Approaches to the Synthesis of Some Tyrosine-Derived Marine Sponge Metabolites: Synthesis of Verongamine and Purealidin N

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The oxidation of tyrosine ethyl ester (**7**) with Na_2WO_4/H_2O_2 in ethanol, dimethyldioxirane in acetone, or methyltrioxorhenium/H_2O_2 in EtOH gave the corresponding tyrosine oxime (**8**) in high yield. Controlled bromination of the aromatic ring gave the monobromo oxime (**9**), the dibromo oxime (**10**), or the spiroisoxazoline (**11**) depending upon reaction conditions. Synthesis of the known metabolite verongamine (**15**) was achieved by oxidation of *O*-methyl bromotyrosine methyl ester and amidation of the resulting oxime ester (**14**) with histamine. The mono- and di-bromotyrosine oxime derivatives (**9** and **10**) were further transformed into the naturally occurring nitriles (**16** and **17**) by base hydrolysis of the ester and acid-catalyzed decarboxylation. Wadsworth−Emmons olefination of the dibromobenzaldehyde (**20b**) with phosphonate (**18**) gave the pyruvate silylenolether (**21b**). Deprotection and in situ oxime formation gave the oxime ester (**23b**). Attempted purification of the pyruvate ester resulted in a homoaldol condensation yielding butenolide (**22**). Amidation of the oxime ester (**23b**) with histamine, followed by deprotection of the MOM ether gave the first synthesis of purealidin N (**28**). Oxidative spirocyclization of the phenolic oxime ester (**23d**) with a polymer-bound iodosyl diacetate gave the spiroisoxazoline (**24**) and represents a formal synthesis of aerothionin (**26a**), homoaerothionin (**26b**), and aerophobin-1 (**25**).

Introduction

Over the past 30 years an ever increasing number of tyrosine (**1**)-derived secondary metabolites have been isolated from marine sponges of the order *Verongida*.[1,2] It was reported that the metabolic pathway employed by the sponge involves bromination of the tyrosine aromatic ring and oxidation of the amine to an oxime (Scheme 1).[3] The tyrosine oximes[4] (**2**), exemplified by verongamine (**15**),[4a] are then further metabolized (via an arene oxide),[5] to form spirocyclic isoxazolines (**3**)[5] such as aerophobin-1 (**25**),[5a] aerothionin (**26a**),[5b] and homoaerothionin (**26b**).[5c] The isoxazolines (**3**) can rearrange to give more stable phenolic oximes (**4**), for example, purealidin N (**28**).[6] Decarboxylation of the oximes leads to the formation of nitriles (**5**),[7] which can also undergo further oxidation to give quinols (**6**).[8] Many of these metabolites exhibit wide ranging biological activity and as a result have become targets for synthesis.[9−13]

Many of the synthetic approaches to these metabolites have concentrated on developing chemistry for the latter steps in the synthesis and rely on an Erlenmeyer condensation for the key carbon−carbon bond forming reaction for the formation of the oximes.[9−11] In particular,

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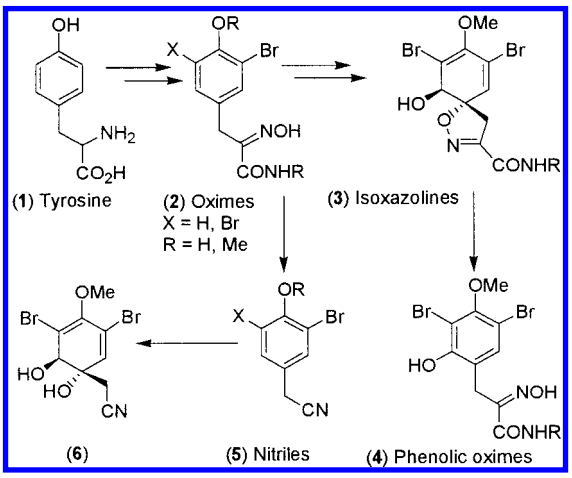
Scheme 1



new methods for the spirocyclization of phenolic oximes have been reported,[10] leading to syntheses of aerothionin (**26a**), homaerothionin (**26b**), and aerophobin-1 (**25**).[11] More recently, Wasserman et al. showed that cyano ylides could be employed in a very efficient preparation of the oximino amides leading to syntheses of verongamine (**15**) and aerothionin (**26a**).[12] In addition, total synthesis of phenolic oxime psammaplin A and the nitrile aeroplysinin-1 (**6**) have been published.[13]

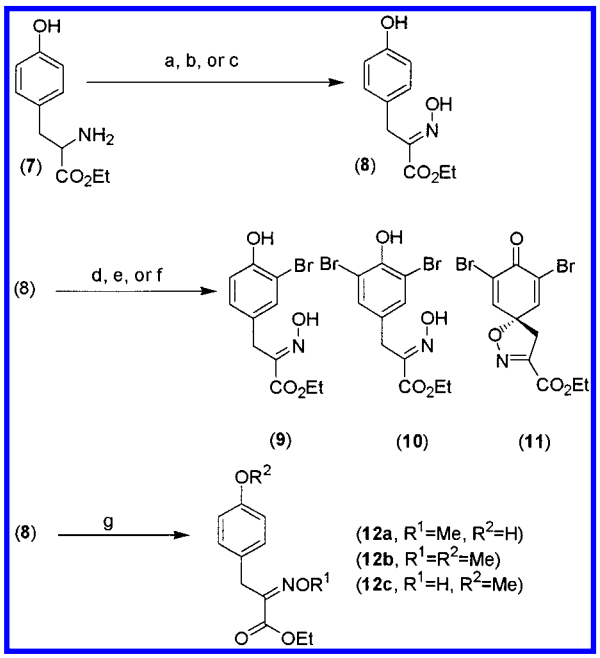
In 1995 we communicated the results of our initial studies on the oxidation, bromination, and decarboxylation of tyrosine esters.[14] We report herein the application of this sequence to the synthesis of the marine sponge metabolite verongamine[4] and a new method of pyruvate oxime preparation using a Wadsworth−Emmons olefination leading to the first synthesis of purealidin N.[6]

Results and Discussion

The oxidation of amines to oximes has been achieved with several oxidizing agents; however, the yields are often variable as a result of side reactions, in particular, overoxidation and nitroso dimer formation.[15] It has been suggested that bromoperoxidase and peroxidase enzymes, which have been isolated from *Verongida*,[16] may be responsible for bromination and amine oxidation in the metabolism of tyrosine. The peroxidase enzymes often contain transition metal oxides (Fe or V) in the active site. Indeed, Di Furia et al.[17] demonstrated that a model system consisting of a combination of NH_4VO_3, H_2O_2, and KBr in a two-phase solvent system would brominate aromatic and olefinic substrates.

We focused our attention on the known[18] oxidation of primary amines with tungstate peroxo complexes as a suitable laboratory mimic (Scheme 2). Treatment of an ethanolic solution of tyrosine ethyl ester (**7**) with sodium tungstate (1 equiv) and 30% aqueous hydrogen peroxide (10 equiv) at room temperature for 1 h gave the corresponding oxime (**8**) in 83% yield as a single geometric isomer.[19] Oxidation of (**7**) using sodium vanadate in place of the sodium tungstate was much slower (30 h) and gave several products from which the oxime (**8**) was isolated in 19% yield. However, oxidation of (**7**) with methyltrioxorhenium ($MeReO_3$) in $EtOH/H_2O_2$, which has rapidly emerged as a versatile oxidizing reagent,[20] afforded the corresponding oxime (**8**) in a high yield (87%).

