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Syntheses of *S*-Enantiomers of Hanishin, Longamide B, and Longamide B Methyl Ester from L-Aspartic Acid *β*-Methyl Ester: Establishment of Absolute Stereochemistry

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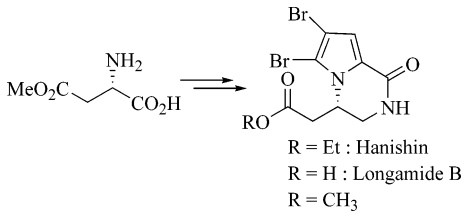
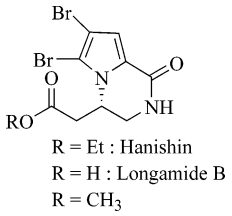


Total syntheses of enantiopure hanishin, longamide B, and longamide B methyl ester are described. Absolute configurations of these natural products have been established.

A large number of bioactive bromopyrrole alkaloids have been isolated from marine sponges.[1] Examples include hanishin,[2] longamide B,[2,3] and longamide B methyl ester[4] (Scheme 1), which have been isolated as a racemic mixture from *Acanthella carteri, Agelas dispar*, and *Homaxinella* sp., respectively. Recently, Venkatteswarlu and co-workers published the isolation of (+)-methyl ester of longamide B from *Agelas* ceylonica.[5] All of these three natural products exhibit interesting biological properties. For example, hanishin is cytotoxic toward NSCLC-N6 human non-small-cellung carcinoma (IC_{50} 9.7 $\mu g \cdot mL^{-1}$), longamide B displays antibiotic activity against Gram-positive bacteria (*Bacillus subtilis* ATCC #6538; MIC 50 $\mu g \cdot mL^{-1}$), and its methyl ester shows an activity against P388 lymphocytic leukemia cells (ED_{50} 30 $\mu g \cdot mL^{-1}$).

Racemic syntheses of hanishin, longamide B, and its methyl ester have been previously reported;[6] however, enantiopure syntheses have not been described. As part of our studies on pyrrole alkaloids,[7] we have decided to synthesize nonracemic (*S*)-hanishin, (*S*)-longamide B, and (*S*)-longamide B methyl ester.

SCHEME 1



We chose the commercially available L-aspartic acid *β*-methyl ester as starting material for the introduction of the stereogenic center. According to a procedure described by Jefford and co-workers,[8] L-aspartic acid *β*-methyl ester was condensed with tetrahydro-2,5-dimethoxyfuran to give the pyrrole **1** (Scheme 2). Reaction of this compound with *N,N*-dibenzylamine, using DCC as the coupling reagent and HOBt/$CuCl_2$ as a deracemizing additive,[9] gave the corresponding amide in poor yield. Replacement of the secondary amine with *N*-benzylamine led to the desired pyrrole which was then treated with a solution of boran tetrahydrofuran complex in THF. Concomitant reduction of ester and amide functions was observed.[10] The obtained secondary amine **2** was subsequently transformed into a tertiary amine by subsequent treatment with benzyl bromide. In the next step, protection of the alcohol function was performed under Williamson's conditions using methyl iodide and sodium hydride.[11] At this stage, the enantiomeric excess of compound **3** was determined by chiral HPLC (column Chiralpak OD) using a racemic standard. It was found to be >99%. Considering the fact that the proton at the chiral center is no longer acidic, further chemical transformations should not induce racemization. Subsequently, trichloroacetylation at the C2 position on the pyrrole ring was carried out. Treatment of the crude material with sodium methoxide in methanol gave the corresponding methyl ester **4**.[12] Deprotection of the amino group under classical conditions[13] followed by heating led to formation of bicyclic compound **5**, which reacts readily with 2 equiv of *N*-bromosuccinimide[14] to give the corresponding 4,5-dibromo derivative. The regioselectivity of this reaction was confirmed by 2D NMR correlation experiments (GCOSY, GHMQC, and GHMBC). Demethylation using boron tribromide afforded

