1,1,1,39,39,39-Hexaphenyl-2,5,8,11,14,17,20,23,26,29,32,35,38-tridecaoxanonatriacontane 4(12): 0.025 molar scale (16.97 g of 3(8)); 25.3 g (98%) of a clear viscous oil; ^{1}H-NMR δ 7.48–7.42 (m, 12 H), 7.32–7.17 (m, 18 H), 3.68–3.60 (m, which contains A of AA'XX', 44 H), 3.26–3.21 (X of AA'XX', 4 H); ^{13}C-NMR δ 144.12, 128.70, 127.72, 126.87, 86.51, 70.72, 70.64, 70.61, 70.52, 70.51, 63.32; IR (NaCl) 3058, 2960–2840, 1490, 1450, 1160–1040 (br) cm^{-1}; FABMS (Xe; matrix: *m*-nitrobenzyl alcohol) 1069 (6, $[M + K]^+$), 1053 (21, $[M + Na]^+$), 1048 (5, $[M + NH_4]^+$), 1031 (1, $[M + H]^+$), 243 (100, $[(C_6H_5)_3C]^+$). Anal. Calcd for $C_{62}H_{78}O_{13}$: C, 72.21; H, 7.62; O, 20.17. Found: C, 72.19; H, 7.63; O, 20.16.

General Procedure for Deprotection of α,ω-Dititylated Ethylene Glycols 4(*n*). A high pressure glass flask is charged with the appropriate **4(*n*)** (0.10 mol), dry CH_2Cl_2 (250 mL), and 10% palladium on carbon (1.5 g). Hydrogenolysis is carried out at 25 °C under 4 atm hydrogen pressure in a Parr apparatus for 4 days. With thin-layer chromatography the course of the reaction is followed [TLC (silica, $CHCl_3$); R_f **4(n)** and **2(n)** 0.05–0.15 [for $n > 4$); R_f triphenylmethane 0.9; R_f **1(n)** 0–0.05]. Upon completion of the reaction, the catalyst is filtered and washed with CH_2Cl_2 (50 mL), and the combined filtrate is concentrated under reduced pressure. The residue is dissolved in boiling MeOH (300 mL). Upon cooling the solution to −25 °C, the sideproduct triphenylmethane crystallizes and is filtered. After concentration of the filtrate, the remaining oily product is stirred with dry hexane (4 × 100 mL) to remove last traces of triphenylmethane. The purity of the oligo(ethylene glycols) was assessed with capillary gas chromatography after trimethylsilylation of the hydroxyl end groups[8] [column 30 m × 0.309 mm, Durabond-5; injector temperature 350 °C, FID detector temperature 250 °C, temperature program 175 °C to 350 °C, rate of 25 °C min^{-1}; carrier gas N_2, flow 1.5 mL min^{-1}].

3,6,9,12-Tetraoxatetradecane-1,15-diol 1(5): 22.98 g (96%) of a clear colorless oil.[5b]

3,6,9,12,15-Pentaoxaheptadecane-1,17-diol 1(6): 26.77 g (95%) of a clear colorless oil.[5d]

3,6,9,12,15,18-Hexaoxaeicosane-1,20-diol 1(7): 31.03 g (95%) of a clear colorless oil.[5d]

3,6,9,12,15,18,21-Heptaoxatricosane-1,23-diol 1(8): 36.06 g (97%) of a clear colorless oil;[5b] ^{1}H-NMR δ 3.72–3.66 (A of AA'MM'X, J(AX) = 6.1 Hz, 4 H), 3.64–3.61 (m, 24 H), 3.59–3.54 (M of AA'MM'X, 4 H), 2.92–2.87 (X of AA'MM'X, J(AX) = 6.1 Hz, 2 H, disappeared upon addition of ^2H_2O); ^{13}C-NMR δ 72.50, 70.54, 70.50, 70.48, 70.27, 61.62; IR (NaCl) 3600–3100 (br), 3000–2800 (br), 1450, 1160–1000 (br) cm^{-1}; FABMS (Xe, no matrix used) 393 (33, $[M + Na]^+$), 371 (32, $[M + H]^+$), 221 (2, $[H(OC_2H_4)_5]^+$), 177 (12, $[H(OC_2H_4)_4]^+$), 133 (39, $[H(OC_2H_4)_3]^+$), 89 (75, $[H(OC_2H_4)_n]^+$), and 45 (100, $[HOC_2H_4]^+$).

