Milolides, New Briarane Diterpenoids from the Western Pacific Octocoral *Briareum stechei*

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Eleven new briarane-type diterpene lactones, designated milolides (**1**−**8**, **10**−**12**), together with four known diterpene lactones (**9**, **13**−**15**), were isolated from the Micronesian octocoral *Briareum stechei* collected at Yap, Federated States of Micronesia. One aspect of the stereochemistry of one of the known compounds, solenolide C (**9**), is revised. Structures of the new compounds were determined from spectral data.

Octocorals of the genus *Briareum* (phylum Cnidaria, class Anthozoa, subclass Octocorallia, order Alcyonacea, family Briareidae) have yielded nearly 200 diterpenoids which fall into three skeletal classes, briarane, asbestinane, and eunicellin, with most belonging to the first two classes.[1] *Briareum asbestinum* (Pallas) is the common Caribbean species and is the source of numerous diterpenoids, while *B. polyanthes* from Bermuda has been the source of only a few. Two *Briareum* species from the Indo-Pacific, *B. stechei* and *B. excavatum*, have also yielded briarane and eunicellin diterpenes. Both of these species have also been reported under the synonym *Solenopodium*. Interestingly, no asbestinin-type diterpenes have been reported from the Indo-Pacific *Briareum* (=*Solenopodium*) sp. to date.[1,2] Briarane diterpenes have been reported to exhibit interesting biological activities including cytotoxic,[3−9] antiinflammatory,[10−13] antiviral,[11,14] insecticidal,[15,16] immunomodulatory,[17] adenosine A_1 receptor binding,[18] and antifouling.[19] Asbestinin diterpenes have been reported to display cytotoxicity, antibacterial activity, and acetylcholine and histamine antagonism.[2]

In continuation of our interest in the comparative chemistry of *Briareum* (*Solenopodium*) species collected at diverse geographical locations,[3,4,13] we obtained specimens of *Briareum stechei* (Kukenthal, 1908) (family Briareidae) from Yap Island, Federated States of Micronesia. We report here the structures of 11 new, one revised, and three known briarane lactones. One of the new lactones has a contracted ring, which results overall in a 8.3.0 bicyclo system.

Results and Discussion

Frozen specimens were freeze-dried and then extracted with MeOH and MeOH−CH_2Cl_2 (1:1). The combined extracts were subjected to solvent partitioning (see Experimental Section), and the CH_2Cl_2-solubles were fractionated by Si gel chromatography. Selected fractions were rechromatographed on reversed-phase C_{18} HPLC and Si gel chromatography using different solvent combinations to yield compounds **1**−**15**. Compounds **9** (solenolide C with revised stereochemistry),[11] **13** (brianolide),[12] **14**,[5,20] and **15** (excavatolide A)[7] were identified by comparison of their spectral data with literature values.

Milolide A (**1**) was obtained as an amorphous solid. The molecular formula $C_{28}H_{38}O_{12}$ was deduced from HRESIMS and NMR data. The IR spectrum suggested the presence of hydroxyl (3480 cm^{-1}), γ-lactone (1775 cm^{-1}), and ester carbonyl groups (1740, 1726, and 1711 cm^{-1}), and NMR data supported the existence of four acetates (Tables 1 and 2) and a γ-lactone (δ_C 177.0). The ^1H and ^{13}C NMR data of **1** also implied the presence of an epoxide, δ (^{13}C) 60.3 d, 63.4 s, and the co-occurrence of **1** with the known compounds **13**−**15** suggested a briarane-type structure. The ^1H NMR spectrum of **1** further revealed the presence of two tertiary methyls (δ 0.99 and 1.42), a secondary methyl at δ 1.27 (d, J = 7.5), an olefinic methyl (δ 2.12), and a olefinic proton (δ 5.56). The ^{13}C NMR spectrum showed signals for six oxygenated carbons (δ 81.5, 78.4, 73.4, 73.0, 72.1, and 70.5) in addition to those of the epoxide. The ^1H−^1H COSY spectrum showed cross-peaks at H-2/H-3, H-3/H-4, H-6/H-7, H-6/H-16, H-9/H-10, H-12/H-13, H-12/H-14 (*W*-coupling), H-13/H-14, and H-17/H-18, thus confirming the following structural fragments: C-2 to C-4, C-5 (C-16)/C-6/C-7, C-9/C-10, C-12 to C-14 and C-17/C-18. These fragments were connected to each other and the two remaining tertiary methyl groups to yield the briarane skeleton by virtue of the HMBC correlations shown in

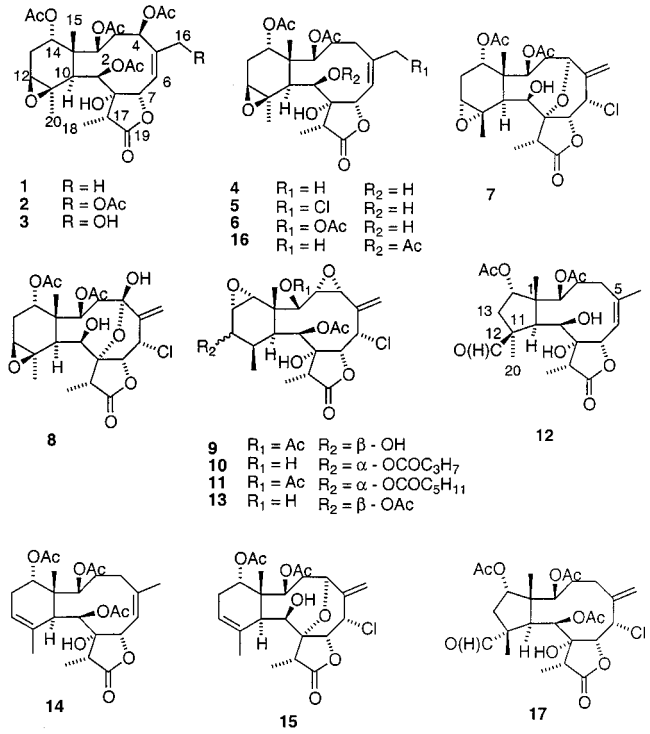

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Table 1. ^{1}H NMR Data for Compounds **1**−**8**[a]

