((1′*S*)-3′,3′-dimethyl-2′,4′-dioxolanyl)-(*R*)-cyclohexanecarboxylate (16b). To a stirred solution of **15** (780 mg, 1.61 mmol) in THF (11 mL) was added lithium diisopropylamide in cyclohexane (1.5 mL, 1.5 M) under nitrogen at −75 °C. The solution was stirred overnight while the temperature was allowed to rise to room temperature. Saturated aqueous NH_4Cl (1.0 mL) was added, and the solution was partitioned between diethyl ether and water. The organic phase was washed with water, dried, and concentrated to give a colorless syrup (527 mg). Column chromatography (diethyl ether–hexane, 1:3) yielded **16a** (393 g, 68%) and **16b** (129 mg, 22%). **16a**: ^{13}C NMR δ 20.5, 24.6, 25.7, 26.5, 26.9, 28.1 (CH_3-Bu), 34.3, 38.0 (2 CH), 67.9 (CH_2O), 72.3, 72.4, 76.4, 80.2 (C-Bu), 107.7, 108.7 (2 $C(CH_3)_2$), 175.5 (CO_2). **16b**: ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 23.1, 25.7, 26.2, 26.8, 28.0 (CH_3-Bu), 28.1, 31.1, 40.0, 40.8 (2 CH_2), 67.5 (CH_2O), 72.9, 74.0, 74.0, 77.5, 80.5 (C-Bu), 108.5, 108.6 (2 $C(CH_3)_2$), 174.0 (CO_2).

3(*R*),4(*S*)-Dihydroxy-5(*R*)-(1′(*S*),2′-dihydroxyethyl)-(*S*)-cyclohexanecarboxylic Acid (1). Compound **16a** (100 mg, 0.28 mmol) was dissolved in aqueous trifluoroacetic acid (1.5 mL, 80%) and the resultant mixture stirred for 40 min at ice bath temperature. The mixture was concentrated, methanol (3.0 mL) was added, and the solution was concentrated to dryness. The residue was purified on a Biogel P-2 column with water as eluant, yielding compound **1**: 59 mg, 96%; $[\alpha]^{22}_D$ +112.5 (*c* 0.64, water); ^{13}C NMR (D_2O, 70 °C) δ 23.0, 28.5 (2 CH_2), 38.8, 40.1 (2 CH), 64.8 (C-2′), 69.4, 69.6, 72.9, 179.6 (CO_2); ^1H NMR (D_2O, 70 °C) δ 1.51 ($J_{1,6_{ax}}$ = 5.3 Hz, H-6_{ax}), 1.67 (H-5), 1.75 ($J_{1,2_{ax}}$ = 5.4 Hz, $J_{2_{ax},3}$ = 12.1 Hz, H-2_{ax}), 1.77 (H-6_{eq}), 2.03 (H-2_{eq}), 2.77 (H-1), 3.56 (H-2′), 3.69 (H-1′), 3.74 ($J_{3,4}$ = 2.8 Hz, H-3), 3.76 (H-2′), 4.13 (H-4).

Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.85; H, 7.18.

3(*R*),4(*S*)-Dihydroxy-5(*R*)-(1′(*S*),2′-dihydroxyethyl)-(*R*)-cyclohexanecarboxylic Acid (2). Compound **16b** (20 mg, 0.056 mmol) was reacted the same way as **1**, yielding **2**: 12 mg, 95%; ^{13}C NMR (D_2O, 70 °C) δ 25.2, 30.9 (2 CH_2), 42.4, 43.1 (2 CH), 64.8 (C-2′), 69.1, 72.1, 72.4, 178.5 (CO_2); ^1H NMR (D_2O, 70 °C) δ 1.41 ($J_{1,6_{ax}}$ = 12.5 Hz, H-6_{ax}), 1.66 ($J_{1,6_{eq}}$ = 3.6 Hz, H-6_{eq}), 1.69 ($J_{1,2_{ax}}$ = 12.6 Hz, $J_{2_{ax},3}$ = 12.3 Hz, H-2_{ax}), 1.94 ($J_{1,2_{eq}}$ = 3.6 Hz, H-2_{eq}), 2.52 (H-1), 3.55 (H-2′), 3.65 ($J_{3,4}$ = 2.8 Hz, H-3), 3.67 (H-1′), 3.75 (H-2′), 4.11 (H-4).

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New Bastadins from the Sponge *Ianthella basta*

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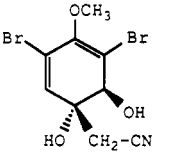
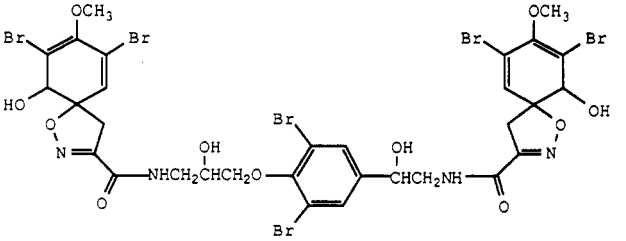
From the sponge *Ianthella basta* collected in Guam, four new bastadin type ethers, bastadin-8 (**7**), -9 (**9**), -10 (**8**), and -11 (**10**) were isolated together with the known bastadin-2 (**4**), -4 (**3**), -5 (**5**), and-6 (**6**). Structures were elucidated by extensive spectroscopic analysis and some derivative formation (methyl ethers). ^{13}C NMR assignments for bastadin-4 and -8 were made by one-bond and long-range H/C correlations. Several of the bastadins were found to exhibit cytotoxic and antiinflammatory activity.

Of the wide variety of nitrogenous natural products isolated from marine sponges, brominated tyrosine-derived metabolites have so far been found exclusively in species of the order Verongida.[1,2] Most of these metabolites consist of simple, modified tyrosines such as **1**[3] or linear combinations of tyrosine-derived units, e.g., fistularin-3 (**2**).[4] However, a unique group of macrocyclic metabolites typified by bastadin-4 (**3**) have been isolated from *Ianthella basta* collected in Australia.[5] We have examined the extracts of *Ianthella basta* collected in Guam and have isolated therefrom four new members of the bastadin series (**7**–**10**) in addition to the known bastadin-2 (**4**), -4 (**3**), -5 (**5**), and -6 (**6**).



