Synthesis of (±)-Phloeodictine A1

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Experimental Section Pages S1-S13

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Supporting Material

General. NMR spectra were recorded at 400 MHz. Chemical shifts are reported in δ and coupling constants in Hz. IR spectra are reported in cm^{-1} .

***exo*-3a,4,7,7a-Tetrahydro-2-(3-hydroxypropyl)-4,7-epoxy-1*H*-isoindole-1,3(2*H*)-dione (9)** was prepared by modification of the procedure to prepare the hydroxyethyl analogue.⁴ 3-Amino-1-propanol (2.04 g, 27.1 mmol) was added dropwise to a solution of *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (**8**) (4.5 g, 27.1 mmol) in MeOH (250 mL). The solution was stirred at 56 °C for 3 d, and concentrated to give a clear oil. This oil was purified by dissolving it in CH_2Cl_2 (100 mL), which was washed with H_2O (3×100 mL). The organic layers were dried over MgSO_4 and concentrated to yield 3.8 g (70%) of **9** as a white solid: mp 118-120 °C; ^1H NMR (CDCl_3) 6.53 (s, 2), 5.28 (s, 2), 3.66 (t, 2, $J = 6.1$), 3.53 (dt, 2, $J = 6.7, 5.5$), 2.89 (s, 2), 2.51 (t, 1, $J = 6.7$, OH), 1.80-1.74 (tt, 2, $J = 6.1, 5.5$); ^{13}C NMR (CDCl_3) 176.9 (2 C), 136.5 (2 C), 80.9 (2 C), 58.6, 47.4 (2 C), 35.1, 30.3; IR (KBr) 3514, 1769, 1701; HRMS (DEI) Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_4$ (M^+) 223.0845, found 223.0849. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 58.82; H, 5.48; N, 6.24.

***exo*-3a,4,7,7a-Tetrahydro-2-(3-[(methanesulfonyl)oxy]propyl)-4,7-epoxy-1*H*-isoindole-1,3(2*H*)-dione (10).** A solution of **9** (2.09 g, 9.3 mmol) in CH_2Cl_2 (93 mL) was cooled to 0 °C. Et_3N (3.3 mL, 23.4 mmol) and then methanesulfonyl chloride (1.1 mL, 14.0 mmol) were added dropwise. The solution was stirred for 10 min, quenched with H_2O (50 mL), and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with H_2O (3×50 mL) and brine (50 mL), dried over

MgSO₄, and concentrated to yield a yellow oil. Upon standing, a yellow solid formed which was washed with Et₂O to yield 2.82 g (100%) of **10** as a white solid: mp 88-90 °C; ¹H NMR (CDCl₃) 6.53 (s, 2), 5.27 (s, 2), 4.18 (t, 2, *J* = 6.1), 3.64 (t, 2, *J* = 6.1), 3.04 (s, 3), 2.88 (s, 2), 2.05 (tt, 2, *J* = 6.1, 6.1); ¹³C NMR (CDCl₃) 176.2 (2 C), 136.4 (2 C), 80.9 (2 C), 66.9, 47.4 (2 C), 37.2, 35.2, 27.0; IR (KBr) 1776, 1709, 1354, 1177; HRMS (DEI) Calcd for C₁₂H₁₅NO₆S (M⁺) 301.0620, found 301.0612. Anal. Calcd for C₁₂H₁₅NO₆S: C, 47.83; H, 5.02; N, 4.65. Found: C, 47.74; H, 4.62; N, 4.63.

***exo*-3a,4,7,7a-Tetrahydro-2-(3-azidopropyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (6).**

Sodium azide (0.86 g, 13.3 mmol) was slowly added to a solution of **10** (1.00 g, 3.3 mmol) in DMF (33 mL). The mixture was stirred for 14 h at 25 °C. CH₂Cl₂ (20 mL) and H₂O (20 mL) were added to quench the reaction. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (4 × 25 mL). The combined organic layers were washed with H₂O (4 × 25 mL) and brine (25 mL), dried over Na₂SO₄, and concentrated to yield **6**. Neat **6** polymerized in 30 min, changing from a clear oil to a white sticky insoluble solid. The ¹H NMR spectrum was obtained immediately from a fresh sample. The ¹³C NMR spectrum was obtained from the toluene solution of **6** used to prepare **5**: ¹H NMR (CDCl₃) 6.52 (s, 2), 5.28 (s, 2), 3.59 (t, 2, *J* = 6.7), 3.30 (t, 2, *J* = 6.7), 2.86 (s, 2), 1.85 (tt, 2, *J* = 6.7, 6.7); ¹³C NMR (CDCl₃) (1:7 **6**/toluene) 176.0 (2 C), 136.3 (2 C), 80.9 (2 C), 48.7, 47.3 (2 C), 36.1, 26.9.

