Total synthesis of naamine C and pyronaamidine, antitumor marine imidazole alkaloids

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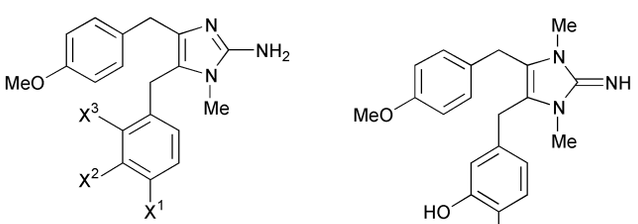
The first total synthesis of naamine C and pyronaamidine, highly substituted and cytotoxic imidazole marine alkaloids of a certain kind of sponge, was achieved through an eight-step reaction starting from 1-methyl-2-phenylthio-1*H*-imidazole.

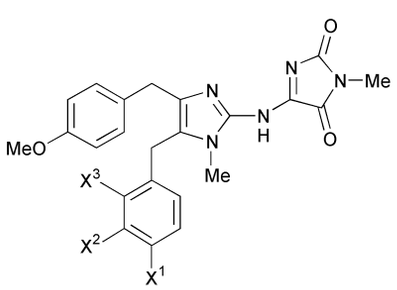
Introduction

Many imidazole alkaloids containing highly substituted imidazole ring(s) have been isolated from a bright yellow sponge, *Leucetta chagosensis*, and several of their structures are shown in Fig 1.[1] These alkaloids generally have interesting biological properties such as antitumor and antifungal activities. For example, it was reported that naamidine A, B and G **5**–**7**[1a–e] showed antifungal activity against *Cryptococcus neoformans*, and, in particular, pyronaamidine **4**[1e] was cytotoxic against KB cells, minimum inhibitory concentration (MIC) = 5 μg mL^{-1}. A structural characteristic of these alkaloids is that one or two alkoxybenzyl group(s) are located at the 4 and/or 5-position of the 1-methyl-1*H*-imidazole ring. So far as the alkaloids **4**–**8** are concerned, the 2-position of the ring is substituted with the (1-methyl-2,5-dioxo-3*H*-imidazolin-4-yl)amino moiety. Pyronaamidine **4** has been considered to be a possible biometabolic intermediate in the biochemical production of the tricyclic alkaloids, kealiiquinone **9**[1e] and 2-deoxy-2-aminokealiiquinone **10**.[1f] We have investigated the total synthesis of these imidazole natural products and already reported the first total synthesis of several marine imidazole alkaloids, **1**,[2] **3**,[3] **5**,[2] **8**[4] and **9**.[5] The most important key step in the total synthesis of **4** may be the construction of the (1-methyl-2,5-dioxo-3*H*-imidazolin-4-yl)amino side chain. In this paper, we report the first total synthesis of **4** through naamine C **2**.

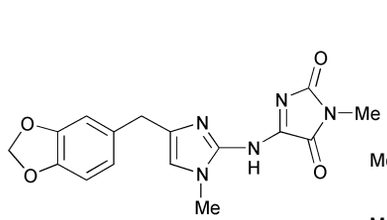


Naamine A (**1**): X^1 = OH, X^2 = X^3 = H
Naamine C (**2**): X^1 = X^2 = OMe, X^3 = OH

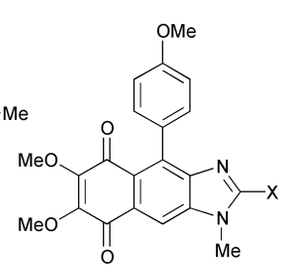
Naamine B (**3**)



Pyronaamidine (**4**): X^1 = OMe, X^2 = OMe, X^3 = OH
Naamidine A (**5**): X^1 = OH, X^2 = X^3 = H
Naamidine B (**6**): X^1 = OMe, X^2 = OH, X^3 = H
Naamidine G (**7**): X^1 = OMe, X^2 = X^3 = H



Clathridine (**8**)



Kealiiquinone (**9**): X = OH
2-Deoxy-2-amino-Kealiiquinone (**10**): X = NH_2

Fig. 1

Results and discussion

First, the preparation of the 1,2,4,5-tetrasubstituted imidazole derivative **17** was attempted (Scheme 1). 1-Methyl-2-phenylthio-1*H*-imidazole **11** was converted to the 5-substituted imidazole **14** according to our previously reported method.[5] When the 4-position of **14** was lithiated by treatment with *tert*-butyllithium, followed by quenching with *p*-anisaldehyde, a diastereomeric mixture of the alcohol **15** was obtained in 43% yield. The TBDMS group was removed by treatment with TBAF. The alcohol **16** was reduced with zinc powder in *conc*. HCl–acetic acid at 80 °C to give not the desired 1,2,4,5-tetrasubstituted imidazole **17** but a tricyclic naphthoimidazole **18** as a major product (yield 75%) along with many minor uncharacterized products. The structure of **18** was supported by a ^{1}H-NMR spectroscopic study based on the data obtained in the previous investigation of the total synthesis of kealiiquinone **9**.[5] It could be considered that an intramolecular Friedel–Crafts type cyclization of **16** occurred under such acidic conditions to give **18**. Reduction of **16** with nickel boride,[6] which was used in the previous report,[2] resulted unfortunately in formation of a complex mixture of many compounds such as the corresponding alcohols and deprotected phenols.

