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## TOTAL SYNTHESIS OF FARGESINE USING A PLATINUM-CATALYZED INTRAMOLECULAR FRIEDEL-CRAFTS-TYPE C–H COUPLING–ALLYLIC AMINATION CASCADE

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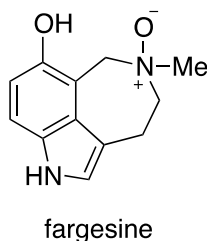
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**Abstract** – Total synthesis of fargesine was described herein. The synthesis was based on the platinum-catalyzed intramolecular Friedel-Crafts-type C–H coupling–allylic amination cascade to construct the 3,4-fused tricyclic indole skeleton.

### INTRODUCTION

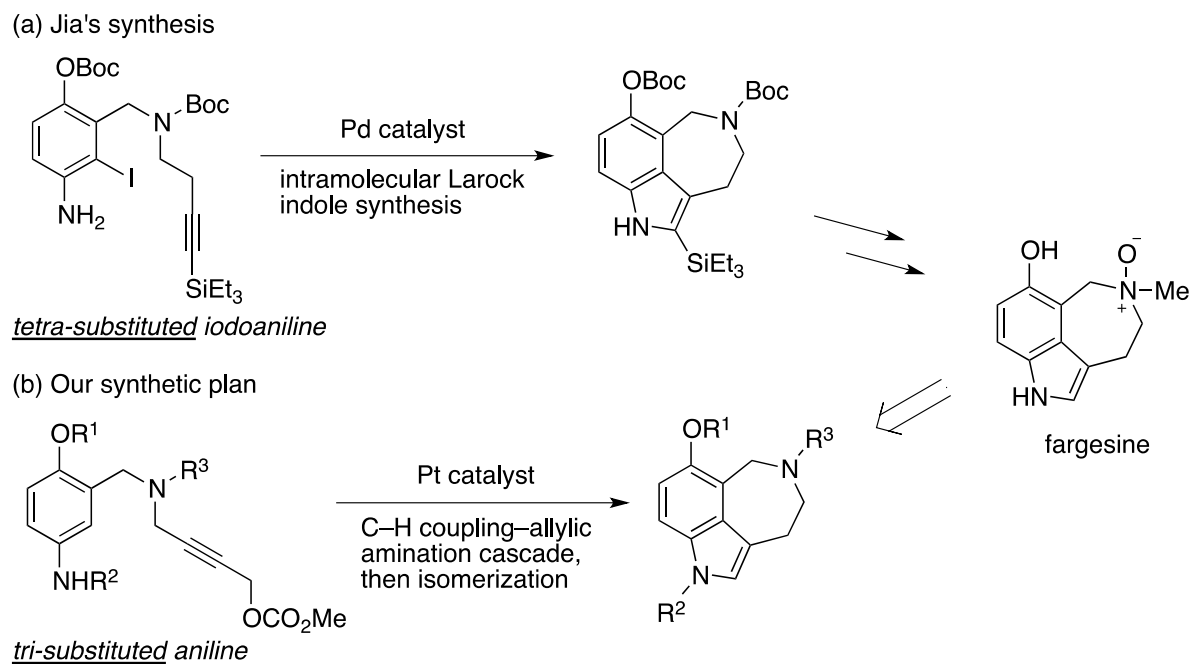
In 2006, Zhu and co-workers isolated an indole *N*-oxide alkaloid, fargesine, from the root and stem of *Evodia fargesii* Dode, whose fruits are used in folk medicine as an analgesic against bellyache and to relieve cough after measles. The structure of fargesine is highlighted by an *N*-oxide-tethered 7-membered ring bridging the C3- and C4-positions of the indole (Figure 1).<sup>1</sup> The characteristic structure of fargesine has attracted the attention of synthetic organic chemists.



