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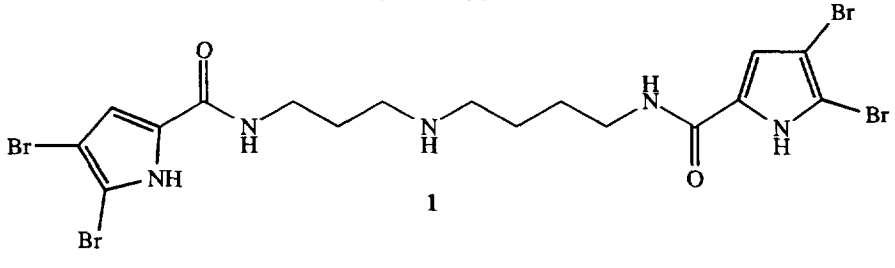
SYNTHESIS OF THE ANTIFOULING POLYAMINE PSEUDOCERATIDINE AND ITS ANALOGS: FACTORS INFLUENCING BIOCIDAL ACTIVITY

James A. Ponasik, Darren J. Kassab, and Bruce Ganem*

Department of Chemistry, Baker Laboratory
Cornell University, Ithaca, NY 14853-1301 USA

Abstract: Syntheses of the title compound **1** and its N^8 and N^1-monoacylated analogs **5** and **8**, respectively, are reported. Assays of **1**, **5**, and **8** indicate that the number and position of the acyl substituents affect bioactivity.

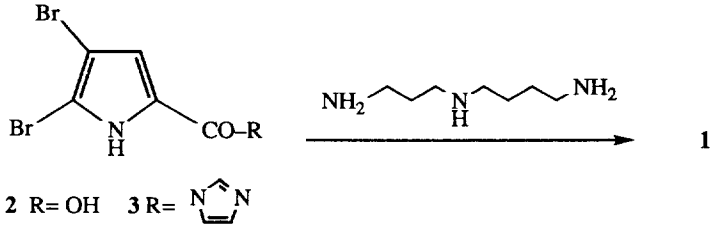
The development of effective, low-cost biocides that are compatible with marine coatings has had a major impact on both the recreational and commercial maritime industries, with worldwide demand for such paints now approaching $2 billion.[1] By preventing barnacles, mollusks, and other organisms from becoming attached to ships' hulls, antifouling agents can block corrosion and significantly improve fuel efficiency. Tributyltin-based compounds, which can be formulated as co-polymers using tributyltin methacrylate, have been the most widely used antifoulants. However, recent concern about their effects on marine mammals[2] and other organisms[3] has led to a ban on the use of tributyltin-containing coatings in the United States, Japan, and other countries. Thus we were intrigued by the report that pseudoceratidine **1**, a derivative of the polyamine spermidine isolated from the marine sponge *Pseudoceratine purpurea*, showed promising properties as an antifouling compound.[4]



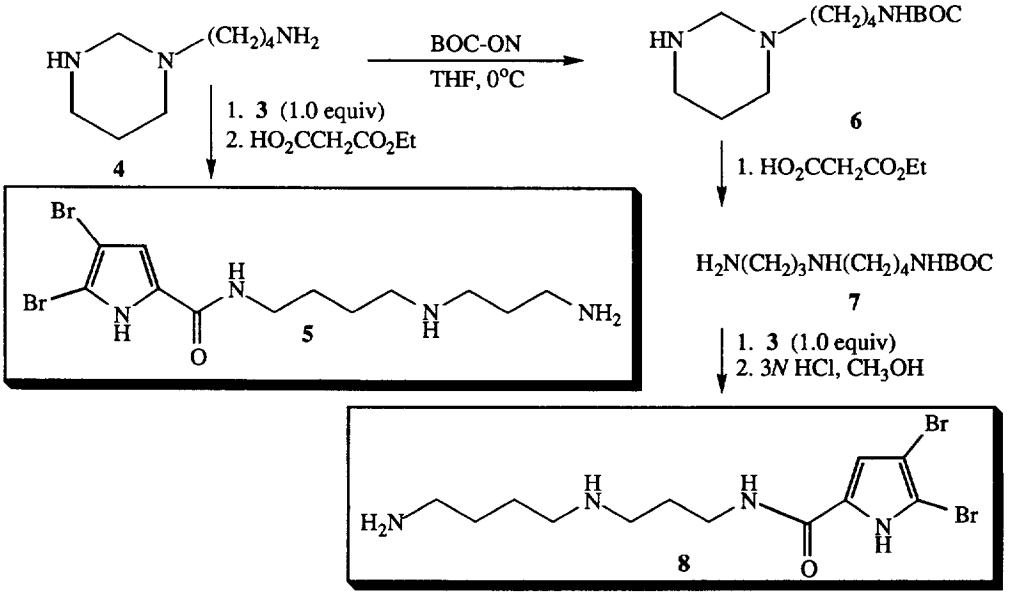
1

Although widely distributed throughout the plant and animal kingdoms,[5] relatively few polyamines are known of marine origin.[6-8] Many of these substances exhibit antimicrobial, cytotoxic, or antifungal activity. Here we report the synthesis of **1** and its N^8 and N^1-monoacylated congeners **5** and **8**, together with additional bioassays that help identify the structural requirements for bioactivity.

