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Total synthesis of proposed structures of jiangrines C and D

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On the basis of the proposed structures of jiangrines C and D, a synthetic strategy was initiated from *D*-glyceraldehyde acetonide, a readily available chiral material. Through a linear seven-step synthesis, the target molecules were accomplished. However, all characteristic data of the synthetic **3** and **4** were found to be different from those of natural jiangrines C and D. Accordingly, the molecular structures of jiangrines should be revised and a possible molecular skeleton for them was proposed.

pyrrole, alkaloid, jiangrine, total synthesis

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1 Introduction

In 2014, isolation of several pyrrole alkaloids from an actinobacterium, *Jiangella gansuensis*, was reported by the Huang group [1]. Jiangrines A–E exhibited inhibitory effect on NO production with IC_{50} ranging from 30.1 to 97.8 μM. Structurally, jiangrines A–D embrace a pyrrole ring and a phenyl ring or an indole ring, as well as several chiral alcohols. Their proposed structures are depicted in Figure 1. Allured by the structures and bioactivity of jiangrines, we initiated total synthesis toward the proposed structures of jiangrines C and D.

2 Experimental

2.1 Reagents and materials

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran was distilled from sodium-benzophenone, dichloromethane and *N*,*N*′-dimethyl formamide were distilled from calcium hydride. All the chemicals pur-

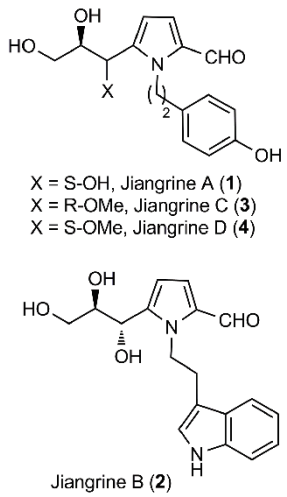

Figure 1 The proposed structures of jiangrines A–D (**1**–**4**).

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chased commercially were used without further purification, unless otherwise stated. Flash chromatography was performed using silica gel (200–300 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254 and 365 nm), I_2 and by developing the plates with *p*-anisaldehyde or phosphomolybdic acid. ^{1}H and ^{13}C NMR were recorded on Bruker DRX-400 MHz NMR (Germany), Bruker DRX-600 MHz NMR (Germany) or Varian Unity INOVA-400 MHz NMR (USA) spectrometer with tetramethyl silane (TMS) as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{1}H NMR=7.26, ^{13}C NMR=77.16). The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Coupling constants (*J*) are reported in Hertz (Hz). Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent. High resolution mass spectra (HRMS) were recorded by using FTMS-7 spectrometer (Bruker, Germany).

2.2 Synthesis of compounds

2.2.1 (*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(1*H*-pyrrol-2-yl)methanol and (*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(1*H*-pyrrol-2-yl) methanol (**6a** and **6b**)

To a solution of pyrrole (11.0 g, 164 mmol, 4.1 eq.) in dichloromethan (100 mL) at 0 °C was added dropwise a freshly prepared solution of EtMgBr (160 mmol) in tetrahydrofuran (THF, 100 mL). The resultant solution was stirred at room temperature for 1 h. Then a solution of *D*-glyceraldehyde acetonide (5.20 g, 40 mmol, 1.0 eq.) in dichloromethane (DCM, 15 mL) was added to the above solution at −78 °C in 5 min. The reaction was stirred at −78 °C and monitored by TLC. After 2 h, the reaction was quenched with saturated NH_4Cl solution (200 mL) and the aqueous layer was extracted with DCM (3×200 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated to afford 6.6 g of inseparable diastereomeric mixture of compounds **6a** and **6b** as yellow oil. The mixture was used directly for the next step without further purification. An aliquot of this sample was collected and detected by ^{1}H NMR, showing that the ratio of **6a** to **6b** was 1.3:1.

