Electronic Supplementary Material (ESI) for Chemical Communications

Total Synthesis and Stereochemical Revision of Lagunamide A

Lu Dai,[a] Bo Chen,[a] Zhuo Wang,[b] Yuqing Liu,[b] ZhengshuangXu,*[a,b] Tao Ye*[a,b]

[a]*Key Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School, University Town of Shenzhen, Xili, Nanshan District, Shenzhen, China, 518055; E-mail: bctaoye@inet.polyu.edu.hk; xuzs@pkusz.edu.cn*
[b] *Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China Tel: +852 34008722; E-mail: bctaoye@inet.polyu.edu.hk*

Supporting Information

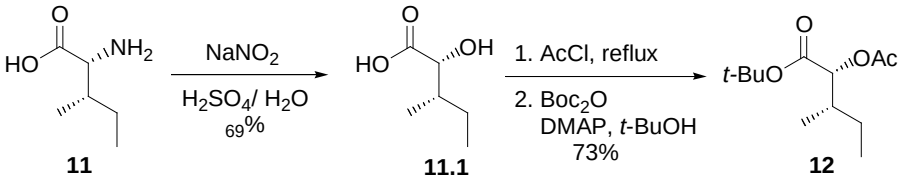
General Experimental

Unless otherwise stated, commercially available reagents were used without further purification. All solvents were distilled prior to use: Toluene, tetrahydrofuran (THF), diethyl ether and benzene were distilled from Na/benzophenone, dichloromethane, DMF, triethylamine (TEA), acetonitrile, collidine and diisopropylethylamine (DIPEA) were distilled from CaH_2. Methanol was distilled under N_2 atmosphere from Mg/I_2. All reactions were conducted in oven-dried (120 ºC) or flame-dried glasswares under N_2 atmosphere, and at ambient temperature (20 to 25 ºC) unless otherwise stated. All non-aqueous reactions were performed by standard syringe in septa techniques. Evaporation and concentration under reduced pressure was performed at 50-500 mbar. ^{1}H NMR (^{13}C NMR) spectra were recorded in $CDCl_3$ (unless stated otherwise) on Bruker Avance AV500, or Bruker Avance AV400, or DPX-300 at 500 MHz (125 MHz) or 400MHz (100 MHz) or 300 MHz (75 MHz), respectively. Chemical shifts are reported as δ values (ppm) referenced to either a tetramethylsilane (TMS) internal standard or the signals due to the solvent residual. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br = broad, d = doublet, t =triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. Some peptide intermediates exist as rotational conformers, the chemical shift for the minor isomers were indicated using parentheses next to the peak for their major isomers. Mass spectra were measured on ABI Q-star Elite. Optical rotations were measured on a Perkin-Elmer 351 polarimeter at 589nm with a 100 mm path length cell at 20 ºC (reported as follows: concentration (*c* in g/100mL, solvent). The reaction progress was checked on pre-coated thin layer chromatography (TLC) plates. TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2 mm) which, after development, were visualized under UV light at 254nm. Flash column chromatography was performed using the indicated solvents on E. Qingdao silica gel 60 (230-400 mesh ASTM). Yields refer to chromatographically purified compounds, unless otherwise stated.

Experimental procedures:

Acid **8** (104.0 mg, 0.30 mmol) and amine **9** (22.0 mg, 0.10 mmol) were dissolved in CH_2Cl_2 (2 mL) at 0 °C. DIPEA (88 μL, 0.50 mmol), HATU (133.0 mg, 0.35 mmol) and HOAt (48.0 mg, 0.35 mmol) were added. The reaction mixture was stirred at room temperature overnight and quenched by adding ice water (4 mL). The aqueous layer was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (10 mL), NH_4Cl (10 mL) and brine (10 mL) successively, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 1) to afford **3** (46.0 mg, 84%) as colorless oil. $[\alpha]_D^{20}$ = + 42.3 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.16 (m, 5H), 6.75-6.56 (m, 1H), 5.82-5.51 (m, 1H), 5.34-5.21 (m, 1H), 4.72-4.58 (m, 1H), 4.51-4.37 (m, 1H), 4.15-3.89 (m, 2H), 3.71 (s, 3H), 3.21-3.10 (m, 1H), 3.10-3.01 (m, 1H), 3.05 (s, 3H), 3.00 (s, 3H), 1.99-1.88 (m, 1H), 1.47-1.32 (m, 9H), 1.32-1.05 (m, 2H), 1.02-0.68 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 172.5, 171.1, 168.3, 155.2, 136.3, 129.2, 128.3, 126.8, 79.5, 55.2, 53.8, 52.6, 52.2, 46.6, 37.5, 36.5, 35.2, 30.3, 28.2, 26.2, 17.7, 14.6, 11.6 ppm; HRMS (ESI) *m/z* calculated for $C_{28}H_{44}N_4NaO_7^+$ $[M+Na]^+$: 571.3102, found: 571.3090.

Compound **3** (137.0 mg, 0.25 mmol) was dissolved in THF-MeOH-H_2O (5 mL, 2 / 2 / 1) at 0 °C. $LiOH \cdot H_2O$ (32.0 mg, 0.75 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. Volatiles were evaporated *in vacuo*. The aqueous layer was washed with diethyl ether (5 mL), then acidified to pH 3 with 1 N HCl and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give acid **10** (129.7 mg, 97%).



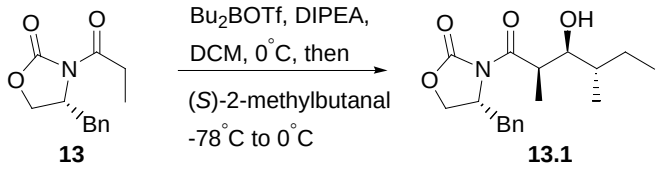
11 **11.1** **12**

D-allo-Isoleucine **11** (26.24 g, 200 mmol) was dissolved in dilute sulfuric acid (500 mL, 400 mmol, 0.8 N) at 0°C. Sodium nitrite (41.40 g, 600 mmol) was added slowly. The mixture was allowed to stir at 0°C for 6 h. The solution was transferred into a separating funnel and extracted with diethyl ether (300 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and recrystallized from hexane-ether to give hydroxyl acid **11.1** (18.33 g, 69%) as a white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.28 (d, J = 2.5 Hz, 1H), 1.98-1.81 (m, 1H), 1.64-1.51 (m, 1H), 1.45-1.31 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.0, 72.9, 38.4, 25.9, 13.1, 11.7 ppm.

The hydroxyl acid **11.1** (2.00 g, 15.13 mmol) was dissolved in acetyl chloride (10 mL) at 0°C. The reaction mixture was then refluxed at 60 °C for 8 h. Excess acetyl chloride was removed under vacuum. Diethyl ether (300 mL) was added, and the solution was washed with water (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue (without further purification) was dissolved in *tert*-butyl alcohol (80 mL). Boc_2O (5.2 mL, 22.70 mmol) and DMAP (486.0 mg, 4.00 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and the solvent was then removed under vacuum. Diethyl ether (300 mL) was added and the solution was washed with water (200 mL) and brine (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 10) to afford **12** (2.98 g, 73%) as a colorless oil. $[\alpha]_D^{20}$ = + 23.1 (*c* 8.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.86 (d, J = 3.2 Hz, 1H), 2.10 (s, 3H), 1.99-1.86 (m, 1H), 1.44 (s, 9H), 1.45-1.36 (m, 1H), 1.29-1.18 (m, 1H), 0.93-0.87 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 169.0, 81.8, 75.0, 36.4, 27.9, 25.8, 20.6, 14.1, 11.6 ppm; HRMS (ESI) *m/z* calculated for $C_{12}H_{22}NaO_4^+$ $[M+Na]^+$: 253.1410, found: 253.1410.

