1). The proton and carbon chemical shifts at position 18 (δ_C 67.6, δ_H 3.60) indicated the presence of a secondary alcohol. Me-21ax (δ 0.52) exhibited a high-field chemical shift observed also in plukenetione F,[12] a compound closely related to compound **5**. This unusual chemical shift has been attributed to shielding effects from the benzoyl group. The last isoprenoid group (C-22 to C-26) showed in the NMR spectra an oxymethine C-23 (δ_C 74.7, δ_H 3.56) linked to a quaternary carbon bearing oxygen C-24 (δ 73.0). The ^{1}H–^{1}H COSY correlation between H_2-22 (δ 2.08) and H-23 (δ 3.56) and the HMBC correlations of Me-25 (δ 1.21) to C-23 (δ 74.7), C-24 (δ 73.0), and C-26 (δ 25.8), Me-26 (δ 1.24) to C-23, C-24, and C-25 (δ 24.1), and H_2-22 to C-24 revealed the presence of a 2,3-dihydroxy-3-methylbutyl group. The HMBC correlations of H_2-22 to C-4 (δ 194.1) and C-9 (δ 210.3) established that the 2,3-dihydroxy-3-methylbutyl group is attached to C-5.

The relative configuration at C-7 was deduced from coupling constants and by NOE data obtained from a ROESY spectrum (Figure 3). An 11 Hz coupling constant between Hα-6 and H-7 required these protons to be diaxial, thus the isopentenyl group at C-7 was α-equatorial. This orientation at C-7 was confirmed by NOE interactions between H-7 and H_β-6 and between Me-32ax and H_α-6. The relative configurations at C-1 and C-5 were deduced from

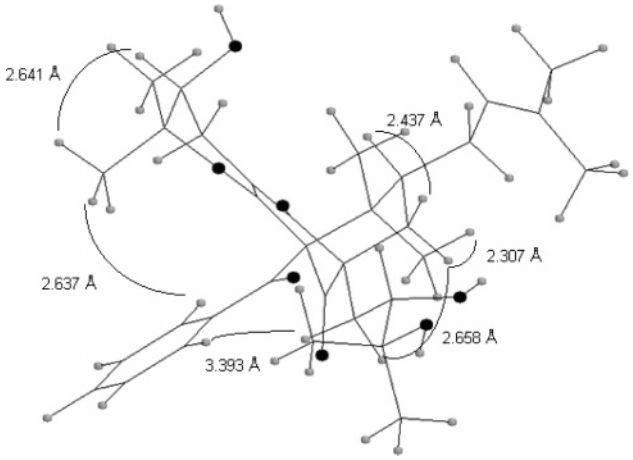

Figure 3. Selected ROESY correlations and relative configuration of **5**.

ROESY cross-peaks of H_2-22/H-12 or H-16, H_2-22/H_α-6, H_β-6/H-7, and H_α-6/Me-32; thus the isoprenoid groups at C-5 and C-7 and the benzoyl moiety at C-1 are cofacial. The ROESY spectrum also clarified the relative configuration at C-18. NOE effects observed between H-18 and Me-21 and between this methyl and the aromatic protons H-12 and H-16 indicated that H-18 has an α-orientation. From crystallographic data of nemorosone[13] (**2**), a compound with the same relative configuration of the bicylo[3.3.1]nonane moiety, a computer-generated 3D structure was obtained by using the molecular modeling program Hyperchem 4.5, with MM+ force-field calculations for energy minimization

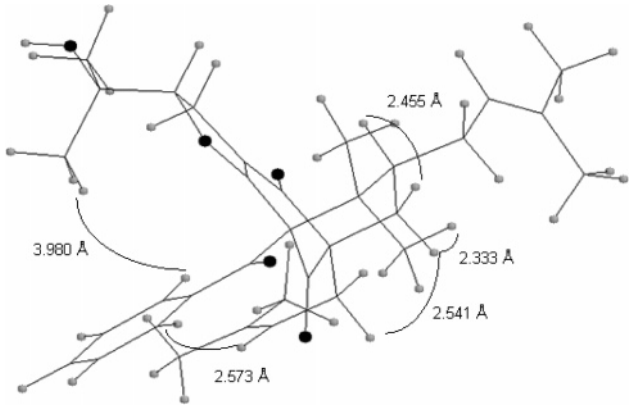

Figure 4. Selected ROESY correlations and relative configuration of **6**.

