# New access to 1,3-dialkyl-2,3-dihydro-2-imino-1*H*-imidazoles and their application to the first total synthesis of naamine B, a marine 2,3-dihydro-2-imino-1,3-dimethyl-1*H*-imidazole alkaloid

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1,3-Dialkyl-2,3-dihydro-2-imino-1*H*-imidazole derivatives are synthesized in 49–86% yield by treatment of 1,3-dialkyl-2-(phenylsulfanyl)imidazolium salts with primary carbamates or amides in the presence of a base such as LDA or NaH, and the first total synthesis of naamine B, a marine 2-imino-2,3-dimethyl-1,3-dihydro-1*H*-imidazole alkaloid, is achieved by application of this reaction as a key step.

# Introduction

Recently, many types of biologically active imidazole alkaloids have been isolated from marine organisms such as sponges, and they have become one of the focuses of scientific attention.<sup>1</sup> 1,3-Dialkyl-2,3-dihydro-2-imino-1H-imidazoles can be seen as basic skeletons of several biologically interesting compounds,<sup>2</sup> and a marine alkaloid, naamine B 1, was isolated from the antifungally active extract of the marine sponge Leucetta chagosensis,1i together with several antitumor (in vivo) imidazole alkaloids,<sup>3</sup> and its structure is shown in Fig. 1. Although there are several examples of the synthesis of 1,3-dialkyl-2,3dihydro-2-imino-1H-imidazoles based on cyclization chemistry,<sup>2d,f</sup> it was reported that attempted direct conversion of an imidazole compound to the 2-imino derivative was not effective.4 We have reported total syntheses of several biologically active imidazole alkaloids such as topsentin,<sup>5</sup> nortopsentins A-D,<sup>6</sup> kealiiquinone,<sup>7</sup> naamine A,<sup>8</sup> naamidine A<sup>8</sup> and clathridine,9 and this time we selected naamine B as a synthetic target, which could be classified in one of the structural categories among the known imidazole marine alkaloids. In this paper, we would like to disclose a new preparation method for 1,3-dialkyl-2,3-dihydro-2-imino-1H-imidazole compounds starting from imidazole compounds and its application to the total synthesis of 1.

### **Results and discussion**

In our previous paper, we reported a new synthetic method for the 1,3-dialkyl-1,3-dihydroimidazol-2-ones **4** by treatment of 1,3-dialkyl-2-phenylsulfanyl-1*H*-imidazolium salts **2** with aqueous alkali, and its application to the synthesis of a regioisomer of kealiiquinone, a marine benzimidazole alkaloid (Scheme 1).<sup>10</sup> This reaction would be initiated by attack of the





hydroxide ion at the 2-position of the imidazolium salts 2 followed by removal of the thiophenoxide ion from the intermediate 3 to produce 4 as shown in Scheme 1. As an expanded application of this reaction, we planned the use of appropriate primary amides or carbamates in the presence of an appropriate base instead of the above-mentioned aqueous alkali. The results are summarized in Table 1.

The 1,3-dialkyl-2-(phenylsulfanyl)imidazolium salts 2a-d were easily prepared by treatment of 1-alkyl-2-phenylsulfanyl-1H-imidazoles<sup>11</sup> with alkyl halides in refluxed AcOEt as previously we reported.<sup>10</sup> Reaction of 2a in THF with acetamide in the presence of 2 equivalents of LDA gave the best result, and the desired 2-acetylimino-1-benzyl-2,3-dihydro-3-methyl-1Himidazole 5a was obtained in 86% yield (entry 2). Decreasing the amount of LDA to 1 equivalent or using 2 equivalents of either NaH or NaOMe instead of LDA lowered the yield of 5a (entries 1, 3 and 4), and in several cases the undesired 2oxoimidazoline 4a was obtained in 48% to quantitative yield (entries 3 and 4). The production of 4a indicated that the unconsumed starting substrate 2a might be hydrolysed during the work-up procedure. The reaction of 2a with benzamide, tert-butyl carbamate or benzyl carbamate in the presence of LDA or NaH in THF at 0 °C to room temperature gave the corresponding iminoimidazolines 5b-d in moderate to fair yield (entries 5-7). Other imidazolium derivatives such as 2b-d could be also converted to the corresponding N-Boc imino derivatives 5e-g in 65-70% yield (Entries 8-10). The present method seems to be efficient for the preparation of multifunctionalized 2-iminoimidazoline derivatives compared with the known methods based on cyclization to afford the imidazoline ring.<sup>2df</sup>

