Total Synthesis, Structural Revision, and Absolute Configuration of (+)- Clavosolide A

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Supporting Information

All reactions were carried out under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus through rubber septa. Tetrahydrofuran (THF), diethyl ether (Et₂O) and toluene were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from phosphorous pentoxide. Triethylamine (TEA) and other nitrogen containing bases were distilled from calcium hydride under nitrogen atmosphere prior to use. Methanol was distilled from sodium. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F₂₅₄). Visualization was accomplished with either UV light, or by immersion in solutions of *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for ~15 sec. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. ¹H-NMR and ¹³C-NMR spectra were obtained using a Varian Gemini-300 (300 MHz for ¹H, and 75 MHz for ¹³C), or a Varian Inova-500 (500 MHz for ¹H, and 125 MHz for ¹³C) spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26) for ¹H NMR and chloroform (δ 77.2) for ¹³C NMR. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz). Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Elemental analyses were performed by the Organic Chemistry Research Center at Sogang University using a Carlo Erba EA 1180 elemental analyzer. Optical rotations were obtained using a Rudolph Autopol III digital polarimeter and optical rotation data was reported as follows: $[\alpha]_D^{25}$ (concentration c =g/100mL, solvent). High resolution mass spectra were recorded on a 4.7 Tesla IonSpec ESI-FTMS or a Micromass LCT ESI-TOF mass spectrometer. All commercially available compounds were used as received unless stated otherwise.

4-(2-[*tert*-Butyldiphenylsilanyloxymethyl]cyclopropyl)- 4-(4-methoxybenzyloxy)-2-methyl-1-butene (5)

Methallylation: Dry TMEDA (4.6 mL, 29.6 mmol) and isobutylene (6.6 g, 118.2 mmol) was added dropwise sequentially to a stirred solution of *n*-butyllithium (12.5 mL, 29.6 mmol, 2.36 M in hexane) in ether (18 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 h and allowed to stand overnight at room temperature. The mixture was added dropwise to the stirred solution of *B*-methoxydiisopinocampheylborane (9.7 g, 30.74 mmol) in Et₂O (35 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, the cooling bath was removed and the reaction mixture was allowed to warm up to rt (~1 h). The reaction mixture was cooled to -78 °C and treated with aldehyde **7** (4 g, 11.82 mmol) in Et₂O (4 mL). The contents were stirred for 2 h at -78 °C and then allowed to warm up to rt. The organoboron intermediate was treated with 11 mL of 3*N* NaOH, followed by 11 mL of 30 % H₂O₂ and the contents were stirred at rt for 3 h. The reaction mixture was extracted with ether (x3), and the extracts were washed with water (x1) and brine (x1), dried over anhydrous MgSO₄, and concentrated *in vacuo*. Purification *via* flash chromatography (Hex:EtOAc = 7:1) gave alcohol (3.5 g, 75%): $[\alpha]_D^{25} = -16.5$ (c 0.525, CHCl₃); IR (film): $\tilde{\nu} = 3435, 3071, 2999, 2959, 2931, 2858, 1648, 1589, 1444, 1111, 889 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.67$ (m, 4 H), 7.43-7.36 (m, 6 H), 4.85 (s, 1 H), 4.80 (s, 1 H), 3.65 (dd, *J* = 6, 10.5 Hz, 1 H), 3.47 (dd, *J* = 6.5, 10.5 Hz, 1 H), 3.17 (m, 1 H), 2.29 (dd, *J* = 4, 13.5 Hz, 1 H), 2.24 (dd, *J* = 8.5, 13.5 Hz, 1 H), 1.75 (s, 3 H), 1.62 (d, *J* = 3 Hz, 1 H), 1.08 (m, 1 H), 1.05 (s, 9 H), 0.79 (m, 1 H), 0.43 ppm (m, 2 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 142.9, 135.8, 134.0, 129.7, 127.8, 113.2, 72.6, 66.7, 45.6, 27.0, 23.5, 22.7, 19.3, 19.0, 7.6$ ppm; HRMS: *m/z* calcd for C₂₅H₃₄O₂SiNa[M+Na]⁺ 417.2226, found 417.2214.

Protection: To a solution of alcohol (494 mg, 1.25 mmol) in CH₂Cl₂/*c*-Hexane (5 mL/ 10 mL) was added a solution of *p*-methoxybenzyl 2,2,2-trichloroacetimidate (707.4 mg, 2.5 mmol) in CH₂Cl₂/*c*-Hexane (5 mL/ 10 mL) at room temperature. A catalytic amount of TsOH was added at room temperature and the reaction mixture was stirred for 24 h at the temperature. The reaction was quenched with TEA, and excess *n*-Hexane was added. Precipitates were filtered off, and the combined filtrates were concentrated *in vacuo*. The residue was diluted with Et₂O and washed with brine (x1). The combined organic layers were dried over MgSO₄, filtered, evaporated to give crude product. The crude residue was purified by column chromatography (Hex:EtOAc = 7:1) to give PMB protected ether **5** in 76% yield (486.5 mg): $[\alpha]_D^{25} = -29.8$ (c 0.585, CHCl₃); IR (film): $\tilde{\nu} = 3071, 2997, 2894, 2857, 1612, 1512, 1463, 1427, 1301, 1247, 1172, 1108, 820, 705 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.67$ (m, 4 H), 7.43-7.36 (m, 6 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 4.79 (s, 1 H), 4.77 (s, 1 H), 4.73 (d, *J* = 11.5 Hz, 1 H), 4.53 (d, *J* = 11.5 Hz, 1 H), 3.79 (s, 3 H), 3.69 (dd, *J* = 5.75, 10.5 Hz, 1 H), 3.50 (dd, *J* = 6.8, 10.5 Hz, 1 H), 2.93 (dt, *J* = 4, 8.5 Hz, 1 H), 2.39 (dd, *J* = 8.5, 14 Hz, 1 H), 2.27 (dd, *J* = 4, 14 Hz, 1 H), 1.72 (s, 3 H), 1.16 (m, 1 H), 1.05 (s, 9 H), 0.83 (tt, *J* = 4, 9 Hz, 1 H), 0.35 (dt, *J* = 5, 9 Hz, 1 H), 0.25 ppm (dt, *J* = 5, 9 Hz, 1 H); ¹³C NMR (125 MHz,

CDCl₃): δ = 159.0, 143.3, 135.8, 134.0, 131.4, 129.7, 129.2, 127.8, 113.7, 112.4, 80.1, 69.9, 67.1, 55.4, 44.0, 27.0, 23.1, 21.0, 20.8, 19.4, 6.1 ppm; HRMS: m/z calcd for C₃₃H₄₂O₃SiNa[M+Na]⁺ 537.2801, found 537.2822

4-(2-Bromomethylcyclopropyl)- 4-(4-methoxybenzyloxy)-2-methyl-1-butene (6)

Deprotection of silyl ether: A solution of silyl ether **5** (2.32 g, 4.50 mmol) in THF (15 mL) was cooled to 0 °C, and TBAF (13.5 mL, 1M in THF) was added. After being stirred for 3 h at rt, the reaction mixture was treated with H₂O and extracted with ether (x3). The extracts were washed with water (x1) and brine (x1), dried over anhydrous MgSO₄, and concentrated *in vacuo*. Purification of the crude product by flash column chromatography on silica gel (Hex:EtOAc = 1:1) provided alcohol (1.16 g, 93%): $[\alpha]_D^{25}$ = -3.91 (*c* 1.17, CHCl₃); IR (film): $\tilde{\nu}$ = 3464, 3071, 2934, 2911, 2867, 1613, 1513, 1463, 1248, 1173, 1038, 821 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.25 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 4.80 (s, 1 H), 4.78 (s, 1 H), 4.61 (d, *J* = 12 Hz, 1 H), 4.50 (d, *J* = 11 Hz, 1 H), 3.79 (s, 3 H), 3.47 (m, 2 H), 2.99 (dt, *J* = 5.1, 7.5 Hz, 1 H), 2.93 (ddd, *J* = 8.25, 8.25, 4.5 Hz, 1 H), 2.39 (dd, *J* = 7.5, 14 Hz, 1 H), 2.27 (dd, *J* = 4, 14 Hz, 1 H), 1.74 (s, 3 H), 1.16 (m, 1 H), 0.81 (tt, *J* = 4.5, 9 Hz, 1 H), 0.46-0.38 ppm (m, 2 H); ¹³C NMR (125 MHz, CDCl₃): δ = 159.2, 143.1, 131.1, 129.3, 113.9, 112.8, 80.0, 70.6, 66.7, 55.4, 43.7, 23.2, 21.4, 20.6, 7.1 ppm; HRMS: m/z calcd for C₁₇H₂₄O₃Na[M+Na]⁺ 299.1623, found 299.1610

