Synthesis of Marine Sponge Alkaloids Oroidin, Clathrodin, and Dispacamides. Preparation and Transformation of 2-Amino-4,5-dialkoxy-4,5-dihydroimidazolines from 2-Aminoimidazoles

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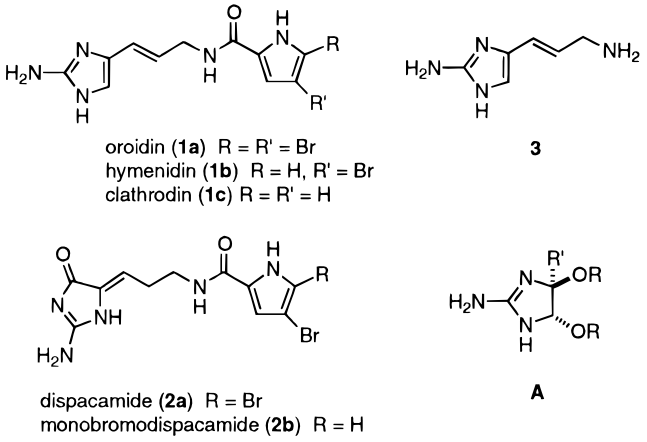
The preparation and transformation of 2-amino-4,5-dialkoxy-4,5-dihydroimidazolines **A** from 2-aminoimidazoles (AIs) is described. The oxidation of 2-aminoimidazole **8** with NCS in methanol affords cyclic guanidine adduct **9** which, upon heating, affords vinylogous AI derivative **3** and 2-aminoimidazolinone (glycocyamidine) **13**. Olefin **3** comprises the core structure found in the oroidin alkaloids. Furthermore, oxidation of **8** with Br_2 and DMSO affords directly α,β-unsaturated imidazolinone **14** which is the key structural unit comprising the dispacamides (**2**). A highly facile and practical synthesis of the $C_{11}N_5$ marine sponge alkaloids oroidin (**1a**), clathrodin (**1c**), and dispacamides (**2**) is outlined.

Marine sponges of the genera *Agelas*, *Hymeniacidon*, and *Phakellia* produce a structurally diverse and pharmacologically interesting class of $C_{11}N_5$, and dimerically related, secondary metabolites.[1,2] The chemical features that distinguish these alkaloids are the presence of either a brominated or nonbrominated pyrrole carboxamide unit, a 2-aminoimidazole or glycocyamidine nucleus, and a functionalized or unfunctionalized 3-carbon alkyl chain connecting these heterocyclic moieties. Collectively, this group of natural products is known as the oroidin alkaloids of which oroidin (**1a**)[3] and dispacamide (**2a**),[4] both from the sponge *Agelas* sp., represent the "simplest" structural entities. The related monobromopyrrole derivatives, hymenidin (**1b**),[5] from the sponge *Hymeniacidon* sp., and monobromodispacamide (**2b**)[4] are also known, as well as the debromooroidin derivative, clathrodin (**1c**).[6] Metabolites **1b** and **2** have been reported as potent antagonists of serotonergic[5] and histaminergic[4] receptors, respectively. Closely related to oroidin (**1a**) is 3-amino-1-(2-aminoimidazol-4-yl)prop-1-ene (**3**)[7] which lacks the pyrrole moiety. This derivative has been isolated from the Axinellidae sponges *T. morchella* and *P. walpersi* and is a potential biosynthetic precursor to oroidin-related metabolites. A synthesis of oroidin (**1a**) and clathrodin (**1c**) has been reported by two research groups.[8,9] Both groups focused on the preparation of **3** in which Wittig chemistry was used to install the olefinic double bond. Moreover, the syntheses relied heavily on the use of protecting groups on nitrogen. Undoubtedly, alkaloids **1**−**3** are biogenetically related and likely derived from a common 2-aminoimidazole (AI) precursor. In this report, we describe the facile synthesis of **1**, **2**, and **3** by the preparation and rearrangement of 2-amino-4,5-dialkoxy-4,5-dihydroimidazolines having the generalized structure **A**.[10]



Imidazolines of the type **A** can be considered dialkoxy adducts of cyclic guanidines. In unpublished investigations from the Büchi group, 4,5-dimethoxyimidazolines were obtained from the reaction of 4-acyl-2-aminoimidazoles with NBS in methanol.[10] A search of the literature revealed no additional examples. Although known, a

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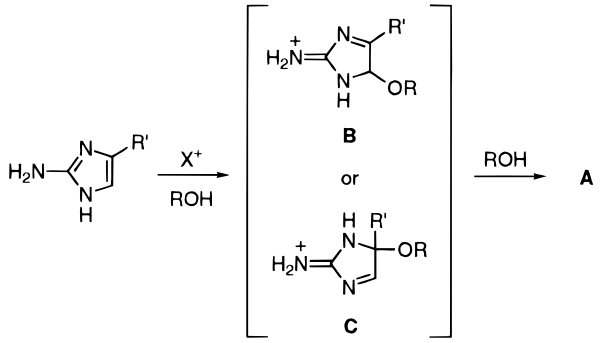
Scheme 1

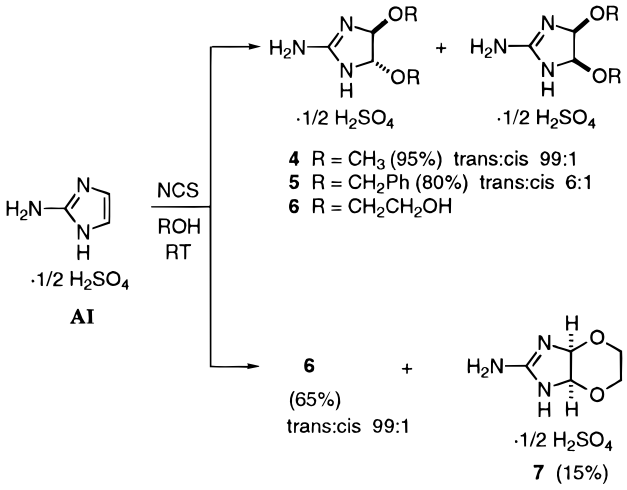


small number of related dihydroxy adducts have been isolated from the condensation of guanidines and α-diketones[11] and/or glyoxal.[12] These limited examples illustrate the stability of imidazoline adducts to isolation. In a continuing effort toward the development of AI chemistry,[13] we focused on further investigating the preparation of various analogues of **A** and examining their utility as key intermediates in alkaloid synthesis. The belief was that these adducts could serve as useful precursors to various members of the oroidin family of marine natural products.

