Nuapapuin A and Sigmosceptrellins D and E: New Norterpene Cyclic Peroxides from a Southern Australian Marine Sponge, *Sigmosceptrella* sp.

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Received May 29, 1998

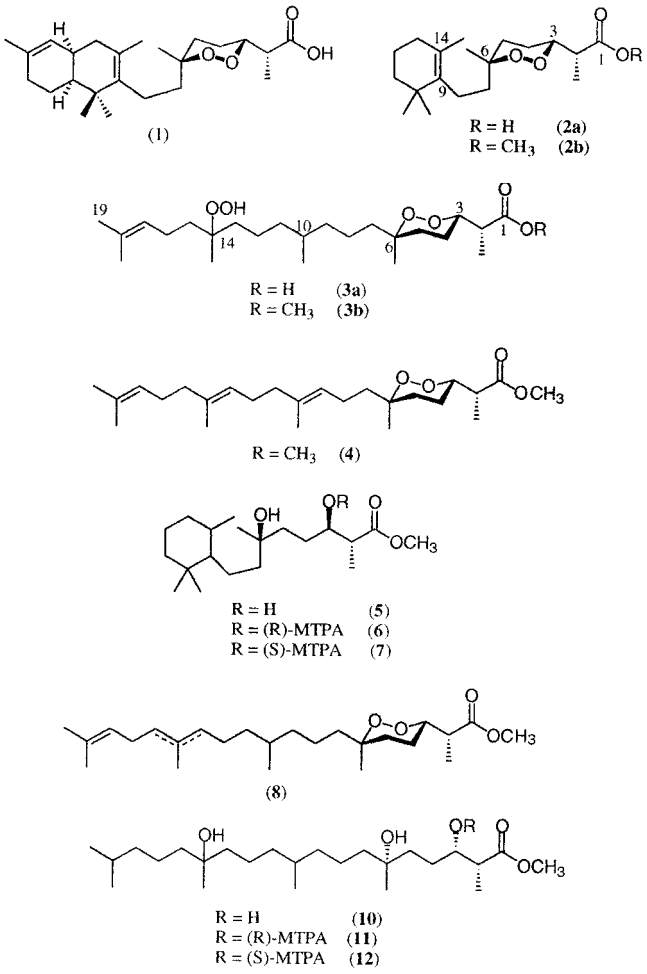
A *Sigmosceptrella* sp. from the Great Australian Bight, Australia, has yielded the new norditerpene cyclic peroxide, nuapapuin A (**2a**), and the norsesterterpene cyclic peroxide sigmosceptrellin D (**3a**), characterized as the corresponding methyl esters **2b** and **3b**. The crude methylated sponge extract also yielded the new norsesterterpene cyclic peroxide sigmosceptrellin E methyl ester (**4**). Relative stereochemistry about C2, C3, and C6 was assigned by established empirical rules and absolute stereochemistry by the advanced Mosher procedure. A plausible biosynthetic pathway has been proposed that rationalizes key transformations in the biosynthesis of all known norterpene cyclic peroxides and related norterpene ketones, dienes and sigmosceptrins.

Over the last two decades, numerous norterpene cyclic peroxides have been reported from marine sponges.[1−13] Southern Australian sponges have been particularly productive in this regard, with specimens of the genera *Latrunculia*,[5,7,8,12] *Mycale*,[4,6,9−11] and *Sigmosceptrella*[2] featuring prominently in the discovery of new norterpene cyclic peroxides. In addition to novel structures, we have come to recognize, through screening by the National Cancer Institute, that selected norterpene cyclic peroxides such as trunculin A (**1**)[5] possess noteworthy antitumor properties. In continuing our investigations into the chemistry of southern Australian marine sponges, we anticipated that discovery of new norterpene cyclic peroxides would provide evidence supporting a biosynthetic origin for this unique class of marine metabolite. Such compounds would also prove useful in defining structure−activity relationships.

Results and Discussion

The crude EtOH extract of a *Sigmosceptrella* sp. obtained during trawling operations in the Great Australian Bight, Australia, displayed growth inhibitory properties against *Micrococcus luteus*, *Serratia marcescens*, and *Staphylococcus aureus*. TLC and ^{1}H NMR analysis suggested the presence of cyclic peroxide carboxylic acids accompanied by minor amounts of related methyl esters. Following established procedures,[4−8,10−12] the crude extract was exhaustively methylated with ethereal CH_2N_2 and subjected to chromatographic fractionation to yield the norditerpene cyclic peroxide methyl ester **2b** and the norsesterterpene cyclic peroxide methyl esters **3b** and **4**.

