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1-METHYL-3-TRIMETHYLSILYLPARABANIC ACID AS AN EFFECTIVE REAGENT FOR THE PREPARATION OF *N*-SUBSTITUTED (1-METHYL-2,5-DIOXO-1,2,5*H*-IMIDAZOLIN-4-YL)-AMINES AND ITS APPLICATION TO THE TOTAL SYNTHESIS OF ISONAAMIDINES A AND C, ANTITUMOR IMIDAZOLE ALKALOIDS

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Abstract – 1-Methyl-3-trimethylsilylparabanic acid (**17**) was successfully used in the final step of the total synthesis of isonaamidine A (**9**), isonaamidine C (**11**) and pyronaamidine (**8**), antitumor marine imidazole alkaloids.

In recent years, many types of biologically active imidazole alkaloids have been isolated from marine organisms such as sponges, and they have become the focus of scientific study.[1,2] For example, several highly substituted imidazole alkaloids, shown in Figure 1, have been isolated from a bright yellow sponge, *Leucetta* sp., and these alkaloids generally have interesting biological properties such as strong antitumor and antifungal activities.[3] In particular, it was reported in 1998 by Ireland that naamidine A (**2**), isonaamidine B (**10**) and isonaamidine C (**11**) acted as inhibitors against the epidermal growth factor receptor, which played an important role in the development of some human tumors.[3c] As far as the alkaloids (**4**-**11**) are concerned, the 2-position of the imidazole ring is substituted with a characteristic (1-methyl-2,5-dioxo-1,2,5*H*-imidazolin-4-yl)amino moiety. In the previous paper,[4] we reported a procedure for the construction of the (1-methyl-2,5-dioxoimidazolin-4-yl)amino moiety at the 2-position of imidazole ring,[5] and we applied it to the first total synthesis of **4**,[4] **5**[6] and **8**;[7] however, the reported reactions were sometimes proceeded in very low yield.[4] In this paper, we would like to report a dramatically improved method for the construction of the moiety, and its successful application to the total synthesis of isonnaamidines A (**9**), C (**11**) and pyronaamidine (**8**).

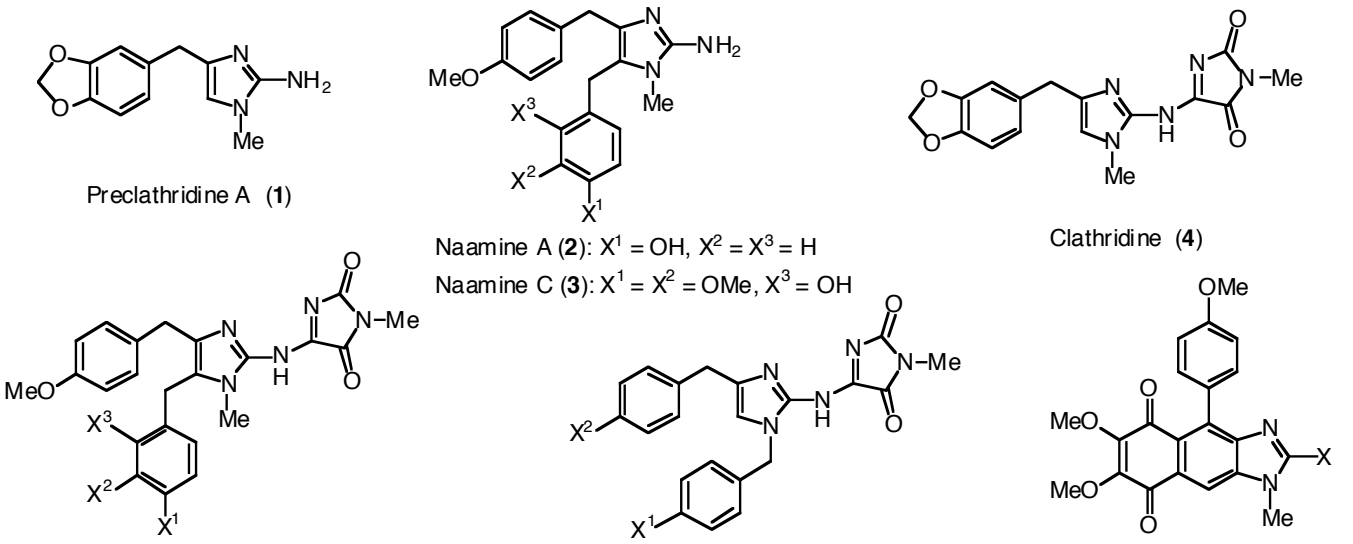
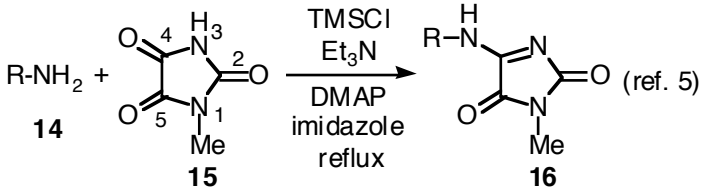
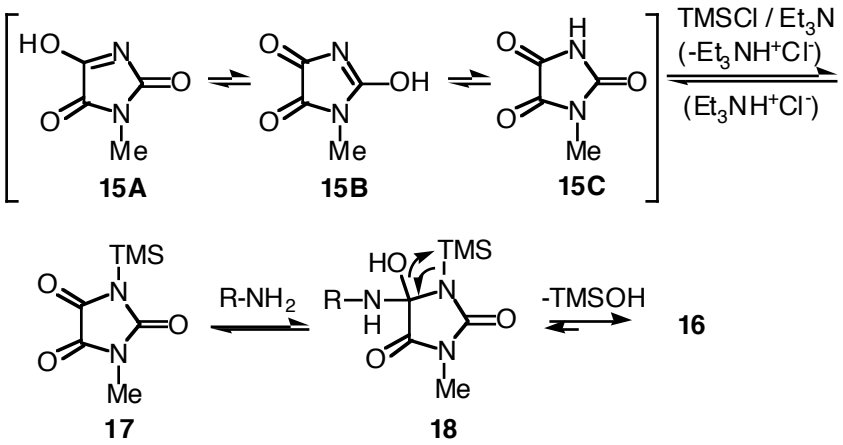


Figure 1

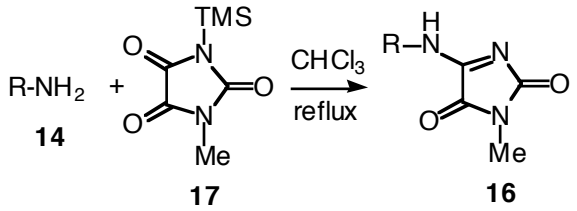
In the previous procedure for the construction of the (1-methyl-2,5-dioxo-1,2,5*H*-imidazolin-4-yl)amino moiety, 1-methylparabanic acid (**15**) was treated with primary amines in the presence of trimethylsilyl chloride, triethylamine and imidazole in chloroform to give the corresponding imidazolines (**16**) in low to fair yields (Scheme 1).[5] We presumed the reaction mechanism as shown in Scheme 2, and in this mechanism the carbonyl group at the 4-position of the initially produced 1-methyl-3-trimethylsilylparabanic acid (**17**) might be activated to accept readily an addition of primary amines and elimination of the hydroxy group from **18** because the intermediate (**17**) did not enolize. The low yields may be due to salt formation as a side reaction between 1-methylparabanic acid and these amines as well as instability of the intermediate 1-methyl-3-trimethylsilylparabanic acid (**17**) in the presence of triethylamine hydrochloride formed.