3,6,9,12,15,18,21,24,27,30,33-Undecaoxapentatriacontane-1,35-diol 1(12): 0.02 molar scale, 10.59 g (97%) of a waxy solid; mp 21.2 °C, maximum of DSC curve; ^{1}H-NMR δ 3.67–3.62 (A of AA'XX', 4 H), 3.62–3.56 (m, 40 H), 3.56–3.51 (X of AA'XX', 4 H), 2.89 (bs, 2 H, disappeared upon addition of ^2H_2O); ^{13}C-NMR δ 72.36, 70.41, 70.37, 70.14, 61.45; IR (NaCl) 3600–3100 (br), 3000–2800 (br), 1450, 1160–1000 (br) cm^{-1}; FABMS (Xe, matrix: glycerol) 1093 (0.2, $[2M - H]^+$), 569 (2.5, $[M + Na]^+$), 547 (45, $[M + H]^+$), 265 (2, $[H(OC_2H_4)_6]^+$), 221 (4, $[H(OC_2H_4)_5]^+$), 177 (15, $[H(OC_2H_4)_4]^+$), 133 (42, $[H(OC_2H_4)_3]^+$), 89 (77, $[H(OC_2H_4)_2]^+$), 45 (100, $[HOC_2H_4]^+$). Anal. Calcd for $C_{24}H_{50}O_{13}$: C, 52.73; H, 9.23. Found: C, 53.14; H, 9.23.

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Supplementary Material Available: Physical data for **1(*n*)** (n = 5, 6, and 7), **3(*n*)** (n = 1, 2, 3, and 4), and **4(*n*)** (n = 5, 6, and 7) and ^{1}H-NMR spectra of compounds **1(*n*)** (n = 5, 6, 7, 8, and 12) (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Theoneberine: The First Brominated Benzyltetrahydroprotoberberine Alkaloid from the Okinawan Marine Sponge *Theonella* sp.

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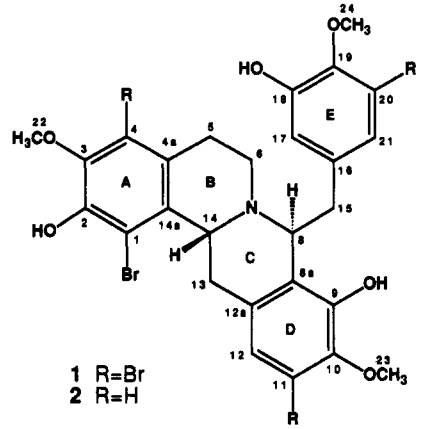
Among a number of tyrosine-derived alkaloids isolated from a variety of marine organisms,[2] several isoquinoline alkaloids have been obtained from marine sponges,[3] starfish,[4] and tunicates.[5] Recent studies have demonstrated that marine sponges of the genus *Theonella* are a rich source of unique bioactive natural products, most of which, however, belong to peptides[6] or polyoxygenated metabolites.[7] During our investigations on bioactive substances from Okinawan marine organisms,[8] we further examined extracts of the *Theonella* sponge of a different collection, resulting in isolation of a novel tetrahydroprotoberberine alkaloid, theoneberine (1). In this paper we describe the isolation and structure elucidation of 1.



