43, 123151-45-1; 44, 123151-46-2; (±)-45, 123151-47-3; (±)-46, 123151-48-4; 47, 123151-49-5; (±)-48, 123151-50-8; (±)-49, 123237-56-9; (±)-50 (isomer 1), 123151-51-9; (±)-50 (isomer 2), 123151-58-6; (±)-51, 123151-52-0; (±)-52, 34160-77-5; (±)-53, 60268-93-1; β-cyclocitral, 432-25-7; 2-isopropylresorcinol, 62858-83-7; 2-methoxy-6-methylphenol, 2896-67-5.

Supplementary Material Available: IR, UV, and mass spectral data for **12–15, 19, 20, 23, 25–30, 34–37, 44, 48, 49, 51, 52**; crystallographic data, ORTEP plots, tables of atomic coordinates, bond lengths, bond angles, and torsional angles for **19a** and **36** (36 pages). Ordering information is given on any current masthead page.

Novel Rearranged Spongian Diterpenes from the Palauan Sponge *Dendrilla* sp.: Reassessment of the Structures of Dendrillolide A and Dendrillolide B

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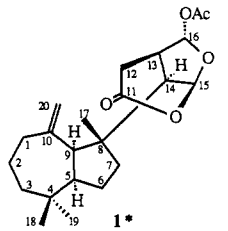
A reinvestigation of the Palauan sponge *Dendrilla* sp. has led to the isolation of four novel rearranged spongian diterpenes in addition to five of the diterpene metabolites previously reported from this sponge. Dehydroambliol A (**9**), 1-bromo-8-ketoambliol A acetate (**10**), norrisolide (**11**), dendrillolide A (**4**), and dendrillolide C (**3**) were reisolated and identified by comparison of spectral data with that of authentic samples. In addition, the novel diterpenes dendrillolide D (**5**), dendrillolide E (**6**), 12-desacetoxypolyrhaphin A (**7**), and 12-desacetoxyshahamin C (**8**) were isolated as minor constituents of this sponge. The structures of the four novel metabolites were determined by interpretation of spectral data. The structure of dendrillolide A (**4**) has been reassigned to that previously proposed for dendrillolide B by interpretation of new spectral data, particularly the two-dimensional heteronuclear NMR shift correlation experiments. The structure of dendrillolide B, which was not reisolated, remains undetermined.

We have previously reported[1] a chemical investigation of the Palauan sponge *Dendrilla* sp., in which the structures of three rearranged spongian diterpenes, dendrillolides A–C (**1–3**), were elucidated by interpretation of spectral data and by application of a biosynthetic hypothesis. Subsequent studies of the rearranged spongian diterpenes from the dorid nudibranch *Chromodoris macfarlandi*[2] revealed that the structure reported for dendrillolide A (**1**) was incorrect and that the structure assigned to dendrillolide B (**2**) was also suspect. This error



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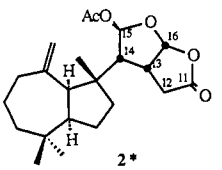

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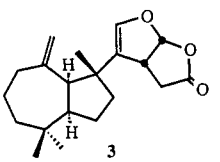
* Asterisk denotes incorrect structures

was confirmed when a different compound, aplyviolene,[3] was determined by X-ray analysis to have the same structure as that proposed for dendrillolide A. We therefore recollected the purple dendroceratid sponge *Dendrilla* sp. from exactly the same location at Kaibaku Island in Iwayama Bay, Palau, in order to determine revised structures for dendrillolides A and B. In this paper we report that the correct structure of dendrillolide A (**4**) is that previously assigned to dendrillolide B and that the structure of dendrillolide B is unknown. In addition, four new diterpenes, dendrillolide D (**5**), dendrillolide E (**6**), 12-desacetoxypolyrhaphin A (**7**), and 12-desacetoxyshahamin C (**8**) are reported.



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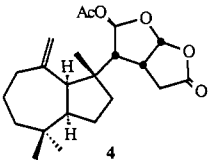

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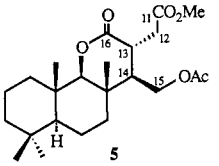

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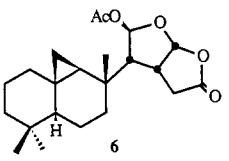

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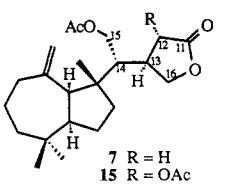
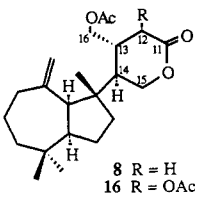


7 R = H
15 R = OAc



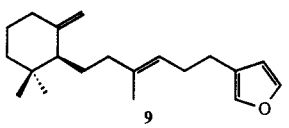
8 R = H
16 R = OAc

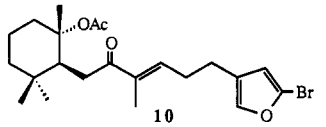
The dichloromethane extract of the lyophilized sponge was separated by flash chromatography on silica to yield four fractions that were determined by ^{1}H NMR spectroscopy to possess diterpene metabolites. Pure compounds were isolated from three of these fractions by HPLC on Partisil while the fourth fraction required additional isolation steps involving Sephadex LH-20 and silica flash chromatography in addition to HPLC on

