Briarellins J−P and Polyanthellin A: New Eunicellin-Based Diterpenes from the Gorgonian Coral *Briareum polyanthes* and Their Antimalarial Activity

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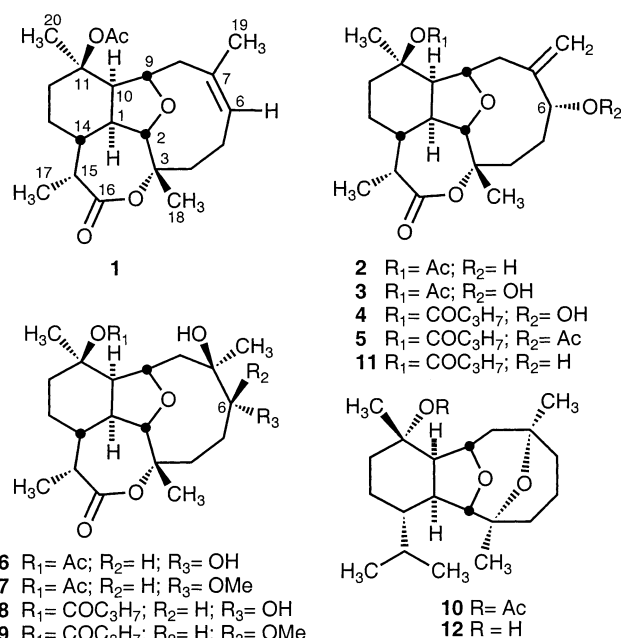
A new chemical study of the hexane extract of the gorgonian *Briareum polyanthes* collected in Puerto Rico afforded 10 new diterpenes of the eunicellin class, briarellins **1**−**9** and polyanthellin A (**10**), along with the known diterpene briarellin D (**11**). The structures and relative stereochemistry of metabolites **1**−**10** were assigned on the basis of NMR studies, chemical methods, and comparisons to the spectral properties of **11**. A reassessment of prior structural assignment for briarellin A and two known sclerophytin-type diterpenes, **13** and **14**, is proposed. Antimalarial tests on **1**−**6** and **8**−**12** indicated that they were active against *Plasmodium falciparum.*

The considerable structural diversity of the terpene metabolites produced by Caribbean gorgonian octocorals is widely recognized by both natural products and synthetic chemists alike. Specifically, specimens from this region belonging to the genus *Briareum* (syn: *Solenopodium*, order Gorgonacea, phylum Cnidaria, family Briareidae) have been the subject of several chemical investigations which thus far have led to the isolation of two related classes of 2,11-cyclized cembranoids.[1] Of these, the asbestinins are the most abundant, whereas the eunicellins (briarellins) constitute a significantly smaller group.[2,3] Briarellin-type diterpenoids have also been isolated from the Taiwanese soft coral *Pachyclavularia violacea.*[4] The unique and complex architecture of these two groups of natural products has made them irresistible targets for total synthesis.[5] Recently, we have focused our attention on the gorgonian *Briareum polyanthes* (Duchassaing & Michelotti) collected on the southwest coast of Puerto Rico. Two previous investigations of this gorgonian from Bermudian and Puerto Rican waters had led largely to complex mixtures of chlorinated and nonchlorinated 3,8-cyclized cembranoids known as briareins (briantheins and briareolides).[6,7] From this soft coral, we now wish to report the isolation and structural elucidation of 10 new eunicellin-type diterpenes (also known as cladiellins and sclerophytins), briarellins J−P (**1**−**9**) and polyanthellin A (**10**). The known compound briarellin D (**11**), previously isolated by us from the gorgonian octocoral *Briareum asbestinum*, was also isolated in the course of this investigation.[3a] This is the first time that diterpenes based on this type of carbon skeleton are reported in *B. polyanthes*.

Results and Discussion

Healthy and robust specimens of *B. polyanthes* were collected by hand using scuba at −10 m in Cabo Rojo, Puerto Rico. The animal specimens were frozen, freeze-dried, cut in small pieces, and homogenized exhaustively using a mixture of $CHCl_3$−MeOH (1:1) to obtain, after in vacuo concentration, an extract that was fractionated using

1

2 R1= Ac; R2= H
3 R1= Ac; R2= OH
4 R1= COC3H7; R2= OH
5 R1= COC3H7; R2= Ac
11 R1= COC3H7; R2= H

6 R1= Ac; R2= H; R3= OH
7 R1= Ac; R2= H; R3= OMe
8 R1= COC3H7; R2= H; R3= OH
9 R1= COC3H7; R2= H; R3= OMe

10 R= Ac
12 R = H

our standard partitioning procedure into several fractions of differing polarity.[8] The hexane fraction was purified by size-exclusion chromatography on a Bio-Beads SX-2 column with toluene followed by repeated chromatography on Si gel flash columns to give pure compounds **1**−**11**. Briarellin D (**11**), a minor component isolated from this gorgonian, was identified from chemical and spectroscopic data and by comparison with literature data.[3a] The spectral properties of compound **11** greatly facilitated the characterization of the new derivatives.

The molecular formula of $C_{22}H_{32}O_5$ for **1**, named briarellin J, was proposed from the LRFABMS pseudomolecular ion at *m/z* 383 [M + Li]⁺ and was verified by subsequent HRFABMS (see Experimental Section). The diterpene structure of compound **1** was directly inferred from its ¹³C NMR spectrum, where it was possible to account for all 20 carbons after subtraction of the two carbons ascribed to an acetate group (Table 1). The briarellin constitution of this diterpene was initially inferred from the oxygenated carbon atoms at δ_C 176.2 (s) and 85.4 (s) in its ¹³C NMR

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Table 1. NMR Spectral Data for Briarellins J−M in CDCl$_3$ [δ_H, mult, J (Hz); δ_C (mult)]^a