2.2.2 2-((*S*)-(*tert*-butyldimethylsilyloxy) ((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-pyrrole (**7a**) and 2-((*R*)-(*tert*-butyldimethylsilyloxy)((*R*)-2,2-dime-thyl-1,3-dioxolan-4-yl)methyl)-1*H*-pyrrole (**7b**)

To a solution of impurified mixture of **6a** and **6b** (1.67 g in total, 8.47 mmol, 1.0 eq.) in DCM (120 mL) at 0 °C was added imidazole (2.31 g, 33.9 mmol, 4.0 eq.), 4-*N*,*N*′-dimethylamino-pyrridine (DMAP, 104 mg, 0.85 mmol, 0.1 eq.) and TBSCl (3.83 g, 25.4 mmol, 3.0 eq.). The resultant solution was stirred overnight before quenching with aqueous saturated $NaHCO_3$ solution (300 mL). The aqueous layer was extracted with DCM (3×120 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica column using petroleum ether-ethyl acetate (20:1) as eluent to give **7a** (1.25 g, 47% yield) and **7b** (1.25 g, 47% yield).

Compound **7a**: pale yellow oil; $[\alpha]_D^{29}$: +33.0 (c 0.68, $CHCl_3$); IR (thin film): 3481, 3380, 2932, 2858, 1468, 1376, 1256, 1071, 839, 780, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 6.73 (dd, *J*=4.0, 2.8 Hz, 1H), 6.14 (q, *J*=5.6, 2.8 Hz, 1H), 6.03–6.05 (m, 1H), 4.73 (d, *J*=5.6Hz, 1H), 4.21 (dd, *J*=12.0, 6.4 Hz, 1H), 3.98 (dd, *J*=8.0, 6.4 Hz, 1H), 3.89 (dd, *J*=8.0, 6.4 Hz, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.4 , 117.3, 109.7, 108.3, 106.3, 79.9, 69.7, 66.3, 26.7, 25.9, 25.6, 18.3; HRMS-ESI: *m/z* [M+Na$^+$] calcd for $C_{16}H_{29}NNaO_3Si$: 334.1809; found: 334.1811.

Compound **7b**: pale yellow oil; $[\alpha]_D^{29}$: −37.7 (c 0.54, $CHCl_3$); IR (thin film): 3461, 3366, 2932, 2858, 1472, 1370, 1255, 1068, 840, 780, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 6.74 (dd, *J*=4.0, 2.4 Hz, 1H), 6.11 (dd, *J*=5.6, 2.8 Hz, 1H), 6.02–6.04 (m, 1H), 4.72 (d, *J*=4.8 Hz, 1H), 4.22 (td, *J*=6.8, 4.8 Hz, 1H), 3.93 (dd, *J*=8.0, 6.8 Hz, 1H), 3.86 (dd, *J*=8.0, 7.2 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.2, 117.6, 109.8, 107.8, 106.5, 79.8, 69.4, 66.0, 26.5, 25.9, 25.8, 18.4; HRMS-ESI: *m/z* [M+Na$^+$] calcd for $C_{16}H_{29}NNaO_3Si$: 334.1809; found: 334.1808.

2.2.3 5-((*S*)-(*tert*-butyldimethylsilyloxy) ((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-pyrrole-2-carbaldehyde (**8a**)

To freshly distilled $POCl_3$ (0.4430 g, 2.889 mmol, 3.0 eq.) in 50 ml flask was added dropwise anhydrous *N*,*N*-dimethylformamide (DMF, 0.2112 g, 2.889 mmol, 3.0 eq.) at 0 °C. A white solid formed immediately, which was dissolved in DCM. Then a solution of compound **7a** (0.2994 g, 0.963 mmol, 1.0 eq.) in DCM (5 mL) was added to the above solution within 30 s. After stirring at 0 °C for 30 min, the reaction was quenched with aqueous saturated $NaHCO_3$ solution and stirred for additional 1 h at room temperature. The aqueous layer was extracted with DCM (3×100 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica column using petroleum ether-ethyl acetate (8:1) as eluent to give **8a** (0.1775 g, 54%) as a pale yellow oil. $[\alpha]_D^{29}$: +13.6 (c 0.96, $CHCl_3$); IR (thin film): 3457, 3257, 2933, 2858, 1650, 1494, 1375, 1255, 1076, 839, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (s, 1H), 9.45 (s, 1H), 6.90 (dd, *J*=4.0, 2.8 Hz, 1H), 6.20 (dd, *J*=3.6, 2.4 Hz, 1H), 4.68 (d, *J*=6.4 Hz, 1H), 4.15 (dd, *J*=12.4, 6.0

Hz, 1H), 4.00 (dd, *J*=8.4, 6.4 Hz, 1H), 3.91 (dd, *J*=8.4, 6.4 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 141.0, 132.4, 121.5, 110.1, 109.3, 79.3, 69.8, 66.4, 26.8, 25.8, 25.4, 18.3; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{17}H_{29}NNaO_4Si$: 362.1758; found: 362.1765.