Scheme 2[a]



[a] Reagents and conditions: (a) Na_2WO_4, EtOH, 30% H_2O_2, 74−83%; (b) dimethyldioxirane, acetone, 91%; (c) $MeReO_3$, 30% H_2O_2, EtOH, 87%; (d) $CH_3CONHBr$, THF, −78 °C, 60%; (e) NBS, DMF, 0 °C, 69%; (f) NBS, DMF, 25 °C, 74%; (g) MeI, Cs_2CO_3 or K_2CO_3, acetone.

Oxidation of the amine with dimethyldioxirane was also investigated. Dimethyldioxirane is a powerful oxidant and has been compared to the monoxygenase enzymes in its oxidation chemistry.[21] Oxidation of primary amines with excess dimethyldioxirane was reported to give nitroalkanes in good yield.[21b] Attempts to limit oxidation by employing 1 equiv of dimethyldioxirane has met with some success for hydroxylamine formation;[21d] however, 1−2 equiv of dimethyldioxirane generally resulted in the formation of several products including hydroxylamines, oximes, nitroso dimers, nitroalkanes, nitrones, and oxaziridines.[21f] Dimethyldioxirane oxidation of amines probably proceeds via the hydroxylamine to the nitroso derivative, which then undergoes a rearrangement to give the oxime.[21f] It was anticipated that the enhanced acidity of the ester α-proton would facilitate

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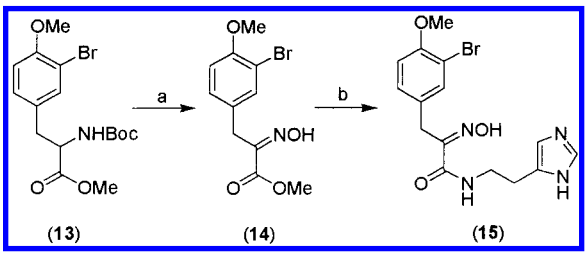
a rapid rearrangement and thus avoid some of the competing reaction pathways of the nitroso compounds. Gratifyingly, it was observed that tyrosine ethyl ester (**7**) was smoothly oxidized with 2 equiv of dimethyldioxirane to give the oxime (**8**) as a single isomer in excellent yield (91%).

It is conceivable that in the biosynthetic pathway bromination of the aromatic ring could take place on either a tyrosine derivative or a corresponding oxime. Bromination of tyrosine is well precedented;[22] however, the effect of the oxime on the stepwise electrophilic bromination of the aromatic ring was uncertain and posed questions about the relative reactivity of these functional groups. However, it was observed that bromination could be controlled by judicious choice of solvent, temperatures and reagent. Addition of 1 equiv of *N*-bromoacetamide to (**8**) in THF at −60 °C gave predominantly the monobromide (**9**), 2 equiv of NBS (in DMF or THF) at 0 °C gave the dibromide (**10**), and 3 equiv at (0 °C to room temperature) cleanly gave the spiroisoxazoline (**11**) (Scheme 2). Interestingly, treatment of oxime (**8**) with Di Furia's bromoperoxidase enzyme mimic (NH_4VO_3, H_2O_2, and KBr in water/chloroform) resulted in the formation of both the monobromo (**9**, 39%) and dibromo (**10**, 27%) oximes. However, none of the spiroisoxazoline (**11**) was observed showing this to be a mild and selective brominating system.

Verongamine (**15**), a histamine H_3 receptor antagonist, was first isolated from the marine sponge *Verongula gigantea*[4] and has been previously synthesized.[12] It appeared that verongamine (**15**) could be synthesized by selective O-methylation of the phenol functionality of monobromo oxime (**9**), followed by amidation with histamine. However, methylation of the oximes proved to be troublesome (Scheme 2). Reaction of the tyrosine oxime (**8**) with methyl iodide and cesium carbonate in refluxing acetone gave a mixture of the two mono methylated (**12a** and **12c**) and the dimethylated (**12b**) products. The oxime methyl ether (**12a**) and dimethyl ether (**12b**) were the major components, with only trace amounts of the desired phenyl methyl ether derivative (**12c**). Unpredictable results occurred using the mono- (**9**) or dibrominated (**10**) oximes, leading to variable mixtures of both mono- and dimethylated products. In each case the products were easily differentiated by IR spectroscopy with the phenol OH (**12a**) stretching frequency appearing at 3410 cm^{-1}, the oxime OH (**12c**) stretching frequency at 3290 cm^{-1}, and the dimethylated compound (**12b**) lacking a peak in the OH region.

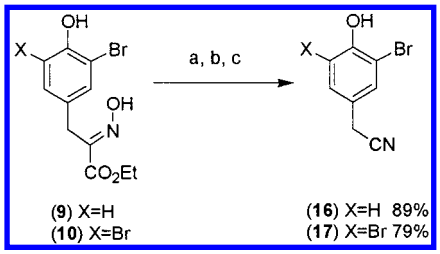
An alternate route to verongamine (**15**) was examined. The known Boc-protected *O*-methyl bromotyrosine methyl ester (**13**)[23] was deprotected by treatment with CF_3CO_2H in CH_2Cl_2, and the crude amine was oxidized with Na_2WO_4/H_2O_2 in ethanol (Scheme 3) to the oxime ester (**14**). Amidation of oxime ester (**14**) with histamine at 60 °C in MeOH for 72 h was successful in yielding verongamine (**15**). When the reaction was conducted in CD_3OD, partial deuterium exchange occurred at the C-2 position of the imidazole ring.[24] The identity of verongamine (**15**) was established through comparison of published ^1H and ^{13}C spectra with natural and synthetic verongamine (**15**).[4,12]

Scheme 3[a]



[a] Reagents and conditions: (a) TFA, CH_2Cl_2 then Na_2WO_4, 30% H_2O_2, EtOH/H_2O, 65% (over two steps); (b) histamine, MeOH, 60 °C, 72 h, 98%.

Scheme 4[a]



[a] Reagents and conditions: (a) KOH, THF; (b) HCl, isolate (>90%); (c) CF_3CO_2H, CH_2Cl_2.

Rinehart and Tymiak demonstrated[3] that the nitrile nitrogen in aeroplysinin-1 is derived from the tyrosine amine nitrogen. It was proposed that nitriles were formed by the decarboxylation of oximino acids. α-Oximino carboxylic acids have been reported to undergo decarboxylation in aqueous solution at elevated temperatures.[25] We believed that these reactions would be accelerated by acids in nonaqueous solution. Hydrolysis (KOH, 10% aq THF) of the ester oximes (**9**) and (**10**) gave the corresponding acids in >90% yield (Scheme 4). Trifluoroacetic acid catalyzed decarboxylation of the acids in CH_2Cl_2 at room temperature gave the naturally occurring nitriles (**16**) and (**17**) in 79% and 89% yield, respectively.[7]

Synthesis of purealidin N (**28**) and the spiroisoxazolines such aerothionin (**26a**) could not be achieved from tyrosine since they required a more elaborate oxime with additional hydroxyl on aromatic ring. As alternative to the Erlenmeyer condensation, the application of the a Wadsworth−Emmons olefination using methyl 2-(*tert*-butyldimethylsilyloxy)-2-(dimethylphosphono) acetate (**18**)[26a] was investigated. The phosphonate (**18**), which can be prepared in large quantities using a two-step procedure,[26a] has previously been used in the synthesis of enol lactams, carbohydrates, and 3-hydroxy pyruvates.[26] Wadsworth−Emmons reaction between phosphonate (**18**) and an aldehyde results in the formation of an silylenolether, which it appeared would yield a pyruvate on hydrolysis and thus an oxime upon further reaction with hydroxylamine.