1 Aeroplysinin-1



2 Fistularin-3

The bastadins were isolated by conventional methods as outlined in the Experimental Section. Bastadin-2, -4, -5, and -6 were identified by comparison of their ^1H and ^{13}C NMR spectral data with that reported in the litera-

(1) Krebs, H. C. *Fortsch. Chem. Org. Naturst.* **1986**, *49*, 184–189.

(2) Bergquist, P. R.; Wells, R. J. In *Marine Natural Products*, Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. 5, pp 1–50.

(3) Fattorusso, E.; Minale, L.; Sodano, G. *J. Chem. Soc., Chem. Commun.* **1970**, 751. Fattorusso, E.; Minale, L.; Sodano, G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 16.

(4) Gopichand, Y.; Schmitz, F. J. *Tetrahedron Lett.* **1979**, 3921.

(5) Kazlauskas, R.; Lidgard, R. O.; Murphy, P. T.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1981**, *34*, 765. Kazlauskas, R.; Lidgard, R. O.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1980**, *21*, 2277.

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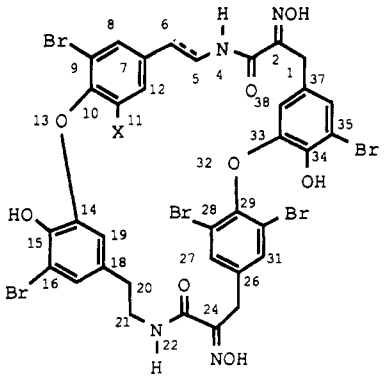
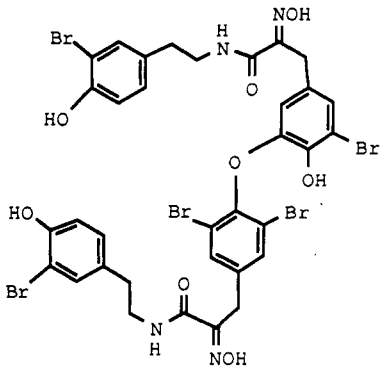


3 Bastadin-4, X = H, Δ^5
5 Bastadin-5, X = H, 5,6-dihydro
6 Bastadin-6, X = Br, 5,6-dihydro

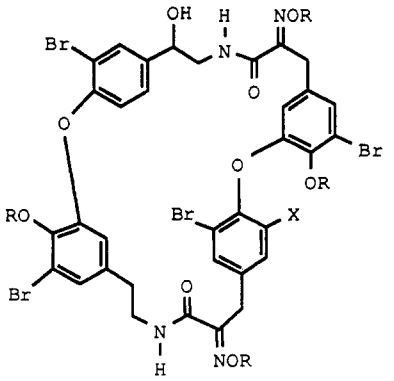


4 Bastadin-2

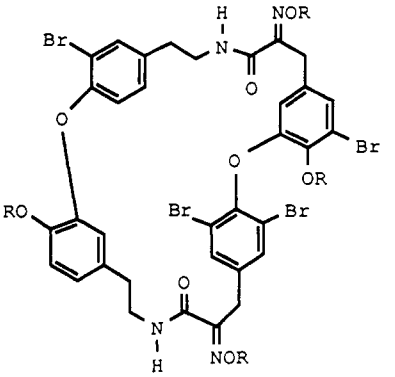
ture.[5] Bastadin-4 (**3**) was the major metabolite. Complete ^1H and ^{13}C NMR chemical shift assignments for this compound, the structure of which had been established by X-ray, were confirmed through HETCOR[6] and INAPT[7] experiments (see Tables I and II). These NMR data served as the reference values for interpreting data of the new bastadins and assigning their structures.

The first of the new metabolites, bastadin-8 (**7**), was slightly more polar than bastadin-4 (**3**). As was the case for all the bastadins reported earlier,[5] no molecular ion was observed in either the EI or FAB mass spectrum of **7**. However, the tetramethyl ether **11**, prepared by heating **7** with methyl iodide and potassium carbonate in dimethylformamide, exhibited a cluster of peaks in the high-resolution FAB mass spectrum beginning at m/z 1110.8194 (see the Experimental Section) that was consistent with the formula $C_{38}H_{35}{}^{79}Br_4{}^{81}BrN_4O_9$. Combining this information with ^{13}C data (chemical shift and multiplicities) and the result of a proton-exchange experiment (six exchangeable signals) the formula $C_{34}H_{27}Br_5N_4O_9$ was deduced for **7**.

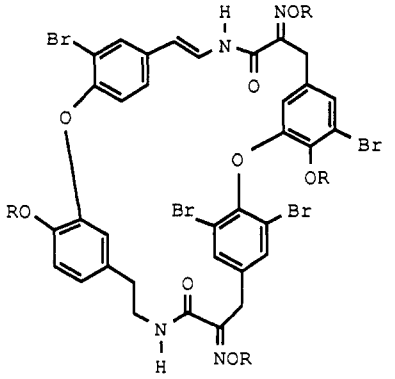
The ^1H NMR spectrum of **7** was similar to that of bastadin-4 (**3**) in that it contained four different sets of aromatic proton resonances indicative of four substituted benzene rings. The presence of CD_3OD-exchangeable proton signals at δ 12.00, 11.83, 9.80, 8.00, and 7.77, in conjunction with infrared absorptions at 3340, 1700, and 1660 cm^{-1}, was suggestive of oxime, phenol, and amide functionalities in **7**. Singlet ^{13}C NMR signals in the spectrum of **7** at δ 162.8, 163.2, and 150.9, 150.4, typical



7 Bastadin-8 (= 6-hydroxybastadin-5), X=Br; R=H
8 Bastadin-10 (= 6-hydroxy-30-debromobastadin-5), X=H; R=H
11 Bastadin-8 tetramethyl ether, X=Br; R=CH_3



9 Bastadin-9 (= 16-debromobastadin-5), R=H
12 Bastadin-9 tetramethyl ether, R=CH_3



10 Bastadin-11 (= 16-debromobastadin-4), R=H
13 Bastadin-11 tetramethyl ether, R=CH_3

resonances for amide carbonyl and oxime carbons, respectively (cf., **3**, Table II), further supported the assumption that compound **7** was a bastadin-type compound, closely related in structure to bastadin-4 (**3**).