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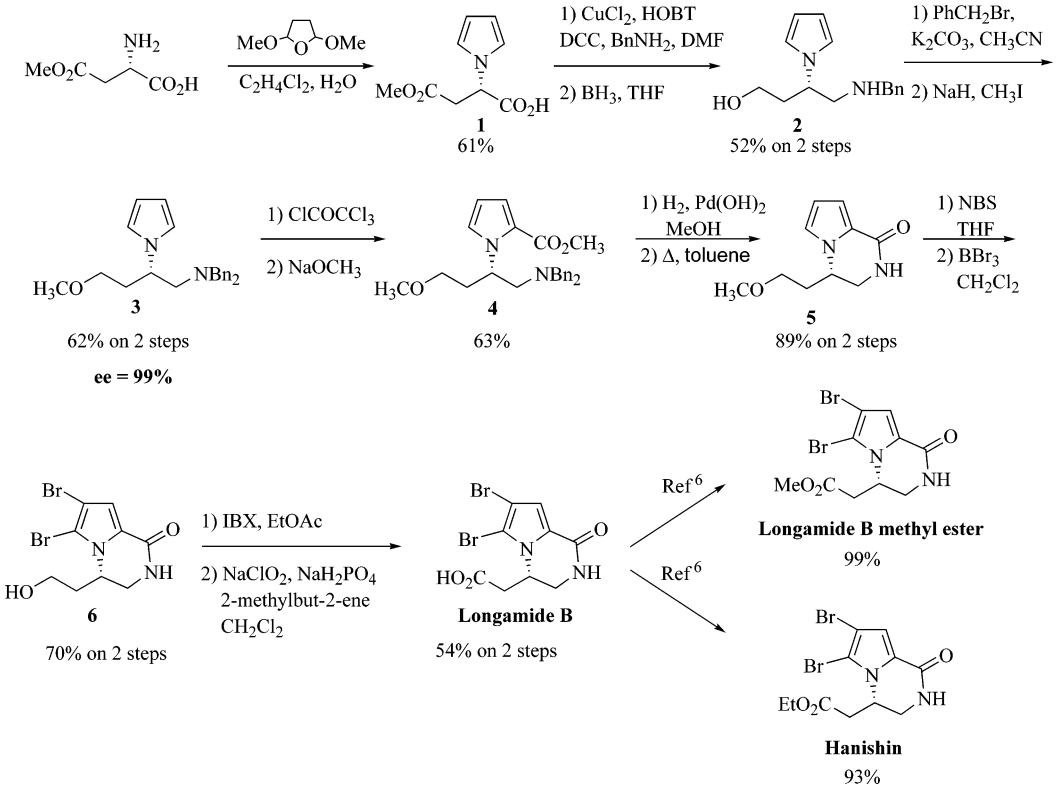
SCHEME 2



alcohol **6**. In a first attempt, we tried to oxidize the primary alcohol to the corresponding carboxylic acid using a sodium periodate−ruthenium trichloride combination; however, these conditions led to the acid in low yield.[15] A two-step strategy was then envisaged involving the treatment of alcohol **6** with *o*-iodoxybenzoic acid[16] followed by oxidation of the resulting aldehyde with sodium chlorite to give longamide B.[17] Spectral properties of the acid were in good agreement with those described in the literature for a racemic sample.[3,6] As described by Banwell et al., we did not observe an infrared absorption band at 1780 cm^{-1}.[6] The optical rotation was −5.5 (*c* 1, MeOH). Finally, to confirm the ee determined for compound **3** (>99%), we synthesized a chiral ester by reacting our longamide B sample with (*S*)-phenylethanol. The corresponding ester exhibited a de >99%, which was determined by HPLC using a standard.

The second target molecule, e.g., hanishin, was prepared by reacting longamide B with acidic ethanol.[6] Once again, spectroscopic data for this product were in agreement with those reported in the literature.[2,6] The optical rotation exhibited by this bromopyrrole alkaloid was −4.3 (*c* 1, MeOH).

