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THE BRIARELLINS, NEW EUNICELLIN-BASED DITERPENOIDS FROM A CARIBBEAN GORGONIAN, *BRIAREUM ASBESTINUM*.

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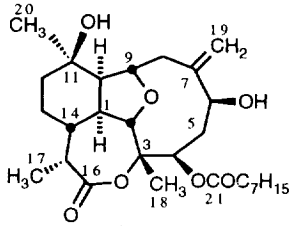
Abstract: The Caribbean gorgonian *Briareum asbestinum* has been shown to contain representatives from three skeletal classes, asbestinins, briareins, and eunicellins. The structural diversity of the diterpenoids isolated suggest a common biosynthetic pathway. Briarellins -A (**1**), -B (**3**), -C (**5**), and -D (**6**) are members of a new class of tetracyclic diterpenoids of the eunicellin family distinguished by the presence of a seven-membered lactone ring formed between C-3 and C-16. *Seco*-briarellin (**7**), which possesses a novel carbon skeleton, is the first representative of a new class of ether-cyclized eunicellin diterpenes known as *seco*-eunicellins. The briarellins are also unique among the compounds in this series in having the opposite relative stereochemistry at C-11 to that found in eunicellin-based compounds isolated from South Pacific soft corals. The structures of the new eunicellin-type diterpenoids were established after extensive analysis of spectral data and those of **3** and **5** were confirmed by chemical interconversions. Briarellin-A (**1**) displayed modest *in vitro* cytotoxicity against HeLa cells.

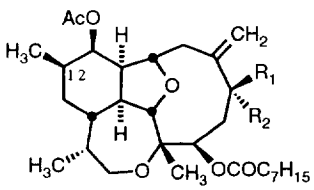
Caribbean gorgonians (phylum Cnidaria, order Gorgonacea) have proven to be a rich source of structurally diverse and pharmacologically important natural products.[1] As part of our continuing search for bioactive substances we have studied the encrusting Caribbean gorgonian *Briareum asbestinum* which was collected near Mona Island off the west coast of Puerto Rico. The genus *Briareum,* which is very difficult to distinguish from the South Pacific *Solenopodium* genus, may be placed taxonomically near the transition between the Alcyonacea and Gorgonacea, the two major groups of octocorals.[2] Previous investigations of Caribbean specimens of *B. asbestinum* have led to the discovery of a variety of diterpenoids, all of which belong to the asbestinane and briarane skeletal classes.[3-12] In addition to species of the genus *Briareum*,[13-17] briareins have also been isolated from another Caribbean species of gorgonian, namely, *Erythropodium caribaeorum*.[17-19] A recent report on *Solenopodium stechei* collected near the Australian Great Barrier Reef described the co-occurrence of over 20 diterpenoids possessing the briarein and eunicellin skeletons and one having the regular cembranoid skeleton.[20] The presence of all three of these classes of compounds has provided key circumstantial evidence for the biosynthetic pathway proposed by Faulkner in which a cembrane skeleton is the precursor to both the briarein skeleton (via C-3/C-8 cyclization) and the eunicellin skeleton (via C-2/C-11 cyclization) (Scheme 1).[4] The carbon skeleton of the asbestinins is related to that of the eunicellins and cladiellins by migration of a methyl group from C-11 to C-12. The asbestinins also contain an additional seven-membered ether ring formed between C-3 and C-16 which has never been detected in any eunicellin-type diterpenoid. Although briarane, cladiellane and cembrane-type diterpenoids have been reported to co-occur in a South Pacific *Briareum* sp.,[21,22] to the best of our knowledge no diterpenoids possessing the asbestinin carbon skeleton have been reported from *Briareum* or *Solenopodium* spp. from that region. Likewise, no cembrane or eunicellin-based diterpenoids have been reported from a Caribbean *Briareum* sp. The present study resulted in the isolation of 24 diterpenoids, of which 19 are known (17 with the asbestinin skeleton, one *seco*-asbestinin, and one with the briarein skeleton)[11,12] and five are new compounds (four with a tetracyclic eunicellin skeleton, which possess a rare C-3 to C-16 lactone link, and

one contains only three rings thus comprising a novel type of ether-cyclized eunicellin-based diterpene). Compounds **1**, **3**, **5**, **6** and **7** are representatives of a new class of eunicellin-based diterpenes distinguished by the presence of a novel ε-lactone moiety and by having an unusual relative configuration at C-11. One of the new metabolites described here, briarellin-A (**1**), was shown to possess modest (*in vitro*) cytotoxic action against HeLa cells.

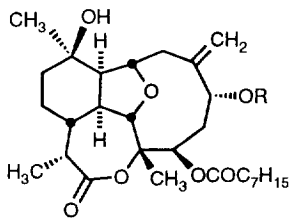
Specimens of *B. asbestinum* were frozen immediately after collection and subsequently freeze-dried. Conventional extraction procedures were used, and the hexane extract was fractionated extensively using normal- and reversed-phase adsorbents to give 23 diterpenoids of several skeletal classes. A preliminary evaluation of the $CHCl_3$ extract obtained from the same specimen of *B. asbestinum* also yielded briarein A (**9**),[3-5] a known chlorinated diterpene, and clearly indicated the presence of additional briarein-type diterpenes (see Experimental). From the pool of hexane-soluble compounds we have isolated and identified five new compounds: four of the more abundant nonchlorinated diterpenes **1**, **3**, **5**, and **6** which we have named the briarellins while the other, *seco*-briarellin (**7**) was a minor component. The structures as well as the chemical and spectroscopic properties of the new briarellins are described below. Since the ^{13}C-nmr spectrum did not contain a signal for a tetrasubstituted carbon atom bearing carbon substituents, as found at the carbocyclic ring junction in the briarein series, nor did it reveal a signal near 31-32 ppm ascribable to the C-13 methylene group, as found in the asbestinin series, these eunicellin diterpenes could not be assigned a structure based on the briarein or the asbestinin carbon skeletons (see Table 1).



