Supporting Information

Total Synthesis and Cytotoxicity of Haterumalides NA and B and their Artificial Analogs

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General experimental.

All chemicals were used as obtained from commercial supplies unless otherwise noted. Organic solvents for moisture-sensitive reactions were distilled by standard procedure. Anhydrous acetone, MeOH, EtOH and DMF were used as obtained from commercial supplies. Column chromatography was performed using silica gel (75–200 μm or 45–75 μm). All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. Optical rotations were measured on digital polarimeter at room temperature, using the sodium D line. CD spectra were measured on spectropolarimeter. Infrared (IR) spectra were recorded on a FT IR system and only selected peaks are reported. ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were run at various field strengths as indicated. Chemical shifts are reported in parts per million (ppm) relative to solvent signals and coupling constants, J , are given in Hz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). High resolution mass spectra were recorded using Electrospray Ionization (ESI) or Atmospheric Pressure Chemical Ionization (APCI).

Procedures and spectroscopic data for the compounds.

DMPM ether 22. To a stirred solution of glycol **21** (2.86 g, 15.3 mmol) in DMF (70 mL) was added NaH (60% in mineral oil, 918 mg, 23.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min, DMPMCl (3.08 g, 16.5 mmol) was added at 0 °C, and the resulting mixture was stirred at room temperature for 11 h. After cooling to 0 °C, the mixture was diluted with MeOH (6 mL) and water (6 mL), and extracted with EtOAc (6×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane–EtOAc 3:1/2% Et_3N) to give DMPM ether **22** (5.14 g, quant) as a colorless oil: $[\alpha]_D^{24} -93.4$ (c 0.32, CHCl_3); IR (film) 2931, 1609, 1517, 1464, 1370, 1264, 1156, 1067 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.89–6.80 (m, 3H), 6.61 (d, J = 2.7 Hz, 1H), 5.26 (dd, J = 2.7, 2.7 Hz, 1H), 4.63 (ddd, J = 7.0, 2.4, 0.8 Hz, 1H), 4.56 (dd, J = 7.0, 2.4 Hz, 1H), 4.48 (d, J = 4.1 Hz, 2H), 4.41 (ddd, J = 7.0, 6.2, 6.2 Hz, 1H), 4.11 (dd, J = 8.4, 6.2 Hz, 1H), 4.00 (dd, J = 8.4, 6.2 Hz, 1H), 3.88 (s, 6H), 1.47 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (67.8 MHz, CDCl_3) δ 150.3, 148.8, 148.4, 130.9, 120.0, 110.8 (2C), 108.6, 101.9, 84.1, 78.9, 73.1, 70.9, 66.0, 55.9, 55.8, 26.6, 25.3; HRMS (ESI) m/z 359.1466, calcd for $\text{C}_{18}\text{H}_{24}\text{NaO}_6$ $[\text{M}+\text{Na}]^+$ 359.1471.

Lactol 23. To a stirred solution of DMPM ether **22** (4.12 g, 12.3 mmol) in THF– H_2O (1:1, 82 mL) was added $\text{Hg}(\text{OAc})_2$ (6.47 g, 20.9 mmol) at room temperature, and the mixture was stirred at room

Alcohol 26. To a stirred Et₂O (35 mL) was added LiAlH₄ (407 mg, 10.7 mmol), and the mixture was stirred at reflux for 1.5 h. After cooling to 0 °C, *trans*-tetrahydrofuran **25** (2.91 g, 7.09 mmol) in Et₂O (20 mL, 2×5 mL rinse) was added, and the resulting mixture was stirred at reflux for 2 h. After cooling to room temperature, the mixture was diluted with saturated aqueous NH₄Cl (10 mL). The mixture was filtered through a Celite pad, and the residue was washed with EtOAc. The filtrate and the washings were combined, dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane–EtOAc 1:1) to give alcohol **26** (2.62 g, 97%) as a colorless oil: $[\alpha]_D^{24}$ –26.4 (*c* 1.6, CHCl₃); IR (film) 3496, 2935, 1517, 1264, 1157, 1067, 1029 cm^{–1}; ¹H NMR (270 MHz, CDCl₃) δ 6.89–6.78 (m, 3H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.35 (m, 1H), 4.35 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H), 4.14 (br.t, 3.8 Hz, 1H), 4.07 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.00 (dd, *J* = 6.5, 3.8 Hz, 1H), 3.93 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 (br.t, *J* = 5.1 Hz, 2H), 2.24 (dd, *J* = 13.2, 5.4 Hz, 1H), 1.80–1.72 (m, 2H), 1.63 (ddd, *J* = 14.6, 10.3, 5.4 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H). A signal due to one proton (OH) was not observed; ¹³C NMR (67.8 MHz, CDCl₃) δ 148.8, 148.4, 130.6, 119.8, 110.8, 110.7, 108.5, 82.7, 78.5 (2C), 73.9, 71.3, 66.9, 61.4, 55.9, 55.8, 38.5, 37.6, 26.7, 25.6; HRMS (ESI) *m/z* 405.1894, calcd for C₂₀H₃₀NaO₇ [M+Na]⁺ 405.1889.

Terminal olefin 28. To a stirred solution of alcohol **26** (2.50 g, 6.54 mmol) in THF (12.2 mL) were added 2-nitrophenyl selenocyanate (2.51 g, 11.1 mmol) and P(*n*-Bu)₃ (3.82 mL, 16.3 mmol) at 0 °C. The mixture was stirred at room temperature for 22.5 h and concentrated. The residual oil was purified by column chromatography on silica gel (250 g, hexane–EtOAc 5:1→3:1→3:2) to give a selenoether **26a** (3.68 g, quant) as a colorless oil: $[\alpha]_D^{24}$ –19.9 (*c* 1.0, CHCl₃); IR (film) 2932, 1515, 1332, 1263, 1157, 1067, 732 cm^{–1}; ¹H NMR (270 MHz, CDCl₃) δ 8.28 (dd, *J* = 8.4, 1.4 Hz, 1H) 7.57 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.52 (dd, *J* = 6.8, 1.4 Hz, 1H), 7.30 (ddd, *J* = 8.4, 6.8, 1.9 Hz, 1H), 6.91–6.81 (m, 3H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.39 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H), 4.36, (m, 1H), 4.17 (m, 1H), 4.11 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.02 (dd, *J* = 8.4, 5.4 Hz, 1H), 3.99 (dd, *J* = 6.8, 6.2 Hz, 1H), 3.88 (s, 6H), 3.07 (m, 1H), 2.95 (m, 1H), 2.26 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.00–1.92 (m, 2H), 1.61 (ddd, *J* = 13.2, 10.0, 4.3 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.0, 148.6, 146.8, 133.6 (2C), 130.8, 128.9, 126.5, 125.3, 119.9, 110.9, 110.8, 108.6, 82.6, 79.0, 78.0, 74.0, 71.4, 67.0, 55.9, 55.8, 38.0, 34.8, 26.8, 25.5, 22.4; HRMS (ESI) *m/z* 590.1277, calcd for C₂₆H₃₃NaNO₈Se [M+Na]⁺ 590.1269.

To a stirred solution of the selenoether **26a** (9.59 g, 16.9 mmol) in THF (369 mL) were added pyridine (8.1 mL, 99.9 mmol) and 30% H₂O₂ (3.3 mL, 41.3 mmol) at 0 °C. The mixture was stirred at room temperature for 7 h, diluted with ice water (85 mL), and extracted with EtOAc (3×100 mL). The combined extracts were washed with brine (500 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (250 g, hexane–EtOAc 3:1) to give terminal olefin **28** (5.84 g, 95%) as a colorless oil: $[\alpha]_D^{24}$ –29.7 (*c* 0.60, CHCl₃); IR (film) 2935, 1517, 1263, 1238, 1158, 1068 cm^{–1}; ¹H NMR (270 MHz, CDCl₃) δ 6.94–6.81 (m, 3H), 5.83 (ddd, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.24

(ddd, $J = 17.0, 1.6, 1.6$ Hz, 1H), 5.10 (ddd, $J = 17.0, 1.6, 1.6$ Hz, 1H), 4.59 (d, $J = 11.6$ Hz, 1H), 4.55, (m, 1H), 4.51 (d, $J = 11.6$ Hz, 1H), 4.39 (ddd, $J = 6.2, 6.2, 6.2$ Hz, 1H), 4.19 (br.t, $J = 3.5$ Hz, 1H), 4.12 (dd, $J = 8.4, 6.2$ Hz, 1H), 4.01 (dd, $J = 8.4, 6.2$ Hz, 1H), 3.99 (dd, $J = 6.8, 3.5$ Hz, 1H), 3.88 (s, 6H), 2.28 (ddd, $J = 13.2, 5.7, 0.8$ Hz, 1H), 1.71 (ddd, $J = 13.2, 10.3, 4.3$ Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (67.8 MHz, CDCl_3) δ 148.7, 148.3, 138.4, 130.1, 120.0, 115.8, 110.7, 110.6, 108.5, 83.0, 79.4, 79.0, 73.8, 71.4, 67.3, 55.9, 55.8, 38.7, 26.9, 25.6; HRMS (ESI) m/z 387.1785, calcd for $\text{C}_{20}\text{H}_{28}\text{NaO}_6$ $[\text{M}+\text{Na}]^+$ 387.1784.

Coupling compound 18. All solvents were degassed by freeze-thawing. To a stirred solution of olefin **28** (900 mg, 2.47 mmol) in THF (8.2 mL) was added a 9-BBN-H dimer (1.20 g, 4.92 mmol) at room temperature in a glove box. The mixture was stirred at room temperature for 7 h in the glove box to give a THF solution of alkylborane **30**.