Bromination: Triphenylphosphine (1.31 g, 4.98 mmol) was added to a mixture of alcohol (1.1 g, 3.98 mmol) and CBr₄ (1.65 g, 4.98 mmol) in THF (10 mL). After being stirred at room temperature for 2.5 hours, the reaction mixture was extracted with ether (x3). The extracts were washed with water and brine, dried over MgSO₄, and concentrated. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc = 10:1) to afford bromide **6** (1.2 g, 89%): $[\alpha]_D^{25}$ = -20.13 (*c* 1, CHCl₃); IR (film): $\tilde{\nu}$ = 3071, 2999, 2934, 2835, 1612, 1513, 1454, 1301, 1247, 1173, 1076, 1035, 893; ¹H NMR (500 MHz, CDCl₃): δ = 7.26 (d, *J* = 9 Hz, 2 H), 6.86 (d, *J* = 9 Hz, 2 H), 4.79 (br d, *J* = 11 Hz, 2 H), 4.66 (d, *J* = 11.5 Hz, 1 H), 4.49 (d, *J* = 11.5 Hz, 1 H), 3.80 (s, 3 H), 3.34 (dd, *J* = 3, 7 Hz, 2 H), 3.02 (dt, *J* = 4.5, 7.5 Hz, 1 H), 2.39 (dd, *J* = 7, 14 Hz, 1 H), 2.27 (dd, *J* = 4.5, 14 Hz, 1 H), 1.73 (s, 3 H), 1.36 (m, 1 H), 0.97 (m, 1 H), 0.62 (dt, *J* = 5.5, 8.5 Hz, 1 H), 0.53 ppm (dt, *J* = 5, 8.5 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃): δ = 159.2, 142.9, 131.1, 129.3, 113.8, 112.9, 79.4, 70.7, 55.4, 43.6, 38.6, 26.1, 23.2, 20.8, 11.7 ppm; HRMS: m/z calcd for C₁₇H₂₃O₂BrNa[M+Na]⁺ 361.0779, found 361.0764

4-(4-Methoxybenzyloxy)-4-(2-methylcyclopropyl)-butan-2-one (7)

Reduction of alkyl boromide: Bromide **6** (1.68 mg, 4.95 mmol) in THF (4.4 mL) was added dropwise to the stirred solution of LAH (7.43 mL, 7.43 mmol, 1M in THF) in THF (8 mL) at room temperature. The reaction mixture was stirred for 1 h, then was quenched at 0 °C with THF/H₂O(1:1, 5 mL), followed by saturated aqueous sodium potassium tartrate (50 mL) and the contents were stirred at rt for 1 h. The aqueous material is extracted with ether (x3) and the combined organic extracts were washed with brine (x1), dried over MgSO₄, and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc = 10:1) to yield olefin (1.23 g, 96%): $[\alpha]_D^{25} = -26.1$ (c 1.13, CHCl₃); IR (film): $\tilde{\nu} = 3070, 2995, 2947, 2866, 1613, 1513, 1443, 1248, 1172, 1075, 820 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.26$ (d, *J* = 9 Hz, 2 H), 6.86 (d, *J* = 9 Hz, 2 H), 4.79 (s, 1 H), 4.77 (s, 1 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 3.80 (s, 3 H), 2.87 (dt, *J* = 4.5, 8 Hz, 1 H), 2.38 (dd, *J* = 8, 14 Hz, 1 H), 2.28 (dd, *J* = 4, 14 Hz, 1 H), 1.73 (s, 3 H), 1.08 (d, *J* = 5 Hz, 3 H), 0.73 (m, 1 H), 0.57 (m, 1 H), 0.23 ppm (m, 2 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 159.1, 143.5, 131.5, 129.1, 113.8, 112.3, 81.4, 70.1, 55.4, 43.8, 24.0, 23.5, 18.5, 13.1, 9.8 \text{ ppm}$; HRMS: *m/z* calcd for C₁₇H₂₄O₂Na[M+Na]⁺ 283.1674, found 283.1675

Ozonolysis: Alkene (1.234 g, 4.74 mmol) and pyridine (2.2 mL) were dissolved in MeOH (47 mL) and the mixture was cooled to -78 °C. Ozone was bubbled through until the starting material was consumed as determined by TLC analysis. The reaction was quenched by adding excess dimethyl sulfide (3.8 mL). The mixture was allowed to warm to ambient temperature and stirred for 4 h. The resulting solution was concentrated directly *in vacuo*. The organic residue was diluted with Et₂O and washed with a saturated aqueous NaHCO₃ solution. Layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by Flash column chromatography on silica gel (Hex:EtOAc = 2:1) to yield methyl ketone **7** (1.19 g, 96 %) as a colorless oil: $[\alpha]_D^{25} = -38.9$ (c 1.26, CHCl₃); IR (film): $\tilde{\nu} = 3065, 2996, 2950, 2865, 1713, 1612, 1513, 1358, 1247, 1076, 823 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.23$ (d, *J* = 8 Hz, 2 H), 6.86 (d, *J* = 8 Hz, 2 H), 4.65 (d, *J* = 11 Hz, 1 H), 4.40 (d, *J* = 11.5 Hz, 1 H), 3.79 (s, 3 H), 3.21 (dt, *J* = 4, 9 Hz, 1 H), 2.82 (dd, *J* = 8.5, 15 Hz, 1 H), 2.56 (dd, *J* = 3.5, 15.5 Hz, 1 H), 2.16 (s, 3 H), 1.08 (d, *J* = 6.5 Hz, 3 H), 0.78 (m, 1 H), 0.57 (m, 1 H), 0.23 ppm (m, 2 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 207.9, 159.2, 130.9, 129.3, 113.9, 79.7, 70.7, 55.4, 49.6, 31.4, 23.7, 18.4, 13.9, 9.4 \text{ ppm}$; HRMS: *m/z* calcd for C₁₆H₂₂O₃Na[M+Na]⁺ 285.1467, found 285.1469.

7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-1-(4-methoxybenzyloxy)-6-methyl-1-(2-methylcyclopropyl)-heptan-3-one (9)

