Syntheses of the Marine Metabolites Verongamine, Hemibastadin-2, and Aerothionin Using the Cyano Ylide Coupling Methodology

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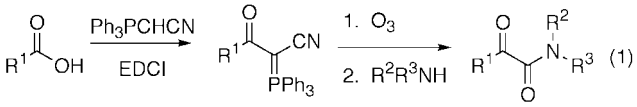
Syntheses of the marine metabolites verongamine, hemibastadin-2, and aerothionin have been accomplished by a methodology involving the conversion of a carboxylic acid to an acyl cyano phosphorane which may be oxidized to an α,*β*-diketo nitrile. This strongly electrophilic intermediate is rapidly converted by amines to α-keto amides.

In recent years, a number of bromotyrosine-derived secondary metabolites have been isolated from marine sponges in oceans ranging from Gallipoli to the Great Barrier Reef.[1] These alkaloids, many of which contain α-oximino amide units, are of special interest because of their biological properties, including antibiotic, antiinflammatory, and cytotoxic activity. Interest in these substances and their analogues has prompted studies on methods for their synthesis, particularly since the isolation of amounts of these substances adequate for more thorough investigation would require collection of very large quantities of the marine sources from which they are derived.

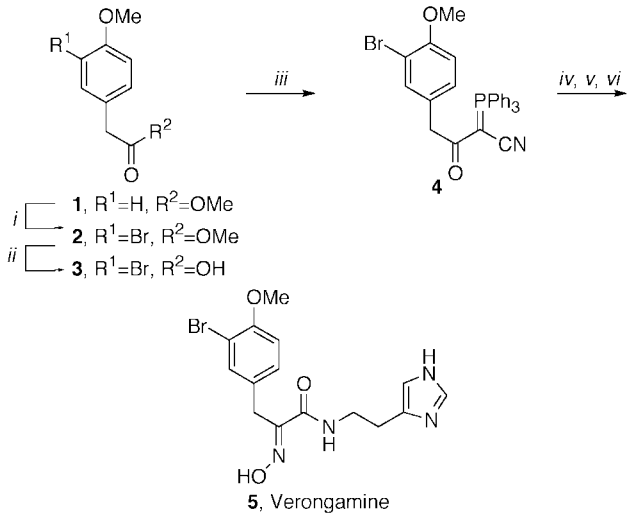
We have recently developed an efficient methodology[2a−d] for forming the key α-keto amido residues common to many members of this family of natural products. The procedure (eq 1) involves the conversion of a carboxylic acid to an acyl cyano phosphorane which may be oxidized to an α,*β*-diketo nitrile. This labile electrophile may then undergo reactions in situ with alcohols, amines, or other nucleophiles to form α-keto carboxylic acid derivatives. In this report we outline the application of this sequence to the syntheses of three of these marine metabolites: verongamine (**5**),[1a] hemibastadin-2 (**13**),[1b] and aerothionin (**28**).[1c] Earlier syntheses of aerothionin[3a,b] have been reported, including a very recent chiral synthesis.[4]



(1)

Verongamine. Our synthesis of verongamine took place according to the procedure outlined in Scheme 1.

Scheme 1[a]



[a]Reagents and Conditions: (*i*) Br_2, $AlCl_3$, CH_2Cl_2. (*ii*) NaOH, MeOH, 73% (two steps). (*iii*) Ph_3P=CHCN, EDCI, CH_2Cl_2, 82%. (*iv*) O_3, CH_2Cl_2, -78 °C. (*v*) histamine, *t*-BuOH. (*vi*) NH_2OH•HCl, NaOAc, EtOH (52%, three steps).

Methyl (3-bromo-4-methoxyphenyl)acetate (**2**)[5] was hydrolyzed in aqueous NaOH to the carboxylic acid **3** which was coupled with (triphenylphosphoranylidene)acetonitrile in the presence of EDCI to form the keto ylide **4**. Ozone was then introduced into a CH_2Cl_2 solution of the keto ylide **4** at −78 °C until the reaction was complete as indicated by the appearance of the characteristic blue color. The resulting α,*β*-diketo nitrile was then reacted in situ with histamine in *tert*-butyl alcohol at low temperature to give an α-keto amide which was not isolated but immediately treated with hydroxylamine in the presence of NaOAc in ethanol to yield the corre-

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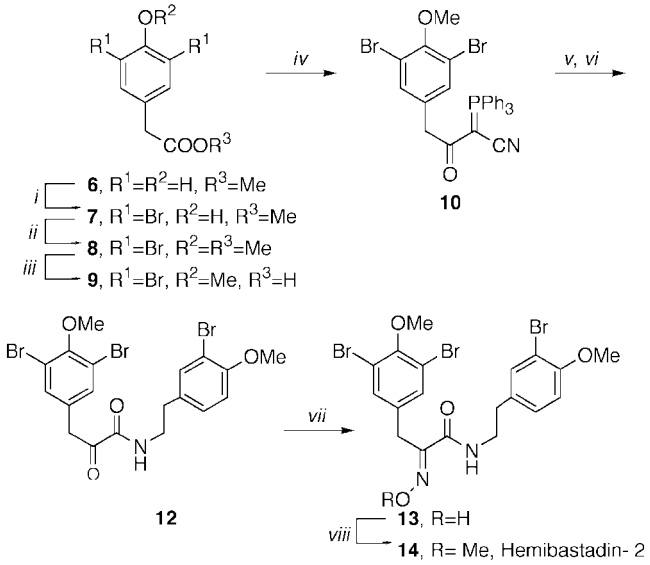
sponding oxime. The resulting reaction mixture was taken up in EtOAc and extracted with dilute HCl, and the extract was worked up in NaOH and EtOAc to yield verongamine **5** (52% from ylide **4**), identical with the natural material (comparison of ^{1}H and ^{13}C NMR). It is interesting to note that in this acylation, the reaction with histamine took place exclusively at the site of the primary amine.[6]

Hemibastadin-2. For the synthesis of hemibastadin-2 (**14**, Scheme 2), methyl (4-hydroxyphenyl)acetate (**6**) was brominated in the presence of *tert*-butylamine to yield the 3,5-dibromo derivative **7** which was converted to the phenolic methyl ether **8** with dimethyl sulfate. The free acid **9**, formed by NaOH hydrolysis of **8**, was then transformed to the ylide **10** by the coupling procedure described above.