The solution of the above-mentioned alkylborane **30** was added via cannula to a stirred solution of iodoalkenylsilane **19** (1.31 g, 3.70 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (202 mg, 0.247 mmol), and 1 M Cs_2CO_3 aq (12.4 mL, 12.4 mmol) in 1,4-dioxane (18.5 mL) in a glove box, and the rinse (1,4-dioxane 10 mL) of the flask of alkylborane **30** was added to the reaction mixture. The resultant mixture was stirred at room temperature for 14.5 h in the glove box, diluted with water and Et_2O , and extracted with EtOAc . The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (90 g, hexane– EtOAc 1:0→8:1→6:1) to give coupling compound **18** (1.48 g, quant) as a colorless oil: $[\alpha]_D^{20} -12.3$ (c 2.7, CHCl_3); IR (film) 2940, 1455, 1369, 1158, 1068, 839 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.92–6.81 (m, 3H), 5.74 (t, $J = 6.8$ Hz, 1H), 4.60 (m, 1H), 4.57 (d, $J = 11.7$ Hz, 1H), 4.48 (d, $J = 11.7$ Hz, 1H), 4.37 (ddd, $J = 6.2, 6.2, 6.2$ Hz, 1H), 4.16–4.08 (m, 3H), 3.97 (dd, $J = 8.6, 6.2$ Hz, 1H), 3.92 (dd, $J = 7.0, 3.5$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.84 (m, 1H), 3.74 (dt, $J = 9.5, 7.3$ Hz, 1H), 3.49 (m, 1H), 3.41 (dt, $J = 9.5, 7.3$ Hz, 1H), 2.41 (q, $J = 6.8$ Hz, 2H), 2.22 (dd, $J = 13.0, 5.4$ Hz, 1H), 2.17–2.05 (m, 2H), 1.83–1.45 (m, 9H), 1.42 (s, 3H), 1.36 (s, 3H), 0.05, (s, 9H); ^{13}C NMR (67.8 MHz, CDCl_3) δ 148.8, 148.3, 142.3, 136.0, 130.9, 120.0, 110.8, 110.7, 108.5, 98.5, 82.5, 79.2, 78.4, 74.0, 71.3, 67.3, 66.8, 62.1, 55.9, 55.8, 38.2, 36.3, 30.7, 29.1, 26.8, 26.1, 25.7, 25.6, 19.5, –1.1 (C3); HRMS (ESI) m/z 615.3328, calcd for $\text{C}_{32}\text{H}_{52}\text{NaO}_8\text{Si}$ $[\text{M}+\text{Na}]^+$ 615.3329.

Vinyl chloride 31. To a stirred solution of coupling compound **18** (35.8 mg, 60.4 μmol) in DMF (1.2 mL) were added K_2CO_3 (4.2 mg, 30.4 μmol) and *N*-chlorosuccinimide (16.1 mg, 0.121 mmol) at 0 °C. The mixture was stirred at 50 °C for 11 h, diluted with water, and extracted with Et_2O (4×10 mL).

Ester 34. To a stirred solution of **17** (399 mg, 847 μmol) in CH_2Cl_2 (8.5 mL) was added Dess–Martin periodinane (899 mg, 2.12 mmol) at 0 °C. The mixture was stirred at room temperature for 40 min, diluted with saturated aqueous NaHCO_3 (6 mL) and saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (6 mL), and extracted with Et_2O (3 $\times$ 12 mL). The combined extracts were washed with brine (50 mL) and dried over MgSO_4 . Removal of the solvent afforded crude aldehyde **17a** (422 mg), which was used for the next reaction without further purification.

To a stirred solution of ethyl 2-(di-*o*-tolylphosphono)propionate **33** (464 mg, 1.28 mmol) in THF (5.1 mL) was added NaH (47.5 mg, 1.19 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After cooling to –78 °C, a solution of the aldehyde **17a** (422 mg) in THF (3.4 mL) was added via cannula. The mixture was stirred at –78 °C for 35 min, diluted with saturated aqueous NH_4Cl (5 mL), and extracted with Et_2O (3 $\times$ 5 mL). The combined extracts were washed with brine (25 mL), dried (MgSO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (26 g, hexane– EtOAc 4:1) to give ester **34** (368 mg, 79% in 2 steps) as a colorless oil: $[\alpha]_{\text{D}}^{24}$ –15.8 (c 0.095, CHCl_3); IR (film) 2928, 1712, 1517, 1265, 1238, 1138, 1068, 846, 760 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.90–6.81 (m, 3H), 5.86 (ddd, J = 7.2, 7.2, 1.3 Hz, 1H), 5.52 (dd, J = 7.2, 7.2 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.36 (ddd, J = 6.4, 6.4, 6.4 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.15–4.10 (m, 2H), 4.08 (dd, J = 8.4, 6.4 Hz, 1H), 3.98–3.93 (m, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.32 (dd, J = 7.2, 7.2 Hz, 2H), 2.47 (m, 1H), 2.39–2.33 (m, 1H), 2.20 (dd, J = 13.5, 5.1 Hz, 1H), 1.89 (d, J = 1.2 Hz, 3H), 1.78–1.73 (m, 2H), 1.56 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.8, 149.0, 148.5, 138.5, 135.3, 130.9, 128.2, 123.1, 119.9, 110.9, 110.8, 108.5, 82.4, 79.1, 77.3, 74.1, 71.3, 67.1, 60.3, 55.9, 55.8, 38.1, 36.2, 33.8, 29.2, 26.8, 25.6, 20.5, 14.3; HRMS (ESI) m/z 575.2392, calcd for $\text{C}_{29}\text{H}_{41}^{35}\text{Cl NaO}_8$ $[\text{M}+\text{Na}]^+$ 575.2388.

Aldehyde 35. To a stirred solution of **34** (668 mg, 1.21 mmol) in toluene (60 mL) was added DIBALH (1.0 M solution in toluene, 3.7 mL, 3.70 mmol) at –78 °C. The mixture was stirred at the same temperature for 45 min then diluted with 0.5 M Na/K tartrate aq (340 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 $\times$ 340 mL). The combined extracts were washed with brine (500 mL) and dried over Na_2SO_4 . Removal of the solvent afforded crude allylic alcohol **34a** (651 mg), which was used for the next reaction without further purification.

To a stirred solution of the allylic alcohol **34a** (651 mg) in CH₂Cl₂ (12 mL) was added Dess-Martin periodinane (770 mg, 1.82 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous NaHCO₃ (12 mL) and saturated aqueous Na₂S₂O₃ (12 mL), and extracted with Et₂O (3×24 mL). The combined extracts were washed with brine (80 mL) and dried over MgSO₄. Removal of the solvent afforded crude aldehyde **35** (660 mg), which was used for the next reaction without further purification.

TBS ether 36. To a stirred solution of isopropyl acetate (0.34 mL, 2.90 mmol) in THF (20.4 mL) was added LHMDS (1.0 M solution in THF, 2.7 mL, 2.70 mmol) at -78 °C. After being stirred at -78 °C for 30 min, a solution of aldehyde **35** (660 mg) in THF (28 mL) was added via cannula. The mixture was stirred at -78 °C for 40 min, diluted with saturated aqueous NH₄Cl (12 mL), and extracted with Et₂O (3×12 mL). The combined extracts were washed with brine (80 mL), dried (MgSO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (26 g, hexane–EtOAc 4:1→3:1→2:1) to give aldol **35a** (562 mg, 76% in 3 steps) as a colorless oil: IR (film) 3472, 2934, 1727, 1517, 1265, 1158, 1066, 849, 757 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.90–6.82 (m, 3H), 5.45 (dd, *J* = 14.1, 7.0 Hz, 1H), 5.22 (dd, *J* = 7.5, 7.5 Hz, 1H), 5.05 (septet, *J* = 6.3 Hz, 1H), 5.02 (m, 1H), 4.55 (dd, *J* = 11.7, 2.9 Hz, 1H), 4.45 (dd, *J* = 11.7, 4.3 Hz, 1H), 4.35 (ddd, *J* = 6.3, 6.3, 6.3 Hz, 1H), 4.14 (dd, *J* = 3.3, 3.3 Hz, 1H), 4.08–4.04 (m, 2H), 3.99–3.91 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.98–2.87 (m, 2H), 2.62 (ddd, *J* = 16.0, 9.7, 2.9 Hz, 1H), 2.46–2.37 (m, 2H), 2.35 (ddd, *J* = 16.0, 3.6, 1.1 Hz, 1H), 2.19 (dd, *J* = 13.2, 5.3 Hz, 1H), 1.80–1.73 (m, 2H), 1.71 (dd, *J* = 7.0, 1.1 Hz, 3H), 1.56 (ddd, *J* = 11.5, 8.3, 3.6 Hz, 1H), 1.42 (d, *J* = 2.9 Hz, 3H), 1.36 (s, 3H), 1.25 (d, *J* = 6.3 Hz, 6H). A signal due to one proton (OH) was not observed; ¹³C NMR (150 MHz, CDCl₃) δ 172.1 (0.5C), 172.1 (0.5C), 149.0, 148.6, 136.5 (0.5C), 136.5 (0.5C), 134.4, 130.9, 124.2 (0.5C), 124.2 (0.5C), 123.8 (0.5C), 123.7 (0.5C), 120.0, 111.0, 110.9, 108.5 (0.5C), 108.5 (0.5C), 82.3, 79.2 (0.5C), 79.1 (0.5C), 74.3 (0.5C), 74.2 (0.5C), 71.4, 68.3, 67.0, 66.8, 66.0, 55.9, 55.8, 40.0, 38.2, 36.2, 33.6 (0.5C), 33.5 (0.5C), 27.0, 26.7, 25.6, (0.5C) 25.5 (0.5C), 21.8, 21.8, 17.6 (0.5C), 17.6 (0.5C); HRMS (ESI) *m/z* 633.2805, calcd for C₃₂H₄₇³⁵ClNaO₉ [M+Na]⁺ 633.2806.