The present reaction described above was applied to the total synthesis of naamine B 1 as follows. The known trisubstituted

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<sup>*a*</sup> Isolated yield. <sup>*b*</sup> Trace amount of **4a** was also obtained. <sup>*c*</sup> A by-product **4a** was isolated in 48% yield. <sup>*d*</sup> Quantitative yield of **4a** was obtained. <sup>*e*</sup> The crude quaternary salt was used.



Scheme 2 Reagents and conditions: (a) Zn, conc. HCl, AcOH, 97%; (b) NBS, THF, 72%; (c) t-BuLi, THF, 63%; (d)  $Et_3SiH$ , TFA, DCM, 80%; (e) MeI, AcOEt; (f) LDA, tert-butyl carbamate, 13: 56% and 14: 21% (2 steps); (g) TFA, DCM, quant. (from 13).

imidazole  $6^{11a}$  was selected as the starting material, and the benzylic hydroxy group of 6 was removed by reduction with a zinc powder–*conc*. HCl system to give the sulfide 7 in 97% yield (Scheme 2). The 4-position of the product was brominated by treatment with NBS in THF,<sup>12</sup> and then the resultant bromide 8 was coupled with the aldehyde 9<sup>13</sup> in the presence of *t*-BuLi to give the alcohol 10 in 63% yield from 8.<sup>14</sup> Reduction of the alcohol 10 with the combination of triethylsilane (5 equiv.) and TFA (6 equiv.)<sup>15</sup> proceeded effectively to give the silyl ether 11 in 80% yield. The imidazolium iodide 12 was prepared in the usual manner, and the salt 12 was treated with *tert*-butyl carbamate in the presence of LDA at -78 °C to give the desired *N*-Boc imino compound 13 in 56% yield accompanied by a 21% yield of the 2-oxoimidazoline 14.

Treatment of iminocarbamate 13 with TFA to remove the Boc and TBDMS groups gave successfully the powdered material 1 in quantitative yield. The spectral data (<sup>1</sup>H-, <sup>13</sup>C-NMR, MS and IR) of the product 1 completely supported the

structure and were well consistent with the reported data of natural naamine B 1.  $\,$ 

In conclusion, we have successfully developed a preparative method for 1,3-dialkyl-2,3-dihydro-2-imino-1*H*-imidazole derivatives starting from imidazole compounds, and have achieved the first total synthesis of naamine B in 20% overall yield from **6**.

# Experimental

All mps were measured with a Yanaco MP micro-melting-point apparatus and are uncorrected. IR spectra were taken with a Shimadzu IR-435 spectrometer. NMR spectra were measured on a Varian UNITY INOVA 400NB (<sup>1</sup>H: 400 MHz, <sup>13</sup>C: 100 MHz) or a JEOL EX-300 (<sup>1</sup>H: 300 MHz, <sup>13</sup>C: 75 MHz) spectrometer with tetramethylsilane as internal standard, and chemical shifts  $\delta$  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) for column chromatography and silica gel 60  $PF_{254}$  (Nacalai Tesque Inc.) for preparative TLC (PLC) were used.

# General procedure for synthesis of 1,3-dialkyl-2,3-dihydro-2-imino-1*H*-imidazoles 5; Synthesis of 1-benzyl-2-*tert*-butoxycarbonylimino-2,3-dihydro-3-methyl-1*H*-imidazole 5c as an example

