Supporting Information for

Synthesis and VATPase inhibitory activity of the archazolid western hemisphere

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Contents

General Experimental Procedures S1

Compound	Procedure/ Characterization	^{1}H NMR spectrum	^{13}C NMR spectrum
11	S2	S17	S17
12	S3	S18	S18
12a	S4	S19	S19
17	S5	S20	S20
16	S6	S21	S21
18a	S7	S22	S22
18	S8	S23	S23
19	S9	S24	S24
4	S10	S25	S25
20	S11	S26	S26

Mosher Ester Data for Compound **4** S12

VATPase Assay Methods S13

Concanamycin Assay Data/Dose-Response Curve S14

Bafilomycin Assay Data/Dose-Response Curve S15

Assay Data for Compounds **3**, **20**, and **21** S16

General: All reactions were carried out under N_2 in flame-dried glassware. IR: Nicolet iS10 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS(EI): 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 UV_{254} plates. Flash chromatography: SilaCycle silica

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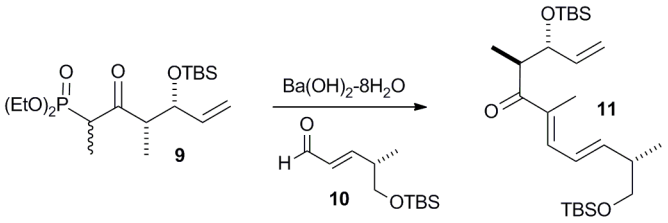
gel P60 (230-400 mesh). NMR: Spectra were recorded on a Varian Mercury 300, or Inova 500 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. The solvent signals were used as references (CD_2Cl_2: $\delta_C \equiv$ 54.0 ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv$ 5.32 ppm; C_6D_6: $\delta_C \equiv$ 128.0 ppm; residual C_6H_6 in C_6D_6: $\delta_H \equiv$ 7.15 ppm; $CDCl_3$: $\delta_C \equiv$ 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv$ 7.26 ppm).

Dienone **11**

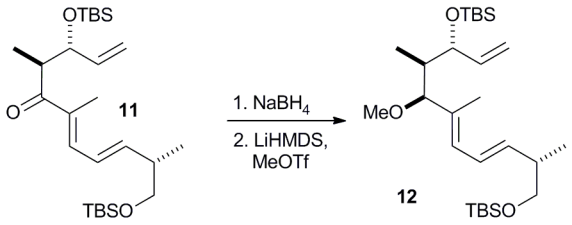


$Ba(OH)_2$•$8H_2O$ (3.78 g, 11.97 mmol) was first activated by heating under vacuum to 120 °C for 1.5 h and then cooled to room temperature before adding THF (17 ml) and phosphonate **9** (2.0 g, 5.01 mmol) and the mixture was stirred for 30 min. Aldehyde **10** (776 mg, 3.40 mmol) was then added and the reaction was stirred for 6 h before quenching with aq. $NaHCO_3$ (30 ml) and extracting with MTBE (2 x 30 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20:1 to 10:1 hexanes:ethyl acetate) afforded **11** (1.14 g, 72%) as an oil.

$[\alpha]_D^{20}$ = -2.8 (*c* 1.0, CH_2Cl_2). IR (ATR) 3064, 2903, 1735, 1640, 1350, 1194, 1067, 910, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, J = 10.1 Hz, 1H), 6.45 (ddd, J = 0.9, 10.5, 14.9 Hz, 1H), 6.06 (dd, J = 7.5, 14.9 Hz, 1H), 5.71 (m, 1H), 5.11 (dt, J = 1.8, 17.1 Hz, 1H), 4.99 (dt, J = 1.3, 10.5 Hz, 1H), 4.23 (dd, J = 6.6, 7.8 Hz, 1H), 3.52 (dd, J = 1.8, 6.6 Hz, 2H), 3.35 (m, 1H), 2.49 (m, 1H), 1.83 (d, J = 0.9 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.88 (m, 18H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.38, 145.99, 139.68, 138.80, 134.83, 126.23, 115.15, 76.28, 67.42, 46.27, 40.18, 25.87, 23.84, 18.30, 18.17, 15.06, 11.69, -

4.24, -4.86, -5.37. HRMS (ESI+): Calcd for $C_{26}H_{50}O_3Si_2Na^+$ $(M + Na)^+$: 489.3196. Found 489.3195.

Methyl Ether **12**



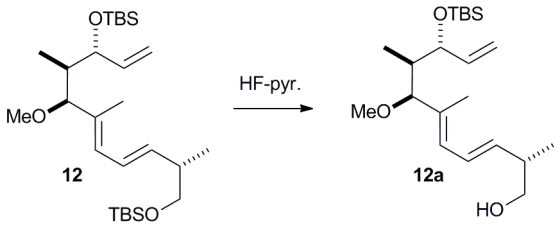
To a solution of ketone **11** (167 mg, 0.36 mmol) in MeOH (1.8 ml) at -0 °C was added $NaBH_4$ (54 mg, 1.44 mmol) and the mixture was stirred and allowed to slowly warm to room temperature for 2 h. The reaction was quenched with brine (15 ml) and extracted with MTBE (2 x 15 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude alcohol product (164 mg, 98%) was used without further purification.

To a solution of the intermediate alcohol (1.0 g, 2.13 mmol) in THF (10.7 ml) at -78 °C was added a solution of LiHMDS (1.0 M, 3.2 ml) at -78 °C and the mixture was stirred for 20 min. Methyl triflate (0.36 ml, 3.20 mmol) was then added and the reaction was stirred for 1 h before quenching with $NaHCO_3$ (30 ml) and extracting with MTBE (2 x 30 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20:1 to 10:1 hexanes:ethyl acetate) afforded **12** (0.82 g, 80%) as an oil.