Finally, longamide B methyl ester was also prepared from longamide B by treatment with diazomethane in diethyl ether.[6] X-ray analysis and spectroscopic data confirmed the structure of this alkaloid.[3,6] However, we observed an $[\alpha]_D$ value with the sign opposite to the one previously described for a sample which was assumed to be (*S*)-(+).[4,5] Our synthetic compound has indeed the absolute *S* configuration[18] but exhibits a (−) sign for its specific rotation. Several measurements were performed using the previously described concentrations.[4,5] In all cases, we found nearly the same absolute value but the opposite sign (experimental results: $[\alpha]_D = -2.8$ (*c* 0.49, MeOH) and −7.7 (*c* 1, MeOH) compared to the literature: $[\alpha]_D = +2.6$ (*c* 0.39, MeOH)[4] and $[\alpha]_D = +7$ (*c* 1, MeOH)[5]).

In conclusion, the first syntheses of enantiopure (*S*)-(−)-longamide B, (*S*)-(−)-hanishin, and (*S*)-(−)-longamide B methyl ester are reported. Their optical rotations are −5.5 (*c* 1, MeOH), −4.3 (*c* 1, MeOH), and −7.7 (*c* 1, MeOH), respectively. Finally, we showed that the *levorotary* enantiomers of these three natural products have the *S* configuration.

Experimental Section

All commercial solvents were distilled before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen atmosphere. Column chromatography purifications were carried out using silica gel (70−230 mesh). ^1H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively. Peak assignments were determined using DEPT and two-dimensional experiments. HPLC analyses were performed on a Shimadzu apparatus (UV diodes array detector) equipped with a chiral column Daicel Chiralpak OD (25 cm) for the separation of enantiomers or a reversed-phase column Kromasil C18 (25 cm) for the separation of diastereoisomers.

(2*S*)-2-Pyrrol-1-ylsuccinic Acid 4-Methyl Ester (1). Sodium acetate (3.385 g, 41.26 mmol) and acetic acid (3 mL) were

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(18) An anomalous dispersion X-ray analysis of longamide B methyl ester confirmed the *S* configuration of our sample.

added to a solution of L-aspartic acid β-methyl ester hydrochloride (7.5 g, 40.85 mmol) in 1,2-dichloroethane (75 mL) and water (45 mL). The resulting mixture was heated at 80 °C, and tetrahydro-2,5-dimethoxyfuran (5.67 g, 42.89 mmol) was then added. After 30 min at 80 °C, the solution was cooled. The aqueous layer was washed with dichloromethane. The combined organic layers were washed with brine and then dried, filtered, and evaporated. The crude residue was purified by chromatography on silica gel (pentane/EtOAc, 7:3) to give compound **1** as a colorless viscous oil (4.91 g, 61% yield): $[\alpha]^{20}_D = -47.9$ (*c* 1, CH_2Cl_2); IR (KBr, cm^{-1}) 3101 (OH), 1732 (CO), 1700 (CO); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.99 (dd, J = 16.8, 7.0 Hz, 1H, H-3), 3.26 (dd, J = 16.8, 7.6 Hz, 1H, H-3), 3.69 (s, 3H, CH_3), 5.13−5.18 (m, 1H, H-2), 6.19 (t, J = 2.1 Hz, 2H, H_{pyr}), 6.71 (t, J = 2.1 Hz, 2H, H_{pyr}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 37.5 (C-3), 52.8 (CH_3), 58.0 (C-2), 109.8 (C_{Ar}), 120.6 (C_{Ar}), 170.8 (C=O), 175.2 (C=O); MS (DCI) *m/z* 198 ($M + H^+$). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.91; H, 5.83; N, 6.98.

(3*S*)-4-Benzylamino-3-pyrrol-1-ylbutan-1-ol (2). A suspension of **1** (4.9 g, 24.97 mmol), anhydrous $CuCl_2$ (4.01 g, 29.85 mmol), and HOBt (4.03 g, 29.85 mmol) in dry DMF (80 mL) was cooled at 0 °C. DCC (6.16 g, 29.85 mmol) in DMF (5 mL) was then added. After the mixture was stirred for 30 min, *N*-benzylamine (5.06 g, 47.26 mmol) was added, and the stirring was continued for 24 h at room temperature. Ethyl acetate (50 mL) was added, and the resulting organic layer was washed subsequently with aqueous HCl (0.1 N), saturated aqueous $NaHCO_3$, and brine. It was then dried, filtered, and concentrated under reduced pressure.