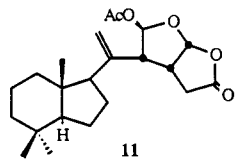
(1) Sullivan, B.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 3204.
(2) Molinski, T. F.; Faulkner, D. J.; Cun-Heng, H.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4564.
(3) Hambley, T. W.; Poiner, A.; Taylor, W. C. *Tetrahedron Lett.* **1986**, *27*, 3281. Buckleton, J. S.; Bergquist, P. R.; Cambie, R. C.; Clark G. R.; Karuso, P.; Richard, C. E. F. *Acta Crystallogr.* **1986**, *C42*, 1846.

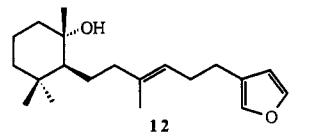
0022-3263/89/1954-5727$01.50/0

Partisil. This isolation scheme led to the reisolation of dehydroambliol A[4] (**9**, 0.005% dry weight), 1-bromo-8-ketoambliol A acetate (**10**, 0.11% dry weight), norrisolide[5] (**11**, 0.06% dry weight), dendrillolide A (**4**, 0.63% dry weight), and dendrillolide C (**3**, 0.004% dry weight). Dendrillolide B was not detected by ^{1}H NMR spectroscopy at any stage during the separation. A number of brominated metabolites related to ambliol A (**12**) were isolated and decomposed before they could be completely characterized. Four new diterpenes, dendrillolide D (**5**, 0.01% dry weight), dendrillolide E (**6**, 0.009% dry weight), 12-desacetoxypolyrhaphin A (**7**, 0.006% dry weight), and 12-desacetoxyshahamin C (**8**, 0.007% dry weight) were isolated as minor constituents of *Dendrilla* sp.

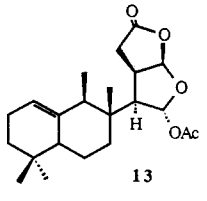


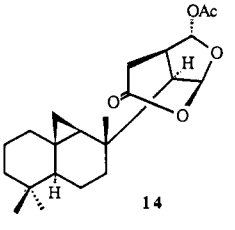






The structures of dendrillolides A (**1**) and B (**2**) were originally assigned by interpretation of spectral data and by comparison of the spectral data with those of known compounds.[1] Both compounds possessed a perhydroazulene hydrocarbon portion, which is not in question. Comparison of the ^{1}H NMR data for the dioxabicyclo portions of dendrillolides A and B with the corresponding data for norrisolide (**11**), the structure of which had been determined by X-ray analysis,[5] suggested that dendrillolide B (**2**) had a dioxabicyclo[3.3.0]octane ring system, and dendrillolide A (**1**) was therefore assigned the alternative dioxabicyclo[3.2.1]octane structure. When it was found that the spectral data for the dioxabicyclo ring system of dendrillolide A closely matched those of the dioxabicyclo[3.3.0]octane ring system of macfarlandin C (**13**), a structure that was also determined by X-ray analysis,[2] it became obvious that the structural assignment of dendrillolides A and B needed to be reinvestigated. The differences in the NMR spectra associated with the dioxabicyclo[3.3.0]octane system of norrisolide (**11**) and macfarlandin C (**13**) are due to the ability of the tetrahydrofuran ring (C13–C16) to adopt two different conformations,[2] depending, presumably, on the influence of the hydrocarbon portion of the compounds.





The sample of dendrillolide A (**4**) isolated from the 1988 collection of *Dendrilla* sp. was determined to be identical to that previously reported[1] by comparison of ^{1}H and ^{13}C NMR, HRMS, and optical rotation data. Extensive two dimensional NMR experiments were run on the new sample in deuterated benzene (20%) in carbon tetrachloride as solvent, which achieved the necessary dispersion of signals in the 2–3 ppm range of the ^{1}H NMR spectrum to allow assignment of each of the individual resonances. ^{1}H–^{1}H COSY and direct (XHCORR) and long-range (COLOC) heteronuclear two-dimensional NMR shift correlation experiments were used to assign all of the resonances in the ^{1}H and ^{13}C NMR spectra (Table I). This information verified the presence of the perhydroazulene moiety in dendrillolide A and suggested the structure possessed a dioxabicyclo[3.3.0]octane ring system rather than the dioxabicyclo[3.2.1]octane ring system originally reported.[1] In particular, the observation of a long-range C–H correlation from the C-11 carbonyl signal at δ 175.1 (s) to the H-16 signal at δ 5.73 (d, 1 H, J = 4.4 Hz) confirmed the presence of the bicyclo[3.3.0]ring system. The ^{1}H–^{1}H COSY spectrum showed that this acetal proton signal was then coupled to a methine proton signal at 2.60 (m, 1 H, J = 10.1, 9.3, 6.6, 4.4 Hz, H-13), which showed couplings to three additional proton signals (H-14 and CH_2-12) [only one additional coupling to H-13 would be observed for the dioxabicyclo[3.2.1]octane ring system]. The infrared band at 1800 cm^{-1} also indicates the presence of a γ-lactone instead of a δ-lactone. It was noted that each of the infrared bands previously reported[1] for dendrillolide A were shifted to lower wavenumber by approximately 15 cm^{-1} when compared with the data obtained for our sample. This calibration error was a significant factor in the incorrect structural assignment. Additional long-range carbon–proton correlations which verify the presence of the dioxabicyclo[3.3.0]octane ring system, and its attachment to the perhydroazulene ring system are presented in Figure 1. The stereochemistry of dendrillolide A (**4**) was determined by NOEDS experiments. Irradiation of