Scheme 1



Scheme 2. Plausible mechanism for the condensation of 1-methylparabanic acid with primary amines



Scheme 3

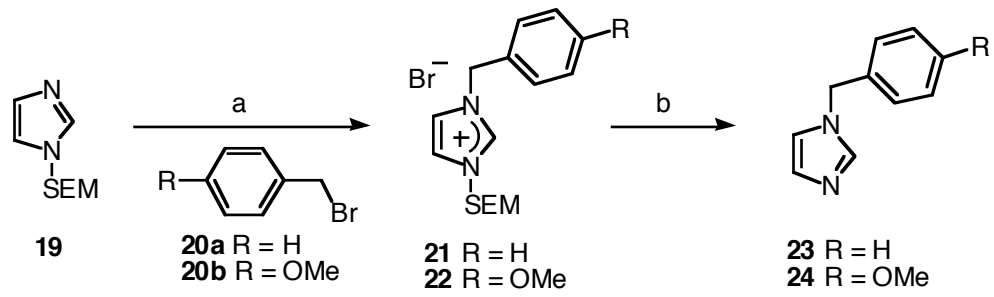
Table 1. Condensation of **17** with primary amines

Entry	R-NH_2	Product No.[a)]	Yield (%)[b)]
1	$C_6H_5NH_2$	**16a**	96 (64)
2	4-$BrC_6H_4NH_2$	**16b**	94 (10)
3	3,5-$Me_2C_6H_3NH_2$	**16c**	84 (72)
4	2-$MeOC_6H_4NH_2$	**16d**	92 (60)
5	3-$MeOC_6H_4NH_2$	**16e**	96 (50)
6	4-$MeOC_6H_4NH_2$	**16f**	96 (30)
7	2-amino-1-methylbenzimidazole	**16g**	77 (25)
8	*c*-$C_6H_{11}NH_2$	**16h**	98 (-)
9	$C_6H_4(CH_2)_3NH_2$	**16i**	98 (-)
10	naamine C (**3**)	pyronaamidine (**8**)	85 (28)

a: Satisfactory analytical and spectral data were obtained.
b: Isolated yield. Yields in parentheses were those of the previous report (ref. 4).

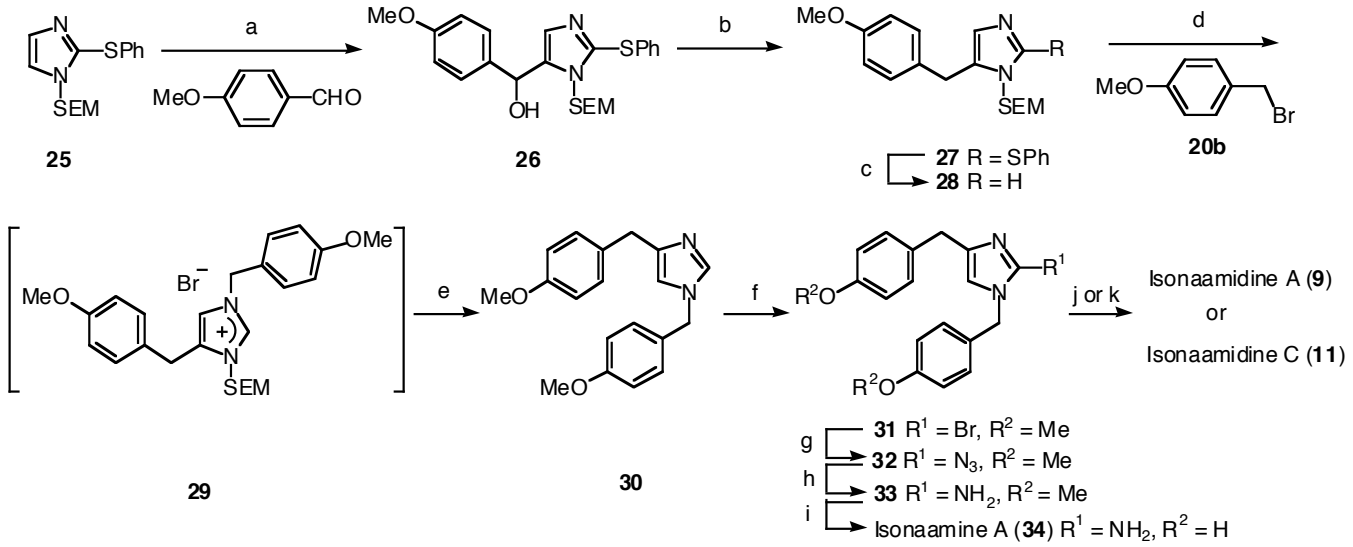
We considered the formation of the salt and triethylamine hydrochloride can be avoided if 1-methyl-3-trimethylsilylparabanic acid (**17**) is used instead of the parabanic acid – TMSCl – triethylamine system, and we planned to prepare and isolate 1-methyl-3-trimethylsilylparabanic acid (**17**). Thus, 1-methylparabanic acid (**15**) was treated with an excess of 1,1,1,3,3,3-hexamethyldisilazane in the presence of imidazole at room temperature, and the product (**17**) was purified by direct distillation *in vacuo* (140 °C, 2 mmHg) from the reaction mixture to give oily **17** in 58 % yield. Because it has been known that trimethylsilylation of succinimide and phthalimide usually gives only the corresponding *N*-silylated product,[8] trimethylsilylation of 1-methylparabanic acid (**15**) would be considered to also occur at the 3-*N*-position but not at the 2- or 4-*O*-position. ^{13}C-NMR signals of the three carbonyl carbons of **17** appeared at 156.9, 157.7 and 161.9 ppm, and these values were very close to those of 1,3-

dimethylparabanic acid[9,10] (154.0 and 156.8 ppm). In the product (**17**), NOE was not observed between the protons of 1-methyl group and TMS group. Furthermore, ^{1}H-NMR signal of the TMS group (s, 9H) was appeared at 0.49 ppm, which was closer to that of *N*-trimethylsilylsuccinimide (0.40 ppm)[8b] rather than that of 1-(trimethylsiloxy)cyclohex-1-ene (0.11 ppm).[11] These data clearly supported that the silylation product (**17**) was 1-methyl-3-*N*-trimethylsilylparabanic acid. As expected, compound (**17**) was moisture-sensitive to give quickly solid 1-methylparabanic acid (**15**) by exposure in air. Reaction of the reagent (**17**) with various primary amines (**14**) without addition of an extra base was examined and the results are summarized in Table 1. Yields of the condensed product (**16**) are much higher than those of the previous method[4] and, in particular, the yield of pyronaamidine (**8**) could be markedly improved. From these results, 1-methyl-3-trimethylsilylparabanic acid (**17**) can be considered as an essential reagent in this reaction.



Scheme 4 Reagents and Conditions: (a) **20**, AcOEt, rt, **21**: 97 %; **22**: quant.; (b) 10 % aq. HCl, rt, **23**: 84 % from **21**; **24**: 86 % from **22**.