1



2 R_1 = OH; R_2 = H
4 R_1 = H; R_2 = OH



3 R = H
5 R = COC_3H_7

A molecular formula of $C_{28}H_{44}O_7$ was established for briarellin-A (**1**) from high-resolution EI mass spectrometry (492.30779, calcd 492.30867), plus ^1H NMR and ^{13}C NMR data (see Table 1). The infrared spectrum indicated the presence of hydroxyl (3413 cm^{-1}, broad) and carbonyl ester (1738, 1714 cm^{-1}) groups and the UV showed only end absorption. Fragments ions in the HREIMS corresponding to M^+-18 $[M-H_2O]^+$, M^+-144 $[M-C_8H_{16}O_2]^+$ and M^+-180 $[M-H_2O-C_8H_{16}O_2-H_2O]^+$, confirmed the presence in **1** for two alcohols and one caprylate group. Subtraction of the 8 carbons associated with the aliphatic ester group left 20 carbons, suggestive of a diterpene skeleton (6 unsaturations). Since the ^{13}C NMR spectrum (Table 1) contained only two olefinic resonances [δ 142.3 (s) and 119.7 (t) assigned to an exocyclic olefin] and two carbon resonances at δ 176.0 (s) and 172.8 (s) for ester carbonyls, the molecule was judged to be tetracyclic. The ^1H NMR spectrum of briarellin-A (**1**) exhibited signals due to an exocyclic methylene [δ 5.56 (1H, br s) and 5.28 (1H, br s)], a β-capryloxy [δ 4.76 (1H, dd, J = 3.6, 10.2 Hz)] proton, three oxymethine protons [δ 4.67 (1H, dd, J = 5.1, 10.8 Hz); 4.14 (1H, br t, J = 6.0 Hz) and 3.77 (1H, d, J = 3.3 Hz)] and four methyls [δ 1.36 (3H, s), 1.32 (3H, d, J = 7.5 Hz),

1.29 (3H, s), and 0.87 (3H, br t, J = 6.9 Hz)]. The ^{1}H NMR spectrum of **1** was similar to that which has been reported for asbestinin-7 (**2**),[7,12] a known compound which was also present in this specimen of *B. asbestinum*. The only major differences are the absence in **1** of an acetoxy group and two diastereotopic oxymethylene protons near δ 4.10 and 3.90 (ascribable to the C-16 protons in **2**) and the observation that in **2** the β-methyl group at C-12, resonating as a sharp doublet at δ 0.87 (J = 7.1 Hz), has been replaced by a sharp 3H singlet at δ 1.29 in briarellin-A (**1**). Comparison of the ^{13}C NMR spectrum of **1** with that of asbestinin-7 (**2**) confirmed the structural similarity of these two compounds and revealed the presence of some features unique to **1**. While the complex tetracyclic ring system along with the caprylate, alcohol, and exomethylene functionalities at C-4, C-6, and C-7, respectively, were shown to be intact in **1** on the basis of similar IR, NMR (^{1}H and ^{13}C), MS and UV data, briarellin-A, however, did not show an oxymethylene carbon signal near δ 67.9 or a tertiary carbon signal at δ 31.4 ascribable in **2** to carbons C-16 and C-12, respectively. Instead, briarellin-A contained new signals at δ 176.0 (s) and 30.3 (t) for C-16 and C-12, respectively. In addition, the C-11 resonance in **2** [δ 73.7 (d)] was replaced in **1** by a new signal at δ 80.5 (s). That carbon C-16 in **1** had indeed undergone complete oxidation to form a ε-lactone ring system was evident from the downfield shift experienced by atoms near that position. For instance, C-15, which resonates at δ 36.8 (d) in **2** appears at δ 45.2 (d) in **1** whereas H-15 resonates at δ 2.96 (1H, m) vs δ 1.59 (1H, m) in **2**. Moreover, compound **1** possessed two oxymethyl groups (vs one in asbestinin-7) as indicated by the ^{1}H NMR signals at δ 1.36 (3H, s) and 1.29 (3H, s) and their corresponding ^{13}C NMR resonances at δ 22.5 (q) and 28.8 (q), respectively. These combined spectroscopic data led us to propose a eunicellin-type skeleton for briarellin-A (**1**). From extensive ^{1}H decoupling experiments and a ^{1}H-^{1}H COSY experiment it was possible to determine the two separate spin systems within the tetracyclic ring moiety which map out the proton sequences H-4 to H-6, and the remaining protons around the cyclohexane, tetrahydrofuran, ε-lactone and 10-membered carbocyclic rings including the more remote exocyclic methylene protons H-19,19'. Allylic couplings were detected in the COSY spectrum between the exomethylene protons and H-6/H-8, thus confirming the C-6 to C-8 with branching C-19 array.

The location of all key substituents around the complex tetracyclic moiety in **1**, including the C-17 and C-20 methyls, was assigned definitively from evidence provided by selective INEPT experiments (Scheme 1). The resonance at δ 172.8 (s) was assigned as the caprylate carbonyl by its coupling with the oxymethine ^{1}H signal at δ 4.76 whose irradiation also caused enhancement to ^{13}C resonances at δ 92.5 (d, C-2), 82.9 (d, C-6), 74.3 (s, C-3), 34.8 (t, C-5), and 22.5 (q, C-18). These long-range couplings definitively positioned the caprylate ester at C-4. The resonance at δ 176.0 (s) was assigned as the lactone carbonyl due to a correlation with the tertiary proton signal at δ 2.96 ascribable to H-15 which in turn showed long-range couplings to ^{13}C signals located at δ 37.5 (d, C-14), 17.5 (q, C-17) and 16.4 (t, C-13). Placement of the hydroxyl at C-6 was confirmed from the coupling observed between the oxymethine proton signal at δ 4.67 (H-6) and the olefin carbons at δ 142.3 (s) and 119.7 (t) and the ^{13}C signals at δ 72.2 (d, C-4), 42.2 (t, C-8), and 34.8 (t, C-5). Key H/C correlations for confirming the skeleton in the cyclohexane ring region of **1** were those observed between the oxymethine proton at δ 4.14 (H-9) and the tertiary carbinol signal [δ 80.5 (s)] and between the signal at δ 1.29 (Me-20) and the carbon resonances at δ 80.5 (s, C-11), 47.6 (d, C-10) and 30.3 (t, C-12). The selective irradiation of H-9 also enhanced the ^{13}C signals ascribable to C-2 (δ 92.5) and C-7 (δ 142.3). Through these and other INAPT experiments (J ≅ 6 Hz) it was possible to correlate each of the quaternary carbons in compound **1** with its neighboring methine, methylene

Table 1. ^{1}H-NMR (300-MHz) and ^{13}C-NMR (75-MHz) Spectral Data of the Briarellins in $CDCl_3$.[a]

[a] Assignments were aided by ^{1}H-^{1}H COSY, spin splitting patterns, selective decoupling experiments, comparison of J values, heteronuclear chemical shift correlation methods, carbon atom multiplicities, and chemical shift values. The δ values are in ppm and are referenced to the residual $CHCl_3$ signal (7.26 and 77.0 ppm, respectively). [b] Values with identical superscripts in each column may be interchanged.