tert-Butyl carbamate (176 mg, 1.5 mmol) was added to a stirred solution of LDA [prepared from diisopropylamine (1 mmol) and n-BuLi (1 mmol; 1.6 M in n-hexane)] in THF (4 mL) under N<sub>2</sub> and ice cooling, and the mixture was stirred for 30 min at 0 °C, then the salt 2a<sup>10</sup> (181 mg, 0.5 mmol) was added to the mixture and stirring was continued for 12 h at ambient temperature. Water (1 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. The product was extracted with CHCl<sub>3</sub> (20 mL  $\times$  4) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was purified by column chromatography (CHCl<sub>3</sub>-MeOH 20:1) on silica gel to give 5c (102 mg, 71%) as colorless crystals, mp 88-91 °C (from AcOEt-n-hexane); v<sub>max</sub> (CHCl<sub>3</sub>) 2954, 1626, 1557, 1361, 1340, 1233, 1157, 1063 cm<sup>-1</sup>;  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 1.51 (s, 9H), 3.48 (s, 3H), 5.01 (s, 2H), 6.34 (d, J = 2.6 Hz, 1H), 6.50 (d, J = 2.6 Hz, 1H), 7.24–7.34 (m, 5H); δ<sub>c</sub> (100 MHz; CDCl<sub>3</sub>) 28.6, 34.0, 49.8, 77.0, 113.9, 116.1, 128.2, 128.4, 128.9, 135.4, 150.9, 159.4 [Calc. for C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.59; H, 7.37; N, 14.41%. FAB-HRMS (pos.) m/z Calc. for  $C_{16}H_{22}N_{3}O_{2}$ : M + H, 288.1712. Found: (M + H)<sup>+</sup>, 288.1707].

### 2-Acetylimino-1-benzyl-2,3-dihydro-3-methyl-1H-imidazole

**5a.** This was prepared in a similar manner to that used for the preparation of **5c** except for the use of acetamide instead of *tert*-butyl carbamate. Title compound was purified by column chromatography (CHCl<sub>3</sub>–MeOH 10 : 1) and obtained as a pale yellow oil (99 mg, 86%);  $v_{max}$  (CHCl<sub>3</sub>) 2954, 1575, 1514, 1380 cm<sup>-1</sup>;  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 2.15 (s, 3H), 3.49 (s, 3H), 4.99 (s, 2H), 6.45 (d, J = 2.6 Hz, 1H), 6.58 (d, J = 2.6 Hz, 1H), 7.25–7.36 (m, 5H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) 25.7, 33.9, 50.1, 114.8, 116.7, 128.4 (×2), 128.9, 134.8, 150.9, 176.3 [EI-HRMS (pos.) *m*/*z* Calc. for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O: *M*, 229.1215. Found: M<sup>+</sup>, 229.1205].

# 2-Benzoylimino-1-benzyl-2,3-dihydro-3-methyl-1*H*-imidazole

**5b.** This was prepared in a similar manner to that used for the preparation of **5c** except for the use of benzamide instead of *tert*-butyl carbamate. Title compound was purified by PLC (CHCl<sub>3</sub>–MeOH 50 : 1) and obtained as a pale yellow oil (72 mg, 49%);  $v_{\text{max}}$  (CHCl<sub>3</sub>) 2950, 1591, 1522, 1375, 1322 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 3.54 (s, 3H), 5.06 (s, 2H), 6.50 (d, J = 2.6 Hz, 1H), 6.61 (d, J = 2.6 Hz, 1H), 7.27–7.46 (m, 8H), 8.23 (dd, J = 8.2, 2.2 Hz, 2H);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 34.1, 49.9, 114.5, 116.6, 127.5, 128.2, 128.4, 128.80, 128.81, 130.1, 135.1, 138.5, 151.9, 170.6 [EI-HRMS (pos.) *m*/*z* Calc. for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O: *M*, 291.1371. Found: M<sup>+</sup>, 291.1361].

### 1-Benzyl-2-benzyloxycarbonylimino-2,3-dihydro-3-methyl-

**1***H*-imidazole 5d. This was prepared in a similar manner to that used for the preparation of 5c except for the use of benzyl carbamate and NaH instead of *tert*-butyl carbamate and LDA respectively. Title compound was purified by column chromatography (CHCl<sub>3</sub>–MeOH 50 : 1) and obtained as pale yellow needles (86 mg, 54%), mp 93–95 °C (from AcOEt–*n*-hexane);  $v_{max}$  (CHCl<sub>3</sub>) 2964, 1627, 1570, 1380, 1079 cm<sup>-1</sup>;  $\delta_{H}$  (400 MHz; CDCl<sub>3</sub>) 3.46 (s, 3H), 4.99 (s, 2H), 5.16 (s, 2H), 6.37 (d, *J* = 2.6 Hz, 1H), 6.50 (d, *J* = 2.6 Hz, 1H), 7.21–7.45 (m, 10H);  $\delta_{C}$  (100 MHz; CDCl<sub>3</sub>) 34.0, 49.9, 66.6, 114.2, 116.3, 127.2, 127.7, 128.1, 128.2, 128.3, 128.7, 135.1, 138.3, 150.7, 159.2 [Calc. for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.77; H, 5.92; N, 12.99%. EI-HRMS (pos.) *m*/*z* Calc. for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>: *M*, 321.1477. Found: M<sup>+</sup>, 321.1466].