The resulting crude ester was dissolved in dry THF (40 mL). A THF solution of BH_3 (90 mL, 1 M solution) was then added, and the resulting mixture was stirred at room temperature for 12 h. The organic layer was removed in vacuo, and water (25 mL) was added. The aqueous layer was neutralized with aqueous NaOH (10%) and the desired compound extracted with EtOAc. Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel (pentane/EtOAc, 5:5). The amino alcohol (3.16 g, 12.98 mmol) was obtained as a red oil (52% yield for two steps): $[\alpha]^{20}_D = -10.3$ (*c* 1, CH_2Cl_2); IR (KBr, cm^{-1}) 3319, 3020, 2929; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.95−1.99 (m, 2H, H-2), 2.40 (bs, 2H, OH and NH), 2.86−3.00 (m, 2H, H-4), 3.41−3.49 (m, 1H, H-1), 3.57−3.64 (m, 1H, H-1), 3.74 (d, 2H, CH_2Ph), 4.19 (m, 1H, H-3), 6.15 (t, J = 2.1 Hz, 2H, H_{pyr}), 6.67 (t, J = 2.1 Hz, 2H, H_{pyr}), 7.21−7.30 (m, 5H, H_{Ph}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 38.2 (C-2), 53.9 (C-3), 54.7 (CH_2Ph), 58.1 (C-1), 59.7 (C-4), 108.7 (C_{pyr}), 119.3 (C_{pyr}), 127.6 (C_{Ar}), 128.5 (C_{Ar}), 128.9 (C_{Ar}), 139.7 (C_{Ar}); MS (DCI) *m/z* 245 ($M + H^+$).

(3*S*)-4-Dibenzylamino-3-pyrrol-1-ylbutan-1-ol. A mixture of compound **2** (2.97 g, 12.17 mmol), K_2CO_3 (5.05 g, 36.51 mmol), and benzyl bromide (3.96 g, 23.13 mmol) in acetonitrile (50 mL) was stirred at room temperature for 24 h. The reaction was stopped by the addition of water (30 mL). Ethyl acetate (50 mL) was used twice for the extraction of the product. The organic layer was then dried to give the desired crude tertiary amine after evaporation. Purification by column chromatography (CH_2Cl_2) yielded the desired amino alcohol as a colorless viscous oil (3.05 g, 9.13 mmol): $[\alpha]^{20}_D = -20.6$ (*c* 1, CH_2Cl_2); IR (KBr, cm^{-1}) 3392 (OH), 3020, 2939, 2802; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.74 (qd, J = 9.3, 4.7 Hz, 1H, H-2), 1.95−2.04 (m, 1H, H-2), 2.76 (ddd, J = 17.9, 13.2, 7.0 Hz, 2H, H-4), 3.33 (ddd, J = 11.0, 8.8, 4.5 Hz, 1H, H-1), 3.43−3.53 (m, 1H, H-1), 3.54−3.59 (m, 4H, CH_2Ph), 4.06−4.16 (m, 1H, H-3), 6.12 (t, J = 2.0 Hz, 2H, H_{pyr}), 6.53 (t, J = 2.2 Hz, 2H, H_{pyr}), 7.21−7.37 (m, 10H, H_{Ph}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 37.7 (C-2), 56.1 (C-3), 59.6 (CH_2Ph), 59.9 (C-4), 60.2 (C-1), 108.4 (C_{pyr}), 119.4 (C_{pyr}), 127.6 (C_{Ar}), 128.7 (C_{Ar}), 129.5 (C_{Ar}), 139.1 (C_{Ar}); MS (DCI) *m/z* 335 ($M + H^+$). Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.01; H, 7.84; N, 8.38. Found: C, 79.30; H, 8.17; N, 8.18.

