An Expeditious Total Syntheses of (±)-Stenine

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Supporting Information

Experimental details for new compounds

Copies of ^1H and ^{13}C spectra of new compounds

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Experimental Details

General Information. α -Keto phosphonate **3**,¹ 3-azidopropionaldehyde **4**,² and compounds **11** and **12a,b**³ are known compounds. *Caution! Low molecular weight alkyl azides are potential explosion hazards and should be used with appropriate caution.*

(E)-8-Azido-5-octen-4-one (5). To a solution of NaH (60%, 1.2 g, 30 mmol) in THF (60 mL) under Ar at -78 °C was added slowly α -keto phosphonate **3**¹ (5.90 g, 30 mmol) in THF (10 mL). The resulting solution was allowed to slowly warm up to -25 °C over 2 h to give a white gel-like suspension. This suspension was cooled in an ice bath followed by dropwise addition of 3-azidopropionaldehyde **4**² (3.0 g, 30 mmol) in THF (10 mL). The mixture was stirred in an ice bath for 1 h and then quenched with water (50 mL). The reaction mixture was partitioned between water and Et₂O. The organic layer was dried (Na₂SO₄), filtered, and concentrated to give an oil. Chromatography (2-10% EtOAc/hexane) afforded 4.6 g (92%) of **5** as an oil. R_f = 0.48 (15% EtOAc/hexane); ¹H NMR (400 MHz, CDCl₃) δ 0.93 (t, J = 7.8 Hz, 2H), 1.63 (h, J = 7.8 Hz, 2H), 2.50 (m, 4H), 3.43 (t, J = 7.7 Hz, 2H), 6.18 (d, J = 16.8 Hz, 1H), 6.75 (m, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 13.7, 17.7, 32.0, 42.3, 49.8, 132.5, 141.8, 200.2; IR (neat) 2100, 1697, 1674 cm⁻¹; MS (ES+) m/z 168 (M^+ +1); HRMS calcd for C₈H₁₄N₃O (M^+ +H): 168.1137, found 168.1116.

[(3Z,5E)-8-Azido-3,5-dien-4-yloxy]trimethylsilane (6). To a solution of enone **5** (1.67 g, 10 mmol) in anhydrous ethyl ether (35 mL) under Ar was added Et₃N

(2.1 g, 20 mmol) at 0 °C followed by the addition of TMSOTf (3.3 g, 15 mmol). The resulting mixture was stirred at 0 °C for 30 min. The organic layer was washed with brine, dried (Na₂SO₄), and evaporated under reduced pressure to give 2.27 g (95%) of **6** as an oil. This diene was used directly for the next step. *R_f* = 0.75 (5:95 EtOAc/hexane); ¹H NMR (400 MHz, CDCl₃) δ 0.23 (s, 9H), 0.99 (t, *J* = 7.0 Hz, 3H), 2.11 (m, 2H), 2.42 (m, 2H), 3.33 (t, *J* = 7.2 Hz, 2H), 4.75 (t, *J* = 7.6 Hz, 1H), 5.68 (m, 1H), 5.98 (d, *J* = 15.3 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 0.6, 14.1, 19.4, 31.7, 51.0, 117.1, 123.5, 131.7, 147.3; IR (neat) 2100 cm⁻¹; MS (ES+) *m/z* 240 (*M*⁺+1); HRMS calcd for C₁₁H₂₂N₃OSi (*M*⁺+H): 240.1532, found 240.1519.

General procedure for the intermolecular Diels–Alder/intramolecular Schmidt reaction involving diene 6. To a cooled (-78 °C) solution of enone (5.0–10 mmol) in CH₂Cl₂ (20–40 mL) under Ar was added a Lewis acid such as SnCl₄ (1 equiv) followed by the addition of diene (1.8 equiv). The resulting mixture was stirred at -78 °C and allowed to warm to -55 °C over 2 h. After slow addition of another portion of the same Lewis acid (1.5 equiv), the mixture was stirred at room temperature for 12 h and quenched with aqueous NH₄Cl. The mixture was partitioned between water and CH₂Cl₂. The organic layer was collected, dried (Na₂SO₄), filtered, and concentrated to give an oil. Chromatography (10–50% EtOAc/hexane followed by 1–2% MeOH/ CH₂Cl₂) afforded the reaction products.