	briarellin J (**1**)^b		briarellin K (**2**)^c		briarellin L (**5**)^b		briarellin M (**6**)^b	
atom	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	2.66, br s	45.7 (d)	2.52, m	44.9 (d)	2.53, br d, 11.0	44.9 (d)	2.68, br d, 9.5	44.5 (d)
2	3.98, br m	91.9 (d)^d	4.12, d, 3.3	91.0 (d)	4.09, d, 3.3	90.6 (d)	3.69, br s	94.9 (d)^d
3		85.4 (s)		85.2 (s)		84.8 (s)		86.4 (s)
4α	2.06, m	34.4 (t)	1.53, m	28.7 (t)	1.58, m	28.3 (t)	2.50, m	35.2 (t)^d
4β	1.82, m		1.97, m		1.58, m		1.86, m	
5α	1.86, m	22.9 (t)	1.71, m	32.7 (t)	1.80, m	30.1 (t)	1.35, m	30.5 (t)
5β	2.32, m		2.18, m		2.14, m		1.65, m	
6	5.64, br t, 8.6	129.7 (d)^d	4.28, dd, 4.9, 9.6	72.6 (d)	5.15, dd, 5.2, 11.0	74.9 (d)	4.49, br d, 6.9	78.8 (d)^d
7		131.5 (s)^d		147.9 (s)		144.5 (s)		76.3 (s)
8α	2.16, dd, 7.4, 14.1	38.5 (t)	2.23, dd, 1.5,13.7	41.3 (t)	2.18, br d, 13.8	41.5 (t)	1.62, dd, 3.3, 14.8	46.6 (t)
8β	2.48, br d, 14.1		2.78, dd, 4.5, 13.7		3.09, dd, 5.1, 13.8		2.10, m	
9	4.02, m	80.6 (d)^d	4.16, ddd, 1.4, 4.6, 8.4	82.5 (d)	4.13, dd, 4.5, 8.6	82.2 (d)	4.27, dt, 3.7, 11.6	78.6 (d)
10	2.67, br s	50.2 (d)^d	2.86, m	47.8 (d)	2.78, dd, 8.9, 11.0	48.0 (d)	2.49, dd, 3.4, 9.5	54.5 (d)
11		81.4 (s)		81.0 (s)		80.9 (s)		81.7 (s)
12α	2.03, m	30.2 (t)	2.02, m	30.4 (t)	2.02, m	30.3 (t)	2.03, m	30.0 (t)
12β	2.03, m		2.02, m		2.02, m		2.03, m	
13α	1.87, m	16.8 (t)	1.86, m	16.8 (t)	1.74, m	16.8 (t)	1.85, m	16.9 (t)
13β	1.87, m		1.75, m		1.90, m		1.85, m	
14	1.67, m	37.4 (d)	1.64, m	37.0 (d)	1.65, m	36.9 (d)	1.71, m	38.2 (d)^d
15	2.94, dq, 4.7, 7.6	46.2 (d)	2.86, m	45.9 (d)	2.87, dq, 5.2, 7.6	45.8 (d)	2.98, dq, 4.5, 7.5	46.3 (d)
16		176.2 (s)		176.1 (s)		176.2 (s)		176.2 (s)
17	1.36, d, 7.6	17.7 (q)	1.36, d, 7.6	17.5 (q)	1.35, d, 7.6	17.4 (q)	1.35, d, 7.5	17.7 (q)
18	1.58, s	23.2 (q)	1.61, s	20.7 (q)	1.63, s	20.5 (q)	1.42, s	23.3 (q)
19α	1.76, br s	26.5 (q)^d	5.09, br s	117.2 (t)	5.08, br s	118.6 (t)	1.16, s	22.5 (q)
19β			5.41, br s		5.32, br s			
20	1.33, s	28.7 (q)	1.31, s	28.9 (q)	1.29, s	28.9 (q)	1.32, s	28.6 (q)
21		169.8 (s)		169.8 (s)		170.7 (s)		169.4 (s)
22	1.99, s	22.4 (q)	1.90, s	22.3 (q)	1.98, s	21.3 (q)	2.08, s	22.3 (q)
23						172.4 (s)		
24					2.11, t, 7.3	37.4 (t)		
25					1.52, m, 7.3	18.4 (t)		
26					0.89, t, 7.4	13.6 (q)		

^{a} Chemical shift values are in ppm relative to TMS. Spectra were recorded at 25°C. ^{13}C NMR multiplicities were obtained from APT experiments. ^{b} ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR data. ^{c} ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data. ^{d} Low-intensity broad resonance line.

spectrum, which are characteristic of the seven-membered lactone ring formed between C-3 and C-16 in the briarellin series.[3]

The planar structure of this new briarellin was defined by ^{1}H NMR, ^{13}C NMR, DEPT, HMQC, and HMBC experiments. Thus, the presence of an acetate group in **1** was suggested by the carbon resonances at δ_C 169.8 (s) and 22.4 (q), and it was confirmed by the HMQC correlation of the latter resonance to the three-proton resonance at δ_H 1.99 (s). Two oxycarbonyl groups linked to tertiary carbons were deduced by the ^{13}C NMR signals at δ_C 85.4 (s) and 81.4 (s), whereas the signals at δ_C 91.9 (d) and 80.6 (d), which correlated by HMQC to two oxymethine protons at δ_H 3.98 (br m) and 4.02 (m), respectively, allowed us to identify the typical tetrahydrofuran ring. Finally, the ^{13}C NMR signals at δ_C 131.5 (s) and 129.7 (d), the last of which correlated by HMQC to an olefinic proton at δ_H 5.64 (br t, J = 8.6 Hz), permitted the identification of a trisubstituted olefin.

HMBC experiments established the connectivity of the isolated proton spin systems deduced from ^{1}H−^{1}H COSY.[9] The comparison of these data to those of other briarellin diterpenes reported in the literature indicated that **1** had a structure similar to that of briarellin D (**11**), also isolated from this specimen of *B. polyanthes*, but differed by the presence of an acetate group at C-11 (instead of a butyrate ester group), the absence of a hydroxyl group at C-6, and a carbon−carbon double bond which in **1** appears shifted to an endocyclic position between C-6,7.

The relative stereochemistry of compound **1** was determined to be comparable to that of **11** by NOESY data.[10] The *Z* geometry of the double bond was deduced from the

^{13}C NMR chemical shifts of the allylic carbon atoms (C-5, C-8, and C-19), as well as by comparison with briarellin H, a closely related analogue obtained from *B. asbestinum*, which displays the opposite *E* geometry.[3b] Thus, the structure of briarellin J (**1**) was unambiguously established.

Briarellin K (**2**) was isolated as a colorless oil whose molecular formula C$_{22}$H$_{32}$O$_6$ was established from HREIMS showing the molecular ion at *m/z* 392.2175 (confirmed by HRFABMS of the [M + Li]$^+$ pseudomolecular ion at *m/z* 399.2366). The structure of **2** was completely solved by a combination of 1D and 2D NMR methods and by comparison with the NMR data of **11** (Table 1). The ^{13}C NMR spectrum of **2** displayed 22 carbon resonances, two of them corresponding to carbonyl groups at δ_C 176.1 and 169.8 characteristic of a seven-membered lactone and ester group, respectively. The ester group was identified as an acetate by the methyl signal observed in the ^{13}C and ^{1}H NMR spectra at δ_C 22.3 (q) and δ_H 1.90 (s, 3H), respectively. The ^{1}H and ^{13}C NMR data of **2** were nearly identical with those of **11** except that the signals corresponding to the propyl group of the butyrate ester in **11** were missing, while an acetate methyl signal was observed in the NMR data of **2**. Since the ^{1}H and ^{13}C NMR spectra of compounds **2** and **11** were virtually identical, and similar NOEs were observed in both compounds,[11] it was concluded that these compounds have the same stereochemistry at all of the ring junctures and chiral centers. Thus, briarellin K, a likely autoxidation product of briarellin J (**1**), was found to be the 11-acetyl analogue of briarellin D (**11**) with the structure as described by formula **2**.