### 2-tert-Butoxycarbonylimino-2,3-dihydro-1,3-dimethyl-1H-

**imidazole 5e.** This was prepared in a similar manner to that used for the preparation of **5c** except for the use of **2b**<sup>10</sup> instead of **2a**. Title compound was purified by column chromatography (CHCl<sub>3</sub>–MeOH 5 : 1) and obtained as colorless needles (73 mg, 69%), mp 146–149 °C (from diethyl ether);  $v_{max}$  (CHCl<sub>3</sub>) 2954, 1625, 1576, 1360, 1318, 1243, 1162, 1049 cm<sup>-1</sup>;  $\delta_{H}$  (400 MHz; CDCl<sub>3</sub>) 1.52 (s, 9H), 3.44 (s, 6H), 6.49 (s, 2H);  $\delta_{C}$  (100 MHz; CDCl<sub>3</sub>) 28.5, 33.8, 76.9, 115.5, 150.8, 159.4 [Calc. for C<sub>10</sub>H<sub>17</sub>-N<sub>3</sub>O<sub>2</sub>: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.55; H, 8.01; N, 20.15%. FAB-HRMS (pos.) *m*/*z* Calc. for C<sub>10</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub>: *M* + H, 212.1399. Found: (*M* + H)<sup>+</sup>, 212.1405].

### 1,3-Dibenzyl-2-phenylsulfanyl-1H-imidazolium bromide 2c

A mixture of 1-benzyl-2-phenylsulfanyl-1*H*-imidazole<sup>11b</sup> (146 mg, 0.55 mmol) and benzyl bromide (0.098 mL, 0.83 mmol) in AcOEt (0.83 mL) was refluxed under stirring for 3 h, and then kept overnight at room temperature. The crude solid was collected and recrystallized from acetone–diethyl ether to give pure **2c** as colorless crystals (229 mg, 95%), mp 170–171 °C;  $v_{max}$  (CHCl<sub>3</sub>) 2917, 1492, 1449, 1234, 1170, 1091 cm<sup>-1</sup>;  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 5.63 (s, 4H), 6.95 (dd, J = 8.2, 1.5 Hz, 2H), 7.27–7.32 (m, 13H), 8.16 (s, 2H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) 53.6, 125.4, 128.9, 129.0, 129.1, 129.2, 129.3 (×2), 130.4, 132.5, 137.9 (Calc. for C<sub>23</sub>H<sub>21</sub>BrN<sub>2</sub>S: C, 63.16; H, 4.84; N, 6.40. Found; C, 63.22; H, 5.04; N, 6.23%).

# 1,3-Dibenzyl-2-*tert*-butoxycarbonylimino-2,3-dihydro-1*H*-imidazole 5f

This was prepared in a similar manner to that used for the preparation of **5c** except for the use of **2c** (87 mg, 0.2 mmol) instead of **2a**. Title compound was purified by column chromatography (CHCl<sub>3</sub>–MeOH 20 : 1) and obtained as colorless crystals (51 mg, 70%), mp 130–132 °C (from AcOEt–*n*-hexane);  $v_{\text{max}}$  (CHCl<sub>3</sub>) 2957, 1625, 1558, 1331, 1287, 1154, 1073, 1016 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 1.52 (s, 9H), 5.03 (s, 4H), 6.29 (s, 2H), 7.26–7.37 (m, 10H);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 28.5, 50.0, 77.1, 114.3, 128.2, 128.5, 128.8, 135.1, 150.4, 159.3 [Calc for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: C, 72.70; H, 6.93; N, 11.56. Found; C, 72.42; H, 6.88; N, 11.62%. FAB-HRMS (pos.) *m*/*z* Calc. for C<sub>22</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>: *M* + H, 364.2025. Found: (*M* + H)<sup>+</sup>, 364.2029].