Our initial investigations focused on the direct generation of adduct **A** by examining various conditions for the oxidation of functionalized AI substrates (Scheme 1). The trapping of a reactive intermediate by nucleophilic solvent molecules was the objective. Since a number of AI derivatives are readily available from known procedures,[14] this overall approach would provide a general method for the preparation of 2-amino-4,5-dialkoxy-4,5-dihydroimidazoline derivatives. Although few in number, related examples in the literature involving the addition to the 4,5-double bond of AIs can be seen in the intramolecular oxidative cycloaddition used for the biomimetic synthesis of dibromophakellin,[15] the intermolecular [2 + 4] cycloaddition for the preparation of tetrahydropurine derivatives,[16] and the acid-facilitated addition of EtOH to a bicyclic[3.3.0] AI system to give a stable 2-aminoimidazolidinium cation.[8]

Preliminary investigations focused on AI (Scheme 2). Upon treatment of AI sulfate with *N*-chlorosuccinimide in methanol, a swift and clean reaction occurred that afforded trans adduct **4** in excellent yield along with trace amounts of the cis diastereomer. With benzyl alcohol, however, a 6:1 trans:cis mixture of adduct **5** was obtained wherein π-stacking of the phenyl rings may contribute to the overall stability of the cis isomer. The use of ethylene glycol produced trans adduct **6** (and trace amounts of cis) as well as the bicyclic imidazoline derivative **7** as a minor coproduct. This bicyclic product can be obtained in pure form as a colorless solid by crystal-

Scheme 2



lization from ethanol after which **6** is separated as an oil. Generally, imidazoline adducts are obtained by trituration from the reaction mixture and are relatively stable. In each instance, the predominant diastereomer formed was the trans isomer except in the case of the bicyclic [4.3.0] imidazoline derivative **7** where the ring fusion is cis. The stereochemistry of the adducts was determined from ^{1}H NMR data. Previous data on related systems established that the 4,5-imidazoline proton resonances for the trans isomers are upfield from those of the cis.[12] In DMSO-d_6, trans adducts **4**−**6** produce singlets at δ 4.86, 5.10, and 4.96, respectively, whereas for the corresponding cis isomers, singlets were observed at lower field at δ 5.12, 5.38, and 5.20, respectively. The reactions in Scheme 2 were model reactions for the study of 2-amino-4-(3-aminopropyl)-1H-imidazole **8** and dihydrooroidin **15**,[15] which bear alkylamine and pyrrolecaboxamide functionalities, respectively.

AI derivative **8** can be considered a hypothetical forerunner to the $C_{11}N_5$ natural products **1** and **2**. It can be prepared readily from ornithine methyl ester using the method of Lancini et al.[17] This procedure, which incorporates an Akabori reduction followed by condensation of the resulting α-amino aldehyde with cyanamide, allows for the preparation of multigram quantities of 2-aminoimidazoles from esters of α-amino acids. Oxidation of **8** with NCS in methanol gave the expected trans dimethoxy adduct **9** in good yield (Scheme 3). An interesting reversal from the model reactions in Scheme 2 is seen with ethylene glycol. When **8** was treated with NCS in ethylene glycol, bicyclic adduct **10** was produced as the only product without formation of the corresponding disubstituted adduct. Evidently, steric interactions between the aminopropyl side chain and the formation of the incipient ethylene glycol unit preclude the generation of the bisglycol adduct.

The trans stereochemistry of adduct **9** was confirmed by 1-D selective NOESY experiments. Irradiation of the C5 ring proton singlet at 4.73 ppm showed NOEs to both methoxyl groups at 3.35 and 3.15 ppm. No enhancement was observed to the methylene protons of the aminopropyl side chain at 1.5−1.9 ppm. Likewise, when the C5 methoxyl group (geminal to the ring proton) was irradi-

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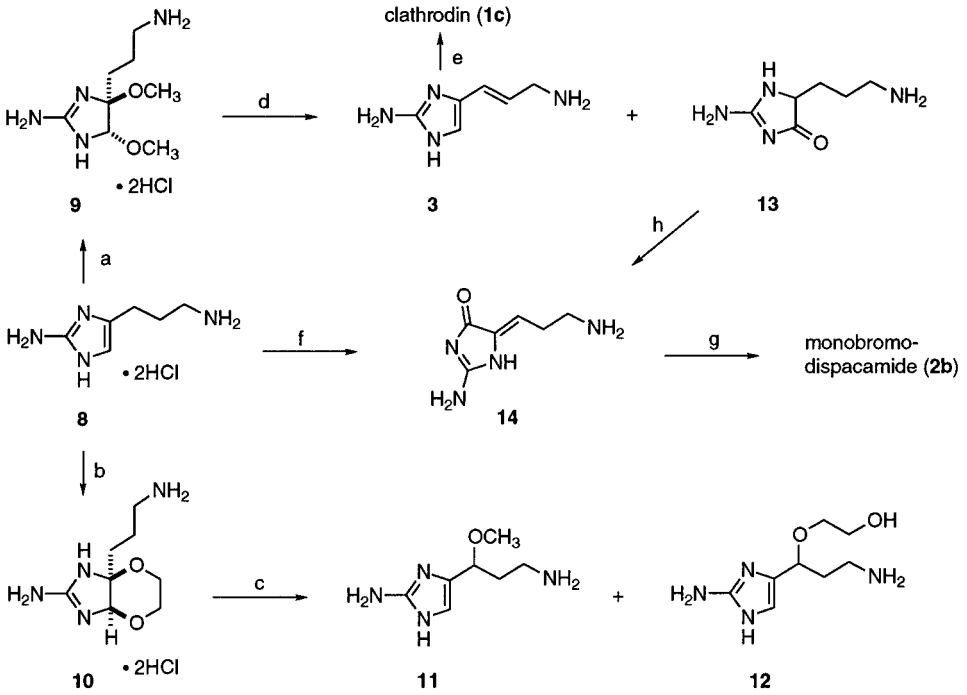
Scheme 3[a]