Compound **2b** was isolated as a stable oil with a molecular formula (M + Na, $C_{20}H_{34}O_4Na$, Δ mmu −1.7) isomeric to the known sponge metabolite nuapapuin A methyl ester[3] (formerly known as methyl nuapauanoate).[13] Comparison of NMR and $[\alpha]_D$ data for **2b** with that reported in the literature[3] revealed **2b** to be identical with nuapapuin A methyl ester. Although nuapapuin A methyl ester has been known since 1984,[3] doubt has been raised about the assigned relative stereochemistry,[14] and the absolute stereochemistry has yet to be assigned. A recent report of **2b** in the chemical literature[13] acknowledged earlier concerns about relative stereochemistry, but did not provide experimental evidence to resolve assignment of either relative or absolute stereochemistry. Our reisolation of **2b** permitted the relative stereochemistry to be determined using established empirical rules.[4] The ^{1}H NMR chemical shift for the 2-CH_3 (δ 1.13), a large $J_{3,4ax}$ (8 Hz), and the ^{13}C NMR chemical shift for the 6-CH_3 (23.4 ppm) were consistent with the 2*R**,3*R**,6*R** stereochemistry as shown. The absolute stereochemistry for **2b** was determined using the advanced Mosher procedure.[15,16] Hydrogenation of **2b** yielded the diol **5**, which was subsequently



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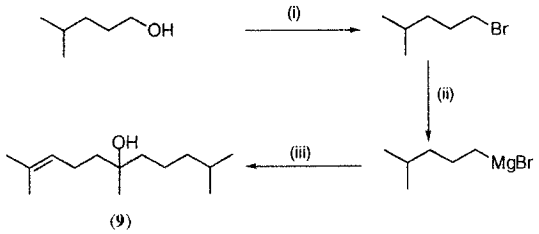
10.1021/np980223r CCC: $18.00
Published on Web 12/05/1998

Scheme 1[a]



[a] Key: (i) H_2SO_4, aq HBr, Δ; (ii) Mg, Et_2O, Δ; (iii) 6-methyl-5-hepten-2-one, Et_2O, Δ.

esterified to yield the *R* and *S* MTPA esters **6** and **7,** respectively. Diagnostic ^{1}H NMR chemical shift differences between the diastereomeric MTPA esters (Δ $\delta S - \delta R$; 2-CH_3 (−21.7 Hz), H-2 (−3.2 Hz), −CO_2CH_3 (−17.1 Hz), 6-CH_3 (+22.7 Hz)) confirmed a 3*R* and hence 2*R*,3*R*,6*R* absolute stereochemistry. Careful analysis of the ^{1}H NMR spectrum of the crude unmethylated sponge extract (relative integration between the *gem*-dimethyls at C-10 and CO_2CH_3) confirmed that **2b** occurred naturally as the free carboxylic acid, nuapapuin A (**2a**). It was not possible to confirm whether nuapapuin A methyl ester (**2b**) occurred naturally in the crude extract—even though trace amounts of norterpene cyclic peroxide methyl esters were clearly present by TLC and ^{1}H NMR (CO_2CH_3 resonance) analysis. This is the first account of nuapapuin A as a natural product.

Sigmosceptrellin D methyl ester (**3b**) was isolated as a stable oil with a molecular formula (M + Na − H_2O, $C_{25}H_{44}O_5Na$, Δ mmu −0.3) consistent with three degrees of unsaturation. Examination of the NMR and IR data for **3b** revealed the presence of a cyclic peroxide methyl ester moiety. Application of empirical rules (^{1}H NMR chemical shift for 2-CH_3 (δ 1.24), a large $J_{3,4ax}$ (8.2 Hz), and ^{13}C NMR chemical shift for the 6-CH_3 (20.2 ppm)) confirmed a 2*R**,3*S**,6*R** relative stereochemistry. Further examination of the NMR data revealed resonances consistent with a single trisubstituted double bond (^{1}H: δ 5.14; ^{13}C: 124.7, 131.7 ppm), which, in the absence of additional sp or sp^2 hybridized carbons, required that the remaining structural unit in **3b** be acyclic. The ^{13}C NMR data for **3b** also revealed a single deshielded quaternary carbon (77.2 ppm), which, given the need to accommodate two remaining oxygen atoms, pointed to the presence of a hydroperoxide moiety. COSY and HMBC NMR experiments established the gross structure for **3b** as shown (or the regioisomer with a C 10-hydroperoxide). The position of the hydroperoxide moiety was confirmed by reduction of **3b** to a mixture of diene regioisomers (**8**). Most significantly, the COSY NMR spectra for the mixed dienes (**8**) displayed a correlation from H15 and H17 to a common bisallylic methylene (δ 2.70), requiring that the hydroperoxide in the natural product **3b** be positioned at C14. Since a hydroperoxide is a rare functional group in the marine natural products literature,[17,18] we undertook to support the assigned structure by preparing the model alcohol **9** (see Scheme 1). Spectroscopic comparisons revealed significant differences between **3b** (^{1}H: 14 H_3, δ 0.87; ^{13}C: C 14, 77.2 ppm) and **9** (^{1}H: 14 H_3, δ 1.16; ^{13}C: C 14, 72.7 ppm), consistent with literature precedence between a tertiary hydroperoxide and a tertiary hydroxide. [17,18]

