Supporting Information

Enantioselective Synthesis of 15-*epi*-Haterumalide NA Methyl Ester and Revised
Structure of Haterumalide NA Methyl Ester

Organic Letters

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Spectral data and experimental sections of key compounds

(+)-*trans*-2,5-Dialkyl-tetrahydrofuran 8 : $[\alpha]_D^{26} +11.1$ (*c* 0.43, CHCl₃); IR (CHCl₃) 1610, 1515, 1460, 1440, 1360, 1250, 1170, 1080, 935, 835 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 7.26 (br d, *J* = 8.6 Hz, 2 H), 6.87 (br d, *J* = 8.6 Hz, 2 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 4.39–4.27 (m, 2 H), 4.03 (ddd, *J* = 6.6, 5.0, 3.6 Hz, 1 H), 3.80 (s, 3 H), 3.59 (dd, *J* = 9.9, 5.0 Hz, 1 H), 3.59 (m, 1 H), 3.47–3.55 (m, 2 H), 2.19–1.79 (m, 3 H), 1.67 (ddd, *J* = 12.5, 9.9, 4.6 Hz, 1 H), 0.88 (s, 9 H), 0.15 (s, 3 H), 0.05 (s, 3 H); ¹³C NMR (67.8 MHz, CDCl₃) δ 159.1, 129.6 (2 C), 113.7 (2 C), 81.6, 77.2, 75.9, 73.1, 73.0, 68.9, 55.3, 41.8, 39.3, 30.0, 25.7 (3 C), 18.0, –4.7, –5.2; HRMS (FAB) *m/z* calcd for C₂₁H₃₅BrNaO₄Si (M+Na)⁺ 481.1386, found 481.1361.

(Z)-Bromovinyl silane 7 : IR (CHCl₃) 1615, 1455, 1440, 1350, 1250, 1135, 1120, 1075, 1030, 980, 890, 840 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 6.33 (t, *J* = 6.6 Hz, 1 H), 4.63 (t, *J* = 4.0 Hz, 1 H), 3.81 (m, 1 H), 3.81 (dt, *J* = 9.6, 6.9 Hz, 1 H), 3.72 (m, 1 H), 3.51 (dt, *J* = 9.6, 6.9 Hz, 1 H), 2.58 (dt, *J* = 6.9, 6.6 Hz, 2 H), 1.90–1.46 (m, 6 H), 0.18 (s, 9 H); ¹³C NMR (67.8 MHz, CDCl₃) δ 149.6, 138.5, 98.6, 65.3, 62.1, 33.1, 30.6, 25.5, 19.4, –1.9 (3 C); HRMS (ESI) *m/z* calcd for C₁₂H₂₃BrNaO₂Si (M+Na)⁺ 329.0548, found 329.0527.

(+)-(E)-Vinyl silane 6 : $[\alpha]_D^{26} +17.2$ (*c* 0.23, CHCl₃); IR (CHCl₃) 1610, 1585, 1515, 1465, 1440, 1340, 1250, 1170, 1120, 1030, 835 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 7.26 (br d, *J* = 8.9 Hz, 2 H), 6.86 (br d, *J* = 8.9 Hz, 2 H), 5.74 (t, *J* = 6.6 Hz, 1 H), 4.61 (t, *J* = 4.0 Hz, 1 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 4.36 (m, 1 H), 4.17 (m, 1 H), 4.04 (m, 1 H), 3.80 (s, 3 H), 3.90–3.69 (m, 2 H), 3.65–3.37 (m, 4 H), 2.42 (dt, *J* = 7.3, 6.8 Hz, 2 H), 2.29–2.03 (m, 2 H), 1.95 (m, 1 H), 1.82 (m, 1 H), 1.71–1.47 (m, 7 H), 1.43 (m, 1 H), 0.88 (s, 9 H), 0.15 (s, 3 H), 0.05 (s, 12 H); ¹³C NMR (67.8 MHz, CDCl₃) δ 159.1, 142.6, 136.1, 130.5, 129.5 (2 C), 113.7 (2 C), 98.6, 81.4, 73.2, 73.1, 69.0, 66.9, 62.1, 55.2, 42.0, 36.4, 30.7, 30.0, 29.0, 26.0, 25.8 (3 C), 25.5, 19.5, 18.0, –1.2 (3 C), –4.7, –5.2; HRMS (FAB) *m/z* calcd for C₃₃H₅₈NaO₆Si₂ (M+Na)⁺ 629.3670, found 629.3667.

