Stereoselective Synthesis of Cyercene A and the Placidenes

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Supporting Information

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Melting points were measured on a Büchi melting point apparatus and are uncorrected. ^1H - and ^{13}C -NMR spectra were recorded on a Bruker DRX 500 or a Bruker AVB 400 spectrometer in CDCl_3 . Infrared spectra (IR) were obtained on NaCl plates with an ATI Mattson Gemini FTIR spectrometer. High-resolution mass spectra (HRMS) were obtained on a VG ProSpec Mass Spectrometer using electron impact (EI) at 70 eV.

Unless otherwise noted, all reaction mixtures were magnetically stirred in oven-dried glassware under a blanket of nitrogen or argon. External bath temperatures were used to record all reaction mixture temperatures. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F₂₅₄ TLC plates. TLC visualization was accomplished using 254 nm UV light or charring solutions of KMnO_4 and ceric ammonium molybdenate. Flash chromatography was performed on ICN siliTech 32-63 D 60 Å silica gel according to the procedure of Still.¹

Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried according to the procedure described by Bergman.² Benzene was distilled from CaH_2 immediately prior to use. DMF was dried over 4 Å molecular sieves. *n*-Butyl lithium was titrated using diphenylacetic acid in THF. CuI was purified by precipitation from hot aqueous NaI . Extracts were dried over anhydrous MgSO_4 and solvents were removed with a rotary evaporator at aspirator pressure.

The preparation of compounds **10** and **11**, **15** and **18**, and the Stille crossing couplings leading to the natural products followed the same general procedures individually. Representative procedures are demonstrated below.

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4-hydroxy-6-((E)-2-iodo-1-methyl-vinyl)-3,5-dimethyl-pyran-2-one (15): To a suspension of NaH (475 mg, 11.9 mmol, 60% in oil) in THF (75 mL) was added 2-methyl-3-oxopentanoic acid ethyl ester (1.60 g, 11.1 mmol) at 0 °C under argon. After 10 min, a solution of *n*-BuLi (4.80 mL, 12.0 mmol, 2.5 M in hexanes) was added. After 10 min, a solution of **13** (1.45 g, 7.40 mmol) in THF (5 mL) was added. After 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) and the two layers were

separated. The aqueous layer was extracted with Et₂O (2 x 40 mL) and the combined organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. The resulting oil was purified by column chromatography (30% EtOAc in hexanes) to provide a mixture of diastereomers that was taken on without characterization. To a solution of this mixture in CH₂Cl₂ taken directly from a squirt bottle (75 mL) was added the Dess-Martin periodinane (3.80 g, 8.96 mmol) at 0 °C open to the air. After addition, the reaction mixture was allowed to warm to rt. After 1 h, a mixture of 1:1:1 H₂O:saturated aqueous NaHCO₃:saturated aqueous Na₂S₂O₃ (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 40 mL) and the combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo*. The resulting oil was purified by column chromatography (20% EtOAc in hexanes) to provide a mixture of diastereomers that was taken on without characterization. To a solution of this diastereomeric mixture in benzene (50 mL) was added 1,8-diazobicyclo[5.4.0]undec-7-ene (1.10 mL, 7.35 mmol). The resulting mixture was heated to 70 °C under argon for 1 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (4% MeOH, 0.1% AcOH in CH₂Cl₂) to provide 1.20 g of **15** (53%) as a white solid: mp 164-166 °C; *R_f* 0.34 (5% MeOH in CH₂Cl₂); IR (thin film) 3070(br), 1661, 1556 cm⁻¹; ¹H NMR (500 MHz): δ_H 6.66 (s, 1 H), 5.63 (s, 1 H), 2.11 (s, 3 H), 2.00 (s, 6 H); ¹³C NMR (100 MHz): δ_C 165.9, 165.8, 154.8, 139.7, 109.0, 100.2, 88.8, 23.1, 11.8, 9.1; HRMS calcd for C₁₀H₁₁IO₃ (M⁺): 305.9753; found: 305.9755.

