Total Synthesis of the Marine Natural Product (-)-Clavosolide A

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SUPPORTING INFORMATION

General Experimental Details

All commercially available compounds were used without further purification except where stated. All moisture or air sensitive reactions were carried out in oven-dried glassware under a positive pressure of nitrogen using standard syringe/septa techniques. Anhydrous solvents were obtained by passing through a modified Grubbs system of alumina columns, manufactured by Anhydrous Engineering. When stated, DMF was dried sequentially over three portions of 10% w/v 3Å MS beads for 24 h each, and then stored under nitrogen. Petroleum ether is of the 40-60 °C boiling point range. Routine monitoring of reactions was performed using precoated Merck-Keisegel 60 F₂₅₄ aluminium backed TLC plates. The spots were visualised by UV₂₅₄ light, or potassium permanganate. Flash column chromatography¹ was performed using silica gel (obtained from Fluorochem Ltd.) as the adsorbent.

Melting points were determined on an electrothermal apparatus and are uncorrected. Optical rotations were recorded using with the sodium D line ($\lambda = 589$ nm) on a Bellingham and Stanley ADP220 polarimeter and the $[\alpha]_D$ values are quoted in units $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer in the solid or liquid state. ¹H and ¹³C NMR spectra were recorded at using either a Jeol Delta/GX 400 MHz or a Jeol Eclipse 400 MHz spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are in Hertz (Hz). Tetramethylsilane was used as the internal reference for proton and carbon chemical shifts. DEPT 135, COSY, HMQC and HMBC NMR spectra were routinely used to definitively assign the signals of ¹H and ¹³C NMR spectra. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on a VG Analytical Autospec mass spectrometer. Electrospray (ESI) mass spectra were recorded on a Micromass LCT mass spectrometer or a VG Quattro mass spectrometer. Methane was the ionisation gas used for chemical ionisation. Conformational searches were carried out in MMFF94 force field² in Spartan.³

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

² Halgren, T. A. *J. Computational Chem.*, **1996**, *17*, 490.

³ Spartan '04, Wavefunction Inc., Irvine, CA, USA.

Experimental Procedures

(+)-Methyl (2*E*, 5*S*, 7*E*)-5-(2-benzyloxyethyl)-4-oxa-non-2,7-dienoate **5**

A solution of methyl propiolate (6.10 ml, 68.4 mmol) in dry DCM (55 ml) was added dropwise over 7 h to a solution of alcohol **4** (13.71 g, 62.2 mmol) and quinuclidine (211 mg, 1.9 mmol) in DCM (70 ml) at room temperature under a nitrogen atmosphere. Upon complete addition, the reaction mixture was added to 5% v/v AcOH_{aq} (125 ml, 0.35M). The layers were separated and the aqueous phase was extracted with Et₂O (4x 100 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution (100 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a brown oil (19.87 g) which was purified by column chromatography on silica gel, eluting with 12% EtOAc/petrol to give *enol ether* **5** (16.64 g, 88%) as a colorless oil: silica gel TLC *R_f* 0.30 (15% EtOAc/petrol); $[\alpha]_D^{23} +56.6$ (*c* 4.4, CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 3028 (CH), 2919 (CH), 2858 (CH), 1713 (C=O), 1640 and 1622 (C=C), 1454, 1437, 1202, 1139; δ_H (400 MHz, CDCl₃) 1.65 (3H, dd, *J* 6.3, 1.2, 9-H₃), 1.78-1.95 (2H, m, 1'-H₂), 2.25-2.31 (2H, m, 6-H₂), 3.46-3.55 (2H, m, 2'-H₂), 3.69 (3H, s, -OMe), 4.14 (1H, m, 5-H), 4.47 (2H, s, -CH₂Ph), 5.27 (1H, d, *J* 12.2, 2-H), 5.35 (1H, dtq, *J* 15.2, 6.9, 1.2, 7-H), 5.50 (1H, dq, *J* 15.2, 6.3, 8-H), 7.25-7.37 (5H, m, 5 x Ar-H), 7.53 (1H, d, *J* 12.2, 3-H); δ_C (100 MHz, CDCl₃) 18.3 (C-9), 36.5 (C-1'), 38.1 (C-6), 51.3 (-OMe), 66.2 (C-2'), 73.5 (CH₂Ph), 81.1 (C-5), 97.0 (C-2), 125.5 (C-7), 128.0, 128.1 and 128.7 (C-Ar), 129.6 (C-8), 138.4 (C-Ar_{ipso}), 163.3 (C-3), 168.9 (C-1); Found (CI): 305.1753 [MH]⁺, (C₁₈H₂₅O₄ requires 305.1751); *m/z* (CI) 305 ([MH]⁺, 20), 273 ([Me]⁺, 23), 203 ([C₄H₅O₃]⁺, 57). Note: In some reactions the by-product, dimethyl *E*-hex-2-en-4-yne-1,6-dioate **8**, was also recovered: δ_H (400 MHz, CDCl₃) 3.79 (3H, s, 6-OMe), 3.83 (3H, s, 1-OMe),

6.48 (1H, d, *J* 16.1, 4-H), 6.79 (1H, d, *J* 16.1, 5-H); δ_{C} (100 MHz, CDCl_3) 52.3 (6-OMe), 53.0 (1-OMe), 81.7 (C-3), 86.7 (C-2), 121.7 (C-4), 135.0 (C-5), 153.5 (C-1), 165.1 (C-6).