$[\alpha]_D^{20}$ = +4.1 (*c* 0.5, CH_2Cl_2). IR (ATR) 2958, 2930, 2859, 1447, 1371, 1308, 1221, 1143, 1085, 1024, 755, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.30 (ddd, *J* = 1.1, 10.6, 15 Hz, 1H), 5.90 (d, *J* = 11 Hz, 1H), 5.83 (ddd, J = 5.5, 10.6, 17.2 Hz, 1H), 5.60 (dd, *J* = 7.3, 15 Hz, 1H), 5.18 (dt, *J* = 1.8, 17.2 Hz, 1H), 5.04 (dt, *J* = 1.8, 10.6 Hz, 1H), 4.64 (dd, *J* = 1.5, 5.5 Hz, 1H), 3.51 (dd, *J* = 6.6, 9.9 Hz, 1H), 3.43 (dd, *J* = 6.9, 9.9 Hz, 1H), 3.30 (d, *J* = 9.9 Hz, 1H), 3.13 (s, 3H), 2.40 (m, 1H), 1.60 (d, *J* = 2.9 Hz, 3H), 1.56 (m, 1H),

1.03 (d, J = 6.6 Hz, 3H), 0.93 (s, 9H), 0.90, 0.89 (s, 9H), 0.62 (d, *J* = 7 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.59, 137.01, 133.88, 130.00, 125.48, 113.70, 71.23, 67.97, 55.52, 41.72, 39.75, 29.70, 25.98, 25.92, 25.88, 18.35, 18.25, 16.50, 10.56, 8.63, -3.95, -5.23, -5.30, -5.32. HRMS (ESI+): Calcd for $C_{27}H_{54}O_3Si_2Na^+$ $(M + Na)^+$: 505.3509. Found 505.3500.

Alcohol **12a**



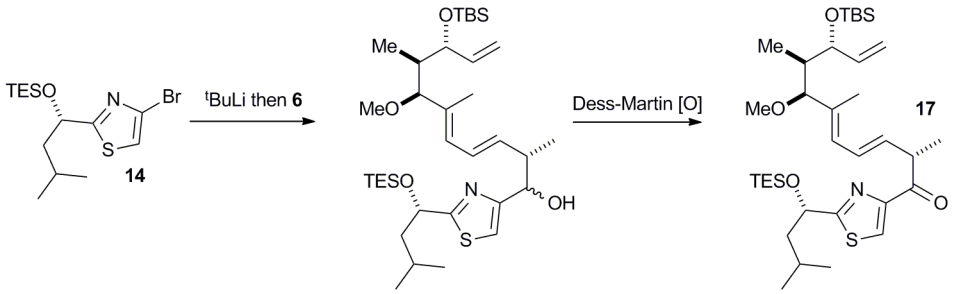
To a solution of **12** (1.0 g, 2.07 mmol) in THF (20 ml) at 0 °C was added HF•pyr (70% HF, 0.56 ml) and the mixture was kept at 4 °C for 15 h. The reaction was quenched with aq. $NaHCO_3$ (50 ml) and extracted with MTBE (2 x 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded the intermediate primary alcohol (702 mg, 92%) as an oil.

$[\alpha]_D^{20}$ = -11.1 (*c* 1.0, CH_2Cl_2). IR (ATR) 3345, 2963, 2928, 1515, 1425, 1294, 1267, 1109, 730 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (dd, *J* = 11.0, 15.4 Hz, 1H), 5.92 (d, *J* = 10.1 Hz, 1H), 5.83 (ddd, *J* = 5.7, 10.5, 17.6 Hz, 1H), 5.57 (dd, *J* = 7.9, 15.4 Hz, 1H), 5.18 (dt, *J* = 1.3, 17.1 Hz, 1H), 5.05 (dt, *J* = 1.3, 10.5 Hz, 1H), 4.64 (dd, *J* = 1.3, 5.7 Hz, 1H) 3.55 (dd, *J* = 5.7, 10.5 Hz, 1H), 3.45 (dd, *J* = 7.9, 10.5 Hz, 1H), 3.37 (d, *J* = 9.7 Hz, 1H), 3.14 (s, 3H), 2.45 (m, 1H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.59 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.93 (s, 9H), 0.62 (d, *J* = 7 Hz, 3H), 0.06 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.53, 136.11, 135.01, 129.41, 126.87, 113.77, 88.19, 76.57, 71.23, 67.40, 55.65, 41.75, 40.07, 25.98, 18.25, 16.48, 10.60, 8.66, -3.93, -5.23. HRMS (ESI+): Calcd for $C_{21}H_{40}O_3SiNa^+$ $(M + Na)^+$: 391.2644. Found 391.2646.

Aldehyde **6**

To a solution of alcohol **12a** (100 mg, 0.27 mmol) in DCM (2.7 ml) at room temperature was added $NaHCO_3$ (114 mg, 1.36 mmol) and Dess-Martin periodinane (173 mg, 0.41 mmol) and the mixture was stirred for 45 min. Aq. $Na_2S_2O_3$ (15 ml) and DCM (15 ml) were then added and the mixture was stirred vigorously for 30 min (until two clear layers developed) before separating. The organic layer was dried over $MgSO_4$, filtered through a short pad of silica, and concentrated *in vacuo*. The somewhat sensitive aldehyde **6** (88 mg, 89%) was used immediately in the next reaction.