Compounds **3** and **4** possessed mass spectral molecular ions that were 16 amu's larger than those of **2** and **11**,

respectively. This difference is consistent with replacement of the C-6 hydroxyl in **2** and **11** with a hydroperoxyl group. The most noticeable ^{13}C NMR chemical shift differences between **2** and **3** (and between compounds **4** and **11**) were at C-5 and C-6, the former carbon atom undergoing a moderate upfield shift and the latter experiencing a noticeable downfield shift relative to those in **2** and **11**. The only significant difference in their ^{1}H NMR spectra was the signal associated with H-6, which in **3** and **4** displays a downfield shift relative to those in **2** and **11**, respectively. As predicted on the basis of the similarities in their ^{1}H and ^{13}C NMR data, briarellins **2**, **3**, **4**, and **11** were shown to have identical relative stereochemistry, a conclusion later confirmed by 2D NOE NMR experiments. Thus, briarellins **3** and **4** were determined to be the hydroperoxyl analogues of compounds **2** and **11**, respectively. Interestingly, a side-by-side comparison of the relevant NMR data of briarellins **3** and **4** with those reported for briarellin A (previously isolated by us from a specimen of *B. asbestinum* from Puerto Rico) prompted us to reexamine our original structural assignment for the latter compound.[3a] From these comparisons we now conclude that **16** (not **15**) is the correct structure for briarellin A. Reexamination of the spectral data for briarellin A, in particular the 2D NOESY NMR and LRFABMS spectra (see Experimental Section), supports this revision.

Briarellin L (**5**) was isolated as a colorless oil with a molecular formula of $C_{26}H_{38}O_7$ established by HRFABMS of the [M + Na]$^+$ ion. The difference of 42 mass units in the molecular formula of **5** in relation to that of **11** suggested that the C-6 hydroxyl group in **11** must be acetylated in **5**. This was corroborated by the spectral data (^{1}H and ^{13}C NMR) of **5**, which were very similar to those of **11** but showed the presence of an additional acetate methyl signal at δ_H 1.98 (s, 3H) as well as a noticeable downfield shift for H-6 (from δ_H 4.29 in **11** to δ_H 5.15 in **5**). Because similar NOEs were observed in both compounds,[12] it was concluded that these compounds have the same stereochemistry at all of the chiral centers. Finally, acetylation of **11** yielded a product identical by ^{1}H and ^{13}C NMR with briarellin L, hence confirming that **5** is the acetylated derivative of **11**.

Briarellin M (**6**) was obtained as a colorless oil, [α]^{26}$_D$ −14.5° (*c* 1.0, CHCl$_3$). A molecular formula of $C_{22}H_{34}O_7$ (found *m/z* 433.2214 for the pseudomolecular ion [M + Na]$^+$, calcd 433.2202) was established from HRFABMS. The ^{1}H NMR spectral data of **6**, measured in CDCl$_3$ (Table 1), also revealed the characteristic signals which suggested that **6** could be a *vic*-glycol derivative of **1**.[13] The ^{13}C NMR spectrum of **6** in CDCl$_3$ gave many weak (broadened) signals, several of which were hardly detected over the baseline noise level. These observations, which were also noticed in the ^{13}C NMR spectra of the closely related compounds **7**−**9**, suggested the existence of slowly interconverting conformations for **6** in CDCl$_3$ solution. The ^{13}C NMR spectrum of **6** is similar to that of **1**, except that the signals for the 6,7-double bond disappeared and were replaced by two signals of oxygenated carbons ascribable to the *vic*-glycol system. The assignments of ^{1}H and ^{13}C NMR spectral data of **6** were accomplished by a series of 2D NMR (^{1}H−^{1}H COSY, HMQC, and HMBC) experiments. The proton of the hydroxy-bearing methine appearing at δ_H 4.49 (1H, br d, *J* = 6.9 Hz) was assigned to H-6. A doublet at δ_H 1.35 (3H, d, *J* = 7.5 Hz) and four singlets at δ_H 1.42, 1.16, 1.32, and 2.08 were attributed to H$_3$-17, H$_3$-18, H$_3$-19, H$_3$-20, and protons of an acetoxy methyl, respectively. On the basis of considerations of the molecular

formula, the second hydroxyl group was placed at C-7. The relative configuration of briarellin M was also deduced using a NOESY spectrum, which showed that the relative configuration of **6** is similar to that of metabolite **1**. In addition, H-6 shows NOE response with H-4β, H-5β, and H$_3$-18, but not with H$_3$-19. Thus, H-6 and H$_3$-19 should be placed on the β and α face, respectively.

The HREIMS of briarellin N (**7**), isolated as a colorless oil, showed no molecular ion peak. Instead, fragment ion peaks at *m/z* 406 [M − H$_2$O]$^+$, 364 [M − CH$_3$CO$_2$H]$^+$, and 332 [M − CH$_3$CO$_2$H − MeOH]$^+$ suggested the molecular formula for **7** of $C_{23}H_{36}O_7$. The ^{1}H and ^{13}C NMR spectra of **7** are very similar to those of **6** (see Tables 1 and 2) but showed the presence of an additional methyl group at δ_H 3.32, indicating that **7** must be the 6- or 7-methoxy derivative of **6**. On the other hand, an intense HMBC cross-peak between the methoxyl carbon at δ_C 56.8 (q) and H-6 at δ_H 4.00 (1H, d, *J* = 6.7 Hz) unambiguously positioned the methoxyl moiety at C-6. This was corroborated by a noticeable downfield shift for C-6 (from δ_C 78.8 in **6** to δ_C 89.3 in **7**) in the ^{13}C NMR spectrum. HMBC and NOESY of **7** also gave results similar to those of **6**, suggesting that **7** is simply a 6-methoxy analogue of **6**. A strong NOE correlation was observed for H-6 and H$_3$-18, revealing that these protons are positioned on the same face. On the other hand, the C-19 methyl must be situated on the α face of the molecule, as H$_3$-19 did not show a correlation with H-6.

Briarellin O (**8**) was also isolated as a colorless oil, [α]^{26}$_D$ −24.4° (*c* 1.1, CHCl$_3$). The pseudomolecular ion [M + Na]$^+$ observed in its LRFABMS at *m/z* 461 along with the intense fragment ion peaks in the HREIMS at *m/z* 350 [M − C$_4$H$_8$O$_2$]$^+$, 332 [M − C$_4$H$_8$O$_2$ − H$_2$O]$^+$, and 314 [M − C$_4$H$_8$O$_2$ − 2H$_2$O]$^+$ suggested the molecular formula for **8** of $C_{24}H_{38}O_7$, which was confirmed by HRFABMS of the [M + Na]$^+$ ion at *m/z* 461.2515 (Δ 0.0 mmu). The spectral data (IR, ^{1}H and ^{13}C NMR) of **8** were remarkably similar to those of **6**, except that **8** showed signals corresponding to an 11-butyryloxyl substituent in lieu of an acetoxyl group. On the basis of all the spectral data, including data from a NOESY experiment, and by comparison of these data with those of briarellin M (**6**), compound **8** was found to be the *n*-butanoyl analogue of **6** with the relative stereochemistry as described by formula **8**.