[a] Key: (a) NCS, MeOH, rt, 83%; (b) NCS, ethylene glycol, rt, 80%; (c) MeOH, reflux, **11** (30%), **12** (15%); (d) 135 °C, *m*-xylene/methanol, **3** (55%), **13** (35%); (e) 2-(trichloroacetyl)pyrrole, DMF, rt, 75%; (f) Br_2, DMSO, rt, 68%; (g) 4-bromo-2-(trichloroacetyl)pyrrole, DMF, rt, 65%; (h) Br_2, CH_3SO_3H, 85 °C, 71%.

ated, an NOE was seen only to the ring proton and the geminal guanidine N1 proton, which resonated at 9.70 ppm. No enhancement was observed for the adjacent C4 methoxyl group. Irradiation of the C4 methoxyl group showed NOEs to both the C5 ring proton and the geminal guanidine N3 proton, but again, no NOE was observed to the vicinal C5 methoxyl group. These data establish the stereochemical relationship of the methoxyl groups as trans.

In the course of these reactions, the mechanistic pathway leading to adduct **A** probably involves initial incorporation of halogen to AI followed by substitution with nucleophilic solvent (Scheme 1). The trans dialkoxy adduct **9** predominates thus implicating the formation of intermediate **B** with the stepwise addition of another ROH from the least hindered face.

An interesting feature of these adducts is their potential for rearrangement. This was investigated thermally by heating adducts **9** and **10** (Scheme 3). Refluxing **9** in methanol afforded mainly the α-substituted side chain derivative **11** and unchanged starting material. Similar results were seen with adduct **10** in refluxing methanol which gave the mixed side chain derivatives **11** and **12** along with a significant amount of recovered starting material. At elevated temperatures (135 °C) using an initial 1:1 solvent mixture of xylene:methanol,[18] adduct **9** rearranged to two products, namely, vinyl imidazole **3** and imidazolinone **13** in 55% and 35% yields, respectively. Acylation of **3** with 2-(trichloroacetyl)pyrrole[19] afforded clathrodin (**1c**). All spectral data of synthetic **1c** and **3** were in satisfactory agreement with those reported for the natural material.[6,7]

Next, the formation of the α,β-unsaturated imidazolinone ring system which comprises the dispacamides (**2**) was investigated. This was done using both AI derivative **8** and imidazolinone **13**. Derivative **8** requires a 2-fold oxidation of the AI nucleus to install both the carbonyl and olefin functionalities. Since the ability of adduct formation occurs readily upon oxidation in protic solvents, similar additions were envisaged with the aprotic but nucleophilic solvent DMSO.[20] The addition of DMSO followed by elimination of dimethyl sulfide would lead directly to the α,β-unsaturated imidazolinone ring system found in the dispacamides. When **8** was treated with 1 equiv of Br_2 in DMSO, transformation to (*Z*)-α,β-unsaturated imidazolinone **14** resulted in good yield.[21] The *Z* stereochemistry of olefin **14** was firmly established by its conversion to monobromodispacamide (**2b**) by acylation with 4-bromo-2-(trichloroacetyl)pyrrole.[22] All spectral data of synthetic **2b** were in satisfactory agreement with those reported for the natural product.[4,23] Alternatively, **14** can be produced from the oxidation of imidazolinone **13** with Br_2 in methanesulfonic acid.

Acylation of AI derivative **8** with the requisite dibromopyrrole unit produced dihydrooroidin (**15**) in 65% yield. This compound is also capable of forming dialkoxy adducts, but the presence of the pyrrolecarboxamide unit necessitated modification of the reaction conditions (Scheme 4). The amide linkage in **15** interferes with

(18) The reaction was heated without a condenser, thus allowing the methanol to boil off.

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(21) The presence of a small amount (5−10%) of the *E*-isomer can be seen in the ^{1}H NMR spectrum (D_2O): δ 3.05 (dt, 2H, *J* = 8.0, 7.1), 3.15 (t, 2H, *J* = 7.1), 6.06 (t, 1H, *J* = 8.0).

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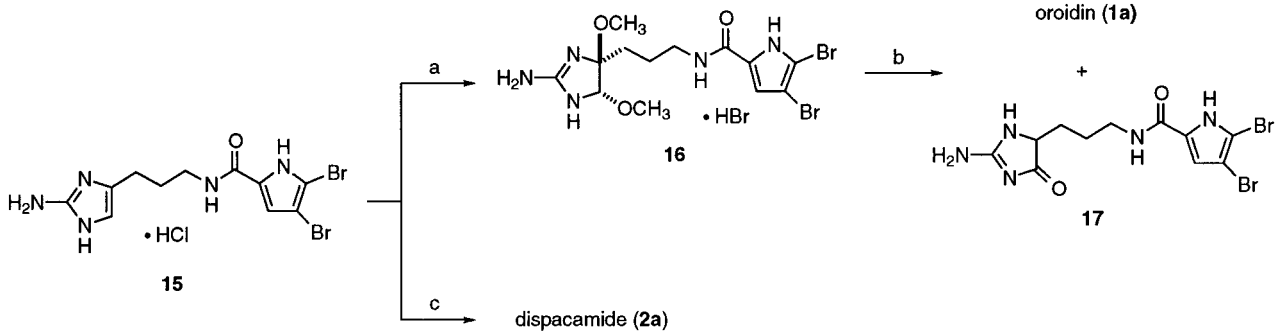
(23) The presence of a small amount (5−10%) of the *E*-isomer can be seen in the ^{1}H NMR spectrum (CD_3OD): δ 2.98 (dt, 2H, *J* = 8.2, 6.6), 3.48 (t, 2H, *J* = 6.6), 6.06 (t, 1H, *J* = 8.2), 6.74 (d, 1H, *J* = 1.5), 6.90 (d, 1H, J = 1.5).

