Total Synthesis of Horsfiline: a Palladium-catalyzed Domino Heck-Cyanation Strategy

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Supporting Information

General information

Melting points (m.p.) were recorded using Büchi B-540 melting point apparatus and are uncorrected. Proton NMR (1H) spectra were recorded at 500 MHz on a Bruker AC-500 spectrometer and carbon NMR (13C) spectra at 75 MHz on a Bruker AC-300 spectrometer. Mass spectra were obtained from an AEI MS-9 using positive electron spray (ES+).

Flash chromatography was performed using SDS silicagel 60 (35-70 µm). Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (SDS Silicagel 60 F254). Visualization was achieved under a UVP mineralight UVGL-58 lamp.

All reagents were obtained from commercial suppliers unless otherwise stated. Organic solvents were routinely distilled prior to use: THF from sodium/benzophenone, CH2Cl2 from calcium chloridehydride, MeOH from Mg/I2. When needed, solvents were degazed using freeze-drying. All reactions were performed in flame- or oven-dried apparatus under an argon atmosphere.

Compound 15

To a degassed solution of iodoanilide 14 (1.90 g, 3.29 mmol, 1.0 equiv) in DMF (16 mL) were added K2Fe(CN)6.3H2O (306.0 mg, 0.72 mmol, 0.22 equiv), Na2CO3 (350.0 mg, 3.30 mmol, 1.0 equiv) and Pd(OAc)2 (22.0 mg, 0.1 mmol, 0.03 equiv). After being stirred at 120 °C under argon atmosphere for 3 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na2SO4) and concentrated. The residue was purified by flash
chromatography (SiO$_2$, Heptane/EtOAc: 95/5 to 90/10) to give the corresponding oxindole 15 (0.94 g, 60%) as a light orange solid.

**Mp:** 84-86 °C

$^1$H NMR (500 MHz, CDCl$_3$) δ ppm 7.06 (d, $J = 2.6$ Hz, 1H), 7.02 (d, $J = 8.6$ Hz, 1H), 6.88 (dd, $J = 8.6$, 2.6 Hz, 1H), 5.17 (d, $J = 11.0$ Hz, 1H), 5.11 (d, $J = 11.0$ Hz, 1H), 3.92 (d, $J = 9.7$ Hz, 1H), 3.80 (s, 3H), 3.73 (d, $J = 9.7$ Hz, 1H), 3.62-3.51 (m, 2H), 3.02 (d, $J = 16.7$ Hz, 1H), 0.92 (t, $J = 8.2$ Hz, 2H), 0.84 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H), -0.03 (s, 9H).

HRMS m/z (ES+) calcd for C$_{24}$H$_{40}$N$_2$O$_4$Si$_2$Na ([M+Na]$^+$): 499.2424, found 499.2415.

To a solution of nitrile 15 (0.85 g, 1.8 mmol, 1.0 equiv) in MeOH (12 mL) was added CoCl$_2$.6H$_2$O (0.85 g, 3.6 mmol, 2.0 equiv). NaBH$_4$ (675 mg, 17.8 mmol, 10.0 equiv) was added portion wise over 45 minutes and the reaction was further stirred for 30 minutes. The reaction mixture was carefully quenched by drop wise addition of HCl (2N) and washed with EtOAc. The aqueous phase was basified with NaOH (2N) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$) and concentrated. The residue was purified by flash chromatography (SiO$_2$, CH$_2$Cl$_2$/MeOH: 100/0 to 90/10) to give the corresponding amine 17 (0.67 g, 78%) as a sticky white foam.

$^1$H NMR (500 MHz, CDCl$_3$) δ ppm 6.94 (d, $J = 8.5$ Hz, 1H), 6.90 (d, $J = 2.3$ Hz, 1H), 6.80 (dd, $J = 8.5$, 2.3 Hz, 1H), 5.10 (d, $J = 11.0$ Hz, 1H), 5.07 (d, $J = 11.0$ Hz, 1H), 3.82 (d, $J = 9.3$ Hz, 1H), 3.79 (s, 3H), 3.72 (d, $J = 9.3$ Hz, 1H), 3.56-3.52 (m, 2H), 2.62-2.48 (m, 2H), 2.13-2.10 (m, 2H), 0.92-0.89 (m, 2H), 0.76 (s, 9H), -0.03 (s, 9H), -0.07 (s, 3H), -0.10 (s, 3H).

NMR (75 MHz, CDCl$_3$) δ ppm 178.5, 156.2, 135.9, 131.4, 113.2, 110.7, 109.9, 69.5, 67.9, 65.9, 55.8, 54.5, 37.5, 34.4, 25.6, 18;1, 17.7, -1.4, -5.6, -5.7.