Compound **12** (9.20 g, 40 mmol) was added to a solution of K_2CO_3 (16.56 g, 120 mmol) in MeOH–H_2O (110 mL, 1 / 10). The reaction solution was stirred vigorously at room temperature for 12 h. Methanol was removed under vacuum, and the aqueous residue was extracted with diethyl ether (150 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 10) to afford the corresponding alcohol **12.1** (6.40 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ = – 3.1(*c* 0.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.05 (d, *J* = 2.7 Hz, 1H), 1.83-1.68 (m, 1H), 1.51 (s, 9H), 1.60-1.48 (m, 1H), 1.39-1.23 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 82.3, 73.0, 38.5, 28.0, 26.0, 12.9, 11.9 ppm; HRMS (ESI) *m/z* calculated for $C_{10}H_{20}NaO_3^+$ $[M+Na]^+$: 211.1305, found: 211.1306.

2-(Diethoxyphosphoryl)-propanoic acid (0.34 g, 1.60 mmol), DIPC (0.25 mL, 1.60 mmol) and collidine (1.1 mL, 1.06 mmol) were added to a solution of alcohol **12.1** (0.20 g, 1.06 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature overnight and quenched by brine (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 1) to afford **5** (0.39 g, 98%) as colorless oil. $[\alpha]_D^{20}$ = + 27.4 (*c* 2.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.86 (dd, *J* = 14.5, 3.4 Hz, 1H), 4.12-4.08 (m, 4H), 3.11-2.98 (m, 1H), 1.95-1.88 (m, 1H), 1.49-1.33 (m, 13H), 1.31-1.25 (m, 7H), 0.93-0.82 (m, 6H) ppm;^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 169.4, 168.9, 168.8, 168.5, 168.3, 81.8, 75.7, 62.6, 62.5, 62.5, 62.4, 62.4, 40.2, 39.3, 39.2, 38.3, 36.6, 36.5, 27.9, 27.9, 27.8, 25.7, 25.7, 16.3, 16.2, 14.1, 11.7, 11.6 ppm; HRMS (ESI) *m/z* calculated for $C_{17}H_{33}NaO_7P^+$ $[M+Na]^+$: 403.1856, found: 403.1853.

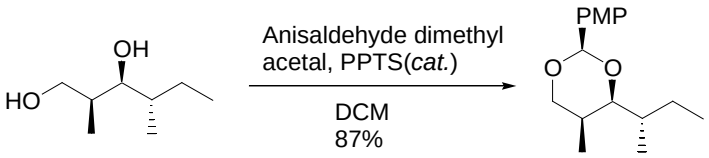


13 **13.1**

Di-*n*-butylborontriflate (5.3 mL, 24.56 mmol) was added to a solution of Evans (*R*)-oxazolidinone **13** (4.80 g, 20.60 mmol) in CH_2Cl_2 (100 mL) at 0 ºC, followed by addition of DIPEA (4.7 mL, 26.96 mmol). The reaction mixture was stirred at 0 ºC for 0.5 h and then cooled to –78 ºC. To the above enolate solution was added a solution of (*S*)-2-methylbutanal (1.96 g, 22.79 mmol, dissolved in 50 ml of CH_2Cl_2) slowly via a syringe. The reaction mixture was stirred at –78 ºC for 20 min, then was allowed to warm to 0 ºC and stirred for an additional 2 h. The reaction was quenched by pH 7.1 phosphate buffer (20 mL) and methanol (60 mL). Then a solution of 30% H_2O_2 (20 mL) and methanol (40 mL) was added slowly to keep the internal temperature below 5 ºC. The mixture was stirred at 0 ºC for an additional 1 h. Volatiles were removed on a rotary evaporator at a bath temperature of 25–30 ºC. The resulting slurry was extracted with diethyl ether (200 mL x 3). The combined organic extracts were washed with aqueous $NaHCO_3$ (400 mL, 5%) and brine (400 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 6) to afford the desired product **13.1** (5.45 g, 83%) as a white amorphous solid. $[\alpha]_D^{20}$ = – 53.6 (*c* 2.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.20 (m, 5H), 4.73-4.69 (m, 1H), 4.24-4.17 (m, 2H), 3.98-3.94 (m, 1H), 3.63 (dd, *J* = 2.1, 9.0 Hz, 1H), 3.25 (dd, *J* = 3.3, 13.4 Hz, 1H), 2.80 (dd, *J* = 9.4, 13.3 Hz, 1H), 1.82-1.77 (m, 1H), 1.54-1.50 (m, 1H), 1.28-1.23 (m, 3H), 1.21-1.18 (m, 1H), 0.97-0.86 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0, 152.8, 135.1, 129.4, 128.9, 127.4, 74.8, 66.1, 55.1, 39.5, 37.8, 37.0, 25.1, 14.7, 10.8, 9.7 ppm; HRMS (ESI) *m/z* calculated for $C_{18}H_{25}NNaO_4^+$ $[M+Na]^+$: 342.1676, found: 342.1676.

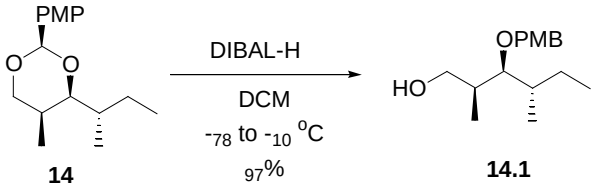
To a solution of alcohol **13.1** (3.33 g，10.43 mmol) in Et_2O–MeOH (55 mL, 10 / 1) at 0 ºC was added sodium borohydride (1.00 g，26.08 mmol). The reaction mixture was stirred at room temperature for 12 h, then cooled to 0 ºC and quenched by addition of saturated aqueous ammonium

chloride solution (50 mL). Volatiles were evaporated under vacuum. Aqueous phase was extracted with diethyl ether (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 1) to afford the diol **13.2** (1.32 g, 87%) as a white amorphous solid. $[\alpha]_D^{20}$ = – 12.3 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79-3.68 (m, 2H), 3.52 (dd, *J* = 2.1, 9.0 Hz, 1H), 2.33-2.28 (m, 2H), 1.85-1.81 (m, 1H), 1.78-1.70 (m, 1H), 1.53-1.46 (m, 1H), 1.20-1.10 (m, 1H), 0.95-0.85 (m, 6H), 0.81 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.7, 67.8, 37.6, 35.9, 25.2, 14.8, 10.8, 8.7 ppm; HRMS (ESI) *m/z* calculated for $C_8H_{18}NaO_2^+$ $[M+Na]^+$: 169.1199, found: 169.1197.



13.2 **14**

Anisaldehyde dimethyl acetal (1.5 mL, 8.79 mmol) and PPTS (150.6 mg, 0.60 mmol) were added to a solution of the diol **13.2** (0.88 g, 6.03 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at room temperature overnight and quenched by triethylamine (10 mL, 71.76 mmol). Ethyl acetate (100 mL) was added, the solution was washed with saturated aqueous solution of $NaHCO_3$ (80 mL) and brine (80 mL) successively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 5) to afford **14** (1.38 g, 87%) as a pale yellow oil. $[\alpha]_D^{20}$ = – 25.6 (*c* 3.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.45 (s, 1H), 4.05 (d, *J* = 1.5 Hz, 2H), 3.81 (s, 3H), 3.49 (dd, *J* = 2.4, 10.2 Hz, 1H),1.90-1.77 (m, 1H), 1.71-1.58 (m, 2H), 1.17 (d, *J*= 6.9 Hz, 3H), 1.21-1.11 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.83 (d,*J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ159.7, 131.7, 127.2, 113.5, 101.6, 83.7, 74.0, 55.2, 35.5, 30.0, 25.0, 13.4, 10.9, 10.6 ppm; HRMS (ESI) *m/z* calculated for $C_{16}H_{24}NaO_3^+$ $[M+Na]^+$: 287.1618, found: 287.1619.