(2*S*)-Dibenzyl(4-methoxy-2-pyrrol-1-ylbutyl)amine (3). The previously obtained alcohol (3.05 g, 9.13 mmol) was treated with sodium hydride in dry THF (60 mL) at 0 °C for 30 min. Methyl iodide (6.48 g, 45.65 mmol) was then added, and the resulting mixture was stirred at room temperature for 24 h. The solution was cooled at 0 °C and quenched with water. The layers were separated, and the aqueous one was extracted twice with EtOAc (2 × 50 mL). The organic layer was dried, the solvent was removed, and the residue was purified by a column chromatography to give a colorless oil (pentane/EtOAc, 5:5, 2.61 g, 82% yield). The ee of this pure compound (99%) was determined by chiral HPLC (debit: 0.3 mL·min^{-1}; cyclohexane/propan-2-ol 99.8:0.2) using a racemic standard (retention times: 17.0 min for the (*S*)-enantiomer and 19.1 min for the (*R*)-enantiomer): $[\alpha]^{20}_D = -3.7$ (*c* 1, CH_2Cl_2); IR (KBr, cm^{-1}) 3028, 2873, 2807, 1493, 1120; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.60−1.71 (m, 1H, H-3), 2.03−2.09 (m, 1H, H-3), 2.65−2.79 (m, 2H, H-1), 2.90−2.97 (m, 1H, H-4), 3.13−3.20 (m, 1H, H-4), 3.21 (s, 3H, OCH_3), 3.51 (s, 2H, CH_2Ph), 3.52 (s, 2H, CH_2Ph), 4.14−4.23 (m, 1H, H-2), 6.12 (t, J = 2.0 Hz, 2H, H_{pyr}), 6.52 (t, J = 2.2 Hz, 2H, H_{pyr}), 7.21−7.28 (m, 10H, H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 34.5 (C-3), 58.9 (C-2), 59.2 (CH_2Ph), 59.4 (C-1), 60.2 (C-4), 108.0 (C_{pyr}), 119.6 (C_{pyr}), 127.3 (C_{Ar}), 128.6 (C_{Ar}), 129.2 (C_{Ar}), 139.6 (C_{Ar}); MS (DCI) *m/z* 349 ($M + H^+$). Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.00; H, 8.25; N, 8.02.

(1*S*)-1-{1-[(Dibenzylamino)methyl]-3-methoxypropyl}-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (4). Compound **3** (2.61 g, 7.5 mmol) in dry THF (10 mL) was added to a solution of trichloroacetyl chloride (3.41 g, 18.75 mmol) and 2,6-lutidine (2.01 g, 18.75 mmol) in THF (70 mL). The resulting mixture was stirred under reflux for 20 h. Then, the reaction was quenched with water and extracted with dichloromethane. The organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$, water, and brine. After drying, filtration, and evaporation of the organic solvent, the corresponding crude trichloroacetyl derivative was obtained and directly dissolved in dry methanol in the presence of sodium methoxide (2.23 g, 41.28 mmol). The reaction was performed at room temperature for 3 h and stopped by adding a saturated aqueous solution of NH_4Cl. Ethyl acetate was added, and the organic layer washed with brine, dried, and evaporated under reduced pressure. The resulting oil was purified by column chromatography (pentane/CH_2Cl_2, 6:4). Ester **4** was obtained as a colorless oil in 63% yield: $[\alpha]^{20}_D = -3.85$ (*c* 1, CH_2Cl_2); IR (KBr, cm^{-1}) 3058, 3021, 2916, 1496; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.77−1.83 (m, 1H, H-2′), 2.04−2.15 (m, 1H, H-2′), 2.59−2.80 (m, 2H, CH_2N), 3.11−3.20 (m, 6H, 2 CH_3), 3.41−3.45 (m, 2H, H-3′), 6.11−6.13 (dd, J = 3.9, 2.7 Hz, 1H, H_{pyr}), 6.64 (bs, 1H, H_{pyr}), 6.95−6.97 (dd, J = 3.9, 1.7 Hz, 1H, H_{pyr}), 7.15−7.25 (m, 10H, H_{Ph}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 34.9 (C-2′), 51.3 (C-1′), 58.2 (CH_2N), 58.8 (CH_2Ph), 58.9 (CH_2Ph), 59.2 (2 CH_3), 109.0 (C_{Ar}), 118.0 (C_{Ar}), 123.0 (C_{Ar}), 127.2 (C_{Ar}), 128.7 (C_{Ar}), 128.9 (C_{Ar}), 129.4 (C_{Ar}), 130.1 (C_{Ar}), 139.7 (C_{Ar}), 162.2 (CO); MS (DCI) *m/z* 407 ($M + H^+$). Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.87; H, 7.44; N, 6.90. Found: C, 73.63; H, 7.46; N, 6.84.