2.2.4 5-((*R*)-(*tert*-butyldimethylsilyloxy)((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-pyrrole-2-carbaldehyde (**8b**)

Similar procedure to that of **8a** in 48% yield. Pale yellow oil; $[\alpha]_D^{29}$: −58.7 (c 0.42, $CHCl_3$); IR (thin film): 3455, 3257, 2932, 2858, 1653, 1493, 1377, 1254, 1101, 841, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (s, 1H), 6.88 (dd, *J*=4.0, 2.8 Hz, 1H), 6.20 (dd, *J*=3.6, 2.4 Hz, 1H), 4.85 (d, *J*=4.8 Hz, 1H), 4.22 (td, *J*=6.8, 4.8 Hz, 1H), 3.95 (dd, *J*=8.4, 6.8 Hz, 1H), 3.74 (dd, *J*=8.5, 6.8Hz, 1H), 1.34 (s, 3H), 1.34 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 140.0, 132.5, 121.1, 110.1, 109.6, 78.5, 69.1, 65.5, 26.2, 25.8, 25.4, 18.4; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{17}H_{29}NnaO_4Si$: 362.1758; found: 362.1762.

2.2.5 1-(2-Bromoethyl)-4-(methoxymethoxy)benzene (**10**)

The commercially available compound **9** was dissolved in 33 wt% HBr solution (10 mL) and the resultant solution was stirred at 80 °C overnight. The reaction was diluted with water (120 mL) and then extracted with DCM (4×80 mL). The combined organic layer was washed with aqueous saturated $NaHCO_3$ solution (100 mL) and dried over Na_2SO_4 and evaporated. The residue was purified by silica column using petroleum ether-ethyl acetate (10:1) as eluent to give the corresponding bromide (2.4782 g, 85%). Then to a solution of the above bromide (0.619 g, 3.08 mmol, 1.0 eq.) in DCM (80 mL) was added diisopropylethylamine (DIPEA, 1.989 g, 15.39 mol, 5.0 eq.) and methoxymethyl chloride (MOMCl, 2.480 g, 30.78 mmol, 10.0 eq.) at 0 °C. The resultant solution was stirred overnight at room temperature.

After quenching the reaction with aqueous saturated $NaHCO_3$ solution (120 mL), the aqueous layer was extracted with DCM (3×80 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica column using petroleum ether-ethyl acetate (20:1) as eluent to give compound **10** (0.6376 g, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.13 (m, 2H), 7.01–6.99 (m, 2H), 5.17 (s, 2H), 3.68 (t, *J*=7.6 Hz, 1H), 3.54 (t, *J*=7.6Hz, 1H), 3.48 (s, 3H), 3.11 (t, *J*=7.6 Hz, 1H), 3.02 (t, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 132.4, 131.6 , 130.0, 129.8, 116.5, 94.6, 56.1, 45.3, 38.8, 38.5, 33.3.

2.2.6 5-((*S*)-(*tert*-butyldimethylsilyloxy)((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1-(4-(methoxymethoxy)phenethyl)-1*H*-pyrrole-2-carbaldehyde (**11a**)

