Sesquiterpene Quinols/Quinones from the Micronesian Sponge *Petrosaspongia metachromia*

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Two new sesquiterpenes, pelorol (**1**) and 5-*epi*-smenospongine (**2**), and seven known ones (**3**−**9**) were isolated from the sponge *Petrosaspongia metachromia*, collected from Yap, Federated States of Micronesia. Their structures were determined from spectral data. Pelorol (**1**) possesses a new carbon skeleton.

In a recent paper on sponges from New Caledonia, Bergquist described the new genus *Petrosaspongia*.[1] Since the description of this new genus, three papers describing sesterterpene lactones from a sponge assigned to this genus, *P. nigra*, have been published.[2−4] In her paper on New Caledonian sponges, a species initially described by de Laubenfels in 1954 as *Hippospongia metachromia* was reassigned by Bergquist as *Petrosaspongia metachromia* (order Dictoceratida, family Thorectidae). Prior to this reassignment several reports on *H. metachromia* had appeared describing the isolation of sesquiterpene-hydroquinones and -quinones.[5−7] The occurrence of marine sesquiterpene-quinones has been reviewed in recent years by Capon.[8] In our continuing studies on the chemistry of some sponges from Yap Island, Federated States of Micronesia, we found that extracts of *P. metachromia* were toxic to brine shrimp, and subsequent investigation resulted in the isolation of nine sesquiterpene hydroquinone/quinone-type compounds, two new ones, **1** and **2**, and seven known compounds, **3**−**9**. One of the new compounds, pelorol (**1**), has a new carbon skeleton.

MeOH and MeOH−CH_2Cl_2 (1:1) extracts of *P. metachromia* were subjected to solvent partitioning to give hexane, CH_2Cl_2, *n*-BuOH, and H_2O fractions. The CH_2Cl_2 fraction, which exhibited toxicity to brine shrimp, was chromatographed over SiO_2, Sephadex LH-20, and reversed-phase C_{18} vacuum flash columns. Selected fractions from these chromatographies were rechromatographed on reversed-phase C_{18} HPLC using different solvent combinations to afford compounds **1**−**9**. The known compounds, smenospongine (**3**),[9,10] dictyoceratin-A (**4**),[11] dictyoceratin-C (**5**),[12] 5-*epi*-ilimaquinone (**7**),[10,13] and ilimaquinone (**8**),[5,9,14] were identified by comparison of their spectral data with literature values. Ilimaquinone (**8**) and 5-*epi*-ilimaquinone (**7**) were by far the major constituents in the mixture (1.5:1 ratio).

Pelorol (**1**) was obtained as an amorphous solid. The molecular formula $C_{23}H_{32}O_4$ was deduced from HRFABMS. The IR spectrum showed bands at 3400 and 1719 cm^{-1}, consistent with the presence of hydroxyl and conjugated ester carbonyl groups. The ^1H NMR spectrum of **1** revealed the presence of four quaternary methyls (δ 0.84, 0.86, 1.05, and 1.22), one methoxyl (δ 3.83), a benzylic methylene [δ 2.48 (m) and 2.62 (dd, J = 14.0, 5.5 Hz)] adjacent to a methine (δ 1.65), and an aromatic hydrogen (δ 7.09). The ^{13}C NMR data, including DEPT and HMQC results, confirmed the presence of a pentasubstituted benzene ring, an ester carbonyl (δ 168.6), four methyl, two methine, six methylene, and two quaternary carbons (Table 1). The aromatic ring and ester group accounted for five of the eight degrees of unsaturation inferred from the molecular formula, thus revealing the presence of three rings. A Decalin ring system was suspected for **1**, based on the nature of the co-occurring metabolites, and the ^{13}C NMR data fitted well for the A/B rings of a drimane skeleton[9] and various sesterterpenes.[3,4] The COSY spectrum showed correlations consistent with spin systems extending from Hs-1 to Hs-3, H-5 to Hs-7, and H-9 to Hs-15. These fragments were confirmed to be part of the A/B ring system of structure **1** by HMBC correlations summarized in Figure 1. The presence of a quaternary methyl at C-8 was also evident from the HMBC results (Figure 1). The connections of the

