Supporting Information for:

An Efficient Total synthesis of (±)-Stemonamine

Yu-Ming,Zhao, Peiming,Gu, Yong-qiang,Tu,* Chun-An Fan, and Qingwei,Zhang

State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou

University, Lanzhou 730000, P R China

E-mail: tuyq@lzu.edu.cn

Supporting Information

Experimental details for new compounds

X-Ray Ellipsoid Plots of **1a** hydrochloride dihydrate

Copies of ¹H and ¹³C spectra of new compounds

Experimental Details

General information

For product purification by flash column chromatography, silica gel (200~300 mesh) and light petroleum ether (bp. 60~90 °C) are used. All solvents were purified and dried by standard techniques, and distilled prior to use. All organic extracts were dried over MgSO₄, unless otherwise noted. IR spectra were recorded on a *Nicolet* FT-170SX spectrometer. ¹H and ¹³C NMR spectra were taken on a *Bruker*, AM-300 or AM-400 spectrometer with TMS as an internal standard and CDCl₃ as solvent. The MS data were obtained with EI (70 eV). HRMS data were determined on a *Bruker Daltonics* APEXII 47e FT-ICR spectrometer. 2-(3-azidopropyl)cyclohex-2-enone **2**¹ are known compounds.

2-(3-azidopropyl)-1-(2-methylenebutyl)cyclohex-2-enol (3). To a suspension of magnesium turnings (4.6 g, 19.1 mmol) and 1,2-dibromoethane (0.1 ml) in dry THF (3 ml) under argon was added ethylallyl chloride (1.0 g, 9.57 mmol) in 7 ml THF over 30 min at -5 °C. This mixture was allowed to stir for 2 h at 0 °C and then at room temperature for 1 h.

The above ethylallylmagnesium chloride solution (3.4 ml) was added to the known compound **2** (185 mg, 1.03 mmol) in dry THF (3 ml) under argon over 10 min at 0 °C. The mixture was allowed to warm to room temperature over 15 min and then was stirred for an additional 1 h. The reaction mixture was diluted with water, and then extracted with ether. The organic phase was washed with NH₄Cl, water, brine, and then dried over MgSO₄ and concentrated. Chromatography afforded the desired allyl alcohol **3** (131 mg, 51% yield; 76% yield based on recovery material); ¹H NMR (300 MHz, CDCl₃) δ 1.01~1.03 (m, 3H), 1.52~1.85 (complex, 5H), 2.21~2.32 (m, 2H), 2.41 (s, 1H), 2.46 (s, 1H), 3.31 (t, 3H, *J* = 7.0Hz), 4.79 (d, 1H, *J* = 1.2Hz), 4.90 (t, 1H, *J* = 1.5Hz), 5.48~5.51 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 12.5, 19.3, 25.5, 27.5, 28.2, 30.6, 36.0, 44.8, 51.4, 72.2, 112.1, 124.6, 140.9, 148.1; MS (EI) *m/z* 249, 221, 152, 149, 123, 97, 95, 81, 69, 55.

1-(3-azidopropyl)-2-(2-methylenebutyl)-7-oxa-bicyclo[4.1.0]heptan-2-ol (4). The allyl alcohol **3** (218 mg, 0.88 mmol) was diluted with benzene (5 mL), Vanadyl(IV) acetylacetonate (12 mg, 0.044 mmol) was added, following *tert*-butyl hydroperoxide (*t*-BuOOH, 0.2 mL, 5.5 M in hexane, 1.1 mmol), after 15 min, the reaction mixture was diluted with water, then extracted with ether. The organic phase was washed with saturated NaHSO₃ solution, water, brine, and then dried over MgSO₄ and concentrated. The residue was chromatographed to give the α -hydroxy epoxide **4** (191 mg, 82% yield); ¹H NMR (400 MHz, CDCl₃) δ 1.02~1.06 (t, 3H), 1.20~1.78 (complex, 8H), 1.80~1.96 (complex, 3H), 2.00~2.35 (m, 4H), 2.40~2.60 (m, 1H), 3.19~3.20 (m, 1H), 3.20~3.30 (m, 2H), 4.75~4.89 (dd, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ 12.4, 17.7, 23.1, 23.7, 27.0, 29.9, 32.3, 41.9, 51.7, 61.2, 64.7, 73.8, 112.1, 147.9; MS (EI) *m/z* 265, 219, 168, 149, 111, 97, 83, 55.