Ketone **17**

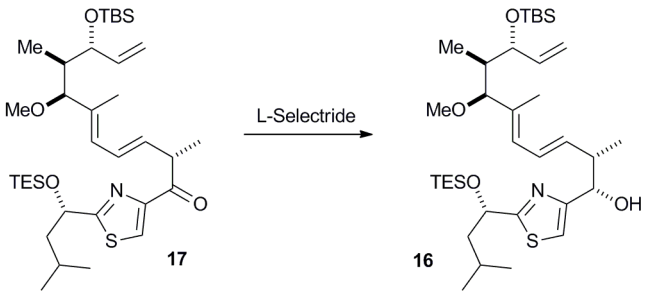


To a solution of ^tBuLi (1.6 M, 0.39 ml) in Et_2O (1.0 ml) at -78 °C was added thiazole **14** (114 mg, 0.31 mmol) and the resulting yellow solution was stirred for 5 min before adding aldehyde **6** (88 mg, 0.24 mmol) as a solution in Et_2O (1.4 ml). The reaction was stirred for 1 h before quenching with aq. NH_4Cl (15 ml) and extracting with MTBE (2 x 15 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded the secondary alcohol product (120 mg, 76%) as an ~2.5:1 (NMR) mixture of stereoisomers.

To a solution of the diastereomeric mixture of alcohols (120 mg, 0.18 mmol) in DCM (1.8 ml) at room temperature was added $NaHCO_3$ (76 mg, 0.9 mmol) and Dess-Martin periodinane (115 mg, 0.27 mmol) and the mixture was stirred for 45 min. Aq. $Na_2S_2O_3$ (15 ml) and DCM (15 ml) were then added and the mixture was stirred vigorously for 30 min (until two clear layers developed) before separating. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded ketone **17** (98 mg, 84%) as an oil.

$[\alpha]_D^{20}$ = +5.9 (*c* 1.0, CH_2Cl_2). IR (ATR) 3064, 2928, 1745, 1460, 1264, 1167, 1104, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 6.44 (dd, *J* = 10.5, 15 Hz, 1H), 5.89 (dd, *J* = 8.1, 15 Hz, 1H), 5.82 (m, 1H), 5.17 (d, *J* = 17.6 Hz, 1H), 5.09 (m, 1H), 5.03 (d, *J* = 10.5 Hz, 1H), 4.62 (dd, *J* = 0.9, 5.7 Hz, 1H), 4.41 (m, 1H), 3.34 (d, *J* = 10.1, 1H), 3.10 (s, 3H), 1.80 (m, 1H), 1.74 (dd, *J* = 7, 13.2 Hz, 1H), 1.65 (m, 2H), 1.60 (m, 1H), 1.59 (s, 3H), 1.36 (d, *J* = 7 Hz, 3H), 1.00 – 0.88 (m, 24H), 0.61 (m, 9H), 0.04 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.88, 177.31, 153.32, 141.48, 135.26, 132.76, 129.58, 127.20, 126.01, 113.76, 88.14, 71.35, 71.17, 55.59, 48.77, 46.27, 41.68, 29.68, 25.94, 24.11, 24.02, 23.05, 22.51, 18.22, 16.59, 10.56, 8.60, 6.70, 4.75, -3.95, -5.29. HRMS (ESI+): Calcd for $C_{35}H_{63}NO_4SSi_2Na^+$ $(M + Na)^+$: 672.3914. Found 672.3914.

Alcohol **16**

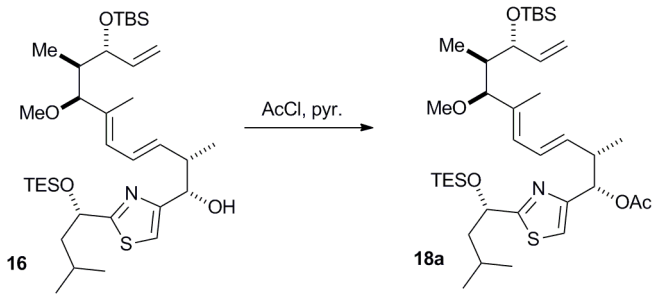


To a solution of ketone **17** (37 mg, 0.06 mmol) in THF (0.57 ml) at -78 °C was added L-Selectride (1.0 M, 85 µl) and the mixture was stirred for 30 min. The reaction was

quenched with aq. NH_4Cl (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 column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded **16** (29 mg, 73%) as a 10:1 (NMR) mixture of stereoisomers.

$[\alpha]_D^{20}$ = -7.7 (*c* 0.5, CH_2Cl_2). IR (ATR) 3327, 2928, 2856, 1628, 1447, 1211, 1157, 1085, 1024, 728 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.05 (s, 1H), 6.38 (dd, *J* = 11, 15.4 Hz, 1H), 5.91 (d, *J* = 10.5 Hz, 1H), 5.83 (m, 1H), 5.64 (dd, *J* = 7.9, 14.9 Hz, 1H), 5.17 (dt, *J* = 1.8, 17.1 Hz, 1H), 5.06 (m, 1H), 5.04 (dt, *J* = 1.8, 10.2 Hz, 1H), 4.63 (dd, *J* = 1.8, 5.7 Hz, 1H), 4.56 (dd, *J* = 5.3, 6.2 Hz, 1H), 3.36 (d, *J* = 10.1 Hz, 1H), 3.13 (s, 3H), 2.79 (dd, *J* = 7, 13.6 Hz, 1H), 2.47 (d, *J* = 5.3 Hz, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.63 (m, 1H), 1.60 (s, 3H), 0.99 (d, *J* = 7 Hz, 3H), 0.96 – 0.86 (m, 24H), 0.61 (m, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.54, 156.99, 141.55, 135.00, 134.94, 129.51, 127.66, 114.23, 113.76, 88.15, 74.42, 71.55, 71.20, 55.65, 48.99, 43.93, 41.71, 25.99, 24.10, 23.32, 22.42, 18.24, 16.59, 10.61, 8.66, 6.76, 4.77, -3.93, -5.25. HRMS (ESI+): Calcd for $C_{35}H_{65}NO_4SSi_2Na^+$ $(M + Na)^+$: 674.4071. Found 674.4078.