(Figure 3). The calculated distances between H_β-6/H-7 (2.437 Å), H_α-6/Me-32 (2.307 Å), H_2-22/ H_α-6 (2.658 Å), H_2-22/H-12 or H-16 (3.393 Å), H-18/Me-21 (2.641 Å), and Me-21/H-12 or H16 (2.637 Å) are all less than 4.00 Å; this is consistent with the well-defined NOESY observed for each of these proton pairs. Thus, the structure of **5** was assigned as shown in Figure 2 and was named propolone B.

The molecular formula of compound **6** was determined as $C_{33}H_{42}O_5$ by MS, ^{13}C NMR, and ^{13}C DEPT NMR analysis. The ESIMS spectrum of **6** exhibited a peak at *m/z* 541, corresponding to the sodium adduct $[M + Na]^+$, and a pseudomolecolar ion $[M + H]^+$ ion at *m/z* 519.

^1H and ^{13}C NMR data suggested that **6** is a bicylo[3.3.1]-nonane derivative with two 3-methyl-2-butenyl side chains attached to C-5 and C-7 (Table 1). These spectra indicated the presence of a 2-(2-hydroxypropyl)dihydrofuran ring in place of the dihydropyran ring of **5**, from the differences observed, mainly in the ^{13}C NMR spectra, for C-18 (δ 93.5 in **6** and 67.6 in **5**), C-19 (δ 70.6 in **6** and 82.1 in **5**), and C-21 (δ 26.4 in **6** and 23.5 in **5**). The presence of a different cyclization of the C_5 unit at C-3 was also confirmed by COSY, HSQC, and HMBC experiments and by comparison with closely related compounds such as hyperibones A−I[11] and sampsoniones K−M.[14] In the HMBC spectrum cross-peaks between methylene protons at C-17 (δ 2.96, 2H) and C-2 (δ 171.9) and C-3 (δ 118.3) indicated that the dihydrofuran ring was formed between C-2 and C-3. Assigment of the relative configuration at C-1, C-5, C-7, and C-18 of **6** was established by a ROESY spectrum and comparison with literature data.[14,15] Although $^3J_{H6ax-H7}$ was not observed, ^{13}C chemical shifts of the *gem*-methyl groups at C-8 permitted definition of an equatorial orientation of the 3-methyl-2-butenyl unit at C-7. The axial C-8 methyl group showed a ^{13}C chemical shift in the range observed for polyprenyl benzophenones with an equatorial isopentenyl group at C-7 (δ_C 15−18). This shielded position is due to a *γ-gauche* interaction between the C-7 3-methyl-2-butenyl group and Me-32.[14,15] The significant NOE correlations in the ROESY spectrum shown in Figure 4 confirmed the relative configuration at C-7. In the same manner, the orientation of the 1-methyl-1-hydroxyethyl group at C-18 in **6** was determined by NOE interactions: cross-peaks between Me-20 and Me-21 and aromatic protons H-12 and H-16 indicated the α-configuration of the C-18 1-methyl-1-hydroxyethyl group as shown in **6**. The shielding of the C-20 and C-21 are due to the anisotropic effect of the aromatic ring. Moreover, a comparison of the NMR data with those of sampsonione M[14] suggested an opposite relative configuration at C-18 in compound **6**. A computer-generated 3D structure was obtained for **6** by using the Hyperchem 4.5 program, with MM+ force-field calculations for energy minimization (Figure 4). The calculated distances between H_β-6/H-7 (2.455 Å), H_α-6/Me-32 (2.333 Å), H-22a/H_α-6 (2.541 Å), H-23/H-12 or H-16 (2.573 Å), and H-12 or H-16/Me-21 (3.980 Å) are all less than 4.00 Å; this is consistent with the well-defined NOESY correlations observed for each of these proton pairs. From all these data the structure of **6** was assigned as reported in Figure 2. Chaturvedula et al.[16] reported the structure of ochrocarpinone B possessing the same structure as that propolone D albeit with unspecified relative configuration. Comparison of ^{13}C NMR data of both compounds showed some consistent differences at C-18, C-3, C-4, and C-5 and other smaller differences.

Compounds **7**−**9** have the same molecular formula as **6** ($C_{33}H_{42}O_5$, determined by MS, ^{13}C NMR, and ^{13}C DEPT NMR analysis), and their NMR data suggested the presence of a bicylo[3.3.1]nonane derivative with a dihydrofuran ring and an equatorial isopentenyl group at C-7.[11,14−15] In **7** this ring was formed between C-4 and C-23, while in **8** and **9** it was formed between C-4 and C-18 (HMBC correlations in **7**: H_2-22/C-5, C-6, C-9, C-23, C-24; HMBC correlations in **8** and **9**: H_2-17/C-3, C-4, C-18, C-19).

