Electronic Supplementary Information

Total Synthesis of (−)-Aplaminal by Buchwald–Hartwig Cross-Coupling of an Aminal

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Experimental Procedures and Spectral Data for All New Compounds.

General methods.

All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. Anhydrous benzene, CH₂Cl₂, MeOH, MeCN, DMF, THF, and toluene were used as obtained from commercial supplies. TLC analyses were conducted on E. Merck precoated silica gel 60 F₂₅₄ (0.25 mm layer thickness). Fuji Silysia silica gel BW-820MH (75–200 μm) and FL-60D (45–75 μm) were used for column chromatography. Optical rotations were measured with a JASCO DIP-370 polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 instrument, and only selected peaks are reported in wavenumbers (cm⁻¹). ¹H and ¹³C NMR spectra were recorded on a Bruker AVANCE 600, a Bruker AVANCE 400, or a Bruker DPX 400 spectrometer. The ¹H and ¹³C chemical shifts (δ) were referenced with CDCl₃ (δH = 7.26 (CHCl₃) and δC = 77.0), acetone-d₆ (δH = 2.50 (CHD₂SOCD₃) and δC = 39.5), or CD₃OD (δH = 3.31 (CHD₂OD) and δC = 49.0). J values are given in Hz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. High resolution ESI/TOF mass spectra were recorded on a JEOL AccuTOFCS JMS-T100CS spectrometer. All new compounds were determined to be >95% pure by ¹H NMR unless otherwise noted.

Alcohol 7.

To a stirred solution of Boc-L-Dap-OH (1.04 g, 5.10 mmol) in THF (25 mL) was added BH₃·THF (1.0 M solution in THF, 25.0 mL, 25.0 mmol) at 0 °C. The mixture was stirred at reflux for 24 h, diluted with 6 M HCl aq. (15 mL), and concentrated. The crude diamine hydrochloride was used for the next reaction without further purification.

To a stirred solution of crude diamine hydrochloride in DMF (13 mL) were added K₂CO₃ (2.72 g, 20.4 mmol) and Boc₂O (3.56 mL, 15.5 mmol) at room temperature. The mixture was stirred at the same temperature for 19 h and filtered through a pad of Celite®, which was rinsed with CHCl₃ (150 mL). The filtrate and a rinse were combined and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane–AcOEt 3:1 → 2:1 → 1:1 → 0:1) to give alcohol 7 (1.36 g, 88%) as a white solid: Mp 112.9–115.5 °C; [α]¹⁹D –8.25 (c 1.33, CHCl₃); IR (CHCl₃) 3453, 2980, 2933, 1683, 1509, 1393, 1268, 1250, 1159 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 4.84 (br, 1H), 3.93 (m, 1H), 3.73–3.68 (m, 2H), 3.41 (m, 1H), 3.24 (m, 1H), 2.86 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 156.4, 79.9, 79.4, 61.3, 57.4, 38.8, 31.3, 28.3 (3C), 28.2 (3C); HRMS (ESI) m/z 327.1924, calcd for C₁₄H₂₉N₂NaO₃ [M+Na]⁺ 327.1896.
TBDPS ether 6.

To a stirred solution of alcohol 7 (100 mg, 0.330 mmol) in CH$_2$Cl$_2$ (3.2 mL) were added imidazole (44.9 mg, 0.660 mmol) and TBDPSCI (0.11 mL, 0.43 mmol) at room temperature. The mixture was stirred at the same temperature for 30 min, diluted with brine (10 mL), and extracted with CHCl$_3$ (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated. The residual oil was purified by column chromatography on silica gel (5.4 g, hexane–AcOEt 10:1 → 5:1) to give TBDPS ether 6 (175 mg, 98%) as a colorless solid; Mp 74.8–76.9°C; [α]$^D_{19}$ −2.60 (c 1.03, CHCl$_3$); IR (CHCl$_3$) 3447, 3009, 2979, 2860, 1707, 1685, 1508, 1252, 1114, 998, 704 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.64–7.62 (m, 4H), 7.45–7.36 (m, 6H), 4.59 [4.71] (m, 1H), 4.29 [4.14] (m, 1H), 3.72–3.62 (m, 2H), 3.31 (m, 1H), 3.20 (m, 1H), 2.79 [2.76] (s, 3H), 1.46 [1.43] (s, 9H), 1.42 (s, 9H), 1.04 (s, 9H) (The rotamer’s signals in the ratio of 1:0.9 are in brackets); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 156.5 [155.8], 155.9, 135.5 (4C), 133.1 (2C), 129.7 (4C), 79.9 [79.5], 79.3 [79.1], 63.1 [63.0], 57.5 [56.3], 39.5, 30.2 [29.6], 28.4 (3C), 28.3 (3C), 26.7 (3C), 19.3 (The rotamer’s signals in the ratio of 1:0.9 are in brackets); HRMS (ESI) m/z 565.3068, calcd for C$_{30}$H$_{46}$N$_2$NaO$_5$Si [M+Na]$^+$ 565.3074.