7,8-Dihydro-4H-pyrrolo[1,2-*a*]pyrimidin-6(5H)-one (11). Sodium azide (0.43 g, 6.6 mmol) was slowly added to a solution of **10** (0.50 g, 1.6 mmol) in DMF (16 mL). The mixture was stirred for 14 h at 25 °C. Toluene (20 mL) and H₂O (20 mL) were added to quench the reaction. The layers were separated and the aqueous layer was extracted with toluene (4 × 20 mL). The combined organic layers were washed with H₂O (6 × 60 mL) and brine (60 mL), dried over Na₂SO₄, and concentrated to yield a solution of **6** in 4 mL of toluene. Additional toluene (to 16 mL) and trioctylphosphine (0.59 g, 1.6 mmol) were added. The reaction mixture was stirred at 25 °C for 30 min and then refluxed for 4 h. The solution was then cooled and filtered through Florisil (19:1 CH₂Cl₂/MeOH) to yield 63 mg of **11** containing some trioctylphosphine oxide. Flash chromatography on silica gel (19:1 CH₂Cl₂/MeOH) gave 36 mg of a white solid (16% from **10**) of pure **11**: mp 102-104 °C; ¹H NMR (CDCl₃) 6.39 (dt, 1, *J* = 7.9, 1.8), 5.23 (dt, 1, *J* = 7.9, 3.0), 4.30 (br s, 2, *w*_{1/2} = 7.2), 2.81-2.78 (m, 2),

2.60-2.56 (m, 2); ^{13}C NMR (CDCl_3) 176.3, 158.6, 132.8, 106.9, 40.2, 27.0, 26.0; IR (KBr) 1729, 1641, 1609.

3,4-Dihydro-pyrrolo[1,2-*a*]pyrimidin-6(2*H*)-one (5). Sodium azide (0.86 g, 13.3 mmol) was slowly added to a solution of **10** (1.00 g, 3.3 mmol) in DMF (33 mL). The mixture was stirred for 14 h at 25 °C. Toluene (20 mL) and H_2O (20 mL) were added to quench the reaction. The layers were separated and the aqueous layer was extracted with toluene (4×25 mL). The combined organic layers were washed with H_2O (4×25 mL) and brine (25 mL), dried over Na_2SO_4 , and concentrated to yield a solution of **6** in 10 mL of toluene. Additional toluene (to 30 mL) and polymer-supported triphenylphosphine (1.1 g, 3.3 mmol P/g resin) were added. The reaction was stirred at 25 °C for 30 min and then refluxed for 4 h. The cooled solution was filtered through Florisil (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to yield 0.193 g (43% from **10**) of **5** as a pale yellow oil: ^1H NMR (CDCl_3) 6.90 (d, 1, $J = 6.1$), 6.45 (d, 1, $J = 6.1$), 3.76 (t, 2, $J = 5.5$), 3.63 (t, 2, $J = 5.8$), 1.94-1.88 (tt, 2, $J = 5.5, 5.8$); ^{13}C NMR (CDCl_3) 169.2, 154.4, 136.4, 130.2, 46.7, 36.7, 20.4; IR (neat) 1714, 1656; MS m/z 135 (31), 136 (100, M^+), 137 (12), 107 (21), 108 (8), 80 (40), 81 (30); HRMS (EI, 70 eV) Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}$ (M^+) 136.0637, found 136.0638.

Refluxing the mixture of **6** and polymer supported Ph_3P for only 2-3 h resulted in 20-25% of **5** and 8-13% of **13**. Flash chromatography on silica gel (CH_2Cl_2 to 99:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) gave **5** followed by **13**: mp 140-142 °C; ^1H NMR (CDCl_3) 6.48 (s, 2), 5.24 (s, 1), 5.20 (s, 1), 3.56 (t, 2, $J = 6.1$), 3.51 (t, 2, $J = 5.5$), 2.89 (d, 1, $J = 7.0$), 2.73 (d, 1, $J = 7.0$), 1.88-1.74 (m, 2); ^{13}C NMR (CDCl_3) 174.0, 155.9, 136.52, 136.49, 83.0, 80.7, 47.0, 45.8, 44.8, 38.0, 19.2; IR (neat) 1735, 1700. Heating **13** (8 mg, 0.039 mmol) in toluene (0.5 mL) at reflux for 1 h and filtration through Florisil (19:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) yielded 5 mg (94%) of **5**.

2,3,4,6-Tetrahydro-6-hydroxy-6-(tetradec-13-enyl)-pyrrolo[1,2-*a*]pyrimidin-1-ium Chloride (14a). Cerium trichloride (54 mg, 0.22 mmol) was added to a solution of **5** (30 mg, 0.22 mmol) in dry THF (3 mL). The mixture was stirred for 3 h, cooled to 0 °C, and 13-tetradecenyl magnesium bromide (0.26 mL, 1.0 M in THF, 0.26 mmol) was quickly added. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (4×5 mL) and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 , filtered

through Celite, and concentrated to give 42 mg (52%) of 70-80% pure **14a** as a dark reddish-brown oil. Flash chromatography on silica gel (9:1 CH₂Cl₂/MeOH) yielded 15 mg (19%) of 95% pure **14a**: ¹H NMR (CDCl₃) 6.98 (d, 1, *J* = 6.1), 6.76 (d, 1, *J* = 6.1), 5.81 (ddt, 1, *J* = 17, 10, 7), 5.00 (dd, 1, *J* = 17, 2), 4.93 (dd, 1, *J* = 10, 2), 3.82-3.78 (m, 1), 3.61-3.54 (m, 1), 3.43-3.38 (m, 1), 3.23-3.16 (m, 1), 2.28-2.19 (m, 1), 2.09-2.00 (m, 3), 2.00-1.93 (m, 1), 1.78-1.71 (m, 1), 1.41-1.19 (m, 18), 1.09-0.95 (m, 2); HRMS (FAB/DCM/NBA) Calcd for C₂₁H₃₇N₂O (M⁺) 333.2906, found 333.2914.