14 **14.1**

To a solution of acetal **14** (2.21 g, 8.37mmol) in CH_2Cl_2 (90 mL) was added diisobutylaluminum hydride (14.0 mL, 16.74 mmol, 1.2 M in CH_2Cl_2) at – 78 ºC. The reaction mixture was stirred at – 78 ºC and allowed to worm to -10 ºC for 2h, then quenched by saturated aqueous potassium sodium tartrate solution (100 mL) and diluted with ethyl acetate (100 mL). The solution was vigorously stirred for 3 h. Layers were separated, and the aqueous phase was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 4) to afford alcohol **14.1** (2.17 g, 97%) as a yellow oil. $[\alpha]_D^{20}$ = + 1.2 (*c* 2.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.52 (q, *J* = 10.8 Hz, 2H), 3.80 (s, 3H), 3.59 (dd, *J* = 3.0, 5.7 Hz, 2H), 3.33 (dd, *J* = 2.7, 7.5 Hz, 1H), 1.98-1.89 (m, 2H), 1.77-1.65 (m, 2H), 1.26-1.10 (m, 1H), 1.02-0.95 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 131.0, 129.2, 113.7, 83.8, 73.9, 66.6, 55.2, 37.4, 37.2, 25.4, 15.6, 11.6, 10.8 ppm; HRMS (ESI) *m/z* calculated for $C_{16}H_{26}NaO_3^+$ $[M+Na]^+$: 289.1774, found: 289.1780.

To a solution of alcohol **14.1** (1.00 g, 3.76 mmol) in CH_2Cl_2 (50 mL) was added sodium bicarbonate (1.58 g, 18.81 mmol) and Dess-Martin periodinane (4.00 g, 9.40 mmol) at 0 ºC. After being stirred for 1 h, the reaction mixture was quenched by saturated aqueous solution of $Na_2S_2O_3$ (30 mL) and $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine (150 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue, without further purification, was dissolved in CH_2Cl_2 (50 mL). After allyltributyltin (1.75 mL, 5.64 mmol) was added, the reaction solution was cooled to – 78 ºC. $BF_3{\cdot}Et_2O$ (0.70 mL, 5.64 mmol) was added dropwise at – 78ºC. 2 h later, the reaction was poured into saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with ethyl

acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 4) to afford **15** and **15a** (1.09 g, 95%) as colorless oil. The ratio of **15** and **15a** was 70 : 30.

Analytical data for **15**: $[\alpha]_D^{20}$ = + 22.9 (*c* 3.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.92-5.81 (m, 1H), 5.18 (s, 1H), 5.14 (d, *J* = 1.8 Hz, 1H), 4.57 (d, *J* = 3.0 Hz, 2H), 3.80 (s, 3H), 3.57 (dd, *J* = 1.8, 7.8 Hz, 2H), 2.46-2.37 (m, 2H), 2.19-2.09 (m, 1H), 1.80-1.66 (m, 3H), 1.20-1.17 (m, 1H), 0.95-0.85 (m, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ159.1, 135.1, 131.3, 129.0, 118.0, 113.7, 82.8, 73.3, 72.7, 55.2, 39.9, 39.7, 37.3, 25.6, 15.7, 11.6, 11.0 ppm; HRMS (ESI) *m/z* calculated for $C_{19}H_{30}NaO_3^+$ $[M+Na]^+$: 329.2087, found: 329.2089.

Analytical data for **15a**: $[\alpha]_D^{20}$ = – 6.7 (*c*1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ7.29 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.91-5.77 (m, 1H), 5.15 (d, *J* = 8.4 Hz, 1H), 5.10 (d, *J* = 1.2 Hz, 1H), 4.70 (q, *J* = 10.5Hz, 2H), 3.93-3.89 (m, 1H),3.80 (s, 3H), 3.60 (dd, *J* = 2.1, 9.6 Hz, 1H), 2.35-2.28 (m, 2H), 1.87-1.75 (m, 2H), 1.69-1.51 (m, 1H), 1.43-1.24 (m, 1H), 0.99-0.85 (m, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 135.1, 130.0, 129.5, 117.5, 114.0, 85.3, 74.5, 74.3, 55.2, 43.3, 39.8, 38.0, 23.6, 13.6, 9.5, 6.3 ppm; HRMS (ESI) *m/z* calculated for $C_{19}H_{30}NaO_3^+$ $[M+Na]^+$: 329.2087, found: 329.2090.

DDQ (127.0 mg, 0.56 mmol) was added to a solution of **15** (118.0 mg, 0.28 mmol) in CH_2Cl_2 (4 mL) aqueous solution of Na_2HPO_4/NaH_2PO_4 buffer (pH 7.1, 2 mL). The reaction mixture was stirred at room temperature for 10 min, then diluted with CH_2Cl_2 (10 mL) and saturated aqueous solution of $NaHCO_3$ (10 mL). Layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford diol **15.1**. Diol **15.1** (52.0 mg, 0.28 mmol) was dissolved in 2,2-dimethoxypropane (2 mL). After *p*-TsOH-H_2O (PTSA) (1.9 mg, 0.01 mmol) was added, the reaction mixture was stirred at room temperature for 5 h and then diluted with ethyl acetate (10 mL).

The organic solution was washed by saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 20) to afford **16** (60.0 mg, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.15-4.99 (m, 2H), 3.40 (dd, J = 10.6, 4.3 Hz, 1H), 3.32 (dd, J = 13.3, 6.3 Hz, 1H), 2.32-2.23 (m, 2H), 1.81-1.68 (m, 2H), 1.53-1.41 (m, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 1.06-0.93 (m, 1H), 0.93-0.83 (m, 6H), 0.79 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 116.4, 100.6, 74.9, 72.9, 39.1, 37.8, 34.0, 25.4, 24.9, 23.9, 14.3, 11.8, 10.7 ppm; HRMS (ESI) *m/z* calculated for $C_{14}H_{27}O_2^+$ $[M+H]^+$: 227.2006, found: 227.2004.

To a solution of **15** (1.09 g, 3.56 mmol) in CH_2Cl_2 (40 mL) were added 2,6-lutidine (1.2 mL, 10.68 mmol) and TESOTf (1.6 mL, 7.12 mmol) at – 78 ºC. The reaction mixture was stirred at – 78 ºC for 1 h and quenched by aqueous solution of $NaHCO_3$ (40 mL). Layers were separated and the aqueous phase was extracted with diethyl ether (50 mL x 3). Combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 30) to afford the corresponding silyl ether (1.30 g, 87%).