Partial structures A–D (Figure 1) were deduced for compound **7** from ^1H NMR decoupling and NOE data. The nature of the substituents and the substitution pattern in each ring was inferred from chemical shift values and coupling constants. The ^{13}C NMR chemical shift assignments, see Table II, were obtained by H/C correlation. Partial structures B, C, and D were recognized as corresponding to the B, C, and D rings in the structure of bastadin-4 (**3**). Partial structure A consisted of a 1,2,4-trisubstituted ring with one substituent being a –CH(OH)– moiety. This benzylic methine proton (δ 4.63, m) was coupled with a set of methylene protons [δ 3.40 (m), and

(6) Bax, A. *J. Magn. Reson.* **1983**, *53*, 517. Bax, A.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 501.
(7) Bax, A.; Ferretti, J. A.; Nashed, N.; Jerina, D. *J. Org. Chem.* **1985**, *50*, 3029.

Table I. ^{1}H NMR Data for Bastadin Compounds 3 and 7–10 (DMSO-d_6, 300 MHz)

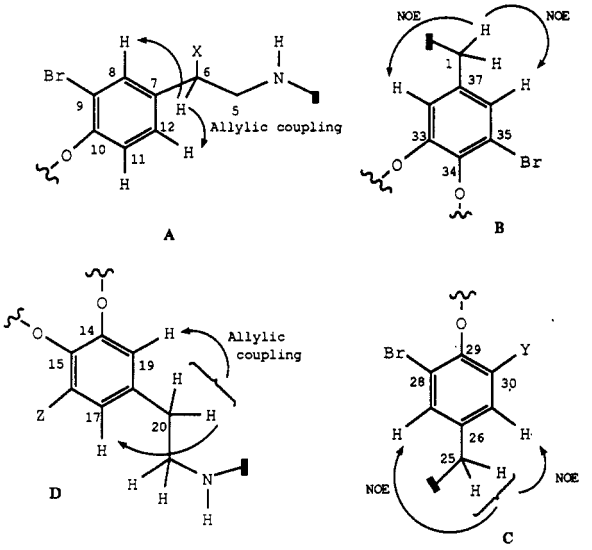
H at carbon	3	7	8	9	10
1	3.64 (2 H, bs)	3.57 (2 H, bs)	3.61 (2 H, bs)	3.54 (2 H, bs)	3.64 (2 H, bs)
4 (NH)	10.2 (1 H, d, 10.2)	7.77 (1 H, t, 6.0)	7.78 (1 H, t, 6.0)	7.97 (1 H, t 6.0)	10.2 (1 H, d, 10.3)
5	7.30 (1 H, dd, 14.7, 10.2)	3.40 (1 H, m) 3.00 (1 H, m)	3.30 (2 H, q)	3.18 (2 H, q)	7.25 (1 H, dd, 14.6, 10.3)
6	6.44 (1 H, d, 14.7)	4.63 (1 H, m)	4.62 (1 H, m)	2.62 (2 H, t)	6.39 (1 H, d, 14.6)
8	7.62 (1 H, d, 2.1)	7.69 (1 H, d, 2.0)	7.64 (1 H, d, 1.7)	7.49 (1 H, d, 2.1)	7.52 (1 H, d, sm)
11	6.92 (1 H, d, 8.4)	6.94 (1 H, d, 8.4)	6.91 (1 H, d, 8.5)	6.75 (1 H, d, 8.4)	6.73 (1 H, d, 8.7)
12	7.47 (1 H, dd, 8.4, 2.1)	7.27 (1 H, dd, 8.4, 2.0)	7.21 (1 H, dd, 8.0, 2.0)	7.10 (1 H, dd, 8.4, 2.1)	7.43 (1 H, dd, 8.7, 2.1)
16	–	–	–	6.85 (1 H, d, 8.1)	6.87 (1 H, d, 8.0)
17	7.12 (1 H, d, 2.1)	7.13 (1 H, d, 2.0)	7.12 (1 H, d, 2.1)	6.81 (1 H, dd, 8.1, 1.8)	6.82 (1 H, dd, 8.0, sm)
19	6.54 (1 H, d, 2.1)	6.60 (1 H, d, 2.0)	6.45 (1 H, d, 1.8)	6.73 (1 H, d, 1.8)	6.72 (1 H, d, sm)
20	2.70 (2 H, t)	2.68 (2 H, t, 6.0)	2.61 (2 H, t, 6.0)	2.67 (2 H, t, 5.7)	2.70 (2 H, bt)
21	3.38 (2 H, q)	3.40 (2 H, q)	3.38 (2 H, q)	3.41 (2 H, q)	3.43 (2 H, q)
22 (NH)	7.82 (1 H, t, 5.7)	8.00 (1 H, t, 6.0)	7.94 (1 H, t, 5.8)	8.03 (1 H, t, 5.7)	7.78 (1 H, t, 6.0)
25	3.52 (2 H, bs)	3.62 (2 H, bs)	3.61 (2 H, bs)	3.52 (2 H, bs)	3.53 (2 H, bs)
27	7.51 (1 H, s)	7.56 (1 H, s)	7.49 (1 H, d, 2.0)	7.59 (1 H, s)	7.51 (1 H, s)
30	–	–	6.78 (1 H, d, 8.5)	–	–
31	7.51 (1 H, s)	7.56 (1 H, s)	7.07 (1 H, dd, 8.5, sm)	7.59 (1 H, s)	7.51 (1 H, s)
36	7.08 (1 H, d, 1.9)	7.07 (1 H, d, 2.0)	7.15 (1 H, d, 1.9)	7.05 (1 H, d, 1.8)	7.07 (1 H, d, 1.9)
38	6.09 (1 H, d, 1.9)	6.24 (1 H, d, 2.0)	6.47 (1 H, d, 1.9)	6.22 (1 H, d, 1.8)	6.14 (1 H, d, 1.9)
6-OH	–	5.62 (1 H, d, 4.2)	5.64 (1 H, d, 4.4)	–	–
N-OH	12.05 br	12.0 br 11.83 bs	11.87 br 11.86 bs	11.96 br 11.73	11.98 bs 11.97 bs
Ar-OH	10.05 br	9.8 br	9.78 bs	10.02 bs	10.04 br 9.38 bs