2,3,4,6-Tetrahydro-6-(tetradec-13-enyl)-pyrrolo[1,2-*a*]pyrimidin-6-ol (4a). A solution of **14a** (15 mg, 0.041 mmol) in CH₂Cl₂ (5 mL) was washed with 1 M NaOH (3 mL). The organic layer was dried over Na₂SO₄, and concentrated to give 10 mg (76%) of **4a** as an 80-90% pure brown oil: ¹H NMR (CDCl₃) 6.48 (d, 1, *J* = 6.1), 6.11 (d, 1, *J* = 6.1), 5.81 (ddt, 1, *J* = 17, 10, 7), 4.99 (dd, 1, *J* = 17, 2), 4.93 (dd, 1, *J* = 10, 2), 3.64-3.34 (m, 4), 3.15-3.09 (m, 1), 2.57-2.51 (m, 1), 2.04 (dt, 2, *J* = 7, 7), 1.85-1.78 (m, 2), 1.41-1.21 (m, 18), 1.15-1.02 (m, 2).

6-(Dodec-11-enyl)-2,3,4,6-tetrahydro-6-hydroxy-pyrrolo[1,2-*a*]pyrimidin-1-ium Chloride (14b). Cerium trichloride (0.33 g, 1.34 mmol) was added to a solution of **5** (0.18 g, 1.34 mmol) in dry THF (13 mL). The mixture was stirred for 3 h, cooled to 0 °C, and 11-dodecenylmagnesium bromide (1.60 mL, 1.0 M in THF, 1.60 mmol) was quickly added. After 30 min, the reaction was quenched with saturated aqueous NH₄Cl solution. The mixture was extracted with CH₂Cl₂ (4 × 25 mL), washed with brine (75 mL), dried over Na₂SO₄, filtered through Celite, and concentrated to a dark reddish-brown oil. The oil was triturated with pentane, leaving 0.187 g (41%) of **14b** as an 80-90% pure brown solid: ¹H NMR (CDCl₃) 6.99 (d, 1, *J* = 6.1), 6.76 (d, 1, *J* = 6.1), 6.58 (br, 1, OH), 5.81 (ddt, 1, *J* = 17, 10, 7), 4.99 (dd, 1, *J* = 17, 2), 4.93 (dd, 1, *J* = 10, 2), 3.82-3.79 (m, 1), 3.59-3.56 (m, 1), 3.42-3.38 (m, 1), 3.23-3.16 (m, 1), 2.28-2.21 (m, 1), 2.10-2.00 (m, 3), 2.00-1.93 (m, 1), 1.78-1.72 (m, 1), 1.37-1.24 (m, 14), 1.03-0.99 (m, 2); ¹³C NMR (CDCl₃) 159.5, 151.7, 139.1, 120.5, 114.0, 97.8, 38.4, 36.1, 34.7, 33.7, 29.4-28.8 (7 C), 23.3, 18.6; IR (neat) 3440-3080, 1735, 1669.

6-(Dodec-11-enyl)-2,3,4,6-tetrahydro-pyrrolo[1,2-*a*]pyrimidin-6-ol (4b). A solution of **14b** (0.187 g, 0.548 mmol) in CH₂Cl₂ (10 mL) was washed with 1 M NaOH (5 mL). The organic layer was dried over Na₂SO₄, and concentrated to give 0.165 g (100%) of **4b** as an 80-90% unstable pure brown oil that was used immediately for the next step: ¹H NMR (CDCl₃) 6.47 (d, 1, *J* = 6.1), 6.12 (d,

1, $J = 6.1$), 5.82 (ddt, 1, $J = 17, 10, 7$), 4.99 (dd, 1, $J = 17, 2$), 4.93 (dd, 1, $J = 10, 2$), 3.60-3.31 (m, 4), 3.18-3.08 (m, 1), 2.59-2.51 (m, 1), 2.04 (dt, 2, $J = 7, 7$), 1.91-1.70 (m, 2), 1.51-1.18 (m, 14), 1.15-0.98 (m, 2); IR (neat) 2926, 2853, 2244, 1736, 1669, 910, 733.

2,3,4,6-Tetrahydro-6-hydroxy-6-tetradecyl-pyrrolo[1,2-*a*]pyrimidin-1-ium Chloride (14c).

Cerium trichloride (0.73 g, 2.96 mmol) was added to a solution of **5** (0.40 g, 2.96 mmol) in dry THF (30 mL). The mixture was stirred for 2 h, cooled to 0 °C, and tetradecylmagnesium chloride (3.6 mL, 1.0 M in THF, 3.6 mmol) was quickly added. The reaction was stirred for 30 min and quenched with 10% aqueous AcOH (15 mL). The mixture was extracted with CH₂Cl₂ (3 × 20 mL), and the organic layer was washed with saturated aqueous NaHCO₃ (30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated to yield a yellow oil. Flash chromatography on silica gel (7:3 MeOH/CH₂Cl₂) gave 0.46 g (42%) of **14c** as a yellow oil: ¹H NMR (CDCl₃) 6.99 (d, 1, $J = 6.1$), 6.58 (d, 1, $J = 6.1$), 3.72-3.60 (m, 2), 3.45-3.38 (m, 1), 3.26-3.19 (m, 1), 2.21-2.09 (m, 1), 2.08-1.96 (m, 3), 1.78-1.72 (m, 2), 1.30-1.25 (m, 20), 1.03-1.02 (m, 2), 0.88 (t, 3, $J = 6.7$); ¹³C NMR (CDCl₃) 159.7, 151.6, 120.8, 97.8, 38.5, 36.2, 34.7, 31.9, 29.7-29.3 (9 C), 23.5, 22.7, 18.6, 14.1.