H	1	2	3	4	5	6	7	8
2	4.76 (d, 7.5)	4.78 (d, 7.5)	4.72 (d, 7.5)	4.80 (d, 8)	4.70 (d, 8)	4.79 (d, 7)	4.90 (d, 6.5)	4.87 (d, 6.5)
3β	2.75 (dd, 14.5, 13)	2.80 (dd, 15, 13)	2.85 (dd, 14, 13)	2.74 (td, 16, 4.5)	2.81 (m)	2.79 (m)	3.26 (ddd, 15, 13, 7)	3.56 (dd, 16, 7)
α	1.88 (m)	1.88 (m)	1.88 (m)	1.49 (m)	1.56 (m)	1.55 (m)	1.32 (m)	1.46 (d, 16)
4	4.96 (dd, 12.5, 5.5)	4.92 (dd, 13, 5)	4.91 (dd, 13, 5)	2.45 (br d, 14)	2.50 (m)	2.43 (m)	4.81 (dd, 13, 4.5)	
				1.81 (td, 15, 4.5)	1.92 (m)	1.77 (m)		
6	5.56 (d, 10)	5.54 (d, 9.5)	5.90 (d, 10)	5.34 (d, 10)	5.77 (d, 9.5)	5.42 (d, 10)	5.49 (br d, 2.5)	5.53 (dd, 3, 2)
7	5.59 (d, 10)	5.60 (d, 10)	5.58 (d, 10.5)	5.46 (d, 10)	5.49 (d, 10)	5.50 (d, 10)	4.64 (d, 3)	4.73 (d, 3)
9	5.96 (d, 3)	5.96 (d, 3)	5.99 (d, 2.5)	4.52 (dd, 6.5, 3.5)	4.52 (dd, 7, 3.5)	4.58 (dd, 6.5, 3.5)	4.86 (d, 7)	4.92 (d, 5.5)
10	2.50 (d, 3)	2.47 (d, 2.5)	2.53 (d, 3)	2.28 (d, 3.5)	2.28 (d, 3.5)	2.25 (d, 3.5)	2.60 (s)	2.40 (s)
12	2.94 (d, 5.5)	2.95 (d, 5.5)	2.95 (d, 5.5)	3.02 (d, 6.5)	3.04 (d, 6)	3.02 (d, 6)	2.97 (d, 3.5)	2.98 (dd, 6, 2)
13	2.05 (m)	2.10 (m)	2.05 (m)	2.13 (m)	2.15 (m)	2.12 (m)	2.24 (m)	2.32 (dd, 17, 3.5)
	2.0 (m)	2.0 (m)	1.98 (m)	2.05 (m)	2.05 (m)	2.05 (m)	2.19 (m)	2.02 (m)
14	4.69 (br d, 1)	4.74 (br d, 1)	4.74 (br s)	4.70 (br s)	4.72 (br s)	4.74 (br s)	4.89 (br s)	5.0 (br s)
15	0.99 (s)	0.98 (s)	1.02 (s)	1.14 (s)	1.16 (s)	1.15 (s)	1.18 (s)	1.30 (s)
16	2.12 (s)	5.17 (dd, 15.5, 1)	4.41 (d, 14.5)	1.96 (br s)	4.30 (d, 14)	4.96 (d, 15.5)	5.43 (d, 2)	5.83 (d, 1.5)
		4.74 (dd, 15.5, 2)	4.28 (d, 15)		4.27 (d, 14)	4.47 (d, 16.5)	5.28 (d, 2)	5.60 (d, 1.5)
17	2.48 (q, 6.5)	2.48 (q, 7)	2.46 (q, 7)	3.25 (q, 7)	3.30 (q, 7)	3.24 (q, 7.5)	2.64 (q, 7)	2.68 (q, 7.5)
18	1.27 (d, 7.5)	1.27 (d, 7)	1.30 (d, 7.5)	1.24 (d, 7.5)	1.26 (d, 7)	1.26 (d, 7.5)	1.31 (d, 7)	1.29 (d, 7)
20	1.42 (s)	1.41 (s)	1.43 (s)	1.36 (s)	1.35 (s)	1.36 (s)	1.53 (s)	1.41 (s)
OAc	2.19, 2.02, 1.98, 1.96	2.19, 2.08, 2.02, 1.98, 1.96	2.21, 2.03, 2.02, 1.95	1.98, 1.87	1.99, 1.95	2.11, 1.98, 1.98	2.00, 1.98	2.05, 2.02

[a] Spectra were recorded in $CDCl_3$ at 500 MHz, referenced to $CDCl_3$ (δ 7.24).

Table 3, in particular, the correlations of H-6, H-9, H-10, H-15, H-16, H-17, and H-20. The epoxide moiety was assigned to the C-11/C-12 position from HMBC correlations (see H-14 and H-20 in Table 3) and because of the characteristic ^{13}C NMR shifts, δ 60.3 and 63.4. Acetate moieties were assigned to C-2 and C-9 because of HMBC correlations of H-2 and H-9 to acetate carbonyl signals. The remaining two acetates were placed at C-4 and C-14 by comparison of the corresponding proton chemical shifts with those of compound **2**, where all of the acetate locations were confirmed by HMBC correlations (see below). Hence the hydroxyl group in **1** is relegated to C-8, where it has been found in related briarane lactones.

Much of the relative stereochemistry of milolide A (**1**) was confirmed to be the same as that of **16** by comparison of the proton chemical shifts and coupling constants for Hs-2, -6, -7, -9, -10 with published values.[20] The configuration of the 11,12-epoxide was established as β, by the C-11 and C-12 chemical shifts (δ 63.4 and 60.3, respectively), because these were significantly different from those of related compounds with an 11α,12α-epoxide.[13,20,21] The relative stereochemistry was also confirmed by observed NOESY correlations between H-10 and H-2/H-20, H-15 and H-3β/H-3α/H-14, H-9 and H_3-20, and H-3β (δ 2.75) and H-7/H-15. The methylene proton signal at δ 2.75 shows NOE to H-15 and H-7 and hence is attributable to H-3β. The geminal partner, H-3α (δ 1.88), shows NOE with only H-4, H-15, and H-3β. On these grounds, the acetate at C-4 is assigned the 4β-configuration. Hence the overall relative configuration of milolide A is as shown in **1**.

Compound **2**, 16-acetoxymilolide A, was assigned the molecular formula $C_{30}H_{40}O_{14}$ on the basis of HRESIMS and NMR data, and its IR spectrum suggested the presence of hydroxyl (3460 cm^{-1}), γ-lactone (1776 cm^{-1}), and ester carbonyl groups (1745, 1726, and 1711 cm^{-1}). The ^{1}H and ^{13}C NMR data of **2** were nearly identical with those of **1** except that the signals for the C-16 vinyl methyl group in **1** were replaced by those for an oxymethylene [δ_H 5.17 (dd, J = 15.5, 1 Hz), 4.74 (dd, J = 15.5, 2 Hz); δ_C 66.3] in **2**, and signals for a additional acetyl group were also noted. Compound **2** was thus formulated as 16-acetoxymilolide A. This conclusion was supported by COSY, HMQC, and HMBC experiments. The location of the OH group was confirmed by the HMBC experiment which showed a correlation between the OH signal at δ 3.31 (exchangeable) and C-9, C-17. Hence, the locations of the acetate groups were fixed as shown in **2**. Compound **2** was assigned the same relative stereochemistry as in **1** because, except for H-16, the chemical shifts and proton coupling constants were essentially identical and most of the same NOESY correlations (see Table 4) were observed for the two compounds.

16-Hydroxymilolide A (**3**) was assigned the molecular formula $C_{28}H_{38}O_{13}$ on the basis of HRESIMS and NMR data. The IR spectrum exhibited absorptions characteristic of the other hydroxybriarane-type γ-lactones (3480, 1778, 1765, and 1738 cm^{-1}). The NMR data of **3** were nearly identical to those of **2** except that there were signals for only four acetate groups in the spectra of **3**. The ^{13}C NMR signals for C-4, C-5, and C-6 in **3** were shifted downfield to δ 70.7, 146.2, and 126.3, respectively, and the signals for H-16 were shifted upfield ~0.6 ppm. This revealed that the 16-acetate in **2** was replaced by a hydroxyl group in **3**. This structure was further supported by COSY, HMQC, and HMBC experiments. The relative stereochemistry of **3** was determined by NOESY experiments (Table 4) and comparison of its ^{1}H NMR coupling constants with those of compounds **1** and **2** and comparison of ^{13}C NMR chemical shifts.

