Highly Convergent Total Synthesis of (+)-Acutiphycin

Supporting Information

Ryan M. Moslin, Timothy, F. Jamison*

Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139

TABLE OF CONTENTS

Compounds 1, 2, 5, 7-26	<i>page</i>	S2-S26
References	<i>page</i>	S27
Spectra	<i>page</i>	S28-S69

Supporting Information

General Methods

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of argon using standard Schlenk-line techniques. Diisopropylamine was distilled from calcium hydride and stored over potassium hydroxide. Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl. Dichloromethane (DCM), xylenes, and toluene were freshly distilled from calcium hydride. Ethoxyethyne was received as a red solution in hexanes from GFS, it was distilled under argon and collected as a clear oil, ^1H NMR was used to determine its weight % in hexanes and it could be stored for up to a month under argon at $-4\text{ }^\circ\text{C}$. All other reagents were used as received unless otherwise noted.

^1H NMR was performed on a 500 MHz Varian instrument, ^{13}C NMR was performed on a 500 MHz Varian instrument equipped with an inverse probe. Deuteriochloroform (CDCl_3), which had been filtered through activated basic alumina prior to use, was used as the solvent. Unless otherwise noted the reference peak was set to δ 7.27 and δ 77.23 ppm from tetramethylsilane for the ^1H and ^{13}C spectra respectively. Infrared (IR) spectra were recorded as a thin film between NaCl plates on a Perkin-Elmer Model 2000 FT-IR System transform spectrometer. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by the Massachusetts Institute of Technology Department of Chemistry Facility.

(+)-5-Benzyloxy-3-(*tert*-butyl-diphenyl-silanyloxy)-methyl pentanoate (17):

To a cold (0 °C) solution of **(S)-methyl 5-(benzyloxy)-3-hydroxypentanoate**¹ (8.74 g, 37 mmol) in DMF (50 mL) was added imidazole (4.9 g, 72 mmol) and chloro-*tert*-butyl-diphenylsilane (11.4 mL, 44 mmol), the mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water and then extracted with diethyl ether. The combined organic extracts were washed with water (2x) and brine, then dried over magnesium sulfate, filtered, concentrated and purified by silica gel chromatography (50:1 hexanes/diethyl ether → 6:1 hexanes/ethyl acetate) to give a clear oil. The oil was placed in a large sublimation apparatus and heated to 70 °C under vacuum (0.01 mmHg) for 24 hours resulting in the collection of an unidentified white solid, recovery of the residual oil gave **17** (15.7 g, 90%). $[\alpha]_D^{25} +16.9$ (*c* 1.0, 22 °C, CHCl₃); chiral HPLC analysis (OD column, 99:1 hexane:isopropanol 0.7 mL/min) R_F (*S*) = 9.70 min, R_F (*R*) = 10.78 min; IR 3071 (m), 2932 (s), 2858 (s), 1741 (s), 1473 (s), 1428 (s), 1362(s), 1169 (s); ¹H NMR (500 MHz, CDCl₃) δ 7.68 (m, 4H), 7.40 (m, 4H), 7.30 (m, 4H), 4.37 (quint, *J* = 6.0 Hz, 1H), 4.33 (s, 2H), 3.53 (s, 3H), 3.49 (m, 1H), 2.53 (d, *J* = 6.0 Hz, 2H), 1.84 (m, 2H), 1.03 (s, 9H); ¹³C (125.8 MHz, CDCl₃) δ 172.0, 138.5, 136.1, 136.1, 134.0, 129.8, 129.8, 128.5, 127.8, 127.7, 127.7, 127.6, 72.9, 68.5, 66.7, 51.6, 42.4, 37.1, 27.1, 19.5; HRMS *m/z* (ESI, M+Na⁺) calcd 499.2275, found 499.2257.

(+)-methyl 3-(tert-butyldiphenylsilyloxy)-5-oxopentanoate (2**):**

17 (450 mg, 0.95 mmol) was dissolved in reagent grade methanol (20 mL) and placed in a high pressure apparatus along with 200 mg of palladium on carbon (10% by weight, 50% water). The vessel was placed under vacuum (20 mmHg) and backfilled with H₂, this cycle was repeated twice, and the vessel was charged to 40 psi with H₂ and stirred overnight. The reaction solution was filtered through celite, eluting with ethyl acetate, and concentrated to give the primary alcohol as a clear oil. The oil was dissolved in DCM (1.8 mL) and added dropwise to a solution of Dess-Martin periodinane (806 mg, 1.9 mmol) and pyridine (338 μ L, 4.2 mmol) in DCM (9 mL) at room temperature. After stirring for 1.5 h, 24 mL of a 1:1 solution of saturated aqueous sodium bicarbonate and sodium bisulfite was added and the biphasic solution was stirred until both phases were clear. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, concentrated, and purified by chromatography (2:1 hexanes/diethyl ether) to give 304 mg (84%) of **2** as a clear oil. $[\alpha]_D^{+0.5}$ (*c* 1.6, 21 °C, CHCl₃); IR 2895 (s), 2933 (s), 2859 (s), 2361 (m), 1733 (s), 1112 (s), 704 (s); ¹H NMR (500 MHz, CDCl₃) δ 9.63 (t, *J* = 2.5 Hz, 1H), 7.67 (m, 4H), 7.46 (m, 2H), 7.40 (m, 4H), 4.62 (quint, *J* = 6.0 Hz, 1H), 3.58 (s, 3H), 2.69 (ddd, *J* = 16.5, 6.5, 2.0 Hz, 1H), 2.58 (m, 3H), 1.04 (s, 9H); ¹³C (125.8 MHz, CDCl₃) δ 201.0, 171.2,

136.0, 136.0, 133.4, 133.2, 130.2, 130.1, 128.0, 127.9, 66.1, 51.8, 50.6, 42.0, 27.0, 19.4;
HRMS m/z (ESI, $M+Na^+$) calcd 407.1649, found 407.1638.

(+)-Non-1-en-4-ol (18):

Copper (I) iodide (78 mg, 0.4 mmol) was placed in a round bottomed flask and cooled to $-78\text{ }^{\circ}\text{C}$. To this was added vinyl magnesium bromide generated from magnesium (535 mg, 22 mmol) and an excess of vinyl bromide (1 M, THF). The vessel was warmed to $-10\text{ }^{\circ}\text{C}$ and (*R*)-1,2-heptene-oxide^{2,3} (1.14 g, 10 mmol) in THF (3.0 mL) was added dropwise. The reaction was allowed to gradually warm to $0\text{ }^{\circ}\text{C}$ over 1.5 hours and then carefully quenched *via* the addition of saturated aqueous ammonium chloride. The solution was extracted with diethyl ether and the combined organics were dried over magnesium sulfate, filtered, concentrated ($0\text{ }^{\circ}\text{C}$, 40 mmHg), and purified by silica gel chromatography (10:1 hexanes/diethyl ether) to give 976 mg (69%) of **18** as a clear oil. Spectral data matched that known in the literature.³ $[\alpha]_D +7.4$ (c 0.9, $21\text{ }^{\circ}\text{C}$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 5.84 (m, 1H), 5.15 (m, 2H), 3.66 (m, 1H), 2.32 (m, 1H), 2.14 (m, 1H), 1.40-1.26 (bm, 8 H), 0.90 (t, $J = 7.0\text{ Hz}$, 3H); ^{13}C (125.8 MHz, CDCl_3) δ 135.1, 118.3, 70.9, 42.2, 37.0, 32.1, 25.6, 22.8, 14.3.