To a solution of compound **8a** (0.0433 g, 0.128 mmol, 1.0 eq.) and compound **10** (0.1719 g, 0.701 mmol, 5.5 eq.) in DMF (1.2 mL) was added anhydrous K_2CO_3 (0.969 g, 0.701 mmol, 5.5 eq.). After the solution was stirred at 110 °C for 0.5 h, another solution of **10** (0.1563 g, 0.637 mmol, 5.0 eq.) in DMF (0.5 mL) was added. After 2 h, aqueous saturated NH_4Cl solution (30 mL) was added to quench the reaction. The aqueous layer was extraced with ethyl acetate (3×30 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica column using petroleum ether-ethyl acetate (15:1) as eluent to give compound **11a** (0.0566 g, 88%) as a colorless oil. $[\alpha]_D^{29}$: +17.1 (c 0.24, $CHCl_3$); IR (thin film): 2931, 2857, 1663, 1512, 1465, 1402, 1235, 1154, 1076, 1006, 837, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 7.22 (d, *J*=8.8 Hz, 2H), 7.00 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=4.0 Hz, 1H), 6.26 (d, *J*=4.4 Hz, 1H), 5.16 (s, 2H), 4.72 (d, *J*=6.8 Hz, 1H), 4.51 (t, *J*=8.4 Hz, 2H), 4.17–4.10 (m, 1H), 4.10–3.99 (m, 2H), 3.48 (s, 3H), 3.04 (dt, *J*=13.2, 8.4 Hz, 1H), 2.91 (dt, *J*=13.2, 8.4 Hz, 1H), 1.41 (s, 3H), 1.31 (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 156.2, 143.4, 131.8, 131.7, 130.0, 125.2, 116.7, 110.1, 94.7, 79.3, 68.9, 67.1, 56.1, 47.7, 37.1, 26.7, 25.8, 25.2, 18.2; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{27}H_{41}NNaO_6Si$: 526.2595; found: 526.2605.

2.2.7 5-((*R*)-(*tert*-butyldimethylsilyloxy)((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1-(4-(methoxymethoxy)phenethyl)-1*H*-pyrrole-2-carbaldehyde (**11b**)

Similar procedure to that of **11a**. Compound **11b**: 81% yield; colorless oil; $[\alpha]_D^{29}$: −18.3 (c 0.22, $CHCl_3$); IR (thin film): 2932, 2857, 1664, 1512, 1468, 1377, 1237, 1153, 1079, 1007, 840, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 7.18 (d, *J*=8.8Hz, 2H), 6.99 (d, *J*=8.4Hz, 2H), 6.93 (d, *J*=4.0 Hz, 1H), 6.24 (d, *J*=4.0 Hz, 1H), 5.16 (s, 2H), 4.89 (d, *J*=6.0 Hz, 1H), 4.62 (ddd, *J*=14.0, 10.4, 6.0 Hz, 1H), 4.47 (ddd, *J*=13.6, 10.4, 5.6 Hz, 1H), 4.29 (dd, *J*=12.8,6.4 Hz, 1H), 3.89 (dd, *J*=8.8, 6.4 Hz, 1H), 3.75 (dd, *J*=8.8, 6.0 Hz, 1H), 3.48 (s, 3H), 3.03 (ddd, *J*=12.8, 10.4, 5.6 Hz, 1H), 2.82 (ddd, *J*=12.8, 10.4, 5.6 Hz, 1H), 1.29 (s, 3H), 1.06 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 156.2, 142.0,131.9, 131.8,130.1, 125.1, 116.6, 110.3, 110.1, 94.7, 78.4, 68.5, 65.4, 56.1, 48.1, 37.0, 26.0, 25.8, 25.4, 18.3; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{27}H_{41}NNaO_6Si$: 526.2595; found: 526.2606.

2.2.8 5-((*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-1-(4-(methoxymethoxy)phenethyl)-1*H*-pyrrole-2-carbaldehyde (**12a**)

To a solution of **11a** (0.160 g, 0.318 mmol, 1.0 eq.) in THF (16 mL) was added tetrabutylammonium fluoride (TBAF, 1 mol/L in THF, 1.6 mL) at room temperature. After 0.5 h, the organic solvent was evaporated and the residue was purified by silica column using petroleum ether-ethyl acetate

(2:1) as eluent to give compound **12a** (0.124 g, >99%) as a pale yellow oil. $[\alpha]_D^{29}$: −9.1 (c 0.396, $CHCl_3$); IR (thin film): 3425, 2931, 2119, 1659, 1512, 1461, 1375, 1235, 1153, 1074, 1007, 922, 852, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 1H), 7.01 (d, *J*=8.8 Hz, 2H), 6.96–6.93 (m, 3H), 6.18 (d, *J*=4.0 Hz, 1H), 5.14 (m, 2H), 4.71 (dt, *J*=13.6, 6.8 Hz, 1H), 4.38 (d, *J*=5.6 Hz, 1H), 4.34 (dd, *J*=13.6, 7.6 Hz, 1H), 4.16 (dd, *J*=12.0,6.0 Hz, 1H), 4.08–3.99 (m, 2H), 3.46 (s, 3H), 2.98 (t, *J*=7.2 Hz, 2H), 1.43 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5, 156.1, 142.2, 132.0, 131.9, 130.3, 125.2, 116.7, 109.8, 108.5, 94.7, 77.7, 66.7, 65.9, 56.1, 47.8, 37.1, 26.6, 24.9; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{21}H_{27}NNaO_6$: 412.1731; found: 412.1735.

