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TOTAL SYNTHESES OF NAAMINE A and NAAMIDINE A, MARINE IMIDAZOLE ALKALOIDS

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Abstract — The first total syntheses of naamine A (**4**) and naamidine A (**5**), marine imidazole alkaloids, were achieved through twelve and thirteen steps of reactions, respectively, starting from 1-methyl-2-phenylthio-1*H*-imidazole (**17**).

Recently, many marine imidazole alkaloids such as **1** - **10** in Table 1 have been isolated from sponges, and their antitumour and antibacterial activities have been also found.[1,2] Structural characteristics of these alkaloids are that one or two alkoxybenzyl group(s) locates at the 1-, 4- and/or 5-positions of the 1*H*-imidazole ring and the 2-position is substituted with a primary amino group or a (1-methyl-2,5-dioxo-3-imidazolin-4-yl)amino moiety[2] (Table 1).

Hitherto, we have reported the total synthesis of several marine imidazole alkaloids such as nortopsentins A - D,[3] topsentin,[4] kealiiquinone (**10**),[5] and clathridine A (**2**).[6] In this paper, we would like to report the first total syntheses of naamine A (**4**) and naamidine A (**5**) starting from 1-methyl-2-phenyl-thio-1*H*-imidazole (**17**).

In previous papers, we reported a procedure for the preparation of 2-aminoimidazoles and preclathridine A (**2**) by using a reaction of 2-bromoimidazole with sodium azide or trimethysilyl azide ($TMSN_3$) in the

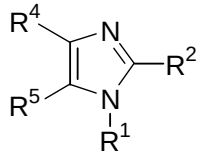
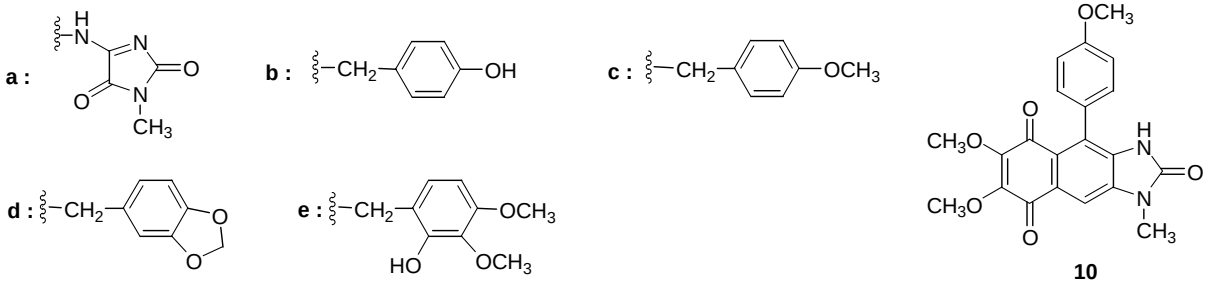
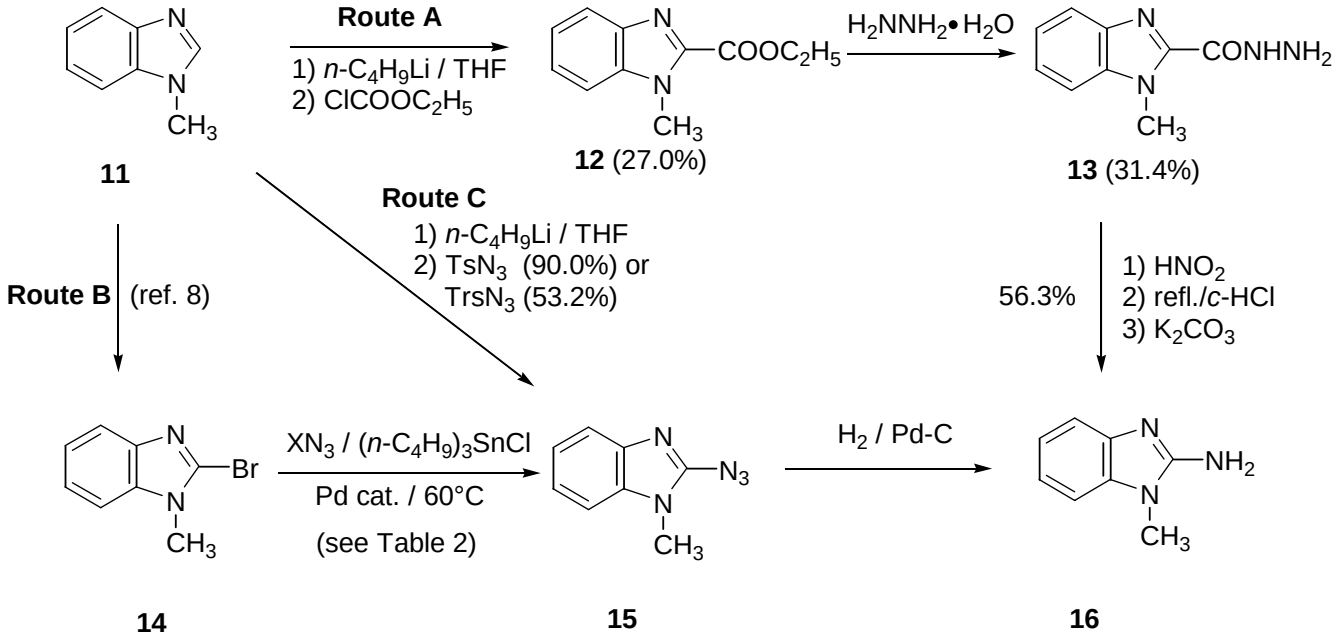


Table 1. Several Marine Imidazole Alkaloids[2]

Name	Compd No.	R^1	R^2	R^4	R^5
Dorimidazole	**1**	CH_3	NH_2	**b**	H
Preclathridine A	**2**	CH_3	NH_2	**b**	H
Isonaamine A	**3**	**c**	H	**b**	H
Naamine A	**4**	CH_3	NH_2	**c**	**b**
Naamidine A	**5**	CH_3	**a**	**c**	**b**
Isonaamidine A	**6**	**b**	**a**	**b**	**b**
Pyrronaamidine A	**7**	CH_3	**a**	**c**	**e**
Clathridine A	**8**	CH_3	**a**	**d**	H
Clathridine B	**9**	CH_3	**a**	**d**	**d**



presence of an appropriate palladium complex followed by catalytic hydrogenation of the intermediate 2-azidoimidazoles.[7] However, subsequent investigations indicated that the reported procedure did not always give good results probably because of the relatively high substrate specificity of the palladium complex used. Therefore, we searched for more general methods for the introduction of a primary amino group into the 2-position of 1-methylbenzimidazole. First, we examined Curtius rearrangement to the imidazole system (Route A in Scheme 1). The hydrazide (**13**), derived from **12**,[7] was treated with nitrous acid followed by heating the intermediate acyl azide in toluene and subsequent hydrolysis with concentrated hydrochloric acid to give 2-amino-1-methylbenzimidazole (**16**). However, overall yield of **16** from **11** *via* Route A was too low to achieve the total synthesis of **5**.