(+)-(Z)-Chloroolefin 19 : To a stirred solution of (*E*)-vinylsilane **6** (970 mg, 1.60 mmol) in DMF (40 mL) were added water (5 μ L) and *N*-chlorosuccinimide (427 mg, 3.20 mmol) under a nitrogen atmosphere. After stirring at 50°C for 6 h, the resulting solution was quenched with saturated aqueous Na₂S₂O₃ (120 mL) and extracted with Et₂O (3 $\times$ 70 mL). The combined extracts were washed with water (50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (60 g, *n*-hexane–Et₂O, 11:1→5:1) to give **19** (407 mg, 45%) and recovered **6** (222 mg, 23%) as colorless oils, respectively; **19**: $[\alpha]_D^{26} +15.1$ (*c* 0.54, CHCl₃); IR (CHCl₃) 1610, 1515, 1460, 1360, 1250, 1170, 1140, 1120, 1030, 835 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 7.26 (br d, *J* = 8.6 Hz, 2 H), 6.87 (br d, *J* = 8.6 Hz, 2 H), 5.57 (t, *J* = 6.1 Hz, 1 H), 4.60 (m, 1 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 4.36 (m, 1 H), 4.20 (m, 1 H), 4.05 (m, 1 H), 3.80 (s, 3 H), 3.85 (m, 1 H), 3.75 (m, 1 H), 3.65–3.38 (m, 4 H), 2.29–2.01 (m, 4 H), 1.93 (ddd, *J* = 12.7, 5.7, 1.7 Hz, 1 H), 1.91–1.63 (m, 9 H), 1.05 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ¹³C NMR (67.8 MHz, CDCl₃) δ 159.1, 135.9, 130.4, 129.5 (2 C), 122.0, 113.7 (2 C), 98.7, 81.4, 77.2, 73.1, 73.1, 69.0, 65.9, 62.3, 55.3, 42.0, 36.3, 33.9, 30.7, 29.7, 25.7 (3 C), 25.4, 19.5, 18.0, –4.7, –5.2; HRMS (FAB) *m/z* calcd for C₃₀H₄₉³⁵ClNaO₆Si (M+Na)⁺ 591.2885, found 591.2864.

(+)- β -Acetoxylactone **35** : To a stirred solution of $\text{RhCl}(\text{PPh}_3)_3$ (5.4 mg, 5 mol%) in THF (4 mL) at 0 °C was added a 1.0 M hexane solution of Et_2Zn (2.4 mL) under an argon flow. After bromoester **4** (57.1 mg, 0.108 mmol) in THF (18 mL) was added dropwise for 4 h at 0 °C, Ac_2O (0.50 mL, 5.3 mmol) was added. After stirring for 1 h at 0 °C, saturated aqueous NaHCO_3 (30 mL) was added. The reaction mixture was filtered on celite, and the filtrate was partitioned between Et_2O and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (1 g, *n*-hexane– EtOAc , 11:1→9:1→7:1→5:1→3:1) and HPTLC (SiO_2 , $100 \times 200 \times 0.25$ mm, 3 plates, *n*-hexane– Et_2O , 1:3) to afford (3*S*,4*Z*)-**35** 4.5 mg (9%) and a mixture of (3*R*,4*Z*)- and (4*E*)-**35** 17.4 mg (36%) as colorless oils, respectively; **35**: $[\alpha]_D^{33} +43.7$ (*c* 0.016, CHCl_3); IR (CHCl_3) 1735(br), 1610(br) ; ^1H NMR (400 MHz, CD_3OD) δ 7.24 (br d, *J* = 8.8 Hz, 2 H), 6.87 (br d, *J* = 8.8 Hz, 2 H), 5.70 (dd, *J* = 11.5, 4.4 Hz, 1 H), 5.69 (m, 1 H), 5.30 (br d, *J* = 6.8 Hz, 1 H), 5.24 (br dd, *J* = 3.4, 3.4 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.38 (d, *J* = 11.7 Hz, 1 H), 4.25 (dt, *J* = 6.3, 3.9 Hz, 1 H), 3.95 (m, 1 H), 3.77 (s, 3 H), 3.59 (dd, *J* = 6.3, 2.0 Hz, 2 H), 3.47 (m, 1 H), 2.68 (dd, *J* = 11.7, 11.5 Hz, 1 H), 2.53 (dd, *J* = 11.7, 4.4 Hz, 1 H), 2.45 (m, 2 H), 2.30 (m, 2 H), 2.12 (m, 1 H), 2.01 (s, 3 H), 1.85 (br s, 3 H), 1.52 (m, 1 H), 1.42 (m, 1 H); HRMS (ESI) *m/z* calcd for $\text{C}_{26}\text{H}_{33}^{35}\text{ClNaO}_7$ ($\text{M}+\text{Na}$)⁺ 515.1812, found 515.1817.

