Supporting Information

A Simple Stereocontrolled Synthesis of Salinosporamide A

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Experimental Details

General. All moisture sensitive reactions were performed under nitrogen gas in glassware that was flame-dried and equipped with a magnetic stir bar. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were freshly distilled from sodium benzophenone ketyl before use. Hexanes, pyridine, triethylamine, pentane and dichloromethane were freshly distilled from CaH_2 before use. Toluene was distilled from sodium. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Flash chromatography was performed using Baker silica gel (40 μm particle size). All products were purified to homogeneity by TLC analysis (single spot/ two solvent systems) using a UV lamp or CAM or PMA or anisaldehyde or basic KMnO_4 for detection purposes. NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometers. ^1H and ^{13}C NMR chemical shifts are

reported as δ using residual solvent as an internal standard. High-resolution mass spectral analyses were performed at Harvard University Mass Spectrometry Center.

Part I. Synthesis of the Salinosporamide A (1)

(4S, 5R) Methyl 4,5-dihydro-2 (4-methoxyphenyl)-5-methyloxazole-4-carboxylate

(4). A mixture of (2S, 3R)-methyl 2-(4-methoxybenzamido)-3-hydroxybutanoate (**3**) (35.0 g, 131 mmol) and *p*-TsOH•H₂O (2.5 g, 13.1 mmol) in toluene (400 mL) was heated at reflux for 12 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3X 200 mL). The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed in vacuo to give crude oxazoline as yellow oil. Flash column chromatography on silica gel (eluent 15% EtOAc-Hexanes) afforded the pure oxazoline (26.1 g, 80%) as solid. *R*_f = 0.51 (50% ethyl acetate in hexanes), mp, 86-87 °C; $[\alpha]_D^{23}$ +69.4 (c 2.0, CHCl₃); FTIR (film) ν_{max} : 2955, 1750, 1545, 1355, 1187, 1011, 810 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.87 (2H, d, *J* = 9.2 Hz), 6.84 (2H, d, *J* = 8.8 Hz), 4.90 (1H, m), 4.40 (1H, d, *J* = 7.6 Hz), 3.79 (3H, s), 3.71 (3H, s), 1.49 (3H, d, *J* = 6.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) : δ 171.93, 165.54, 162.64, 130.52, 119.80, 113.85, 78.91, 75.16, 55.51, 52.73, 21.14; HRMS (ESI) calcd for C₁₃H₁₆NO₄ (M + H)⁺. 250.1079, found 250.1084.

(4*R*, 5*R*)-Methyl 4-((benzyloxy) methyl)-4,5-dihydro-2- (4-methoxyphenyl)-5-methyloxazole-4-carboxylate (5). To a solution of LDA (50 mmol, 1.0M stock solution in THF) was added HMPA (24 mL, 215 mmol) at $-78\text{ }^{\circ}\text{C}$ and then oxazoline **4** (12.45 g, 50 mmol, in 20 mL THF) was added dropwise with stirring at $-78\text{ }^{\circ}\text{C}$ for 1 h to allow complete enolate formation. Benzyloxy chloromethyl ether (8.35 mL, 60 mmol) was added at this temperature and after stirring the mixture at $-78\text{ }^{\circ}\text{C}$ for 4 h, it was quenched with water (50 mL) and warmed to $23\text{ }^{\circ}\text{C}$ for 30 min. Then the mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were dried (MgSO_4) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexanes, 1:4 then 1:3) to give the benzyl ether **5** (12.7 g, 69%). $R_f = 0.59$ (50% ethyl acetate in hexanes). $[\alpha]_D^{23} -6.3$ (c 1.0, CHCl_3); FTIR (film) ν_{max} : 3050, 2975, 1724, 1642, 1607, 1252, 1027, 745, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.96 (2H, d, $J = 9.2\text{ Hz}$), 7.26 (5H, m), 6.90 (2H, $J = 8.8\text{ Hz}$), 4.80 (1H, m), 4.61 (2H, s), 3.87 (3H, m), 3.81 (3H, s), 3.73 (3H, s), 1.34 (3H, d, $J = 6.8\text{ Hz}$); ^{13}C NMR (CDCl_3 , 100MHz): δ 171.23, 165.47, 162.63, 138.25, 130.64, 128.52, 127.87, 127.77, 120.15, 113.87, 81.40, 79.92, 73.91, 73.43, 55.58, 52.45, 16.92; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{24}\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 370.1654, found 370.1644.