(4*S*)-4-(2-Methoxy-ethyl)-3,4-dihydro-2*H*-pyrrolo[1,2-*a*]-pyrazin-1-one (5). To a solution of **4** (2.3 g, 5.66 mmol) in methanol (75 mL) was added $Pd(OH)_2$/C. After the reaction flask was purged with argon, the reaction mixture was stirred for 12 h under hydrogen. It was then filtered through Celite and concentrated in vacuo. The residue was dissolved in toluene (50 mL) and heated under reflux in an argon atmosphere for 20 h. The reaction mixture was then cooled and the solvent removed under reduced pressure. Column chromatography (pentane/EtOAc, 8:2) yielded the desired compound as a colorless oil (89% yield): $[\alpha]^{20}_D = -5.6$ (*c* 1, CH_2Cl_2); IR (KBr, cm^{-1}) 3198, 2924, 2879, 1662; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.98−2.11 (m, 2H, H-1′), 3.17−3.28 (m, 1H, H-3), 3.34 (s, 3H, CH_3), 3.38−3.45 (m, 2H, H-2′ and H-3), 3.87−3.92 (dd, J = 11.9, 4.6 Hz, 1H, H-2′), 4.36−4.43 (m, 1H, H-4), 6.21−6.23 (dd, J = 3.8, 2.6 Hz, 1H, H_{pyr}), 6.49 (bs, 1H, NH), 6.82−6.83 (m, 1H, H_{pyr}), 6.94−6.96 (m, 1H, H_{pyr}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 33.2 (C-1′), 45.2 (C-3), 51.7 (CH_3), 59.0 (C-4), 68.9 (C-2′), 109.7 (C_{pyr}), 114.2 (C_{pyr}), 123.7 (C_{pyr}), 125.0 (C_{pyr}), 161.7 (CO); MS (DCI) *m/z* 195 ($M + H^+$). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.43. Found: C, 61.97; H, 7.47; N, 14.01.

(4*S*)-6,7-Dibromo-4-(2′-methoxyethyl)-3,4-dihydro-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one. NBS (1.798 g, 10.1 mmol) was added to a solution of compound **5** (0.89 g, 5.05 mmol) in THF (35 mL). The resulting mixture was then stirred for 50 min at room temperature. Then, an aqueous solution of $NaHCO_3$ (5%) and dichloromethane were added. The layers were separated, and the organic phase was successively washed with aqueous $NaHCO_3$ (5%), water, and brine. After evaporation of the organic solvent, the residue was purified by column chromatography on silica gel to give a white solid (CH_2Cl_2/MeOH, 98:2, yield 83%): mp 109−110 °C; $[\alpha]^{20}_D = -31.6$ (*c* 1, CH_3OH); IR (KBr, cm^{-1}) 3220 (NH), 3077, 2918, 1652 (CO); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.87−1.98 (m, *J* = 14.3, 11.1, 5.5 Hz, 1H, H-1′), 2.02−2.17 (m, 1H, H-1′), 3.35 (s, 3H, CH_3), 3.40−3.48 (m, 2H, H-2′), 3.64 (ddd, *J* = 13.1, 5.4, 1.3 Hz, 1H, H-3), 3.84 (dd, *J* = 13.1, 4.1 Hz, 1H, H-3), 4.45−4.53 (m, 1H, H-4), 6.96 (bs, 1H, NH), 6.98 (s, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 31.9 (C-1′), 43.2 (C-3), 52.4 (CH_3), 58.8 (C-4), 68.9 (C-2′), 100.7 (C-7), 106.7 (C-6), 115.9 (C-8), 124.9 (C-8a), 159.4 (C=O); MS (DCI) *m/z* 351, 353, 355; HRMS (EI) *m/z* calcd for $C_{10}H_{12}{}^{79}Br_2N_2O_2$ 349.9265, found 349.9270.