	Briarellin-A		Briarellin-B		Briarellin-C		Briarellin-D		*Seco*-Briarellin	
Position	(1)		(3)		(5)		(6)		(7)	
	^{1}H mult (J)	^{13}C	^{1}H mult (J)	^{13}C	^{1}H mult (J)	^{13}C	^{1}H mult (J)	^{13}C	^{1}H mult (J)	^{13}C
1	2.74 m	44.7	2.81 m	44.6	2.77 m	44.8	2.53 m	44.9	2.73 m	43.6
2	3.77 d (3.3)	92.5	3.83 d (4.8)	92.1	3.77 d (3.9)	92.5	4.14 d (2.7)	91.1	3.77 d (6.0)	88.7
3	-	74.3	-	73.9	-	74.2	-	81.0	-	74.1
4	4.76 dd (3.6,10.2)	72.2	4.64 t (4.2)	72.7	4.80 dd (4.2, 9.0)	71.9	2.01 m; 1.96 m	30.3	6.84 d (15.9)	160.7
5	2.23 m; 1.94 d (4)	34.8	2.76 t (4.2); 1.76 m	38.2	2.15 m; 2.10 m	36.3	2.20 m; 1.58 m	32.8	6.34 dd (7.8, 15.6)	130.3
6	4.67 dd (5.1,10.8)	82.9	4.18 br m	72.0	5.26 dd (5.1, 9.6)	72.4	4.29 dd (4.8, 7.8)	72.6	9.58 d (7.8)	193.4
7	-	142.3	-	145.4	-	142.7	-	147.9	-	206.4
8	2.83 m; 2.28 m	42.2	2.49 dd; 2.28, dd	39.8	2.94 t (5.1); 2.18 m	41.0	2.77 d (4.8); 2.09 d (2.4)	41.4	2.79 m	47.9
9	4.14 brt (6.0)	82.4	4.22 dd (3.0, 6.3)	82.9	4.15 brt (5.7)	82.4	4.19 m	82.4	4.04 m	77.6
10	2.78 brd (7.8)	47.6	3.05 dd (6.3, 10.8)	47.4	2.82 brd (7.8)	47.5	2.83 m	47.7	2.59 m	51.1
11	-	80.5	-	81.4	-	80.6	-	84.9	-	80.0
12	2.01 m	30.3	1.99 m	29.9	2.00 m	30.2	1.91 m; 1.50 m	28.7	2.08 m	29.7
13	1.90 m; 1.65 m	16.4	1.81 m	16.3	1.86 m; 1.75 m	16.3	1.65 m	16.8	2.25 m	16.1
14	1.63 m	37.5	1.73 m	36.8	1.66 m	37.5	1.59 m	37.0	1.61 m	36.0
15	2.96 m	45.2	2.92 m	45.6	2.97 m	45.3	2.88 m	45.9	2.97 m	45.6
16	-	176.0	-	175.9	-	175.9	-	176.1	-	175.4
Me_{17}	1.32 d (7.5)	17.5	1.36 d (6.9)	17.9	1.33 d (7.8)	17.5	1.36 d (7.8)	17.5	1.38 d (7.5)	17.8
Me_{18}	1.36 s	22.5	1.37 s	22.6	1.34 s	22.7	1.63 s	20.7	1.25 s	23.6
19	5.56 s; 5.28 s	119.7	5.73 s; 5.13 s	118.4	5.50 s; 5.15 s	119.5	5.42 s; 5.10 s	117.3	2.18 s	31.3
Me_{20}	1.29 s	28.8	1.33 s	28.4	1.28 s	28.7	1.32 s	28.9	1.24 s	28.7
21	-	172.8	-	175.0	-	173.0	-	172.4	-	-
22	2.31 t (7.5)	34.4	2.36 t (7.5)	34.6	2.31 t (6.9)	34.4	2.08 t (7.2)	37.4	-	-
23	1.60 m	24.9	1.64 m	24.9	1.60 m	24.8	1.54 m	18.4	-	-
24	1.27 m	29.0[b]	1.29 m	29.0[b]	1.24 m	28.8[b]	0.91 t (7.2)	13.6	-	-
25	1.27 m	28.8[b]	1.29 m	28.9[b]	1.24 m	29.0[b]	-	-	-	-
26	1.27 m	31.6	1.29 m	31.6	1.24 m	31.6	-	-	-	-
27	1.27 m	23.0	1.29 m	22.5	1.24 m	22.5	-	-	-	-
28	0.87 brt (6.9)	14.0	0.87 brt (6.9)	14.0	0.87 brt (6.9)	13.6	-	-	-	-
29	-	-	-	-	-	172.9	-	-	-	-
30	-	-	-	-	2.21 t (6.6)	36.3	-	-	-	-
31	-	-	-	-	1.60 m	18.3	-	-	-	-
32	-	-	-	-	0.90 t (7.2)	14.0	-	-	-	-

or methyl groups. The connectivities between each structural unit deduced from these two- and three-bond ^{1}H-^{13}C couplings are in full agreement with the eunicellin-based structure for briarellin-A (**1**).