Reaction of 2-hydroxy-4-methoxybenzaldehyde (**19a**) with MOMCl and $EtNiPr_2$ in CH_2Cl_2 gave the protected

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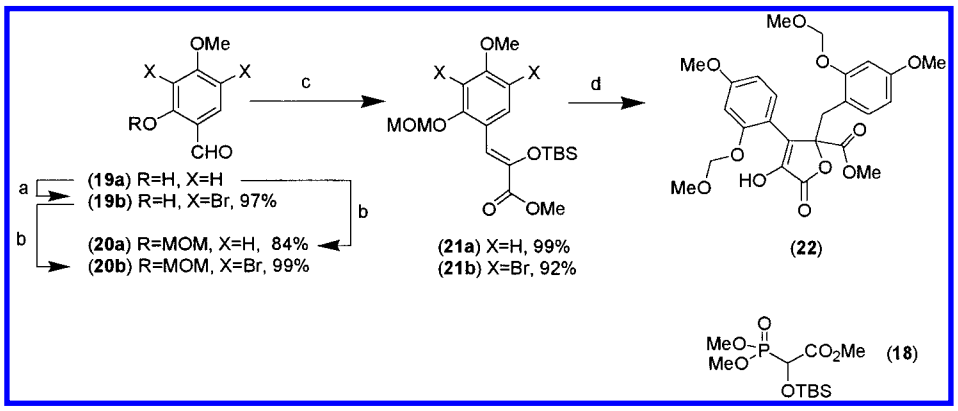
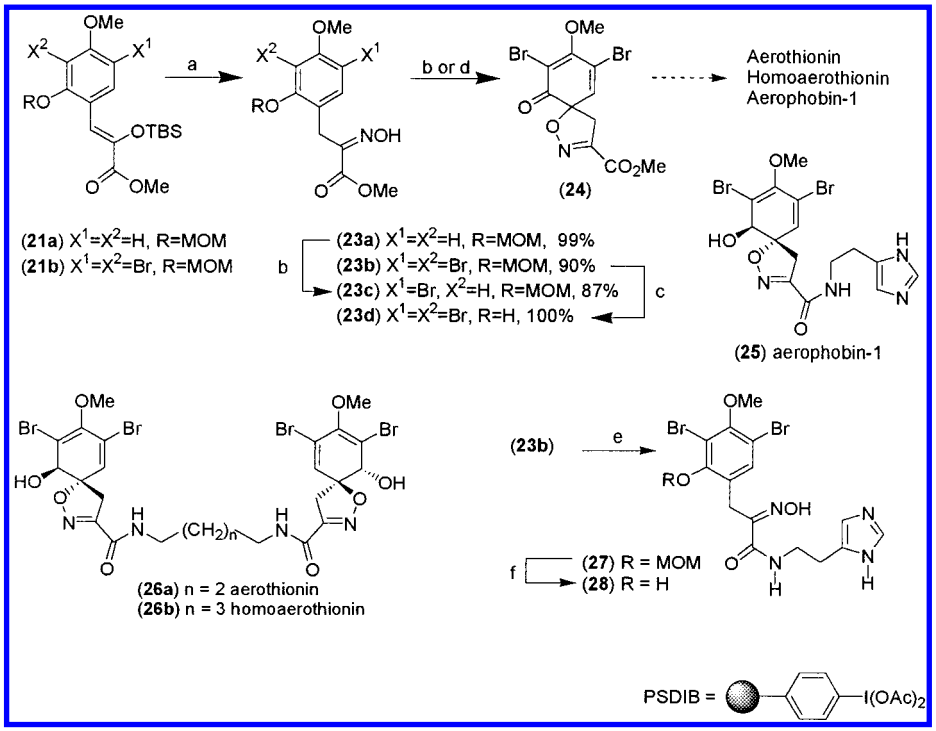
Scheme 5[a]



[a] Reagents and conditions: (a) NBS, DMF, 0 °C; (b) MOMCl, EtN*i*Pr$_2$, THF; (c) **18**, LDA, THF; (d) HF·Et$_3$N, MeOH, silica.

Scheme 6[a]



[a] Reagents and conditions: (a) HF·Et$_3$N, MeOH then NH$_2$OH·HCl; (b) NBS, DMF, 0 °C; (c) TsOH, MeOH, 100%; (d) PSDIB, MeCN, 99%; (e) histamine, 60 °C, MeOH, 96%; (f) TsOH, MeOH, 87%.

aldehyde (**20a**) in excellent yield (Scheme 5). Reaction of the protected aldehyde with methyl 2-(*tert*-butyldimethylsilyloxy)-2-(dimethylphosphono) acetate (**18**) gave the silylenolether (**21a**) in quantitative yield. Deprotection of the silylenolether (**21a**) with Et$_3$N·HF in MeOH proceeded smoothly. However, attempted workup and purification by SiO$_2$ chromatography gave the butenolide (**22**). It is probable that the butenolide is formed by a homo-aldol condensation of the pyruvate, followed by a lactonization.[27] The structure of the butenolide was ultimately proved by X-ray crystallography.[28]

Fortunately, deprotection of the silylenolether (**21a**) with Et$_3$N·HF in MeOH followed by immediate addition of NH$_2$OH·HCl and Et$_3$N yielded the required oxime (**23a**) in excellent yield (Scheme 6). However, attempted dibromination of (**23a**) with NBS in DMF only resulted in mono-bromination to give (**23c**) in 87% yield. Under more forcing conditions multiple compounds were formed. It was decided to introduce the bromine substituents at the earliest stage of the synthesis. Bromination of 2-hydroxy-4-methoxy-benzaldehyde (**19a**) with NBS in DMF produced the dibromoaldehyde (**19b**) in a 97% yield. Again reaction with MOMCl yielded the protected aldehyde (**20b**) in high yield. Reaction of the protected aldehyde (**20b**) with phosphonate (**18**), deprotection of the silylenolether (**21b**), and in situ oxime formation proceeded as before to yield the oxime (**23b**). The synthesis of the key oxime (**23b**) is efficient and scalable (performed on a 40-g scale) and proceeds with high overall yield (83% in four steps).

