Supporting Information for

Total Synthesis of (–)-Callystatin A

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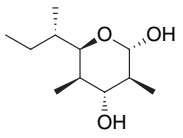
Preparation of Lactol (+)-14

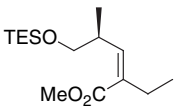


(+)-**14**

A solution of alcohol (+)-**13** (400 mg, 1.07 mmol) in tetrahydrofuran (8 mL) at -78 °C was treated with DIBAL-H (1.5 M in toluene, 2.85 mL, 4.27 mmol). The reaction was allowed to warm to -15 °C over 45 min, and was quenched with a saturated solution of Rochelle's salt (8 mL). After 16 h of vigorous stirring, the aqueous portion was extracted with ethyl acetate (4 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes / ethyl acetate 2:1) gave lactol (+)-**14** (141 mg, 65% yield) as a white solid: mp 79-81 °C; $[\alpha]_D^{23}$ +16° (*c* 0.25, acetone); IR ($CHCl_3$) 3480 (s), 2900 (s), 1700 (w), 1320 (s), 1200 (m), 1000 (s) cm^{-1}; ^1H NMR (500 MHz, acetone) δ 5.00 (d, *J* = 5.78 Hz, 1H), 4.68-4.71 (m, 1H), 3.89-3.92 (m, 1H), 3.78 (dd, *J* = 9.98, 3.81 Hz, 1H), 3.21-3.28 (m, 1H), 2.70 (s, 1H), 1.71-1.84 (m, 1H), 1.38-1.50 (m, 2H), 1.02 (d, *J* = 7.15 Hz, 3H), 0.95 (d, *J* = 7.17 Hz, 3H), 0.91 (d, *J* = 6.46 Hz, 3H), 0.89 (t, *J* = 7.15 Hz, 3H) ; ^{13}C NMR (125 MHz, acetone) δ 97.34, 76.64, 70.57, 40.16, 38.60, 34.90, 24.60, 15.28, 15.09, 12.46, 10.40; high resolution mass spectrum (CI, CH_4) *m/z* 203.1640 [$(M+H)^+$; calcd for $C_{11}H_{23}O_3$: 203.1647].

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.50; H, 10.98.

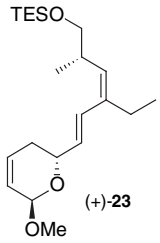
Preparation of Ester (+)-20



(+)-**20**

To a solution of phosphonate **19** (760 mg, 2.2 mmol) and 18-crown-6 (2.9 g, 11 mmol) in THF (10 mL) at 0 °C was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 4.4 mL, 2.2 mmol). After three min, the resulting brown solution was chilled to -78 °C, and aldehyde (–)-**18** (486 mg, 2.4 mmol) was added. The reaction was allowed to warm to 20 °C over 40 min, and then quenched with brine (200 mL) and ether (100 mL). After separation, the aqueous phase was extracted with ether (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (hexanes/ethyl acetate, 95:5) gave ester (+)-**20** (461 mg, 72%) as a colorless oil: $[\alpha]_D^{23}$ +18.8° (*c* 0.4, $CHCl_3$); IR (neat) 2940 (s), 2860 (s), 1720 (s), 1450 (w), 1230 (w), 1120 (m), 1060 (s), 990 (m), 725 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (d, *J* = 9.73 Hz, 1H), 3.73 (s, 3H), 3.51 (dd, *J* = 9.71, 5.93 Hz, 1H), 3.45 (dd, *J* = 9.68, 6.27 Hz, 1H), 3.2-3.1 (m, 1H), 2.26 (dq, *J* = 7.45, 1.25 Hz, 1H), 2.25 (dq, *J* = 7.39, 1.16, 1H), 1.02 (t, *J* = 7.43 Hz, 3H), 1.00 (d, *J* = 6.71 Hz, 3H), 0.94 (t, *J* = 7.93 Hz, 9H), 0.576 (q, *J* = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, CDCl3) δ 168.65, 142.53, 133.60, 67.39, 51.09, 36.36, 27.62, 16.93, 13.49, 6.83, 4.41; high resolution mass spectrum (CI, CH_4) *m/z* 285.1878 [(M - H)$^+$; calcd for $C_{15}H_{29}O_3Si$: 285.1886].