The silyl ether (1.30 g, 3.10 mmol) was dissolved in dioxane-water (24 mL, 3 / 1). 2,6–Lutidine (0.8 mL, 4.00 mmol) was added, followed by the addition of OsO_4 (0.6 mL, 0.05 mmol, 0.02 M in *tert*-butanol) and $NaIO_4$ (1.53 g, 7.14 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. When the starting material was consumed, the reaction was quenched by addition of saturated solution of Na_2SO_3 (20 mL) and diluted with CH_2Cl_2 (40 mL). Layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (40 mL x 3). The combined organic layers were washed with saturated aqueous solution of Na_2SO_3 (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 10) to afford the corresponding aldehyde **6**

(1.24 g, 95%) as colorless oil. $[\alpha]_D^{20}$ = – 3.3 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.53 (d, *J* = 10.5 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 4.25-4.23 (m, 1H), 3.81 (s, 3H), 3.21-3.19 (m, 1H), 2.61-2.56 (m, 1H), 2.49-2.46 (m, 1H), 1.95-1.93 (m, 1H), 1.72-1.68 (m, 1H), 1.60-1.55 (m, 1H), 1.27-1.19 (m, 1H), 0.98-0.93 (m, 18H), 0.60 (t, *J* = 7.5 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.4, 159.1, 131.1, 128.8, 113.7, 83.7, 72.9, 71.0, 55.2, 47.4, 41.3, 37.6, 25.0, 15.6, 11.9, 9.3, 6.8, 5.1 ppm; HRMS (ESI) *m/z* calculated for $C_{24}H_{42}NaO_4Si^+$ $[M+Na]^+$: 445.2745, found: 445.2746.

A solution of **5** (0.72 g, 1.90 mmol) in acetonitrile (4 mL) was added to pre-activated LiCl (0.16 g, 3.80 mmol) in acetonitrile (4 mL), followed by DIPEA (0.26 mL, 1.52 mmol). The reaction mixture was stirred at room temperature for 20 min. Aldehyde **6** (0.32 g, 0.76 mmol) in acetonitrile (4 mL) was added. Then the reaction mixture was stirred at room temperature for 20 h and quenched by the addition of saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with diethyl ether (20 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 10) to afford **17** (0.41 g, 84%) as a colorless oil. $[\alpha]_D^{20}$ = + 5.0 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.97 (t, *J* = 6.5 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.95 (d, *J* = 3.5 Hz, 1H), 4.50 (q, *J* = 10.5 Hz, 2H), 3.84-3.81 (m, 1H), 3.81 (s, 3H), 3.30 (t, *J* = 4.0 Hz, 1H), 2.47-2.40 (m, 1H),2.34-2.27 (m, 1H), 2.05-1.96 (m, 1H), 1.86 (s, 3H), 1.88-1.85 (m, 1H), 1.67-1.62 (m, 1H), 1.59-1.52 (m, 1H), 1.49 (s, 9H), 1.51-1.45 (m, 1H), 1.35-1.29 (m, 1H), 1.27-1.21 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.98-0.92 (m, 21H), 0.65-0.55 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 167.4, 159.0, 140.3, 131.6, 128.7, 128.5, 113.8, 83.7, 81.6, 75.2, 74.2, 73.3, 55.3, 41.3, 38.0, 36.8, 33.0, 28.0, 26.2, 24.9, 15.8, 14.2, 12.7, 11.9, 11.6, 10.0, 6.9, 5.4 ppm; HRMS (ESI) *m/z* calculated for $C_{37}H_{64}NaO_7Si^+$ $[M+Na]^+$: 671.4314, found: 671.4293.

Compound **17a** was prepared from aldehyde **6a** using procedures for **17**. Analytical data for **17a**: $[\alpha]_D^{20}$ = – 21.5 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.94 (t, *J* = 6.5 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.95 (d, *J* = 3.5 Hz, 1H), 4.50 (q, *J* = 10.5 Hz, 2H), 4.15-4.05 (m, 1H), 3.80 (s, 3H), 3.31 (t, *J* = 4.0 Hz, 1H), 2.47-2.40 (m, 1H), 2.40-2.32 (m, 1H), 2.09-1.97 (m, 1H), 1.85 (s, 3H), 1.88-1.69 (m, 1H), 1.68-1.45 (m, 12H), 1.35-1.28 (m, 1H), 1.28-1.15 (m, 1H), 1.10-0.89 (m, 24H), 0.61 (t, *J* = 8.0 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 167.4, 159.0, 140.3, 131.7, 128.7, 128.5, 113.7, 84.0, 81.6, 75.2, 74.6, 73.8, 55.3, 41.0, 38.0, 36.8, 33.1, 28.2, 26.2, 24.7, 15.9, 14.2, 12.7, 11.9, 11.6, 10.2, 6.9, 5.4 ppm; HRMS (ESI) *m/z* calculated for $C_{37}H_{64}NaO_7Si^+$ $[M+Na]^+$: 671.4314, found: 671.4293.

DDQ (153.0 mg, 0.68 mmol) was added to a solution of **17** (219.0 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) and aqueous solution of Na_2HPO_4/NaH_2PO_4 buffer (pH 7.1, 2 mL). The reaction mixture was stirred at room temperature for 10 min and then diluted with CH_2Cl_2 (20 mL) and saturated aqueous solution of $NaHCO_3$ (20 mL). Layers were separated, the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 10) to afford **19** (89.0 mg, 64%) and **18** (45.0 mg, 32%) as colorless oil.

Analytical data for compound **19**: $[\alpha]_D^{20}$ = + 3.5 (*c* 2.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 (t, *J* = 7.5 Hz, 1H), 4.95 (d, *J* = 3.0 Hz, 1H), 3.96 (t, *J* = 8.0 Hz, 1H), 3.64 (d, *J* = 6.5 Hz, 2H), 2.65-2.55 (m, 1H), 2.55-2.48 (m, 1H), 2.04-1.98(m, 1H), 1.91 (s, 3H), 1.85-1.79 (m, 1H), 1.66-1.63(m, 1H), 1.46 (s, 9H), 1.50-1.42 (m, 1H), 1.33-1.26 (m, 2H), 1.15-1.08 (m, 1H), 1.11-0.96 (m, 15H), 0.94-0.89 (m, 6H), 0.70 (d, *J* = 6.0 Hz, 3H), 0.64 (q, *J* = 8.0 Hz, 6H) ppm; ^{13}C NMR (125

MHz, $CDCl_3$): δ169.0, 167.3, 138.0, 129.2, 81.7, 78.0, 75.3, 74.1, 37.3, 36.8, 36.7, 35.0, 28.0, 26.1, 25.2, 14.6, 14.3, 12.8, 11.6, 10.9, 10.8, 6.8, 5.0 ppm; HRMS (ESI) *m/z* calculated for $C_{29}H_{57}O_6Si^+$ $[M+H]^+$: 529.3919, found: 529.3918.

Analytical data for compound **18**: $[\alpha]_D^{20}$ = – 6.1 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (t, *J* = 7.1 Hz, 1H), 4.93 (d, *J* = 3.3 Hz, 1H), 3.83-3.73 (m, 1H), 3.67 (d, *J* = 9.5 Hz, 1H), 2.72 (s, 2H), 2.55-2.47 (m, 1H), 2.47-2.36 (m, 1H), 2.03-1.98 (m, 1H), 1.90 (s, 3H), 1.81-1.73 (m, 1H), 1.73-1.66 (m, 1H), 1.48-1.39 (m, 2H), 1.46 (s, 9H), 1.35-1.25 (m, 1H), 1.18-1.10 (m, 1H), 0.97 (t, *J* = 6.8 Hz, 6H), 0.91 (q, *J* = 7.2 Hz, 6H), 0.76 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 167.4, 139.1, 129.4, 81.8, 75.4, 75.2, 74.7, 38.2, 37.6, 36.8, 35.0, 28.0, 26.2, 25.4, 14.8, 14.3, 12.7, 11.6, 10.8, 10.2 ppm; HRMS (ESI) *m/z* calculated for $C_{23}H_{42}NaO_6^+$ $[M+Na]^+$: 415.3054, found: 415.3054.