2.2.9 5-((*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy) mthyl)-1-(4-(methoxymethoxy)phenethyl)-1*H*-pyrrole-2-carbaldehyde (**12b**)

Similar procedure to that of **12a**. Compound **12b**: pale yellow oil; yield: >99%; $[\alpha]_D^{29}$: −15.0 (c 0.466, $CHCl_3$). IR (thin film): 3440, 2929, 2119, 1662, 1512, 1464, 1372, 1235, 1153, 1070, 1005, 921, 885, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 6.98 (d, *J*=8.4 Hz, 2H), 6.92 (d, *J*=8.8 Hz, 2H), 6.92 (d, *J*=4.4 Hz, 1H), 6.17 (d, *J*=4.0 Hz, 1H), 5.14 (s, 2H), 4.65–4.49 (m, 2H), 4.27 (dd, *J*=12.4,6.0Hz, 1H), 4.04 (t, *J*=5.6 Hz, 1H), 3.91 (dd, *J*=8.8, 6.8 Hz, 1H), 3.49 (dd, *J*=8.8, 6.4 Hz, 1H), 3.47 (s, 3H), 3.03–2.97 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 156.3, 141.3, 132.2, 132.1, 130.3, 124.7, 116.6, 110.3, 108.8, 94.7, 77.3, 66.4, 66.3, 56.1, 47.9, 37.0, 26.8, 25.5; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{21}H_{27}NNaO_6$: 412.1731; found: 412.1740.

2.2.10 5-((*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(methoxy)methyl)-1-(4-(methoxymethoxy)phenethyl)-1*H*-pyrrole-2-carbaldehyde (**13a**)

To a reaction tube containing NaH (60% in mineral oil, 0.0201 g, 0503 mmol, 10 eq.) was added a solution of **12a** (0.0196 g, 0.050 mmol, 1.0 eq.) in THF (1.0 mL) at 0 °C. Then excess methyl iodide (0.2 mL) was added. After stirring at 0 °C for 0.5 h, the reaction was quenched with aqueous saturated NH_4Cl solution (10 mL). The aqueous layer was extraced with ethyl acetate (3×10 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica column using petroleum ether-ethyl acetate (2:1) as eluent to give compound **13a** (0.0181 g, 90%) as a pale yellow oil. $[\alpha]_D^{29}$: +12.2 (c 0.238, $CHCl_3$); IR (thin film): 2933, 1662, 1511, 1460, 1376, 1234, 1154, 1078, 1005, 922, 827, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.13 (d, *J*=8.4 Hz, 2H), 6.98–6.95 (m, 3H), 6.24 (d, *J*=4.0 Hz, 1H), 5.14 (s, 2H), 4.62 (ddd, *J*=14.0, 8.8, 6.0 Hz, 1H), 4.49–4.41 (m, 1H), 4.20–4.15 (m, 1H), 4.11 (dd, *J*=8.4, 6.0 Hz, 2H), 4.01 (dd, *J*=8.4, 5.6 Hz, 1H), 3.46 (s, 3H), 3.10 (s, 3H), 3.02–2.94 (m, 2H), 1.42 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 156.2, 141.0, 132.4, 131.8, 130.2, 125.3, 116.6, 110.0, 109.8, 94.6,78.0, 67.4, 57.1, 56.1, 47.8, 37.0, 26.6, 25.0; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{22}H_{29}NNaO_6$: 426.1887; found: 426.1889.