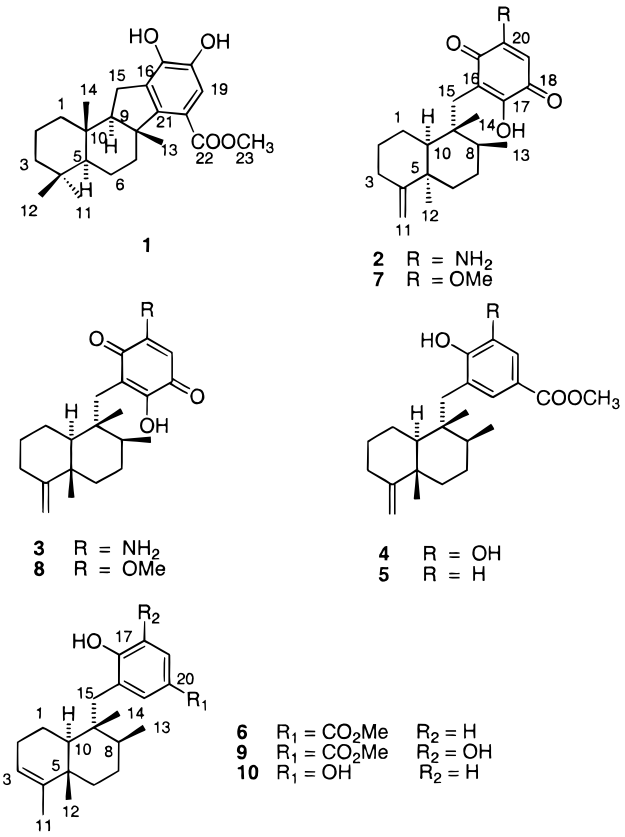

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Table 1. ^{13}C NMR Data for Pelorol (**1**), 5-*epi*-Smenospongine (**2**), Dictyoceratin C (**5**), and 18-Hydroxyhyrtiophenol (**9**)[a]

C	**1**[b,c]	**2**[e]	**5**[b,c]	**9**[b,c]
1	40.1 (t)	22.5	23.2 (t)	19.8 (t)
2	19.5 (t)	25.0	27.8 (t)	26.1 (t)
3	42.4 (t)	32.7	33.0 (t)	120.6 (d)
4	33.0 (s)	153.5	159.9 (s)	144.1 (s)
5	57.1 (d)	39.4	40.1 (s)	38.3 (s)
6	18.3 (t)	37.9	36.5 (t)	35.8 (t)
7	36.5 (t)	27.8	27.6 (t)	27.7 (t)
8	48.5 (s)	39.3	36.3 (d)	36.0 (d)
9	65.1 (d)	44.5	42.0 (s)	41.8 (s)
10	37.1 (s)	48.2	47.9 (d)	45.6 (d)
11	21.1 (q)	105.7	102.8 (d)	18.1 (q)
12	33.3 (q)	33.1	20.6 (q)	20.0 (q)
13	19.8 (q)	18.6	17.6 (q)	17.5 (q)
14	16.3 (q)	18.3	17.6 (q)	17.8 (q)
15	24.3 (t)	32.0	37.0 (t)	37.1 (t)
16	130.0 (s)	114.3	125.1 (s)	125.2 (s)
17	143.7 (s)[d]	156.0	159.0 (s)	148.5 (s)
18	140.6 (s)[d]	179.7	115.3 (d)	142.2 (s)
19	114.8 (d)	95.6	129.2 (d)	113.8 (d)
20	117.8 (s)	150.6	121.7 (s)	120.5 (s)
21	149.3 (s)	183.0	135.0 (d)	127.6 (d)
22	168.6 (s)		167.3 (s)	167.1 (s)
23	51.8 (q)		51.9 (q)	52.0 (q)

[a] Spectra were recorded in $CDCl_3$ at 125 MHz, referenced to $CDCl_3$ (δ 77). [b] Assignments made by HMQC and HMBC experiments. [c] Multiplicities were implied from DEPT experiments (*C* = s, CH = d, CH_2 = t, CH_3 = q). [d] May be interchanged. [e] Assignments are by analogy only, due to lack of sample for assignment experiments.

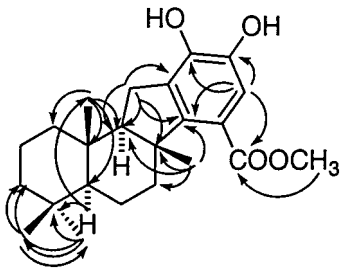

Figure 1. Selected HMBC correlations for pelorol (**1**).