Compound **18** could be transformed into silyl ether **19**: Thus, to a solution of **18** (89.0 mg, 0.21 mmol) in CH_2Cl_2 (4 mL) were added 2,6–lutidine (49 μL, 0.42 mmol) and TESOTf (48 μL, 0.21 mmol) at – 78 ºC. The reaction mixture was stirred at – 78 ºC for 1 h and quenched by aqueous solution of $NaHCO_3$ (5 mL). Layers were separated and the aqueous phase was extracted with diethyl ether (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 10) to afford **19** (86.0 mg, 78%). The analytical data of compound **19** produced in this procedure was identical to that of the product obtained from DDQ treatment of compound **17**.

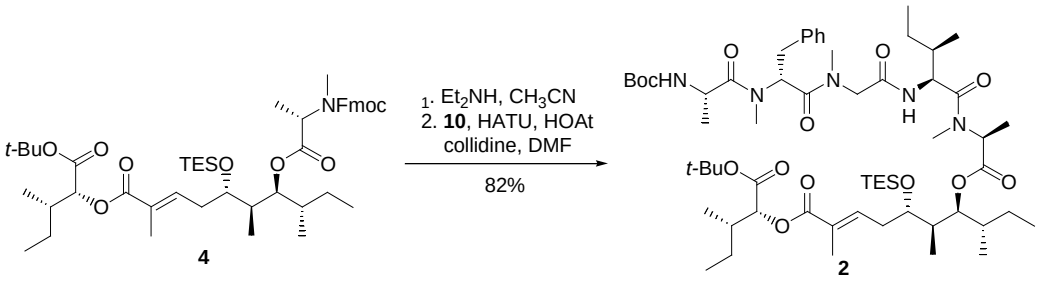
Analytical data for compound **19a**: $[\alpha]_D^{20}$ = – 18.1 (*c* 3.6, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD): δ 6.96 (t, *J* = 6.8 Hz, 1H), 4.88 (d, *J* = 3.4 Hz, 1H), 4.00-3.90 (m, 1H), 3.35 (dd, *J* = 7.9, 3.0 Hz, 1H), 2.65-2.54 (m, 1H), 2.54-2.43 (m, 1H), 2.03-1.98 (m, 1H), 1.89 (s, 3H), 1.81-1.62 (m, 3H), 1.58-1.41 (m, 1H), 1.50 (s, 9H), 1.40-1.25 (m, 1H), 1.22-1.08 (m, 1H), 1.08-0.85 (m, 22H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.68-0.62 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 169.3, 167.6, 140.0, 128.3, 81.7, 75.2,

74.9, 74.4, 40.1, 37.8, 36.7, 33.7, 27.0, 25.9, 24.4, 14.6, 13.5, 11.6, 10.6, 10.1, 8.1, 6.0, 4.9 ppm; HRMS (ESI) *m/z* calculated for $C_{29}H_{56}NaO_6Si^+$ $[M+Na]^+$: 551.3738, found: 551.3739.

Collidine (111 μL, 0.83 mmol) and DMAP (2.3 mg, 0.019 mmol) were added to a solution of **19** (44.0 mg, 0.083 mmol) in toluene (1 mL) at 0 °C, followed by slowly addition of freshly prepared Fmoc-N(Me)-Val-Cl (**7**) (143.0 mg, 0.42 mmol) in toluene (4 mL). The reaction mixture was stirred at 60 °C for 8 h, then cooled to room temperature and poured into saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (25 mL), NH_4Cl (25 mL) and brine (25 mL) successively, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 4) to afford compound **4** (45.0 mg, 65%) as colorless oil. $[\alpha]_D^{20}$ = – 2.0 (*c* 3.0, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD): δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.65-7.52 (m, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 6.96 (t, *J* = 6.5 Hz, 1H), 5.05-4.93 (m, 1H), 4.91-4.84 (m, 1H), 4.75-4.65 (m, 1H), 4.46-4.32 (m, 2H), 4.25-4.16 (m, 1H), 3.79-3.69 (m, 1H), 2.90-2.81 (m, 3H), 2.45-2.35 (m, 1H), 2.35-2.26 (m, 1H), 2.02-1.95 (m, 1H), 1.86 (s, 3H), 1.91-1.84 (m, 1H), 1.67-1.58 (m, 1H), 1.53-1.39 (m, 13H), 1.39-1.23 (m, 2H), 1.14-1.03 (m, 1H), 1.02-0.89 (m, 15H), 0.85-0.78 (m, 9H),0.61 (q, *J* = 8.0, 6H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 171.7, 169.3, 167.4, 156.7, 143.9, 141.3, 139.5, 128.6, 127.5, 126.8, 124.6, 119.6, 81.7, 78.2, 75.2, 72.7, 67.6, 54.8, 40.2, 36.9, 36.9, 32.6, 30.0, 27.0, 25.9, 24.1, 24.0, 14.8, 13.8, 13.5, 11.6, 10.6, 10.3, 9.0, 6.1, 4.8 ppm; HRMS (ESI) *m/z* calculated for $C_{48}H_{73}NNaO_9Si^+$ $[M+Na]^+$: 858.4947, found: 858.4941.

Analytical data for compound **4a**: $[\alpha]_D^{20}$ = – 12.5 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD): δ

7.80 (d, *J* = 7.4 Hz, 2H), 7.63-7.58 (m, 2H), 7.39 (dd, *J* = 9.6, 5.0 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 6.91-6.85 (m, 1H), 4.90-4.86 (m, 1H),4.75-4.62 (m, 1H), 4.62-4.53 (m, 1H), 4.48-4.31 (m, 2H), 4.31-4.15 (m, 1H), 3.78-3.69 (m, 1H), 2.89-2.81 (m, 3H), 2.62-2.43 (m, 1H), 2.36-2.25 (m, 1H), 2.03-1.91 (m, 1H), 1.88 (s, 3H), 1.91-1.80 (m, 1H), 1.77-1.62 (m, 1H), 1.49-1.36 (m, 13H), 1.36-1.27 (m, 3H), 1.11-0.86 (m, 15H), 0.83 (t, *J* = 7.5 Hz, 9H), 0.65-0.54 (m, 6H) ppm; ^{13}C NMR (100 MHz, MeOD): δ 171.8, 169.2, 167.4, 156.7, 143.8, 141.3, 139.2, 128.6, 127.5, 126.9, 124.6, 119.6, 81.7, 77.9, 75.1, 72.9, 67.9, 55.0, 39.5, 36.6, 36.5, 33.5, 30.1, 26.9, 25.9, 24.9, 24.0, 14.5, 13.8, 13.4, 11.6, 10.6, 10.1, 9.5, 6.0, 5.8, 4.7, 4.4 ppm; HRMS (ESI) *m/z* calculated for $C_{48}H_{73}NNaO_9Si^+$ $[M+Na]^+$: 858.4947, found: 858.4949.



Diethylamine (1.0 mL, 0.97 mmol) was added to a solution of **4** (100.0 mg, 0.12 mmol) in acetonitrile (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Volatiles were removed *in vacuo* to give the corresponding amine.