Next, we applied the present reaction to the first total synthesis of isonaamidine C (**11**),[3c] which had a unique structure bearing a 4-methoxybenzyl group at the 1-position. In general, reaction of 2-, 4- or 5-lithio-1-benzylimidazole with an electrophile usually produces a complex mixture because lithiation at the benzylic methylene is always concomitant with the deprotonation at these positions.[12] Therefore, a new strategy different from that of the previous synthesis of such as clathridine (**4**) and pyronaamidine (**8**) should be used for the synthesis of **11**. For this purpose, 2-phenylthio-1-{[2-(trimethylsilyl)ethoxy]methyl}-*1H*-imidazole (**25**) was selected as the starting material because the 1-protecting group could be easily removed and exchanged to a 4-methoxybenzyl group at a later step by applying the 1,3-substituents replacement technique *via* imidazolium salt.[13] First, replacement of the [2-(trimethylsilyl)ethoxy]methyl (SEM) group of 1-SEM-imidazole with a benzyl group was tested as follows. When the 1-SEM-imidazole (**19**) was treated with benzyl bromide such as **20a** and **20b** in ethyl acetate, the resulting imidazolium salts (**21**) and (**22**) were hydrolyzed with aqueous 10 % hydrochloric acid to give successfully 1-benzylimidazole (**23**) and 1-(4-methoxybenzyl)imidazole (**24**) in 84 % and 86 % yields from **19**, respectively (Scheme 4).[14]



Scheme 5 Reagents and Conditions: (a) *n*-BuLi, *p*-anisaldehyde, THF, 87 %; (b) Et_3SiH, CF_3COOH, CH_2Cl_2, quant.; (C) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, THF, MeOH, 95 %; (d) **20b**, AcOEt (e) 10 % aq. HCl, 78 % from **28**; (f) NBS, THF, 78 %; (g) (i) *tert*-BuLi, THF; (ii) trisyl azide, 62 %; (h) H_2, 10 % Pd-C, EtOH, quant.; (i) BBr_3, CH_2Cl_2, quant.; (j) (i) **17**, $CHCl_3$, (ii) CsF, THF; isonaamidine A (**9**), 80 % from **34**; (k) **17**, $CHCl_3$; isonaamidine C (**11**), 90 % from **33**.

Lithiation of the sulfide (**25**) with *n*-BuLi[15] followed by addition of *p*-anisaldehyde gave the alcohol (**26**, 87 % yield), the hydroxyl group of which was removed by reduction with triethylsilane in the presence of trifluoroacetic acid according to the procedure reported by Kobayashi[16] to give quantitatively the 5-benzylimidazole (**27**). The sulfide (**27**) was desulfurized by reducing with a combination of $NaBH_4$ and nickel(II) dichloride[17] to give (**28**, 95 % yield), a solution in ethyl acetate of which was heated in the presence of 4-methoxybenzyl bromide to give almost quantitatively the corresponding imidazolium salt (**29**) as precipitates. Hydrolysis of the quaternary salt (**29**) with 10 % hydrochloric acid gave 1,4-di(4-methoxybenzyl)imidazole (**30**, 78 % yield from **28**), ^{1}H-NMR spectrum of which revealed the presence of the 5-position proton (s, 1H, 6.48 ppm). Bromination of **30** with NBS gave the 2-bromoimidazole (**31**, 78 % yield), lithiation of which with *tert*-BuLi followed by treatment with trisyl azide[18] and then by hydrogenation over 10 % Pd-C afforded 2-amino-1,4-bis(4- methoxybenzyl)imidazole (**33**, 62 % yield from **31**), a precursor for isonaamidine C (**11**). On the other hand, demethylation of **33** with boron tribromide gave isonaamine A (**34**), a natural product.[3g, h, 19] Finally, isonaamidine A (**9**) and isonaamidine C (**11**) were obtained in 80 % and 90 % yields respectively by refluxing solutions of **34** and **33** in $CHCl_3$ with 1-methyl-3-trimethylsilylparabanic acid (**17**) (Scheme 5).[20, 21]

In conclusion, we have found **17** was a useful and versatile reagent for the condensation of 1-methylparabanic acid with various primary amines to prepare effectively *N*-substituted 2-(1-methyl-2,5-

dioxo-1,2,5*H*-imidazolin-4-yl)amines (**16**), and the reagent could be successfully applied to the first total synthesis of isonaamidine A (**9**), isonaamidine C (**11**) and a new synthesis of pyronaamidine (**8**).

EXPERIMENTAL

All melting points were measured with a Yanaco MP micro-melting points apparatus without correction. IR spectra were taken with a Shimadzu IR-435 spectrophotometer. NMR spectra were measured on a Varian UNITY INOBA 400NB (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) spectrometer with tetramethylsilane as an internal standard and chemical shifts □ are reported in ppm. HRMS was measured on a JEOL JMS-SX 102A QQ (FAB) or a JEOL JMS BU-20 (EI) spectrometer, respectively. Silica gel (Merck Art. 7734) was used for column chromatography.

1-Methyl-3-trimethylsilylparabanic acid (17) 1,1,1,3,3,3-Hexamethyldisilazane (3.38 mL, 16.00 mmol) was added to a solution of 1-methylparabanic acid (**15**; 1.025 g, 8.00 mmol) and imidazole (55 mg, 0.80 mmol) in $CHCl_3$ (3 mL) under N_2, and then the whole was stirred at rt for 1 h. The reaction mixture was filtrated, and the filtrate was purified by direct distillation *in vacuo* (140 °C, 2 mmHg) to give a colorless oil (**17**; 927 mg, 58 %). IR ($CHCl_3$): 1751, 1722, 1440, 1385, 1335, 1110, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 0.49 (s, 9H, $Si(CH_3)_3$), 3.15 (s, 3H, NCH_3); ^{13}C-NMR □: -0.6, 24.9, 156.9, 157.7, 161.9. CI-HRMS (pos.) *m/z* Calcd for $C_7H_{13}N_2O_3Si$: *M* + H, 201.0695. Found: $(M + 1)^+$, 201.0703.

1-Methyl-4-(*N*-phenylamino)-1*H*-imidazole-2,5-dione (16a) (General Procedure) A solution of aniline (25 mg, 0.268 mmol) in $CHCl_3$ (0.5 mL) was added to a solution of 1-methyl-3-trimethylsilylparabanic acid (**17**; 215 mg, 1.074 mmol) in $CHCl_3$ (0.5 mL) under N_2, and the whole was refluxed for 5 h at 80 °C. After cooling, the reaction mixture was purified by column chromatography ($CHCl_3$) to give compound (**16a**; 53 mg, 96 %), mp 237.5-238.5 °C (colorless needles; recrystallized from MeOH). IR (KBr): 3252, 1730, 1639, 1587, 1496, 1447, 1129 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.18 (s, 3H, NCH_3), 7.28 (tt, 1H, J = 1.1, 7.3 Hz, ArH), 7.45 (dd, 2H, J = 7.5, 8.6 Hz, ArH), 7.83 (dd, 2H, J = 1.1, 8.8 Hz, ArH), 8.14 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) □: 25.4, 120.7, 126.7, 129.6, 135.5, 160.2, 163.1, 165.6. *Anal.* Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.90; H, 4.55; N, 20.43. EI-HRMS (pos.) *m/z* Calcd for $C_{10}H_9N_3O_2$: *M*, 203.0695. Found: M^+, 203.0691. The following compounds were prepared similarly.