Pure (3*R*,4*Z*)-isomer was obtained as (3*R*,4*Z*)-**3** after the removal of the MPM group and subsequent HPLC separation.

HPLC chart of **35**

Haterumalide NA methyl ester (36) : To a stirred solution of alcohol **34** (0.80 mg, 2.1 μmol) in CH_2Cl_2 (1 mL) was added at 0 °C the Dess-Martin periodinane (5.2 mg, 12.3 μmol) under nitrogen atmosphere. After stirring at room temperature for 3.5 h, saturated aqueous Na_2SO_3 (5 mL) and

saturated aqueous NaHCO_3 (5 mL) were added. After stirring at room temperature for 1 h, the resulting mixture was extracted with Et_2O (3×10 mL), and the combined extracts were washed with water (10 mL), and brine (10 mL), dried (Na_2SO_4) and concentrated to give aldehyde **4** (1 mg) as a colorless oil, which was used in the next experiment without purification. To a stirred solution of **4** (1 mg) and iodide **2** (41.0 mg, 0.170 mmol) in DMSO (0.5 mL) was added at room temperature CrCl_2 containing 1% NiCl_2 (58 mg) under an argon flow. After stirring for 20 h, the reaction mixture was diluted with Et_2O (5 mL), poured into water (5 mL), and extracted with Et_2O (3×5 mL). The combined extracts were washed with saturated aqueous NaHCO_3 (5 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (1 g, *n*-hexane– Et_2O , 5:1, then EtOAc), HPTLC (SiO_2 , $100 \times 200 \times 0.25$ mm, *n*-hexane– EtOAc , 1:2) to give a mixture of **36** and its 15*R* isomer (0.59 mg, 57%, *S*:*R* = 11:1). The diastereomer mixture was purified by HPLC (Develosil ODS HG-5, ϕ 4.6 $\times$ 250 mm, 60% aqueous MeOH, 1 mL/min, UV 215 nm) to give haterumalide NA methyl ester (**36**) (*ca.* 0.2 mg) as a colorless oil: CD (MeOH) λ_{ext} 220.0 nm ($\Delta\epsilon$ -0.72); ^1H NMR (800 MHz, CD_3OD) δ 5.79 (dd, J = 11.4, 4.6 Hz, 1 H), 5.70 (br dd, J = 9.2, 7.4 Hz, 1 H), 5.37 (br d, J = 8.7 Hz, 1 H), 5.31 (br d, J = 7.3 Hz, 1 H), 5.30 (br t, J = 3.4 Hz, 1 H), 4.53 (br t, J = 8.5 Hz, 1 H), 3.93 (br tt, J = 11.4, 3.6 Hz, 1 H), 3.90 (dd, J = 8.7, 3.7 Hz, 1 H), 3.67 (s, 3 H), 3.49 (m, 1 H), 3.08 (s, 2 H), 2.82 (dd, J = 11.5, 4.6 Hz, 1 H), 2.77 (dd, J = 11.5, 11.4 Hz, 1 H), 2.47 (m, 2 H), 2.29 (m, 2 H), 2.10 (br dd, J = 12.8, 3.2 Hz, 1 H), 2.02 (s, 3 H), 1.88 (br s, 3 H), 1.81 (d, J = 1.4 Hz, 3 H), 1.52 (br dt, J = 12.8, 3.2 Hz, 1 H), 1.39 (m, 1 H); HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{33}^{35}\text{ClNaO}_8$ ($\text{M}+\text{Na}$) $^+$ 507.1762, found 507.1753.

HPLC chart of **36**

¹H NMR spectrum of haterumalide NA methyl ester (**36**) (800 MHz, CD₃OD)

CD spectra of natural and synthetic haterumalide NA methyl ester (**1** and **36**)