Compound **18a**

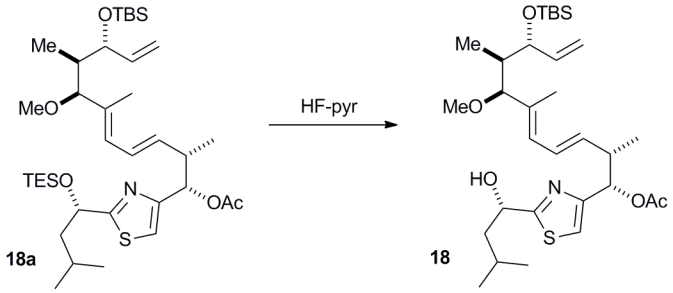


To a solution of alcohol **16** (74 mg, 0.11 mmol) in DCM at 0 °C was added pyridine (23 µl, 0.29 mmol) and acetyl chloride (12 µl, 0.17 mmol) and the resulting mixture was stirred for 2 h. The reaction was quenched with aq. NH_4Cl (15 ml) and extracted with DCM (15 ml). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in*

vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded **18a** (70 mg, 94%) as an oil.

$[\alpha]_D^{20}$ = -11.2 (*c* 0.5, CH_2Cl_2). IR (ATR) 2929, 2860, 1739, 1447, 1288, 1232, 1144, 1084, 1024, 998, 911, 753, 728, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (s, 1H), 6.33 (dd, *J* = 11.0, 15.4 Hz, 1H), 5.88 (m, 1H), 5.82 (m, 1H), 5.75 (d, *J* = 8.4 Hz, 1H), 5.57 (dd, *J* = 8.3, 14.9 Hz, 1H), 5.18 (dt, *J* = 1.8, 17.8 Hz, 1H), 5.06 (m, 1H), 5.05 (dt, *J* = 1.4, 17.1 Hz, 1H), 4.63 (d, *J* = 5.3 Hz, 1H), 3.35 (d, *J* = 9.7 Hz, 1H), 3.11 (s, 3H), 3.01 (m, 1H), 2.05 (s, 3H), 1.80 – 1.70 (m, 2H), 1.76 (m, 2H), 1.58 (s, 3H), 0.92 (m, 27H), 0.64 – 0.58 (m, 9H), 0.059 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.15, 170.23, 152.93, 141.53, 134.77, 134.51, 129.61, 127.05, 116.61, 113.74, 88.12, 75.06, 71.58, 71.14, 55.50, 48.95, 41.65, 41.39, 29.68, 25.98, 24.07, 23.35, 22.39, 21.12, 18.24, 16.77, 10.50, 8.61, 6.73, 4.73, -3.96, -5.25. HRMS (ESI+): Calcd for $C_{37}H_{67}NO_5SSi_2Na^+$ $(M + Na)^+$: 716.4176. Found 716.4283.

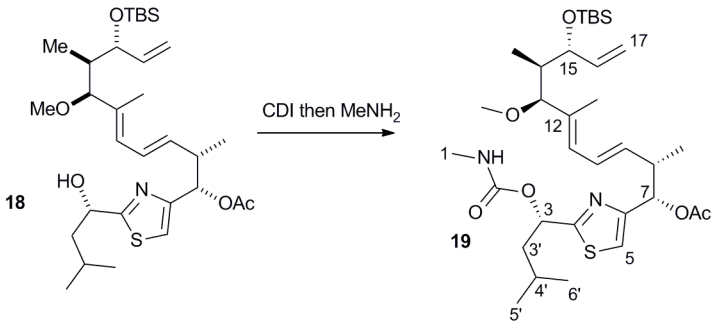
Compound **18**



To a solution of **18a** (50 mg, 0.07 mmol) in THF (1.0 ml) at 0 °C was added HF•pyr (70% HF, 50 µl) and the resulting mixture was kept at 4 °C 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 column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded **18** (45 mg, 99%) as an oil.

$[\alpha]_D^{20}$ = -4.6 (*c* 0.5, CH_2Cl_2). IR (ATR) 2918, 2850, 1649, 1602, 1448, 1412, 1306, 1270, 1171, 1037, 1008, 831, 711 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.14 (s, 1H), 6.32 (dd, *J* = 10.5, 14.9 Hz, 1H), 5.88 (d, *J* = 11.4 Hz, 1H), 5.81 (m, 1H), 5.75 (d, *J* = 8.3 Hz, 1H), 5.56 (dd, J = 8.4, 14.9 Hz, 1H), 5.17 (dd, *J* = 1.8, 17.1 Hz, 1H), 5.04 (dd, *J* = 1.3, 10.5 Hz, 1H), 5.03 (m, 1H), 4.62 (dd, *J* = 1.1, 5.4 Hz, 1H), 3.34 (d, *J* = 10.1 Hz, 1H), 3.11 (s, 3H), 3.00 (m, 1H), 2.69 (d, *J* = 4.8 Hz, 1H), 2.04 (s, 3H), 1.87 (m, 1H), 1.76 (m, 1H), 1.73 (m, 1H), 1.57 (s, 3H), 1.55 (m, 1H), 0.99 (d, *J* = 6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.93 (m, 12H), 0.60 (d, *J* = 7 Hz, 3H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 175.98, 170.25, 153.28, 141.51, 134.57, 129.49, 127.17, 116.98, 113.77, 88.11, 74.93, 71.13, 70.45, 55.53, 47.34, 41.65, 41.37, 25.99, 24.60, 23.30, 21.81, 21.14, 18.24, 16.80, 10.53, 8.63, -3.95, -5.23. HRMS (CI+): Calcd for $C_{31}H_{53}NO_5SSiNa^+$ $(M + Na)^+$: 602.3311. Found 602.3308.

