Supporting Information

Efficient Total Synthesis of (-)-*cis*-Clavicipitic Acid

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S2	General information
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General information

Proton NMR (^1H) were recorded at 300 MHz or 400 MHz NMR spectrometer, Carbon NMR (^{13}C) at 75 MHz or 100 MHz NMR spectrometer and NOESY at 400 MHz NMR spectrometer unless otherwise stated. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, br s: broad singlet for proton spectra. Coupling constants (J) are reported in Hertz (Hz).

Infrared spectra were recorded with a thin layer of the product on a KBr disk.

Flash chromatography was performed using silica gel (200-300 mesh) with solvents distilled prior to use. Visualization was achieved under a UV lamp (254 nm and 365 nm), and by developing the plates with phosphomolybdic acid in ethanol.

All reagents were obtained from commercial suppliers unless otherwise stated.

The following abbreviations are used: **FCC**: flash column chromatography; **PE**: petroleum ether; **EtOAc**: ethyl acetate; **DCM**: dichloromethane; **Boc₂O**: di-*tert*-butyl dicarbonate; **TMSOTf**: trimethylsilyl trifluoromethanesulfonate; **PCy₃**: tricyclohexylphosphine; **XPhos**: 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-propyl-1,1'-biphenyl; **JohnPhos**: 2-(di-*t*-butylphosphino)biphenyl; **Cyclohexyl JohnPhos**: 2-(dicyclohexylphosphino)-biphenyl.

Experimental procedure and physical data

3-Chloro-2-iodobenzenamine **4**¹: 1-Chloro-2-iodo-3-nitrobenzene **6**

(1.42 g, 5.0 mmol, 1.0 equiv), which was prepared followed the literature process from 1-chloro-3-nitrobenzene², and SnCl₂·2H₂O (5.64 g, 25.0 mmol, 5.0 equiv) were dissolved in 10.0 mL of dry EtOH. The result reaction mixture was heated at 70 °C under argon atmosphere for 30 min until the starting material disappeared. The solution was allowed to cool down and the pH was made slightly basic (pH 7-8) by addition of sat. aq. Na₂CO₃ before being extracted with EtOAc. The combined organic phases were washed with brine and dried over Na₂SO₄. The crude product was purified by FCC (PE-CH₂Cl₂, 5 : 1) to give **4** (1.24 g, 98%) as a light yellowish solid: ¹H NMR (300 MHz, CDCl₃) δ 7.04 (t, *J* = 7.8 Hz, 1H), 6.84 (dd, *J* = 0.6, 7.8 Hz, 1H), 6.59 (dd, *J* = 0.6, 7.8 Hz, 1H), 4.26 (br s, 2H); EIMS *m/e* (*rel. int.*) 255.1 (33), 253.1 (100), 127.1 (15), 126.0 (55), 99.1 (17), 90.1 (98), 73.1 (9), 65.1 (10), 64.1 (15), 63.1 (42).

Compound **3**³: A mixture of 3-chloro-2-iodo-benzenamine **4**

(794 mg, 3.13 mmol, 2.0 equiv), (*S*)-2-*N,N*-di-*tert*-butoxycarbonyl-5-oxopentane **5** (540 mg, 1.57 mmol, 1.0 equiv) and DABCO (1.04 g, 4.71 mmol, 3.0 equiv) in dry DMF (10.0 mL) was degassed for 20 min. Pd(OAc)₂ (69.6 mg, 0.31 mmol, 0.1 equiv) was added to the reaction, and the resulting reaction mixture was heated at 80 °C under argon atmosphere for 12 h. The reaction mixture was cooled to room temperature and diluted with water followed by extraction with EtOAc. The combined organic phases were washed with brine and dried over Na₂SO₄. Purification by FCC (PE-EtOAc, 4 : 1) to give the starting aniline **4** (357 mg, 45% based on **4**) and the desired product **3** (570 mg, 80% based on **5**) as white foam: [α]_D²³ -179.3 (*c* 1.22, EtOH); IR (KBr) 3326, 2980, 1782, 1748, 1434, 1370, 1278, 1141, 1094, 936, 853, 781, 742 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.84 (br s, 1H), 7.29 (dd, *J* = 2.4, 6.9 Hz, 1H), 6.95-7.02 (m, 2H), 6.90 (d, *J* = 1.8 Hz, 1H), 5.44 (dd, *J* = 3.9, 11.4 Hz, 1H), 4.09 (dd, *J* = 3.9, 14.4 Hz, 1H), 3.79 (s, 3H), 3.28 (dd, *J* = 11.4, 14.4 Hz,

¹ Bellamy, F. D. ; Ou, K. *Tetrahedron Lett.* **1984**, 25, 839-842.

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³ (a). Jia, Y. ; Zhu, J. *Synlett* **2005**, 2469-2472. (b). Jia, Y.; Zhu, J. *J. Org. Chem.* **2006**, 71, 7826-7834. (c). Xu, Z.; Hu, W.; Zhang, F.; Li, Q.; Lü, Z.; Zhang, L.; Jia, Y. *Synthesis* **2008**, 3981-3987.