4-[*N*-(4-Bromophenyl)amino]-1-methyl-1*H*-imidazole-2,5-dione (16b) Pale yellow needles (72 mg, 94 %); mp 280.5-281.5 °C (recrystallized from AcOEt). IR (KBr): 3184, 1708, 1604, 1567, 1447, 1390, 1131 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.18 (s, 3H, NCH_3), 7.57 (d, 2H, J = 9.0 Hz, ArH), 7.74 (d, 2H, J = 9.0 Hz, ArH), 8.11 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) □: 25.5, 119.9, 122.2, 132.7, 134.6, 160.9, 162.8,

165.3. *Anal.* Calcd for $C_{10}H_8N_3O_2Br$: C, 42.58; H, 2.86; N, 14.90. Found: C, 42.72; H, 2.93; N, 14.76. EI-HRMS (pos.) *m/z* Calcd for $C_{10}H_8N_3O_2Br$: *M*, 280.9799. Found: M^+, 280.9801.

1-Methyl-4-[*N*-(3,5-dimethylphenyl)amino]-1*H*-imidazole-2,5-dione (16c) Colorless needles (27 mg, 84 %); mp 220.0-221.0 °C (recrystallized from AcOEt). IR ($CHCl_3$): 3325, 2975, 1737, 1629, 1588, 1444, 1392, 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 2.35 (s, 6H, $ArCH_3$), 3.16 (s, 3H, NCH_3), 6.90 (s, 1H, ArH), 7.46 (s, 2H, ArH), 8.23 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) □: 21.3, 25.4, 118.4, 128.5, 135.4, 139.6, 159.9, 163.2, 165.8. *Anal.* Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.27; H, 5.76; N, 17.98. EI-HRMS (pos.) *m/z* Calcd for $C_{12}H_{13}N_3O_2$: *M*, 231.1008. Found: M^+, 231.1005.

4-[*N*-(2-Methoxyphenyl)amino]-1-methyl-1*H*-imidazole-2,5-dione (16d) Pale yellow needles (35 mg , 92 %); mp 215.0-216.0 °C (recrystallized from AcOEt). IR ($CHCl_3$): 3325, 2974, 1730, 1628, 1590, 1446, 1386, 1253, 1130, 1096 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.17 (s, 3H, NCH_3), 3.97 (s, 3H, OCH_3), 6.97 (dd, 1H, J = 1.3, 8.2 Hz, ArH), 7.05 (ddd, 1H, J = 1.3, 8.1, 8.6 Hz, ArH), 7.21 (ddd, 1H, J = 1.7, 7.7, 8.1 Hz, ArH), 8.56 (dd, 1H, J = 1.7, 8.1 Hz, ArH), 8.78 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) □: 25.3, 55.9, 110.4, 121.4, 121.6, 125.0, 126.8, 149.2, 159.6, 163.0, 165.8. *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.85; H, 4.77; N, 17.82. EI-HRMS (pos.) *m/z* Calcd for $C_{11}H_{11}N_3O_3$: *M*, 233.0800. Found: M^+, 233.0803.

4-[*N*-(3-Methoxyphenyl)amino]-1-methyl-1*H*-imidazole-2,5-dione (16e) Colorless needles (87 mg, 96 %); mp 216.5-217.5 °C (recrystallized from AcOEt-*n*-hexane). IR (KBr): 3261, 1729, 1640, 1585, 1494, 1452, 1254, 1135 cm^{-1}; ^{1}H-NMR ^{1}H-NMR ($CDCl_3$) □: 3.17 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 6.80-6.83 (m, 1H, ArH), 7.30-7.52 (m, 3H, ArH), 8.08 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) □: 25.4, 55.6, 106.4, 112.6, 112.9, 130.4, 136.6, 160.2, 160.5, 163.1, 165.6. *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.74; H, 4.88; N, 17.87. EI-HRMS (pos.) *m/z* Calcd for $C_{11}H_{11}N_3O_3$: *M*, 233.0800. Found: M^+, 233.0793.

4-[*N*-(4-Methoxyphenyl)amino]-1-methyl-1*H*-imidazole-2,5-dione (16f) Yellow needles (45 mg, 96 %); mp 221.5-222.0 °C (recrystallized from AcOEt). IR (KBr): 3400, 1710, 1610, 1579, 1508, 1443, 1260, 1134 cm^{-1}; ^{1}H-NMR (DMSO-d_6) □: 2.96 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 7.00 (d, 2H, J = 8.8 Hz, ArH), 7.95 (br, 2H, ArH), 11.34 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6) □: 24.7, 55.3, 114.2, 122.9, 130.4, 156.9, 160.5, 163.0, 165.8. *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.84; H, 4.77; N, 17.75. EI-HRMS (pos.) *m/z* Calcd for $C_{11}H_{11}N_3O_3$: *M*, 233.0800. Found: M^+, 233.0809.

1-Methyl-4-[*N*-(1-methyl-1*H*-benzimidazol-2-yl)amino]-1*H*-imidazole-2,5-dione (16g) Yellow needles (27 mg, 77 %); mp 243.0-244.0 °C (recrystallized from AcOEt). IR ($CHCl_3$): 3200, 2975, 1791, 1739, 1716, 1668, 1540, 1440, 1387, 1325, 1137 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.19 (s, 3H, C

(=O)N(C)CH_3), 3.93 (s, 3H, ArN(C)CH_3), 7.35-7.62 (m, 4H, ArH); ^{13}C-NMR ($CDCl_3$) □: 24.9, 29.3, 110.0, 116.4, 124.1, 124.2, 132.5, 135.0, 152.2, 156.1, 159, 1, 163.0. *Anal.* Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.95; H, 4.33; N, 26.96. EI-HRMS (pos.) *m/z* Calcd for $C_{12}H_{11}N_5O_2$: *M*, 257.0912. Found: M^+, 257.0909.

4-(*N*-Cyclohexylamino)-1-methyl-1*H*-imidazole-2,5-dione (16h) Colorless needles (41 mg, 98 %); mp 156.5-157.5 °C (recrystallized from AcOEt-*n*-hexane). IR ($CHCl_3$): 3355, 2919, 1738, 1624, 1445, 1391, 1127, 1085 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 1.17-1.46 (m, 5H, CH_2), 1.66-1.82 (m, 3H, CH_2), 2.05-2.08 (m, 2H, CH_2), 3.09 (s, 3H, NCH_3), 3.88-3.98 (br m, 1H, NHC*H*(CH_2)CH_2), 6.68 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) □: 24.4, 25.0, 25.1, 32.0, 52.6, 162.5, 163.0, 165.4. *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.11; H, 7.22; N, 19.81. EI-HRMS (pos.) *m/z* Calcd for $C_{10}H_{15}N_3O_2$: *M*, 209.1164. Found: M^+, 209.1168.