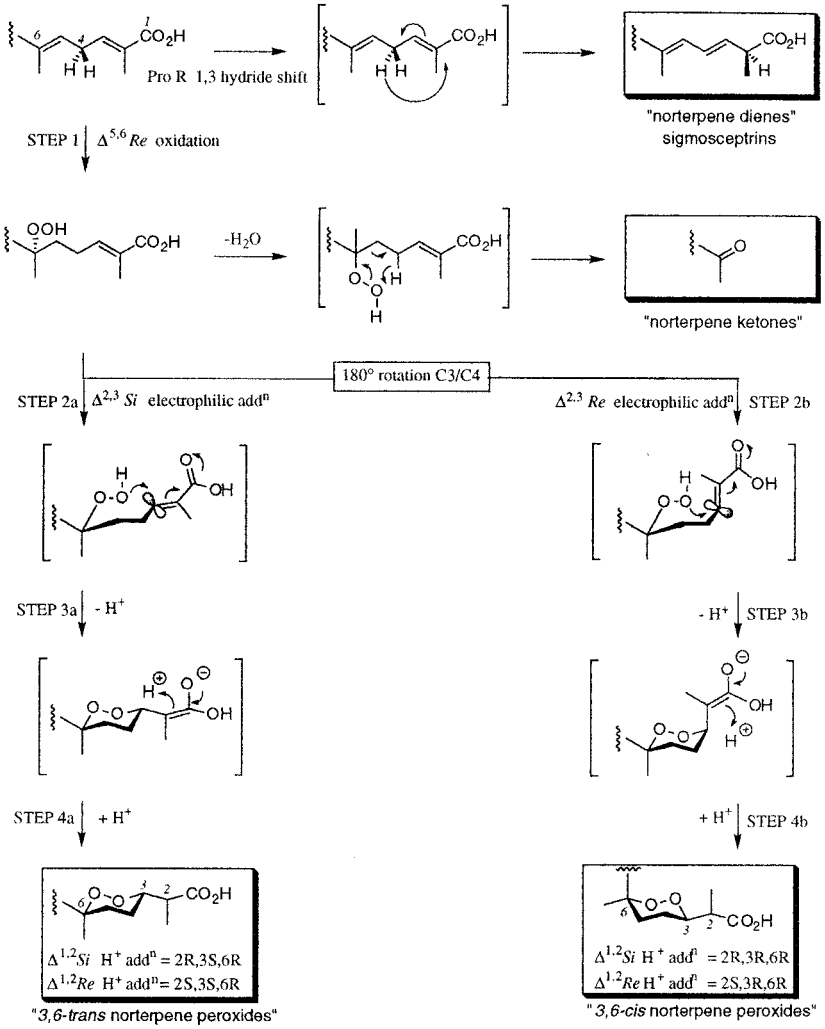
The absolute stereochemistry of **3b** was determined using the advanced Mosher procedure.[15,16] Hydrogenation of **3b** yielded the eriol **10**, which was esterified with *R* and *S* MTPA acid to yield the corresponding MTPA esters **11** and **12**, respectively. Diagnostic ^{1}H NMR chemical shift differences between the diastereomeric MTPA esters (Δ $\delta S - \delta R$; 2-CH_3 (+13.7 Hz), H-2 (+4.4 Hz), −CO_2CH_3 (+12.2 Hz), 6-CH_3 (−18.1 Hz)) were consistent with a 3*S* and hence 2*R*,3*S*,6*R* absolute stereochemistry. Stereochemical determinations about C10 and C14 remain unassigned. As with nuapapuin A methyl ester (**2b**), careful analysis of the ^{1}H NMR (relative integration between H-17 and CO_2CH_3) and TLC data for the crude unmethylated sponge extract confirmed that sigmosceptrellin D occurred naturally as its carboxylic acid **3a**. It was not possible to unambiguously determine whether the corresponding methyl ester **3b** occurred naturally, although as noted earlier methyl esters were present in minor amounts in the initial ethanol extract.