The ylide **10** was oxidized by ozone to an intermediate α,β-diketo nitrile in CH_2Cl_2 at −78 °C and then coupled with 3-bromo-4-methoxyphenethylamine (**11**) in CH_2Cl_2, yielding the desired α-keto amide **12**. Formation of the oxime mixture (*E*:*Z* = 97:3) resulted under the conditions outlined in our verongamine synthesis (Scheme 1). After purification, the *E*-oxime **13** was converted by methyla-

Scheme 2[a]

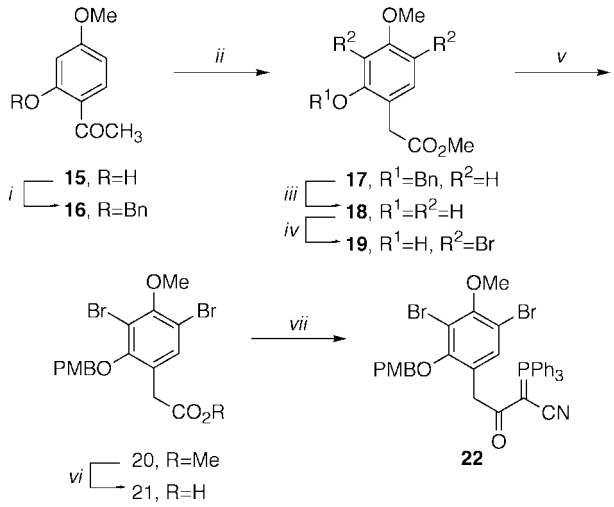


[a]Reagents and Conditions: (*i*)Br_2, *t*-$BuNH_2$, CH_2Cl_2, 95%. (*ii*) Me_2SO_4, K_2CO_3, acetone, 93%. (*iii*) 2N NaOH, 95%. (*iv*) Ph_3P=CHCN, EDCI, CH_2Cl_2, 85%. (*v*) O_3, CH_2Cl_2. (*vi*) **11**, CH_2Cl_2. (*vii*) NH_2OH•HCl, NaOAc, EtOH, (85% two steps, E:Z = 97:3). (*viii*) Me_2SO_4, Na_2CO_3, acetone, 86%

tion to hemibastadin-2 (**14**), identified by comparison of the spectroscopic properties of natural and synthetic materials.

Aerothionin. A key step in our synthesis of aerothionin (**28**) involved the coupling of 1,4-diaminobutane with the α,β-diketo nitrile **23**, derived from the oxidation of the corresponding ylide **22**. The generation of **22** from 2-hydroxy-4-methoxyacetophenone (**15**) was accomplished according to the sequence outlined in Scheme 3 by protection of the phenolic hydroxyl as the benzyl ether **16**, rearrangement with $Tl(NO_3)_3$ to **17**, deprotection to

Scheme 3[a]



[a]Reagents and Conditions: (*i*) BnBr, K_2CO_3, acetone, 97%. (*ii*)$Tl(NO_3)_3$, MeOH, 76%. (*iii*) H_2, Pd/C,MeOH, 96%. (*iv*) Br_2, pyridine, 90%. (*v*) PMBCl, K_2CO_3, acetone, 93%. (*vi*) 2N NaOH, MeOH, 94%. (*vii*) Ph_3P=CHCN, EDCI, CH_2Cl_2, 88%.

18,[8] and bromination (Br_2, pyridine) to form the dibromide **19**.[9] Following reprotection (*p*-methoxybenzyl bromide) to **20** and hydrolysis of the ester to the acid **21**, coupling with Ph_3P=CHCN in the presence of EDCI yielded **22**.

After the ylide **22** was oxidized by O_3 to the labile diketo nitrile **23** (Scheme 4), generation of the bis-α-keto amide **24** took place on treatment of **23** as formed in CH_2Cl_2 with 1,4-diaminobutane. Conversion of **24** to the bis-*E*-oxime **25** and deprotection with TFA provided the substrate **26** for intramolecular ring closure to the bis-spiro isoxazolidine **27**. In the latter cyclization, we followed the earlier precedent of Forrester,[10a,b] who used 2,4,4,6-tetrabromo-2,5-cyclohexadienone in acetonitrile for the oxidative cyclization. This reaction took place readily to yield **27** in 70% yield.

The final conversion of **27** to aerothionin **28** called for a reduction of the cyclohexadienone ketonic centers in a stereospecific manner in order to generate both of the newly formed hydroxyl groups in trans relationships to the corresponding spiro oxazoline rings. Although an earlier reduction of this system with $NaBH_4$ gave a mixture of products containing mostly cis/cis stereochemistry, we were successful in preparing the desired trans/trans reduction product **28** using $NaCNBH_3$ in TFA. The identity of the synthetic aerothionin with the natural substance was established by comparison of the ^{1}H and ^{13}C NMR spectra of the synthetic product, purified by silica gel chromatography, with the corresponding spectra of the natural material kindly supplied by Dr. E. Fattorusso.[1c,11]

Experimental Section

General. Melting points were determined on a capillary melting point apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$, DMSO-d_6, CD_3OD, and acetone-d_6 with

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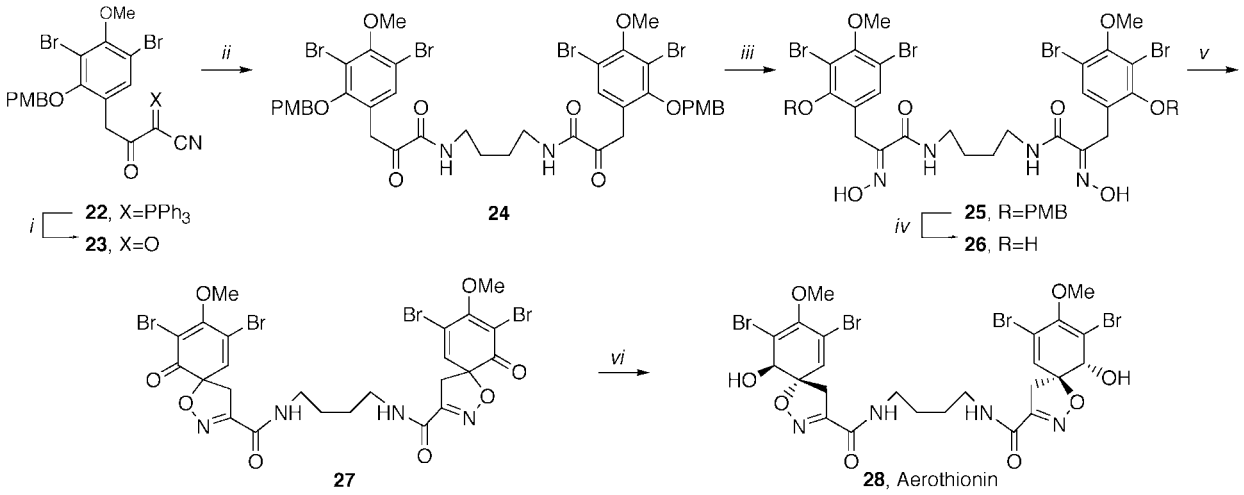
(11) While the NMR spectra of our synthetic material indicate only one substance, it is possible that there may be both *meso* and *d,l* forms present in the product. Our purification methods including HPLC analyses of synthetic and natural materials have not resolved this question.