(±)-(5*S*, **7aR**, 10*R*, 10*aR*)-10-ethyloctahydroazipino[3,2,1-*h,i*]indol-4,9(1*H*, 5*H*)dione (**7a**) and (±)-(5*S*, **7aS**, 10*S*, 10*aR*)-10-ethyl-octahydroazipino[3,2,1-*h,i*]indol-4,9(1*H*, 5*H*)dione (**7b**). 2-Cyclohexenone (95%, 500 mg, 5.0 mmol) was reacted with **6** using SnCl₄ as Lewis acid to afford 820 mg (70%) of **7a** and **7b**, an oil, as a ca. 3: 1 (**7a** : **7b**) mixture of diastereomers based on HPLCMS analysis. Repeat chromatography afforded **7a** (600 mg, 52%) and **7b** (200 mg, 17%) as brown syrups (**7b** as isolated contained a few percent of **7a** as a contaminant). Lactam **7a**: *R_f* = 0.38 (1:10

MeOH/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.92 (t, $J = 7.8$ Hz, 3H), 1.45 (m, 2H), 1.62-2.70 (complex, 13H), 3.40 (dd, $J = 8.9, 12.2$ Hz, 1H), 3.53 (dt, $J = 6.7, 11.2$ Hz, 1H), 3.73 (dd, $J = 8.9, 12.3$ Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 12.9, 21.0, 22.5, 24.9, 28.3, 32.9, 38.4, 38.7, 43.4, 46.9, 53.5, 62.2, 171.0, 212.0. IR (neat) 1707, 1612 cm^{-1} ; MS (CI) m/z 236 ($\text{M}^+ + 1$); HRMS calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_2$ ($\text{M}^+ + \text{H}$): 236.1651, found 236.1634.

Lactam **7b**: $R_f = 0.32$ (1:10 MeOH/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.94 (t, $J = 7.2$ Hz, 3H), 1.03 (m, 1H), 1.26 (septet, $J = 7.2$ Hz, 1H), 1.52-2.54 (complex, 10H), 2.88 (sextet, $J = 6.1$ Hz, 1H), 3.40 (dt, $J = 6.6, 11.9$ Hz, 1H), 3.88 (dd, $J = 9.6, 12.5$ Hz, 1H), 4.40 (dd, $J = 5.8, 9.3$ Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 12.4, 19.3, 21.6, 21.9, 27.3, 33.3, 37.1, 37.7, 39.4, 44.8, 52.1, 59.9, 171.9, 211.2. IR (neat) 1713, 1624 cm^{-1} ; MS (CI) m/z 236 ($\text{M}^+ + 1$); HRMS calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_2$ ($\text{M}^+ + \text{H}$): 236.1651, found 236.1644.

Compound **7b** was obtained as the only product in 35% yield (415 mg) when $\text{BF}_3 \cdot \text{OEt}_2$ as Lewis acid; the physical and spectra data were identical as above.

($\pm$)-Ethyl 2-(5 *R* , 7 a *R* , 8 *R* , 1 0 *R* , 1 0 a *R*)-10-ethyl-4,9-dioxo-dodecahydroazipino[3,2,1-*h,i*]indol-8-yl)acetate (**8**). Ketone **7a** (500 mg, 2.12 mmol) in THF (10 mL) was added to a solution of LiHMDS (1 M, 3.8 mL, 3.8 mmol) in THF (30 mL) at -78°C under Ar. After stirring at -78°C for 1 h, ethyl 2-bromoacetate (1.78 g, 10.6 mmol) was added followed by HMPA (1.14 g, 6.4 mmol). The resulting mixture was stirred for 3.5 h and then quenched with aq 2 N HCl. After warming up to room temperature, the mixture was partitioned between water and CH_2Cl_2 . The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated to give an oil. Chromatography (10-50% EtOAc/hexane followed by 1-2% MeOH/EtOAc and finally 1-2% MeOH/ CH_2Cl_2) afforded **8** (500 mg, 73%) as a yellow syrup. $R_f = 0.42$ (1:10 MeOH/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.92 (t, $J = 7.3$ Hz, 3H), 1.26 (t, $J = 6.8$ Hz, 3H), 1.45 (m, 2H), 1.60-2.09 (complex, 7H), 2.30-2.47 (m, 4H), 2.57 (dd, $J = 5.0$,

