111, 44; HRMS (M^+) calcd for $C_{12}H_{21}ON$ 195.1623, found 195.1601.

Supplementary Material Available: ^1H NMR spectra of 7-19 and intermediates and ^{13}C NMR spectrum of 18 (35 pages). Ordering information is given on any current masthead page.

Manzacidins A-C, Novel Tetrahydropyrimidine Alkaloids from the Okinawan Marine Sponge *Hymeniacidon* sp.

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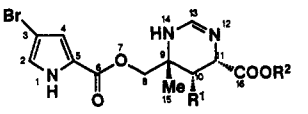
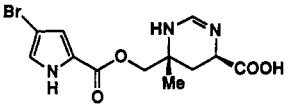
Bromopyrrole alkaloids comprise a typical class of marine natural products, frequently encountered as secondary metabolites of marine sponges of various species.[1] During our studies on bioactive substances from Okinawan marine organisms,[2] we have examined the extracts of numerous marine sponges and isolated several bromopyrrole alkaloids, which were found to be pharmacologically useful as α-adrenoceptor blockers,[3] antagonists of serotonergic receptor,[4] and actomyosin ATPase activators.[5] Recently, we investigated bioactive constituents of another Okinawan sponge *Hymeniacidon* sp. and isolated three novel compounds, named manzacidins A-C (1-3), belonging to an unprecedented class of bromopyrrole alkaloids with an unusual 3,4,5,6-tetrahydropyrimidine ring. Here, we describe the isolation and structure elucidation of 1-3.

The sponge *Hymeniacidon* sp., collected at Manza Beach, Okinawa, was extracted with methanol. The



1 R^1=R^2=H
2 R^1=OH, R^2=H
4 R^1=H, R^2=Me



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methanol extract was dissolved in a mixture of ethyl acetate and water, and then the aqueous layer was extracted with ethyl acetate and 1-butanol. The 1-butanol-soluble fraction was subjected to silica gel flash chromatography with chloroform/1-butanol/acetic acid/water (1.5:6:1:1) followed by reversed-phase HPLC on ODS (acetonitrile/water/trifluoroacetic acid (22:78:0.1)) to give manzacidins A (1; 3.5×10^{-3}% yield, wet weight), B (2; 2.1×10^{-3}%), and C (3; 1.0×10^{-3}%) as colorless oils, concurrently with previously reported bromopyrroles, dibromophakelin,[1d] and debromohymenialdisine.[1i]

Manzacidin A (1) showed a UV maximum at 272 (ϵ 5800) nm, suggestive of the presence of a substituted pyrrole chromophore.[6] A broad IR absorption band was observed at 3600-2800 cm^{-1}, which was attributable to a carboxyl group, and strong IR bands at 1710 and 1685 cm^{-1} were indicative of the presence of carbonyl (conjugated ester and carboxyl) groups. The presence of a carboxylic acid group in 1 was confirmed by the fact that a methyl ester (4) was obtained on treatment of 1 with HCl/MeOH. The positive-ion FABMS of manzacidin A (1) gave prominent quasi-molecular ions at m/z 344 and 346 $(M + H)^+$ with an intensity ratio of ca. 1:1, implying that 1 contains one bromine atom. The molecular formula was established to be $C_{12}H_{14}N_3O_4Br$ by HRFABMS (m/z 344.0251 $(M + H)^+$ for $C_{12}H_{15}N_3O_4{}^{79}Br$, Δ +0.5 mmu). The ^1H and ^{13}C NMR spectra of manzacidin A (1) showed signals characteristic corresponding to a 3-bromopyrrole-5-carboxylic acid derivative moiety (C_5H_3NOBr) (δ_H 12.32 (1 H, br s, exchangeable; NH-1), 7.25 (1 H, br t, H-2), and 6.98 (1 H, br t, H-4); δ_C 124.3 (d, C-2), 96.0 (s, C-3), 117.0 (s, C-4), 121.9 (s, C-5), and 158.6 (s, C-6)[7]). These assignments were fully corroborated by comparison of the NMR data of hymenidin,[4a] sceptrin,[1c] or ageliferin.[5a] The rest of the molecule consisting of $C_7H_{11}N_2O_3$, therefore, remains to be accounted for. Interpretation of the ^1H and ^{13}C NMR data of this part leading to the unusual structure, 3,4,5,6-tetrahydro-4-(hydroxymethyl)-4-methyl-6-pyrimidinecarboxylic acid, was achieved as follows with the aid of extensive application of one- and two-dimensional NMR techniques (DEPT,[8] difference NOE,[9] ^1H-^1H COSY,[10] INEPTNON,[11] HMQC,[12] and HMBC[13] experiments). Seven carbons of this portion of 1 were characterized as