1-(3-azidopropyl)-2-(2-methylenebutyl)-7-oxa-bicyclo[4.1.0]heptan-2-yloxy)trimethylsilane (5). The α -hydroxy epoxide **4** (336 mg, 1.28 mmol) was treated with TMSCl (0.50 mL, 3.84 mmol) and imidazole (416 mg, 6.4 mmol) in 10 mL of DMF at room temperature under argon. After 4 h, the mixture was diluted with ether, and washed with water twice, and dried over MgSO₄, concentrated, and chromatographed to give the desired Siloxy-Epoxy-Azide **5** (344 mg, 81% yield); ¹H NMR (300 MHz, CDCl₃) δ 0 (s, 9H), 1.01~1.06 (t, 3H), 1.30~1.90 (complex, 10H), 2.00~2.50 (complex, 4H), 3.00~3.15 (m, 1H), 3.20~3.40 (m, 2H), 4.70~4.90 (dd, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ 2.5, 12.5, 19.0, 21.9, 23.1, 25.5, 29.6, 29.8, 42.3, 51.8, 58.7, 64.3, 78.8, 112.1, 148.3; MS (EI) *m/z* 337, 279, 271, 240, 167, 73.

Hexahydro-9-hydroxy-9a-(2-methylenebutyl)-1H-pyrrolo[1,2-a]azepin-5(6H)-one (6). To a cool (-78 °C) solution of the Siloxy-Epoxy-Azide **5** (124 mg, 0.36 mmol) in CH₂Cl₂ (5 mL) under argon was added TiCl₄ (0.72 mL, 1M in CH₂Cl₂). The result mixture was stirred -78 °C for 15 minutes. Then the mixture was warmed slowly to 0 °C over 2 h, and stirred additional 1 h at 0 °C, then it was quenched with 1 mL water. The mixture was partitioned between water and CH₂Cl₂. The organic layer was collected, dried over MgSO₄, filtered, and concentrated to give a solid.

Chromatography afforded **6** (59 mg, 68% yield) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 1.00~1.10 (t, 3H), 1.58~2.22 (complex, 11H), 2.34~2.44 (m, 1H), 2.56~2.86 (complex, 3H), 3.46~3.66 (m, 2H), 3.74~3.84 (m, 1H), 4.80~5.00 (dd, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 12.6, 16.9, 21.5, 29.8, 30.6, 36.1, 37.4, 42.1, 50.3, 68.1, 72.8, 113.7, 147.2, 173.4; MS (EI) m/z 237, 208, 168, 138, 122, 55, 41; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{24}\text{NO}$ (M^++H): 238.1802, found 238.1802, Error: 0 ppm.

Tetrahydro-9a-(2-methylenebutyl)-1H-pyrrolo[1,2-a]azepine-5,9-dione (7). PCC (713 mg, 3.3 mmol), silica (1.4 g), and NaOAc (271 mg, 3.3 mmol) were well mixed, then added into the solution of **6** (261 mg, 1.1 mmol) in CH_2Cl_2 (10 ml). After 18 h, the mixture was subjected to a column of Al_2O_3 , washed with CHCl_3 , the organic solvent was evaporated and chromatographed to give the ketone **7** (220 mg, 85% yield) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 0.89~1.00 (m, 3H), 1.82~2.10 (m, 7H), 1.82~2.15 (m, 1H), 2.23~2.25 (m, 2H), 2.38~2.58 (m, 2H), 2.70~2.80 (m, 2H), 3.48~3.62 (m, 1H), 3.62~3.78 (m, 1H), 4.85 (d, $J = 1.6\text{Hz}$, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 12.4, 21.0, 22.9, 29.7, 33.0, 35.1, 37.9, 39.8, 47.4, 74.6, 114.6, 146.5, 171.2, 211.2; IR (neat) 1649, 1714 cm^{-1} ; MS (EI) m/z 235, 178, 166, 150, 138, 123; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2\text{N}$ (M^++H): 236.1645, Found 236.1648, Error: 1.3 ppm.