Compounds **4**, **5**, and **6** were obtained as amorphous solids, and their molecular formulas were established by HRESIMS and NMR data as $C_{24}H_{34}O_9$, $C_{24}H_{33}O_9Cl$, and $C_{26}H_{36}O_{11}$, respectively. These three compounds each showed absorptions for hydroxyl, γ-lactone, and ester carbonyl groups in their IR spectra, and their NMR data were nearly identical except for some signals associated with H/C-16. The COSY spectra of **4**−**6** revealed that these compounds have the same partial skeletal fragments as do **1**−**3**, and HMBC spectra for **5** and **6** firmly established that these metabolites had the same briarane skeleton as **1**−**3**.

Milolide B (**4**) was assigned the structure shown on the basis of the above information and comparison of its ^{1}H

Table 2. ^{13}C NMR Data for Compounds **1**−**11** and **13**[a,b]

C	**1**[c]	**2**[c]	**3**[c]	**4**[d]	**5**[c]	**6**[c]	**7**[c]	**8**[d]	**9**[c,e]	**10**[d]	**11**[c]	**13**[c,e]
1	45.3 (s)	45.2 (s)	45.3 (s)	45.4 (s)	45.4 (s)	45.4 (s)	44.1 (s)	44.9 (s)	39.4 (s)	38.7 (s)	38.5 (s)	40.0 (s)
2	73.0 (d)	72.8 (d)	73.9 (d)	75.7 (d)	75.6 (d)	75.6 (d)	73.1 (d)	73.4 (d)	77.4 (d)	73.9 (d)	75.4 (d)	74.3 (d)
3	38.0 (t)	38.1 (t)	37.9 (t)	31.9 (t)	31.8 (t)	31.8 (t)	34.8 (t)	41.4 (t)	61.3 (d)	62.1 (d)	59.9 (d)	63.4 (d)
4	72.1 (d)	68.5 (d)	70.7 (d)	28.7 (t)	26.2 (t)	25.0 (t)	76.7 (d)	96.9 (s)	58.1 (d)	57.8 (d)	57.0 (d)	58.5 (d)
5	144.4 (s)	141.3 (s)	146.2 (s)	146.9 (s)	143.5 (s)	142.9 (s)	137.7 (s)	138.9 (s)	137.8 (s)	134.8 (s)	133.8 (s)	138.5 (s)
6	122.9 (d)	122.6 (d)	126.3 (d)	117.7 (d)	121.9 (d)	117.7 (d)	55.1 (d)	56.2 (d)	61.3 (d)	61.1 (d)	61.1 (d)	61.3 (d)
7	78.4 (d)	77.5 (d)	77.5 (d)	78.4 (d)	78.0 (d)	77.2 (d)	80.6 (d)	80.0 (d)	80.0 (d)	76.3 (d)	76.2 (d)	79.9 (d)
8	81.5 (s)	81.6 (s)	81.7 (s)	82.8 (s)	83.2 (s)	83.0 (s)	82.6 (s)	82.5 (s)	84.7 (s)	84.7 (s)	84.7 (s)	84.7 (s)
9	70.5 (d)	70.6 (d)	70.7 (d)	73.1 (d)	73.0 (d)	73.3 (d)	75.8 (d)	76.4 (d)	70.6 (d)	68.6 (d)	68.8 (d)	70.2 (d)
10	38.5 (d)	38.3 (d)	38.3 (d)	39.2 (d)	39.3 (d)	39.2 (d)	42.1 (d)	39.3 (d)	38.7 (d)	32.7 (d)	32.6 (d)	38.2 (d)
11	63.4 (s)	63.4 (s)	63.5 (s)	65.2 (s)	65.0 (s)	64.9 (s)	59.2 (s)	61.0 (s)	40.4 (d)	35.8 (d)	35.8 (d)	37.5 (d)
12	60.3 (d)	60.4 (d)	60.1 (d)	61.1 (d)	61.2 (d)	61.1 (d)	58.5 (d)	57.4 (d)	70.8 (d)	69.6 (d)	69.1 (d)	74.0 (d)
13	25.2 (t)	25.2 (t)	25.2 (t)	25.4 (t)	25.4 (t)	25.4 (t)	26.8 (t)	26.4 (t)	59.9 (d)	52.9 (d)	52.3 (d)	64.0 (d)
14	73.4 (d)	73.1 (d)	73.3 (d)	73.7 (d)	73.6 (d)	73.5 (d)	71.5 (d)	72.2 (d)	63.3 (d)	62.4 (d)	61.4 (d)	58.6 (d)
15	15.1 (q)	15.0 (q)	15.0 (q)	15.5 (q)	15.5 (q)	15.5 (q)	14.5 (q)	16.0 (q)	17.1 (q)	15.6 (q)	16.3 (q)	16.5 (q)
16	25.7 (q)	66.3 (t)	66.8 (t)	25.3 (q)	50.5 (t)	67.7 (t)	115.7 (t)	116.7 (t)	118.8 (t)	118.8 (t)	120.6 (t)	117.6 (t)
17	43.3 (d)	43.1 (d)	43.3 (d)	43.7 (d)	43.7 (d)	43.6 (d)	50.7 (d)	49.8 (d)	45.9 (d)	45.2 (d)	45.3 (d)	45.8 (d)
18	6.7 (q)	6.8 (q)	6.8 (q)	6.9 (q)	7.0 (q)	7.0 (q)	7.3 (q)	8.3 (q)	6.2 (q)	6.1 (q)	6.1 (q)	6.2 (q)
19	177.0 (s)	176.5 (s)	176.7 (s)	177.9 (s)	177.8 (s)	177.3 (s)	176.1 (s)	176.0 (s)	177.1 (s)	174.4 (s)	174.0 (s)	177.1 (s)
20	25.2 (q)	25.0 (q)	24.9 (q)	25.3 (q)	25.3 (q)	25.2 (q)	23.4 (q)	23.7 (q)	9.6 (q)	13.0 (q)	13.0 (q)	10.2 (q)
OAc	170.8, 170.4, 170.3, 168.2, 21.6, 21.2, 21.1, 21.0	171.0, 170.6, 170.5, 170.1, 168.2, 21.6, 21.0 (3C), 20.8	171.9, 170.7, 170.6, 168.2, 21.7, 21.2, 21.1(2C)	171.0, 170.7, 21.4, 21.2	171.1, 170.9, 21.3, 21.2	171.1, 170.9, 170.6, 21.2, 21.1, 20.1	170.6, 170.4, 21.2, 21.0	173.3, 170.1, 21.2, 20.9	172.2, 171.3, 22.0, 20.9	169.7, 21.9[f]	169.4, 169.1, 21.9, 21.0[g]	172.5, 172.2, 22.0, 20.9

[a] Spectra were recorded in $CDCl_3$ at 125 MHz, referenced to $CDCl_3$ (δ 77) except where otherwise noted. [b] Multiplicities were determined from DEPT experiments. [c] Assignments made by HMQC and HMBC experiments. [d] Assignments aided by H/H COSY and HMQC experiments. [e] Spectra recorded in CD_3OD (δ 49) at 125 MHz. [f] Butyrate C's: 172.8 (s), 35.9 (t), 18.6 (t), 13.7 (q). [g] Hexanoate C's:172.9 (s), 34.0 (t), 31.4 (t), 24.7 (t), 22.3 (t), 14.0 (q).

and ^{13}C NMR data with that of **1**. A hydroxyl group was assigned to C-9 because coupling of an OH signal with H-9 was observed and also the chemical shift of H-9 was significantly upfield from that observed for **1**−**3**. The relative stereochemistry is assumed to be the same as in **1**−**3** and **5** (supported by NOE data), since the proton chemical shift and coupling data are essentially the same at the relevant sites. The 11β,12β-epoxide configuration was assigned to **4** as well as **5** and **6** because of the ^{13}C NMR shifts of C-11 and C-12 (> 60 ppm) as discussed above for **1**.