(1) Agelasiidae family.[4b] (a) Forenza, S.; Minale, L.; Riccio, R. *J. Chem. Soc., Chem. Commun.* **1971**, 1129-1130. (b) Garcia, E. E.; Benjamine, L. E.; Ian Fryer, R. *J. Chem. Soc., Chem. Commun.* **1973**, 78-79. (c) Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772-6773. (d) Fedreyev, S. A.; Ilyin, S. G.; Utkina, N. K.; Maximov, O. B.; Reshetnyak, M. V.; Antipin, M. Y.; Struchkov, Y. T. *Tetrahedron* **1989**, *45*, 3487-3492. Axinellidae family: (e) Sharma, G.; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118-4124. (f) Sharma, G. M.; Buyer, J. S.; Pomerantz, M. W. *Chem. Soc., Chem. Commun.* **1980**, 435-436. (g) De Nanteuil, G.; Ahond, A.; Guilhem, J.; Poupat, C.; Tran Huu Dau, E.; Potier, P.; Pusset, M.; Pusset, J.; Laboute, P. *Tetrahedron* **1985**, *41*, 6019-6033. (h) Fedoreyev, S. A.; Utkina, N. K.; Ilyin, S. G.; Reshetnyak, M. V.; Maximov, O. B. *Tetrahedron Lett.* **1986**, *27*, 3177-3180. (i) Pettit, G. R.; Herald, C. L.; Leet, J. E.; Gupta, R.; Schaufelberger, D. E.; Bates, R. B.; Clewlow, P. J.; Doubek, D. L.; Manfredi, K. P.; Rützler, K.; Schmidt, J. M.; Tackett, L. P.; Ward, F. B.; Bruck, M.; Camou, F. *Can. J. Chem.* **1990**, *68*, 1621-1624. Hymeniacidonidae family:[3a,4a] (j) Kitagawa, I.; Kobayashi, M.; Kitanaka, K.; Kido, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2321-2328. (k) Schmitz, F. J.; Gunasekera, S. P.; Lakshmi, V.; Tillekeratne, L. M. V. *J. Nat. Prod.* **1985**, *48*, 47-53.

(2) (a) Kobayashi, J.; Murayama, T.; Ishibashi, M.; Kosuge, S.; Takamatsu, M.; Ohizumi, Y.; Kobayashi, H.; Ohta, T.; Nozoe, S.; Sasaki, T. *Tetrahedron* **1990**, *46*, 7699-7702. (b) Kobayashi, J.; Murayama, T.; Kosuge, S.; Kanda, F.; Ishibashi, M.; Kobayashi, H.; Ohizumi, Y.; Ohta, T.; Nozoe, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3301-3303. (c) Kobayashi, J.; Cheng, J.-F.; Kikuchi, Y.; Ishibashi, M.; Yamamura, S.; Ohizumi, Y.; Ohta, T.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 4617-4620. (d) Kobayashi, J.; Cheng, J.-F.; Ohta, T.; Nozoe, S.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3666-3670. (e) Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3421-3423.

(3) (a) Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y.; Wakamatsu, K.; Miyazawa, T. *Experientia* **1986**, *42*, 1064-1065. (b) Kobayashi, J.; Nakamura, H.; Ohizumi, Y. *Experientia* **1988**, *44*, 86-87.