### 1-Benzyl-3-ethyl-2-phenylsulfanyl-1H-imidazolium bromide 2d

n-BuLi (1.6 M in n-hexane; 8.03 mL, 12.84 mmol) was added to a stirred solution of 1-ethyl-1*H*-imidazole<sup>16</sup> (1.029 g, 10.70 mmol) in THF (43 mL) under  $N_2$  at -78 °C. After stirring of the mixture for 15 min at the same temperature, diphenyl disulfide (2.803 g, 12.84 mmol) was added and the whole was stirred for 3 h at -78 °C. The mixture was acidified with 10% HCl and washed with diethyl ether. The aqueous layer was basified with  $K_2CO_3$  powder and extracted with AcOEt (20 mL × 2). 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 1-ethyl-2-phenylsulfanyl-1H-imidazole (2.069 mg, 95%) as a colorless oil; v<sub>max</sub> (CHCl<sub>3</sub>) 2949, 1580, 1474, 1428, 1270, 1087  $cm^{-1}$ ;  $\delta_{H}$  (400 MHz; CDCl<sub>3</sub>) 1.28 (t, J = 7.3 Hz, 3H), 4.04 (q, J = 7.3 Hz, 2H), 7.11–7.27 (m, 7H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) 16.1, 42.0, 121.7, 126.5, 127.9, 129.1, 130.5, 135.2, 137.2 [EI-HRMS (pos.) *m/z* Calc. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>S: *M*, 204.0721. Found: M<sup>+</sup>, 204.0724].

A mixture of 1-ethyl-2-phenylsulfanyl-1*H*-imidazole (390 mg, 1.91 mmol) and benzyl bromide (0.341 mL, 2.87 mmol) in AcOEt (2.9 mL) was refluxed under stirring for 3 h, and then kept overnight at room temperature. The solvent was evaporated off to give a brown syrup, which was washed with AcOEt (5 mL  $\times$  2) and evaporated to give a crude salt **2d** (676 mg, 94%) as a brown gum, which was used in the next reaction without further purification;  $v_{max}$  (CHCl<sub>3</sub>) 2919, 1477, 1439, 1233,

1090 cm<sup>-1</sup>;  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 1.39 (t, J = 7.3 Hz, 3H), 4.44 (q, J = 7.3 Hz, 2H), 5.70 (s, 2H), 7.02–7.04 (m, 2H), 7.19–7.37 (m, 8H), 8.30 (d, J = 2.0 Hz, 1H), 8.40 (d, J = 2.0 Hz, 1H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) 15.3, 45.4, 53.4, 125.2, 125.7, 128.7, 128.9, 129.0, 129.08, 129.10, 129.11, 130.4, 132.8, 136.9 [FAB-HRMS (pos.) m/z Calc. for C<sub>18</sub>H<sub>19</sub>N<sub>2</sub>S: M – Br, 302.1869. Found: (M – Br)<sup>+</sup>, 302.1863].

# 1-Benzyl-2-*tert*-butoxycarbonylimino-3-ethyl-2,3-dihydro-1*H*-imidazole 5g

This was prepared in a similar manner to that used for the preparation of **5c** except for the use of a solution of **2d** (128 mg, 0.34 mmol) in THF (1.0 mL)–CH<sub>2</sub>Cl<sub>2</sub> (0.2 mL) instead of crystalline **2a**. Title compound was purified by column chromatography (CHCl<sub>3</sub>–MeOH 20 : 1) and obtained as colorless crystals (67 mg, 65%), mp 156–157 °C (from AcOEt–*n*-hexane);  $v_{max}$  (CHCl<sub>3</sub>) 2958, 1625, 1558, 1331, 1290, 1158, 1085, 1017 cm<sup>-1</sup>;  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 1.36 (t, J = 7.3 Hz, 3H), 1.51 (s, 9H), 3.90 (q, J = 7.3 Hz, 2H), 5.00 (s, 2H), 6.34 (d, J = 2.6 Hz, 1H), 6.54 (d, J = 2.6 Hz, 1H), 7.25–7.37 (m, 5H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) 14.1, 28.4, 41.1, 49.9, 76.8, 113.7, 114.2, 128.1, 128.5, 128.7, 135.1, 149.9, 159.2 [Calc. for C<sub>17</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.46; H, 7.53; N, 14.20%. FAB-HRMS (pos.) *m*/*z* Calc. for C<sub>17</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>: *M* + H, 302.1869. Found: (M + H)<sup>+</sup>, 302.1863].