Much of the stereochemistry of compound **1**, which was fully defined by a phase-sensitive NOESY experiment (Table 2), was found to be similar to that previously established for asbestinin-7 (**2**). Large NOE crosspeaks were observed for the methine proton at C-4 (δ 4.76) with those located at C-1 (δ 2.74) and C-6 (δ 4.67) suggesting that all three protons are on the same side of the molecule arbitrarily assigned as the α face. An intense NOE response was observed between H-6 and H-10 (δ 2.78), which, in turn, exhibited a similarly strong NOE response to H-1. This established the orientation of the latter resonances in the α orientation. Given the orientation of the H-1α proton as a starting point, we could immediately establish the orientations of the key protons at the 2 and 14 positions as β because they failed to exhibit an NOE response correlating them with H-1α. However, an intense NOE response was observed between H-2 at δ 3.77 and the H-14 and Me-18 resonances at δ 1.63 and δ 1.36, respectively. This established the orientation of the latter resonances in the β orientation. The determination of the β-orientation of H-15 resonating at δ 2.96 in the ε-lactone ring was also consistent with the proposed stereochemistry on the basis of observed NOE responses with the H-14β proton. Also, the methyl substituent attached to C-15 (δ 1.32) failed to exhibit an NOE response correlating it with 14β, thus confirming the orientation of the Me-15 substituent in the α orientation. Examination of a Dreiding model reveals that, like in the asbestinins, the cyclohexane structural unit in **1** is locked in a boat conformation.[23] Therefore, if the Me-11 substituent, resonating at δ 1.29, were located in a flagpole (axial) position it would fail to exhibit an NOE response correlating it with H-10α and a strong NOE response with H-14β would be expected. The Me-20 group, however, failed to exhibit an NOE with H-14β but produced instead strong NOE responses which correlated it with H-9 and H-10. Although the NOE to H-9 would be more consistent with a β configuration for the Me-20 group, it does not provide reliable information about the stereochemical identity at C-11 (an NOE between H-9 and Me-20 would be expected in both C-11 α and β epimers). A weak NOE response between Me-20 and the upfield H-19' proton also supports the orientation of the former in the α-orientation. These NOE responses established the orientation of this key resonance in the α orientation (equatorial). Many of the NOE correlations, which are summarized in Table 2, suggest a very flexible ten-membered ring in briarellin-A. For instance, strong NOE's between H-19 (δ 5.56) and the upfield H-5' resonance (δ 1.94), betweeen H-10 and H-19' (δ 5.28), and those observed between H-6 and Me-18, suggest a ring conformation wherein the C-6 hydroxyl is hydrogen-bonded to the tetrahydrofuran oxygen and where all the atoms connected to C-3, C-4, C-5, C-6, C-7, and C-8 adopt a staggered conformation. Since the ^{1}H and ^{13}C NMR spectra of briarellin-A (**1**) and asbestinin-7 (**2**) are remarkably similar, and since similar NOE's were observed in both compounds, it was concluded that these compounds have the same stereochemistry at all the ring junctures and common chiral centers in their structures. Interestingly, the C-11 stereochemistry in briarellin-A does not compare favorably with that found in all the eunicellin-based compounds isolated from South Pacific *Briareum* or *Solenopodium* spp.[20,21] This could be confirmed easily by virtue of the downfield shift of the C-11 resonance in the ^{13}C NMR spectrum of **1**. In fact, the α configuration is assigned to Me-20 in briarellins A-D (**1**, **3**, **5**, and **6**) since the C-11 carbon chemical shifts, 80.5-85.0 ppm, are distinctly different from those observed in South Pacific eunicellins having the opposite configuration at that center, i.e., 70.3-73.2 ppm.[20,21,24]

Compound **3** (briarellin-B) shared many spectral features in common with compound **1**. Its infrared spectrum indicated the presence of two ester (1732 and 1715 cm^{-1}) functionalities and contained a broad

absorption for hydroxyl groups (3465 cm^{-1}). A molecular formula of $C_{28}H_{44}O_7$, established for this compound by high-resolution EI mass spectrometry, was supported by ^1H and ^{13}C NMR data (Table 1) indicating that **3** was an isomer of **1**. Comparison of the ^1H and ^{13}C NMR spectra of briarellins -A (**1**) and -B (**3**) revealed that the major differences were associated with a change in **3** in its relative configuration at C-6. A broad signal at δ 4.18 (1H, br m), assigned to an allylic α-hydroxyl proton, was correlated in the ^{13}C NMR spectrum to a carbon resonance at δ 72.0 (d). The stereochemistry at C-6 in **3** is based on the chemical shift difference of the C-6 carbon (δ 72.0) and the H-6 resonance (δ 4.18) which appear shifted downfield to 82.9 and 4.67 ppm, respectively, in **1**. A similar empirical relationship between the C-6 methine carbon chemical shift and the H-6 proton chemical shift with the α or β configuration of the allylic hydroxyl group at C-6 has been observed for related compounds in the asbestinane series[12] [i.e. asbestinin-7 (**2**) and asbestinin-13 (**4**) which were both isolated along with **1** and **3** from the same specimen of *B. asbestinum*]. The remainder of the ^1H and ^{13}C NMR spectra of **3** were virtually superimposable with those of **1**. Consequently, it was assumed that the rest of the structure of **3** was the same as in **1**. This was confirmed by ^1H-^{13}C correlations from HETCOR and selective INEPT experiments. Except for C-6, the relative stereochemistry of briarellin-B (**3**), determined by a PSNOESY experiment (Table 2), was also found to be identical with that of **1**. NOE intereactions that were not seen in compound **3**, but were detected in **1**, were those between the proton at C-6 with H-4 and Me-18. This, presumably, may be caused by the inability of the α-hydroxyl group at C-6 to hydrogen-bond to the tetrahydrofuran oxygen atom suggesting that the section of the 10-membered ring bearing the exocyclic double bond is now folded downward relative to the axial (β) ring juncture methyl (Me-18).