To a stirred solution of **35a** (558 mg, 913 μmol) in DMF (1.8 mL) were added imidazole (373 mg, 5.48 mmol) and TBSCl (413 mg, 2.74 mmol) at 0 °C. The mixture was stirred at room temperature for 17 h, diluted with saturated aqueous NaHCO₃ (12 mL), and extracted with EtOAc (3×16 mL). The combined extracts were washed with brine (50 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (23 g, hexane–EtOAc 10:1→4:1) to give **36** (604 mg, 91%) as a colorless oil: IR (film) 2932, 1731, 1517, 1260, 1069, 957, 837, 778 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.90–6.81 (m, 3H), 5.42 (dd, *J* = 6.9, 6.9 Hz, 1H), 5.09 (dd, *J* = 7.2, 7.2 Hz, 1H), 5.04 (dd, *J* = 9.0, 4.5 Hz, 1H), 4.97 (septet, *J* = 6.2 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.35 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 4.15–4.06 (m, 3H), 3.96–3.93 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.00 (m, 1H), 2.89 (m,

1H), 2.58 (dd, $J = 14.4, 9.0$ Hz, 1H), 2.45 (m, 1H), 2.34 (m, 1H), 2.27 (dd, $J = 14.4, 4.5$ Hz, 1H), 2.20 (dd, $J = 13.5, 5.4$ Hz, 1H), 1.77–1.71 (m, 2H), 1.67 (s, 3H), 1.56 (ddd, $J = 13.5, 9.7, 4.1$ Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.23 (d, $J = 6.2$ Hz, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 149.0, 148.5, 137.9, 134.5, 130.9, 123.7, 122.6, 119.9, 110.9, 110.8, 108.5, 82.4, 79.1, 77.4, 74.1, 71.3, 67.7, 67.2, 67.0, 55.9, 55.8, 42.2, 38.1, 36.2, 33.8, 27.1, 26.7, 25.7 (3C), 25.6, 21.9, 21.8, 18.0, 17.5, –5.0, –5.2; HRMS (ESI) m/z 747.3671, calcd for $\text{C}_{38}\text{H}_{61}^{35}\text{ClNaO}_9\text{Si}$ $[\text{M}+\text{Na}]^+$ 747.3671.

Trityl ether 39. To a stirred solution of **36** (42.4 mg, 58.4 μmol) in 2-propanol (0.85 mL) were added CSA (1.0 mg, 4.30 μmol) and ethylene glycol (0.165 mL, 2.96 mmol) at 0 °C. The mixture was stirred at room temperature for 19 h, diluted with H_2O (1 mL), and extracted with benzene (7 $\times$ 3 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane–EtOAc 2:1 $\rightarrow$ 0:1) to give a diol **36a** (31.7 mg, 79%), recovered **36** (5.2 mg, 12%), and triol (2.2 mg, 8%) as colorless oils respectively; diol: IR (film) 3441, 2930, 1731, 1517, 1260, 1076, 957, 836, 777 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.89–6.79 (m, 3H), 5.42 (dd, $J = 7.0, 7.0$ Hz, 1H), 5.09 (brt, $J = 7.2$ Hz, 1H), 5.03 (dd, $J = 8.9, 4.5$ Hz, 1H), 4.96 (septet, $J = 6.2$ Hz, 1H), 4.60 (d, $J = 11.5$ Hz, 1H), 4.35 (d, $J = 11.5$ Hz, 1H), 4.29 (m, 1H), 4.14 (m, 1H), 3.94 (m, 1H), 3.90 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.78 (dd, 11.0, 2.5 Hz, 1H), 3.66 (dd, 11.2, 5.5 Hz, 1H), 3.00 (m, 1H), 2.91 (m, 1H), 2.58 (dd, $J = 14.4, 8.9$ Hz, 1H), 2.45 (m, 1H), 2.33 (m, 1H), 2.27 (dd, $J = 14.4, 4.5$ Hz, 1H), 2.23 (dd, $J = 13.2, 5.6$ Hz, 1H), 1.76–1.70 (m, 2H), 1.66 (s, 3H), 1.61 (m, 1H), 1.23 (d, $J = 6.2$ Hz, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H). Signals due to two protons (OH) were not observed; ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 149.2, 148.9, 137.9, 134.3, 129.9, 123.8, 122.5, 120.3, 111.1, 111.0, 80.8, 79.7, 77.1, 77.1, 71.3, 70.2, 67.7, 67.2, 64.8, 55.9, 42.2, 37.3, 36.1, 33.6, 27.1, 25.7 (3C), 21.9, 21.8, 18.0, 17.5, –5.0, –5.2; HRMS (ESI) m/z 707.3355, calcd for $\text{C}_{35}\text{H}_{57}^{35}\text{ClNaO}_9\text{Si}$ $[\text{M}+\text{Na}]^+$ 707.3358.

To a stirred solution of the diol **36a** (237 mg, 346 μmol) in 1,4-dioxane (5.0 mL) and H_2O (2.5 mL) was added NaIO_4 (111 mg, 519 μmol) at 0 °C. The mixture was stirred at room temperature for 4 h then NaBH_4 (20.6 mg, 545 μmol) was added at room temperature. The resultant mixture was stirred at room temperature for 45 min, diluted with saturated aqueous NH_4Cl (6 mL) and saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (6 mL), and extracted with EtOAc (4 $\times$ 12 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (7 g, hexane–EtOAc 2:1 $\rightarrow$ 0:1) to give alcohol **36b** (213 mg, 94%) as a colorless oil: IR (film) 3473, 2930, 1730, 1516, 1260, 1160, 1078, 957, 836, 777 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.89–6.80 (m, 3H), 5.44 (dd, $J = 6.9, 6.9$ Hz, 1H), 5.10 (dd, $J = 7.4, 7.5$ Hz, 1H), 5.04 (dd, $J = 8.9, 4.5$ Hz, 1H), 4.97 (septet, $J = 6.2$ Hz, 1H), 4.57 (d, $J = 11.6$ Hz, 1H), 4.35 (d, $J = 11.6$ Hz, 1H), 4.25 (brt, $J = 4.3$ Hz, 1H), 4.20 (m,

1H), 4.06 (dd, $J = 10.0, 5.0$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (m, 1H), 3.81 (m, 1H), 3.01 (m, 1H), 2.89 (m, 1H), 2.59 (dd, $J = 14.4, 8.9$ Hz, 1H), 2.47 (m, 1H), 2.42–2.33 (m, 2H), 2.28 (dd, $J = 14.4, 4.5$ Hz, 1H), 2.21 (dd, $J = 13.2, 5.8$ Hz, 1H), 1.77 (dd, $J = 14.5, 7.3$ Hz, 2H), 1.67 (s, 3H), 1.23 (d, $J = 6.2$ Hz, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 149.1, 148.8, 137.9, 134.5, 130.2, 123.7, 122.6, 120.1, 111.0, 110.8, 80.6, 80.3, 76.9, 76.9, 71.4, 67.7, 67.3, 62.1, 55.9, 55.9, 42.2, 37.8, 36.1, 33.8, 27.1, 25.7, 25.7, 21.9, 21.8, 18.0, 17.6, –4.9, –5.2; HRMS (ESI) m/z 677.3252, calcd for $\text{C}_{34}\text{H}_{55}^{35}\text{ClNaO}_8\text{Si}$ $[\text{M}+\text{Na}]^+$ 677.3252.

To a stirred solution of the alcohol **36b** (46.8 mg, 71.4 μmol) in CH_2Cl_2 (0.72 mL) were added DMAP (2.7 mg 21.4 μmol), pyridine (46 μL , 569 μmol), and triphenylmethyl chloride (77.8 mg, 279 μmol) at 0 °C. The mixture was stirred at room temperature for 41 h, diluted with saturated aqueous NH_4Cl (1 mL), and extracted with EtOAc (3 $\times$ 3 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (6 g, toluene 100% $\rightarrow$ hexane–EtOAc 3:1) to give a trityl ether **39** (62.6 mg, 98%) as a colorless oil: IR (film) 2931, 1731, 1516, 1267, 1076, 1031, 836, 776, 706 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.48–7.20 (m, 18H), 5.44 (dd, $J = 6.9, 6.9$ Hz, 1H), 5.10 (brt, $J = 7.1$ Hz, 1H), 5.05 (dd, $J = 8.9, 4.5$ Hz, 1H), 4.98 (septet, $J = 6.2$ Hz, 1H), 4.45 (d, $J = 11.8$ Hz, 1H), 4.32 (d, $J = 11.8$ Hz, 1H), 4.21–4.17 (m, 2H), 4.10 (m, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.45 (dd, $J = 9.3, 5.9$ Hz, 1H), 3.28 (dd, $J = 9.3, 5.9$ Hz, 1H), 3.02 (m, 1H), 2.90 (m, 1H), 2.60 (dd, $J = 14.4, 8.9$ Hz, 1H), 2.51 (m, 1H), 2.36 (m, 1H), 2.28 (dd, $J = 14.4, 4.5$ Hz, 1H), 2.16 (dd, $J = 13.1, 5.7$ Hz, 1H), 1.78 (dd, $J = 14.9, 6.9$ Hz, 2H), 1.68 (s, 3H), 1.61 (m, 1H), 1.24 (d, $J = 6.2$ Hz, 3H), 1.23 (d, $J = 6.2$ Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 149.2, 148.8, 144.6 (3C), 138.3, 135.1, 131.3, 129.2 (6C), 128.1 (6C), 127.3 (3C), 124.0, 123.1, 120.4, 111.3, 111.2, 87.1, 81.1, 79.5, 77.0, 71.8, 68.2, 67.7, 62.8, 56.3, 56.2, 42.7, 38.6, 36.8, 34.4, 27.6, 26.1 (3C), 22.3 (3C), 18.5 (0.5C), 18.0 (0.5C), –4.5, –4.8; HRMS (ESI) m/z 919.4355, calcd for $\text{C}_{53}\text{H}_{69}^{35}\text{ClNaO}_8\text{Si}$ $[\text{M}+\text{Na}]^+$ 919.4348.