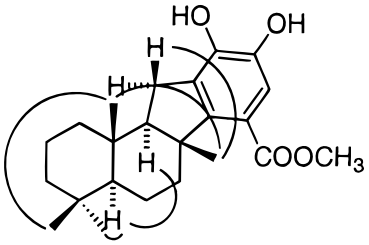

Figure 2. Selected NOE correlations for pelorol (**1**).

sesquiterpene skeleton to the aromatic ring were established from HMBC correlations from the H-15 signals to two of the aromatic carbon signals (C-16, -21) and from the methyl-13 signal to one of these carbon resonances (C-21). The substitution pattern on the aromatic ring was revealed by the HMBC correlations noted between the signals for the aromatic proton and the ester carbonyl, both oxygenated aromatic carbons, and C-21. Assuming these are all two- or three-bond couplings, the substitution pattern is limited to that shown in **1**. The relative stereochemistry of **1** was established by GOESY (gradient enhanced nuclear Overhauser effect spectroscopy)[15] (Figure 2) and NOESY data. Saturation of the H-5 proton at δ 0.92 enhanced the H-9 signal (δ 1.65) and a methyl (δ 0.86, H-11) signal. When the H-13 methyl group was irradiated, an NOE was observed for the proton signals at δ 1.05 (14-CH_3) and 2.48 (H-15ax). Also, irradiation of the H-12 signal (δ 0.84) caused enhancement of the H-14 methyl signal at δ 1.05. Similar results were observed in a NOESY experiment at 500 MHz, but some signals were overlapped, thus making assignments from the NOESY data alone questionable. Thus, pelorol was confirmed to have structure **1**. During preparation of this paper we became aware of the independent isolation and structure elucidation of **1** by Goclik et al.,[16] and we have adopted the name coined by these authors.

5-*epi*-Smenospongine (**2**) was obtained as a purple powder. The EIMS exhibited a molecular ion peak at *m*/*z* 343, and the molecular formula $C_{21}H_{29}NO_3$ was established by HRFABMS and ^1H and ^{13}C NMR data. Compound **2** showed absorptions compatible with hydroxyl, amino (3450, 3320 cm^{-1}), and carbonyl (1642 cm^{-1}) groups in the IR spectrum. The ^1H NMR spectrum exhibited two methyl singlets (δ 1.04 and 0.85), a methyl doublet (δ 0.90, J = 5.5 Hz), a benzylic methylene AB quartet (δ 2.43 and 2.52, each, J = 14.0 Hz), exocylic methylene signals (δ 4.65 and 4.68), and one olefinic proton resonance (δ 5.62). The ^{13}C NMR spectrum of **2** revealed 21 carbon signals, including six that matched nearly exactly those for the amino-substituted quinone ring of **3**, and one for an exocyclic methylene carbon (δ 105.7). These data indicated that **2** contains a hydroxyl and amino-substituted quinone moiety linked to a sesquiterpene unit. Close similarity between the ^1H NMR data for **2** and that reported for smenospongine (**3**)[9,10] suggested that **2** was a stereoisomer of **3**. Comparison of the ^{13}C NMR data for **2** with that of 5-*epi*-ilimaquinone (**7**)[10,13] indicated that **2** and **7** have the same sesquiterpene skeleton and relative stereochemistry, as the ^{13}C NMR chemical shifts of C-4/-11/-12 are diagnostic for the cis ring junction in the sesquiterpenes with the substituted decalin system.[10] Thus, structure **2** was assigned, and it is designated 5-*epi*-smenospongine.

Compound **6** was assigned the molecular formula $C_{23}H_{32}O_3$ based on EIMS and NMR data, and its IR spectrum suggested the presence of hydroxyl (3300 cm^{-1}) and conjugated ester carbonyl groups (1713 cm^{-1}). ^1H NMR data indicated the presence of a 1,2,5-trisubstituted benzene ring (δ 7.78, d, J = 2.5 Hz; 7.75, dd, J = 8, 2 Hz; 6.72, d, J = 8.5 Hz). ^{13}C NMR data for the aliphatic portion of the molecule matched that of several avarol analogues (avarol = **10**) reported by Kashman.[17] Combining these data and confirming the connections via HMBC experiments led to structure **6**. This was further confirmed by comparison of the data published for hyrtiophenol (**6**) during preparation of this paper.[18]