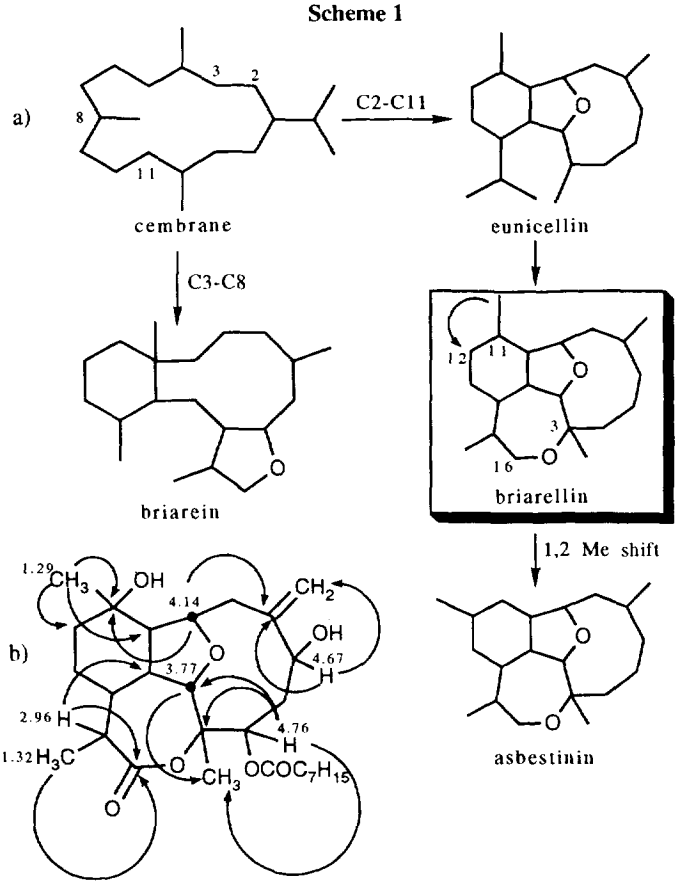
Analysis of the spectral data for briarellin-C (**5**) established a molecular formula of $C_{32}H_{50}O_8$. Thus, compound **5** possessed a mass spectral molecular ion which was 70 amu's larger than that of **3** the difference being consistent with replacement of a hydrogen in **3** with a butyroxy group. The ^1H and ^{13}C NMR spectra indicated the presence of a butyrate ester, a caprylate ester, and one proton exchangeable with CD_3OD. Fragment ions corresponding to sequential losses of butyric acid (*m/z* = 474.29710 for $C_{28}H_{42}O_6$) and caprylic acid (*m/z* = 418.23574 for $C_{24}H_{34}O_6$) from the molecular ion were evident. The ^1H NMR spectrum of **5** was quite similar to that of **3** suggesting that these two compounds possessed the same type of substituted eunicellin-based skeleton. The similarity, however, was not extended to the H-6 signal which had now shifted from δ 4.18 (1H, br m) in **3** to δ 5.26 (1H, dd, J = 5.1, 9.6 Hz) in **5**. A small allylic coupling was observed between H-6 and each of the H-19 exomethylene protons. The ^1H and ^{13}C NMR chemical shift assignments are based on data from ^1H-^{13}C correlation experiments (CSCMBB, J ≅ 140 Hz). The location of each of the aliphatic ester groups was assigned definitively from chemical evidence and also from data provided by a selective INEPT experiment. Thus, butyrylation of **3** with butyric anhydride/pyridine after 24 h at 25°C gave a reaction product indistinguishable from **5** with regard to IR, NMR (^1H and ^{13}C), MS and TLC retention time. Through INAPT experiments (J ≅ 6 Hz) it was possible to correlate each ester carbonyl with its neighboring oxymethine proton. The signal at δ 172.9 (s) was coupled with the oxymethine signal at δ 5.26 and was consequently assigned as the butyrate carbonyl; the resonance at δ 173.0 (s) was assigned as the caprylate carbonyl due to a correlation with the oxymethine signal at δ 4.80. Finally, placement of the Me-20 at C-11 of the cyclohexane ring was deduced from the coupling observed between the quaternary methyl protons at δ 1.28 (3H, s) and the tertiary carbinol carbon at δ 80.6 (s). Additional key H/C correlations for confirming the skeleton in the cyclohexane region of **5** were those observed between the signal at δ 1.28 (Me-20) and the carbon resonances at δ 47.5 (d, C-10) and 30.2 (t, C-12).

Table 2. Selected NOE Data for Briarellins A-D[a]

atom	Briarellin-A (1)	Briarellin-B (3)	Briarellin-C (5)	Briarellin-D (6)
1	H-4, H-10, H-17	H-4, H-10, H-17	H-4, H-10, H-17	H10, H17
2	H-14, H-18	H-14, H-18	H-14, H-18	H-14
4	H-1, H-6, H-10	H-1, H-10	H-1, H-10	
6	H-4, H-10, H-18	H-5, H-8	H-8, H-18	H-18
9	H-20	H-8, H-20	H-8, H-20	H-20
10	H-1, H-4, H-6, H-19', H-20	H-1, H-4, H-19', H-20	H-1, H-4, H-19', H-20	H-1, H-20
14	H-2, H13, H-15	H-2, H13, H-15	H-2, H13, H-15	H-2, H-15
15	H-14	H-14	H-14	H-14
17	H-1, H-13'	H-1, H-13'	H-1, H-13'	H-1
18	H-2, H-5', H-6	H-2, H-5'	H-2, H-5', H-6	H-6
19	H-5'	H-5'	H-5'	H-5'
19'	H-8', H-10, H-20	H-8', H-10, H-20	H-8', H-10	H-8'
20	H-9, H-10, H-19'	H-9, H-10, H-19'	H-9, H-10	H-9, H-10

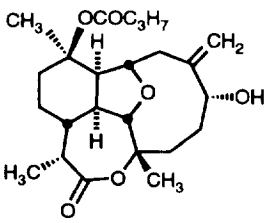
[a] Spectra were recorded at room temperature in $CDCl_3$ solutions.

Scheme 1

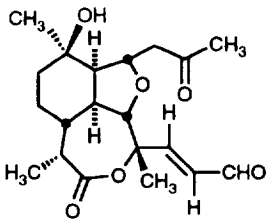


Scheme 1. a) The proposed biosynthetic relationship between the cembrane skeleton and the asbestinin skeleton suggested by Faulkner *et. al.* has been expanded to include the briarellins as logical biosynthetic intermediates formed from a eunicellin carbon skeleton. The discovery of the briarellins most likely suggests that the biosynthesis of the asbestinins involves cyclization (via lactone formation between C-3 and C-16) of the eunicellin carbon skeleton prior to methyl migration. b) Selected long-range ^1H-^{13}C correlations for briarellin-A (**1**) established by a series of selective INEPT ($J \cong 6$ Hz) experiments.