Table I. ^{13}C NMR [50 MHz, Chemical Shift (δ), Multiplicity] and ^{1}H NMR [200 MHz, Chemical Shift (δ), Multiplicity, Number of Hydrogens, Coupling Constants (Hz)] Data for Dendrillolide A (4) (20% C_6D_6 in CCl_4)

carbon no.[a]	^{13}C	^{1}H
1	37.8 (t)	2.28 (m, 1 H)
		1.73 (m, 1 H)
2	28.8 (t)	1.62 (m, 1 H)
		1.26 (m, 1 H)
3	38.1 (t)	1.60 (m, 1 H)
		1.30 (m, 1 H)
4	36.2 (s)	
5	54.5 (d)	1.65 (m, 1 H)
6	27.2 (t)	1.58 (br, 2 H)
7	38.3 (t)	1.48 (m, 1 H)
		1.16 (m, 1 H)
8	47.0 (s)	
9	56.0 (d)	2.52 (d, 1 H, 9.0)
10	153.6 (s)	
11	175.1 (s)	
12	28.9 (t)	2.34 (dd, 1 H, 17.5, 10.1)
		2.09 (dd, 1 H, 17.5, 9.3)
13	42.0 (d)	2.60 (m, 1 H, 10.1, 9.3, 6.6, 4.4)
14	54.8 (d)	2.40 (dd, 1 H, 6.6, 6.2)
15	97.0 (d)	6.33 (d, 1 H, 6.2)
16	105.0 (d)	5.73 (d, 1 H, 4.4)
17	24.3 (q)	0.76 (s, 3 H)
18	26.0 (q)	0.91 (s, 3 H)
19	34.7 (q)	0.93 (s, 3 H)
20	114.7 (t)	4.60 (d, 1 H, 2.3)
		4.46 (d, 1 H, 2.3)
$OCOCH_3$	168.9 (s)	
$OCOCH_3$	21.2 (q)	1.92 (s, 3 H)

[a] Assignments were made by the analysis of ^{1}H–^{13}C 2D NMR shift correlation experiments. Experiments to detect direct couplings (XHCORR) and long-range couplings (COLOC) were conducted on a Bruker WP200 SY spectrometer. The delays were optimized for one-bond couplings of J = 135 Hz (XHCORR) or for long-range couplings of J = 7 or 10 Hz (COLOC).

(4) Walker, R. P.; Faulkner, D. J. *J. Org. Chem.* **1981**, *46*, 1098.
(5) Hochlowski, J. E.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1983**, *48*, 1141.

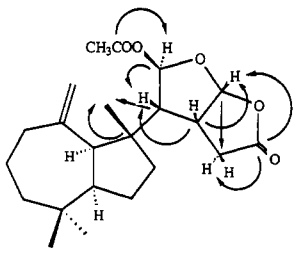


Figure 1. Selected long-range carbon–proton correlations of dendrillolide A (**4**) observed by COLOC (parameters maximized for J_{CCH} = 7 or 10 Hz). [The arrows indicate a correlation from carbon (tail) to hydrogen (head)].

the resonance for H-13 resulted in enhancement of the H-16 signal at 5.73 (8.0%) and the H-14 signal at 2.40 (7.3%) while irradiation of the H-9 resonance at 2.52 produced enhancements of the H-15 signal at 6.33 (5.6%) and the H-5 signal at 1.65 (4.4%).