1-Methyl-4-[*N*-(3-phenylpropyl)amino]-1*H*-imidazole-2,5-dione (16i) Colorless needles (46 mg, 98 %); mp 89.5-90.5 °C (recrystallized from AcOEt-*n*-hexane). IR ($CHCl_3$): 3362, 2925, 1731, 1634, 1444, 1391, 1129, 1084 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 2.05 (tt, 2H, J = 7.3, 7.7 Hz, $CH_2CH_2CH_2$), 2.71 (t, 2H, J = 7.6 Hz, ArCH_2CH_2), 3.06 (s, 3H, NCH_3), 3.60 (t, 2H, J = 7.2 Hz, CH_2CH_2NH), 7.16-7.30 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) □: 25.1, 29.9, 32.9, 42.8, 126.3, 128.2, 128.5, 140.4, 162.2, 164.1, 165.4. *Anal.* Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.73; H, 6.27; N, 16.98. EI-HRMS (pos.) *m/z* Calcd for $C_{13}H_{15}N_3O_2$: *M*, 245.1164. Found: M^+, 245.1161.

Pyronaamidine (8)[7] This was prepared in a similar manner to that used for the preparation of pyronaamidine (**8**) except for the use of naamine C (**3**; 21 mg, 0.055 mmol) instead of aniline. Title compound was obtained as yellow crystals (23 mg, 85 %). ^{1}H-NMR (CD_2Cl_2) □: 3.09 (s, 3H, NCH_3), 3.54 (s, 3H, NCH_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, ArH), 6.44 (d, 1H, *J* = 8.6 Hz, ArH), 6.79 (d, 2H, *J* = 8.8 Hz, ArH), 7.10 (d, 2H, *J* = 8.8 Hz, ArH). ^{1}H-NMR spectrum of this product was consistent with the reported data (ref. 3*f*) of natural pyronaamidine (**8**).

1-Benzyl-3-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazolium bromide (21) To a solution of **19** (100 mg, 0.50 mmol) in AcOEt (1 mL) was added a solution of benzyl bromide (**20a**; 0.09 mL, 0.76 mmol). The solution was stirred for 2 h under N_2 at rt and the solvent was evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1) on silica gel to give **21** (180 mg, 97 %) as a colorless viscous syrup. IR ($CHCl_3$): 2926, 1246, 1118, 856 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: -0.01 (s, 9H, $Si(CH_3)_3$), 0.94 (t, 2H, *J* = 8.2 Hz, C$H_2Si(CH_3)_3$), 3.69 (t, 2H, *J* = 8.2 Hz, OCH_2CH_2), 5.62 (s, 2H, NCH_2Ar or NCH_2O), 5.73 (s, 2H, NCH_2Ar or NCH_2O), 7.29-7.51 (m, 7H, ArH), 10.99 (s, 1H, ArH); ^{13}C-NMR ($CDCl_3$) □: -1.4, 17.8, 53.6, 68.6, 78.8, 120.8, 122.0, 129.0, 129.5, 129.7, 132.6, 137.5. FAB-

HRMS (pos.) *m/z* Calcd for $C_{16}H_{25}N_2OSi$: (*M* - Br), 289.1736. Found: $(M - Br)^+$, 289.1738. FAB-MS (pos.) *m/z*: 289 (100 %, M^+), 657 (5 %, 2 $M^{+ \cdot 79}Br^-$), 659 (5 %, 2 $M^{+ \cdot 81}Br^-$).

1-Benzyl-1*H*-imidazole (23) A solution of **21** (89 mg, 0.24 mmol) in 10 % HCl (0.5 mL) was stirred for 2 h at 80 °C. The reaction mixture was basified by addition of K_2CO_3 powder and extracted with $CHCl_3$. The crude product was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1) on silica gel to afford **23** (32 mg, 84 %) as a white solid. ^{1}H-NMR ($CDCl_3$) □: 5.12 (s, 2H, $ArCH_2Im$), 6.90 (s, 1H, ImH), 7.09 (s, 1H, ImH), 7.15 (d, 2H, *J* = 7.9 Hz, ArH), 7.32-7.36 (m, 3H, ArH), 7.54 (s, 1H, ImH). ^{1}H-NMR spectrum of this product (**23**) supported the structure and was consistent with the reported data.[14]

1-(4-Methoxybenzyl)-3-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazolium bromide (22) To a solution of 4-methoxybenzyl alcohol (0.17 mL, 1.33 mmol) in $CHCl_3$ (2 mL) was added a solution of bromotrimethylsilane (0.26 mL, 2.00 mmol). The solution was stirred for 1 h under N_2 at rt and the solvent was evaporated off. The obtained 4-methoxybenzyl bromide (**20b**) was added to a solution of **19** (176 mg, 0.89 mmol) in AcOEt (1 mL), and the whole was stirred for 2 h at rt. The solvent was evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$: MeOH = 20 : 1) on silica gel to give **22** (354 mg, quant.) as a colorless viscous syrup. IR ($CHCl_3$): 2930, 1609, 1510, 1247, 1110, 855 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: -0.01 (s, 9H, $Si(CH_3)_3$), 0.93 (t, 2H, *J* = 8.2 Hz, $CH_2Si(CH_3)_3$), 3.68 (t, 2H, *J* = 8.2 Hz, OCH_2CH_2), 3.79 (s, 3H, OCH_3), 5.53 (s, 2H, NCH_2Ar or NCH_2O), 5.72 (s, 2H, NCH_2Ar or NCH_2O), 6.91 (d, 2H, *J* = 8.6 Hz, ArH), 7.30 (t, 1H, *J* = 1.7 Hz, ArH), 7.37 (t, 1H, *J* = 1.8 Hz, ArH), 7.45 (d, 2H, *J* = 8.8 Hz, ArH), 10.93 (br s, 1H, ArH); ^{13}C-NMR ($CDCl_3$) □: –1.4, 17.8, 53.2, 55.3, 68.6, 78.8, 114.8, 120.7, 121.9, 124.5, 130.7, 137.2, 160.5. FAB-HRMS (pos.) *m/z* Calcd for $C_{17}H_{27}N_2O_2Si$: (*M* - Br), 319.1842. Found: $(M - Br)^+$, 319.1839. FAB-MS (pos.) *m/z*: 319 (100 %, M^+), 717 (4 %, 2 $M^{+ \cdot 79}Br^-$), 719 (5 %, 2 $M^{+ \cdot 81}Br^-$).

1-(4-Methoxybenzyl)-1*H*-imidazole (24) A solution of **22** (30 mg, 0.075 mmol) in 10 % HCl (0.5 mL) was stirred for 2 h at 80 °C. The reaction mixture was basified by addition of K_2CO_3 powder and extracted with $CHCl_3$. The crude product was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1) on silica gel to afford **24** (12 mg, 86 %) as a white solid. ^{1}H-NMR ($CDCl_3$) □: 3.80 (s, 3H, OCH_3), 5.05 (s, 2H, $ArCH_2Im$), 6.86-6.90 (m, 3H, ArH, ImH), 7.07 (t, 1H, *J* = 1.0 Hz, ImH), 7.11 (d, 2H, *J* = 9.0 Hz, ArH), 7.53 (s, 1H, ImH). ^{1}H-NMR spectrum of this product (**24**) supported the structure and was consistent with the reported data.[14]

