An Efficient Synthesis of ($\pm$)-Lycoricidine Featuring a Stille-IMDAF Cycloaddition Cascade

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Experimental Section

6-Iodo-benzo[1,3]dioxole-5-carboxylic Acid Furan-2-yl Amide (12). To a solution of 4.5 g (25 mmol) of furan-2-yl-carbamic acid 2-*tert*-butyl ester (**10a**)¹ in 40 mL of THF at 0 °C was added 11 mL (27 mmol) of a 2.5 M *n*-BuLi in hexane solution. The reaction mixture was stirred for 20 min and was then added dropwise through a cannula to a solution containing 6.4 g (21 mmol) of 6-iodo-benzo[1,3]-dioxole-5-carbonyl chloride (**9**)² in 40 mL of THF at 0 °C. The resulting solution was stirred at 0 °C for 20 min, diluted with 200 mL of H₂O, and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried over MgSO₄ and concentrated under reduced pressure to afford carbamate **11** as a brown oil.

To this oil was added 50 mL of CH₃CN and 1.9 g (6.2 mmol) of Mg(ClO₄)₂. The reaction mixture was heated to 50 °C for 1 h, cooled to room temperature, diluted with 300 mL of H₂O, and extracted with EtOAc. The combined organic layers were washed with H₂O, brine and dried over MgSO₄. After removing the solvent under reduced pressure, the residue was recrystallized from EtOAc to give 3.4 g (46%) of the titled compound **12** as a white solid. The filtrate was subjected to silica gel chromatography to give an additional 2.1 g for an overall yield of 75%; mp 192-193 °C; IR (neat) 3228, 1660, 1531, 1476, and 1243 cm⁻¹; ¹H-NMR (acetone-d₆, 600 MHz) δ 6.12 (s, 2H), 6.40 (d, 1H, *J* = 2.4 Hz), 6.46 (t, 1H, *J* = 2.4 Hz), 7.10 (s, 1H), 7.23 (dd, 1H, *J* = 2.4 and 1.2 Hz), 7.36 (s, 1H), and 10.07 (brs, 1H); ¹³C-NMR (acetone-d₆, 150 MHz) δ 82.5, 95.5, 97.8, 103.5, 109.6, 112.2, 119.8, 136.4, 147.5, 149.2, 150.7, and 165.5; Anal. Calcd for C₁₂H₁₈INO₄: C, 40.36; H, 2.26; N, 3.92. Found: C, 40.51; H, 2.12; N, 3.93.

6-Iodo-benzo[1,3]dioxole-5-carboxylic Acid Furan-2-yl-(4-methoxy-benzyl)-Amide (7). To a solution of 0.7 g (1.9 mmol) of the above amide **12** in 8 mL of DMF at 0 °C was added 0.09 g (2.3 mmol) of NaH (60% in mineral oil) in several

portions. After stirring for 10 min, the reaction mixture was warmed to room temperature and was stirred for an additional 30 min. The reaction mixture was cooled to 0 °C and 0.4 mL (2.8 mmol) of 4-methoxybenzyl chloride was added dropwise. After stirring for 15 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 4 h. The mixture was quenched with H₂O and extracted with EtOAc. The combined extracts were washed with H₂O, brine, and dried over MgSO₄. After concentration under reduced pressure, the residue was subjected to silica gel chromatography to give 0.7 g (83%) of iodide **7** as a white solid: mp 119.5-120.5 °C; IR (neat) 1671, 1610, 1512, 1478, and 1237 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 3.79 (s, 3H), 4.90 (s, 2H), 5.76 (d, 1H, *J* = 3.2 Hz), 5.91 (s, 2H), 6.07 (dd, 1H, *J* = 3.2 and 2.4 Hz), 6.62 (s, 1H), 6.83 (d, 2H, *J* = 8.8 Hz), 7.08 (s, 1H), 7.08-7.10 (brm, 1H), and 7.29 (d, 2H, *J* = 8.8 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ 51.1, 55.4, 82.2, 102.0, 105.8, 108.0, 111.1, 113.9, 118.7, 128.8, 130.6, 135.7, 140.0, 147.3, 147.8, 148.7, 159.3, and 170.3; Anal. Calcd for C₂₀H₁₆INO₅: C, 50.33; H, 3.38; N, 2.93. Found: C, 50.21; H, 3.34; N, 2.81.