Scheme 4[a]



[a]Reagents and Conditions: (*i*) O_3, CH_2Cl_2. (*ii*) 1,4-diaminobutane,CH_2Cl_2, 64% (two steps). (*iii*) NH_2OH•HCl, NaOAc, EtOH, 95%. (*iv*) TFA, CH_2Cl_2, 92%. (*v*) 2,4,4,6-tetrabromo-2,5-cyclohexadienone, CH_3CN, 70%. (*vi*) $NaCNBH_3$, TFA,25%.,

a 500 MHz spectrometer for ^1H and at 125 MHz for ^{13}C. TMS was used as an internal standard, and chemical shifts are reported as δ values (ppm from TMS). IR spectra vibrational frequencies are expressed in wavenumbers (cm^{-1}). High-resolution mass spectra were recorded by using EI unless specified as FAB (m-NBA as a matrix). Preparative thin-layer chromatography (TLC) was performed on 20 × 20 cm plates coated with Merck-EM type 60 GF-254 silica gel. Analytical TLC was performed using silica gel 60 F254 precoated plates (0.25 mm). Silica gel (particle size 0.032−0.063 mm) was used for flash chromatography. Analytical high-performance liquid chromatography (HPLC) was carried out on a reverse phase column (4.6 × 150 mm), which was eluted with a linear gradient of CH_3CN (60−90%, 25 min) in 0.1% aqueous TFA at a flow rate of 1.0 mL/min. All reactions were run under a nitrogen atmosphere unless otherwise stated. All solvents were distilled prior to use. All other commercially obtained reagents were used as received.

Synthesis of Verongamine (5). Methyl (3-Bromo-4-methoxyphenyl)acetate (2). Bromine (9.8 g, 61.6 mmol) was added slowly at 0 °C to a solution of methyl (4-methoxyphenyl)acetate (10 g, 55.6 mmol) and $AlCl_3$ (7.3 g, 55.6 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at 0 °C for 20 min and then poured into ice−water (200 mL). The product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic solution was washed with saturated $NaHCO_3$ (150 mL) and brine (200 mL) and then dried over anhydrous $MgSO_4$. Evaporation of solvent gave the product **2** (11.4 g, 79%) as colorless crystals, mp 45−47 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 2940, 2820, 1730, 1600, 1490, 1450, 1430, 1295, 1250, 1115, 1050, 1005. ^1H NMR ($CDCl_3$): 7.49 (s, 1H); 7.18 (d, J = 7.5, 1H); 6.85 (d, J = 7.5, 1H); 3.88 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 3.55 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 171.9 (COO); 155.2; 134.0; 129.5; 128.4; 112.1; 111.8; 56.3; 52.2; 39.8. HRMS FAB (m-NBA) Calcd for $C_{10}H_{11}{}^{79}BrO_3$: $(M + H)^+$ 257.9892; found 257.9897.

(3-Bromo-4-methoxyphenyl)acetic Acid (3). To a solution of methyl (3-bromo-4-methoxyphenyl)acetate (**2**) (10 g, 38.6 mmol) in CH_3OH (50 mL) was added aqueous NaOH (2 N, 30 mL) dropwise at room temperature. After the reaction mixture was stirred for 1.5 h, most of the methanol was removed in vacuo, water (50 mL) was added, and the resulting aqueous solution was adjusted to pH 2 with HCl (2 N). The solid was filtered and washed with water (10 mL) to afford the product (8.5 g, 90%) as a white solid, mp 116−117 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 3000, 2940, 2820, 1705, 1600, 1500, 1435, 1275, 1250, 1050, 1010. ^1H NMR ($CDCl_3$): 7.47 (d, J = 2, 1H); 7.18 (dd, J = 8.4, J = 2, 1H); 6.86 (d, J = 8, 1H); 3.89 (s, 3H, OCH_3); 3.56 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 177.6 (COO); 155.2; 134.1; 129.4; 126.7; 111.9; 111.6; 56.2; 39.7. HRMS FAB (m-NBA) Calcd for $C_9H_9{}^{79}BrO_3$: $(M + H)^+$ 243.9735; found 243.9737.

(Triphenylphosphoranylidene)(3-bromo-4-methoxyphenylacetyl)acetonitrile (4). A solution of carboxylic acid **3** (3.5 g, 14.3 mmol), ylide (4.3 g, 14.3 mmol), and EDCI (3.2 g, 17.2 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 4 h. The reaction mixture was then diluted by addition of CH_2Cl_2 (150 mL), washed with water (200 mL) and brine (150 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by chromatography on silica gel. The fraction eluted with AcOEt/hexane/CH_2Cl_2 (1:1:1) was collected. Removal of the solvents gave the product **4** (6.2 g, 82%) as a white crystal, mp 196−197 °C (from EtOAc). IR ($CHCl_3$): 3000, 2180, 1580, 1500, 1430, 1340, 1250, 1100, 1050. ^1H NMR ($CDCl_3$): 7.61−7.32 (m, 16H); 7.33 (dd, J = 7.6, J = 2, 1H); 6.85 (d, J = 7.6, 1H); 3.88 (s, 3H, OCH_3); 3.86 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 193.8 (CO); 154.4; 133.5; 133.4 (d J = 10, 6C); 133.0 (3C); 130.1; 130.0; 129.0 (d, J = 13, 6C); 122.8 (d, J = 93, 3C); 122.4 (d, J = 16, CN); 111.7; 111.2; 56.1; 48.6 (d, J = 125); 45.6 (d, J = 7). HRMS FAB (m-NBA) Calcd for $C_{29}H_{23}{}^{79}BrNO_2P$: $(M + H)^+$ 528.0728; found 528.0726.