(4) (a) Kayabashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Experientia* **1986**, *42*, 1176-1177. (b) Nakamura, H.; Ohizumi, Y.; Kobayashi, J.; Hirata, Y. *Tetrahedron Lett.* **1984**, *25*, 2475-2478.

(5) (a) Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron* **1990**, *46*, 5579-5586. (b) Kobayashi, J.; Tsuda, M.; Ohizumi, Y. *Experientia* **1991**, *47*, 301-304.

(6) Scott, A. I. In *Interpretation of the Ultraviolet Spectra of Natural Products*; Pergamon Press: New York, 1964; pp 165-169.

(7) Multiplicities were determined by DEPT experiments.[8]

(8) Pegg, D. T.; Doddrell, D. M.; Bendall, M. R. *J. Chem. Phys.* **1982**, *77*, 2745-2752.

(9) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703-5711.

(10) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542-561.

(11) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101*, 760-762.

(12) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565-569.

(13) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093-2094.

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Table I. ^1H and ^{13}C NMR Data of Manzacidin A (1) in DMSO-d_6[a,b]

position	^1H	J(Hz)	^{13}C	HMBC correlations (^1H)
1	12.32 (br s)			
2	7.25 (br t)		124.3 (d)	H-4
3			96.0 (s)	H-2
4	6.98 (br t)		117.0 (s)	H-2
5			121.9 (s)	H-2, H-4
6			158.6 (s)	H_2-8
7				
8a	4.26 (d)	11.5	67.5 (t)	H_3-15
8b	4.15 (d)	11.5		
9			51.8 (s)	H_2-8, H_2-10, H-13, H_3-15
10_{eq}	2.25 (dd)	13.2, 4.9	29.3 (t)	H_2-8, H_3-15
10_{ax}	2.13 (dd)	13.2, 9.9		
11	4.43 (dd)	4.9, 9.9	48.0 (d)	H_2-10, H-13
12				
13	8.18 (br s)		150.7 (d)	
14	10.14 (br s)			
15	1.35 (3 H, s)		23.2 (q)	H_2-8, H_2-10
16			170.3 (s)	H-11

[a] ^1H-^1H COSY correlations: H-1/H-2, H-1/H-3, H-2/H-3, H-8a/H-8b, H-10_{eq}/H-10_{ax}, H-10_{eq}/H-11, H-10_{ax}/H-11, and H-13/H-14. [b] NOE results [H(irradiated) → H(enhanced)]: H-1 → H-2, H-4 → H_3-15, H-8a → H_3-15, H-10_{eq} → H-10_{ax}, H-10_{ax} → H-10_{eq}, H-11 → H_3-15, and H-14 → H-13.

