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Efficient Synthesis of Tyrosine-Derived Marine Sponge Metabolites via Acylation of Amines with a Coumarin

J. Jonathan Harburn, Nigam P. Rath, and Christopher D. Spilling*

Department of Chemistry and Biochemistry, University of Missouri—St. Louis, One University Boulevard, St. Louis, Missouri 63121-4499

cspill@umsl.edu

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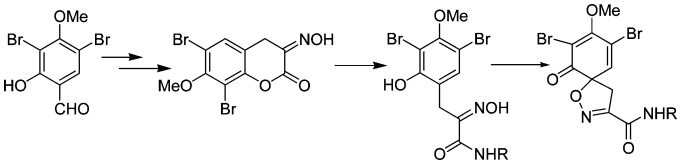

Condensation of *N*-acetylglycine with aldehyde **15** in acetic anhydride gave acetamido coumarin **16**. Hydrolysis to the enol coumarin **17** and reaction with hydroxylamine gave the oximino coumarin **18**. Reaction of the oximino coumarin **18** with a range of nucleophiles gave the phenolic oximes in excellent yield. The rates of acylation of histamine with the oximino coumarin **18** and methyl ester **9** were compared. Oxidative spirocyclization of three representative phenolic oximes with polymer-supported (diacetoxyiodo) benzene gave the spiroisoxazolines.

Introduction

Marine sponges of the order *Verongida* and related organisms have provided a vast array of tyrosine **1** derived secondary metabolites.[1,2] It was reported that the metabolic pathway[3] involves bromination of the tyrosine **1** aromatic ring and oxidation of the amine to an oxime (**2**−**5)** (Scheme 1). The tyrosine oximes **2** are methylated and coupled with amines to form oximino amides **5**[4] which react further via an arene oxide[5] to form spirocyclic isoxazolines **6**.[6] The isoxazolines **6** can rearrange to give the more stable phenolic oximes **7**.[7]

These metabolites exhibit wide-ranging biological activity and as a result have become targets for synthesis.[8−12] In particular, new methods for the spirocyclization of phenolic oximes have been reported,[8] leading to syntheses of aerothionin **6a**, homoaerothionin **6b**, and aerophobin-1 **6c**.[9] Wasserman et al. showed that cyano ylides could be employed in a very efficient preparation of the oximino amides leading syntheses of verongamine **5a** and aerothionin **6a**.[10]

In general, the metabolites can be considered as derivatives of di-, tri-, and higher peptides containing one or more oximino amide or spiroisoxazoline moiety. Much

(1) Berquist, P. R.; Wells, R. J. Chemotaxonomy of the Porifera: The Development and Current Status of the Field. In *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: 1993, *5*, 1−50.

(2) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, 113; Faulkner, D. J. *Nat. Prod. Rep.* **1997**, 259 and previous reports in this series.

(3) (a) Tymiak, A. A.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 6763. (b) De Rosa, M.; Minale, L.; Sodano, G. *Comput. Biochem. Physiol.* **1973**, *45B*, 883. (c) Carney, J. R.; Rinehart, K. L. *J. Nat. Prod.* **1995**, *58*, 971.

(4) For examples of oximino amides, see: (a) Mierzwa, R.; King, A.; Conover, M. A.; Tozzi, S.; Puar, M. S.; Patel, M.; Coval, S. J.; Pomponi, S. A. *J. Nat. Prod.* **1994**, *57*, 175. (b) Rodriguez, A. D.; Akee, R. K.; Scheuer, P. J. *Tetrahedron Lett.* **1987**, *28*, 4989.

(5) Roll, D. M.; Chang, C. W. J.; Scheuer, P. J.; Gray, G. A.; Shoolery, J. N.; Matsumoto, G. K.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 2916.

(6) For examples of spiroisoxazolines, see: (a) Cimino, G.; De Rosa, S.; De Stefano, S.; Self, R.; Sodano, G. *Tetrahedron Lett.* **1983**, *24*, 3029. (b) Fattorusso, E.; Minale, L.; Sodano, G.; Moody, K.; Thompson, R. H. *Chem. Commun.* **1970**, 752. (c) Moody, K.; Thomson, R. H.; Fattorusso, E.; Minale, L.; Sodano, G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 18.

(7) For examples of phenolic oximino amides, see: Kobayashi, J.; Honma, K.; Sasaki, T.; Tsuda, M. *Chem. Pharm. Bull.* **1995**, *43*, 403.

(8) (a) Murakata, M.; Yamada, K.; Hoshino, O. *Heterocycles* **1998**, *47*, 921. (b) Murakata, M.; Yamada, K.; Hoshino, O. *Tetrahedron* **1996**, *52*, 14713. (c) Murakata, M.; Yamada, K.; Hoshino, O. *Chem. Commun.* **1994**, 443. (d) Kacan, M.; Koyuncu, D.; McKillop, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1771. (e) Noda, H.; Niwa, M.; Yamamura S. *Tetrahedron Lett.* **1981**, *22*, 3247. (f) Forrester, A. R.; Thomson, R. H.; Woo S.-O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2340. (g) Forrester, A. R.; Thomson, R. H.; Woo S.-O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2348. (h) Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 4969.