5-(4-Methoxy-benzyl)-2,4*a*-epoxy-6-oxo-2,4*a*,5,6-tetrahydro-1*H*-[1,3]dioxolo-[4,5-*j*]phenanthridine-11*b*-carboxylic Acid Methyl Ester (6**).** A Schlenck tube charged with 0.3 g (6.3 mmol) of LiCl was dried with a flame under vacuum. Upon cooling, 0.12 g (0.10 mmol) of Pd(PPh₃)₄, and 0.5 g (0.5 mmol) of CuCl were added and the mixture was degassed 3 times under vacuum using an argon purge. To this mixture was added 8.4 mL of anhydrous DMSO, 0.5 g (1.0 mmol) of iodide **7**, and 0.47 g (1.3 mmol) of 2-tributylstananyl-acrylic acid methyl ester.³ The resulting mixture was vigorously degassed by several freeze-thaw cycles (-78 °C to 25 °C). After stirring at room temperature for 1 h, the reaction mixture was heated at 60 °C for 20 h. The mixture was then cooled to room temperature, diluted with 200 mL of EtOAc, 50 mL of a saturated NaHCO₃ solution, 150 mL of H₂O, and filtered over a celite pad. The organic layer was

separated, washed with H₂O and brine, and dried over MgSO₄. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography with a hexane/EtOAc/Et₃N mixture to give 0.37 g (82%) of **6** as a pale yellow oil: IR (neat) 1733, 1655, 1513, 1447, 1383, and 1249 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 2.51 (dd, 1H, *J* = 12.0 and 4.8 Hz), 2.76 (d, 1H, *J* = 12.0 Hz), 3.46 (s, 3H), 3.79 (s, 3H), 4.32 (d, 1H, *J* = 15.6 Hz), 4.87 (dd, 1H, *J* = 4.8 and 1.5 Hz), 5.43 (d, 1H, *J* = 15.6 Hz), 6.01 (s, 2H), 6.14 (d, 1H, *J* = 5.4 Hz), 6.54 (dd, 1H, *J* = 5.4 and 1.5 Hz), 6.73 (s, 1H), 6.85 (d, 2H, *J* = 8.4 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), and 7.67 (s, 1H); ¹³C-NMR (CDCl₃, 150 MHz) δ 42.1, 48.4, 52.7, 54.3, 55.4, 74.4, 100.5, 102.1, 107.7, 108.9, 113.9, 121.6, 128.6, 130.7, 133.4, 134.7, 139.4, 147.9, 151.5, 158.8, 163.9, and 171.6; HRMS Calcd for [(C₂₄H₂₁NO₇) + H]⁺: 436.1391. Found: 436.1395.

4-(4-Methoxy-benzyl)-3*b*,12-epoxy-2,2-dimethyl-5-oxo-3*a*,4,5,11,12,12*a*-hexahydro-3*bH*-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthrene-10*b*-carboxylic Acid Methyl Ester (15**).** To a solution of 0.9 g (2.1 mmol) of alkene **6** in 30 mL of CH₃CN and 3 mL of H₂O was added 0.4 g (4.4 mmol) of 4-methylmorpholine-*N*-oxide and a catalytic amount of OsO₄. The reaction mixture was stirred at room temperature overnight and was then diluted with 200 mL of H₂O and extracted with CH₂Cl₂. The organic extracts were washed with H₂O, brine, and dried over MgSO₄. Removal of the solvent afforded diol **14** which was immediately taken up in 2 mL of DMF and 4 mL of 2,2-dimethoxypropane and 0.1 g (0.4 mmol) of pyridinium *p*-toluenesulfonate was added. The reaction mixture was stirred at room temperature overnight, quenched with a saturated NaHCO₃ solution, and extracted with EtOAc. The organic layer was washed with H₂O, brine, and dried over MgSO₄. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to afford 0.9 g (80%) of **15** as a pale yellow oil: IR (neat) 1731, 1655, 1513, 1484, 1448, and 1246 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.19 (s, 3H), 1.37 (s, 3H), 2.26 (dd, 1H, *J* = 12.6

and 6.0 Hz), 2.92 (d, 1H, J = 12.6 Hz), 3.56 (s, 3H), 3.77 (s, 3H), 4.14 (d, 1H, J = 4.8 Hz), 4.30 (d, 1H, J = 6.6 Hz), 4.42 (d, 1H, J = 5.4 Hz), 5.18 (d, 1H, J = 15.6 Hz), 5.37 (d, 1H, J = 15.6 Hz), 6.00 (s, 2H), 6.50 (s, 1H), 6.80 (d, 2H, J = 8.4 Hz), 7.23 (d, 2H, J = 8.4 Hz), and 7.61 (s, 1H); ^{13}C -NMR (CDCl_3 , 150 MHz) δ 25.1, 25.8, 39.2, 46.9, 53.4, 54.9, 55.5, 74.9, 80.6, 82.6, 96.5, 102.1, 105.5, 108.5, 112.6, 113.4, 120.9, 128.2, 132.2, 135.6, 147.8, 152.0, 158.1, 164.7, and 171.4; HRMS Calcd for $[(\text{C}_{27}\text{H}_{27}\text{NO}_9) + \text{H}]^+$: 510.1759. Found: 510.1756.