(+)-Methyl (3*S*, 4*S*, 5*S*, 7*R*, 9*S*, 10*E*)-[7-(2-hydroxypent-3-enyl)-4-methyl-5-(triisopropylsilyloxy)-tetrahydropyran-2-yl]-acetate **10**

and

(+)-Methyl (3*S*, 4*S*, 5*S*, 7*R*, 9*R*, 10*E*)-[7-(2-hydroxypent-3-enyl)-4-methyl-5-(triisopropylsilyloxy)-tetrahydropyran-2-yl]-acetate **11**

Chromium (II) chloride (9.10 g, 74.04 mmol) and nickel (II) chloride (110 mg, 0.85 mmol) were added to a solution of aldehyde **9** (5.70 g, 14.65 mmol) and *E*-1-bromo-1-propene (2.60 ml, 30.26 mmol) in dry DMF (150 ml) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 20 h. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (250 ml). The mixture was stirred vigorously for 30 min. and then added to saturated aqueous potassium sodium tartarate solution (250 ml) and Et_2O (300 ml). The layers were separated and the aqueous phase was extracted with Et_2O (4 x 300 ml). The combined organic extracts were washed with water (2 x 300 ml) and brine (300 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give a pale green oil which was purified by column chromatography on silica gel, eluting with 30% Et_2O /hexane to give *alcohol* **10** (lower-running diastereomer by TLC) as a colorless oil (2.41 g, 39%) and *alcohol* **11** (higher-running diastereomer by TLC) as a colorless oil (2.29 g, 36%): Data for **10**; silica gel TLC *R_f* 0.24 (20% EtOAc /petrol); $[\alpha]_{\text{D}}^{23} +13.3$ (*c* 1.2, CHCl_3); ν_{max} (neat)/ cm^{-1} 3526, 2945, 2892 and 2867 (CH), 1744 (C=O), 1464, 1438, 1092; δ_{H} (400 MHz, CDCl_3) 0.98 (3H, d, *J* 6.6, 4- CH_3), 1.02-1.08 (3H, m, 3 x Si-CH), 1.06 (18H, s, 3 x SiCH(CH_3)₂), 1.34 (1H, tq, *J* 9.8, 6.5, 4-H), 1.43 (1H, dt, *J* 12.6, 11.2, 6- H_{ax}), 1.56 (1H, dt, *J* 14.5, 2.6, 8-*HH*), 1.67 (3H, dd, *J* 6.5, 1.4, 12- H_3), 1.74 (1H, dt, *J* 14.5, 10.0, 8-*HH*), 1.87 (1H, ddd, *J* 12.6, 4.6, 1.7, 6- H_{eq}), 2.41 (1H, dd, *J* 14.9, 10.0, 2-*HH*), 2.67 (1H, dd, *J* 14.9, 2.7, 2-*HH*), 3.39 (1H, br s, -OH), 3.47-3.65 (3H, m, 3-H, 5-H and 7-H),

Reaction scheme showing the conversion of compound **11** to compound **11a** using Dess-Martin Periodinane in DCM.

Compound **11** is a 6-membered cyclic acetal with a TIPS group at C4, a methyl ester at C2, and a 3-hydroxyprop-1-en-1-yl group at C6. The reaction conditions are Dess-Martin Periodinane and DCM.

Compound **11a** is the corresponding lactone where the hydroxyl group has been oxidized to a ketone, forming a 5-membered lactone ring. The numbering 11, 9, 7, 5, 2 is shown on the lactone ring in **11a**.