Pseudoceratidine is likely biosynthesized from spermidine and 4,5-dibromo-2-pyrrolic acid **2**, a known immunosuppressive agent that was first isolated from deep-water marine sponges.[9] Published syntheses of acid **2** involve bromination of methyl 2-pyrrolecarboxylate with subsequent deesterification.[10] However, we found that compound **2** (mp 148 °C) was more conveniently prepared in nearly quantitative yield by the direct bromination of pyrrole-2-carboxylic acid.[11] Conversion of **2** to the corresponding acylimidazole and *in situ* coupling of **3** (2 equiv) with spermidine by the method of Joshua and Scott[12] gave **1** in 73% yield after chromatography (SiO_2, 75:25:3 CH_2Cl_2:CH_3OH:NH_4OH). Spectral data on synthetic **1** matched published values for the natural product.



We have previously used adduct **4** of spermidine and formaldehyde[13] to prepare N^1 and N^8-acetyl-spermidines.[14] A variation of that approach, shown below, afforded the corresponding monoacyl analogs of **1**.



To synthesize N^8-(dibromopyrroloyl)-spermidine **5**, the primary amine in **4** was selectively acylated with **3**, then the hexahydropyrimidine protecting group was removed in a Knoevenagel condensation with ethyl

hydrogen malonate. The overall yield of **5** from **4** was 68%.[15] To prepare N^1-(dibromopyrroloyl)-spermidine **8**, triamine **4** was first transformed to its N^8-BOC-derivative **6**, then deprotected to afford N^8-BOC-spermidine **7**.[16,17] Acylation of **7** with **3** followed by acid treatment gave **8** in 30% yield from **6**.[18]

Pseudoceratidine was reported to inhibit metamorphosis of the barnacle *Balanus amphitrite* (ED_{50} = 8 μg/mL),[4] suggesting a potential effect on chitinase; however, no inhibition of *Streptomyces griseus* chitinase was observed. Compounds **1**, **5**, and **8** were also assayed against a variety of other microorganisms (see Table). While both **5** and **8** were less active than pseudoceratidine, isomer **5** was significantly more potent than **8** against *Staphylococcus aureus* and *Escherichia coli*. Discrimination of the two ends of the polyamine chain appeared to play a significant role in biological activity.

Compound **Antibiotic Activity** *(Minimum Inhibitory Concentration; values in μg/mL)*

	S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*
1	4	32	128	32
5	64	128	256	128
8	>256	256	>256	>256

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11. Bromine (9.2 mmol) in HOAc (6.2 mL) was added to **2** (4.6 mmol) in HOAc (25 mL). The solution was heated to 60 °C for 1 h, then decolorized (Norit) and concentrated *in vacuo*. Recrystallization from H_2O:EtOH gave **2** (1.17 g, 94%): mp 170 °C (d); lit. mps: 165 °C (Ref 9b), 165-175 °C (ref 10a).

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15. For **5**: ^{1}H NMR (D_2O, 300 MHz) δ 8.49 (1H, s), 7.27 (1H, d, J = 1.1 Hz), 6.55 (1H, s), 3.13 (2H, t, J = 6.7 Hz), 2.82-2.99 (6H, m), 1.42-1.57 (4H, m); CMR (D_2O, dioxane, 75 MHz) δ 160.9, 126.5, 113.5, 105.5, 98.9, 47.3, 44.4, 38.4, 36.5, 25.8, 23.7, 23.0; FABMS (magic bullet) *m/z* 397 (M^+).

16. Although patented (Ref 17), **7** has not been described in the primary literature: ^{1}H NMR (DMSO-d_6, 300 MHz, 87 °C) δ 2.95 (2H, t, J = 6.3 Hz), 2.73 (3H, br. s), 2.68 (2H, t, J = 6.7 Hz), 2.59 (2H, t, J = 6.8 Hz), 2.53 (2H, t, J = 6.6 Hz), 1.53 (2H, quintet, J = 6.7 Hz) 1.37-1.47 (13H, m); CMR (DMSO-d_6, 75 MHz) δ 155.6, 79.2, 59.7, 48.9, 46.9, 31.3, 28.3, 27.4, 26.6.

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18. For **8**: ^{1}H NMR (D_2O, 300 MHz) δ 6.61 (1H, s), 3.20 (2H, t, J = 6.5 Hz), 2.74-2.82 (6H, m), 1.70 (2H, quintet, J = 7.4 Hz) 1.48-1.50 (4H, m); CMR (D_2O, dioxane, 75 MHz) δ 162.3, 127.7, 114.0, 108.0, 98.1, 47.1, 45.2, 39.0, 36.2, 26.5, 24.6, 23.5; FABMS (magic bullet) *m/z* 397 (M^+).

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