**Figure 1.** Structure of fargesine

Jia and co-workers recently reported the first total synthesis of fargesine.<sup>2</sup> Palladium-catalyzed intramolecular Larock indolization using a tetra-substituted iodoaniline derivative was utilized to construct the 3,4-fused tricyclic indole skeleton [Scheme 1(a)].<sup>3</sup> As part of our ongoing studies aimed at developing an efficient catalytic synthetic method based on Friedel-Crafts-type chemistry,<sup>4</sup> we recently

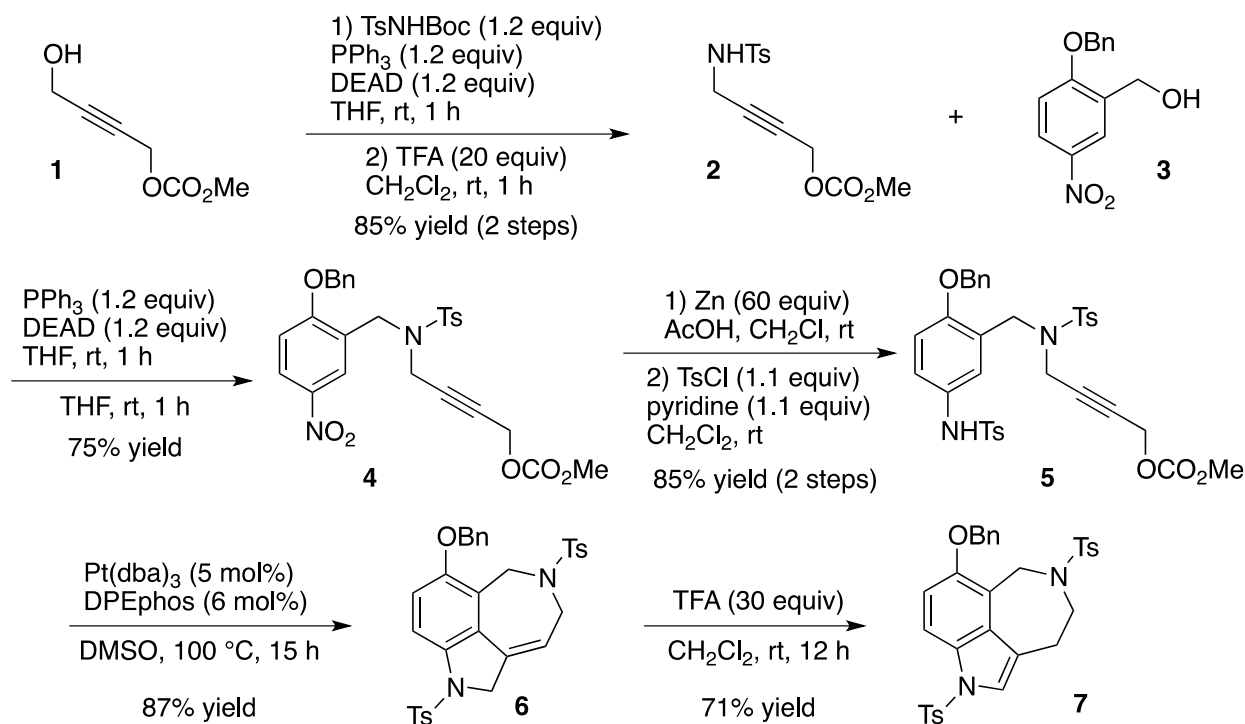
reported the synthesis of 3,4-fused tricyclic indoles using a platinum-catalyzed intramolecular Friedel-Crafts type C–H coupling–allylic amination cascade.<sup>5,6</sup> We envisioned that the present cascade process would be applicable to the synthesis of fargesine by using a more easily accessible tri-substituted aniline derivative as a substrate [Scheme 1(b)]. Herein we report the total synthesis of fargesine using a platinum-catalyzed Friedel-Crafts-type C–H coupling–allylic amination cascade to construct the core structure.