S4

δ_{H} (400 MHz, CDCl_3) 0.97 (3H, d, J 6.6, 4- CH_3), 1.01-1.08 (3H, m, 3 x SiCH), 1.06 (18H, s, 3 x SiCH(CH_3)₂), 1.32 (1H, tq, J 9.8, 6.6, 4-H), 1.34 (1H, dt, J 12.5, 11.5, 6- H_{ax}), 1.90 (3H, dd, J 6.8, 1.2, 12- H_3), 1.99 (1H, ddd, J 12.5, 4.6, 1.7, 6- H_{eq}), 2.36 (1H, dd, J 14.7, 9.5, 2- HH), 2.48 (1H, dd, J 15.3, 5.4, 8- HH), 2.62 (1H, dd, J 14.7, 3.4, 2- HH), 2.86 (1H, dd, J 15.3, 7.2, 8- HH), 3.48 (1H, td, J 9.8, 3.4, 3-H), 3.56 (1H, ddd, J 11.5, 9.8, 4.6, 5-H), 3.63 (3H, s, OMe), 3.82 (1H, m 7-H), 6.11 (1H, dq, J 15.6, 1.2, 10-H), 6.83 (1H, dq, J 15.6, 6.8, 11-H); δ_{C} (100 MHz, CDCl_3) 12.9 (3 x SiCH), 13.3 (4- CH_3), 18.2 and 18.3 (3 x SiCH(CH_3)₂), 39.4 (C-2), 41.8 (C-6), 44.3 (C-4), 46.0 (C-8), 51.6 (OMe), 72.2 (C-7), 74.0 (C-5), 78.1 (C-3), 132.5 (C-10), 143.5 (C-11), 172.0 (C-1), 198.2 (C-9); Found (ESI): 449.2686 $[\text{MNa}]^+$, ($\text{C}_{23}\text{H}_{42}\text{O}_5\text{Si}$ requires 449.2694); m/z (ESI) 449 $[\text{MNa}]^+$, 100%.

Luche Reduction

Sodium borohydride (1 eq, 0.26 mmol, 9.9 mg) was added in small portions to a stirred solution of enone **11a** (0.26 mmol, 112 mg) and cerium trichloride heptahydrate (0.26 mmol, 97.8 mg) at 0 °C in MeOH (8 ml). The mixture was stirred for 3 h and the volatiles removed *in vacuo* to give a yellow precipitate which was purified by column chromatography on silica gel, eluting with 20% EtOAc in petrol to give a 2:1 (**11**:**10**) mixture of diastereomers (101 mg, 90%) as a colorless oil: Spectroscopic data as above.

(+)-Methyl (3*S*, 4*S*, 5*S*, 7*R*, 9*S*, 10*E*)-[7-(2-(*tert*-butyldimethylsilyloxy)-pent-3-enyl)-4-methyl-5-(triisopropylsilyloxy)-tetrahydropyran-2-yl]-acetate **10a**

tert-Butyldimethylsilyltriflate (0.177 ml, 0.77 mmol) was added to a solution of imidazole (72 mg, 1.05 mmol) and alcohol **10** (300 mg, 0.70 mmol) in dry DMF (5 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred for 19 h and then water (25 ml) and Et₂O (25 ml) were added. The layers were separated and the aqueous phase was extracted with Et₂O (3 x 25 ml). The combined organic extracts were washed with water (2 x 25 ml) and brine (25 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a colorless oil which was purified by flash column chromatography on silica gel, eluting with 5% Et₂O/hexanes to give *alkene 10a* (376 mg, 92%) as a colorless oil: silica gel TLC *R_f* 0.63 (20% EtOAc/petrol); $[\alpha]_D^{25} +21.0$ (*c* 2.0, CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 2948, 2892 and 2867 (CH), 1747 (C=O), 1464, 1437; δ_H (400 MHz, CDCl₃) 0.01 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.86 (9H, s, 3 x Si(CH₃)₃), 0.95 (3H, d, *J* 6.6, 4-CH₃), 1.01-1.07 (3H, m, 3 x SiCH), 1.05 (18H, s, 3 x SiCH(CH₃)₂), 1.30 (1H, tq, *J* 9.8, 6.6, 4-H), 1.34 (1H, dt, *J* 12.5, 11.5, 6-H_{ax}), 1.42 (1H, ddd, *J* 13.3, 8.0, 4.0, 8-HH), 1.68 (3H, dd, *J* 6.4, 1.5, 12-H₃), 1.78 (1H, ddd, *J* 13.3, 9.1, 4.9, 8-HH), 1.85 (1H, ddd, *J* 12.5, 4.6, 1.7, 6-H_{eq}), 2.38 (1H, dd, *J* 14.7, 10.0, 2-HH), 2.61 (1H, dd, *J* 14.7, 3.2, 2-HH), 3.27 (1H, dddd, *J* 11.0, 9.1, 4.0, 1.7, 7-H), 3.39 (1H, td, *J* 9.8, 3.2, 3-H), 3.49 (1H, ddd, *J* 11.5, 9.8, 4.6, 5-H), 3.68 (3H, s, OMe), 4.17 (1H, td, *J* 8.0, 4.9, 9-H), 5.34 (1H, ddq, *J* 15.4, 8.0, 1.5, 10-H), 5.52 (1H, dqd, *J* 15.4, 6.4, 0.7, 11-H); δ_C (100 MHz, CDCl₃) -4.9 (SiMe), -4.3 (SiMe), 12.8 (3 x SiCH), 13.3 (4-CH₃), 17.7 (C-12), 18.2 and 18.3 (3 x SiCH(CH₃)₂), 25.9 (SiC(CH₃)₃), 39.2 (C-2), 41.9 (C-6), 44.4 (C-4), 44.5 (C-8), 51.5 (OMe), 70.8 (C-9), 72.1 (C-7), 74.3 (C-5), 77.8 (C-3), 125.9 (C-11), 134.0 (C-10), 172.3 (C-1); Found (ESI): 565.3696 [MNa]⁺, (C₂₉H₅₈O₅Si₂Na requires, 565.3715); *m/z* (ESI) 565 ([MNa]⁺, 100).