Preparation of Triene (+)-23

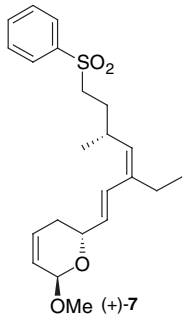


(+)-**23**

In a flask wrapped in aluminum foil, a solution of aldehyde (+)-**8** (1.5 g, 5.9 mmol), sulfone (+)-**9** (2.02 g, 6.0 mmol), and HMPA (1.25 mL) in DME (15 mL) at -78 °C was treated with NaHMDS (1.0 M solution in THF, 6.0 mL, 6.0 mmol). After 1.5 h, the reaction bath temperature had risen to -20 °C. The reaction was quenched with 50% NaCl(aq) (100 mL) and extracted with

CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography gave 1.5 g of a colorless oil, corresponding to a mixture of isomers containing predominantly the desired triene. The mixture was used in the next reaction without further purification. A sample of (+)-**23** was purified by flash chromatography: $[\alpha]_D^{23}$ +36.8° (*c* 0.50, acetone); IR (neat) 2900 (s), 1725 (w), 1673 (w), 1455 (m), 1390 (m), 1330 (w), 1230 (m), 1180 (s), 1000-1100(s), 950 (s), 800 (s), 725 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.62 (d, *J* = 15.95 Hz, 1H), 5.99-6.06 (m, 1H), 5.72-5.79 (m, 2H), 5.15 (d, *J* = 9.39 Hz, 1H). 4.90 (s, 1H), 4.37-4.44 (m, 1H), 3.50-3.32 (m, 2H), 3.42 (s, 3H), 2.72-2.82 (m, 1H), 2.21 (q, *J* = 7.43 Hz, 2H), 2.00-2.17 (m, 2H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.97 (d, *J* = 6.66 Hz, 3H), 0.93 (t, *J* = 7.78 Hz, 6H), 0.56 (q, *J* = 7.86 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.39, 132.22, 128.77, 128.71, 127.62, 125.51, 95.93, 67.72, 67.40, 55.15, 34.78, 30.86, 26.37, 17.64, 13.30, 6.78, 4.48; high resolution mass spectrum (CI, CH_4) *m/z* 366.2590 [$(M)^+$; calcd for $C_{21}H_{38}O_3Si$: 366.2583].

Preparation of Sulfone (+)-7

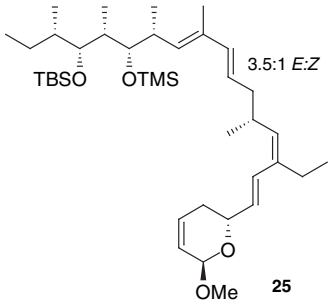


(+)-**7**

A solution of phenyl methyl sulfone (312 mg, 2 mmol) in THF (2 mL) and HMPA (359 mg, 2 mmol) at 0 °C was treated with *n*-BuLi (1.66 M solution in hexanes, 1.20 mL, 2 mmol) the solution was allowed to warm to room temperature to generate a homogeneous solution. Iodide (–)-**24** (40 mg, 0.11 mmol) in benzene (0.4 mL) was then treated with an aliquot of the sulfone anion solution (0.20 mL, 0.11 mmol, 1.0 eq). After 10 min, the reaction was quenched with water (150 μL); flash chromatography furnished sulfone (+)-**7** (28 mg, 65%) as a colorless oil: $[\alpha]_D^{23}$

+38.8° (*c* 0.99, CH_2Cl_2); IR (neat) 2900 (m), 1440 (w), 1300 (m), 1180 (m), 1135 (s), 1100 (m), 1080 (m), 1030 (m), 950 (m), 860 (w), 790 (w), 735 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.90 (m, 2H), 7.62-7.66 (m, 1H), 7.54-7.58 (m, 2H),. 6.46 (d, *J* = 15.87 Hz, 1H), 5.99-6.04 (m, 1H), 5.76 (dd, *J* = 15.95, 6.06 Hz, 1H), 5.76 (ddd, *J* = 10.13, 2.83, 1.37 Hz, 1H), 4.98 (d, *J* = 9.85 Hz, 1H), 4.89 (d, *J* = 1.16 Hz, 1H), 4.37-4.42 (m, 1H), 3.42 (s, 3H), 2.95-3.08 (m, 2H), 2.60-2.70 (m, 1H), 2.17 (q, *J* = 7.4 Hz, 2H), 1.97-2.12 (m, 2H), 1.77-1.84 (m, 1H), 1.49-1.64 (m, 1H), 1.02 (t, *J* = 7.44, Hz, 3H), 0.96 (d, *J* = 6.62 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.22, 137.88, 133.51, 132.84, 129.72, 129.17, 128.55, 127.93, 126.28, 125.45, 95.85, 67.04, 55.16, 54.58, 30.72, 30.59, 29.98, 26.32, 21.22, 13.37; high resolution mass spectrum (CI, CH_4) *m/z* 390.1874 [$(M)^+$; calcd for $C_{22}H_{30}O_4S$: 390.1865].

