Supporting Information

Latonduines A and B, New Alkaloids Isolated from the Marine Sponge *Stylissa carteri*: Structure Elucidation, Synthesis, and Biogenetic Implications

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Experimental

Stylissa carteri (Dendy) (Demospongiae, order Halichondrida, family Dictyonellidae) was harvested by hand using SCUBA on Latondu Island, Taka Bonerate, 80 miles south of southern Sulawesi, Indonesia. Freshly collected sponge (50 g) was initially preserved in EtOH for two days at room temperature after which the EtOH was discarded and the sample frozen. The frozen sponge was subsequently repeatedly extracted with MeOH. The combined extracts were concentrated *in vacuo*, and the resulting aqueous suspension was partitioned between H₂O and EtOAc. Fractionation of the EtOAc soluble material, by sequential application of Sephadex LH20 chromatography (80% MeOH/CH₂Cl₂) and reversed phase HPLC (45% MeOH/H₂O), yielded latonduine A (**6**) (2.8 mg, pale yellow solid), latonduine B ethyl ester B (**8**) (2.9 mg, pale yellow crystalline solid) and latonduine B methyl ester (**9**) (0.4 mg, pale yellow crystalline solid).

Latonduine A (**6**): mp decomposes at ~290°C; UV (MeOH) λ max 245 (ϵ 19830), 284 (ϵ 14222) nm; HREIMS [M]⁺ *m/z* 372.9002 (C₁₀H₇ON₅Br₂, calc 372.8997); ¹H NMR (500 MHz, DMSO-*d*₆): δ 13.10 (s, 1H), 8.76 (s, 1H), 8.14 (t, *J* = 5.2 Hz, 1H), 6.88 (bs, 2H), 3.90 (bd, *J* = 5.2 Hz, 2H) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆): δ 163.7, 162.1, 161.8, 155.9, 125.1, 120.0, 113.4, 107.9, 96.0, 46.4 ppm.

Latonduine B ethyl ester (8): mp 228-231°C; UV (MeOH) λ max 203 (ϵ 24131), 252 (ϵ 25922), 284 (shoulder), 348 (ϵ 5887) nm; HREIMS $[M]^+$ m/z 444.9193 ($C_{13}H_{11}O_3N_5Br_2$, calc 444.9195); 1H NMR (500 MHz, $DMSO-d_6$): δ 13.10 (s, 1H), 8.26 (m, 1H), 7.24 (bs, 2H), 4.19 (m, 2H), 4.10 (dd, J = 14.5, 3.1 Hz, 1H), 3.77 (dd, J = 14.5, 7.1 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 168.8, 165.1, 162.0, 161.4, 155.4, 125.4, 120.2, 111.3, 106.4, 99.1, 61.5, 46.8, 13.5 ppm.

Latonduine B methyl ester (9): UV (MeOH) λ max 209 (ϵ 11181), 252 (ϵ 13507), 345 (ϵ 3032) nm; HREIMS $[M]^+$ m/z 430.9050 ($C_{12}H_9O_3N_5Br_2$, calc 430.9053); 1H NMR (500 MHz, $DMSO-d_6$): δ 13.12 (bs, 1H), 8.26 (m, 1H), 7.25 (bs, 2H), 4.09 (bd, J = 14.4, 1H), 3.77 (dd, J = 14.4, 6.9 Hz, 1H), 3.75 (s, 3H) ppm; ^{13}C NMR (100 MHz, $DMSO-d_6$) (only partial ^{13}C NMR assignments possible from HMQC and HMBC data): δ 168.8, 165.5, 162.1, 111.3, 52.6, 46.8 ppm.

Preparation of 4,5-dibromopyrrol-2-yl trichloromethyl ketone.

To a stirred solution of pyrrol-2-yl trichloromethyl ketone (11.5 g, 54.1 mmol) in acetic acid (25 mL), was added a solution of bromine (5.86 mL, 113.7 mmol) in acetic acid (225 mL). After the solution had been stirred for 24 hours, an additional quantity of bromine (0.5 mL, 9.7 mmol) was added and the reaction mixture stirred for a further 3 hours. The reaction mixture was concentrated to dryness *in vacuo* and partitioned between aqueous K_2CO_3 (10% w/w, 250 mL) and Et_2O (200 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 x 200 mL). The combined organic phases were dried ($MgSO_4$), filtered through CeliteTM and concentrated to dryness *in vacuo*. Purification of the crude product by flash

chromatography (40 x 150 mm, hexanes/EtOAc 19:1) and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 18.65 g (93%) of the bromopyrrole as a pale pink solid.