Briarellin-D (**6**) had the molecular formula $C_{24}H_{36}O_6$. The ^1H NMR spectrum again indicated the presence of an allylic α-hydroxy proton [δ 4.29 (1H, dd, J = 4.8, 7.8 Hz)] and a butyrate group [δ 0.91 (3H, t, J = 7.2 Hz), 1.54 (m, 2H), and 2.08 (2H, t, J = 7.2 Hz)]. The infrared spectrum contained a hydroxyl band (3443 cm^{-1}) and two ester bands at 1730 and 1714 cm^{-1}. The ^{13}C NMR spectrum contained two ester signals at δ 176.1 (s) and 172.4 (s), olefinic carbon signals at δ 147.9 (s) and 117.3 (t), and only five signals for carbon atoms bearing oxygen at δ 91.1 (d), 84.9 (s), 82.4 (d), 81.0 (s), and 72.6 (d). The downfield shift experienced by the quaternary ^{13}C resonance at δ 84.9 ascribed to C-11 (see Table 1), coupled with the absence of a downfield signal that could be assigned to a butyroxy proton, placed the butyrate ester group at C-11. Decoupling experiments established that **6** has a methylene group at C-4 rather than an oxygenated methine as in **1**, **3**, and **5**. The subtle shifts experienced by some of the ^{13}C resonances assigned to carbon atoms near C-4 (i.e. C-3, C-5, and Me-18) agree with C-4 being deoxygenated in **6** (see Table 1). Thus, briarellin-D (**6**) is 11-butyroxy-4-decapryloxybriarellin-B. Several minor metabolites of the asbestinin class with a methylene at C-4 (the 4-deoxyasbestinin series) were also isolated from this specimen of *B. asbestinum*.[12] Since the remaining ^1H and ^{13}C NMR signals were similar to those observed for the other compounds in the briarellin series, we assigned structure **6** to briarellin-D.



6



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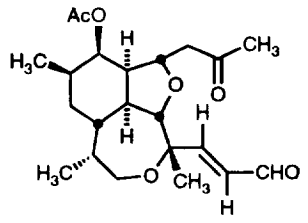


8

The low-resolution FAB^+ mass spectrum of the UV active metabolite *seco*-briarellin (**7**) [λ_{max} (MeOH) 222 nm (ε 4,570)] agreed with a molecular formula for this compound of $C_{20}H_{28}O_6$ (found *m/z* 387 $[M+Na]^+$, calcd 387], which was supported by ^1H and ^{13}C NMR data. The high-resolution EI mass spectrum gave the highest mass peak at *m/z* 346.17750 for $C_{20}H_{26}O_5$, which reflects a fragmentation of $[M-H_2O]^+$ from the actual molecular composition of $C_{20}H_{28}O_6$. The HREIMS showed the base peak at *m/z* 265.14396 for $C_{15}H_{21}O_4$ reflecting a fragmentation of $[M-C_5H_7O_2]^+$ from the molecular ion. The base peak in turn fragments to another ion peak at *m/z* 207.10187 for $C_{12}H_{15}O_3$ representing the loss of one molecule of acetone. Absorptions in the infrared indicated the presence of ester (1742 cm^{-1}), ketone (1711 cm^{-1}), and α,β-unsaturated carbonyl (1688 cm^{-1}) functionalities. The ^1H NMR spectrum of compound **7** contained signals for two sp^2 methine protons [δ 6.84 (1H, d, J = 15.9 Hz) and 6.34 (1H, dd, J = 7.8, 15.6 Hz)], three oxymethine protons: one sp^2 [δ 9.58 (1H, d, J = 7.8 Hz)] and two sp^3 [δ 4.04 (1H, m) and 3.77 (1H, d, J = 6.0 Hz)], and four methyl groups [δ 2.18 (3H, s), 1.38 (3H, d, J = 7.5 Hz), 1.25 (3H, s), and 1.24 (3H, s)]. The ^{13}C NMR spectrum showed the presence of twenty carbon atoms three of which are carbonyl signals at δ 206.4 (s), 193.4 (d), and 175.4 (s), two are olefinic carbons at δ 160.7 (d) and 130.3 (d), and four represent signals for carbon atoms bearing oxygen at δ 88.7 (d), 80.0 (s), 77.6 (d), and 74.1 (s). The ^{13}C NMR resonances at δ 206.4, 193.4, 160.7 and 130.3 supported the presence of a ketone and α,β-unsaturated aldehyde groups and the signal at δ 175.4 was indicative of an ε-lactone

functionality. These three carbonyl groups and the carbon-carbon double bond accounted for four of the seven double-bond equivalents required by the molecular formula. Compound **7**, therefore, contained three rings in its structure. Comparison of the ^1H and ^{13}C NMR spectra of **7** with those of **1**, **3**, **5**, and **6** (see Table 1) confirmed many structural similarities among these compounds and also suggested the presence of some features unique to **7**. For instance, while the cyclohexane, tetrahydrofuran and ε-lactone ring moieties appeared to be intact in **7** on the basis of similar IR, MS, and NMR data, the remaining spectroscopic features indicated that the C6,7 bond of the ten-membered ring had been ruptured oxidatively to produce an aldehyde and ketone, respectively. Also unique to **7** was the aldehyde proton signal at δ 9.58 (1H, d, J = 7.8 Hz) which was shown by COSY to be coupled only to the olefinic methine proton at δ 6.34 (1H, dd, J = 7.8, 15.6 Hz) which in turn was likewise shown by COSY to be coupled to the remaining olefinic proton at δ 6.84 (1H, d, J = 15.9 Hz). The large coupling (15.9 Hz) observed between H-4 (δ 6.84) and H-5 (δ 6.34) suggested a *trans* orientation of these two protons. The presence of an α,β-unsaturated aldehyde functionality in **7**, which may arise by β elimination of caprylic acid from a suitable intermediate, was also supported by the UV absorption at λ_{max} 222 nm. The loss of acetone observed in the HREIMS spectrum of **7** and the ^1H NMR signal at δ 2.18 (3H, s) combined with resonances in the ^{13}C NMR spectrum at δ 206.4 (s) and 31.3 (q), indicated the presence in this compound of a methyl ketone moiety, a feature not found in any previously reported eunicellin-type diterpene. Moreover, comparison of the NMR (^1H and ^{13}C), NOESY, and MS spectra of *seco*-briarellin (**7**) with those of known *seco*-asbestinin (**8**), a rare metabolite which co-occurs with briarellins A-D and **7** in *B. asbestinum*,[11] confirmed many structural similarities among these compounds. Since the ^1H and ^{13}C NMR spectra of **7** and **8** are remarkably similar, and since similar NOE's were observed in both compounds, it was concluded that these compounds have the same stereochemistry at all the ring junctures and common chiral centers in their structures. The C-11 stereochemistry in *seco*-briarellin (**7**) compared favorably with that found in briarellins A-D on the basis of ^{13}C NMR chemical shift and NOE arguments. Compound **7**, with these unprecedented structural features, thus comprises a new group of ether-cyclized eunicellins possessing a novel carbon skeleton named the *seco*-eunicellins.