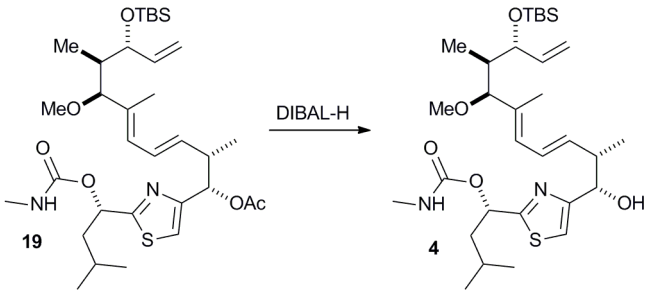
Compound **19**



To a solution **18** (45 mg, 0.08 mmol) in DCM at room temperature was added carbonyl diimidazole (50 mg, 0.31 mmol) portionwise over 1 h. The mixture was then cooled to 0 °C before adding methyl amine (1.0 M, 0.47 ml) and the reaction was allowed to slowly warm to room temperature for 3 h. The reaction was quenched with aq. $NaHCO_3$ (15 ml) and extracted with DCM (2 x 15 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded **19** (46 mg, 91%) as an oil.

$[\alpha]_D^{20}$ = -5.2 (*c* 0.5, CH_2Cl_2). IR (ATR) 3062, 2983, 1736, 1614, 1415, 1274, 1267, 1129, 1078, 930 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H, H(5)), 6.23 (dd, *J* = 10.6, 14.9 Hz, 1H, H(10)), 6.07 (dd, *J* = 4.9, 8.9 Hz, 1H, H(3)), 5.88 (d, *J* = 11.1 Hz, 1H, H(11)), 5.83 (m, 1H, H(16)), 5.79 (d, *J* = 7.7 Hz, 1H, H(7)) 5.55 (dd, *J* = 8.3, 14.9 Hz, 1H, H(9)), 5.18 (dd, *J* =1.4, 17.2 Hz, 1H, H(17a)), 5.04 (dd, *J* = 1.4, 10.6 Hz, 1H, H(17b)), 4.79 (m, 1H, *N*H), 4.63 (dd, *J* = 1.4, 5.7 Hz, 1H, H(15)), 3.34 (d, *J* = 9.7 Hz, 1H, H(13)), 3.11 (s, 3H, *O*Me(13)), 3.02 (m, 1H, H(8)), 2.82 (d, *J* = 4.9, 3H, *N*Me(1)), 2.05 (s, 3H, *Ac* (7)), 1.89 (m, 1H, H(3'a)), 1.84 (m, 1H, H(3'b)), 1.72 (m, 1H, H(4')), 1.57 (s, 3H, Me(12)), 1.55 (m, 1H, H(16)), 0.97 (d, *J* = 6.6 Hz, 3H, Me(5'/6')), 0.95 (d, *J* = 6.9 Hz, 3H, Me(5'/6')), 0.93 (s, 3H, Me(8)), 0.92 (s, 9H, (*Si*-CMe_3)), 0.60 (d, *J* = 7.2 Hz, 3H, Me(16)), 0.05 (s, 3H, (*Si*-Me)), 0.01 (s, 3H, (*Si*-Me)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.98, 170.25, 153.28, 141.51, 134.57, 129.49, 127.17, 116.98, 113.77, 88.11, 74.93, 71.13, 70.45, 55.53, 47.34, 41.65, 41.37, 25.99, 24.60, 23.30, 21.81, 21.14, 18.24, 16.80, 10.53, 8.63, -3.95, -5.23. HRMS (ESI+): Calcd for $C_{33}H_{57}N_2O_6SSi$ $(M + H)^+$: 637.3707. Found 637.3708.

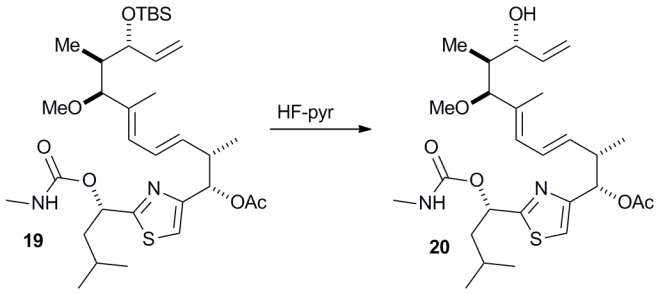
Compound **4**



To a solution of **19** (25 mg, 0.04 mmol) in DCM at -78 °C was added DIBAL-H (1.0 M, 0.13 ml) and the mixture was stirred for 30 min. The reaction was quenched with aq. Rochelle's salt (15 ml) and stirred vigorously with EtOAc (15 ml) until two clear layers developed. The layers were separated and the organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1:1 hexanes:ethyl acetate) afforded **4** (18 mg, 74%) as an oil.