**Scheme 1.** Synthetic plan

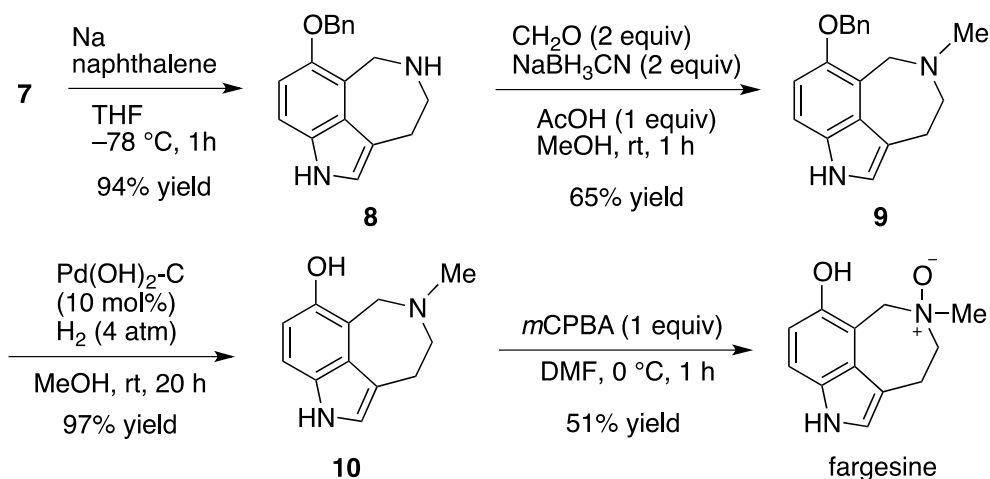
## RESULTS AND DISCUSSION

Our synthesis began with readily available mono-protected 1,4-butanediol **1**<sup>7</sup> (Scheme 2). Compound **1** was first reacted with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide in the presence of PPh<sub>3</sub> and diethyl azodicarboxylate (DEAD), providing the corresponding propargylamine derivative, which was then treated with 20 equiv of trifluoroacetic acid (TFA) to give compound **2** in 85% yield. Compound **2** was subsequently coupled with the known benzyl alcohol derivative **3**<sup>8</sup> under PPh<sub>3</sub>/DEAD conditions and compound **4** was obtained in 75% yield. After reduction of the nitro group in compound **4** with zinc powder, the resulting amine was protected with a tosyl group to give compound **5** in 85% yield. We next applied the platinum-catalyzed intramolecular Friedel-Crafts-type C–H coupling–allylic amination cascade to construct the 3,4-fused tricyclic indole framework. We performed the reaction using 5 mol% of Pt(dba)<sub>3</sub> and 6 mol% of DPEphos in DMSO (0.05 M) at 100 °C. The cascade cyclization proceeded smoothly to give the corresponding 3-alkylidene indoline derivative **6** in 87% yield. The obtained product was isomerized into the 3,4-fused tricyclic indole derivative **7** in 71% yield by treating with 30 equiv of TFA.



**Scheme 2.** Construction of the 3,4-fused tricyclic indole skeleton

With key intermediate **7** in hand, the stage was set for completion of the synthesis of fargesine (Scheme 3). Both of the tosyl groups were removed by treatment with Na/naphthalene in THF at  $-78$  °C and the desired product **8** was obtained in 94% yield. Reductive methylation of the secondary amine under conventional conditions gave compound **9** in 65% yield. Subsequent removal of the benzyl group in the presence of Pd(OH)<sub>2</sub>-C under a hydrogen atmosphere (4 atm) afforded compound **10** in 97% yield. Finally, selective oxidation of the *tert*-amine moiety in compound **10** using *m*CPBA proceeded in DMF at room temperature, producing fargesine in 51% yield.



**Scheme 3.** Total synthesis of fargesine

In conclusion, we achieved the total synthesis of fargesine with 10.1% overall yield in 11 steps from compound **1**. The core 3,4-fused tricyclic indole skeleton was constructed by the platinum-catalyzed intramolecular Friedel-Crafts-type C–H coupling–allylic amination cascade developed by our group. The present synthesis successfully demonstrated the usefulness of our catalytic synthetic method.