Compound **9**, named briarellin P, possessed a mass spectral molecular ion which was 14 amu's larger than that of **8**. This difference is consistent with replacement of a hydroxyl proton in **8** with a methyl group. The ^{1}H NMR spectrum of **9** showed a new set of methyl protons deshielded by oxygen at δ_H 3.32, which were coupled to the carbon signal at δ_C 89.4 assigned to C-6. Since the remainder of the spectra of this compound was nearly identical to those of **8**, it was concluded that **9** was the 6-methoxyl version of **8**. Comparison of the ^{1}H and ^{13}C NMR and NOESY spectra of **9** with those of briarellin N (**7**) (see Table 2) confirmed the structural similarity of these two compounds. Thus, the complete structure of briarellin P with all the relative stereochemistry is described by formula **9**.

Polyanthellin A (**10**) was obtained as a colorless oil, [α]^{20}$_D$ −9.9° (*c* 1.0, CHCl$_3$). The molecular formula $C_{22}H_{36}O_4$ was deduced from the pseudomolecular ion at *m/z* 387.2512 [M + Na]$^+$ obtained from a HRFABMS determination, which was supported by the NMR data (see Table 2). No absorptions ascribable to hydroxyl functions were detected in the IR spectrum of an exhaustively dried sample of **10**. On the other hand, the intense IR band at 1730 cm^{-1}, the ^{1}H NMR signals at δ_H 1.99 (3H, s), and the ^{13}C NMR signals at δ_C 170.3 (s) and 22.5 (q) indicated the presence of an acetate

Table 2. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) Spectral Data for Briarellins N−P and Polyanthellin A in CDCl$_3$ [δ_H, mult, J (Hz); δ_C (mult)]^a

	briarellin N (7)		briarellin O (8)		briarellin P (9)		polyanthellin A (10)	
atom	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	2.68, br d, 9.4	44.5 (d)	2.66, br d, 9.4	44.4 (d)	2.67, br d, 9.2	44.5 (d)	2.30, m	41.6 (d)
2	3.66, br s	95.4 (d)^b	3.69, br s	94.9 (d)^b	3.67, br s	95.5 (d)^b	3.54, br s	93.7 (d)
3		86.4 (s)		86.1 (s)		86.1 (s)		75.5 (s)
4α	2.62, dd, 8.7, 14.2	35.9 (t)^b	2.48, m	35.2 (t)^b	2.64, m	36.0 (t)^b	1.41, m	36.2 (t)
4β	1.75, m		1.82, m		1.76, m		1.79, m	
5α	1.24, m	26.3 (t)	1.34, m	30.4 (t)	1.25, m	26.2 (t)	1.49, m	18.1 (t)
5β	1.62, m		1.64, m		1.64, m		2.32, m	
6	4.00, d, 6.7	89.3 (d)^b	4.47, d, 7.0	78.8 (d)^b	3.99, d, 6.8	89.4 (d)^b	1.42, m	39.6 (t)
7		75.5 (s)		76.3 (s)		75.5 (s)		74.3 (s)
8α	1.61, m	45.8 (t)	1.61, m	46.6 (t)	1.61, m	45.8 (t)	1.86, br d, 14.2	47.5 (t)
8β	2.01, m		2.02, m		2.02, m		2.19, dd, 4.9, 14.2	
9	4.28, dt, 4.1, 11.8	78.8 (d)	4.26, dt, 3.8, 11.7	78.6 (d)	4.28, dt, 4.0, 11.7	78.8 (d)	3.89, t, 5.3	77.2 (d)
10	2.49, dd, 4.6, 9.7	54.5 (d)	2.49, dd, 4.3, 9.1	54.4 (d)	2.50, dd, 4.6, 9.8	54.5 (d)	3.21, t, 6.0	51.0 (d)
11		81.7 (s)		81.7 (s)		81.7 (s)		83.1 (s)
12α	2.07, m	30.0 (t)	2.04, m	30.1 (t)	2.07, m	30.0 (t)	2.41, m	29.7 (t)
12β	2.07, m		2.04, m		2.07, m		1.25, m	
13α	1.86, m	16.9 (t)	1.84, m	16.9 (t)	1.84, m	16.9 (t)	1.14, m	17.5 (t)
13β	1.86, m		1.84, m		1.84, m		1.40, m	
14	1.73, m	38.4 (d)^b	1.70, m	38.2 (d)^b	1.72, m	38.4 (d)^b	1.15, m	42.3 (d)
15	2.99, dq, 4.6, 7.5	46.2 (d)	2.96, dq, 4.4, 7.2	46.3 (d)	2.98, dq, 4.7, 7.4	46.2 (d)	1.67, m	29.6 (d)
16		176.2 (s)		176.2 (s)		176.2 (s)	0.92, d, 6.9^c	21.7 (q)^c
17	1.36, d, 7.5	17.6 (q)	1.34, d, 7.5	17.6 (q)	1.36, d, 7.6	17.6 (q)	0.79, d, 6.9^c	15.5 (q)^c
18	1.42, s	23.3 (q)	1.41, s	23.4 (q)	1.41, s	23.4 (q)	1.07, s	27.5 (q)
19	1.11, s	23.2 (q)	1.13, s	22.4 (q)	1.10, s	23.3 (q)	1.33, s	35.6 (q)
20	1.32, s	28.7 (q)	1.31, s	28.6 (q)	1.33, s	28.7 (q)	1.48, s	24.0 (q)
21		169.5 (s)		172.1 (s)		172.1 (s)		170.3 (s)
22	2.09, s	22.3 (q)	2.27, m	37.1 (t)	2.30, m	37.1 (t)	1.99, s	22.5 (q)
23			1.59, m	18.2 (t)	1.66, m	18.2 (t)		
24			0.96, t, 7.4	13.6 (q)	0.97, t, 7.4	13.6 (q)		
25								
26								
-OMe	3.32, s	56.8 (q)			3.32, s	56.8 (q)		

^{a} Chemical shift values are in ppm relative to TMS. Spectra were recorded at 25 °C. ^{13}C NMR multiplicities were obtained from APT experiments. ^{b} Low-intensity broad resonance line. ^{c} Values with the same superscript are interchangeable.