To a solution of the methyl ketone **7** (415 mg, 1.58 mmol) in 7 mL of ether was added *i*-Pr₂NEt (0.4 mL, 2.26 mmol). The solution was cooled to -78 °C and Bu₂BOTf (2.1 mL, 2.1 mmol) was added dropwise. The resulting white heterogeneous mixture was stirred 30 minutes at -78 °C followed by the slow addition of aldehyde **8** (639 mg, 3.16 mmol) in 3 mL of ether over a period of 40 minutes. The mixture was stirred 2 h at -78 °C and 11 mL of a pH=7 buffer/MeOH (1/6, v/v) solution was added. This resulting clear solution was placed at 0 °C followed by the addition of 3.8 mL of a 30 % H₂O₂/MeOH (1/2, v/v) solution. The ice bath was removed and the reaction was stirred 1 h at room temperature. The mixture was extracted with Et₂O (x3). The combined organic layers were washed with brine, dried over MgSO₄, and evaporated. Purification of the crude product by flash column chromatography on silica gel (Hex:EtOAc = 2:1) provided β-hydroxy ketone **9** (713 mg, 93%): $[\alpha]_D^{25} = -24.93$ (*c* 1.68, CHCl₃); IR (film): $\tilde{\nu} = 3502, 2954, 2925, 2857, 1715, 1613, 1514, 1471, 1250, 1095, 1036, 837 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.21$ (d, *J* = 9 Hz, 2 H), 6.85 (d, *J* = 8 Hz, 2 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.39 (d, *J* = 11.5 Hz, 1 H), 4.25 (ddd, *J* = 5.5, 11, 15 Hz, 1 H), 3.79 (s, 3 H), 3.66 (dd, *J* = 5, 10 Hz, 1 H), 3.60 (dd, *J* = 5.5, 10 Hz, 1 H), 3.29 (d, *J* = 3.5 Hz, 1 H), 3.25 (dt, *J* = 4, 9.5 Hz, 1 H), 2.86 (dd, *J* = 9.5, 15 Hz, 1 H), 2.67 (dd, *J* = 9.5, 16.5 Hz, 1 H), 2.57 (dd, *J* = 3.5, 15 Hz, 1 H), 2.53 (dd, *J* = 3.5, 16.5 Hz, 1 H), 1.67 (m, 1 H), 1.07 (d, *J* = 6 Hz, 3 H), 0.89 (s, 9 H), 0.87 (d, *J* = 7 Hz, 3 H), 0.77 (m, 1 H), 0.57 (m, 1 H), 0.23 (m, 2 H), 0.06 ppm (s, 6 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 210.2, 159.3, 130.9, 129.4, 113.9, 79.8, 70.8, 69.6, 67.0, 55.4, 49.5, 49.7, 39.5, 26.1, 23.7, 18.41, 18.39, 14.1, 11.0, 9.5, -5.3, -5.4$ ppm; HRMS: *m/z* calcd for C₂₆H₄₄NaO₅Si[M+Na]⁺ 487.2856, found 487.2853

4-[1-(*tert*-Butyldimethylsilyloxy)-2-methyl]ethyl-6-[2-(4-methoxybenzyloxy)-2-(2-methylcyclopropyl)]ethyl-2,2-dimethyl-[1,3]-dioxan (10)

Reduction: To a solution of 7.7 g (29.3 mmol) of tetramethylammonium triacetoxyborohydride in 14 mL of acetonitrile was added 14 mL of acetic acid and the mixture was stirred at ambient temperature for 30 min. The mixture was cooled to -20°C , and a solution of 1.7 g (3.66 mmol) of β -hydroxy ketone **9** in 5.3 mL of acetonitrile was added *via* cannula. The mixture was stirred at -20°C for 2 d. The reaction was quenched with 45 mL of 0.5N aqueous sodium potassium tartrate and the mixture was allowed to warm slowly to ambient temperature. The mixture was diluted with CH_2Cl_2 and washed with aqueous saturated NaHCO_3 . The aqueous layer was back extracted with CH_2Cl_2 four times, and the combined organic layers were washed with aqueous saturated NaHCO_3 . The aqueous layer was back extracted with CH_2Cl_2 four times, and the combined organic layers were dried over MgSO_4 , and concentrated under reduced pressure. Purification *via* flash chromatography (Hex:EtOAc = 1:2) gave diol (1.62 g, 95%): $[\alpha]_D^{25} = -55.0$ (*c* 1, CHCl_3); IR (film): $\tilde{\nu} = 3462, 2944, 2862, 1613, 1514, 1248, 1094, 1038, 842\text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.25$ (d, $J = 8.5\text{ Hz}$, 2 H), 6.86 (d, $J = 8.5\text{ Hz}$, 2 H), 4.79 (d, $J = 11\text{ Hz}$, 1 H), 4.39 (d, $J = 11\text{ Hz}$, 1 H), 4.16 (s, 1 H), 4.09 (m, 2 H), 3.79 (s, 3 H), 3.74 (dd, $J = 4.5, 9.5\text{ Hz}$, 1 H), 3.64 (dd, $J = 5.5, 9.5\text{ Hz}$, 1 H), 3.51 (d, $J = 3\text{ Hz}$, 1 H), 3.00 (dt, $J = 3, 9.5\text{ Hz}$, 1 H), 1.84 (dt, $J = 10, 15\text{ Hz}$, 1 H), 1.73 (br d, $J = 14.5\text{ Hz}$, 1 H), 1.69-1.61 (m, 2 H), 1.43 (ddd, $J = 2, 8.5, 13.8\text{ Hz}$, 1 H), 1.09 (d, $J = 6\text{ Hz}$, 3 H), 0.93 (d, $J = 7\text{ Hz}$, 3 H), 0.89 (s, 9 H), 0.77 (m, 1 H), 0.55 (tt, $J = 4.5, 9\text{ Hz}$, 1 H), 0.26 (dt, $J = 5, 9\text{ Hz}$, 1 H), 0.19 (dt, $J = 5, 8\text{ Hz}$, 1 H), 0.06 ppm (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 159.4, 130.5, 129.4, 114.1, 85.0, 71.1, 70.3, 69.6, 68.3, 55.5, 42.2, 41.6, 39.9, 26.1, 23.9, 18.4, 18.3, 14.4, 10.9, 9.2, -5.4, -5.5\text{ ppm}$; HRMS: m/z calcd for $\text{C}_{26}\text{H}_{46}\text{NaO}_5\text{Si}[M+\text{Na}]^+$ 489.3012, found 489.3021

Protection: To a solution of diol (1.62 g, 3.47 mmol) in 2,2-dimethoxypropane (4.3 mL, 34.71 mmol) and CH_2Cl_2 (18 mL) at room temperature was added a few crystal of PPTS (87.2 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 5 h before it was concentrated *in vacuo*. The remaining organic residue was removed by concentration under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc = 7:1) to give acetone **10** (1.46 g, 83%): $[\alpha]_D^{25} = -43.11$ (*c* 1.06, CHCl_3); IR (film): $\tilde{\nu} = 2987, 2951, 2858, 1613, 1513, 1248, 1089, 1038, 840\text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.26$ (d, $J = 9\text{ Hz}$, 2 H), 6.87 (d, $J = 9\text{ Hz}$, 2 H), 4.64 (d, $J = 11\text{ Hz}$, 1 H), 4.40 (d, $J = 9\text{ Hz}$, 1 H), 4.01 (ddd, $J = 7, 9, 13\text{ Hz}$, 1 H), 3.80 (s, 3 H), 3.77 (dt, $J = 6, 10\text{ Hz}$, 1 H), 3.51 (dd, $J = 5.5, 10\text{ Hz}$, 1 H), 3.43 (dd, $J = 5, 10\text{ Hz}$, 1 H), 2.80 (dt, $J = 5.5, 8\text{ Hz}$, 1 H), 2.02 (dt, $J = 7, 14\text{ Hz}$, 1 H), 1.71 (ddd, $J = 6, 10, 12\text{ Hz}$, 1 H), 1.68-1.56 (m, 2 H), 1.46 (ddd, $J = 6, 9.5, 12.5\text{ Hz}$, 1 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.11 (d, $J = 6\text{ Hz}$, 3 H), 0.94 (d, $J = 7\text{ Hz}$, 3 H), 0.91 (s, 9 H), 0.75 (m, 1 H), 0.58 (tt, $J = 4.5, 9\text{ Hz}$, 1 H), 0.29 (dt, $J = 5, 8\text{ Hz}$, 1 H), 0.27 (dt, $J = 4.5, 8\text{ Hz}$, 1 H), 0.05 ppm (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 159.2, 131.4, 129.3, 113.9, 100.3, 79.2, 70.1, 67.2, 64.8, 64.3, 55.5, 42.4, 40.6, 36.6, 26.1, 25.2, 24.8, 24.0, 18.6, 18.4, 13.0, 12.5, 9.8, -5.2, -5.3\text{ ppm}$; HRMS: m/z calcd for $\text{C}_{29}\text{H}_{50}\text{NaO}_5\text{Si}[M+\text{Na}]^+$ 529.3325, found 529.3334