(+)-Methyl (3*S*, 4*S*, 5*S*, 7*R*, 9*S*, 10*R*, 11*R*)-9-(*tert*-butyldimethylsilyloxy)-4-methyl-5-triisopropylsilyloxy-bicyclo-methano-[1^{10,11}]-oxa-[1^{3,7}]-dodecanoate **12**

Chloriodomethane (10 eq, 9.10 mmol, 663 μ L) was added to a solution of diethyl zinc (5 eq, 1.0 M in hexanes, 4.55 mmol, 4.55 ml) in dry DCM (12 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 0.5 h (white ppt forms) and then a solution of *alkene 10a* (0.91 mmol, 495 mg) in dry DCM (6 ml) was added *via* syringe followed by dry DCM washings (5 ml). The mixture was stirred for

5 h slowly warming to 15 °C and was then quenched by addition to saturated aqueous ammonium chloride solution (120 ml). Et₂O (70 ml) was added, the layers were separated and the aqueous phase was extracted with Et₂O (2 x 70 ml). The combined organic extracts were washed with brine (70 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a slightly opaque oil which was purified by flash column chromatography on silica gel, eluting with 5% Et₂O/hexanes to give *cyclopropane* **12** (366 mg, 72%) as a colorless oil: silica gel TLC *R_f* 0.48 (10% EtOAc/petrol); $[\alpha]_D^{25} +22.0$ (*c* 2.0, CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 2948, 2893 and 2866 (C-H), 1747 (C=O); δ_H (400 MHz, CDCl₃) 0.01 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.17 (1H, dt, *J* 8.1, 4.6, 13-*HH*), 0.37 (1H, dt, *J* 8.1, 4.6, 13-*HH*), 0.50-0.60 (2H, m, 10-H and 11-H), 0.87 (9H, s, 3 x Si(CH₃)₃), 0.97 (3H, d, *J* 6.6, 14-H₃), 1.02 (3H, d, *J* 5.6, 12-H₃), 1.06 (21H, s, 3 x Si-CH and 3 x SiCH(CH₃)₂), 1.25-1.37 (2H, m, 4-H and 6-H_{ax}), 1.55 (1H, ddd, *J* 13.4, 8.1, 4.0, 8-*HH*), 1.78 (1H, ddd, *J* 13.4, 9.1, 4.7, 8-*HH*), 1.87 (1H, ddd, *J* 12.2, 4.4, 1.7, 6-H_{eq}), 2.37 (1H, dd, *J* 14.6, 9.9, 2-*HH*), 2.61 (1H, dd, *J* 14.6, 3.0, 2-*HH*), 3.14 (1H, td, *J* 8.1, 4.7, 9-H), 3.41 (1H, td, *J* 9.9, 3.0, 3-H), 3.47-3.57 (2H, m, 5-H and 7-H), 3.65 (3H, s, OMe); δ_C (100 MHz, CDCl₃) -4.6 (SiMe), -4.3 (SiMe), 10.7 (C-13), 10.9 (C-11), 12.8 (3 x SiCH), 13.4 (C-14), 18.1 (SiC-(CH₃)₃), 18.2 and 18.3 (3 x SiCH(CH₃)₂), 18.7 (C-12), 25.7 (C-10), 25.9 (SiC-(CH₃)₃), 39.3 (C-2), 42.3 (C-6), 44.4 (C-4), 45.1 (C-8), 51.5 (OMe), 72.2 (C-5 or C-7), 73.2 (C-9), 74.3 (C-5 or C-7), 77.8 (C-3), 172.3 (C-1); Found (ESI): 579.3878 [MNa]⁺, (C₃₀H₆₀O₅Si₂Na requires, 579.3871); *m/z* (ESI) 579 ([MNa]⁺, 100).

(+)-Methyl (3*S*, 4*S*, 5*S*, 7*R*, 9*S*, 10*R*, 11*R*)-9-hydroxy-4-methyl-5-triisopropylsilanyloxy-bicyclo-methano-[1^{10,11}]-oxa-[1^{3,7}]-dodecanoate **13**