group, and this was further substantiated by the intense (100%) mass fragment at m/z 304 in the HREIMS, corresponding to the loss of AcOH from the molecular ion. In addition, the ^{1}H NMR spectrum showed three methyl singlets at δ_H 1.48, 1.33, and 1.07 and two methyl doublets at δ_H 0.92 and 0.79 (each J = 6.9 Hz) coupled with a methine at δ_H 1.67 (m, H-15), which in turn linked to a proton (H-14) resonating at δ_H 1.15 from the ^{1}H–^{1}H COSY. Since the molecular formula of **10** requires five degrees of unsaturation, **10** must be tetracyclic. Moreover, the presence of two ^{13}C NMR signals at δ_C 93.7 (d) and 77.2 (d) that were correlated in the HMQC experiment to the ^{1}H NMR signals at δ_H 3.54 (1H, br s; H-2) and 3.89 (1H, t, J = 5.3 Hz; H-9), respectively, suggested a eunicellin (cladiellane) carbon skeleton. The location of the acetoxyl group on the eunicellin skeleton was defined by HMQC and HMBC experiments. Since the methyl geminal to the acetoxyl (δ_H 1.48) was correlated in the HMBC experiment to C-10, C-11, and C-12, the acetoxyl group must be located on C-11. Furthermore, the locus of two quaternary carbons each bearing an ether bridge [δ_{C-3} 75.5 (s) and δ_{C-7} 74.3 (s)] and a methyl group [δ_H 1.07 (s) and 1.33 (s)] was also established by the HMBC experiment, which showed the following key correlations: H-1, H-2, and H$_3$-18 to C-3; H$_3$-18 to C-2 and C-4; H-8α, H-9, and H$_3$-19 to C-7; and H$_3$-19 to C-6 and C-8. That the ether oxygen bridged carbons C-3 and C-7 across the 10-membered carbocyclic ring in **10** was also evident from the strong downfield chemical shift experienced by C-18 [δ_C 27.5 (q)] and C-19 [δ_C 35.6 (q)]. The relative stereochemistry of **10** was determined from NOESY (H$_3$-20 and H-9; H-1 and H-10, H$_3$-17), which indicated the stereochemistry for the six-membered ring and for the H-1, H-10 ring junction protons. The presence

of NOEs between H-2 and H-14 confirmed the orientation of the isopropyl group, while the NOE correlations of H-1 with H$_3$-18 and H-10 with H$_3$-19 defined the stereochemistry at C-3 and C-7, respectively. Other NOEs are in accord with the proposed structure of **10**.[14] Thus, the overall relative stereochemistry for polyanthellin A (**10**) is 1S*,2S*,3S*,7R*,9S*,10R*,11S*,14S*. Reduction of **10** with lithium aluminum hydride gave tertiary alcohol **12** in excellent yield with C-11 at δ_C 70.3 and C-20 at δ_C 29.7. As a matter of interest, the compounds formulated as **10** and **12** in this investigation appear to be spectroscopically identical to a pair of natural products isolated by Bowden et al. from an Australian *Briareum* species for which structures **13** and **14** were assigned.[15] However, the optical rotations for **13** and **14**, [α]$_D$ +8.9° (c 0.22, CHCl$_3$) and [α]$_D$ +19.4° (c 0.57, CHCl$_3$), were weakly positive in a manner contrary to those recorded for **10** and **12**, [α]$^{20}_D$ −9.9° (c 1.0, CHCl$_3$) and [α]$^{20}_D$ −11.0° (c 0.6, CHCl$_3$), respectively, indicating that both congeneric pairs are enantiomeric. As there are noticeable structural differences between the proposed molecular formulas for **10** and **13** (and **12** and **14**), it seems conceivable that structures **13** and **14** were

13 R= Ac
14 R= H

15 R$_1$= OH; R$_2$= H
16 R$_1$= H; R$_2$= OOH
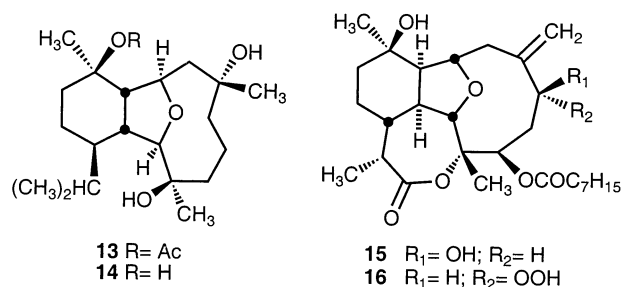
misformulated and that these compounds' structural assignments require revision.[16]

The majority of the compounds isolated were tested for the inhibition of *Plasmodium falciparum*, the parasite responsible for the most severe forms of malaria.[17] Among briarellins **2**, **3**, **4**, **5**, and **11**, with a Δ^7 exocyclic double bond and an −OR group (R = H, OH, or Ac) at C-6, compounds **3**−**5** demonstrated the most toxic effect (IC$_{50}$ 15, 9, 9, 8, and 13 μg/mL, respectively). Briarellin K (**2**) exhibited antiplasmodial activity comparable with briarellin D (**11**). Interestingly, it seems that the absence of an −OR group at C-6 in the briarellins leads to a significant decrease in antimalarial activity. The lack of significant antiplamodial activity in briarellin J (**1**) is consistent with this hypothesis. Curiously, eunicellins **10** and **12**, which unlike the briarellins lack the ϵ-lactone functionality and bear an extra ether bridge, were approximately equipotent. The IC$_{50}$'s for **1**, **6**, **8**, **9**, **10**, and **12** are >50, 22, 24, 14, 16, and 16 μg/mL, respectively.

Briarellin K (**2**) and briarellin D (**11**) were evaluated in the National Cancer Institute (NCI) 3-cell line, one dose, primary anticancer assay. At a concentration of 100 μM, each compound was deemed inactive against the MCF (breast), NCI-H460 (lung), and SF-268 (CNS) cell lines. In vitro antituberculosis screening of briarellin K (**2**), briarellin N (**7**), polyanthellin A (**10**), and briarellin D (**11**) against *Mycobacterium tuberculosis* H$_{37}$Rv at a concentration of 6.25 μg/mL showed no significant inhibitory activity. Briarellins **2**, **7**, and **11** also proved to be inactive as potential inhibitors of the cell cycle regulators cdc2/cyclin B kinase and cdc25 phosphatase.[18]

Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer polarimeter Model 243B. IR spectra were recorded on a Nicolet Magna 750 FT-IR spectrophotometer, and UV data were recorded on a Hewlett-Packard diode array spectrophotometer Model 8452A. NMR data were recorded either on a Bruker DPX-300 spectrometer operating at 300 MHz for ¹H NMR and 75 MHz for ¹³C NMR or on a Bruker DRX-500 spectrometer operating at 500 MHz for ¹H NMR and 125 MHz for ¹³C NMR. All ¹H NMR and ¹³C NMR chemical shifts are referenced to residual CHCl$_3$ in the deuterated solvent (7.26 ppm for ¹H NMR and 77.0 ppm for ¹³C NMR). EIMS and FABMS were obtained from the Material Characterization Center at the University of Puerto Rico, Río Piedras, the Midwest Center for Mass Spectrometry at the University of Nebraska−Lincoln, and the Mass Spectrometry Laboratory of the University of Illinois at Urbana−Champaign. Column chromatography was performed in Si gel (35−75 mesh), and TLC analyses were carried out using Analtech glass precoated Si gel plates. All solvents used were spectral grade or were distilled from glass prior to use.