In addition to the previously reported metabolites, four new rearranged spongian diterpenes were also isolated from this collection of *Dendrilla* sp. Dendrillolide D (**5**) was isolated as crystalline needles, mp 120 °C, and displayed a molecular ion at m/z = 408.2519 ($C_{22}H_{36}O_6$) in the high-resolution mass spectrum. A strong, broad infrared band at 1730 cm^{-1} suggested the presence of more than one ester functionality in the molecule, and the ^{13}C NMR data revealed three ester carbonyl resonances [δ 173.2 (s), 172.2 (s), 170.6 (s)]. ^{13}C NMR signals at δ 52.0 (q) and 21.4 (q) along with ^1H NMR signals at 3.71 (s, 3 H) and 2.05 (s, 3 H) suggested the presence of methyl ester and acetate moieties in the molecule, leaving the third ester functionality to be incorporated into a δ-lactone ring. The relative arrangement of these three groups was determined by analysis of ^1H NMR and ^1H–^1H COSY data. The signals at δ 4.28 (dd, 1 H, J = 11.8, 4.4 Hz, H-15β) and 3.84 (dd, 1 H, J = 11.8, 5.7 Hz, H-15α) due to methylene protons attached to a carbon-bearing oxygen were coupled to a methine proton signal at δ 1.88 (ddd, 1 H, J = 11.2, 5.7, 4.4 Hz, H-14), which was further coupled to a signal at δ 2.54 (ddd, 1 H, J = 11.2, 4.4, 3.7 Hz, H-13) that was assigned to a methine proton adjacent to a carbonyl group. The methine proton signal at δ 2.54 was also coupled to two signals at δ 3.24 (dd, 1 H, J = 17.8, 4.4 Hz, H-12β) and 2.82 (dd, 1 H, J = 17.8, 3.7 Hz, H-12α) assigned to methylene protons adjacent to a second carbonyl group. The large coupling constant of 11.2 Hz between H-13 and H-14 indicated that these protons were in a trans-diaxial orientation on the δ-lactone ring. None of the four methylene protons (CH_2-12 or CH_2-15) exhibited the large coupling constants with H-13 or H-14 which would have been expected if these methylene groups were also contained within the δ-lactone ring. These data are compatible with a δ-lactone bearing an equatorial carbomethoxymethylene group at C-13 and an equatorial acetoxymethylene group at C-14 with the oxygen of the δ-lactone ring being joined to C-9 of the decalin ring system. This analysis was supported by the observation of a fragment ion in the mass spectrum at m/z 208 (100%, $C_{14}H_{24}O$), which corresponds to the loss of the C-11 to C-16 portion of the molecule. The stereochemistry of dendrillolide D (**5**) was determined by NOEDS experiments run in benzene-d_6. Irradiation of the signal at δ 3.83 (s, 1 H, H-9) produced enhancements in the signals at δ 1.88 (H-14, 13.6%) and 0.54 (dd, 1 H, H-5, 3.5%). These results require a trans-fused decalin ring system bearing a substituted δ-lactone ring in the orientation shown for dendrillolide D (**5**).

Dendrillolide E (**6**) was isolated as a clear oil and was determined to have a molecular fromula of $C_{22}H_{32}O_5$ (m/z 376.2271). ^{13}C NMR signals at δ 24.7 (d, C-9), 23.1 (s, C-10), and 13.2 (t, C-20) along with mutually coupled ^1H NMR signals at δ 0.47 (br s, 1 H), 0.44 (m, 1 H), and 0.24 (m, 1 H) indicated the presence of a cyclopropyl ring and were similar to the signals observed for polyrhaphin C (**14**)[6] as were the remainder of the ^{13}C NMR resonances for the hydrocarbon portion of dendrillolide E (**6**). The observation of a major fragment ion in the mass spectrum of both compounds at m/z 190 (100%, $C_{14}H_{22}$) provided further evidence for the tricyclic hydrocarbon portion in dendrillolide E (**6**). The remaining ^{13}C NMR signals for dendrillolide E matched the signals for dendrillolide A (**4**), suggesting a dioxabicyclo[3.3.0]octane ring system for dendrillolide E (**6**) rather than the dioxabicyclo[3.2.1]octane ring system seen in polyrhaphin C (**14**). The ^1H NMR spectrum of dendrillolide E (**6**) included six signals comprising a single spin system similar to that observed for dendrillolide A (**4**). The methylene proton signals at δ 3.05 (dd, 1 H, J = 17.9, 8.9 Hz, H-12) and 2.54 (dd, 1 H, J = 17.9, 8.9 Hz, H-12′) that were assigned as α-carbonyl protons were coupled to a methine proton signal at δ 3.20 (m, 1 H, J = 8.9, 8.9, 4.8, 2.7 Hz, H-13). This methine signal was also coupled to an acetal signal at δ 6.06 (d, 1 H, J = 4.8 Hz, H-16) and another methine signal at δ 2.57 (dd, 1 H, J = 5.5, 2.7 Hz, H-14) which was further coupled to a second acetal proton at δ 6.46 (d, 1 H, J = 5.5 Hz, H-15). An infrared band at 1795 cm^{-1} indicated a γ-lactone ring and allowed assignment of the dioxabicyclo[3.3.0]octane ring system to dendrillolide E (**6**). The stereochemistry about this ring system was shown to be the same as in dendrillolide A (**4**) by a single NOEDS experiment: irradiation of the H-13 signal resulted in enhancement of the signals for H-14 (5.3%) and H-16 (8.1%).