2,3,4,6-Tetrahydro-6-tetradecyl-6-pyrrolo[1,2-*a*]pyrimidin-6-ol (4c). To a solution of **14c** (0.56 g, 1.7 mmol) in CH₂Cl₂ (5 mL) was added 1 M NaOH (5 mL). The solution was stirred for 3 min, and the organic layer was separated, dried over Na₂SO₄ and concentrated to yield 0.55 g (99%) of **4c** as a yellow oil: ¹H NMR (CDCl₃) 6.47 (d, 1, $J = 6.1$), 6.10 (d, 1, $J = 6.1$), 3.71-3.35 (m, 4), 3.15-3.08 (m, 1), 2.57-2.48 (m, 1), 1.89-1.71 (m, 4), 1.34-1.21 (m, 20), 1.09-1.01 (m, 2), 0.88 (t, 3, $J = 6.7$); ¹³C NMR (CDCl₃) 158.3, 143.9, 126.8, 93.9, 43.5, 37.0, 35.4, 31.8, 29.6-29.3 (9 C), 23.7, 22.6, 20.7, 14.0.

***N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-(4-hydroxybutyl)guanidine (16a)** was prepared according to the literature procedure.¹² A solution of *N,N'*-bis(*tert*-butoxycarbonyl)-*S*-methylisothiurea (1.0 g, 3.4 mmol) in THF (10 mL) was added to a solution of 4-amino-1-butanol (0.61 g, 6.8 mmol) in THF (20 mL). The reaction was heated at 50 °C for 2 h and cooled to 25 °C. H₂O (30 mL) and CH₂Cl₂ (50 mL) were added. The organic layer was removed and the aqueous layer was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layers were washed with H₂O (90 mL) and brine (90 mL), dried over Na₂SO₄, filtered, and concentrated to give 1.14 g (100%) of **16a** as a white solid: ¹H

NMR (CDCl₃) 11.49 (br s, 1, NH), 8.39 (br s, 1, NH), 3.71 (t, 2, $J = 6.0$), 3.46 (dt, 2, $J = 6.8, 6.0$), 1.71-1.61 (m, 4), 1.502 (s, 9), 1.495 (s, 9).

***N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-(4-[(methanesulfonyl)oxy]butyl)guanidine (17a).** A solution of **16a** in CH₂Cl₂ (33 mL) was cooled to 0 °C. Et₃N (1.16 mL, 8.3 mmol) and methanesulfonylchloride (0.39 mL, 5.3 mmol) were added dropwise. After 10 min, H₂O (30 mL) was added to the solution and the reaction allowed to warm to 25 °C. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed with H₂O (6 × 90 mL) and brine (90 mL), dried over Na₂SO₄, filtered, and concentrated to give 1.36 g (100%) of **17a** as a yellow oil: ¹H NMR (CDCl₃) 11.50 (br s, 1, NH), 8.36 (br s, 1, NH), 4.27 (t, 2, $J = 6.0$), 3.48 (dt, 2, $J = 6.8, 6.0$), 3.03 (s, 3), 1.84-1.79 (m, 2), 1.75-1.69 (m, 2), 1.502 (s, 9), 1.497 (s, 9).

***N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-(5-[(methanesulfonyl)oxy]pentyl)guanidine (17b)** was prepared from *N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-(5-hydroxypentyl)guanidine (**16b**)¹² (1.27 g, 3.7 mmol), Et₃N (1.28 mL, 9.2 mmol), methanesulfonyl chloride (0.43 mL, 5.5 mmol) and CH₂Cl₂ (37 mL) following the procedure for **17a** to afford 1.56 g (100%) of **17b** as a yellow oil: ¹H NMR (CDCl₃) 11.50 (br s, 1, NH), 8.33 (br s, 1, NH), 4.24 (t, 2, $J = 6.4$), 3.43 (dt, 2, $J = 5.1, 7.0$), 3.01 (s, 3), 1.80 (tt, 2, $J = 7.0, 6.4$), 1.63 (tt, 2, $J = 7.0, 7.0$), 1.51 (s, 9), 1.50 (s, 9), 1.50-1.46 (m, 2).

***N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-(4-iodobutyl)guanidine (18a).** NaHCO₃ (0.70 g, 8.3 mmol), Na₂SO₃ (0.50 g, 3.98 mmol), and NaI (2.99 g, 19.9 mmol) were added to a solution of **17a** (1.36 g, 3.30 mmol) in acetone (94 mL). The solution was refluxed for 3 h, cooled to 25 °C and poured into a 1:1 mixture of Et₂O/H₂O (300 mL total). The organic layer was separated and washed with saturated aqueous Na₂S₂O₃ solution (150 mL), saturated aqueous NaHCO₃ solution (150 mL), and brine (150 mL), filtered and concentrated to give an orange oil. Flash chromatography on silica gel (CH₂Cl₂) yielded 1.14 g (78%) of pure **18a** as a white solid: mp 76-78 °C; ¹H NMR (DMSO-*d*₆) 11.49 (br s, 1, NH), 8.34 (br s, 1, NH), 3.33-3.28 (m, 4), 1.80-1.73 (m, 2), 1.60-1.55 (m, 2), 1.48 (s, 9), 1.39 (s, 9); ¹H NMR (CDCl₃) 11.50 (br s, 1, NH), 8.33 (br s, 1, NH), 3.45 (dt, 2, $J = 7.0, 7.0$), 3.22 (t, 2, $J = 7.0$), 1.88 (tt, 2, $J = 7.0, 7.0$), 1.70 (tt, 2, $J = 7.0, 7.0$), 1.50 (s, 18); ¹³C NMR (CDCl₃) 163.6,

156.2, 153.3, 83.2, 79.3, 39.7, 30.6, 30.0, 28.3 (3 C), 28.1 (3 C), 5.9; IR (KBr) 3332, 2978, 2931, 1738, 1652, 1370, 1139.