Sigmosceptrellin E methyl ester (**4**) was isolated as a stable oil with a molecular formula ($C_{25}H_{42}O_4Na$, Δmmu 0.7) consistent with five degrees of unsaturation. Examination of the NMR and IR data for **4** revealed a cyclic peroxide methyl ester moiety common with that for **3b** (^{1}H NMR chemical shift for the 2-CH_3 (δ 1.25), a large $J_{3,4ax}$ (7.6 Hz), and ^{13}C NMR chemical shift for the 6-CH_3 (20.6 ppm)). Further examination of the NMR data revealed the presence of three trisubstituted double bonds (^{1}H: δ 5.09; ^{13}C: 135.5, 135.0, 131.3, 124.4, 124.1, 123.9), which, in the absence of additional sp or sp^2 hybridized carbons, required that the remaining structural unit in **4** be acyclic. COSY NMR analysis confirmed the gross structure for **4** as shown, while ^{13}C NMR chemical shifts for C10-CH_3 and C14-CH_3 (16.0 and 16.0 ppm) were consistent with *E* geometries about $\Delta^{10,11}$ and $\Delta^{14,15}$. The limited supply of **4** isolated during this investigation precluded an independent experimental determination of absolute stereochemistry; however, a 2*R*,3*S*,6*R* absolute stereochemistry was *tentatively* assigned on biosynthetic considerations (given the co-occurrence of the closely related **3b**). The low yield of "sigmosceptrellin E" in the crude extract made it impossible to establish whether it occurred naturally as either the carboxylic acid, the methyl ester, or both.

Although a large number of norterpene cyclic peroxides and related co-metabolites have been reported from marine sponges, no attempt has been made to propose a biosynthetic pathway that satisfactorily accounts for all stereoisomeric forms of the terminal cyclic peroxide moiety and related analogues. In an earlier report we isolated, characterized, identified, and speculated on the possible biosynthetic role of norterpene dienes.[19] More recently,[20] we proposed that norterpene dienes were biosynthetic precursors to the sigmosceptrins. The norterpene cyclic peroxides encountered in this paper have prompted us to review the array of known norterpene cyclic peroxides and propose a common biosynthetic pathway that accounts for key structural and stereochemical features. This proposal is outlined in Scheme 2.

Key to proposing this biosynthetic pathway was the discovery of sigmosceptrellin D (**3a**), with a hydroperoxide moiety strategically positioned in such a way as to mimic the cyclic peroxide moiety at the opposite end of the molecule. This observation encouraged a belief that the biosynthetic origin of some or all marine norterpene cyclic peroxides involved a common intermediate C6 hydroperoxide (Scheme 2, step 1), undergoing a "Michael addition" to an adjacent α,β-unsaturated carboxylic acid or ester moiety (Scheme 2, step 2). Initial formation of the C6 hydroperoxide could occur on either the *Re* or *Si* face of a $\Delta^{5,6}$ precursor, thereby defining the absolute stereochemical outcome of the biosynthetic process. Scheme 2 arbitrarily illustrates this process occurring via oxidation of the *Re* face of a $\Delta^{5,6}$ precursor, although the antipodal pathway

Scheme 2. Proposed Biosynthetic Pathway



could be evidenced by known norterpene cyclic peroxides. Depending on the conformation of the hydroperoxy carboxylic acid precursor, the electrophilic $\Delta^{2,3}$ addition can proceed via the *Si* face (Scheme 2, step 2a) or the *Re* face (Scheme 2, step 2b), leading to epimers about C3. Quenching of the resulting $\Delta^{1,2}$ "enolate" can proceed via both *Re* and/or *Si* facial addition of H^+ to yield the full suite of C2 and C3 stereoisomers. Those isomers originating via the process step 2b−3b−4b also experience inversion of the cyclic peroxide chair conformation to attain the more stable conformer bearing an equatorial C 3 substituent. This inversion has the effect of repositioning the C 6 "terpene" side chain from an equatorial to axial conformation. That the C 14 hydroperoxide in sigmosceptrellin D (**3a**) did not yield a cyclic peroxide is readily explained in that, lacking a C19 carboxylic acid, $\Delta^{17,18}$ is not sufficiently activated toward electrophilic attack by the C 14 hydroperoxide. This proposed biosynthetic pathway not only provides an efficient route to the key structural feature in norterpene cyclic peroxides but also provides ready access to known cometabolites. Oxidative degradation through loss of water from the hydroperoxide carboxylic acid precursor, with accompanying intramolecular abstraction of an allylic C 4 proton and cleavage of C5−C6 (see Scheme 2), can yield norterpene ketones. Such ketones are increasingly being identified[10,11] as minor cometabolites with norterpene cyclic peroxides. Likewise, a *pro-R* 1,3 hydride shift from C4 to C2 can yield norterpene dienes, which are known cometabolites[19] and have been proposed as biosynthetic precursors for the closely related sigmosceptrins.[20] It should be emphasized that in the proposed biosynthetic scheme the conjugated norterpene dienes described above are not biosynthetic precursors to the cyclic peroxides, but are rather an offshoot of the biosynthetic pathway. This proposal differs from an earlier hypothesis[19] that required the 2+4 cycloaddition of oxygen to conjugated norterpene dienes. Although no experimental evidence is presented to support the biosynthetic pathway outlined in Scheme 2, it is an attractive proposal in that it goes a long way toward explaining the stereochemical versatility encountered among known marine norterpene cyclic peroxides, and accounts for the occurrence of related metabolites.