# 5-(4-Methoxybenzyl)-1-methyl-2-phenylsulfanyl-1*H*-imidazole 7

Zn powder (320 mg) was added to a mixture of **6**<sup>11a</sup> (261 mg, 0.8 mmol) and conc. HCl (0.8 mL) in AcOH (8 mL), and the whole was stirred at 80 °C for 3 h. The reaction mixture was filtered and the filtrate was concentrated, diluted with water (3 mL), and basified by addition of K<sub>2</sub>CO<sub>3</sub> powder. The products was extracted with AcOEt (20 mL × 4), and the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated off to give an oily residue, which was purified by PLC (AcOEt) to give **7** (151 mg, 97%) as a pale yellow oil;  $v_{\rm max}$  (CHCl<sub>3</sub>) 2935, 1608, 1506, 1449, 1241, 1173, 1093, 1031 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 3.39 (s, 3H), 3.79 (s, 3H), 3.89 (s, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.97–7.26 (m, 8H);  $\delta_{\rm C}$  (75 MHz; CDCl<sub>3</sub>) 30.5, 31.2, 55.2, 114.1, 126.3, 127.6, 129.0 (×2), 129.1, 129.3, 134.4, 135.3, 137.6, 158.4 [EI-HRMS (pos.) *m/z* Calc. for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>OS: *M*, 310.1140. Found: M<sup>+</sup>, 310.1135].

# 4-Bromo-5-(4-methoxybenzyl)-1-methyl-2-phenylsulfanyl-1*H*-imidazole 8

NBS (251 mg, 1.41 mmol) was added to a solution of 7 (364 mg, 1.17 mmol) in THF (2.3 mL) at 0 °C under N<sub>2</sub>, and the whole was stirred at 0 °C for 4 h. After addition of water (15 mL), the product was extracted with AcOEt (50 mL  $\times$  2), and the the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated off to give an oily residue, which was purified column chromatography (AcOEt-n-hexane 1:5) on silica gel to give 8 (327 mg, 72%) as colorless needles, mp 73–77 °C (from *n*-hexane);  $\nu_{max}$  (CHCl<sub>3</sub>) 2965, 1607, 1506, 1239, 1093 cm<sup>-1</sup>;  $\delta_{H}$  (400 MHz; CDCl<sub>3</sub>) 3.38 (s, 3H), 3.78 (s, 3H), 3.94 (s, 2H), 6.83 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 7.12–7.27 (m, 5H); δ<sub>c</sub> (75 MHz; CDCl<sub>3</sub>) 29.8, 32.3, 55.3, 114.2, 115.7, 126.7, 127.9, 128.4, 128.8, 129.2, 132.1, 134.2, 137.1, 158.3 [Calc. for  $C_{18}H_{17}BrN_2OS$ : C, 55.53; H, 4.40; N, 7.20. Found: C, 55.62; H, 4.59; N, 6.99%. EI-HRMS (pos.) m/z Calc. for C<sub>18</sub>H<sub>17</sub>BrN<sub>2</sub>OS: *M*, 388.0244. Found: M<sup>+</sup>, 388.0243. EI-MS (pos.) m/z (% base): 391 (9), 390 (39), 389 (16), 388 (38), 387 (8), 121 (100)].

