Supporting Information

Facile Synthesis of 1,2,3,4-Tetrahydro- β -carboline by One-Pot Domino Three-Component Indole Formation and Nucleophilic Cyclization

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Experimental Section

General Methods. IR spectra were determined on a JASCO FT/IR-4100 spectrometer. Exact mass (HRMS) spectra were recorded on JMS-HX/HX 110A mass spectrometer. ^1H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in CDCl_3) as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-500 and referenced to the residual CHCl_3 signal. Optical rotations were measured with a JASCO P-1020 polarimeter. Melting points were measured by a hot stage melting points apparatus (uncorrected). Microwave reaction was conducted in a sealed glass vessel (capacity 10 mL) using CEM Discover microwave reactor with a run time of no more than 10 min. The temperature was monitored using IR sensor mounted under the reaction vessel. For column chromatography, Wakosil C-300 was employed. For HPLC separations, a CHIRALCEL OD-H analytical column (DICEL CHEMICAL INDUSTRIES LTD., 4.6×150 mm, flow rate 0.5 mL/min) was employed, and eluting products were detected by UV at 256 nm. A solvent system consisting of 0.1% Et_2NH in *n*-hexane (v/v, solvent A) and 0.1% Et_2NH in *i*-PrOH (v/v, solvent B) was used for HPLC elution with a linear gradient of *i*-PrOH (20-40% over 45 min).

General Procedure for Synthesis of 1,2,3,4-Tetrahydro- β -carboline by Domino Copper-Catalyzed Three-Component Indole Formation and Cyclization with *t*-BuOK: Synthesis of 2-Methyl-1-propyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (6a) and 2-Methyl-1-propyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole (8a) (Table 1, Entry 9). A mixture of *N*-(4-chlorophenyl)sulfonyl-2-ethynylaniline **1f** (53.6 mg, 0.18 mmol), *n*-butyraldehyde **2a** (33.2 μL , 0.37 mmol), 2-(methylamino)ethanol **3a** (16.3 μL , 0.21 mmol), and CuBr (1.3 mg, 0.0092 mmol) in dioxane (1 mL) was stirred at 50 $^\circ\text{C}$ for 1.5 h [for the reaction with **2b** (Table 2, entry 1) and **2c** (Table 2, entry 2), the mixture was stirred at 100 $^\circ\text{C}$ for an additional 0.5 h]. After the three-component indole formation was completed on TLC, hexane (2 mL) was added at room temperature and the mixture was cooled to 0 $^\circ\text{C}$. *t*-BuOK (62.0 mg, 0.55 mmol) was added at 0 $^\circ\text{C}$ and the reaction mixture was stirred for 5 min at 0 $^\circ\text{C}$ and additional 30 min at rt. The reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel with hexane/EtOAc (3 : 1 to 1 : 3) as the eluent to give **6a** (31.8 mg, 75%) and **8a** (10.7 mg, 25%) both as a yellow oil.

Compound 6a: ^1H NMR (500 MHz, CDCl_3) δ 0.94 (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 1.31-1.41 (m, 1H, *CHH*), 1.45-1.56 (m, 1H, *CHH*), 1.69-1.76 (m, 1H, *CHH*), 1.81-1.89

(m, 1H, CHH), 2.47 (s, 3H, NMe), 2.69-2.82 (m, 3H, 3 × CH), 3.14-3.20 (m, 1H, CH), 3.51 (t, $J = 5.4$ Hz, 1H, 1-H), 7.08-7.11 (m, 1H, Ar), 7.12-7.15 (m, 1H, Ar), 7.31 (d, $J = 8.0$ Hz, 1H, Ar), 7.48 (d, $J = 7.4$ Hz, 1H, Ar), 7.72 (br s, 1H, NH); ^{13}C NMR (125 MHz, CDCl_3) δ 14.3, 18.7, 19.0, 35.3, 41.9, 49.6, 59.8, 108.2, 110.6, 118.0, 119.3, 121.3, 127.3, 135.1, 135.8; MS (FAB) m/z (%): 229 (MH^+ , 50), 185 (100); HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2$ (MH^+): 229.1705; found: 229.1713.