Scheme 1

Next, we also tried the conversion of the bromide (**14**)[8] to the azide **(15)**, in which the bromide (**14**) was treated with sodium azide in the presence of tributyltin chloride, 15-crown-5 ether and an appropriate palladium catalyst in tetrahydrofuran (THF) (Route B in Scheme 1).[9] As shown in Table 2, the combination of $TMSN_3$ and $PdCl_2[P(o\text{-tolyl})_3]_2$ was not effective (Entries 3 ~ 5), while that of NaN_3, $PdCl_2(PPh_3)_2$, and 15-crown-5 ether gave the best result (81.2% yield of **15**), though the reaction took 48 h to complete. (Entry 2).

Table 2. Conversion of the Bromide (**14**) to the Azide (**15**)

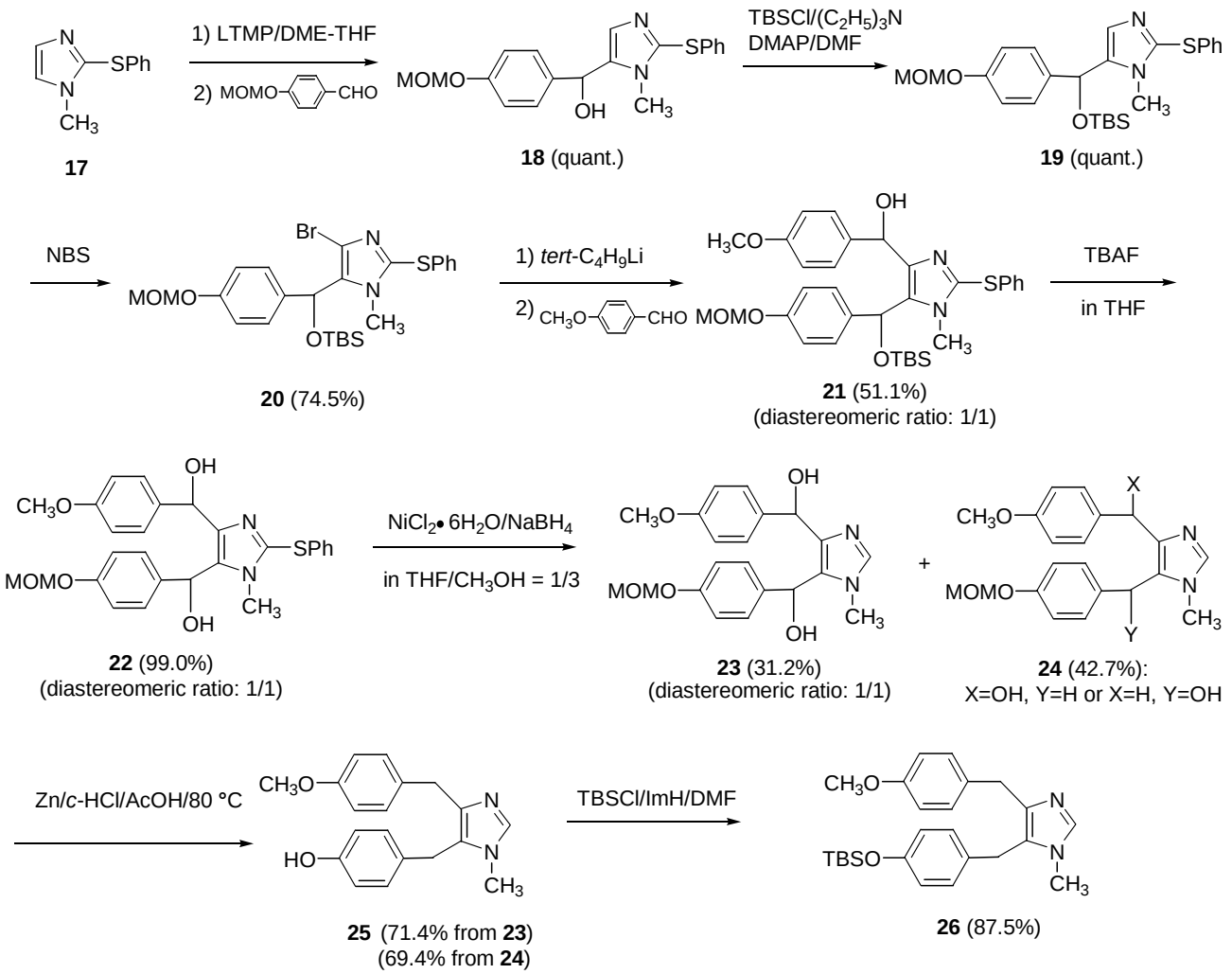
Entry	XN_3	Pd-Catalyst	Coadditive	Reaction Time (h)	Yield of **15** (%)[a]
1	NaN_3	$PdCl_2(PPh_3)_2$	None	48	73.2
2	NaN_3	$PdCl_2(PPh_3)_2$	15-Crown[b]	48	81.2
3	NaN_3	$PdCl_2[P(o\text{-tolyl})_3]_2$	15-Crown[b]	48	No Reaction
4	NaN_3	$PdCl_2[P(o\text{-tolyl})_3]_2$	15-Crown[b]	72	No Reaction
5	$TMSN_3$	$PdCl_2(PPh_3)_2$	None	48	No Reaction

a: Isolated yields. b: 15-Crown-5 ether.