Aminal 8.

To a stirred solution of TBDPS ether 6 (1.31 g, 2.42 mmol) in CH$_2$Cl$_2$ (32 mL) was added TFA (7.0 mL, 91.5 mmol) at 0 °C. After being stirred at same temperature for 3 h, the reaction mixture was concentrated. The crude diamine TFA salt 6a was used for the next reaction without further purification.

To a stirred solution of crude diamine TFA salt 6a in DMF (17 mL) were added Na$_2$SO$_4$ (7.73 g, 5.12 mmol) and dimethyl 2-oxomalonate (5) (0.37 mL, 3.21 mmol) at room temperature. The mixture was stirred at the same temperature for 2 d, diluted with saturated aqueous NaHCO$_3$ (15 mL), filtered, and extracted with AcOEt (2×30 mL). The combined extracts were washed with brine (30 mL), dried (Na$_2$SO$_4$), and concentrated. The residual oil was purified by column chromatography on silica gel (70 g, hexane–acetone 6:1) to give aminal 8 (970 mg, 85%) as a colorless oil; [α]$^D_{24}$ −0.80 (c 2.5, CHCl$_3$); IR (CHCl$_3$) 2955, 2858, 1736, 1472, 1227, 824, 788 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, $J = $ 6.6 Hz, 4H), 7.45–7.36 (m, 6H), 3.78 (s, 3H), 3.77 (s, 3H), 3.67 (dd, $J = $ 10.3, 4.3 Hz, 1H), 3.53 (dd, $J = $ 10.3, 5.7 Hz, 1H), 3.31 (dd, $J = $ 10.1, 7.7 Hz, 1H), 3.24–3.19 (m, 2H), 3.09 (dd, $J = $ 10.1, 4.8 Hz, 1H), 2.56 (s, 3H), 1.07 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.7, 169.4, 135.6 (4C), 133.5 (2C), 129.7 (2C), 127.7 (4C), 79.9 [79.5], 79.3 [79.1], 63.1 [63.0], 57.5 [56.3], 39.5, 30.2 [29.6], 28.4 (3C), 28.3 (3C), 26.7 (3C), 19.3 (The rotamer’s signals in the ratio of 1:0.9 are in brackets); HRMS (ESI) m/z 493.2135, calcd for C$_{25}$H$_{34}$N$_2$NaO$_5$Si [M+Na]$^+$ 493.2142.

S3
Alcohol 4.
To a stirred solution of aminal 8 (4.25 g, 9.12 mmol) in THF (150 mL) was added TBAF (1.0 M solution in THF, 12.5 mL, 12.5 mmol) at 0 °C. The mixture was stirred at room temperature for 1.5 h, diluted with AcOH (1.0 M solution in THF, 12.5 mL, 12.5 mmol), and concentrated. The residual oil was purified by column chromatography on silica gel (250 g, hexane–acetone 3:1→2:1→1:1) to give alcohol 4 (1.82 g, 86%) as a yellow oil: [α]₂⁴ D +0.06 (c 2.7, CHCl₃); IR (CHCl₃) 3347, 2956, 2882, 1736, 1437 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.83 (s, 3H), 3.78 (s, 3H), 3.70 (dd, J=11.4, 2.8 Hz, 1H), 3.46 (d, J = 11.4 Hz, 1H), 3.26–3.11 (m, 3H), 2.59 (s, 3H), Signals due to two protons (NH, OH) were not observed; ¹³C NMR (100 MHz, CDCl₃) δ 169.5, 169.4, 85.2, 65.2, 60.2, 53.0, 52.3, 46.9, 34.1; HRMS (ESI) m/z 255.0957, calcd for C₉H₁₆N₂NaO₅ [M+Na]^+ 255.0957.