To overcome these problems, the Et_3SiH reduction method[7] was applied to the present system (Scheme 2). The benzyl alcohol **20** having a TBDMS group instead of the MOM group of

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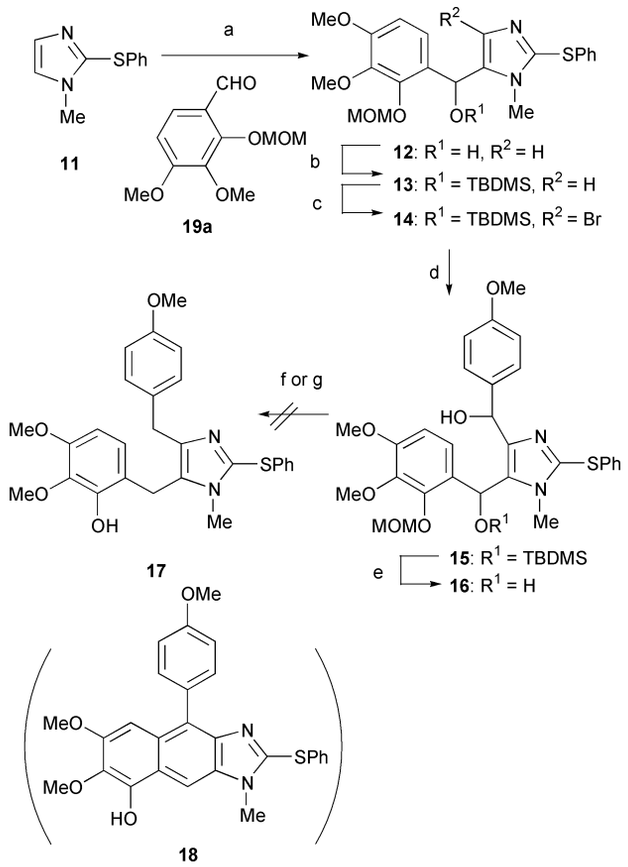
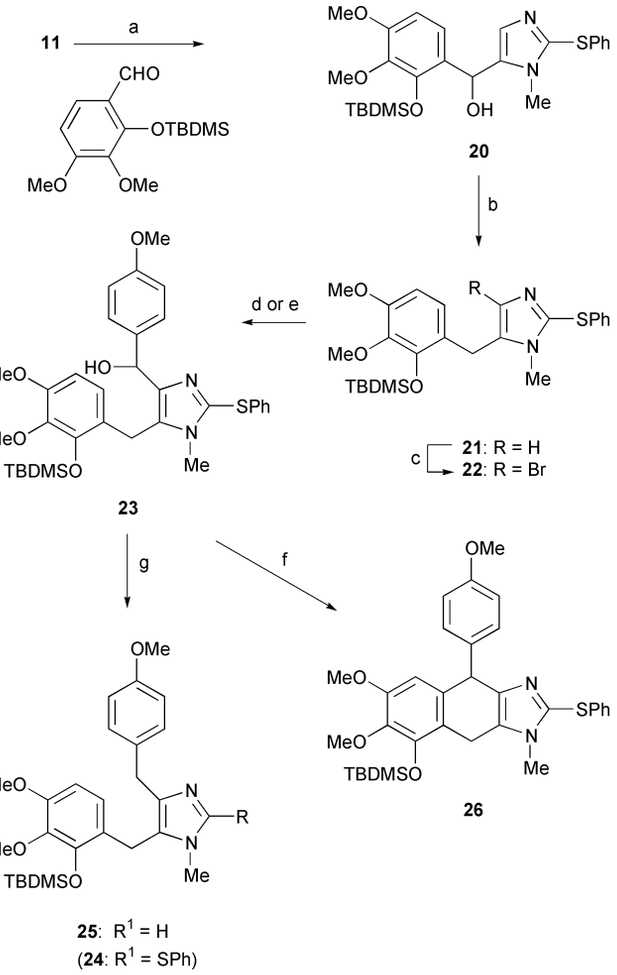
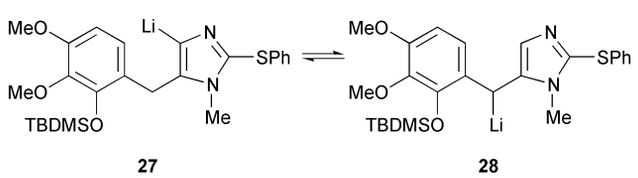


Scheme 1 *Reagents*: (a) lithium 2,2,6,6,-tetramethylpiperidinide (LTMP), THF, 89%; (b) TBDMSCl, imidazole, DMF, quant; (c) NBS, THF, 64%; (d) (i) *tert*-BuLi THF; (ii) *p*-anisaldehyde, 43%; (e) TBAF, THF, quant: (f) Zn, *conc.* HCl, AcOH, **18**: 75%; (g) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, THF, MeOH, produced complex mixture.



Scheme 2 *Reagents*: (a) LTMP, THF, 78%; (b) Et_3SiH, TFA, DCM, 98%; (c) NBS, THF, 81%; (d) (i) *tert*-BuLi (2 equiv.), THF; (ii) *p*-anisaldehyde (5 equiv.), 15%; (e) *tert*-BuLi (6 equiv.), *p*-anisaldehyde (5 equiv.), THF, 89%; (f) Et_3SiH, TFA, DCM, **26**: 79%; (g) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, THF, MeOH, **25** 62%.



Scheme 3 A possible equilibrium after the lithiation of **22**.

12 was prepared starting from **11** and the aldehyde **19b**[8] (R = TBDMS) similarly as above. The compound **20** was smoothly reduced to the 5-benzylimidazole **21** in 98% yield by treatment with triethylsilane in the presence of trifluoroacetic acid according to Kobayashi's procedure.[7] The 5-benzylimidazole **21** was brominated by NBS to give the 4-bromoimidazole **22** in 81% yield. When the bromide **22** was subjected to lithiation with *tert*-butyllithium at −78 °C for 15 min followed by quenching with *p*-anisaldehyde, the required 4-alkylated product **23** was obtained in only 15% yield along with a mixture of many minor uncharacterized products. This result might be attributable to intermediate formation of an equilibrium mixture containing the kinetic product **27** and the thermodynamic product **28** before addition of *p*-anisaldehyde (Scheme 3). Thus, *tert*-butyllithium was added into a mixed solution of **23** and *p*-anisaldehyde in THF at −78 °C in order to avoid the equilibrium, and the yield of **23** increased as expected, and reached 89%.