(2*R*,3*R*)-Methyl 2-(4-methoxybenzylamino)-2-((benzyloxy)methyl)-3-hydroxybutanoate (6). To a solution of oxazoline **5** (18.45 g, 50 mmol) in AcOH (25 mL) at 23 °C was added in portions NaCNBH₃ (9.3 g, 150 mmol). The reaction mixture was then stirred at 40 °C for 12 h to allow complete consumption of the starting material. The reaction mixture was diluted with water (100 mL), neutralized with solid Na₂CO₃ and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic phases were dried over NaSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexanes, 1: 5) to give the *N*-PMB amino alcohol **6** (16.78 g, 90%). *R_f* = 0.50 (50% ethyl acetate in hexanes). [α]_D²³ −9.1(*c* 1.0, CHCl₃); FTIR (film) ν_{max} : 3354, 2949, 1731, 1511, 1242, 1070, 1030, 820, 736, 697 cm^{−1}; ¹H NMR (CDCl₃, 400 MHz): δ 7.32 (7H, m), 6.87 (2H, d, *J* = 8.8 Hz), 4.55 (2H, m), 4.10 (1H, q, *J* = 6.4 Hz), 3.85 (2H, dd, *J* = 17.2, 10.0 Hz), 3.81 (3H, s), 3.77 (3H, s), 3.69 (2H, dd, *J* = 22.8, 11.6 Hz), 3.22 (2H, bs), 1.16 (3H, d, *J* = 6.0 Hz); ¹³C NMR (CDCl₃, 100MHz): δ 173.34, 159.03, 137.92, 132.51, 129.78, 128.67, 128.07, 127.98, 114.07, 73.80, 70.55, 69.82, 69.65, 55.51, 55.29, 47.68, 18.15; HRMS (ESI) calcd. for C₂₁H₂₈NO₅ (*M* + *H*)⁺ 374.1967, found 374.1974.

(2*R*,3*R*)-Methyl-2-(*N*-(4-methoxybenzyl)acrylamido)-2-(benzyloxy)methyl-3-

hydroxybutanoate (7). A solution of amino alcohol **6** (26.2 g, 68.5 mmol) in Et₂O (200 mL) was treated with Et₃N (14.2 mL, 102.8 mmol) and trimethylchlorosilane (10.4 mL, 82.2 mmol) at 23 °C and stirred for 12 h. After completion, the reaction mixture was diluted with ether (200 mL) and then resulting suspension was filtered through celite. The solvent was removed to furnish the crude product (31.2 g, 99%) in quantitative yield as viscous oil. A solution of this crude trimethylsilyl ether (31.1 g) in CH₂Cl₂ (200 mL) was charged with diisopropylethylamine (14.2 mL, 81.6 mmol) and then cooled to 0 °C. Acryloyl chloride (6.64 mL, 82.2 mmol) was added dropwise with vigorous stirring and the reaction temperature was maintained at 0 °C until completion (1 h). The reaction mixture was then diluted with CH₂Cl₂ (100 mL) and the organic layer was washed with water and brine. The organic layer was separated and dried over Na₂SO₄. The solvent was removed to afford the crude acrylamide **7** as a viscous oil. The crude product was then dissolved in Et₂O (200 mL) and stirred with 6N HCl (40 mL) at 23 °C for 1 h. The reaction mixture was diluted with water (100 mL) and concentrated to provide crude product. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes, 1: 5 to 1:1) to give pure amide **7** (28.3 g, 96%) as colorless solid, mp 88-89 °C. *R*_f = 0.40 (50% ethyl acetate in hexanes). [α]_D²³ −31.1 (*c* 0.45, CHCl₃), FTIR (film) ν_{max} : 3435, 2990, 1725, 1649, 1610, 1512, 1415, 1287, 1242, 1175, 1087, 1029,

732, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.25 (5H, m), 7.15 (2H, d, J = 6.0 Hz), 6.85 (2H, d, J = 7.5 Hz), 6.38 (2H, d, J = 6.0 Hz), 5.55 (1H, t, J = 6.0 Hz), 4.81 (2H, s), 4.71 (1H, q, J = 6.5 Hz), 4.35 (2H, s), 4.00 (1H, d, J = 10.0 Hz), 3.80 (1H, d, J = 10.0 Hz), 3.76 (3H, s), 3.75 (3H, s), 3.28 (1H, bs), 1.22 (3H, d, J = 6.0 Hz); ^{13}C NMR (CDCl_3 , 125MHz): δ 171.87, 168.74, 158.81, 137.73, 131.04, 129.68, 128.58, 128.51, 127.94, 127.72, 127.20, 127.14, 114.21, 73.71, 70.42, 69.76, 67.65, 55.45, 52.52, 49.09, 18.88; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{30}\text{NO}_6$ ($\text{M} + \text{H}$) $^+$ 428.2073, found 428.2073.

(R)-Methyl-2-(N-(4-methoxybenzyl)acrylamido)-2-(benzyloxy)methyl-3-

oxybutanoate (8). To a solution of amide **7** (10.67 g, 25.0 mmol) in CH_2Cl_2 (100 mL) was added Dess-Martin periodinane reagent (12.75 g, 30.0 mmol, Aldrich Co.) at 23 °C. After stirring for 1 h, the reaction mixture was quenched with aq NaHCO_3 — $\text{Na}_2\text{S}_2\text{O}_3$ (1:1, 50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was dried and concentrated in vacuo to afford the crude ketone. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexanes) to give pure keto amide **8** (10.2 g, 96%). R_f = 0.80 (50% ethyl acetate in hexanes), mp 85 to 86 °C; $[\alpha]_D^{23}$ -12.8 (c 1.45, CHCl_3); FTIR (film) ν_{max} : 3030, 2995, 1733, 1717, 1510, 1256, 1178, 1088, 1027, 733, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.30 (2H, d, J = 8.0), 7.25 (3H, m), 7.11 (2H, m), 6.88 (2H, d, J = 9.0 Hz), 6.38 (2H, m), 5.63 (1H, dd, J = 8.5, 3.5 Hz), 4.93 (1H, d, J = 18.5, Hz), 4.78 (1H, d, J = 18.5, Hz), 4.27 (2H, m), 3.78 (3H, s), 3.76 (3H,

s), 2.42 (3H, s); ^{13}C NMR (CDCl_3 , 125MHz): δ 198.12, 169.23, 168.62, 158.01, 136.95, 130.64, 130.38, 128.63, 128.13, 127.77, 127.32, 114.33, 77.49, 73.97, 70.66, 55.49, 53.09, 49.03, 28.24; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{28}\text{NO}_6$ ($\text{M} + \text{H}^+$) 426.1916, found 426.1909.

(2R,3S)-Methyl-1-(4-methoxybenzyl)-2-((benzyloxy)methyl)-3-hydroxy-3-methyl-4-methylene-5-oxopyrrolidine-2-carboxylate (9** + **10**).** A mixture of keto amide **8** (8.5 g, 20.0 mmol) and quinuclidine (2.22 g, 20.0 mmol) in DME (10 mL) was stirred rapidly for 7 d at 0 °C. After completion, the reaction mixture was diluted with ethyl acetate (50 mL) washed with 2N HCl, followed by water and dried over Na_2SO_4 . The solvent was removed in vacuo to give the crude adduct (7.65 g, 90%, 9:1 ratio of **9** to **10 dr**) as a viscous oil. The diastereomeric mixture was separated at the next step, although small amounts of **9** and **10** were purified by column chromatography (silica gel, ethyl acetate/hexanes, 1:10 to 1:2) for analytical purposes.

Major Diastereomer (**9**).