Moreover, the preparation of **16** *via* Route C in Scheme 1 was examined. 2-Lithio-1-methyl-

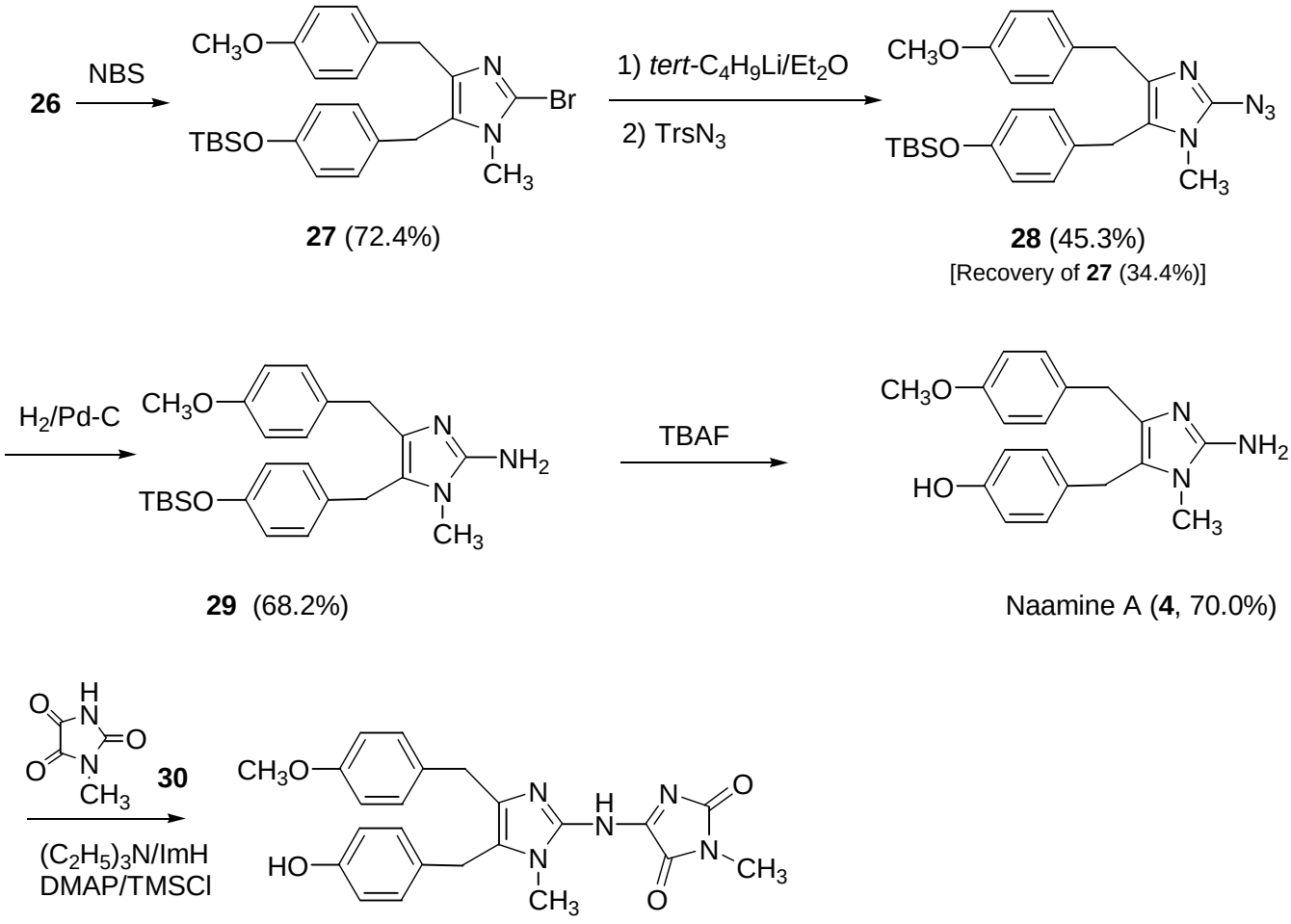
benzimidazole was quenched with tosyl azide or trisyl azide to give the oily 2-azidobenzimidazole (**15**) in 90.0 or 53.2% yield, respectively. Thus, we were able to develop several applicable methods for the introduction of an azide group into the 2-position of the imidazole ring. The azide (**15**) could be hydrogenated over palladium-charcoal to **16** in high yield.

The preparation of a naamine A precursor (**26**) was started from 1-methyl-2-phenylthio-1*H*-imidazole (**17**)[10] as shown in Scheme 2. Reaction of 4-methoxymethoxybenzaldehyde with the 5-lithio derivative of **17** gave the alcohol (**18**), which was subjected to protection of the OH group with *tert*-butyldimethylsilyl (TBS) group in the usual manner, followed by bromination of the 4-position with *N*-bromosuccinimide (NBS) to give the bromide (**20**) in 74.5% yield from **17**. The 4-position in **20** was lithiated by treatment with *tert*-butyllithium, followed by quenching with 4-methoxybenzaldehyde to



Scheme 2

give the tetrasubstituted imidazole (**21**), which was desilylated by treatment with tetrabutylammonium fluoride (TBAF) to afford a diastereomeric mixture (ratio: about 1/1 on the basis of ^{1}H-NMR) of the diol (**22)** in 50.6% yield from **20**. Reduction of **22** with nickel boride[11] gave a mixture of the 2-unsubstituted diol (**23**) (31.2% yield) and the 2-unsubstituted monool (**24**) (42.7% yield); however, reductive desulfurization of **22** with Raney nickel (W-2) or sodium metal in liquid ammonia did not proceed at all. The compounds **23** and **24** were each further treated with zinc powder in *conc*.-HCl - acetic acid at 80 ℃ to reduce to 4,5-dibenzylimidazole (**25**),[12] and the phenolic hydroxy group of **25** was silylated with TBS chloride in the usual manner to give **26**.



Scheme 3

The next steps were lithiation of the 2-position of the TBS ether (**26**) with *n*-butyllithium and subsequent introduction of an azide group with trisyl azide; however, most of the starting material (**26**) was recovered. This result would be attributed to lithiation at the benzyl methylene group of the 5-position rather than the 2-position and difficulty in the subsequent approach of trisyl azide to the relatively hindered lithiated position. On the other hand, fortunately, bromination of the 2-position in **26** with NBS followed by lithiation with *tert*-butyllithium and subsequent treatment with trisyl azide proceeded to afford the azide (**28**) in 32.8% yield from **26**. Hydrogenation of the azide (**28**) over palladium-charcoal gave the amine (**29**) in 68.2 % yield, and the TBS group was removed by treatment with TBAF to give naamine A (**4**)[2d,13] in 70.0% yield. Conversion of **4** to naamidine A (**5**) was achieved by the condensation of **4** with 1-methylparabanic acid (**30**) in the presence of trimethylsilyl chloride and triethylamine as previously reported[6] to give naamidine A (**5**) as yellow granules in 43.5% yield. The structure of the synthetic naamidine A (**5**) was confirmed by comparison of its ^{1}H-NMR, ^{13}C-NMR, IR and MS spectral data with those of the natural naamidine A.[2d, 14] (Scheme 3)

ACKNOWLEDGMENT

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EXPERIMENTAL

All melting points were measured with a Yanaco MP micro-melting points apparatus and are not corrected. IR were taken with a Shimadzu IR-435 spectrophotometer. ^{1}H-NMR was measured on a Varian XL-300 (^{1}H: 300 MHz, ^{13}C: 75.4 MHz) and a Varian UNITY *INOVA* 400NB (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) with tetramethylsilane as an internal standard, and chemical shifts are reported in ppm. Low-resolution MS (LRMS) and high-resolution MS (HRMS) were measured on JEOL JMS-SX 102A QQ and JEOL JMS BU-20 spectrometers. Silica gel (Merck Art. 7734) and Silica Gel 60PF_{254} (Nacalai Tesque) were used for column chromatography and preparative TLC (PTLC), respectively.