Seco acid 40. DDQ (20.9 mg 92.0 μmol) was added to a stirred solution of the trityl ether **39** (59.0 mg, 65.7 μmol) in CH_2Cl_2 (16.6 mL), t -BuOH (0.91 mL), and pH 6.6 phosphate buffer (0.91 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, diluted with saturated aqueous NaHCO_3 (8 mL), and extracted with EtOAc (3 $\times$ 8 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, hexane–EtOAc 5:1) to give an alcohol **39a** (46 mg, 93%) as a colorless oil: IR (film) 3460, 2928, 1731, 1448, 1251, 1173, 1074, 835, 775, 705 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.47–7.25 (m, 15H), 5.45 (dd, $J = 6.9, 6.9$ Hz, 1H), 5.09 (dd, $J = 7.5, 7.5$ Hz, 1H), 5.05 (dd, $J = 8.9, 4.5$ Hz, 1H), 4.99 (septet, $J = 6.2$ Hz, 1H), 4.56 (brdd, $J = 7.6, 3.7$ Hz, 1H), 4.24 (dddd, $J = 11.0, 5.6, 5.6, 5.6$ Hz, 1H), 4.16 (ddd, $J = 7.8, 3.9, 3.9$ Hz,

1H), 3.47 (dd, $J = 9.5, 4.5$ Hz, 1H), 3.31 (dd, $J = 9.5, 7.4$ Hz, 1H), 3.01 (m, 1H), 2.90 (m, 1H), 2.65 (brs, 1H), 2.60 (dd, $J = 14.4, 8.9$ Hz, 1H), 2.49 (m, 1H), 2.37 (m, 1H), 2.29 (dd, $J = 14.4, 4.5$ Hz, 1H), 2.11 (dd, $J = 13.0, 5.4$ Hz, 1H), 1.80–1.70 (m, 3H), 1.68 (s, 3H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.24 (d, $J = 6.2$ Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 143.5 (3C), 137.9, 134.5, 128.4 (6C), 128.0 (6C), 127.2 (3C), 123.7, 122.6, 87.2, 80.1, 77.3, 73.6, 67.7, 67.3, 62.6, 42.2, 41.2, 36.3, 33.8, 27.1, 25.7 (3C), 21.9, 21.8 (2C), 18.0 (0.5C), 17.5 (0.5C), $-4.9, -5.2$; HRMS (ESI) m/z 769.3669, calcd for $\text{C}_{44}\text{H}_{59}^{35}\text{ClNaO}_6\text{Si}$ $[\text{M}+\text{Na}]^+$ 769.3667.

To a stirred solution of the alcohol **39a** (66.9 mg, 89.5 μmol) in THF (0.75 mL) and MeOH (0.375 mL) was added 3 M LiOH *aq* (0.375 mL, 1.13 mmol) at 0 °C. The mixture was stirred at room temperature for 42 h, diluted with saturated NaH_2PO_4 to pH 3, and extracted with EtOAc (4 $\times$ 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane–EtOAc 4:1) to give seco acid **40** (48.3 mg, 77%) as a colorless oil: IR (film) 3422, 2928, 1712, 1448, 1252, 1076, 836, 759, 706 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44–7.22 (m, 15H), 5.50 (dd, $J = 7.1, 7.1$ Hz, 0.5H), 5.40 (dd, $J = 6.7, 6.7$ Hz, 0.5H), 5.28 (brt, $J = 7.8$ Hz, 0.5H), 5.18 (brt, $J = 7.8$ Hz, 0.5H), 4.99 (dd, $J = 14.5, 7.2$ Hz, 1H), 4.52 (dd, $J = 4.1, 4.1$ Hz, 0.5H), 4.43 (dd, $J = 4.1, 4.0$ Hz, 0.5H), 4.22 (m, 1H), 4.10 (m, 1H), 3.45 (dd, $J = 9.6, 4.8$ Hz, 0.5H), 3.40 (dd, $J = 9.9, 5.5$ Hz, 0.5H), 3.35 (dd, $J = 9.8, 6.4$ Hz, 0.5H), 3.29 (dd, $J = 9.6, 7.2$ Hz, 0.5H), 2.92–2.87 (m, 2H), 2.58 (dd, $J = 13.6, 7.1$ Hz, 0.5H), 2.56 (dd, $J = 14.2, 7.4$ Hz, 0.5H), 2.50–2.35 (m, 3H), 2.16 (m, 1H), 1.79–1.67 (m, 3H), 1.68 (s, 3H), 0.87 (s, 4.5H), 0.87 (s, 4.5H), 0.08 (s, 1.5H), 0.07 (s, 1.5H), 0.03 (s, 1.5H), 0.02 (s, 1.5H). Signals due to two protons (COOH, OH) were not observed; ^{13}C NMR (125 MHz, CDCl_3) δ 174.0 (0.5C), 173.6 (0.5C), 143.5 (1.5C), 143.5 (1.5C), 137.2 (0.5C), 137.2 (0.5C), 134.0 (0.5C), 133.6 (0.5C), 128.5 (3C), 128.4 (3C), 128.0 (3C), 127.9 (3C), 127.2 (1.5C), 127.2 (1.5C), 124.6 (0.5C), 124.2 (0.5C), 123.4 (0.5C), 123.2 (0.5C), 87.2 (0.5C), 87.1 (0.5C), 80.7 (0.5C), 80.2 (0.5C), 76.0, 73.7 (0.5C), 73.4 (0.5C), 67.2 (0.5C), 67.0 (0.5C), 62.4 (0.5C), 62.2 (0.5C), 41.7 (0.5C), 41.4 (0.5C), 41.1 (0.5C), 41.0 (0.5C), 36.1 (0.5C), 36.0 (0.5C), 33.2 (0.5C), 33.1 (0.5C), 27.1 (0.5C), 26.8 (0.5C), 25.7 (3C), 18.0, 17.3 (0.5C), 17.1 (0.5C), -4.9 (0.5C), -4.9 (0.5C), -5.1 (0.5C), -5.2 (0.5C); HRMS (ESI) m/z 727.3195, calcd for $\text{C}_{41}\text{H}_{53}^{35}\text{ClNaO}_6\text{Si}$ $[\text{M}+\text{Na}]^+$ 727.3198.

Lactone 41. To a stirred solution of seco acid **40** (27.6 mg, 39.1 μmol) in THF (1.6 mL) were added Et_3N (65.5 μL , 469 μmol) and 2,4,6-trichlorobenzoyl chloride (65 μL , 0.416 μmol) at 0 °C. The mixture was stirred at room temperature for 2 h and diluted with toluene (14 mL) to give a solution of mixed anhydride. The mixed anhydride was added slowly to a solution of 4-(dimethylamino)pyridine (120 mg, 0.978 mmol) in toluene (122 mL) through a syringe pump over 22 h. After stirring for an additional 13 h at room temperature, the mixture was diluted with saturated aqueous NH_4Cl (16 mL) and extracted with EtOAc (3 $\times$ 16 mL). The combined extracts were washed with brine (180 mL), dried

(Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 3 g, hexane–EtOAc 10:1) and by recycle HPLC [JAIGEL-1H-40 (600×20 mm) and JAIGEL-2H-40 (600×20 mm); flow rate 3.8 mL/min; detection, UV 254 nm; solvent CHCl₃] to give lactone **41** (16.5 mg, 61%) as a colorless oil: IR (film) 2928, 1730, 1448, 1289, 1252, 1074, 836, 759, 706 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.46–7.20 (m, 15H), 5.46 (dd, *J* = 10.3, 7.1 Hz, 1H), 5.32 (dd, *J* = 3.2, 3.2 Hz, 1H), 5.21 (brd, *J* = 7.3 Hz, 1H), 4.50 (dd, *J* = 10.8, 4.4 Hz, 1H), 4.36 (m, 1H), 3.76 (dddd, *J* = 11.5, 11.5, 3.7, 3.7 Hz 1H), 3.45 (m, 1H), 3.19 (m, 1H), 3.16 (dd, *J* = 8.3, 8.3 Hz, 1H), 2.69–2.07 (m, 7H), 1.82 (s, 3H), 1.50–1.40 (m, 2H), 0.87 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.4 (0.5C), 168.8 (0.5C), 143.9 (1.5C), 143.8 (1.5C), 138.1 (0.5C), 136.2 (0.5C), 133.7 (0.5C), 131.7 (0.5C), 128.7 (3C), 128.6 (3C), 127.8 (3C), 127.7 (3C), 127.0 (1.5C), 127.0 (1.5C), 125.9 (0.5C), 124.9 (0.5C), 123.8 (0.5C), 122.2 (0.5C), 86.6 (0.5C), 86.5 (0.5C), 79.4 (0.5C), 79.2 (0.5C), 76.9 (0.5C), 76.0 (0.5C), 75.1 (0.5C), 74.9 (0.5C), 66.8 (0.5C), 66.1 (0.5C), 61.9 (0.5C), 61.2 (0.5C), 42.3 (0.5C), 41.5 (0.5C), 37.7 (0.5C), 37.6 (0.5C), 36.0 (0.5C), 34.7 (0.5C), 28.8 (0.5C), 27.8 (0.5C), 26.8 (0.5C), 25.6 (1.5C), 25.6 (1.5C), 25.5 (0.5C), 17.9, 17.6 (0.5C), 17.2 (0.5C), –4.7, –4.8; HRMS (APCI) *m/z* 685.3125, calcd for C₄₁H₅₀³⁵ClNaO₅Si [M–H]⁺ 685.3116.

Diastereomer: ¹H NMR (500 MHz, CDCl₃) δ 7.46–7.20 (m, 15H), 5.52 (dd, *J* = 9.8, 7.8 Hz, 1H), 5.38 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.10 (dd, *J* = 4.1, 4.1 Hz, 1H), 4.64 (dd, *J* = 10.6, 3.6 Hz, 1H), 4.42 (m, 1H), 3.68 (dddd, *J* = 11.4, 11.4, 3.3, 3.3 Hz, 1H), 3.45 (m, 1H), 3.03 (dd, *J* = 9.3, 6.3 Hz, 1H), 2.77 (m, 1H), 2.69–2.07 (m, 7H), 1.31 (s, 3H), 1.50–1.40 (m, 2H), 0.85 (s, 9H), 0.07 (s, 3H), 0.00 (s, 3H).