12-Hydroxy-4-(4-methoxy-benzyl)-2,2-dimethyl-5-oxo-3a,4,5,11,12,12a-hexahydro-3bH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthrene-10b-carboxylic Acid Methyl Ester (5). To a solution of 0.2 g (0.4 mmol) of acetone **15** in 6 mL of CH_2Cl_2 at -78°C was added 3.1 mL (0.8 mmol) of a 0.25 M solution of $\text{Zn}(\text{BH}_4)_2$ in Et_2O ,⁴ and 0.14 mL (0.8 mmol) of TMSOTf, respectively. After stirring for 20 min at -78°C , the reaction mixture was allowed to warm to room temperature and was stirred for an additional 4 h. The mixture was quenched with a saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2 . The combined organic extracts were washed with H_2O , brine, and dried over MgSO_4 . After removing the solvent under reduced pressure, the residue was dissolved in 5 mL of THF, and this was followed by the addition of 0.4 mL (0.4 mmol) of TBAF (1.0 M in THF) at room temperature. After stirring for 5 min, the mixture was diluted with a saturated NH_4Cl solution and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine and dried over MgSO_4 . After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to afford 0.15 g (74%) of alcohol **5** as a white solid: mp $204.5\text{--}205.5^\circ\text{C}$; IR (neat) 3396, 1728, 1639, 1512, 1456, and 1244 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz) δ 1.39 (s, 3H), 1.43 (s, 3H), 2.04 (dd, 1H, J = 13.6 and 10.4 Hz), 2.24 (d, 1H, J = 8.8 Hz), 2.69 (dd, 1H, J = 13.6 and 5.2 Hz), 3.32 (s, 3H), 3.77 (s, 3H), 4.02 (d, 1H, J = 8.8 Hz), 4.02-4.08 (m, 1H),

4.47 (dd, 1H, $J = 5.2$ and 4.4 Hz), 4.73 (d, 1H, $J = 15.6$ Hz), 4.88 (dd, 1H, $J = 8.4$ and 5.6 Hz), 5.37 (d, 1H, $J = 15.6$ Hz), 6.03 (d, 1H, $J = 1.2$ Hz), 6.04 (d, 1H, $J = 1.2$ Hz), 6.80 (d, 2H, $J = 8.8$ Hz), 6.86 (s, 1H), 7.23 (d, 2H, $J = 8.8$ Hz), and 7.59 (s, 1H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 26.4, 28.4, 35.4, 45.9, 50.2, 52.8, 55.4, 63.8, 65.6, 74.8, 75.9, 102.1, 105.1, 108.8, 109.9, 113.7, 123.7, 129.1, 132.2, 135.3, 147.9, 151.3, 158.6, 165.6, and 172.; Anal. Calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_9$: C, 63.4; H, 5.71; N, 2.74. Found: C, 63.0; H, 5.60; N, 2.70.