Compound 8a: ^1H NMR (500 MHz, CDCl_3) δ 0.94 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.34-1.53 (m, 2H, CH_2CH_3), 1.82-1.89 (m, 1H, CHH), 1.91-1.99 (m, 1H, CHH), 2.43 (s, 3H, NMe), 2.92 (ddd, $J = 12.6, 9.2, 4.6$ Hz, 1H, CHH), 3.26-3.30 (m, 1H, CHH), 3.65 (t, $J = 4.6$ Hz, 1H, 1-H), 4.01-4.10 (m, 2H, CH_2), 6.24 (s, 1H, 9-H), 7.08-7.11 (m, 1H, Ar), 7.13-7.17 (m, 1H, Ar), 7.26 (d, $J = 8.0$ Hz, 1H, Ar), 7.56 (d, $J = 7.4$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.4, 17.8, 34.2, 39.9, 41.0, 50.9, 60.8, 96.8, 108.6, 119.7, 119.9, 120.5, 128.2, 136.0, 138.1; MS (FAB) m/z (%): 229 (MH^+ , 50), 185 (100); HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2$ (MH^+): 229.1705; found: 229.1703.

General Procedure for Synthesis of 1,2,3,4-Tetrahydro- β -carboline by Domino Copper-Catalyzed Three-Component Indole Formation and Cyclization with MsOH: Synthesis of 2-Methyl-2,3-dihydro-1*H*-pyrido[3,4-*b*]indol-4(9*H*)-one (7a) (Table 3, Entry 1). A mixture of *N*-methyl-2-ethynylaniline **1g** (25.0 mg, 0.19 mmol), paraformaldehyde **2d** (11.4 mg, 0.38 mmol), *N*-methylglycine ethyl ester **3b** (26.8 mg, 0.23 mmol), and CuI (1.8 mg, 0.0095 mmol) in dioxane (0.5 mL) was stirred at 170 °C for 1 h under the microwave irradiation (300 W). After the three-component indole formation was completed monitored by TLC, MsOH (1 mL) was added at room temperature and the mixture was stirred at 80 °C for 30 min. The reaction mixture was diluted with H_2O followed by neutralization with saturated aqueous NaHCO_3 . The aqueous solution was extracted with EtOAc (twice). The organic layer was washed with brine and dried over MgSO_4 . The filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography over silica gel with $\text{CHCl}_3/\text{CH}_3\text{OH}$ (50 : 1) as the eluent to give **7a** (32.6 mg, 72%) as a pale yellow solid, which was recrystallized by CHCl_3 -hexane: colorless crystals; mp 183 °C; IR (neat) 1639 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (500 MHz, CDCl_3) δ 2.55 (s, 3H, 2-NMe), 3.26 (s, 2H, 3- CH_2), 3.63 (s, 3H, 9-NMe), 3.76 (s, 2H, 1- CH_2), 7.27-7.29 (m, 3H, Ar), 8.18-8.20 (m, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 30.0, 45.1, 50.4, 63.3, 109.3, 110.7, 121.5, 122.7, 123.2, 124.1, 137.6, 149.8, 189.9; MS (FAB) m/z (%): 215 (MH^+ , 100); HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}$ (MH^+): 215.1184; found: 215.1180.

single pulse decoupled gated NMR

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single pulse decoupled gated NMR

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single pulse decoupled gated NMR

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single pulse decoupled gated NMR

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hexane - iPrOH in 0.1% Et₃NH
20% → 40% / 45 min

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** CALCULATION REPORT **

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Analysis FILE : 9:@FIL11.FIL

Dt M18 20% → 40% / 45min in 10-1% 1

2-RSA CHROMATOPAC CH=1 Report No.=53 DATA=1:CHRM1.C00 09/03/30 13:25:50

** CALCULATION REPORT **

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	23	34.101	340148	5024			2.3271	
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TOTAL			14617025	214371			100	

95% ee

Analysis FILE : 9:0FIL11.FIL