Scheme 4[a]



[a] Key: (a) Br_2, tBuOK, CH_3OH, −78 °C, 75%; (b) 135 °C, *m*-xylene/MeOH, **1a** (48%), **17** (30%); (c) Br_2, DMSO, 60%.

adductformation under the usual conditions of NCS and methanol. This is due to competing intramolecular processes of the pyrrolecarboxamide group. To overcome this problem, a slight excess of base (tBuOK) was added and bromine was used instead of NCS as the halogen source. The slight excess of base generates the more nucleophilic methoxide species which readily adds to the oxidized AI nucleus. This afforded dimethoxy adduct **16** in good yields. The trans stereochemical assignment of adduct **16** was inferred from comparison with NMR data of trans adduct **9**. Adduct **16** can be converted to oroidin (**1a**) and dihydrodispacamide (**17**) when heated in xylene/methanol. In addition, oxidation of dihydrooroidin (**15**) with Br_2 and DMSO gave dispacamide **2a**. Starting from commercially available ornithine methyl ester, the overall synthesis of **1** and **2** required only four and three steps, respectively, and proceeded without the use of a single protecting group on nitrogen. AI derivative **8** serves as a common intermediate to metabolites **1**-**3**.

In conclusion, the preparation of 2-amino-4,5-dialkoxy-4,5-dihydroimidazoline derivatives having various functionalities from 2-aminoimidazoles is described. The method appears general, and the utility of these interesting derivatives is demonstrated in their imidazoline to vinyl imidazole and imidazolinone transformations. The facile synthesis of **1**, **2**, and **3** is illustrative of the chemistry. Furthermore, we have shown that the AI nucleus can serve as a direct precursor to the α,β-unsaturated imidazolinone system found in the dispacamides and related AI alkaloids. Perhaps a similar oxidative pathway is operative in the biogenesis of glycocyamidine-containing metabolites such as **2**.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification except for solvents which were dried and distilled. Silica gel (particle size 32−63 μ) was used for flash chromatography. ^{1}H NMR spectra were measured at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz. Abbreviations are as follows: AI = 2-aminoimidazole and NCS = *N*-chlorosuccinimide.

***trans*-2-Amino-4,5-dihydro-4,5-dimethoxy-2-imidazoline (4).** To a stirred solution of AI sulfate (0.60 g, 4.5 mmol) in 10 mL of methanol at rt was added NCS (0.67 g, 5.0 mmol). After 30 min, methanol was removed by evaporation under reduced pressure without heat. The resulting residue was washed with ether (3 × 100 mL) and acetone (100 mL), and the solid was collected by filtration to give **4** as a colorless solid (0.84 g, 95%). The ^{1}H NMR of **4** showed trace amounts of cis isomer. **4**: ^{1}H NMR (DMSO-d_6) δ 9.56 (s, 2H), 8.35 (s, 2H), 4.86 (s, 2H), 3.30 (s, 6H); (D_2O) δ 5.03 (s, 2H), 3.39 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 158.6 (s), 90.3 (d × 2), 54.7 (q × 2); IR (KBr) 3153, 2822, 1700, 1583, 1211 cm^{-1}; MS *m*/*z* (relative intensity) 146 (M^+ + 1, 100), 114 (10). Anal. Calcd for $C_5H_{11}N_3O_2 \cdot {}^1/_2H_2SO_4$: C, 30.92; H, 6.23; N, 21.64. Found: C, 30.89; H, 6.25; N, 21.60.

***trans*-2-Amino-4,5-dihydro-4,5-ibs(benzyloxy)-2-imidazoline (5).** To a stirred mixture of AI sulfate (0.60 g, 4.5 mmol) in 10 mL of benzyl alcohol at rt was added NCS (0.67 g, 5.0 mmol). After 20 h, the reaction mixture was diluted with ether and decanted (3 × 100 mL). The resulting residue was dissolved in 10 mL of acetone, and the small amount of unreacted starting material was removed by filtration. Concentration of the filtrate afforded a gum that was washed with ether (100 mL) and dried to give **5** as a pale yellow oil (1.26 g, 80%). The ^{1}H NMR of **5** showed 15% of cis isomer. **5**: ^{1}H NMR (DMSO-d_6) δ 9.78 (bs, 2H), 8.49 (bs, 2H), 7.34 (m, 10H), 5.10 (s, 2H), 4.64 (d, 2H, *J* = 11.7), 4.55 (d, 2H, *J* = 11.7); ^{13}C NMR (DMSO-d_6) δ 158.8 (s), 137.0 (s × 2), 128.4 and 128.0 (d × 10), 89.1 (d × 2), 68.8 (t × 2); IR (Nujol) 3194, 2851, 1695, 1576, 1093 cm^{-1}; MS *m*/*z* (relative intensity) 298 (M^+ + 1, 100), 208 (60), 190 (10). HRMS calcd for $C_{17}H_{20}N_3O_2$ (MH^+) 298.1557, found 298.1551.

***trans*-2-Amino-4,5-dihydro-4,5-bis(2-hydroxyethoxy)-2-imidazoline (6) and 6-Amino-5*H*-imidazo[4,5-*b*]-1,4-dioxane (7).** To a stirred mixture of AI sulfate (0.60 g, 4.5 mmol) in 10 mL of ethylene glycol at rt was added NCS (0.67 g, 5.0 mmol). After 20 h, the reaction mixture was diluted with ether and decanted (3 × 100 mL). The resulting residue was washed with acetone (3 × 100 mL) to give a mixture of **6** and **7** (0.7 g, 80%) as a colorless oil. The ^{1}H NMR in DMSO-d_6 showed a 6:1 ratio of **6**:**7** with a trace amount of the cis isomer of **6**. Addition of a small amount of ethanol to this oil and filtration gave pure **7** as a colorless solid. The filtrate, after evaporation, yielded a colorless oil consisting of **6** with a trace of **7**. **6**: ^{1}H NMR (DMSO-d_6) δ 9.64 (bs, 2H), 8.44 (bs, 2H), 4.96 (s, 2H), 4.85 (br, 2H), 3.51 (m × 2, 8H); ^{13}C NMR (DMSO-d_6) δ 158.7 (s), 89.8 (d × 2), 69.1 (t × 2), 60.0 (t × 2). **7**: ^{1}H NMR (DMSO-d_6) δ 9.08 (bs, 2H), 8.48 (bs, 2H), 5.31 (s, 2H), 3.69 (m, 4H); ^{1}H NMR (D_2O) δ 5.46 (s, 2H), 3.90 (ddd, $2H_{eq}$, *J* = 8.4, 7.1, 6.9), 3.82 (ddd, $2H_{ax}$, *J* = 8.4, 7.1, 6.9); ^{13}C NMR (DMSO-d_6) δ 159.2 (s), 78.8 (d × 2), 58.0 (t × 2); IR (KBr) 3180, 2956, 1700, 1667, 1261 cm^{-1}; MS *m*/*z* (relative intensity) 143 (M^+, 45), 114 (30), 86 (100). Anal. Calcd for $C_5H_9N_3O_2 \cdot {}^1/_2H_2SO_4$: C, 31.25; H, 5.24; N, 21.86. Found: C, 31.30; H, 5.27; N, 21.87.