# 4-{[3(-*tert*-Butyldimethylsiloxy)-4-methoxyphenyl]hydroxymethyl}-5-(4-methoxybenzyl)-1-methyl-2-phenylsulfanyl-1*H*-imidazole 10

t-BuLi (1.56 M in pentane; 0.58 ml, 0.90 mmol) was added

dropwise to a stirred solution of 8 (72 mg, 0.18 mmol) and 9 (253 mg, 0.95 mmol) in THF (1 mL) under N<sub>2</sub> at -78 °C. After stirring of the mixture for 10 min at the same temperature, water (2 mL) was added. The product was extracted with AcOEt (10 mL  $\times$  3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated off to give an oily residue, which was purified by column chromatography (AcOEt-n-hexane 1 : 3) on silica gel to give 10 (65 mg, 63%) as a pale yellow oil;  $v_{\text{max}}$  (CHCl<sub>3</sub>) 2913, 1606, 1579, 1504, 1447, 1270, 1243, 841 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 0.10 (s, 6H), 0.96 (s, 9H), 3.27 (s, 3H), 3.74 (s, 3H), 3.76 (s, 3H), 3.77 (s, 2H), 5.74 (br s, 1H), 6.72-6.83 (m, 5H), 6.94-7.26 (m, 7H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) -4.7, 18.4, 25.7, 29.0, 31.4, 55.2, 55.5, 69.7, 111.8, 114.0, 119.5, 120.0, 126.3, 127.2, 128.8, 129.1, 129.2, 129.4, 135.1, 135.8, 136.2, 142.5, 144.8, 150.3, 158.2 [EI-HRMS (pos.) m/z Calc. for C<sub>32</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>SSi: M, 576.2478. Found: M<sup>+</sup>, 576.2482].

# 4-[3(-*tert*-Butyldimethylsiloxy)-4-methoxybenzyl]-5-(4-methoxybenzyl)-1-methyl-2-phenylsulfanyl-1*H*-imidazole 11

To a stirred solution of 10 (23 mg, 0.04 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) were added triethylsilane (0.032 mL, 0.20 mmol) and TFA (0.018 mL, 0.24 mmol) under N<sub>2</sub> and ice-cooling. The solution was stirred for 3.5 h at ambient temperature and quenched by the addition of saturated aq. NaHCO<sub>3</sub> (3 mL). The products were extracted with AcOEt (10 mL  $\times$  2) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated off to give an oily residue, which was purified by PLC (AcOEt-n-hexane 1 : 1) on silica gel to give 11 (18 mg, 80%) as a pale yellow oil;  $v_{max}$  (CHCl<sub>3</sub>) 2918, 1505, 1458, 1438, 1272, 1240, 839 cm<sup>-1</sup>;  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 0.11 (s, 6H), 0.96 (s, 9H), 3.28 (s, 3H), 3.76 (s, 6H), 3.84 (s, 2H), 3.90 (s, 2H), 6.71–6.86 (m, 7H), 7.04–7.24 (m, 5H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) -4.7, 18.4, 25.7, 29.2, 31.5, 33.3, 55.2, 55.6, 112.1, 114.0, 121.3, 121.5, 126.0, 127.0, 128.8, 129.1, 129.6, 129.9, 133.3, 135.3, 135.9, 140.3, 144.8, 149.2, 158.2 [EI-HRMS (pos.) m/z Calc. for C<sub>32</sub>H<sub>40</sub>N<sub>2</sub>O<sub>3</sub>SSi: M, 560.2529. Found: M<sup>+</sup>, 560.2519].

# 2-*tert*-Butoxycarbonylimino-4-[3(-*tert*-butyldimethylsiloxy)-4-methoxybenzyl]-2,3-dihydro-5-(4-methoxybenzyl)-1,3-dimethyl-1*H*-imidazole 13 and 4-[3(-*tert*-butyldimethylsiloxy)-4-methoxybenzyl]-5-(4-methoxybenzyl)-1,3-dimethyl-2,3-dihydro-1*H*-imidazol-2-one 14

A mixture of **11** (72 mg, 0.13 mmol) and methyl iodide (0.1 mL, 1.6 mmol) in AcOEt (1 mL) was refluxed under stirring for 1 h. The solvent was evaporated off to give the crude salt **12**, which was used in the next reaction without further purification.