Preparation of Pentaenes 25

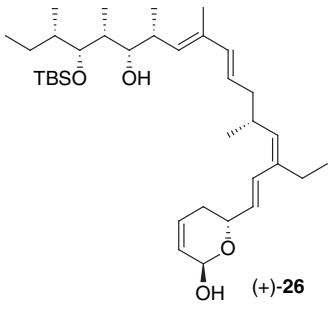


25

A solution of the acetate products derived from the Julia coupling between sulfone (+)-**7** and aldehyde (+)-**6** (50 mg, 0.058 mmol) in THF (0.8 mL) and methanol (0.16 mL) was added to sodium amalgam (7%, 541 mg) and K_2HPO_4 (100 mg, 0.57 mmol) at 0 °C under argon. After one hour of stirring, the reaction was quenched by the addition of water (20 mL) and ethyl acetate (20 mL). The reaction was partitioned, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel using hexanes/ethyl acetate (95/5) gave pentaenes **25** (32 mg,

83%) and the des-TMS-compound (3 mg, 9%) total yield = 92%. These products were combined and subjected to the next reaction without further purification.

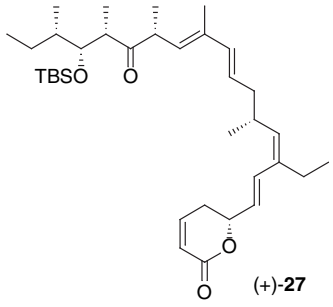
Preparation of Diol (+)-26



(+)-**26**

A solution of pentaenes **25** (10 mg, 0.015 mmol) in THF (0.50 mL), water (0.10 mL), and acetic acid (0.40 mL) was allowed to stir for 24 h, in the dark, under Ar. Preparative TLC, eluting with hexanes/ethyl acetate (80/20) gave diol (+)-**26** (6.2 mg, 72% yield) as a colorless oil: $[\alpha]_D^{23}$ +57.5° (*c* 0.12, acetone); IR (neat) 3401 (m), 2953 (s), 1717 (w), 1675 (w), 1648 (w), 1456 (m), 1376 (m), 1248 (m), 1178 (m), 1092 (s), 1050 (s), 963 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.61 (d, *J* = 15.95 Hz, 1 H), 6.03-6.08 (m, 1H), 5.99 (d, *J* = 15.55 Hz, 1H), 5.80-5.85 (m, 1H), 5.74 (dd, *J* = 15.86, 6.52 Hz, 1H), 5.51 (dt, *J* = 15.53, 7.80 Hz, 1H), 5.45 (s, broad, 1H), 5.19 (d, *J* = 9.60 Hz, 1H), 5.07 (d, *J* = 9.72 Hz, 1H), 3.63 (t, *J* = 3.6 Hz, 1H), 3.37 (d, *J* = 9.23 Hz, 1H), 2.52-2.76 (m, 3H), 2.19 (dq, *J* = 7.45, 3.50 Hz, 2H), 2.03-2.16 (m, 5H), 1.76-1.79 (m, 1H), 1.72 (s, 3H), 1.60-1.49 (m, 2H), 1.08-1.15 (m, 1H), 1.04 (t, *J* = 6.47 Hz, 3H), 1.04 (obscured d, 3H), 0.97 (d, *J* = 6.60 Hz, 3H), 0.91 (s, 9H), 0.87 (t, *J* = 7.13 Hz, 3H), 0.84 (d, *J* = 7.03 Hz, 3H), 0.82 (d, *J* = 6.83 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.19, 135.89, 135.70, 133.20, 133.02, 128.78, 128.23, 127.71, 126.16, 125.87, 89.33, 79.84, 79.16, 67.57, 40.85, 39.96, 37.72, 36.94, 32.02, 30.85, 26.46, 26.15, 25.90, 20.67, 18.37, 17.58, 14.63, 13.59, 12.85, 12.54, 8.48, -3.44, -4.19; high resolution mass spectrum (ESI, positive ion) *m/z* 597.4293 $[(M)^+$; calcd for $C_{35}H_{62}O_4NaSi$: 597.4315].