Allylic alcohol 42a, 42b. To a stirred solution of lactone **41** (6.8 mg, 9.9 μmol) in THF (0.65 mL) was added TBAF (25 μL, 25 μmol) at 0 °C. The mixture was stirred at room temperature for 40 min, diluted with Et₂O (3.1 mL) and saturated aqueous NH₄Cl (2 mL), and extracted with Et₂O (3×5 mL). The combined extracts were dried (MgSO₄) and concentrated. The residual oil was purified by column chromatography on silica gel (0.5 g, hexane–EtOAc 5:1) to give allylic alcohol **42a** (3.2 mg, 56%) and **42b** (2.2 mg, 39%) as colorless oils, respectively; **42a**: [α]_D²⁴ +63.4 (*c* 0.41, CHCl₃); IR (film) 3418, 2928, 1728, 1448, 1138, 1075, 1003, 758, 707, 633 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.21 (m, 15H), 5.63 (brt, *J* = 8.1 Hz, 1H), 5.43 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.26 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.65 (dd, *J* = 9.4, 4.3 Hz, 1H), 4.42 (ddd, *J* = 6.7, 6.7, 4.5 Hz, 1H), 3.71 (dddd, *J* = 11.3, 11.3, 3.3, 3.3 Hz, 1H), 3.43 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.05 (dd, *J* = 9.2, 6.6 Hz, 1H), 2.86 (m, 1H), 2.72 (m, 1H), 2.53 (dd, *J* = 12.1, 9.4 Hz, 1H), 2.47 (dd, *J* = 12.1, 4.3 Hz, 1H), 2.41 (ddd, *J* = 12.7, 3.5, 3.5 Hz, 1H), 2.32–2.18 (m, 3 H), 1.53–1.42 (m, 2H), 1.40 (s, 3H). A signal due to one proton (OH) was not observed; ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 143.8 (3C), 135.7, 133.7, 128.7 (6C), 127.8 (6C), 127.0 (3C), 125.1, 123.9, 86.6, 79.3, 76.6, 75.4, 66.7, 61.9, 40.5, 38.3, 36.0, 28.8, 25.7, 17.4; HRMS (ESI) *m/z* 595.2232, calcd for C₃₅H₃₇³⁵ClNaO₅ [M+Na]⁺ 595.2227; **42b**: [α]_D²⁴ –12.1 (*c* 0.31, CHCl₃); IR (film) 3435, 2927, 1736, 1447, 1233, 1074,

767, 706, 633 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42–7.22 (m, 15H), 5.61 (brdd, $J = 9.3, 7.5$ Hz, 1H), 5.37 (dd, $J = 3.3, 3.3$ Hz, 1H), 5.18 (d, $J = 7.0$ Hz, 1H), 4.56 (dd, $J = 11.3, 4.0$ Hz, 1H), 4.32 (ddd, $J = 7.9, 5.4, 3.6$ Hz, 1H), 3.79 (dddd, $J = 11.6, 11.6, 3.8, 3.8$ Hz, 1H), 3.39 (dd, $J = 8.9, 5.6$ Hz, 1H), 3.20 (dd, $J = 8.4, 8.4$ Hz, 1H), 3.20 (m, 1H), 2.58 (dd, $J = 11.3, 11.3$ Hz, 1H), 2.60–2.48 (m, 2H), 2.40 (dd, $J = 11.3, 4.0$ Hz, 1H), 2.34 (m, 1H), 2.15 (ddd, 13.2, 7.8, 5.4 Hz, 1H), 2.03 (dd, $J = 12.8, 3.3$ Hz, 1H), 1.87 (s, 3H), 1.48 (ddd, $J = 12.6, 12.4, 3.3$ Hz, 1H), 1.35 (m, 1H). A signal due to one proton (OH) was not observed; ^{13}C NMR (125 MHz, CDCl_3) δ 168.8, 143.8 (3C), 137.5, 131.8, 128.6 (6C), 127.8 (6C), 127.4, 127.0 (3C), 125.6, 86.5, 79.2, 76.1, 75.0, 65.9, 61.3, 39.9, 37.7, 34.8, 28.0, 26.3, 17.6; HRMS (ESI) m/z 595.2229, calcd for $\text{C}_{35}\text{H}_{37}^{35}\text{ClNaO}_5$ $[\text{M}+\text{Na}]^+$ 595.2227.

Allylic alcohol 42b. To a stirred solution of allylic alcohol **42a** (5.4 mg, 9.4 μmol) in CH_2Cl_2 (0.38 mL) was added Dess–Martin periodinane (16 mg, 37 μmol) at 0 $^\circ\text{C}$. The mixture was stirred at room temperature for 2 h, and Dess–Martin periodinane (16 mg, 38 μmol) was added at 0 $^\circ\text{C}$. The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (3.5 mL), and extracted with EtOAc (4 $\times$ 8 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (0.4 g, hexane–EtOAc 5:1) to give an enone **42aa** (5.1 mg, 94%) as a colorless oil: $[\alpha]_D^{24} +132$ (c 0.63, CHCl_3); IR (film) 2927, 1745, 1687, 1448, 1240, 1076, 757, 706, 633 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.43–7.23 (m, 15H), 6.26 (brt, $J = 9.2$ Hz, 1H), 5.57–5.52 (m, 2H), 4.41 (ddd, $J = 8.2, 5.8, 3.9$ Hz, 1H), 3.67 (dddd, $J = 11.3, 11.3, 3.5, 3.5$ Hz, 1H), 3.46 (d, $J = 11.8$ Hz, 1H), 3.19 (d, $J = 11.8$ Hz, 1H), 3.10 (dd, $J = 8.4, 8.4$ Hz, 1H), 3.46 (m, 1H), 3.23–3.14 (m, 2H), 2.43 (m, 1H), 2.26 (dddd, $J = 12.6, 12.6, 4.1, 4.1$ Hz, 1H), 2.16 (ddd, $J = 13.1, 13.1, 4.1$ Hz, 1H), 1.94 (dd, $J = 13.0, 3.3$ Hz, 1H), 1.83 (s, 3H), 1.50 (ddd, $J = 12.4, 12.4, 3.2$ Hz, 1H), 1.43 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 194.2, 165.3, 143.7 (3C), 141.0, 133.5, 133.1, 128.6 (6C), 127.8 (6C), 127.0 (3C), 123.4, 86.5, 78.9, 75.9, 75.7, 61.1, 48.0, 38.2, 35.5, 28.9, 27.3, 22.3; HRMS (ESI) m/z 593.2073, calcd for $\text{C}_{35}\text{H}_{35}^{35}\text{ClNaO}_5$ $[\text{M}+\text{Na}]^+$ 593.2071.

To a stirred solution of the enone **42aa** (1.6 mg, 2.8 μmol) in EtOH (0.12 mL) was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.7 mg, 2.8 μmol) at 0 $^\circ\text{C}$, and the mixture was stirred at room temperature for 35 min. After cooling to -30°C , NaBH_4 (0.2 mg, 5.6 μmol) was added. The mixture was stirred at -30°C for 30 min, diluted with saturated 0.2 M phosphate buffer (1 mL) and extracted with EtOAc (4 $\times$ 2 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.5 g, hexane–EtOAc 5:1) to give allylic alcohol **42b** (1.5 mg, 94%) as a colorless oil.

Acetate 43. To a stirred solution of allylic alcohol **42b** (11.7 mg, 20.4 μmol) in CH_2Cl_2 (1.2 mL) were added pyridine (20 μL , 247 μmol), DMAP (1.2 mg, 9.82 μmol), and acetyl chloride (14.5 μL , 204 μmol) at 0 $^\circ\text{C}$. The mixture was stirred at room temperature for 22 h, diluted with H_2O (2 mL), and extracted with Et_2O (3 $\times$ 5 mL). The combined extracts were dried (MgSO_4) and concentrated. Removal of the solvent afforded a crude acetate **42ba** (20.5 mg), which was used for the next reaction without further purification.

The acetate **42ba** was treated with 80% AcOH in H_2O (1.3 mL) at room temperature for 12 h. The reaction mixture was diluted with saturated aqueous NaHCO_3 (20 mL) and extracted with Et_2O (3 $\times$ 20 mL). The combined extracts were dried (MgSO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (0.6 g, hexane– EtOAc 1:1 $\rightarrow$ 3:2 $\rightarrow$ 1:2) to give alcohol **43** (7.2 mg, 95% in 2 steps) as a colorless oil: $[\alpha]_D^{24}$ –11.7 (*c* 0.18, CHCl_3); IR (film) 3443, 1738, 1435, 1295, 1231, 1147, 1047 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 5.76 (dd, *J* = 9.7, 6.3 Hz, 1H), 5.69 (m, 1H), 5.31 (brd, *J* = 8.1 Hz, 1H), 5.30 (dd, *J* = 3.6, 3.6 Hz, 1H), 4.15 (ddd, *J* = 6.7, 6.7, 3.9 Hz, 1H), 3.91 (dddd, *J* = 11.7, 11.7, 3.3, 3.3 Hz, 1H), 3.71–3.64 (m, 2H), 3.48 (brddd, *J* = 17.6, 10.1, 7.5 Hz, 1H), 2.77–2.75 (m, 2H), 2.50–2.45 (m, 2H), 2.35–2.29 (m, 2H), 2.09 (dd, *J* = 13.1, 3.3 Hz, 1H), 2.01 (s, 3H), 1.87 (s, 3H), 1.52 (ddd, *J* = 12.5, 12.5, 3.3 Hz, 1H), 1.43 (m, 1H). A signal due to one proton (OH) was not observed; ^{13}C NMR (125 MHz, CD_3OD) δ 172.0, 170.2, 135.4, 133.9, 131.7, 127.8, 82.9, 78.3, 77.6, 69.4, 62.1, 39.5 (2C), 36.3, 29.7, 28.5, 21.7, 19.3; HRMS (ESI) *m/z* 395.1243, calcd for $\text{C}_{18}\text{H}_{25}^{35}\text{ClNaO}_6$ [$\text{M}+\text{Na}$] $^+$ 395.1237.

2,4-dimethoxybenzyl ester 46. To a stirred solution of **44** (52.0 mg, 230 μmol) in CH_2Cl_2 (1.4 mL) were added 2,4-dimethoxybenzyl alcohol (194 mg, 1.15 mmol), DMAP (61.9 mg, 507 μmol), and PyBOP (146 mg, 281 μmol) at 0 $^\circ\text{C}$. The mixture was stirred at room temperature for 13.5 h. The resulting solution was diluted with CHCl_3 (5 mL), and washed with H_2O (5 mL). The organic layer was washed with brine (5 mL), dried (MgSO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (11.1 g, hexane– Et_2O 8:1 $\rightarrow$ 3:1 $\rightarrow$ 1:1) to give 2,4-dimethoxybenzyl ester **46** (46.4 mg, 54%) as a colorless oil: IR (film) 3442, 3001, 1730, 1616, 1510, 1292, 1209, 1159, 1036, 835, 542 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 7.22 (d, *J* = 8.9 Hz, 1H), 6.48–6.44 (m, 2H), 6.13 (brd, *J* = 1.1 Hz, 1H), 5.10 (s, 2H), 3.82 (s, 6H), 3.20 (d, *J* = 1.1 Hz, 2H), 1.90 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (67.8 MHz, CDCl_3) δ 169.8, 161.2, 158.8, 140.4, 131.4, 116.1, 103.8, 98.4, 79.4, 62.3, 55.5, 55.4, 44.2, 24.0; HRMS (ESI) *m/z* 399.0066, calcd for $\text{C}_{14}\text{H}_{17}\text{INaO}_4$ [$\text{M}+\text{Na}$] $^+$ 399.0069.