Experimental Section

General Methods. For general experimental details see ref 12.

Collection, Extraction, and Isolation. A specimen of *Sigmosceptrellin* sp. (154 g dry weight, Museum of Victoria registry no. F79981) collected by epibenthic sled at a depth of 150 m from the Great Australian Bight, Australia, was frozen and transported to the laboratory where it was diced, steeped in EtOH, and stored at −18 °C [growth form: macrobenthic, fixed directly to the substrate, massive-lobate; color: pink-beige on deck, beige-white in ethanol; texture: compressible, tough, leathery; surface: opaque, optically smooth, irregular with long papillose-fistulose projections flattened apically; oscules: raised on small fistules; megascleres: styles (slight constriction, occasionally deformed, 360−430 μm) microscleres: sanidastoid discorhabds (four symmetrical whorls of spines 30−100 μm);

Table 1. NMR Data ($CDCl_3$, 400 MHz) for Sigmosceptrellin D Methyl Ester (**3b**)[b]

no.	^{13}C δ	^{1}H δ	m	COSY	gHMBC ^{1}H to ^{13}C
1	174.2				
2	42.9	2.63	dq	H-3, 2-CH_3	C-1, C-3, CH_3-2
3	80.5	4.11	ddd	H-2	C-1, C-2, CH_3-2
4	23.5[a]	*	m		
5	32.3[a]	*	m		
6	81.3				
7	35.6[a]	*	m		
8	22.3[a]	*	m		
9	43.2[a]	*	m		
10	37.8	*	m		
11	29.3[a]	*	m		
12	32.8[a]	*	m		
13	30.4[a]	*	m		
14	77.2				
15	32.6	*	m	H-16	
16	21.8	1.99	m	H-15, H-17	C-15, C-17, C-18
17	124.7	5.14	br t	H-16, H-19, CH_3-18	C-15, C-16, C-19, CH_3-18
18	131.7				
19	25.7	1.69	s	H-17	C-17, C-18, CH_3-18
CO_2CH_3	51.8	3.69	s		C-1, C-2
2-CH_3	13.5	1.24	d	H-2	C-1, C-2, C-3
6-CH_3	20.2	1.27	s		C-5, C-6, C-7
10-CH_3	12.7	0.84	d		C-9, C-10, C-11
14-CH_3	16.9	0.87	s		C-14
18-CH_3	17.6	1.62	s	H-17	C-17, C-18, C-19

[a] Indicates that assignments may be interchanged. *Refers to an overlapping envelope. [b] $J_{2,2-Me} = 7.0$ Hz, $J_{2,3ax} = 8.2$ Hz, $J_{3,4ax} = 8.2$ Hz, $J_{3,4eq} = 3.4$ Hz.

ectosome: a continuous palisade of megascleres just protruding the surface obscured by a dense layer of discorhabd microscleres (approx 1 mm thick); choanosome: dense and disorganized styles centrally becoming more organized into multispicular almost radial tracts subectosomally with discorhabd microscleres scattered throughout the light interstitial collagen].

The decanted crude EtOH extract was concentrated in vacuo and partitioned into CH_2Cl_2-soluble and -insoluble fractions. The CH_2Cl_2-soluble fraction was methylated with ethereal CH_2N_2 and subjected to rapid filtration through silica (20% stepwise gradient from petroleum ether to CH_2Cl_2 to EtOAc). Interesting fractions identified by TLC and ^{1}H NMR were subjected to further purification by HPLC (2 mL/min, 10% EtOAc/petroleum ether through a Phenomenex 5 μm silica 250 mm × 10 mm column) to yield nuapapuin A methyl ester (**2b**) (270 mg, 0.18%), sigmosceptrellin D methyl ester (**3b**) (130 mg, 0.08%), and sigmosceptrellin E methyl ester (**4**) (3 mg, 0.002%).

Nuapapuin A methyl ester (2b): a stable oil; $[\alpha]_D$ +61.7° (*c* 0.78, $CHCl_3$); IR (film) ν_{max} 1740 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$) identical in all respects to published results[3]; EIMS (70 eV) *m*/*z* 338 (0.4, M^+), 282 (1), 251 (1), 193 (1), 175 (2), 95 (9), 83 (100); HRESIMS (M+Na) 361.2355 ($C_{20}H_{34}O_4Na$ requires 361.2355).

Sigmosceptrellin D methyl ester (3b): a stable oil; $[\alpha]_D$ −57.8° (*c* 5.9, $CHCl_3$); IR (film) ν_{max} 1734 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$) see Table 1; ESIMS (40 kV) *m*/*z* 443 (M + H, 31); HRESIMS (M + Na − H_2O) 447.3089 ($C_{25}H_{44}O_5Na$ requires 447.3086).