Animal Material. The gorgonian octocoral was identified by J. A. Sánchez of the Department of Biological Sciences, The State University of New York at Buffalo, as *Briareum polyanthes* (Duchassaing & Michelotti). A voucher specimen has been deposited at the Department of Chemistry, University of Puerto Rico, Río Piedras, Puerto Rico (deposit number BPPR01-1).

Collection, Extraction, and Isolation. *B. polyanthes* was collected by scuba divers near Cabo Rojo, Puerto Rico, at a depth of 10−15 m on October 4, 2000, and frozen until used. The freeze-dried coral (0.97 kg) was extracted exhaustively with CHCl$_3$−MeOH (1:1) (13 L), and after concentration the crude extract (74.8 g) was partitioned against H$_2$O with hexane, CHCl$_3$, EtOAc, and *n*-butanol. The hexane extract (27.8 g) was subsequently purified by size exclusion chromatography on a Bio-Beads SX-2 column with toluene to yield 12 fractions (1−12). Fraction 7 in turn was concentrated to

an orange oil (1.5 g) and chromatographed over Si gel (50 g) with 10% EtOAc in hexane to yield 21 subfractions, denoted A−T. Subfraction P (119 mg) was purified further by column chromatography over Si gel (4 g) with 0.5% MeOH in CHCl$_3$ to give briarellin L (**5**) (37 mg). Fraction 9 was concentrated to a yellow oil (2.8 g) and chromatographed over Si gel (100 g) with 10% EtOAc in hexane to yield 30 subfractions, denoted I−XXX. Subfraction III was identified as polyanthellin A (**10**) (17 mg). Purification of subfraction XVIII (32 mg) by column chromatography over Si gel (2 g) with 0.3% MeOH in CHCl$_3$ gave briarellin J (**1**) (10 mg). Subfraction XXVI (203 mg) was chromatographed over Si gel (7 g) and eluted with 1% MeOH in CHCl$_3$ to give briarellin K hydroperoxide (**3**) (7 mg) and briarellin D hydroperoxide (**4**) (50 mg). Subfractions XXVII (196 mg) and XXIX (156 mg) were fractionated separately over a Si gel column with 0.05% MeOH in CHCl$_3$ to give briarellin P (**9**) (17 mg) and briarellin M (**6**) (26 mg), respectively. Subfraction XXVIII (293 mg) was chromatographed over Si gel (10 g) using a CHCl$_3$−MeOH mixture (95.5:0.5) to yield known briarellin D[3a] (**11**) (36 mg) and briarellin K (**2**) (24 mg). Briarellin O (**8**) (39 mg) was obtained from subfraction XXX (478 mg) after purification on a Si gel column with 0.1% MeOH in CHCl$_3$. The crude CHCl$_3$ extract (1 g) was fractionated over Si gel (30 g) with CHCl$_3$−MeOH (95.5:0.5) to yield 25 fractions, denoted 1−25. Fraction 9 was identified as briarellin N (**7**) (12 mg). Fraction 10 (47 mg) was chromatographed over Si gel (3 g) with 1% MeOH in CHCl$_3$ to give additional quantities of briarellin K (**2**) (16 mg) and briarellin D (**11**) (8 mg).

Briarellin J (1): white semisolid; [α]$^{26}_D$ −7.3° (*c* 1.1, CHCl$_3$); IR (neat) 2982, 2967, 2940, 1726, 1710, 1372, 1253 cm^{-1}; ¹H NMR (CDCl$_3$, 300 MHz) and ¹³C NMR (CDCl$_3$, 75 MHz) (see Table 1); HRFABMS (3-NBA) *m/z* [M + Li]$^+$ 383.2422 (calcd for C$_{22}$H$_{32}$O$_5$Li, 383.2410).

Briarellin K (2): colorless oil; [α]$^{26}_D$ −14.9° (*c* 1.2, CHCl$_3$); IR (neat) 3447 (br), 2977, 2943, 1726 (br), 1373, 1248, 754 cm^{-1}; ¹H NMR (CDCl$_3$, 500 MHz) and ¹³C NMR (CDCl$_3$, 125 MHz) (see Table 1); EIMS *m/z* 392 [M]$^+$ (7), 332 (43), 207 (30), 109 (41), 107 (44), 95 (46), 85 (64), 83 (100); HREIMS *m/z* 392.2175 (calcd for C$_{22}$H$_{32}$O$_6$, 392.2198); HRFABMS (3-NBA) *m/z* [M + Li]$^+$ 399.2366 (calcd for C$_{22}$H$_{32}$O$_6$Li, 399.2359).

Briarellin K hydroperoxide (3): colorless oil; [α]$^{20}_D$ −25.6° (*c* 1.0, CHCl$_3$); IR (neat) 3395 (br), 2968, 2938, 2878, 1728 (br), 1379, 1246, 1132, 1085, 751 cm^{-1}; ¹H NMR (CDCl$_3$, 500 MHz) δ 2.55 (br d, *J* = 11.2 Hz, H-1), 4.09 (br d, *J* = 3.4 Hz, H-2), 4.65 (dd, *J* = 4.9, 11.5 Hz, H-6), 2.30 (br d, *J* = 13.5 Hz, H-8α), 2.86 (dd, *J* = 4.5, 13.5 Hz, H-8β), 4.15 (dd, *J* = 5.0, 8.7 Hz, H-9), 2.78 (dd, *J* = 9.2, 10.8 Hz, H-10), 2.90 (dq, *J* = 5.0, 7.5 Hz, H-15), 1.37 (d, *J* = 7.6 Hz, Me-17), 1.65 (s, Me-18), 5.22 (br s, H-19α), 5.40 (br s, H-19β), 1.32 (s, Me-20), 1.91 (s, Me-22), 7.87 (br s, −OOH); ¹³C NMR (CDCl$_3$, 125 MHz) δ 44.9 (d, C-1), 90.6 (d, C-2), 85.2 (s, C-3), 28.5 (t, C-4), 28.2 (t, C-5), 85.6 (d, C-6), 144.1 (s, C-7), 42.7 (t, C-8), 82.2 (d, C-9), 48.0 (d, C-10), 80.8 (s, C-11), 30.4 (t, C-12), 16.8 (t, C-13), 37.0 (d, C-14), 45.9 (d, C-15), 176.2 (s, C-16), 17.5 (q, C-17), 20.5 (q, C-18), 118.5 (t, C-19), 29.0 (q, C-20), 169.8 (s, C-21), 22.4 (q, C-22); HRFABMS (3-NBA) *m/z* [M + Na]$^+$ 431.2040 (calcd for C$_{22}$H$_{32}$O$_7$Na, 431.2046).

