Verrillin: A Highly Oxygenated Marine Diterpene Based on the Novel Verrillane Carbon Skeleton

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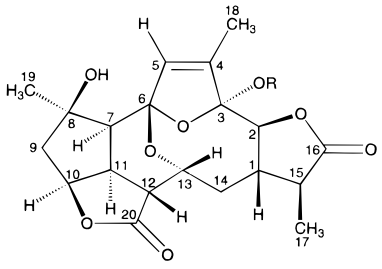
Introduction

Caribbean gorgonians (sea whips, sea feathers, and sea fans; phylum Cnidaria, order Gorgonacea) are prolific producers of structurally interesting natural products. Terpenoid metabolites are especially plentiful, and these include the sesquiterpenes, diterpenes, bis-diterpenes, steroids, and some carotenoids.[1,2] The cembranes, gersolanes, and the pseudopteranes, isolated from *Pseudopterogorgia bipinnata* (Verrill, 1864), are examples of diterpenoid members of this group.[3] In connection with our interest in the development of new agents for the treatment of tuberculosis, we now wish to report the isolation and structure elucidation of verrillin (**1**) from a Colombian specimen of *P. bipinnata*. Verrillin is a hexacyclic diterpene related in structure to some bipinnatins,[4] but possesses a novel carbon skeleton. Since both the bipinnatin class of compounds and the verrillin class are found within the same source, the latter must arise from a significantly different pathway that yields a novel pattern of cyclization. So far, only two examples of hexacyclic diterpenoids of coelenterate origin (each a trisepoxycembranolide) have been reported in the literature.[4,5]



1 R = H
2 R = Ac

Specimens of *P. bipinnata* were collected by hand using scuba (−25 to −30 m) near San Andrés Island, Colombia, and kept frozen until workup. Freeze-dried samples *of P. bipinnata* were homogenized and extracted with MeOH−$CHCl_3$ (1:1) to give a crude extract. This extract was partitioned between hexane, $CHCl_3$, ethyl acetate, and water. The $CHCl_3$ extract soluble material was further fractionated by gradient silica gel flash chromatography (first using 0−100% ethyl acetate in hexane followed by 0−100% MeOH in $CHCl_3$) and separated into 30 fractions. Samples were inspected by TLC and ^{1}H and ^{13}C NMR spectroscopy. Fraction XX was purified further by successive silica gel column chromatography to give verrillin (**1**) as a colorless gum.

Results and Discussion

The molecular formula of verrillin (**1**) was assigned as $C_{20}H_{24}O_8$ on the basis of high-resolution mass measurement of the $[M + Na]^+$ ion at $m/z = 415.1389$ and overall NMR information indicating the presence of nine degrees of unsaturation in the molecule. There was no molecular ion observed in the HREI-MS; however, a peak at $m/z = 374.1366$, which represented the fragment $[C_{20}H_{24}O_8 - H_2O]^+$, was consistent with the molecular formula. The IR data for **1** indicated the presence of hydroxyl(s) (3430 cm^{-1}) and carbonyl(s) (1765 cm^{-1}) bands, the latter band strongly suggesting the presence of nonconjugated γ-lactone moieties. Inspection of the ^{1}H NMR spectral data of **1** in $CDCl_3$ (Table 1) showed two broad one-proton resonances at δ 3.15 and 2.92 assigned to two exchangeable hydroxyl protons, one noncoupled alkene proton, three methyl groups, and nine complex proton resonances between δ 1.80 and 3.65, suggestive of a polycyclic terpenoid structure. The chemical shift of the remaining three signals (between δ 4.15 and 5.07) were indicative of protons attached to carbons bearing either hydroxyl or ether functionalities. Acetylation of **1** afforded the monoacetate (**2**) whose molecular formula was determined as $C_{22}H_{26}O_9$ on the basis of high-resolution mass measurement of the $[M + H]^+$ ion at $m/z = 435.1659$. The ^{1}H NMR spectral data for **2** were very similar to those of **1**, except for the presence of the acetyl group at δ 2.09 suggesting that a tertiary hemiacetal hydroxyl group was acetylated.[6] The only significant variation in the ^{1}H NMR data was the chemical shift of H-2 (δ 4.15 versus 4.37), which was consistent with the presence of a nearby hydroxyl substituent on the same face of the molecule (i.e., cis to H-2).