The MOM group was removed using a catalytic amount of TsOH in methanol to give the known phenolic oxime (**23d**) in high overall yield.[11] The oxime ester (**23d**) was cyclized with NBS in DMF to give the spiro isoxazoline

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(**24**), which displayed spectral characteristics that compared well with those reported previously.[11b] In our hands the isoxazoline (**24**) was sensitive to chromatography with any attempted purification resulting in degradation. Oxidative cyclization using the polymer-supported (diacetoxyiodo)benzene (PSDIB) reagent[29] in MeCN at room temperature gave the isoxazoline (**24**) in excellent yield and purity. The spirocyclization occurred rapidly, and workup involved only filtration, thus removing the need for chromatography. The synthesis of the known spiroisoxazoline (**24**) represents a formal synthesis of aerophobin-1 (**25**), aerothionin (**26a**), and homoaerothionin (**26b**) through routes developed by Nishiyama et al.[11] and Wasserman.[12]

Purealdin N (**28**) was first isolated from the marine sponge *Psammaplysilla purea*[6] and was reported to possess potent antitumor activity (murine lymphoma L1210 cells $IC_{50} = 0.07$ μg/mL and human epidermoid carcinoma KB cells $IC_{50} = 0.074$ μg/mL). Purealidin N (**28**) was synthesized in a manner analogous to that used for verongamine (**15**). The MOM-protected oxime (**23b**) was reacted with histamine in MeOH at 60 °C for 72 h to give the corresponding amide (**27**) in an excellent yield of 96%. Simple deprotection of the MOM group with TsOH in MeOH gave purealidin N (**28**). This represents the first total synthesis of purealidin N (**28**), and was achieved in a 67% overall yield in six steps from the commercially available 2-hydroxy-4-methoxybenzaldehyde (**19a**). The structure of (**28**) was confirmed by ^{1}H and ^{13}C NMR spectroscopy (in d_6-DMSO and d_4-MeOH) and HR-FAB-MS. The ^{1}H NMR shifts of the imidazole protons for **28** (δ 7.40 and 8.89 ppm) in DMSO with added TFA are in agreement with those reported for natural purealidin N (**28**).[6] Therefore, natural purealidin N (**28**), chromatographed with a $H_2O/CH_3CN/CF_3CO_2H$ eluent, is most likely the TFA salt.

Synthetic purealidin N (**28**) and related oximes (**23a**, **23c**, and **23d**) were tested against three sensitive cancer cell lines, lung NCI-H460, breast MCF7, and CNS SF-268.[30] At concentrations of 10^{-4} M, all of the compounds were essentially inactive, showing inhibition of cell growth of between 30% and 93% of the control. This is in contrast to the high activity previously reported for purealidin N isolated from natural sources.[6]

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of dry argon in oven-dried glassware unless otherwise noted. Reaction temperatures were recorded at bath temperatures. Elemental analyses were determined by Atlantic Microlab, Inc., Norcross, Georgia. Column chromatography was performed on E. Merck silica gel 60, 230−400 mesh ASTM. Analytical thin-layer chromatography (TLC) was performed on precoated glass plates (Merck Kieselgel 60 F_{254} 0.25 mm), and visualization was effected by UV irradiation and vanillin/H_2SO_4 dip followed by charring. Infrared spectra were recorded on a Perkin-Elmer 1600 series Fourier Transform spectrophotometer, and only the principal bands are listed; nuclear magnetic resonance (NMR) spectra were obtained on a Varian XL-300 or Bruker ARX-500. Melting points were determined on a Electrothermal melting point apparatus and are uncorrected. High-resolution mass spectometry was performed upon JEOL Mstation (JMS-700) mass spectrometer. The polymer-supported (diacetoxyiodo)benzene (PSDIB) was prepared in accordance with Togo et al.[29a]

Ethyl 3-(4-Hydroxyphenyl)-2(*E*)-(hydroxyimino)propanoate (8). Method A. Tyrosine ethyl ester (**7**) (0.250 g, 1.19 mmol) was dissolved in a solution of DMD (35 mL, 0.69 M, 23.8 mmol) in acetone, and the resulting mixture was stirred until the reaction was complete as indicated by TLC (SiO_2, 100% Et_2O). The solution was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The resulting solid was recrystallized from toluene to give the title compound (**8**) (0.24 g, 91%).

Method B. To a solution of tyrosine ethyl ester (**7**) (4.64 g, 22 mmol) in absolute EtOH (50 mL) at 0 °C were added Na_2WO_4 (7.32 g, 22 mmol), H_2O_2 (30%, 22 mL), and H_2O (38 mL). The resulting mixture was stirred until the reaction was complete as indicated by TLC (SiO_2, hexanes/Et_2O/CH_2Cl_2, 5:5:1). The solution was extracted with EtOAc (3 × 50 mL) and washed with aqueous $NaHSO_3$ (2 × 50 mL) and H_2O (2 × 50 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo to yield a pale yellow solid (**8**) (3.61 g, 74%)

Method C. A solution of $MeReO_3$ (0.02 g, 0.08 mmol) in H_2O_2 (1 mL, 30% H_2O_2) and absolute EtOH (1 mL) was added to a stirred solution of tyrosine ethyl ester (**7**) (0.211 g, 1 mmol) in EtOH (5 mL) until everything dissolved. The resulting solution was stirred for an additional 15 min, and then the reaction was diluted with Et_2O (50 mL) and washed with H_2O (50 mL) and saturated $Na_2S_2O_3$ (50 mL). The organic layer was tested for peroxides (KI paper), dried over Na_2SO_4, and filtered, and then the solvent was removed in vacuo to yield (**8**) (0.195 g, 87%) as a light yellow solid: mp 140.5−141.5 °C (toluene); IR (KBr) 3466, 3293, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.10 (d, $J = 8.7$ Hz, 1H), 6.72 (d, $J = 8.5$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 2H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) 164.5, 156.6, 151.9, 130.8, 128.0, 115.9, 61.7, 30.18, 14.5. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.83; N, 6.28. Found: C, 59.16; H, 5.88; N, 6.25.

Ethyl 3-(3-Bromo-4-hydroxyphenyl)-2(*E*)-(hydroxyimino)propanoate (9). NBA (0.165 g, 11.9 mmol) in THF (5 mL) was added dropwise to a solution of oxime (**8**) (0.250 g, 11.9 mmol) in THF (2 mL) over 5 min at −78 °C. The resulting mixture was stirred until the reaction was complete as indicated by TLC (SiO_2, hexanes/Et_2O/CH_2Cl_2, 5:5:1). The reaction mixture was diluted with Et_2O (50 mL), washed with H_2O (2 × 50 mL) and saturated $Na_2S_2O_3$ (50 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated in vacuo to yield a yellow solid residue (0.317 g). The residue was separated by chromatography (SiO_2, hexanes/EtOAc, 7:3) and then recrystallized from toluene to produce a colorless crystalline solid (**9**) (0.197 g, 57%): mp 135.5−136.5 °C; IR (KBr) 3435, 3280, 1723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, $J = 2.0$ Hz, 1H), 7.19 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 4.31 (q, $J = 7.0$ Hz, 2H), 3.89 (s, 2H), 1.35 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 150.9, 132.5, 130.1, 129.1, 115.9, 110.0, 62.1, 29.4, 14.2. Anal.Calcd for $C_{11}H_{12}BrNO_4$: C, 43.73; H, 4.00. Found: C, 43.81; H, 4.04.

