Supporting Information
for DOI: 10.1055/s-0036-1588413
© Georg Thieme Verlag KG Stuttgart · New York 2017
Supporting Information for

Synthesis of the C₁-C₂₃ Fragment of the Archazolids and Evidence for V-ATPase but not COX Inhibition

Gregory W. O’Neil,* Alexander M. Craig, John R. Williams, Jeffery C. Young, and P. Clint Spiegel

Department of Chemistry, Western Washington University, Bellingham, WA, 98225

Contents

General Experimental Procedures S1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Procedure/ Characterization</th>
<th>(^1\text{H} \text{ NMR spectrum})</th>
<th>(^{13}\text{C} \text{ NMR spectrum})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>S2</td>
<td>S11</td>
<td>S11</td>
</tr>
<tr>
<td>4</td>
<td>S3</td>
<td>S13</td>
<td>S13</td>
</tr>
<tr>
<td>7</td>
<td>S4</td>
<td>S14</td>
<td>S14</td>
</tr>
<tr>
<td>8</td>
<td>S5</td>
<td>S15</td>
<td>S15</td>
</tr>
<tr>
<td>9</td>
<td>S6</td>
<td>S16</td>
<td>S16</td>
</tr>
<tr>
<td>10</td>
<td>S6</td>
<td>S17</td>
<td>S17</td>
</tr>
<tr>
<td>11</td>
<td>S7</td>
<td>S18</td>
<td>S18</td>
</tr>
<tr>
<td>1</td>
<td>S8</td>
<td>S19</td>
<td>S19</td>
</tr>
</tbody>
</table>

VATPase Assay S9

COX Assay S10

* Corresponding Author: oneil@chem.wwu.edu
General: All reactions were carried out under N₂ in flame-dried glassware. IR: Nicolet iS10 spectrometer, wavenumbers (ν) in cm⁻¹. MS(El): JEOL JMS-AX505HA mass spectrometer. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. All other reagents were purchased and used as received unless otherwise mentioned. All TLC analysis used 0.25 mm silica layer fluorescence UV254 plates. Flash chromatography: SilaCycle silica gel P60 (230-400 mesh). NMR: Spectra were recorded on a Varian Mercury 300, or Inova 500 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. The solvent signals were used as references (CD₃OD: δC = 49.3 ppm; residual CH₃OD in CD₃OD: δH = 4.78 ppm; C₆D₆: δC = 128.0 ppm; residual C₆H₆ in C₆D₆: δH = 7.15 ppm; CDCl₃: δC = 77.0 ppm; residual CHCl₃ in CDCl₃: δH = 7.26 ppm).

Compound 3. To a solution of ethyl triphenylphosphonium iodide (1.4 g, 3.2 mmol, 2.0 equiv.) in THF (13 mL) at room temperature was added NaHMDS (1.0 M, 3.33 mL, 2.08 equiv.) and the mixture was stirred for 30 min. The resulting red homogeneous solution was transferred via cannula to a dropping funnel and added to a solution of iodine (0.81 g, 3.2 mmol, 2.0 equiv.) in THF (26 mL) at -78 ºC over 1h and then stirred for 15 min. NaHMDS (1.0M, 3.2 mL) was then added and the mixture was stirred for 30 min before adding aldehyde 2 (0.75 g, 1.6 mmol, 1.0 equiv.) as a solution in THF (1.8 mL). The mixture was stirred for 1.5 h and then warmed to -20 ºC over 15 min. before quenching with aq. NH₄Cl (50 mL), filtered through Celite, and extracted with MTBE (2 x 50 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 hexanes:ethyl acetate) gave 3 (0.83 g, 85%) as an 8:1 Z,Z,Z,E mixture of stereoisomers.