**2-{6-[2-(4-methoxybenzyloxy)-2-(2-methylcyclopropyl)ethyl]-2,2-dimethyl-[1,3]dioxan-4-yl}propionaldehyde
(11)**

Deprotection of silyl group: A solution of silyl ether **10** (1.46 g, 2.88 mmol) in THF (15 mL) was treated with TBAF (5.8 mL 1 M in THF, 5.8 mmol) at 0 °C, and then the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with H₂O, and extracted with Et₂O (x3). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and then concentrated *in vacuo*. Purification *via* flash chromatography (Hex:EtOAc = 4:1) provided 1.12 g of primary alcohol (99%): $[\alpha]_D^{25} = -62$ (c 0.84, CHCl₃); IR (film): $\tilde{\nu} = 3446, 2991, 2945, 1613, 1513, 1378, 1246, 1035, 845 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.28$ (d, $J = 8.5$ Hz, 2 H), 6.90 (d, $J = 8.5$ Hz, 2 H), 4.67 (d, $J = 11$ Hz, 1 H), 4.43 (d, $J = 11$ Hz, 1 H), 4.05 (ddd, $J = 7, 9, 13$ Hz, 1 H), 3.97 (dt, $J = 5.5, 9$ Hz, 1 H), 3.82 (s, 3 H), 3.69 (m, 1 H), 3.54 (m, 1 H), 2.81 (dt, $J = 5.5, 8$ Hz, 1 H), 2.57 (br s, 1 H), 2.02 (dt, $J = 7.5, 13.5$ Hz, 1 H), 1.88 (m, 1 H), 1.76-1.65 (m, 2 H), 1.40 (m, 1 H), 1.35 (s, 6 H), 1.11 (d, $J = 6$ Hz, 3 H), 0.90 (d, $J = 7$ Hz, 3 H), 0.75 (m, 1 H), 0.58 (m, 1 H), 0.27 ppm (br t, $J = 7$ Hz, 2 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 159.3, 131.4, 129.4, 114.0, 100.5, 78.9, 70.0, 69.7, 65.9, 64.4, 55.5, 42.2, 38.8, 34.3, 25.1, 24.9, 24.0, 18.6, 13.0, 11.8, 9.8$ ppm; HRMS: m/z calcd for C₂₃H₃₆NaO₅[*M*+Na]⁺ 415.2460, found 415.2456

Oxidation: To a solution of alcohol (1.12 g, 2.853 mmol) in 28 mL CH₂Cl₂ is added 720 mg (8.559 mmol) solid NaHCO₃ followed by 1.45 g (3.424 mmol) of the Dess-Martin periodinane. After stirring for 2 h, the mixture is diluted with 20 mL ether, 20 mL saturated aqueous NaHCO₃ and 40 mL saturated aqueous Na₂S₂O₃ and stirred for 30 min. The aqueous phase is extracted with Et₂O and the combined organic layers washed with 50 mL each saturated aqueous Na₂S₂O₃, saturated aqueous NaHCO₃ and brine then dried over Na₂SO₄ and concentrated *in vacuo* to give the aldehyde **11** (1.09 g, 98%) as a light yellow liquid. The crude product was used immediately in the next reaction: $[\alpha]_D^{25} = -81$ (c 0.4, CHCl₃); IR (film): $\tilde{\nu} = 3063, 2989, 2945, 2867, 1727, 1612, 1513, 1455, 1379, 1247, 1174, 1083, 1035, 821 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 9.71$ (d, $J = 1.5$ Hz, 1 H), 7.24 (d, $J = 8.5$ Hz, 2 H), 6.87 (d, $J = 8.5$ Hz, 2 H), 4.64 (d, $J = 11.5$ Hz, 1 H), 4.39 (d, $J = 11.5$ Hz, 1 H), 4.13 (dt, 1 H, $J = 10, 6$ Hz), 4.03 (ddd, $J = 13.5, 9, 6.5$ Hz, 1 H), 3.80 (s, 3 H), 2.77 (dt, $J = 8.5, 5$ Hz, 1 H), 2.43 (dt, $J = 13, 6.5$ Hz, 1 H), 1.99 (dt, $J =$

15, 7 Hz, 1 H), 1.68-1.62 (m, 2 H), 1.52 (ddd, $J = 13, 9.5, 6.5$ Hz, 1 H), 1.33 (s, 3 H), 1.32 (s, 3 H), 1.10 (d, $J = 6.5$ Hz, 3 H), 1.09 (d, $J = 6$ Hz, 3 H), 0.73 (m, 1 H), 0.55 (m, 1 H), 0.25 ppm (t, $J = 7$ Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 204.2, 159.2, 131.3, 129.4, 113.9, 100.7, 78.9, 70.0, 66.3, 64.1, 55.5, 50.7, 42.1, 35.7, 24.9, 24.8, 23.9, 18.5, 13.1, 9.7, 9.0$ ppm; HRMS: m/z calcd for $\text{C}_{23}\text{H}_{34}\text{NaO}_5[M+\text{Na}]^+$ 413.2304, found 413.2306

5,7-Dihydroxy-9-(4-methoxybenzyloxy)-4-methyl-9-(2-methylcyclopropyl)-non-2-enoic acid methyl ester (12)

To a solution of aldehyde **11** (1.09 g, 2.791 mmol), trimethylphosphonoacetate (0.9 mL, 5.582 mmol), and $i\text{Pr}_2\text{NEt}$ (1.46 mL, 8.374 mmol) in 23.3 mL MeCN at 0°C was added LiCl (473 mg, 11.165 mmol). The reaction mixture was allowed to slowly warm to room temperature and stirred for 5 h, during which time the reaction became cloudy. Aqueous NaHCO_3 was added and the mixture was diluted with ether. Layers were separated and the aqueous layer was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by Flash column chromatography on silica gel (Hex:EtOAc = 4:1) to yield ester (1.11 g, 89 %) as a colorless oil: $[\alpha]_D^{25} = -69.5$ (c 0.55, CDCl_3); IR (film): $\tilde{\nu} = 3067, 2989, 2947, 2865, 2837, 1725, 1658, 1612, 1513, 1455, 1379, 1248, 1174, 1035, 822\text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.24$ (d, $J = 8.5$ Hz, 2 H), 6.88 (d, $J = 8.5$ Hz, 2 H), 6.86 (dd, $J = 7.5, 15.5$ Hz, 1 H), 5.85 (d, $J = 15.5$ Hz, 1 H), 4.63 (d, $J = 11$ Hz, 1 H), 4.39 (d, $J = 11$ Hz, 1 H), 4.00 (m, 1 H), 3.81 (s, 3 H), 3.73 (s, 3 H), 3.61 (m, 1 H), 2.77 (dt, $J = 5, 8$ Hz, 1 H), 2.36 (m, 1 H), 1.96 (dt, $J = 7, 14$ Hz, 1 H), 1.61 (ddd, $J = 5, 7.5, 13.5$ Hz, 1 H), 1.52 (ddd, $J = 6.5, 10.12.5$ Hz, 1 H), 1.39 (m, 1 H), 1.33 (s, 3 H), 1.32 (s, 3 H), 1.08 (d, $J = 6$ Hz, 3 H), 1.07 (d, $J = 7$ Hz, 3 H), 0.72 (m, 1 H), 0.54 (tt, $J = 5, 8.5$ Hz, 1 H), 0.25 ppm (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 167.2, 159.2, 150.3, 131.3, 129.4, 121.5, 113.9, 100.6, 78.8, 70.0, 69.3, 64.2, 55.5, 51.7, 42.1, 41.9, 36.6, 25.0, 24.7, 24.0, 18.6, 15.7, 13.0, 9.8$ ppm; HRMS: m/z calcd for $\text{C}_{26}\text{H}_{38}\text{NaO}_6[M+\text{Na}]^+$ 469.2566, found 469.2581