2-Ethoxycarbonyl-1-methylbenzimidazole (12)[7] *n*-C_4H_9Li (1.6 M in *n*-hexane, 0.325 mL, 2.5 mmol) was added dropwise to a solution of 1-methylbenzimidazole (**11**; 264 mg, 2.00 mmol) in THF (2 mL) at –78 ℃ under N_2 and the whole was stirred for 30 min at the same temperature. To the reaction mixture, a solution of ethyl chloroformate (239 mg, 2.20 mmol) in THF (4 mL) was added dropwise at –78 ℃ and the whole was stirred for 30 min. After addition of water (2 mL), the mixture was extracted with AcOEt. The organic layer was washed with water, dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (AcOEt / *n*-hexane = 1 / 3) to give **12**. Yield, 110 mg (27.0%). Colorless powder (ethyl acetate - *n*-hexane), mp 148.8~150.1 ℃. IR ($CHCl_3$): 2965, 1782, 1720, 1687, 1654, 1610, 1522, 1404, 1454, 1229 cm^{-1}. ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 1.50 (t, 3H, *J*=7.1 Hz, $OCH_2C\underline{H}_3$), 4.17 (s, 3H, N-CH_3), 4.52 (q, 2H, *J*=7.1 Hz, O-$C\underline{H}_2$-CH_3), 7.33~7.45 (m, 4H, Ar-H). HRMS *m/z*: Calcd for $C_{11}H_{12}N_2O_2$, 204.0899. Found, 204.0907 (M^+).

1-Methylbenzimidazole-2-carboxylic Acid Hydrazide (13) A mixture of **12** (174 mg, 0.85 mmol), hydrazine monohydrate (255 mg, 5.10 mmol), and EtOH (1.5 mL) was refluxed overnight. After addition of water, the mixture was extracted with AcOEt. The organic phase was washed with water and dried over sodium sulfate. Evaporation of the solvent gave a solid mass, which was purified by column chromatography (AcOEt) to give **13**. Yield, 51 mg (31.4%). Colorless needles (AcOEt), mp 133.7~134.9 ℃. IR ($CHCl_3$): 3396, 2980, 1674, 1610, 1509, 1462, 1392, 1329, 1257 cm^{-1}. ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 4.23 (s, 3H, N-CH_3), 7.32~7.79 (m, 3H, Ar-H), 7.79 (d, 1H, *J*=1.2 Hz, Ar-H). HRMS *m/z*: Calcd for $C_9H_{10}N_4O$, 190.0854. Found, 190.0852 (M^+).

2-Azido-1-methylbenzimidazole (15)[15] a) From **14** with NaN_3 NaN_3 (24 mg, 0.36 mmol) and 15-crown-5 ether (79 mg, 0.36 mmol) were added to a solution of tributyltin chloride (117 mg, 0.36 mmol) in THF (1 mL) under N_2, and the mixture was stirred for 2 h at rt. A solution of **14** (51 mg, 0.24 mmol) in THF (1 mL) and $PdCl_2(PPh_3)_2$ (8.0 mg, 0.01 mmol) were added to the mixture, and the whole was refluxed for 48 h. After addition of aqueous 10% KF solution (1 mL), the mixture was

extracted with AcOEt and the organic phase was dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crystalline solid, which was purified by column chromatography (AcOEt / *n*-hexane = 1 / 2) to give **15** as pale yellow needles. Yield, 34 mg (81.2%). IR ($CHCl_3$): 2965, 2167, 1616, 1492, 1445, 1405, 1258 cm^{-1}. ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 3.54 (s, 3H, N-CH_3), 7.19~7.26 (m, 3H, Ar-H), 7.60~7.63 (m, 1H, Ar-H). HRMS *m/z*: Calcd for $C_8H_7N_5$, 173.0700. Found, 173.0703 (M^+).

b) From **11** with $TrsN_3$ *n*-C_4H_9Li (1.6 M in *n*-hexane, 0.34 mL, 0.55 mmol) was added to a solution of **11** (66 mg, 0.50 mmol) in THF (2 mL) at –78 ℃ under N_2, and the mixture was stirred for 30 min. Trisyl azide (170 mg, 0.55 mmol) in THF (1.0 mL) was added to the mixture, and the whole was stirred for 30 min. After dilution with AcOEt (20 mL), the reaction mixture was washed with water (2 mL), and the separated organic phase was dried over anhydrous sodium sulfate. A solid mass, obtained by evaporation of the solvent, was purified by column chromatography (AcOEt / *n*-hexane = 1 / 2). Yield, 46 mg (53.2%).

c) From **11** with TsN_3 Reaction was carried out in a similar manner as that for b) except for use of TsN_3 (108 mg, 0.55 mmol) instead of $TrsN_3$. Yield, 78 mg (90.0%).

2-Amino-1-methylbenzimidazole (16)[15,16] a) From **13** A solution of $NaNO_2$ (93 mg, 1.35 mmol) in water (1.0 mL) was added to an ice-cooled and stirred solution of **13** (52 mg, 0.27 mmol) in *conc*-HCl (0.5 mL), and the whole was stirred at rt for 1 h. The reaction mixture was basified with powdered K_2CO_3, and extracted with toluene. After evaporation of the solvent, the residual solid was dissolved in *conc*-HCl (1.0 mL) and the whole mixture was heated at 80 ℃ for 1 h. The mixture was basified with powdered K_2CO_3, and extracted with AcOEt. The organic phase was dried over sodium sulfate followed by evaporation under reduced pressure to give a solid mass. The residue was purified by column chromatography ($CHCl_3$ / MeOH = 10 / 1) to give **16**. Yield, 22 mg (56.3%). Colorless needles (AcOEt - *n*-hexane), mp 196.4~197.3 ℃ (lit., mp 201~202 ℃). IR ($CHCl_3$): 3381, 2928, 1630, 1551, 1456, 1240, 1085 cm^{-1}. ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 3.53 (s, 3H, N-CH_3), 7.04~7.16 (m, 3H, Ar-H), 7.38~7.40 (m, 1H, Ar-H). HRMS *m/z*: Calcd for $C_8H_9N_3$, 147.0800. Found, 147.0793 (M^+).

b) From **15** A mixture of **15** (65 mg, 0.38 mmol), 10% Pd-C (30 mg), and EtOH (3 mL) was stirred under hydrogen atmosphere of usual pressure at rt for 3 h. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to give a crystalline solid, which was purified by column chromatography ($CHCl_3$ / MeOH = 10 / 1) to give **16**. Yield 50 mg (89.5%).