2-Amino-4-(3-aminopropyl)-1*H*-imidazole (8). A solution of L-ornithine methyl ester dihydrochloride (25 g, 0.11 mol) in 250 mL of water was cooled between 0 and 5 °C. The pH was adjusted to 1.5−2.0 by addition of 15% HCl. Over the course of 1 h, 5% Na/Hg (546 g, 1.1 mol) was added to the solution while the temperature and pH within were maintained the given range. When the pH remained constant and the evolution of gas had ceased, the solution was decanted to remove Hg. The pH was then adjusted to 4.3 by the addition of 1 N NaOH. Cyanamide (48 mL, 0.57 mol) was added and the solution heated at 95 °C for 2.5 h. Removal of the solvent in vacuo afforded a thick, light yellow residue which was

washed with ether (3 × 200 mL). Methanol was added to the residue and NaCl removed by filtration. The filtrate, after evaporation, gave a pale yellow solid. Recrystallization from ethanol gave **8** as colorless needles (14.9 g, 62%): mp 213-215 °C; ^{1}H NMR (DMSO-d_6) δ 12.30 (s, 1H), 11.76 (s, 1H), 8.25 (s, 3H), 7.39 (s, 2H), 6.62 (s, 1H), 2.72 (t, 2H, J = 6.3), 2.5 (t, 2H, J = 7.4), 1.82 (p, 2H, J = 7.3); ^{1}H NMR (D_2O) δ 6.54 (s, 1H), 3.01 (t, 2H, J = 7.6), 2.61 (t, 2H, J = 7.4), 1.94 (p, 2H, J = 7.6); ^{13}C NMR (CD_3OD) δ 148.7 (s), 127.2 (s), 110.4 (d), 39.9 (t), 27.1 (t), 22.5 (t); IR (KBr) 3310, 1667, 1473, 1140 cm^{-1}; UV λ_{max} (MeOH) 215 nm; MS m/z (relative intensity) 141 (M^+ + 1, 100), 124 (65). Anal. Calcd for $C_6H_{12}N_4$·2HCl: C, 33.82; H, 6.62; N, 26.29. Found: C, 33.78; H, 6.59; N, 26.33.

***trans*-2-Amino-4,5-dimethoxy-4-(3-aminopropyl)-2-imidazoline (9).** To a stirred solution of **8** (0.60 g, 2.8 mmol) in 10 mL of methanol at rt was added NCS (0.41 g, 3.1 mmol). After 1 h, methanol was removed in vacuo without heat and the resulting residue was washed with ether (3 × 100 mL) and acetone (3 × 100 mL) to give **9** as an unstable colorless oil (0.64 g, 83%): ^{1}H NMR (DMSO-d_6) δ 9.75 (bs, 1H), 9.70 (bs, 1H), 8.28 (bs, 2H), 8.14 (bs, 3H), 4.73 (s, 1H), 3.36 (s, 3H), 3.15 (s, 3H), 2.75 (q, 2H, J = 5.7), 1.95−1.58 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 158.0 (s), 94.4 (s), 90.1 (d), 55.9 (q), 48.8 (q), 38.7 (t), 27.6 (t), 21.8 (t); IR (Nujol) 3136, 2855, 1692, 1570, 1184 cm^{-1}; MS m/z (relative intensity) 203 (M^+ + 1, 25), 171 (90). HRMS calcd for $C_8H_{19}N_4O_2$ (MH^+) 203.1509, found 203.1500.

6-Amino-4a-(3-aminopropyl)-5*H*-imidazo[4,5-*b*]-1,4-dioxane (10). To a stirred solution of **8** (0.60 g, 2.8 mmol) in 10 mL of ethylene glycol at rt was added 1.1 equiv of NCS (0.41 g, 3.1 mmol). After 20 h, the reaction mixture was diluted with ether and decanted (3 × 100 mL). The resulting residue was washed with acetone (3 × 100 mL) to give **10** as an unstable colorless oil (0.61 g, 80%): ^{1}H NMR (DMSO-d_6) δ 9.40 (bs, 1H), 9.22 (bs, 1H), 8.42 (bs, 2H), 8.27 (bs, 3H), 5.18 (s, 1H), 3.76−3.62 (m, 4H), 2.78 (q, 2H, J = 5.9), 1.82−1.69 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 158.0 (s), 87.5 (s), 81.5 (d), 62.8 (t), 56.8 (t), 38.4 (t), 33.8 (t), 20.5 (t); IR (Nujol) 3404, 2740, 1695, 1571, 1272, cm^{-1}; MS m/z (relative intensity) 201 (M^+ + 1, 100); HRMS calcd for $C_8H_{17}N_4O_2$ (MH^+) 201.1353, found 201.1350.

2-Amino-4-(3-amino-1-methoxypropyl)-1*H*-imidazole (11). A stirred solution of **9** (0.75 g, 2.7 mmol) was refluxed in 10 mL of methanol for 2 d. The solvent was removed in vacuo to afford a residue which consisted of starting material **9** and **11** as determined by NMR. Purification of the residue by column chromatography (MeOH saturated with NH_3) gave **11** (free base, 0.14 g, 30%) as a pale yellow oil: ^{1}H NMR (DMSO-d_6) δ 6.35 (s, 1H), 5.11 (bs, 2H), 4.42 (br, 3H), 4.00 (t, 1H, J = 6.6), 3.05 (s, 3H), 2.52 (t, 2H, J = 6.7), 1.84−1.67 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 149.9 (s), 131.8 (s), 113.9 (s), 74.3 (d), 54.8 (q), 38.6 (t), 38.5 (t); IR (KBr) 2944, 1584, 1489, 1344, 1193 cm^{-1}; MS m/z (relative intensity) 171 (M^+ + 1, 100); HRMS, calcd for $C_7H_{15}N_4O$ (MH^+) 171.1247, found 171.1250.