12-Desacetoxypolyrhaphin A (**7**) was isolated as a clear oil and was found to have a molecular formula of $C_{22}H_{34}O_4$ (m/z 362.2447). The ^{13}C and ^1H NMR data for 12-desacetoxypolyrhaphin A (**7**) were nearly identical with those of polyrhaphin A (**15**)[6] except that the ^1H NMR spectrum of 12-desacetoxypolyrhaphin A (**7**) lacked an acetate signal and a methine proton signal at δ 5.69 (d, 1 H, H-12), which were replaced by a methylene signal at 2.43 (d, 2 H, J = 9.7 Hz, CH_2-12). Comparison of the ^{13}C NMR data (Table II) also suggested that the new compound (**7**) was simply the 12-desacetoxy analogue of polyrhaphin A (**15**). The presence of a γ-lactone ring was verified by the observation of a band at 1775 cm^{-1} in the infrared spectrum. The perhydroazulene hydrocarbon portion of the molecule gave rise to a prominent fragment ion in the mass spectrum at m/z 191 (22%, $C_{14}H_{23}$). The stereochemistry of 12-desacetoxypolyrhaphin A (**7**) was determined to be identical with that of polyrhaphin A (**15**) by the observation of NOE enhancements in the signals for H-5 [1.85 (m, 1 H, 8.7%)] and H-13 [3.07 (m, 1 H, 11.2%)] upon irradiation of the signal for H-9 [2.56 (d, 1 H, J = 8.3 Hz)]. The small coupling constant between H-13 and H-14 ($J_{13,14}$ = 3.7 Hz), which was also observed for polyrhaphin A (**15**), indicated that both compounds had the same stereochemistry at C-14.

12-Desacetoxyshahamin C (**8**) was isolated as a clear oil and was found to be an isomer of 12-desacetoxypolyrhaphin A (**7**) by observation of the molecular ion (m/z 362.2456) in the high-resolution mass spectrum. The ^1H and ^{13}C NMR data for 12-desacetoxyshahamin C (**8**) were very similar to those of shahamin C (**16**).[7] Differences in the ^1H NMR data of 12-desacetoxyshahamin C (**8**) in-

(6) Bobzin, S. C.; Faulkner, D. J. *J. Org. Chem.*, 1989, *54*, 3902.
(7) Carmely, S.; Cojocaru, M.; Loya, Y.; Kashman, Y. *J. Org. Chem.* 1988, *53*, 4801.

Table II. ^{13}C NMR Data [50 MHz, $CDCl_3$ Chemical Shift (δ), Multiplicity] for 12-Desacetoxypolyrhaphin A (7), Polyrhaphin A (15), 12-Desacetoxyshahamin C (8), and Shahamin C (16)

carbon no.[a]	7	15	8	16
1	37.0 (t)[b]	37.0 (t)[b]	37.1 (t)[b]	37.1 (t)
2	28.9 (t)[c]	28.9 (t)[c]	28.8 (t)[c]	28.8 (t)
3	37.8 (t)[b]	37.9 (t)[b]	37.7 (t)[b]	37.6 (t)
4	36.1 (s)	36.1 (s)	36.2 (s)	36.1 (s)
5	54.3 (d)	54.7 (d)	54.4 (d)	54.6 (d)
6	26.5 (t)[c]	26.4 (t)[c]	25.9 (t)[c]	26.0 (t)
7	38.9 (t)[b]	39.0 (t)[b]	37.6 (t)[b]	37.6 (t)
8	48.8 (s)	48.4 (s)	48.5 (s)	48.2 (s)
9	57.2 (d)	56.3 (d)	54.8 (d)	54.8 (d)
10	154.1 (s)	153.9 (s)	153.7 (s)	153.2 (s)
11	169.1 (s)[d]	169.3 (s)[d]	170.8 (s)[d]	168.8 (s)[b]
12	30.8 (t)	69.3 (d)	32.2 (t)	66.8 (d)
13	35.2 (d)	40.7 (d)	32.0 (d)	36.4 (d)
14	48.6 (d)	48.6 (d)	44.1 (d)	45.2 (d)
15	73.6 (t)	70.7 (t)	68.2 (t)	65.9 (t)
16	63.1 (t)	63.6 (t)	67.5 (t)	64.2 (t)
17	21.4 (q)[e]	21.4 (q)[e]	21.3 (q)[e]	20.7 (q)[c]
18	25.5 (q)	25.5 (q)	25.6 (q)	25.5 (q)
19	34.5 (q)	34.4 (q)	34.4 (q)	34.4 (q)
20	115.0 (t)	115.0 (t)	115.0 (t)	115.2 (t)
$OCOCH_3$	170.7 (s)[d]	170.3 (s)[d]	172.9 (s)[d]	170.6 (s)[b]
		172.4 (s)[d]		169.4 (s)[b]
$OCOCH_3$	21.0 (q)[e]	20.9 (q)[e]	20.8 (q)[e]	20.6 (q)[c]
		20.5 (q)[e]		20.4 (q)[c]

[a] Assignments of 12-desacetoxypolyrhaphin A (7) and 12-desacetoxyshahamin C (8) were made by comparison to polyrhaphin A[6] (14) and shahamin C[7] (16), respectively. [b-e] Assignments may be interchanged within a column.