Sigmosceptrellin E methyl ester (4): a stable oil; $[\alpha]_D$ −16.7° (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.09 (br s, H9, H13, H17), 4.13 (ddd, J = 7.6, 7.6, 3.5 Hz, H3), 3.70 (s, CO_2CH_3), 2.65 (dq, J = 7.6, 6.9 Hz, H2), 1.68 (s, $H_3$19), 1.60 (s, 10-CH_3, 14-CH_3, 18-CH_3), 1.40−2.05 (br envelope, $H_2$4, $H_2$5, $H_2$7, $H_2$8, $H_2$11, $H_2$12, $H_2$15, $H_2$16), 1.29 (s, 6-CH_3), 1.25 (d, J = 6.9 Hz, 2-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3 (s, C1), 135.5, 135.0, 131.3 (3s, C10, C14, C18), 124.4, 124.1, 123.9 (3d, C9, C13, C17), 81.2 (d, C3), 80.1 (s, C6), 51.9 (q, CO_2CH_3), 43.0 (d, C2), 39.9, 39.7, 39.6 (3t, C7, C11, C15), 32.0 (t, C8), 26.7, 26.5 (2t, C12, C16), 25.7 (q, C19), 23.5 (t, C4), 21.7 (t, C16), 20.6 (q, 6-CH_3), 17.7 (q, 18-CH_3), 16.0 (q, 14-CH_3), 16.0 (q, 10-CH_3), 13.6 (q, 2-CH_3); EIMS (30 eV) *m*/*z* 406 (M^+, 1), 371 (3), 315 (4), 253 (7), 185 (9), 147 (32); HRESIMS (M + Na) 429.2988 ($C_{25}H_{42}O_4Na$ requires 429.2981).

Hydrogenation of 2b. A sample of **2b** (58.7 mg, 0.17 mmol) in ether (10 mL) was treated with 10% palladium on carbon (20 mg) and stirred under an atmosphere of H_2 for 16 h. The reaction mixture was then filtered through Celite and concentrated in vacuo to yield the saturated diol **5** (49.8 mg, 88%): $[\alpha]_D$ −1.8° (*c* 1.42, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3610, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.71 (s, CO_2CH_3), 3.68 (m, H3), 2.55 (m, H2), 0.80−1.90 (br envelope, $H_2$4, $H_2$5, $H_2$7, $H_2$8, H9, $H_2$11, $H_2$12, $H_2$13, H14, 10-CH_3, 10-CH_3, 14-CH_3), 1.20 (d, J = 7.2 Hz, 2-CH_3), 1.18 (s, 6-CH_3); ESIMS (25 kV) *m*/*z* 381 (M + K, 40), 365 (M + Na, 55), 343 (M + H, 55). EIMS (70 eV) *m*/*z* 324 (M − H_2O, 4), 322 (26), 281 (29), 215 (49), 183 (30); HRESIMS (M + Na) 366.2683 ($C_{20}H_{38}O_4Na$ requires 366.2667)

Reduction of Sigmosceptrellin D Methyl Ester (3b). To a sample of **3b** (12.3 mg, 0.021 mmol) in dry benzene (10 mL) was added 25 mg (0.22 mmol) of freshly sublimed oxalic acid and the mixture refluxed for 24 h, during which time the reaction mixture was allowed to evaporate to dryness. The crude product was then extracted with ether (2 × 20 mL), and the organic phase was washed with saturated Na_2CO_3 (2 × 40 mL) and brine (1 × 40 mL) and then dried with anhydrous $MgSO_4$ to yield **8** (8.3 mg, 95%) as a stable oil: $[\alpha]_D$ −12.5° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.14 (m, H13, $\Delta^{13,14}$), 5.07 (m, H17), 5.01 (t, J = 6.4 Hz, H15, $\Delta^{14,15}$), 4.10 (ddd, J = 8.2, 8.2, 3.4 Hz, H3), 3.69 (s, CO_2CH_3), 2.70 (br t, J = 6.7 Hz, $H_2$16, $\Delta^{14,15}$), 2.63 (m, H2), 2.10−0.80 (br envelope, $H_2$4, $H_2$5, $H_2$7, $H_2$8, $H_2$9, H10, $H_2$11, $H_2$12), 1.69 (s, 18-CH_3), 1.67 (s, 14-CH_3, $\Delta^{14,15}$), 1.62 (s, 18-CH_3), 1.60 (s, 14-CH_3, $\Delta^{13,14}$), 1.25 (s, 6-CH_3), 1.25 (d, J = 6.9 Hz, 2-CH_3), 0.81 (d, J = 6.8 Hz, 10-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 174.3 (s, C1), 142.8, 140.8 (2s, C14$\Delta^{13,14}$, C14$\Delta^{14,15}$), 131.1 (s, C18), 124.9, 124.0 (2d, C17$\Delta^{13,14}$, C17$\Delta^{14,15}$), 121.9, 121.8 (2d, C13Δ,^{13,14} C14$\Delta^{14,15}$), 81.4 (s, C6), 80.4 (d, C3), 51.8 (q, CO_2CH_3), 42.4 (d, C2), 43.0, 40.4, 33.9, 33.5, 32.1, 30.1, 29.3, 23.6, 21.4 (10t, C 4, C 5, C 7, C 8, C 9, C 11, C 12, C 13Δ^{14-15}, C 15$\Delta^{13,14}$, C 16), 38.8 (d, C 10), 25.7 (q, C 19), 20.7 (q, 6-CH_3), 17.7 (q, 18-CH_3), 15.9, 15.7 (2q, 10-CH_3, 14-CH_3), 13.6 (q, 2-CH_3); ESIMS (25 kV) *m*/*z* 409 (M + H, 70); EIMS (30 eV) *m*/*z* 408 (M, 1), 388 (8), 331 (4), 301 (15), 245 (16).