The ^{13}C NMR spectrum of **1** (Table 1) showed signals characteristic of two lactone carbonyls, two alkene carbons (one quaternary), six oxygenated carbons (δ 107.6, 105.7, 86.7, 81.8, 77.7, and 70.2), and 10 carbons between δ 49.2 and 12.2, while the DEPT spectrum indicated that three CH_3, two CH_2, nine CH, and six quaternary carbons were present. Because the UV spectrum of **1** showed only

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Table 1. ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), ^{1}H−^{1}H COSY, NOESY, and HMBC Spectral Data of Verrillin (1) in $CDCl_3$[a]

position	δ_H, mult, intgr, (*J* in Hz)	δ_C (mult)[b]	^{1}H−^{1}H COSY	NOESY	HMBC[c]
1	2.28, m, 1H	42.1 (d)	H2, H14α*β*	H17	H13, H15, H17
2	4.15, d, 1H (10.5)	86.7 (d)	H1	H14α, H15	H1, H14α*β*
3		107.6 (s)			H2, H5, H18
4		144.2 (s)			H2, H5, H18
5	6.14, q, 1H (1.8)	128.3 (d)	H18	H18, H19	H7, H18
6		105.7 (s)			H5, H7, H13
7	2.11, br d, 1H (9.3)	49.2 (d)	H11	H11	H9*β*, H10, H12, H19
8		77.7 (s)			H9*β*, H10, H11, H19
9α	1.80, dd, 1H (5.7, 15.0)	48.0 (t)	H9*β*, H10	H9*β*, H10, H19	H19
9*β*	2.35, br d, 1H (15.0)		H9α	H9α, H−12	
10	5.07, dd, 1H (5.7, 7.5)	81.8 (d)	H9α, H11	H9α, H11	H9*β*
11	3.65, ddd, 1H (7.5, 9.3, 12.0)	38.2 (d)	H7, H10, H12	H7, H10, H14α	H7, H9*β*, H12
12	2.56, dd, 1H (0.6, 12.0)	41.3 (d)	H11	H9*β*, H13	H7, H11, H13
13	4.60, t, 1H (9.6)	70.2 (d)	H14α*β*	H12, H14*β*	H12, H14α*β*
14α	2.20, m, 1H	37.5 (t)	H1, H13, H14*β*	H2, H11	H2, H12, H13, H15
14*β*	2.08, m, 1H		H1, H13, H14α	H13	
15	2.35, q, 1H (6.6)	41.0 (d)	H17	H2, H17	H1, H2, H14α*β*, H17
16		176.9 (s)			H15, H17
17	1.25, d, 3H (6.6)	12.2 (q)	H15	H1, H15	H15
18	1.99, d, 3H (1.8)	12.9 (q)	H5	H5	H5
19	1.43, s, 3H	27.2 (q)		H5, H9α, 8-OH	
20		177.4 (s)			H10, H11, H12, H13
3-OH	2.92, br s, 1H				
8-OH	3.15, br s, 1H			H19	

[a] Chemical shift values are in ppm relative to TMS. Spectra were recorded at room temperature. [b] ^{13}C NMR multiplicities were obtained from a DEPT experiment. [c] Protons correlated to carbon resonances in ^{13}C column. Parameters were optimized for $^{2,3}J_{CH} = 6$ and 8 Hz.

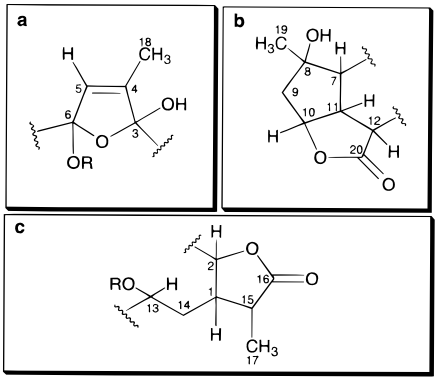

Figure 1. Substructures of verrillin (**1**).

end absorption, the carbonyl groups were nonconjugated. Spectral evidence thus demanded that compound **1** was hexacyclic with one olefin and two carbonyl groups. Since these spectroscopic data were not reminiscent of any known class of alcyonarian metabolites, it appeared that compound **1** contained a novel carbon skeleton.

The three partial structures (**a**−**c**) were deduced from extensive analyses of the 2D NMR data of **1** and **2** including COSY, TOCSY, NOESY, HMQC, and HMBC spectra in $CDCl_3$ (Figure 1). The COSY, NOESY, and HMBC correlations for verrillin (**1**) are presented in Table 1.