12M HCl_{aq} (5 eq, 3.14 mmol, 260 μ L) was mixed with 95% EtOH (14 ml) and added to a vigorously stirring solution of cyclopropane **12** (0.63 mmol, 350 mg) in 95% EtOH (12 ml). The mixture was stirred at room temperature for 50 min and then added to saturated aqueous sodium hydrogen carbonate solution (160 ml) and DCM (160 ml). The layers were separated and the aqueous phase was extracted with DCM (2 x 120 ml). The combined organic extracts were washed with water (140 ml) and brine (140 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale yellow oil which was

purified by flash column chromatography on silica gel, eluting with 40% Et₂O/petrol to give *alcohol 13* (262 mg, 94%) as a colorless oil: silica gel TLC *R_f* 0.28 (40% EtOAc/petrol); $[\alpha]_D^{25} +4.5$ (*c* 2.7, CHCl₃); $\nu_{\max}$ (neat)/cm⁻¹ 3530 (OH), 2946, 2893 and 2867 (C-H), 1743 (C=O); δ_H (400 MHz, CDCl₃) 0.15 (1H, dt, *J* 8.4, 4.6, 13-*HH*), 0.30 (1H, dt, *J* 8.4, 4.6, 13-*HH*), 0.58 (1H, tt, *J* 8.4, 4.6, 10-*HH*), 0.77 (1H, m, 11-H), 0.97 (3H, d, *J* 6.6, 14-H₃), 1.05 (3H, d, *J* 6.1, 12-H₃), 1.06 (21H, s, 3 x Si-*CH* and 3 x SiCH(CH₃)₂), 1.34 (1H, tq, *J* 9.8, 6.6, 4-H), 1.42 (1H, dt, *J* 12.3, 11.2, 6-H_{ax}), 1.65 (1H, dt, *J* 14.5, 2.7, 8-*HH*), 1.75 (1H, dt, *J* 14.5, 9.6, 8-*HH*), 1.87 (1H, ddd, *J* 12.3, 4.6, 1.8, 6-H_{eq}), 2.40 (1H, dd, *J* 15.2, 9.8, 2-*HH*), 2.65 (1H, dd, *J* 15.2, 2.8, 2-*HH*), 3.11 (1H, td, *J* 8.4, 2.7, 9-H), 3.49 (1H, td, *J* 9.8, 2.8, 3-H), 3.48-3.60 (2H, m, 5-H and 7-H), 3.68 (3H, s, OMe); δ_C (100 MHz, CDCl₃) 10.0 (C-13), 11.2 (C-11), 12.8 (SiCH), 13.3 (C-14), 18.2 and 18.3 (SiCH(CH₃)₂), 18.7 (C-12), 26.1 (C-10), 38.6 (C-2), 42.2 (C-6), 42.6 (C-8), 44.0 (C-4), 51.9 (OMe), 73.8 and 76.1 (C-5 and C-7), 76.3 (C-9), 77.9 (C-3), 172.1 (C-1); Found (ESI): 465.3006 [MNa]⁺, (C₃₀H₆₀O₅Si₂Na requires, 465.3007); *m/z* (ESI) 465 ([MNa]⁺, 100).

(-)-(3*S*,4*S*,5*S*,7*R*,9*S*,10*R*,11*R*)-9-Hydroxy-4-methyl-5-triisopropylsilyloxy-bicyclo-methano-[1^{10,11}]-oxa-[1^{3,7}]-dodecanoic acid 14

Sodium trimethylsilylanolate (1M in DCM, 2 eq, 1.45 mmol, 1.45 ml) was added to a stirred solution of ester **13** (0.72 mmol, 320 mg) in dry DCM (18 ml) at RT under a nitrogen atmosphere. The mixture was stirred for 18 h and then the volatiles were removed *in vacuo* to give the sodium salt as a pale yellow solid which was purified by column chromatography on silica gel, eluting with 67% EtOAc in petrol followed by 67% EtOAc in petrol + 4% AcOH to give *acid 14* (307 mg, 99%) as a pale yellow oil: silica gel TLC *R_f* 0.61 (67% EtOAc/petrol + 4% AcOH); $[\alpha]_D^{24} -5.6$ (*c* 5.0, CH₂Cl₂); $\nu_{\max}$ (neat)/cm⁻¹ 3456 (OH), 2943, 2893 and 2866 (CH), 1715, 1463; δ_H (400 MHz, CDCl₃) 0.17 (1H, dt, *J* 8.5 and 5.0, 13-*HH*), 0.27 (1H, dt, *J* 8.5 and 5.0, 13-*HH*), 0.59 (1H, tt, *J* 8.5 and 5.0, 10-H), 0.77 (1H, m, 11-H), 0.98 (3H, d, *J* 7.0, 14-H₃), 1.02 (3H, d, *J* 5.0, 12-H₃), 1.03-1.08 (3H, m, 3 x SiCH), 1.06 (18H, s, 3 x SiCH(CH₃)₂), 1.34 (1H, m, 4-H), 1.44 (1H, dt, *J* 12.0 and 11.5, 6-H_{ax}), 1.67 (1H, br d, *J* 14.0, 8-*HH*), 1.79 (1H, m, 8-*HH*), 1.88 (1H, ddd, *J* 12.0, 5.0 and 1.5, 6-H_{eq}), 2.40 (1H, dd, *J* 15.0 and 11.0, 2-*HH*), 2.66 (1H, dd, *J* 15.0 and 2.0, 2-*HH*), 3.16 (1H, dt, *J* 8.5 and 2.0, 9-H), 3.46-3.62 (3H, m, 3-H, 5-H and