(9) (a) Forrester, A. R.; Thomson, R. H.; Woo, S.-O. *Liebigs Ann. Chem.* **1978**, 66. (b) Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 3351. (c) Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3453. (d) Murakata, M.; Masafumi, T.; Hoshino, O. *J. Org. Chem.* **1997**, *62*, 4428.

(10) Wasserman, H. H.; Wang, J. *J. Org. Chem.* **1998**, *63*, 5581.

(11) (a) Hoshino, O.; Murakata, M.; Yamada, K. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1561. (b) Goldstein K.; Fendert, T.; Proksch, P.; Winterfeldt, E. *Tetrahedron* **2000**, *56*, 4173. (c) Hirotani, S.; Kaji, E. *Tetrahedron* **1999**, *55*, 4255. (d) Nicolaou, K. C.; Hughes, R.; Pfefferkorn, J. A.; Barluenga, S.; Roecker, A. J. *Chem.−Eur. J.* **2001**, *7*, 4280. (e) Nicolaou, K. C.; Hughes, R.; Pfefferkorn, J. A.; Barluenga, S. *Chem.−Eur. J.* **2001**, *7*, 4296.

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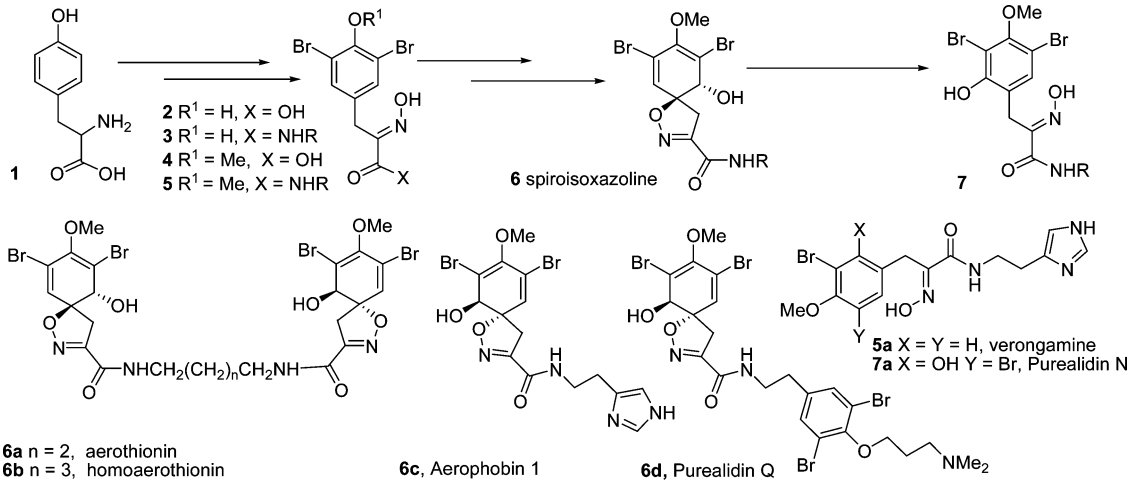
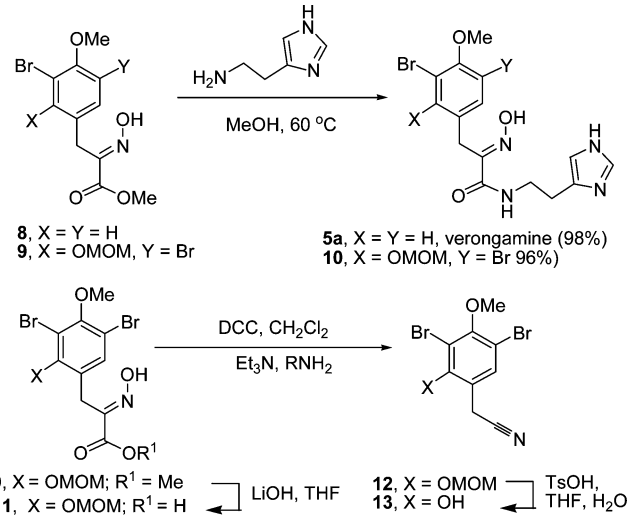
SCHEME 1. Biosynthesis of Tyrosine-Derived Secondary Metabolites