HRMS m/z (ES+) calcd for C$_{28}$H$_{45}$N$_2$O$_4$Si$_2$ ([M+H]$^+$): 481.2918, found 481.2901.
To a solution of amine 17 (0.65 g, 1.35 mmol, 1.0 equiv) in MeOH (14 mL) were added 20 drops of HCl (12N). The reaction was stirred for 3 h at room temperature, quenched with an aqueous saturated solution of Na₂CO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated to afford crude amino alcohol. To a solution of this crude in THF (14 mL) was added Boc₂O (385 mg, 1.76 mmol, 1.3 equiv). The reaction was stirred for 2 h at room temperature, quenched with an aqueous saturated solution of Na₂CO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (SiO₂, Heptane/EtOAc: 5/1 to 2/1) to give the corresponding amino alcohol 18 (0.52 g, 83%) as a white wax.

**¹H NMR** (500 MHz, CDCl₃) δ ppm: 6.97 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.81 (dd, J = 8.5, 2.3 Hz, 1H), 5.15 (d, J = 10.9 Hz, 1H), 5.08 (d, J = 10.9 Hz, 1H), 4.5 (bs, 1H, NH), 3.83-3.79 (m, 1H), 3.78 (s, 3H), 3.74 (dd, J = 10.8, 3.5 Hz, 1H), 3.56-3.48 (m, 2H), 2.96-2.90 (m, 1H), 2.89-2.82 (m, 1H), 2.42-2.35 (d, J = 5.2 Hz, 1H, OH), 2.24-2.15 (m, 1H), 2.05-1.98 (m, 1H), 1.36 (s, 9H), 0.91-0.86 (m, 2H), -0.06 (s, 9H).

**NMR** (75 MHz, CDCl₃) δ ppm: 178.9, 156.5, 155.5, 135.7, 130.2, 112.9, 110.6, 110.1, 79.2, 69.4, 67.3, 65.9, 55.7, 53.9, 36.5, 32.8, 28.3, 17.7, -1.5

**HRMS m/z (ES+)** calcd for C₂₃H₃₈N₂O₆SiNa ([M+Na]+): 489.2397, found 489.2395.

**Compound 19**

To a solution of amino alcohol 18 (0.50 g, 1.1 mmol, 1.0 equiv) in CH₂Cl₂ (21 mL) at 0 °C were added Et₃N (0.31 mL, 2.25 mmol, 2.1 equiv) and MsCl (0.15 mL, 2.0 mmol, 1.8 equiv). The reaction was stirred for 4 h at room temperature, quenched with an aqueous saturated solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated to afford crude mesylated compound. To a solution of this crude in THF (20 mL) at 0 °C was added NaH 60% (85 mg, 2.2 mmol, 2.0 equiv). The reaction was stirred for 15 h at room temperature, quenched with an aqueous saturated saturated solution of NH₄Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (SiO₂, Heptane/EtOAc: 8/1 to 4/1) to give the corresponding spirooxindole 19 (0.46 g, 95%) as a white solid.

**Mp:** 69-71 °C
**1H NMR** (500 MHz, CDCl₃, mixture of rotamers) δ ppm 6.97 (d, J = 7.6 Hz, 1H), 6.82-6.79 (m, 2H), 5.15-5.10 (m, 2H), 3.78 (s, 3H), 3.85-3.60 (m, 4H), 3.55-3.51 (m, 2H), 2.42-2.37 (m, 1H), 2.09-2.06 (m, 1H), 1.50 and 1.44 (s, 9H), 0.91-0.88 (m, 2H), -0.05 (s, 9H).

**13C NMR** (75 MHz, CDCl₃, mixture of rotamers) δ ppm 177.6, 156.6, 154.3, 134.7 and 134.5, 133.4, 112.7 and 112.4, 110.2, 109.8, 79.8, 69.5, 55.8, 54.6 and 54.1, 53.5 and 52.5, 45.4 and 45.2, 36.6 and 35.7, 28.4, 17.7, -1.5.

**HRMS** m/z (ES+) calcd for C₁₂H₁₈N₂O₅SiNa([M+Na]⁺): 471.2291, found 471.2299.

**Compound 20**

To a solution of spirooxindole 19 (0.25 g, 0.56 mmol, 1.0 equiv) in DMF (3.8 mL) and in ethylenediamine (1.6 mL) was added TBAF·3H₂O (600 mg, 1.9 mmol, 3.4 equiv). The reaction was stirred for 24 h at 110 °C, quenched with H₂O and extracted with Et₂O. The combined organic layers were washed with HCl (1N), an aqueous saturated solution of NaHCO₃, dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (SiO₂, Heptane/EtOAc: 7/1 to 3/1) to give the corresponding spirooxindole 20 (0.15 g, 84%) as a white solid.