NMR data of compound **7** were identical with those reported for hyperibone G. Although differences were observed with respect to optical rotation values ($[\alpha]_D$ = +48.5° for **7**, $[\alpha]_D$ = −29.3° for hyperibone G), these compounds are probably enantiomeric. Since $[\alpha]_D$ values depend on several factors, e.g., concentration, solvent, temperature, equipment, and the purity of the isolated compound, reported enantiomers have shown differences similar to those recorded for **7** and hyperibone G, e.g., guttiferone E[17,18] and garcinol.[19] Thus, the structure of compound **7**, named propolone D, was assigned as shown in Figure 2.

The NMR data of **8** and **9** were very similar, but some differences in their ^{13}C NMR chemical shifts were observed for C-18 (δ 93.1 in **8** and δ 92.5 in **9**), for the carbons near C-18, and for the 1-methyl-1-hydroxyethyl side chain, consistent with these compounds being epimeric at C-18. Other differences were also observed in the chemical shifts of H_2-22 (δ 2.54, 2H, br d in **8**; δ 2.45 dd, 10.3, 7.8, and 2.60 dd, 10.3, 6.6 in **9**), C-23 (δ 120.3 in **8** and 118.3 in **9**), and C-24 (δ 134.7 in **8** and 135.5 in **9**). These differences are consistent with different orientations of the substituent at C-18 in these compounds and due to the steric effects between the C-18 1-methyl-1-hydroxyethyl and C-5 2-methylbut-2-enyl groups. 1D and 2D NMR data of **8** and **9** were identical to those reported for garcinielliptone I[10] and hyperibone B,[11] respectively.

Various enantiomers of polyisoprenylated benzophenone derivatives have been isolated from plants of the family Guttiferae.[10,11,17−19] A literature search reveals homology of the sign of optical rotation in compounds isolated from the same plants. The presence of polyisoprenylated benzophenones with different absolute configuration in our propolis sample could be due to the different plant sources collected by the honeybees.The bees in Cuba collect floral resins from *Clusia rosea*, a tree widely distributed in the Isle, but from this source only nemorosone[9] and hydroxynemorosone[20] have been isolated so far. This suggests the contribution of some other species producing resins that bees combine in order to produce propolis.

Experimental Section

General Experimental Procedures. Melting points were determined using a Bausch & Lomb apparatus. Optical rotations were measured on a Perkin-Elmer 192 polarimeter

equipped with a sodium lamp (589 nm) and a 10 cm microcell. UV spectra were obtained with a Beckman DU 670 spectrophotometer and IR spectra with a Bruker IFS-48 spectophotometer. A Bruker DRX-600 spectrometer, operating at 599.19 MHz for ^{1}H and 150.858 for ^{13}C, using the UXNMR software package was used for NMR experiments in $CDCl_3$. ^{1}H−^{1}H DQF-COSY, ^{1}H−^{13}C HSQC, HMBC, and NOESY experiments were obtained using conventional pulse sequences. ESIMS was performed using a Finnigan LC-Q Advantage Max instrument (Termoquest, San Jose, CA) equipped with Excalibur software. Exact masses were measured by a Q-Star Pulsar (Applied Biosystems) triple-quadrupole orthogonal time-of-flight instrument. HPLC separations were performed on a Waters 590 series pumping system equipped with a Waters R401 refractive index detector and a Waters 10 μm μ-Bondapak C18 column (300 × 7.8 mm). TLC analysis was performed with Macherey-Nagel precoated silica gel 60 F_{254} plates.

Biological Material. Propolis sample was collected in Guantanamo Province (Cuba) in April 2003. The sample and the dried methanol extract were stored at 5 °C in a dark place.