2-((E)-2-iodo-1-methyl-vinyl)-6-methoxy-3,5-dimethyl-pyran-4-one (10): To a suspension of **11** (890 mg, 2.91 mmol) in CH₂Cl₂ (30 mL) was added MeOSO₂F (1.20 mL, 15.0 mmol) at 0 °C under argon. After the addition was complete the mixture was allowed to warm to rt. After 12 h, the reaction mixture was concentrated *in vacuo* taking great care to avoid exposure to the volatile and highly toxic MeOSO₂F. The residue was dissolved in CH₂Cl₂ and concentrated three more times to remove all MeOSO₂F. This residue was then taken up in CH₂Cl₂ (25 mL) and 1 N NaOH (50 mL). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined organics were dried (MgSO₄), filtered, and concentrated *in vacuo* to provide 888 mg of **10** (95%) as a white solid: mp 90-93 °C; *R_f* 0.36 (40% EtOAc in hexanes); IR (thin film) 1655, 1611, 1590 cm⁻¹; ¹H NMR (500 MHz): δ_H 6.72 (s, 1 H), 3.93 (s, 3 H), 2.11 (s, 3 H), 1.95 (s, 3 H), 1.82 (s, 3 H); ¹³C NMR (100 MHz): δ_C 181.0, 161.9, 154.6, 139.3, 119.2, 99.9, 89.5, 55.6, 22.9, 11.9, 7.1; HRMS calcd for C₁₁H₁₃IO₃ (M⁺): 319.9909; found: 319.9912.

4-hydroxy-6-((Z)-2-iodo-1-methyl-vinyl)-3,5-dimethyl-pyran-2-one (18)

White solid. mp 193.0-194.5 °C; R_f 0.21 (33% EtOAc in hex); IR (thin film) 3093(br), 1665, 1611, 1561 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ_{H} 6.66 (s, 1 H), 2.01 (s, 3 H), 1.89 (s, 3 H), 1.86 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ_{C} 168.2, 167.6, 157., 142.4, 110.1, 100.4, 83.6, 23.4, 11.2, 9.2; HRMS calcd for $\text{C}_{10}\text{H}_{11}\text{IO}_3$ (M^+): 305.9753; found: 305.9750.

2-((Z)-2-iodo-1-methyl-vinyl)-6-methoxy-3,5-dimethyl-pyran-4-one (11)

Colorless oil. R_f 0.20 (25% EtOAc in hexanes); IR (thin film) 1663, 1612, 1586 cm^{-1} ; ^1H NMR (400 MHz) δ_{H} 6.37 (q, $J = 1.5$ Hz, 1 H), 3.94 (s, 3 H), 2.08 (d, $J = 1.5$ Hz, 3 H), 1.88 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR (100 MHz) δ_{C} 180.7, 162.4, 155.8, 140.4, 118.9, 100.0, 83., 55.6, 23.5, 10.6, 6.9; HRMS calcd for $\text{C}_{11}\text{H}_{13}\text{IO}_3$ (M^+): 319.9909; found: 319.9913.

cyercene A (1) A mixture of **10** (20.5 mg, 64 μmol), **19** (21.3 mg, 91 μmol), $\text{Pd}(\text{PPh}_3)_4$ (4.3 mg, 3.7 μmol), CuI (1.9 mg, 10 μmol) and CsF (24.1 mg, 0.16 mmol) in DMF (0.5 mL) was heated to 45 °C under argon for 1.5 h. The reaction mixture was taken up in H_2O (10 mL) and Et_2O (3 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (2 x 3 mL) and the combined organic layers were then washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried (MgSO_4), filtered, concentrated *in vacuo* and purified by column chromatography (30% EtOAc in hexanes) to provide 10.8 mg (64%) of **Cyercene A (1)** as a white solid: mp 52-55 °C; R_f 0.39 (40% EtOAc in hexanes); IR (thin film) 2960, 2927, 1658, 1612, 1600 cm^{-1} ; ^1H NMR (500 MHz) δ_{H} 6.10 (s, 1 H), 5.52 (app t, $J = 17.2$ Hz, 1 H), 3.95 (s, 3 H), 2.15 (app quint, $J = 17.4$ Hz, 2 H), 2.06 (d, $J = 1.3$ Hz, 3 H), 2.01 (s, 3 H), 1.86 (s, 3 H), 1.84 (s, 3 H), 1.03 (t, $J = 17.5$ Hz, 3 H); ^{13}C (125 MHz): δ_{C} 181.8, 162.1, 159.3,

139.7, 136.1, 131.2, 125.6, 118.0, 99.4, 55.4, 21.8, 16.6, 16.3, 14.1, 12.1, 7.1; HRMS calcd for C₁₆H₂₂O₃ (M⁺): 262.1569; found: 262.1566.