Ethyl 3-(3,5-Dibromo-4-hydroxyphenyl)-2(*E*)-(hydroxyimino)propanoate (10). NBS (0.16 g, 0.92 mmol) was added portionwise to the oxime (**8**) (0.104 g, 0.46 mmol) in THF (4 mL) at 0 °C until the reaction was complete as indicated by TLC (SiO_2, hexanes/Et_2O/CH_2Cl_2, 5:5:1). The reaction mixture was diluted with Et_2O (50 mL) and washed with H_2O (50 mL) and saturated $Na_2S_2O_3$ (2 × 50 mL). The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The resulting red solid was purified by chromatography (SiO_2, hexanes/Et_2O 9:1) to yield a colorless solid (**10**) (0.123 g, 70%): mp 194.0−194.7 °C; IR (KBr) 3405, 3246, 1726 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 11.61 (s, 1H), 8.44 (s, 1H), 7.46 (s, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.85 (s, 2H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 162.2, 150.7, 149.9, 133.5, 131.9, 111.1, 61.8, 30.6, 14.4. Anal. Calcd for $C_{10}H_9Br_2NO_4$: C, 34.68; H, 2.91. Found: C, 34.94; H, 2.95.

Bromination of Tyrosine Oxime (8) with Di Furia's Bromoperoxidase Enzyme Mimic. A solution of NH_4VO_3 (0.072 g, 0.61 mmol) and KBr (0.362 g, 3.0 mmol) in H_2O (3

(29) (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.

(30) These compounds were screened through the National Cancer Institute developmental therapeutics program (www.dtp.nci.nih.gov).

mL) was then added to a solution of (**8**) (0.138 g, 0.61 mmol) in $CHCl_3$ (5 mL). Next, 30% aqueous H_2O_2 (0.122 mL, 1.22 mmol) was added, and the resulting biphasic mixture was stirred until the reaction was complete as indicated by TLC (SiO_2, hexanes/Et_2O/CH_2Cl_2, 5:5:1). The reaction was diluted with $CHCl_3$ (25 mL), washed with H_2O (2 × 25 mL) and Na_2S_2O4 (2 × 25 mL), dried over Na_2SO_4, and filtered; the solvent removed in vacuo to give a yellow solid (0.180 g). Chromatography (SiO_2, hexanes/Et_2O/CH_2Cl_2, 8:2:1) yielded the monobromotyrosine oxime (**9**) (0.064 g, 28%) and the dibromotyrosine oxime (**10**) (0.073 g, 40%).

Ethyl 7,9-Dibromo-8-oxo-1-azaspiro[4,5]-deca-2,6,9-triene-3-carboxylate (11). NBS (2.68 g, 15 mmol) in DMF (30 mL) was added dropwise to oxime (**8**) (1.05 g, 4.7 mmol) in DMF (10 mL) at 0 °C over a 15 min period. The reaction mixture was diluted with Et_2O (50 mL), washed with H_2O (3 × 50 mL) and saturated $Na_2S_2O_3$ (2 × 50 mL), dried over Na_2SO_4, and filtered; the solvent was removed in vacuo to yield a purple solid (3.03 g). Chromatography (SiO_2, hexanes/Et_2O/CH_2Cl_2, 8:2:1) gave a white crystalline solid (**11**) (1.38 g, 78%): mp 170.0−170.1 °C; IR (KBr) 1735, 1680, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.52 (s, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz,-$CDCl_3$) δ 171.1, 158.9, 151.3, 144.1, 123.6, 86.1, 62.8, 43.0, 14.1. Anal. Calcd for $C_{11}H_9Br_2NO_4$: C, 34.83; H, 2.37; N, 3.69. Found: C, 34.85; H, 2.43; N, 3.65.

Methylation of Tyrosine Oxime (8). CH_3I (0.7 mL, 11.3 mmol) was added to a stirred solution of oxime (**7**) (2.10 g, 9.41 mmol) and Cs_2CO_3 (3.06 g, 9.41 mmol) in anhydrous acetone (70 mL). The mixture was heated at reflux until all the starting material had been consumed as indicated by TLC (SiO_2, 100% Et_2O) at which point the solvent was removed in vacuo to give a brown gum. The gum was dissolved in EtOAc (100 mL), washed successively with H_2O (100 mL), HCl (1M, 2 × 100 mL), and H_2O (100 mL), dried over Na_2SO_4, and filtered; solvent was removed in vacuo to give a brown gum (1.4 g). The mixture was separated by chromatography (SiO_2, hexanes/EtOAc, 3:1) to yield **12a** (0.56 g, 20%) as a colorless crystalline solid: mp 106.5−107.5 °C ($CHCl_3$); IR ($CHCl_3$ slurry) 3410, 2981, 1716, 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 8.3 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.11 (s, 3H), 3.88 (s, 2H), 1.29 (t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 154.7, 151.1, 130.2, 127.4, 115.5, 63.4, 62.3, 30.5, 14.; HRMS (EI) calcd for $C_{12}H_{15}NO_4$ 237.1001, found (M^+) 237.0998. Also obtained was **12b** (0.41 g, 14%) as an orange oil: IR (neat) 2939, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 3.28 (q, J = 7.1 Hz, 2H), 4.12 (s, 3H), 3.90 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 158.2, 151.0, 130.0, 127.9, 114.1, 113.9, 63.3, 61.9, 55.3, 30.5, 14.3; HRMS (EI) calcd for $C_{13}H_{17}NO_4$ 251.1158, found (M^+) 251.1153.

Methyl 3-(5-Bromo-4methoxyphenyl)-2(*E*)-(hydroxyimino)propanoate (14). TFA (0.048 mL, 0.62 mmol) was added dropwise to the Boc-protected tyrosine derivative (**13**)[23] (0.2 g, 0.52 mmol) in CH_2Cl_2 (3 mL). After the addition was complete, the mixture was stirred for 3 h. The solvent was removed in vacuo, and the residue was dissolved in EtOAc (50 mL). The EtOAc solution was washed with saturated $NaHCO_3$ (2 × 50 mL) and saturated NaCl (50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to give an orange gum (0.150 g). The crude amine was dissolved in absolute EtOH (5 mL). Na_2WO_4 (0.172 g, 0.52 mmol) and then 30% aqueous H_2O_2 (5.2 mL, 52 mmol) were added, and the mixture was stirred until reaction was complete as indicated by TLC (SiO_2, hexanes/Et_2O/CH_2Cl_2, 5:5:1). The reaction mixture was extracted with EtOAc (2 × 25 mL), and the combined EtOAc extracts were washed with $NaHSO_3$ (25 mL) and H_2O (25 mL), dried over Na_2SO_4 and filtered. The solvent was removed in vacuo to yield a pale yellow solid (0.201 g). Chromatography (SiO_2, hexanes/Et_2O/CH_2Cl_2, 10:5:1) gave the title oxime (**14**) (0.102 g, 65%) as a colorless solid: mp 103.5−104.5 °C ($CHCl_3$); IR ($CHCl_3$) 3287, 2952, 2848, 1721, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (br. s, 1H), 7.55 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 8.4, 2.2 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 3.94 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 154.8, 150.9, 134.1, 129.4, 129.2, 112.1, 111.7, 56.5, 53.1, 29.6, 14.3; HRMS (EI) calcd for $C_{11}H_{12}BrNO_4$ 300.9950, found (M^+) 300.9947.

