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

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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). The characteristic structure of fargesine has attracted the attention of synthetic organic chemists.

![fargesine](image)

Figure 1. Structure of fargesine

Jia and co-workers recently reported the first total synthesis of fargesine. 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)]. As part of our ongoing studies aimed at developing an efficient catalytic synthetic method based on Friedel-Crafts-type chemistry, 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.\textsuperscript{5,6} 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.

(a) Jia's synthesis

(b) Our synthetic plan

\textbf{Scheme 1.} Synthetic plan

**RESULTS AND DISCUSSION**

Our synthesis began with readily available mono-protected 1,4-butyn-diol 1\textsuperscript{7} (Scheme 2). Compound 1 was first reacted with \textit{N-}\textit{(tert-butoxycarbonyl)}-\textit{p}-toluenesulfonamide in the presence of PPh\textsubscript{3} 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\textsuperscript{8} under PPh\textsubscript{3}/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)\textsubscript{3} 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.
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)$_2$-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 mCPBA proceeded in DMF at room temperature, producing fargesine in 51% yield.
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 CDCl3 were reported downfield from TMS (= 0 ppm) for 1H NMR. For 13C NMR, chemical shifts were reported in the scale relative to the solvent signal [CHCl3 (77.0 ppm)] as an internal reference. Chemical shifts in CD3OD were reported in the scale relative to the solvent signal as an internal reference [MeOH (3.30 ppm for 1H NMR, 49.0 ppm for 13C NMR)]. Chemical shifts in D2O/DMSO-d6 were reported in the scale relative to the solvent signal as an internal reference [DMSO (2.50 ppm for 1H NMR, 39.5 ppm for 13C 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 PPh3 (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 CH2Cl2 (8.0 mL) at room temperature was added TFA (2.0 mL), and the resulting solution was stirred at the same temperature. 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 CH2Cl2 (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, CHCl3/AcOEt = 30/1) to give 2 (252 mg, 85% yield, 2 steps) as white solid. mp 50–51 °C; IR (ATR) ν 1749, 1444, 1329, 1262, 1156, 1092, 1059, 949, 814 cm⁻¹; 1H NMR (CDCl3): δ 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); 13C NMR (CDCl3): δ 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 C13H15NNaO5S⁺ (M+Na⁺): 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 PPh3 (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, CHCl₃/AcOEt = 50/1) to give 4 (40.2 mg, 75% yield) as white solid. mp 121–122 °C; IR (ATR) ν 1752, 1594, 1518, 1494, 1444, 1341, 1263, 1161, 1091, 954 cm⁻¹; ¹H NMR (CDCl₃): δ 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); ¹³C NMR (CDCl₃): δ 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 C₂₇H₂₆N₂NaO₈S⁺ (M+Na⁺): 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 CH₂Cl₂ (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. NaHCO₃ was added to the filtrate. The obtained mixture was extracted with AcOEt and the organic layer was washed with brine, dried over Na₂SO₄, 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 µL, 0.453 mmol) in CH₂Cl₂ (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) ν 1751, 1499, 1445, 1328, 1261, 1155, 1091, 951, 814 cm⁻¹; ¹H NMR (CDCl₃): δ 2.34 (s, 3H), 2.37 (s, 3H), 3.75 (t, J = 2.0 Hz, 2H), 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); ¹³C NMR (CDCl₃): δ 21.4, 21.5, 24.7, 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
C32H30N2NaO5S2

Compound 7: To a solution of 6 (83.7 mg, 0.143 mmol) in CH2Cl2 (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) ν
1374, 1331, 1173, 1153, 1134, 1091, 748, 660 cm

1H NMR (CDCl3): δ 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); 13C NMR (CDCl3): δ 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 C32H30N2NaO5S2

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
Na2SO4, and concentrated in vacuo. The obtained residue was purified by column chromatography (silica
gel 60N, CHCl3/MeOH = 3/1) to give 8 (25.4 mg, 94% yield) as yellow solid. mp 148–149 °C; IR (ATR)
ν 2857, 1454, 1365, 1239, 737, 695, 652, 631 cm

1H NMR (CDCl3): δ 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); 13C NMR (CDCl3): δ 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 C18H19N2O+ (M+H+): 279.1492. Found: 279.1498.

Compound 9: To a solution of 8 (9.8 mg, 0.035 mmol) and acetic acid (2.0 µL, 0.035 mmol) in MeOH
(0.35 mL) was added a solution of 37% aqueous formaldehyde (5.2 µL, 0.070 mmol). The resulting
mixture was stirred at room temperature for 15 min, and then NaBH3CN (4.4 mg, 0.070 mmol) was added
at 0 °C. After 1 h, the reaction was quenched with aq. NaHCO3 and diluted with AcOEt. The organic
layer was separated and then washed with brine, dried over Na2SO4, and concentrated in vacuo. The
obtained residue was purified by column chromatography (silica gel 60N, CHCl3/MeOH = 5/1) to give 9
(6.7 mg, 65% yield) as yellow solid. mp 141–142 °C; IR (ATR) ν 2923, 1579, 1376, 1232, 1123, 1052,
782, 736, 632, 610 cm

1H NMR (CDCl3): δ 2.57 (s, 3H), 3.08 (t, J = 5.6 Hz, 2H), 3.09 (t, J = 5.6 Hz,
Compound 10: 9 (41.2 mg, 0.141 mmol) and Pd(OH)$_2$-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, CHCl$_3$/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 cm$^{-1}$; $^1$H NMR (CD$_3$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); $^{13}$C NMR (CD$_3$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 C$_{12}$H$_{15}$N$_2$O+ (M+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 mCPBA (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, CHCl$_3$/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 cm$^{-1}$; $^1$H NMR (CD$_3$OD): $\delta$ 3.07 (ddd, $J = 3.2$, 8.8, 17.2 Hz, 1H), 3.22 (s, 3H), 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); $^1$H NMR (D$_2$O/DMSO-d$_6$ = 1/1): $\delta$ 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); $^{13}$C NMR (D$_2$O/DMSO-d$_6$ = 1/1): $\delta$ 22.5, 56.6, 70.0, 74.4, 107.7, 112.6, 113.3, 114.3, 124.7, 127.9, 131.7, 148.2; $^{13}$C NMR (CD$_3$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 C$_{12}$H$_{15}$N$_2$O$_2^+$ (M+H$^+$): 219.1128. Found: 219.1134.

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7. Compound 1 was prepared according to the known procedure, see: P. James, F.-X. Felpin, Y. Landais, and K. Schenk, *J. Org. Chem.*, 2005, **70**, 7985.

8. Compound 3 could be prepared from commercially available 2-hydroxy-5-nitrobenzyl alcohol in a single step according to the reported procedure, see: C. Dugave, *J. Org. Chem.*, 1995, **60**, 601.