The NMR spectral data for **5**, 16-chloromilolide B, were nearly identical to those of **4** except that the vinyl methyl signal (H/C-16) was missing and in its place was a H/C signal for a deshielded methylene group (see H/C-16 in Tables 1 and 2, respectively). The chlorine atom was evident from the mass spectrum of **5** and was assigned at C-16 on the basis of the ^{13}C NMR shift (δ 50.5). The similarity of the NMR chemical shifts and coupling constants of **5** compared to **4** supports similar relative stereochemistry for these two compounds.

The NMR data of **6**, 16-acetoxymilolide B, were the same as that of **4** except for the presence of signals for an additional acetate moiety and downfield shifts for the proton and carbon signals of the C-16 methylene group. HMBC data (Table 3) confirmed that **6** bears an acetoxy group at C-16. The stereochemistry of **6** is assumed to be the same as in **4** and **5** on the basis of common NMR chemical shift and coupling features.

Milolide C (**7**), molecular formula $C_{24}H_{31}O_9Cl$ by HRESIMS, exhibited ^1H and ^{13}C NMR data similar in most parts to those of **1**−**3**. The COSY, HMQC, and HMBC spectra revealed that **7** has the conventional briarane skeleton with oxygenation at the same positions as in **1**−**3**. However, the double bond in **7** is positioned as an exocyclic methylene group at C-5/C-16, as evidenced by the relevant NMR data (δ_H 5.43, 5.28; δ_C 115.7, 137.7), the position being confirmed by HMBC correlations between H_2-16 and the neighboring ring carbons (Table 3). The chlorine group was fixed at C-6 on the basis of the chemical shift of this carbon (δ 55.1), in agreement with that reported for lactone **15** (excavatolide A).[7] A hydroxyl doublet signal at δ 2.83 (exchangeable) was assigned to a 9-OH on the basis of its coupling with H-9. An epoxide at C-11,12 was deduced from the ^{13}C NMR shifts of these carbons (see Table 2). The remaining oxygen in the formula was assigned to an ether connection between C-4 and C-8 to account for the chemical shift of these carbons and also the last degree of unsaturation inferred from the molecular formula. This ether link is supported by an HMBC correlation between H-4 and C-8 (Table 3). The chlorine was relegated to C-6 on the basis of the modest downfield shift of that atom and by analogy with related briaranes.[7,10−13]

The relative stereochemistry at C-1, -2, -10 and, -14 was assigned on the grounds of NOE correlations between H-2/H-10 and H-14/H-15 (Table 4). The H-3 proton resonating at δ 3.26 showed an NOE with H-15, confirming that this proton is H-3β. H-3β also exhibited an NOE with H-6, which in turn showed an NOE with H-7. These results indicated the substituents at C-6 and C-7 were both α-oriented. The small coupling constant between H-6 and H-7 parallels that reported for **15** and also argues for the C-6α, C-7α substitution shown. The stereochemistry assigned to C-8 and C-9 is by analogy with compounds **1**−**6** and literature examples, e.g., **14**−**16**.[5,7,20] The 11,12-epoxide was assigned the α-configuration because the chemical shifts of both these carbons were <60 ppm, as has been

Table 3. Selected HMBC Correlations of **1**−**3**, **5**−**7**, **9**, and **11**[a]

H	1	2	3	5	6	7	9	11
2	C-1, 4, 15, 2-OAc	C-1, 3, 4, 10, 15, 2-OAc	C-1, 4, 15, 2-OAc	C-1, 4, 10, 15, 2-OAc	C-1, 4, 15, 2-OAc	C-1, 3, 4, 15, 2-OAc	C-1, 3, 15, 2-OAc	C-3, 14, 15, 2-OAc
3	C-4	C-4, 5	C-1, 2, 4, 5	C-4		C-1, 2, 4	C-2	
4						C-8, 16	C-5, 16	
6	C-4, 7, 16	C-4, 7	C-4, 16	C-4, 16	C-5		C-5, 7, 8	
7	C-5, 6	C-6	C-5	C-5	C-6	C-5, 6	C-6	
9	C-7, 8, 10, 11, 17, 9-OAc	C-7, 8, 10, 11, 17, 9-OAc	C-1, 7, 8, 10, 11, 17, 9-OAc	C-7, 8, 11	C-8, 11	C-1, 11, 17	C-7, 8, 10, 11, 17, 9-OAc	C-7, 8, 11, 17, 9-OAc
10	C-1, 2, 9, 11, 14, 15	C-1, 2, 8, 9, 11, 15	C-1, 2, 8, 9, 11, 15	C-1, 2, 8, 9, 15	C-1, 2, 8, 11, 15	C-1, 2, 8, 11, 12, 14, 15	C-1, 2, 8, 9, 15, 20	C-2, 9, 15
11								
12	C-13, 20		C-13	C-13	C-13, 14, 20		C-13, 20	
13			C-12	C-12		C-1, 11, 12, 14	C-14	
14	C-10, 12	C-10, 12, 14-OAc	C-10, 12, 14-OAc	C-12	C-13	C-10, 12	C-1	
15	C-1, 2, 10, 14	C-1, 2, 10, 14	C-1, 2, 10, 14	C-1, 2, 10, 14	C-1, 2, 10, 14	C-1, 2, 14	C-1, 2, 14	C-1, 2, 10, 14
16	C-4, 5, 6	C-5, 6, 16-OAc	C-4, 5, 6	C-4, 5, 6	C-5, 6, 16-OAc	C-4, 5, 6	C-4, 5, 6	C-4, 6
17	C-8, 18, 19	C-8, 18, 19	C-18, 19	C-18, 19	C-18, 19	C-9, 18, 19	C-8, 18, 19	C-19
18	C-8, 17, 19	C-8, 17, 19	C-8, 17, 19	C-8, 17, 19	C-8, 17, 19	C-8, 17, 19	C-8, 17, 19	C-8, 17, 19
20	C-10, 11, 12	C-10, 11, 12	C-10, 11, 12	C-10, 11, 12	C-10, 11, 12	C-10, 11, 12	C-10, 11, 12	C-10, 11, 12

[a] HMBC experiments maximized for $J = 9$ Hz except for **6**, $J = 5.5$ Hz, and **11**, $J = 7$ Hz.