^1H NMR (400 MHz, CDCl_3) δ 7.35 (s, 1H), 10.27 (bs, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 93.8, 102.4, 113.5, 123.2, 123.8, 172.1.

Exact mass calculated for $\text{C}_6\text{H}_2\text{ON}^{79}\text{Br}_2^{35}\text{Cl}_2^{37}\text{Cl}$: 368.7539; found: 368.7540.

Preparation of the amide **12**.

To a solution of the bromopyrrole (7.52 g, 20.3 mmol) in MeCN (40 mL) was added, dropwise, 2-(2-ethylamino)-1,3-dioxolane (2.24 mL, 20.4 mmol). After the reaction mixture had been stirred for 17 hours at rt it was filtered and the precipitate washed with MeCN (30 mL) to yield 6.16 g (81%) of the amide **12** as a white solid which required no further purification.

^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 1.90 (m, 2H), 3.48 (q, 2H), 3.80 (m, 2H), 3.92 (m, 2H), 4.89 (t, 1H), 6.86 (s, 1H), 7.58 (bs, 1H), 11.97 (bs, 1H).

^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$) δ 34.3, 35.5, 65.5, 99.4, 103.5, 105.3, 113.0, 129.2, 160.0.

Exact mass calculated for $\text{C}_{10}\text{H}_{12}\text{O}_3\text{N}_2^{79}\text{Br}^{81}\text{Br}$: 367.9194; found: 367.9194.

Preparation of the olefin **13**.

A stirred solution of the amide **12** (2.82 g, 7.68 mmol) in MeSO_3H (15 mL) was heated to 35 °C. After the solution had been stirred for 20 hours an additional quantity of MeSO_3H (10 mL) was added. After the solution had been stirred for a further 22 hours an additional quantity of MeSO_3H (10 mL) was added and the solution was stirred for 5 days. The solution was cooled to room temperature and poured into cold (0 °C) water (400 mL). The resultant suspension was filtered to give a grey solid. Purification of the crude product by flash chromatography (40 x 270 mm, EtOAc/hexanes 7:3) and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 1.602 g (69%) of the olefin **13** as a pale yellow solid.

^1H NMR (400 MHz, CD_3OD) δ 3.56 (d, 2H, J = 6.4 Hz), 6.00 (dt, 1H, J = 6.4, 10.3 Hz), 6.64 (d, 1H, J = 10.3 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ 39.7, 100.2, 108.4, 126.5, 126.7, 126.8, 127.1, 164.7.

Exact mass calculated for $\text{C}_8\text{H}_6\text{ON}_2^{79}\text{Br}^{81}\text{Br}$: 305.8826; found: 305.8830.

Preparation of the alcohol **14**.

To a stirred solution of the olefin **13** (338 mg, 1.105 mmol) in dry THF (10 mL) was added LiBH_4 (3 mg, 0.136 mmol). The reaction was placed under an inert atmosphere ($\text{Ar}_{(\text{g})}$) and 1,3,2-benzodioxaborole (141 μL , 1.325 mmol) was added as a solution in dry THF (5 mL). After the mixture had been stirred for 1 hour it was quenched with 1N NaOH (1 mL) and treated with 30% H_2O_2 (1.3 mL, 1.325 mmol). The reaction mixture was concentrated to dryness *in vacuo* and partitioned between water (100 mL) and EtOAc (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were concentrated to dryness *in vacuo*. Purification of the crude product by flash chromatography (45 x 170 mm, EtOAc then EtOAc/MeOH 9:1) and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 254 mg (71%) of the alcohol **14** as a white solid and 44 mg (13%) of the starting material **13**.

^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ 2.53 (dd, 1H, $J = 8.8, 16.8$ Hz), 2.84 (dd, 1H, $J = 4.9, 16.8$ Hz), 3.10 - 3.19 (m, 2H), 3.88 (m, 1H), 5.17 (d, 1H, $J = 4.1$ Hz) 7.71 (t, 1H, $J = 5.4$ Hz) 12.44 (s, 1H).