Verongamine (15).[4,12] A solution of oxime (**14**) (0.045 g, 0.15 mmol) and histamine (0.049 g, 0.45 mmol) in MeOH (1 mL) was heated for 72 h at 60 °C. The solvent was removed, and the yellow gum obtained was purified by chromatography (SiO_2, CH_2Cl_2/MeOH, 5:1) to give a colorless solid (0.055 g, 97%): mp 121.5−123.0 °C ($CHCl_3$); IR (KBr) 3408, 2927 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.62 (s, 1H), 7.48 (d, J = 1.2 Hz, 1H), 7.25 (dd, J = 8.4, 1.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.85 (s,1H), 3.86 (s, 5H), 3.54 (t, J = 7.1 Hz, 2H), 2.84 (t, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.8, 156.1, 153.2, 136.2, 134.9, 132.0, 130.6, 118.1, 113.1, 112.3, 56.8, 40.4, 28.8, 27.8; HRMS (FAB, *m*-nitro benzyl alcohol) calcd for $C_{15}H_{18}BrN_4O_3$ $(M + H)^+$ 381.0562, found 381.0563.

2-Bromo-4-cyanomethylphenol (16).[7] KOH (0.05 g, 1.46 mmol) was added to a solution of oxime (**9**) (0.147 g, 0.48 mmol) in THF/H_2O (2 mL, 1:1) at room temperature, and the mixture was stirred overnight. The solution was acidified with 1 M HCl (15 mL) and extracted with EtOAc (30 mL). The organic extract was successively washed with H_2O (1 × 25 mL) and HCl (1 M, 25 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to yield a white solid (0.131 g, 99%).

The crude solid (0.081 g, 0.295 mmol) was dissolved in CH_2Cl_2 (5 mL), TFA (3 mL) was added, and the resulting solution was stirred overnight. The reaction mixture was diluted with H_2O (20 mL), neutralized with saturated $NaHCO_3$ (20 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo to yield a yellow solid (0.058 g). Chromatography (SiO_2, hexanes/Et_2O, 8:2) yielded a pale yellow solid (**16**) (0.056 g, 89%): mp 118−119 °C (lit.[7] 117−118 °C); ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 7.54 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 8.4, 2.2 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 3.88 (s, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 154.5, 133.2, 129.1, 124.4, 119.0, 117.5, 110.4, 22.1.

2,6-Dibromo-4-cyanomethylphenol (17). KOH (0.372 g, 9.3 mmol) was added to a solution of oxime (**10**) (0.515 g, 2.30 mmol) in THF/H_2O (4 mL, 1:1) at room temperature, and the resulting mixture was stirred overnight. The solution was acidified with 1 M HCl (15 mL) and extracted with EtOAc (100 mL). The organic extract was successively washed with H_2O (1 × 75 mL) and HCl (1M, 75 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to yield a white solid (0.439 g, 99%).

The crude acid (0.207 g, 0.54 mmol) was dissolved in CH_2Cl_2 (2 mL), and TFA (1 mL) was added dropwise. The resulting solution was stirred until the reaction was complete as indicated by TLC (SiO_2, Et_2O). The reaction was diluted with H_2O (20 mL), neutralized with saturated $NaHCO_3$ (20 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo to yield a yellow solid. Chromatography (SiO_2, hexanes/Et_2O, 7:3) yielded a pale yellow solid (**17**) (0.161 g, 79%): mp 176.5−176.5 °C; IR (KBr) 3368, 2262 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 7.60 (s, 2H), 3.94 (s, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 151.1, 132.8, 126.5, 118.6, 111.6, 21.0. Anal. Calcd for $C_8H_5Br_2NO$: C, 33.03; H, 1.73. Found: C, 32.85; H, 1.75.

3,5-Dibromo-2-hydroxy-4-methoxybenzaldehyde (19b). A solution of NBS (6.20 g, 34.8 mmol) in DMF (5 mL) was added to a solution of 2-hydroxy-4-methoxybenzaldehyde (**19a**) (2.41 g, 15.8 mmol) in DMF (5 mL) over 15 min at 0 °C. When the addition was complete, the reaction mixture was diluted with Et_2O (200 mL), washed with H_2O (3 × 50 mL) and $Na_2S_2O_3$ (3 × 50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to yield a pale yellow solid (4.88 g). Recrystallization from hexanes/Et_2O yielded a white fibrous solid (4.76 g, 97%): mp 100−100.5 °C; IR (KBr) 3052, 2988, 2943, 1654, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.78 (s, 1H), 9.79 (s, 1H), 7.78 (s, 1H), 4.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 161.0, 159.4, 136.2, 118.6, 107.9,

107.8, 61.0. Anal. Calcd for $C_8H_6Br_2O_3$: C, 31.18; H, 1.96. Found: C, 31.27; H, 2.01.

2-(*O*-Methoxymethylenoxy)-4-methoxybenzaldehyde (20a). To a solution of 2-hydroxy-4-methoxybenzaldehyde (**19a**) (1.05 g, 6.9 mmol) and Et*N*iPr_2 (1.16 g, 8.9 mmol) in THF (5 mL) at 0 °C was added MOMCl (0.712 g, 8.9 mmol) over a 5 min period. The solution was stirred overnight, then diluted with Et_2O (75 mL), washed with H_2O (2 × 50 mL) and HCl (1 M, 2 × 50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to yield a pale yellow liquid. Chromatography (SiO_2, hexanes/Et_2O, 8:2) yielded the pure aldehyde (**20a**) as a colorless solid (84%): mp 62−62.5 °C; IR (KBr) 2940, 2846, 2759, 1684 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.82 (d, 1H, J = 9.0 Hz), 6.72 (d, 1H, J = 2.3 Hz), 6.62 (dd, 1H, J = 9.0, 2.3 Hz), 5.30 (s, 2H), 3.87 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.8, 165.6, 161.2, 129.9, 119.2, 107.5, 100.4, 94.4, 56.3, 55.5. Anal. Calcd for $C_{10}H_{12}O_3$: C, 61.20; H, 6.17. Found: C, 60.95; H, 6.16.

3,5-Dibromo-2-(*O*-methoxymethylenoxy)-4-methoxybenzaldehyde (20b). To a solution of dibromo aldehyde (**19b**) (2.06 g, 6.6 mmol) and Et*N*iPr_2 (1.28 g, 9.9 mmol) in THF (5 mL) at 0 °C was added MOMCl (0.80 g, 9.9 mmol) over a 5 min period. The solution was stirred overnight, then diluted with Et_2O (75 mL), washed with H_2O (2 × 50 mL) and HCl (1M, 2 × 50 mL), dried over Na_2SO_4, and the solvent was removed in vacuo to yield a pale yellow solid (**20b**) (2.3 g, 99%): mp 79.9−80.1 °C; IR (KBr) 3000, 2949, 2889, 1734, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.06 (s, 1H), 5.21 (s, 2H), 3.98 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 159.8, 157.9, 131.3, 128.3, 115.0, 114.4, 101.0, 60.8, 58.3. Anal. Calcd for $C_{10}H_{10}Br_2O_4$: C, 34.10; H, 2.86. Found: C, 33.99; H, 2.80.