Compound (8). Alkene **7** (1.0 g, 4.25 mmol) was dissolved in CH_2Cl_2 (15 ml) at room temperature. The reaction mixture was cooled to -78°C , after a brief oxygen purge (ca. 5 min), ozone was bubbled through the reaction mixture until the solution turned blue (approximately 2 h). The reaction solution was then purged with nitrogen for about 20 min to remove excess ozone. After dimethylsulfide addition, the reaction was stirred at room temperature for 10 h. Concentration of the reaction mixture to give a solid. Chromatography afforded **8** (970 mg, 96% yield) as a colorless solid; ^1H NMR (400 MHz, CDCl_3) δ 0.94~0.98 (m, 3H), 1.80~2.18 (complex, 5H), 2.20~2.45 (m, 5H), 2.45~2.70 (m, 2H), 2.70~2.86 (m, 2H), 3.42~3.57 (m, 1H), 3.57~3.70 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 7.4, 21.0, 22.7, 33.1, 34.6, 35.2, 38.2, 43.7, 46.9, 73.9, 170.2, 207.7, 210.4; IR (neat) 1647, 1713 cm^{-1} ; MS (EI) m/z 237, 152, 140, 138, 124, 110, 96, 84; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3\text{N}$ (M^++H): 238.1438, Found 238.1437, Error: 0.4 ppm.

Compound (9). To a solution of **8** (500 mg, 2.1 mmol) in 10 ml of *tert*-BuOH was added KO^tBu (270 mg, 2.4 mmol) at 40 °C under argon. After 30 min, the reaction mixture was evaporated, and the residue was taken in 100 mL of CHCl₃. The mixture was washed with water and brine, dried over MgSO₄, and evaporated under reduced pressure. The residue was purified by column chromatography to give cyclic enone **9** (370 mg, 80% yield) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.47~1.50 (m, 1H), 1.68 (s, 3H), 1.77~2.29 (complex, 7H), 2.46-2.56 (m, 2H), 2.71-2.77 (m, 1H), 3.46~3.58 (m, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ 7.7, 21.2, 22.0, 23.4, 32.5, 40.3, 46.6, 49.4, 69.3, 136.0, 170.6, 170.8, 203.0; IR (neat) 1629, 1700 cm⁻¹; MS (EI) *m/z* 219, 204, 191, 176, 163, 148, 135, 55, 41; HRMS (ESI) Calcd for C₁₃H₁₈O₂N (M⁺+H): 220.1332, Found 220.1332, Error: 0 ppm.

Compound (10). To a solution of 200 mg (0.91 mmol) of ketone **9** in THF (5 ml) at -78 °C under argon was added LHMDs (1.0 M, 1.06 mL, 1.1 mmol). After stirring at -78 °C for 30 min, CNCO₂Me (88 ul, 1.1 mmol) was added and followed HMPA (0.11 ml, 1.1 mmol). The resulting mixture was stirred for 30 min and then quenched with water. After warming up to room temperature, the mixture was partitioned between water and CH₂Cl₂. The organic layer was collected, dried over MgSO₄, filtered and concentrated. Chromatography afforded **10** (241 mg, 95% yield) as a white crystalline solid; ¹H NMR (400 MHz, CDCl₃) δ 1.12~1.51 (m, 1H), 1.71 (s, 3H), 2.50~2.65 (m, 1H), 2.70~2.80 (m, 1H), 3.29 (s, 1H), 3.21~3.35 (m, 1H), 3.52 (s, 3H), 3.55~3.65 (m, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 7.9, 20.7, 22.2, 22.8, 31.9, 41.2, 46.9, 52.2, 62.8, 72.1, 137.3, 168.0, 169.8, 171.9, 198.7; IR (neat) 1644, 1706, 1739, 2954 cm⁻¹; MS (EI) *m/z* 277, 249, 221, 204, 190, 176, 162, 148, 91, 84, 77, 55, 49; HRMS (ESI) calcd for C₁₅H₂₀NO₄ (M⁺+H): 278.1387, found 278.1388, Error: 0.4 ppm.

Compound (11a) and Compound (11b). CeCl₃•7H₂O (24 mg, 0.0655 mmol) was added to a solution of **10** (364 mg, 1.31 mmol) in *i*PrOH (7 ml). The flask was then evacuated to 300 mbar, flushed with O₂, and the reaction mixture was stirred at 25 °C for 20 h, while a slow stream of oxygen (ca., 50 cm³h⁻¹) was passed through. After removal of the solvent, the residue was purified

by column chromatography to give **11a** and **11b** (354 mg, 92% yield, ca. 1:1.05 diastereoselectivity) as a white solid.

Lactam 11a: ^1H NMR (400 MHz, CDCl_3) δ 1.70~2.42 (complex, 10H), 1.86 (s, 3H), 2.65~2.80 (m, 1H), 2.80~2.90 (m, 1H), 3.25~3.40 (m, 1H), 3.70 (s, 3H), 3.75~3.85 (m, 1H), 4.01 (bs, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 8.5, 20.6, 22.7, 23.0, 32.3, 35.9, 46.9, 53.2, 76.3, 84.5, 136.9, 169.1, 170.6, 172.3, 199.7; MS (EI) m/z 293, 275, 234, 205, 177, 149; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_5$ ($\text{M}^+\text{+H}$): 294.1336, found 294.1338, Error:0.7ppm.