Nosylamide 3.
To a stirred solution of alcohol 4 (43.0 mg, 185μmol) in benzene (0.6 mL) were added NsNHoNB (105 mg, 311 μmol), nBu₃P (75 μL, 311 μmol), and TMAD (52.8 mg, 311 μmol) at 0 °C. The mixture was stirred at 30 °C for 24 h and concentrated. The residual oil was purified by column chromatography on silica gel (15 g, toluene–AcOEt 1:0→5:1) to give nosylamide 3 (32.2 mg, 32%) as a yellow oil: [α]₂⁴ D −2.5 (c 0.69, CHCl₃); IR (CHCl₃) 2360, 1735, 1542, 1353, 925, 853, 771 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (dd, J = 8.1, 1.0 Hz, 1H), 7.94 (dd, J = 7.8, 1.1 Hz, 1H), 7.73–7.61 (m, 4H), 7.55 (dddd, J = 7.8, 6.9, 1.1 Hz, 1H), 7.41 (dddd, J = 8.1, 7.3, 1.0 Hz, 1H), 5.10 (d, J = 18.0 Hz, 1H), 5.02 (d, J = 18.0 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.44–3.42 (m, 2H), 3.13–3.09 (m, 2H), 2.96–2.93 (m, 2H), 2.45 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2 (2C), 148.3, 148.0, 134.0, 133.6, 132.9, 132.0, 131.9, 129.3, 128.6, 84.8, 63.8, 53.0 52.3, 51.3, 50.0, 48.2, 34.8; HRMS (ESI) m/z 574.1220, calcd for C₂₂H₂₃N₅NaO₁₀S [M+Na]^+ 574.1220.

Lactam 9.
To a stirred solution of nosylamide 3 (1.01 g, 1.83 mmol) in MeCN (10 mL) were added K₂CO₃ (2.54 g, 18.3
mmol) and PhSH (0.93 mL, 9.15 mmol) at 0 °C. The mixture was stirred at room temperature for 3.5 h, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (45 g, CHCl₃–MeOH 1:0 → 30:1) to give amine 3a (contaminated with unidentified impurities).

To a stirred solution of amine 3a in MeOH (20 mL) was added K₂CO₃ (1.26 g, 9.16 mmol) at room temperature. The mixture was stirred at the same temperature for 15 h, diluted with H₂O (10 mL), and extracted with CHCl₃ (7×15 mL). The combined extracts were washed with brine (20 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (45 g, CHCl₃–MeOH 1:0 → 20:1) to give lactam 9 (592 mg, 97% in 2 steps) as a yellow solid. [α]₂₄⁺D +0.18 (c 0.48, CHCl₃); IR (CHCl₃) 3014, 2400, 1752, 1672, 1494, 1440, 1125, 669 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.99 (dd, J = 7.9, 1.0 Hz, 1H), 7.63 (ddd, J = 7.8, 7.8, 1.0 Hz, 1H), 7.44–7.40 (m, 2H), 5.06 (d, J = 16.7 Hz, 1H), 4.63 (d, J = 16.7 Hz, 1H), 4.39 (s, 3H), 3.65 (m, 1H), 3.55–3.49 (m, 2H), 2.92 (d, J = 11.0 Hz, 1H), 2.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 166.6, 148.7, 134.0, 132.1, 128.7, 128.2, 125.0, 87.0, 60.9, 53.2, 53.0, 46.5, 45.9, 37.0; HRMS (ESI) m/z 357.1175, calcd for C₁₅H₁₈N₄NaO₅ [M+Na]⁺ 357.1157.