***N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-(5-iodopentyl)guanidine (18b)** was prepared from **17b** (1.58 g, 3.7 mmol), NaHCO₃ (0.79 g, 9.3 mmol), Na₂SO₃ (0.57 g, 4.5 mmol), NaI (2.8 g, 18.7 mmol) and acetone (105 mL) following the procedure for **18a**. Flash chromatography on silica gel (24:1 hexanes/EtOAc) yielded 1.2 g (75%) of **18b** as a white solid: mp 89-92 °C; ¹H NMR (DMSO-*d*₆) 11.50 (br s, 1, NH), 8.31 (br s, 1, NH), 3.31-3.25 (m, 4), 1.80-1.74 (m, 2), 1.53-1.45 (m, 2), 1.47 (s, 9), 1.42-1.32 (m, 2), 1.39 (s, 9); ¹H NMR (CDCl₃) 11.51 (br s, 1, NH), 8.33 (br s, 1, NH), 3.43 (dt, 2, *J* = 5.1, 7.0), 3.20 (t, 2, *J* = 7.0), 1.86 (tt, 2, *J* = 7.0, 7.0), 1.64-1.56 (m, 2), 1.51 (s, 9), 1.50 (s, 9), 1.51-1.44 (m, 2); ¹³C NMR (CDCl₃) 163.6, 156.1, 153.3, 83.1, 79.3, 40.5, 32.9, 28.3 (3 C), 28.1 (3 C), 28.0, 27.7, 6.4; IR (KBr) 3335, 2978, 2932, 1737, 1650, 1370, 1148.

Acetone adduct 20. Iodopentyl guanidine **18b** (21 mg, 0.045 mmol) was added to a solution of **4c** (15 mg, 0.045 mmol) in acetone (0.5 mL). The solution was stirred for 2 h at 25 °C and concentrated to give a reddish-orange liquid. Flash chromatography on silica gel (19:1 CH₂Cl₂/MeOH) gave 35 mg (92%) of **20** as a yellow oil: ¹H NMR (CDCl₃) 11.50 (br s, 1, NH), 8.33 (br s, 1, NH), 4.67 (dd, 1, *J* = 5.2, <1), 3.95-3.87 (m, 1), 3.85 (dd, 1, *J* = 17.5, 5.2), 3.65-3.55 (m, 1), 3.53-3.40 (m, 6), 2.96 (dd, 1, *J* = 17.5, <1), 2.41-2.28 (m, 2), 2.01-1.82 (m, 2), 1.79-1.76 (m, 1), 1.66-1.62 (m, 3), 1.50 (s, 18), 1.41 (s, 3), 1.35 (s, 3), 1.41-1.25 (m, 26), 0.88 (t, 3, *J* = 6.9); ¹³C NMR (CDCl₃) 163.6, 161.3, 156.2, 153.3, 112.9, 106.0, 83.3, 79.4, 76.2, 52.3, 45.1, 40.2, 36.9, 36.8, 31.9, 31.7, 29.7-29.3 (9 C), 28.6, 28.3 (3 C), 28.2, 28.1 (3 C), 27.0, 26.8, 24.1, 23.8, 22.7, 19.3, 14.1. The HSQC and HMBC data are shown below.

HSQC and HMBC Data for **20**

HSQC and HMBC in CDCl ₃			
Atom	Carbon	Proton	HMBC correlations
2	45.1	3.93 3.43	
3	19.3	2.40 1.91	
4	36.9	3.63 3.45	
6	106.0		H ₇ , H ₈ (δ 2.99)
7	76.2	4.68	H ₈ (δ 2.99)
8	36.8	3.87 2.99	H ₇
8a	161.3		H _{7,8,9}
9'	52.3	3.52	H _{10',11'}
10'	26.8	1.78 1.64	H _{11'}
11'	24.1	1.37	H _{10',12'}
12'	27.0	1.64	H _{11'}
13'	40.2	3.44	H _{11',12'}
14'	163.6		
COCMe ₃	153.3		
COCMe ₃	79.4		δ 1.5
COCMe ₃	28.1	1.50	
COCMe ₃	156.2		H _{13'}
COCMe ₃	83.3		δ 1.5
COCMe ₃	28.3	1.50	
O ₂ CMe ₂	112.9		δ 1.41, 1.35
O ₂ CMe ₂	28.2	1.41	
O ₂ CMe ₂	28.6	1.35	
14	31.7	2.31 1.99	H _{15,16}
15	23.8	1.40	H ₁₄
16-24	29.7-29.3	1.40-1.25	H _{15,25}
25	31.9	1.24	H _{26,27}
26	22.7	1.26	H _{25,27}
27	14.1	0.88	H ₂₆

Phloeodictine A1 (2). Iodopentyl guanidine **18b** (30.2 mg, 0.07 mmol) was added to a solution of **4b** (20 mg, 0.07 mmol) in DMSO-*d*₆ (1.0 mL). The solution was stirred for 24 h, giving a 2:1 mixture of **21** and **14b** as determined by NMR analysis of the alkene region: ¹H NMR (DMSO-*d*₆) 7.30 (d, 1, *J* = 6.1), 6.52 (d, 1, *J* = 6.1) and 6.51 (d, 1, *J* = 6.1), 6.00 (d, 1, *J* = 6.1), and 7.39 (d, 1, *J* = 6.1), 7.13 (d, 1, *J* = 6.1) for **14b**, **4b**, and **21** respectively. Removal of **14b** and DMSO was achieved

by pouring the solution into a 1:1 mixture of $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (15 mL total). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with H_2O (5×10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated to give 40 mg of a brown oil containing **21**.