Table II. ^{13}C NMR Data for Compounds 3 and 7–10[a]

carbon	3[b]	7[b]	8[c]	9[c]	10[c]
1	27.3 (t)	27.3 (t)	27.5 (t)	27.6 (t)	27.3 (t)
2	151.3 (s)*	150.9 (s)*	151.1 (s)	151.4 (s)	151.3 (s)
3	161.4 (s)*	162.8 (s)*	162.8 (s)	162.9 (s)	161.4 (s)
5	123.9 (d)	47.3 (t)	46.9 (t)	40.9 (t)	123.6 (d)
6	110.8 (d)	70.4 (d)	70.1 (d)	34.0 (t)	110.9 (d)
7	134.5 (s)*	140.6 (s)*	140.9 (s)	135.4 (s)	133.3 (s)
8	130.2 (d)	130.2 (d)	130.5 (d)	132.8 (d)	130.5 (d)
9	113.9 (s)*	112.0 (s)*	113.2 (s)	111.8 (s)	112.5 (s)
10	150.9 (s)*	151.8 (s)*	151.7 (s)	152.4 (s)	152.3 (s)
11	121.1 (d)	119.5 (d)	119.8 (d)	120.3 (d)	119.9 (d)
12	124.9 (d)	126.5 (d)	126.7 (d)	125.7 (d)	124.1 (d)
14	145.0 (s)*	144.7 (s)*	144.9 (s)	148.0 (s)	146.7 (s)
15	143.3 (s)*	143.8 (s)*	143.4 (s)	143.0 (s)	143.0 (s)
16	110.4 (s)*	110.6 (s)	110.6 (s)	116.5 (d)	116.7 (d)
17	127.8 (d)	128.1 (d)	127.9 (d)	128.9 (d)	125.8 (d)
18	131.5 (s)	131.4 (s)	131.6 (s)	130.6 (s)	130.6 (s)
19	117.0 (d)	118.0 (d)	117.4 (d)	118.0 (d)	119.1 (d)
20	32.8 (t)	33.4 (t)	33.5 (t)	34.0 (t)	33.5 (t)
21	38.5 (t)	39.2 (t)	40.6 (t)	39.4 (t)	38.5 (t)
23	162.9 (s)*	163.2 (s)*	163.1 (s)	163.0 (s)	162.7 (s)
24	150.1 (s)*	150.4 (s)*	150.7 (s)	150.4 (s)	150.1 (s)
25	28.9 (t)	28.7 (t)	28.5 (t)	28.8 (t)	28.9 (t)
26	137.6 (s)*	137.6 (s)*	133.5 (s)	137.7 (s)	137.6 (s)
27	133.6 (d)	133.5 (d)	129.5 (d)	133.1 (d)	133.5 (d)
28	116.8 (s)*	117.1 (s)*	117.4 (s)	117.2 (s)	116.9 (d)
29	145.9 (s)*	145.9 (s)*	151.1 (s)	145.9 (s)	145.9 (s)
30	116.8 (s)*	117.1 (s)*	119.0 (d)	117.2 (s)	116.9 (s)
31	133.6 (d)	133.5 (d)	128.7 (d)	133.1 (d)	133.5 (d)
33	144.8 (s)	144.7 (s)*	143.3 (s)	144.8 (s)	144.8 (s)
34	141.9 (s)*	141.9 (s)*	134.4 (s)	141.9 (s)	141.9 (s)
35	109.8 (s)*	109.7 (s)*	110.5 (s)	109.8 (s)	110.1 (s)
36	126.7 (d)	126.8 (d)	126.7 (d)	126.8 (d)	126.8 (d)
37	127.6 (s)*	127.9 (s)*	127.7 (s)	128.1 (s)	127.6 (s)
38	112.3 (d)	112.9 (d)	113.3 (d)	112.8 (d)	112.4 (s)

[a] Obtained in DMSO-d_6 at 75 MHz. Multiplicities obtained by DEPT. [b] Protonated carbons assigned by HETCOR. [c] Assignments based on analogy. * Assigned by long-range HETCOR and INAPT.

3.00 (m)] as well as with the hydroxyl proton (δ 5.62, d) and showed both allylic coupling and NOE with the aromatic proton signals at δ 7.69 and 7.27, thereby establishing the structure indicated. Thirty of the thirty-four carbons



7 Bastadin-8, X=OH; Y=Z=Br

8 Bastadin-10, X=OH; Y=H; Z=Br

9 Bastadin-9, X=H; Y=Br; Z=H

10 Bastadin-11, X=H, Δ^5, Y=Z=Br

Figure 1. Partial structures for bastadin-8 (**7**), -9 (**9**), -10 (**8**), -11 (**10**).