2-Amino-4-(3-amino-1-(2-hydroxyethoxy)propyl)-1*H*-imidazole (12). A solution of **10** (0.75 g, 2.7 mmol) was refluxed in 10 mL of methanol for 2 d. The solvent was removed in vacuo to afford a residue which consisted of a mixture of starting material **10**, along with **11** and **12**, as determined by ^{1}H NMR. Purification of the residue by flash chromatography (MeOH saturated with NH_3) gave **11** (0.14 g, 30%) and **12** (0.081 g, 15%) as free bases, both of which were pale yellow oils. **12**: ^{1}H NMR (DMSO-d_6) δ 6.32 (s, 1H), 5.08 (bs, 2H), 4.40 (br, 4H), 4.18 (t, 1H, J = 6.7), 3.42 (t, 2H, J = 5.1), 3.36−3.23 (m, 2H), 2.55 (t, 2H, J = 6.6), 1.83−1.67 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 150.0 (s), 132.9 (s), 113.7 (s), 73.4 (d), 69.4 (t), 60.7 (t), 38.4 (t), 37.8 (t); IR (KBr) 2812, 1693, 1560, 1166, 1010 cm^{-1}; MS m/z (relative intensity) 201 (M^+ + 1, 40), 139 (15), 97 (100); HRMS calcd for $C_8H_{17}N_4O_2$ (MH^+) 201.1353, found 201.1351.

3-Amino-1-(2-aminoimidazol-4-yl)prop-1-ene (3) and 2-Amino-5-(3-aminopropyl)-2-imidazolin-4-one (13). A solution of **9** (1.5 g, 5.5 mmol) in 10 mL of methanol was added to 10 mL of *m*-xylene and heated at 135 °C for 3 h without a condenser. During this time, the methanol evaporated. After the solution was cooled to rt, the xylene was decanted and the residue washed with ether (3 × 100 mL) and acetone (2 × 100 mL). Addition of 5 mL of methanol to the residue and filtration yielded pure **3**·2HCl as a colorless solid (0.46 g, 40%). Concentration of the filtrate followed by purification of the resulting residue by flash chromatography (CH_2Cl_2/MeOH saturated with NH_3 1:1) afforded additional **3** (0.11 g, 15%) and **13** (0.30 g, 35%) as free bases. Addition of concentrated HCl to a methanol solution of the corresponding free base and concentration in vacuo afforded **3**·2HCl and **13**·2HCl. **3·2HCl**: ^{1}H NMR (DMSO-d_6) δ 12.99 (br, 1H), 12.2 (br, 1H), 8.40 (bs, 3H), 7.58 (s, 2H), 7.01 (s, 1H), 6.47 (d, 1H, J = 16.1), 6.11 (dt, 1H, J = 16.1, 6.3), 3.53 (bs, 2H, changes to do with D_2O, J = 6.3); ^{1}H NMR (CD_3OD) δ 6.93 (s, 1H), 6.59 (s, 1H, J = 16.1), 6.16 (dt, 1H, J = 16.1 and 7.0), 3.70 (d, 2H, J = 7.0); ^{13}C NMR (CD_3OD) δ 149.5 (s), 125.9 (s), 123.1 (d), 121.5 (d), 114.0(d), 42.1 (t); UV λ_{max} (MeOH) 265 nm; MS m/z (relative intensity) 139 (M^+ + 1, 100), 122 (30). Anal. Calcd for $C_6H_{10}N_4$·2HCl: C, 34.14; H, 5.73; N, 26.54. Found: C, 33.99; H, 5.70; N, 26.53. **13·2HCl**: ^{1}H NMR (DMSO-d_6) δ 12.37 (bs, 1H), 9.87 (s, 1H), 9.18 (bs, 1H), 8.91 (bs, 1H), 8.02 (bs, 3H), 4.34 (t, 1H, J = 5.1), 2.78 (q, 2H, J = 6.5), 1.86−1.55 (m, 4H, J = 7.7); ^{13}C NMR (DMSO-d_6) δ 174.9 (s), 157.9 (s), 58.5 (d), 38.4 (t), 27.6 (t), 22.4 (t); IR (KBr) 3283, 2644, 1713, 1545, 1397 cm^{-1}; UV λ_{max} (MeOH) 205 nm; MS m/z (relative intensity) 157 (M^+ + 1, 100), 102 (10). Anal. Calcd for $C_6H_{12}N_4O$·2HCl: C, 31.45; H, 6.16; N, 24.45. Found: C, 31.39; H, 6.12; N, 24.50.

(*Z*)-2-Amino-5-(3-aminopropylidenyl)-2-imidazolin-4-one (14). Method A. To a stirred solution of **13**·2HCl (0.10 g, 0.44 mmol) in 1 mL of CH_3SO_3H was added bromine (20 μL, 0.44 mmol). The reaction was heated between 80 and 90 °C for 1 h. After cooling, the reaction mixture was diluted with ether and decanted (3 × 25 mL). The resulting solid was washed with acetone and filtered to give **14**·2CH_3SO_3H as a tan solid (0.11 g, 71%). **Method B.** To a stirred solution of **8** (0.50 g, 2.3 mmol) in 6 mL of DMSO at rt was added bromine (120 μL, 2.3 mmol). After 1 h, the reaction mixture was diluted with ether and decanted (3 × 75 mL). The resulting residue was purified by flash chromatography (MeOH saturated with NH_3) to give **14** as a pale yellow solid. Addition of concentrated HCl to a methanol solution of the free base and concentration in vacuo afforded **14**·2HCl (0.36 g, 68%) as a colorless solid. **14·2HCl**: ^{1}H NMR (DMSO-d_6) δ 12.45 (br, 2H), 9.39 (br, 2H), 8.18 (bs, 3H), 5.98 (t, 1H, J = 7.7), 2.97 (q, 2H, J = 6.9), 2.67 (q, 2H, J = 7.2); ^{1}H NMR (D_2O) δ 6.13 (t, 1H, J = 7.9), 3.20 (t, 2H, J = 7.1), 2.71 (dt, 2H, J = 7.9 and 7.1); ^{13}C NMR (D_2O) δ 164.8 (s), 156.2 (s), 130.7 (s), 117.0 (d), 38.9 (t), 25.8 (t); IR (KBr) 3100, 1690, 1540, 1310, 1250 cm^{-};[1] UV λ_{max} (MeOH) 226 and 271 nm; MS m/z (relative intensity) 155 (M^+ + 1, 100), 138 (90). Anal. Calcd for $C_6H_{10}N_4O$·2HCl: C, 31.73; H, 5.33; N, 24.67. Found: C, 31.79; H, 5.30; N, 24.59.