7-H); δ_{C} (100 MHz, CDCl_3) 10.2 (C-13), 11.7 (C-11), 12.8 (3 x SiCH), 13.3 (C-14), 18.2 and 18.3 (3 x SiCH(CH₃)₂), 18.6 (C-12), 25.8 (C-10), 38.6 (C-2), 41.8 (C-6), 42.1 (C-8), 44.0 (C-4), 73.7 and 76.5 (C-5 and C-7), 77.2 (C-9), 78.2 (C-3), 173.4 (C-1); Found (ESI): 451.2856 $[\text{MNa}]^+$, ($\text{C}_{23}\text{H}_{44}\text{O}_5\text{Si}$ requires 451.2850); m/z (ESI) 451 $[\text{MNa}]^+$, 100%).

(-)-(3*S*,4*S*,5*S*,7*R*,9*S*,10*R*,11*R*,3'*S*,4'*S*,5'*S*,7'*R*,9'*S*,10'*R*,11'*R*)-4,4'-Dimethyl-9,9'-bis-(2-methylcyclopropyl)-5,5'-triisopropylsilanyloxy-15,16,15',16'-tetraoxy-tricyclo[15.3.1.1^{3,7}]docosane-1,1'-dione **14a**

2,4,6-Trichlorobenzoyl chloride (1.1 eq, 0.44 mmol, 68.2 μL) was added to a stirred solution of seco-acid **14** (0.40 mmol, 170 mg) and triethylamine (1.3 eq, 0.52 mmol, 71.9 μL) in dry THF (1.4 ml) at RT under a nitrogen atmosphere. The mixture was stirred for 2.5 h. The TEA.HCl salt was filtered off and the filtrate diluted with dry toluene (15 ml). This solution was then added slowly to a solution of dimethylaminopyridine (5.1 eq, 2.02 mmol, 247 mg) in dry toluene (70 ml) under reflux. The mixture was stirred for a further 17 h and diluted with water (75) at RT. The layers were separated and the aqueous layer was extracted with Et₂O (2 x 35 ml). The combined organic fractions washed with brine (50 ml), dried (MgSO_4), filtered and concentrated *in vacuo* to give a white solid which was purified by flash column chromatography on silica gel, eluting with 10% Et₂O in hexane to give *dimer 14a* (121 mg, 74%) as a white solid (which could not be recrystallised): silica gel TLC R_f 0.75 (50% Et₂O/hexane); $[\alpha]_{\text{D}}^{24}$ -3.2 (c 2.5, CH_2Cl_2); ν_{max} (neat)/ cm^{-1} 2944, 2925, 2893 and 2866 (CH), 1754 (C=O), 1464, 1054; δ_{H} (400 MHz, CDCl_3) 0.23 (2H, dt, J 8.6, 4.6, 13-*HH* and 13'-*HH*), 0.36 (2H, dt, J

8.6, 4.6, 13-*HH* and 13'-*HH*), 0.69 (2H, tt, *J* 8.6, 4.6, 10-H and 10'-H), 0.79 (2H, m, 11-H and 11'-H), 0.92 (6H, d, *J* 6.6, 14-H₃ and 14'-H₃), 0.97 (6H, d, *J* 5.9, 12-H₃ and 12'-H₃), 1.02-1.09 (6H, m, 6 x SiCH), 1.06 (36H, s, 6 x SiCH(CH₃)₂), 1.27 (2H, m, 4-H and 4'-H), 1.32 (2H, dt, *J*, 12.0, 11.5, 6-H_{ax} and 6'-H_{ax}), 1.65 (2H, dt, *J* 14.9, 2.0, 8-*HH* and 8'-*HH*), 1.75 (2H, ddd, *J* 12.0, 4.9, 1.7, 6-H_{eq} and 6'-H_{eq}), 1.88 (2H, dt, *J* 14.9, 8.6, 8-*HH* and 8'-*HH*), 2.43 (2H, dd, *J* 17.8, 5.6, 2-*HH* and 2'-*HH*), 2.54 (2H, dd, *J* 17.8, 4.4, 2-*HH* and 2'-*HH*), 3.43-3.54 (6H, m, 3-H and 3'-H, 5-H and 5'-H, 7-H and 7'-H), 4.45 (2H, td, *J* 8.6, 1.7, 9-H and 9'-H); δ_c (100 MHz, CDCl₃) 11.0 (C-11 and C-11'), 11.7 (C-13 and C-13'), 12.8 (SiCH), 13.2 (C-14 and C-14'), 18.2 and 18.3 (SiCH(CH₃)₂), 18.5 (C-12 and C-12'), 24.7 (C-10 and C-10'), 39.4 (C-2 and C-2'), 41.4 (C-8 and C-8'), 42.5 (C-6 and C-6'), 44.8 (C-4 and C-4'), 74.3 (C-5 and C-5'), 74.9 (C-7 and C-7'), 77.0 (C-3 and C-3'), 77.2 (C-9 and C-9'), 171.2 (C-1 and C-1'); Found (ESI): 843.5614 [MNa]⁺, (C₄₆H₈₄O₈Si₂Na requires 843.5597); *m/z* (ESI) 843 ([MNa]⁺, 100).