## EXPERIMENTAL

**General:** Infrared (IR) spectra were recorded on a Fourier transform infrared spectrophotometer, equipped with ATR. NMR spectra were recorded with a 400 MHz spectrometer. Chemical shifts in CDCl<sub>3</sub> were reported downfield from TMS (= 0 ppm) for <sup>1</sup>H NMR. For <sup>13</sup>C NMR, chemical shifts were reported in the scale relative to the solvent signal [CHCl<sub>3</sub> (77.0 ppm)] as an internal reference. Chemical shifts in CD<sub>3</sub>OD were reported in the scale relative to the solvent signal as an internal reference [MeOH (3.30 ppm for <sup>1</sup>H NMR, 49.0 ppm for <sup>13</sup>C NMR)]. Chemical shifts in D<sub>2</sub>O/DMSO-*d*<sub>6</sub> were reported in the scale relative to the solvent signal as an internal reference [DMSO (2.50 ppm for <sup>1</sup>H NMR, 39.5 ppm for <sup>13</sup>C NMR)]. Positive-ion mass spectra were recorded by electrospray ionization (ESI-TOF). Column chromatography was performed with silica gel 60N (spherical, neutral, 40–60 μm mesh) (Kanto Chemical) or CHROMATOREX NH-DM1020 (Fuji Silysia Chemical). Reactions were carried out in dry solvent. Other reagents were purified by the usual methods.

**Compound 2:** To a stirred solution of **1** (148 mg, 1.03 mmol), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (334 mg, 1.23 mmol) and PPh<sub>3</sub> (278 mg, 1.23 mmol) in THF (3.4 mL) at 0 °C was added DEAD (2.2 M solution in toluene, 0.56 mL, 1.23 mmol), and the resulting mixture was stirred at room temperature for 1 h. After evaporation, the crude mixture was filtered through a short pad of silica gel and the obtained residue was used for the next reaction without further purification. To a stirred solution of the crude sample in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) at room temperature was added TFA (2.0 mL), and the resulting solution was stirred at the same temperature. After 1 h, the reaction mixture was evaporated *in vacuo* and the obtained residue was purified by column chromatography (silica gel 60N, CHCl<sub>3</sub>/AcOEt = 30/1) to give **2** (252 mg, 85% yield, 2 steps) as white solid. mp 50–51 °C; IR (ATR)  $\nu$  1749, 1444, 1329, 1262, 1156, 1092, 1059, 949, 814 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.43 (s, 3H), 3.80 (s, 3H), 3.87 (dt, *J* = 2.0 Hz, 6.0 Hz, 2H), 4.50 (t, *J* = 2.0 Hz, 2H), 4.85 (br-s, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 8.6 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  21.5, 33.0, 55.1, 55.1, 78.1, 81.7, 127.4 (2C), 129.6 (2C), 136.5, 143.8, 155.0; (+)-ESI-HRMS. Calcd for C<sub>13</sub>H<sub>15</sub>NNaO<sub>5</sub>S<sup>+</sup> (M+Na<sup>+</sup>): 320.0563. Found: 320.0565.

**Compound 4:** To a stirred solution of **3** (25.9 mg, 0.100 mmol), **2** (29.7 mg, 0.100 mmol) and PPh<sub>3</sub> (31.5 mg, 0.120 mmol) in THF (0.33 mL) at 0 °C was added DEAD (2.2 M solution in toluene, 0.055 mL, 0.120 mmol), and the resulting mixture was stirred at room temperature for 1 h. After evaporation, the