(4*S*)-6,7-Dibromo-4-(2′-hydroxyethyl)-3,4-dihydro-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (6). A 1 M solution of BBr_3 (42.32 mmol) in dichloromethane was slowly added to a solution of the previous ether (1.49 g, 4.23 mmol) in CH_2Cl_2 (50 mL) at −20 °C. The resulting mixture was stirred at room temperature for 20 h and treated with water. The aqueous phase was extracted twice with ethyl acetate, and the combined organic layers were dried and concentrated under vacuum. Chromatography of the residue gave pure title alcohol as a white powder in 84% yield: mp 138−140 °C; $[\alpha]^{20}_D = -32.8$ (*c* 1, CH_3OH); IR (KBr, cm^{-1}) 3434, 3245, 3129, 1648, 1617; ^1H NMR (300 MHz, CD_3OD) δ (ppm) 1.75−1.86 (m, 1H, H-1′), 2.90−2.02 (m, 1H, H-1′), 3.59−3.65 (m, 3H, 2 H-3 and H-2′), 3.77 (ddd, *J* = 13.5, 4.1, 0.9 Hz, 1H, H-2′), 3.75−3.81 (m, 1H, H-4), 6.88 (s, 1H, H-8); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 34.7 (C-1′), 43.3 (C-3), 52.9 (C-4), 59.4 (C-2′), 101.7 (C-7), 108.5 (C-6), 116.2 (C-8), 126.4 (C-8a), 161.2 (C=O); MS (DCI) *m/z* 337, 339, 341; HRMS (EI) *m/z* calcd for $C_9H_{10}{}^{79}Br_2N_2O_2$ 335.91090, found 335.9116; calcd for $C_9H_{10}{}^{79}Br^{81}BrN_2O_2$ 337.90885, found 337.9072.

(*S*)-(-)-Longamide B. The alcohol **6** (1.2 g, 3.55 mmol) was dissolved in ethyl acetate (60 mL), and *o*-iodoxybenzoic acid (2.98 g, 10.65 mmol) was added. The resulting suspension was heated at 80 °C for 3 h. The solution was then cooled to room temperature, filtered through Celite, and concentrated in vacuo. Purification of the resulting residue on silica gel (MeOH/EtOAc, 5:95) gave the corresponding aldehyde which was immediately dissolved in THF (50 mL) and water (50 mL) at 0 °C, in the presence of 2-methylbut-2-ene (50 mL), $NaClO_2$ (2.05 g, 20.62 mmol), and $NaH_2PO_4{\cdot}H_2O$ (3.51 g, 25.44 mmol). The mixture was then stirred at room temperature for 5 h and then diluted with dichloromethane. The layers were separated, and the aqueous one was extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated in vacuo. Purification after a classical acid−base treatment gave longamide B as a white powder (667 mg, 1.92 mmol): mp 208−210 °C; $[\alpha]^{20}_D = -5.51$ (*c* 1, CH_3OH); IR (KBr, cm^{-1}) 3270, 3214, 3044, 1728, 1643; ^1H NMR (300 MHz, CD_3OD) δ (ppm) 2.57 (ddd, *J* = 16.3, 3.4, 1.4 Hz, 1H, H-10), 2.87 (dd, *J* = 16.4, 10.8 Hz, 1H, H-10), 3.67 (dd, *J* = 13.5, 1.3 Hz, 1H, H-8), 3.91 (ddd, *J* = 13.6, 4.1, 1.5 Hz, 1H, H-8), 4.81 (m, 1H, H-9), 6.96 (s, 1H, H_{pyr}); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 36.7 (C-10), 44.2 (C-8), 52.4 (C-9), 102.1 (C-4), 108.4 (C-5), 117.0 (C-3), 126.7 (C-2), 161.4 (C=O), 173.2 (C=O); MS (DCI) *m/z* 349.5, 351.1, 352.9; HRMS (EI) *m/z* calcd for $C_9H_8N_2O_3{}^{79}Br^{81}Br$ 351.88812, found 351.8889. Anal. Calcd for $C_9H_8Br_2N_2O_3$: C, 30.72; H, 2.3; N, 7.96, Found: C, 30.56; H, 2.29; N, 7.65.