two sp^3 methylene, one of which bore oxygen (δ_C 67.5 (t, C-8) and 29.3 (t, C-10)), one sp^3 quaternary carbon (δ_C 51.8 (s, C-9)), one sp^3 methine (δ_C 48.0 (d, C-11)), one sp^2 methine (δ_C 150.7 (d, C-13)), one methyl (δ_C 23.2 (q, C-15)), and one carboxyl group (δ_C 170.3 (s, C-16)). ^1H-^{13}C correlations via one-bond coupling were directly disclosed from the HMQC spectrum, and the proton connectivities obtained by the ^1H-^1H COSY spectrum showed that ^1H signals of this part could be divided into four groups: an AB quartet (δ_H 4.26 and 4.15 (each d, H_2-8)), an ABX system (δ_H 2.13, 2.25, and 4.43 (each dd, H_2-10 and H-11, respectively)), two broad singlets long-range coupled to each other (δ_H 8.18 and 10.14 (exchangeable, H-13 and H-14, respectively)), and a methyl group (δ_H 1.35 (s, H_3-15)). These four proton systems and nonprotonated carbon signals were shown to be connected on the basis of ^1H-^{13}C long-range connectivities provided by the HMBC experiment (Table I). The sp^3 quaternary carbon (δ_C 51.8 (s, C-9)) showed HMBC cross-peaks with H_2-8, H_2-10, H-13, and H_3-15, and the carboxyl carbon (δ_C 170.3 (s, C-16)) was revealed to be correlated with H-11. Nitrogen atoms were inferred to be attached to C-9 and C-11 from their ^{13}C chemical shifts (δ_C 51.8 and 48.0, respectively). The ^{13}C chemical shift of C-13 (δ_C 150.7)[14] implied that this carbon is situated between two nitrogen atoms, which was supported by the relatively large ^1H-^{13}C one-bond coupling constant[15] ($^1J_{C-H}$ = 198.6 Hz) observed from the INEPTNON experiment. On the basis of the combination of these NMR spectroscopic results, a tetrahydropyrimidine ring was deduced for the structure of the $C_7H_{11}N_2O_3$ unit of manzacidin A (1). Since H-11 did not show the ^1H-^1H COSY correlation with the exchangeable NH signal (δ_H 10.14), the NH (hydrogen on secondary amine) was located at N-14 and an imine bond exists between N-12 and C-13. The oxymethylene protons on C-8 (δ_H 4.26 and 4.15) revealed HMBC long-range correlations with the C-6 carbonyl carbon (δ_C 158.6), suggesting that C-8 was connected with the bromopyrrolecarboxylic acid moiety through an ester linkage. The relative stereochemistry of the tetrahydropyrimidine ring portion was defined by the ^1H-^1H coupling constants along with difference NOE experiments (Figure 1). From the $J_{10_{ax},11}$ and $J_{10_{eq},11}$ values (9.9 and 4.9 Hz, respectively), H-11 was shown to be axially oriented and the carboxyl group was therefore equatorial. Irradiation of H-11 yielded a significant NOE for H_3-15, thus revealing that the C-15 methyl group and H-11 were in a 1,3-diaxial relationship. From all of the observations described above, the structure of manzacidin A was concluded to be 1.

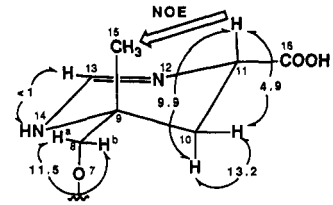

Figure 1. ^1H-^1H coupling constants and NOE results of tetrahydropyrimidine ring of manzacidin A (1).

Manzacidin B (2) showed UV and IR absorption spectra similar to those of manzacidin A (1). The molecular weight of 2 (FABMS, m/z 360 and 362 $(M + H)^+$, ca. 1:1) was larger than that of 1 only by 16 Da, indicating that 2 was an oxygenated compound of 1, which was firmly verified by determination of the molecular formula as $C_{12}H_{14}N_3O_5Br$ based on HRFABMS (m/z 360.0211 $(M + H)^+$ for $C_{12}H_{15}N_3O_5{}^{79}Br$, Δ + 1.1 mmu). The differences of the ^1H and ^{13}C NMR data of 2[16] from those of 1 were found only in the signals for C-10 and its neighboring groups. The ^{13}C signal due to C-10 was observed at δ_C 65.2 (d),[7] which was assignable to an oxymethine carbon. The H-10 resonated in the lower field (δ_H 4.46) as a doublet and was coupled with H-11 (δ_H 4.75, br d) by 2.2 Hz, suggesting that a hydroxyl group is attached to C-10 and oriented axially.

The FABMS of manzacidin C (3) showed quasi-molecular ions at m/z 344 and 346 ($(M + H)^+$, ca. 1:1), which was the same as those of 1, and the ^1H and ^{13}C NMR spectra of 3 were also analogous to those of 1, thus implying that 3 was an isomer of 1. The primary difference was the ^1H coupling pattern of the ABX system due to H_2-10 and H-11. The $J_{10_{ax},11}$ and $J_{10_{eq},11}$ were observed to be 3.8 and 2.8 Hz for 3, suggesting that the H-11 was equatorial and the carboxyl group (C-16) was axial. This finding was consistent with the observation that no NOE was detected at H_3-15 on irradiation of H-11. Thus, manzacidin C (3) was shown to be a C-11 stereoisomer of manzacidin A (1).