observed in the ^{13}C NMR spectrum of **7** were accounted for by the partial structures shown in Figure 1. Positions of the remaining four carbons (two amide carbonyl and two oxime carbons) were established by long-range HETCOR (J = 10 Hz) as follows. The methylene protons (δ 3.57) of partial structure B were coupled with both the oxime carbon at δ 150.9 and the amide carbonyl at δ 162.8. The other methylene protons (δ 3.62) of partial structure C were coupled with the oxime carbon at δ 150.4 and the amide carbonyl at δ 163.2. This information led to the extension of partial structures B and C to the partial structures B′

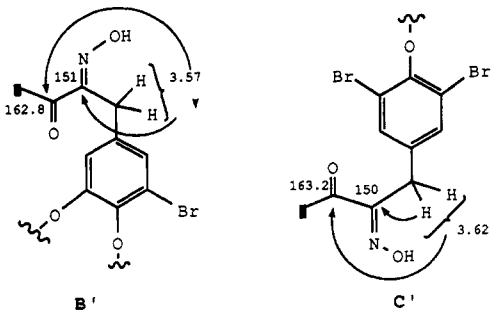
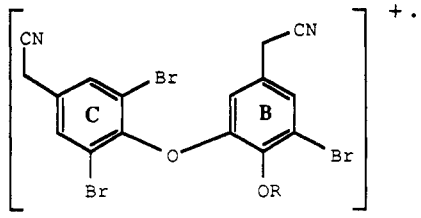


Figure 2. Partial structures for bastadin-8 (7) as deduced from long-range HETCOR.

and C′ shown in Figure 2. The stereochemistry of both the oxime groups was assigned as *E* on the basis of ^{13}C NMR data. The chemical shifts of the methylene carbons in partial structures B′ and C′ were 27.3 and 28.3 ppm, respectively, which are typical values for the α-methylene carbon in *E* oximes, in contrast to ~35 ppm expected for the *Z* isomer.[8]

Although no molecular ion was observed in the EI mass spectrum of bastadin-4 (3) or bastadin-8 (7), spectra of both these compounds contained a dominant ion fragment cluster at *m/z* 498, 500, 502, 504. In 3 these peaks were assigned to the cation radical shown below, which results from cleavage of the two oximino amide C–C bonds. Since



R = H, m/z = 498
R = CH_3, m/z = 512

the mass spectrum of 7 also contained the peaks at *m/z* 498–504, it was inferred that partial structures B′ and C′ were connected via an ether link to give the right-hand hemisphere of structure 7. To determine whether this ether link was indeed at the meta rather than the para position of the benzene ring of partial structure B, difference NOE experiments were performed on the tetramethyl ether 11. Irradiation of each of the methyl signals in the ^1H NMR spectrum of 11 failed to induce NOE enhancements of any of the other proton signals. This was negative evidence in favor of linkage between rings B and C in compound 7 via the meta oxygen on ring B just as in 3. If the ether link were at the para position in ring B, an NOE interaction between the proton (δ 6.24) ortho to the methoxy substituent and the methoxy group would have been expected.

Evidence for the ether connection between partial structures A and D came from the observation of an NOE between H-11 (6.94 ppm) and H-19 (6.60 ppm) of rings A and D. This NOE supported the presence of the ether link and confirmed that the ring D–A connection was via the oxygen at the meta rather than the para position of partial structure D.

To arrive at the final structure for 7, evidence for the amide linkages was obtained through INAPT experiments (*J* = 10 Hz), in which each of the N-H proton triplet signals was irradiated to detect the associated carbonyl carbons.

(8) Arabshahi, L.; Schmitz, F. J. *J. Org. Chem.* **1987**, *52*, 3584.

Table III. Some Long-Range H/C Correlations for Bastadin-8 (7)

H	C	H	C
H-1	C-2, -3, -36, -37	H-19	C-14, -15, -17
NH-4	C-3	NH-22	C-23
H-5	C-7	H-25	C-24, -26, -27/31
H-6	C-7, -8,	H-27/31	C-28/30, -29
H-11	C-7, -9, -12	H-36	C-34, -35
H-12	C-6, -10	H-38	C-33, -34, -36, -37
H-17	C-15		

Table IV. NOE Data for Bastadin-9 Tetramethyl Ether (12)

irr signal	enhanced signal (%)
H-11	H-19 (2)
MeO-15	H-16 (12)
MeON-2	H-38, H-19 (4.5)

These and other H/C correlations observed in INAPT and HETCOR experiments that support structure 7 are shown in Table III.

The ^1H NMR spectrum of the minor metabolite 8 (bastadin-10) closely resembled that of bastadin-8 (7). An obvious difference was the absence in the spectrum of 8 of the two-proton singlet peak at δ 7.51, assigned to the aromatic protons in ring C of bastadin-8 (7), and the presence of a new set of three aromatic signals at δ 7.49, 6.78, and 7.07 consistent with the 1,2,4-trisubstituted benzene ring shown in fragment C in Figure 1. The other three aromatic rings in 8 appeared to be identical with those in 3 by comparison of NMR data (see Tables I and II), and hence bastadin-10 was assigned structure 8. Corresponding differences in the ^{13}C NMR spectrum were also observed that supported this structure, i.e., there was one more aromatic methine carbon (δ 119.0) in the spectrum of 8 when compared to that of 3, and the signals at δ 116.8 and 133.6 in the spectrum of 3, which were twice as tall as the other signals (indicating 2 C's for each signal), were replaced in the spectrum of 8 by shorter peaks at δ 117.4, 129.5, 128.7, respectively. Chemical shift differences in the other ring C carbons (C-26 to 31, see Table II) were also fully compatible with having one less bromine substituent in the ring.