$[\alpha]_D^{20}$ = -1.2 (*c* 0.25, CH_2Cl_2). IR (ATR) 3098, 2926, 2876, 1720, 1635, 1574, 1410, 1315, 1264, 1200, 1159, 835 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.37 (dd, *J* = 16, 11.5 Hz, 1H), 6.05 (dd, *J* = 9, 5.5 Hz, 1H), 5.91 (d, *J* = 11 Hz, 1H), 5.83 (m, 1H), 5.63 (dd, *J* = 15.5, 8 Hz, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 4.75 (bs, *N*H), 4.64 (dd, *J* = 5.5, 1H), 4.60 (dd, *J* = 5.5, 5.5 Hz, 1H), 3.36 (d, *J* = 9.5 Hz, 1H), 3.13 (s, 3H), 2.82 (d, *J* = 5 Hz, 3H), 2.81 (m, 1H), 2.46 (m, 1H), 1.90 (m, 1H), 1.84 (m, 1H), 1.74 (m, 1H), 1.60 (m, 3H), 1.25 (m, 1H) 1.02 – 0.94 (m, 15H), 1.01 (d, *J* = 7 Hz, 3H), 0.61 (d, *J* = 7 Hz, 3H) 0.06 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.93, 157.98, 155.96, 141.56, 135.03, 134.74, 129.46, 127.88, 114.41, 113.75, 88.15, 74.47, 72.11, 71.23, 55.66, 43.81, 41.73, 25.99, 24.62, 23.30, 22.99, 22.11, 21.83, 18.25, 16.63, 10.63, 8.66, -3.95, -5.23. HRMS (FAB+): Calcd for $C_{31}H_{55}N_2O_5SSi$ $(M + H)^+$: 595.3601. Found 595.3614.

Compound **20**

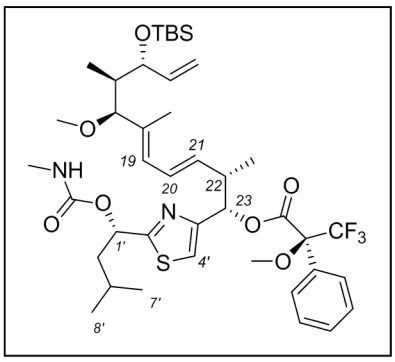


To a solution of **19** (45 mg, 0.07 mmol) in THF (0.4 ml) at 0 °C was added HF•pyr (70% HF, 0.1 ml) and the mixture was warmed to room temperature for 6 h. The reaction was quenched with aq. $NaHCO_3$ (15 ml) and extracted with EtOAc (2 x 15 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded **20** (35 mg, 94%) as an oil.

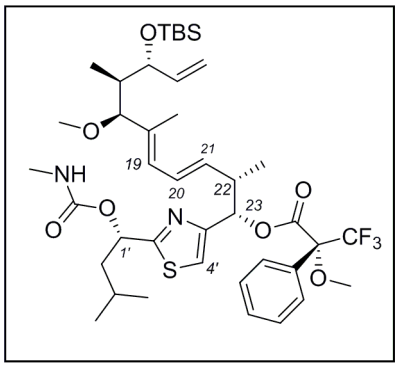
$[\alpha]_D^{20}$ = +4.7 (*c* 0.3, CH_2Cl_2). IR (ATR) 3098, 2926, 2876, 1720, 1635, 1574, 1410, 1315, 1264, 1200, 1159, 835 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.32 (dd, *J* =

10.8, 15.3 Hz, 1H), 6.06 (dd, *J* = 4.8, 8.7 Hz, 1H), 5.94 (dd, *J* = 5.4, 10.5 Hz, 1H), 5.88 (m, 1H), 5.77 (d, *J* = 7.8 Hz, 1H), 5.56 (dd, *J* = 8.4, 15 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.21 (d, *J* = 10.8 Hz, 1H), 4.80 (m, 1H), 4.20 (m, 1H), 3.71 (d, *J* = 7.8 Hz, 1H), 3.41 (d, *J* = 9.6 Hz, 1H), 3.12 (s, 3H), 3.03 (m, 1H), 2.82 (d, *J* = 4.8 Hz, 3H), 2.07 (m, 1H), 2.05 (s, 3H), 1.85 (m, 1H), 1.69 (m, 1H), 1.59 (s, 3H), 0.97 (d, *J* = 6 Hz, 3H), 0.94 (d, *J* = 5.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (m, 1H), 0.68 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.77, 170.20, 155.89, 153.80, 138.13, 133.31, 129.41, 126.82, 116.55, 115.15, 90.58, 75.58, 75.02, 72.29, 55.59, 44.51, 41.16, 39.72, 27.62, 24.59, 23.01, 22.04, 21.08, 16.64, 12.93, 10.90. HRMS (FAB+): Calcd for $C_{27}H_{43}N_2O_6S$ $(M + H)^+$: 523.2842. Found 523.2838.

^{1}H NMR data for the bis-Mosher esters of Compound 4 (selected signals).[1]



(S)-Mosher Ester



(R)-Mosher Ester

H	δ [ppm], S-Mosher ester	δ [ppm], R-Mosher ester	$\Delta\delta=\delta_S-\delta_R$
19	5.94	5.95	-0.01
20	6.25	6.31	-0.06
21	5.47	5.58	-0.11
22	3.10	3.34	-0.24
22-Me	0.87	0.94	-0.07
4'	7.12	6.97	+0.15
1'	6.03	5.96	+0.07
7'	1.85	1.83	+0.02
8'	1.85	1.83	+0.02

[1] Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451.