Manzacidins A–C (1–3) are the first bromopyrrole alkaloids with a tetrahydropyrimidine ring attached through an ester linkage. Most of the pyrrole-2-carboxylic acid derivatives obtained from marine sources possess amide bonds.[1,3-6] Agelin B is an example of a pyrrole-2-carboxylic acid derivative attached to the terpenoid group through an ester bond.[17] Natural products containing a tetrahydropyrimidine ring are rare, and these apparently are the first examples from marine sources.[18] 1,4,5,6-Tetrahydro-2-methyl-4-pyrimidinecarboxylic acid, named "ectoine", was isolated from halophilic phototrophic bacteria of the genus *Ectothiorhodospira*.[14,19] Biosyntheti-

(14) Galinski, E. A.; Pfeiffer, H.-P.; Trüper, H. G. *Eur. J. Biochem.* **1985**, *149*, 135–139.
(15) Carroll, A. R.; Scheuer, P. J. *J. Org. Chem.* **1990**, *55*, 4426–4431.
(16) The NMR signals of 2 were firmly assigned on the basis of DEPT, ^1H-^1H COSY, HMQC, and HMBC experiments.
(17) Capon, R. J.; Faulkner, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 1819–1822.
(18) Faulkner, D. J. *Natl. Prod. Rep.* **1984**, *1*, 251–280, 551–598; **1986**, *3*, 1–33; **1987**, *4*, 539–576; **1988**, *5*, 613–663; **1990**, *7*, 269–309.
(19) Unusual amino acids containing the 3,4,5,6-tetrahydropyrimidine moiety were identified in a bacterial siderophore: Demange, P.; Bateman, A.; Macleod, J. K.; Dell, A.; Abdallah, M. A. *Tetrahedron Lett.* **1990**, *31*, 7611–7614.

cally, the tetrahydropyrimidine ring in manzacidins A-C (1-3) may have been generated through a condensation between formic acid and an unusual amino acid like γ-amino-δ-hydroxyleucine.

Experimental Section

General Methods. Optical rotations were measured on a JASCO DIP-370 polarimeter. The IR and UV spectra were recorded on a JASCO A-102 and Shimadzu UV-220 spectrophotometer, respectively. ^1H and ^{13}C NMR spectra were recorded on a JEOL GX-270 and EX-400 spectrometers. FAB mass spectra were obtained on a JEOL HX-110 spectrometer using glycerol as a matrix. EI mass spectra were recorded on a JEOL DX-303 spectrometer. Wako C-300 silica gel (Wako Pure Chemical) was used for glass column chromatography, and TLC was carried out on Merck silica gel GF_{254}.

Collection, Extraction, and Separation. The sponge *Hymeniacidon* sp. was collected by SCUBA at Manza Beach, Okinawa island, and was kept frozen until used. The methanol extract (43 g) was dissolved in ethyl acetate and water (1:4, 200 mL) and then partitioned between ethyl acetate (400 mL × 3) and water (400 mL). The aqueous layer was subsequently extracted with 1-butanol (400 mL × 3). The 1-butanol-soluble fraction (6.3 g) was partially (2.0 g) subjected to flash column chromatography on silica gel (4.3 × 20 cm) eluted with chloroform/1-butanol/acetic acid/water (1.5:6:1:1). The fraction eluting from 560 to 780 mL was further purified by reversed-phase HPLC on ODS (Develosil ODS-5, Nomura Chemical, 10 × 250 mm; eluent acetonitrile/water/trifluoroacetic acid (22:78:0.1); flow rate 2.5 mL/min; UV detection at 254 nm) to give manzacidins A (1; 3.5×10^{-3}% yield, wet weight; t_R 24.6 min), B (2; 2.1×10^{-3}%; t_R 21.9 min), and C (3; 1.0×10^{-3}%; t_R 23.7 min).