Deprotection: To a solution of acetonide (1.11 g, 2.486 mmol) in MeOH (25 mL) was added 10-camphorsulfonic acid (578 mg, 2.486 mmol) and H_2O (2.5 mL). The mixture was stirred at ambient temperature for 2.5 h, and quenched with aqueous saturated NaHCO_3 solution. The methanol was removed *in vacuo*, and the residue was diluted with CH_2Cl_2 , and the resulting aqueous solution was washed with CH_2Cl_2 (x3). The combined organic extracts were washed with brine, dried over MgSO_4 , filtered, and then concentrated *in vacuo*. Purification *via* flash chromatography (Hex:EtOAc = 1:1) provided 975.1 mg of diol **12** (97%): $[\alpha]_D^{25} = -76.4$ (c 0.3, CDCl_3); IR (film): $\tilde{\nu} = 3462, 3054, 2950, 2870, 1720, 1656, 1612, 1436, 1266, 1083\text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.24$ (d, $J = 8.5$ Hz, 2 H), 6.93 (dd, $J = 8, 16$ Hz, 1 H), 6.88 (d, $J = 8.5$ Hz, 2 H), 5.84 (d, $J = 16$ Hz, 1 H), 4.80 (d, $J = 10.5$ Hz,

1 H), 4.41 (d, $J = 4$ Hz, 1 H), 4.39 (d, $J = 11.5$ Hz, 1 H), 4.08 (m, 1 H), 3.84 (m, 1 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.50 (d, $J = 3.5$ Hz, 1 H), 2.95 (br t, $J = 8.5$ Hz, 1 H), 2.44 (m, 1 H), 1.66-1.56 (m, 3 H), 1.49 (ddd, $J = 2, 6.5, 10.5$ Hz, 1 H), 1.10 (d, $J = 7$ Hz, 6 H), 0.78 (m, 1 H), 0.55 (tt, $J = 4, 9$ Hz, 1 H), 0.27 (dt, $J = 5, 8.5$ Hz, 1 H), 0.18 ppm (dt, $J = 4.5, 8.5$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 167.2, 159.5, 151.6, 130.2, 129.4, 121.1, 114.2, 85.1, 71.7, 70.6, 70.2, 55.5, 51.6, 43.0, 41.2, 39.9, 23.7, 18.2, 15.3, 14.5, 9.2$ ppm; HRMS: m/z calcd for $\text{C}_{23}\text{H}_{34}\text{NaO}_6[M+\text{Na}]^+$ 429.2253, found 429.2257

{4-Hydroxy-6-[2-(4-methoxybenzyloxy)-2-methylcyclopropyl]ethyl}-3-methyltetrahydropyran-2-yl}acetic acid methyl ester (13**)**

To a solution of diol **12** (439.7 mg, 1.08 mmol) in 10.8 mL of THF at room temperature was added NaH (65 mg, 1.62 mmol). After stirring for 4 h at ambient temperature, the reaction was quenched with water at 0 °C. The reaction mixture was extracted with ether (x3), and the extracts were washed with water and brine, dried over MgSO_4 , and concentrated. The residue was purified by flash column chromatography on silica gel (Hex:EtOAc = 1:1) to afford pyran **13** (361.8 mg, 82%): $[\alpha]_D^{25} = -25.7$ (c 0.46, CHCl_3); IR (film): $\tilde{\nu} = 3509, 3021, 2994, 1949, 2868, 1739, 1612, 1513, 1374, 1246, 1043, 823$ cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.24$ (d, $J = 9$ Hz, 2 H), 6.87 (d, $J = 9$ Hz, 2 H), 4.61 (d, $J = 11$ Hz, 1 H), 4.37 (d, $J = 11$ Hz, 1 H), 3.80 (s, 3 H), 3.63 (m, 1 H), 3.61 (s, 3 H), 3.42 (td, $J = 10, 3.5$ Hz, 1 H), 3.35 (m, 1 H), 2.78 (dt, $J = 6.5, 9$ Hz, 1 H), 2.62 (dd, $J = 3, 14.5$ Hz, 1 H), 2.38 (dd, $J = 9.5, 14.5$ Hz, 1 H), 1.98 (ddd, $J = 7, 8.5, 14.3$ Hz, 1 H), 1.88 (ddd, $J = 1.5, 5, 6.5$ Hz, 1 H), 1.62 (ddd, $J = 5, 7, 13.5$ Hz, 1 H), 1.44 (d, $J = 5$ Hz, 1 H), 1.29-1.20 (m, 2 H), 1.08 (d, $J = 6.5$ Hz, 3 H), 0.98 (d, $J = 6.5$ Hz, 3 H), 0.65 (m, 1 H), 0.49 (tt, $J = 5, 8.5$ Hz, 1 H), 0.28 (dt, $J = 5, 8.5$ Hz, 1 H), 0.22 ppm (dt, $J = 4.5, 8.5$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 172.3, 159.2, 131.4, 129.3, 113.9, 79.4, 77.8, 73.5, 72.6, 70.2, 55.5, 51.8, 44.0, 42.0, 41.3, 39.3, 23.4, 18.6, 13.0, 12.7, 9.6$ ppm; HRMS: m/z calcd for $\text{C}_{23}\text{H}_{34}\text{NaO}_6[M+\text{Na}]^+$ 429.2253, found 429.2213

NOESY (500 MHz, CDCl₃) of 13

{4-(*tert*-Butyldimethylsilanyloxy)-6-[2-hydroxy-2-(2-methylcyclopropyl)ethyl]-3-methyltetrahydropyran-2-yl}acetic acid (14**)**

Protection: To a solution of secondary alcohol **13** (378.2 mg, 1.24 mmol) and TEA (0.52 mL, 3.72 mmol) in CH₂Cl₂ (7.2 mL) was added TBSOTf (0.43 mL, 1.86 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with H₂O and aqueous layer was extracted with CH₂Cl₂ (x3), washed with brine (x1), and dried over anhydrous MgSO₄. Filtration was followed by concentration *in vacuo* gave crude product. The crude product was purified on silica gel (Hex:EtOAc = 5:1) to afford silyl ether (335.8 mg, 69 %) as a clear liquid: $[\alpha]_D^{25} = -1.0$ (c 1, CHCl₃); IR (film): $\tilde{\nu} = 2951, 2858, 1744, 1613, 1513, 1248, 1080, 830 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.25$ (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 4.63 (d, *J* = 11 Hz, 1 H), 4.40 (d, *J* = 11 Hz, 1 H), 3.82 (s, 3 H), 3.63 (m, 1 H), 3.62 (s, 3 H), 3.44 (td, *J* = 10, 3 Hz, 1 H), 3.37 (td, *J* = 10, 4.5 Hz, 1 H), 2.83 (dt, *J* = 6, 8 Hz, 1 H), 2.64 (dd, *J* = 3, 15 Hz, 1 H), 2.39 (dd, *J* = 10, 15 Hz, 1 H), 1.99 (ddd, *J* = 5.5, 8, 14 Hz, 1 H), 1.81 (dd, *J* = 4.5, 12 Hz, 1 H), 1.63 (ddd, *J* = 5, 8.5, 12.5 Hz, 1 H), 1.32 (m, 2 H), 1.10 (d, *J* = 6 Hz, 3 H), 0.92 (d, *J* = 6 Hz, 3 H), 0.91 (s, 9 H), 0.66 (m, 1 H), 0.51 (tt, *J* = 4.5, 9 Hz, 1 H), 0.34 (dt, *J* = 5, 8.5 Hz, 1 H), 0.25 (dt, *J* = 4.5, 8.5 Hz, 1 H), 0.09 (s, 3 H), 0.07 ppm (s, 3 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 172.5, 159.2, 131.6, 129.3, 114.0, 79.8, 78.0, 74.2, 72.5, 70.3, 55.5, 51.8, 44.3, 42.2, 42.0, 39.6, 26.1, 23.6, 18.7, 18.3, 13.5, 12.6, 9.8, -3.7, -4.4 \text{ ppm}$; HRMS: *m/z* calcd for C₂₉H₄₈NaO₆Si[M+Na]⁺ 543.3118 found 543.3145