Compound **9** was assigned the molecular formula $C_{23}H_{32}O_4$ based on EIMS and NMR data. The ^1H and ^{13}C NMR data of **9** revealed that it possessed a 1,2,3,5-tetrasubstituted aromatic ring as in dictyoceratin A[11] and smenospondiols.[9,10] The ^{13}C NMR data for the sesquiterpene portion of **9** were the same as those for **6**, and the shift assignments were confirmed by HMQC and HMBC data. Thus, structure **9** was proposed, and this conclusion was further confirmed by noting that the NMR data matched those of 18-hydroxyhyrtiophenol, which were reported during preparation of this report.[18]

Because the known metabolites such as ilimaquinone (**8**), 5-*epi*-ilimaquinone (**7**), and dictyoceratin A (**4**) isolated in this work have nearly the same optical rotations as those reported previously, we assume that all of the compounds isolated from this sponge source, which was collected in one area, have a common biogenetic origin and that hence all have the absolute configuration shown here, including

1. Pelorol (**1**) was toxic to brine shrimp[19] with an LC_{50} value of between 5 and 10 μg/mL.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Rudolph Autopol III automatic polarimeter. IR spectra were recorded on a Bio-Rad FTS-155 FT-IR spectrometer. UV spectra were obtained on Hewlett-Packard HP 8453 diode array instrument. EIMS and FABMS were measured on a Hewlett-Packard 5985 GC/MS system and VG-ZAB-E mass spectrometer, respectively. NMR experiments were performed on a Varian VXR-500 spectrometer equipped with a 3-mm $^1H/^{13}C$ switchable gradient microprobe (MDG-500-3) and a pulsed field gradient driver, using standard Varian software. NMR signals are reported in parts per million (δ), referenced to the solvent used. The GOESY experiment was executed on a Varian INOVA-600 NMR spectrometer. Vacuum flash chromatography was carried out on Merck Si gel 60 H(230−240 mesh), Sephadex LH-20, and Whatman LRP-2 C_{18} material. Preparative HPLC was performed using a Phenomenex ODS-2 (300 × 10 mm) column and a UV dectector (254 nm).

Animal Material. The sponge was collected at Yap Archipelago, Federated States of Micronesia, in 1995. It forms a thick, semispherical encrustation with regularly spaced conules on the surface. The sponge is barely compressible but rather fleshy to the touch. The color in life is bright yellow. The sponge emits a thick-copious mucus in life. The skeleton consists of a very dense network of laminated secondary fibers, which coalesce to form cored primary fibers near the surface of the sponge. A thin layer of sand grains can be found on the surface, and sand particles are scattered within the choanosome. The sponge was first described as *H. metachromia* by de Laubenfels (1954), but it is now more appropriately situated within a new genus *Petrosaspongia* by Bergquist (1995).[1] The sponge is *P. metachromia* de Laubenfels (order Dictyoceratida, family Thorectidae, subfamily Thorectinae). A voucher specimen has been deposited at the Natural History Museum, London, United Kingdom (BMNH 1999. 7.23.3), and another voucher specimen is maintained at the University of Oklahoma (18YA95).