Aldehyde 13. To a stirred solution of the alcohol **43** (7.2 mg, 19.3 μmol) in CH_2Cl_2 (3.4 mL) was added Dess–Martin periodinane (0.3 M solution in CH_2Cl_2 , 0.24 mL, 72.0 μmol) at 0 °C. The mixture was stirred at 0 °C for 35 min, and the mixture was stirred at room temperature for 1.5 h, diluted with aqueous NaHCO_3 (3 mL) and half saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (6 mL), and extracted with Et_2O (5×10 mL). The combined extracts were washed with brine (30 mL), dried (MgSO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.6 g, hexane– EtOAc 3:1 $\rightarrow$ 2:1 $\rightarrow$ 3:2 $\rightarrow$ 1:1) to give aldehyde **13** (7.1 mg, 99%) as a colorless oil: ^1H NMR (270 MHz, CDCl_3) δ 9.69 (d, J = 1.9 Hz, 1H), 5.69 (dd, J = 11.6, 4.6 Hz, 1H), 5.67 (m, 1H), 5.52 (t, J = 4.1 Hz, 1H), 5.23 (dd, J = 8.0, 1.5 Hz, 1H), 4.39 (dd, J = 4.7, 2.0 Hz, 1H), 4.13 (dddd, J = 11.6, 11.6, 3.5, 3.5 Hz, 1H), 3.53 (m, 1H), 2.75 (dd, J = 11.6, 11.6 Hz, 1H), 2.62 (dd, J = 11.6, 4.5 Hz, 1H), 2.61–2.45 (m, 3H), 2.25–2.17 (m, 2H), 1.56–1.41 (m, 2H).

Haterumalide NA 2,4-dimethoxybenzyl ester (48). DMSO was degassed by freeze-thawing. To a stirred solution of aldehyde **13** (5.6 mg, 15.1 μmol) and 2,4-dimethoxybenzyl ester **46** (34.9 mg, 92.8 μmol) in DMSO (1.3 mL) was added CrCl_2 doped with NiCl_2 (0.5%) (35.1 mg, CrCl_2 : 284 μmol , NiCl_2 : 1.35 μmol) at room temperature in glove box. The mixture was stirred at room temperature for 37 h, diluted with Et_2O (10 mL) and H_2O (10 mL), and extracted with Et_2O (7×5 mL). The combined extracts were dried (MgSO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (0.8 g, hexane– EtOAc 1:1 $\rightarrow$ 1:2) to give haterumalide NA 2,4-dimethoxybenzyl ester (**48**) (4.6 mg, 49%) as a colorless oil: $[\alpha]_D^{24}$ -2.0 (c 0.23, CHCl_3); IR (film) 3446, 2924, 1734, 1439, 1294, 1230, 1159, 1066, 1034, 833, 756 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.23 (d, J = 8.9 Hz, 1H), 6.47–6.45 (m, 2H), 5.77 (dd, J = 11.0, 5.0 Hz, 1H), 5.67 (ddd, J = 11.0, 7.1, 1.4 Hz, 1H), 5.42 (dq, J = 8.3, 1.2 Hz, 1H), 5.31 (dd, J = 3.4, 3.4 Hz, 1H), 5.21 (dd, J = 7.9, 1.4 Hz, 1H), 5.09 (s, 2H), 4.60 (brdd, J = 8.1, 8.1 Hz, 1H), 3.96 (m, 1H), 3.94 (dd, J = 8.0, 3.8 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.55 (ddd, J = 17.9, 10.7, 7.6 Hz, 1H), 3.08 (brs, 2H), 2.82–2.70 (m, 2H), 2.56–2.48 (m, 2H), 2.39 (m, 1H), 2.17 (m, 1H), 2.12 (dd, J = 12.8, 3.8 Hz, 1H), 2.04 (s, 3H), 1.89 (s, 3H), 1.84 (d, J = 1.3 Hz, 3H), 1.46 (ddd, J = 12.4, 12.4, 3.2 Hz, 1H), 1.40 (m, 1H). A signal due to one proton (OH) was not observed; ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 169.5, 168.0, 161.3, 159.0, 134.9, 133.2, 132.0, 131.4, 129.8, 129.1, 125.5, 116.6, 104.0, 98.6, 82.7, 77.4, 75.8, 67.4, 66.5, 61.9, 55.5, 55.4, 45.1, 38.0, 37.8, 34.8, 27.9, 26.7, 21.1, 18.3, 17.3; HRMS (ESI) m/z 643.2283, calcd for $\text{C}_{32}\text{H}_{41}^{35}\text{ClNaO}_{10}$ $[\text{M} + \text{Na}]^+$ 643.2286.

Haterumalide NA (2). To a stirred solution of **48** (4.6 mg, 7.41 μmol) in CH_2Cl_2 (3.0 ml) were added anisole (4.6 mg, 40.6 μmol) and TFA (2.5 μL , 32.5 μmol) at room temperature for 5 h. The solution was concentrated by blowing of nitrogen gas and the residue was purified by column chromatography on silica gel (0.4 g, CHCl_3 –MeOH 50:1→30:1→10:1) and by HPLC (Develosil ODS-HG-5 (250×20 mm), flow rate 5 mL/min; detection, UV 215 nm; solvent 75% MeOH/0.1% TFA) to give haterumalide NA (**2**) (2.3 mg, 66%) as a colorless oil: CD (MeOH) λ_{ext} 220 nm, $\Delta\epsilon$ +0.12; ^1H NMR (500 MHz, CD_3OD) δ 5.79 (dd, J = 11.3, 4.5 Hz, 1H), 5.70 (dd, J = 9.6, 7.7 Hz, 1H), 5.39–5.30 (m, 3H), 4.54 (dd, J = 8.6, 8.6 Hz, 1H), 3.90 (dd, J = 8.7, 3.6 Hz, 1H), 3.93 (m, 1H), 3.48 (m, 1H), 3.05 (brs, 2H), 2.82 (dd, J = 11.5, 4.6 Hz, 1H), 2.77 (dd, J = 11.5, 11.5 Hz, 1H), 2.54–2.38 (m, 2H), 2.32–2.25 (m, 2H), 2.09 (dd, J = 12.7, 3.1 Hz, 1H), 2.02 (s, 3H), 1.88 (brs, 3H), 1.82 (brs, 3H), 1.52 (ddd, J = 12.4, 12.4, 3.0 Hz, 1H), 1.39 (m, 1H). Signals due to two protons (COOH, OH) were not observed; ^{13}C NMR (125 MHz, CD_3OD) δ 175.4, 171.3, 169.5, 135.0, 134.7, 133.2, 130.9, 130.8, 127.0, 84.5, 78.1, 76.6, 68.7, 66.5, 45.7, 38.9, 38.8, 35.5, 29.0, 27.7, 21.0, 18.6, 17.3; HRMS (ESI) m/z 493.1612, calcd for $\text{C}_{23}\text{H}_{31}^{35}\text{ClNaO}_8$ [$\text{M} + \text{Na}$] $^+$ 493.1605.

(S)-MTPA ester of 53. A solution of **53** (0.9 mg, 0.0013 mmol) in pyridine (0.26 mL) was treated with (*R*)-(+)-MTPACl (6.9 mg, 0.027 mmol). The reaction mixture was stirred at room temperature for 45 min and concentrated. The residual oil was purified by column chromatography on silica gel (0.6 g, hexane–EtOAc 8:1→6:1→4:1) to give (*S*)-MTPA ester of **53** (1.1 mg, quant) as a colorless oil.

(R)-MTPA ester of 53. A solution of **53** (1.0 mg, 0.0015 mmol) in pyridine (0.30 mL) was similarly treated with (*S*)-(–)-MTPACl to afford (*R*)-MTPA ester of **53** (1.2 mg, 92%). The $\Delta\delta$ values for these MTPA esters are described below:

$\Delta\delta$ values ($\delta_S - \delta_R$) for the MTPA esters in ppm (600 MHz).

Acetate 58. To a stirred solution of DMPM ether **28** (210 mg, 576 μmol) in CH_2Cl_2 (5 mL) and H_2O (0.25 mL) was added DDQ (183 mg, 806 μmol) at 0 °C. The mixture was stirred at room temperature for 2.5 h, diluted with saturated aqueous NaHCO_3 , and extracted with CHCl_3 . The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, $\text{CHCl}_3\text{-MeOH}$ 40:1; 0.7 g, CHCl_3) to give alcohol **28a** (125 mg, quant) as a colorless oil: $[\alpha]_D^{24} -9.78$ (c 1.86, CHCl_3); IR (film) 3464, 2985, 2935, 2879, 1371, 1255, 1215, 1153, 1066, 991 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.80 (ddd, $J = 17.0, 10.3, 6.8$ Hz, 1H), 5.26 (ddd, $J = 17.3, 1.4, 1.4$ Hz, 1H), 5.11 (ddd, $J = 10.3, 1.4, 0.9$ Hz, 1H), 4.66 (ddd, $J = 10.5, 5.8, 5.8$ Hz, 1H), 4.52 (ddd, $J = 3.5, 3.5, 3.5$ Hz, 1H), 4.27 (ddd, $J = 8.4, 5.9, 4.9$ Hz, 1H), 4.16 (dd, $J = 8.5, 6.1$ Hz, 1H), 3.97 (dd, $J = 8.6, 4.9$ Hz, 1H), 3.86 (dd, $J = 8.5, 3.6$ Hz, 1H), 2.55 (brs, 1H), 2.16 (ddd, $J = 13.2, 5.5, 0.9$ Hz, 1H), 1.83 (ddd, $J = 11.7, 11.7, 5.4$ Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (67.8 MHz, CDCl_3) δ 138.1, 116.1, 109.2, 83.5, 79.6, 74.1, 73.0, 68.1, 41.5, 27.0, 25.3; HRMS (ESI) m/z 237.1102, calcd for $\text{C}_{11}\text{H}_{18}\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 237.1103.