Extraction and Isolation. Propolis sample (40 g) was extracted with MeOH (200 mL × 3) for 3 h, and after filtration, the MeOH extract was taken to dryness under reduced pressure to yield a black gum (24.1 g). A portion of this extract (9 g) was fractionated over a Sephadex LH-20 column using MeOH as solvent to furnish nine fractions (1/1−1/9). Fraction 1/3 (1.04 g) on Vacuum-LC over silica gel eluting with 0−100% hexane−EtOAc mixtures yielded eight fractions (2/1−2/8). Fraction 2/3 (497.9 mg) on medium-pressure column chromatography over silica gel eluting with 0−100% hexane−EtOAc and 0−100% EtOAc−MeOH mixtures yielded 38 factions (3/1−3/38). Fraction 3/14 (40.5 mg) was purified by RP-HPLC (μ-Bondapack C-18 column, MeOH−H_2O, 75:25, flow rate 2.5 mL/min) to give **6** (3.6 mg). Fractions 3/15−17 (83.2 mg) were subjected to RP-HPLC (μ-Bondapack C-18 column, MeOH−H_2O, 75:25, flow rate 2.5 mL/min) to give **6** (7.9 mg), **8** (17.3 mg), **9** (22.8 mg), and **7** (7.3 mg). Fraction 3/29 (98.9 mg) was purified by HPLC (μ-Bondapack C-18 column, MeOH−H_2O, 80:20, flow rate 2.5 mL/min) to give **5** (5.1 mg).

Propolone B (5): colorless oil; $[\alpha]_D$ +38.2° (*c* 0.6, $CHCl_3$); IR (KBr) ν_{max} 3498, 1726, 1690, 1601 cm^{-1}; UV(MeOH) λ_{max} 248 and 277 nm; ^{1}H and ^{13}C NMR data, Table 1; ESIMS (positive mode) *m/z* 553 $[M + H]^+$, MS/MS *m/z* 535 $[M + H - H_2O]^+$; HRESI-MS (*m/z*), calcd for $C_{33}H_{44}O_7$, 553.3165, found, 553.3172.

Propolone C (6): colorless oil; $[\alpha]_D$ +35.7° (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 3504, 1740, 1710, 1698, 1654, 1032, cm^{-1}; UV (MeOH) λ_{max} 245 and 268 nm; ^{1}H and ^{13}C NMR data, Table 1; ESIMS (positive mode) *m/z* 519 $[M + H]^+$ and *m/z* 541 $[M + Na]^+$, (negative mode) *m/z* 517 $[M - H]^-$; ESI-MS/MS (positive mode) *m/z* 501 $[M + H - H_2O]^+$, 463 $[M + H - 56]^+$, 451 $[M + H - 68]^+$, 397 $[M + H - 122]^+$, 359 $[M + H - 160]^+$, 327 $[M + H - 192]^+$; HRESI-MS (*m/z*), calcd for $C_{33}H_{42}O_5$, 519.3111, found, 519.3119.

Propolone D (7): colorless oil; $[\alpha]_D$ +48.5° (*c* 0.71, $CHCl_3$); ^{1}H and ^{13}C NMR data were consistent with those previously reported for hyperibone G;[11] ESIMS (positive mode) *m/z* 519 $[M + H]^+$ and *m/z* 541 $[M + Na]^+$, (negative mode) *m/z* 517 $[M - H]^-$, ESIMS/MS (positive mode) *m/z* 501 $[M + H - H_2O]^+$, 441 $[M + H - 78]^+$, 397 $[M + H - 122]^+$, 383 $[M + H - 136]^+$, 327 $[M + H - 192]^+$; HRESI-MS (*m/z*), calcd for $C_{33}H_{42}O_5$, 519.3111, found, 519.3098.

Garcinielliptone I (8): colorless oil; $[\alpha]_D$ +63.7° (*c* 0.37, $CHCl_3$); ^{1}H and ^{13}C NMR data were consistent with those previously reported for garcinielliptone I;[10] ESIMS (positive mode) *m/z* 519 $[M + H]^+$ and *m/z* 541 $[M + Na]^+$ (negative mode) *m/z* 517 $[M - H]^-$, ESIMS/MS (positive mode) *m/z* 463 $[M + H - 56]^+$, 451 $[M + H - 68]^+$, 397 $[M + H - 122]^+$, 359 $[M + H - 160]^+$, 327 $[M + H - 192]^+$; HRESI-MS (*m/z*), calcd for $C_{33}H_{42}O_5$, 519.3111, found, 519.3117.

Hyperibone B (9): colorless oil; $[\alpha]_D$ −42.2° (*c* 0.14, $CHCl_3$); ^{1}H and ^{13}C NMR data were consistent with those previously reported;[11] ESIMS (positive mode) *m/z* 519 $[M + H]^+$ and *m/z* 541 $[M + Na]^+$, (negative mode) *m/z* 517 $[M - H]^-$, ESIMS/MS (positive mode) *m/z* 463 $[M + H - 56]^+$, 451 $[M + H - 68]^+$, 397 $[M + H - 122]^+$, 359 $[M + H - 160]^+$, 327 $[M + H - 192]^+$.

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