(-)-(3*S*,4*S*,5*S*,7*R*,9*S*,10*R*,11*R*,3'*S*,4'*S*,5'*S*,7'*R*,9'*S*,10'*R*,11'*R*)-4,4'-Dimethyl-9,9'-bis-(2-methylcyclopropyl)-5,5'-bis-hydroxy-15,16,15',16'-tetraoxy-tricyclo[15.3.1.1^{3,7}]docosane-1,1'-dione 15

TBAF (8 eq, 1 M in THF, 1.12 mmol, 1.12 ml) was added to a solution of dimer **14a** (0.115 mmol, 121 mg) in dry THF (5 ml) at RT under a nitrogen atmosphere. The mixture was stirred for 3 h and then added to 1:1 water/EtOAc (30 ml). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 25 ml). The combined organic fractions were washed with water (2 x 25 ml) and brine (25 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel, eluting with 40% EtOAc in petrol to give diolide **15** (54 mg, 72%) as a white solid (which could not be recrystallised): silica gel TLC *R_f* 0.07 (50% Et₂O/hexane); $[\alpha]_D^{23}$ -54.0 (*c* 3.3, CH₂Cl₂), Lit.² $[\alpha]_D^{25}$ -49.6 (*c* 0.165, CHCl₃); ν_{max} (neat)/cm⁻¹ 3305 (OH), 2960, 2920 and 2854 (CH), 1722 (C=O), 1024; δ_H (400 MHz, CDCl₃) 0.24 (2H, dt, *J* 8.6, 4.6, 13-*HH* and 13'-*HH*), 0.36 (2H, dt, *J* 8.6, 4.6, 13-*HH* and 13'-*HH*), 0.73 (2H, tt, *J* 8.6, 4.6, 10-H and 10'-H), 0.82 (2H, m, 11-H and 11'-H), 0.95 (6H, d, *J* 6.6, 14-H₃ and 14'-H₃), 0.98 (6H, d, *J* 6.1, 12-H₃ and 12'-H₃), 1.23 (2H, m, 4-H and 4'-H), 1.26 (2H, dt, *J*, 12.0, 11.5, 6-H_{ax} and 6'-H_{ax}), 1.70 (2H, ddd, *J* 15.1, 3.4,

2.0, 8-*HH* and 8'-*HH*), 1.88-1.96 (4H, m, 6-*H*_{eq} and 6'-*H*_{eq}, 8-*HH* and 8'-*HH*), 2.43 (2H, dd, *J* 17.1, 6.6, 2-*HH* and 2'-*HH*), 2.56 (2H, dd, *J* 17.1, 3.7, 2-*HH* and 2'-*HH*), 3.36 (2H, td, *J* 11.5, 4.4, 5-*H* and 5'-*H*), 3.42 (2H, dt, *J* 6.6, 3.7, 3-*H* and 3'-*H*), 3.49 (2H, m, 7-*H* and 7'-*H*), 4.42 (2H, td, *J* 8.6, 1.5, 9-*H* and 9'-*H*); δ_c (100 MHz, CDCl₃) 10.9 (C-13 and C-13'), 11.9 (C-11 and C-11'), 12.7 (C-14 and C-14'), 18.5 (C-12 and C-12'), 24.7 (C-10 and C-10'), 39.1 (C-2 and C-2'), 41.3 (C-8 and C-8'), 41.4 (C-6 and C-6'), 44.0 (C-4 and C-4'), 73.1 (C-5 and C-5'), 74.8 (C-7 and C-7'), 76.9 (C-9 and C-9'), 77.0 (C-3 and C-3'), 171.1 (C-1 and C-1'); Found (ESI): 531.2934 [MNa]⁺, (C₂₈H₄₄O₈Na requires 531.2928); *m/z* (ESI) 531 ([MNa]⁺, 100).

² Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.*, **2006**, 8 661.