To a stirred solution of alcohol **28a** (122 mg, 569 μmol) in pyridine (3 mL) was added Ac_2O (0.1 mL) at 0 °C. The mixture was stirred at room temperature for 8 h and Ac_2O (0.1 mL) was added at 0 °C. The mixture was stirred for 11 h and Ac_2O (0.2 mL) was added at 0 °C. After 2 h stirring, removal of the solvent afforded crude acetate **58**, which was used for the next reaction without purification: ^1H NMR (270 MHz, CDCl_3) δ 5.82 (ddd, $J = 17.0, 10.3, 6.8$ Hz, 1H), 5.46 (dd, $J = 3.9, 3.9$ Hz, 1H), 5.27 (ddd, $J = 17.0, 1.4, 1.4$ Hz, 1H), 5.14 (ddd, $J = 10.3, 1.4, 1.4$ Hz, 1H), 4.57 (m, 1H), 4.22 (ddd, $J = 7.6, 5.7, 5.7$ Hz, 1H), 4.09 (dd, $J = 8.4, 6.2$ Hz, 1H), 4.03–3.97 (m, 2H), 2.22 (ddd, $J = 14.0, 5.8, 1.2$ Hz, 1H), 2.10 (s, 3H), 1.96 (ddd, $J = 14.0, 9.7, 4.6$ Hz, 1H), 1.39 (s, 3H), 1.33 (s, 3H).

Aldehyde 59. To a stirred solution of acetate **58** (157 mg) in THF (4 mL) was added 70% AcOH (8 mL) at 0 °C. The mixture was stirred at 50 °C for 24 h, diluted with saturated aqueous NaHCO_3 , and extracted with EtOAc . The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (6 g, hexane- EtOAc 3:1→1:1→0:1) to give diol **58a** (112 mg, 91%) as a colorless oil: $[\alpha]_D^{25} +16.6$ (c 0.32, CHCl_3); IR (film) 3332, 2934, 2874, 1731, 1252, 1092, 1047, 945 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.83 (ddd, $J = 17.0, 10.3, 6.5$ Hz, 1H), 5.46 (dd, $J = 3.7, 3.7$ Hz, 1H), 5.27 (ddd, $J = 17.0, 1.4, 1.4$ Hz, 1H), 5.14 (ddd, $J = 10.5, 1.4, 1.4$ Hz, 1H), 4.65 (ddd, $J = 9.7, 6.5, 6.5$ Hz, 1H), 3.93 (dd, $J = 8.8, 2.8$ Hz, 1H), 3.86 (m, 1H), 3.72 (m, 1H), 3.62 (m, 1H), 3.12 (brs, 1H), 2.26 (ddd, $J = 13.9, 6.5, 0.8$ Hz, 1H), 2.16 (s, 3H), 1.97 (ddd, $J = 13.9, 9.7, 4.3$ Hz, 1H). Signals due to two protons (OH) were not observed; ^{13}C NMR (67.8 MHz, CDCl_3) δ 171.8, 137.8, 116.0, 82.1, 79.2,

75.6, 68.9, 64.6, 39.1, 21.2; HRMS (ESI) m/z 239.0895, calcd for $C_{10}H_{16}NaO_5$ $[M + Na]^+$ 239.0907. m/z 217.1076, calcd for $C_{10}H_{17}O_5$ $[M + H]^+$ 217.1079.

To a stirred solution of diol **58a** (65.0 mg, 301 μ mol) in 1,4-dioxane (5 mL) and H_2O (2.5 mL) was added $NaIO_4$ (97.2 mg, 454 μ mol) at 0 °C. The mixture was stirred at room temperature for 1 h and extracted with EtOAc (7 $\times$ 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (1.7 g, Hexane–EtOAc 4:1 $\rightarrow$ 3:1 $\rightarrow$ 2:1) to give aldehyde **59** (47.0 mg, 85%) as a colorless oil: $[\alpha]_D^{23}$ -64.5 (c 0.705, $CHCl_3$); IR (film) 3453, 2988, 2933, 1740, 1645, 1428, 1232, 1061 cm^{-1} ; ^1H NMR (270 MHz, $CDCl_3$) δ 9.64 (d, J = 1.6 Hz, 1H), 5.87 (ddd, J = 17.0, 10.3, 6.6 Hz, 1H), 5.71 (ddd, J = 5.1, 5.1, 1.4 Hz, 1H), 5.37 (ddd, J = 17.3, 1.4, 1.4 Hz, 1H), 5.23 (ddd, J = 10.3, 1.4, 1.4 Hz, 1H), 4.81 (m, 1H), 4.52 (dd, J = 4.9, 1.4 Hz, 1H), 2.28 (ddd, J = 13.8, 5.4, 1.4 Hz, 1H), 2.04 (s, 3H), 1.97 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 199.0, 169.6, 136.5, 117.3, 84.7, 80.7, 75.9, 39.6, 20.9; HRMS (ESI) m/z 207.0642, calcd for $C_9H_{12}NaO_4$ $[M + Na]^+$ 207.0633.

2,4-dimethoxybenzyl ester 61. DMSO was degassed by freeze-thawing. To a stirred solution of aldehyde **59** (4.8 mg, 26.1 μ mol) and iodide **46** (31.1 mg, 82.7 μ mol) in DMSO (2.6 mL) was added $CrCl_2$ doped with 1% $NiCl_2$ (28.9 mg, $CrCl_2$: 233 μ mol, $NiCl_2$: 2.2 μ mol) at room temperature in a glove box. The mixture was stirred at room temperature for 13.5 h, diluted with Et_2O (3 mL) and H_2O (1 mL), and extracted with Et_2O (7 $\times$ 4 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residual oil was purified by column chromatography on silica gel (3.7 g, hexane–EtOAc 10:1 $\rightarrow$ 8:1 $\rightarrow$ 6:1 $\rightarrow$ 4:1 $\rightarrow$ 2:1 $\rightarrow$ 1:1 $\rightarrow$ 1:2) to give 2,4-dimethoxybenzyl ester **61** (4.2 mg, 37%) as a colorless oil: IR (film) 3456, 2936, 1732, 1615, 1210, 1159, 1036, 947, 835 cm^{-1} ; ^1H NMR (270 MHz, $CDCl_3$) δ 7.23 (m, 1H), 6.46–6.44 (m, 2H), 5.83 (ddd, J = 17.0, 10.4, 6.7 Hz, 1H), 5.47 (m, 1H), 5.27 (m, 1H), 5.18–5.07 (m, 2H), 5.09 (s, 2H), 4.63 (m, 1H), 4.47 (m, 1H), 3.93 (dd, J = 7.2, 3.4 Hz, 1H), 3.81 (s, 6H), 3.07 (brs, 2H), 2.21 (dd, J = 14.0, 5.9 Hz, 1H), 2.12 (s, 3H), 1.96 (ddd, J = 14.0, 9.5, 4.6 Hz, 1H), 1.81 (brs, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.2, 170.7, 161.1, 158.8, 138.0, 134.4, 131.3, 128.3, 116.5, 116.0, 103.9, 98.5, 83.4, 79.0, 74.9, 66.3, 61.9, 55.5, 55.4, 45.1, 39.4, 21.3, 17.2; HRMS (ESI) m/z 457.1846, calcd for $C_{23}H_{30}NaO_8$ $[M + Na]^+$ 457.1838.

Artificial analog of haterumalide NA 55. To a stirred solution of 2,4-dimethoxybenzyl ester **61** (6.3 mg, 14.5 μmol) was added the stock solution (0.67 mL) prepared from anisole (90 μL , 827 μmol) and TFA (48 μL , 624 μmol) in CH_2Cl_2 (6.5 mL). The mixture was stirred at room temperature for 13 h and concentrated. The residue was purified by column chromatography on silica gel (0.6 g, CHCl_3 –MeOH 1:0 $\rightarrow$ 100:1 $\rightarrow$ 80:1 $\rightarrow$ 60:1 $\rightarrow$ 40:1 $\rightarrow$ 20:1 $\rightarrow$ 10:1) to give artificial analog **55** of haterumalide NA (1.1 mg, 27%) as a colorless oil: $[\alpha]_D^{26}$ -4.21 (c 0.095, CHCl_3); IR (film) 3418, 2925, 2855, 1732, 1250, 1034, 947 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.83 (ddd, $J = 17.0$ 10.3, 6.8 Hz, 1H), 5.65–5.30 (m, 2H), 5.26 (ddd, $J = 17.0$, 1.1, 1.1 Hz, 1H), 5.14 (ddd, $J = 10.3$, 1.1, 1.1 Hz, 1H), 4.65 (m, 1H), 4.46 (dd, $J = 7.8$, 7.8 Hz, 1H), 3.94 (dd, $J = 7.8$, 3.4 Hz, 1H), 3.10 (brs, 2H), 2.25 (ddd, $J = 14.0$, 5.9, 1.1 Hz, 1H), 2.14 (s, 3H), 2.00 (ddd, $J = 14.0$, 9.5, 4.6 Hz, 1H), 1.84 (brs, 3H). Signals due to two protons (COOH, OH) were not observed; ^{13}C NMR (125 MHz, CDCl_3) δ 176.3, 171.1, 137.8, 129.1, 116.3, 100.9, 83.6, 79.2, 75.0, 66.2, 44.7, 39.4, 21.3, 17.4; HRMS (ESI) m/z 307.1168, calcd for $\text{C}_{14}\text{H}_{20}\text{NaO}_6$ $[\text{M} + \text{Na}]^+$ 307.1158.