SCHEME 2



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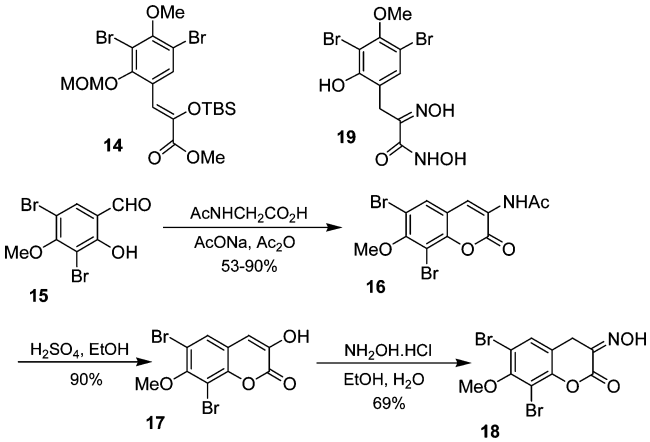


of the structural variation exists in the amine component, which is typically derived from metabolites of ornithine, lysine, tryramine, cystamine, and histamine. The large number and structure of the metabolites, and the potential for designing synthetic analogues with improved biological activity, make these compounds ideal targets for parallel synthesis. Indeed, using a similar rationale, Nicolaou reported the formation of a combinatorial library of antibacterial heterodisulfides based on the homodimeric disulfide tyrosine-derived marine sponge metabolite psammaplin A.[11d,e,f] Parallel synthesis of amides would require an efficient method for the rapid coupling of the phenolic oxime (and/or spirocyclic) moiety to a large variety of amines. An ideal solution would be a reactive acylating agent that required no protection of the oxime or phenolic groups and hence no additional deprotection steps.

In 1995 we communicated the results of our initial studies on the oxidation, bromination, and decarboxylation of tyrosine esters[12a] and later reported the synthesis of verongamine and purealidin N by the direct displacement of methyl esters **8** and **9**, respectively, with histamine.[12b] However, although this direct amidation reaction worked well with histamine, other amines, particularly more the complex amines and diamines, gave less than satisfactory results. In our hands, attempts to couple the free acid **11**, formed by hydrolysis of the methyl ester **9**, with amines using standard peptide coupling reactions resulted in a decarboxylation leading to formation of the nitrile **12**. Hydrolytic deprotection of the nitrile **12** led to the known[13] phenol **13**, which was characterized by X-ray crystallography.[14] Clearly, the presence of the free oxime presents a problem in the coupling reaction. Although, protection of the oxime was an option,[15] this would add additional deprotection steps and thereby reducing the overall efficiency of the synthesis. In a serendipitous development, an archived sample of silylenol ether **14**[12b] was examined by NMR spectroscopy prior to further reaction. The ^{1}H NMR spectrum revealed that upon storage the silylenol ether **14** had cleanly converted to the enol coumarin **17**, presumably through deprotection and lactonization. It was envisaged that an oxime **18**, derived from coumarin **17**, could serve as a self-protected active acylating agent. However, more expeditious synthesis of coumarin **18** was required.

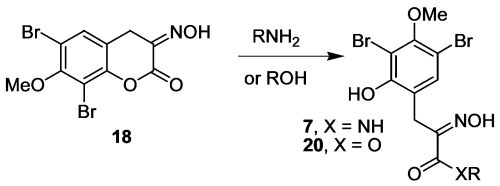
(12) (a) Boehlow, T. R.; Spilling, C. D. *Nat. Prod. Lett.* **1995**, *7*, 1. (b) Boehlow, T. R.; Harburn, J. J.; Spilling, C. D. *J. Org. Chem.* **2001**, *66*, 3111.

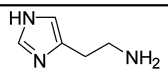
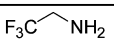
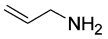
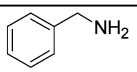
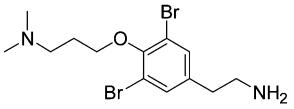
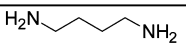
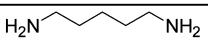
(13) Anderson, R. J.; Faulkner, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 936.

(14) Full details of the X-ray structure determination can be found in the Supporting Information.

(15) Bailey, K. L.; Molinski, T. F. *Tetrahedron Lett.* **2002**, *43*, 9657.

TABLE 1.



Entry	NuH	Product	Conditions	Yield (%)
1		**7a**	Amine, MeOH, reflux	98
2	H_2O	**20a**	NaOH, THF, H_2O	98
3	MeOH	**20b**	NaOMe, MeOH	97
4		**7b**	Neat amine, reflux	99
5		**7c**	Neat amine, reflux	95
6		**7d**	Neat amine, reflux	93
7		**7e**	Amine, MeOH, Et_3N, reflux	63
8		**7f**	Amine, MeOH, Et_3N, reflux	68
9		**7g**	Amine, MeOH, Et_3N, reflux	72