The sponge *Theonella* sp. was collected off Ie Island, Okinawa, and kept frozen until used. The methanol ex-

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Table I. ^1H and ^{13}C NMR Data of Theoneberine (1) in C_6D_6[a]

position	^1H	J (Hz)	^{13}C	HMBC correlations (^1H)
1			109.4 s	H-14
2			145.8 s	
3			144.1 s	H_3-22
4			119.4 s	H_2-5
4a			127.8 s	H_2-5, H-6α, H-14
5 (α)	2.73 ddd	16.1, 11.2, 7.3	30.7 t	H_2-6
(β)	2.49 dd	16.1, 3.9		
6 (α)	2.30 dd	11.2, 7.3	45.4 t	H_2-5, H-8, H-14
(β)	2.66 td	11.2, 3.9		
8	4.16 dd	9.8, 2.4	63.0 d	H-6α, H_2-15
8a			124.2 s	H-8, H-12, H_2-13
9			147.3 s	H-8, H-12[b]
10			142.6 s	H-12, H_3-23
11			113.8 s	H-12
12	6.76 s		124.3 d	H_2-13
12a			131.7 s	H-8, H_2-13
13 (α)	2.33 dd	17.6, 11.7	25.8 t	H-12, H-14
(β)	2.95 dd	17.6, 4.9		
14	4.72 dd	11.7, 4.9	50.7 d	H_2-6, H-8, H_2-13
14a			136.0 s	H_2-5, H-13α, H-14
15 (a)	2.86 dd	14.2, 9.8	39.6 t	H-8, H-17, H-21
(b)	2.98 dd	14.2, 2.4		
16			140.0 s	H-8, H_2-15
17	7.14 d	2.0	116.4 d	H_2-15, H-21
18			150.3 s	H-21[b]
19			143.3 s	H-17, H-21, H_3-24
20			115.8 s	H-21
21	7.34 d	2.0	125.3 d	H_2-15, H-17
22	3.36 s		60.2 q	
23	3.46 s		60.7 q	
24	3.32 s		60.4 q	
OH	5.38 br s (3 H)			

[a] Recorded on a JEOL EX-400 spectrometer. [b] Correlations representing 4-bond couplings observed by the HMBC experiment using the duration Δ_2 = 120 ms, while other correlations were obtained in the usual HMBC spectrum using Δ_2 = 62.5 ms. ^1H–^1H COSY correlations: H-5α/H-5β, H-5α/H-6α, H-5α/H-6β, H-5β/H-6β, H-6α/H-6β, H-8/H_2-15, H-13α/H-13β, H_2-13/H-14, H-15a/H-15b, and H-17/H-21. NOESY correlations: H-5α/H-5β, H-6α/H-6β, H-6α/H-8, H-8/H-15b, H-12/H-13β, H-13α/H-13β, H-13β/H-14, H-14/H-15a, H-15a/H-15b, and H-15b/H-21.

tract of the sponge was partitioned between ethyl acetate and water. The ethyl acetate soluble material was subjected to a silica gel column ($CHCl_3$/MeOH, 95:5) followed by an ODS column (MeOH/H_2O, 90:10), reversed-phase HPLC (ODS; MeOH/H_2O, 85:15), and a Sephadex LH-20 column ($CHCl_3$/MeOH, 1:1) to give theoneberine (1, 0.0004%, wet weight).