Hydrogenation of Sigmosceptrellin D Methyl Ester (3b). Treatment of a sample of **3b** (32.4 mg, 0.073 mmol) as described above for **2b** yielded the saturated diol **10** (28 mg, 86%): $[\alpha]_D$ −4.4° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3610, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.88 (m, H3), 3.71 (s, CO_2CH_3), 2.56 (m, H2), 1.00−2.00 (br envelope, $H_2$4, $H_2$5, $H_2$7, $H_2$8, $H_2$9, H10, $H_2$11, $H_2$12, $H_2$13, $H_2$15, $H_2$16, $H_2$17, H18), 1.25 (s, 6-CH_3), 1.21 (d, J = 7.1 Hz, 2-CH_3), 0.88 (m, 10-CH_3, 14-CH_3, 18-CH_3, 18-CH_3); ESIMS (25 kV) *m*/*z* 431 (M + H, 10), 453 (M + Na, 10); HRESIMS (M + Na − 2H) 451.3391 ($C_{25}H_{48}O_5Na$ requires 451.3399).

Reaction of Diol 5 with (*R*)-MTPA Acid. To a solution of **5** (24 mg) in 5 mL of dry CH_2Cl_2 were added DCC (82.7 mg), DMAP (28 mg), and (*R*)-MTPA acid (82.7 mg) and the solution stirred for 16 h. The reaction mixture was concentrated, prepurified on a silica Sep-Pak (20% gradient elution from petrol to EtOAc), and subjected to HPLC chromatography (2 mL/min 20% EtOAc/petroleum ether, Phenomenex 5 μm silica 250 × 10 mm column) to yield the (*R*)-MTPA ester **6** (13 mg, 33%): $[\alpha]_D$ −71.2° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (m, H3′, H5′), 7.40 (m, H2′, H4′, H6′), 5.38 (m, H3), 3.64 (s, CO_2CH_3), 3.54 (s, MTPA-OCH_3), 2.86 (s, H2), 0.80−1.90 (br envelope, $H_2$4, $H_2$5, $H_2$7, $H_2$8, $H_2$11, $H_2$12, $H_2$13, 10-CH_3, 10-CH_3, 14-CH_3), 1.18 (d, J = 7.3 Hz, 2-CH_3), 1.04 (s, 6-CH_3); EIMS (70 eV) *m*/*z* 541 (M − OH, 1), 405 (2), 307 (17), 237 (4), 197 (7), 189 (40).

Reaction of Diol 5 with (*S*)-MTPA Acid. To a solution of **5** (24 mg) in 5 mL of dry CH_2Cl_2 were added DCC (82.7 mg), DMAP (28 mg), and (*S*)-MTPA acid (82.7 mg), and the solution was stirred for 16 h. The reaction mixture was concentrated and purified as described above for **5** to yield the (*S*)-MTPA ester **7** (24 mg, 61%): $[\alpha]_D$ −37.8° (*c* 0.79, $CHCl_3$);

IR ($CHCl_3$) ν_{max} 3600, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (m, H3′, H5′), 7.40 (m, H2′, H4′, H6′), 5.38 (m, H5), 3.58 (s, CO_2CH_3), 3.51 (s, MTPA-OCH_3), 2.85 (m, H2), 0.80−1.90 (br envelope, $H_2$4, $H_2$5, $H_2$7, $H_2$8, $H_2$11, $H_2$12, $H_2$13, 10-CH_3, 10-CH_3, 14-CH_3), 1.12 (m, 2-CH_3, 6-CH_3); EIMS (70 eV) *m/z* 540 (M − H_2O, 0.4), 525 (0.4), 385 (2), 359 (4), 251 (12).