5-[1-Hydroxy-1-(4-methoxymethoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (18)

n-C_4H_9Li (1.6 M in *n*-hexane, 26.6 mL, 42.5 mmol) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (4.99 g, 35.4 mmol), DME (12 mL) and THF (4 mL) at –78 ℃ under N_2 atmosphere, and the mixture was stirred for 15 min. A solution of **17** (6.73 g, 35.4 mmol) in THF (5 mL) was added dropwise to the mixture, and the mixture was stirred for 1 h at -78 ℃. A solution of 4-methoxymethoxybenzaldehyde (5.89 g, 35.4 mmol) in THF (5 mL) was added dropwise to the mixture and the whole was stirred at the same temperature for 2 h. After dilution with AcOEt (50 mL), the mixture was washed with water (10 mL), and the separated organic phase was dried over anhydrous sodium sulfate followed by evaporation under reduced pressure to give an oily residue. The crude product was purified by column chromatography (AcOEt / *n*-hexane = 1 / 1) to give **18**. Yield, 12.6 g (quant.). Colorless needles (AcOEt - *n*-hexane), mp 86.4~87.8 ℃. IR ($CHCl_3$): 3547, 3239, 2940, 1718, 1607, 1529, 1221, 1148, 1075 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 3.47 (s, 6H, N-CH_3 and O-CH_3), 5.16 (s, 2H, O-CH_2-O), 5.76 (s, 1H, Ar-C(OH)H-Ar), 6.72 (s, 1H, C4-H), 6.95~7.01 (m, 2H, Ar-H), 7.02~7.10 (m, 2H, Ar-H), 7.11~7.22 (m, 3H, Ar-H), 7.24~7.30 (m, 2H, Ar-H). HRMS *m/z*: Calcd for $C_{19}H_{20}N_2O_3S$, 356.1194. Found, 356.1199 (M^+). *Anal*. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86. Found: C, 64.42; H, 5.81; N, 7.60.

5-[1-*tert*-Butyldimethylsiloxy-1-(4-methoxymethoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (19) *tert*-Butyldimethylsilyl cholide (TBSCl, 29.2 g, 194 mmol) was added to a solution of **18** (12.5 g, 35.1 mmol), and imidazole (18.0 g, 265 mmol) in DMF (100 mL) under N_2 atmosphere and ice-cooling, and the mixture was stirred at 60 ℃ overnight. After dilution with ether (200 mL), the mixture was washed with water (40 mL), and the separated organic layer was dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography

(AcOEt / *n*-hexane = 1 / 3) to give **19**. Colorless viscous oil. Yield, 16.5 g (quant.). IR ($CHCl_3$): 2935, 1607, 1581, 1503, 1474, 1454, 1248, 1215, 1164, 1072 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: -0.06 (s, 3H, Si-CH_3), 0.19 (s, 3H, Si-CH_3), 1.02 (s, 9H, Si-C(CH_3)$_3$), 3.43 (s, 3H, N-CH_3), 3.59 (s, 3H, O-CH_3), 5.29 (s, 2H, O-CH_2-O), 6.00 (s, 1H, Ar-C(OTBS)H-Ar), 7.25 (s, 1H, C4-H), 7.02~7.08 (m, 2H, Ar-H), 7.09~7.14 (m, 2H, Ar-H), 7.17~7.23 (m, 2H, Ar-H), 7.24~7.32 (m, 3H, Ar-H). HRMS *m/z*: Calcd for $C_{25}H_{34}N_2O_3SSi$, 470.2059. Found, 470.2055 (M^+).

4-Bromo-5-[1-*tert*-butyldimethylsiloxy-1-(4-methoxymethoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (20) *N*-Bromosuccimide (18 mg, 0.10 mmol) was added to a solution of **19** (47 mg, 0.10 mmol) in THF (1 mL) at 0 ℃, and the mixture was stirred for 3 h at 0 ℃. The mixture was diluted with ether, washed with aqueous 5% $Na_2S_2O_3$ (2 mL), and the separated organic phase was dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane = 1 / 5) to give **20** as a pale yellow viscous oil. Yield, 41 mg (74.5%). IR ($CHCl_3$): 2938, 1723, 1607, 1580, 1503, 1474, 1445, 1250, 1228, 1163, 1073 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: -0.06 (s, 3H, Si-CH_3), 0.18 (s, 3H, Si-CH_3), 0.91 (s, 9H, Si-C(CH_3)$_3$), 3.47 (s, 3H, N-CH_3), 3.63 (s, 3H, O-CH_3), 5.16 (s, 2H, O-CH_2-O), 6.07 (s, 1H, Ar-C(OTBS)H-Ar), 6.99 (d, 2H, *J*=8.8 Hz, Ar-H), 7.08 (d, 2H, *J*=8.8 Hz, Ar-H) , 7.14~7.33 (m, 5H, Ar-H). HRMS *m/z*: Calcd for $C_{25}H_{33}N_2O_3BrSSi$, 548.1164. Found, 548.1156 (M^+).

5-[1-*tert*-Butyldimethylsiloxy-1-(4-methoxymethoxyphenyl)methyl]-4-[1-hydroxy-1-(4-methoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (21) *tert*-C_4H_9Li (1.51 M in *n*-pentane, 0.26 mL, 0.40 mmol) was added to a solution of **20** (110 mg, 0.20 mmol) in ether (4 mL) at -78 ℃ under N_2 atmosphere, and the mixture was stirred for 30 min. *p*-Anisaldehyde (136 mg, 1.0 mmol) was added, and the whole was stirred at the same temperature for 3 h. After dilution with AcOEt (10 mL), the mixture was washed with water (3 mL), and the separated organic phase was dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (AcOEt / *n*-hexane = 1 / 2) to give a diastereomeric mixture (1:1) of **21** as a pale yellow viscous oil. Yield, 62 mg (51.1%). IR ($CHCl_3$): 3437, 2936, 1723, 1608, 1581, 1505, 1459, 1240,

1167, 1073, 1000 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: -0.30 (s, 3H, Si-CH_3), -0.09 (s, 3H, Si-CH_3), -0.04 (s, 3H, Si-CH_3), 0.16 (s, 3H, Si-CH_3), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.90 (s, 9H, Si-C(CH_3)$_3$), 3.26 (s, 3H, N-CH_3), 3.33 (s, 3H, N-CH_3), 3.44 (s, 3H, O-CH_3), 3.47 (s, 3H, O-CH_3), 3.78 (s, 3H, O-CH_3), 3.79 (s, 3H, O-CH_3), 5.11 (s, 2H, O-CH_2-O), 5.15 (s, 2H, O-CH_2-O), 5.83 (s, 1H, Ar-C(OTBS)H-Ar), 5.90 (s, 1H, Ar-C(OTBS)H-Ar), 5.97 (s, 1H, Ar-C(OH)H-Ar), 6.09 (s, 1H, Ar-C(OH)H-Ar), 6.82~6.89 (m, 6H, Ar-H), 6.90~6.98 (m, 4H, Ar-H), 7.00~7.29 (m, 12H, Ar-H), 7.36~7.46 (m, 4H, Ar-H). HRMS *m/z*: Calcd for $C_{33}H_{42}N_2O_5SSi$, 606.2583. Found, 606.2592 (M^+).