5-{(1-Hydroxy)-[1-(4-methoxyphenyl)methyl]}-2-phenylthio-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (26) A solution of *n*-BuLi in *n*-hexane (1.60 M; 9.62 mL, 15.38 mmol) was added dropwise to a solution of **25** (3.627 g, 11.83 mmol) in THF (24 mL) under N_2 at –78 °C. Stirring was continued for 30 min, then a solution of *p*-anisaldehyde (7.20 mL, 59.15 mmol) in THF (3 mL) was

added dropwise at -78 °C. Stirring was continued for 1 h at -78 °C, then water (10 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 followed by recrystallization from *n*-hexane-AcOEt to afford **26** (4.564 g, 87 %). mp 102.5-104.0 °C (colorless needles). IR ($CHCl_3$): 2935, 1608, 1507, 1246, 1071, 856 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: -0.07 (s, 9H, $Si(CH_3)_3$), 0.83 (t, 2H, *J* = 8.5 Hz, $CH_2Si(CH_3)_3$), 3.36 (t, 2H, *J* = 8.5 Hz, OCH_2CH_2), 3.82 (s, 3H, OCH_3), 5.33 (d, 1H, *J* = 10.8 Hz, NCH_aH_bO), 5.38 (d, 1H, *J* = 10.8 Hz, NCH_aH_bO), 5.90 (d, 1H, *J* = 5.5 Hz, ArCH(OH)Im), 6.89-6.91 (m, 3H, ArH), 7.16-7.35 (m, 7H, ArH); ^{13}C-NMR ($CDCl_3$) □: –1.6, 17.9, 55.3, 66.6, 67.2, 73.6, 113.8, 126.9, 127.6, 128.2, 129.3, 130.6, 132.3, 134.4, 137.5, 139.7, 159.3. *Anal.* Calcd for $C_{23}H_{30}N_2O_3SSi \cdot 1/2H_2O$: C, 61.16; H, 6.92; N, 6.20. Found; C, 61.42; H, 6.62; N, 6.58. EI-HRMS *m/z* Calcd for $C_{23}H_{30}N_2O_3SSi$: *M*, 442.1746. Found: M^+, 442.1745.

5-(4-Methoxybenzyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2-phenylthio-1*H*-imidazole (27) To a solution of **26** (327 mg, 0.74 mmol) in CH_2Cl_2 (4 mL) were added a solution of triethylsilane (0.47 mL, 2.96 mmol) and a solution of TFA (0.29 mL, 3.69 mmol). The solution was stirred for 12 hr under N_2 at rt and quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 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 **27** (314 mg, quant.) as a pale yellow viscous material. IR ($CHCl_3$): 2935, 1608, 1506, 1244, 1070, 857 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: -0.08 (s, 9H, $Si(CH_3)_3$), 0.75 (t, 2H, *J* = 8.3 Hz, $CH_2Si(CH_3)_3$), 3.30 (t, 2H, *J* = 8.2 Hz, OCH_2CH_2), 3.79 (s, 3H, OCH_3), 3.98 (s, 2H, $ArCH_2Im$), 5.24 (s, 2H, NCH_2O), 6.84 (d, 2H, *J* = 8.8 Hz, ArH), 6.94 (s, 1H, ImH), 7.11 (d, 2H, *J* = 8.8 Hz, ArH), 7.13-7.26 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) □: -1.5, 17.8, 30.1, 55.3, 65.9, 73.4, 114.0, 126.6, 127.9, 129.18, 129.24, 129.6, 129.8, 134.8, 135.2, 138.2, 158.4. EI-HRMS *m/z* Calcd for $C_{23}H_{30}N_2O_2SSi$: *M*, 426.1797 Found: M^+, 426.1799.

5-(4-Methoxybenzyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (28) Sodium borohydride (1.750 g, 46.27 mmol) was added to a solution of **27** (940 mg, 2.20 mmol) and nickel(II) chloride hexahydrate (3.666 g, 15.42 mmol) in MeOH (20 mL) and THF (8 mL) under N_2 at 0 °C, and the whole were stirred for 12 h at rt. 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 = 50 : 1) on silica gel to give **28** (668 mg, 95 %) as a pale yellow viscous material. IR ($CHCl_3$): 2950, 1607, 1506, 1244, 1084, 855 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: -0.03 (s, 9H, $Si(CH_3)_3$), 0.83 (t, 2H, *J* = 8.2 Hz, $CH_2Si(CH_3)_3$), 3.37 (t, 2H, *J* = 8.2 Hz, OCH_2CH_2), 3.78 (s, 3H, OCH_3), 3.94 (s, 2H, $ArCH_2Im$),

5.06 (s, 2H, NCH_2O), 6.82 (s, 1H, ImH), 6.83 (d, 2H, J = 8.6 Hz, ArH), 7.09 (d, 2H, J = 8.8 Hz, ArH), 7.49 (s, 1H, ImH); ^{13}C-NMR ($CDCl_3$) □: -1.5, 17.6, 29.2, 55.2, 65.7, 74.1, 113.9, 128.7, 129.4, 129.9, 130.8, 138.0, 158.3. EI-HRMS *m/z* Calcd for $C_{17}H_{26}N_2O_2Si$: *M*, 318.1763 Found: M^+, 318.1757.

1,4-Bis(4-methoxybenzyl)-3-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazolium Bromide (29) To a solution of 4-methoxybenzyl alcohol (0.37 mL, 2.95 mmol) in $CHCl_3$ (1 mL) was added a solution of bromotrimethylsilane (0.58 mL, 4.42 mmol). The solution was stirred for 1 h under N_2 at rt, and the solvent was evaporated off. The obtained 4-methoxybenzyl bromide (**20b**) was added to a solution of **28** (626 mg, 1.97 mmol) in AcOEt (3 mL), and the whole was stirred for 2 h at rt. The solvent was evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$: MeOH = 20 : 1) on silica gel to give **29** (978 mg, 96 %) as a colorless viscous material. IR ($CHCl_3$): 2926, 1609, 1507, 1245, 1093, 853 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: -0.02 (s, 9H, $Si(CH_3)_3$), 0.88 (t, 2H, J = 8.2 Hz, $CH_2Si(CH_3)_3$), 3.63 (t, 2H, J = 8.2 Hz, OCH_2CH_2), 3.77 (s, 6H, OCH_3), 3.94 (s, 2H, $ArCH_2Im$), 5.42 (s, 2H, NCH_2O or NCH_2Ar), 5.55 (s, 2H, NCH_2O or NCH_2Ar), 6.78 (s, 1H, ImH), 6.83 (d, 2H, J = 8.8 Hz, ArH), 6.87 (d, 2H, J = 8.6 Hz, ArH), 7.04 (d, 2H, J = 8.6 Hz, ArH), 7.39 (d, 2H, J = 8.6 Hz, ArH), 10.89 (s, 1H, ImH); ^{13}C-NMR ($CDCl_3$) □: -1.4, 17.7, 29.1, 53.0, 55.25, 55.28, 67.9, 76.6, 114.5, 114.7, 119.3, 124.7, 125.9, 129.7, 130.4, 135.3, 138.0, 159.0, 160.4. FAB-HRMS *m/z* Calcd for $C_{25}H_{35}N_2O_3Si$: (*M* - Br), 439.2417 Found: $(M - Br)^+$, 439.2425. FAB-MS (pos.) *m/z*: 439 (100 %, M^+), 957 (2 %, 2 $M^+ \cdot {}^{79}Br^-$), 959 (2 %, 2 $M^+ \cdot {}^{81}Br^-$).