Table 4. Selected NOE Correlations of **1**−**3**, **5**, and **7**−**12**

H	1	2	3	5	7	8	9	10	11	12
2	H-10	H-10	H-3,10	H-10	H-10	H-10(4-OH)	H-10,16	H-10,16	H-10,16	H-10
3	H-4,7,15	H-4,7,15	H-7,15	H-7,15	H-6,15	H-6,15	H-4,15(9-OAc)	H-4,15(9-OAc)	H-4,15(9-OAc)	H-7
4	H-3,16	H-3,16	H-16		H-16		H-3,6,7	H-3,6,7	H-3,7	
6	H-16	H-7	H-7	H-7,16	H-3,7	H-3,7,16	H-4,7	H-4,7	H-7	H-7,16
7	H-3,17	H-3,6,17	H-3,6	H-3	H-6	H-6	H-4,6,17	H-4,6,17	H-4,6,17	H-3,6
9	H-10,18,20	H-10,17,18,20	H-10,18,20	H-18,20	H-17,20(9-OH)	H-17,20	H-11,17, 18,20	H-11,17, 18,20	H-11,18,20	H-10,18, 20(9-OH)
10	H-2,9,20	H-2,9,20	H-2,9,20	H-2,20	H-2	H-2,18	H-2,11,12	H-2,11	H-2	H-2,9,20
11							H-9,10,12, 20	H-9,10,20	H-9,20	
12	H-20	H-13,20	H-13,20	H-13,20	H-13,20	H-20	H-10,11	H-13,20	H-13,20	
13	H-14	H-12,14	H-12,14	H-12,14	H-12,14,15	H-15	H-14	H-12,14	H-12,14	H-14
14	H-13,15	H-13,15	H-13,15	H-13,15	H-13,15	H-15	H-13,15	H-13,15	H-13,15	H-13,15
15	H-3,14(2,9-OAc)	H-3,14(2,9-OAc)	H-3,14(2,9-OAc)	H-3,14	H-3,14,13β	H-3,13β,14	H-3,14,20	H-3,14	H-3,14	H-14(9-OH)
16	H-4,6	H-4	H-4	H-6	H-4	H-6	H-2	H-2	H-2	H-6
17	H-7,18	H-7,9.18	H-18	H-18	H-9,18	H-9,18	H-7,9,18	H-7,9.18	H-7,18	H-18
18	H-9,17	H-9,17	H-17	H-9,17	H-17	H-10,17	H-9,17	H-9,17	H-9,17	H-17
20	H-9,10,12	H-9,10,12	H-9,10,12	H-9,10,12	H-9,12	H-9,12	H-9,11,15	H-9,11,12	H-9,11,12	H-9,10

observed for other 11α,12α-epoxides in closely related examples.[13,20,21] Also H-12 shows a decidedly different vicinal J (3.5 Hz) with one of the H_2-13, whereas in all the 11β,12β-epoxides described in this paper, **1**−**6** and **8**, $J_{H12,13}$ is 5−6 Hz.

Compound **8** (4-hydroxymilolide C), $C_{24}H_{31}O_{10}Cl$, exhibited ^{1}H and ^{13}C NMR data similar to those of **7** except the proton signal for H-4 was missing and the signal for C-4 was replaced by a quaternary carbon signal resonating at 96.9 ppm, indicative of a ketal carbon. Of the two exchangeable OH signals at δ 6.45 (br s) and δ 3.60 ($J = 5.5$ Hz), the latter was shown to be coupled in the COSY experiment to H-9. A COSY experiment confirmed the same coupled systems as in compound **7** except for H-4. The stereochemistry of **8** was determined to be the same as **7**, except for the epoxide configuration, based on observance of nearly the same NOE correlations and coupling constants. An 11β,12β-epoxide configuration was assigned since $J_{H12,13\alpha}$ is 6 Hz as in **1**−**6** and δ_C for C-11 is >60 ppm as in **1**−**6** and **14**−**16**. The J values for H-12, H_2-13, and H-14 of **8** were definitively assigned with the aid of homo 2D J resolved spectra and single-frequency decoupling (irr. H-14): $H_{12,13\alpha}$ $J = 5.9$ Hz; $H_{12,13\beta}$ $J = \sim 0$; $H_{12,14}$ $J = 1.8$ Hz; $H_{13\alpha,14}$ $J = 2.8$ Hz; $H_{13\beta,14}$ $J = 3.9$ Hz. Proton-13β was identified by its NOE interaction with H-15.

The molecular formula of **9** was established as $C_{24}H_{30}O_{10}$-Cl by HRESIMS and NMR data. The ^{1}H and ^{13}C NMR chemical shift data for **9** (Tables 5 and 2) and its proton coupling data are the same as those reported for solenolide C,[11] although the carbon chemical shifts are assigned differently owing to the use of HMQC and HMBC data in the current work. Solenolide C was initially assigned a 12α-OH configuration, but on the basis of Kobayashi's study of brianolide (**13**) by X-ray and NMR analysis,[12] it appears that solenolide C should be assigned a 12β-OH configuration. Since we observed a $J_{H12,13} \sim 0$ for **9** as was found for brianolide (**13**) and an NOE was observed between H-10 and H-12, solenolide C (**9**) is depicted here with the 12β-OH. Finally, it may be noted that the chemical shifts of C-20 in both **9** and **13** are ~3 ppm farther upfield than the corresponding signals in **10** and **11**, which have 12α-substituents. This trend is expected due to the γ-gauche interactions of C-20 with the C-12 substituents in **9** and **13**. Hence, the ^{13}C NMR chemical shift of C-20 is a good predictor of C-12 stereochemistry of briaranes having a 11β-methyl substituent, i.e., $\delta_{C20} \sim 10 = 12\beta$-X; $\delta_{C20} \sim 13-$

Table 5. ^{1}H NMR Data for Compounds **9**−**13**

H	**9**[a]	**10**[b]	**11**[b]	**12**[b]	**13**[a]
2	5.10 (d, 9.5)	3.64 (d, 9)	5.20 (d, 9.5)	5.02 (d, 7.5)	3.16 (d, 9)
3	3.47 (dd, 9, 4)	3.37 (dd, 9, 4)	3.38 (dd, 9.5, 3.5)	2.52 (m), 1.62 (m)	3.70 (dd, 9, 4)
4	3.85 (d, 4)	3.70 (d, 4)	3.62 (d, 3)	2.50 (m), 1.94 (m)	3.85 (d, 4)
6	5.40 (dd, 3.5, 2)	5.38 (dd, 3.5, 2.5)	5.40 (dd, 3, 2.5)	5.30 (d, 9.5)	5.41 (dd, 3.5, 2.5)
7	5.21 (d, 3.5)	5.02 (d, 3.5)	4.99 (d, 3)	5.42 (d, 9.5)	5.23 (d, 4)
9	5.32 (d, 8.5)	5.28 (d, 9)	5.31 (d, 8.5)	4.01 (d, 5)	5.28 (d, 9)
10	1.74 (dd, 8, 2.5)	1.87 (dd, 9.5, 2.5)	2.01 (dd, 8.5, 2)	2.43 (br s)	1.74 (dd, 9, 2.5)
11	2.26 (m)	2.27 (m)	2.28 (m)		2.38 (m)
12	3.53 (d, 4.5)	4.66 (dd, 5.5, 2.5)	4.68 (dd, 5, 2.5)	9.43 (d. 0.5)	4.49 (d, 4.5)
13	3.05 (d, 3.5)	3.58 (dd, 5.5, 3)	3.52 (dd, 5, 3.5)	2.31 (dd, 15.5, 5.5), 1.46 (d, 15.5)	3.21 (d, 4)
14	2.91 (d, 3.5)	3.23 (d, 3.5)	2.85 (d, 3.5)	4.80 (d, 5.5)	3.15 (d, 3.5)
15	1.21 (s)	1.09 (s)	1.16 (s)	1.08 (s)	1.13 (s)
16	5.96 (d, 2.5)	5.96 (d, 2.5)	6.08 (d, 3)	2.02 (s)	5.94 (d, 2.5)
	5.82 (d, 2.5)	5.58 (d, 3)	6.05 (d, 3)		5.48 (d, 3)
17	2.63 (q, 7)	2.41 (q, 7)	2.39 (q, 7)	3.24 (q, 7)	2.64 (q, 7)
18	1.09 (d, 7)	1.15 (d, 7)	1.17 (d, 7.5)	1.09 (d, 7.5)	1.09 (d, 7.5)
20	0.98 (d, 7.5)	1.03 (d, 7.5)	1.04 (d, 7.5)	1.33 (s)	1.04 (d, 7)
OAc	2.22, 2.09	2.18[c]	2.20, 2.12[d]	2.0, 1.93	2.22, 2.09

[a] Spectra obtained in CD_3OD at 500 MHz and referenced thereto (δ 3.30). [b] Spectra recorded in $CDCl_3$ at 500 MHz and referenced to $CDCl_3$ (δ 7.24). [c] Butyrate residue: 2.25 (td, 7.5, 1.5), 1.63 (m, 7.5), 0.94 (t, 7.5). [d] Hexanoate residue: 2.28 (t, 7.5), 1.61 (m, 7.5), 1.31 (m), 1.31 (m), 0.89 (t, 7).