Spectral data for the major stereoisomer: [α]D²⁰ = -8.0 (c 3.0, CH₂Cl₂). IR (ATR) 2927, 2954, 2855, 1251, 1099, 1058, 1030, 832, 811, 772 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 6.16 (s, 1H), 5.12 (dt, J = 10.0, 1.5 Hz, 1H), 5.08 (dd, J = 9.0, 1.0 Hz, 1H), 4.13 (dd, J = 8.9, 5.7 Hz, 1H), 3.60 (t, J = 6.0 Hz, 2H), 2.53 (d, J = 1.5 Hz, 3H), 2.31 (m, 1H), 1.97 (m, 2H), 1.77 (s, 3H), 1.58 (s, 3H), 1.50 – 1.40 (m, 4H), 0.90 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.06 (s, 6H), -0.01 (s, 3H), -0.04 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 136.2, 135.4, 134.1, 132.4, 127.2, 100.6, 72.8, 63.0, 41.1, 39.4, 34.0, 32.5, 26.0, 25.9, 24.1, 22.2, 16.8, 15.6, -4.3, -4.8, -5.3. HRMS (ESI⁺): Calcd for C₂₈H₅₆O₂Si₂Na⁺ (M + Na)⁺: 629.2683. Found 629.2668.
Compound 4. To a solution of amide 5 (0.7 g, 2.4 mmol, 1.0 equiv.) in DCM (13 mL) at 0 °C was added PdCl₂(PPh₃)₂ (0.17 g, 0.24 mmol, 0.1 equiv.) and Bu₃SnH (0.73 mL, 2.7 mmol, 1.1 equiv.) and the mixture was allowed to warm to room temperature for 1 h. Concentration of the mixture in vacuo and purification by flash chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave the vinyl stannane Weinreb amide (1.32 g, 96%) as a 6:1 mixture of β:α regioisomers.

Spectral data for the major isomer: [α]D²⁰ = -5.0 (c 1.0, CH₂Cl₂). IR (ATR) 3064, 2903, 1640, 1350, 1194, 1067, 910, 730 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 6.14 (d, J = 19.1 Hz, 1H), 5.98 (dd, J = 19.1, 6.1 Hz, 1H), 4.21 (m, 1H), 3.66 (s, 3H), 3.15 (s, 3H), 3.00 (m, 1H), 1.49 (m, 6H), 1.31 (m, 12H), 1.20 (d, J = 7.0 Hz, 3H), 0.93 (s, 9H), 0.90 (t, J = 8.0 Hz, 9H), 0.09 (s, 3H), 0.04 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 149.9, 128.8, 78.3, 61.5, 42.7, 29.1, 27.3, 25.9, 18.3, 14.6, 13.7, 9.4, -4.2, -4.8. HRMS (ESI⁺): Calcd for C₂₆H₅₅NO₃Si₂SnNa⁺ (M + Na)⁺: 600.2890. Found 600.2875.

To a solution of diethyl ethyl phosphonate (0.37 mL, 2.3 mmol, 2.5 equiv.) in THF (4.6 mL) at -78 °C was added BuLi (1.6M, 0.85 mL, 2.3 equiv.) and the mixture was stirred for 20 min. The Weinreb amide vinyl stannane (0.53 g, 0.92 mmol, 1.0 equiv.) was then added and the reaction was stirred for 30 min before quenching with aq. NH₄Cl (30 mL) and extracting with MTBE (2 x 25 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave 4 (0.49 g, 78%) as a ~1:1 mixture of diastereomers.

Spectral data for the mixture of diastereomers: IR (ATR) 3345, 2963, 2928, 1515, 1425, 1294, 1267, 1109, 730 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 6.10 (dd, J = 19.2, 0.9 Hz, 1H), 6.03 (19.2, 1.0 Hz, 1H), 5.91 (dd, J = 19.1, 5.8 Hz, 1H), 5.80 (dd, J = 19.1, 6.6 Hz, 1H), 4.35 (td, J = 5.8, 1.1 Hz, 1H), 4.16 – 4.05 (m, 8H), 4.02 (dd, J = 6.4, 6.4 Hz, 1H), 3.55 (dq, Jₕ,P = 25.6 Hz, Jₕ,H = 7.3 Hz, 1H), 3.32 (dq, Jₕ,H = 6.1 Hz, 1H), 3.27 (qd, J = 7.2, 6.1 Hz, 1H), 2.88 (qd, J = 7.1, 5.5 Hz, 1H), 1.46 (m, 12H), 1.35 (dd, Jₕ,p = 18.2 Hz, Jₕ,HH = 7.3 Hz, 3H), 1.32 – 1.26 (m, 24H), 1.30 (s, 9H), 1.28 (s, 9H), 1.22 (dd, Jₕ,P = 17.4 Hz, Jₕ,HH = 7.3 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.90 – 0.84 (m, 30H), 0.04 (s, 3H), 0.03 (s, 3H), -0.01 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 208.3 (d, Jₜ,P = 5.2 Hz, 1C), 208.0 (d, Jₜ,C = 4.5 Hz, 1C), 149.2, 147.9, 130.5, 129.2, 79.72, 76.1, 62.5 (d, Jₜ,C = 3.1 Hz, 1C), 62.44 (d, Jₜ,C = 3.4 Hz, 1C), 62.4, 62.3, 53.58, 51.87, 48.1 (d, 1C), 45.3 (d, 1C), 44.78, 29.1, 29.0, 27.49, 27.28, 27.06, 25.89, 25.81, 18.21, 18.16, 16.45, 16.41, 16.38, 16.36, 16.33, 13.69, 13.67, 13.02, 12.70, 11.60, 11.55, 10.36, 10.31,
9.46, 9.39, 8.09, -4.14, -4.21, -4.84, -4.94. HRMS (ESI+): Calcd for C_{30}H_{63}O_{5}PSiSnNa^{+} (M + Na)^+: 705.3108. Found 705.3097.