Lactam 11b: ^1H NMR (300 MHz, CDCl_3) δ 1.35~1.58 (m, 1H), 1.78 (s, 3H), 1.79~2.00 (complex, 3H), 2.00~2.40 (complex, 4H), 2.70~2.96 (m, 2H), 3.40~3.55 (m, 1H), 3.62~3.80 (m, 1H), 3.85 (s, 3H), 5.06 (bs, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 8.1, 20.0, 22.4, 23.5, 32.0, 36.2, 46.7, 53.2, 76.0, 81.2, 134.2, 171.4, 174.0, 198.6; MS (EI) m/z 293, 275, 234, 205, 177, 149; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_5$ ($\text{M}^+\text{+H}$): 294.1336, found 294.1338, Error:0.7ppm.

Compound (12a). A solution of **11a** (385 mg, 1.31 mmol) in anhydrous CH_2Cl_2 (10ml) under argon was treated with Et_3N (0.55 ml, 3.94 mmol), DMAP (80 mg, 0.66 mmol), and propionic anhydride (0.42 ml, 3.3 mmol) at room temperature. The reaction mixture was stirred for 24 h and then quenched with water (5 ml). The aqueous layer was extracted with CH_2Cl_2 (2×100 ml). The combined extracts were washed with brine, dried over MgSO_4 , filtered and concentrated. Chromatography afforded **12a** (436 mg, 95% yield) as a clean oil; ^1H NMR (400 MHz, CDCl_3) δ 0.98~1.02 (m, 3H), 1.69 (s, 3H), 1.76~2.18 (complex, 8H), 2.26~2.41 (m, 3H), 2.63~2.69 (m, 1H), 3.26~3.32 (m, 1H), 3.48 (s, 3H), 3.60~3.68 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 7.9, 8.4, 19.9, 21.8, 22.9, 17.0, 31.5, 36.5, 46.6, 52.2, 74.3, 87.7, 136.3, 164.9, 166.8, 171.2, 171.5, 194.3; IR (neat) 1645, 1717, 1752 cm^{-1} ; MS (EI) m/z 293, 275, 234, 205, 177, 149; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_3$ ($\text{M}^+\text{+H}$): 350.1598, found 350.1594, Error: 1.1 ppm.

Compound (12b). Using a procedure similar to that for the preparation of **12a**, A solution of **11b** (115 mg, 0.39 mmol) in anhydrous CH_2Cl_2 (8 ml) under argon was treated with Et_3N (0.19 ml, 1.365 mmol), DMAP (24 mg, 0.18 mmol), and propionic anhydride (0.16 ml, 1.17 mmol) at room temperature. The reaction mixture was stirred for 16 h and then quenched with water (3 ml). The aqueous layer was extracted with CH_2Cl_2 (2×50 ml). The combined extracts were washed with brine, dried over MgSO_4 , filtered and concentrated. Chromatography afforded **12b** (127 mg, 93% yield) as a clean oil; ^1H NMR (400 MHz, CDCl_3) δ 0.93~0.97 (m, 3H), 1.55~1.59 (m, 1H), 1.70 (s, 3H), 1.80~2.11 (complex, 5H), 2.12~2.25 (m, 4H), 2.64~2.76 (m, 2H), 3.37 (dd, J = 10.4, 12 Hz, 1H), 3.67 (s, 1H), 3.67~3.73 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 8.12, 8.3, 19.5, 21.8, 22.8, 26.9, 32.1, 36.1, 46.8, 52.3, 74.6, 82.6, 134.3, 166.5, 168.2, 171.2, 172.6, 193.1; IR (neat) 1646, 1718, 1745, 1765 cm^{-1} ; MS (EI) m/z 293, 275, 234, 205, 177, 149; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_3$ ($\text{M}^+\text{+H}$): 350.1598, found 350.1594, Error: 1.1 ppm.