(+)-4-Triethylsilyloxylnonene (19):

To a cold (0 °C) solution of **18** (47 mg, 0.33 mmol) in DMF (1 mL) was added imidazole (112 mg, 1.6 mmol) and chlorotriethylsilane (221 μ L, 1.3 mmol), the mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with water and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, concentrated (rt, 60 mmHg) and purified by chromatography (hexanes) to give **19** as a clear oil (68 mg, 80%). $[\alpha]_D^{+11.4}$ (*c* 0.78, 22 °C, CHCl₃); IR 2956 (s), 2876 (s), 1458 (m), 1239 (m), 1005 (m), 911 (m), 724 (s); ¹H NMR (500 MHz, CDCl₃) δ 5.83 (ddt, $J_t = 7.0$, $J_d = 17.5$, 10.0 Hz, 1H), 5.04 (m, 2H), 3.69 (quint, $J = 6.0$, 1H), 2.22 (m, 2H), 1.50-1.25 (bm, 8H), 0.97 (t, $J = 7.5$, 9H), 0.89 (t, $J = 7.0$, 3H), 0.61 (q, $J = 7.5$, 6H); ¹³C (125.8 MHz, CDCl₃) δ 135.6, 116.8, 72.3, 42.3, 37.1, 32.2, 25.3, 22.9, 14.3, 7.2, 5.2; HRMS *m/z* (ESI, M+Na⁺) calcd 279.2115, found 279.2106.

(–)-3-(triethylsilyloxy)-octanal (5**):**

Ozone was bubbled through a cold (–78 °C) solution of **19** (48 mg, 0.18 mmol) in DCM (4 mL) until a pale blue color was observed, the solution was degassed with argon until clear and triphenylphosphine (~400 mg) in DCM (~ 1 g/mL) was added. The solution was allowed to slowly (2 h) warm to –15 °C, concentrated and purified by silica gel chromatography (50:1 hexanes/DCM $\rightarrow$ 5:1 hexanes/diethyl ether) to give **5** as a colorless oil (46 mg, 96%). $[\alpha]_D^{-7.9}$ (*c* 0.43, 21 °C, CHCl₃); IR 2956 (s), 2877 (s), 1727 (s), 1457 (w), 1379 (w), 1240 (w), 1102 (m), 1005 (m); ¹H NMR (500 MHz, CDCl₃) δ

9.82 (t, $J = 2.5$ Hz, 1H), 4.20 (q, $J = 6.0$ Hz, 1H), 2.53 (m, 2H), 1.60-1.49 (bm, 2H), 1.37-1.25 (bm, 6H), 0.96 (t, $J = 8.0$ Hz, 9H), 0.90 (t, $J = 7.0$ Hz, 3H), 0.61 (q, $J = 8.0$ Hz, 6H); ^{13}C (125.8 MHz, CDCl_3) δ 202.7, 68.4, 51.1, 38.2, 32.0, 25.1, 22.8, 14.2, 7.0, 5.2; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 281.1907, found 281.1898.

(–)-5-Hydroxy-4,4,6-trimethyl-oct-7-yn-3-one (7):

To a cold (-78 °C) orange solution of $\text{Pd}(\text{OAc})_2$ (65 mg, 0.29 mmol) in THF (120 mL) was added powdered PPh_3 (76 mg, 0.29 mmol) and the solution stirred until it dissolved, at which point the solution turned yellow. (*R*)-(+)-3-Butyn-2-ol methanesulfonate⁴ (3.0 g, 20.2 mmol) and 2,2-dimethyl-3-pentanone-al⁵ (1.99 g, 15.5 mmol) were added, followed by dropwise addition of diethylzinc (1 M hexanes, 58 mL, 58 mmol) over 15 minutes. The reaction was stirred at -78 °C for 15 minutes and then placed in an ice bath, which was maintained at 0 °C for 2.5 h, during which time the reaction solution turned dark. The reaction was quenched *via* the careful addition of saturated aqueous ammonium chloride, and then diluted with diethyl ether. The phases were separated and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with brine and stirred for 20 minutes with magnesium sulfate and decolorizing agent. The slurry was filtered, concentrated and then purified by silica gel chromatography (3:1 hexanes/diethyl ether) to give a clear oil which crystallized upon

standing (2.69 g, 95%, > 95:5 dr, 90% ee). Relative stereochemistry of **7** was determined by X-ray crystallography (see CIF file in supporting information). $[\alpha]_D -11.1$ (c 0.81, 21 °C, CHCl₃); chiral GC analysis (β -PH column, 88 °C, 1.5 ml/min H₂) R_T (*S*, *S*) = 46.85 min, R_T (*R*, *R*) = 47.91 min; IR 3415 (bs), 3265 (s), 2975 (s), 1681 (s), 1386 (m), 972 (m); ¹H NMR (500 MHz, CDCl₃) δ 3.50 (dd, J = 9.0, 2.0 Hz, 1H), 3.35 (d, J = 9.0 Hz, 1H), 2.70 (m, 1H), 2.65 (dq, J_d = 18.5, J_q = 7.0 Hz, 1H), 2.54 (dq, J_d = 18.5, J_q = 7.0 Hz, 1H), 2.14 (d, J = 2.0 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H), 1.27 (s, 3H), 1.22 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H); ¹³C (125.8 MHz, CDCl₃) δ 218.1, 84.9, 73.0, 51.1, 32.4, 28.9, 23.5, 21.5, 20.4, 7.8; HRMS m/z (ESI, M+Na⁺) calcd 205.1205, found 205.1195.

(+)-3,5,5-Trimethyl-4,6-bis-triethylsilyloxy-oct-5-en-1-yne (20):

To a cold (−78 °C) solution of **7** (1.129 g, 6.2 mmol) and NEt₃ (4.3 mL, 30.8 mmol) in DCM (12 mL) was added triethylsilyltriflate (TESOTf) (5.6 mL, 24.8 mmol), the reaction was warmed to room temperature and stirred overnight. The reaction was quenched with saturated sodium bicarbonate and diluted with diethyl ether, the layers were separated and the organic layer was washed with brine, dried over magnesium sulfate, filtered, concentrated and purified by silica gel chromatography (hexanes) to give **20** as a clear oil (2.49 g, 98%). $[\alpha]_D +9.4$ (c 4.08, 21 °C, CHCl₃); IR 3314 (m), 2956 (s), 2878 (s), 1664 (m), 1459 (m), 1317 (m), 1240 (m), 1136 (s), 1008 (s), 738 (s); ¹H NMR (500 MHz, CDCl₃) δ 4.65 (q, J = 7.0 Hz, 1H), 3.66 (d, J = 1.0 Hz, 1H), 2.72 (ddq, J_q =

7.0, $J_d = 2.5, 1.5$ Hz, 1H), 2.00 (d, $J = 2.5$ Hz, 1H), 1.52 (d, $J = 7.0$ Hz, 3H), 1.22 (d, $J = 7.0$ Hz, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 1.01 (t, $J = 8.0$ Hz, 9H), 1.00 (t, $J = 8.0$ Hz, 9H), 0.73 (q, $J = 8.0$ Hz, 6H), 0.66 (apparent dt, $J_t = 8.0, J_d = 1.5$ Hz, 6H); ^{13}C (125.8 MHz, CDCl_3) δ 157.2, 99.5, 87.5, 79.4, 70.4, 46.5, 28.9, 25.4, 21.9, 20.3, 11.7, 7.4, 7.2, 6.4, 5.9; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 433.2929, found 433.2911.