Trivedi and Sethna had described[16] a simple large-scale method for the preparation of 3-hydroxycoumarins via the condensation of the appropriate salicylaldehyde with *N*-acetylglycine followed by acid-catalyzed hydrolysis. Reaction of the dibromosalicylaldeyde **15**[12b] with *N*-acetyl glycine in acetic anhydride gave the acetamido coumarin **16** in yields ranging from 53 to 90%.[16a] Careful reaction with an ethanolic solution of sulfuric acid led to the selective hydrolysis of the enamide to give the enol **17**. Reaction of the enol **17** with 8.5 equiv of hydroxylamine in refluxing 80% EtOH for 1−2 h yielded the oximino coumarin **18**. Prolonged reaction of enol **17** with an excess of hydroxylamine lead to formation and isolation of the hydroxamic acid **19**. The enol **17** and the hydroxamic acid **19** were characterized by X-ray crystallography.[14] The oximino coumarin **18** was reacted with a variety of nucleophiles (Table 1). Reaction with aqueous hydroxide gave the corresponding carboxylic acid **20a** in excellent yield (Table 1, entry 2). Similarly, the addition of methoxide to coumarin **18** gave the known methyl ester **20b** in high yield.[12b] However, since most of the natural products of interest are amides, a series of amines were investigated. For the volatile amines (entries 4−6), the coumarin **18** was dissolved in the neat amine. After the reaction was complete, the excess amine was evaporated to give the amides in high yield and purity. The more complex amines (entries 1 and 7) were reacted with 1 equiv of the coumarin in methanol solution at 60 °C to give the corresponding amides in good to excellent yield. Reaction of the diamines (entries 8 and 9) also proceeded in methanol solution to give the diamide precursors to aerothionin and homoaerothionin in good yield. However between 2 and 4 equiv of the coumarin were used to ensure complete reaction.

It was clear that the coumarin oxime **18** was a superior acylating agent for amines than the methyl ester **9**. To get a quantitative measure, the relative reactions rates of ester **9** and coumarin **18** with histamine were compared. Coumarin **18** (1 equiv) and the methyl ester **9** (1 equiv) (in separate NMR tubes) were reacted with 3 equiv of histamine in d_4-MeOH solution at 60 °C. The reactions were followed by ^{1}H NMR spectroscopy. The peak for aromatic hydrogen in each starting material was integrated and compared to the integration of an internal standard (0.1 equiv hexamethylbenzene). The coumarin **18** was consumed (Figure 1) approximately six times faster than the methyl ester **9** under identical reaction conditions.

We had previously reported[12b] that the oxime ester **20b** could be cyclized with NBS in DMF or with polymer-supported (diacetoxyiodo)benzene (PSDIB) reagent[17] in acetonitrile to give the isoxazoline **21**.[12b] Since, in our hands, the isoxazoline **21** was sensitive to chromatography, the excellent yield and purity provided by the oxidative cyclization using the PSDIB proved it to be the superior method. Two additional amide substrates **7d**

(16) (a) Trivedi, K. N.; Sethna, S. *J. Org. Chem.* **1960**, *25*, 1817. (b) Kokotos, G.; Tzougraki, C. *J. Heterocycl. Chem.* **1986**, *23*, 87. (c) Shaw, K. N. F.; McMillan, A.; Armstrong, M. D. *J. Org. Chem.* **1956**, *21*, 601.

(17) (a) Togo, H.; Nogami, G.; Yokoyama, M. *Synlett* **1998**, 534. (b) Ley, S. V.; Thomas, A. W.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 669.

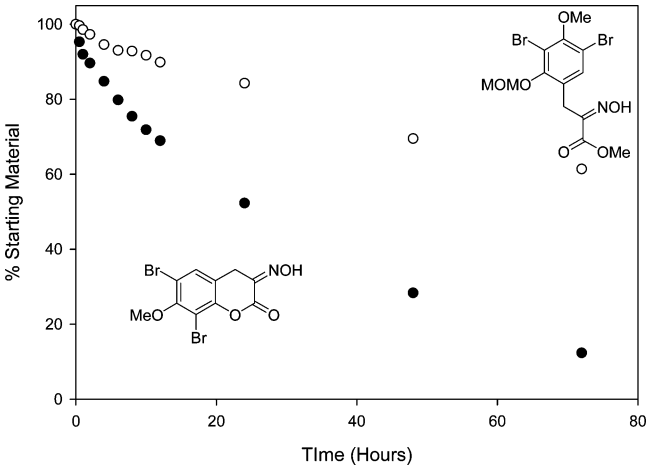
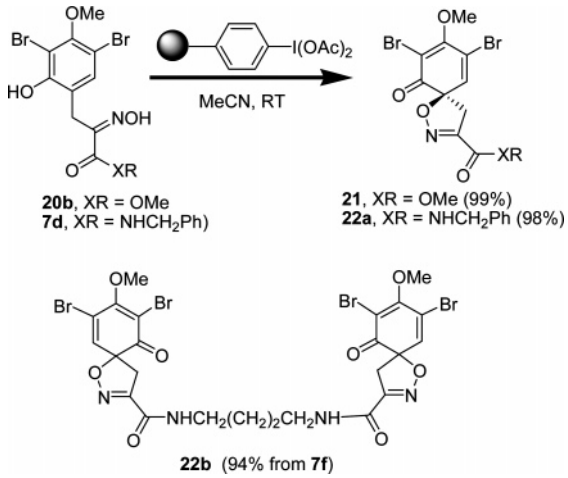


FIGURE 1. A graph comparing the rate of the reaction of the methyl ester **9** and coumarin **18** with histamine.

SCHEME 4



and **7f** were cyclized with PSDIB to give **22a** and **22b**, respectively. The spirocyclization occurred rapidly, and workup only involved filtration, thus removing the need for chromatography.