Reaction of Diol 10 with (*R*)-MTPA Acid. A solution of **10** (15 mg) in 5 mL of dry CH_2Cl_2 was treated as above for the conversion of **5** into **6** to yield the (*R*)-MTPA ester **11** (5.3 mg, 24%): $[\alpha]_D$ −90.7° (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3610, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (m, H3′, H5′), 7.40 (m, H2′, H4′, H6′), 5.41 (m, H3), 3.62 (s, CO_2CH_3), 3.52 (s, MTPA-OCH_3), 2.77 (m, H2), 1.10−1.98 (br envelope, $H_2$4, $H_2$5, $H_2$7, $H_2$8, $H_2$9, H10, $H_2$11, $H_2$12, $H_2$13, $H_2$15, $H_2$16, $H_2$17, H18), 1.14 (d, J = 5.3 Hz, 2-CH_3), 1.13 (s, 6-CH_3), 0.87 (m, 10-CH_3, 14-CH_3, 18-CH_3, $H_3$19); ESIMS (25 kV) *m/z* 631 (M + H, 5), 653 (M + Na, 1), 669 (M + K, 10).

Reaction of Diol 10 with (*S*)-MTPA Acid. A solution of **10** (10 mg) in 5 mL of dry CH_2Cl_2 was treated as above for conversion of **5** into **7** to yield the (*S*)-MTPA ester **12** (13.6 mg, 94%): $[\alpha]_D$ −99.1° (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3610, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (m, H3′, H5′), 7.40 (m, H2′, H4′, H6′), 5.41 (m, H3), 3.66 (s, CO_2CH_3), 3.55 (s, MTPA-OCH_3), 2.79 (m, H2), 1.10−1.98 (br envelope, $H_2$4, $H_2$5, $H_2$7, $H_2$8, $H_2$9, H10, $H_2$11, $H_2$12, $H_2$13, $H_2$15, $H_2$16, $H_2$17, H18), 1.18 (d, J = 7.3 Hz, 2-CH_3), 1.07 (s, 6-CH_3), 0.87 (12H, m, 10-CH_3, 14-CH_3, 18-CH_3, $H_3$19); ESIMS (25 kV) *m/z* 631 (M + H, 5), 653 (M + Na, 1), 669 (M + K, 10).

Synthesis of Alcohol 9. Concentrated H_2SO_4 (0.48 g, 4.9 mmol) was slowly added to 4-methyl-1-pentanol (1 g, 9.8 mmol), followed by slow addition of 48% hydrobromic acid (2.48 g, 0.015 mol), and the resulting mixture was refluxed for 5 h. The reaction mixture was then diluted with H_2O (100 mL) and extracted into Et_2O (3 × 50 mL). The combined ether extract was washed with $NaHCO_3$ (3 × 50 mL) and then brine (100 mL) and finally dried over anhydrous $MgSO_4$ to yield 4-methyl-1-bromopentane (740 mg, 46%). The crude bromide was dissolved in Et_2O (20 mL) and added dropwise to Mg turnings (0.108 g, 4.5 mmol) in Et_2O (10 mL) and refluxed for 2 h. After this time, 6-methyl-5-hepten-2-one (0.57 g, 4.5 mmol) in Et_2O (20 mL) was added dropwise and the reaction mixture refluxed for 30 min. The reaction mixture was diluted with H_2O (50 mL) and 5 mL of 10% HCl added to dissolve the precipitate. This mixture was then extracted into Et_2O (3 × 50 mL), washed with $NaHCO_3$ (2 × 50 mL) and brine (100 mL), and subjected to normal-phase HPLC (2.0 mL/min 10% EtOAc/petroleum ether, Phenomenex 5 μm silica 250 × 10 mm column) to yield 2,6,10-trimethyl-2-undecen-6-ol (**9**) (210 mg, 22%): IR ($CHCl_3$) ν_{max} 3610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.13 (br t, J = 7.1 Hz, H 3), 2.04 (m, H_2 4), 1.69 (s, 2 CH_3), 1.62 (s, 1-CH_3), 1.10−1.70 (br envelope, H_2 5, H_2 7, H_2 8, H_2 9, H 10), 1.16 (s, 6-CH_3), 0.88 (m, 10-CH_3, 11-CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), 131.4 (s, C 2), 124.5 (d, C 3), 72.7 (s, C 6), 42.1, 41.5, 39.5 (3t, C 4, C 5, C 7), 27.9, 26.8, 25.6, 22.6 (4q, C 1, C 11, 6-CH_3, 10-CH_3), 22.6 (t, C 9), 22.5 (d, C 10), 21.6 (t, C 8), 17.5 (q, 2-CH_3); ESIMS (25 kV) *m/z* 213 (M + H, 20), 235 (M + Na, 5); HRESIMS (M + Na) 235.2046 ($C_{14}H_{28}ONa$ requires 235.2038).

Acknowledgment. We acknowledge L. Goudie and the CSIRO Division of Oceanography, along with the crew and scientific personnel aboard the O. R. V. Franklin, for the collection of sponge specimens. We also acknowledge taxonomic classification by L. Goudie, technical support by P. Niclasen, and financial assistance from the Australian Research Council.

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NP980223R