14 = 12α-X. Our conclusions for correlating $J_{H12,13}$ with C-12 stereochemistry in **9**−**11** and **13** are in agreement with Kobayashi's observations, i.e., $J_{12,13}$ ~0 = 12β-X; $J_{12,13}$ ~4−6 = 12α-X. Using these criteria it would appear that solenolide B−D[11] all have 12β-substituents.

Mililide D (**10**), molecular formula $C_{26}H_{34}O_{10}Cl$, exhibited ^{1}H and ^{13}C NMR data quite similar to those of **9** and **13** (Tables 5 and 2). The COSY experiment confirmed the presence of the same substituted skeletal fragments in all three compounds. NMR data supported the presence of one acetate (δ_H 2.18 H_3; δ_C 169.7) and one butyrate group (Tables 5 and 2). Comparison of proton chemical shifts of H-2 in the spectra of **10**, **9**, and **13** confirmed the presence of a free OH at C-2 in **10**. The acetoxy group was confirmed to be at C-9 in view of an NOE detected between H-3 and the acetyl methyl signal. Hence the butyrate ester is at C-12. The same relative stereochemistry, except at C-12, was assigned to **10** as found in **9** and **13** because of the similarity in coupling constants, ^{13}C NMR chemical shifts, and NOESY correlations (Table 4). A 5.5 Hz coupling observed between H-12/H-13 and hence the butyrate group is assigned as α-oriented, in agreement with the data published by Kobayashi[12] and the fact that δ_C of C-20 is farther downfield than those found for **9** and **13**.

Mililide E (**11**), $C_{30}H_{40}O_{11}Cl$ by HRESIMS and NMR data, showed nearly the same ^{1}H and ^{13}C NMR data for the briarane framework atoms as found for **10**, except for the downfield shift of the H-2 signal to δ 5.20, indicating esterification at this position in **11**. NMR data (Tables 5 and 2) provided evidence for two acetate groups and one hexanoate group. Acetate esters were assigned at C-2 and C-9 on the basis of HMBC correlations of H-2 and H-9 with carbonyl signals that were in turn correlated with acetate methyl signals. This fixed the hexanoate group at C-12, and this was supported by the chemical shift of H-12 (δ 4.68). The NOEs found (Table 4) for **11** were the same as observed for **10**, and since $J_{H12,13}$ was large (5.5 Hz) as for **10**, both compounds have the same relative stereochemistry.

Mililide F (**12**) had the molecular formula $C_{24}H_{34}O_9$ on the basis of HRESIMS and NMR data. Its ^{1}H NMR spectrum confirmed the presence of two tertiary, one secondary, and one vinyl methyl group as in **1**, **4**, and **16**, in addition to two acetate groups (Table 5). In contrast to the spectra of all the preceding compounds the spectrum of **12** contained an aldehyde proton doublet signal (δ 9.43, J = 0.5 Hz). The ^{1}H−^{1}H COSY spectrum confirmed the same proton spin systems for the 10-membered ring and lactone moiety as in **4** and **16**. Correlations were also observed for H-14/H-13β, but the oxygen-deshielded H-12 signal observed for **1**−**13** was missing in the spectrum of **12**. The aldehyde proton doublet showed a COSY correlation to H-10, and on the basis of this observation the aldehyde group was attached to C-11 in the β-configuration, which creates a W-arrangement between H-10 and the aldehyde proton. An OH doublet at δ 3.53 (J = 5) was coupled to H-9 (COSY), and hence the acetate residues were assigned to the oxygens at C-2 and C-14, which is also consistent with the chemical shifts of H-2 and H-14. The NOESY spectrum of **12** possesses nearly all the same correlations as that of **5**, and hence the relative stereochemistry of both compounds is assumed to be the same. Although compound **12** appears to be the first of the naturally occurring briarane lactones to have a contracted ring-A, the type of rearranged product, e.g., **17**, has been reported by Faulkner's group as arising from BF_3/Et_2O treatment of stylatulide.[20]

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Rudolph Autopol III automatic polarimeter. IR spectra were obtained on a Bio-Rad FTS-155 FT-IR spectrometer. FABMS and ESIMS were measured on VG ZAB-E and Micromass Q-TOF mass spectrometers, respectively. NMR experiments were performed on aVarian VXR-500 spectrometer equipped with a 3 mm ^{1}H/^{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. Merck Si gel 60 H (230−240 mesh) was used for vacuum flash column chromatography, and preparative HPLC was performed using an RI detector and Phenomenex ODS Prep (250 × 10 mm) column.

Animal Material. The soft coral (specimens 24YA95) for this study was collected in August 1995 at ~30 ft depths in Mil channel, Yap, Micronesia. The material used in the present paper most closely resembles the scleraxonian gorgonian *Briareum stechei* (Kükenthal, 1908) (order Alcyonacea, family Briareidae; type locality Moluccas, Indonesia), especially in the shape and size of sclerites. The genus *Briareum* is known to occur in shallow water of coral reef communities in both the tropical western Atlantic and the Indo-Pacific. One species is

known from the West Indian region, *Briareum asbestinum* (Pallas, 1766), while several species are most likely present in the Indo-Pacific region. *Briareum marquesarum* (Kükenthal, 1916), from Polynesia, differs from *B. stechei* in that the maxium length of sclerites is 0.36 mm. The original description of *B. stechei* notes that the sclerites can attain 0.60 mm in length. The maximum length of sclerites in the material for this study is slightly over 0.50 mm. The range of morphological variation for *B. stechei* is not known, but the species probably has a relatively widespread distribution in the tropical western Pacific, including Indonesia, the Philippines, and Micronesia (Palau and Yap) and recently reported from New Caledonia.[22] A voucher specimen has been deposited at the California Academy of Sciences (CAS #117221). Indo-Pacific species of *Briareum* are preyed upon by the nudibranch mollusk *Phyllodesmium briareus* (Bergh, 1896).[23]

Extraction and Isolation. Frozen specimens were cut into small pieces and freeze-dried (2.04 kg wet wt; 850 g dry wt after extraction). The dry specimens were extracted with MeOH (1.7 L × 2) and MeOH−CH_2Cl_2 (1:1, 1.7 L × 2). All extracts were combined and concentrated, and the residue was partitioned between aqueous MeOH and organic solvents. The extract was dissolved in MeOH−H_2O (9:1, 700 mL) and partitioned with hexane (700 mL × 2), and then the aqueous MeOH solution was diluted with H_2O (200 mL) to 30% of H_2O in MeOH. The aqueous MeOH solution was extracted with CH_2Cl_2 (800 mL × 2) and then concentrated in vacuo. The aqueous residue was diluted with H_2O to 400 mL and extracted with *n*-BuOH (400 mL × 2). Each of the extracts was evaporated under reduced pressure to obtain hexane (8.39 g), CH_2Cl_2 (16.16 g), *n*-BuOH (1.42 g), and H_2O (25.38 g) solubles.