In summary, whereas attempted coupling of α-oximinoacid **11** with amines using carbodiimides resulted in decarboxylation to the corresponding nitrile **12**, reaction of the coumarin oxime **18** with a range of nucleophiles proceeded smoothly to give phenolic oximes **7a**−**g** and **20a**−**b.** The rate of acylation with the coumarin oxime **18** was approximately six times faster than the methyl ester **9** (with histamine). The phenolic oximes **7d** and **7f** reacted with PSDIB to give spiroisoxazolines **22a** and **22b**, respectively. These reactions are potentially useful in the parallel synthesis of a wide range of sponge metabolite analogues.

Experimental Section

3-Acetamido-6,8-dibromo-7-methoxy-coumarin (16). A solution of 3,5-dibromo-2-hydroxy-4-methoxybenzaldehyde[12b] **15** (25.4 g, 82.5 mmol), acetylglycine (9.66 g, 82.5 mmol), and anhydrous NaOAc (13.5 g, 165 mmol) in Ac_2O (250 mL) was heated at reflux overnight. The mixture was allowed to cool to room temperature, and the crystalline solid which precipitated was collected by filtration. The solid was successively washed with copious amounts of H_2O, $CHCl_3$, and Et_2O and dried in vacuo to give **16** as a tan crystalline solid (17.1 g, 53%): mp 291−292.5 °C (lit. 292−294 °C, DMSO/H_2O);[6c] IR (KBr) 3347, 1715, 1681 cm^{-1}; ^1H NMR (d_6-DMSO, 100 °C) δ 9.43 (s, 1H), 8.49 (s, 1H), 8.01 (s, 1H), 3.91 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (d_6 DMSO, 100 °C) δ 169.4, 156.0, 153.9, 146.4, 129.6, 124.0, 121.5, 118.1, 112.0, 104.9, 60.4, 23.3; HRMS (EI, M^+) calcd for $C_{12}H_9{}^{79}Br^{81}BrNO_4$ 390.8898, found 390.8875. Anal. Calcd for $C_{12}H_9Br_2NO_4$: C, 36.86; H, 2.32; N 3.58. Found: C, 36.92; H, 2.29; N 3.57.

6,8-Dibromo-3-hydroxy-7-methoxy-coumarin (17). A solution of 3-acetamido-6,8-dibromo-7-methoxycoumarin **16** (10 g, 25.7 mmol) in absolute EtOH (100 mL) and 6 N HCl (50 mL) was heated at reflux overnight. The reaction mixture was concentrated in vacuo to give a yellow precipitate, which was collected by filtration. The filtrate was washed successively with copious amounts of H_2O, hexanes, and cold Et_2O (50 mL) and dried in vacuo to give **17** as a pale-yellow crystalline solid (8.02 g, 90%): mp 178−179 °C ($CHCl_3$); IR (KBr) 3367, 1695, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (s, 1H), 6.94 (s, 1H), 6.33 (s, 1H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6, 154.7, 146.5, 140.4, 129.0, 119.0, 114.3, 113.1, 107.3, 61.3; HRMS (CI, M^+) calcd for $C_{10}H_7{}^{79}Br^{81}BrO_4$ 350.8691, found 350.8699. Anal. Calcd for $C_{10}H_6Br_2O_4$: C, 34.32; H, 1.73. Found: C, 34.25; H, 1.72.

6,8-Dibromo-7-methoxy-3-hydroximino-3,4-dihydrocoumarin (18). A solution of 6,8-dibromo-3-hydroxy-7-methoxycoumarin **17** (1 g, 2.87 mmol), hydroxylamine hydrochloride (1.69 g, 24.3 mmol), and NaOAc (2.35 g, 28.7 mmol) in aqueous EtOH (80%, 50 mL) was heated at reflux until no starting material remained (usually 1−2 h, thin-layer chromatography (TLC), SiO_2, EtOAc:CH_2Cl_2, 2:1). The reaction mixture was concentrated in vacuo and the pale-yellow solid was collected by filtration. The solid was washed with copious amounts of H_2O and $CHCl_3$ and dried in vacuo. Further purification by chromatography (SiO_2, hexanes:EtOAc) gave **18** as a pale-yellow solid (0.721 g, 69%): mp 193.5−195 °C; IR (KBr) 3354, 1718, 1526 cm^{-1}; ^1H NMR (d_6-DMSO) δ 9.28 (s, 1H), 7.28 (s, 1H), 3.74 (s, 3H), 3.71 (s, 2H); ^{13}C NMR (d_6 DMSO) δ 163.0, 154.4, 154.1, 150.2, 134.6, 121.3, 108.4, 106.3, 60.1, 25.6; HRMS (EI, M^+) calcd for $C_{10}H_7{}^{79}Br^{81}BrNO_4$ 364.8742, found 364.8725. If the reaction mixture is heated at reflux for longer than 1−2 h, formation of increasing amounts of the hydroxamic acid **19** was observed (>5 h, TLC, SiO_2, EtOAc:CH_2Cl_2, 2:1). The hydroxamic acid was separated from the coumarin **18** by column chromatography (SiO_2, EtOAc:CH_2Cl_2, 1:1) to give a beige solid, IR (ATR) 3471, 3318, 3234, 1647, 1618 cm^{-1}; ^1H NMR (d_6-acetone) δ 7.57 (s, 1H), 3.82 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (d_6-acetone) δ 163.9, 155.3, 155.0, 151.5, 122.2, 109.2, 107.2, 61.0, 26.6; Anal. Calcd for $C_{10}H_{10}Br_2N_2O_5$: C, 30.18; H, 2.53; N, 7.04. Found: C, 30.40; H, 2.51; N. 6.90.