Crude **21** (40 mg) was stirred in a 1:1 mixture of TFA/ CH_2Cl_2 (1 mL total) for 2 h. The reddish solution was concentrated to give a reddish-brown oil. Purification by flash chromatography on BakerbondTM Octadecyl (C_{18}) 40 μm PrepLC Packing using a step gradient of MeOH-NaCl (0.2 M)-THF (56:43:1 to 66:33:1), adjusted to pH 2 with HCl, yielded salty **2**. Washing with methanol several times removed the NaCl, yielding 11 mg (26% from **5**) of phloeodictine A1 (**2**): ^1H NMR (CD_3OD) 7.30 (d, 1, $J = 6.1$), 7.03 (d, 1, $J = 6.1$), 5.80 (ddt, 1, $J = 17, 10, 7$), 4.97 (dd, 1, $J = 17, 2$), 4.91 (dd, 1, $J = 10, 2$), 3.84-3.42 (m, 5), 3.39-3.26 (m, 1), 3.21 (t, 2, $J = 6.7$), 2.28-2.20 (m, 1), 2.19-2.11 (m, 1), 2.06-1.96 (m, 3), 1.82-1.70 (m, 3), 1.70-1.61 (m, 2), 1.48-1.40 (m, 2), 1.38-1.24 (m, 14), 1.22-1.12 (m, 2); ^{13}C NMR (CD_3OD) 160.4, 158.8, 154.6, 140.3, 120.5, 114.9, 99.4, 53.6, 46.8, 42.3, 37.1, 36.1, 35.0, 30.8-30.3 (7 C), 29.6, 28.9, 24.9, 24.6, 20.5; ^1H NMR (500 MHz, D_2O) 7.27 (d, 1, $J = 5.5$), 7.05 (d, 1, $J = 5.5$), 5.89-5.80 (m, 1), 5.03 (d, 1, $J = 17$), 4.97 (d, 1, $J = 10$), 3.86-3.46 (m, 5), 3.36-3.28 (m, 1), 3.28-3.21 (m, 2), 2.29-2.12 (m, 2), 2.10-1.98 (m, 3), 1.88-1.74 (m, 3), 1.74-1.66 (m, 2), 1.51-1.27 (m, 16), 1.22-1.14 (m, 2); ^{13}C NMR (400 MHz, D_2O) 159.4, 157.3, 152.4, 139.5, 120.5, 114.8, 97.9, 53.0, 46.0, 41.6, 36.5, 35.2, 34.3, 30.1-29.4 (7 C), 28.3, 27.8, 24.1, 23.5, 19.5; MS m/z 468 (10, $\text{M} + \text{HCl}^+$), 433 (32), 432 (100, M^+), 415 (8), 414 (14), 305 (5), 154 (14), 137 (13), 136 (13); HRMS (FAB/MeOH/NBA) Calcd for $\text{C}_{25}\text{H}_{46}\text{N}_5\text{O}^+$ (M^+) 432.3702, found 432.3720. The HSQC data shown below are identical to those reported for the natural product.^{1b}

HSQC Data for Phloeodictine A1

Atom	HSQC (500 MHz, D ₂ O)		HSQC (400 MHz, CD ₃ OD)	
2	46.0	3.54 3.64	46.8	3.65
3	19.5	2.09 2.16	20.5	2.07 2.24
4	36.5	3.25 3.53	37.1	3.35 3.60
6	97.9		99.4	
7	152.4	7.27	154.6	7.30
8	120.5	7.01	120.5	7.03
8a	159.4		158.8	
9'	53.0	3.64	53.6	3.70
10'	27.8	1.74	28.9	1.78
11'	23.5	1.40	24.6	1.46
12'	28.3	1.61	29.6	1.68
13'	41.6	3.18	42.3	3.23
14'	157.3		160.4	
14	35.2	1.75 2.01	36.1	2.01 1.80
15	24.1	1.10 1.23	24.9	1.19
16-22	30.1-29.4	1.51-1.27	30.8-30.3	1.38-1.24
CH ₂ CH=CH ₂	34.3	2.05	35.0	2.05
CH ₂ CH=CH ₂	139.5	5.74	140.3	5.80
CH ₂ CH=CH ₂	114.8	5.03 4.97	114.9	4.97 4.91

Carbon shifts for quaternary carbons were obtained from ¹³C NMR spectra.

*N*¹-(4-Bromobutyl)-*N*¹,*N*²,*N*³-tris(*tert*-butoxycarbonyl)guanidine (**26a**) was prepared by Goodman's procedure.¹⁵ A solution of 4-bromo-1-butanol (43 mg, 0.28 mmol) in THF (0.3 mL) was added dropwise to a solution of Ph₃P (0.11 g, 0.42 mmol) and *N*¹,*N*²,*N*³-tris(*tert*-butoxycarbonyl)guanidine (**25**)¹⁵ (0.20 g, 0.56 mmol) in THF (5 mL). A solution of DEAD (66 μL, 0.42 mmol) in THF (0.3 mL) was added dropwise at a rate such that the reaction mixture was completely colorless before addition of the next drop. After the addition was complete, the reaction mixture was refluxed for 2 h. The solution was then cooled and excess **25** was filtered off. The filtrate was concentrated and purified by flash chromatography on silica gel (23:1 hexanes/EtOAc), which gave a mixture of **26a** and **25**. Flash chromatography on silica gel (CH₂Cl₂ to 19:1 CH₂Cl₂/EtOAc) gave 80 mg of recovered **25** and 102 mg (74%) of **26a** as a clear oil: ¹H NMR

(CDCl₃) 10.67 (s, 1, NH), 3.83 (t, 2, $J = 6.7$), 3.44 (t, 2, $J = 6.7$), 1.92-1.87 (m, 2), 1.83-1.77 (m, 2), 1.51 (s, 9), 1.49 (s, 18).