Preparation of Ketolactone (+)-27



(+)-**27**

A solution of diol (+)-**26** (1.5 mg, 0.0026 mmol) in benzene (300 μL) was treated with PCC (4.5 mg, 0.021 mmol), 4Å molecular seives (1, crushed), and acetic acid (25 μL, 0.26 mmol). After 45 min, the reaction was transferred directly to a pipette column loaded with silica gel. Chromatography (hexanes/ethyl acetate, 85:15) gave ketolactone (+)-**27** (1.3 mg, 86%) as a colorless oil: $[\alpha]_D^{23}$ -82° (*c* 0.05, CH_2Cl_2); IR (neat) 2925 (s), 2851 (s), 1731 (s), 1710 (s), 1458 (m), 1378 (m), 1245 (m), 1058 (m), 833 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (dt, *J* = 9.4, 4.37 Hz, 1 H), 6.64 (d, *J* = 15.67 Hz, 1H), 6.06 (dt, *J* = 9.78, 1.72 Hz, 1H), 6.01 (d, *J* = 15.63 Hz, 1H), 5.77 (dd, *J* = 15.91, 6.79 Hz, 1H), 5.57 (dt, *J* = 15.57, 7.16 Hz, 1H), 5.25 (d, *J* = 9.81 Hz, 1H), 5.18 (d, *J* = 9.78 Hz, 1H), 4.99 (ddd, *J* = 7.85, 7.85, 7.28 Hz, 1H), 3.88 (dd, *J* = 7.76, 2.01 Hz, 1H), 3.69-3.62 (m, 1H), 2.79-2.85 (m, 1H), 2.62-2.71 (m, 1H), 2.44-2.49 (m, 2H), 2.28-2.38 (m, 1H), 2.15-2.22 (m, 2H), 1.98-2.12 (m, 3H), 1.81 (d, *J* = 1.11 Hz, 3H), 1.11 (d, *J* = 7.10 Hz, 3H), 1.08 (d, *J* = 7.15 Hz, 3H), 1.04 (t, *J* = 7.45 Hz, 3H), 0.96 (d, *J* = 6.64 Hz, 3H), 0.89 (s, 9H), 0.84 (t, *J* = 7.40 Hz, 3H), 0.72 (d, *J* = 6.67 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); 13C NMR (125 MHz, CDCl3) _ 214.23, 163.97, 144.54, 137.28, 135.76, 135.36, 129.75, 129.06, 127.08, 124.86, 121.73, 78.75, 75.50, 48.96, 45.69, 40.81, 40.36, 32.11, 30.09, 26.99, 26.40, 26.19, 20.63, 18.49, 16.71, 15.25, 13.44, 13.37, 12.99, 12.41, -3.68, -3.93; high resolution mass spectrum (ESI, positive ion) m/z 593.3973 [(M)+; calcd for C35H58O4NaSi: 593.4002].

Preparation of (–)-Callystatin A (1)

A solution of ketolactone (+)-27 (4.0 mg, 0.0070 mmol) in THF (400 _L) in a plastic vial was treated with HF·Pyr (Fluka, 70%, 260 mg). The reaction was allowed to stir for 36 h, and then transferred directly to a pipette column loaded with silica gel. Elution (hexanes/ethyl acetate, 70/30) gave (–)-callystatin A (2.5 mg, 79% yield) as a colorless oil: $[\alpha]_D^{23}$ -82° (c 0.055, methanol), $[\alpha]_D^{23}$ (lit[1]) -107° (*c*=0.1, MeOH); IR (neat) 3472 (w), 2919 (s), 2848 (s), 1731 (s), 1708 (s), 1455 (m), 1378 (m), 1243 (m) cm-1; 1H NMR (500 MHz, CDCl3) _ 6.90 (dt, J = 9.74, 4.21 Hz, 1H), 6.64 (d, J = 15.82 Hz, 1H), 6.01 (d, J = 15.54 Hz, 1H), 5.76 (dd, J = 15.77, 6.83 Hz, 1H), 5.58 (dt, J = 15.49, 7.64 Hz, 1H), 5.25 (d, J = 9.76 Hz, 1H), 5.13 (d, J = 9.78 Hz, 1H), 4.98 (dt, J = 7.28, 7.28 Hz, 1H), 3.63-3.68 (m, 1H), 3.58 (dd, J = 6.66, 4.33 Hz, 1H), 2.86 (dq, J = 7.25, 4.29 Hz, 1H), 2.64-2.70 (m, 1H), 2.45-2.48 (m, 2H), 2.14-2.23 (m, 2H), 2.09 (dd, J = 6.8, 6.8 Hz, 2H), 1.82 (d, J = 1.2 Hz, 3H), 1.31-1.44 (m, 3H), 1.14 (d, J = 6.66 Hz, 3H), 1.12 (d, J = 7.13 Hz, 3H), 1.05 (t, J = 7.45 Hz, 3H), 0.97 (d, J = 6.64 Hz, 3H), 0.89 (d, J = 6.55 Hz, 3H), 0.85 (t, J = 7.35 Hz, 3H); 13C NMR (125 MHz, CDCl3) _ 216.38, 164.04, 144.62, 132.2, 136.23, 135.42, 135.32, 129.90, 128.35, 127.65, 124.81, 121.71, 78.83, 74.46, 45.78, 45.64, 40.79, 36.72, 32.16, 30.11, 26.39, 25.79, 20.73, 16.16, 14.20, 13.46, 13.05, 11.19, 10.90; high resolution mass spectrum (ESI, positive ion) *m/z* 479.3141 [$(M)^+$; calcd for $C_{29}H_{44}O_4Na$: 479.3137].