Reductive removal of the hydroxy group of **23** with Et_3SiH in the presence of TFA unfortunately resulted in formation of the tricyclic imidazole derivative **26** in 79% yield instead of the desired reductant **24** because intramolecular Friedel–Crafts type cyclization of **23** occurred under such acidic conditions. On the other hand, reduction of **23** with nickel boride[6] gave successfully the 2-unsubstituted 4,5-dibenzylimidazole **25** in 62% yield. The structure of **25** was supported by ^{1}H-NMR spectra and other analytical data (Scheme 2).

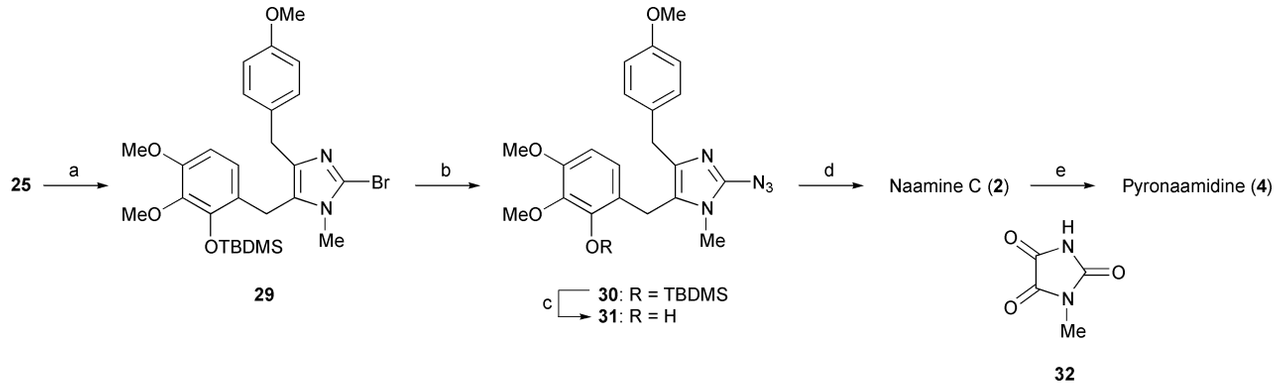
The imidazole **25** was brominated by NBS to give the 2-bromoimidazole **29**, which was subjected to lithiation with *tert*-butyllithium followed by treatment with trisyl azide[9]† to afford the 2-azido **30** in 46% overall yield from **25**. The TBDMS group of **30** was removed by treatment with TBAF, and the subsequent hydrogenation over 10% Pd–C gave naamine C **2** in 84% yield from **30** in 2 steps. Naamine C **2** was isolated as a yellow powder, the physical and spectral data of which almost agreed with those of the natural product reported[1f,10] (Scheme 4).

The final step was construction of the 2-(1-methyl-2,5-dioxo-3*H*-imidazolin-4-yl)amino moiety. We have already reported a method for the regio-selective condensation of arylamine with 1-methylparabanic acid ‡ **32** for constructing the side chain, and its application to the total synthesis of clathridine **8**.[4] This time, naamine C **2** was treated with **32** in the presence of TMSCl and *N,N*-diisopropylethylamine according to the previous procedure[11] to give successfully pyronaamidine **4** in 28% yield as yellow needles, the melting point and spectral data of which were all consistent with those of the natural product reported by Scheuer[1e,12] (Scheme 4).

While pyrronaamidine **4** was isolated at a relatively early stage among many imidazole alkaloids of sponges, its total

† The IUPAC name for trisyl azide is azidotriphenylsilane.

‡ The IUPAC name for parabanic acid is imidazolidinetrione.



Scheme 4 *Reagents*: (a) NBS, THF, 59%; (b) (i) *tert*-BuLi, THF, (ii) trisyl azide, 78%; (c) TBAF, THF, 87%; (d) H_2, 10% Pd–C, EtOH, 97%; (e) *N,N*-diisopropylethylamine, TMSCl, $CHCl_3$, 28%.

synthesis had not been reported, and we were fortunately able to achieve the first total synthesis of **4** through **2**.

Experimental

All melting points were measured with a Yanaco MP micro-melting points apparatus without correction. IR was taken with a Shimadzu IR-435 spectrometer. ^{1}H-NMR spectra were measured on a Varian INOBA 400NB (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) with tetramethylsilane as an internal standard and chemical shifts δ are reported in ppm. Abbreviations of ^{1}H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); m (multiplet). Mass spectra (MS) and high-resonance MS (HRMS) were obtained on a JEOL JMS BU-20 spectrometer under EI ionizing conditions. Silica gel (Merck Art. 7734) was used for column chromatography.

5-[1-(*tert*-Butyldimethylsiloxy)-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)methyl]-4-[1-hydroxy-1-(4-methoxyphenyl)-methyl]-1-methyl-2-phenylthio-1*H*-imidazole (15)