The above amine (73.6 mg, 0.12 mmol), which was dried under high vacuum for 2 h, and acid **10** (129.7 mg, 0.24 mmol) were dissolved in DMF (4 mL) at 0 °C. HATU (137.0 mg, 0.36 mmol), HOAt (33.0 mg, 0.24 mmol) and collidine (80 μL, 0.60 mmol) were added. The reaction mixture was stirred at room temperature for 14 h and quenched by ice water (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (40 mL), NH_4Cl (40 mL) and brine (40 mL) successively, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 2) to afford **2** (112.0 mg, 82%) as a yellow oil. $[\alpha]_D^{20}$ = + 19.2 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) existed as rotational conformers: δ 7.30-7.13 (m, 5H), 7.04-6.94 (m, 1H), 5.90-5.80 (m, 1H), 5.21 (d, *J* = 7.4 Hz, 1H), 5.03-5.01 (m, 1H), 4.92-4.90 (m, 1H), 4.47-4.24 (m, 1H), 4.19-3.98 (m, 1H), 3.95-3.85 (m, 1H), 3.19-2.87 (m, 11H),

2.55-2.45 (m, 1H), 2.45-2.32 (m, 1H), 2.03-1.97 (m, 1H), 1.95-1.86 (m, 1H),1.88 (s, 3H), 1.74-1.63 (m, 1H), 1.57-1.25 (m, 27H), 1.18-1.09 (m, 2H), 1.08-0.85 (m, 30H), 0.72-0.65 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD) existed as rotamers: δ 173.8, 172.2, 171.4, 171.1, 169.3, 167.4, 156.2, 140.0, 139.6, 139.5, 136.9, 129.3, 128.6, 128.1, 127.9, 127.5, 127.2, 126.8, 126.3, 124.7, 124.2, 119.9, 119.4, 81.8, 79.2, 79.0, 78.4, 75.2, 72.8, 67.9, 54.7, 52.8, 40.2, 37.0, 36.8, 36.7, 35.8, 34.7, 32.6, 31.0, 29.7, 27.3, 26.9, 26.2, 25.9, 24.0, 15.7, 14.7, 13.4, 13.2, 11.5, 10.8, 10.6, 10.2, 9.1, 6.0, 4.8 ppm; HRMS (ESI) *m/z* calculated for $C_{60}H_{107}N_6O_{13}Si^+$ $[M+NH_4]^+$: 1147.7660, found: 1147.7657.

Analytical data for compound **2a**: $[\alpha]_D^{20}$ = + 11.1 (*c* 2.4, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) existed as rotational conformers: δ 7.26-7.11 (m, 5H), 6.91 (t, *J* = 7.3 Hz, 1H), 5.81-5.66 (m, 1H), 5.21-5.17 (m, 1H), 4.99-4.85 (m, 3H), 4.40 (q, *J* = 6.8 Hz, 1H), 4.18-3.99 (m, 1H), 3.80 (dd, *J* = 10.7, 5.3 Hz, 1H), 3.18-2.89 (m, 11H), 2.61-2.50 (m, 1H), 2.50-2.37 (m, 1H), 2.05-1.97 (m, 1H), 1.92-1.82 (m, 5H), 1.79-1.73 (m, 1H), 1.54-1.36 (m, 25H), 1.34-1.25 (m, 3H), 1.24-1.15 (m, 1H), 1.12-1.03 (m, 1H), 1.00-0.83 (m, 33H), 0.75-0.66 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD) existed as rotamers: δ 173.8, 172.2, 171.5, 171.1, 169.3, 169.2, 167.4, 156.0, 139.1, 136.9, 129.3, 129.0, 128.8, 127.9, 127.2, 126.3, 119.6, 81.7, 79.0, 78.5, 75.2, 72.9, 54.7, 52.9, 52.6, 51.2, 39.5, 36.9, 36.7, 36.4, 35.8, 34.7, 33.7, 31.0, 29.7, 29.3, 27.4, 27.0, 26.3, 26.2, 25.9, 23.7, 15.8, 14.7, 13.5, 13.4, 13.3, 11.6, 10.9, 10.8, 10.6, 10.3, 9.4, 6.0, 5.9, 5.5, 4.8, 3.5 ppm; HRMS (ESI) *m/z* calculated for $C_{60}H_{103}N_5NaO_{13}Si^+$ $[M+Na]^+$: 1152.7214, found: 1152.7210.

Trifluoroacetic acid (2 mL) was added to compound **2** (63.0 mg, 0.056 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 2 h. Volatiles were removed *in vacuo*. The residue was dried under high vacuum for 2 h and dissolved in DMF (60 mL). After HATU (213.0 mg, 0.56 mmol), HOAt (38.0 mg, 0.28 mmol) and collidine (220μL, 1.68 mmol) were added, the reaction mixture was stirred at room temperature for 48 h. Solvent was evaporated under high vacuum. The residue was dissolved in ethyl acetate (50 mL) and washed with saturated aqueous solution of $NaHCO_3$ (40 mL), NH_4Cl (40 mL) and brine (40 mL) successively, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification was performed with semi-preparative HPLC (Agilent 1200 system, using Agilent XB-C18 column (7 μm, 21.2 × 250 mm), eluting with a gradient consisting of water / MeOH from 20 : 80 to 0 : 100 within 10 min, flow rate was 10 mL min^{-1}, temperature was 25 °C and the DAD detector was set at 230 nm wave length), to afford **1** (23.0 mg, 71%, Retention time for HPLC: 10.125 min) after lyophilization as an amorphous powder. $[\alpha]_D^{20}$ = – 31.0 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, MeOD): δ 8.27 (d, *J* = 6.4 Hz, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.29-7.14 (m, 6H), 5.54 (dd, *J* = 10.4, 5.1 Hz, 1H), 5.11 (d, *J* = 10.3 Hz, 1H), 5.01-4.98 (m, 1H), 4.91 (d, *J* = 3.2 Hz, 1H), 4.56-4.48 (m, 1H), 4.28 (d, *J* = 18.2 Hz, 1H), 4.09-4.02 (m, 1H), 3.91 (q, *J* = 6.9 Hz, 1H), 3.36 (s, 3H), 3.05 (s, 3H), 3.10-3.02 (m, 1H), 3.02-2.96 (m, 1H), 2.84 (s, 3H), 2.48 (d, *J* = 16.9 Hz, 1H), 2.27-2.19 (m, 1H), 1.95 (s, 3H), 1.94-1.87 (m, 2H), 1.85-1.79 (m, 4H), 1.57-1.50 (m, 1H), 1.51 (d, *J* = 6.5, 3H), 1.42-1.26 (m, 3H), 1.16-1.10 (m, 2H), 1.06-0.87 (m, 25H), 0.82 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 173.7, 172.5, 172.0, 171.2, 171.1, 169.1, 169.0, 144.8, 137.1, 129.3, 127.7, 127.2, 126.0, 78.7, 76.0, 71.2, 60.8, 53.8, 52.6, 51.5, 45.0, 40.8, 37.4, 37.3, 37.0, 35.2, 34.6, 34.4, 33.3, 29.2, 26.2, 26.0, 25.4, 14.4, 13.8, 13.4, 12.9, 12.9, 11.4, 10.7, 10.6, 9.5, 8.5 ppm; HRMS (ESI) *m/z* calculated for $C_{45}H_{71}N_5NaO_{10}^+$ $[M+Na]^+$: 864.5093, found: 864.5018.