16.4 Hz, 1H), 2.57 (dd, $J = 5.0, 16.4$ Hz, 1H), 2.73 (dd, $J = 5.0, 16.4$ Hz, 1H), 3.51 (m, 2H), 3.71 (dd, $J = 9.2, 12.8$ Hz, 1H), 4.13 (q, $J = 6.8$ Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 12.4, 14.2, 21.8, 22.4, 25.2, 26.8, 32.9, 34.7, 38.0, 42.6, 46.6, 49.2, 53.2, 60.9, 62.1, 171.0, 171.3, 213.0. IR (neat) 1732, 1713, 1632 cm^{-1} ; MS (ES+) m/z 322 ($\text{M}^+ + 1$); HRMS calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_4$ ($\text{M}^+ + \text{H}$): 322.2018, found 322.2015.

(±)-14-Desmethyl-4-oxostenine (9). To a solution of keto ester (**8**) (400 mg, 1.25 mmol) in MeOH (30 mL) at 0°C was added NaBH_4 (118 mg, 3.8 mmol). The resulting mixture was stirred under for 1.5 h and then quenched with aq 2 N HCl. After concentration to ca 20 mL, the mixture was partitioned between water and CH_2Cl_2 . The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated to give a light yellow syrup. Chromatography (50% EtOAc/hexane followed by 2-5% MeOH/EtOAc and then 2-5% MeOH/ CH_2Cl_2) afforded **9** (220 mg, 64%) as off-white crystalline solid. Mp 143-144 °C; $R_f = 0.28$ (1:10 MeOH/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.96 (t, $J = 7.4$ Hz, 3H), 1.37-1.75 (complex, 7H), 1.80-2.10 (complex, 4H), 2.26-2.59 (m, 4H), 2.78 (dd, $J = 10.0, 17.8$ Hz, 1H), 3.43 (m, 1H), 3.70 (dd, $J = 9.0, 12.2$ Hz, 1H), 4.56 (dd, $J = 9.3, 11.7$ Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 10.2, 22.5, 23.0, 23.5, 27.8, 33.0, 33.1, 35.5, 37.4, 42.5, 44.2, 46.7, 60.6, 81.6, 171.1, 176.0. IR (neat) 1772, 1628 cm^{-1} ; MS (ES+) m/z 278 ($\text{M}^+ + 1$); HRMS calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_3$ ($\text{M}^+ + \text{H}$): 278.1756, found 278.1734. Crystals for X-ray crystallographic analyses were obtained by recrystallization from EtOAc/hexane.