(+)-4,6,6-Trimethyl-5,7-bis-triethylsilanyloxy-non-7-en-2-yne (8):

$n\text{BuLi}$ (2.5 M in hexanes, 10.8 mL, 27 mmol) was added dropwise to a cold (-10 °C) solution of $i\text{Pr}_2\text{NH}$ (3.96 mL, 28.2 mmol) in THF (100 mL) the solution was stirred for 15 minutes, then cooled to -78 °C. **20** (2.42 g, 5.88 mmol), DMPU (aldrich, 5.92 mL, 48.8 mmol), and MeI (filtered through activated basic alumina, 1.75 mL, 28.1 mmol) were added to the solution at -78 °C, the solution was warmed to 0 °C (5 minutes) then to room temperature (2.5 h). The reaction was quenched *via* the addition of water, and the product extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, concentrated and purified by chromatography (hexanes) to give **8** (2.26 g, 91%). $[\alpha]_D +11.0$ (c 3.1, 21 °C, CHCl_3); IR 2956 (s), 2916 (s), 2878 (s), 2361 (w), 1664 (m), 1458 (m), 1317 (m), 1116 (s), 1004 (s), 845 (m), 737 (s); ^1H NMR (500 MHz, CDCl_3) δ 4.62 (q, $J = 6.5$ Hz, 1H), 3.63 (d, $J = 1.5$ Hz, 1H), 2.63 (m, 1H), 1.76 (d, $J = 2.0$ Hz, 1H), 1.50 (d, $J = 7.0$ Hz, 3H), 1.16 (d, $J = 7.5$ Hz, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.00 (t, $J = 8.0$ Hz, 9H), 1.00 (t, $J = 8.0$ Hz, 9H), 0.72

(q, $J = 8.0$ Hz, 6H), 0.64 (q, $J = 8.0$, 6H); ^{13}C (125.8 MHz, CDCl_3) δ 157.4, 99.3, 82.2, 79.6, 77.3, 46.4, 29.0, 25.3, 22.2, 20.4, 11.7, 7.3, 7.2, 6.4, 5.9, 3.9; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 447.3085, found 447.3076.

(+)- γ -Lactone (9):

In a darkened fume hood a solution of $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ (694 mg, 2.7 mmol) and **8** (1.10 g, 2.6 mmol) in toluene (20 mL) was heated to 43 °C for 80 minutes then cooled to –65 °C. Dimethylzinc (2 M in toluene, 1.31 mL, 2.62 mmol) was slowly added to the cold solution followed by α,α -diphenyl-N-methyl-D-prolinol (107 mg, 0.40 mmol). The reaction was allowed to gradually warm up to –30 °C over 90 minutes, at which point **2** (768 mg, 2.0 mmol) in 5 mL toluene was added followed by a 3 mL rinse (toluene). The reaction was warmed to –25 °C and stirred for 50 minutes then warmed to –15 °C and stirred overnight. The reaction was warmed to room temperature then heated to 35 °C for 20 minutes, this was done to ensure complete conversion to the lactone. The reaction was cooled to 0 °C and quenched *via* the careful addition of saturated aqueous ammonium chloride. The aqueous layer was extracted with diethyl ether and the combined organics were washed with 0.1 M NaHSO_4 and brine, dried over magnesium sulfate, filtered, concentrated and subject to chromatography: 50:1 hexanes/diethyl ether,

80 mL (removes excess **8** and related) $\rightarrow$ 9:1 hexanes/diethyl ether, 1 L (**9**) $\rightarrow$ 6:1 hexanes/diethyl ether (*epi*-C(7)-**9**), to give 810 mg **9** (52%) and 154 mg *epi*-C(7)-**9** (10%) as clear oils (data for **9** only). $[\alpha]_D^{25} +16.0$ (c 1.85, 22 °C, CHCl₃); IR 2957 (s), 2877 (s), 1747 (s), 1664 (w), 1460 (w), 1381 (w), 1317 (w), 1231 (m), 1111 (s), 1008 (s), 738 (s); ¹H NMR (500 MHz, CDCl₃) δ 7.65 (m, 4H), 7.46 (m, 2H), 7.40 (m, 4H), 5.63 (nOe 14.5%) (d, J = 9.5 Hz, 1H), 4.51 (q, J = 6.5 Hz, 1H), 4.31 (nOe 14.5%, 9.4%) (dd, J = 6.5, 3.5 Hz, 1H), 4.12 (nOe 9.4%) (m, 1H), 3.77 (s, 1H), 2.70 (ddd, J = 17.0, 6.0, 1.0 Hz, 1H), 2.62 (m, 1H), 2.49 (dd, J = 17.0, 8.0 Hz, 1H), 1.87 (m, 2H), 1.55 (d, J = 1.0 Hz, 3H), 1.50 (d, J = 6.5 Hz, 3H), 1.07 (s, 9H), 1.03–0.96 (m, 21 H), 0.89 (d, J = 7.0 Hz, 3H), 0.82 (s, 3H), 0.73 (q, J = 8.0 Hz, 6H), 0.64 (q, J = 8.0 Hz, 6 H); ¹³C (125.8 MHz, CDCl₃) δ 171.3, 157.4, 135.9, 133.7, 133.4, 133.0, 130.3, 130.2, 128.9, 128.1, 128.0, 99.1, 82.9, 81.2, 77.2, 65.7, 46.1, 40.1, 37.4, 34.2, 27.0, 25.7, 21.2, 20.6, 19.2, 11.6, 7.5, 7.2, 6.4, 5.9; HRMS m/z (ESI, M+Na⁺) calcd 801.4738, found 801.4721.

α -Bromo-ketone (10):

To a cooled (0 °C) solution of **9** (800 mg, 1.03 mmol) in THF (45 mL) was added re-crystallized N-Bromosuccinimide (NBS) (201 mg, 1.1 mmol) and the reaction was stirred for 45 minutes then quenched with sodium bicarbonate. The solution was poured

in to a mixture of brine and saturated aqueous sodium bicarbonate and the product extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, concentrated and purified by chromatography (hexanes $\rightarrow$ 10:1 hexanes/ethyl acetate $\rightarrow$ 6:1 hexanes/ethyl acetate) to give 765 mg (100%) of **10** as a 3:1 mixture of diastereomers (spectral data for major diastereomer only). IR 3473 (bw), 3072 (w), 2959 (s), 2877 (s), 1742 (s), 1711 (m), 1472 (m), 1428 (m), 1233 (s), 1113 (s), 1009 (s) 703 (s); ^1H NMR (500 MHz, CDCl_3) δ 7.65 (m, 4H), 7.46 (m, 2H), 7.40 (ψ t, $J = 7.0$ Hz, 4H), 5.60 (d, $J = 9.5$ Hz, 1H), 4.72 (q, $J = 6.5$ Hz, 1H), 4.30 (dd, $J = 11.5, 3.0$ Hz, 1H), 4.12 (m, 1H), 3.40 (d, $J = 1.0$ Hz, 1H), 2.71 (dd, $J = 17.5, 6.0$ Hz, 1H), 2.49 (dd, $J = 17.5, 8.0$ Hz, 1H), 2.38 (apparent quintet, $J = 7.5$ Hz, 1H), 1.90 (m, 1H), 1.83 (m, 1H), 1.68 (d, $J = 6.5$ Hz, 3H), 1.56 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.07 (s, 9H), 1.00 (m, 9H), 0.93 (d, $J = 7.5$ Hz, 3H), 0.68 (m, 6H); ^{13}C (125.8 MHz, CDCl_3) δ 209.5, 170.9, 135.8, 133.6, 133.3, 131.0, 130.4, 130.3, 130.2, 128.1, 128.0, 124.9, 82.2, 81.5, 65.6, 54.2, 41.4, 40.0, 37.3, 35.4, 27.0, 25.4, 21.3, 21.1, 19.2, 11.9, 7.4, 7.4, 5.8, 5.8; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 765.2977, found 765.2975.