Verongamine (5). A solution of (triphenylphosphoranylidene)acetonitrile **4** (500 mg, 0.947 mmol) in dry CH_2Cl_2 (30 mL) was treated with O_3 for 4 min at −78 °C, and the resulting pale green solution was purged with N_2 for 5 min. To this pale solution was added a solution of histamine (100 mg, 0.90 mmol) in *tert*-butyl alcohol (5 mL) via cannula, and the mixture was stirred at −78 °C for 5 min and then room temperature for 1 h. The solvents were evaporated in vacuo, and the residue was dissolved in ethanol (15 mL). To this solution were added NH_2OH•HCl (75 mg, 1.09 mmol) and NaOAc (112 mg, 1.37 mmol). The resulting reaction mixture was stirred at room temperature for 16 h and then partitioned between EtOAc (200 mL) and water (100 mL). The EtOAc fraction was extracted with HCl (1 N, 3 × 100 mL). The aqueous HCl was treated with NaOH (5 N) to adjust the pH to 9−10. The resulting alkaline solution was extracted with EtOAc (3 × 200 mL) and the EtOAc extract concentrated in vacuo to give an oily residue which was purified by chromatography on silica gel. The fraction eluted with CH_2Cl_2/CH_3OH/NH_3•H_2O was collected. Evaporation of solvents gave the product **5** (verongamine 178 mg, 52%) as a pale solid, mp120−122 °C (from EtOAc). IR (KBr, cm^{-1}): 3380, 3200, 2920, 1650, 1630, 1530, 1500, 1460, 1420, 1380, 1300, 1280, 1270, 1260, 1200, 1150, 1050, 1020, 100, 770. ^1H NMR (CD_3OD): 7.56 (s, 1H); 7.42 (d J = 2, 1H); 7.18 (dd, J = 8.4, J = 2, 1H); 6.88 (d, J = 8.4, 1H); 6.80 (s, 1H); 3.81 (s 3H, OCH_3); 3.80 (s, 2H, $PhCH_2$); 3.47 (t, J = 7.2, 2H); 2.76 (t, J = 7.2, 2H). ^{13}C NMR (CD_3OD): 165.7, 155.9, 153.0, 136.1, 134.7, 131.8, 130.4, 130.3,

118.0, 113.1, 112.1, 56.7, 40.3, 28.7, 27.7. (Both ^{1}H NMR and ^{13}C NMR spectra were identical to the corresponding spectra of the natural material[1a]). HRMS FAB (m-NBA) Calcd for $C_{15}H_{18}{}^{79}BrN_4O_3$: $(M + H)^+$ 381.0562; found 381.0558.

Synthesis of Hemibastadin-2 (14). Methyl (3,5-Dibromo-4-hydroxylphenyl)acetate (7). To a solution of *tert*-butylamine (1.5 g, 20.0 mmol) in toluene (20 mL) was added bromine (3.2 g, 20.0 mmol) at −78 °C followed by addition of the solution of methyl (4-hydroxyphenyl)acetate (**6**) in CH_2Cl_2 (20 mL). The resulting reaction mixture was allowed to warm to room temperature and stirring continued. After 3 h, CH_2Cl_2 (100 mL) was added, and the resulting solution was washed with aqueous HCl (0.1 N, 120 mL) and brine (100 mL). The organic solution was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvents gave the product **7** (3.1 g, 95%) as a white solid, mp 115−117 °C (from AcOEt/*n*-hexane). IR ($CHCl_3$): 3500; 3000; 2960; 1730; 1560; 1460; 1420; 1320; 1280; 1160; 1010. ^{1}H NMR ($CDCl_3$): 7.38 (s, 2H); 5.93 (s, 1H, OH); 3.71 (s, 3H, OCH_3); 3.51 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 171.2 (COO); 148.6; 132.7(2C); 128.3; 109.7(2C); 52.3; 39.3. HRMS EI Calcd for $C_9H_8{}^{79}Br^{81}BrO_3$: M^+ 323.8820; found 323.8816.

Methyl (3,5-Dibromo-4-methoxyphenyl)acetate (8). A mixture of **7** (10 g, 30.8 mmol), K_2CO_3 (7.0 g, 50.7 mmol), and Me_2SO_4 (5 g, 39.7 mmol) in acetone (200 mL) was stirred at room temperature for 4 h. After most of the acetone was removed in vacuo, the residue was dissolved in CH_2Cl_2 (200 mL) and H_2O (200 mL). The organic solution was separated and washed with H_2O (200 mL) and brine (200 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvents gave the product **8** (9.7 g, 93%) as a colorless oil. IR ($CHCl_3$): 3000; 2960; 1730; 1550; 1460; 1420; 1250; 1160; 1000. ^{1}H NMR ($CDCl_3$): 7.43 (s, 2H); 3.87 (s, 3H, OCH_3); 3.72 (s, 3H, OCH_3); 3.54 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 170.9 (COO); 153.2; 133.4 (2C), 131.1; 118.0 (2C); 60.5; 52.3; 39.5. HRMS EI Calcd for $C_{10}H_{10}{}^{79}Br_2O_3$: M^+ 335.8997; found 335.8994.

3,5-Dibromo-4-methoxyphenylacetic Acid (9). To a solution of **8** (10 g, 29.6 mmol) in CH_3OH (200 mL) was added NaOH (2 N, 20 mL) at room temperature. The resulting reaction mixture was stirred for 1.5 h. After most of the CH_3OH was removed in vacuo, H_2O (200 mL) was added. The resulting solution was adjusted to pH 2.0 by the addition of HCl (2 N). The solid was filtered and washed with H_2O (10 mL) to afford the product **9** (9.1 g, 95%) as a white solid, mp 143−145 °C (from AcOEt/*n*-hexane). IR ($CHCl_3$): 3000; 2920; 1710; 1550; 1470; 1410; 1260; 1000. ^{1}H NMR ($CDCl_3$): 7.45 (s, 2H); 3.89 (s, 3H, OCH_3); 3.58 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 176.7 (COO); 153.5; 133.6 (2C), 131.5; 118.2 (2C); 60.6; 39.4. HRMS EI Calcd for $C_9H_8{}^{79}Br^{81}BrO_3$: M^+ 323.8820; found 323.8820.

(Triphenylphosphoranylidene)(3,5-dibromo-4-methoxyphenylacetyl)acetonitrile (10). A solution of carboxylic acid **10** (6.5 g, 20.0 mmol), Ph_3PCHCN (6.0 g, 20.0 mmol), and EDCI (4.5 g, 23.5 mmol) in CH_2Cl_2 (150 mL) was stirred at room temperature for 4 h. The reaction mixture was then diluted by addition of CH_2Cl_2 (150 mL), washed with water (200 mL) and brine (200 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography on silica gel. The fraction eluted with AcOEt/hexane/CH_2Cl_2 (1:1:1) was collected. Removal of the solvents gave the product **10** (11.0 g, 90%) as a white crystal, mp 215−217 °C (from AcOEt). IR ($CHCl_3$): 3000; 2180; 1580; 1470; 1430; 1340; 1250; 1100; 1000. ^{1}H NMR ($CDCl_3$): 7.67−7.50 (m, 17H); 3.88 (s, 3H, OCH_3); 3.86 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 192.6 (CO); 152.6; 135.1; 133.5 (d J = 10, 6C); 133.3 (3C); 133.2 (2C); 129.2 (d, J = 13, 6C); 122.7 (d, J = 93, 3C); 122.4 (d, J = 16, CN); 117.7 (2C); 60.5; 49.3 (d, J = 125); 44.6 (d, J = 7). HRMS FAB (m-NBA) Calcd for $C_{29}H_{23}{}^{79}Br_2NO_2P$: $(M + H)^+$ 605.9833; found 605.9832.