(*S*)-(-)-Hanishin. We followed the procedure described by Banwell et al.,[6] starting from 30 mg of longamide B: mp 158−160 °C; $[\alpha]^{20}_D = -4.3$ (*c* 1, CH_3OH); IR (KBr, cm^{-1}) 3180, 3064, 2978, 2924, 1722, 1684; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ (ppm) 1.27 (t, *J* = 7.1 Hz, 3H, CH_3), 2.68 (ddd, *J* = 15.9, 3.8, 1.3 Hz, 1H, H-10), 3.00 (ddd, *J* = 15.9, 10.0, 1.3 Hz, 1H, H-10), 3.67 (s, 3H, OCH_3), 3.71 (ddd, *J* = 13.4, 5.3, 1.3 Hz, 1H, H-8), 4.03 (ddd, *J* = 13.4, 4.1, 1.1 Hz, 1H, H-8), 4.19 (q, *J* = 7.1 Hz, 2H, CH_2), 4.86 (m, 1H, H-9), 6.89 (s, 1H, H_{pyr}), 6.94 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.3 (CH_3), 36.5 (C-10), 43.6 (C-8), 51.6 (C-9), 61.5 (OCH_2), 100.6 (C-4), 106.1 (C-5), 115.2 (C-3), 127.0 (C-2), 158.6 (C=O), 170.2 (C=O); MS (DCI) *m/z* 379.0, 381, 383; HRMS (EI) *m/z* calcd for $C_{11}H_{12}N_2O_3{}^{79}Br_2$ 377.92146, found 377.9224.

(*S*)-(-)-Longamide B Methyl Ester. We followed the procedure described by Banwell et al.[6] starting from 80 mg of longamide B: mp 150−151 °C; $[\alpha]^{20}_D = -7.7$ (*c* 1, CH_3OH), $[\alpha]^{20}_D = -2.8$ (*c* 0.49, CH_3OH); CD (c 0.013, CH_3OH, 25 °C) ($\Delta\epsilon$) 226 nm (+3.02); IR (KBr, cm^{-1}) 3218, 1728, 1671; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.54 (ddd, *J* = 16.8, 3.1, 1.5 Hz, 1H, H-10), 2.95 (dd, *J* = 16.7, 10.8 Hz, 1H, H-10), 3.61 (ddd, *J* = 13.4, 5.3, 1.3 Hz, 1H, H-8), 3.67 (s, 3H, OCH_3), 3.86 (ddd, *J* = 13.3, 4.0, 1.4 Hz, 1H, H-8), 4.68 (m, 1H, H-9), 6.26 (bs, 1H, NH), 6.93 (s, 1H, H_{pyr}); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 35.6 (C-10), 43.5 (C-8), 50.7 (C-9), 52.6 (OCH_3), 101.7 (C-4), 107.0 (C-5), 116.7 (C-3), 125.1 (C-2), 159.9 (C=O), 170.5 (C=O); MS (DCI) *m/z* 363.3, 365.2, 367.1; HRMS (EI) *m/z* calcd for $C_{10}H_{19}N_2O_3{}^{79}Br_2$ 363.90581, found 363.9052.

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Supporting Information Available: Copies of ^1H NMR spectra of all compounds, CD spectrum of (*S*)-(−)-longamide B methyl ester, and crystallographic data for (*S*)-(−)-longamide B methyl ester. This material is available free of charge via the Internet at http://pubs.acs.org.

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