Clathrodin (1c). To a stirred solution of **3**·2HCl (0.2 g, 0.95 mmol) in 2 mL of DMF at rt were added Na_2CO_3 (0.11 g, 1.0 mmol) and 2-(trichloroacetyl)pyrrole[19] (0.25 g, 1.1 mmol). The mixture was stirred for 1 h and then diluted with ether and decanted (3 × 50 mL). The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH saturated with NH_3 17:3) to give **1c** as the free base. Addition of concentrated HCl to a methanol solution of the free base and concentration in vacuo gave **1c**·HCl (0.19 g, 75%). **1c·HCl**: ^{1}H NMR (DMSO-d_6) δ 12.39 (bs, 1H), 11.80 (bs, 1H), 11.49 (s, 1H), 8.33 (t, 1H, J = 5.9), 7.46 (s, 2H), 6.91 (s, 1H), 6.85 (m, 1H), 6.80 (m, 1H), 6.21 (d, 1H, J = 16.2), 6.15 (dt, 1H, J = 16.2, 4.9), 6.08 (m, 1H), 3.96 (t, 2H, J = 4.9); IR (KBr) 1682, 1620, 1565, 1410, 1325; UV λ_{max} (MeOH) 270 nm; MS m/z (relative intensity) 232 (M^+ + 1, 100). HRMS calcd for $C_{11}H_{14}N_5O$ (MH^+) 232.1199, found 232.1198.

Monobromodispacamide (2b). To a stirred solution of **14** (0.30 g, 1.9 mmol) in 5 mL of DMF under argon was added 4-bromo-2-(trichloroacetyl)pyrrole[22] (0.67 g, 2.3 mmol) at rt. After 72 h, the reaction mixture was diluted with ether and decanted (2 × 100 mL). The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH saturated with NH_3 8:2) to give **2b** as a white solid (0.53 g, 65%). **2b** (free base): ^{1}H NMR (CD_3OD) δ 6.90 (d, 1H, J = 1.5), 6.75 (d, 1H, J = 1.5), 5.73 (t, 1H, J = 7.8), 3.43 (t, 2H, J = 6.9), 2.49 (dt, 2H, J

= 7.8, 6.9); ^{13}C NMR (CD_3OD) δ 179.0 (s), 168.0 (s), 162.7 (s), 137.0 (s), 127.5 (s), 122.8 (d), 113.3 (d), 111.6 (d), 97.5 (s), 39.5 (t), 28.6 (t); IR (KBr) 3133, 2767, 1633, 1567, 1328 cm^{-1}; UV λ_{max} (MeOH) 250 and 270(sh) nm; MS *m/z* (relative intensity) 326 (M^+, 100). Anal. Calcd for $C_{11}H_{12}BrN_5O_2$: C, 40.51; H, 3.71; N, 21.47. Found: C, 40.49; H, 3.72; N, 21.40. **2b·HCl**: ^{1}H NMR (CD_3OD) δ 6.91 (d, 1H, J = 1.5), 6.77 (d, 1H, J = 1.5), 6.16 (t, 1H, J = 8.0), 3.48 (t, 2H, J = 6.7), 2.6 (dt, 2H, J = 8.0, 6.7); ^{13}C NMR (CD_3OD) δ 163.8 (s), 162.8 (s), 157.1 (s), 133.0 (s), 130.5 (s), 122.9 (d), 119.2 (d), 113.4 (d), 97.5 (s), 38.9 (t), 28.7 (t); UV λ_{max}(MeOH) 232 and 272 nm. Anal. Calcd for $C_{11}H_{12}BrN_5O_2$·HCl: C, 36.44; H, 3.61; N, 19.31. Found: C, 36.40; H, 3.68; N, 19.28.

Dihydrooroidin (15). To a stirred solution of **8** (free base, 0.66 g, 4.7 mmol) in 5 mL of DMF at rt was added 4,5-dibromo-2-(trichloroacetyl)pyrrole[24] (1.9 g, 5.2 mmol). The mixture was stirred for 1 d and diluted with ether and decanted (3 × 75 mL). The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH saturated with NH_3 8:2) to afford **15** as the free base. Addition of concentrated HCl to a methanol solution of the free base and concentration in vacuo gave **15** as a white solid (1.3 g, 65%). **15**: ^{1}H NMR (DMSO-d_6) δ 12.76 (s, 1H), 12.07 (s, 1H), 11.60 (s, 1H), 8.35 (t, 1H, J = 5.7), 7.33 (s, 2H), 6.95 (d, 1H, J = 2.7), 6.61 (s, 1H), 3.21 (q, 2H, J = 5.9), 2.44 (t, 2H, J = 7.3), 1.77−1.70 (m, 2H); ^{13}C NMR (D_2O) δ 162.0 (s), 147.2 (s), 127.7 (s), 127.3 (s), 114.3 (d), 109.5 (d), 106.5 (s), 99.8 (s), 39.5 (t), 27.9 (t), 22.5 (t); MS *m/z* (relative intensity) 394 (M^+ + 5, 50), 392 (M^+ + 3, 100), 390 (M^+ + 1, 50). Anal. Calcd for $C_{11}H_{13}Br_2N_5O$·HCl: C, 30.90; H, 3.30; N, 16.38. Found: C, 30.80; H, 3.48; N, 16.12.