2.2.11 5-((*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(methoxy)methyl)-1-(4-(methoxymethoxy)phenethyl)-1*H*-pyrrole-2-carbaldehyde (**13b**)

Similar procedure to that of **13a**. Compound **13b**: pale yellow oil; yield: 83%; $[\alpha]_D^{29}$: −18.6 (c 0.226, $CHCl_3$); IR (thin film): 2931, 1663, 1512, 1465, 1380, 1234, 1153, 1079, 1006, 920, 827, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 7.14–7.07 (m, 2H), 6.99–6.92 (m, 3H), 6.18 (d, *J*=4.0 Hz, 1H), 5.14 (s, 2H), 4.60 (ddd, *J*=14.0, 8.4, 6.0 Hz, 1H), 4.48 (ddd, *J*=14.0, 8.4, 7.2 Hz, 1H), 4.40 (dd, *J*=13.2,6.4 Hz, 1H), 4.22 (d, *J*=7.2 Hz, 1H), 3.83 (dd, *J*=8.8, 6.8 Hz, 1H), 3.54 (dd, *J*=8.8, 6.4 Hz, 1H), 3.46 (s, 3H), 3.16 (s, 3H), 3.02–2.88 (m, 2H), 1.33 (s, 3H), 1.25 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 156.3, 139.1, 132.6, 131.8, 130.2, 125.1, 116.6, 110.4, 110.3, 94.6, 77.0, 76.9, 65.9, 57.1, 56.1, 48.2, 37.0, 29.8, 26.4, 25.4; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{22}H_{29}NNaO_6$: 426.1887; found: 426.1886.

2.2.12 5-((1*S*,2*R*)-2,3-dihydroxy-1-methoxypropyl)-1-(4-hydroxyphenethyl)-1*H*-pyrrole-2-carbaldehyde (**4**)

To a solution of **13a** (0.0205 g, 0.051 mmol, 1.0 eq.) in DCM (4.0 mL) was added a solution of BBr_3 (0.1279 g, 0.510 mmol, 10.0 eq.) in DCM (1.0 mL) at −60 °C. 5 min later, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (15 mL). The aqueous layer was extraced with ethyl acetate (3×15 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica column using petroleum ether-ethyl acetate (1:2) as eluent to give compound **4** (0.0123 g, 75%) as a white oil. $[\alpha]_D^{29}$: +14.5 (c 0.172, $CHCl_3$); IR (thin film): 3787, 3662, 3379, 2924, 2854, 1640, 1516, 1460, 1374, 1240, 1105, 787 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 9.41 (s, 1H), 7.07 (d, *J*=4.1Hz, 1H), 7.06–7.02 (m, 2H), 6.71–6.67 (m, 2H), 6.28 (d, *J*=4.1 Hz, 1H), 4.60 (ddd, *J*=14.0, 8.8, 5.6 Hz, 1H), 4.46 (dt, *J*=13.6, 8.4 Hz, 1H), 4.32 (d, *J*=7.2 Hz, 1H), 3.75–3.70 (m, 1H), 3.68 (s, 1H), 3.67 (d, *J*=1.6 Hz, 1H), 3.09 (s, 3H), 2.97–2.87 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 180.4, 157.2, 144.4, 133.4, 131.1(2C), 130.6, 127.0, 116.4(2C), 111.0, 77.7, 75.6, 64.2, 61.6, 57.5, 49.0, 37.8, ; HRMS-ESI: *m*/*z* [M+Na^+] calcd for $C_{17}H_{21}NNaO_5$: 342.1312; found: 342.1322.

2.2.13 5-((1*R*,2*R*)-2,3-dihydroxy-1-methoxypropyl)-1-(4-hydroxyphenethyl)-1*H*-pyrrole-2-carbaldehyde (**3**)