A solution of *tert*-BuLi in *n*-pentane (1.51 M; 0.44 mL, 0.66 mmol) was added dropwise to a solution of **14**[5] (200 mg, 0.33 mmol) in THF (2 mL) under an N_2 atmosphere at −78 °C. Stirring was continued for 1 h, then a solution of *p*-anisaldehyde (0.20 mL, 1.64 mmol) in THF (0.5 mL) was added dropwise at −78 °C. Stirring was continued for 3 h at −78 °C, then water (2 mL) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOEt–*n*-hexane 1 : 5) on silica gel to give **15** (95 mg, 43%), a diastereomeric mixture (*ca.* 1 : 1) as a pale yellow viscous material; ν_{max} ($CHCl_3$) 2917, 1473, 1242, 1083, 834 cm^{-1}; δ_H ($CDCl_3$) −0.28 (s, 3H, SiCH_3), −0.11 (s, 3H, SiCH_3), −0.07 (s, 3H, SiCH_3), 0.04 (s, 3H, SiCH_3), 0.84 [s, 9H, SiC(CH_3)$_3$], 0.85 [s, 9H, SiC(CH_3)$_3$], 3.29 (s, 3H, NCH_3), 3.40 (s, 3H, NCH_3), 3.56 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.78 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.61 (d, 1H, J = 4.9 Hz, OCH_aH$_b$O), 4.92 (d, 1H, J = 5.0 Hz, OCH_aH$_b$O), 4.97 (d, 1H, J = 5.1 Hz, OCH$_a$$H_b$O), 5.09 (d, 1H, J = 4.9 Hz, OCH$_a$$H_b$O), 5.78 (d, 1H, J = 7.5 Hz, ArCH(OH)Ar), 6.00 (d, 1H, J = 7.5 Hz, ArCH(OH)Ar), 6.28 (s, 1H, ArCH(OTBDMS)Ar), 6.37 (s, 1H, ArCH(OTBDMS)-Ar), 6.67 (d, 2H, J = 8.8 Hz, Ar–H), 6.796 (d, 2H, J = 8.8 Hz, Ar–H), 6.802 (d, 2H, J = 8.8 Hz, Ar–H), 7.03–7.38 (m, 16H, Ar–H) [HRMS *m*/*z* Calc. for $C_{35}H_{46}N_2O_7SSi$: *M*, 666.2795. Found: M$^+$, 666.2799].

5-[1-Hydroxy-1-(3,4-dimethoxy-2-methoxymethoxyphenyl)-methyl]-4-[1-hydroxy-1-(4-methoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (16)

A solution of TBAF in THF (1 M; 0.14 mL, 0.14 mmol) was added dropwise to a solution of **15** (78 mg, 0.12 mmol) in THF at room temperature. The mixture was stirred for 10 min at room temperature. Water (0.5 mL) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOEt) on silica gel to give **16** (57 mg, 88%), a diastereomeric mixture (*ca.* 1 : 1), as a pale yellow viscous material; ν_{max} ($CHCl_3$) 3384, 2920, 1596, 1450, 1240, 1090 cm^{-1}; δ_H ($CDCl_3$) 3.37 (s, 3H, NCH_3), 3.42 (s, 3H, NCH_3), 3.50 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 6H, 2 × OCH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.137 (d, 1H, J = 5.7 Hz, OCH_aH$_b$O), 5.141 (d, 1H, J = 5.9 Hz, OCH_aH$_b$O), 5.16 (d, 1H, J = 5.9 Hz, OCH$_a$$H_b$O), 5.18 (d, 1H, J = 5.0 Hz, OCH$_a$$H_b$O), 5.94 (s, 1H, ArC$H$(OH)Ar), 6.00 (s, 1H, ArCH(OH)Ar), 6.19 (s, 2H, 2 × ArCH(OH)Ar), 6.36 (d, 1H, J = 8.4 Hz, Ar–H), 6.47 (d, 1H, J = 8.8 Hz, Ar–H), 6.55 (d, 1H, J = 8.8 Hz, Ar–H), 6.58 (d, 1H, J = 8.6 Hz, Ar–H), 6.76 (d, 2H, J = 8.8 Hz, Ar–H), 6.82 (d, 2H, J = 8.8 Hz, Ar–H), 7.09–7.41 (m, 14H, Ar–H) [HRMS *m*/*z* Calc. for $C_{29}H_{32}N_2O_7S$: *M*, 552.1930. Found: M$^+$ 552.1933].

6,7-Dimethoxy-8-hydroxy-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho[2,3-*d*]imidazole (18)

Zn powder (114 mg) was added to a mixture of acetic acid (0.5 mL), *conc.* HCl (0.05 mL) and **16** (42 mg, 0.08 mmol), and then the whole was stirred at 80 °C for 1 h. The reaction mixture was filtered through a cotton plug, and the filtrate was evaporated under reduced pressure. After addition of water (0.5 mL), K_2CO_3 powder was added to basify, and the whole was extracted with AcOEt (2 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1) on silica gel to give **18** (27 mg, 75%) as a pale yellow viscous material; ν_{max} ($CHCl_3$) 3484, 2979, 1655, 1477, 1240, 1096 cm^{-1}; δ_H ($CDCl_3$) 3.75 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.33 (s, 1H, ArOH), 6.97 (s, 1H, Ar–H), 7.08 (d, 2H, J = 8.8 Hz, Ar–H), 7.21–7.36 (m, 5H, Ar–H), 7.59 (d, 2H, J = 8.8 Hz, Ar–H), 7.94 (s, 1H, Ar–H); δ ($CDCl_3$) 31.0, 55.3, 55.5, 61.4, 97.0, 99.1, 113.8, 118.6, 125.9, 127.29, 127.32, 128.8, 129.3, 129.5, 132.1, 132.4, 132.6, 135.2, 141.6, 143.2, 150.3, 150.8, 158.9 [HRMS *m*/*z* Calc. for $C_{27}H_{24}N_2O_4S$: *M*, 472.1457. Found: M$^+$, 472.1458].

5-[1-Hydroxy-1-(2-*tert*-butyldimethylsiloxy-3,4-dimethoxy-phenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (20)

A solution of *n*-BuLi in *n*-hexane (1.6 M; 12.7 mL, 20.3 mmol) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (3.8 mL, 22.3 mmol) in THF (50 mL) under an N_2 atmosphere at −78 °C, and the mixture was stirred for 15 min. A solution of **11** (3.86 g, 20.3 mmol) in THF (6 mL) was added