3-(3,5-Dibromo-2-hydroxy-4-methoxyphenyl)-2(*E*)-(hydroximino)propanoic Acid (20a). KOH (0.154 g, 2.74 mmol) was added to a solution of 6,8-dibromo-7-methoxy-3-oximinocoumarin **18** (0.5 g, 1.37 mmol) in THF (15 mL) and H_2O (5 mL). The mixture was stirred for 18 h, then the solvent was removed in vacuo. The residue was dissolved in distilled H_2O (10 mL) and acidified to pH 1 with dilute HCl (0.1 M) at which point a pale-tan precipitate formed. The mixture was extracted with EtOAc (3 × 15 mL), and the combined extracts were washed with saturated NaCl solution (2 × 25 mL) and H_2O (2 × 25 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a pale-tan solid (0.512 g, 98%): mp 141−143 °C (PhMe); IR (ATR) 3472, 3319, 3235,1689 cm^{-1}; ^1H NMR (d_6-DMSO) δ 10.74 (br. s, 3H), 7.42 (s, 1H), 3.95 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (d_6-DMSO) δ 166.1, 154.0, 153.1, 150.0, 133.2, 121.9, 107.8, 106.8, 60.2, 25.4.

Methyl 3-(3,5-Dibromo-2-hydroxy-4-methoxy-phenyl)-2(*E*)-(hydroximino)propanoate (20b). A solution of the coumarin oxime **18** (0.10 g, 0.276 mmol) and NaOMe (0.07 mL, 25 wt %, 0.303 mmol) in MeOH (1 mL) was stirred until the starting material had been consumed (TLC, SiO_2, EtOAc:hexanes:CH_2Cl_2, 5:5:1). The solvent was evaporated in vacuo. The residue was dissolved in EtOAc (10 mL) and washed with

dilute HCl (0.1M, 2 × 10 mL) and saturated NaCl (10 mL), dried over Na_2SO_4, and evaporated in vacuo to give a colorless solid (0.105 g, 97%), mp 146−147 °C (lit. 148−149 °C).[8a,12b] Spectroscopic data were identical with those previously reported.

General Procedure for the Reaction of Volatile Amines with Coumarin (18). 6,8-Dibromo-7-methoxy-3-oximino coumarin **18** (0.5 g, 1.37 mmol) and amine (13.7 mmol) were heated at reflux until no starting material remained by TLC (SiO_2, hexanes:EtOAc:CH_2Cl_2, 5:5:1). The remaining amine was evaporated in vacuo, and the residue was purified by chromatography. Yields and characterization data given below.

***N*-(2,2,2 Trifluoroethyl) 3-(3,5-dibromo-2-hydroxy-4-methoxyphenyl)-2(*E*)-(hydroximino)propanamide (7b).** Tan crystalline solid (0.665 g, 99%): mp 139.5−141 °C; IR (ATR) 3474, 3373, 3239, 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.91 (br. s, 1H, OH), 7.43 (s, 1H), 7.16 (t, 1H, J = 6.2 Hz, 1H) 3.95 (m, 2H), 3.79 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 165.6, 154.5, 153.0, 151.0, 134.3, 125.1 (q, J_{CF} = 277 Hz), 120.0, 108.9, 107.9, 61.0, 41.5 (q, J_{CF} = 35.5 Hz), 24.86; HRMS (FAB, CsI/NBA/PEG 600, M + Cs^+) calcd for $C_{12}H_{11}{}^{79}Br^{81}BrN_2O_4Cs$: 596.8072, found 596.8041. Anal. Calcd for $C_{12}H_9Br_2NO_4$: C, 31.06; H, 2.39; N 6.04. Found: C, 30.83; H, 2.37; N 5.92.