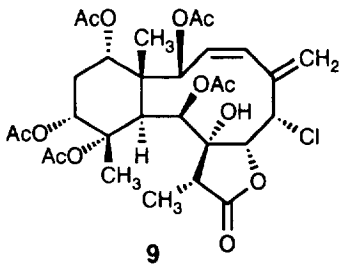
CONCLUSIONS

The diterpenes from *B. asbestinum* (briarellins) possess certain structural features so far unreported in the literature for compounds of this type. Briarellins -A (**1**), -B(**3**), -C (**5**), -D (**6**) and *seco*-briarellin (**7**), have a 11*R** tertiary carbinol moiety in the six-membered ring while eunicellins of this type isolated from Pacific *Briareum* (or *Solenopodium*) sp. octocorals have the opposite relative configuration at C-11. All of the briarellins, which possess a C-3 to C-16 ε-lactone bridge, thus comprise a new group of lactone-cyclized eunicellins. The isolation of all three skeletal classes, asbestinins, briareins, and eunicellins from the same specimen of *B. asbestinum* provides additional circumstantial support that these ring systems might indeed be synthesized *in vivo* by different cyclizations of the cembrane ring skeleton. Our results suggest that the biosynthesis of the asbestinins most likely involves the cyclization of a cembrane to an eunicellin followed by lactone formation to a briarellin followed by methyl migration (Scheme 1). As a practical extension of this study, an important finding would be to demonstrate that a cembranoid metabolite co-occurs with the asbestinin, briarein and eunicellin-type diterpenes. This would be consistent with a biosynthetic pathway wherein a cembrene intermediate serves as a precursor to these diterpene skeletons. Although a cembrane metabolite has been found in the Australian gorgonian *Briareum*

steckii,[21] a species not found in Caribbean waters, the fact that the majority of the Caribbean cembrane-producing gorgonians are taxonomically within the same family Plexauridae could explain why the isolation of cembranoids from a Caribbean *Briareum* species (which taxonomically belongs to a different family, namely, Briareidae) continues to be an elusive goal.

EXPERIMENTAL

General Experimental Procedures.- Infrared spectra were recorded on a Nicolet 600 FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a General Electric Multinuclear QE-300; ^1H NMR chemical shifts are recorded with respect to the residual $CHCl_3$ signal (7.26 ppm) and ^{13}C NMR chemical shifts are reported in ppm relative to $CDCl_3$ (77.0 ppm). Optical rotations were determined on a Perkin-Elmer Polarimeter Model 243B. HREIMS and LRFABMS were determined in the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln. Column chromatography was performed on Analtech Si gel (35-75 mesh) and TLC analyses were carried out using Analtech glass packed precoated Si gel plates. All solvents used were either spectral grade or were distilled from glass prior to use.



9

Collection, Extraction, and Isolation. Minced and freeze-dried specimens of *B. asbestinum* (4.01 Kg) collected at Mona Island, Puerto Rico were extracted exhaustively with $CHCl_3$-MeOH (1:1) (7 x 1L) and after filtration the crude extract was evaporated under vacuum to yield a residue (300.74 g) that was partitioned against H_2O with hexane and $CHCl_3$ (6 x 1L). The hexane extract was subsequently filtered and the filtrate was concentrated *in vacuo* to yield 208.38 g of a dark green oily residue. The toluene soluble portion (156.92 g) was fractionated by size exclusion chromatography on a Bio-Beads SX-2 column. The combined diterpene-containing fractions (TLC guided) were concentrated to an orange oil (41.40 g) and chromatographed over a Si gel column (800 g) with 10% EtOAc in hexane. The less polar portion of the lipids was fractionated roughly into fractions A through J on the basis of TLC analyses. Subsequent purification of fractions A-I led to the isolation of 18 known diterpenoids of the asbestinane class including asbestinin-7 (**2**), asbestinin-13 (**4**), and the rare *seco*-asbestinin (**8**).[11,12] Fraction J (*ca* 11.34 g) was fractionated over a Si gel column (350 g) with 1% MeOH in $CHCl_3$ into 13 fractions (1-13). Sub-fraction 4 (*ca* 224 mg) was fractionated via HPLC [ODS Si gel with 30% H_2O in MeOH] to yield pure briarellin-C (**5**) (43.2 mg, 0.0010% dry wt). Briarellin-B (**3**) (22.1 mg, 0.0005% dry wt) was isolated from sub-fraction 5 (*ca* 2.48 g) via reversed-phase HPLC using a Zorbax C-8 Si gel column [MeOH-H_2O (70:30)]. Sub-fraction 7 in turn (*ca* 885 mg) was subjected to successive chromatographic purifications [first by HPLC using a Zorbax C-8 Si gel with MeOH-H_2O (85:15) followed by a Si gel column using 45% EtOAc in hexane as eluent] to yield 43.2 mg (0.0010% dry wt) of pure briarellin-A (**1**) and 3.1 mg (0.00007%) of briarellin-D (**6**). Finally, *seco*-briarellin (**7**) (*ca* 5.0 mg; 0.00012%) was obtained from sub-fraction 13 after

HPLC [Zorbax C-8 Si gel [MeOH-H_20 (80:20)] followed by column chromatography (Si gel using 40% EtOAc-hexane). Briarein A (**9**), which was isolated from the $CHCl_3$ extract of *B. asbestinum* after repeated chromatography, was identified by comparison of its NMR (^1H and ^{13}C), IR, UV, and MS data with values reported in the literature.[5]