dropwise to the mixture, and the mixture was stirred for 1 h at −78 °C. A solution of 2-*tert*-butyldimethylsiloxy-3,4-dimethoxybenzaldehyde **19**[8] (6.02 g, 20.3 mmol) in THF (6 mL) was added dropwise to the mixture and the whole was stirred at the same temperature for 2 h. Water (20 mL) was added, and the mixture was extracted with AcOEt (50 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to give a crystalline mass, which was purified by column chromatography (AcOEt–*n*-hexane = 1 : 1) on silica gel followed by recrystallization from *n*-hexane–AcOEt to afford **20** (7.70 g, 78%), mp 122.3–122.5 °C (colorless needles); ν_{max} ($CHCl_3$) 3150, 2928, 1597, 1455, 1277, 1098, 834 cm^{-1}; δ_H ($CDCl_3$) 0.09 (s, 3H, SiCH_3), 0.23 (s, 3H, SiCH_3), 0.88 [s, 9H, SiC(CH_3)$_3$], 3.63 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.09 (s, 1H, ArC*H*(OH)Im), 6.60 (d, 1H, *J* = 8.6 Hz, Ar–H), 6.69 (s, 1H, Im–H), 7.01 (d, 1H, *J* = 8.8 Hz, Ar–H), 7.12–7.26 (m, 5H, Ar–H); δ ($CDCl_3$) −4.5, −4.3, 18.6, 25.9, 31.8, 55.9, 60.4, 63.1, 105.2, 122.2, 124.9, 126.5, 128.0, 129.2, 129.5, 134.8, 136.7, 139.0, 139.4, 146.5, 153.4 [Calcd for $C_{25}H_{34}N_2O_4SSi$: C, 61.69; H, 7.04; N, 5.76. Found; C, 61.45; H, 7.07; N, 5.99%. HRMS *m*/*z* Calc. for $C_{25}H_{34}N_2O_4SSi$: *M*, 486.2008. Found: M^+, 486.2015].

5-[1-(2-*tert*-Butyldimethylsiloxy-3,4-dimethoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (21)

To a solution of **20** (2.0 g, 4.1 mmol) in 12 ml of CH_2Cl_2 were added a solution of triethylsilane (3.3 ml, 20.5 mmol) and a solution of TFA (1.9 ml, 24.6 mmol). The solution was stirred for 12 h at rt under N_2 and quenched by the addition of saturated aqueous $NaHCO_3$ solution (15 ml). The mixture was extracted with $CHCl_3$ (15 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane = 1 : 2) on silica gel to give **21** (1.90 g, 98%) as a pale yellow viscous material; ν_{max} ($CHCl_3$) 2916, 1457, 1098, 834 cm^{-1}; δ_H ($CDCl_3$) 0.21 [s, 6H, Si(CH_3)$_2$], 0.97 [s, 9H, SiC(CH_3)$_3$], 3.40 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 2H, ArCH_2Im), 6.47 (d, 1H, *J* = 8.6 Hz, Ar–H), 6.55 (d, 1H, *J* = 8.6 Hz, Ar–H), 6.90 (s, 1H, Im–H), 7.10–7.26 (m, 5H, Ar–H); δ ($CDCl_3$) −4.2, 18.7, 25.4, 26.0, 31.1, 55.8, 60.3, 105.0, 121.4, 123.5, 126.3, 127.6, 129.1, 129.2, 134.3, 135.4, 137.2, 139.8, 147.1, 152.4 [HRMS *m*/*z* Calc. for $C_{25}H_{34}N_2O_3SSi$: *M*, 470.2059. Found: M^+, 470.2050].

4-Bromo-5-[1-(2-*tert*-butyldimethylsiloxy-3,4-dimethoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (22)

NBS (182 mg, 1.02 mmol) was added to a solution of **21** (482 mg, 1.02 mmol) in THF (4 ml) under an N_2 atmosphere at 0 °C, and the whole was stirred for 1 h at 0 °C. Then water (1 ml) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOEt–*n*-hexane = 1 : 2) on silica gel to afford **22** (454 mg, 81%), mp 86.6–88.4 °C (colorless crystals, recrystallized from *n*-hexane–AcOEt); ν_{max} ($CHCl_3$) 2915, 1599, 1457, 1253, 1098, 834 cm^{-1}; δ_H ($CDCl_3$) 0.25 [s, 6H, Si(CH_3)$_2$], 1.03 [s, 9H, SiC(CH_3)$_3$], 3.36 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.92 (s, 2H, ArCH_2Im), 6.38 (d, 1H, *J* = 8.6 Hz, Ar–H), 6.44 (d, 1H, *J* = 8.6 Hz, Ar–H), 7.16–7.29 (m, 5H, Ar–H); δ ($CDCl_3$) −4.1, 18.8, 24.3, 26.1, 32.0, 55.8, 60.3, 105.2, 116.1, 120.8, 122.4, 126.8, 128.0, 129.3, 132.1, 134.4, 137.1, 139.8, 146.9, 152.4 [Calc. For $C_{25}H_{33}BrN_2O_3SSi$: C, 54.63; H, 6.05; N, 5.10. Found: C, 54.41; H, 5.99; N, 5.19%. MS *m*/*z* (% base): 551 (3), 550 (7), 549 (2), 548 (6), 496 (2), 495 (12), 494 (28), 493 (100), 492 (26), 491 (92), 478 (18), 476 (15), 397 (15), 209 (27), 199 (24). HRMS *m*/*z* Calc. for $C_{25}H_{33}BrN_2O_3SSi$: *M*, 548.1164. Found: M^+, 548.1177].

5-[1-(2-*tert*-Butyldimethylsiloxy-3,4-dimethoxyphenyl)methyl]-4-[1-hydroxy-1-(4-methoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (23)

[Method A]. A solution of *tert*-BuLi in *n*-pentane (1.56 M; 0.17 mL, 0.26 mmol) was added dropwise to a solution of **22** (72 mg, 0.13 mmol) in THF (1.0 mL) under an N_2 atmosphere at −78 °C. Stirring was continued for 1 h, then a solution of *p*-anisaldehyde (0.08 mL, 0.66 mmol) in THF (0.5 mL) was added dropwise at −78 °C. Stirring was continued for 3 h at −78 °C, then water (2 mL) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOEt–*n*-hexane = 1 : 2) on silica gel to give **23** (12 mg, 15%) as a pale yellow viscous material.