cluded the absence of an acetate signal and a methine proton signal at δ 5.44 (d, 1 H, H-12), which were replaced by a methylene signal at δ 2.55 (m, 2 H, CH_2-12). The ^{13}C NMR data showed appreciable chemical shift differences for C-12 and adjacent carbons only (Table II). These NMR data suggested that the new compound (8) was simply the 12-desacetoxy analogue of shahamin C (16). The presence of a δ-lactone ring was verified by the observation of an infrared band at 1745 cm^{-1}. The perhydroazulene hydrocarbon portion of the molecule was responsible for a major fragment ion in the mass spectrum at m/z 191 (25%, $C_{14}H_{23}$). The stereochemistry of 12-desacetoxyshahamin C (8) was determined to be identical with that of shahamin C (16) by analysis of data from NOEDS experiments and by comparison of ^1H–^1H coupling constants. Irradiation of the signal at δ 2.73 (d, 1 H, J = 8.7 Hz, H-9) caused NOE enhancements of the signals at δ 1.90 (m, 1 H, H-5) and 4.32 (dd, 1 H, J = 11.8, 6.1 Hz, H-15α). Although an enhancement of H-14 was not observed, the α-orientation of this proton was assigned by analysis of its coupling constants with the adjacent methylene protons. The magnitude of the coupling constants ($J_{14,15\alpha}$ = 6.1 Hz, $J_{14,15\beta}$ = 10.0 Hz) indicated that H-14 and H-15β must both be axially oriented. The observation of an NOE between H-9 and H-15α confirmed the α-orientation of this proton, therefore placing the axial proton of the methylene group on the β-face of the lactone ring. An enhancement of the signal for H-13 [2.11 (m, 1 H, 3.6%)] upon irradiation of the CH_3-17 signal at 0.59 (s, 3 H)[8] completed the stereochemical assignments of 12-desacetoxyshahamin C (8).

The original structural elucidations of dendrillolides A (1) and B (2) were incorrect due to an invalid assumption that the dioxabicyclo[3.3.0]octane ring system could adopt only one conformation and hence give rise to only one set of coupling constants. The similarity of the ^1H NMR chemical shifts and coupling constants indicated that dendrillolide B (2) had the dioxabicyclo[3.3.0]octane ring system of norrisolide (11), which was the only model compound available at that time. Since dendrillolide A (1) appeared to have the same hydrocarbon portion as dendrillolide B (2) it was assigned the alternative dioxabicyclo[3.2.1]octane ring system, which appeared at that time to fit the ^1H NMR data and the (incorrect) IR data. The reassignment of the structure of dendrillolide A from 1 to 4 leaves the structure of dendrillolide B unknown. The spectral data of dendrillolide B do not match those reported for any of the known spongian diterpenes. Until a new specimen of dendrillolide B can be reisolated, any further speculation concerning this compound seems pointless.

(8) This experiment was run in a benzene-d_6 solution.

Experimental Section

Extraction and Chromatography. The purple dendritic sponge *Dendrilla* sp. was collected by hand at a depth of 1–5 m in a marine lake on Kaibaku Island, Iwayama Bay, Palau. The sponge was stored at −10 °C for approximately 2 weeks and then freeze-dried. The lyophilized sponge tissue (109.5 g) was extracted with dichloromethane (4 × 1 L) and methanol (3 × 1 L). The dichloromethane extract (5.8 g) was separated by silica flash chromatography (Kieselgel 60, 230–400 mesh, bed size 6 × 10 cm) using a solvent gradient from hexane/diethyl ether (8:2) through 100% diethyl ether to ethyl acetate, and finally methanol. Four of the fractions that were eluted with hexane/diethyl ether mixtures consisted of mixtures of diterpenes as indicated by ^1H NMR spectroscopy.

The least polar fraction of the four (412 mg) was recognized as a mixture of ambliol derivatives and was separated by HPLC on Partisil using hexane/diethyl ether (1:1) to yield nearly pure fractions of six unstable compounds. The six compounds were tentatively identified by ^1H NMR analysis as 1-bromo-8-ketoambliol A (8.5 mg, 0.008% dry weight), dehydroambliol A (9, 5.9 mg, 0.005% dry weight), 8-ketoambliol A (16.2 mg, 0.015% dry weight), 1-bromo-8-ketoambliol A acetate (10, 121 mg, 0.11% dry weight), ambliol A (12, 13.4 mg, 0.012% dry weight), and 1-bromoambliol A (29.8 mg, 0.027% dry weight). All six compounds decomposed within 48 h, preventing verification of the structural assignments. The instability of these compounds is most likely due to autocatalytic decomposition with release of hydrogen bromide from the bromofuran moiety.

The second fraction (325 mg) was separated by HPLC on Partisil using hexane/diethyl ether (4:6). A number of unstable ambliol diterpene derivatives were again isolated, but they quickly decomposed. In addition, two impure fractions of spongian diterpenes were isolated. The first fraction (24.8 mg, 0.023% dry weight) was also unstable and decomposed before any additional data could be collected. The second fraction (14.0 mg) was further purified by HPLC on Partisil in hexane/diethyl ether (55:45) to yield dendrillolide C (3, 4.0 mg, 0.004% dry weight).