5-[1-Hydroxy-1-(4-methoxymethoxyphenyl)methyl]-4-[1-hydroxy-1-(4-methoxyphenyl)methyl]-1-methyl-2-phenylthio-1*H*-imidazole (22) Tetrabutylammonium fluoride (1.0 M in THF, 0.20 mL, 0.20 mmol) was added to a solution of **21** (121 mg, 0.20 mmol) in THF (1 mL) at rt and the mixture was stirred for 10 min. After dilution with AcOEt (10 mL), the mixture was washed with water (1 mL), and the separated organic phase was dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane = 1 / 1) to give a diastereomeric mixture (1:1) of **22** as a pale yellow viscous oil. Yield, 97 mg (99.0%). IR ($CHCl_3$): 3305, 2974, 1724, 1608, 1580, 1505, 1474, 1448, 1235, 1213, 1167 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 3.23 (s, 3H, N-CH_3), 3.28 (s, 3H, N-CH_3), 3.44 (s, 3H, O-CH_3), 3.45 (s, 3H, O-CH_3), 3.72 (s, 3H, O-CH_3), 3.73 (s, 3H, O-CH_3), 5.10 (s, 2H, O-CH_2-O), 5.11 (s, 2H, O-CH_2-O), 5.70 (s, 1H, Ar-C(OH)H-Ar), 5.92 (s, 1H, Ar-C(OH)H-Ar), 5.95 (s, 1H, Ar-C(OH)H-Ar), 6.05 (s, 1H, Ar-C(OH)H-Ar), 6.70~6.77 (m, 4H, Ar-H), 6.81~6.88 (m, 4H, Ar-H), 6.91~7.02 (m, 8H, Ar-H), 7.03~7.18 (m, 6H, Ar-H), 7.19~7.30 (m, 4H, Ar-H). HRMS *m/z*: Calcd for $C_{27}H_{28}N_2O_5S$, 492.1719. Found, 492.1718 (M^+).

5-[1-Hydroxy-1-(4-methoxymethoxyphenyl)methyl]-4-[1-hydroxy-1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (23) and 5(4)-[1-Hydroxy-1-(4-methoxymethoxyphenyl)methyl]-4(5)-[1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (24) Nickel(II) chloride hexahydrate (2.17 g, 9.12 mmol) and $NaBH_4$ (1.23 g, 32.6 mmol) were added to a solution of **22** (642 mg, 1.30 mmol) in MeOH / THF = 3 / 1 (8 mL), and the mixture was stirred at rt for 1.5 h. The reaction mixture was passed

through a florisil column to remove Ni colloid. The eluate was diluted with water (20 mL) and extracted with AcOEt (50 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 = 20 / 1) to give a diastereomeric mixture (1:1) of **23** and **24**. **23:** Colorless oil. Yield, 156 mg (31.2%). IR ($CHCl_3$): 3324, 2980, 1723, 1607, 1505, 1236, 1167, 1074, 1028 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 3.27 (s, 3H, N-CH_3), 3.28 (s, 3H, N-CH_3), 3.46 (s, 3H, O-CH_3), 3.46 (s, 3H, O-CH_3), 3.74 (s, 3H, O-CH_3), 3.75 (s, 3H, O-CH_3), 5.14 (s, 4H, O-CH_2-O), 5.70 (s, 1H, Ar-C(OH)H-Ar), 5.79 (s, 1H, Ar-C(OH)H-Ar), 5.98 (s, 1H, Ar-C(OH)H-Ar), 5.98 (s, 1H, Ar-C(OH)H-Ar), 6.79 (d, 4H, *J*=8.6 Hz, Ar-H), 6.92 (d, 4H, *J*=8.8 Hz, Ar-H), 7.19 (s, 1H, C2-H), 7.20 (s, 1H, C2-H), 7.07 (dd, 4H, *J*=8.4, 2.4 Hz, Ar-H), 7.24 - 7.40 (m, 4H, Ar-H). HRMS *m/z*: Calcd for $C_{21}H_{24}N_2O_5$, 384.1685. Found, 384.1691 (M^+). **24**: Colorless oil. Yield, 205 mg (42.7%). IR ($CHCl_3$): 3089, 2981, 2820, 1607, 1581, 1504, 1459, 1234, 1166, 1075, 1002 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 3.28 (s, 3H, N-CH_3), 3.47 (s, 3H, O-CH_3), 3.74 (s, 3H, O-CH_3), 3.77 (d, 1H, *J*=15.6 Hz, Ar-CH_2-Ar), 3.82 (d, 1H, *J*=15.6 Hz, Ar-CH_2-Ar), 5.15 (s, 2H, O-CH_2-O), 6.00 (s, 1H, r-C(OH)H-Ar), 6.75 (d, 2H, *J*=8.6 Hz, Ar-H), 6.94 (d, 2H, *J*=8.8 Hz, Ar-H), 7.09~7.18 (m, 5H, Ar-H). HRMS *m/z*: Calcd for $C_{21}H_{24}N_2O_4$, 368.1736. Found, 368.1732 (M^+).