***N*¹-(4-Iodobutyl)-*N*¹,*N*²,*N*³-tris(*tert*-butoxycarbonyl)guanidine (26b).** NaI (171 mg, 0.86 mmol) was added to a solution of **26a** (85 mg, 0.17 mmol) in acetone (0.2 mL). The solution was stirred at 25 °C for 13 h and concentrated to give a yellow solid. The yellow solid was dissolved in CHCl₃ (5 mL), which was washed with H₂O (5 mL) and brine (5 mL), dried over MgSO₄, filtered and concentrated to yield a yellow oil. Flash chromatography on silica gel (3:19 hexanes/EtOAc) gave 66 mg (71%) of **26b** as a yellow oil: ¹H NMR (DMSO-*d*₆) 3.51 (t, 2, $J = 6.7$), 3.27 (t, 2, $J = 6.7$), 1.78-1.75 (m, 2), 1.58-1.53 (m, 2), 1.42 (br s, 18); ¹H NMR (CDCl₃) 10.68 (br s, 1, NH), 3.82 (t, 2, $J = 7.0$), 3.22 (t, 2, $J = 7.0$), 1.85 (tt, 2, $J = 7.0, 7.0$), 1.75 (tt, 2, $J = 7.0, 7.0$), 1.51 (s, 9), 1.50 (s, 18); ¹³C NMR (CDCl₃) 153.4 (2 C), 152.6, 83.3 (3 C), 46.5, 30.7, 29.7, 28.1 (6 C), 28.0 (3 C), 6.39 (1 C was not observed).

Bis(1,1-dimethylethyl) 2-[[1,1-Dimethylethoxy]carbonyl]imino]-hexahydro-1*H*-1,3-diazepine-1,3-dicarboxylate (28). 2,4,6-Collidine (10 μL, 0.08 mmol) was added to a solution of **26b** (20 mg, 0.04 mmol) in DMSO-*d*₆ (0.5 mL). The reaction rate was monitored by NMR analysis of the disappearance of the peaks at 3.27 and 1.76 and the half-life was determined to be 24 h. After 7 d, the reaction mixture was poured into H₂O (5 mL), CH₂Cl₂ (5 mL) was added and the organic layer was removed. The aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL), and the combined organic layers were washed with H₂O (6 × 10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated to a clear oil. Flash chromatography on silica gel (9:1 CH₂Cl₂/EtOAc) gave 14 mg (90%) of **28** as a clear oil: ¹H NMR (DMSO-*d*₆) 3.55-3.42 (br, 4), 1.59-1.55 (br, 4), 1.42 (s, 18), 1.38 (s, 9); ¹H NMR (CDCl₃) 3.64-3.58 (br, 4), 1.65-1.52 (br, 4), 1.49 (s, 27); ¹³C NMR (CDCl₃) 158.3, 151.8 (2 C), 149.3, 82.7 (2 C), 80.3, 47.0 (2 C), 28.10 (3 C), 28.06 (6 C), 25.9 (2 C).

***N*¹,*N*²-Bis(benzyloxycarbonyl)-*N*¹-(4-[(methanesulfonyl)oxy]butyl)guanidine** was prepared from the known alcohol¹⁷ (78 mg, 0.20 mmol), Et₃N (70 μL, 0.49 mmol), methanesulfonyl chloride (23 μL, 0.29 mmol) and CH₂Cl₂ (2 mL) following the procedure for **17a** to afford 85 mg (92%) of mesylate as a yellow oil: ¹H NMR (CDCl₃) 9.45 (br s, 1, NH), 9.28 (br s, 1, NH), 7.43-7.28 (m, 10), 5.25 (s, 2), 5.13 (s, 2), 4.20 (t, 2, $J = 7.0$), 4.03 (t, 2, $J = 7.0$), 2.86 (s, 3), 1.73-1.69 (m, 4).

***N*¹,*N*²-Bis(benzyloxycarbonyl)-*N*¹-(4-iodobutyl)guanidine (29a)** was prepared from the above mesylate (85 mg, 0.18 mmol), NaHCO₃ (38 mg, 0.45 mmol), Na₂SO₃ (27 mg, 0.21 mmol), NaI (130 mg, 0.89 mmol) and acetone (5 mL) following the procedure for **18a**. Flash chromatography on silica gel (9:1 hexanes/EtOAc) yielded 68 mg (75%) of **29a** as a clear oil: ¹H NMR (CDCl₃) 9.45 (br s, 1, NH), 9.27 (br s, 1, NH), 7.40-7.25 (m, 10), 5.24 (s, 2), 5.15 (s, 2), 4.00 (t, 2, *J* = 7.0), 3.13 (t, 2, *J* = 7.0), 1.81-1.74 (m, 2), 1.72-1.65 (m, 2); ¹³C NMR (CDCl₃) 163.8, 160.4, 155.8, 136.9, 134.5, 128.81, 128.75 (2 C), 128.4 (2 C), 128.3 (2 C), 127.8 (2 C), 127.7, 68.9, 66.9, 43.4, 30.4, 29.7, 6.1.