Deprotection of PMB group: To a solution of PMB ether (90.7 mg, 0.174 mmol) in CH₂Cl₂ (4.4 mL) and water (0.25 mL) was added DDQ (43.5 mg, 0.192 mmol). The reaction mixture was stirred for 30 min. After which time the mixture was filtered through a plug of filter aid, washed with CH₂Cl₂, dried over MgSO₄ and concentrated. The residue was purified on silica gel using (Hex:EtOAc = 5:1) as eluant, which gave the secondary alcohol (61.3 mg, 88%) as a colorless oil: $[\alpha]_D^{25} = -3.5$ (c 0.58, CHCl₃); IR (film): $\tilde{\nu} = 3526, 2952, 2857, 1742, 1437, 1373, 1252, 1082 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 3.68$ (s, 3 H), 3.57 (br t, *J* = 11 Hz, 1 H), 3.47 (td, *J* = 9.5, 3 Hz, 1 H), 3.33 (td, *J* = 10, 4.5 Hz, 1 H), 3.28 (s, 1 H), 3.11 (td, *J* = 8.5, 2.5 Hz, 1 H), 2.64 (dd, *J* = 3, 15 Hz, 1 H), 2.40 (dd, *J* = 9.5, 15 Hz, 1 H), 1.79-1.70 (m, 2 H), 1.65 (dt, *J* = 2.5, 14 Hz, 1 H), 1.39 (q, *J* = 11.5 Hz, 1 H), 1.33 (m, 1 H), 1.04 (d, *J* = 6 Hz, 3 H), 0.90 (d, *J* = 7 Hz, 3 H), 0.88 (s, 9 H), 0.76 (m, 1 H), 0.57 (tt, *J* = 4.5, 8.5 Hz, 1 H), 0.29 (dt, *J* = 5, 8.5 Hz, 1 H), 0.15 (dt, *J* = 5, 8 Hz, 1 H), 0.06 (s, 3 H), 0.05 ppm (s, 3 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 172.3, 78.1, 76.5, 76.3, 73.7, 52.1, 43.7, 42.7, 42.2, 38.8, 26.3, 18.9, 18.2, 13.4, 11.4, 10.3, -3.8, -4.5 \text{ ppm}$; HRMS: *m/z* calcd for C₂₁H₄₀NaO₅Si[M+Na]⁺ 423.2543, found 423.2532

Hydrolysis: To a solution of methyl ester (73.3 mg, 0.18 mmol) in 18.3 mL (10 : 1 : 1, THF : H₂O : MeOH) is added 9.2 mL of a 1 M aqueous solution of LiOH. This suspension is stirred for 18 h and then diluted with water. The reaction solvent was removed *in vacuo*. The aqueous material is extracted with ether and then acidified with 2 N HCl to give a clear solution of pH 6-7. This aqueous solution was extracted with ether (x3) and the combined organic extracts washed with brine, dried MgSO₄ and concentrated *in vacuo*. The residue is purified by flash chromatography (Hex:EtOAc = 1:2) to give hydroxy acid **14** (56.7 mg, 81%): $[\alpha]_D^{25} = -10.3$ (c 2.6, CHCl₃); IR (film): $\tilde{\nu} = 3465, 2951, 2858, 1731, 1434, 1375, 1254 \text{ cm}^{-1}$; ¹H NMR (500 MHz, CDCl₃): $\delta = 3.60$ (br t, *J* = 11 Hz, 1 H), 3.50 (br t, *J* = 9.5 Hz, 1 H), 3.34 (td, *J* = 10, 4 Hz, 1 H), 3.17 (br t, *J* = 8.5 Hz, 1 H), 2.65 (d, *J* = 14.5 Hz, 1 H), 2.38 (dd, *J* = 10.5, 14.5 Hz, 1 H), 1.82-1.76 (m, 2 H), 1.67 (d, *J* = 15 Hz, 1 H), 1.32 (m, 1 H), 1.01 (d, *J* = 6 Hz, 3 H), 0.91 (d, *J* = 7 Hz, 3 H), 0.88 (s, 9 H), 0.76 (m, 1 H), 0.58 (tt, *J* = 4, 8.5 Hz, 1 H), 0.25 (dt, *J* = 4.5, 8.5 Hz, 1 H), 0.17 (dt, *J* = 5, 8.5 Hz, 1 H), 0.06 (s, 3 H), 0.05 ppm (s, 3 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 173.7, 78.4, 77.6, 76.8, 73.5, 43.8, 42.1, 41.9, 38.8, 26.0, 25.9, 18.7, 18.2, 13.4, 11.9, 10.4, -3.8, -4.5 \text{ ppm}$; HRMS: *m/z* calcd for C₂₀H₃₈NaO₅Si[M+Na]⁺ 409.2386, found 409.2381

2,3,4-tri-*O*-methyl-D-xylopyranose (**15**)

Methylation: To a vigorously stirred solution of D-xylose (1 g, 6.66 mmol) in 18.1 mL DMSO was introduced 1.8 mL of 50% aqueous sodium hydroxide to form a gel-like suspension. Methyl iodide (2.49 mL, 40.0 mmol) was immediately added dropwise, and the mixture was stirred for 1 h. The resulting suspension was then poured into 100 mL of water and the aqueous layer was extracted with ether (x3). The combined organic extracts were washed with water (x1), dried over MgSO₄, and concentrated under reduced pressure. Purification of the residue by flash chromatography (Hex:EtOAc = 1:1) to give the methyl 2,3,4-tri-*O*-methyl-D-xylopyranosides (2.64 g, 53%): (α) ¹H NMR (500 MHz, CDCl₃): $\delta = 4.79$ (d, *J* = 3.5 Hz, 1 H), 3.72 (dd, *J* = 5.5 Hz, 1 H), 3.64 (s, 3 H), 3.54 (s, 3 H), 3.51 (s, 3 H), 3.46 (t, *J* = 9 Hz, 2 H), 3.43 (s, 3 H), 3.26 (m, 1 H), 3.18 (dd, *J* = 3, 9 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 97.8, 82.8, 81.9, 79.9, 61.2, 59.5, 59.2, 59.1, 55.3$; (β) ¹H NMR (500 MHz, CDCl₃): $\delta = 4.14$ (d, *J* = 7.5 Hz, 1 H), 3.99 (dd, *J* = 5.5, 11 Hz, 1 H), 3.60 (s, 3 H), 3.56 (s, 3 H), 3.51 (s, 3 H), 3.47 (s, 3 H), 3.26 (m, 1 H), 3.14 (dd, *J* = 9.5, 11.5 Hz, 1 H), 3.13 (t, *J* = 8.5 Hz, 1 H), 2.97 ppm (dd, *J* = 7.5, 8.5 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 104.9, 85.2, 83.4, 79.5, 63.3, 60.8, 60.6, 58.9, 57.0 \text{ ppm}$; HRMS: *m/z* calcd for C₉H₁₈NaO₅[M+Na]⁺ 229.1052, found 229.1059

Hydrolysis: To a solution of the methyl 2,3,4-tri-*O*-methyl-D-xylopyranosides (2.37 g, 11.49 mmol) in 1,4-

dioxane (41 mL) was added 2N HCl (41 mL). The reaction mixture was refluxed for 24 h. After allowing the mixture to cool to rt, the solvent removed *in vacuo*. The mixture was diluted with ethyl acetate and then neutralized with aqueous NaHCO₃ to give a solution of pH 6-7. This aqueous solution was extracted with ether (x3) and the combined organic extracts washed with brine, dried MgSO₄ and concentrated *in vacuo*. The residue is purified by flash chromatography (Hex:EtOAc = 3:1) to give mixture hemiacetal **15** (1.32 g, 60%) as a solid: mp. 93.3 °C; IR (film): $\tilde{\nu}$ = 3421, 2942, 2835, 1465, 1011 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 5.22 (t, *J* = 6 Hz, 1 H), 4.60 (t, *J* = 11 Hz, 1 H), 4.00 (dd, *J* = 4.5, 16.5 Hz, 1 H), 3.72 (d, *J* = 12.5 Hz, 2 H), 3.60 (s, 6 H), 3.59 (s, 3 H), 3.53 (s, 3 H), 3.47 (s, 3 H), 3.46 (s, 3 H), 3.43 (m, 2 H), 3.30-3.15 (m, 6 H), 3.05 (d, *J* = 5.5 Hz, 1 H), 2.97 ppm (t, *J* = 11.5 Hz, 1 H); HRMS: *m/z* calcd for C₈H₁₆NaO₅[*M*+Na]⁺ 215.0895, found 215.0890