$[\alpha]_D^{23}$ -37.8 (c 0.51, CHCl_3); FTIR (film) ν_{max} : 3450, 3055, 2990, 1733, 1683, 1507, 1107, 1028, 808, 734 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.29 (5H, m), 7.15 (2H, d, J = 7.5 Hz), 6.74 (2H, d, J = 8.5 Hz), 6.13 (1H, s), 5.57 (1H, s), 4.81 (1H, d, J = 14.5 Hz), 4.45 (1H, d, J = 15.0 Hz), 4.20 (1H, d, J = 12.0 Hz), 4.10 (1H, d, J = 12.0 Hz), 3.75 (3H, s), 3.70 (1H, d, J = 10.5 Hz), 3.64 (3H, s), 3.54 (1H, d, J = 10.5 Hz), 2.55 (1H, bs, OH),

1.50 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.67, 168.42, 158.97, 145.96, 137.57, 130.19, 130.12, 128.53, 127.83, 127.44, 116.79, 113.71, 76.32, 76.00, 73.16, 68.29, 55.45, 52.63, 45.36, 22.64; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{28}\text{NO}_6$ ($\text{M} + \text{H}$) $^+$ 426.1916, found 426.1915.

Minor Diastereomer 10.

$[\alpha]_{\text{D}}^{23}$ -50.1 (c 0.40, CHCl_3); FTIR (film) ν_{max} : 3450, 3055, 2990, 1733, 1683, 1507, 1107, 1028, 808, 734 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.29 (5H, m), 7.12 (2H, d, J = 7.5 Hz), 6.73 (2H, d, J = 8.5 Hz), 6.12 (1H, s), 5.57 (1H, s), 4.88 (1H, d, J = 15.5 Hz), 4.31 (1H, d, J = 15.0 Hz), 4.08 (3H, m), 3.99 (1H, d, J = 12.0 Hz) 3.73 (3H, s), 3.62 (3H, s), 3.47 (1H, bs, OH), 3.43 (1H, d, J = 10.0 Hz), 1.31 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.65, 167.89, 159.13, 147.19, 136.95, 130.29, 129.76, 128.74, 128.19, 127.55, 116.80, 113.82, 76.21, 75.66, 73.27, 68.02, 55.45, 52.52, 45.24, 25.25; HRMS (ESI) calcd. for ($\text{M} + \text{H}$) $^+$ $\text{C}_{24}\text{H}_{28}\text{NO}_6$ 426.1916, found 426.1915.

Silylation of 9 and 10 and Purification of 11.

To a solution of lactams **9** and **10** (7.65 g, 18 mmol) in CH_2Cl_2 (25 ml) was added Et_3N (7.54 ml, 54 mmol), and DMAP (2.2 g, 18 mmol) at 0 $^\circ\text{C}$, and then bromomethyldimethylchlorosilane (5.05 g, 27 mmol) (added dropwise). After stirring the mixture for 30 min at 0 $^\circ\text{C}$, it was quenched with aq NaHCO_3 and the resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed in vacuo to give a mixture of the silylated derivatives of **9** and **10** (9.83 g, 95%). The diastereomers were purified by column chromatography (silica gel, ethyl acetate/hexanes, 1 : 5 to 1 : 4) to give pure diastereomer **11** (8.8 g) and its diastereomer (0.95 g).

Silyl Ether 11. $R_f = 0.80$ (30% ethyl acetate in hexanes). $[\alpha]_D^{23} -58.9$ (c 0.55, CHCl_3); FTIR (film) ν_{max} : 3050, 2995, 1738, 1697, 1512, 1405, 1243, 1108, 1003, 809, 732 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.27 (5H, m), 7.05 (2H, d, $J = 7.0$ Hz), 6.71 (2H, d, $J = 8.5$ Hz), 6.18 (1H, s), 5.53 (1H, s), 4.95 (1H, d, $J = 15.5$ Hz), 4.45 (1H, d, $J = 15.0$ Hz), 4.02 (1H, $J = 12.0$ Hz), 3.86 (1H, d, $J = 11.5$ Hz) 3.72 (3H, s), 3.68 (3H, s), 3.65 (1H, d, $J = 10.5$ Hz), 3.30 (1H, d, $J = 10.0$ Hz), 2.34 (2H, d, $J = 2.0$ Hz), 1.58 (3H, s), 0.19 (3H, s), 0.18 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ 168.62, 168.12, 158.93, 145.24, 137.53, 130.32, 130.30, 128.49, 127.76, 127.22, 117.26, 113.60, 78.55, 78.03, 72.89, 68.45, 55.43, 52.37, 45.74, 21.87, 17.32, -0.72, -0.80; HRMS (ESI) Calcd. for $\text{C}_{27}\text{H}_{35}\text{BrNO}_6\text{Si}$ ($\text{M} + \text{H}$) $^+$ 576.1417, found 576.1407