**Mp:** 155-157 °C

**1H NMR** (500 MHz, CDCl₃, mixture of rotamers) δ ppm 9.05 and 9.03 (s, 1H, NH), 6.86 (d, J = 8.2 Hz, 1H), 6.79-6.75 (m, 2H), 3.87-3.53 (m, 4H), 3.77 (s, 3H), 2.44-2.38 (m, 1H), 2.08-1.95 (m, 1H), 1.48 and 1.43 (s, 9H).

**13C NMR** (75 MHz, CDCl₃, mixture of rotamers) δ ppm 180.2 and 180.0, 156.2 and 156.1, 154.4, 134.4 and 134.0, 133.6 and 133.5, 112.7 and 112.4, 110.4 and 110.3, 110.0, 79.8, 55.8, 54.3, 53.8 and 52.8, 45.4 and 45.2, 36.3 and 35.5, 28.4.

**HRMS** m/z (ES+) calcd for C₁₇H₂₂N₂O₄Na([M+Na]⁺): 341.1477, found 341.1448.

**Compound 21**

To a solution of 20 (50 mg, 0.15 mmol, 1.0 equiv) in CH₂Cl₂ (1.5 mL) was added TFA (0.125 mL, 1.6 mmol, 5.4 equiv). The reaction was stirred for 6 h at room temperature, dilute with CH₂Cl₂, quenched with water and extracted with CH₂Cl₂. The aqueous phase was basified with NaOH (2N) and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated to afford the
crude amine. To a solution of this crude in AcOH (0.7 mL) were added a 37% aqueous solution of CH₂O (0.2 mL) and NaBH₃CN (30 mg, 0.48 mmol, 3.4 equiv). The reaction was stirred for 45 minutes at room temperature, diluted with EtOAc, quenched with NaOH (2N) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (SiO₂, CH₂Cl₂/MeOH: 100/0 to 95/5) to give the compound 21 (32 mg, 88%) as a white wax.

**¹H NMR** (500 MHz, CDCl₃) δ ppm 7.08 (d, J = 2.5 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 6.78 (dd, J = 8.5, 2.5 Hz, 1H), 5.23 (d, J = 11.2 Hz, 1H), 5.20 (d, J = 11.2 Hz, 1H), 4.32 (bs, 1H), 3.78 (s, 3H), 3.11-3.08 (m, 1H), 2.94 (d, J = 9.7 Hz, 1H), 2.80 (d, J = 9.7 Hz, 1H), 2.80-2.74 (m, 1H), 2.46 (s, 3H), 2.33-2.28 (m, 1H), 2.11-2.04 (m, 1H).

**¹³C NMR** (75 MHz, CDCl₃) δ ppm 180.4, 156.7, 135.9, 134.9, 112.7, 110.2, 109.4, 65.6, 64.1, 56.4, 55.8, 53.8, 41.6, 38.1.

**HRMS** m/z (ES⁺) calcd for C₁₄H₁₉N₂O₃ ([M+H]⁺) 263.1396, found 263.1390.

**Compound 4, Horsfiline**

To a solution of 21 (20 mg, 0.076 mmol, 1.0 equiv) in MeOH (0.3 mL) was added Et₃N (0.1 mL). The reaction was stirred for 48 h at reflux and concentrated. The residue was purified by preparative TLC (SiO₂, CH₂Cl₂/MeOH: 9/1) to give horsfiline 21 (15 mg, 85%) as a white wax.

**¹H NMR** (500 MHz, CDCl₃) δ ppm 7.62 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.72 (dd, J = 8.4, 2.4 Hz, 1H), 3.79 (s, 3H), 3.16 (m, 1H), 3.05 (d, J = 9.8 Hz, 1H), 2.93 (d, J = 9.8 Hz, 1H), 2.91-2.86 (m, 1H), 2.54 (s, 3H), 2.43-2.38 (m, 1H), 2.23-2.16 (m, 1H).

**¹³C NMR** (75 MHz, CDCl₃) δ ppm 182.5, 156.2, 137.6, 133.3, 112.4, 110.3, 109.7, 66.3, 56.7, 55.9, 54.1, 41.8, 38.1.

**HRMS** m/z (ES⁺) calcd for C₁₃H₁₇N₂O₂ ([M+H]⁺) 233.1290, found 233.1285.
$^1$H NMR spectra of compound 15

$^1$H NMR spectra of compound 17
$^1$H NMR spectra of compound 18

$^1$H NMR spectra of compound 19
$^1$H NMR spectra of compound 20

$^1$H NMR spectra of compound 21
$^1$H NMR spectra of compound 4, Horsfiline