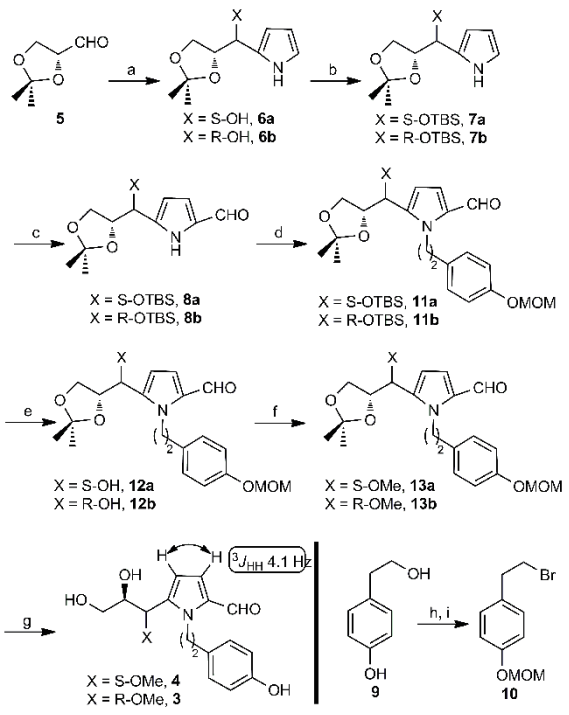
Similar procedure to that of **4**. Compound **3**: white oil; yield: 78%; $[\alpha]_D^{29}$: −6.3 (c 0.128, $CHCl_3$); IR (thin film): 3788, 3662, 3379, 2922, 2847, 1657, 1515, 1455, 1377, 1265, 1042, 790 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 9.45 (s, 1H), 7.07

(d, *J*=4.1 Hz, 1H), 7.05–6.99 (m, 2H), 6.72–6.65 (m, 2H), 6.28 (d, *J*=4.1 Hz, 1H), 4.64–4.57 (m, 2H), 4.49–4.41 (m, 1H), 4.39 (d, *J*=5.6 Hz, 1H), 3.76 (dd, *J*=10.4, 5.6 Hz, 1H), 3.54 (dd, *J*=11.2, 4.8 Hz, 1H), 3.15 (s, 3H), 2.94–2.87 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 180.5, 157.3, 143.1, 133.5, 131.1(2C), 130.4, 126.9, 116.4(2C), 111.6, 77.6, 75.4, 63.6, 57.6, 48.9, 37.9, ; HRMS-ESI: *m/z* [M+Na$^+$] calcd for $C_{17}H_{21}NNaO_5$: 342.1312; found: 342.1317.

3 Results and discussion

Our synthesis commenced from *D*-glyceraldehyde acetonide (**5**), facilely available from *D*-mannitol (Scheme 1) [2]. Nucleophilic attack of pyrrole on **5** in the presence of Grignard reagent afforded a diastereomeric mixture of compounds **6a** and **6b** with about 1:1 ratio [3]. These diastereomers are inseparable by column chromatography and thus were directly transformed to their *tert*-butyldimethylsilyl (TBS) ethers, i.e. **7a** and **7b**, which were separable to each other in this step. Subsequently, compounds **7a** and **7b** were respectively transformed to compounds **3** and **4** along the same synthetic strategy.

Thus, to introduce an aldehyde on pyrrole, Vilsmeier-Haack formylation was employed to produce compound **8a** from **7a** and produce compound **8b** from **7b** in moderate

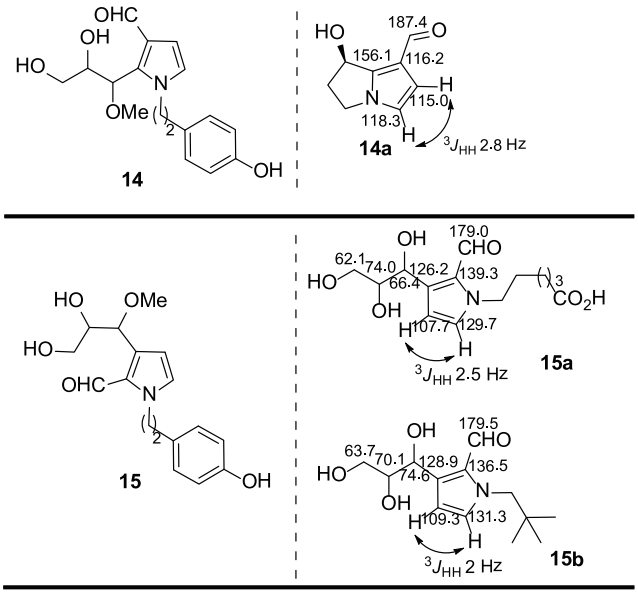


Scheme 1 The synthesis of compounds. Reagents and conditions are: (a) pyrrole, EtMgBr, THF, 0 °C to r.t.; **5** in DCM, −78 °C; (b) TBSCl, imidazole, DMAP, DCM, r.t.; (c) $POCl_3$, DMF, DCM, 0 °C; (d) K_2CO_3, **9**, DMF, 110 °C; (e) TBAF, THF, r.t.; (f) NaH, MeI, THF, 0 °C; (g) BBr_3, DCM, −60 °C; (h) 33% HBr, H_2O, 80 °C; (i) MOMCl, DIPEA, DCM, r.t..