2

placidene-A (2)

White solid. mp: 47.0-48.0 °C; R_f 0.33 (25% EtOAc in hexanes); IR 2961, 2932, 2874, 1656, 1614, 1597 cm⁻¹; ¹H NMR (400 MHz) δ_H 6.18 (s, 1 H), 5.40 (t, *J* = 7.2 Hz, 1 H), 3.97 (s, 3 H), 2.05 (s, 3 H), 1.99 (m, 2 H), 1.91 (s, 3 H), 1.88 (s, 3 H), 1.85 (s, 3 H), 0.98 (t, *J* = 7.5 Hz, 3 H); ¹³C NMR (100 MHz) δ_C 181.5, 161.9, 158.3, 135.2, 132.4, 130.3, 128.0, 118.0, 99.3, 55.2, 23.2, 22.7, 16.1, 14.0, 12.0, 6.9; HRMS calcd for C₁₆H₂₂O₃ (M⁺): 262.1569; found: 262.1570.

3

isoplacidene-A (3)

White solid. mp: 68.0-69.0 °C; R_f 0.34 (25% EtOAc in hexanes); IR (thin film) 2961, 2926, 2873, 1661, 1613, 1594 cm⁻¹; ¹H NMR (400 MHz) δ_H 6.42 (s, 1 H), 5.31 (t, *J* = 7.2 Hz, 1 H), 3.94 (s, 3 H), 2.08-1.95 (m, 5 H), 1.87 (s, 3 H), 1.83 (s, 3 H), 1.57 (s, 3 H), 0.94 (t, *J* = 7.4 Hz, 3 H); ¹³C NMR (100 MHz) δ_C 180.8, 162.4, 156.3, 134.8, 132.1, 130.3, 126.8, 119.5, 99.7, 55.4, 23.1, 21.8, 21.7, 14.1, 10.8, 6.9; HRMS calcd for C₁₆H₂₂O₃ (M⁺): 262.1569; found: 262.1566.

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placidene-B (4)

White solid. mp: 76.0-77.0 °C; R_f 0.30 (25% EtOAc in hexanes); IR 2957, 2921, 1656, 1610, 1596 cm⁻¹; ¹H NMR (400 MHz) δ_H 6.15 (s, 1 H), 5.49 (q, *J* = 6.9 Hz, 1 H), 3.98 (s, 3 H), 2.06

(s, 3 H), 1.90 (s, 3 H), 1.88 (s, 3 H), 1.85 (s, 3 H), 1.61 (d, $J = 6.9$ Hz, 3 H); ^{13}C NMR (100 MHz) δ_{C} 181.5, 161.9, 158.3, 135.0, 131.9, 128.1, 124.5, 118.1, 99.4, 55.3, 23.2, 16.1, 15.1, 12.1, 6.9; HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3$ (M^+): 248.1412; found: 248.1416.

isoplacidene-B (5)

White solid. mp: 80.0-81.0 °C; R_f 0.31 (25% EtOAc in hexanes); IR (thin film) 2954, 2917, 1655, 1611, 1591 cm^{-1} ; ^1H NMR (400 MHz) δ_{H} 6.41 (s, 1 H), 5.40 (q, $J = 7.0$ Hz, 1 H), 3.94 (s, 3 H), 2.06 (s, 3 H), 1.87 (s, 3 H), 1.83 (s, 3 H), 1.61 (d, $J = 7.0$ Hz, 3 H), 1.57 (s, 3 H); ^{13}C NMR (100 MHz) δ_{C} 180.9, 162.4, 156.3, 132.0, 131.8, 126.8, 119.5, 99.7, 55.4, 23.1, 21.8, 14.1, 10.8, 6.9 (The missing carbon signal is assumed to be due to the isochronicity of two quaternary carbons. By correlation with isoplacidene-A, this appears to be the 131.8 ppm signal. An APT spectrum is attached in addition to the normal ^{13}C spectrum.); HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3$ (M^+): 248.1412; found: 248.1408.

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

² Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.