Compound 9 (bastadin-9) was obtained as a white powder by reversed-phase HPLC. A molecular formula of $C_{34}H_{28}Br_4N_4O_8$ for 9 was suggested by the FAB mass spectrum (molecular ion cluster, *m/z* 936–942). This compound was also judged to be a bastadin derivative based on IR (3420–3200, 3060, 2920, 1710, 1660 cm^{-1}), UV [λ_{max} (MeOH) 208 (log ε 5.1), 280 (log ε 4.0)], and NMR data (four sets of aromatic protons and 34 carbons) which were similar to those of bastadin-4 (3), -8 (7), -10 (8). The ^1H NMR spectrum of 9, like that of the other bastadins, contained aromatic resonances that could readily be assigned to the protons of four different aromatic rings (see Table I). Decoupling and NOE experiments led to the elucidation of partial structures A–D for bastadin-9 (see Figure 1) similar to those for 7. The B–C connection in 9 was confirmed from the high-resolution EI mass spectrum of the tetramethyl derivative of 9 (compound 12), which showed a dominant ion fragment with *m/e* 511.8354 ($C_{17}H_{11}O_2N_2{}^{79}Br_3$ requires 511.8371). This corresponds to the *m/z* 498 ion observed in the mass spectrum of 7. That compound 9 did not possess a C-6 hydroxyl group in partial structure A was evident from the presence in the ^1H NMR spectrum of 9 of two sets of upfield methylene triplet signals (δ 2.62 and 2.67), each allylically coupled to two aromatic protons. The aromatic ring in partial structure D of 9 lacked the bromine substituent that was present

Table V. Some Long-Range H/C Correlations for Bastadin-9 Tetramethyl Ether (12)

H	C	H	C
H-1	C-2, -3, -36	H-25	C-23, -24, -26, -27/31
H-5	C-7	MeO-34	C-34
H-8	C-10, -12	H-36	C-34
MeO-15	C-15	H-38	C-34
H-21	C-18		

in **7**. This was deduced from ^1H and ^{13}C NMR data and confirmed by the NOE observed between the proton at δ 6.97 (H-16) and the methoxy protons at δ 3.98 (MeO-15) of **12**, the tetramethyl ether derivative of **9** (see Table IV). Linking the partial structures deduced for bastadin-9 (Figure 1) in a manner analogous to that observed in the other bastadins resulted in structure **9**. This structure was also supported by NOE (Table IV), long-range HETCOR, and INAPT data (Table V) obtained on the tetramethyl derivative **12**. The NOE's observed between the protons at δ 6.66 (H-19) and 6.85 (H-11), and between the proton at δ 6.97 (H-16) and the C-15 methoxy methyl signal (δ 3.98) supported the assigned position of the ether link between rings A and D. An NOE observed between the proton at δ 6.66 (H-19) and a methoxy methyl group (δ 3.48), presumably on the C-2 oxime, was in agreement with the X-ray structure of the closely related tetramethyl ether of bastadin-5 (**5**) in which this methoxyimino group was shown to be oriented toward the center of the macrocycle.[5]

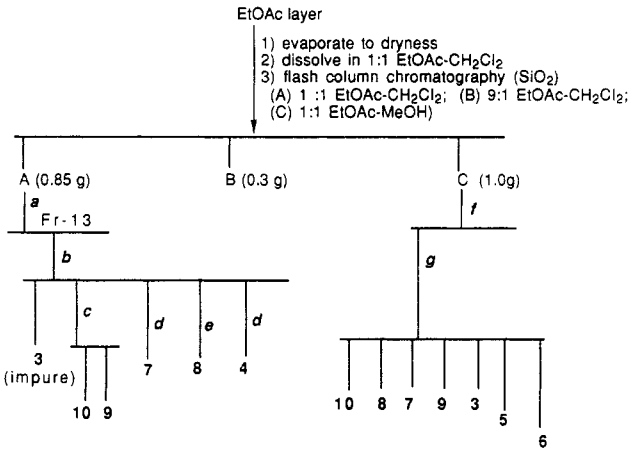
From examination of the ^1H NMR spectrum of bastadin-11 (**10**), it was clear that this bastadin derivative had a structure that combined features of bastadin-4 (**3**) and bastadin-9 (**9**). Partial structure A for **10** (Figure 1), obtained by analysis of ^1H homodecoupling data, featured an enamide side chain on a 1,2,4-trisubstituted ring. This was identical with ring A in bastadin-4 (**3**) (see Tables I and II for pertinent NMR data). Partial structure D was recognized as identical with ring D of bastadin-9 (**9**). The other half of the structure of bastadin-11, i.e., rings B and C, was inferred to be the same as in bastadins-4 (**3**), -8 (**7**), and -9 (**9**), based on a close agreement of NMR data for this section of the molecule in all these four compounds (see Tables I and II). Bastadin-11 was thus assigned structure **10**. Methylation of **10** (MeI, K_2CO_3, DMF) yielded the tetramethyl ether **13**. Unfortunately, as was the case for the natural product **10**, no molecular ion was observed for **13** in either FAB or EI mass spectra. However, comparison of the ^1H NMR spectra of **13** and **12**, the tetramethyl ether derivative of bastadin-9 (**9**) (see the Experimental Section for data), revealed a close similarity between these two compounds and thus further supported the assigned structure for bastadin-11 (**10**).

Bastadin-4 (**3**), -8 (**7**), and -9 (**9**) are cytotoxic against P-388 leukemia cells with ED_{50} values of 2.0, 3.6, and 2.7 μg/mL, respectively. These compounds also show anti-inflammatory activity in the mouse ear assay. At a dose of 50 μg/ear, bastadin-4, bastadin-8, and bastadin-9 inhibited inflammation by 89%, 93%, and 94%, respectively.[9] These data taken together with the bioactivity reported earlier for other bastadins[5] demonstrate that these macrocyclic amides may provide models for drug synthesis and are good candidates for mechanism of action studies.

Experimental Section

^1H and ^{13}C NMR chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Ultraviolet spectra were taken in methanol. Melting points are uncorrected. An Altex 9.6 mm × 29.9 cm semipreparative 5 μm Adsorbosphere reverse-phase C_{18} column and an Altex 5 μm, 10 mm × 30 mm semipreparative Econosphere silica gel column were used for HPLC separations and purification. Kieselgel 60 H silica gel was used for vacuum flash column chromatography. Thin-layer chromatography was performed using Kodak chromagram precoated silica TLC sheets and Whatman C-18 reverse-phase precoated TLC plates.