Manzacidin A (1): colorless oil; $[\alpha]^{27}_D$ -28° (*c* 0.67, MeOH); IR (KBr) ν_{max} 3600-2800, 1710, 1685, 1625, 1400, 1320, 1205, 1190, and 1140 cm^{-1}; UV (MeOH) λ_{max} 209 (ε 5100) and 272 (5800) nm; ^1H and ^{13}C NMR (Table I); FABMS (positive) *m/z* 368 and 366 $(M + Na)^+$ and 346 and 344 $(M + H)^+$; exact mass found *m/z* 344.0251, calcd for $C_{12}H_{15}N_3O_4{}^{79}Br$ M + H 344.0246.

Manzacidin B (2): colorless oil; $[\alpha]^{22}_D$ -71° (*c* 0.43, MeOH); IR (KBr) ν_{max} 3600-2800, 1705, 1665, 1620, 1380, 1310, 1195, 1175, and 1125 cm^{-1}; UV (MeOH) λ_{max} 214 (ε 10300) and 273 (11600) nm; ^1H NMR (CD_3OD) δ_H 8.04 (1 H, s, H-13), 7.05 (1 H, d, *J* = 1.5 Hz, H-2), 6.98 (1 H, d, *J* = 1.5 Hz, H-4), 4.75 (1 H, br d, H-11), 4.46 (1 H, d, *J* = 2.2 Hz, H-10), 4.45 (1 H, d, *J* = 11.0 Hz, H-8a), 4.38 (1 H, d, *J* = 11.0 Hz, H-8b), and 1.44 (3 H, s, H_3-15); ^{13}C NMR (CD_3OD) δ_C 160.8 (s, C-6), 151.7 (d, C-13), 125.4 (d, C-2), 123.4 (s, C-5), 118.6 (d, C-4), 98.2 (s, C-3), 66.7 (t, C-8), 65.2 (d, C-10), 58.1 (s, C-9), and 23.7 (q, C-15); ^1H-^1H COSY correlations H-2/H-4, H-8a/H-8b, and H-10/H-11; HMBC correlations C-2/H-4, C-3/H-2, C-4/H-2, C-5/H-2, C-5/H-4, C-8/H_3-15, C-9/H_3-15, C-10/H_3-15, and C-15/H_2-8; FABMS (positive) *m/z* 384 and 382 $(M + Na)^+$ and 362 and 360 $(M + H)^+$; exact mass found *m/z* 360.0211, calcd for $C_{12}H_{15}N_3O_5{}^{79}Br$ M + H 360.0200.

Manzacidin C (3): colorless oil; $[\alpha]^{22}_D$ +37° (*c* 0.23, MeOH); IR (KBr) ν_{max} 3600-2800, 1700, 1680, 1625, 1400, 1380, 1315, 1205, 1180 and 1135 cm^{-1}; UV (MeOH) λ_{max} 224 (ε 7500) and 273 (7700) nm; ^1H NMR (CD_3OD) δ_H 8.13 (1 H, s, H-13), 7.10 (1 H, d, *J* = 1.5 Hz, H-2), 6.94 (1 H, d, *J* = 1.5 Hz, H-4), 4.50 (1 H, m, H-11), 4.43 (1 H, d, *J* = 11.4 Hz, H-8a), 4.33 (1 H, d, *J* = 11.4 Hz, H-8b), 2.65 (1 H, m, H-10a), 2.07 (1 H, m, H-10b), and 1.50 (3 H, s, H_3-15); ^{13}C NMR (DMSO-d_6) δ_C 169.9 (s, C-16), 158.8 (s, C-6), 150.5 (d, C-13), 124.5 (d, C-2), 122.0 (s, C-5), 116.8 (d, C-4), 96.1 (s, C-3), 68.2 (t, C-8), 51.6 (s, C-9), 48.6 (d, C-11), 30.9 (t, C-10), and 23.0 (q, C-15); ^1H-^1H COSY correlations H-2/H-4, H-8a/H-8b, H-10a/H-11, H-10b/H-11, and H-10a/H-10b; FABMS (positive) *m/z* 344 and 346 $(M + H^+)$; exact mass found *m/z* 344.0262, calcd for $C_{12}H_{15}N_3O_4{}^{79}Br$ M + H 344.0246.