yields [4]. Then compounds **8a** and **8b** were subjected to comcoupling in the presence of potassium carbonate with compound **10**, prepared from the commercially available compound (**9**) over two steps, to afford compounds **11a** and **11b** respectivley. Deprotection of the TBS silyl ether with TBAF and transformation of the resultant alcohol to methyl ether with NaH/MeI resulted in formation of compounds **13a** and **13b** smoothly. Finally, simultaneous deprotection of acetonide and MOM ether gave compounds **4** and **3** from **13a** and **13b** respectively.

However, neither the characterization data of our synthetic **3** nor those of our synthetic **4** were in accordance with the reported data of jiangrines C and D. In the original isolation literature [1], jiangrines C and D were obtained as an inseperable mixture in a 1.2:1 ratio. Wondering if there are any shifts of signals between the spectra of pure **3** or **4** and those of their mixture, we mixed **3** and **4** in a 1.2:1 ratio and recorded ^{1}H NMR and ^{13}C NMR spectra. Unfortunately, spectra of the mixture are just composite spectra of **3** and **4**, and are obviously different from those of mixture of natural jiangrines C and D. Thus, one may argue that whether our synthetic samples are structurally correct or not. The structures of our synthetic **3** and **4** were confirmed through full characterization. Moreover, the 2,5-disubstitution on pyrrole of the synthetic **3** and **4** is confirmed by the coupling constant between two adjacent pyrrole hydrogens ($^3J_{HH}$ 4.1 Hz), which is consistent with those of known compounds with similar substitution pattern reported in literatures [5]. However, the corresponding coupling constants of jiangrines C and D are 1.8 and 2.4 Hz respectively [1]. This discrepance indicate that the structures of jiangrines C and D should be modified on the basis of our current synthesis. Based on the characterization data of jiangrine A, its molecular structure should be highly related to jiangrines C and D. Re-investigation on 2D NMR spectra of jiangrines A, C and D, including ^{1}H-^{1}H COSY, HSQC, HMBC and NOESY, revealed that the two hydrogen atoms on pyrrole ring in these natural molecules should be adjacent to each other. But a 2,5-disubstitution pattern has been proved incorrect according to our total synthesis. Combining all information made us propose the following two possible molecular skeletons for jiangrines C and D, i.e. compounds **14** and **15** (Figure 2).

^{13}C NMR data of the known compound **14a** [6], a structural analog of our proposed structure **14**, are actually very different from those of compound **14**, although the coupling constants are close between them. However, ^{13}C NMR data of the known compounds **15a** and **15b** are very close to those of compound **15** [7], which indicates the structure of compound **15** represent the molecular skeleton of jiangrines C and D (tables for comparison of NMR data among jiangrines C&D, synthetic **3** and **4**, compounds **15a** and **15b** were provided in the Supporting Information online).



Representative ^{13}C NMR

Natural Jiangrine C: 180.9, 137.7, 132.9, 129.5, 110.0, 79.0, 76.9, 63.9

Natural Jiangrine D: 181.3, 137.7, 132.7, 129.9, 110.3, 79.1, 75.7, 64.2

Figure 2 Possible molecular skeletons of jiangrines C and D (**14** and **15**) and NMR data of several known compounds.

4 Conclusions

In conclusion, we accomplished total synthesis of the proposed structures of jiangrines C and D in seven steps from *D*-glyceraldehyde acetonide. The notable difference between spectra of our samples and those of natural jiangrines C and D indicates their authentic molecular structures should be reassigned from **3** and **4**. After scrupulous analysis, we proposed a most possible molecular skeleton of jiangrines C and D as **15**. Total synthesis and identification of authentic structures of jiangrines is underway in our laboratory.

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Conflict of interest The authors declare that they have no conflict of interest.

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