**Coupling compound 11.**

To the mixture of lactam 9 (14.4 mg, 45 μmol), methyl 4-bromobenzoate (28.9 mg, 135 μmol), Pd(dba)₂ (25.8 mg, 45 μmol), SPhos (18.4 mg, 45 μmol), and Cs₂CO₃ (87.6 mg, 269 μmol) was added degassed toluene (0.5 mL). The mixture was stirred at reflux for 24 h, filtered through a pad of Celite®, and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–acetone 5:1 → 1:1) to give coupling compound 11 (16.6 mg, 82%) as a yellow solid; [α]₂₄⁻D −13.7 (c 0.78, CHCl₃); IR (CHCl₃) 3019, 1759, 1704, 1675, 1606, 1527, 1287, 1192, 910, 842 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.93–7.90 (m, 3H), 7.30 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.12 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.89–6.84 (m, 3H), 5.12 (d, J = 16.6 Hz, 1H), 4.46 (d, J = 16.6 Hz, 1H), 4.54 (ddd, J = 9.2, 5.6, 1.7 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.76 (ddd, J = 11.3, 4.5, 1.7 Hz, 1H), 3.67 (m, 1H), 3.29 (d, J = 9.2 Hz, 1H), 3.06 (d, J = 11.3 Hz, 1H), 2.56 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 165.2, 163.8, 148.7, 148.6, 133.7, 131.5, 130.5 (2C), 128.4, 128.3, 124.9, 120.1, 115.3 (2C), 86.1, 58.6, 53.2, 53.1, 52.8, 51.7, 45.9, 38.4; HRMS (ESI) m/z 491.1543, calcd for C₂₃H₂₅N₄NaO₇ [M+Na]⁺ 491.1577.
Aplaminal (1).

The solution of coupling compound 11 (16.6 mg, 35 μmol) in trifluoroethanol (12 mL) was stirred at room temperature for 24 h under 365 irradiation and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, CHCl₃–MeOH 1:0 → 50:1) to give aplaminal (1) (8.6 mg, 73%) as a white solid; Mp 232–234 °C; [α]²⁴D –107 (c 0.22, MeOH); IR (MeOH) 3407, 1747, 1654, 1605, 1284, 1192, 826, 789 cm⁻¹; ¹H NMR (600 MHz, acetone-d₆) δ 7.77 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 6.61 (brs, 1H), 4.27 (ddd, J = 9.2, 5.8, 1.5 Hz, 1H), 3.85–3.75 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.68 (dd, J = 11.5, 4.3 Hz, 1H), 3.37 (d, J = 9.2 Hz, 1H), 3.24 (m, 1H), 2.47 (s, 3H); ¹³C NMR (151 MHz, acetone-d₆) δ 167.3, 166.3, 164.8, 150.7, 130.5 (2C), 119.8, 116.2 (2C), 86.9, 58.5, 53.5, 52.7, 51.6, 47.4, 38.2; HRMS (ESI) m/z 356.1222, calcd for C₁₆H₁₅N₃NaO₅ [M+Na]⁺ 356.1222.

Comparison of the ¹H data of synthetic aplaminal and natural sample

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Amine 12.
To a stirred solution of alcohol 7 (41.7 mg, 137 μmol) in CH₂Cl₂ (1.9 mL) was added Dess–Martin periodinane (116 mg, 274 μmol) at 0 °C. After being stirred at room temperature for 2 h, the mixture was diluted with saturated aqueous NaHCO₃ (1.0 mL), saturated aqueous Na₂S₂O₅ (1.0 mL), and H₂O (1.0 mL). The mixture was extracted with Et₂O (3×3 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The crude aldehyde 7a was used for the next reaction without further purification.