Conversion of 11 to 12. To a solution of compound **11** (5.67 g 10 mmol) in benzene (250 mL) at 80 °C under nitrogen was added a mixture of tributyltin hydride (4.03 mL, 15 mmol) and AIBN (164 mg, 1 mmol) in 50 mL benzene by syringe pump over 4 h. After the addition was complete, the reaction mixture was stirred for an additional 4 h at 80 °C and the solvent was removed in vacuo. The residue was dissolved in hexanes (20 mL) and washed with saturated NaHCO_3 (3 x 25 mL), water and dried over Na_2SO_4 . The solvent was removed in vacuo to give crude product. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexanes, 1: 5) to afford the pure **12**

(4.42 g, 89%). $R_f = 0.80$ (30% ethyl acetate in hexanes). $[\alpha]_D^{23} -38.8$ (c 0.25, CHCl_3); FTIR (film) ν_{max} : 3025, 2985, 1756, 1692, 1513, 1247, 1177, 1059, 667 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.28 (5H, m), 7.09 (2H, d, $J = 7.0$ Hz), 6.73 (2H, d, $J = 9.0$ Hz), 4.96 (1H, d, $J = 15.0$ Hz), 4.35 (1H, d, $J = 15.5$ Hz), 3.97 (1H, d, $J = 12.5$ Hz), 3.86 (1H, d, $J = 12.0$ Hz), 3.80 (1H, d, $J = 10.0$ Hz), 3.72 (3H, s), 3.65 (3H, s), 3.27 (1H, d, $J = 10.5$ Hz), 2.67 (1H, t, $J = 4.0$ Hz), 2.41 (1H, m), 1.79 (1H, m), 1.46 (3H, s), 0.77 (1H, m), 0.46 (1H, m), 0.10 (3H, s), 0.19 (3H, s); ^{13}C NMR (CDCl_3 , 125MHz): δ 175.48, 169.46, 158.76, 137.59, 131.04, 129.90, 128.58, 127.88, 127.52, 113.59, 113.60, 81.05, 78.88, 73.12, 69.03, 55.45, 51.94, 48.81, 45.50, 22.79, 17.06, 7.76, 0.54; HRMS (ESI) calcd. for $(\text{M} + \text{H})^+ \text{C}_{27}\text{H}_{36}\text{NO}_6\text{Si}$ 498.2312, found 498.2309.

Debenzylation of 12. A solution of **12** (3.98 g, 8 mmol) in EtOH (50 ml) at 23 °C was treated with 10% Pd-C (~1 g) under an argon atmosphere. The reaction mixture was evacuated and flushed with H₂ gas (four times) and then stirred vigorously under an atmosphere of H₂ (1 atm, H₂ balloon) at 23 °C. After 12 h, the reaction mixture was filtered through Celite and concentrated in vacuo to give the crude debenzylation product (3.08 g, 95%) which was used for the next step. A small amount crude product was purified by column chromatography (silica gel, ethyl acetate/hexanes, 1: 3) for analytical purposes. R_f = 0.41 (50% ethyl acetate in hexanes). mp, 45 – 47 °C; $[\alpha]_D^{23}$ –30.9 (c 0.55, CHCl₃); FTIR (film) ν_{max} : 3432, 3020, 2926, 1735, 1692, 1512, 1244,