3-Bromo-4-methoxyphenethylamine (11). A mixture of *N*-benzoyl-3-bromo-4-methoxyphenethylamine (1.4 g, 4.2 mmol), AcOH (5 mL), and HCl (6 N, 20 mL) was refluxed for 48 h under N_2. After the benzoic acid was removed by extraction with CH_2Cl_2 (2 × 50 mL), the aqueous solution was adjusted to pH 0−1 by the addition of solid NaOH. The product was extracted with CH_2Cl_2 (3 × 100 mL) and dried over NaOH. Evaporation of solvent gave the product (0.8 g, 84% as a colorless oil. IR ($CHCl_3$): 3000; 2960; 2840; 1600; 1500; 1460; 1420; 1280; 1250; 1050; 1020. ^{1}H NMR ($CDCl_3$): 7.38 (d J = 1.6, 1H), 7.09 (dd, J = 8.4, 1.6, 1H); 6.83 (d, J = 8.4, 1H); 3.87 (s, 3H, OCH_3); 2.92 (m, 2H); 2.66 (t, J = 6.8, 2H); 1.02 (s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): 154.3, 133.6, 133.4, 129.7, 111.9, 111.5, 56.2, 43.5, 38.8. HRMS EI Calcd for $C_9H_{12}{}^{79}BrNO$: M^+ 229.0102; found 229.0100.

Coupling Product 12 of 3-Bromo-4-methoxyphenethylamine (11) with 10. Ozone was added to a solution of ylide **10** (500 mg, 0.82 mmol) in CH_2Cl_2 (30 mL) for 5 min at −78 °C, and the resulting greenish solution was purged with N_2 for 5 min. To this yellowish solution was added a solution of amine **11** (150 mg, 0.66 mmol) in CH_2Cl_2 (5 mL) via cannula, and the mixture was stirred at −78 °C for 5 min and room temperature for 1 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel. The fraction eluted with EtOAc/*n*-hexane (1:3) was collected. Removal of the solvents gave **12** (281 mg, 76%) as a pale yellow oil. IR ($CHCl_3$): 3400; 3000; 2920; 1680; 1520; 1500; 1480; 1420; 1250; 1110; 1060; 990. ^{1}H NMR ($CDCl_3$): 7.38 (s, 2H); 7.36 (d, J = 2.0, 1H); 7.05 (dd, J = 8.3, 2.0, 1H); 7.01 (t, J = 6.7, 1H, NH); 6.82 (d, J = 8.3, 1H); 4.12 (s, 2H, CH_2); 3.87 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.53 (q, J = 6.7, 2H); 2.77 (t, J = 6.7, 2H). ^{13}C NMR ($CDCl_3$): 162.9; 154.6; 152.6; 151.9; 134.8; 133.4 (2C); 133.3; 132.1, 128. 6; 117.8 (2C); 112.1; 111.7; 60.5; 56.2; 40.7; 34.2; 27.9. HRMS FAB (m-NBA) Calcd for $C_{19}H_{19}{}^{79}Br_2{}^{81}BrNO_4$: $(M + H)^+$ 563.8844; found 563.8847.

Compound 13 (*E*-Oxime of 12). A mixture of **12** (200 mg, 0.345 mmol), $NH_2OH{\cdot}HCl$ (200 mg, 2.89 mmol) and NaOAc (300 mg, 3.66 mmol) in EtOH (20 mL) was stirred at room temperature for 24 h and then partitioned between CH_2Cl_2 (200 mL) and water (100 mL). The CH_2Cl_2 fraction was washed with brine (200 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvents gave a residue which was purified by column chromatography on silica gel. The fraction eluted with EtOAc/*n*-hexane (1:3) was collected. Removal of the solvents afforded the product **13** (174 mg, 85%) as a yellowish oil. IR ($CHCl_3$): 3550; 3400; 3000; 2920; 1670; 1600; 1530; 1500; 1480; 1420; 1250; 1000. ^{1}H NMR ($CDCl_3$): 7.49 (s, 2H); 7.33 (d, J = 2.1, 1H); 7.01 (dd, J = 8.4, 2.1, 1H); 7.01 (t, J = 7.2, 1H, NH); 6.77 (d, J = 8.4, 1H); 4.12 (s, 2H, CH_2); 3.84 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 3.49 (q, J = 7.2, 2H); 2.72 (t, J = 7.2, 2H). ^{13}C NMR ($CDCl_3$): 194.8; 159.5; 154.8; 153.3; 133.9 (2C); 133.3; 131.5; 131.2; 128.5; 118.1 (2C); 112.1; 118.8; 60.5; 56.2; 41.5; 40.6; 34.0. HRMS FAB (m-NBA) Calcd for $C_{19}H_{20}{}^{79}Br_3N_2O_4$: $(M + H)^+$ 576.8973; found 576.8955.

Hemibastadin-2 (14). A mixture of **13** (150 mg, 0.26 mmol), Me_2SO_4 (200 mg, 1.58 mmol), and Na_2CO_3 (250 mg, 2.34 mmol) in acetone (15 mL) was stirred at room temperature for 18 h. To this reaction mixture was added CH_2Cl_2 (150 mL). The resulting solution was washed with water (2 × 50 mL) and brine (100 mL). Removal of the solvents gave a residue which was purified by column chromagraphy on silica gel. The fraction eluted with EtOAc/*n*-hexane (1:3) was collected. Evaporation of the solvents afforded the product hemibastadin-2 (**14**) (132 mg, 86%) as a yellowish oil. The spectroscopic properties (IR, ^{1}H NMR, and ^{13}C NMR were identical to the corresponding values for the natural hemibastadin-2. IR ($CHCl_3$): 3400; 3000; 1940; 1670; 1600; 1520; 1500; 1470; 1420; 1250; 1050; 990. ^{1}H NMR ($CDCl_3$): 7.43 (s, 2H); 7.38 (d, J = 2.1, 1H); 7.08 (dd, J = 8.4, 2.1, 1H); 6.83 (d, J = 8.4, 1H); 6.78 (t, J = 7.1, 1H, NH); 4.00 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 3.85 (s 3H, OCH_3); 3.82 (s, 2H, CH_2); 3.52 (q, J = 7.2, 2H); 2.77 (t, J = 7.2, 2H). ^{13}C NMR ($CDCl_3$): 162.1; 154.6; 152.7; 150.7; 134.8; 133.5; 133.3 (2C); 132.3; 128.7; 117.8 (2C); 112.1; 111.7; 63.2; 60.5; 56.3; 40.7; 34.4; 28.5. (Both ^{1}H NMR and ^{13}C NMR spectra were identical to the corresponding spectra of the natural material[1b]). HRMS FAB (m-NBA) Calcd for $C_{20}H_{22}{}^{79}Br_3NO_4$: $(M + H)^+$ 590.9129; found 590.9119.