(+)-Enone (11):

SmI₂ (Strem, 0.1 M THF, 50 mL, 5.0 mmol) was added to a 500 mL teardrop flask which had been thoroughly purged with argon and cooled to –78 °C. A solution of **10** (765 mg, 1.03 mmol) and **5** (282 mg, 1.09 mmol) in THF (52mL) was added to the reaction vessel over 70 minutes. Excess SmI₂ was oxidized by bubbling dry air through the solution until the solution turned yellow, the solution was poured into a separation funnel containing aqueous sodium thiosulfate, sodium bicarbonate and diethyl ether, the layers were separated and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with saturated aqueous sodium thiosulfate (2x), dried over magnesium sulfate, filtered, concentrated and purified by chromatography: hexanes (flush out iodine) → 10:1 hexanes/ethyl acetate → 6:1 hexanes/ethyl acetate to give **21** as a mixture of 4 diastereomers (852 mg, 90%). IR 3503 (bm), 2957 (s), 2876 (s), 1744 (s), 1700 (s), 1462 (s), 1379 (s), 1235 (s), 1112 (s), 1009 (s), 739 (s), 702 (s); HRMS *m/z* (ESI, M+Na⁺) calcd 945.5887, found 945.5880. To a cold (0 °C) solution of **21** (852 mg, 0.924 mmol) in DCM (70 mL) was added Martin sulfurane (aldrich, 4.3 g, 6.39 mmol) and the reaction was stirred at 0 °C for 2 h, sealed and placed in a freezer (–4 °C) for 50 h. The reaction was quenched with saturated aqueous sodium bicarbonate and the product extracted with diethyl ether. The combined organic layers were washed four times with 1 M NaOH and once with brine, dried over magnesium sulfate, filtered, concentrated and purified by chromatography: hexanes → 15:1 hexanes:diethyl ether (400 mL flush) → 13:1 hexanes:ethyl acetate to give 665 mg (80%) **11** as a single detectable isomer. [α]_D +20.5 (*c* 1.28, 21 °C, CHCl₃); IR 2957 (s), 2933 (s), 2876 (s); 1746 (m), 1654 (w), 1463 (w), 1379 (w), 1231 (m), 1112 (s), 1008 (m), 739 (s); ¹H NMR (500 MHz, CDCl₃) δ 7.65 (m, 4H), 7.46 (m, 2H), 7.40 (ψt, *J* = 7.5 Hz, 4H), 6.05 (t, *J* = 9.5 Hz, 1H), 4.29 (dd, *J* =

7.0, 3.0 Hz, 1H), 4.18 (s, 1H), 4.11 (m, 1H), 3.78 (q, $J = 5.5$ Hz, 1H), 2.71 (dd, $J = 17.5$, 6.0 Hz, 1H), 2.49 (dd, $J = 17.5$, 8.5 Hz, 1H), 2.38 (q, $J = 8.0$ Hz, 1H), 2.32 (t, $J = 6.0$ Hz, 2H), 1.91 (m, 1H), 1.83 (m, 1H), 1.78 (s, 3H), 1.56 (s, 3H), 1.42 (bm, 3H), 1.32–1.24 (bm, 6H), 1.17 (s, 3H), 1.07 (s, 9 H), 1.03 (s, 3H), 1.01–0.93 (bm, 20H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.66 (q, $J = 8.0$ Hz, 6H), 0.60 (q, $J = 8.0$ Hz, 6H); ^{13}C (125.8 MHz, CDCl_3) δ 211.2, 171.0, 138.0, 135.8, 133.6, 133.4, 132.1, 131.9, 130.8, 130.3, 130.2, 129.7, 128.1, 128.0, 82.3, 80.9, 71.6, 65.7, 54.2, 40.1, 37.3, 37.3, 36.5, 35.3, 32.2, 27.0, 25.5, 25.4, 22.9, 21.1, 20.8, 19.2, 14.8, 14.3, 12.0, 7.4, 7.1, 5.9, 5.2; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 927.5781, found 927.5770.

(–)- β -Hydroxy-enone (22):

A solution of HF (49% aqueous, 800 μL , 24.4 mmol) in MeCN (7.2 mL) was added to **11** (88 mg, 97 μmol) in a plastic vial. After 4 minutes the vial was rinsed (diethyl ether) into a separation funnel containing aqueous sodium bicarbonate. The two phases were separated and the aqueous phase was extracted twice with ethyl acetate, the combined organic layers were washed with sodium bicarbonate and brine, dried over sodium sulfate, filtered, concentrated and purified by silica gel chromatography (8:1 hexanes:ethyl acetate $\rightarrow$ 3:1 hexanes:ethyl acetate) to give **22** as a clear oil (45 mg, 68%).

$[\alpha]_D -11.1$ (c 0.33, 24 °C, CHCl_3); IR 3446 (bm), 2958 (s), 2930 (s), 2858 (s), 1734 (s), 1653 (w), 1472 (m), 1428 (m), 1379 (m), 1240 (m), 1112 (s); ^1H NMR (500 MHz, CDCl_3) δ 7.64 (apparent dd, $J = 8.0, 1.5$ Hz, 4H), 7.47 (m, 2H), 7.41 (apparent dt, $J_t = 7.5, J_d = 1.5$ Hz, 4H), 5.97 (dt, $J_t = 7.0, J_d = 1.5$ Hz, 1H), 5.44 (d, $J = 10.5$ Hz, 1H), 4.34 (dd, $J = 12.0, 3.5$ Hz, 1H), 4.11 (m, 1H), 3.85 (d, $J = 7.5$ Hz, 1H), 3.71 (m, 1H), 3.56 (dd, $J = 7.5, 2.5$ Hz, 1H), 2.67 (m, 2H), 2.47 (dd, $J = 17.5, 8.0$ Hz, 1H), 2.30 (m, 1H), 2.23 (m, 1H), 2.13 (d, $J = 5.0$ Hz, 1H), 1.90 (m, 1H), 1.84 (m, 1H), 1.78 (s, 3H), 1.62 (d, $J = 1.0$ Hz, 3H), 1.45 (m, 3H), 1.30 (bm, 8 H), 1.20 (s, 3H), 1.06 (s, 9H), 1.02 (d, $J = 7.0$ Hz, 3H), 0.89 (t, $J = 7.0$ Hz, 3H); ^{13}C (125.8 MHz, CDCl_3) δ 216.0, 171.2, 138.0, 135.8, 135.8, 133.5, 133.3, 132.3, 131.2, 131.2, 130.3, 130.3, 128.1, 128.1, 82.8, 77.4, 71.0, 65.5, 50.2, 40.0, 37.6, 37.4, 36.1, 34.4, 32.1, 27.0, 25.9, 25.6, 22.8, 22.8, 19.9, 19.2, 15.0, 14.3, 11.3; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 699.4051, found 699.4055.