The FABMS spectrum of theoneberine (1) showed $(M + H)^+$ ions at m/z 784, 782, 780, 778, and 776 in the ratio of ca. 1:4:6:4:1, implying the presence of four bromine atoms. The molecular formula of 1 was revealed to be $C_{27}H_{25}Br_4NO_6$ by the HRFABMS [m/z 779.8447 $(M + H)^+$, for $C_{27}H_{26}{}^{79}Br_2{}^{81}Br_2NO_6$, Δ −0.5 mmu]. The IR spectrum indicated the presence of hydroxyl group(s) (3450 cm^{-1}) and the UV absorption at 284 nm (ϵ 5300) showed a bathochromic shift to 300 nm (ϵ 6800) on addition of NaOH, suggesting the presence of phenol chromophore(s). The ^{13}C NMR spectrum of 1 facilitated by DEPT experiments revealed 27 carbons consisting of 9 sp^3 and 18 sp^2 ones, the latter of which corresponded to three aromatic rings. Since 12 of the 14 unsaturations were thus accounted for, 1 was inferred to contain two other rings. The ^1H NMR spectrum of 1 in C_6D_6 (Table I) revealed signals due to three aromatic protons (one sharp singlet and two doublets being meta-coupled with each other by J = 2.0 Hz), three methoxy groups, two sp^3 methines, and four sp^3 methylenes. Three deuterium-exchangeable protons were observed at δ 5.38 (3 H, br s), which were attributed to three phenolic protons. The assignments of all protonated carbons were enabled by interpretation of the heteronuclear single quantum coherence (HSQC)[9] spectrum (Table I). The ^1H–^1H COSY spectrum of 1 revealed spin systems due to three segments [one AA′BB′ (C-5–C-6) and two ABX patterns (C-8–C-15 and C-13–C-14)]. These three segments were connected with one another through the nitrogen atom (N-7) by the ^1H–^{13}C long-range couplings observed in the HMBC[10] spectrum of 1 (cross peaks: H-8/C-6, H-14/C-6, H-6α/C-8, H_2-6/C-14, and H-8/C-14). The ^{13}C chemical shifts of C-6 (δ_C 45.4), C-8 (δ_C 63.0), and C-14 (δ_C 50.7) coincided with the fact that these carbons were adjacent to a nitrogen atom. These segments were shown to be further connected with three aromatic rings as follows. The connection with the aromatic ring A was suggested by the HMBC connectivities for H_2-5/C-4, H_2-5/C-4a, H-6α/C-4a, H-14/C-1, H_2-5/C-14a, H-13α/C-14a, and H-14/C-14a, while the aromatic ring D was connected by the HMBC correlations for H-8/C-8a, H_2-13/C-8a, H-8/C-9, H_2-13/C-12, H-8/C-12a, and H_2-13/C-12a. The third aromatic ring E was attached to C-15 position (HMBC cross peaks: H_2-15/C-16, H_2-15/C-17, and H_2-15/C-21). From these results a benzyltetrahydroprotoberberine[11] ring system was deduced for theonebereine (1). On the three aromatic rings were attached three hydrogens, three hydroxyl groups, three methoxy groups, and four bromine atoms. The sp^2 carbon signals bearing these substituents were clearly distinguished by the ^{13}C chemical shifts as well as the HMBC spectrum. Particularly, the HMBC correlations from the methoxy protons to the carbons bearing the methoxy groups were useful to discriminate methoxy-bearing carbons from hydroxy-bearing carbons. Furthermore, the HMBC data (Table I) provided evidence for the positions of these substituents except for the locations of one hydroxyl group and one methoxy group to be placed on C-2 or C-3, because of few HMBC informations on ring A resulting from the lack of aromatic proton on this ring. The substituents on C-2 and C-3 was, however, obviously recognized by the NOE experiment of tridebromotheoneberine (2),[12] which was prepared by hydrogenolysis of 1 (H_2, 10% Pd/C). On irradiation of H-5α (δ_H 2.58) a significant NOE (8.5%) was observed at a singlet aromatic proton at δ_H 6.58, which suggested that this aromatic proton was assignable to H-4 and the bromine atom on C-1 remained unchanged under the hydrogenolysis. Irradiation of H-4 yielded a strong NOE (11.3%) at the methoxy protons at δ_H 3.88 (H_3-22), while irradiation of H_3-22 caused an appreciable NOE (4.4%) at H-4. These observations clearly revealed that the methoxy group was located on C-3 and the hydroxyl group, therefore, on C-2. Theoneberine (1) was most likely to adopt a cis form at the B/C ring juncture because of the steric interaction between the C-1 bromine and the C-13 hydrogens,[13] which was supported by the ^1H chemical shift of H-14 (δ_H 4.72)[14] and the ^{13}C chemical shift of C-6 (δ_C 45.4)[15] as well as the absence of Bohlmann bands in the region of 2900–2700 cm^{-1} in the IR spectrum of 1 in $CHCl_3$ solution.[16] Since