1174, 1094, 1024, 870, 795 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.36 (2H, d, J = 8.5 Hz), 6.83 (2H, d, J = 8.5 Hz), 5.16 (1H, d, J = 15.0 Hz), 4.29 (1H, d, J = 15.0 Hz), 3.92 (1H, m), 3.78 (3H, s), 3.68 (3H, s), 3.45 (1H, m), 2.53 (1H, t, J = 4.0 Hz), 2.42 (1H, m), 1.82 (1H, m), 1.50 (3H, s), 1.28 (1H, m), 0.75 (1H, m), 0.47 (1H, m), 0.11 (3H, s), 0.02 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ 175.82, 169.51, 159.32, 131.00, 129.72, 114.52, 80.79, 80.13, 61.85, 55.48, 51.99, 49.29, 45.06, 23.11, 17.03, 7.44, 0.54; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{30}\text{NO}_6\text{Si}$ ($\text{M} + \text{H}$) $^+$ 408.1842, found 408.1846.

Oxidation to Form Aldehyde 13. To a solution of the above alcohol from debenzylation of **12** (2.84 g, 7 mmol) in CH_2Cl_2 (30 mL) was added Dess-Martin reagent (3.57 g, 8.4 mmol) at 23 °C. After stirring for 1 h at 23 °C, the reaction mixture was quenched with aq NaHCO_3 – $\text{Na}_2\text{S}_2\text{O}_3$ (1:1, 50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was dried and concentrated in vacuo to afford the crude aldehyde. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexanes, 1:5) to give pure aldehyde **13** (2.68 g, 95%). R_f = 0.56 (50% ethyl acetate in hexanes). mp, 54–56 °C; $[\alpha]_D^{23}$ –16.5 (c 0.60, CHCl_3); FTIR (film) ν_{max} : 3015, 2925, 1724, 1702, 1297, 1247, 1170, 1096, 987, 794 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 9.62 (1H, s), 7.07 (2H, d, J = 8.0 Hz), 6.73 (2H, d, J = 8.5 Hz), 4.49 (1H, quart, J = 8.5 Hz), 3.70 (3H, s), 3.67 (3H, s), 2.36 (2H, m), 1.75 (1H, m), 1.37 (3H, s), 0.73 (1H, m), 0.48 (1H, m), 0.07 (3H, s), 0.004 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ 197.26, 174.70, 167.36, 158.07, 130.49, 128.96, 113.81, 83.97, 82.36, 55.34, 52.43, 47.74, 46.32, 23.83, 16.90, 7.52, 0.56, 0.45; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{28}\text{NO}_6\text{Si}$ ($\text{M} + \text{H}$) $^+$ 406.1686, found 406.1692.

Conversion of 13 to 14. To a solution of freshly prepared cyclohexenyl zinc chloride (10 mL, 0.5 M solution in THF, 5 mmol) (see p. S16 below) at $-78\text{ }^{\circ}\text{C}$ under nitrogen was added a $-78\text{ }^{\circ}\text{C}$ solution of aldehyde **13** (1.01 g, in 3 mL of THF, 2.5 mmol). After stirring for 5 h at $-78\text{ }^{\circ}\text{C}$ reaction mixture was quenched with water (10 mL) then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed in vacuo to give crude product (20 : 1 *dr*). The diastereomers were purified by column chromatography (silica gel, ethyl acetate/hexanes, 1:10 to 1:2 affords the pure major diastereomer **14** (1.0 g, 83%) and a minor diastereomer (50 mg 5%). For **14**: R_f = 0.56 (50% ethyl acetate in hexanes); mp, $79\text{--}81\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{23}$ -28.5 (c 1.45, CHCl_3); FTIR (film) ν_{max} : 3267, 2927, 2894, 2829, 1742, 1667, 1509, 1248, 1164, 1024, 795 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.34 (2H, d, J = 8.5 Hz), 6.81 (2H, d, J = 9.0 Hz), 5.84 (1H, m), 5.73 (1H, m), 4.88 (1H, d, J = 15.5 Hz), 4.39 (1H, d, J = 14.5 Hz), 4.11 (1H, t, J = 6.5 Hz), 3.77 (3H, s), 3.58 (3H, s), 3.00 (1H, m), 2.95 (1H, d, J = 9.0 Hz), 2.83 (1H, t, J = 3.5 Hz), 3.36 (1H, m), 2.27 (1H, m), 1.98 (2H, m), 1.74 (3H, m), 1.62 (3H, s), 1.14 (2H, m), 0.59 (1H, m), 0.39 (1H, m), 0.13 (3H, s), 0.03 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz): δ 176.80, 170.03, 158.27, 131.86, 131.34, 128.50, 126.15, 113.40, 83.96, 82.45, 77.17, 55.45, 51.46, 48.34, 48.29, 39.08, 28.34, 25.29, 22.45, 21.09, 17.30, 7.75, 0.39, 0.28; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{38}\text{NO}_6\text{Si}$ ($M + \text{H}$) $^{+}$ 488.2468, found 488.2477.