Synthesis of Aerothionin (28). 2-(Benzyloxy)-4-methoxyacetophenone (16). A mixture of 2′-hydroxy-4′-methoxyacetophenone (**15**) (3.5 g, 21.1 mmol), benzyl bromide (4.5

g, 26.3 mmol), K_2CO_3 (5 g, 43.5 mmol), and 18-crown-6 (200 mg) in acetone (150 mL) was refluxed for 5 h. After most of acetone was removed, the residue was partitioned between CH_2Cl_2 (200 mL) and water (150 mL). The organic solution was washed with brine (150 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the product **16** (5.2 g, 97%) as a white solid, mp 78−80 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 3000; 2940; 2840; 1660; 1600; 1500; 1440; 1360; 1270; 1170; 1140; 1020; 830. ^{1}H NMR ($CDCl_3$): 7.85 (d, J = 8.4, 1H); 7.46−7.36 (m, 5H); 6.54 (d, J = 8.4, 1H); 6.53 (s, 1H); 5.14 (s, 2H, $PhCH_2O$); 3.83 (s, 3H, OCH_3); 2.57 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 197.8(CO); 164.3; 160.1; 136.0; 132.7; 128.7 (2C); 128.2; 127.6 (2C); 121.5; 105.3; 99.4; 70.7; 55.5; 32.1. HRMS EI Calcd for $C_{16}H_{16}O_3$: M^+ 256.1100; found 256.1108.

Methyl [2-(Benzyloxy)-4-methoxyphenyl]acetate (17). To a solution of **17** (4.5 g, 17.6 mmol) in methanol (50 mL) was added dropwise a solution of thallium nitrate trihydrate (7.8 g, 17.6 mmol) in methanol (20 mL) containing HNO_3 (2 mL). The resulting reaction mixture was stirred at room temperature for 18 h. After most of methanol was removed in vacuo, the residue was partitioned between AcOEt (300 mL) and water (300 mL). The organic solution was washed with brine (200 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a residue which was purified by column chromatography on silica gel. The fraction eluted with EtOAc/*n*-hexane (1:3) was collected. Removal of the solvents afforded the ester **17** (3.8 g, 76%) as a white solid, mp 51−52 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 3000; 2970; 2860; 1735; 1610; 1590; 1510; 1430; 1290; 1260; 1170; 1120; 1020; 830. ^{1}H NMR ($CDCl_3$): 7.43−7.33 (m, 5H); 7.12 (d, J = 8.2, 1H); 6.53 (d, J = 2.0, 1H); 6.48 (dd, J = 8.2, 2, 1H); 5.07 (s, 2H, $PhCH_2O$); 3.79 (s, 3H, OCH_3); 3.65 (s, 3H, OCH_3); 3.63 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 172.5(COO); 160.1; 157.4; 136.9; 131.2; 128.4 (2C); 127.7; 127.0 (2C); 115.8; 104.4; 99.8; 69.9; 55.3; 51.7; 35.3. HRMS EI Calcd for $C_{17}H_{18}O_4$: M^+ 286.1205; found 286.1192.

Methyl (2-Hydroxy-4-methoxyphenyl)acetate (18). A mixture of ester **17** (3 g, 10.5 mmol), Pd/C (5%, 500 mg) in methanol (60 mL) was stirred at room temperature under 1 atm. of H_2 for 7 h. After catalyst was removed by fitration, the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel. The fraction eluted with EtOAc/*n*-hexane (1:3) was collected. Removal of the solvents gave the phenol **18** (1.97 g, 96%) as a white solid, mp 68−69 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 3300; 3000; 2960; 2840; 1700; 1620; 1590; 1510; 1440; 1350; 1270; 1240; 1150; 1100; 1040; 1000; 960; 840. ^{1}H NMR ($CDCl_3$): 7.56 (s, 1H); 6.98 (d, J = 8.3, 1H); 6.49 (d, J = 2.5, 1H); 6.44 (dd, J = 8.3, 2.5, 1H); 3.75 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3); 3.62 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 174.6(COO); 160.4; 156.0; 131.3; 112.7; 106.5; 103.1; 55.2; 52.6; 36.7.HRMS EI Calcd for $C_{10}H_{12}O_4$: M^+ 196.0736; found 196.0747.

Methyl (3,5-Dibromo-2-hydroxy-4-methoxylphenyl) acetate (19). To a solution of **18** (2 g, 10.2 mmol) in CH_2Cl_2(50 mL) was added dropwise a solution of pyridium hydrobromide perbromide (6.5 g, 20.4 mmol) in pyridine (15 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h and then partitioned between CH_2Cl_2 (300 mL) and water (200 mL). The organic solution was washed with HCl (3 N, 2 × 200 mL) and brine (200 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave the dibromide **19** (3.25 g, 90%) as a white solid, mp 74−75 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 3500; 3000; 2960; 2840; 1740; 1600; 1470; 1440; 1400; 1350; 1320; 1180; 1060; 970; 860. ^{1}H NMR ($CDCl_3$): 7.35 (s, 1H); 3.86 (s, 3H, OCH_3); 3.72 (s, 3H, OCH_3); 3.64 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 171.8(COO); 153.6; 151.4; 133.4; 118.9; 107.5; 107.4; 60.5; 52.4; 35.8. HRMS EI Calcd for $C_{10}H_{10}{}^{79}Br_2O_4$: M^+ 351.8946; found 351.8937.