To a stirred solution of crude aldehyde 7a in CH₂Cl₂ (1.5 mL) was added oNBNH₂·HCl (51.7 mg, 274 μmol) at room temperature. After the mixture was stirred at the same temperature for 1 h, NaBH(OAc)₃ (87.1 mg, 411 μmol) was added to the mixture. The mixture was stirred at the same temperature for 12 h and diluted with saturated aqueous NaHCO₃ (2.0 mL). The mixture was extracted with CH₂Cl₂ (3×3 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, hexane–acetone 10:1 → 5:1) to give amine 12 (54.1 mg, 90% in 2 steps) as a colorless oil; [α]²³°D +4.3 (c 1.89, CHCl₃); IR (CHCl₃) 3445, 3017, 1684, 1525, 1367, 1225, 1160, 798, 787 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 7.90 (d, J = 8.1 Hz, 1H), 7.71–7.64 (m, 2H), 7.49 (dd, J = 8.1, 7.8 Hz, 1H), 6.34 (brs, 1H), 4.09 (m, 1H), 3.96 (s, 2H), 3.12–2.94 (m, 2H), 2.64 (s, 3H), 2.71–2.50 (m, 2H), 1.40 (s, 9H), 1.39 (s, 9H); ¹³C NMR (100 MHz, DMSO-d₆) δ 155.1 (2C), 148.7, 135.1, 132.4, 130.2, 127.5, 123.6, 78.7, 77.9, 77.2, 59.8, 48.7, 47.9, 38.9, 27.9 (3C), 27.7 (3C); HRMS (ESI) m/z 461.2393, calcd for C₂₁H₃₄N₄NaO₆ [M+Na]⁺ 461.2376.

Nosylamide 13.
To a stirred solution of amine 12 (54.1 mg, 123 μmol) in CH₂Cl₂ (1.0 mL) were added Et₃N (34 μL, 246 μmol), NsCl (41.0 mg, 185 μmol), and DMAP (7.5 mg, 62 μmol) at room temperature. The mixture was stirred at the same temperature for 19 h, diluted with saturated aqueous NaHCO₃ (2.0 mL), and extracted with CH₂Cl₂ (3×3 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, hexane–acetone 5:1 → 3:1) to give nosylamide 13 (69.0 mg, 90%) as a yellow solid; Mp 68.0–69.0 °C; [α]²³°D –3.8 (c 0.60, CHCl₃); IR (CHCl₃) 3452, 3018, 1709, 1545, 1529, 1368, 1226, 1053, 795 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 8.01 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.86 (dd, J = 8.0, 7.6 Hz, 1H), 7.76 (dd, J = 8.0, 7.6 Hz, 1H), 7.61 (dd, J = 7.9, 7.7 Hz, 1H), 7.51 (dd, J = 7.9, 7.7 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 6.45 (brs, 1H), 4.93 (s, 2H), 4.26–4.03 (m, 2H), 3.67 (dd, J = 14.2, 9.3 Hz, 1H),
3.40 (d, $J = 15.4$ Hz, 1H), 3.04 (m, 1H), 2.54 (s, 3H), 1.35 (s, 18H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 155.8 (2C), 148.4, 147.9, 135.2, 134.0, 132.9, 132.1, 131.6, 130.7, 129.3, 129.1, 125.3, 124.9, 79.6, 79.4, 78.3, 55.2, 48.7, 48.6, 39.8, 28.6 (3C), 28.5(3C); HRMS (ESI) $m/z$ 646.2177, calcd for C$_{27}$H$_{37}$N$_5$NaO$_{10}$S $[M+Na]^+$ 646.2159.

**Aminal 3.**

To a stirred solution of nosylamide 13 (69.0 mg, 110 μmol) in CH$_2$Cl$_2$ (2.8 mL) was added TFA (0.8 mL, 821 μmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was concentrated. The crude diamine TFA salt 13a was used for the next reaction without further purification.

To a stirred solution of crude diamine TFA salt 13a in DMF (0.8 mL) were added Na$_2$SO$_4$ (312 mg, 2.20 mmol) and dimethyl 2-oxomalonate (5) (16 μL, 143 μmol) at room temperature. The mixture was stirred at the same temperature for 2 d, diluted with saturated aqueous NaHCO$_3$ (2.0 mL), filtered, and extracted with CHCl$_3$ (3×5 mL). The combined extracts were washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated. The residual oil was purified by column chromatography on silica gel (7 g, hexane–acetone 5:1 → 3:1) to give aminal 3 (61.0 mg, quant. in 2 steps) as a yellow oil.