4-(4-Methoxy-benzyl)-2,2-dimethyl-5-oxo-3a,4,5,12a-tetrahydro-3bH-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthrene-10b-carboxylic Acid Methyl Ester (16). To a solution of 0.4 g (0.7 mmol) of alcohol **5** in 7 mL of THF was added 0.09 g (2.2 mmol) of NaH (60% in mineral oil) at 0 °C. After stirring for 10 min, the mixture was warmed to room temperature and was stirred for an additional 30 min. The solution was cooled to 0 °C, and 0.26 mL (4.4 mmol) of CS_2 was added and the mixture was stirred for 1 h at this temperature and then 0.5 mL (8.8 mmol) of MeI was added. After stirring for 10 min, the mixture was warmed to room temperature and was stirred for an additional 20 min. The solution was quenched with a saturated NH_4Cl solution and then extracted with EtOAc. The combined organic extracts were washed with H_2O , brine, and dried over MgSO_4 . After concentration under reduced pressure, the residue was dissolved in 20 mL of 1,2-dichlorobenzene and was heated at reflux for 12 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.34 g (94%) of alkene **16** as a pale yellow oil; IR (neat) 1733, 1650, 1512, 1275, 1244, 1210 and 1037 cm^{-1} ; ^1H -NMR (CDCl_3 , 600 MHz) δ 1.43 (s, 3H), 1.44 (s, 3H), 3.25 (s, 3H), 3.77 (s, 3H), 3.91 (d, 1H, $J = 9.0$ Hz), 4.68 (d, 1H, $J = 15.6$ Hz), 4.81 (dt, 1H, $J = 7.2$ and 1.8 Hz), 4.99 (dd, 1H, $J = 9.0$ and 7.2 Hz), 5.49 (d, 1H, $J = 15.6$ Hz), 6.05 (s, 2H), 6.18 (dd, 1H, $J = 9.6$, and 1.8 Hz), 6.26 (dd, 1H, $J = 9.6$ and 1.2 Hz), 6.80 (d, 2H, $J = 9.0$ Hz), 6.93 (s, 1H), 7.23 (d, 2H, $J = 9.0$ Hz), and 7.64 (s, 1H); ^{13}C -

NMR (CDCl₃, 150 MHz) δ 24.8, 27.5, 45.6, 52.5, 53.1, 55.5, 64.3, 72.2, 72.9, 102.1, 105.0, 109.4, 109.5, 113.9, 124.7, 126.6, 129.1, 130.2, 132.7, 133.8, 147.8, 151.2, 158.6, 165.9, and 170.8; HRMS Calcd for [(C₂₇H₂₇NO₈) + H]⁺: 494.1809. Found: 494.1805.

Methanesulfonic Acid 4-(4-Methoxy-benzyl)-2,2-dimethyl-5,10*b*-dioxo-3*a*,3*b*, 4, 5,10*b*,11,12,12*a*-octahydro-1,3,7,9,12-pentaoxa-4-aza-dicyclopenta[*a,h*]phenanthren-11-yl Ester (19). To a solution of 0.25 g (0.5 mmol) of alkene **16** in 8 mL of acetone and 0.8 mL of H₂O was added 0.08 g (0.7 mmol) of 4-methylmorpholine-*N*-oxide and a catalytic amount of OsO₄. The reaction mixture was stirred at room temperature for 12 h, quenched with a saturated Na₂S₂O₃ solution and extracted with EtOAc. The combined organic layer was washed with H₂O, brine, and dried over MgSO₄. After concentration under reduced pressure, the residue was dissolved in 10 mL of THF and a catalytic amount of NaOMe was added. After stirring for 20 min, the mixture was quenched with 50 mL of H₂O and extracted with EtOAc. The combined organic layer was dried over MgSO₄, and concentrated under reduced pressure. To the resulting residue was added 20 mL of THF, 0.4 mL (3.1 mmol) of Et₃N, and 0.12 mL (1.5 mmol) of MsCl. The mixture was stirred at room temperature for 6 h and was then quenched with a saturated NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with H₂O, brine, and dried over MgSO₄. After removing the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.22 g (76%) of **19** as a white solid: mp 179-180 °C; IR (neat) 1788, 1653, 1608, 1508, 1245, 1179, and 1037 cm⁻¹; ¹H-NMR (CDCl₃, 600 MHz) δ 1.35 (s, 3H), 1.52 (s, 3H), 3.22 (s, 3H), 3.76 (s, 3H), 4.27 (d, 1H, *J* = 5.4 Hz), 4.48-4.51 (m, 2H), 4.57 (d, 1H, *J* = 16.2 Hz), 5.12 (d, 1H, *J* = 3.6 Hz), 5.37 (d, 1H, *J* = 16.2 Hz), 5.63 (s, 1H), 6.04 (s, 1H), 6.06 (s, 1H), 6.82 (d, 2H, *J* = 8.4 Hz), 7.13 (d, 2H, *J* = 8.4 Hz), 7.31 (s, 1H), and 7.75 (s, 1H); ¹³C-NMR (CDCl₃, 150 MHz) δ 25.7, 27.7, 39.7, 46.3, 50.8, 5.4, 66.0, 73.2, 74.3, 79.4, 81.4,

102.4, 106.6, 109.8, 113.1, 114.3, 125.4, 126.2, 127.7, 130.7, 148.7, 151.5, 158.8, 164.6, and 170.1; Anal. Calcd for $C_{27}H_{27}NO_{11}S$: C, 56.54; H, 4.74; N, 2.44. Found: C, 56.29; H, 4.55; N, 2.18