1H), 1.22 (s, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.0, 151.4, 138.2, 125.9, 125.6, 124.0, 122.0, 119.8, 110.7, 110.0, 83.3, 59.7, 52.1, 27.3, 26.5; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{29}\text{ClN}_2\text{O}_6\text{K}$ ($\text{M} + \text{K}$) $^+$ 491.1346; found 491.1332.

Compound 2: A mixture of **3** (360 mg, 0.79 mmol, 1.0 equiv), 2-methyl-3-buten-2-ol (3.41 g, 39.70 mmol, 50 equiv) and K_2CO_3 (122 mg, 0.95 mmol, 1.2 equiv) in dry dioxane (13.2 mL, 0.06 M) was degassed for 20 min. $\text{Pd}(\text{OAc})_2$ (17.8 mg, 0.079 mmol, 0.1 equiv) and PCy_3 (44.5 mg, 0.159 mmol, 0.2 equiv) were added to the reaction, and the resulting reaction mixture was heated at 120 $^\circ\text{C}$ under argon atmosphere for 12 h. After cooling, the solvent was evaporated under reduced pressure, and purified by FCC (PE-EtOAc, 2 : 1) to give **2** (191 mg, 48%) as white foam: $[\alpha]_{\text{D}}^{23}$ -71.6 (c 1.00, CHCl_3); IR (KBr) 3537, 3350, 2972, 1787, 1736, 1457, 1438, 1369, 1283, 1141, 1094, 994, 971, 910, 854, 782, 745 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.99 (br s, 1H), 7.30 (d, J = 15.9 Hz, 1H), 7.25-7.28 (m, 1H), 7.07-7.08 (m, 2H), 6.91 (s, 1H), 6.23 (d, J = 15.9 Hz, 1H), 5.17 (dd, J = 2.4, 11.4 Hz, 1H), 3.95 (dd, J = 2.4, 15.0 Hz, 1H), 3.78 (s, 3H), 3.33 (dd, J = 11.4, 15.0 Hz, 1H), 2.29 (br s, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.20 (s, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.6, 151.2, 140.3, 137.3, 131.1, 124.7, 124.6, 124.4, 121.9, 117.5, 111.0, 110.8, 83.0, 70.9, 59.8, 52.2, 29.6, 27.8, 27.3; HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_7\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 525.2571; found 525.2570.

Compound 7: To a stirred solution of **3** (1.12 g, 2.47 mmol, 1.0 equiv) and DMAP (57 mg, 0.49 mmol, 0.2 equiv) in dry CH_3CN (10 mL) was added Boc_2O (808 mg, 3.71 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature overnight. The reaction was evaporated to dryness under reduced pressure and purified by FCC (PE-EtOAc, 10 : 1) to give **7** (1.34 g, 98%) as white foam: $[\alpha]_{\text{D}}^{23}$ -98.6 (c 1.00, CHCl_3); IR (KBr) 2981, 1744, 1427, 1370, 1280, 1256, 1142, 1096, 876, 851, 807, 779, 747 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.05 (br s, 1H), 7.29 (s, 1H), 7.13-7.14 (m, 2H), 5.38 (dd, J = 4.2, 11.1 Hz, 1H), 3.90 (dd, J = 4.2, 14.7 Hz, 1H), 3.74 (s, 3H), 3.31 (dd, J = 11.1, 14.7 Hz, 1H), 1.60 (s, 9H), 1.25 (s, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.7, 151.6, 148.9, 137.1, 126.9, 126.24, 126.16, 124.9, 123.6, 115.8, 113.9, 83.9, 82.6, 58.5, 52.1, 27.8, 27.4, 26.4. HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{37}\text{ClN}_2\text{O}_8\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 575.2131; found 575.2137.

(-)-cis-N-Boc-Clavicipitic acid methyl ester 10a: To a stirred solution of **9a** (150 mg, 0.31 mmol, 1.0 equiv) and 2,6-lutidine (166 mg, 1.55 mmol, 5.0 equiv) in DCM (1.5 mL) at 0 °C was added TMSOTf (225 μ L, 1.24 mmol, 4.0 equiv) dropwise. The reaction mixture was stirred at 0 °C for 20 min, and sat. aq. NH_4Cl was added followed by extraction with EtOAc three

times. The combined organic phases were washed with sat. NaHCO_3 , brine successively, and dried over Na_2SO_4 . Purification by FCC afforded the **10a** (113 mg, 95%) as colorless oil: $[\alpha]_{\text{D}}^{23}$ -133.8 (c 1.00, CHCl_3) [lit.⁴, $[\alpha]_{\text{D}}^{23}$ -82.5 (c 0.71, CHCl_3)]; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, J = 6.0 Hz, 1H), 7.40 (s, 1H), 7.19 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 6.8 Hz, 1H), 5.40 (d, J = 8.0 Hz, 1H), 5.29 (d, J = 8.0 Hz, 1H), 4.11 (d, J = 9.2 Hz, 1H), 3.78 (s, 3H), 3.37 (d, J = 14.8 Hz, 1H), 3.20 (t, J = 14.8 Hz, 1H), 2.53 (br s, 1H), 1.83 (s, 3H), 1.80 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5, 149.5, 139.4, 136.1, 134.2, 128.4, 125.7, 124.0, 122.2, 120.3, 117.8, 113.3, 83.3, 56.5, 55.5, 52.1, 31.7, 28.1, 25.8, 18.2.