***N*-Allyl 3-(3,5-dibromo-2-hydroxy-4-methoxyphenyl)-2(*E*)-(hydroximino)propanamide (7c).** Colorless needles (95%): mp 198−199 °C (acetone), IR (KBr) 3346, 3192, 3089, 1620 cm^{-1}; ^1H NMR (d_6-acetone) δ 11.51 (br. s, 1H), 10.74 (br. s, 1H), 8.04 (br. s, 1H), 7.51 (s, 1H), 5.77 (ddd, 1H, J = 5.5, 10.3, 17.2 Hz,), 5.03 (ddd, 1H, J = 1.6, 3.0, 17.2 Hz), 4.95 (ddd, 1H, J = 1.6, 3.0, 10.3 Hz), 3.85 (dt, 2H, J = 1.6 Hz, 5.5 Hz), 3.70 (s, 2H), 3.67 (s, 3H); ^{13}C NMR (rotomers) (d_6-acetone) δ 166.58, 154.95, 154.81, 151.46, 135.2, 134.9, 122.0, 116.5, 108.9, 106.8, 60.7, 39.4, 26.5, 25.1; (CD_3OD) δ 167.0, 155.1, 154.7, 151.7, 136.1, 134.9, 134.8, 123.0, 117.9, 109.0, 107.4, 60.9, 40.7, 27.7, 25.8; HRMS (FAB CsI/NBA/PEG 600, M + Cs^+) calcd for $C_{13}H_{14}{}^{79}Br^{81}BrN_2O_4Cs$ 554.8355, found 554.8356. Anal. Calcd for $C_{13}H_{14}Br_2N_2O_4$: C, 37.15; H, 3.36. Found: C, 37.14; H, 3.33.

***N*-Benzyl 3-(3,5-dibromo-2-hydroxy-4-methoxyphenyl)-2(*E*)-(hydroximino)propanamide (7d).** Colorless crystalline solid (0.619 g, 93%); mp 143.5−145 °C (acetone); IR (ATR) 3353, 3212, 3089, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.10 (br s, 1H, OH), 8.80 (br s, 1H, OH), 7.54 (s, 1H), 7.38 (m, 5H), 4.52 (s, 1H), 4.51 (s, 1H), 3.87 (s, 3H), 3.840 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 165.2, 154.5, 153.4, 151.3, 137.0, 134.5, 129.3, 128.3, 128.2, 120.4, 109.0, 107.6, 60.9, 44.4, 25.2; HRMS (EI, M^+) calcd for $C_{17}H_{16}{}^{79}Br^{81}BrN_2O_4$ 471.9455, found 471.9455.

Purealidin N 7a. A solution of the coumarin oxime **18** (0.50 g, 1.37 mmol) and histamine (0.153 g, 1.37 mmol) in MeOH (10 mL) was heated at reflux until no starting material was visible by TLC (SiO_2, $CHCl_3$:MeOH, 5:1), at which point the solvent was evaporated in vacuo to give a yellow gum. Chromatography (SiO_2, hexanes:EtOAc then $CHCl_3$ to MeOH) gave a pale-yellow hygroscopic solid (0.641 g, 98%). Physical and spectroscopic data were identical those previously reported.[12b]

***N*-[3,5-Dibromo-4-(3-dimethylaminopropoxy)phenethyl] 3-(3,5-dibromo-2-hydroxy-4-methoxyphenyl)-2(*E*)-(hydroximino)propanamide (7e).** A solution of coumarin oxime **18** (0.250 g, 0.69 mmol), NEt_3 (0.02 mL, 0.137 mmol), and 3,5-dibromo-4-(3-dimethylaminopropoxy) phenethylamine (0.260 g, 0.69 mmol) in MeOH (10 mL) was heated at reflux until no starting material was visible by TLC (SiO_2, $CHCl_3$:MeOH, 5:1), at which point the solvent was evaporated in vacuo to give a yellow gum. Chromatography (SiO_2, $CHCl_3$ to MeOH) gave a yellow gum, which was titrated with acetone to give a colorless solid (0.321 g, 63%): mp 131−132.5 °C (acetone); IR (ATR) 3334, 3214, 3111, 1625 cm^{-1}; ^1H NMR (CD_3OD) δ 7.41 (s, 2H), 7.06 (s, 1H), 4.00 (t, 2H, J = 6.1 Hz), 3.78 (s, 3H), 3.57 (s, 2H), 3.46 (t, 2H, J = 7.0 Hz), 2.86 (t, 2H, J = 7.0 Hz), 2.67 (m, 2H), 2.31 (s, 6H), 2.06 (m, 2H); ^{13}C NMR (CD_3OD) δ 169.8, 165.5, 155.9, 153.4, 138.5, 134.4, 132.5, 122.0, 119.3, 112.1, 99.4, 72.8, 60.6, 57.6, 45.9, 43.9, 37.0, 33.7, 29.1; HRMS [FAB (MH − $NMe_2)^+$] calcd. for $C_{21}H_{22}{}^{79}Br_2{}^{81}Br_2N_2O_5$ 701.8825, found 701.8871.