A portion (6.8 g) of the CH_2Cl_2 solubles was fractionated on a Si gel vacuum flash column eluting sequentially with CH_2Cl_2−MeOH (50:1, 30:1, 20:1, 10:1, 5:1, 3:1, and 1:1). Fractions were combined according to their TLC patterns to yield fractions F008−F015. Fraction F009 was rechromatographed over C_{18} reversed-phase HPLC with 35% H_2O−MeOH as eluent to obtain compounds **4**, **5**, **6**, **10**, and **13** (5.2, 6.2, 11, 6 and 9.3 mg, respectively) and mixtures of compounds. The mixtures were again applied over C_{18} reversed-phase HPLC using water−methanol mixtures and Si gel chromatography using hexanes−EtOAc (1:1.3) as eluent to separate compounds **1**, **2**, **7**, **8**, and **12** (7.8, 17, 4.5, 9.7, and 1 mg, respectively). Fraction F010 was fractionated by C_{18} reversed-phase HPLC (35% H_2O−MeOH) to yield compounds **3** and **9** (6.5 and 52.1 mg, respectively). Compounds **11**, **14**, and **15** (2, 33.6, and 3.3 mg, respectively) were obtained by Si gel chromatography [hexanes−EtOAc (1.5:1)] and C_{18} reversed-phase HPLC (27% H_2O−MeOH) from the fraction F008.

Milolide A (1): $[\alpha]_D^{23}$ +47.7° (*c* 0.65, CH_2Cl_2); IR (neat) ν_{max} 3480, 1775, 1740, 1726, 1711, 1380, and 1250 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; FABMS *m/z* 567 $[M + H]^+$; HRESIMS *m/z* 589.2258 $[M + Na]^+$ (calcd for $C_{28}H_{38}O_{12}Na$, 589.2261).

16-Acetoxymilolide A (2): $[\alpha]_D^{23}$ +44.2° (*c* 0.6, CH_2Cl_2); IR (neat) ν_{max} 3460, 1776, 1745, 1726, 1711, 1370, and 1250 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; FABMS *m/z* 625 $[M + H]^+$; HRESIMS *m/z* 647.2312 $[M + Na]^+$ (calcd for $C_{30}H_{40}O_{14}Na$, 647.2316).

16-Hydroxymilolide A (3): $[\alpha]_D^{23}$ +50.4° (*c* 0.42, CH_2Cl_2); IR (neat) ν_{max} 3480, 1778, 1765, 1738, 1373, 1254, 1219, and 1033 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; FABMS *m/z* 583 $[M + H]^+$, 605 $[M + Na]^+$; ESIMS *m/z* 605 $[M + Na]^+$; HRESIMS *m/z* 605.2208 $[M + Na]^+$ (calcd for $C_{28}H_{38}O_{13}Na$, 605.2210).

Milolide B (4): $[\alpha]_D^{23}$ +7.1° (*c* 0.28, CH_2Cl_2); IR (neat) ν_{max} 3470, 1775, 1740, and 1720 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; ESIMS *m/z* 489 $[M + Na]^+$; HRESIMS *m/z* 489.2082 $[M + Na]^+$ (calcd for $C_{24}H_{34}O_9Na$, 489.2101).

16-Chloromilolide B(5): $[\alpha]_D^{23}$ −10° (*c* 0.25, CH_2Cl_2); IR (neat) ν_{max} 3400, 1770, 1738, and 1717 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; FABMS *m/z* 501 $[M + H]^+$; HRESIMS *m/z* 523.1724 $[M + Na]^+$ (calcd for $C_{24}H_{33}O_9ClNa$, 523.1711).

16-Acetoxymilolide B (6): $[\alpha]_D^{23}$ −0.8° (*c* 0.38, CH_2Cl_2); IR (neat) ν_{max} 3400, 1780, 1737, 1720, and 1717 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; FABMS *m/z* 525 $[M + H]^+$, 547 $[M + Na]^+$; HRESIMS *m/z* 547.2156 $[M + Na]^+$ (calcd for $C_{26}H_{36}O_{11}Na$, 547.2155).

Milolide C (7): $[\alpha]_D^{23}$ −9.8° (*c* 0.23, MeOH); ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; ^1H NMR (CD_3OD) δ 5.61 (1H, d, *J* = 3 Hz, H-6), 5.37 (1H, d, *J* = 2 Hz, H-16), 5.25 (1H, d, *J* = 2 Hz, H-16), 4.91 (1H, d, *J* = 6.5 Hz, H-2), 4.89 (1H, d, *J* = 6 Hz, H-9), 4.84 (1H, br s, H-14), 4.70 (1H, d, *J* = 3.5 Hz, H-7), 4.69 (1H, dd, *J* = 12.5, 4.5 Hz, H-4), 3.51 (1H, ddd, *J* = 15.5, 13, 7 Hz, H-3), 3.01 (1H, d, *J* = 3 Hz, H-12), 2.98 (1H, q, *J* = 7 Hz, H-17), 2.53 (1H, s, H-10), 2.27 (1H, ddd, *J* = 17, 5, 3 Hz, H-13), 2.06 (1H, d, *J* = 17 Hz, H-13), 1.97 (3H, s, OAc), 1.94 (3H, s, OAc), 1.55 (3H, s, H-20), 1.29 (1H, dd, *J* = 15.5, 4.5 Hz, H-3), 1.23 (3H, s, H-15), 1.23 (3H, d, *J* = 7 Hz, H-18); ^{13}C NMR (CD_3OD) δ 178.5 (C-19, s), 140.9 (C-5, s), 115 (C-16, t), 85.2 (C-8, s), 82.3 (C-7, d), 78.5 (C-4, d), 75.0 (C-14, d), 75.0 (C-2, d), 73.5 (C-9, d), 61.0 (C-12, d), 60.9 (C-11, s), 56.5 (C-6, d), 50.9 (C-17, d), 45.4 (C-1, s), 43.1 (C-10, d), 36.0 (C-3, t), 27.9 (C-13, t), 23.3 (C-20, q), 14.9 (C-15, q), 7.7 (C-18, q), 172.6, 172.0, 21.1, 21.0 (OAc × 2); ESIMS *m/z* 521 $[M + Na]^+$; HRESIMS *m/z* 521.1541 $[M + Na]^+$ (calcd for $C_{24}H_{31}O_9ClNa$, 521.1554).

4-Hydroxymilolide C (8): $[\alpha]_D^{23}$ +8.4° (*c* 0.47, CH_2Cl_2); ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; ESIMS *m/z* 537 $[M + Na]^+$; HRESIMS *m/z* 537.1461 $[M + Na]^+$ (calcd for $C_{24}H_{31}O_{10}ClNa$, 537.1503).