Analytical data for **1a**: $[\alpha]_D^{20}$ = – 4.6 (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, MeOD): δ 7.24 (d, *J* = 12.3 Hz, 1H), 7.20-7.07 (m, 5H), 5.48 (dd, *J* = 10.5, 5.1 Hz, 1H), 4.93-4.89 (m, 3H), 4.45 (q, *J* = 7.0 Hz, 1H), 4.21 (d, *J* = 18.3 Hz, 1H), 3.90-3.76 (m, 2H), 3.29 (s, 3H), 3.19 (d, *J* = 18.4 Hz, 1H), 3.01 (s, 3H), 3.05-2.96 (m, 1H), 2.93 (dd, *J* = 14.2, 4.9 Hz, 1H), 2.83 (s, 3H), 2.61 (d, *J* = 10.5 Hz, 1H), 2.16 (dd, *J* = 23.9, 10.8 Hz, 1H), 1.91 (s, 3H), 1.89-1.83 (m, 1H), 1.80-1.71 (m, 3H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.47-1.38 (m, 2H), 1.38-1.25 (m, 2H), 1.25-1.15 (m, 2H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.98-0.83 (m, 16H), 0.80 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, MeOD): δ 173.4, 170.9, 170.8, 170.7, 170.3, 168.7, 168.5, 143.9, 136.1, 128.6, 127.4, 127.2, 125.6, 77.8, 75.2, 71.2, 59.7, 53.3, 52.3,50.8, 44.8, 39.9, 37.0, 36.8, 36.7, 35.4, 34.5, 33.8, 33.6, 28.8, 25.5, 24.9, 24.3, 13.5, 13.3, 13.0, 12.4, 12.3, 11.6, 10.8, 10.7, 9.4, 8.5 ppm; HRMS (ESI) *m/z* calculated for $C_{45}H_{71}N_5NaO_{10}^+$ $[M+Na]^+$: 864.5093, found: 864.5118.

2,6-Lutidine (7.7 mL, 66.11 mmol) and TESOTf (11.4 mL，49.60 mmol) were added to a solution of **20** (4.72 g, 21.45 mmol) in CH_2Cl_2 (200 mL) at – 78 °C. The reaction mixture was stirred at – 78 °C for 1 h and then poured into saturated aqueous solution of $NaHCO_3$ (200 mL). Layers were separated, the aqueous phase was extracted with diethyl ether (150 mL x 3). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (400 mL) and brine (400 mL), then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 30) to afford the silyl ether **20.1** (6.83 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ = – 9.1 (*c* 2.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 5.86-5.74 (m, 1H), 5.04 (d, *J* = 0.9 Hz, 1H), 5.02-4.99 (m, 1H), 4.51 (q, *J* = 11.9 Hz, 2H), 3.88-3.83 (m, 1H), 3.58-3.53 (m, 2H), 2.36-2.28 (m, 1H), 1.80-1.65 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.98 (t, *J*

= 7.9 Hz, 9H), 0.62 (q, *J* = 7.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.7, 138.7, 128.3, 127.7, 127.5, 114.6, 73.0, 72.7, 67.5, 43.7, 33.5, 14.6, 7.0, 5.2 ppm; HRMS (ESI) *m/z* calculated for $C_{20}H_{34}NaO_2Si^+$ $[M+Na]^+$: 357.2220, found: 357.2218.

Silyl ether **20.1** (2.74 g, 8.20 mmol) was dissolved in dioxane-water (40 mL, 3:1) at room temperature, after 2,6-lutidine (1.9 mL, 16.31 mmol), OsO_4 (1.5 mL, 0.13mmol, 0.02 M in *tert*-butanol) and $NaIO_4$ (3.50 g, 16.37mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After all the starting material was consumed, the reaction was diluted with CH_2Cl_2 (50 mL) and quenched by saturated aqueous solution of Na_2SO_3 (50 mL). Layers were separated, the aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with saturated aqueous solution of Na_2SO_3 (150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford aldehyde **20.2**.

A solution of potassium *tert*-butoxide (1.14 g, 9.84mmol, dried at 0.5 mmHg and 80 °C for 8 h) in THF (50 mL) was cooled to – 78 °C, *trans*-2-Butene (1.38 g, 24.64 mmol), followed by *n*-BuLi (4.9 mL, 9.84 mmol, 2.0 M in THF), was added to form an orange solution. This solution was stirred at -50 °C for 1 h, then re-cooled to -78 °C before (+)-Ipc_2BOMe (3.63 g, 11.48 mmol, 1.0 M in THF) was dropwise added. 30 min later, boron trifluoride etherate (1.6 mL, 12.62 mmol) was dropwise added to the reaction mixture at – 78 °C, followed by aldehyde **20.2** dissolved in THF (25 mL). The reaction mixture was stirred at – 78 °C for 5 h. Triethylamine (25 mL) and H_2O_2 (30 mL, 30% aqueous solution) were added to quench the reaction at room temperature. The resulting solution was refluxed for 1 h. After being cooled to room temperature, volatiles were removed *in vacuo*. The residue was extracted with diethyl ether (150 mL x 3). The combined organic layers were washed with water (300 mL) and brine (300 mL), then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 5) to afford **21** (2.09 g, 65%) as a colorless oil. $[\alpha]_D^{20}$ = – 2.8 (*c* 1.1,CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.92-5.78 (m, 1H), 5.07 (t, *J* = 14.8 Hz, 2H), 4.57-4.42 (m, 2H),

4.06-3.96 (m, 1H), 3.66 (d, *J* = 9.1 Hz, 1H), 3.53-3.41 (m, 2H), 2.29-2.21 (m, 1H), 2.01-1.90 (m, 2H), 1.69-1.66 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.98-0.93 (m, 9H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.62 (q, *J* = 7.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.4, 138.3, 128.3, 127.7, 127.6, 114.3, 75.7, 74.2, 73.0, 66.8, 41.4, 36.8, 35.1, 16.4, 10.6, 6.8, 5.0 ppm; HRMS (ESI) *m/z* calculated for $C_{23}H_{40}NaO_3Si^+$ $[M+Na]^+$: 415.2639, found: 415.2636.

Homoallylic alcohol **21** (1.00 g, 2.55 mmol) was dissolved in HCl-MeOH (25 mL, 2N) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 min. Volatiles were evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 5) to afford the corresponding diol **21.1** (0.61 g, 90%) as a viscous oil. $[\alpha]_D^{20}$ = + 4.1 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.82-5.75 (m, 1H), 5.22-5.04 (m, 2H), 4.54 (s, 2H), 3.93-3.80 (m, 1H), 3.80-3.60 (m, 3H), 2.78 (br, s, 2H), 2.32-2.24 (m, 1H), 2.02-1.86 (m, 1H), 1.86-1.74 (m, 1H), 1.71-1.67 (m, 1H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 8.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.0, 138.0, 128.5, 127.8, 127.7, 115.9, 75.3, 73.8, 73.4, 69.5, 42.1, 38.7, 35.0, 16.4, 10.1 ppm; HRMS (ESI) *m/z* calculated for $C_{17}H_{26}NaO_3^+$ $[M+Na]^+$: 301.1774, found: 301.1777.

PPTS (25.0 mg, 0.10 mmol) was added to a solution of diol **21.1** (0.60 g, 2.16 mmol, dissolved in 25 ml of 2,2-dimethoxypropane), and the reaction mixture was stirred at 60 °C for 4 h before it was quenched by saturated aqueous solution of $NaHCO_3$ (25 mL) and concentrated *in vacuo*. The residue was extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (80 mL) and brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 20) to afford **22** (0.68 g, 99%) as a colorless oil. $[\alpha]_D^{20}$ = – 1.8 (*c* 3.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.92-5.83 (m, 1H), 5.09-4.95 (m, 2H), 4.57-4.45 (m, 2H), 3.63-3.54 (m, 2H), 3.50 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.50-3.43 (m, 1H), 2.34-2.23 (m, 1H), 1.94-1.85 (m, 1H), 1.83-1.66 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H), 0.95-0.89 (m, 6H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 138.6, 128.4, 127.6, 127.5, 113.4, 100.8, 77.4, 77.1, 76.7, 73.1, 72.9, 72.0, 67.1, 38.6, 37.1, 35.0, 24.7, 23.8, 15.9, 11.5 ppm; HRMS (ESI) *m/z* calculated for $C_{20}H_{30}NaO_3^+$ $[M+Na]^+$: 341.2087, found: 341.2079.