crude mixture was filtered through a short pad of silica gel (hexane/AcOEt = 2/1) and the obtained residue was purified by column chromatography (silica gel 60N, CHCl<sub>3</sub>/AcOEt = 50/1) to give **4** (40.2 mg, 75% yield) as white solid. mp 121–122 °C; IR (ATR)  $\nu$  1752, 1594, 1518, 1494, 1444, 1341, 1263, 1161, 1091, 954 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.44 (s, 3H), 3.78 (s, 3H), 4.08 (t,  $J$  = 2.0 Hz, 2H), 4.39 (t,  $J$  = 2.0 Hz, 2H), 4.48 (s, 2H), 5.21 (s, 2H), 6.97 (d,  $J$  = 9.2 Hz, 1H), 7.32 (d,  $J$  = 8.4 Hz, 2H), 7.36–7.41 (m, 5H), 7.77 (d,  $J$  = 8.4 Hz, 2H), 8.15 (dd,  $J$  = 2.4 Hz, 8.4 Hz, 1H), 8.25 (d,  $J$  = 2.4 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  21.5, 37.5, 45.1, 55.1, 55.1, 70.9, 79.4, 80.4, 111.5, 125.4, 125.5, 125.7, 127.3 (2C), 127.8 (2C), 128.5, 128.8 (2C), 129.6 (2C), 135.3, 135.6, 141.5, 144.0, 155.7, 161.4; (+)-ESI-HRMS. Calcd for C<sub>27</sub>H<sub>26</sub>N<sub>2</sub>NaO<sub>8</sub>S<sup>+</sup> (M+Na<sup>+</sup>): 561.1302. Found: 561.1318.

**Compound 5:** To a solution of **4** (222 mg, 0.412 mmol) and zinc powder (1.62 g, 24.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.2 mL) was added AcOH (0.62 mL) at 0 °C, and the mixture was stirred at room temperature. After 1 h, the reaction mixture was filtered through a short pad of celite, and aq. NaHCO<sub>3</sub> was added to the filtrate. The obtained mixture was extracted with AcOEt and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The obtained residue was used for the next reaction without further purification. To a stirred solution of crude aniline (0.412 mmol), pyridine (37  $\mu$ L, 0.453 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.41 mL) at 0 °C was added TsCl (137 mg, 0.453 mmol) and the reaction was stirred at room temperature. After 1 h, the reaction mixture was concentrated *in vacuo*. The obtained residue was purified by column chromatography (silica gel 60N, hexane/AcOEt = 3/1) to give **5** (231 mg, 85% yield, 2 steps) as colorless oil. IR (ATR)  $\nu$  1751, 1499, 1445, 1328, 1261, 1155, 1091, 951, 907, 814 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.38 (s, 3H), 2.42 (s, 3H), 3.78 (t,  $J$  = 1.8 Hz, 2H), 3.81 (s, 3H), 4.28 (s, 2H), 4.35 (t,  $J$  = 1.8 Hz, 2H), 5.02 (s, 2H), 6.72 (br-s, 1H), 6.82 (d,  $J$  = 9.2 Hz, 1H), 6.91 (d,  $J$  = 2.8 Hz, 1H), 7.16–7.22 (m, 3H), 7.27–7.39 (m, 7H), 7.58 (d,  $J$  = 8.4 Hz, 2H), 7.71 (d,  $J$  = 8.0 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  21.5, 21.5, 36.6, 44.8, 55.1, 55.3, 79.1, 80.6, 112.7, 124.4, 124.5, 125.3, 127.2 (2C), 127.3 (2C), 127.8 (2C), 128.0, 128.5 (2C), 129.4 (2C), 129.5, 129.5 (2C), 135.6, 135.9, 136.5, 143.6, 143.6, 143.7, 154.8, 155.2; (+)-ESI-HRMS. Calcd for C<sub>34</sub>H<sub>34</sub>N<sub>2</sub>NaO<sub>8</sub>S<sub>2</sub><sup>+</sup> (M+Na<sup>+</sup>): 685.1649. Found: 685.1650.