Briarellin D hydroperoxide (4): colorless oil; [α]$^{20}_D$ −25.2° (*c* 1.0, CHCl$_3$); IR (neat) 3377 (br), 3077, 2967, 2937, 2878, 1722, 1717, 1377, 1253, 1185, 1084, 1009, 755 cm^{-1}; ¹H NMR (CDCl$_3$, 500 MHz) δ 2.52 (br d, *J* = 11.1 Hz, H-1), 4.07 (br d, *J* = 3.3 Hz, H-2), 4.62 (dd, *J* = 5.0, 11.4 Hz, H-6), 2.27 (br d, *J* = 13.9 Hz, H-8α), 2.83 (dd, *J* = 4.8, 13.9 Hz, H-8β), 4.12 (dd, *J* = 4.9, 8.7 Hz, H-9), 2.77 (dd, *J* = 8.9, 11.0 Hz, H-10), 2.86 (dq, *J* = 5.2, 7.6 Hz, H-15), 1.34 (d, *J* = 7.6 Hz, Me-17), 1.62 (s, Me-18), 5.19 (br s, H-19α), 5.37 (br s, H-19β), 1.29 (s, Me-20), 2.10 (t, *J* = 7.2 Hz, H-22), 0.88 (t, *J* = 7.4 Hz, Me-24), 8.36 (br s, −OOH); ¹³C NMR (CDCl$_3$, 125 MHz) δ 44.9 (d, C-1), 90.7 (d, C-2), 84.9 (s, C-3), 28.5 (t, C-4), 28.2 (t, C-5), 85.5 (d, C-6), 144.1 (s, C-7), 42.7 (t, C-8), 82.2 (d, C-9), 48.0 (d, C-10), 80.8 (s, C-11), 30.3 (t, C-12), 16.7 (t, C-13), 37.0 (d, C-14), 45.8 (d, C-15), 176.0 (s, C-16), 17.4 (q, C-17), 20.5 (q, C-18), 118.5 (t, C-19), 28.9 (q, C-20), 172.3 (s, C-21), 37.4 (t, C-22), 18.4 (t, C-23), 13.5 (q, C-24); HRFABMS (3-NBA) *m/z* [M + Na]$^+$ 459.2352 (calcd for C$_{24}$H$_{36}$O$_7$Na, 459.2359).

Briarellin L (5): colorless oil; $[\alpha]^{26}_D$ −20.8° (*c* 1.2, CHCl$_3$); IR (neat) 2963, 2938, 1727 (br), 1377, 1248, 1185, 1087 cm^{-1} (br); ^{1}H NMR (CDCl$_3$, 300 MHz) and ^{13}C NMR (CDCl$_3$, 75 MHz) (see Table 1); EIMS *m/z* 402 [M − AcOH]$^+$ (2), 374 [M − C$_4$H$_8$O$_2$]$^+$ (12), 314 [M − AcOH − C$_4$H$_8$O$_2$]$^+$ (9), 296 (47), 268 (100), 205 (38), 71(49); HREIMS *m/z* [M − AcOH]$^+$ 402.2458 (calcd for C$_{24}$H$_{34}$O$_5$, 402.2406); HRFABMS (3-NBA) *m/z* [M + Na]$^+$ 485.2530 (calcd for C$_{26}$H$_{38}$O$_7$Na, 485.2515).

Briarellin M (6): colorless oil; $[\alpha]^{26}_D$ −14.5° (*c* 1.0, CHCl$_3$); IR (neat) 3459 (br), 2971, 2928, 1738, 1707, 1373, 1243, 1007, 746 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) and ^{13}C NMR (CDCl$_3$, 75 MHz) (see Table 1); EIMS *m/z* 350 [M − AcOH]$^+$ (8), 332 [M − AcOH − H$_2$O]$^+$ (50), 314 [M − AcOH − 2H$_2$O]$^+$ (10), 307 (75), 209 (30), 207 (48), 127(95), 119 (100); HREIMS *m/z* [M − AcOH]$^+$ 350.2094 (calcd for C$_{20}$H$_{30}$O$_5$, 350.2093); HRFABMS (3-NBA) *m/z* [M + Na]$^+$ 433.2214 (calcd for C$_{22}$H$_{34}$O$_7$Na, 433.2202).

Briarellin N (7): colorless oil; $[\alpha]^{20}_D$ −13.6° (*c* 1.1, CHCl$_3$); IR (neat) 3448 (br), 2960, 2935, 1738, 1713, 1378, 1242, 1082 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) and ^{13}C NMR (CDCl$_3$, 75 MHz) (see Table 2); EIMS *m/z* 406 [M − H$_2$O]$^+$ (3), 364 [M − AcOH]$^+$ (15), 332 [M − AcOH − MeOH]$^+$ (4), 305 (10), 221 (18), 127 (100), 83 (40); HREIMS *m/z* [M − H$_2$O]$^+$ 406.2345 (calcd for C$_{23}$H$_{34}$O$_6$, 406.2355).

Briarellin O (8): colorless oil; $[\alpha]^{26}_D$ −24.4° (*c* 1.1, CHCl$_3$); IR (neat) 3440 (br), 2971, 2938, 1732, 1713, 1379, 1253, 1175, 1074, 1011, 755 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) and ^{13}C NMR (CDCl$_3$, 75 MHz) (see Table 2); EIMS *m/z* 350 [M − C$_4$H$_8$O$_2$]$^+$ (8), 332 [M − C$_4$H$_8$O$_2$ − H$_2$O]$^+$ (18), 314 [M − C$_4$H$_8$O$_2$ − 2H$_2$O]$^+$ (5), 307 (34), 249 (23), 221 (37), 133 (40), 109 (35), 93 (41), 71(100); HREIMS *m/z* [M − C$_4$H$_8$O$_2$]$^+$ 350.2096 (calcd for C$_{20}$H$_{30}$O$_5$, 350.2093); HRFABMS (3-NBA) *m/z* [M + Na]$^+$ 461.2515 (calcd for C$_{24}$H$_{38}$O$_7$Na, 461.2515).

Briarellin P (9): colorless oil; $[\alpha]^{26}_D$ −8.8° (*c* 1.1, CHCl$_3$); IR (neat) 3452 (br), 2967, 2934, 2878, 1729, 1714, 1382, 1250, 1085, 1003, 971, 751 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) and ^{13}C NMR (CDCl$_3$, 75 MHz) (see Table 2); EIMS *m/z* 434 [M − H$_2$O]$^+$ (14), 364 [M − C$_4$H$_8$O$_2$]$^+$ (18), 332 [M − C$_4$H$_8$O$_2$ − MeOH]$^+$ (5), 207 (36), 201 (32), 168 (46), 145 (41), 133 (47), 119 (52), 82 (46), 71(100); HRFABMS (glycerol) *m/z* [M + Li]$^+$ 459.2911 (calcd for C$_{25}$H$_{40}$O$_7$Li, 459.2934).