Methyl Ester 4. Manzacidin A (1, 0.6 mg) was treated with 5% hydrogen chloride in methanol (0.5 mL) under reflux for 30 min. Evaporation of the solvent afforded the methyl ester 4 (0.5 mg): ^1H NMR (CD_3OD) δ_H 8.14 (1 H, s, H-13), 7.05 (1 H, d, *J* = 1.8 Hz, H-2), 4.35 (1 H, d, *J* = 11.7 Hz, H-8a), 4.22 (1 H, d, *J* = 11.7 Hz, H-8b), 3.81 (3 H, s, MeO), 2.37 (1 H, dd, H-10a), 2.27 (1 H, dd, H-10b), and 1.48 (3 H, s, H_3-15); EIMS *m/z* 359, 357 (M^+, 1:1), 300, and 298 ($M^+ - COOCH_3$, 1:1).

Acknowledgment. We thank Mr. Z. Nagahama for his help in collecting the sponge and Dr. J. Fromont, James Cook University of North Queensland, for identification of the sponge.

Registry No. 1, 134029-41-7; 2, 134029-42-8; 3, 134107-38-3.

Supplementary Material Available: Copies of all spectra of manzacidins A-C (22 pages). Ordering information is given on any current masthead page.

Synthesis of an Unsymmetrical Naphthalein Indicator Dye from an Indole-6-sulfonamide

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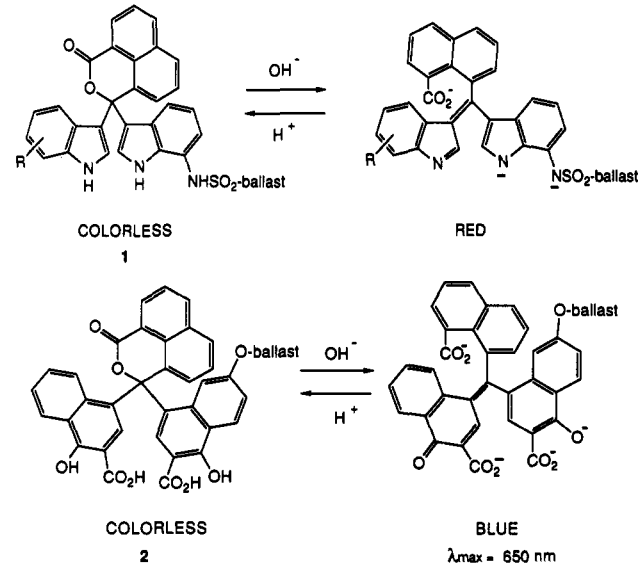
Naphthalein indicator dyes such as **1** and **2** can be used in integral format instant photography as opacification media to protect the latent image so that exposed film can be ejected immediately from the camera into ambient light.[1] These opacification dyes are designed to be colored



in the highly alkaline (pH ~14) photographic reagent while the chemistry of image development takes place but to begin to become colorless at pH ~12 to permit the image to be seen within 1-2 min. The dyes are designed to be completely colorless at the final system pH (close to neutrality) so that the color photograph can be viewed free from any residual visible absorptions of the opacification dyes. The position and nature of the substituents on the indole and naphthol moieties have a profound effect on the pK_a values of the indicator dyes.[2] The ballast groups are alkyl chains that limit the migration of the dyes. While working on indole naphthalein dyes of type 1, we required an efficient synthesis of indole sulfonamides. We report

(1) Land, E. H. *Photogr. J.* **1974**, *7*, 1.

(2) (a) Simon, M. S.; Waller, D. P. U.S. Patent 3,702,245, November 7, 1972. (b) Borror, A. L.; Chinoporos, E.; Filosa, M. P.; Herchen, S. R.; Petersen, C. P.; Stern, C. A.; Onan, K. D. *J. Org. Chem.* **1988**, *53*, 2047. (c) Borror, A. L.; Chinoporos, E.; Petersen, C. P. U.S. Patent 4,615,966, October 7, 1986.

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