Methyl 2-{(1,1dimethylethyl)dimethylsilyloxy}-3-{4-methoxy-2-(*O*-methoxymethylenoxy)phenyl}prop-2-enoate (21a). To a solution of diisopropylamine (3.79 g, 37.5 mmol) in THF (25 mL) at −78 °C was added *n*-BuLi (15 mL, 2.5 M, 37.5 mmol), and the resulting mixture was stirred for 1 h, allowed to warm to room temperature, and then recooled to −78 °C. Methyl 2-(*tert*-butyldimethylsilyloxy)-2-(dimethylphosphono) acetate (**18**)[26] (5.00 g, 25 mmol) in THF (10 mL) was added over 10 min. The reaction mixture was stirred for an additional 30 min and then a solution of the aldehyde (**20a**) (8.6 g, 27.5 mmol) in THF (25 mL) was added. The mixture was stirred until the reaction was complete as indicated by TLC (SiO_2, hexanes/Et_2O/CH_2Cl_2, 5:5:1). The solution was allowed to warm to room temperature, quenched with saturated NH_4Cl (20 mL), and diluted with EtOAc (200 mL). The EtOAc solution was washed with saturated NH_4Cl (3 × 100 mL) and H_2O (3 × 100 mL), dried over Na_2SO_4, and filtered, and the solvent evaporated in vacuo to yield a red oil (10.19 g). Chromatography (SiO_2, hexanes/Et_2O, 9:1) yielded a pale yellow oil (**21a**) (7.71 g, 99%): IR ($CDCl_3$) 2952, 2857, 1732, 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 6.45 (s, 1H), 5.16 (s, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 3.47 (s, 3H), 1.01 (s, 9H), 0.24 (s, 6H);^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 160.1, 155.3, 140.8, 130.6, 116.9, 106.0, 101.1, 94.6, 56.0, 55.3, 51.4, 25.7, 18.3. Anal. Calcd for $C_{19}H_{30}O_6Si$: C, 59.66; H, 7.91. Found: C, 59.64; H, 7.93.

Methyl 2-{(1,1dimethylethyl)dimethylsilyloxy}-3-{3,5-dibromo-4-methoxy-2-(*O*-methoxymethylenoxy)phenyl}-prop-2-enoate (21b). To a solution of diisopropylamine (0.497 g, 4.9 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (2.5 M, mL, 4.9 mmol), and the resulting solution was stirred for 1 h. A solution of methyl 2-(*tert*-butyldimethylsilyloxy)-2-(dimethylphosphono) acetate (**18**)[26] (1.53 g, 4.9 mmol) in THF (10 mL) was added via syringe over 10 min, and then the reaction mixture was stirred for a further 30 min. A solution of the dibromobenzaldehyde (**20b**) (1.45 g, 4.09 mmol) in THF (10 mL) was added over 10 min, and the mixture was stirred until the reaction was complete as indicated by TLC (SiO_2, hexanes/Et_2O/CH_2Cl_2, 5:5:1). The reaction mixture was quenched with saturated NH_4Cl (20 mL), diluted with EtOAc (75 mL), washed with H_2O (3 × 50 mL) and saturated NH_4Cl (3 × 50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to yield a red oil (2.57 g). Purification by chromatography (SiO_2, hexanes/Et_2O, 9:1) yielded a clear oil (**21b**) (1.95 g, 92%): IR (neat) 2930, 1732, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.19 (s, 1H), 4.91 (s, 2H), 3.75 (s, 3H), 3.53 (s, 3H), 3.47 (s, 3H), 0.84 (s, 9H), 0.09 (s, 6H); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 164.5, 153.9, 152.4, 143.4, 132.6, 127.6, 114.2, 114.0, 112.1, 99.6, 60.5, 58.1, 51.8, 25.5, 18.2. Anal. Calcd for $C_{19}H_{28}Br_2O_6Si$: C, 42.38; H, 5.25. Found: C, 42.29; H, 5.22.

Methyl 4-Hydroxy-3-{4-methoxy-2-(methoxymethylenoxy)-phenyl}-2-[{4-methoxy-2-(methoxymethylenoxy)phenyl}-methyl]-5-oxo-2,5-dihydrofuran-2-carboxylate (22).[28] To solution of silylenolether (**21a**) (0.62 g,1.6 mmol) in MeOH (10 mL) was added Et_3N·HF (1 mL). When the reaction was complete as indicated by TLC (hexanes/Et_2O/CH_2Cl_2, 5:5:1), the solvent was removed in vacuo. The resulting white solid was dissolved in CH_2Cl_2 (75 mL), washed with H_2O (2 × 50 mL) and $NaHCO_3$ (saturated, 50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The residue was purified by chromatography (SiO_2, hexanes/Et_2O, 1:1) to yield a colorless solid which crystallized directly from the eluent (0.41 g, 95%): mp 152.5−154.0 °C; IR (KBr) 3314, 2943, 1728, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 2.5 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 8.9, 2.6 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.38 (s, 1H), 6.36 (dd, J = 8.9, 2.5 Hz, 1H), 5.16 (d, J = 6.9 Hz, 1H), 5.08 (d, J = 6.9 Hz, 1H), 4.83 (d, J = 6.9 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.71 (d, J = 14.8 Hz, 1H), 3.53 (s, 3H), 3.50 (d, J = 14.7 Hz, 1H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.3, 161.5, 159.7, 156.8, 155.1, 138.2, 132.0, 130.9, 126.7, 114.5, 112.6, 107.7, 105.9, 101.8, 101.0, 94.9, 94.4, 87.5, 56.7, 55.8, 55.6, 55.3, 53.0, 31.0.

Methyl 2(*E*)-(Hydroxyimino)-3-(4-methoxy-2-*O*-methoxymethylenoxyphenyl)propanoate (23a). To a solution of the silylenolether (**21a**) (5.64 g,14.7 mmol) in MeOH (20 mL) was added Et_3N·HF (2 mL). When the starting material had been consumed as indicated by TLC (SiO_2, hexanes/Et_2O/CH_2Cl_2, 5:5:1), NH_2OH·HCl (1.22 g, 17.6 mmol) was added and stirring was continued. When complete reaction was observed TLC (SiO_2, Et_2O), the solvent was removed in vacuo. The resulting solid was dissolved in CH_2Cl_2 (75 mL), washed with H_2O (2 × 50 mL) and $NaHCO_3$ (saturated, 50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to give a yellow solid (4.16 g, 99%): mp 68.5−69.5 °C; IR (KBr) 3314, 2949, 2837, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 8.3 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.47 (dd, J = 2.4, 8.3 Hz, 1H), 5.16 (s, 2H), 3.93 (s, 2H), 3.81 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 159.2, 155.4, 151.1, 130.0, 116.8, 105.1, 101.0, 94.2, 55.9, 55.2, 52.5, 25.1. Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.10; H, 6.05. Found: C, 55.05; H, 6.04.

Methyl 3-{3,5-Dibromo-4-methoxy-2-(*O*-methoxymethylenoxy)phenyl}2(*E*)-(hydroxyimino)propanoate (23b). To a solution of silylenolether (**21b**) (1.94 g, 3.66 mmol) in MeOH (5 mL) was added Et_3N·HF (1 mL). When the starting material had been consumed as indicated by TLC (SiO_2, hexanes/Et_2O/ CH_2Cl_2, 5:5:1), NH_2OH·HCl (0.305 g, 4.39 mmol) was added and stirring was continued. When the reaction was complete as indicated by TLC (SiO_2, Et_2O), the solvent was removed in vacuo. The resulting white solid was dissolved in EtOAc (75 mL), washed with H_2O (2 × 50 mL) and saturated $NaHCO_3$ (50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to give a colorless solid (1.46 g, 90%): mp 138−139 °C (MeOH); IR ($CDCl_3$) 3350, 2954, 1732, 1684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.52 (br. s, 1H), 7.21 (s, 1H), 5.15 (s, 2H), 4.06 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 153.9, 153.4, 150.5, 131.6, 128.3, 114.6, 113.1, 99.9, 60.6, 58.1, 53.0, 25.3; HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{13}H_{16}BrNO_6$ (M + H)$^+$ 441.9344, found 441.9315. Anal. Calcd for $C_{13}H_{15}Br_2NO_5$: C, 35.54; H, 3.44. Found: C, 35.36; H, 3.36.