4-[1-(4-Methoxyphenyl)methyl]-5-[1-(4-hydroxyphenyl)methyl]-1-methyl-1*H*-imidazole (25) a) From **24**. Zn powder (5.0 g) were added to a mixture of acetic acid (20 mL), *conc*.-HCl (5 mL) and **24** (598 mg, 1.63 mmol), and the whole was stirred at 80 ℃ for 1 h. The reaction mixture was filtered through a cotton plug, and the filtrate was evaporated under reduced pressure. After addition of water (5 mL), K_2CO_3 powder was added to basify, and the whole was extracted with AcOEt. 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 = 30 / 1) to give **25**. Yield, 347 mg (69.4%). Colorless crystals (AcOEt – MeOH), mp 222.8 - 225.2 ℃. IR (KBr): 3400, 2900, 1607, 1507, 1450, 1242, 1170, 1080 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 3.33 (s, 3H, N-CH_3), 3.75 (s, 3H, O-CH_3), 3.86 (s, 2H, Ar-CH_2-Ar), 3.87 (s, 2H, Ar-CH_2-Ar), 6.68 (d, 2H, *J*=8.4 Hz, Ar-H), 6.78 (d, 2H, *J*=8.6 Hz, Ar-H), 6.83

(d, 2H, *J*=8.6 Hz, Ar-H), 7.15 (d, 2H, *J*=8.6 Hz, Ar-H), 7.41 (s, 1H, C2-H). HRMS *m/z*: Calcd for $C_{19}H_{20}N_2O_2$, 308.1525. Found, 308.1521 (M^+). *Anal*. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.76; H, 6.66; N, 8.92.

b) From **23**. Reaction was carried out in a similar manner as that for a) except for use of **23** (9 mg, 0.02 mmol) instead of **24**. Yield, 5 mg (71.4%).

5-[1-(4-*tert*-Butyldimethylsiloxyphenyl)methyl]-4-[1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (26) This compound was prepared in a similar manner as that used for preparation of **19** except for use of **25** (257 mg, 0.83 mmol) instead of **18**. The obtained crude product was purified by column chromatography ($CHCl_3$ / MeOH = 30 / 1) to give **26** as a pale yellow viscous oil. Yield, 306 mg (87.5%). IR ($CHCl_3$): 2915, 1605, 1505, 1459, 1247, 1223, 1167, 1097, 1032 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 0.17 (s, 6H, Si-CH_3), 0.97 (s, 9H, Si-C(CH_3)$_3$), 3.31 (s, 3H, N-CH_3), 3.76 (s, 3H, O-CH_3), 3.86 (s, 2H, Ar-CH_2-Ar), 3.87 (s, 2H, Ar-CH_2-Ar), 6.71 (d, 2H, *J*=8.6 Hz, Ar-H), 6.80 (d, 2H, *J*=8.6 Hz, Ar-H), 6.85 (d, 2H, *J*=8.6 Hz, Ar-H), 7.16 (d, 2H, *J*=8.6 Hz, Ar-H), 7.26 (s, 1H, C2-H). HRMS *m/z*: Calcd for $C_{25}H_{34}N_2O_2Si$, 422.2389. Found, 422.2379 (M^+).

2-Bromo-5-[1-(4-*tert*-butyldimethylsiloxyphenyl)methyl]-4-[1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (27) *N*-Bromosuccinimide (148 mg, 0.83 mmol) was added to a solution of **26** (352 mg, 0.83 mmol) in THF (5 mL) at 0 ℃ and the mixture was stirred for 1 h at 0 ℃. After dilution with AcOEt (10 mL), the mixture was washed with aqueous 5% $Na_2S_2O_3$ (2 mL), and the separated organic phase was dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (AcOEt / *n*-hexane = 1 / 2) to give **27** as a pale yellow viscous oil. Yield, 301 mg (72.4%). IR ($CHCl_3$): 2932, 1723, 1605, 1504, 1482, 1245, 1170, 1099, 1033 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 0.18 (s, 6H, Si-CH_3), 0.97 (s, 9H, Si-C(CH_3)$_3$), 3.26 (s, 3H, N-CH_3), 3.76 (s, 3H, O-CH_3), 3.84 (s, 2H, Ar-CH_2-Ar), 3.86 (s, 2H, Ar-CH_2-Ar), 6.71 (d, 2H, *J*=8.6 Hz, Ar-H), 6.78 (d, 2H, *J*=8.8 Hz, Ar-H), 6.84 (d, 2H, *J*=8.8 Hz, Ar-H), 7.12 (d, 2H, *J*=8.8 Hz, Ar-H). ^{13}C-NMR (100.6 MHz in $CDCl_3$) δ: 18.1, 25.6, 29.2, 29.7, 32.2, 32.9, 55.2, 113.8, 118.4, 120.2, 128.6, 128.8, 129.4, 130.2, 132.5, 139.5, 154.3, 157.9. HRMS *m/z*: Calcd for $C_{25}H_{33}N_2O_2BrSi$, 500.1495.

Found, 500.1486 (M^+).

2-Azido-5-[1-(4-*tert*-butyldimethylsiloxyphenyl)methyl]-4-[1-(4-methoxyphenyl)methyl]-1-methyl-1*H*-imidazole (28) *tert*-C_4H_9Li (1.51 M in *n*-pentane, 0.44 mL, 0.67 mmol) was added dropwise to a solution of **27** (160 mg, 0.32 mmol) in ether (1 mL) at –78 ℃, and the mixture was stirred for 30 min. Trisylazide (109 mg, 0.35 mmol) was added to the mixture at -78 ℃, and the whole was stirred for 1 h. After dilution with AcOEt (10mL), the mixture was washed with water (2 mL), and the separated organic phase was dried over sodium sulfate. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (AcOEt / *n*-hexane = 1 / 5) to give **28** as a pale yellow viscous oil and **27** (55 mg, 34.4%). Yield, 67 mg (45.3%). IR ($CHCl_3$): 2912, 2119, 1604, 1503, 1250, 909 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 0.17 (s, 6H, Si-CH_3), 0.97 (s, 9H, Si-C(CH_3)$_3$), 3.06 (s, 3H, N-CH_3), 3.77 (s, 3H, O-CH_3), 3.78 (s, 2H, Ar-CH_2-Ar), 3.83 (s, 2H, Ar-CH_2-Ar), 6.71 (d, 2H, *J*=8.4 Hz, Ar-H), 6.80 (d, 2H, *J*=8.4 Hz, Ar-H), 6.85 (d, 2H, *J*=8.4 Hz, Ar-H), 7.12 (d, 2H, *J*=8.8 Hz, Ar-H). ^{13}C-NMR (100.6 MHz in $CDCl_3$) δ: 18.2, 25.7, 28.7, 29.4, 32.7, 55.2, 113.8, 120.2, 123.7, 124.9, 128.8, 129.4, 130.7, 132.7, 136.2, 138.9, 154.2, 157.9. HRMS *m/z*: Calcd for $C_{25}H_{33}N_5O_2Si$, 463.2403. Found, 463.2405 (M^+).