Scheme I.[a] **Isolation of *Ianthella basta* Metabolites via Procedure b**



[a] (a) SiO_2 flash column chromatography, $CHCl_3$ with step increase in MeOH; (b) SiO_2 HPLC, acetone–hexane (4:6); (c) C-18 reversed-phase HPLC, MeOH–H_2O (67:33); (d) C-18 reversed-phase HPLC, MeOH–H_2O (7:3); (e) C-18 reversed-phase HPLC, MeOH–H_2O (65:35); (f) SiO_2 flash column chromatography, CH_2Cl_2 with step increase in 2-propanol; (g) C-18 reversed-phase HPLC, MeOH–H_2O (75:25).

Extraction and Isolation. (a) The blue, thin, vase-shaped sponge *Ianthella basta* used in this investigation was collected in Guam in 1985 and then again in 1986. Fresh sponge specimens were cut into strips, frozen, and shipped to Oklahoma. A portion of the first collection was cut into smaller pieces and freeze-dried to give 46 g of dry sponge, which was then soaked sequentially at room temperature in hexane, dichloromethane, and finally chloroform–methanol (1:1) (1 day in each solvent). Upon removal of the solvents by evaporation under vacuum, 0.4 g of hexane extract, 0.3 g of dichloromethane extract, and 6.0 g of 1:1 chloroform–methanol extract were obtained. The chloroform–methanol extract was fractionated on silica gel by vacuum flash chromatography using gradient elution beginning with $CHCl_3$ then increasing the polarity with MeOH. Silica HPLC of the third of 20 column fractions using 1:1 acetone–hexane resulted in the isolation of compound **9**. Reversed-phase HPLC of the fourth column fraction using H_2O–MeOH (28:72) yielded compounds **3** and **7**, which were further purified by silica HPLC (using 1:4 acetone–hexane and 1:1 acetone–hexane, respectively).

(b) The remainder of the specimens from the first batch as well as all of the second batch were each extracted separately using the following procedure. The sponge was freeze-dried to give 127 g of dry sponge tissue which was pulverized in a blender and then percolated sequentially with hexane, chloroform, and methanol in a Soxhlet extractor (1 day in each solvent). The solvent was evaporated under vacuum from each extract to give 1.4, 0.9, and 23 g of hexane, chloroform, and methanol extract, respectively. The methanol extract was redissolved in methanol (500 mL), water (500 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 500 mL). Approximately 3 g of a dark reddish gummy material was obtained upon vacuum evaporation of the solvent from the organic layer. This contained the bastadin compounds and was further chromatographed, as outlined in Scheme I.

Bastadin-4 (3): ~100 mg; yellow needles; $C_{34}H_{25}O_8Br_5N_4$; UV (MeOH) λ_{max} 209 (log ϵ 5.1), 288.5 (log ϵ 4.3), 300 (sh) (log ϵ 4.2), 310 nm (log ϵ 4.2); IR (film on NaCl plate) 3600–2800, 1657, 1633, 1490, 1250 cm^{-1}; low-resolution MS (EI$^+$, 12 eV), m/z (relative intensity) 504 (4), 502 (11), 500 (11), 498 (4), 342 (28), 340 (28);

(9) Antiinflammatory activity testing was carried out by Dr. R. S. Jacobs' group, University of California, Santa Barbara.

^{1}H NMR, Table I; ^{13}C NMR, Table II.

Bastadin-8 (7): 65 mg; white film; $C_{34}H_{27}O_9N_4Br_5$; UV (MeOH) λ_{max} 208 (log ϵ 5.1), 280 nm (log ϵ 3.9); IR (film on NaCl plate) 3340, 1700, 1660, 1590, 1530, 1490, 1450, 1420, 1360, 1280, 1240, 990 cm^{-1}; low-resolution MS (EI$^+$, 12 eV) m/z (relative intensity) 504 (7.0), 502 (18.7), 500 (18.7), 498 (5.8), 342 (15.8), 340 (21.1), 199 (7.6), 199 (7.0); ^{1}H NMR (DMSO-d_6, 300 MHz), Table I; ^{13}C NMR (DMSO-d_6, 75.4 MHz), Table II.

Bastadin-8 Tetramethyl Ether (11). Bastadin-8 (7) (3.3 mg) was stirred at room temperature in dimethylformamide (1.5 mL), with potassium carbonate (100 mg) and methyl iodide (180 μL) for 18 h. The reaction mixture was diluted with dichloromethane and filtered. Evaporation of the solvent gave the crude methylated derivative, which was purified by HPLC on silica gel (acetone–hexane, 4:6) to give the product as a white powder (2.3 mg, 66% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (H-8, d, 2.0), 7.52 (H-27, H-31, s), 7.28 (H-12, dd, 8.0, 2.0), 7.16 (H-36, d, 2.0), 7.14 (H-17, d, 2.0), 6.97 (H-11, d, 8.0), 6.87 (H-4 (NH), t, 6.0), 6.76 (H-22, t, 6.0), 6.65 (H-19, d, 2.0), 6.28 (H-38, d, 2.0), 4.88 (H-6, m), 3.79 (H-1, bs), 3.78 (H-25, bs), 3.72, 3.38 (H-5), 3.46, 3.55 (H-21), 2.75 (H-20, m), 4.02 (3 H, s), 4.01 (3 H, s), 3.97 (3 H, s), 3.70 (3 H, s); LRMS (FAB$^+$, p-nitrobenzyl alcohol/magic bullet (dithiothreitol/dithioerythritol) matrix m/z (relative intensity) 1076.9 (33.2), 1074.9 (52.5), 1072.8 (24.7), 1070.8 (19.9); HR FAB m/z (formula) 1110.8194 ($C_{38}H_{35}N_4O_9{}^{79}Br_4{}^{81}BrNa$ requires 1110.8198), 1112.8194 ($C_{38}H_{35}N_4O_9{}^{79}Br_3{}^{81}Br_2Na$ requires 1112.8178), 1114.8035 ($C_{38}H_{35}N_4O_9{}^{79}Br_2{}^{81}Br_3Na$ requires 1114.8157), 1116.7491 ($C_{38}H_{35}N_4O_9{}^{79}Br^{81}Br_4Na$ requires 1116.8137).