[Method B]. A solution of *tert*-BuLi in *n*-pentane (1.56 M; 0.23 mL, 0.36 mmol) was added dropwise to a mixed solution of **22** (100 mg, 0.18 mmol) and *p*-anisaldehyde (0.11 mL, 0.91 mmol) in THF (1.5 mL) under an N_2 atmosphere at −78 °C. Stirring was continued at −78 °C and a solution of *tert*-BuLi in *n*-pentane [1.56 M; 0.46 mL (0.23 mL × 2), 0.72 mmol] was added to the reaction mixture every 15 min until TLC of the reaction mixture indicated disappearance of the starting compound **22**. After stirring was continued for 1 h at −78 °C, water (1 mL) was added to the mixture. The mixture was extracted with AcOEt, and the organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOEt–*n*-hexane = 1 : 2) on silica gel to give **23** (98 mg, 89%) as a pale yellow viscous material; ν_{max} ($CHCl_3$) 3400, 2916, 1602, 1457, 1246, 1098, 834 cm^{-1}; δ_H ($CDCl_3$) 0.197 (s, 3H, SiCH_3), 0.203 (s, 3H, SiCH_3), 0.98 [s, 9H, SiC(CH_3)$_3$], 3.29 (s, 3H, NCH_3), 3.61 (br s, 1H, O*H*), 3.73 (s, 3H, OCH_3), 3.75 (s, 2H, ArCH_2Im), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.73 (d, 1H, *J* = 3.7 Hz, ArC*H*(OH)Im), 6.10 (d, 1H, *J* = 8.6 Hz, Ar–H), 6.32 (d, 1H, *J* = 8.6 Hz, Ar–H), 6.79 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.10–7.35 (m, 7H, Ar–*H*); δ ($CDCl_3$) −4.2, 18.7, 24.0, 26.1, 31.1, 55.2, 55.8, 60.3, 69.7, 104.9, 113.6, 121.4, 122.3, 126.4, 127.4, 127.9, 127.9, 129.2, 135.1, 135.6, 136.0, 139.7, 142.8, 146.8, 152.2, 158.9 [HRMS *m*/*z* Calc. for $C_{33}H_{42}N_2O_5SSi$: *M*, 606.2583. Found: M^+, 606.2591].

8-(*tert*-Butyldimethylsilyloxy)-6,7-dimethoxy-4-(4-methoxyphenyl)-1-methyl-2-phenylthio-4,9-dihydro-1*H*-naphtho[2,3-*d*]-imidazole (26)

To a solution of **23** (54 mg, 0.09 mmol) in 1.5 ml of CH_2Cl_2 were added a solution of triethylsilane (0.02 mL, 0.13 mmol) and a solution of TFA (0.02 mL, 0.27 mmol). The solution was stirred for 12 h at rt under N_2 and quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 ml). The mixture was extracted with $CHCl_3$ (2 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane = 1 : 1) on silica gel to give **26** (41 mg, 79%) as colorless crystals; ν_{max} ($CHCl_3$) 2917, 1603, 1490, 1246, 1126, 834 cm^{-1}; δ_H ($CDCl_3$) 0.27 (s, 3H, SiCH_3), 0.28 (s, 3H, SiCH_3), 1.07 [s, 9H, SiC(CH_3)$_3$], 3.55 (s, 3H, NCH_3), 3.746 (s, 3H, OCH_3), 3.752 (s, 3H, OCH_3), 3.754 (s, 3H, OCH_3), 3.83 (d, 1H, *J* = 3.7 Hz, ArC$H_a$$H_b$Im), 3.87 (d, 1H, *J* = 3.5 Hz, ArCH$_a$$H_b$Im), 5.22 (t, 1H, *J* = 3.4 Hz, ArC*H*(Ar)Im), 6.40 (s, 1H, Ar–H), 6.78 (d, 2H, *J* = 8.6 Hz, Ar–H), 7.02–7.22 (m, 7H, Ar–H) [HRMS *m*/*z* Calc. for $C_{33}H_{40}N_2O_4SSi$: *M*, 588.2478. Found: M^+, 588.2470].

5-[1-(2-*tert*-Butyldimethylsiloxy-3,4-dimethoxyphenyl)methyl]-4-[1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (25)

Sodium borohydride (1.08 g, 28.51 mmol) was added to a solution of **23** (412 mg, 0.68 mmol) and nickel(II) chloride

hexahydrate (2.26 g, 9.51 mmol) in MeOH–THF = 1 : 1 (20 mL) under an N_2 atmosphere at 0 °C, and the whole was refluxed for 2 h. The solvent was evaporated off, then water (20 mL) was added to the residue. The mixture was extracted with $CHCl_3$. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography ($CHCl_3$–MeOH = 20 : 1) on silica gel to give **25** (202 mg, 62%) as a pale yellow viscous material; ν_{max} ($CHCl_3$) 2918, 1601, 1457, 1241, 1099, 834 cm^{-1}; δ_H ($CDCl_3$) 0.25 [s, 6H, Si(CH_3)$_2$], 1.03 [s, 9H, SiC(CH_3)$_3$], 3.33 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.82 (s, 2H, ArCH_2Im), 3.84 (s, 2H, ArCH_2Im), 6.21 (d, 1H, J = 8.6 Hz, Ar–H), 6.36 (d, 1H, J = 8.6 Hz, Ar–H), 6.77 (d, 2H, J = 8.6 Hz, Ar–H), 7.16 (d, 2H, J = 8.6 Hz, Ar–H), 7.37 (s, 1H, Im–H); δ ($CDCl_3$) −4.1, 18.8, 23.0, 26.1, 31.4, 33.0, 55.2, 55.8, 60.3, 104.8, 113.7, 122.5, 122.7, 125.1, 129.5, 133.0, 136.6, 139.2, 146.8, 152.1, 157.7 [HRMS *m*/*z* Calc. for $C_{27}H_{38}N_2O_4Si$: *M*, 482.2601. Found: M^+, 482.2592].