Extraction and Isolation. Freshly thawed specimens of the sponge (1.81 kg wet wt; 157 g dry wt after extraction) were cut into small pieces and soaked in MeOH (2 L × 2) followed by MeOH−CH_2Cl_2 (1:1, 2 L × 2) at room temperature. All extracts were combined, the solvents removed under reduced pressure, and the residue was dissolved in MeOH−H_2O (9:1, 200 mL). The resulting solution was partitioned with hexane (200 mL x 2), and then the aqueous MeOH solution was diluted with H_2O (57 mL) to 30% of H_2O in MeOH and extracted with CH_2Cl_2 (200 mL × 2). The aqueous MeOH solution was concentrated in vacuo, and the aqueous residue was diluted with H_2O to 200 mL and then extracted with *n*-BuOH (200 mL × 2). Each of the organic fractions was evaporated under reduced pressure to give hexane (3.06 g), CH_2Cl_2 (5.10 g), *n*-BuOH (12.84 g), and H_2O (2.22 g) extracts. The CH_2Cl_2 extract, which showed toxicity to brine shrimp, was subjected to vacuum flash chromatography over Si gel eluting sequentially with hexane−EtOAc (4:1), hexane−EtOAc (2:1), and EtOAc. Fractions were combined according to their TLC patterns to yield fractions F008−F011. Further rechromatography of fraction F009 over Sephadex LH-20 (MeOH) afforded five fractions, F012−F016. Fractions F014 and F015 were each chromatographed on a RP_{18} vacuum flash column and eluted with 25% H_2O to 0% H_2O in MeOH to furnish 20 fractions designated as F017− F026 and F027−F036, respectively. Fraction F031 was rechromatographed over C_{18} reversed-phase HPLC using 10% H_2O−MeOH as eluent to yield compounds **1**−**4** (23, 0.7, 1.5, and 17 mg, respectively). Similarly, fraction F023 was fractionated by reversed-phase HPLC using 8% H_2O−MeOH as eluent, to obtain compounds **5** (15 mg) and **6** (1.3 mg). Also, HPLC of fraction F021 over a C_{18} column using MeOH−H_2O−HOAc (90:10:1) as eluent afforded compounds **4**, **7**, and **8** (9, 7, and 5 mg, respectively). Fraction F031 was applied over C_{18} reversed-phase HPLC (10% H_2O−MeOH) to yield compounds **4** and **9** (7.3 mg) (0.7 mg). Ilimaquinone (**8**) and 5-*epi*-ilimaquinone (**7**) were the major constituents in the mixture, F021−F023 containing ca. 2 g of these compounds in a 1.5:1 ratio.

Pelorol (1): $[\alpha]^{23}_D$ −72.1° (*c* 0.33, CH_2Cl_2); IR (film) ν_{max} 3400, 1719, 1686, 1560, 1376, 1291, 1225 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 218 (12 362), 260 (4033), 292 (1687); ^1H NMR ($CDCl_3$) δ 7.09 (1H, br s, H-19), 3.83 (3H, s, OCH_3), 2.62 (1H, dd, *J* = 14.0, 5.5 Hz, H-15), 2.48 (1H, m, H-15′), 2.50, 1.38 (2H, m, H-7), 1.68, 1.40 (2H, m, H-6), 1.65 (1H, m, H-9), 1.65, 1.55 (2H, m, H-2), 1.53 (1H, m, H-1), 1.38 (1H, m, H-3), 1.22 (3H, s, 13-CH_3), 1.15 (1H, td, *J* = 13.8, 4.8 Hz, H-3′), 1.05 (3H, s, 14-CH_3), 0.98 (1H, td, *J* = 12.6, 3.0 Hz, H-1′), 0.92 (1H, dd, *J* = 12.6, 2.4 Hz, H-5), 0.86 (3H, s, 11-CH_3), 0.84 (3H, s, 12-CH_3); ^{13}C NMR, see Table 1; EIMS *m*/*z* 372 (75), 357 (100), 325 (22), 232 (15), 221 (20), 219 (17); FABMS *m*/*z* 373 $[M + H]^+$; HRFABMS *m*/*z* 373.2362 $[M + H]^+$ (calcd for $C_{23}H_{33}O_4$, 373.2379).

5-*epi*-Smenospongine (2): $[\alpha]^{23}_D$ +73.1° (*c* 0.03, $CHCl_3$); IR (film) ν_{max} 3450, 3320, 1642 cm^{-1}; ^1H NMR ($CDCl_3$), δ 5.62 (1H, s, H-19), 4.68 (1H, br s, H-11), 4.65 (1H, br s, H-11′), 2.52 (1H, d, *J* = 14.0 Hz, H-15), 2.43 (1H, d, *J* = 14.0 Hz, H-15′), 2.42, 2.08 (2H, m, H-3), 1.18 (1H, m, H-8), 1.04 (3H, s, 12-CH_3), 0.90 (3H, d, *J* = 5.5 Hz, 13-CH_3), 0.85 (3H, s, 14-CH_3); ^{13}C NMR, see Table 1; EIMS *m*/*z* 343 (2, M^+), 225 (3), 191 (12), 189 (4), 153 (100); HRFABMS *m*/*z* 344.2254 $[M + H]^+$ (calcd for $C_{21}H_{30}NO_3$, 344.2226).