Methyl 3-{5-Bromo-4-methoxy-2-(*O*-methoxymethylenoxy)phenyl}-2(*E*)-(hydroxyimino)propanoate (23c). To a solution of (**23a**) (0.254 g, 0.67 mmol) in DMF (2 mL) was

added a solution of NBS (0.239 g, 1.3 mmol) in DMF (4 mL) dropwise. The mixture was stirred until the reaction was complete as indicated by TLC (SiO_2, Et_2O). It was then diluted with Et_2O (50 mL), washed with H_2O (50 mL) and saturated $Na_2S_2O_3$ (50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to yield a deep purple oil (0.408 g). Purification by chromatography (SiO_2, hexane/Ether, 8:3) yielded a colorless solid (**23c**) (0.257 g, 87%): mp 108.8−109 °C; IR (KBr) 3285, 2955, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.74 (s, 1H), 5.19 (s, 2H), 3.91 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 163.7, 155.1, 154.9, 150.7, 133.4, 118.2, 102.9, 99.5, 94.6, 56.3, 56.1, 52.7, 24.8. Anal. Calcd for $C_{13}H_{15}Br_2NO_6$: C, 43.11; H, 4.47. Found: C, 43.17; H, 4.43.

Methyl 3-(3,5-Dibromo-2-hydroxy-4-methoxyphenyl)-2(*E*)-(hydroxyimino)propanoate (23d).[10,11] To a solution of MOM ether (**23b**) (1.03 g, 2.3 mmol) in MeOH (5 mL) was added TsOH (4 crystals), and the resulting solution was stirred overnight. The MeOH was removed in vacuo, and the resulting solid was redissolved in EtOAc (50 mL), washed with H_2O (25 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo to yield a colorless solid (0.920 g, 99%): mp 146−147 °C (lit.[11b] 148−149 °C); IR (KBr) 3510, 3302, 3063, 2954, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 153.6, 151.4, 149.8, 133.3, 119.3, 107.6, 60.6, 53.5, 25.6. Anal. Calcd for $C_{11}H_{11}Br_2NO_5$: C, 33.43; H, 2.81. Found: C, 33.59; H, 2.77.

Methyl 7,9-Dibromo-8-methoxy-6-oxo-1-oxa-2-azaspiro-[4,5]deca-2,7,9-triene-3-carboxylate (24).[10,11] Method A. To a room-temperature solution of phenolic oxime (**23d**) (0.104 g, 0.26 mmol) in DMF (1 mL) was added NBS (0.056 g, 0.31 mmol). When the reaction was complete as indicated TLC (SiO_2, Et_2O), the mixture was diluted with Et_2O (2 × 50 mL), washed with H_2O (2 × 50 mL) and saturated $NaHSO_3$ (2 × 50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to give the crude spiroisoxazoline (**24**) (0.096 g, 93%). The spectral properties were identical to those reported by Nishiyama.[11b]

Method B. PSDIB (0.5 g, 3.5 mmol g^{-1}, 1.75 mmol) was stirred in MeCN (10 mL) and allowed to swell. A solution of the phenolic oxime (**23d**) (0.2 g, 0.51 mmol) in MeCN (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 MeCN (3 × 25 mL). The solvent was removed in vacuo to give a colorless solid (**24**) (0.198 g, 99%). The spectral properties were identical to those reported by Nishiyama.[11b] ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.18 (s, 3H), 3.91 (s, 3H), 3.64 (d, J = 17.8 Hz, 1H), 3.34 (d, J = 17.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 163.3, 159.7, 150.0, 136.0, 121.0, 106.7, 87.0, 62.4, 53.4, 60.1, 44.6.

Purealidin N (28).[6] A solution of the oxime (**25b**) (0.1 g, 0.23 mmol) and histamine (0.1 g, 0.90 mmol) in MeOH (1 mL) were heated for 72 h at 60 °C. The solvent was removed, and the yellow gum obtained was purified by chromatography (SiO_2, solvent gradient 100% CH_2Cl_2 to 100% MeOH) to give MOM-protected purealidin (**27**) as a colorless solid (0.113 g, 96%): mp 154.5−155.5 °C (MeOH), IR (KBr) 3395, 3219, 2938, 1652; ^1H NMR (500 MHz, CD_3OD) δ 7.60 (s, 1H), 7.18 (s, 1H), 6.85 (s, 1H), 5.13 (s, 2H), 3.97 (s, 2H), 3.81 (s, 3H), 3.63 (s, 2H), 3.51 (t, J = 7.1 Hz, 2H), 2.82 (t, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 165.7, 155.0, 154.9, 152.5, 136.2, 136.0, 132.9, 131.1, 118.0, 115.5, 113.8, 101.2, 61.2, 58.6, 40.5, 27.8, 25.2; HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{17}H_{21}Br_2N_4O_5$ $(M + H)^+$ 520.9878, found 520.9844. A solution of the MOM-protected purealidin N (**27**) (0.1 g, 0.19 mmol) and TsOH (0.005 g, 0.03 mmol) in MeOH (2 mL) was stirred overnight at room temperature. The methanol was removed in vacuo, and the residue was purified by chromatography (SiO_2, solvent gradient 100% CH_2Cl_2 to 100% MeOH) to give purealidin N (**28**) (0.078 g, 87%) as a colorless hygroscopic powder: mp 127.5−129 °C (MeOH), IR (KBr) 3396, 3226, 2930, 2869, 1650; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 8.54 (t, J = 5.7 Hz, 1H), 7.58 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 3.73 (s, 3H), 3.70 (s, 2H), 3.39 (dt, J = 5.7, 7.1 Hz, 2H), 2.50 (t, J = 7.1 Hz, 2H);^1H NMR (500 MHz, CD_3OD) δ 7.60 (s, 1H), 7.42 (s, 1H), 6.85 (s, 1H), 3.80 (s, 3H), 3.78 (s, 2H), 3.51 (t, J = 7.1 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz $(CD_3)_2SO$) δ 164.6, 153.4, 152.8, 150.6, 132.6, 122.1, 107.7, 105.1, 60.1, 39.4 (masked by DMSO, visible in DEPT135), 26.5, 25.1;^{13}C NMR (125 MHz, 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, TFA) calcd for $C_{15}H_{16}Br_2N_4O_2$ $(M + H)^+$ 476.9596, found 476.9600.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for verongamine (**15**), purealidin N (**28**), and spiroisoxazoline (**24**); a comparison of ^1H and ^{13}C NMR data for natural and synthetic verongamine and purealidin N; a HPLC chromatogram for compound **24**; and National Cancer Institute biological screening data for compounds **23a**, **23c**, **23d**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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