2-Bromo-5-[1-(2-*tert*-butyldimethylsiloxy-3,4-dimethoxyphenyl)-methyl]-4-[1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (29)

NBS (9 mg, 0.05 mmol) was added to a solution of **25** (25 mg, 0.05 mmol) in THF (0.5 ml) under an N_2 atmosphere at 0 °C, and then the whole was stirred for 1 h at 0 °C. Then water (0.5 ml) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOEt–*n*-hexane = 1 : 2) on silica gel to give **29** (17 mg, 59%) as a pale yellow viscous material; ν_{max} ($CHCl_3$) 2917, 1602, 1460, 1244, 1098, 834 cm^{-1}; δ_H ($CDCl_3$) 0.24 [s, 6H, Si(CH_3)$_2$], 1.02 [s, 9H, SiC(CH_3)$_3$], 3.27 (s, 3H, NCH_3), 3.76 (s, 6H, 2 × OCH_3), 3.810 (s, 2H, ArCH_2Im), 3.813 (s, 3H, OCH_3), 3.83 (s, 2H, ArCH_2Im), 6.24 (d, 1H, J = 8.6 Hz, Ar–H), 6.38 (d, 1H, J = 8.6 Hz, Ar–H), 6.77 (d, 2H, J = 8.8 Hz, Ar–H), 7.15 (d, 2H, J = 8.8 Hz, Ar–H); δ ($CDCl_3$) −4.1, 18.8, 23.9, 26.1, 32.0, 33.0, 55.2, 55.8, 60.3, 104.9, 113.7, 118.3, 121.9, 122.5, 128.3, 129.5, 132.5, 139.7, 139.8, 146.8, 152.2, 157.8 [MS *m*/*z* (% base): 562 (2), 560 (2), 507 (2), 506 (8), 505 (28), 504 (8), 503 (26), 383 (10), 381 (10), 279 (6), 209 (6), 121 (100). HRMS *m*/*z* Calc. for $C_{27}H_{37}BrN_2O_4Si$: *M*, 560.1705. Found: M^+, 560.1714].

2-Azido-5-[1-(2-*tert*-butyldimethylsiloxy-3,4-dimethoxyphenyl)-methyl]-4-[1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (30)

A solution of *tert*-BuLi in *n*-pentane (1.56 M; 0.43 mL, 0.66 mmol) was added dropwise to a solution of **29** (124 mg, 0.22 mmol) under an N_2 atmosphere at −78 °C. The mixture was stirred for 15 min at −78 °C, then trisyl azide (205 mg, 0.66 mmol) was added, and then the whole was stirred for 1 h at −78 °C. Water (1 mL) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography (AcOEt–*n*-hexane = 1 : 3) on silica gel to give **30** (90 mg, 78%) as a pale yellow viscous material; ν_{max} ($CHCl_3$) 2916, 2120, 1601, 1499, 1245, 1098, 834 cm^{-1}; δ_H ($CDCl_3$) 0.23 [s, 6H, Si(CH_3)$_2$], 1.01 [s, 9H, SiC(CH_3)$_3$], 3.07 (s, 3H, NCH_3), 3.746 (s, 3H, OCH_3), 3.753 (s, 2H, ArCH_2Im), 3.76 (s, 3H, OCH_3), 3.79 (s, 2H, ArCH_2Im), 3.81 (s, 3H, OCH_3), 6.27 (d, 1H, J = 8.6 Hz, Ar–H), 6.37 (d, 1H, J = 8.6 Hz, Ar–H), 6.78 (d, 2H, J = 8.8 Hz, Ar–H), 7.16 (d, 2H, J = 8.8 Hz, Ar–H); δ ($CDCl_3$) −4.1, 18.8, 23.3, 26.1, 29.2, 32.7, 55.2, 55.8, 60.3, 104.9, 113.7, 122.4, 122.5, 124.5, 129.4, 132.7, 136.5, 138.9, 139.7, 146.8, 152.1, 157.8 [HRMS *m*/*z* Calc. for $C_{27}H_{37}N_5O_4Si$: *M*, 523.2614. Found: M^+, 523.2612].

2-Azido-5-[1-(2-hydroxy-3,4-dimethoxyphenyl)methyl]-4-[1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (31)

A solution of TBAF in THF (1 M; 1.00 mL, 1.00 mmol) was added dropwise to a solution of **30** (476 mg, 0.91 mmol) in THF (5 mL) at room temperature. The mixture was stirred for 5 min at room temperature. Water (2 mL) was added, and the mixture was extracted with AcOEt. The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue. The crude product was purified by column chromatography ($CHCl_3$–MeOH = 50 : 1) on silica gel to give **31**, yellow crystals (322 mg, 87%), mp 140 °C dec. (recrystallized from $CHCl_3$–*n*-hexane); ν_{max} ($CHCl_3$) 3475, 2924, 2121, 1607, 1500, 1458, 1240, 1169, 1093 cm^{-1}; δ_H ($CDCl_3$) 3.13 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 3.78 (s, 2H, ArCH_2Im), 3.816 (s, 3H, OCH_3), 3.823 (s, 2H, ArCH_2Im), 3.89 (s, 3H, OCH_3), 6.31 (d, 1H, J = 8.8 Hz, Ar–H), 6.38 (d, 1H, J = 8.6 Hz, Ar–H), 6.78 (d, 2H, J = 8.8 Hz, Ar–H), 7.16 (d, 2H, J = 8.8 Hz, Ar–H); δ ($CDCl_3$) 22.4, 29.3, 32.6, 55.2, 55.8, 60.9, 103.5, 113.7, 117.1, 123.3, 124.4, 129.4, 132.8, 135.2, 136.2, 138.8, 146.9, 150.9, 157.8 [HRMS *m*/*z* Calc. for $C_{21}H_{23}N_5O_4$: *M*, 409.1750. Found: M^+, 409.1749].