Unit a. The presence of a 3-methyl-2,5-dihydrofuran moiety in the molecule was deduced from the ^{1}H−^{1}H COSY and HMQC spectra and proton and carbon chemical shifts at positions C-4, C-5, and C-18.[7] The HMBC NMR correlations between the olefinic proton H-5 (δ_H = 6.14) and the ketal-bearing carbons C-3 (δ_C = 107.6) and C-6 (δ_C = 105.7), and long-range couplings between H-5 with C-4 and C-18 allowed us to confirm the proposed structure for unit **a**. This was upheld by complementary HMBC correlations between methyl protons H-18 and C-3, C-4, and C-5.

Unit b. For partial structure **b** (C-7, C-8, C-9, C-10, C-11, C-12, C19, and C-20), connectivities from C-9 through C-12 and from C-7 to C-11 were clearly revealed by the COSY and HMQC spectra. TOCSY correlations from the methine proton H-10 (δ_H = 5.07) to H-12 and between protons H-9*β* and H-11 allowed us to further link these spin systems. The connectivity of unit **b** was completed by HMBC correlations for H9*β*/C-8, H-10/C-8, H-11/C-8, and H-19/C-7/C-8/C-9, and correlations between C-20 (δ_C = 177.4) and H-10, H-11, and H-12. Interestingly, the chemical shifts of all proton and carbon atoms in unit **b** (as well as the multiplicities and coupling constants of all the protons) were remarkably similar to those of the corresponding substructures of ophiobolin A lactone, ophiobolin B lactone, and rameswaralide implying that the structures of these metabolites are similar to that of verrillin (**1**).[8,9]

Unit c. COSY experiments gave straightforward connectivities from H-13 to H-14α*β*, H-1 to H-2, and from H-15 to H-17. It was, however, difficult to obtain unambiguous evidence for connecting H-1 (δ_H = 2.28) to the methine H-15 (δ_H = 2.35, δ_C = 41.0) and the methylene protons H-14α*β* (δ_H = 2.20/2.08, δ_C = 37.5), due to the heavy overlapping of these proton signals. Fortunately, HMBC techniques unambiguously revealed that these fragments were linked through cross-peaks due to $^2J_{CH}$ and $^3J_{CH}$ coupling (Table 1). Thus, long-range couplings between C-1 and the methine protons H-13 and H-15, and those between C-2 and H-1 and H-14α*β* were consistent with partial structure **c**. Furthermore, the lactone methine in substructure **c**, which appears unusually shielded to δ 4.15, indicated that it must be forced

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into the electron cloud of the nearby oxygens of substructure **a**. Units **a**−**c** were connected using a number of key HMBC NMR correlations. Substructures **a** and **b**, for example, were linked by correlations between H-7 and C-5 and between H-7 and C-6. Substructures **a** and **c**, on the other hand, were connected by the observation of strong HMBC correlations between H-13 and C-6 and between H-2 and C-3. This coupled with the observation of a three-bond proton−carbon connectivity in the HMBC experiment between carbon resonance C-4 ($\delta_C = 144.2$) and H-2 ($\delta_H = 4.15$) allowed the attachment of the two rings of units **a** and **c** through C-3 and C-2, respectively. Furthermore, HMBC cross-peaks between the oxymethine proton H-13 ($\delta_H = 4.60$) (unit **c**) and carbons C-11 and C-12 (unit **b**) connected the latter substructures. The long-range correlation between the lactone carbonyl carbon at δ 177.4 (C-20) and H-13 further confirmed this connectivity. At this point, the link between units **b** and **c** through C-12 and C-13, allowed the complete planar structure for **1** to be assigned. Applying these combined NMR methods resulted in the unambiguous assignment of all the protons and carbons as listed in Table 1.