Briarellin-A (1)- Colorless oil: $[\alpha]^{28}_D$ -25.24° (*c* = 14.9, $CHCl_3$); IR (neat) 3413, 3076, 1738, 1714 cm^{-1}; HREIMS $[M]^+$ 492.30779, $C_{28}H_{44}O_7$ (Δ -0.8 mmu), $[M-H_2O]^+$ 474.29743, $C_{28}H_{42}O_6$ (Δ -0.6 mmu), $[M-C_8H_{16}O_2]^+$ 348.19263, $C_{20}H_{28}O_5$ (Δ -1.0 mmu), $[M-H_2O-C_8H_{16}O_2]^+$ 330.18217, $C_{20}H_{26}O_4$ (Δ -0.9 mmu), $[M-H_2O-C_8H_{16}O_2-H_2O]^+$ 312.17163, $C_{20}H_{24}O_3$ (Δ -0.9 mmu); ^1H and ^{13}C NMR, see Table 1.

Briarellin-B (3)- Colorless oil: $[\alpha]^{30}_D$ -7.89° (*c* = 5.70, $CHCl_3$); IR (neat) 3465, 3079, 1732, 1715 cm^{-1}; HREIMS $[M]^+$ 492.30982, $C_{28}H_{44}O_7$ (Δ +1.1 mmu), $[M-H_2O]^+$ 474.29691, $C_{28}H_{42}O_6$ (Δ +1.2 mmu), $[M-H_2O-C_8H_{16}O_2]^+$ 330.18220, $C_{20}H_{26}O_4$ (Δ -0.9 mmu), $[M-H_2O-C_8H_{16}O_2-H_2O]^+$ 312.17035, $C_{20}H_{24}O_3$ (Δ +2.1 mmu); ^1H and ^{13}C NMR, see Table 1.

Briarellin-C (5)- Colorless oil: $[\alpha]^{28}_D$ -29.75° (*c* = 11.8, $CHCl_3$); IR (neat) 3489, 3083, 1730, 1714 cm^{-1}; HREIMS $[M]^+$ 562.35298, $C_{32}H_{50}O_8$ (Δ +2.4 mmu), $[M-H_2O]^+$ 544.33997, $C_{32}H_{48}O_7$ (Δ 0.0 mmu), $[M-C_4H_8O_2]^+$ 474.29710, $C_{28}H_{42}O_6$ (Δ -1.0 mmu), $[M-H_2O-C_4H_8O_2]^+$ 456.28696, $C_{28}H_{40}O_5$ (Δ -0.5 mmu), $[M-C_8H_{16}O_2]^+$ 418.23574, $C_{24}H_{34}O_6$ (Δ +0.2 mmu), $[M-C_4H_8O_2-C_8H_{16}O_2]^+$ 330.18320, $C_{20}H_{26}O_4$ (Δ +0.1 mmu), $[M-H_2O-C_4H_8O_2-C_8H_{16}O_2]^+$ 312.17216, $C_{20}H_{24}O_3$ (Δ -0.3 mmu); ^1H and ^{13}C NMR, see Table 1.

Briarellin-D (6)- Colorless oil: $[\alpha]^{30}_D$ -17.89° (*c* = 0.33, $CHCl_3$); IR (neat) 3443, 3082, 1730, 1714 cm^{-1}; HREIMS $[M-H_2O]^+$ 402.25237, $C_{24}H_{34}O_5$ (Δ +1.2 mmu), $[M-C_4H_8O_2]^+$ 332.19862, $C_{20}H_{28}O_4$ (Δ -0.1 mmu), $[M-H_2O-C_4H_8O_2]^+$ 314.18843, $C_{20}H_{26}O_3$ (Δ +0.2 mmu); LRFABMS $[M + Na]^+$ 443, $C_{24}H_{36}O_6Na$; ^1H and ^{13}C NMR, see Table 1.

***Seco*-Briarellin (7)**- Colorless oil: $[\alpha]^{26}_D$ -11.49° (*c* = 1.56, $CHCl_3$); IR (neat) 3447, 1742, 1711, 1688 cm^{-1}; HREIMS $[M-H_2O]^+$ 346.17750, $C_{20}H_{26}O_5$ (Δ -0.5 mmu), $[M-H_2O-C_2HO]^+$ 305.17512, $C_{18}H_{25}O_3$ (Δ -0.1 mmu), $[M-C_5H_7O_2]^+$ 265.14369, $C_{15}H_{21}O_4$ (Δ 0.0 mmu), $[M-C_5H_7O_2-C_3H_6O]^+$ 207.10187, $C_{12}H_{15}O_3$ (Δ -0.2 mmu); LRFABMS $[M + Na]^+$ 387, $C_{20}H_{28}O_6Na$; UV (MeOH) λ_{max} 222 (log ε 3.66); ^1H and ^{13}C NMR, see Table 1.

Butyrylation of Briarellin-B (3).- A solution of briarellin-B (15 mg, 0.030 mmol) in a mixture of butyric anhydride (0.5 mL) and pyridine (1.0 mL) was stirred at 25°C for 24 h. Excess reagents were removed by rotaevaporation *in vacuo* and the residue obtained was partitioned against ether and water. The combined ether extract was dried over Na_2SO_4 and evaporated to give 14.3 mg of the crude butyrate. The NMR (^1H and ^{13}C), MS, IR and COSY spectra of the product obtained after purification by Si gel column chromatography were indistinguishable from those recorded for briarellin-C (**5**).

Biological Activity- Briarellin-A (**1**), which was the only briarellin assessed for pharmacological activity in the present study, displayed modest *in vitro* cytotoxicity against HeLa cells with an estimated IC_{50} = 20.0 μg/mL.

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24. Shortly after we submitted this manuscript for publication a group of five additional eunicellins was isolated by us from the same specimens of *B. asbestinum* . These compounds, named briarellins E-I, have the same relative stereochemistry at C-11 found in South Pacific *Briareum* or *Solenopodium* spp. The β configuration was assigned to the Me-20 group in these compounds since the C-11 carbon chemical shifts, 71.1-72.2 ppm, are virtually identical to those of Pacific eunicellins. As expected, very strong NOE's were observed between H-14 and Me-20 confirming the orientation of the latter group in the β orientation.

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