Approximately half of the third fraction (1.009 g) was separated on Sephadex LH-20 (column size 95 × 3 cm) using hexane/dichloromethane/methanol (2:1:1) as eluant. The major UV active fraction (716 mg) was again subjected to Sephadex LH-20 (column size 95 × 3 cm) using dichloromethane/methanol (1:1) as eluant. Approximately half of the major fraction from LH-20 chromatography (336 mg) was separated by silica flash chromatography (Kieselgel 60, 230–400 mesh, column size 23 × 2 cm) using an elution gradient from hexane/diethyl (1:1) to 100% diethyl ether. The major fraction (193 mg) was further purified by HPLC on Partisil using hexane/diethyl ether (45:55) to yield pure dendrillolide A (4, 147 mg, 0.63% dry weight). The following fraction from the flash chromatography was separated by HPLC on Partisil in hexane/diethyl ether (55:45) to yield dendrillolide E (6, 2.5 mg, 0.009% dry weight) and 12-desacetoxypolyrhaphin A (7, 1.7 mg, 0.006% dry weight).

The most polar fraction from the original flash chromatography (113 mg) was separated by HPLC on Partisil in hexane/diethyl ether (3:7) to yield norrisolide (11, 16.6 mg, 0.061% dry weight), dendrillolide D (5, 2.6 mg, 0.01% dry weight), and 12-desacet-

oxyshahamin C (8, 1.9 mg, 0.007% dry weight).

Dendrillolide A (4): clear oil; $[\alpha]_D$ +87.0° (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 1800, 1750, 1215, 990 cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table I; HRMS (EI) *m/z* 376.2246 (M^+), $C_{22}H_{32}O_5$ requires 376.2250.

Dendrillolide D (5): crystals from diethyl ether/hexanes; mp 120 °C; $[\alpha]_D$ +35.8° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 1730, 1370, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 3 H), 0.88 (s, 3 H), 0.96 (s, 3 H), 1.01 (s, 3 H), 1.20 (m, 1 H), 1.28 (m, 1 H), 1.42 (br d, 1 H, *J* = 13.3 Hz), 1.48 (m, 1 H), 1.60 (dd, 2 H, *J* = 13.5, 2.1 Hz), 1.88 (ddd, *J* = 11.2, 5.7 4.4 Hz), 1.93 (dt, 1 H, *J* = 13.3, 2.8 Hz), 2.03 (br d, 1 H, *J* = 11.4 Hz), 2.05 (s, 3 H), 2.54 (ddd, 1 H, *J* = 11.2, 4.4, 3.7 Hz), 2.82 (dd, 1 H, *J* = 17.8, 3.7 Hz), 3.24 (dd, 1 H, *J* = 17.8, 4.4 Hz), 3.71 (s, 3 H), 3.83 (s, 1 H), 3.84 (dd, 1 H, *J* = 11.8, 5.7 Hz), 4.28 (dd, 1 H, *J* = 11.8, 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 173.2 (s), 172.2 (s), 170.6 (s), 92.7 (d), 63.3 (t), 53.0 (d), 52.0 (q), 48.9 (d), 41.7 (t), 39.4 (d), 38.8 (s), 38.4 (t), 37.1 (t), 37.1 (s), 34.7 (t), 33.1 (q), 32.9 (s), 21.4 (q), 21.0 (q), 17.8 (t), 17.7 (t), 14.6 (q), 14.0 (q); HRMS (EI) *m/z* 408.2519 (M^+), $C_{23}H_{36}O_6$ requires 408.2512.

Dendrillolide E (6): clear oil; $[\alpha]_D$ +21.4° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 1795, 1750, 1215, 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.24 (m, 1 H), 0.44 (m, 1 H), 0.47 (br s, 1 H), 0.82 (s, 3 H), 0.92 (s, 3 H), 0.94 (s, 3 H), 2.07 (s, 3 H), 2.54 (dd, 1 H, *J* = 17.9, 8.9 Hz), 2.57 (dd, 1 H, *J* = 5.5, 2.7 Hz), 3.05 (dd, 1 H, *J* = 17.9, 8.9 Hz), 3.20 (m, 1 H, *J* = 8.9, 8.9, 4.8, 2.7 Hz), 6.06 (d, 1 H, *J* = 4.8 Hz), 6.46 (d, 1 H, *J* = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 175.5 (s), 169.8 (s), 105.8 (d), 97.7 (d), 56.9 (d), 47.3 (d), 42.2 (t), 41.2 (d), 38.3 (t), 36.5 (t), 34.5 (s), 32.6 (s), 30.5 (q), 28.3 (t), 28.0 (q), 24.7 (d), 23.1 (s), 21.4 (t), 21.2 (q), 20.3 (q), 17.5 (t), 13.2 (t); HRMS (EI) *m/z* 376.2271 (M^+), $C_{22}H_{32}O_5$ requires 376.2250.