**Bicyclic core 2.**

The solution of lactam 9 (20.1 mg, 60 μmol) in MeCN–H$_2$O (4:1) (1.0 mL) was stirred at room temperature for 24 h under 365 irradiation and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, CHCl$_3$–MeOH 1:0 → 10:1) to give bicyclic core 2 (8.8 mg, 73%) as a white solid; Mp 207.0–208.0 °C; [α]$^{23}_{D}$ +30.4 (c 0.22, CHCl$_3$); IR (CHCl$_3$) 3685, 3410, 3018, 1752, 1690, 1455, 1301, 1120 cm$^{-1}$; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.85 (s, 3H), 3.59 (m, 1H), 3.52 (dd, $J = 11.5$, 3.4 Hz, 1H), 3.45 (dd, $J = 10.8$, 6.4 Hz, 1H), 3.02 (d, $J = 11.5$ Hz, 1H), 2.83 (d, $J = 10.8$ Hz, 1H), 2.26 (s, 3H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 169.4, 168.0, 88.3, 61.3, 53.2, 47.7, 47.0, 36.9; HRMS (ESI) $m/z$ 222.0835, calcd for C$_8$H$_{13}$N$_3$NaO$_3$ $[M+Na]^+$ 222.0855.
Aplaminal analog 10.

To the mixture of bicyclic core 2 (8.8 mg, 44 μmol), methyl 4-bromobenzoate (33.1 mg, 154 μmol), Pd(dba)$_2$ (25.4 mg, 44 μmol), SPhos (18.1 mg, 44 μmol), and Cs$_2$CO$_3$ (144 mg, 440 μmol) was added degassed toluene (1.5 mL). The mixture was stirred at reflux for 24 h, filtered through a pad of Celite$^\text{®}$, and concentrated. The residual oil was purified by column chromatography on silica gel (2.5 g, CHCl$_3$–MeOH 1:0 → 15:1) to give aplaminal analog 10 (9.6 mg, 65%) as a yellow solid; [$\alpha$]$^\text{23}$$D$ +73.1(c 0.29, CHCl$_3$); IR (CHCl$_3$) 3358, 3021, 1752, 1719, 1681, 1604, 1510, 1437, 1282, 795, 760 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.04 (d, $J$ = 8.9 Hz, 2H), 7.44 (d, $J$ = 8.9 Hz, 2H), 4.15 (dd, $J$ = 10.8, 3.7 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.68 (m, 1H), 3.58 (m, 1H), 3.36–3.33 (m, 2H), 3.08 (d, $J$ = 10.3 Hz, 1H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.3, 166.5, 165.4, 145.1, 130.6 (2C), 128.1, 124.6 (2C), 87.7, 61.2, 55.1, 53.3, 52.3, 46.2, 37.3; HRMS (ESI) $m/z$ 356.1271, calcd for C$_{16}$H$_{18}$N$_3$NaO$_5$ [M+Na]$^+$ 356.1245.

General procedure for the aplaminal analogs 14, 16, and 17.

To the mixture of lactam 9 (ca. 20 μmol), bromide (3–5 eq), Pd(dba)$_2$ (1.0 eq), SPhos (2.0 eq), and Cs$_2$CO$_3$ (5–10 eq) was added degassed toluene (2.0 mL). The mixture was stirred at reflux for 24 h, filtered through a pad of Celite$^\text{®}$, and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, CHCl$_3$–MeOH) to give coupling compound.

The solution of crude coupling compound in MeCN/H$_2$O (6/1) (2.0 mL) was stirred at room temperature for 24 h under 365 irradiation and concentrated. The residual oil was purified by column chromatography on silica gel (CHCl$_3$–MeOH) and by HPLC (Develosil ODS-HG-5, 45% MeOH) to give aplaminal analog.

$m$-carbomethoxy analog 14.