(-)-Triol (12):

To a cold (-10 °C) solution of **22** (140 mg, 0.207 mmol) in THF (14 mL) was added catecholborane (442 μL , 4.13 mmol) and the reaction was stirred at -10 °C for 6 h. Methanol (4 mL) was carefully added to the reaction, followed by saturated aqueous potassium sodium tartrate (4 mL), and pinacol (300 mg). The reaction was warmed to

room temperature and stirred overnight. The solution was diluted with ethyl acetate and then washed with 0.5 M NaOH until the aqueous layer was colorless and then once with brine. The organic layer was dried over sodium sulfate, filtered, concentrated and purified by chromatography (4:1 hexanes/ethyl acetate $\rightarrow$ 1:1 hexanes/ethyl acetate) to give 122 mg (87%) of **12** as a clear oil. Stereochemistry of the diol, and olefin geometry was confirmed by nOe analysis of the acetonide (**23**). **12** (3.1 mg, 4.6 μ mole) was reacted with 2,2-dimethoxypropane (2 eq) in acetone (0.01 M) and catalytic CSA (0.2 eq) to give **23** (3.1 mg, 95%) after chromatography (hexanes $\rightarrow$ 3:1 hexane/ethyl acetate).

12: $[\alpha]_D -4.8$ (*c* 0.18, 22 °C, CHCl₃); IR 3386 (bm), 2958 (s), 2930 (s), 2858 (s), 1734 (s), 1428 (s), 1379 (s), 1260 (m), 1112 (s), 1011 (s), 823 (w); ¹H NMR (500 MHz, CDCl₃) δ 7.65 (apparent dd, *J* = 8.0, 1.5 Hz, 4H); 7.46 (m, 2H), 7.40 (m, 4H), 5.70 (d, *J* = 10.0 Hz, 1H), 5.47 (t, *J* = 7.5 Hz, 1H), 4.38 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.12 (m, 1H), 3.98 (s, 1H), 3.67 (bs, 1H), 3.55 (s, 1H), 3.52 (bs, 1H), 2.68 (m, 2H), 2.48 (dd, *J* = 17.0, 8.5 Hz, 1H), 2.22 (t, *J* = 7.0 Hz, 2H), 1.94 (dt, *J*_t = 3.5, *J*_d = 13.0 Hz, 1H), 1.87 (m, 1H), 1.68 (s, 3H), 1.64 (d, *J* = 1.0 Hz, 3H), 1.49–1.44 (bm, 3H), 1.36–1.26 (bm, 6H), 1.07 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 3H), 0.71 (s, 3H); ¹³C (125.8 MHz, CDCl₃) δ 171.1, 138.5, 135.9, 135.8, 133.6, 133.4, 131.5, 130.3, 130.2, 130.0, 128.1, 128.0, 126.0, 87.3, 83.8, 82.6, 71.9, 65.7, 42.6, 40.1, 37.4, 37.4, 35.9, 34.1, 32.1, 27.0, 25.6, 22.8, 20.3, 19.2, 15.9, 15.3, 14.3, 11.5; HRMS *m/z* (ESI, M+Na⁺) calcd 701.4208, found 701.4212. **23**: $[\alpha]_D -16.5$ (*c* 0.5, 24 °C, CHCl₃); IR 3447 (bm), 2959 (s), 2931(s), 2859 (s), 1741 (s), 1465 (m), 1428 (m), 1378 (s), 1254 (s), 1168 (m), 1112 (s), 702 (s); ¹H NMR (500 MHz, CDCl₃) δ 7.65 (m, 4H), 7.46 (apparent t, *J* = 7.0 Hz, 2H), 7.40 (m, 4H), 5.71 (d, *J* = 9.5 Hz, 1H), 5.38 (nOe 7.1%) (t, *J* = 7.0 Hz, 1H), 4.37 (dd, *J* = 12.5, 3.0 Hz,

1H), 4.12 (m, 1H), 3.91 (nOe 7.1%, 5.0%) (s, 1H), 3.66 (m, 1H), 3.43 (nOe 5.0%) (s, 1H), 2.68 (m, 2H), 2.49 (dd, $J = 17.0, 8.0$ Hz, 1H), 2.23 (m, 2H), 1.94 (dt, $J_t = 3.5, J_d = 13.0$ Hz, 1H), 1.86 (m, 1H), 1.66 (s, 3H), 1.63 (d, $J = 1.0$ Hz, 3H), 1.46 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.32–1.26 (m, 6H), 1.07 (s, 9H), 0.97 (d, $J = 7.0$ Hz, 3H), 0.90 (t, $J = 7.0$ Hz, 3H), 0.76 (s, 3H), 0.74 (s, 3H); ^{13}C (125.8 MHz, CDCl_3) δ 171.2, 135.9, 135.8, 135.4, 133.6, 133.4, 132.7, 130.3, 130.2, 129.1, 128.1, 128.0, 126.0, 98.8, 84.3, 82.6, 82.0, 71.9, 65.7, 40.1, 38.3, 37.3, 37.2, 36.2, 32.1, 31.8, 31.8, 30.2, 27.0, 25.6, 22.8, 22.2, 20.7, 19.4, 19.2, 15.6, 15.3, 14.3, 11.6; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 741.4521, found 741.4504.

(–)-Alkoxyacetylene-tetraol (13):

$n\text{BuLi}$ (2.5 M in hexanes, 117 μL , 0.29 mmol) was added dropwise to a cold (-10 $^{\circ}\text{C}$) solution of $i\text{Pr}_2\text{NH}$ (40 μL , 0.29 mmol) in THF (7.2 mL) and the solution stirred for 15 minutes then cooled to -78 $^{\circ}\text{C}$. Ethoxyethyne (63 wt% in hexanes, 45 μL , 0.29 mmol)⁶ was subsequently added, and the solution stirred for 50 minutes. After dry (azeotroped with anhydrous toluene) **12** (20 mg, 0.029 mmol) in THF (500 μL) was added dropwise down the side of the reaction vessel the reaction was stirred for 10 minutes at -78 $^{\circ}\text{C}$ and then warmed to -42 $^{\circ}\text{C}$ for 45 minutes. The reaction was

quenched with pH 7.2 phosphate buffer and diluted with diethyl ether. The aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed with sodium bicarbonate and brine, and dried over sodium sulfate. The slurry was filtered, concentrated, and purified by chromatography (3:2 hexanes:ethyl acetate → 4:5 hexanes:ethyl acetate) to give **13** as a clear oil (15.9 mg, 72%). Stereochemistry is unassigned, $dr > 10:1$. $[\alpha]_D -16.1$ (c 0.4, 21 °C, $CHCl_3$); IR 3365 (bm), 2929 (s), 2857 (s), 2226 (s), 1717 (w), 1654 (m), 1471 (m), 1428 (m), 1111 (s), 1008 (s), 703 (s); 1H NMR (500 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.45 (m, 2H), 7.40 (m, 4H), 5.50 (d, $J = 10.5$ Hz, 1H), 5.46 (t, $J = 7.0$ Hz, 1H), 4.46 (apparent quint, $J = 5.5$ Hz, 1H), 4.25 (q, $J = 7.0$, 2H), 4.16 (d, $J = 9.0$ Hz, 1H), 3.99 (s, 1H), 3.66 (m, 1H), 3.50 (d, $J = 2.0$ Hz, 1H), 3.01 (bs, 1H), 2.82 (dd, $J = 15.0, 7.5$ Hz, 1H), 2.72 (dd, $J = 15.0, 6.0$ Hz, 1H), 2.65 (m, 1H), 2.48 (d, $J = 2.5$ Hz, 1H), 2.23 (t, $J = 7.0$ Hz, 2H), 1.75 (m, 1H), 1.69 (s, 3H), 1.50–1.40 (bm, 8H), 1.35–1.25 (bm, 9H), 1.06 (s, 9H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 3H), 0.90 (t, $J = 7.0$ Hz, 3H), 0.72 (s, 3H); ^{13}C (125.8 MHz, $CDCl_3$) δ 185.4, 138.7, 136.2, 136.2, 135.6, 133.5, 133.4, 130.1, 130.1, 127.9, 127.9, 127.0, 125.7, 103.6, 86.9, 84.3, 77.6, 74.0, 71.9, 69.2, 52.2, 45.3, 42.7, 41.3, 37.3, 36.0, 34.1, 32.1, 29.9, 27.1, 25.6, 22.9, 20.6, 19.5, 15.9, 15.2, 14.6, 14.3, 11.9; HRMS m/z (ESI, $M+Na^+$) calcd 771.4627, found 771.4639.