10

(±)-4-Oxostenine (10). To a solution of 56 mg (0.2 mmol) of lactone **9** in 10 mL of THF at -78°C under Ar was added LiHMDS (1 M, 0.3 mL, 0.3 mmol). After stirring at -78°C for 1 h, MeI (142 mg, 1 mmol) was added. The resulting mixture was stirred for 2 h and then quenched with aq 2 N HCl. After warming up to room temperature, the mixture was partitioned between water and CH_2Cl_2 . The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated to give a yellow syrup. Chromatography (10-50% EtOAc/hexane followed by, 1-2% MeOH/EtOAc) afforded **10** (46 mg, 79%) as light yellow crystalline solid. An analytical sample was furnished by reverse-phase preparative HPLC (50% acetonitrile/50%water/0.1% TFA). Mp $164\text{--}165^{\circ}\text{C}$; $R_f = 0.34$ (1:10 MeOH/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.98 (t, $J = 7.5$ Hz, 3H), 1.35 (d, $J = 7.1$ Hz, 3H), 1.40-1.75 (complex, 7H), 1.84-2.04 (complex, 4H), 2.14-2.21 (m, 2H), 2.31 (dd, $J = 4.6, 12.8$ Hz, 1H), 2.43 (m, 2H), 3.48 (m, 1H), 3.73 (dd, $J = 9.2, 12.0$ Hz, 1H), 4.46 (dd, $J = 9.3, 12.2$ Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 10.2, 15.4, 22.5, 22.8, 23.4, 27.8, 33.0, 35.8, 39.8, 42.3, 44.3, 45.7, 46.9, 60.5, 79.2, 171.1, 178.7. IR (neat) 1763, 1634 cm^{-1} ; MS (ES+) m/z 292 ($\text{M}^+ + 1$); HRMS calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_3$ ($\text{M}^+ + \text{H}$): 292.1913, found 292.1906. ^1H and ^{13}C NMR spectra matched data reported by Wipf et al for (±)-**10**.⁴

A

(±)-4-Thiostenine (A). To a solution of 24 mg (0.082 mmol) of **10** in 5 mL of CH_2Cl_2 was added at room temperature 49 mg (0.123 mmol) of Lawesson's reagent. After 3 h, the reaction mixture was concentrated under reduced pressure and chromatographed on SiO_2 (EtOAc/hexane, 1: 3 to 1: 1) to give 24 mg (93%) of (±)-4-

thiostenine (**A**) as a colorless solid. Mp 180-181 °C; R_f = 0.49 (1:1 EtOAc/hexane); ^1H NMR (400 MHz, CDCl_3) δ 0.97 (t, J = 7.4 Hz, 3H), 1.37 (d, J = 7.1 Hz, 3H), 1.49-1.75 (complex, 7H), 2.00 (m, 2H), 2.20 (m, 3H), 2.46 (m, 2H), 2.87 (dt, J = 5.6, 13.0 Hz, 1H), 3.02 (dd, J = 3.9, 12.8 Hz, 1H), 3.73 (m, 2H), 4.14 (dd, J = 8.7, 13.9 Hz, 1H), 4.44 (dd, J = 8.9, 12.1 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 10.1, 15.6, 22.6, 23.2, 24.7, 27.8, 35.6, 39.7, 42.2, 42.7, 44.6, 45.5, 55.2, 65.8, 78.8, 178.4, 199.3. IR (neat) 1768 cm^{-1} ; MS (ES+) m/z 308 (M^+ +1); HRMS calcd for $\text{C}_{17}\text{H}_{26}\text{NSO}_2$ (M^+ +H): 308.1684, found 308.1667.

1

($\pm$)-**Stenine (1)**. A solution of 20 mg (0.065 mmol) of the thioamide **A** in 10 mL of 95% EtOH was treated at room temperature with 350 mg of Raney Ni. The reaction mixture was shaken for 30 min and filtered through a cotton filter. The solvent was removed under reduced pressure, and the solid residue was chromatographed on SiO_2 (EtOAc) to give 16 mg (89%) of **1** as a light yellow oil. R_f = 0.1 (1:10 MeOH/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.92 (t, J = 7.4 Hz, 3H), 1.28 (d, J = 7.1 Hz, 3H), 1.30-1.75 (complex, 10H), 1.90 (m, 2H), 2.05-2.50 (m, 2H), 2.86 (dt, J = 4.2, 13.0 Hz, 1H), 3.17 (dt, J = 3.5, 9.0 Hz, 1H), 4.46 (dd, J = 9.2, 12.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 9.8, 15.0, 22.3, 26.2, 27.5, 29.5, 29.8, 39.8, 40.4, 42.5, 43.2, 47.4, 53.1, 55.0, 68.0, 80.5, 179.6. IR (neat) 1770 cm^{-1} ; MS (ES+) m/z 278 (M^+ +1); HRMS calcd for $\text{C}_{17}\text{H}_{28}\text{NO}_2$ (M^+ +H): 278.2120, found 278.2106.

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