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the ^1H chemical shifts along with the splitting pattern of H-14[13] of 1 and 2 were similar to each other (in $CDCl_3$: 1: δ_H 4.59, dd, J = 11.7 and 4.9 Hz; 2: δ_H 4.60, dd, J = 11.6 and 4.4 Hz), the tridebromo derivative (2) was suggested to be also B/C cis. The relative configurations of 1 at C-8 and C-14 were deduced by the NOESY correlations for H-14/H-15a and H-6α/H-8, indicating that H-14 and C-15 methylene group were oriented to the same side of ring C. Thus the structure of theoneberine was concluded to be 1,[17] and this structure was consistent with the fragment ion peaks observed in the FABMS of 1. The intense peaks at m/z 566, 564, 562, and 560 (ca. 1:3:3:1) were ascribed to the fragment ions generated by loss of the benzyl group ($C_8H_8BrO_2$) at C-8, which was characteristic of 1-benzylisoquinolines,[18] whereas the fragment peaks at m/z 338, 336, and 334 (ca. 1:2:1) corresponded to the A and B rings resulting from the cleavage of C-13/C-14 and N-7/C-8 bonds via retro-Diels-Alder fragmentation.[4]

Theoneberine (1) is the first tetrahydroprotoberberine alkaloid isolated from marine organisms. Theoneberine (1) is also the first example as a naturally-occurring tetrahydroprotoberberine alkaloid with substitution by bromine atoms. Biogenetically theoneberine (1) seems to be classified as a hybrid between 1-benzylisoquinolines and protoberberines, which has been hitherto unknown from natural sources. Theoneberine (1) exhibited antimicrobial activity against Gram-positive bacteria (MIC values: *Staphylococcus aureus*, 16 μg/mL; *Sarcina lutea*, 2 μg/mL; *Bacillus subtilis*, 66 μg/mL; *Mycobacterium* sp. 607, 4 μg/mL).[19] Compound 1 also showed cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells in vitro with the IC_{50} values of 2.9 and ca. 10 μg/mL, respectively.

Experimental Section[20]

Isolation. The sponge *Theonella* sp. was collected off Ie Island, Okinawa, and kept frozen until used. The sponge (1 kg, wet weight) was extracted with methanol (1 L × 2). After evaporation under reduced pressure, the residue (39 g) was partitioned between ethyl acetate (400 mL × 3) and 1 M NaCl aqueous solution (400 mL). The ethyl acetate soluble fraction (1.0 g) was subjected to a silica gel column (Wako gel C-300, Wako Pure Chemical, 2.3 × 38 cm) with $CHCl_3$/MeOH (95:5). The fraction eluting from 230 to 320 mL was further separated by a reversed-phase column (YMC gel ODS-A 120-S30/50, 2.3 × 10 cm) with MeOH/H_2O (90:10). The fraction eluting from 430 to 500 mL was then purified by a reversed-phase HPLC [YMC-Pack ODS-AM, 5 μm, 10 × 300 mm; flow rate, 2.0 mL/min; UV detection at 254 nm; eluent, MeOH/H_2O (85:15)], followed by purification through a Sephadex LH-20 column (Pharmacia Fine Chemcials, 2 × 100 cm) with $CHCl_3$/MeOH (1:1) to give theoneberine (1, 3.6 mg, 0.0004% wet weight).

Theoneberine (1): colorless solid; mp 128 °C; $[\alpha]^{20}_D$ -53° (c 0.6, $CHCl_3$); UV λ_{max} (MeOH) 284 nm (ϵ 5300), (0.01 N HCl-MeOH) 286 nm (ϵ 5300), and (0.01 N NaOH-MeOH) 300 nm (ϵ 6800); IR (KBr) ν_{max} 3450, 2920, 1565, 1480, 1455, 1420, 1410, 1240, and 995 cm^{-1}; IR ($CHCl_3$) ν_{max} 3675, 3610, 3000, 1520, and 1420 cm^{-1}; ^1H and ^{13}C NMR (Table I); FABMS m/z 784, 782, 780, 778, 776 $(M + H)^+$, 566, 564, 562, 560 $(M - C_8H_8BrO_2)^+$ and 338, 336, 334; HRFABMS m/z 779.8447 $(M + H)^+$, calcd for $C_{27}H_{28}{}^{79}Br_2{}^{81}Br_2NO_6$ 779.8452.