**Compound 7.** Ba(OH)_{2}•8H_{2}O (0.23 g, 1.0 equiv.) was first activated by heating to 130 °C under vacuum for 2 h. Phosphonate 4 (0.5 g, 0.73 mmol, 1.0 equiv.) was then added and the mixture was stirred for 1.5 h. Aldehyde 6 (0.17 g, 1.0 equiv.) was then added and the mixture was stirred for 18 h. The reaction was filtered through Celite and concentrated in vacuo. Purification by flash chromatography on silica (10:1 hexanes:ethyl acetate) gave 7 (0.41 g, 75%) as a 10:1 mixture of E:Z isomers.

$[\alpha]^{20}_{D} = -2.8$ (c 1.0, CH_{2}Cl_{2}). IR (ATR) 3064, 2903, 1735, 1640, 1350, 1194, 1067, 910, 730 cm^{-1}. $^{1}$H NMR (500 MHz, CDCl_{3}): $\delta$ 6.99 (d, $J = 10.8$ Hz, 1H), 6.44 (ddd, $J = 15.3$, 10.8, 1.0 Hz, 1H), 6.03 (dd, $J = 15.1$, 7.6 Hz, 1H), 6.01 (dd, $J = 19.1$, 0.9 Hz, 1H), 5.83 (dd, $J = 19.1$, 6.2 Hz, 1H), 4.16 (ddd, $J = 8.1$, 7.2, 0.7 Hz, 1H), 3.53 (dd, $J = 9.7$, 6.7 Hz, 1H), 3.48 (dd, $J = 9.7$, 6.4 Hz, 1H), 3.36 (dq, $J = 13.7$, 6.8 Hz, 1H), 2.48 (m, 1H), 1.58 (s, 3H), 1.43 (m, 6H), 1.26 (m, 12H), 1.13 (d, $J = 7.0$ Hz, 3H), 1.05 (d, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.86 (t, $J = 7.4$ Hz, 6H), 0.80 (t, $J = 8.1$ Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H). $^{13}$C NMR (125 MHz, CDCl_{3}): $\delta$ $^{13}$C NMR (126 MHz, CDCl_{3}) $\delta$ 204.5, 149.7, 145.7, 138.7, 135.0, 128.7, 126.3, 79.1, 67.5, 46.3, 40.3, 29.0, 27.2, 25.9, 25.8, 25.7, 18.3, 18.2, 16.3, 15.0, 13.7, 11.7, 9.4, -4.1, -4.8, -5.3, -5.4. HRMS (ESI+): Calcd for C_{38}H_{76}O_{3}Si_{2}SnNa^{+} (M + Na)^+: 779.4260. Found 779.4289.
Compound 8. To a solution of 7 (0.21 g, 0.28 mmol) in THF/MeOH (1.8 mL/1.8 mL) at 0 °C was added NaBH₄ (0.04 g, 1.1 mmol, 4.0 equiv.) and the mixture was stirred for 1 h. The reaction was quenched with aq. Brine (20 mL) and extracted with MTBE (2 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 hexanes:ethyl acetate) gave the corresponding alcohol as a 10:1 mixture of diastereomers that was used without further purification.