$^1$H NMR (400 MHz, acetone-$d_6$) δ 7.48 (s, 1H), 7.35 (d, $J$ = 7.8 Hz, 1H), 7.20 (dd, $J$ = 8.2, 7.8 Hz, 1H), 7.11 (d, $J$ = 8.2 Hz, 1H), 6.57 (brs, 1H), 4.29 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.77 (m, 1H), 3.65 (dd, $J$ = 11.4, 4.2 Hz, 1H), 3.30 (d, $J$ = 8.6 Hz, 1H), 3.22 (m, 1H), 2.47 (s, 3H); HRMS (ESI) $m/z$ 356.1222, calcd for C$_{16}$H$_{18}$N$_3$NaO$_5$ [M+Na]$^+$ 356.1222.
**p-Chloro analog 16.**

\(^1\)H NMR (400 MHz, acetone-\(d_6\)) \(\delta\) 7.09 (dd, \(J = 9.7, 2.2\) Hz, 2H), 6.83 (dd, \(J = 9.7, 2.2\) Hz, 2H), 6.58 (brs, 1H), 4.23 (ddd, \(J = 8.6, 3.7, 1.4\) Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.64 (m, 1H), 3.24 (d, \(J = 8.6\) Hz, 1H), 3.21 (m, 1H), 2.45 (s, 3H); HRMS (ESI) \(m/z\) 332.0778, calcd for C\(_{14}\)H\(_{16}\)ClN\(_3\)NaO\(_3\) [M+Na]\(^+\) 332.0743.

**p-Nitrile analog 17.**

\(^1\)H NMR (400 MHz, acetone-\(d_6\)) \(\delta\) 7.46 (d, \(J = 8.8\) Hz, 2H), 6.92 (d, \(J = 8.8\) Hz, 2H), 6.67 (brs, 1H), 4.28 (m, 1H), 3.81 (s, 3H), 3.70–3.67 (m, 2H), 3.38 (d, \(J = 9.2\) Hz, 1H), 3.26 (d, \(J = 10.2\) Hz, 1H), 2.46 (s, 3H); HRMS (ESI) \(m/z\) 323.1120, calcd for C\(_{15}\)H\(_{16}\)N\(_4\)NaO\(_3\) [M+Na]\(^+\) 323.1154.

**Cytotoxic activity**

Stock cultures of HeLa S3 cells were maintained in Dulbecco’s Modified Eagle Medium containing 10% fetal bovine serum, 100 \(\mu\)g/mL of penicillin, and 100 \(\mu\)g/mL streptomycin at 37 °C under 5% CO\(_2\). For the purpose of the experiment, \(5\times10^3\) cells suspended in 100 \(\mu\)L of medium per well were plated in 96-well plate, and incubated at 37 °C under 5% CO\(_2\). After incubation for 24 h, a solution of compound in DMSO (1 \(\mu\)L, concentration: 0.001, 0.01, 0.1, 1, 10 mM, respectively) was added to the above-mentioned well, resulting in various concentrations of the compound (0.01, 0.1, 1, 10, 100 \(\mu\)M) or solvent control (1% DMSO). After incubation for 96 h under the same conditions, 5 \(\mu\)L of WST-8 reagent solution was added to the cell culture, and the cell culture was further incubated for 2 h. Colorimetric determination of WST-8 was conducted at 450 nm with an optical reference wavelength at 595 nm using a microplate reader. The absorbance obtained upon the addition of the vehicle was considered as 100%. Data are expressed from the dose-response curve at three independent experiments. The cytotoxic effects of each compound were obtained as IC\(_{50}\) values calculated by probit analysis using the PriProbit 1.63 software.
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{1}$H NMR (600 MHz, acetone-$d_6$)

$^{13}$C NMR (151 MHz, acetone-$d_6$)
$\text{H NMR (400 MHz, DMSO-d}_6\text{)}$

$\text{C NMR (100 MHz, DMSO-d}_6\text{)}$
$^1$H NMR (400 MHz, DMSO-$d_6$)

$^{13}$C NMR (100 MHz, DMSO-$d_6$)
$^{1}H$ NMR (400 MHz, CD$_3$OD)

$^{13}C$ NMR (100 MHz, CD$_3$OD)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, acetone-$d_6$)
$^1$H NMR (400 MHz, acetone-$d_6$)
$^1$H NMR (400 MHz, acetone-$d_6$)