(–)-Macrocycle, hemi-ketal (15):

Dry (azeotroped with anhydrous toluene) **13** (13 mg, 17.4 μ mol) in dry xylenes (24 mL) was added dropwise over 5 hours to refluxing (150 °C) xylenes (48 mL) and tri-*n*butylamine (48 μ L, 0.20 mmol). The reaction was stirred for an additional 20 minutes after the slow addition was complete, then poured into a separation funnel containing ice, and diluted with ethyl acetate. The organic layer was washed with 0.1 M NaHSO₄ and brine, dried over magnesium sulfate, filtered, concentrated and purified by silica gel chromatography (20:1 hexanes:ethyl acetate $\rightarrow$ 4:1 hexanes:ethyl acetate) to give 11.3 mg (90%) of **15** as a single diastereomer. $[\alpha]_D -8.1$ (*c* 0.19, 21 °C, CHCl₃); IR 3452 (bm), 2929 (s), 2858 (s), 1710 (m), 1428 (m), 1378 (m), 1208 (s), 1112 (s), 1058 (s), 998 (s), 702 (s); ¹H NMR (500 MHz, CDCl₃) δ 7.67 (m, 4H), 7.43 (m, 2H), 7.38 (apparent t, *J* = 7.5 Hz, 4H), 5.42 (d, *J* = 10.5 Hz, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 5.12 (d, *J* = 2.0 Hz, 1H), 4.92 (m, 1H), 4.29 (apparent sept, *J* = 5.0 Hz, 1H), 4.12 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.92 (s, 1H), 3.56 (s, 1H), 2.88 (m, 1H), 2.55 (d, *J* = 14.0 Hz, 1H), 2.47 (d, *J* = 14.0 Hz, 1H), 2.37 (m, 1H), 2.04 (d, *J* = 14.0 Hz, 1H), 1.99 (dd, *J* = 12.0, 3.5 Hz, 1H), 1.71 (m, 1H), 1.66 (s, 3H), 1.62 (d, *J* = 1.0 Hz, 3H), 1.55–1.48 (bm, 2H), 1.40–1.32 (bm, 2H), 1.30–1.23 (bm, 8H), 1.06 (s, 9H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 3H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.64 (s, 3H); ¹³C (125.8 MHz, CDCl₃) δ 172.4, 136.3, 135.9, 134.5, 131.9, 131.4, 129.8, 129.8, 127.8, 127.8, 96.6, 81.2, 79.8, 76.5, 74.4, 66.5, 44.8, 44.2, 43.3, 38.6, 35.8, 34.1, 32.8, 31.8, 27.2, 25.1, 22.7, 22.2, 19.4, 19.4, 18.8, 14.2, 13.0, 11.1; HRMS *m/z* (ESI, M+Na⁺) calcd 743.4314, found 743.4334.

(+)-Macrocycle, methyl-ketal (24):

15 (11.3 mg, 15.7 μmol), citric acid (3.8 mg, 19.8 μmol) and methanol (30 mL) were combined in a sealed tube and then heated to 75 $^{\circ}\text{C}$ overnight. The crude mixture was concentrated and purified by chromatography (20:1 hexanes:ethyl acetate $\rightarrow$ 4:1 hexanes:ethyl acetate) to give 11.5 mg (100%) of **24**. $[\alpha]_{\text{D}} +15.2$ (c 0.083, 22 $^{\circ}\text{C}$, CHCl_3); IR 3447 (bm), 2926 (s), 2855 (s), 1725 (m), 1462 (m), 1378 (m), 1201 (m), 1113 (s), 1063 (s), 702 (s); ^1H NMR (500 MHz, CDCl_3) δ 7.67 (d, J = 7.0 Hz, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 5.63 (t, J = 7.0 Hz, 1H), 5.50 (d, J = 10.5 Hz, 1H), 4.78 (m, 1H), 4.17 (s, 1H), 4.12 (m, 1H), 3.76 (d, J = 11.5 Hz, 1H), 3.41 (d, J = 6.5 Hz, 1H), 2.98 (s, 3H), 2.86 (m, 1H), 2.74 (d, J = 13.5 Hz, 1H), 2.46 (d, J = 13.5 Hz, 1H), 2.44 (m, 1H), 2.20 (m, 1H), 2.01 (dd, J = 7.5, 4.5 Hz, 1H), 1.77 (m, 1H), 1.71 (s, 3H), 1.66 (m, 3H), 1.49 (bm, 2H), 1.37 (q, J = 11.5 Hz, 1H), 1.32–1.20 (bm, 9H), 1.05 (s, 9H), 1.01 (d, J = 7.0 Hz, 3H), 0.99 (s, 3H), 0.89 (s, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C (125.8 MHz, CDCl_3) δ 169.7, 136.4, 136.4, 135.1, 135.0, 132.1, 130.4, 130.3, 128.5, 128.3, 128.3, 126.4, 100.4, 83.4, 80.4, 77.9, 75.3, 75.1, 67.1, 49.6, 44.5, 44.3, 43.7, 39.1, 35.0, 34.4, 32.4, 31.9, 30.4, 27.6, 25.8, 24.6, 23.2, 21.9, 20.7, 19.8, 14.8, 14.7, 13.5, 13.4; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 757.4470, found 757.4464.

(+)-TES Ether (25):

24 (6 mg, 8.2 μ mol) was loaded into a 5 mL RBF and azeotroped with anhydrous toluene, placed under argon and cooled to -78 $^{\circ}\text{C}$. Portions (200 μL) of a cold (0 $^{\circ}\text{C}$) stock solution of triethylsilyltriflate (TESOTf) (70 μL , 0.31 mmol), 2,6-lutidine (71 μL , 0.61 mmol) in CH_2Cl_2 (6.0 mL) were added, and the reaction progress checked by TLC (6:1 hexanes:ethyl acetate). Additional portions of the stock solution were added until TLC indicated that all the **24** was consumed. The reaction was quenched with methanol (70 μL) diluted with diethyl ether and washed with 0.1 M NaHSO_4 and brine, dried over magnesium sulfate, filtered, concentrated and purified by chromatography (hexanes $\rightarrow$ 13:1 hexanes:ethyl acetate) to give **25** as a clear oil (5.8 mg, 83%). $[\alpha]_{\text{D}}^{22} +34.9$ (c 0.25, 22 $^{\circ}\text{C}$, CHCl_3); IR 3546 (bw), 2955 (s), 2930 (s), 2875 (s), 1728 (s), 1458 (m), 1379 (m), 1238 (m), 1112 (s), 1066 (s), 1045 (s), 1008 (s), 702 (s); ^1H NMR (500 MHz, CDCl_3) δ 7.68 (dd, $J = 8.0, 1.5$ Hz, 2H), 7.65 (dd, $J = 8.0, 1.5$ Hz, 2H), 7.44 (m, 2H), 7.38 (m, 4H), 5.80 (bs, 1H), 5.60 (d, $J = 11.0$ Hz, 1H), 4.88 (m, 1H), 4.20 (s, 1H), 4.14 (m, 1H), 3.64 (d, $J = 12.0$ Hz, 1H), 3.28 (d, $J = 11.0$ Hz, 1H), 2.96 (s, 3H), 2.92 (d, $J = 14.5$ Hz, 1H), 2.85 (m, 1H), 2.44 (m, 1H), 2.41 (d, $J = 14.5$ Hz, 1H), 1.97 (m, 2H), 1.90 (m, 1H), 1.72–1.67 (bm, 1H), 1.70 (s, 3H), 1.52 (s, 3H), 1.48–1.42 (bm, 1H), 1.34–1.24 (bm, 10H), 1.05 (s, 9H), 1.02 (bs, 2H), 0.98 (d, $J = 6.5$ Hz, 3H), 0.92 (t, $J = 8.0$ Hz, 9H), 0.92 (d, $J = 5.0$ Hz, 3H), 0.88 (t, $J = 6.5$ Hz, 3H), 0.54 (q, $J = 8.0$ Hz, 6H); ^{13}C (125.8 MHz, CDCl_3) δ