(-)-trans-N-Boc-Clavicipitic acid methyl ester 10b: Obtained in 95% yield followed the same procedure as that of **10a**. colorless oil, $[\alpha]_{\text{D}}^{23}$ -52.7 (c 1.00, CHCl_3) [lit.³, $[\alpha]_{\text{D}}^{23}$ -32.2 (c 0.51, CHCl_3)]; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 5.46 (d, J = 8.8 Hz, 1H), 4.87 (d, J = 8.8 Hz, 1H), 3.81-3.84 (m,

1H), 3.81 (s, 3H), 3.51 (dd, J = 2.0, 15.6 Hz, 1H), 3.02 (ddd, J = 2.0, 11.2, 15.6 Hz, 1H), 2.71 (br s, 1H), 1.87 (s, 3H), 1.82 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 149.6, 138.1, 136.4, 134.7, 128.2, 127.2, 123.9, 122.9, 121.1, 117.7, 113.4, 83.4, 61.2, 60.9, 52.5, 33.5, 28.2, 25.8, 18.3.

(-)-cis-Clavicipitic acid 1a: To a stirred suspension of **10a** (66.4 mg, 0.713 mmol, 1.0 equiv.) and K_2CO_3 (71.5 mg, 0.518 mmol, 3.0 equiv.) in MeOH (1.2 mL) was added water (0.4 mL). The result reaction mixture was stirred at reflux for 2 days. The reaction mixture was subjected to the ion-exchange resin (Amberlite[®] IRC-50) column chromatography after cooling down

and washed with MeOH to give (-)-cis-clavicipitic acid **1a** (44.4 mg, 95%) as white powder: ^1H NMR (300 MHz, MeOD) δ 7.34 (d, J = 8.1 Hz, 1H), 7.22 (s, 1H), 7.10 (t,

⁴ Shinohara, H. ; Fukuda, T. ; Iwao, M. *Tetrahedron* **1999**, 55, 10989-11000.

$J = 8.1$ Hz, 1H), 6.84 (d, $J = 8.1$ Hz, 1H), 5.94 (d, $J = 9.3$ Hz, 1H), 5.49 (d, $J = 9.0$ Hz, 1H), 4.30 (dd, $J = 3.3, 11.7$ Hz, 1H), 3.72 (dd, $J = 3.3, 16.2$ Hz, 1H), 3.45 (dd, $J = 11.7, 16.2$ Hz, 1H), 1.92 (s, 3H), 1.89 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O_2$ ($M + H$)⁺ 271.1441; found 271.1443.

(-)-*trans*-Clavicipitic acid 1b: Obtained in 94% yield followed the same procedure as that of **1a**, white powder, ¹H NMR (300 MHz, MeOD) δ 7.37 (d, $J = 7.8$ Hz, 1H), 7.24 (s, 1H), 7.11 (t, $J = 7.8$ Hz, 1H), 6.85 (d, $J = 7.8$ Hz, 1H), 5.63 (d, $J = 10.2$ Hz, 1H), 5.57 (d, $J = 9.9$ Hz, 1H), 4.14 (dd, $J = 3.0, 11.1$ Hz, 1H), 3.84 (dd, $J = 4.2, 16.5$ Hz, 1H), 3.20 (dd, $J = 11.1, 16.5$ Hz, 1H), 1.99 (s, 3H), 1.95 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O_2$ ($M + H$)⁺ 271.1441; found 271.1443.

^1H -NMR of compound 4

¹H-NMR of compound 3

^{13}C -NMR of compound 3

¹H-NMR of compound 2

^{13}C -NMR of compound 2

¹H-NMR of compound 7

¹³C-NMR of compound 7

¹H-NMR and ¹³C-NMR of compound 8

^{13}C -NMR of compound 8

¹H-NMR of compound 9a (cis)

¹³C-NMR of compound 9a (*cis*)

NOESY spectra of compound 9a (*cis*)

¹H-NMR of compound 9b (*trans*)

¹³C-NMR of compound 9b (*trans*)

NOESY spectra of compound 9b (*trans*)

¹H-NMR of compound 10a (*cis*)

¹³C-NMR of compound 10a (*cis*)

^1H -NMR and ^{13}C -NMR of compound 10b (*trans*)

^{13}C -NMR of compound 10b (*trans*)

¹H-NMR of (-)-*cis*-clavicipitic acid 1a

¹H-NMR of (-)-*trans*-clavicipitic acid 1b