To a solution of the alcohol in THF (3.0 mL) at -78 °C was added LiHMDS (1.0M, 0.56 mL) and the mixture was stirred for 20 min before adding MeI (0.05 mL, 0.84 mmol, 3.0 equiv.). The reaction was allowed to slowly warm to room temperature for 15 h before quenching with aq. NH₄Cl (25 mL) and extracting with MTBE (2 x 25 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 hexanes:ethyl acetate) gave 8 (0.13 g, 63% 2-steps) as an oil.

\[ \alpha_{D}^{20} = +4.1 \ (c \ 0.5, \ \text{CH}_2\text{Cl}_2) \]. IR (ATR) 2958, 2930, 2859, 1447, 1371, 1308, 1221, 1143, 1085, 1024, 755, 699 cm⁻¹.¹H NMR (500 MHz, CDCl₃): δ 6.44 (ddd, \( J = 15.2, 10.7, \ 1.1 \text{ Hz, 1H} \)), 6.37 (dd, \( J = 19.1, 1.0 \text{ Hz, 1H} \)), 6.29 (dd, \( J = 19.1, 5.0 \text{ Hz, 1H} \)), 6.18 (d, \( J = 11.0 \text{ Hz, 1H} \)), 5.58 (dd, \( J = 15.3, 7.8 \text{ Hz, 1H} \)), 5.03 (ddd, \( J = 4.9, 1.2, 1.2 \text{ Hz, 1H} \)), 3.65 (d, \( J = 9.9 \text{ Hz, 1H} \)), 3.48 (dd, \( J = 9.7, 6.1 \text{ Hz, 1H} \)), 3.38 (dd, \( J = 9.8, 7.0 \text{ Hz, 1H} \)), 3.20 (s, 3H), 2.42 (m, 1H), 1.97 (m, 1H), 1.68 (s, 3H), 1.62 (m, 6H), 1.39 (m, 12H), 1.11 (s, 9H), 1.04 (d, \( J = 7.0 \text{ Hz, 3H} \)), 1.00 (d, \( J = 7.0 \text{ Hz, 3H} \)), 0.98 (s, 9H), 0.95 (t, \( J = 8.3 \text{ Hz, 9H} \)), 0.22 (s, 3H), 0.21 (s, 3H), 0.22 (s, 3H), 0.05 (s, 6H).¹³C NMR (125 MHz, CDCl₃): δ 152.3, 137.0, 134.2, 130.1, 126.1, 125.6, 88.4, 74.0, 67.8, 55.2, 42.3, 39.9, 29.3, 27.3, 26.0, 25.8, 18.3, 18.2, 16.4, 13.6, 10.5, 9.5, 8.9, -3.9, -5.1, -5.5, -5.6. HRMS (ESI⁺): Calcd for C₃₉H₇₀O₃Si₂SnNa⁺ (M + Na)⁺: 795.4573. Found 795.4593.
**Compound 9.** To a solution of 8 (0.39 g, 0.50 mmol, 1.0 equiv.) in DCM (4 mL) at -10 ºC was added iodine (0.14 g, 0.55 mmol, 1.1 equiv.) as a solution in DCM (1.0 mL) over 10 min. The reaction was stirred for 20 min. before quenching with aq. Na₂S₂O₃ (25 mL) and extracting with MTBE (2 x 25 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 hexanes:ethyl acetate) gave 9 (0.21 g, 70%) as an oil.

\[ [\alpha]_{D}^{20} = -11.1 \; (c \; 1.0, \; \text{CH}_2\text{Cl}_2) \]. IR (ATR) 3345, 2963, 2928, 1515, 1425, 1294, 1267, 1109, 730 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 6.55 (dd, \( J = 14.6, 6.3, 1H \)), 6.30 (ddd, \( J = 15.2, 10.8, 1.1 \) Hz, 1H), 6.19 (dd, \( J = 14.4, 1.3, 1H \)), 5.89 (d, \( J = 10.7 \) Hz, 1H), 5.61 (dd, \( J = 15.1, 7.3 \) Hz, 1H), 4.62 (ddd, \( J = 6.0, 1.5, 1.5 \) Hz, 1H), 3.52 (dd, \( J = 9.8, 6.4 \) Hz, 1H), 3.44 (dd, \( J = 9.8, 6.8 \) Hz, 1H), 3.32 (d, \( J = 10.0 \) Hz, 1H), 3.12 (s, 3H), 2.41 (m, 1H), 1.62 (m, 1H), 1.60 (s, 3H), 1.03 (d, \( J = 7.0 \) Hz, 3H), 0.93 (s, 9H), 0.90 (s, 9H), 0.64 (d, \( J = 7.0 \) Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 149.2, 137.3, 133.4, 130.3, 125.4, 87.9, 75.5, 73.2, 67.9, 55.5, 41.2, 39.7, 29.7, 18.4, 18.2, 16.5, 10.5, 8.9, -4.1, -5.2, -5.3.