13a

Compound 13a. To a solution of **12a** (251 mg, 0.72 mmol) in freshly distilled benzene (10 ml) at 25 °C under argon was added 18-crown-6 (571 mg, 2.16 mmol) and potassium *tert*-butoxide (202 mg, 1.80 mmol). The reaction mixture was stirred for 3 h at room temperature, and then treated with 2N HCl to PH = 2. The mixture was partitioned between water and CHCl₃. The aqueous layer was extracted with CHCl₃ (2×50ml). The combined extracts were dried over MgSO₄, filtered, concentrated. Flash column Chromatography afforded crude product.

The above crude product was treated with Et₃N (89 ul, 0.64 mmol) and Me₂SO₄ (0.1 ml, 1.12 mmol) in CH₂Cl₂ (5 ml) for 24 h. the reaction mixture were concentrated under reduce pressure. Chromatography afforded **13a** (105 mg, 44% yield) as a white solid; ¹H NMR (300 MHz, CDCl₃) δ 1.88 (s, 3H), 1.88~1.97 (m, 4H), 2.01 (s, 3H), 2.07~2.17 (m, 1H), 2.21~2.22 (m, 1H), 2.32~2.36 (m, 1H), 2.39~2.48 (m, 1H), 2.80~2.86 (m, 1H), 2.88~2.95 (m, 1H), 3.26~3.31 (m, 1H), 3.84~3.91 (m, 1H), 3.99 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 8.6, 8.8, 20.3, 22.2, 22.8, 32.8, 37.5, 47.2, 59.1, 74.5, 88.4, 98.4, 137.3, 169.6, 169.7, 172.6, 173.5, 195.9; IR (neat) 1643, 1665, 1719, 1765 cm⁻¹; MS (EI) *m/z* 331, 276, 149, 148, 84, 83, 57; HRMS (ESI) calcd for C₁₈H₂₂NO₅ (M⁺+H): 332.1492, found 332.1491, Error: 0.3 ppm.

14a

Compound 14a. To a solution of **13a** (18 mg, 0.0544 mmol) in CH₂Cl₂ (2.5 ml) was added 33 mg (0.082 mmol) of Lawesson's reagent at room temperature. After 2 h, the reaction mixture was concentrated under reduced pressure and chromatographed to give **14a** (18.4 mg, 98% yield) as a white solid; ¹H NMR (300 MHz, CDCl₃) δ 1.87 (s, 3H), 2.07 (s, 3H), 1.90~2.15 (m, 1H), 2.15~2.35 (m, 3H), 2.44~2.55 (m, 1H), 2.91~2.98 (m, 1H), 3.08~3.18 (b, 1H), 3.25~3.40 (m, 1H), 3.52~3.65 (m, 1H), 3.99 (s, 3H), 4.26~4.41 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 8.6, 8.9, 20.1, 22.7, 24.0, 37.4, 42.4, 55.6, 59.5, 79.5, 87.6, 98.6, 137.2, 169.0, 169.2, 173.2, 195.0, 204.2; IR (neat) 1732, 1713, 1632 cm⁻¹; MS (EI) *m/z* 347, 314, 288, 149, 99, 83, 44; HRMS (ESI) calcd for C₁₈H₂₂NO₄S (M⁺+H): 348.1264, found 348.1269, Error 0.4ppm.

Stemonamine (1a). A solution of **14a** (16.9 mg, 0.0487 mmol) in THF (3 mL) was treated with W2-Raney Ni at room temperature. The reaction mixture was stirred for 30 min and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed to give **1a** (14.7 mg, 95% yield) as a white solid; ^1H NMR (300 MHz, CDCl_3) δ 1.10~1.30 (m, 1H), 1.30~1.50 (m, 1H), 1.77 (s, 3H), 2.01 (s, 3H), 1.60-2.20 (complex, 8H); ^{13}C NMR (75 MHz, CDCl_3) δ 8.2, 9.1, 24.5, 24.7, 26.7, 26.9, 28.2, 29.7, 35.5, 38.9, 48.9, 51.4, 58.6, 91.7, 97.5, 102.3, 135.1, 171.8, 174.8, 198.7; IR (its hydrochloride dihydrate) 1670, 1736, 1773 cm^{-1} ; MS (EI) m/z 317, 190, 129, 71, 57; HRMS calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_4$ ($\text{M}^+ + \text{H}$): 317.1622, found 317.1617, Error: 1.6ppm..

References:

- (1) Milligan, G. L.; Mossman C. J.; Aubé, J. J. *Am. Chem. Soc.* **1995**, *117*, 10449-10459.

The structure of our synthetic Stemonamine (**1a**) was corroborated by single-crystal of its hydrochloride dihydrate.

Datablock y2473 - ellipsoid plot