Methanesulfonic Acid 2,2-Dimethyl-5,10*b*-dioxo-3*a*,3*b*,4,5,10*b*,11,12,12*a*-octanhydro-1,3,7,9,12-pentaoxa-4-aza-dicyclopenta[*a,h*]phenanthren-11-yl

Ester. To a solution of 0.07 g (0.12 mmol) of mesylate **19** in 1.0 mL of EtOAc was added 1.0 mL of CH_3COOH and 0.04 g (0.24 mmol) of $PdCl_2$. The resulting suspension was stirred under a hydrogen atmosphere (80 psi) overnight. The mixture was diluted with EtOAc and filtered over a celite pad. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 0.04 g (65%) of the titled compound as a white solid: mp 240 °C; IR (neat) 1793, 1678, 1180 and 1035 cm^{-1} ; 1H -NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 3H), 1.56 (s, 3H), 3.25 (s, 3H), 4.04 (d, 1H, $J = 6.8$ Hz), 4.22 (t, 1H, $J = 6.4$ Hz), 4.73 (dd, 1H, $J = 5.6$ and 4.4 Hz), 5.24 (d, 1H, $J = 4.4$ Hz), 5.59 (s, 1H), 5.98 (brs, 1H), 6.05 (d, 1H, $J = 1.2$ Hz), 6.08 (d, 1H, $J = 1.2$ Hz), 7.28 (s, 1H), and 7.69 (s, 1H); ^{13}C -NMR ($CDCl_3$, 150 MHz) δ 26.0, 28.0, 39.8, 50.6, 60.1, 60.6, 73.7, 79.7, 81.8, 102.6, 107.3, 109.4, 114.3, 124.8, 127.1, 148.8, 152.0, 164.4, and 169.6; HRMS Calcd for $[(C_{19}H_{19}NO_{10}S) + H]^+$: 454.0802. Found: 454.0803.

12-Hydroxy-2,2-dimethyl-3*b*,4,12,12*a*-tetrahydro-3*aH*-1,3,7,9-tetraoxa-4-aza-dicyclopenta[*a,h*]phenanthren-5-one (20). To a solution containing 5 mg (0.01 mmol) of the above compound in 2 mL of THF was added a solution of 2 mg (0.1 mmol) of LiOH in 0.5 mL of H_2O . The reaction mixture was stirred at room temperature for 20 min and then heated to 60 °C for 10 min. After cooling to room temperature, the mixture was diluted with a saturated NH_4Cl solution and EtOAc was added. The organic layer was washed with H_2O , brine, and dried over $MgSO_4$. Concentration under reduced pressure afforded 3.4 mg (93%) of alcohol **20** as a white solid whose spectral properties were identical to that reported in the literature⁵: IR (neat) 3350, 1653, 1475, 1257, 1059, and 1035 cm^{-1} .

1; ^1H -NMR (CDCl_3 , 600 MHz) δ 1.38 (s, 3H), 1.53 (s, 3H), 1.64 (brs, 1H), 4.13-4.15 (m, 3H), 4.38-4.40 (m, 1H), 6.03 (d, 1H, $J = 1.8$ Hz), 6.04 (d, 1H, $J = 1.8$ Hz), 6.25 (brs, 1H), 7.04 (s, 1H), and 7.60 (s, 1H); ^{13}C -NMR (CDCl_3 , 150 MHz) δ 24.9, 27.2, 56.2, 73.2, 79.1, 79.7, 101.6, 102.2, 107.9, 111.7, 121.0, 124.1, 127.8, 128.5, 148.9, 152.1, and 162.6.

($\pm$)-Lycoricidine (1). To a flask containing 3 mg (0.01 mmol) of alcohol **20** at 0 °C was added 0.3 mL of cold (-20 °C) TFA. After stirring for 40 min, the solution was diluted with 2 mL of cold dioxane and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.3 mg (90%) of ($\pm$)-Lycoricidine (**1**) as a white solid whose ^1H -NMR properties were identical to that reported in the literature⁵: ^1H -NMR (methanol- d_4 , 400 MHz) δ 3.89-3.92 (m, 2H), 4.24 (ddd, 1H, $J = 4.8$, 2.0, and 1.6 Hz), 4.37 (ddd, 1H, $J = 8.0$, 2.4, and 1.6 Hz), 6.04 (d, 1H, $J = 1.2$ Hz), 6.05 (d, 1H, $J = 1.2$ Hz), 6.16 (m, 1H), 7.15 (s, 1H), and 7.38 (s, 1H).

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