**Compound 10.** To a solution of tBuLi (1.7M, 0.56 mL, 3.0 equiv.) in Et₂O (3.2 mL) was added 3 (0.2 g, 0.32 mmol) and the mixture was stirred for 10 min before adding Bu₃SnCl (0.17 mL, 0.63 mmol, 2.0 equiv.) and stirring for 1 h. The reaction was quenched with H₂O (25 mL) and extracted with MTBE (2 x 25 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (10:1 hexanes:ethyl acetate) gave 10 (0.22 g, 90%) as an oil.

\[ [\alpha]_{D}^{20} = 19.67 \; (c \; 3.6, \; \text{CH}_2\text{Cl}_2) \]. IR (ATR) 2954, 2926, 2854, 1463, 1250, 1101, 1070, 773 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 6.83 (s, 1H), 5.13 (dd, \( J = 9.1, 1.2 \) Hz, 1H), 5.02 (dt, \( J = 9.5, 1.2 \) Hz,
1H), 4.17 (dd, J = 8.9, 5.6 Hz, 1H), 3.63 (t, J = 6.1 Hz, 2H), 2.60 (m, 1H), 2.01 (d, J = 1.7 Hz, 3H), 2.00 (m, 2H), 1.77 (s, 3H), 1.63 (m, 6H), 1.59 (d, J = 1.1 Hz, 3H), 1.54 – 1.45 (m, 4H), 1.44 – 1.29 (m, 12H), 1.12 (s, 9H), 0.97 – 0.89 (m, 12H), 0.92 (s, 9H), 0.07 (s, 6H), 0.02 (s, 3H), -0.01 (s, 3H).  

$^1$H NMR (125 MHz, CDCl$_3$):  δ $^1$H NMR (126 MHz, CDCl$_3$) δ 140.5, 140.1, 135.2, 134.2, 132.0, 127.1, 72.7, 63.0, 39.7, 39.4, 32.5, 30.8, 29.4, 29.3, 28.8, 27.7, 27.4, 26.0, 25.9, 24.1, 18.4, 16.6, 13.7, 13.6, 10.5, 7.9, -4.3, -4.8, -5.3. HRMS (ESI+): Calcd for C$_{40}$H$_{82}$O$_2$Si$_2$SnNa$^+$ (M + Na$^+$): 793.4875. Found 793.4874.

**Compound 11.** To a solution of 9 (36 mg, 0.058 mmol, 1.0 equiv.) and 10 (45 mg, 0.058 mmol, 1.0 equiv) in degassed THF (1.2 mL) was added [Ph$_2$PO$_2$][NBu$_4$] (75 mg, 0.17 mmol, 3.0 equiv.), CuTC (28 mg, 0.07 mmol, 2.5 equiv.) and Pd(PPh$_3$)$_4$ (7 mg, 0.006 mmol, 0.1 equiv.) and the mixture was stirred for 15 h. The reaction was quenched with aq. NaHCO$_3$ (15 mL) and extracted with MTBE (2 x 15 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica (20:1 to 10:1 hexanes:ethyl acetate) gave 11 (46 mg, 82%) as an oil.