**Compound 6:** **5** (109 mg, 0.164 mmol), Pt(dba)<sub>3</sub> (7.4 mg, 0.0082 mmol) and DPEphos (5.3 mg, 0.0099 mmol) were dissolved in DMSO (3.3 mL), and the resulting solution was stirred at 100 °C. After 15 h, the reaction was quenched with water, and the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated *in vacuo*. The obtained residue was purified by column chromatography (silica gel 60N, hexane/AcOEt = 3/1) to give **6** (83.7 mg, 87% yield) as white solid. mp 178–179 °C; IR (ATR)  $\nu$  1596, 1440, 1351, 1332, 1255, 1155, 1119, 1090, 1033, 760, 662 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.34 (s, 3H), 2.37 (s, 3H), 4.21 (s, 4H), 4.68 (s, 2H), 5.08 (s, 2H), 5.41–5.43 (m, 1H), 6.78 (d,  $J$  = 8.8 Hz, 1H), 6.97 (d,  $J$  = 8.0 Hz, 2H), 7.23 (d,  $J$  = 7.6 Hz, 2H), 7.34–7.44 (m, 6H), 7.49 (d,  $J$  = 7.8 Hz, 2H), 7.61 (d,  $J$  = 8.4 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  21.4, 21.5, 47.4, 50.4,

54.9, 71.3, 113.5, 114.1, 118.2, 124.2, 127.1 (2C), 127.2 (2C), 127.5 (2C), 128.1, 128.3, 128.6 (2C), 128.7 (2C), 129.8 (2C), 133.5, 133.6, 136.5, 136.8, 138.9, 143.3, 144.3, 151.5; (+)-ESI-HRMS. Calcd for  $C_{32}H_{30}N_2NaO_5S_2^+$  (M+Na<sup>+</sup>): 609.1488. Found: 609.1475.

**Compound 7:** To a solution of **6** (83.7 mg, 0.143 mmol) in  $CH_2Cl_2$  (2.9 mL) at 0 °C was added TFA (0.33 mL, 4.29 mmol), and the resulting mixture was stirred at room temperature for 12 h. After evaporation, the crude mixture was purified by column chromatography (silica gel 60N, hexane/AcOEt = 4/1) to give **7** (59.6 mg, 71% yield) as white solid. mp 106–107 °C; IR (ATR)  $\nu$  1374, 1331, 1173, 1153, 1134, 1091, 748, 660  $cm^{-1}$ ; <sup>1</sup>H NMR ( $CDCl_3$ ):  $\delta$  2.35 (s, 3H), 2.38 (s, 3H), 3.11 (t,  $J$  = 5.8 Hz, 2H), 3.58 (t,  $J$  = 5.8 Hz, 2H), 4.69 (s, 2H), 5.10 (s, 2H), 6.92 (d,  $J$  = 8.8 Hz, 1H), 7.19 (d,  $J$  = 8.4 Hz, 2H), 7.22 (d,  $J$  = 8.0 Hz, 2H), 7.30 (s, 1H), 7.34–7.45 (m, 5H), 7.62 (d,  $J$  = 8.4 Hz, 2H), 7.70 (d,  $J$  = 8.4 Hz, 2H), 7.80 (d,  $J$  = 8.8 Hz, 1H); <sup>13</sup>C NMR ( $CDCl_3$ ):  $\delta$  21.5, 21.6, 28.9, 48.9, 49.4, 71.4, 110.5, 112.6, 119.8, 120.5, 124.1, 126.7 (2C), 126.9 (2C), 127.2 (2C), 127.9, 128.6 (2C), 129.6 (2C), 129.9 (2C), 130.0, 130.7, 135.0, 136.3, 137.2, 143.2, 144.6, 151.1; (+)-ESI-HRMS. Calcd for  $C_{32}H_{30}N_2NaO_5S_2^+$  (M+Na<sup>+</sup>): 609.1488. Found: 609.1475.