Tamao-Fleming Oxidation of 14 to 15. To a solution of **14** (0.974 g, 2 mmol) in THF (5 mL) and MeOH (5 mL) at 23 °C was added KHCO_3 (0.8 g 8 mmol) and KF (0.348 g, 6 mmol). Hydrogen peroxide (30% in water, 5 mL) was then introduced to this mixture. The reaction mixture was vigorously stirred at 23 °C and additional hydrogen peroxide (2 mL) was added after 12 h. After 18 h, the reaction mixture was quenched carefully with NaHSO_3 solution (15 mL). The mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers were washed with water and dried over Na_2SO_4 . The solvent was removed in vacuo to give the crude product. The crude product was purified by column chromatography (silica gel, ethyl acetate) to give the pure triol **15** (0.82 g, 92%). $R_f = 0.15$ (in ethyl acetate). mp, 83-84 °C; $[\alpha]_D^{23}$: +5.2 (c 0.60, CHCl_3); FTIR (film) ν_{max} : 3317, 2920, 2827, 1741, 1654, 1502, 1246, 1170, 1018, 802 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 7.77 (2H, d, $J = 8.0$ Hz), 6.28 (2H, d, $J = 8.0$ Hz), 5.76 (1H, m), 5.63 (1H, d, $J = 10.0$ Hz), 4.74 (1H, d, $J = 15.5$ Hz), 4.54 (1H, d, $J = 15.0$ Hz), 4.12 (1H, d, $J = 2.5$ Hz), 3.80 (1H, m), 3.76 (3H, s), 3.72 (1H, m), 3.68 (3H, s), 3.00 (1H, m), 2.60 (1H, br), 2.20 (1H, m), 1.98 (2H, s), 1.87 (1H, m), 1.80 (1H, m), 1.71 (2H, m), 1.61 (3H, s), 1.14 (2H, m); ^{13}C NMR (CDCl_3 , 125 MHz): δ 178.99, 170.12, 158.27, 131.30, 130.55, 128.13, 126.39, 113.74, 81.93, 80.75, 76.87, 61.61, 55.45, 51.97, 51.32, 48.07, 39.17, 27.71, 27.13, 25.22, 21.35, 21.22; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{34}\text{NO}_7$ ($M + \text{H}$) $^+$ 448.2335, found 448.2334.

Deprotection of 15 to 16. To a solution of **15** (0.670 g, 1.5 mmol) in acetonitrile (8 mL) at 0 °C was added a pre-cooled solution of ceric ammonium nitrate (CAN) (2.46 g 4.5 mmol in 2 mL H₂O). After stirring for 1h at 0 °C the reaction mixture was diluted with ethyl acetate (50 mL), washed with saturated NaCl solution (5 mL) and organic layers was dried over Na₂SO₄. The solvent was removed in vacuo to give the crude product which was purified by column chromatography (silica gel, ethyl acetate) to give the pure **16** (0.4 g, 83%). R_f = 0.10 (5% MeOH in ethyl acetate). mp, 138 to 140 °C; $[\alpha]_D^{23}$ +14.5 (c 1.05, CHCl₃); FTIR (film) ν_{max} : 3301, 2949, 2911, 2850, 1723, 1673, 1437, 1371, 1239, 1156, 1008, 689 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz): δ 8.48 (1H, br), 6.08 (1H, m), 5.75 (1H, d, J = 9.6 Hz), 5.29 (1H, br), 4.13 (1H, d, J = 6.6 Hz), 3.83 (3H, m), 3.79 (1H, m), 3.72 (1H, m), 2.84 (1H, d, J = 10.2 Hz), 2.20 (1H, m), 2.16 (1H, br), 1.98 (3H, m), 1.77 (3H, m), 1.59 (1H, m), 1.54 (3H, s), 1.25 (1H, m). ¹³C NMR (CDCl₃, 125 MHz): δ 180.84, 172.95, 135.27, 123.75, 82.00, 80.11, 75.56, 62.39, 53.14, 51.78, 38.95, 28.79, 26.48, 25.04, 20.66, 19.99; HRMS (ESI) calcd. (M + H)⁺ for C₁₆H₂₆NO₆ 328.1760, found 328.1752.