(-)-(3*S*, 4*S*, 5*S*, 7*R*, 9*S*, 10*R*, 11*R*, 15*S*, 16*R*, 17*S*, 18*R*, 3'*S*, 4'*S*, 5'*S*, 7'*R*, 9'*S*, 10'*R*, 11'*R*, 15'*S*, 16'*R*, 17'*S*, 18'*R*)-4,4'-Dimethyl-9,9'-bis-(2-methylcyclopropyl)-5,5'-bis-(3,4,5-trimethoxy tetrahydropyran -2-yloxy)-15,16,15',16'-tetraoxa-tricyclo[15.3.1.1^{3,7}]docosane-1,1'-dione 2

A solution of NBS (8 eq, 0.88 mmol, 157 mg) in dry MeCN (3 ml) and washings (1 ml MeCN) was added slowly to a stirred solution of diolide **17** (0.11 mmol, 56 mg), thioglycoside (4 eq, 0.44 mmol, 126 mg) and activated powdered 4Å molecular sieves (250 mg) in dry MeCN (3 ml) and washings (2 ml DCM) at -40 C under a nitrogen atmosphere. The mixture was stirred for 1 h slowly warming to RT (white → orange) and for a further 0.5 h at RT. The solution was then filtered into saturated aqueous sodium hydrogen carbonate solution (25 ml) and diluted with EtOAc (20 ml). The layers were

separated and the aqueous fraction extracted with EtOAc (2 x 20 ml). The combined organic fractions were washed with brine (30 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale yellow oil which was purified by column chromatography on silica gel, eluting with 60% EtOAc in petrol to give diolide **2** (17 mg, 18%) as a white solid: silica gel TLC *R_f* 0.43 (60% EtOAc/petrol); mp 252-254 °C, Lit.² 256.8 °C; $[\alpha]_{\text{D}}^{23}$ -38.0 (*c* 1.0, CHCl₃); ν_{max} (film)/cm⁻¹ 2944 (CH), 1736 (C=O), 1072; δ_{H} (400 MHz, CDCl₃) 0.22 (2H, dt, *J* 8.3, 4.9, 13-*HH* and 13'-*HH*), 0.34 (2H, dt, *J* 8.3, 4.9, 13-*HH* and 13'-*HH*), 0.71 (2H, tt, *J* 8.3, 4.9, 10-H and 10'-H), 0.81 (2H, m, 11-H and 11'-H), 0.97 (12H, d, *J* 6.5, 12-H₃ and 12'-H₃, 14-H₃ and 14'-H₃), 1.37 (2H, q, *J* 11.5, 6-H_{ax} and 6'-H_{ax}), 1.38 (2H, m, 4-H and 4'-H), 1.68 (2H, br d, *J* 15.1, 8-*HH* and 8'-*HH*), 1.89 (2H, dt, *J* 15.1, 9.0, 8-*HH* and 8'-*HH*), 2.05 (2H, ddd, *J* 11.5, 4.6, 1.5, 6-H_{eq} and 6'-H_{eq}), 2.41 (2H, dd, *J* 17.3, 6.6, 2-*HH* and 2'-*HH*), 2.55 (2H, dd, *J* 17.3, 3.7, 2-*HH* and 2'-*HH*), 2.96 (2H, dd, *J* 9.0, 7.8, 16-H and 16'-H), 3.09 (2H, dd, *J* 11.2, 10.0, 19-H_{ax} and 19'-H_{ax}), 3.10 (2H, t, *J* 9.0, 17-H and 17'-H), 3.21-3.28 (4H, m, 5-H and 5'-H, 18-H and 18'-H), 3.41-3.49 (4H, m, 3-H and 3'-H, 7-H and 7'-H), 3.47 (6H, s, 22-H₃ and 22'-H₃), 3.57 (6H, s, 20-H₃ and 20'-H₃), 3.61 (6H, s, 21-H₃ and 21'-H₃), 3.96 (2H, dd, *J* 11.2, 5.1, 19-H_{eq} and 19'-H_{eq}), 4.27 (2H, d, *J* 7.8, 15-H and 15'-H), 4.41 (2H, td, *J* 9.0, 2.0, 9-H and 9'-H); δ_{C} (100 MHz, CDCl₃) 10.9 (C-13 and C-13'), 11.9 (C-11 and C-11'), 12.6 (C-14 and C-14'), 18.5 (C-12 and C-12'), 24.7 (C-10 and C-10'), 39.2 (C-2 and C-2'), 40.7 (C-6 and C-6'), 41.3 (C-8 and C-8'), 42.6 (C-4 and C-4'), 58.8 (C-22 and C-22'), 60.4 (C-20 and C-20'), 60.8 (C-21 and C-21'), 63.2 (C-19 and C-19'), 74.8 (C-7 and C-7'), 77.0 (C-3 and C-3'), 77.1 (C-9 and C-9'), 79.4 (C-18 and C-18'), 83.2 (C-5 and C-5'), 83.8 (C-16 and C-16'), 85.6 (C-17 and C-17'), 105.5 (C-15 and C-15'), 171.0 (C-1 and C-1'); Found (ESI): 879.4737 [MNa]⁺, (C₄₄H₇₂O₁₆Na requires 879.4713); *m/z* (ESI) 879 ([MNa]⁺, 100).

The ¹H- and ¹³C NMR spectra of the aglycone **15** and synthetic clavosolide A **2** are given below.

^1H Aglycone **15**.

^{13}C Aglycone **15**.

¹H Synthetic (-)-Clavosolide A 2.

^{13}C Synthetic (-)-Clavosolide A **2**.