Dictyoceratin-C (5): $[\alpha]^{23}_D$ +16.7° (*c* 0.03, $CHCl_3$); ^1H NMR ($CDCl_3$), δ 7.74, (2H, d, *J* = 2.0 Hz, H-21), 7.73 (1H, dd, overlapped with 7.74), 6.73, (1H, d, *J* = 9.5 Hz, H-18), 5.71 (1H, br s, OH), 4.39 (1H, br s, H-11) 4.34 (1H, br s, H-11′), 3.85 (3H, s, OCH_3), 2.65 (1H, d, *J* = 14.5 Hz, H-15), 2.61 (1H, d, *J* = 14.5 Hz, H-15′), 2.31 (1H, td, *J* = 13.5, 5.5 Hz, H-3), 2.06 (2H, m, H-1, 3′), 1.90 (1H, m, H-2), 1.56 (1H, qd, *J* = 13.5, 3.5 Hz, H-1′), 1.45 (1H, ddd, *J* = 12.0, 3.0, 3.0 Hz, H-6), 1.42−1.30 (3H, m, H-2′, -7, -7′), 1.26 (1H, m, H-8), 1.19 (1H, m, H-6), 1.04 (3H, s, 12-CH_3), 1.01 (3H, d, *J* = 6.5 Hz, 13-CH_3), 0.93 (1H, dd, *J* = 12.0, 2.2 Hz, H-10), 0.86 (3H, s, 14-CH_3); ^{13}C NMR, See Table 1.

Hyrtiophenol (6): $[\alpha]^{23}_D$ −15.2° (*c* 0.125, $CHCl_3$); IR (film) ν_{max} 3300, 1713, 1601, 1289 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (1H, d, *J* = 2.5 Hz, H-21), 7.75 (1H, dd, *J* = 8.0, 2.0 Hz, H-19), 6.72 (1H, d, *J* = 8.5 Hz, H-18), 5.13 (1H, br s, H-3), 3.84 (3H, s, OCH_3), 2.68, 2.67 (2H, br d, H-15), 2.19, 2.10 (2H, m, H-2), 2.02, 1.60 (2H, m, H-1), 1.54 (1H, br d, *J* = 13.0 Hz, H-6), 1.48 (3H, s, 11-CH_3), 1.35, 1.27 (2H, m, H-7), 1.29 (1H, m, H-8), 1.16 (1H, br d, *J* = 12.0 Hz, H-10), 1.01 (3H, d, *J* = 6.5 Hz, 13-CH_3), 1.0 (3H, s, 12-CH_3), 0.86 (3H, s, 14-CH_3), 0.83 (1H, m, H-6′); ^{13}C NMR, see Hirsch et al.[17] EIMS *m*/*z* 356 (M^+).

5-*epi*-Ilimaquinone (7): $[\alpha]^{23}_D$ +26.2° (*c* 0.27, $CHCl_3$); lit.[9] +29.8°.

Ilimaquinone (8): $[\alpha]^{23}_D$ −27° (*c* 0.1, $CHCl_3$); lit.[5,8,10] −23.2°, −24°, −27.7°.

18-Hydroxyhyrtiophenol (9): $[\alpha]^{23}_D$ −37.5° (*c* 0.008, $CHCl_3$); IR (film) ν_{max} 3400, 2929, 1715, 1435, 1300, 1220 cm^{-1}; ^1H NMR (CDCl3) δ 7.42 (1H, d, *J* = 2.0 Hz, H-21), 7.40 (1H, d, *J* = 2.0 Hz, H-19), 5.12 (1H, br s, H-3), 3.84 (3H, s, OCH_3), 2.71 (1H, d, *J* = 14.5 Hz, H-15), 2.68 (1H, d, *J* = 14.5 Hz, H-15′), 2.16, 2.05 (2H, m, H-2), 2.02, 1.59 (2H, m, H-1), 1.55 (1H, m, H-6), 1.48 (3H, s, 11-CH_3), 1.33 (2H, m, H-7), 1.31 (1H, m, H-8), 1.16 (1H, br d, *J* = 12.5 Hz, H-10), 1.01 (3H, d, *J* = 5.5 Hz, 13-CH_3), 1.0 (3H, s, 12-CH_3), 0.85 (3H, s, 14-CH_3), 0.83 (1H, m, H-6′); ^{13}C NMR, see Table 1; EIMS *m*/*z* 372 (M^+).

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