Methyl [3,5-Dibromo-2-(*p*-methoxybenzyloxy)-4-methoxyphenyl]acetate (20). A mixture of **19** (4 g, 11.3 mmol), K_2CO_3 (4 g, 28.9 mmol), *p*-methoxybenzyl chloride (2 g, 12.8 mmol), 18-crown-6 (200 mg), and (n-Bu)$_4$NI (200 mg) in acetone (100 mL) was refluxed for 3 h. After most of acetone was removed in vacuo, the residue was partitioned between CH_2Cl_2 and water (200 mL). The organic solution was washed with brine (200 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a residue which was purified by column chromatography on silica gel. The fraction eluted with EtOAc/*n*-hexane (1:4) was collected. Removal of the solvents gave the product **20** (5.0 g, 93%) as a colorless oil. IR ($CHCl_3$): 3000; 2960; 2860; 1740; 1610; 1520; 1470; 1430; 1250; 1180; 1060; 1040; 820. ^{1}H NMR ($CDCl_3$): 7.45 (s, 1H); 7.41 (d, J = 8.6, 2H); 6.93 (d, J = 8.6, 2H); 4.93 (s, 2H, $PhCH_2O$); 3.91 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 3.69 (s, 3H, OCH_3); 3.57 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 171.8 (COO); 159.8; 154.6; 133.5; 130.1 (2C); 130.0; 128.4; 126.9; 113.9 (2C); 113.8; 112.8; 75.1; 60.6; 55.3;,52.2; 35.2. HRMS (FAB^+) Calcd for $C_{18}H_{18}{}^{79}Br_2NaO_5$: $(M + Na)^+$ 494.9419; found 494.9414.

Methyl 3,5-Dibromo-2-(*p*-methoxybenzyloxy)-4-methoxyphenylacetic Acid (21). To a solution of **20** (6.0 g, 12.7 mmol) in methanol (100 mL) was added aqueous NaOH (2 N, 25 mL) dropwise at room temperature. After stirring the mixture for 1.5 h, most of methanol was removed in vacuo. The residue was dissolved in water (50 mL), and the resulting aqueous solution was adjusted to pH 2 with HCl (2 N). The solid was filtered and washed with water (10 mL) to afford the free acid **21** (5.5 g, 94%) as a white solid, mp 140−142 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 3400; 3040; 2980; 2860; 1730; 1630; 1540; 1490; 1450; 1390; 1270; 1200; 1080; 1060; 850. ^{1}H NMR ($CDCl_3$): 7.44 (s, 1H); 7.39 (d, J = 8.5, 2H); 6.90 (d, J = 8.5, 2H); 4.95 (s, 2H, $PhCH_2O$); 3.92 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 3.57 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$): 176.6 (COO); 159.9; 154.7; 133.6; 130.2 (2C); 129.9; 128.2; 126.2; 114.0 (2C); 113.9; 112.8; 75.3; 60.6; 55.3; 35.1. HRMS (FAB^+) Calcd for $C_{17}H_{16}{}^{79}Br_2NaO_5$: $(M + Na)^+$ 480.9262; found 480.9258.

Compound 22. Coupling Product of 21 with (Triphenylphosphoranylidene)acetonitrile. A solution of **21** (3.5 g, 7.6 mmol), ylide (2.3 g, 7.6 mmol), and EDCI (1.7 g, 8.9 mmol) in CH_2Cl_2 (70 mL) was stirred at room temperature for 4 h. The reaction mixture was then diluted by addition of CH_2Cl_2 (200 mL), washed with water (200 mL) and brine (150 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel chromatography. The fraction eluted with (AcOEt/*n*-hexane/CHCl, 1:1:1) was collected. Removal of the solvents gave the cyano ylide **22** (5.0 g, 88%) as a white solid, mp 95−97 °C (from EtOAc). IR ($CHCl_3$): 3000; 2940; 2180; 1600; 1520; 1470; 1430; 1350; 1250; 1180; 1100; 1050; 830. ^{1}H NMR ($CDCl_3$): 7.61−7.46 (m, 17H); 7.40 (s 1H); 6.89 (d, J = 8.6, 2H); 4.92 (s, 2H, $PhCH_2O$); 4.08 (s, 2H, CH_2); 3.87 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 192.7(CO); 159.6; 154.6; 153.7; 133.8; 133.5 (d J = 10, 6C); 133.0 (3C); 130.5 (2C); 129.4; 129.0 (d, J = 13, 6C); 128.9; 122.7 (d, J = 93, 3C); 122.4 (d, J = 16, CN); 114.5; 113.8 (2C); 112.5; 74.5; 60.5; 55.2; 49.2 (d, J = 125); 40.5 (d, J = 7). HRMS FAB (m-NBA) Calcd for $C_{37}H_{31}{}^{79}Br^{81}BrNO_4P$: $(M + H)^+$ 744.0337; found 744.0317.

Bis-α-keto Amide 24. A solution of ylide **22** (2.5 g, 3.36 mmol) in CH_2Cl_2 (30 mL) was treated with O_3 for 5 min at −78 °C, and the resulting pale green solution was purged with N_2 for 5 min. To this solution was added a solution of 1,4-diaminobutane (130 mg, 1.48 mmol) in CH_2Cl_2 (5 mL) via cannula, and the mixture was stirred at −78 °C for 5 min and then room temperature for 1 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography. The fraction eluted with EtOAc/*n*-hexane (1:1) was collected. Removal of the solvents gave the bis-keto amide **24** (1.0 g, 64%) as a white solid, mp 151−153 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 3400; 3020; 2940; 2840; 1690; 1610; 1520; 1470; 1430; 1320; 1250; 1180; 1120; 1060; 850. ^{1}H NMR ($CDCl_3$): 7.36 (d, J = 8.7, 4H); 7.34 (s, 2H); 6.88 (d, J = 8.7, 4H); 4.90 (s, 4H,2 × $PhCH_2O$); 4.14 (s, 4H, 2 × CH_2); 3.91 (s, 6H, 2 × OCH_3); 3.84 (s, 6H, 2 × OCH_3); 3.26 (q, J = 6.1, 4H); 1.49 (br, 4H). ^{13}C NMR ($CDCl_3$): 195.2 (2C); 159.8 (4C); 154.5 (4C); 133.7 (2C); 130.2 (4C); 128.2 (2C); 126.6 (2C); 114.5 (2C); 113.9 (4C); 112.8 (2C); 74.9 (2C); 60.6 (2C); 55.3 (2C); 38.8 (2C); 38.0 (2C); 26.5 (2C). HRMS FAB (m-NBA) Calcd for $C_{40}H_{41}{}^{79}Br_2{}^{81}Br_2N_2O_{10}$: $(M + H)^+$ 1028.9454; found 1028.9427.