^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{SO}$) δ 36.4, 47.9, 67.4, 100.2, 105.5, 121.9, 123.7, 161.5.

Exact mass calculated for $\text{C}_8\text{H}_8\text{O}_2\text{N}_2^{79}\text{Br}^{81}\text{Br}$: 323.8932; found: 323.8932.

Preparation of the ketone **15**.

To a solution of the alcohol **14** (96 mg, 0.296 mmol) in THF (5 mL) was added Dess-Martin periodinane (452 mg, 1.066 mmol) and the resulting mixture was stirred for 15 minutes. The reaction mixture was concentrated to dryness *in vacuo* and partitioned between water (100 mL) and EtOAc (100 mL). The phases were separated and the organic phase was washed with water (2 x 100 mL). The organic phase was concentrated to dryness *in vacuo*. Purification of the crude product by flash chromatography (3 x 270 mm, EtOAc/hexanes 9:1) and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 79 mg (83%) of the ketone **15** as a white solid and 14 mg (15%) of the starting material **14**.

^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 3.70 (s, 2H), 3.91 (d, 2H, $J = 4.9$ Hz), 7.15 (bs, 1H), 11.85 (bs, 1H).

^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$) δ 41.5, 52.1, 100.7, 106.9, 121.1, 125.7, 164.1, 205.9.

Exact mass calculated for $\text{C}_8\text{H}_6\text{O}_2\text{N}_2^{81}\text{Br}_2$: 323.8755; found: 323.8757.

Preparation of the ethyl ether **16**.

To a stirred solution of the ketone **15** (25 mg, 0.078 mmol) in triethylorthoformate (10 mL, 60.12 mmol) was added trifluoroacetic acid (200 μ L, 0.003 mmol). The reaction was placed under an inert atmosphere ($\text{Ar}_{(\text{g})}$) and refluxed for 18 hours, after which the reaction mixture was concentrated to dryness *in vacuo*. Purification of the crude product by flash chromatography (16 x 250 mm, EtOAc/hexanes 3:7) and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 10 mg (35%) of the ethyl ether **16** as a white solid.

^1H NMR (500 MHz, CDCl_3) δ 1.40 (t, $J = 7.1$ Hz, 3H), 3.86 (bs, 2H), 4.24 (q, $J = 7.1$ Hz, 2H), 6.40 (bs, 1H), 7.63 (s, 1H), 11.00 (bs, 1H).

Exact mass calculated for $\text{C}_{11}\text{H}_{10}\text{O}_3\text{N}_2^{79}\text{Br}^{81}\text{Br}$: 377.9038; found: 377.9038.

Preparation of latonduine A (**17**).

To a stirred solution of the ethyl ether **16** (3.5 mg, 0.009 mmol) in THF (5 mL) and water (1 mL) were added K_2CO_3 (3.8 mg, 0.028 mmol) and guanidine hydrochloride (2.3 mg, 0.024 mmol) and the solution stirred at

reflux for 19 hrs. The reaction mixture was concentrated to dryness *in vacuo* and partitioned between water (20 mL) and EtOAc (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were concentrated to dryness *in vacuo*. Purification of the crude product by reversed phase C₁₈ high performance liquid chromatography (46% MeOH/H₂O) and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 2.8 mg (82%) of latonduine A (**17**) as a white solid.

¹H NMR (500 MHz, (CD₃)₂SO) δ 3.90 (bd, *J* = 5.2 Hz, 2H), 6.88 (bs, 2H), 8.14 (t, *J* = 5.2 Hz, 1H), 8.76 (s, 1H), 13.10 (s, 1H).

Exact mass calculated for C₁₀H₇ON₅⁸¹Br₂: 374.8976; found: 374.8978.

Latondaine A acquired at 500MHz in DMSO-*d*₆

Latondeine A acquired at 100 MHz in DMSO-*d*₆

Latondeine B ethyl ester acquired at 500 MHz in DMSO-*d*₆

Latondeine B ethyl ester acquired at 500 MHz in DMSO-*d*₆

Latondeine B methyl ester acquired at 500 MHz in DMSO-*d*₆

Synthetic Material

Natural Product