1,4-Bis(4-methoxybenzyl)-1*H*-imidazole (30) To a solution of 4-methoxybenzyl alcohol (0.61 mL, 4.93 mmol) in $CHCl_3$ (5 mL) was added a solution of bromotrimethylsilane (0.98 ml, 7.40 mmol). The solution was stirred for 1 h under N_2 at rt and the solvent was evaporated off. The obtained 4-methoxybenzyl bromide (**20b**) was added to a solution of **28** (1.046 g, 3.28 mmol) in AcOEt (3 mL), and the whole was stirred for 2 h at rt. The solvent was evaporated off to give an oily residue, which was washed with Et_2O (5 mL x 2) and evaporated to give a crude salt as a colorless viscous oil. The imidazolium salt was stirred in 10 % HCl (3 mL) for 2 h at 80 °C. The reaction mixture was basified by addition of K_2CO_3 powder and extracted with $CHCl_3$. The crude product was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1) on silica gel followed by recrystallization from *n*-hexane-AcOEt to afford **30** (790 mg, 78 %), mp 84-85 °C (colorless needles). IR ($CHCl_3$): 2917, 1609, 1506, 1242, 1094, 816 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.84 (s, 2H, CCH_2Ar), 4.93 (s, 2H, NCH_2Ar), 6.48 (s, 1H, ImH), 6.82 (d, 2H, J = 8.6 Hz, ArH), 6.86 (d, 2H, J = 8.8 Hz, ArH), 7.08 (d, 2H, J = 8.8 Hz, ArH), 7.18 (d, 2H, J = 8.6 Hz, ArH), 7.43 (s, 1H, ImH); ^{13}C-NMR ($CDCl_3$) □: 34.2, 50.3, 55.2, 55.3, 113.8, 114.3, 115.8, 128.2, 128.8, 129.8, 132.4, 136.7, 143.3, 157.9, 159.5. *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found; C, 73.75; H, 6.32; N, 8.83. EI-

HRMS *m/z* Calcd for $C_{19}H_{20}N_2O_2$: *M*, 308.1525 Found: M^+, 308.1529.

2-Bromo-1,4-bis(4-methoxybenzyl)-1*H*-imidazole (31) NBS (196 mg, 1.10 mmol) was added to a solution of **30** (324 mg, 1.05 mmol) in THF (2.5 mL) under N_2 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 ($CHCl_3$: MeOH = 20 : 1) on silica gel to afford **31** (317 mg, 78 %), mp 98-99 °C (colorless needles, recrystallized from *n*-hexane-AcOEt). IR ($CHCl_3$): 2935, 1609, 1507, 1244, 1174, 1031 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.83 (s, 2H, CCH_2Ar), 4.98 (s, 2H, NCH_2Ar), 6.81 (d, 2H, *J* = 8.8 Hz, ArH), 6.87 (d, 2H, *J* = 8.8 Hz, ArH), 7.10 (d, 2H, *J* = 9.0 Hz, ArH), 7.21 (d, 2H, *J* = 8.8 Hz, ArH), 7.48 (s, 1H, ImH); ^{13}C-NMR ($CDCl_3$) □: 32.9, 49.4, 55.17, 55.24, 100.8, 113.8, 114.3, 127.2, 128.8, 129.5, 131.7, 137.2, 140.3,157.9, 159.4. *Anal.* Calcd for $C_{19}H_{19}N_2O_2Br$: C, 58.93; H, 4.95; N, 7.23. Found; C, 58.69; H, 5.00; N, 7.00. EI-HRMS *m/z* Calcd for $C_{19}H_{19}N_2O_2Br$: *M*, 386.0629 Found: M^+, 386.0622. EI-MS (pos.) *m/z* (% base): 388 (7), 386 (7), 121 (100), 78 (11).

2-Azide-1,4-bis(4-methoxybenzyl)-1*H*-imidazole (32) A solution of *tert*-BuLi in *n*-pentane (1.47 M; 1.41 mL, 2.08 mmol) was added dropwise to a solution of **31** (268 mg, 0.69 mmol) in THF (6 mL) under N_2 at –78 °C. The mixture was stirred for 15 min at -78 °C followed by addition of trisyl azide (642 mg, 2.08 mmol), and then the whole was stirred for 1 h at -78 °C. Water (2 mL) was added. 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 **32** (150 mg, 62 %) as a pale yellow viscous oil. IR ($CHCl_3$): 2939, 2123, 1608, 1505, 1243, 1031, 817 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.77 (s, 2H, CCH_2Ar), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.72 (s, 2H, NCH_2Ar), 6.22 (s, 1H, ImH), 6.83 (d, 2H, *J* = 8.8 Hz, ArH), 6.85 (d, 2H, *J* = 8.8 Hz, ArH), 7.07 (d, 2H, *J* = 8.8 Hz, ArH), 7.17 (d, 2H, *J* = 8.6 Hz, ArH); ^{13}C-NMR ($CDCl_3$) □: 34.2, 48.1, 55.2, 55.3, 113.8, 114.2, 114.8, 128.1, 128.7, 129.8, 131.6, 139.5, 140.7, 158.0, 159.4. EI-HRMS *m/z* Calcd for $C_{19}H_{19}N_5O_2$: *M*, 349.1538 Found: M^+, 349.1547.

2-Amino-1,4-bis(4-methoxybenzyl)-1*H*-imidazole (33) A mixture of **32** (153 mg, 0.44 mmol) and 10 % Pd / C (30 mg) in EtOH (2 mL) was stirred for 4 h under H_2 at rt. The Pd / C 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 = 10 : 1) on silica gel to give **33** (142 mg, quant.) as a yellow powder. IR ($CHCl_3$): 3350, 2925, 1609, 1521, 1242, 1030 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.72 (s, 2H, CCH_2Ar), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.75 (s, 2H, NCH_2Ar), 6.13 (s, 1H, ImH), 6.83 (d, 2H, *J* = 8.8 Hz, ArH), 6.87 (d, 2H, *J* = 8.8 Hz, ArH), 7.07 (d, 2H, *J* = 8.8 Hz, ArH), 7.19 (d, 2H, *J* = 8.8 Hz,

ArH); ^{13}C-NMR ($CDCl_3$) □: 33.8, 48.2, 55.2, 55.3, 112.4, 113.8, 114.4, 127.8, 128.3, 129.8, 132.0, 136.8, 147.3, 157.9, 159.4. EI-HRMS *m/z* Calcd for $C_{19}H_{21}N_3O_2$: *M*, 323.1634 Found: M^+, 323.1639.