**Compound 8:** To a solution of naphthalene (250 mg, 1.95 mmol) in THF (3.9 mL) was added sodium metal (44.7 mg, 1.95 mmol), and the resulting mixture was stirred at room temperature for 2 h. The obtained solution was added dropwise to a solution of **7** (57.1 mg, 0.097 mmol) in THF (3.9 mL) at –78 °C until dark blue color persisted. After 1 h, the reaction was quenched with water. The resulting mixture was extracted with AcOEt and the combined organic layers were washed with brine, dried over  $Na_2SO_4$ , and concentrated *in vacuo*. The obtained residue was purified by column chromatography (silica gel 60N,  $CHCl_3/MeOH$  = 3/1) to give **8** (25.4 mg, 94% yield) as yellow solid. mp 148–149 °C; IR (ATR)  $\nu$  2857, 1454, 1365, 1239, 737, 695, 652, 631  $cm^{-1}$ ; <sup>1</sup>H NMR ( $CDCl_3$ ):  $\delta$  2.36 (broad peak, 1H), 3.05 (t,  $J$  = 5.2 Hz, 2H), 3.22 (t,  $J$  = 5.2 Hz, 2H), 4.43 (s, 2H), 5.06 (s, 2H), 6.90 (d,  $J$  = 8.4 Hz, 1H), 6.98 (s, 1H), 7.15 (d,  $J$  = 8.4 Hz, 1H), 7.30 (t,  $J$  = 7.2 Hz, 1H), 7.37 (dd,  $J$  = 7.2, 7.2 Hz, 2H), 7.45 (d,  $J$  = 7.2 Hz, 2H), 8.10 (br-s, 1H); <sup>13</sup>C NMR ( $CDCl_3$ ):  $\delta$  31.1, 50.0, 50.3, 72.3, 109.0, 110.2, 115.0, 122.4, 126.4, 127.3 (2C), 127.7, 127.7, 128.4 (2C), 132.7, 138.0, 148.3; Calcd for  $C_{18}H_{19}N_2O^+$  (M+H<sup>+</sup>): 279.1492. Found: 279.1498.

**Compound 9:** To a solution of **8** (9.8 mg, 0.035 mmol) and acetic acid (2.0  $\mu$ L, 0.035 mmol) in MeOH (0.35 mL) was added a solution of 37% aqueous formaldehyde (5.2  $\mu$ L, 0.070 mmol). The resulting mixture was stirred at room temperature for 15 min, and then  $NaBH_3CN$  (4.4 mg, 0.070 mmol) was added at 0 °C. After 1 h, the reaction was quenched with aq.  $NaHCO_3$  and diluted with AcOEt. The organic layer was separated and then washed with brine, dried over  $Na_2SO_4$ , and concentrated *in vacuo*. The obtained residue was purified by column chromatography (silica gel 60N,  $CHCl_3/MeOH$  = 5/1) to give **9** (6.7 mg, 65% yield) as yellow solid. mp 141–142 °C; IR (ATR)  $\nu$  2923, 1579, 1376, 1232, 1123, 1052, 782, 736, 632, 610  $cm^{-1}$ ; <sup>1</sup>H NMR ( $CDCl_3$ ):  $\delta$  2.57 (s, 3H), 3.08 (t,  $J$  = 5.6 Hz, 2H), 3.09 (t,  $J$  = 5.6 Hz,

2H), 4.26 (s, 2H), 5.07 (s, 2H), 6.90 (d,  $J = 8.4$  Hz, 1H), 6.93 (s, 1H), 7.10 (d,  $J = 8.4$  Hz, 1H), 7.30 (t,  $J = 7.2$  Hz, 1H), 7.37 (dd,  $J = 7.2, 7.2$  Hz, 2H), 7.44 (d,  $J = 7.2$  Hz, 2H), 8.12 (br-s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  27.0, 44.3, 57.0, 58.2, 72.7, 109.0, 110.7, 115.1, 121.4, 122.1, 126.7, 127.4 (2C), 127.6, 128.4 (2C), 132.4, 138.1, 148.9; (+)-ESI-HRMS. Calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}^+$  ( $\text{M}+\text{H}^+$ ): 293.1648. Found: 293.1648.