Bastadin-10 (8): 2.7 mg; colorless oil; $C_{34}H_{28}O_9N_4Br_4$; UV (MeOH) λ_{max} 210 (log ϵ 4.7), 277 nm (log ϵ 3.7); IR (film on NaCl plate) 3340 br, 1698, 1662, 1590, 1545, 1483, 1421, 1290, 1240 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz), Table I. ^{13}C NMR (DMSO-d_6, 75.4 MHz), Table II.

Bastadin-9 (9): 45 mg; white powder from methanol–water; $C_{34}H_{28}O_8N_4Br_4$; UV (MeOH) λ_{max} 208 (log ϵ 5.1), 280 nm (log ϵ 4.0); IR (film on NaCl plate) 3420–3200, 1710, 1660, 1620, 1585, 1450, 1420, 1360, 1230 cm^{-1}; low-resolution MS (FAB$^+$, magic bullet matrix) m/z (relative intensity) 942 (1), 940 (2), 938 (2), 936 (1, M$^+$); ^{1}H NMR (DMSO-d_6, 300 MHz), Table I; ^{13}C NMR (DMSO-d_6, 75.4 MHz), Table II.

Bastadin-9 Tetramethyl Ether (12). Methylation of bastadin-9 (9) (5.2 mg) was carried out using the same procedure described for the methylation of bastadin-8 (7). Purification by HPLC on silica gel gave 3.5 mg of 12 (64% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (H-27, H-31, s), 7.44 (H-8, d, 2.0), 7.19 (H-36, d, 2.0), 7.03 (H-12, dd, 8.3, 2.0), 6.97 (H-16, d, 8.3), 6.91 (H-17, dd, 8.3, 2.0), 6.85 (H-11, d, 8.0), 6.79 (H-4 (NH), t, 6.0), 6.66 (H-19, d, 2.0), 6.61 (NH, t, 6.0), 6.27 (H-38, d, 2.0), 3.67 (H-1, bs), 3.86 (H-25, bs), 3.53 (2 H, q, 6.3), 3.46 (2 H, q), 2.75 (2 H, t), 2.73 (2 H, t), 4.05 (3 H, s), 4.00 (3 H, s), 3.90 [OCH_3, (C-15), s], 3.49 (s H, s); low-resolution MS (FAB$^+$) m/e (relative intensity) 1014 [7.1 (M + Na)$^+$], 1016 (21.1), 1018 (28.3), 1020 (26.3), 1022 (1.2); high-resolution MS (EI$^+$) m/e (relative intensity) 511.8354 [$C_{17}H_{11}O_2N_2{}^{79}Br_3$, calcd 511.8371, –3.3 ppm (34.4)], 513.8460 (95.8), 515.8416 (100), 517.8291 (37.5).

Bastadin-11 (10): 4.3 mg; whitish film; $C_{34}H_{26}O_8N_4Br_4$; UV (MeOH) λ_{max} 208 (log ϵ 4.3), 285 (log ϵ 3.4), 331 nm (log ϵ 3.5); IR (film on NaCl plate), 3300 br, 1718, 1662, 1646, 1544, 1495, 1479, 1447, 1418, 1284, 1243 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz), Table I; ^{13}C NMR (DMSO-d_6, 75.4 MHz), Table II.

Bastadin-11 Tetramethyl Ether (13). To bastadin-11 (10) (2.0 mg) in dimethylformamide was added excess ethereal diazomethane, and the mixture was allowed to stand for 3 h. The solvent was evaporated, and the residue was purified by HPLC on silica gel to give the tetramethyl derivative (<1 mg): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (H-4 (NH), d, 11.4), 7.54 (H-8, d, 2.7), 7.46 (H-27, H-31, s), 7.38 (H-12, dd), 7.34 (H-5, dd), 7.12 (1 H, d, 2.0), 6.96 (H-16, d, 8.4), 6.90 (H-17, dd), 6.90 (H-11, d, 8.4), 6.71 (H-19, d, 2.1), 6.58 (NH, t, 5.4), 6.25 (H-38, d, 2.0), 6.17 (H-6, d, 14.7), 3.73 (2 H, bs), 3.65 (2 H, bs), 3.58 (2 H, q, 5.4), 2.82 (2 H, t, 5.4), 4.01 (6 H, s), 3.93 (3 H, s), 3.92 (3 H, s).

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Acid-Catalyzed Rearrangement of Arenerol

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Upon treatment with p-toluenesulfonic acid in benzene, the sesquiterpene quinol arenerol (1) underwent skeletal rearrangement and intramolecular ether formation. The structure of the rearranged and cyclized product 4 was determined by X-ray analysis.

Some time ago we reported the structure of the sesquiterpene quinol arenerol (1), which had been isolated from the Pacific sponge *Dysidea areneria*.[1] In the course of trying to establish the structure of 1 (Chart I) by spectral and chemical methods, prior to obtaining crystals of 1 diacetate for X-ray analysis, we had treated 1 with p-toluenesulfonic acid in benzene to see if it would readily form a cyclic ether as would have been expected if the exocyclic methylene group were at position 8,13; cf. cyclization of zonarol.[2] Treatment of 1 in this acid solution overnight at room temperature followed by 1/2 h at reflux temperature resulted in the formation of a new product isomeric with 1 (MS analysis) in approximately 60% isolated yield. This rearranged product possessed one secondary and three quaternary methyl groups, but no exocyclic double bond. It formed only a monoacetate (acetic anhydride/pyridine) and hence was considered to contain a new ether ring. The proton NMR spectral data did not conform to that reported for some possible rearrangement

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