Compound 25 (Bis-Oxime of 24). A mixture of **24** (320 mg, 0.34 mmol), NH_2OH·HCl (200 mg, 2.89 mmol), and NaOAc (300 mg, 3.66 mmol) in a mixture of solvents (EtOH/THF, 1:2)

was heated at 50−60 °C for 4 h and then partitioned between CH_2Cl_2 (200 mL) and water (100 mL). The organic solution was washed with brine (200 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents gave a residue which was purified by column chromatography. The fraction eluted with EtOAc/*n*-hexane (1:1) was collected. Removal of the solvents afforded the bis oxime **25** (340 mg, 95%) as a white solid, mp 105−107 °C (from EtOAc/*n*-hexane). IR ($CHCl_3$): 3300; 3010; 1680; 1610; 1520; 1470; 1430; 1380; 1250; 1060; 930; 850. ^{1}H NMR ($CDCl_3$ + 20% CD_3OD): 7.45 (d, J = 8.5, 4H); 7.17 (s, 2H); 6.87 (d, J = 8.5, 4H); 4.96 (s, 4H, 2 × $PhCH_2O$); 3.90 (s, 4H, 2 × CH_2); 3.81 (s, 6H, 2 × OCH_3); 3.77 (s, 6H, 2 × OCH_3); 3.21 (br, 4H); 1.49 (br, 4H). ^{13}C NMR ($CDCl_3$ + 20% CD_3OD): 163.5 (2C); 159.6 (2C); 154.1 (2C); 153.3 (2C); 151.1 (2C); 131.7 (2C); 130.1 (4C); 129.3 (2C); 128.7 (2C); 114.4 (2C); 113.7 (4C); 112.6 (2C); 74.4 (2C); 60.5 (2C); 55.2 (2C); 38.8 (2C); 26.5 (2C); 23.6 (2C). HRMS FAB (m-NBA) Calcd for $C_{40}H_{43}{}^{79}Br_2{}^{81}Br_2N_4O_{10}$: $(M + H)^+$ 1058.9672; found 1058.9706.

Compound 26. De-*p*-Methoxybenzylation of 2. To a suspension of **25** (300 mg, 0.28 mmol) in CH_2Cl_2 (15 mL) was added TFA (2 mL) dropwise at 0 °C. The resulting pale solution was stirred at room temperature for 20 min and then diluted with CH_2Cl_2 (300 mL) and washed with saturated $NaHCO_3$ (150 mL) and brine (150 mL). The organic solution was dried over anhudrous Na_2SO_4. Evaporation of the solvent gave a residue which was purified by recrystalization from CH_2Cl_2. The solid was filtered and washed with CH_2Cl_2 (3 mL) to give the phenol **26** (218 mg, 92%) as a white solid, mp 185−187 °C (from CH_2Cl_2/Et_2O). IR (KBr): 3340, 3200, 2940, 1650, 1610, 1550, 1460, 1400, 1320, 1230, 1210, 1160, 1050, 1000, 960. ^{1}H NMR (acetone-d_6): 8.08 (br, 2H, 2 × NH); 7.58 (s, 2H); 5.61 (s 2H, 2 × OH); 3.80 (s, 4H, 2 × CH_2); 3.79 (s, 6H, 2 × OCH_3); 3.36 (q, J = 6.1, 4H); 1.60 (br, 4H). ^{13}C NMR (acetone-d_6): 166.6 (2C); 154.8 (2C); 154.7 (2C); 151.4 (2C); 135.1 (2C); 121.9 (2C); 108.8 (2C); 106.6 (2C); 60.6 (2C); 40.0 (2C); 27.2 (2C); 25.9 (2C). HRMS FAB (m-NBA) Calcd for $C_{24}H_{27}{}^{79}Br_2{}^{81}Br_2N_4O_8$: $(M + H)^+$ 818.8521; found 818.8510.

Compound 27 (Bis-Spiro Product from Oxidation of 26). To a warm solution of the diphenolic dioxime **26** (50 mg, 0.061 mmol) in acetonitrile (10 mL) was added 2,4,4,6-tetrabromo-2,5-cyclohexadienone (65 mg, 0.159 mmol). The resulting solution was heated for a few minutes and then allowed to stand a room temperature for 24 h. The precipitate which separated was filtered, and the filtrate was concentrated to give a further quantity of solid. The combined solids were crystallized from EtOAc to give the product **27** (35 mg, 70%) as a pale solid, mp 245 °C (from EtOAc, dec). IR (KBr): 3300, 2940, 1680, 1650, 1610, 1500, 1460, 1420, 1320, 1280, 1230, 1170, 1000, 940, 890, 800, 740.

^{1}H NMR (DMSO-d_6): 8.64 (t, J = 5.3, 2H, 2 × NH); 7.23 (s, 2H); 4.03 (s, 6H, 2 × OCH_3); 3.51 (d, J = 18.2, 2H); 3.43 (d, J = 18.2, 2H), 3.15 (br, 4H); 1.46 (br, 4H). ^{13}C NMR (DMSO-d_6): 189.7; 163.1; 158.0; 153.7; 138.3; 118.4; 107.5; 85.9; 61.8; 45.1; 38.5; 26.3. HRMS FAB (m-NBA) Calcd for $C_{24}H_{23}{}^{79}Br_2{}^{81}Br_2N_4O_8$: $(M + H)^+$ 814.8208; found 814.8204.

Aerothionin (28). Sodium cyanoborohydride (20 mg 0.339 mmol) was added in portions to a stirred solution of **27** (30 mg, 0.037 mmol) in TFA (2 mL) and CH_2Cl_2 (10 mL) at 0 °C, and the stirring was continued for 20 min. The resulting solution was poured into CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by preparative TLC on silica gel (ethyl acetate/*n*-hexane, 2:1) to give aerothionin **28** (7.5 mg, 25%) as a pale solid. Analytical HPLC showed that the synthetic aerothionin **28** had the same retention time as the natural substance. The ^{1}H NMR and ^{13}C NMR spectra of synthetic aerothionin were identical to the spectra of the natural material except for the broad peak at 5.40 ppm and the sharp singlet at 4.16 ppm in the ^{1}H spectrum of the synthetic product compared to the doublets shown at the same locations in the ^{1}H spectrum of the natural material. Identical ^{1}H NMR effects (associated with the silica gel purification) were observed when a small amount of silica gel was added to the sample of natural aerothionin. IR (KBr): 3350, 2940, 1670, 1650, 1600, 1550, 1430, 1330, 1260, 1220, 1180, 990, 960, 920, 750. ^{1}H NMR (acetone-d_6): 7.63 (b, 2H, 2 × NH); 6.51 (s, 2H); 5.41 (b, 2H, 2 × OH); 4.16 (s, 2H); 3.83 (d, J = 18.3, 2H); 3.71 (s, 6H); 3.33 (m, 4H); 3.16 (d, J = 18.3, 2H); 1.60 (m, 4H). ^{13}C NMR (acetone-d_6): 159.9; 155.3; 148.7; 132.4; 122.0; 113.8; 91.5; 75.2; 60.2; 40.2; 39.4; 27.5.

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Supporting Information Available: Copies of NMR spectra (50 pages). This material is contained in 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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