**Compound 10: 9** (41.2 mg, 0.141 mmol) and  $\text{Pd}(\text{OH})_2\text{-C}$  (9.9 mg, 0.014 mmol) were dissolved in MeOH (1.4 mL), and the mixture was stirred under hydrogen (4 atm) for 20 h. The mixture was filtered through a short pad of celite and the filtrate was purified by column chromatography (silica gel 60N,  $\text{CHCl}_3/\text{MeOH} = 3/1$ ) to give **10** (27.8 mg, 97% yield) as yellow solid. mp  $> 200$  °C; IR (ATR)  $\nu$  2922, 1579, 1436, 1376, 1263, 1122, 984, 791, 734, 639  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  2.85 (s, 3H), 3.20 (t,  $J = 5.6$  Hz, 2H), 3.43 (t,  $J = 5.6$  Hz, 2H), 4.46 (s, 2H), 6.69 (d,  $J = 8.8$  Hz, 1H), 7.05 (s, 1H), 7.13 (d,  $J = 8.8$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  27.1, 45.5, 59.2, 59.3, 111.0, 112.2, 113.6, 114.7, 123.4, 127.5, 133.1, 147.4; (+)-ESI-HRMS. Calcd for  $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}^+$  ( $\text{M}+\text{H}^+$ ): 203.1179. Found: 203.1177.

**Fargesine**: To a solution of **10** (9.8 mg, 0.049 mmol) in DMF (0.48 mL) was added *m*CPBA (8.4 mg, 0.049 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and the residue was purified by column chromatography (CHROMATOREX NH-DM1020,  $\text{CHCl}_3/\text{MeOH} = 10/1$ ) to give fargesine (5.4 mg, 51% yield) as yellow solid. IR (ATR)  $\nu$  3191, 1586, 1441, 1244, 1154, 1011, 799, 631  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  3.07 (ddd,  $J = 3.2, 8.8, 17.2$  Hz, 1H), 3.22 (s, 3H), 3.46 (ddd,  $J = 3.2, 7.2, 17.2$  Hz, 1H), 3.87 (dd,  $J = 3.2, 7.2$  Hz, 1H), 3.90 (dd,  $J = 3.2, 8.8$  Hz, 1H), 4.80 (d,  $J = 14.4$  Hz, 1H), 5.02 (d,  $J = 14.4$  Hz, 1H), 6.69 (d,  $J = 8.8$  Hz, 1H), 7.04 (s, 1H), 7.16 (d,  $J = 8.8$  Hz, 1H);  $^1\text{H}$  NMR ( $\text{D}_2\text{O}/\text{DMSO}-d_6 = 1/1$ )<sup>2</sup>:  $\delta$  2.97 (ddd,  $J = 3.2, 9.6, 18.0$  Hz, 1H), 3.05 (s, 3H), 3.26 (ddd,  $J = 3.2, 6.8, 18.0$  Hz, 1H), 3.72 (dd,  $J = 3.2, 6.8$  Hz, 1H), 3.75 (dd,  $J = 3.2, 9.6$  Hz, 1H), 4.59 (d,  $J = 15.2$  Hz, 1H), 4.80 (d,  $J = 15.2$  Hz, 1H), 6.67 (d,  $J = 8.8$  Hz, 1H), 7.07 (s, 1H), 7.17 (d,  $J = 8.8$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}/\text{DMSO}-d_6 = 1/1$ )<sup>2</sup>:  $\delta$  22.5, 56.6, 70.0, 74.4, 107.7, 112.6, 113.3, 114.3, 124.7, 127.9, 131.7, 148.2;  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  22.7, 56.7, 70.0, 75.1, 107.0, 112.7, 112.8, 113.8, 124.0, 128.5, 132.3, 149.4; (+)-ESI-HRMS. Calcd for  $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_2^+$  ( $\text{M}+\text{H}^+$ ): 219.1128. Found: 219.1134.

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