2-Amino-5-[1-(4-*tert*-butyldimethylsiloxyphenyl)methyl]-4-[1-(4-methoxypheny)methyl]-1-methyl-1*H*-imidazole (29) This compound was prepared in a similar manner as that used for the preparation of **16** from **15** except for use of **28** (34 mg, 0.074 mmol) instead of **15**. The crude oily product was purified by column chromatography ($CHCl_3$ / MeOH = 7 / 3) to give **29** as a pale yellow viscous oil. Yield, 22 mg (68.2%). IR ($CHCl_3$): 3288, 2916, 1723, 1667, 1605, 1505, 1459, 1246, 1220 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 0.18 (s, 6H, Si-CH_3), 0.97 (s, 9H, Si-C(CH_3)$_3$), 3.05 (s, 3H, N-CH_3), 3.76 (s, 3H, O-CH_3), 3.76 (s, 2H, Ar-CH_2-Ar), 3.78 (s, 2H, Ar-CH_2-Ar), 5.23 (br, 2H, NH_2), 6.73 (d, 2H, *J*=8.8 Hz, Ar-H), 6.79 (d, 2H, *J*=8.8 Hz, Ar-H), 6.89 (d, 2H, *J*=8.8 Hz, Ar-H), 7.15 (d, 2H, *J*=8.4 Hz, Ar-H). ^{13}C-NMR (100.6 MHz in $CDCl_3$) δ: 18.2, 28.4, 29.1, 31.3, 38.7, 55.2, 113.9, 120.3, 120.8, 128.8, 129.5, 130.5, 130,.9 131.9, 154.3, 158.0. HRMS *m/z*: Calcd for $C_{25}H_{35}N_3O_2Si$, 437.2498. Found, 437.2508 (M^+).

Naamine A (4) TBAF (1.0 M in THF, 0.032 mL, 0.032 mmol) was added to a solution of **29** (14 mg, 0.032 mmol) in THF(1 mL) at rt under N_2 atmosphere, and the mixture was stirred for 10 min. After dilution with $CHCl_3$ (10 mL), the mixture was washed with water (1 mL), and the separated organic phase was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave an oily residue, which was purified by column chromatography ($CHCl_3$ / MeOH = 7 / 3) to give **4** as a pale yellow powder. Yield, 7 mg (70.0%). mp 202.0 - 204.5 ℃. IR (KBr): 3350, 1668, 1568, 1507, 1417, 1240 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 3.05 (s, 3H, N-CH_3), 3.65 (s, 3H, Ar-CH_3), 3.72 (s, 2H, Ar-CH_2-Ar), 3.73 (s, 2H, Ar-CH_2-Ar), 6.72 - 6.82 (m, 6H, Ar-H), 7.10 (d, 2H, *J*=8.4 Hz, Ar-H). HRMS *m/z*: Calcd for $C_{21}H_{19}N_3O_2$, 323.1634. Found, 323.1643 (M^+). These data were almost agreed with those of the natural naamine A.[2d, 13]

Naamidine A (5) A mixture of 1-methylparabanic acid (**30;** 7 mg, 0.053 mmol), 4-*N*,*N*-dimethyl-aminopyridine (1 mg), imidazole (4 mg, 0.059 mmol), triethylamine (11 mg, 0.11 mmol), and trimethylsilyl chloride (12 mg, 0.111 mmol) in $CHCl_3$ (0.5 mL) was stirred for 5 min under ice-cooling and N_2 atmosphere, and then the stirring was continued for 2 h at rt. A solution of naamine A (**4**; 17 mg, 0.053 mmol) in $CHCl_3$(1 mL) was added to the mixture, and the whole was refluxed for 72 h. After dilution with $CHCl_3$ (10 mL), the mixture was washed with water (1 mL), and the separated organic phase was dried over anhydrous sodium sulfate. The organic phase was evaporated under reduced pressure to give a crystalline residue, which was triturated with $CHCl_3$ followed by filtration to give pure **5** as yellow granules. Yield, 10 mg (43.5%). mp 186.5 – 190.0 ℃. IR ($CHCl_3$): 3410, 1725, 1668, 1635, 1608, 1508, 1440, 1240 cm^{-1}. ^{1}H-NMR (400 MHz in $CDCl_3$ + CD_3OD) δ: 3.04 (s, 3H, N-CH_3), 3.15 (s, 3H, N-CH_3), 3.78 (s, 3H, O-CH_3), 3.79 (s, 2H, Ar-CH_2-Ar), 3.83 (s, 2H, Ar-CH_2-Ar), 6.75 (d, 2H, *J*=8.4 Hz, Ar-H), 6.82 (d, 2H, *J*=8.8 Hz, Ar-H), 6.91 (d, 2H, *J*=8.4 Hz, Ar-H), 7.13 (d, 2H, *J*=8.4 Hz, Ar-H). ^{13}C-NMR (75.4 MHz in $CDCl_3$ + CD_3OD) δ: 24.9, 27.4, 28.4, 29.7, 54.5, 113.4, 115.0, 127.5, 128.4, 128.8, 129.9, 130.4, 131.8, 146.6, 148.4, 155.3, 157.8, 162.5. HRMS *m/z*: Calcd for $C_{23}H_{23}N_5O_4$, 433.1750. Found, 433.1742 (M^+). These data were almost agreed with those of the natural naamidine A.[2d, 14]

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12. Catalytic hydrogenolysis of the benzylic hydroxyl group for **23** and **24** in the presence of 5 or 10% Pd-C did not proceed at all.
13. The reported data for the natural naamine A (ref. 2d): IR (KBr): 3500 (br), 2920, 1670, 1615 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.15 (br s, 3H), 3.69 (s, 3H), 3.79 (br s, 2H), 3.84 (br s, 2H), 6.70 (d, 2H, *J*=8.6 Hz), 6.83 (d, 2H, *J*=8.6 Hz), 6.89 (d, 2H, *J*=8.6 Hz), 7.16 (d, 2H, *J*=8.6 Hz), 7.60 (br s, 2H).

Mp was not reported in ref. 2d.

14. The reported data for the natural naamidine A (ref. 2d): Yellow foaming oil. IR (KBr): 3650-3100 (br), 2930, 1707, 1570, 1510, 1440, 1250, 1170, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + CD_3OD) δ: 3.13 (s, 3H), 3.48 (br s, 3H), 3.77 (s, 3H), 3.88 (br s, 2H), 3.91 (br s, 2H), 6.72 (d, 2H *J*=8.6 Hz), 6.81 (d, 2H *J*=8.6 Hz), 6.84 (d, 2H *J*=8.6 Hz), 7.11 (d, 2H *J*=8.6 Hz). ^{13}C-NMR ($CDCl_3$ + CD_3OD) δ: 24.4, 28.2, 29.6, 31.3, 55.0, 113.9, 115.6, 126.7, 127.4, 128.7, 129.1, 130.7, 132.9, 146.2, 148.4, 155.6, 158.3, 163.3. Mp was not reported in ref. 2d.
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