12-Desacetoxypolyrhaphin A (7): clear oil; $[\alpha]_D$ +14.3° (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 1775, 1740, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 0.92 (s, 3 H), 0.96 (s, 3 H), 1.85 (m, 1 H), 2.04 (s, 3 H), 2.34 (m, 1 H), 2.43 (d, 2 H, *J* = 9.7 Hz), 2.56 (d, 1 H, *J* = 8.3 Hz), 3.07 (m, 1 H, *J* = 9.7, 8.8, 8.8, 3.7 Hz), 3.99 (dd, 1 H, *J* = 11.8, 9.1 Hz), 4.10 (t, 1 H, *J* = 8.8 Hz), 4.38 (dd, 1 H, *J* = 11.8, 4.0 Hz), 4.43 (t, 1 H, *J* = 8.8 Hz), 4.61 (d, 1 H, *J* = 1.7 Hz), 4.84 (d, 1 H, *J* = 1.7 Hz); ^{13}C NMR, see Table II; HRMS (EI) *m/z* 362.2447 (M^+), $C_{22}H_{34}O_4$ requires 362.2457.

12-Desacetoxyshahamin C (8): clear oil; $[\alpha]_D$ +54.0° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 1745, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 3 H), 0.95 (s, 3 H), 1.00 (s, 3 H), 1.78 (m, 1 H), 1.82 (m, 1 H), 1.90 (m, 1 H), 2.09 (s, 3 H), 2.36 (m, 1 H), 2.48 (m, 1 H), 2.55 (m, 2 H), 2.73 (d, 1 H, *J* = 8.7 Hz), 3.84 (dd, 1 H, *J* = 11.2, 7.8 Hz), 4.19 (dd, 1 H, *J* = 11.2, 4.3 Hz), 4.21 (dd, 1 H, *J* = 11.8, 10.0 Hz), 4.32 (dd, 1 H, *J* = 11.8, 6.1 Hz), 4.63 (d, 1 H, *J* = 2.0 Hz), 4.86 (d, 1 H, *J* = 2.0 Hz); ^{13}C NMR, see Table II; HRMS (EI) *m/z* 362.2456 (M^+), $C_{22}H_{34}O_4$ requires 362.2457.

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Synthesis of an N^1-Phosphotryptophan-Containing Tripeptide: Glutamyl-N^1-phosphotryptophylleucine[1]

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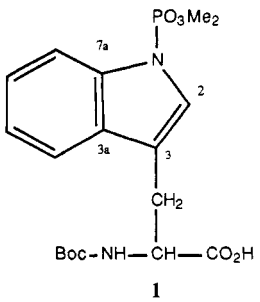
The novel protected amino acid N^α-(*tert*-butyloxycarbonyl)-N^1-(dimethylphosphono)tryptophan, or Boc-Trp(Dmop)-OH, was used in the solution-phase synthesis of the tripeptide Z-Glu(OBzl)-Trp(Dmop)-Leu-OBzl. The N^1-phosphotryptophan-containing peptide H-Glu-Trp(PO_3H_2)-Leu-OH was obtained by the selective deprotection of the protected tripeptide with CF_3SO_3H/CF_3CO_2H/*m*-cresol/DMS or thioanisole. The dimethylphosphate group was also evaluated as a new protecting group for the tryptophan indole moiety and was found to effectively suppress *tert*-butylation of the indole ring during acidolytic removal of the Boc group and to be stable to "high" HF conditions, palladium-catalyzed hydrogenation, and CF_3SO_3H/CF_3CO_2H/*m*-cresol treatment. The Dmop group was cleaved by 1 M NaOH, and the N^1-(methylphosphono)tryptophan peptide, H-Glu-Trp($MeOPO_2H$)-Leu-OH, was obtained by mild base (e.g., piperidine) treatment of H-Glu-Trp-(Dmop)-Leu-OH.

We recently reported[2] the synthesis of the N^1-(dimethylphosphono)tryptophan derivative, Boc-Trp-(Dmop)-OH (1), which can be deprotected selectively to give the novel amino acid N^1-phosphotryptophan, *P*Trp (2), or fully to yield the parent amino acid. Modern peptide synthesis methods permit the efficient incorporation of tryptophan into peptides without difficulties. However, decomposition of tryptophan frequently occurs during the acidolytic removal of side-chain protection and cleavage from the resin in solid-phase peptide synthesis of tryptophan-containing peptides. Relatively little research has been concerned with the development of indole protecting groups[3,4] to overcome the problems of oxidative degrada-



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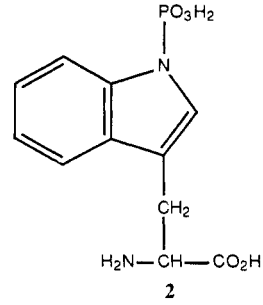

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(1) The abbreviations for natural amino acids and nomenclature for peptide structures follow the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature. Other abbreviations used: Dmop = dimethylphosphono, TFA = trifluoroacetic acid, TFMSA = trifluoromethanesulfonic acid, Z = benzyloxycarbonyl, Boc = *tert*-butyloxycarbonyl, DMS = dimethyl sulfide, Bzl = benzyl, EDT = ethane-1,2-dithiol, THF = tetrahydrofuran.

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