169.4, 136.0, 135.9, 134.6, 134.5, 131.0, 129.8, 127.8, 124.1, 99.6, 84.9, 79.8, 74.6, 73.0, 66.8, 48.1, 45.3, 43.4, 42.6, 39.0, 33.9, 33.5, 32.0, 31.1, 29.9, 27.1, 25.7, 22.8, 21.5, 19.2, 14.3, 14.1, 13.8, 7.3, 5.2; HRMS m/z (ESI, $M+Na^+$) calcd 871.5335, found 871.5358.

(+)-Ketone (26):

A portion (3.4 mL) of a stock solution of Dess-Martin periodinane (100 mg, 0.23 mmol) and pyridine (93 μ L, 1.15 mmol) in DCM (7.14 mL) was added to **25** (5.6 mg, 6.6 μ mol) and the solution was stirred for 20 minutes. The solvent was removed *in vacu.* and the crude material was purified by silica gel chromatography (hexanes $\rightarrow$ 11:1 hexanes/ethyl acetate) to give **26** as a clear oil (5.5 mg, 98%). $[\alpha]_D +116.8$ (c 0.17, 22 $^{\circ}$ C, $CHCl_3$); IR 3361 (bw), 2926 (s), 2856 (s), 1726 (m), 1709 (w), 1380 (m), 1238 (w), 1111 (s), 1072 (s), 1046 (s), 702 (s); 1H NMR (500 MHz, $CDCl_3$) δ 7.68 (apparent dd, J = 8.0, 1.5 Hz, 2H), 7.65 (dd, J = 8.0, 1.5 Hz, 2H), 7.44 (m, 2H), 7.38 (m, 4H), 5.40 (d, J = 10.3 Hz, 1H), 5.25 (t, J = 6.6 Hz, 1H), 4.89 (m, 1H), 4.18 (s, 1H), 4.10 (m, 1H), 3.97 (m, 1H), 3.68 (d, J = 11.7 Hz, 1H), 2.94 (s, 3H), 2.88 (d, J = 14.3 Hz, 1H), 2.38 (d, J = 14.3 Hz, 1H), 2.27 (m, 2H), 1.97 (ddd, J = 12.8, 4.8, 1.6 Hz, 1H), 1.86 (dt, J_t = 2.2, J_d = 12.2 Hz, 1H), 1.78 (dd, J = 12.7, 10.7 Hz, 1H), 1.67–1.61 (bm, 1H), 1.59 (s, 3H), 1.56 (s, 3H), 1.43–1.33 (bm, 1H), 1.32–1.22 (bm, 6H), 1.29 (s, 3H), 1.17 (q, J = 11.9 Hz, 1H), 1.05 (s,

9H), 1.01 (d, $J = 6.6$ Hz, 3H), 1.00 (s, 3H), 0.97 (t, $J = 7.8$ Hz, 9H), 0.87 (t, $J = 7.0$ Hz, 3H), 0.60 (q, $J = 8.0$ Hz, 6H); ^{13}C (125.8 MHz, CDCl_3) δ 214.8, 169.6, 137.8, 136.0, 135.9, 134.6, 134.4, 133.9, 129.9, 127.8, 125.3, 123.3, 99.5, 80.2, 74.6, 72.5, 66.6, 56.4, 48.4, 43.6, 42.0, 40.6, 38.9, 33.3, 32.1, 30.8, 27.1, 25.7, 24.4, 22.8, 19.4, 19.2, 18.8, 14.3, 13.8, 13.3, 7.3, 5.0; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 869.5178, found 869.5146.

(+)-(5)-(tert-butyl-diphenyl-silanyloxy)-acutiphycin (16):

Et_2O and disorder in C_5H_{11} chain omitted for clarity

26 (8.3 mg, 9.8 μmol) was treated with 49% aqueous HF (74 μL , 2.3 mmol) in MeCN (667 μL) at room temperature. After 3 minutes the reaction was poured into a separation funnel containing aqueous sodium bicarbonate and diluted with diethyl ether. The organic layer was washed with sodium bicarbonate and brine, dried over magnesium sulfate, filtered, concentrated, and purified by silica gel chromatography (2:1 hexanes:diethyl ether) to give **16** as a white solid (6.1 mg, 87%). The solid was crystallized using slow vapor diffusion of pentanes into diethyl ether (CIF file included in supporting information). mp 154-155 $^\circ\text{C}$; $[\alpha]_{\text{D}} +131.2$ (c 0.155, 22 $^\circ\text{C}$, CHCl_3); IR 3428 (bs), 2957 (s), 2929 (s), 1703 (s), 1428 (m), 1379 (s), 1210 (m), 1112 (s). ^1H NMR (500 MHz, CDCl_3) δ 7.67 (apparent d, $J = 6.5$ Hz, 4H), 7.43 (m, 2H), 7.38 (m, 4H), 5.25 (d, $J = 9.8$ Hz, 1H), 5.18 (dd, $J = 11.1, 1.1$ Hz, 1H), 5.15 (d, $J = 2.6$ Hz, 1H), 4.94 (m, 1H),

4.61 (d, $J = 4.2$ Hz, 1H), 4.28 (m, 1H), 4.12 (dd, $J = 11.7, 2.2$ Hz, 1H), 3.90 (m, 1H), 2.59 (d, $J = 14.6$ Hz, 1H), 2.50 (d, $J = 14.6$ Hz, 1H), 2.39 (ddd, $J = 15.2, 10.7, 2.1$ Hz, 1H), 2.08 (t, $J = 13.5$ Hz, 1H), 1.99 (dd, $J = 12.2, 4.5$ Hz, 1H), 1.75 (d, $J = 1.1$ Hz, 3H), 1.73–1.69 (m, 1H), 1.64 (s, 3H), 1.57–1.48 (m, 3H), 1.37 (dt, $J_d = 2.4, J_t = 11.5$ Hz, 1H), 1.32–1.22 (m, 7H), 1.09 (s, 3H), 1.07 (s, 9H), 1.02 (d, $J = 6.4$ Hz, 3H), 0.87 (t, $J = 6.9$ Hz, 3H), 0.83 (s, 3H); ^{13}C (125.8 MHz, CDCl_3) δ 215.7, 172.6, 135.9, 135.3, 134.9, 134.4, 134.4, 130.7, 129.9, 129.9, 127.8, 126.6, 96.8, 79.9, 75.9, 74.2, 66.3, 52.8, 44.8, 44.2, 43.3, 38.5, 35.5, 32.9, 31.8, 27.2, 25.8, 25.2, 22.7, 19.4, 19.3, 16.2, 14.2, 13.1, 11.3; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 741.4157, found 741.4150.