Relative Configuration. The relative configurations for the 11 stereocenters in the complex hexacyclic nuclei of verrillin (**1**) were assigned primarily on the basis of ^{1}H NMR coupling constants and NOESY data supported by distance calculations using the INSIGHT-II molecular mechanics program. The proton at C-12 showed an axial-axial ($J_{H-11/H-12} = 12.0$ Hz) coupling constant with the methine proton H-11, whereas H-2 occurred as a doublet signal exhibiting large coupling ($J = 10.5$ Hz) with H-1. These coupling constants indicated that these protons were trans-coupled. On the other hand, the small axial−equatorial ($J_{H-12/H-13} = 0.6$ Hz) coupling constant between H-12 and H-13 indicated that these protons were cis-coupled. A weak but very diagnostic NOE between these protons defined their cis relative stereochemistry. In agreement with the relevant signals assigned for ophiobolin A lactone, ophiobolin B lactone, and rameswaralide the coupling constants between H-7 and H-11 ($J_{H-7/H-11} = 9.3$ Hz) and between H-10 and H-11 ($J_{H-10/H-11} = 7.5$ Hz) indicated that these proton pairs were cis-coupled.[8,9] Similarly, NOESY correlations between H-7 and H-11, H-9β and H-12, and H-10 and H-11 established the spatial proximities of these protons on the same face of the molecule. Furthermore, the coupling constants between H_2-9 and H-10 ($J_{H-9\alpha/H-10} = 5.7$ Hz; $J_{H-9\beta/H-10} \leq 1$ Hz) required a dihedral angle between H-9β and H-10 close to 90°. These orientations bring H-9α within 2.6 Å of the H-19 methyl protons, in accord with the observed NOE (all distance estimates come from molecular modeling studies). The C-15 methyl group was predicted to be on the same molecular face as the C-1 methine, based upon the lack of any significant coupling between H-1 and H-15 ($J_{H-1/H-15} \leq 1$ Hz) and the strong cross-peaks in the NOESY spectrum between H-2 and H-15 and between H-1 and H-17. All these geometric constraints dictated by the observed NOEs and coupling constants were incompatible with a C-15 methyl substituent having the α-orientation. Strong dipolar coupling (NOEs) between H-2 with H-14α and H-15, H-11 with H-14α, and most importantly, between H-5 and H-19 were observed. These geometric constraints require the relative stereochemistry at the C-3 and C-6 stereocenters to be as shown (3*S**,6*S**). In molecular modeling studies of all the other alternative stereoisomers [(3*S**,6*R**), (3*R**,6*R**), and (3*R**,6*S**)] it proved to be impossible to bring these protons, especially H-5 and H-19, simultaneously within observable NOE distances. The distances between protons experiencing these NOEs in **1** all lie within 2.4−2.6 Å according to molecular modeling studies, while the distance between H-5 and H-19 was calculated to be 2.6 Å. The cis relationship between H-2 and CH_3-22 in **2** was also attributed on the basis of a strong cross-peak in the NOESY spectrum of verrillin acetate. These results definitely supported the relative stereochemistry of **1** with the tetrahydropyran ring and the eight-membered cyclic ketal having the chair and distorted crown conformation, respectively. In such conformation, compound **1** achieves additional molecular stability via intramolecular hydrogen bonding between the C-8 hydroxyl proton and the tetrahydropyran oxygen. Thus, the overall relative stereochemistry for verrillin (**1**) was assigned as 1*S**,2*S**,3*S**,6*S**,7*S**,8*R**,10*S**,11*S**,12*R**,13*R**,15*S**.

A careful substructure search of the *cis*-bicyclo[9.3.0]-tetradecane nucleus of verrillin (**1**) revealed no natural products composed of this specific bicyclic ring architecture. Thus, verrillin represents a new class of regular diterpenes. The name verrillane is proposed for this structurally unique carbon framework. Although not yet proven, the carbobicyclic ring system of **1** appears to be produced by subsequent transannular cyclization of a suitable cembranoid precursor. The isolation of both skeletal classes from the same specimen of *P. bipinnata* provides circumstantial support that the verrillane ring system might be synthesized in vivo by subsequent cyclization of the cembrane skeleton via [$C_7 \rightarrow C_{11}$] bond formation.[3] In an in vitro antituberculosis screen against *Mycobacterium tuberculosis* H_{37}Rv at 6.25 μg/mL, verrillin (**1**) caused 0% inhibition in the primary screen. Unfortunately, scarcity of material precluded more extensive probing of the biological properties of **1**.

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR were measured at 500 and 125 MHz, respectively. IR spectra were determined as thin films, and UV spectra were recorded in MeOH solution. Column chromatography was performed in silica gel (35−75 mesh) and TLC analyses were carried out using glass precoated silica gel plates. Molecular mechanic calculations were performed on INSIGHT-II (version 98.0) 3.0/Discover Packages (Biosym Technologies, 9685 Scranton Rd., San Diego, CA 92121-2777). All chemicals and solvents used were of analytical grade. The percentage yield of natural product **1** is based on the weight of the crude gorgonian extract.