Tridebromotheoneberine (2). A solution of theoneberine (1, 1.0 mg) in MeOH (0.5 mL) containing 10% Pd-C (0.8 mg) was stirred at room temperature under H_2 for 1 day. After removal of the catalyst by filtration and evaporation of the filtrate, the residue was purified by a silica gel column (Wako gel C-300, 0.5 × 5 cm) with $CHCl_3$/MeOH (95:5) to give tridebromotheoneberine (2, 0.3 mg, 51%): colorless solid; $[\alpha]^{26}_D$ -24° (c 0.05, $CHCl_3$); UV λ_{max} (MeOH) 283 nm (ϵ 5100), IR (film) ν_{max} 3400, 2920, 1490, and 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (1 H, d, J = 2.0 Hz, H-17), 6.79 (1 H, dd, J = 8.3, 2.0 Hz, H-21), 6.77 (1 H, d, J = 11.7 Hz, H-11), 6.72 (1 H, d, J = 8.3 Hz, H-20), 6.62 (1 H, d, J = 11.2 Hz, H-12), 6.58 (1 H, s, H-4), 4.60 (1 H, dd, J = 11.6, 4.4 Hz, H-14), 4.12 (1 H, dd, J = 8.3, 4.4 Hz, H-8), 3.90 (3 H, s, H_3-23), 3.88 (3 H, s, H_3-22), 3.85 (3 H, s, H_3-24), 3.14 (1 H, dd, J = 17.6, 4.4 Hz, H-13β), 3.03 (1 H, m, H-6β), 2.96 (2 H, m, H_2-15), 2.67 (1 H, m, H-13α), 2.58 (2 H, m, H-5α and H-6α), and 2.33 (1 H, m, H-5β); FABMS m/z 544, 542 $(M + H)^+$, 464 $(M + H - Br + H)^+$, and 406, 404 $(M + H - C_8H_{10}O_2)^+$; HRFABMS m/z 542.1177 $(M + H)^+$, calcd for $C_{27}H_{29}{}^{79}BrNO_6$ 542.1179.

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Supplementary Material Available: All spectra of compounds 1 and 2 (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(19) Compound 1 was inactive against fungi or Gram-negative bacteria. The antimicrobial activity of tetrahydroberberine was also examined for reference to show fairly weak activity (MIC values: *Staphylococcus aureus*, 133 μg/mL; *Sarcina lutea*, 266 μg/mL; *Bacillus subtilis*, >266 μg/mL; *Mycobacterium* sp. 607, 266 μg/mL).
(20) The general procedures are the same as described in the previous papers.[8]

Conformational Analysis of 1,2:5,6:9,10-Tribenzododeca-1,5,9-triene by ^1H NMR at 173 K

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In 1978, Brickwood, Ollis, Stephanidou-Stephanatou, and Stoddart[1] studied the conformational behavior of 1,2:5,6:9,10-tribenzododeca-1,5,9-triene (1) (called by these authors, 5,6,11,12,17,18-hexahydrotribenzo[*a*,*e*,*i*]cyclododecene). By means of proton-decoupled ^{13}C NMR spectroscopy at -104 °C in a 2:1 mixture of CD_2Cl_2-CS_2, they determined that the sole conformation present in solution is that of C_2 symmetry. Only this conformation is consistent with the observation of three methylene signals. Recently,[2] we have determined the X-ray structure

(1) Brickwood, D. J.; Ollis, W. D.; Stephanidou-Stephanatou, J.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1398.
(2) Domiano, P.; Cozzini, P.; Claramunt, R. M.; Lavandera, J. L.; Sanz, D.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1609.

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