Polyanthellin A (10): colorless oil; $[\alpha]^{20}_D$ −9.9° (*c* 1.0, CHCl$_3$); IR (neat) 2958, 2927, 2872, 2853, 1730, 1369, 1254, 1241, 1079, 1015 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) and ^{13}C NMR (CDCl$_3$, 75 MHz) (see Table 2); EIMS *m/z* 304 [M − AcOH]$^+$ (100), 275 (8), 243 (15), 179 (22), 149 (17), 121 (23), 109 (25), 105 (25), 81 (25); HREIMS *m/z* [M − AcOH]$^+$ 304.2502 (calcd for C$_{20}$H$_{32}$O$_2$, 304.2402); HRFABMS (3-NBA) *m/z* [M + Na]$^+$ 387.2512 (calcd for C$_{22}$H$_{36}$O$_4$Na, 387.2511).

Reduction of 10 with Lithium Aluminum Hydride. A solution of **10** (5 mg, 0.013 mmol) and 1.0 M LiAlH$_4$ (27 μL, 0.027 mmol) in dry ether (2.5 mL) was stirred at 25 °C for 3 h. After this time the reaction mixture was quenched with a 0.1 N HCl solution, the product extracted with ether (3 × 15 mL), and the organic layer evaporated to dryness. The residue was chromatographed over Si gel, eluting with a hexane− EtOAc (9:1) mixture, to afford **12** (4.1 mg, 93%): clear oil; $[\alpha]^{20}_D$ −11.0° (*c* 0.6, CHCl$_3$); EIMS *m/z* 322 [M]$^+$ (11), 304 [M − H$_2$O]$^+$ (47), 264 (31), 195 (34), 135 (47), 121 (65), 93 (100), 81(89), 69 (77). The synthetic material was found to be spectroscopically identical to a natural product formulated as **14** by Bowden and co-workers.[15,16]

Acetylation of Briarellin D (11). A solution of briarellin D (**11**) (17.1 mg, 0.041 mmol) in a mixture of Ac$_2$O (0.5 mL) and pyridine (0.5 mL) was stirred at 25 °C for 19 h. Excess reagents were removed in vacuo to give 14.2 mg of the crude acetate. The synthetic material was found to be spectroscopically identical to the natural briarellin L (**5**).

Briarellin A (16):[3a] LRFABMS (Gly/3-NBA/TFA) *m/z* [M + H]$^+$ 509 (calcd for C$_{28}$H$_{45}$O$_8$, 509); LRFABMS (3-NBA/NaI) *m/z* [M + Na]$^+$ 531 (calcd for C$_{28}$H$_{44}$O$_8$Na, 531); restatement of NOEs for briarellin A: H-1/H-4, H-2/H-14, H-2/Me-18, H-4/ H-5α, H-5β/H-6, H-6/H-8β, H-6/Me-18, H-8α/H-9, H-8α/H-19α, H-8β/H-9, H-9/Me-20, H-10/H-19α, H-10/Me-20, H-14/H-15, H-15/Me-17, H-19α/H-19β.

Bioassay. Compounds **1**−**6** and **8**−**12** were tested for antimalarial activity against *P. falciparum* using a novel microfluorometric assay that measures inhibition based on the detection of parasite DNA by intercalation with Pico Green. A complete description of this test has been previously described.[19]

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(9) Selected correlations observed in the HMBC spectrum of briarellin J (**1**): C-2 [H$_3$-18], C-3 [H$_3$-18], C-4 [H-2, H$_3$-18], C-6 [H$_3$-19], C-7 [H$_3$-19], C-8 [H-6, H-10, H$_3$-19], C-9 [H-2], C-10 [H$_3$-20], C-11 [H-9, H-12αβ, H$_3$-20], C-12 [H$_3$-20], C-13 [H-1], C-14 [H-2, H-12αβ, H$_3$-17], C-15 [H-13αβ, H$_3$-17], C-16 [H$_3$-17], C-17 [H-15], C-18 [H-2], C-19 [H-6], C-21 [H$_3$-22].
(10) Selected NOEs for briarellin J (**1**): H-2/H-14, H-2/Me-18, H-4β/H-6, H-5β/H-6, H-6/Me-19, H-8β/H-9, H-9/Me-19, H-9/Me-20, H-10/Me-20, H-12α/Me-20, H-13β/H-15, H-14/H-15, H-15/Me-17.
(11) Selected NOEs for briarellin K (**2**): H-1/H-10, H-2/H-14, H-2/Me-18, H-6/H-8β, H-6/H-9, H-6/Me-18, H-8β/H-9, H-9/H-12β, H-9/Me-20, H-10/Me-20, H-14/H-15, H-15/Me-17, H-19α/H-19β.
(12) Selected NOEs for briarellin L (**5**): H-1/H-10, H-2/H-14, H-2/Me-18, H-5β/H-6, H-6/H-8β, H-8α/H-9, H-8α/H-10, H-8α/H-19α, H-8β/H-9, H-9/Me-20, H-10/H-19α, H-14/H-15, H-15/Me-17, H-19α/H-19β.
(13) There exist experimental data to suggest that a strained (6*E*)-eunicellane (rather than an unstrained *Z*-cycloalkene such as **1**) could undergo spontaneous addition of MeOH to produce derivatives like **7** and **9** with identical configuration at C-6,7. This could explain why **1** was isolated unaltered after extraction under the same conditions and also suggests that briarellin M (**6**), briarellin O (**8**), and their respective methyl ethers **7** and **9** may be artifacts from the isolation process; see: Mancini, I.; Guella, G.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **2000**, *83*, 1561−1575.

(14) Selected NOEs for polyanthellin A (**10**): H-1/H-10, H-1/Me-17, H-1/Me-18, H-2/H-4β, H-2/H-14, H-2/H-15, H-2/Me-18, H-4α/Me-18, H-8α/H-9, H8α/H-10, H-8α/Me-19, H-8α/Me-20, H-8β/H-9, H-9/Me-20, H-10/Me-19, H-10/Me-20, H-15/Me-16, H-15/Me-17.

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(16) Despite having dissimilar structures, the ^{1}H and ^{13}C NMR data reported for **13** and **14** correspond very well to those of compounds **10** and **12**, respectively. Therefore, we surmise that the relationship between each pair of analogues appears to be antipodal in nature. Besides the presence of two ether bridges in **10** and **12**, our proposed formulas also differ from those of **13** and **14** in their relative stereochemistry at C-7. Dr. Bowden and co-workers have reevaluated the evidence suggesting structures **13** and **14**, and they have agreed that they should be reformulated, respectively, to the corresponding mirror images of **10** and **12** (personal communication).

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