Solenolide C (9): $[\alpha]_D^{23}$ −28° (*c* 0.3, MeOH); lit.[9] −25° (*c* 0.76, MeOH); ^1H NMR, see Table 5; ^{13}C NMR, see Table 2; ^1H NMR (acetone-d_6) δ 5.92 (1H, d, *J* = 2.5 Hz, H-16), 5.89 (1H, d, *J* = 2 Hz, H-16), 5.51 (1H, dd, *J* = 3, 2 Hz, H-6), 5.40 (1H, d, *J* = 8.5 Hz, H-9), 5.38 (1H, d, *J* = 3.5 Hz, H-7), 5.14 (1H, d, *J* = 9.5 Hz, H-2), 3.94 (1H, d, *J* = 3.5 Hz, H-4), 3.59 (1H, d, *J* = 4.5, H-12), 3.51 (1H, dd, *J* = 9.5, 4 Hz, H-3), 3.04 (1H, d, *J* = 4 Hz, H-13), 2.92 (1H, d, *J* = 3.5 Hz, H-14), 2.70 (1H, q, *J* = 7 Hz), 2.33 (3H, s, OAc), 2.24 (1H, m, H-11), 2.07 (3H, s, OAc), 1.78 (1H, dd, *J* = 8.5, 2.3 Hz, H-10), 1.24 (3H, s, H-15), 1.10 (3H, d, *J* = 7 Hz, H-18), 1.03 (3H, d, *J* = 7.0, H-20); ^{13}C NMR (acetone-d_6) δ 174.9 (C-19, s), 137.5 (C-5, s), 118.4 (C-16, t), 84.5 (C-8, s), 78.4 (C-7, d), 76.3 (C-2, d), 70.1 (C-12, d), 70.0 (C-9, d), 62.5 (C-14, d), 61.6 (C-3 or C-6, d), 60.8 (C-6 or C-3, d), 59.3 (C-13, d), 57.5 (C-4, d), 45.4 (C-17, d), 40.1 (C-11, d), 39.0 (C-1, s), 38.2 (C-10, d), 16.9 (C-15, q), 9.6 (C-20, q), 6.3 (C-18, q), 171.5, 169.1, 22.1, 20.9 (OAc × 2); ESIMS *m/z* 537 $[M + Na]^+$; HRESIMS *m/z* 537.1463 $[M + Na]^+$ (calcd for $C_{24}H_{31}O_{10}ClNa$, 537.1503).

Milolide D (10): $[\alpha]_D^{23}$ −45° (*c* 0.43, CH_2Cl_2); ^1H NMR, see Table 5; ^{13}C NMR, see Table 2; ESIMS *m/z* 565 $[M + Na]^+$; HRESIMS *m/z* 565.1811 $[M + Na]^+$ (calcd for $C_{26}H_{35}O_{10}ClNa$, 565.1816).

Milolide E (11): $[\alpha]_D^{23}$ −53.6° (*c* 0.084, CH_2Cl_2); ^1H NMR, see Table 5; ^{13}C NMR, see Table 2; ESIMS *m/z* 635 $[M + Na]^+$; HRESIMS *m/z* 635.2208 $[M + Na]^+$ (calcd for $C_{30}H_{41}O_{11}ClNa$, 635.2235).

Milolide F (12): $[\alpha]_D^{23}$ +18.8° (*c* 0.016, CH_2Cl_2); ^1H NMR, see Table 5; ESIMS *m/z* 489 $[M + Na]^+$; HRESIMS *m/z* 489.2101 $[M + Na]^+$ (calcd for $C_{24}H_{34}O_9Na$, 489.2101).

Brianolide (13): $[\alpha]_D^{23}$ −11.2° (*c* 0.66, MeOH); lit.[12] −15° (*c* 0.1, MeOH); ^1H NMR, see Table 5; ^{13}C NMR, see Table 2; ^1H NMR ($CDCl_3$) δ 6.0 (1H, d, *J* = 2.5 Hz, H-16), 5.56 (1H, d, *J* = 2.5 Hz, H-16), 5.33 (1H, dd, *J* = 3.5, 2 Hz, H-6), 5.31 (1H, d, *J* = 9 Hz, H-9), 5.0 (1H, d, *J* = 3.5 Hz, H-7), 4.56 (1H, d, *J* = 4.5 Hz, H-12), 3.63 (1H, d, *J* = 4 Hz, H-4), 3.60 (1H, d, *J* = 9.5 Hz, H-2), 3.36 (1H, dd, H-9.5, 4 Hz, H-3), 3.23 (1H, d, *J* = 3 Hz, H-13), 3.18 (1H, d, *J* = 3 Hz, H-14), 2.43 (1H, q, *J* = 6.5 Hz, H-17), 2.23 (1H, m, H-11), 2.19 (3H, s, OAc), 2.10 (3H, s, OAc), 1.59 (1H, dd, *J* = 8.5, 2 Hz, H-10), 1.16 (3H, d, *J* = 6.5 Hz, H-18), 1.14 (3H, s, H-15), 1.02 (3H, d, *J* = 7.5 Hz, H-20); ^{13}C NMR ($CDCl_3$) δ 174.1 (C-19, s), 134.2 (C-5, s), 119.4 (C-16, t), 84.1 (C-8, s), 76.4 (C-7, d), 73.5 (C-2, d), 72.1 (C-12, d), 69.2 (C-9, d), 62.3 (C-13, d), 62.1 (C-3, d), 61.1 (C-6, d), 57.9 (C-4, d), 57.5 (C-14, d), 45.4 (C-17, d), 38.5 (C-1, s), 37.3 (C-10, d), 35.8 (C-11, d), 15.8 (C-15, q), 9.7 (C-20, q), 6.2 (C-18, q), 170.1, 169.6, 22.0, 21.0 (OAc × 2); ESIMS *m/z* 537 $[M + Na]^+$.

Compound 14: $[\alpha]_D^{23}$ −20.9° (*c* 0.33, CH_2Cl_2); lit.[5,20] −7° (*c* 0.1, $CHCl_3$).

Excavatolide A (15): $[\alpha]_D^{23}$ +23° (*c* 0.25, pyridine); lit.[7] +38° (*c* 0.05, pyridine); ^{1}H NMR ($CDCl_3$); δ 5.63 (1H, m, H-12), 5.52 (1H, d, J = 2.5 Hz, H-6), 5.46 (1H, d, J = 2 Hz, H-16), 5.31 (1H, d, J = 2 Hz, H-16), 5.01 (1H, m, H-14), 4.99 (1H, d, J = 7 Hz, H-7), 4.98 (1H, d, J = 6 Hz, H-6), 4.85 (1H, dd, J = 13, 5 Hz, H-4), 4.69 (1H, d, J = 3 Hz, H-7), 3.29 (1H, ddd, J = 15, 13, 7 Hz, H-3), 2.88 (1H, br s, H-10), 2.60 (1H, q, J = 7.0 Hz, H-17), 2.39 (1H, m, H-13), 2.25 (1H, d, J = 5.5 Hz, 9-OH), 2.05 (3H, s, OAc), 2.01 (3H, s, OAc), 2.01 (1H, m, H-13), 1.88 (3H, s, H-20), 1.39 (1H, dd, J = 15.5, 5 Hz, H-3), 1.28 (3H, d, J = 6.5 Hz, H-18), 1.17 (3H, s, H-15); ^{13}C NMR ($CDCl_3$) δ 175.5 (C-19), 137.9 (C-5), 131.2 (C-11), 123.2 (C-12), 115.7 (C-16), 82.4 (C-8), 80.6 (C-7), 76.6 (C-4), 75.9 (C-9), 73.5 (C-2), 72.1 (C-14), 55.1 (C-6), 50.7 (C-17), 44.0 (C-1), 41.2 (C-10), 35.4 (C-3), 28.4 (C-13), 24.6 (C-20), 14.7 (C-15), 7.6 (C-18), 170.7, 170.4, 21.2, 21.1 (OAc x 2).

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