2,2,2-Trichloroacetimidic acid 3,4,5-trimethoxytetrahydro-pyran-2-yl ester (16)

To a solution of hemiacetal **15** (220 mg, 1.145 mmol) in trichloroacetonitrile (0.51 mL, 5.04 mmol) and CH₂Cl₂ (7.6 mL) is added NaH (27.5 mg, 0.69 mmol). After 2.5 h reaction time, the mixture is filtered through Celite, the solvents are evaporated, and the residue is purified by flash chromatography (Hex:EtOAc = 2:1) to give imidate **16** (311.6 mg, 81%) as a pale yellow oil: ¹H NMR (500 MHz, CDCl₃): δ = 8.59 (s, 1 H), 6.40 (d, *J* = 4 Hz, 1 H), 3.88 (dd, *J* = 5.5, 11 Hz, 1 H), 3.65 (s, 3 H), 3.64 (t, *J* = 11 Hz, 1 H), 3.51 (m, 2 H), 3.50 (s, 3 H), 3.49 (s, 3 H), 3.34 ppm (dd, *J* = 3.5, 9.5 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃): δ = 161.8, 94.1, 82.4, 81.1, 79.3, 62.2, 61.3, 59.3, 59.1 ppm.

**9,19-Dihydroxy-10,20-dimethyl-5,15-bis-(2-methylcyclopropyl)-4,14,21,22-tetraoxa-
tricyclo[15.3.1.17,11]docosane-3,13-dione (17)**

Dimerization: To a solution of the hydroxy acid **14** (127.4 mg, 0.33 mmol) in dry THF (1.2 mL) were added TEA (59 μ L, 0.428 mmol) and 2,4,6-trichlorobenzoyl chloride (55.4 μ L, 0.354 mmol). After the reaction mixture was stirred at room temperature for 2 h, TEA-HCl salt was then filtered off, and the filtrate was diluted with dry toluene (15 mL) under N_2 . This solution was then added slowly to a solution of DMAP (205 mg, 1.68 mmol) in toluene (70 mL) under reflux. The reaction mixture was further stirred under reflux for 17 h and then diluted with water at room temperature. The mixture was extracted with ether (x3). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (Hex:EtOAc = 7:1) to give the lactone (91 mg): $[\alpha]_D^{25} = -10.3$ (c 2.6, $CHCl_3$); IR (film): $\tilde{\nu} = 3064$, 2955, 2857, 1732, 1257, 1182, 1077 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): $\delta = 4.44$ (t, $J = 9$ Hz, 2 H), 3.44 (m, 4 H), 3.32 (td, $J = 10$, 4 Hz, 2 H), 2.53 (dd, $J = 4.5$, 17.5 Hz, 2 H), 2.42 (dd, $J = 6$, 17.5 Hz, 2 H), 1.88 (tt, $J = 9$, 15.5 Hz, 2 H), 1.74 (dd, $J = 5$, 13 Hz, 2 H), 1.66 (br d, $J = 15.5$ Hz, 2 H), 1.32-1.20 (m, 4 Hz), 0.97 (d, $J = 5.5$ Hz, 6 H), 0.88 (s, 18 H), 0.85 (d, $J = 7$ Hz, 6 H), 0.80 (m, 2 H), 0.70 (tt, $J = 4.5$, 8.5 Hz, 2 H), 0.36 (dt, $J = 4.5$, 8.5 Hz, 2 H), 0.23 (dt, $J = 5$, 9 Hz, 2 H), 0.05 ppm (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.4$, 77.1, 76.9, 75.0, 74.2, 44.5, 42.4, 41.6, 39.5, 26.0, 24.9, 18.7, 18.2, 13.3, 11.9, 11.2, -3.8, -4.5 ppm; HRMS: m/z calcd for $C_{40}H_{72}NaO_8Si_2[M+Na]^+$ 759.4663, found 759.4661

Deprotection: A solution of TBS protected lactone (91 mg, 0.123 mmol) in THF (0.82 mL) at 0 $^\circ C$ was treated with Bu_4NF (0.62 mL, 0.62 mmol, 1.0 M in THF), and the mixture was stirred for 3 h at room temperature. Water was added, and the aqueous phase was extracted with Et_2O (x3). The organic extracts were dried over $MgSO_4$ and the solvent was evaporated. Purification of the residue by flash chromatography (Hex:EtOAc = 1:2) afforded diol **17** (35.1 mg, 2 steps 41%) as a white solid: mp : 210 $^\circ C$; $[\alpha]_D^{25} = -49.6$ (c 0.165, $CHCl_3$); IR (film): $\tilde{\nu} = 3346$, 3067, 2998, 2930, 2884, 1736, 1188, 1042 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): $\delta = 4.35$ (t, $J = 9.5$ Hz, 2 H), 3.42 (br t, $J = 7.5$ Hz, 2 H), 3.37 (ddd, $J = 3.5$, 6.5, 10 Hz, 2 H), 3.30 (td, $J = 10$, 4 Hz, 2H), 2.48 (dd, $J = 3.5$, 17.5 Hz, 2 H), 2.36 (dd, $J = 6.5$, 17.5 Hz, 2 H), 1.88-1.84 (m, 4 H), 1.64 (dq, $J = 4$, 15 Hz, 2H), 1.23-1.14 (m, 4 H), 0.91 (d, $J = 6$ Hz, 6

H), 0.88 (d, $J = 6.5$ Hz, 6 H), 0.75 (m, 2 H), 0.66 (tt, $J = 5, 9$ Hz, 2 H), 0.29 (dt, $J = 5, 8.5$ Hz, 2 H), 0.17 ppm (dt, $J = 5, 8.5$ Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 171.3, 77.15, 77.1, 75.0, 73.4, 44.2, 41.64, 41.56, 39.3, 24.9, 18.7, 12.9, 12.1, 11.1$ ppm; HRMS: m/z calcd for $\text{C}_{28}\text{H}_{44}\text{NaO}_8[M+\text{Na}]^+$ 531.2934, found 531.2936

Clavosolide A (**3**)

A mixture of trichloroacetimidate **16** (0.11 mL, 0.11 mmol, 1.0 M in CH_2Cl_2), diol **17** (20.8 mg, 0.04 mmol), and molecular sieves $4\text{\AA}$ in CH_2Cl_2 (0.5 mL) is stirred for 30 min at ambient temperature. The solution is then cooled to -78°C prior to the addition of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (8.2 μL , 8.2 μmol , 1.0 M in CH_2Cl_2) and stirring is continued at -40°C for 2 h. The cooling bath is removed and the mixture is stirred for 30 min before it is filtered through a pad of Celite. The filtrate is diluted with CH_2Cl_2 and washed with sat. aq. NaHCO_3 , the organic layer is dried over MgSO_4 and evaporated, and the crude product is purified by flash chromatography (Hex:EtOAc = 1:2) to give Clavosolide A (**3**) (4 mg, 11%) as a white solid: mp. 256.8°C ; $[\alpha]_D^{25} = +52.0$ (c 0.165, CHCl_3); IR (film): $\tilde{\nu} = 3065, 2928, 2855, 1740, 1092\text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 4.41$ (t, $J = 9$ Hz, 2 H), 4.26 (d, $J = 8$ Hz, 2 H), 3.95 (dd, $J = 5, 11.5$ Hz, 2 H), 3.61 (s, 6 H), 3.58 (s, 6 H), 3.46 (s, 6 H), 3.43 (m, 2 H), 3.42 (m, 2 H), 3.24 (t, $J = 11.5$ Hz, 2 H), 3.24 (td, $J = 8.5, 5$ Hz, 2 H), 3.09 (t, $J = 8.5$ Hz, 2 H), 3.08 (dd, $J = 8.5, 11.5$ Hz, 2 H), 2.95 (t, $J = 8.5$ Hz, 2 H), 2.54 (dd, $J = 3, 17$ Hz, 2 H), 2.41 (dd, $J = 6.5, 17$ Hz, 2 H), 2.04 (dd, $J = 4.5, 11.5$ Hz, 2 H), 1.88 (dt, $J = 9, 15$ Hz, 2 H), 1.68 (br d, $J = 15$ Hz, 2 H), 1.38 (m, 2 H), 1.37 (q, $J = 11.5$ Hz, 2 H), 0.96 (d, $J = 6.5$ Hz, 6 H), 0.81 (m, 2 H), 0.71 (tt, $J = 5, 9$ Hz, 2 H), 0.34 (dt, $J = 5, 8.5$ Hz, 2 H), 0.22 ppm (dt, $J = 5, 8.5$ Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 171.2, 105.7, 85.7, 84.0, 83.4, 79.5, 77.2, 77.0, 75.0, 63.4, 61.0(2), 59.0, 42.7, 41.4, 40.9, 39.4, 24.9, 18.7, 12.8, 12.1, 11.1$ ppm; HRMS: m/z calcd for $\text{C}_{44}\text{H}_{72}\text{NaO}_{16}[M+\text{Na}]^+$ 879.4718, found 879.4718