***trans*-4,5-Dihydro-4,5-dimethoxydihydrooroidin (16).** To a stirred solution of dihydrooroidin hydrochloride (**15**) (0.40 g, 0.94 mmol) in 15 mL of methanol at −78 °C was added *t*-BuOK (0.0734 g, 6.5 mmol) followed by bromine (53 μL, 1.0 mmol). After 10 min, the reaction mixture was quenched with CH_3SO_3H (0.45 g, 4.7 mmol), warmed to rt, and filtered. Concentration of the filtrate gave a residue that was purified by flash chromatography (CH_2Cl_2/MeOH 8:2) to give **16** as a yellow solid (0.37 g, 75%): ^{1}H NMR (DMSO-d_6) δ 12.67 (s, 1H), 9.42 (s, 1H), 9.36 (s, 1H), 8.20 (t, 1H, J = 5.5), 8.13 (bs, 2H), 6.92 (s, 1H), 4.71 (s, 1H), 3.32 (s, 3H), 3.24−3.16 (m, 2H), 3.11 (s, 3H), 1.90−1.50 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 158.8 (s), 157.6 (s), 128.2 (s), 112.4 (d), 104.4 (s), 97.7 (s), 94.7 (s), 90.1 (d), 55.8 (q), 48.9 (q), 38.4 (t), 27.7 (t), 23.9 (t); IR (KBr) 2941, 1693, 1567, 1416, 1241, cm^{-1} MS *m/z* (relative intensity) 454 (M^+ + 5, 30), 454 (M^+ + 3, 60), 454 (M^+ + 1, 30), 422 (40), 390 (20), 307 (100), 289 (60). HRMS calcd for $C_{13}H_{20}N_5O_3Br_2$ (MH^+) 451.9928, found 451.9926.

Oroidin (1a) and Dihydrodispacamide (17). A solution of **16** (0.30 g, 0.56 mmol) in 10 mL of methanol was added to 10 mL of *m*-xylene, and the whole was heated at 135 °C for 3 h without a condenser. During this time, the methanol evaporated. After cooling, the xylene was decanted and the residue washed with ether (3 × 100 mL) and acetone (2 × 100 mL). Purification of the resulting residue by flash chromatography (CH_2Cl_2/MeOH saturated with NH_3 8:2) gave oroidin (**1a**) (0.10 g, 48%) and dihydrodispacamide (**17**) (0.69 g, 30%). Addition of concentrated HCl to a methanol solution of the free base and concentration in vacuo gave **1a**·HCl and **17**·HCl. **1a·HCl**: ^{1}H NMR (DMSO-d_6) δ 12.78 (bs, 1H), 12.48 (bs, 1H), 11.85 (bs, 1H), 8.55 (t, 1H, J = 4.9), 7.49 (bs, 2H), 6.99 (d, 1H, J = 2.9), 6.91 (s, 1H), 6.21 (d, 1H, J = 16.1), 6.13 (dt, 1H, J = 16.1, 4.9), 3.95 (t, 2H, J = 4.9); IR (KBr) 3290, 3160, 1685, 1564 cm^{-1}; UV λ_{max} (MeOH) 275 nm; MS *m/z* (relative intensity) 394 (M^+ + 5, 50), 392 (M^+ + 3, 100), 390 (M^+ + 1, 50). **17·HCl**: ^{1}H NMR (DMSO-d_6) δ 12.73 (bs, 1H), 12.28 (bs, 1H), 9.76 (bs, 1H), 9.03 (br, 1H), 8.87 (br, 1H), 8.29 (t, 1H, J = 6.6), 6.93 (bs, 1H), 4.32 (t, 1H, J = 6.1), 3.21 (q, 2H, J = 6.6), 1.82−1.45 (m, 4H); MS *m/z* (relative intensity) 410 (M^+ + 5, 50), 408 (M^+ + 3, 100), 406 (M^+ + 1, 50); HRMS calcd for $C_{11}H_{14}N_5O_2Br_2$ (MH^+) 405.9513, found 405.9510.

Dispacamide (2a). Method A. To a stirred solution of **15** (0.10 g, 0.23 mmol) in 1 mL of DMSO at rt was added bromine (13 μL, 0.23 mmol). After 1 h, the reaction mixture was diluted with ether and decanted (3 × 50 mL). The resulting residue was then purified by flash chromatography (CH_2Cl_2:MeOH saturated with NH_3 8:2) to give **2a** as a white solid (56 mg, 60%). **Method B.** To a stirred solution of **14** (0.32 g, 2.1 mmol) in DMF under argon at rt was added 4,5-dibromo-2-(trichloroacetyl)pyrrole (0.93 g, 2.5 mmol). After 72 h, the reaction mixture was diluted with ether and decanted (2 × 100 mL). The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH saturated with NH_3 8:2) to give **2a** as a white solid (0.69 g, 60%). ^{1}H NMR (CD_3OD) δ 6.78 (s, 1H), 5.72 (t, 1H, J = 7.9), 3.42 (t, 2H, J = 6.9), 2.50 (dt, 2H, J = 7.9, 6.9); ^{13}C NMR (CD_3OD) δ 178.8 (s), 168.0 (s), 161.9 (s), 137.1 (s), 128.8 (s), 114.3 (d), 111.6 (d), 106.1 (s), 99.9 (s), 39.5 (t), 28.6 (t); UV λ_{max} (MeOH) 250 and 274 nm; MS *m/z* (relative intensity) 405 (M^+, 100), 325 (30). Anal. Calcd for $C_{11}H_{11}Br_2N_5O_2$: C, 32.62; H, 2.74; N, 17.29. Found: C, 32.57; H, 2.72; N, 17.30. **2a·HCl**: mp >215 °C; ^{1}H NMR (CD_3OD) δ 6.82 (s, 1H), 6.15 (t, 1H, J = 8.0), 3.48 (t, 2H, J = 6.9), 2.62 (dt, 2H, J = 8.0, 6.9); ^{13}C NMR (CD_3OD) δ 163.8 (s), 161.9 (s), 156.4 (s), 128.6 (s), 119.2 (d), 114.4 (d), 106.3 (s), 99.9 (s), 38.9 (t), 28.7 (t); IR (KBr) 3111, 2722, 1700, 1556, 1522 cm^{-1}; UV λ_{max} (MeOH) 224 and 278 nm. Anal. Calcd for $C_{11}H_{11}Br_2N_5O_2$·HCl: C, 29.92; H, 2.74; N, 15.86. Found: C, 29.88; H, 2.78; N, 15.78.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1a**, **1c**, and **2**−**17** (44 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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