Conversion of 16 to Salinosporamide A (1). A solution of triol ester **16** (0.164 g, 0.5 mmol) in 3 N aq LiOH (3 mL) and THF (1 mL) was stirred at 5 °C for 4 days until hydrolysis was complete. The reaction mixture was acidified with phosphoric acid (to pH 3.5). The solvent was removed in vacuo and the residue was extracted with EtOAc, separated, and concentrated in vacuo to give the crude trihydroxy carboxylic acid. The crude acid was suspended in dry CH₂Cl₂ (2 mL), treated with pyridine (0.5 mL) and stirred vigorously at 23 °C for 5 min. To this solution was added BOPCI (152 mg, 0.6 mmol) at 23 °C under argon, and stirring was continued for 1h. The solvent was removed under high vacuum and the residue was suspended in dry CH₃CN (1 mL) and treated with pyridine (1 mL). To this solution was added PPh₃Cl₂ (333 mg, 1.0 mmol) at 23 °C under argon with stirring. After 1 h the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, ethyl acetate–CH₂Cl₂, 1 : 5) to give the pure β -lactone **1** (100 mg, 64%) as a colorless solid. R_f = 0.55 (50% ethyl acetate in hexane). mp, 168-170 °C (authentic sample: 168-170 °C, in lit¹: 169-171 °C); mixture mp, 168-170 °C. $[\alpha]_D^{23}$ –73.2 (c 0.49, MeOH) , –72.9 (c 0.55, MeOH, in lit²); FTIR (film) $\nu_{\max}$: 3406, 2955, 2920, 2844, 1823, 1701, 1257, 1076, 1012, 785, 691 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 10.62 (1H, br), 6.42 (1H, d, J = 10.5 Hz), 5.88 (1H, m), 4.25 (1H, d, J = 9.0 Hz), 4.14 (1H, m), 4.01 (1H, m), 3.17 (1H, t, J = 7.0 Hz), 2.85

¹ Feling, R.H.; Buchanan, G. O.; Mincer, T. J.; Kauffmam, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 355-357.

(1H, m), 2.48 (1H, m), 2.32 (2H, m), 2.07 (3H, s), 1.91 (2H, m), 1.66 (2H, m), 1.38 (1H, m); ^{13}C NMR (CDCl_3 , 125 MHz): δ 176.92, 169.43, 129.08, 128.69, 86.32, 80.35, 70.98, 46.18, 43.28, 39.31, 29.01, 26.47, 25.35, 21.73, 20.00; HRMS (ESI) calcd. for $(\text{M} - \text{H})^- \text{C}_{15}\text{H}_{19}\text{ClNO}_4$ 312.1003, found 312.1003.

Part 2. Synthesis of the 2-Cyclohexenylzinc chloride

Synthesis of the Cyclohexenylzinc chloride. To a solution of Cyclohexenyltributyl tin² (1.85 g 5 mmol) in THF (5ml) at -78°C under nitrogen was added $n\text{BuLi}$ (2 ml, 2.5M solution in hexane, 5 mmol). After an additional 30 min stirring, ZnCl_2 (5 ml, 1 M solution in THF, 5 mmol) was added and stirring was continued at this temperature for 30 min at -78°C to give a 0.5M solution of 2-cyclohexenylzinc chloride for reaction with the aldehyde **13** (see p S12).

² Miyake, H.; Yamamura, K.; *Chem. Lett.* **1992**, 507-508.