Collection and Extraction Procedures. Verrillin (**1**) was isolated from the gorgonian octocoral *P. bipinnata* (Verrill, 1864) collected in May 1996 near San Andrés Island, Colombia. A voucher specimen is stored at the Chemistry Department of the University of Puerto Rico. The dry animal (2.1 kg) was blended with MeOH−$CHCl_3$ (1:1) (5 × 1L), and after filtration, the crude extract was evaporated under vacuum to yield a green residue (167.5 g). After the crude extract was partitioned between hexane and H_2O, the aqueous suspension was extracted with $CHCl_3$ (4 × 1 L). The resulting extract was concentrated in vacuo to yield 43.3 g of an oil, which was chromatographed over silica gel (400 g) using a step gradient of EtOAc−hexane (0−100%) followed by a step gradient of MeOH−$CHCl_3$ (0−100%), and separated into 30 fractions (I−XIX and XX−XXX, respectively) on the basis of TLC and NMR analyses. Purification of fraction XX (0.33 g) by successive silica gel column chromatography (first using 18 g of silica gel with a 25:1 mixture of $CHCl_3$−MeOH as eluant and then 2.2 g of silica gel eluting with a 2:1 mixture of $CHCl_3$−acetone) led to pure verrillin (**1**) (2.7 mg, yield = 1.6×10^{-3}%).

Verrillin (1): colorless gum; $[\alpha]^{24}_D$ +225° (*c* 0.2, $CHCl_3$); IR (film) 3430, 3018, 1765, 1657, 1371, 1012, 961, 762 cm^{-1}; UV λ_{max} (MeOH) 206 nm (ϵ 7200); ^1H NMR (500 MHz, $CDCl_3$) see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$) see Table 1; HRFAB-MS (glycerol) *m*/*z* $[M + Na]^+$ 415.1389 (calcd for $C_{20}H_{24}O_8Na$, 415.1369); $[M - H_2O + Na]^+$ 397.1331 (calcd for $C_{20}H_{22}O_7Na$, 397.1263); HREI-MS *m*/*z* $[M - H_2O]^+$ calcd for $C_{20}H_{22}O_7$ 374.1366, found 374.1384 (67), 356 (78), 328 (28), 312 (77), 310 (78), 230 (67), 174 (79), 150 (100).

Acetylation of Verrillin (1). A solution of **1** (1.0 mg, 0.002 mmol) in a 1:1 mixture of Ac_2O−pyridine (0.50 mL) was stirred at 25 °C for 24 h. TLC analysis of a small aliquot revealed that the starting material had completely disappeared. After adding ice−water (0.5 mL) the mixture was stirred for 10 min, concentrated, and stored overnight under vacuum. The residue was purified by column chromatography over silica gel (0.8 g) [$CHCl_3$−acetone (4:1) as eluant] to give ca. 0.7 mg (63%) of verrillin acetate (**2**) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 2.33 (m, 1H, H-1), 4.37 (d, 1H, J = 10.2 Hz, H-2), 6.17 (q, 1H, J = 1.8 Hz, H-5), 2.25 (br d, 1H, J = 9.6 Hz, H-7), 1.80 (dd, 1H, J = 5.8, 14.9 Hz, H-9α), 2.34 (br d, 1H, J = 14.8 Hz, H-9β), 5.06 (dd, 1H, J = 5.8, 7.3 Hz, H-10), 3.62 (ddd, 1H, J = 7.3, 9.6, 11.7 Hz, H-11), 2.57 (br d, 1H, J = 11.7 Hz, H-12), 4.64 (t, 1H, J = 9.1 Hz, H-13), 2.08 (m, 1H, H-14α), 2.22 (m, 1H, H-14β), 2.33 (m, 1H, H-15), 1.26 (d, 3H, J = 6.6 Hz, Me-17), 1.92 (d, 3H, J = 1.8 Hz, Me-18), 1.44 (s, 3H, Me-19), 2.09 (s, 3H, $OCOCH_3$), 3.07 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.5 (d, C-1), 85.4 (d, C-2), 109.9 (s, C-3), 140.7 (s, C-4), 128.7 (d, C-5), 108.2 (s, C-6), 47.8 (d, C-7), 77.7 (s, C-8), 47.8 (t, C-9), 81.9 (d, C-10), 38.3 (d, C-11), 41.5 (d, C-12), 70.3 (d, C-13), 37.5 (t, C-14), 40.7 (d, C-15), 176.8 (s, C-16), 12.2 (q, C-17), 12.8 (q, C-18), 27.1 (q, C-19), 177.5 (s, C-20), 168.1 (s, C-21), 22.1 (q, C-22); HRFAB-MS (glycerol) *m*/*z* $[M + H]^+$ 435.1659 (calcd for $C_{22}H_{27}O_9$, 435.1655).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for verrillin acetate (**2**) and HREI-MS and HRFAB-MS spectral data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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