(+)-Acutiphycin (1):

16 (3.9 mg, 5.4 μmol) was dissolved in THF (2.1 mL) and treated with 980 μL of TBAF/HOAc solution (TBAF 1 M THF, 2.5 mL; acetic acid 0.15 mL). The reaction was stirred at room temperature for 52 hours, diluted with ethyl acetate and washed with sodium bicarbonate (2x) and brine, dried over magnesium sulfate, filtered, concentrated and purified by silica gel chromatography (3:2 diethyl ether:hexanes) to give **1** as a white solid (2.4 mg, 92%). mp 150–151 $^{\circ}\text{C}$; $[\alpha]_D +151.6$ (c 0.095, 21 $^{\circ}\text{C}$, CH_2Cl_2); IR (solution in CDCl_3) 3608 (m), 3457 (bw), 2985 (s), 2932 (m), 2902 (s), 1702 (m), 1643 (m), 1562

(m), 1298 (m), 1261 (m), 1216 (s), 1167 (s); ^1H NMR (500 MHz, CDCl_3) δ 5.39 (d, J = 2.4 Hz, 1H), 5.29 (m, 2H), 4.98 (m, 1H), 4.64 (d, J = 3.8 Hz, 1H), 4.33 (dd, J = 12.0, 2.1 Hz, 1H), 4.28 (m, 1H), 4.95 (m, 1H), 2.67 (d, J = 14.6 Hz, 1H), 2.62 (d, J = 14.6 Hz, 1H), 2.42 (ddd, J = 15.1, 10.7, 1.9 Hz, 1H), 2.18 (ddd, J = 11.9, 4.6, 1.3 Hz, 1H), 2.10 (apparent t, J = 13.6 Hz, 1H), 1.89 (dt, J_{d} = 12.2, J_{t} = 2.2 Hz, 1H), 1.78 (d, J = 1.3 Hz, 3H), 1.67 (s, 3H), 1.61–1.51 (m, 3H), 1.33–1.24 (m, 9H), 1.12 (s, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.89 (s, 3H), 0.88 (t, J = 6.9 Hz, 3H); ^1H NMR (500 MHz, 1:1 C_6D_6 : CDCl_3) δ 5.37 (bs, 1H), 5.21 (d, J = 10.4 Hz, 1H), 5.16 (d, J = 11.2 Hz, 1H), 4.91 (m, 1H), 4.52 (s, 1H), 4.18 (d, J = 11.9 Hz, 1H), 4.01 (tt, J = 11.1, 4.3 Hz, 1H), 3.87 (m, 1H), 2.42 (d, J = 14.4 Hz, 1H), 2.29 (d, J = 14.4 Hz, 1H), 2.20 (ddd, J = 14.9, 10.7, 1.8 Hz, 1H), 1.97 (d, J = 12.8 Hz, 1H), 1.91 (m, 1H), 1.63 (s, 3H), 1.54 (m, 1H), 1.44 (s, 3H), 1.30 (m, 1H), 1.22–1.10 (m, 11H), 1.04 (m, 3H), 1.00 (dt, J_{d} = 2.2, J_{t} = 11.5 Hz, 1H), 0.85 (s, 3H), 0.82 (m, 3H); ^{13}C (125.8 MHz, CDCl_3) δ 215.7, 172.6, 135.1, 135.0, 131.1, 126.6, 96.8, 79.9, 76.1, 74.4, 64.7, 52.8, 44.8, 43.9, 43.3, 38.2, 35.5, 32.9, 31.8, 25.8, 25.2, 22.7, 19.3, 16.3, 14.2, 13.1, 11.3; ^{13}C (125.8 MHz, $\text{DMSO}-d_6$) δ 214.5, 170.9, 136.2, 134.9, 128.0, 123.6, 96.2, 77.3, 74.1, 73.8, 62.7, 53.1, 45.9, 43.5, 41.3, 38.2, 34.4, 31.7, 31.0, 24.4, 23.3, 22.0, 20.7, 16.7, 13.9, 12.9, 11.9; HRMS m/z (ESI, $\text{M}+\text{Na}^+$) calcd 503.2979, found 503.2987.

For comparison the chemical shifts for (**1**) as reported by Moore are listed below.⁷

^1H NMR (300 MHz, 1:1 C_6D_6 : CDCl_3) (carbon on which the protons are located given in parenthesis) δ 5.36 (OH on C3), 5.20 (C15), 5.15 (C9), 4.89 (C17), 4.51 (C13), 4.16 (C7), 4.0 (C5), 3.86 (C10), 2.39 (C2), 2.28 (C2), 2.19 (C16 α), 1.97 (C16 β), 1.62 (C23 *methyl group at C8*), 1.54 (C6), 1.43 (C27 *methyl group at C14*), 1.30 (C6), 1.16 (C18, C19,

C20, C21), 1.09 (C26 methyl group at C12), 1.03 (C24 methyl group at C10), 0.99 (C4), 0.84 (C25 methyl group at C12), 0.80 (C22); ^{13}C (75 MHz, $\text{Me}_2\text{SO}-d_6$) δ 124.4 (likely a typo and was meant to be 214.4 as observed by ourselves and by Smith) (C11), 170.9 (C1), 136.1 (C8 or C14), 134.9 (C8 or C14), 128.1 (C9), 123.6 (C15), 96.2 (C3), 77.3 (C13), 74.2 (C7), 73.8 (C17), 62.6 (C5), 53.0 (C12), 49.9 (C2), 43.5 (C4), 41.3 (C10), 38.2 (C6), 34.4 (C16), 31.8 (C20), 31.0 (C18), 24.4 (C19), 23.4 (C26 methyl group at C12), 22.0 (C21), 20.6 (C25 methyl group at C12), 16.7 (C24 methyl group at C10), 13.9 (C22), 12.9 (C27 methyl group at C14), 11.9 (C23 methyl group at C8).

Figure 1: (+)-acutiphycin (**1**) in CDCl_3

-
- ¹ Eggen, M.; Mossman, C. J.; Buck, S. B.; Nair, S. K.; Bhat, L.; Ali, S. M.; Reiff, E. A.; Boge, T. C.; Georg, G. I. *J. Org. Chem.* **2000**, *65*, 7792-7799.
- ² Tokunaga, M.; Larrow, J. F.; Kakuchi, F.; Jacobsen, E. N. *Science*, **1997**, *277*, 936-938. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.
- ³ Gupta, P. S.; Naidu, V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849-851.
- ⁴ Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **2002**, *67*, 733-740.
- ⁵ Shioji, K.; Kawaoka, H.; Miura, A.; Okuma, K. *Synth. Commun.* **2001**, *31*, 3569-3575.
- ⁶ Although not utilized here, lithiated ethoxyethyne can be generated *in situ* and added directly to aldehydes and ketones: Raucher, S.; Bray, B. L. *J. Org. Chem.* **1987**, *52*, 2332-2333.
- ⁷ Barchi, J. J., Jr.; Moore, R. E.; Patterson, F. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 8193-8197.

2

19

19

5

7

20

20

(+) -acutiphycin (1), CDC13