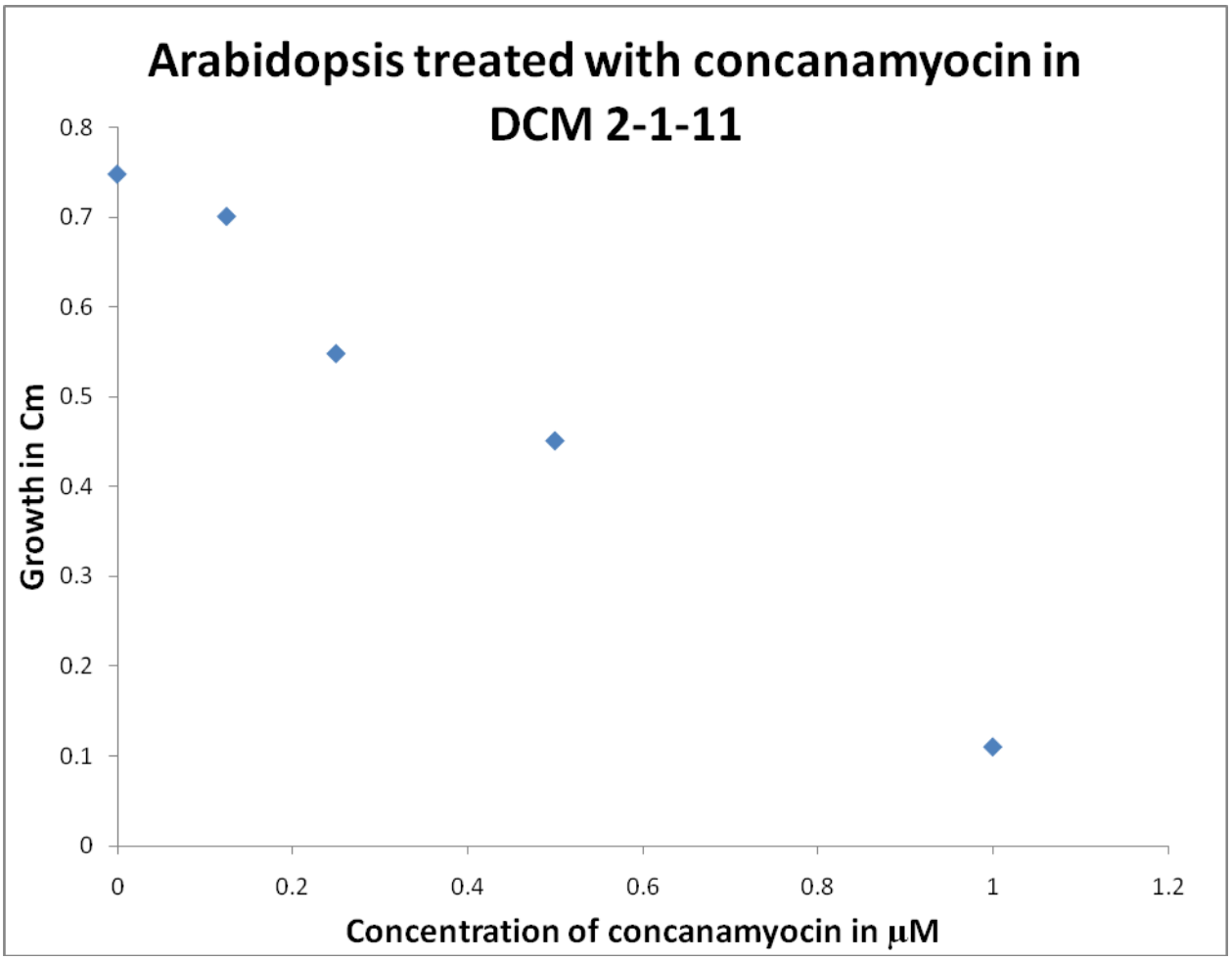
VATPase Assay

A bioassay was performed to test inhibition of V-ATPases in *Arabidopsis thaliana*. Young *Arabidopsis* plants grown in the absence of light undergo etiolation, a process by which the hypocotyl elongates at an abnormally rapid rate. This process, which increases the likelihood that a light-deprived cotyledon will reach light, relies on an increase in water potential in the lumen of a vacuole. V-ATPases create this water potential through active transport of protons into the vacuole. 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 .5x Murasinghe and Skoog Media. Concanamycin in DCM and Bafilomycin in DMSO 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 concanamycin and bafilomycin in equivalent amounts of DCM and DMSO. All plants were placed in a 4˚C dark room for three days before being exposed to light for two days to promote germination followed by four days in aluminum foil to promote etiolation. Hypocotyls were measured to the $5 \bullet 10^{-4}$ using a ruler.

Compound **3**, **20**, and **21** assays were performed using the same procedure as the concanamycin and bafilomycin assays. All synthetic compounds were dissolved in DCM as a solvent. Compound **3** was added to media to a total concentration of 4.08 μM, 8.14 μM, 16.45 μM and 32.1 μM. Compounds **20** and **21** were added to media to a total concentration of 1 μM, 2μM, 10μM and 100μM. Controls were performed for each assay using an equivalent amount of DCM with no added inhibitors and are shown as 0μM concentrations.