[$\alpha$]$_{D}^{20}$ = -5.2 (c 0.5, CH$_2$Cl$_2$). IR (ATR) 3062, 2983, 1736, 1614, 1415, 1274, 1267, 1129, 1078, 930 cm$^{-1}$. $^1$H NMR (500 MHz, C$_6$D$_6$): δ 6.80 (d, J = 16.0 Hz, 1H), 6.44 (ddd, J = 15.3, 10.7, 0.9 Hz, 1H), 6.17 (d, J = 10.4 Hz, 1H), 6.02 (s, 1H), 5.90 (ddd, J = 16.0, 7.2 Hz, 1H), 5.58 (ddd, J = 15.4, 8.0 Hz, 1H), 5.34 (dd, J = 8.4, 0.8 Hz, 1H), 5.29 (ddd, J = 9.8, 2.0, 1.0 Hz, 1H), 5.07 (d, J = 7.4 Hz, 1H), 4.29 (dd, J = 9.0, 6.0 Hz, 1H), 3.63 (d, J = 10.0 Hz, 1H), 3.58 – 3.53 (m, 2H), 3.47 (dd, J = 9.7, 6.2 Hz, 1H), 3.38 (dd, J = 9.7, 6.8 Hz, 1H), 3.18 (s, 3H), 2.71 (m, 1H), 2.42 (m, 1H), 1.96 (m, 2H), 1.91 (s, 3H), 1.86 (m, 1H), 1.89 (d, J = 1.0 Hz, 3H), 1.71 (d, J = 1.0 Hz, 3H), 1.59 (s, 3H), 1.50 (m, 2H), 1.39 (m, 2H), 1.08 (s, 6H), 1.03 (s, 6H), 1.02 (s, 3H), 1.01 (s, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.98 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.95 (s, 6H), 0.94 (d, J = 7.0 Hz, 3H), 0.93 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H), 0.13 (s, 6H), 0.08 (s, 6H), 0.05 (s, 6H). $^{13}$C NMR (125 MHz, C$_6$D$_6$):  δ $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ 137.8, 136.0, 134.9, 134.7, 133.4, 133.3, 133.0,
132.5, 130.9, 130.3, 126.3, 125.4, 73.8, 72.9, 68.5, 63.4, 63.4, 56.0, 43.7, 41.5, 40.6, 40.1, 33.1, 31.4, 30.3, 28.5, 26.7, 26.6, 26.5 25.4, 24.8, 24.8, 24.0, 21.0, 19.1, 18.9, 18.8, 17.4, 17.2, 17.1, 16.2, 14.3, 11.2, 9.8, 8.7, -3.0, -3.6, -4.2, -4.3, -4.4, -4.7, -4.8, -4.9. HRMS (ESI+): Calcd for C₅₅H₁₀₈O₅Si₄Na⁺ (M + Na)⁺: 983.7172. Found 983.7179.

**Tetrol 1.** To a solution of 11 (25 mg, 0.026 mmol) in THF (1.2 mL) at 0 °C was added pyridine (0.3 mL) and HF•pyr. (60% HF, 0.2 mL) and the mixture was allowed to slowly warm to room temperature for 42 h. The reaction was cooled to 0 °C, diluted with ethyl acetate (15 mL) and quenched with aq. NaHCO₃ (15 mL). The layers were separated and the aqueous phase was re-extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica (1:1 to 1:2 to 0:1 hexanes:ethyl acetate) gave 1 (7 mg, 58%) as an oil.

\[ [\alpha]_{D}^{20} = -6.0 \ (c \ 0.5, \ CH₂Cl₂) \]