*tert*-Butyl carbamate (46 mg, 0.39 mmol) was added to a stirred solution of LDA [prepared from diisopropylamine (0.312 mmol) and *n*-BuLi (0.26 mmol; 1.6 M in *n*-hexane)] in THF (1 mL) under N<sub>2</sub> and ice-cooling, and the mixture was stirred for 30 min at 0 °C, then a solution of the salt **12** in THF (0.8 mL) was added to the mixture and stirring was continued for 12 h at ambient temperature. Water (3 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. The product was extracted with CHCl<sub>3</sub> (15 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated off to give an oily residue, which was purified by PLC (CHCl<sub>3</sub>–MeOH 20 : 1) on silica gel to give **13** ( $R_{\rm f}$  0.20, 42 mg, 56%) and **14** ( $R_{\rm f}$  0.34, 13 mg, 21%) as a colorless oil.

Compound **13**;  $v_{max}$  (CHCl<sub>3</sub>) 2910, 1623, 1551, 1521, 1335, 1244, 1163, 1047, 838 cm<sup>-1</sup>;  $\delta_{H}$  (400 MHz; CDCl<sub>3</sub>) 0.12 (s, 6H), 0.96 (s, 9H), 1.48 (s, 9H), 3.27 (s, 3H), 3.28 (s, 3H), 3.775 (s, 3H), 3.783 (s, 3H), 3.82 (s, 2H), 3.87 (s, 2H), 6.58 (dd, J = 8.2, 2.2 Hz, 1H), 6.63 (d, J = 2.2 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H);  $\delta_{C}$  (100 MHz; CDCl<sub>3</sub>) -4.7, 18.4, 25.6, 28.2, 28.5 (×2), 31.0, 31.1, 55.2, 55.4, 77.5,

112.3, 114.3, 120.7, 120.8, 122.8, 123.0, 128.3, 128.75, 128.80, 145.2, 148.4, 149.9, 158.0, 158.5 [FAB-HRMS (pos.) m/z Calc. for C<sub>32</sub>H<sub>48</sub>N<sub>3</sub>O<sub>5</sub>Si: M + H, 582.3363. Found: (M + H)<sup>+</sup>, 582.3358].

Compound **14**;  $v_{max}$  (CHCl<sub>3</sub>) 2916, 1669, 1646, 1506, 1457, 1243, 1092, 838 cm<sup>-1</sup>;  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 0.12 (s, 6H), 0.98 (s, 9H), 3.030 (s, 3H), 3.034 (s, 3H), 3.73 (s, 2H), 3.78 (s, 5H), 3.79 (s, 3H), 6.64–6.66 (m, 2H), 6.75 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) –4.7, 18.4, 25.6, 27.7, 27.8, 28.2, 28.4, 55.2, 55.5, 112.1, 114.1, 117.4, 117.6, 120.7, 120.8, 128.8, 129.8, 130.3, 145.1, 149.7, 153.7, 158.3 [EI-HRMS (pos.) *m*/*z* Calc. for C<sub>27</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>Si: *M*, 482.2601. Found: M<sup>+</sup>, 482.2597].

# Naamine B 1

TFA (0.2 mL) was added to a solution of 13 (24 mg, 0.04 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) at 0 °C under N<sub>2</sub>, and the solution was stirred for 48 h at ambient temperature. The products were extracted with  $CHCl_3$  (10 mL  $\times$  3) after addition of saturated aq. NaHCO<sub>3</sub> (1 mL), and the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was purified column chromatography (CHCl<sub>3</sub>-MeOH 5 : 1) on silica gel to give 1 (15 mg, 100%) as a white amorphous powder; v<sub>max</sub> (KBr) 3312, 3143, 2907, 1680, 1609, 1508 cm<sup>-1</sup>;  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub> + CD<sub>3</sub>OD) 3.26 (br s, 3H), 3.27 (br s, 3H), 3.80 (s, 3H), 3.85 (br s, 2H), 3.87 (s, 3H), 3.89 (br s, 2H), 6.57 (dd, J = 8.2, 2.2 Hz, 1H), 6.62 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub> + CD<sub>3</sub>OD) 27.8, 27.9, 29.7, 29.8, 55.2, 55.8, 111.4, 114.1, 114.4, 118.8, 122.67, 122.73, 127.4, 128.4, 128.7, 146.3, 146.4, 146.6, 158.7 [EI-HRMS (pos.) m/z Calc. for C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>: M, 367.1896. Found: M<sup>+</sup>, 367.1889].

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