Artificial analog of haterumalide NA methyl ester 56. DMSO was degassed by freeze-thawing. To a stirred solution of aldehyde **59** (4.3 mg, 23.3 μmol) and iodide **60** (20.8 mg, 86.7 μmol) in DMSO (2.3 mL) was added CrCl_2 doped with 1% NiCl_2 (25.1 mg, CrCl_2 : 202 μmol , NiCl_2 : 1.9 μmol) at room temperature in a glove box. The mixture was stirred at room temperature for 13.5 h, diluted with Et_2O (3 mL) and H_2O (1 mL), and extracted with Et_2O (7 $\times$ 5 mL). The combined extracts were dried (MgSO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (1.5 g, hexane– EtOAc 10:1 $\rightarrow$ 8:1 $\rightarrow$ 6:1 $\rightarrow$ 4:1 $\rightarrow$ 2:1 $\rightarrow$ 1:1 $\rightarrow$ 1:2) to give artificial analog **56** of haterumalide NA methyl ester (1.7 mg, 24%) as a colorless oil: IR (film) 3462, 2987, 1739, 1436, 1250, 1161, 1036, 947 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.84 (ddd, $J = 17.0$, 10.4, 6.6 Hz, 1H), 5.47 (m, 1H), 5.28 (m, 1H), 5.16 (m, 1H), 4.64 (m, 1H), 4.46 (dd, $J = 7.6$, 7.6 Hz, 1H), 3.94 (dd, $J = 7.6$, 3.4 Hz, 1H), 3.68 (s, 3H), 3.06 (brs, 2H), 2.35 (brs, 1H), 2.23 (dd, $J = 14.0$, 6.1 Hz, 1H), 2.14 (s, 3H), 1.98 (ddd, $J = 14.0$, 9.5, 4.6 Hz, 1H), 1.82 (brs, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, CDCl_3) δ 171.6, 170.8, 138.0, 134.1, 128.4, 116.0, 83.5, 79.0, 75.0, 66.3, 51.9, 44.8, 39.4, 21.3, 17.3; HRMS (ESI) m/z 321.1290, calcd for $\text{C}_{15}\text{H}_{22}\text{NaO}_6$ $[\text{M} + \text{Na}]^+$ 321.1314.

MPM ether 62. DMSO was degassed by freeze-thawing. To a stirred solution of aldehyde **59** (5.5 mg, 29.9 μmol) and iodide ($\pm$)-**15** (90.6 mg, 211 μmol) in DMSO (3.0 mL) was added CrCl_2 doped with 1% NiCl_2 (83.6 mg, CrCl_2 : 673 μmol , NiCl_2 : 6.5 μmol) at room temperature in a glove box. The mixture was stirred at room temperature for 14 h, diluted with Et_2O (3 mL) and H_2O (1 mL), and extracted with Et_2O (5 $\times$ 5 mL). The combined extracts were washed with brine, dried (MgSO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2.0 g, hexane– EtOAc 10:1 $\rightarrow$ 8:1 $\rightarrow$ 6:1 $\rightarrow$ 4:1) to give MPM ether **62** (6.8 mg, 47%) as a colorless oil: IR (film) 3464, 2979, 2930, 1739, 1613, 1514, 1247, 1035, 822 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.83 (ddd, J = 17.0, 10.3, 6.8 Hz, 1H), 5.50–5.45 (m, 2H), 5.26 (m, 1H), 5.20 (brs, 2H), 5.13 (ddd, J = 10.3, 1.1, 1.1 Hz, 1H), 4.65 (m, 1H), 4.66 (s, 2H), 4.46 (m, 1H), 4.46 (d, J = 11.1 Hz, 1H), 4.27 (d, J = 11.3 Hz, 1H), 4.02 (q, J = 6.8 Hz, 1H), 3.91 (ddd, J = 6.9, 6.9, 3.2 Hz, 1H), 3.80 (s, 3H), 3.10 (brs, 2H), 2.23 (ddd, J = 14.0, 6.5, 0.8 Hz, 1H), 2.13 (s, 3H), 2.04 (m, 1H), 1.83 (d, J = 1.4 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, CDCl_3) δ 170.8, 170.7, 159.0, 144.4, 138.0, 134.0, 130.3, 129.2 (2C), 128.7, 116.0, 114.0, 113.7 (2C), 83.5, 79.0, 76.0, 74.9, 69.8, 66.2, 63.5, 55.3, 45.1, 39.4, 21.3, 20.6, 17.4; HRMS (ESI) m/z 511.2301, calcd for $\text{C}_{27}\text{H}_{36}\text{NaO}_8$ $[\text{M} + \text{Na}]^+$ 511.2308.

Allylic alcohol 63. To a stirred solution of MPM ether **62** (23.3 mg, 47.7 μmol) in CH_2Cl_2 (12.5 mL), $t\text{-BuOH}$ (0.75 mL), and pH 6.6 phosphate buffer (0.75 mL) was added DDQ (15.5 mg, 68.3 μmol) at 0 $^\circ\text{C}$. The mixture was stirred at 0 $^\circ\text{C}$ for 2.5 h, and pH 6.6 phosphate buffer (0.75 mL) and DDQ (15.7 mg, 69.2 μmol) were added at 0 $^\circ\text{C}$. The mixture was stirred at 0 $^\circ\text{C}$ for 26.5 h, diluted with saturated aqueous NaHCO_3 (3 mL), and extracted with EtOAc (3 $\times$ 8 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (1.1 g, hexane– EtOAc 3:1 $\rightarrow$ 2:1 $\rightarrow$ 3:2 $\rightarrow$ 1:1 $\rightarrow$ 1:2) to give diol **63** (15.4 mg, 88%) as a yellow oil: IR (film) 3419, 2979, 2926, 1738, 1375, 1251, 1156, 1037 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.58 (ddd, J = 17.0, 10.3, 6.5 Hz, 1H), 5.50–5.45 (m, 2H), 5.26 (m, 1H), 5.22 (s, 1H), 5.13 (m, 1H), 5.13 (s, 1H), 4.73 (d, J = 12.7 Hz, 1H), 4.64 (m, 1H), 4.61 (d, J = 12.7 Hz, 1H), 4.44 (dd, J = 7.8, 7.8 Hz, 1H), 4.35 (q, J = 6.8 Hz, 1H), 3.92 (dd, J = 7.8, 3.2 Hz, 1H), 3.08 (s, 2H), 2.23 (ddd, J = 14.0, 6.5, 1.4 Hz, 1H), 2.14 (s, 3H), 1.98 (ddd, J = 14.0, 9.5, 4.6 Hz, 1H), 1.82 (d, J = 1.1 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H). Signals due to two protons (OH) were not observed; ^{13}C NMR (67.8 MHz, CDCl_3) δ 170.9, 170.7, 147.0 (0.5C), 146.9 (0.5C), 138.0, 134.1 (0.5C), 134.1 (0.5C), 128.8 (0.5C), 128.6 (0.5C), 116.1 (0.5C), 116.0 (0.5C), 113.7 (0.5C), 113.6 (0.5C), 83.5, 79.1, 74.9, 68.7, 66.1, 64.7 (0.5C), 64.7 (0.5C), 45.2, 39.4, 22.0, 21.3, 17.5; HRMS (ESI) m/z 391.1724, calcd for $\text{C}_{19}\text{H}_{28}\text{NaO}_7$ $[\text{M} + \text{Na}]^+$ 391.1733.

Artificial analog of haterumalide B 57. To a stirred solution of diol **63** (2.4 mg, 6.5 μmol) in CH_2Cl_2 (0.65 mL) was added MnO_2 (28.3 mg, 325 μmol) at 0 $^\circ\text{C}$. The mixture was stirred at room temperature for 21 h, filtrated through a pad of Celite, and concentrated. The residual oil was purified by column chromatography on silica gel (0.6 g, hexane–EtOAc 1:1) to give artificial analog **57** of haterumalide B (1.3 mg, 54%) as a colorless oil: IR (film) 3472, 2986, 2927, 1731, 1681, 1157, 1125, 1037 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.17 (s, 1H), 6.02 (t, $J = 1.4$ Hz, 1H), 5.83 (ddd, $J = 17.0, 10.3, 6.8$ Hz, 1H), 5.48 (m, 1H), 5.49 (brs, 1H), 5.25 (ddd, $J = 17.0, 1.4, 1.4$ Hz, 1H), 5.13 (ddd, $J = 10.3, 1.4, 1.4$ Hz, 1H), 4.81 (brs, 2H), 4.64 (dd, $J = 14.0, 6.8$ Hz, 1H), 4.45 (t, $J = 7.6$ Hz, 1H), 3.93 (dd, $J = 7.6, 3.2$ Hz, 1H), 3.10 (brs, 2H), 2.36 (s, 3H), 2.23 (ddd, $J = 13.8, 6.2, 1.1$ Hz, 1H), 2.14 (s, 3H), 1.98 (ddd, $J = 14.0, 9.5, 4.6$ Hz, 1H), 1.83 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, CDCl_3) δ 197.8, 170.9, 170.5, 143.0, 138.1, 133.9, 128.8, 126.8, 116.0, 83.5, 79.1, 75.0, 66.2, 62.2, 45.0, 39.4, 25.9, 21.3, 17.4; HRMS (ESI) m/z 389.1603, calcd for $\text{C}_{19}\text{H}_{26}\text{NaO}_7$ $[\text{M} + \text{Na}]^+$ 389.1576.

Cytotoxicity assay

Stock cultures of HeLa S₃ cells were maintained in Eagle's Minimum Essential Medium containing Earle's Balanced Salts and 10% fetal bovine serum (DS Pharma Biomedical Co., Ltd.) and 1% kanamycin at 37 $^\circ\text{C}$ under 5% CO_2 .

For the purpose of the experiment, 2×10^3 cells suspended in 100 μL of medium per well were plated in 96-well plate. After 18 h incubation at 37 $^\circ\text{C}$ under 5% CO_2 to allow cell attachment, compounds in 100 μL of medium were added to the well at defferent concentrations and incubated for 96 h under the same conditions. After 3 h of the MTT (1.44 mg/mL, 30 μL) addition to each well, the medium/MTT mixtures were removed, and the formazan crystals formed were dissolved in 150 μL of DMSO per well. After 30 min, optical absorbance at 540 nm were measured with a microplate reader. The cytotoxic effects of each compound were obtained as IC_{50} values.

YI-6-DMPMether(070111)

YI-6-DMPMether-13C(070111)

YI-Wittig(070109)

YI-Wittig-13C(070109)

YI-1-151-2(041124)

YI-0-alkohol-13C(060510)

C:\WINNIR96\K190511\DISC1\011-0-SELENIUM (070111).010
 YI-6-selenide(070111)

YI-6-selenide-13C(070111)

terminalorefine(061229)

28

terminalorefine-13(061229)

YI-6-Suzuki(070109)

YI-6-Suzuki-13C(070109)

40

MU-VI-41-1

D:\M-ueda\MU-VI-41-1-13C.als
MU-VI-41-1

MU-VI-76-2

Synthetic

Natural

MU-VIII-66-2

MU-VIII-66-2-130