IR (ATR) 3350, 3955, 2929, 2872, 1716, 1688, 1525, 1471, 1418, 1369, 1244, 1126, 1084, 1008, 963, 919, 828, 730 cm⁻¹. ¹H NMR (500 MHz, CD₃OD): δ 6.52 (dd, \( J = 16.0, 0.7 \text{ Hz, 1H, (H13)} \)), 6.29 (ddd, \( J = 15.0, 10.8, 0.7 \text{ Hz, 1H, (H20)} \)), 5.90 (d, \( J = 11.0 \text{ Hz, 1H, (H19)} \)), 5.74 (s, 1H, H(11)), 5.70 (dd, \( J = 15.8, 5.9 \text{ Hz, 1H, (H14)} \)), 5.57 (dd, \( J = 15.2, 7.6 \text{ Hz, 1H, (H21)} \)), 5.09 (d, \( J = 9.0 \text{ Hz, 1H, (H9)} \)), 5.07 (d, \( J = 8.0, 1.0 \text{ Hz, 1H, (H6)} \)), 4.46 (dd, \( J = 6.0, 3.5 \text{ Hz, 1H (H15)} \)), 4.05 (dd, \( J = 9.0, 6.1 \text{ Hz, 1H, (H7)} \)), 3.48 (t, \( J = 6.0 \text{ Hz, 2H, (H1a/b)} \)), 3.38 (d, \( J = 8.4 \text{ Hz, 1H, (H17)} \)), 3.37 (dd, \( J = 10.6, 5.5 \text{ Hz, 1H, H23a)} \)), 3.33 (dd, \( J = 10.6, 6.5 \text{ Hz, 1H, H23b)} \)), 3.09 (s, 3H, (OMe)), 2.36 – 2.28 (m, 2H, (H8/22)), 1.97 (t, \( J = 7.3 \text{ Hz, 2H, (H4a/b)} \)), 1.81 (d, \( J = 1.2 \text{ Hz, 3H, (Me10)} \)), 1.70 (s, 3H, (Me12)), 1.64 (m, 1H, (H16)) 1.58 (d, \( J = 1.0 \text{ Hz, 3H, (Me5)} \)), 1.56 (d, \( J = 1.0 \text{ Hz, 3H, (Me18)} \)), 1.48 – 1.40 (m, 4H, (H2/3)), 0.96 (d, \( J = 7.0 \text{ Hz, 3H, (Me22)} \)), 0.81 (d, \( J = 7.0 \text{ Hz, 3H, (Me8)} \)), 0.59 (d, \( J = 7.0 \text{ Hz, 3H, (Me16)} \)). ¹³C NMR (125 MHz, CD₃OD): δ 139.3, 138.7, 134.7, 134.4, 133.6, 132.7, 131.5, 130.5, 129.9, 127.3, 126.9, 90.4, 73.1, 73.0, 71.7, 68.2, 63.0, 56.3, 42.8, 41.3, 41.2, 40.7, 33.3, 25.3, 25.0, 20.5, 17.2, 17.0, 16.3, 11.1, 10.7. HRMS (ESI+): Calcd for C₅₁H₅₂O₅Na⁺ (M + Na)⁺: 527.3712. Found 527.3729.
VATPase Assay

A bioassay was performed to test inhibition of V-ATPases in *Arabidopsis thaliana*. Dark grown *Arabidopsis* seedlings undergo etiolation, a process in which the hypocotyl elongates at a rapid rate. This process, which increases the likelihood that embryotic leaves will reach light, relies on increased cell turgor and subsequent cell elongation. V-ATPases create this change in turgor through active transport of protons into the vacuole, thus lowering water potential. Wild-type *Arabidopsis thaliana* of the ecotype Colombia were vernalized (4°C dark treatment for one week after harvesting) then planted on 1% agar plates pH 5.7 containing .1x Murasinghe and Skoog Media. Compound 1 (Figure 3) and Concanamycin in DCM were administered by adding to the media to a total concentration of 0.125 µM, 0.25 µM, 0.5 µM and 1.0 µM. Additionally, control plants were grown in the absence of compound 1 and concanamycin in equivalent amounts of DCM. All plants were placed in a 4°C dark room for two days before being exposed to light for 24 hours to promote germination followed by seven days in aluminum foil to promote etiolation. Hypocotyls were photographed and measured using ImageJ.

![Graph 1](image1.png)

![Graph 2](image2.png)
**COX Inhibition Assay**

Compound 1 was serially diluted from 250 to 1.5625 µM in DMSO and assayed with an ELISA-based COX (ovine/human) Inhibitor Screening Assay Kit (Cayman Chemical, Ann Arbor, MI) according to the manufacturer’s instructions. This is a competition-based assay between prostaglandins (PGs) and a PG-acetylcholinesterase conjugate (PG-AChE) for a limiting amount of PG antiserum. Following the pre-incubation of both COX-1 (ovine) and COX-2 (human recombinant) with compound 1 for 10 minutes at 37°C, the reactions were mixed with arachidonic acid and subsequently quenched with Stannous Chloride. The ELISA-based detection of cyclooxygenase activity indicated no dose-dependent inhibition for either COX-1 or COX-2 by compound 1. All of the internal controls for this assay were verified, including a standard curve of PG standards.