Isonaamine A (34) To a solution of **33** (103 mg, 0.32 mL) in CH_2Cl_2 (15 mL) was added dropwise a solution of BBr_3 in CH_2Cl_2 (1.00 M; 3.19 mL, 3.19 mmol) at rt, and the whole was refluxed for 1 h at 55 °C. The reaction mixture was basified by addition of K_2CO_3 powder and extracted with $CHCl_3$. The crude product was purified by column chromatography ($CHCl_3$: MeOH = 2 : 1) on silica gel to afford **34** (94 mg, quant.) as pale yellow solid. IR (KBr): 3116, 1656, 1608, 1510, 1437, 1214 cm^{-1}; ^{1}H-NMR (DMSO-*d*$_6$) □: 3.61 (s, 2H, CCH_2Ar), 4.87 (s, 2H, NCH_2Ar), 6.54 (s, 1H, ImH), 6.68 (d, 2H, *J* = 8.4 Hz, ArH), 6.74 (d, 2H, *J* = 8.6 Hz, ArH), 6.99 (d, 2H, *J* = 8.6 Hz, ArH), 7.11 (d, 2H, *J* = 8.4 Hz, ArH),7.44 (br s, 2H, NH_2), 9.31 (br s, 1H, OH), 9.56 (br s, 1H, OH). EI-HRMS *m/z* Calcd for $C_{17}H_{17}N_3O_2$: *M*, 295.1321 Found: M^+, 295.1325. The synthesis of isonaamine A (**34**) was already reported based on cyclization chemistry.[19] The IR, ^{1}H-NMR, and MS spectra of this product (**34**) supported the structure and were consistent with the data of natural product.[3g, h]

Isonaamidine A (9) A solution of **34** (18 mg, 0.061 mmol) in $CHCl_3$ (0.5 mL) was added to a solution of 1-methyl-3-trimethylsilylparabanic acid (**17**; 73 mg, 0.366 mmol) in $CHCl_3$ (0.5 mL) under N_2, and the whole was refluxed for 5 h at 80 °C and the solvent was evaporated off. CsF (37 mg, 0.24 mmol) was added to the reaction mixture in THF (2 mL) under N_2, and then the whole was stirred for 10 h at rt. The solvent was evaporated to give an solid residue, which was purified by column chromatography ($CHCl_3$: MeOH = 10 : 1) on silica gel to give isonaamidine A (**9**; 20 mg, 80 %) as a pale yellow granules. IR (KBr): 3320, 1784, 1717, 1651, 1609, 1561, 1510, 1441, 1252 cm^{-1}; ^{1}H-NMR (CD_3OD) □: 3.08 (s, 3H, NCH_3), 3.80 (s, 2H, CCH_2Ar), 5.16 (s, 2H, NCH_2Ar), 6.696 (s, 1H, ImH), 6.697 (d, 2H, *J* = 8.6 Hz, ArH), 6.71 (d, 2H, *J* = 8.8 Hz, ArH), 7.04 (d, 2H, *J* = 8.8 Hz, ArH), 7.14 (d, 2H, *J* = 8.6 Hz, ArH) ; ^{13}C-NMR ($CDCl_3$ + CD_3OD) □: 24.2, 32.3, 48.2, 115.1, 115.2, 115.3, 126.4, 128.4, 129.36, 129.40, 136.1, 146.0, 151.4, 155.3, 156.7, 159.4, 163.6. EI-HRMS *m/z* Calcd for $C_{21}H_{19}N_5O_4$: *M*, 405.1437 Found: M^+, 405.1433. EI-MS (pos.) *m/z* (% base): 405 (35), 299 (100), 106 (40), 78 (19).

Isonaamidine C (11) A solution of **33** (22 mg, 0.068 mmol) in $CHCl_3$ (0.5 mL) was added to a solution of 1-methyl-3-trimethylsilylparabanic acid (**17**; 55 mg, 0.272 mmol) in $CHCl_3$ (0.5 mL) under N_2, and the whole was refluxed for 5 h at 80 °C. After cooling, the reaction mixture was purified by column chromatography ($CHCl_3$) to give isonaamidine C (**11**; 27 mg, 90 %), mp 67.5-68.5 °C (pale yellow needles, recrystallized from *n*-hexane-AcOEt). IR ($CHCl_3$): 3200, 2925, 1785, 1732, 1663, 1609, 1557, 1506, 1441, 1387,1298, 1244, 1173, 1111, 1032 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.19 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.80 (s, 2H, CCH_2Ar), 5.19 (s, 2H, NCH_2Ar), 6.45 (s, 1H, ImH), 6.83 (d, 2H, *J* = 8.8 Hz, ArH), 6.84 (d, 2H, *J* = 8.8 Hz, ArH), 7.13 (d, 2H, *J* = 8.8 Hz, ArH), 7.16 (d, 2H, *J* = 8.8

Hz, ArH); ^{13}C-NMR ($CDCl_3$) □: 24.7, 33.8, 48.3, 55.25, 55.26, 113.9, 114.2, 115.9, 128.2, 129.4, 129.7, 130.8, 139.9, 144.8, 146.6, 155.2, 158.2, 159.4, 162.0. *Anal.* Calcd for $C_{23}H_{23}N_5O_4$: C, 63.73; H, 5.35; N, 16.16. Found; C, 63.66; H, 5.14; N, 15.99. EI-HRMS *m/z* Calcd for $C_{23}H_{23}N_5O_4$: *M*, 433.1750 Found: M^+, 433.1760.

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20. In ref. 3*g* and ref. 3*h*, NMR solvent for isonaamidine A (**9**) was not described exactly. In this time, ^{1}H-NMR and ^{13}C-NMR solvent for synthetic **9** was CD_3OD and $CDCl_3$ + CD_3OD used, respectively. The spectral data of the synthetic **9** were almost agreed with that of the natural product except for the signal of imidazole ring (6.70 ppm) in ^{1}H-NMR. We assumed this deviation reflected different solvent system. The reported physical data for the natural isonaamidine A in ref. 3g, h: IR (KBr) cm^{-1}: 3600-3000br, 2930, 1710, 1670, 1616, 1565, 1515, 1445, 1245 cm^{-1}; ^{1}H-NMR (360.1 MHz) □: 2.95 (s, 3H, NCH_3), 3.75 (br s, 2H, CCH_2Ar), 5.09 (br s, 2H, NCH_2Ar), 6.66 (d, 2H, *J* = 8.6 Hz, ArH), 6.69 (d, 2H, *J* = 8.6 Hz, ArH), 6.89 (br s, 1H, ImH), 7.04 (d, 2H, *J* = 8.6 Hz, ArH), 7.09 (d, 2H, *J* = 8.6 Hz, ArH) ; ^{13}C-NMR (90.5 MHz) □: 24.5, 32.5, 47.5, 115.2, 115.4, 116.0, 125.6, 127.4, 129.3,

129.4, 137.5, 145.9, 148.6, 155.8, 157.1, 157.2, 162.5. CI-MS (pos.) *m/z* (% base): 406 (42), 300 (100), 243 (40), 190 (26), 127 (65), 107 (28), 85 (47).

21. The spectral data of the synthetic **11** were almost agreed with those of the natural product as well as other physical properties. The reported physical data for the natural isonaamidine C (ref. 3*c*): yellow solid; IR (film): 3441, 2929, 1793, 1738, 1668, 1613, 1514, 1446, 1392, 1303, 1249, 1177, 1114, 1034 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) □: 3.16 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.78 (s, 2H, CCH_2Ar), 5.16 (s, 2H, NCH_2Ar), 6.44 (s, 1H, ImH), 6.81 (d, 2H, *J* = 8.5 Hz, ArH), 6.82 (d, 2H, *J* = 8.5 Hz, ArH), 7.11 (d, 2H, *J* = 8.5 Hz, ArH), 7.14 (d, 2H, *J* = 8.5 Hz, ArH); ^{13}C-NMR ($CDCl_3$, 125 MHz) □: 24.7, 33.8, 48.3, 55.23, 55.24, 114.0, 114.2, 115.9, 128.3, 129.4, 129.7, 130.8, 139.9, 144.7, 146.6, 155.1, 158.2, 159.4, 162.0. EI-HRMS *m/z* Calcd for $C_{23}H_{23}N_5O_4$: *M*, 433.1750 Found: M^+, 433.1746. Elementary analysis was not reported in ref. 3c.