***N*¹,*N*²-Bis(benzyloxycarbonyl)-*N*¹-(5-[(methanesulfonyl)oxy]pentyl)guanidine** was prepared from the known alcohol¹⁷ (70 mg, 0.17 mmol), Et₃N (59 μL, 0.42 mmol), methanesulfonyl chloride (20 μL, 0.25 mmol) and CH₂Cl₂ (2 mL) following the procedure for **17a** to afford 80 mg (96%) of mesylate as a yellow oil: ¹H NMR (CDCl₃) 9.45 (br s, 1, NH), 9.28 (br s, 1, NH), 7.40-7.26 (m, 10), 5.24 (s, 2), 5.14 (s, 2), 4.14 (t, 2, *J* = 7.3), 3.98 (t, 2, *J* = 7.3), 2.90 (s, 3), 1.70 (tt, 2, *J* = 7.3, 7.3), 1.61 (tt, 2, *J* = 7.3, 7.3), 1.36 (tt, 2, *J* = 7.3, 7.3).

***N*¹,*N*²-Bis(benzyloxycarbonyl)-*N*¹-(5-iodopentyl)guanidine (29b)** was prepared from the above mesylate (84 mg, 0.17 mmol), NaHCO₃ (36 mg, 0.43 mmol), Na₂SO₃ (26 mg, 0.21 mmol), NaI (129 mg, 0.86 mmol) and acetone (5 mL) following the procedure for **18a**. Flash chromatography on silica gel (9:1 hexanes/EtOAc) yielded 70 mg (78%) of **29b** as a white solid: ¹H NMR (CDCl₃) 9.46 (br s, 1, NH), 9.27 (br s, 1, NH), 7.41-7.29 (m, 10), 5.25 (s, 2), 5.15 (s, 2), 3.98 (t, 2, *J* = 7.3), 3.11 (t, 2, *J* = 7.3), 1.77 (tt, 2, *J* = 7.3, 7.3), 1.59 (tt, 2, *J* = 7.3, 7.3), 1.35 (tt, 2, *J* = 7.3, 7.3); ¹H NMR (DMSO-*d*₆) 9.16 (br s, 2, NH), 7.45-7.31 (m, 10), 5.25 (s, 2), 5.06 (s, 2), 3.83 (t, 2, *J* = 7.3), 3.19 (t, 2, *J* = 7.3), 1.68 (tt, 2, *J* = 7.3, 7.3), 1.27 (tt, 2, *J* = 7.3, 7.3).

4-[[Imino[[benzyloxycarbonyl]amino]methyl][benzyloxycarbonyl]amino]butyl-2,3,4,6,7,8-hexahydro-pyrrolo[1,2-*a*]pyrimidinium Chloride (31a). DBN (4 μL, 0.04 mmol) was added to a solution of **29a** (18 mg, 0.04 mmol) in DMSO-*d*₆ (0.5 mL). The solution was stirred for 24 h. The reaction mixture was poured into H₂O (5 mL) and CH₂Cl₂ (5 mL) was added. The organic layer was removed and the aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL). The combined organic layers were washed with H₂O (5 × 15 mL) and brine (15 mL), dried over Na₂SO₄, filtered and concentrated

to an oil. Flash chromatography on silica gel (19:1 to 1:1 CH₂Cl₂/EtOAc) gave 3 mg (23%) of **33**, 2 mg (15%) of **32**, and 11 mg (50%) of 80% pure **31a**, respectively.

Data for **31a**: ¹H NMR (CDCl₃) 9.42 (br s, 1, NH), 9.30 (br s, 1, NH), 7.41-7.31 (m, 10), 5.28 (s, 2), 5.11 (s, 2), 3.98 (t, 2, *J* = 7.0), 3.74 (t, 2, *J* = 7.0), 3.47-3.39 (m, 6), 3.09 (t, 2, *J* = 7.9), 2.12-2.08 (m, 2), 2.05-2.00 (m, 2), 1.70-1.65 (m, 2), 1.63-1.58 (m, 2).

Data for bis(benzyl) 2-imino-hexahydro-1*H*-1,3-diazepine-1,3-dicarboxylate (**32**): ¹H NMR (CDCl₃) 9.21 (br s, 1, NH), 7.37-7.33 (m, 10), 5.24 (s, 4), 3.70-3.61 (br, 4), 1.71-1.64 (br, 4).

Data for benzyl 2-[[[(benzyloxy)carbonyl]imino]-hexahydro-1*H*-1,3-diazepine-1-carboxylate (**33**): ¹H NMR (CDCl₃) 9.68 (br s, 1, NH), 7.42-7.26 (m, 10), 5.20 (s, 2), 5.15 (s, 2), 3.70-3.60 (br, 2), 3.35-3.29 (br, 2), 1.79-1.73 (m, 2), 1.66-1.65 (m, 2).

5-[[[Imino[[benzyloxycarbonyl]amino]methyl][benzyloxycarbonyl]amino]pentyl-2,3,4,6,7,8-hexahydro-pyrrolo[1,2-*a*]pyrimidinium Iodide (31b**)** was prepared from DBN (5 μL, 0.04 mmol) and **29b** (20 mg, 0.04 mmol) in DMSO-*d*₆ (0.5 mL) following the procedure for **31a**. Normal workup gave 14 mg (87%) of **31b** as a clear oil: ¹H NMR (CDCl₃) 9.45 (br s, 1, NH), 9.32 (br s, 1, NH), 7.43-7.29 (m, 10), 5.27 (s, 2), 5.12 (s, 2), 3.96 (t, 2, *J* = 7.3), 3.77 (t, 2, *J* = 7.3), 3.46-3.41 (m, 4), 3.38 (t, 2, *J* = 7.3), 3.08 (t, 2, *J* = 7.9), 2.17-2.09 (m, 2), 2.08-2.02 (m, 2), 1.71-1.58 (m, 4), 1.34-1.25 (m, 2).