Naamine C 2

A mixture of **31** (52 mg, 0.13 mmol) and 10% Pd/C (10 mg) in EtOH (3 mL) was stirred for 24 h under an H_2 atmosphere at room temperature. The catalyst was removed by filtration with $CHCl_3$ and the filtrate was evaporated to give an oily residue. The crude product was purified by column chromatography ($CHCl_3$: MeOH = 5 : 1) on silica gel to give **2** as a yellow powder[1f,10] (47 mg, 97%); ν_{max} ($CHCl_3$) 3251, 3107, 2932, 1660, 1608, 1504, 1458, 1236, 1093 cm^{-1}; δ_H ($CDCl_3$) 3.25 (s, 3H, NCH_3), 3.736 (br s, 2H, ArCH_2Im), 3.742 (s, 3H, OCH_3), 3.75 (br s, 2H, ArCH_2Im), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.35 (d, 1H, J = 8.6 Hz, Ar–H), 6.47 (d, 1H, J = 8.6 Hz, Ar–H), 6.77 (d, 2H, J = 8.8 Hz, Ar–H), 7.10 (d, 2H, J = 8.8 Hz, Ar–H); δ ($CDCl_3$) 22.1, 29.7, 29.9, 55.2, 55.8, 61.0, 103.7, 114.0, 115.9, 120.9, 123.3, 124.7, 129.5, 130.1, 135.5, 146.7, 147.2, 151.3, 158.2 [HRMS *m*/*z* Calc. for $C_{21}H_{25}N_3O_4$: *M*, 383.1845. Found: M^+, 383.1843].

Pyronaamidine 4

A solution of 1-methylparabanic acid **32** (30 mg, 0.24 mmol) and *N,N*-diisopropylethylamine (0.11 mL, 0.61 mmol) and trimethylsilyl chloride (0.06 mL, 0.49 mmol) in $CHCl_3$ (0.5 mL) was stirred for 5 min under an N_2 atmosphere at 0 °C, and then the stirring was continued for 2 h at room temperature. A solution of naamine C **2** (90 mg, 0.24 mmol) in $CHCl_3$ (0.5 mL) was added to the mixture, the whole was refluxed for 48 h. The solution was evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$–MeOH = 5 : 1) on silica gel to afford **4**, yellow crystals (32 mg, 28%), mp 182.3–184.5 °C (recrystallized from $CHCl_3$–*n*-hexane; lit.[1e,12] mp 185–187 °C); ν_{max} ($CHCl_3$) 3476, 2977, 1783, 1732, 1659, 1609, 1563, 1504, 1457, 1388, 1297, 1240, 1172, 1144, 1094, 1031 cm^{-1}; δ_H (CD_2Cl_2) 3.09 (s, 3H, NCH_3), 3.54 (s, 3H, –OCH_3), 3.75 (s, 3H, –OCH_3), 3.80 (s, 3H, –OCH_3), 3.87 (s, 3H, –OCH_3), 3.88 (s, 2H, ArCH_2Im), 3.90 (s, 2H, ArCH_2Im), 6.35 (d, 1H, J = 8.6 Hz, Ar–H), 6.44 (d, 1H, J = 8.6 Hz, Ar–H), 6.79 (d, 2H, J = 8.8 Hz, Ar–H), 7.10 (d, 2H, J = 8.8 Hz, Ar–H); δ (CD_2Cl_2) 23.2, 24.7, 30.0, 32.2, 55.5, 56.1, 61.2, 104.0, 114.1, 116.4, 123.7, 126.9, 129.7, 131.9, 135.2, 135.8, 146.5, 146.8, 147.5, 151.6, 156.4, 158.5, 162.7 [Calc. For $C_{25}H_{27}N_5O_6 \cdot \frac{1}{2}H_2O$: C, 59.75; H, 5.62; N, 13.94. Found: C, 59.56; H, 5.53; N, 13.81%. HRMS *m*/*z* Calc. for $C_{25}H_{27}N_5O_6$: *M*, 493.1961. Found: M^+, 493.1974].

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10 The reported physical data for the natural naamine C (ref. 1*f*): yellow powder; δ_H (500 MHz; $CDCl_3$) 3.26 (s, 3H), 3.72 (s, 3H), 3.73 (br s, 4H), 3.81 (s, 3H), 3.87 (s, 3H), 6.34 (d, 1H, J = 8.7 Hz), 6.46 (d, 1H, J = 8.7 Hz), 6.76 (d, 2H, J = 8.7 Hz), 7.06 (d, 2H, J = 8.7 Hz); δ (125 MHz; $CDCl_3$) 22.6, 29.3, 29.6, 55.3, 55.8, 61.0, 103.8, 114.2, 115.1, 121.1, 122.7, 123.3, 129.0, 129.5, 135.5, 146.4, 147.1, 151.5, 158.5. IR was not reported in ref. 1*f*.

11 At this time *N,N*-diisopropylethylamine was used instead of Et_3N and imidazole, which were used in ref. 4. Although use of the latter bases resulted in low yield of **4** (10% yield), use of the former base somewhat improved the yield of **4** (28% yield).

12 The reported physical data for the natural pyronaamidine (ref. 1*e*): mp 185–187 °C (yellow feathery crystals); ν_{max} ($CHCl_3$) 3403 (br) 1790, 1732, 1664, 1613, 1567, 1510, 1444, 1392, 1302, 1246, 1178, 1148, 1096, 1034, 968, 752, 606 cm^{-1}; δ_H (500 MHz; CD_2Cl_2) 3.09 (s, 3H), 3.54 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 3.88 (s, 2H), 3.90 (s, 2H), 6.34 (d, 1H), 6.44 (d, 1H), 6.78 (d, 2H), 7.15 (d, 2H), 8.14 (br s, 1H), 8.14 (br s, 1H); δ (125 MHz; CD_2Cl_2) 23.2, 24.7, 29.9, 32.1, 55.5, 56.0, 61.1, 104.0, 114.1, 116.4, 123.7, 126.9, 129.7, 131.9, 135.1, 135.8, 146.5, 146.7, 147.5, 151.7, 156.4, 158.5, 162.7.