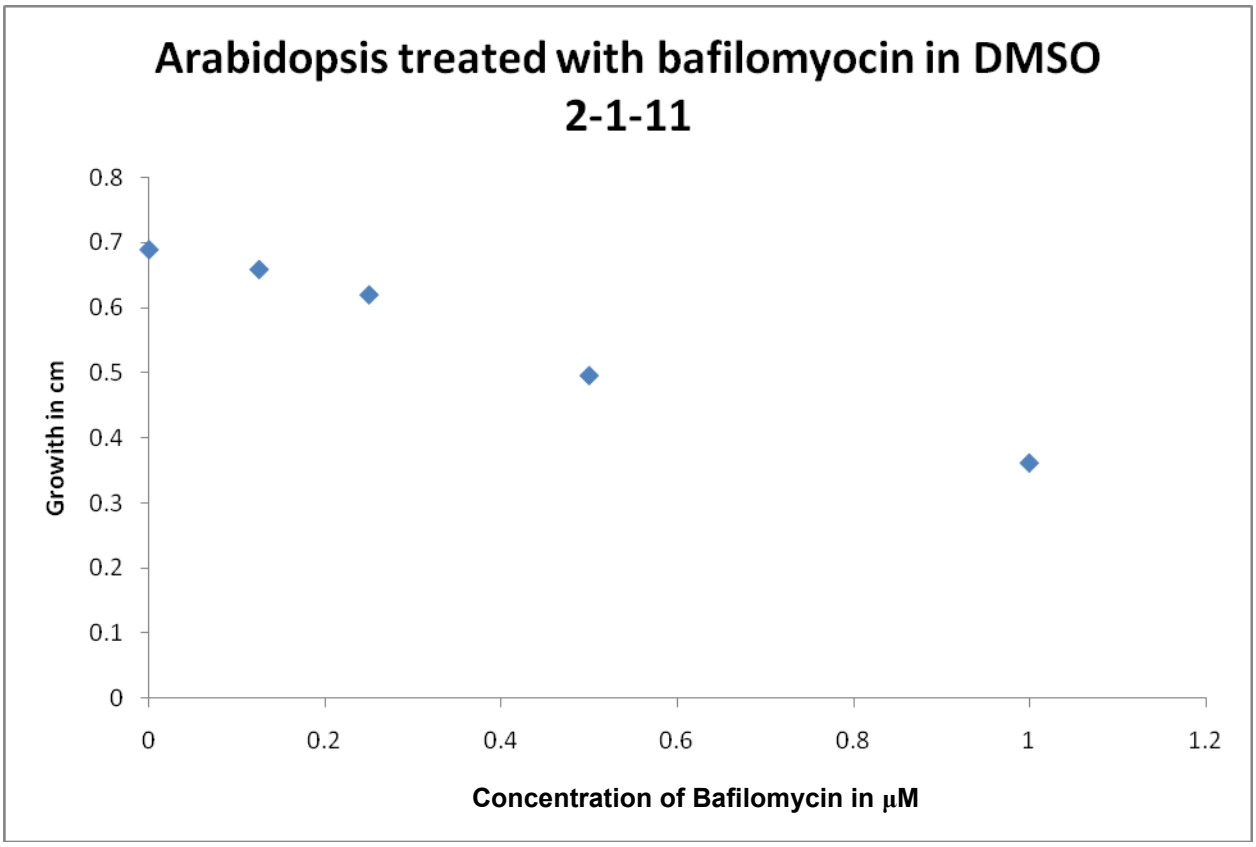
Average and Standard Deviation for Concanamycin A (growth in cm)

Average	Average	Average	Average	Average
0 µM	0.125 µM	0.25 µM	0.5 µM	1 µM
0.7774 cm	0.7175 cm	0.5350 cm	0.4445 cm	0.1071 cm
0 µM	1 µM	2 µM	10 µM	100 µM
Stan Dev	Stan Dev	Stan Dev	Stan Dev	Stan Dev
0.1557	0.1689	0.1375	0.1116	0.0546



Average and Standard Deviation for Bafilomycin A (growth in cm)

Average	Average	Average	Average	Average
0 µM	0.125 µM	0.25 µM	0.5 µM	1 µM
0.6886 cm	0.6582 cm	0.6191 cm	0.4949 cm	0.3604 cm
0 µM	1 µM	2 µM	10 µM	100 µM
Stan Dev	Stan Dev	Stan Dev	Stan Dev	Stan Dev
0.1931	0.1650	0.1579	0.1354	0.1224



Average and Standard Deviation for Compound 3 (growth in cm)

Average	Average	Average	Average
4.08 μM	8.14 μM	16.45 μM	32.1 μM
0.9914 cm	0.7000 cm	1.0221 cm	1.0382 cm
4.08 μM	8.14 μM	16.45 μM	32.1 μM
Stan Dev	Stan Dev	Stan Dev	Stan Dev
0.2036	0.1648	0.1410	0.1409

Average and Standard Deviation for Compound 21 (growth in cm)

Average	Average	Average	Average	Average
0 μM	1 μM	2 μM	10 μM	100 μM
0.7841 cm	0.8134 cm	0.7500 cm	0.7744 cm	0.7716 cm
0 μM	1 μM	2 μM	10 μM	100 μM
Stan Dev	Stan Dev	Stan Dev	Stan Dev	Stan Dev
0.1472	0.1538	0.1027	0.1159	0.1542

Average and Standard Deviation for Compound 20 (growth in cm)

Average	Average	Average	Average	Average
0 μM	1 μM	2 μM	10 μM	100 μM
0.8385 cm	0.8413 cm	0.8759 cm	0.8257 cm	0.7524 cm
0 μM	1 μM	2 μM	10 μM	100 μM
Stan Dev	Stan Dev	Stan Dev	Stan Dev	Stan Dev
0.1715	0.1810	0.1264	0.1477	0.1207