Synthetic Compound 1

mp : 246.2 °C; $[\alpha]_D^{25}$ -3.13 (c 0.180, CH₃Cl); IR (neat, cm⁻¹) 2958, 2921, 2852, 1736, 1467, 1258, 1066; ¹H NMR (CDCl₃, 500 MHz) δ 4.41 (t, *J* = 8.5 Hz, 2 H), 4.27 (d, *J* = 8 Hz, 2 H), 3.96 (dd, *J* = 11, 5 Hz, 2 H), 3.61 (s, 6 H), 3.58 (s, 6 H), 3.46 (s, 6 H), 3.45-3.41(m, 4H), 3.28-3.20 (m, 4 H), 3.11-3.05 (m, 4 H), 2.96 (t, *J* = 8 Hz, 2 H), 2.55(dd, *J* = 18, 4 Hz, 2 H), 2.41 (dd, *J* = 17.5, 4.5 Hz, 2 H), 2.05 (dd, *J* = 11, 4.5 Hz, 2 H), 1.92 (dt, *J* = 15, 8.5 Hz, 2 H), 1.70 (br d, *J* = 15 Hz, 2 H), 1.43-1.32 (m, 4 H), 1.00 (d, *J* = 5.5 Hz, 6 H), 0.96 (d, *J* = 6 Hz, 6 H), 0.72-0.66(m, 2 H), 0.61-0.56 (m, 4 H), 0.23-0.19 (m, 2 H), 0.22 (dt, *J* = 5, 8.5 Hz, 2 H); ¹³C NMR (CDCl₃, 125 MHz) δ 171.2, 105.7, 85.7, 84.0, 83.4, 79.6, 77.2, 77.0, 75.0, 63.4, 61.0(2), 59.0, 42.7, 42.0, 40.9, 39.4, 25.1, 18.6, 12.8, 12.6, 11.2; HRMS (EI):*m/z* calcd for C₄₄H₇₂NaO₁₆(M⁺) 856.4820, found 856.4831

Comparison of ^{13}C NMR Spectra for Isolated and Synthetic Clavosolide A (3)

Assignment	Isolated Clavosolide A (100 MHz, CDCl_3)	Synthetic Clavosolide A (3) (125 MHz, CDCl_3)
1, 1'	170.7	171.2
2, 2'	39.3	39.4
3, 3'	77.0	77.0
4, 4'	42.6	42.7
5, 5'	83.1	83.4
6, 6'	40.8	40.9
7, 7'	74.8	75.0
8, 8'	41.1	41.4
9, 9'	77.1	77.2
10, 10'	24.8	24.9
11, 11'	12.0	12.0
12, 12'	18.6	18.7
13, 13'	11.0	11.1
14, 14'	12.7	12.8
15, 15'	105.4	105.7
16, 16'	83.8	84.0
17, 17'	85.6	85.7
18, 18'	79.4	79.5
19, 19'	63.2	63.4
20, 20'	60.7	61.0
21, 21'	60.8	61.0
22, 22'	58.5	59.0

Comparison of ^1H NMR Spectra for Isolated and Synthetic Clavosolide A (3)

Assignment	Isolated Clavosolide A (400 MHz, CDCl_3)		Synthetic Clavosolide A (3) (500 MHz, CDCl_3)	
1, 1'				
2, 2'	2.55	dd, 3, 17.5	2.54	dd, 3, 17
	2.41	dd, 7, 17.5	2.41	dd, 6.5, 17
3, 3'	3.42	m	3.43	m
4, 4'	1.38	m	1.38	m
5, 5'	3.25	t, 11.5	3.24	t, 11.5
6, 6'	2.05	dd, 5, 11.5	2.04	dd, 4.5, 11.5
	1.37	q, 11.5	1.37	q, 11.5
7, 7'	3.42	m	3.43	m
8, 8'	1.87	dt, 9, 15	1.88	dt, 9, 15
	1.66	br d, 15	1.68	br d, 15
9, 9'	4.41	br t, 9	4.41	br t, 9
10, 10'	0.72	tt, 5, 9	0.71	tt, 5, 9
11, 11'	0.83	m	0.81	m
12, 12'	0.96	d, 6.5	0.96	d, 6.5
13, 13'	0.22	dt, 5, 8	0.22	dt, 5, 8.5
	0.33	dt, 5, 8	0.34	dt, 5, 8.5
14, 14'	0.96	d, 6.5	0.96	d, 6.5
15, 15'	4.27	d, 8	4.26	d, 8
16, 16'	2.96	t, 8	2.95	t
17, 17'	3.12	t, 8	3.09	t, 8.5
18, 18'	3.25	td, 8, 5	3.24	td, 8.5, 5
19, 19'	3.96	dd, 5, 11	3.95	dd, 5, 11.5
	3.10	dd, 8, 11	3.08	dd, 8.5, 11.5
20, 20'	3.57	s	3.58	s
21, 21'	3.62	s	3.61	s
22, 22'	3.47	s	3.46	s

SJ8-2005-0503 1-1H
 Pulse Sequence: szpul
 Solvent: CDCl₃
 Ambient temperature
 INOVA-500 "Chemmr3"
 Relax. delay 3.000 sec
 Pulse 58.7 degrees
 Acq. time 1.592 sec
 Spectrosc. 400 MHz
 32 repetition
 OBSERVE H1, 499.7465732 MHz
 DATA PROCESSING
 FT size 32768
 Total time 2 min, 36 sec

¹H NMR Spectrum (500 MHz, CDCl₃) of Synthetic Compound 1

¹³C NMR Spectrum (125 MHz, CDCl₃) of Synthetic Compound 1

SJB-2005-0929 1H
 Pulse Sequence: presat
 Solvent: CDCl3
 Acquisition temperature
 INOVA-500 "Chemmer3"
 Relax delay 2.000 sec
 Pulse 58.70 sec
 Acq time 1.080 sec
 Width 8000.0 Hz
 64 repetitions
 OBSERVE H1, 499.7485737 MHz
 DATA PROCESSING
 FT size 32768
 Total time 17 min, 7 sec

¹H NMR Spectrum (500 MHz, CDCl₃) of Synthetic Clavosolide A (3)

SUB-2005-0913 13C
 Pulse Sequence: szpul
 Solvent: CDCl3
 Ambient temperature
 User: 1-14-87
 INOVA-S00 "Chemmr3"
 Relax. delay 1.000 sec
 Pulse delay 0.000 sec
 Acq. time 1.380 sec
 Width 40000.0 Hz
 7000 Repetitions
 OBSERVE C13, 125.6618539 MHz
 DECOUPLE H1, 499.7502305 MHz
 Power 37 dB, 499.7502305 MHz
 on during acquisition
 off during delay
 WALTZ-16 modulated
 DATA PROCESSING
 Time Resolution 0.5 Hz
 FT size 131072
 Total time 4 hr, 29 min, 25 sec

¹³C NMR Spectrum (125 MHz, CDCl₃) of Synthetic Clavosolide A (3)

Comparison of ^1H NMR Spectra for Synthetic Compound 1 (top), Isolated (middle) and Synthetic Clavosolide A (3) (bottom)