Aerothionin Precussor (7f). A solution of coumarin oxime **18** (0.50 g, 1.37 mmol), NEt_3 (0.02 mL, 0.069 mmol), and 1,4-diaminobutane (0.033 g, 0.323 mmol) in MeOH (10 mL) was heated at reflux until no starting material was visible by TLC (SiO_2, $CHCl_3$:MeOH, 5:1) at which point the solvent was evaporated in vacuo to give a yellow gum. Chromatography (SiO_2, hexanes/EtOAc then CH_2Cl_2 to CH_3CN to MeOH) gave a pale-yellow solid (0.384 g, 67%): mp 187−189.5 °C (Et_2O/$CHCl_3$) (lit. 188.5−189.5);[6c,10] IR (ATR) 3352, 3215, 3087, 1651 cm^{-1}; ^1H NMR (d_6-acetone) δ 8.11 (br s, 2H), 7.61 (s, 2H), 3.83 (s, 4H), 3.82 (s, 6H), 3.40 (m, 4H), 2.80 (m, 4H); ^{13}C NMR (d_6-acetone) δ 166.1, 154.4, 154.3, 150.9, 134.6, 121.4, 108.4, 106.2, 60.1, 39.6, 26.8, 25.4; HRMS (FAB, CsI:NBA, M + Cs^+) calcd for $C_{24}H_{26}{}^{79}Br_2{}^{81}Br_2N_4O_8Cs$ 950.7500, found 950.7509.

Homoaerothionin Precusor (7g). A solution of the coumarin oxime **18** (0.250 g, 0.685 mmol), NEt_3 (0.01 mL, 0.069 mmol), and 1,5-diaminopentane (0.033 g, 0.323 mmol) in MeOH (10 mL) was treated as above to give a pale-yellow gum (0.191 g, 70%): IR (Diamond) 3350, 32.15, 3086, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.24, (br s, 4H), 8.05 (t, 2H, J = 5.8 Hz), 7.59 (s, 2H), 3.81 (s, 4H), 3.80 (s, 6H), 3.36 (m, 4H), 2.06 (m, 4H), 1.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 167.1, 155.4, 155.3, 152.0, 135.6, 122.5, 109.4, 107.2, 61.1, 40.8, 31.1, 26.4, 25.3; HRMS (FAB NBA, M + H^+) calcd. for $C_{25}H_{29}{}^{79}Br_2N_4O_8$ 832.8681, found 832.8669.

A Comparison of the Rate of Reaction of the Methyl Ester 9 and Coumarin 18 with Histamine. In two separate NMR tubes were placed **18** (0.05 g, 0.137 mmol) or **9** (0.06 g, 0.137 mmol), histamine (0.046 g, 0.411 mmol), internal standard hexamethylbenzene (0.002 g, 0.0137 mmol), and CD_3OD (1.5 mL). The NMR tubes were heated at 60 °C (water bath temperature), and ^1H NMR spectra were recorded at regular intervals. The integrals were corrected to the internal standard and plotted against time.

General Procedure for Oxidative Spirocyclization. PSDIB[17] (1.0 g, 3.5 mmol/g, 3.5 mmol) was stirred in acetonitrile (10 mL) and allowed to swell. A solution of the phenolic oxime (0.05 g) in acetonitrile (1 mL) was added via syringe to the swelled polymer, and the mixture was stirred for 1 h. The polymer was removed by filtration, washing with additional acetonitrile (3 × 25 mL), and then the solvent was evaporated in vacuo. Yields and characterization data are given below.

***N*-Benzyl 7,9-dibromo-8-methoxy-6-oxo-1-oxa-2-azaspiro-[4,5]deca-2,7,9-triene-3-carbamide (22a).** Pale-yellow gum (0.049 g, 98%); IR (ATR) 3339, 3063, 3031, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (m, 5H), 7.00 (t, 1H, J = 5.7 Hz), 6.80, (s, 1H), 4.59 (m, 2H), 4.20 (s, 3H), 3.66 (d, 1H, J = 18.0 Hz), 3.42 (d, 1H, J = 18.0 Hz); ^{13}C NMR ($CDCl_3$) δ 189.6, 163.7, 158.6, 152.9, 137.4, 136.8, 129.3, 128.1, 120.8, 107.1, 87.2, 65.5, 45.4, 44.1; HRMS (EI, M − NOH^+) calcd. for $C_{17}H_{13}{}^{79}Br^{81}BrNO_3$ 438.9243, found 438.9245.

Aerothionin Precursor (22b). Pale-yellow gum (0.047 g, 94%); IR (ATR) 3342, 3066, 3031, 1662 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.65 (t, J = 5.7 Hz, 2H, 2 × NH), 7.24 (s, 2H), 4.06, (s, 6H, 2 × OCH_3), 3.51 (br, 4H), 3.18 (br 4H), 1.48 (br, 4H); ^{13}C NMR (DMSO-d_6) δ 190.5, 163.9, 158.9, 154.6, 139.6, 119.3, 108.4, 86.8, 62.7, 45.9, 39.4, 27.1; HRMS (FAB, NBA, M + H^+) calcd. for $C_{24}H_{23}{}^{79}Br_2{}^{81}Br_2N_4O_8$ 814.8204, found 814.8245.

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Supporting Information Available: General experimental details, experimental for compounds **11**, **12**, and **13**, ^{1}H and ^{13}C NMR spectra for compounds **11**, **12**, **13**, **16**, **17**, **18**, **20a**, **20b**, **7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **7g**, **22a**, and **22b**, X-ray crystallographic data for compounds **13**, **17**, and **19**, and stack plots of the ^{1}H NMR spectra for the reaction of **9** and **18** with histamine. This material is provided free of charge via the Internet at http://pubs.acs.org.

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