Pd/C (*cat.*) was added to a solution of **22** (0.68 g, 2.14 mmol) in methanol (20 mL) under N_2 atmosphere. The reaction vessel was sealed and the mixture was stirred under H_2 atmosphere (balloon) for 12 h. The catalyst was filtered off through a pad of celite. The filtrate was concentrated *in vacuo* to give **22.1** (0.45 g, 92%) as a colorless oil, which was dissolved in CH_2Cl_2 (20 mL) at 0 °C and treated with Dess-Martin Periodinane (1.84 g, 4.35 mmol) in the presence of $NaHCO_3$ (0.58 g, 6.96 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched by a solution of $Na_2S_2O_3$ (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford aldehyde **23**. Under the HWE reaction condition for the synthesis of compound **17**, compound **23** (0.45 g, 1.96 mmol) was transformed into ester **23.1** (0.76 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ = + 13.0 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92-6.82 (m, 1H), 4.94 (dd, *J* = 6.5, 3.4 Hz, 1H), 3.50-3.31 (m, 2H), 2.43-2.35 (m, 2H), 2.03-1.95 (m, 1H), 1.87 (s, 3H), 1.79-1.67 (m, 2H), 1.46 (s, 9H), 1.51-1.42 (m, 4H), 1.33 (s, 3H), 1.31 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.96-0.91 (m, 3H), 0.90-0.85 (m, 3H), 0.79 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 167.3, 139.6, 128.8, 100.8, 81.6, 75.1, 74.4, 73.0, 38.3, 36.8, 34.0, 34.0, 28.0, 26.3, 25.4, 24.8, 23.8, 14.3, 14.3, 12.6, 11.8, 11.6, 10.6 ppm; HRMS (ESI) *m/z* calculated for $C_{26}H_{46}NaO_6^+$ $[M+Na]^+$: 477.3187, found: 477.3185.

Acetonide **23.1** (0.41 g, 0.90 mmol) was dissolved in methanol (10 mL). After PTSA (3.8 mg, 0.02

mmol) was added, the reaction mixture was stirred at room temperature for 2 h and quenched by addition of saturated aqueous solution of $NaHCO_3$ (10 mL). Volatiles were evaporated in vacuum. The aqueous phase was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / hexanes, 1 / 5) to afford **18** (0.35 g, 95%) as a colorless oil. The analytical data of **18** was identical with the same compound obtained via the procedures ilustracted in scheme 4 of the manuscript.

Synthetic route and data for lagunamide A **1b**:

The synthesis of lagunamide A **1b** commenced with compound **20** according to procedures for the preparation of the corresponding intermediates and **1** (Schemes 4-6). Analytical data for key intermediates were listed below:

Analytical data for compound **23.1b**: $[\alpha]_D^{20}$ = + 5.2 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD): δ 7.02 (t, *J* = 6.5 Hz, 1H), 4.86 (d, *J* = 3.3 Hz, 1H), 3.75-3.69 (m, 1H), 3.56 (dd, *J* = 10.2, 2.0 Hz, 1H), 2.57-2.51 (m, 1H), 2.46-2.34 (m, 1H), 2.03-1.98 (m, 1H), 1.87 (s, 3H), 1.67-1.55 (m, 1H), 1.53-1.42 (m, 3H), 1.43 (s, 9H), 1.41 (s, 3H), 1.41-1.32 (m, 2H), 1.31 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.98-0.89 (m, 6H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82-0.77 (m, 3H)ppm;^{13}C NMR (125 MHz, MeOD): δ 169.5, 167.6, 140.1, 128.0, 97.7, 81.8, 75.1, 73.8, 36.7, 34.9, 32.0, 29.0, 26.9, 26.5, 26.0, 18.5, 13.4, 11.4,

11.2, 10.9, 10.6, 10.4 ppm; HRMS (ESI) *m/z* calculated for $C_{26}H_{46}NaO_6^+$ $[M+Na]^+$: 477.3187, found: 477.3185.

Analytical data for compound **18b**: $[\alpha]_D^{20}$ = – 1.1 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00 (t, *J* = 6.6 Hz, 1H), 4.94 (d, *J* = 3.3 Hz, 1H), 3.88-3.85 (m, 1H), 3.62-3.51 (m, 1H), 2.53-2.46 (m, 1H), 2.46-2.35 (m, 1H), 2.08-1.95 (m, 1H),1.90 (s, 3H), 1.79-1.72 (m, 1H), 1.59-1.50 (m, 1H), 1.51-1.43 (m, 1H), 1.46 (s, 9H), 1.42-1.36 (m, 1H), 1.35-1.26 (m, 2H), 0.99 (t, *J* = 5.8 Hz, 3H), 0.96-0.90 (m, 6H), 0.85 (t, *J* = 5.7 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 167.4, 139.5, 129.3, 81.8, 78.9,75.7, 75.2, 40.9, 36.9, 36.8, 34.4, 28.0, 27.0, 26.2, 14.3, 13.0, 12.7, 12.0, 11.7, 11.5 ppm; HRMS (ESI) *m/z* calculated for $C_{23}H_{42}NaO_6^+$ $[M+Na]^+$: 437.2874, found: 437.2875.

Analytical data for compound **19b**: $[\alpha]_D^{20}$ = + 0.3 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD): δ 7.00 (t, *J* = 6.6 Hz, 1H), 4.88 (d, *J* = 3.4 Hz, 1H), 4.35-4.30 (m, 1H), 3.35 (dd, *J* = 10.2, 1.7 Hz, 1H), 2.38-2.33 (m, 2H), 2.05-1.97 (m, 1H), 1.95-1.87 (m, 1H), 1.88 (s, 3H), 1.58-1.41 (m, 3H), 1.47 (s, 9H), 1.41-1.27 (m, 2H), 1.11-0.90 (m, 18H), 0.90-0.85 (m, 6H), 0.75-0.58 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 169.4, 167.7, 142.1, 127.9, 81.7, 75.1, 74.6, 72.0,42.5, 36.7, 36.7, 30.5, 26.9, 25.9, 13.5, 11.4, 11.0, 10.7, 10.6, 9.0, 6.0, 4.7 ppm; HRMS (ESI) *m/z* calculated for $C_{29}H_{56}NaO_6Si^+$ $[M+Na]^+$: 551.3738, found: 551.3742.

Analytical data for compound **4b**: $[\alpha]_D^{20}$ = – 29.3 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD): δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.71-7.54 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 6.89-6.81 (m, 1H), 4.92 (d, *J* = 10.3 Hz, 2H), 4.77-4.62 (m, 1H), 4.59-4.50 (m, 1H), 4.50-4.41 (m, 1H), 4.31-4.29 (m, 1H), 3.85-3.68 (m, 1H), 2.82 (s, 3H), 2.39-2.32 (m, 1H), 2.32-2.21 (m, 1H), 2.14-2.09 (m, 1H), 1.99-1.89 (m, 1H), 1.83 (s, 3H), 1.72-1.65 (m, 1H), 1.49-1.39 (m, 12H), 1.37-1.23 (m, 3H), 1.23-1.18 (m, 1H), 1.09-0.75 (m, 24H), 0.69-0.51 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 172.1, 169.3, 167.6, 156.7, 143.9,141.3,127.4, 126.8, 124.7, 119.6, 81.7, 77.9, 75.1, 71.2,71.1, 67.5, 54.6, 54.1, 53.4, 41.3, 36.7, 36.2, 30.5, 29.5, 26.9, 26.9, 25.9, 25.8, 14.1, 13.5, 11.6, 11.5, 10.8, 10.8, 10.5, 8.7, 5.9, 4.7 ppm; HRMS (ESI) *m/z* calculated for $C_{48}H_{73}NNaO_9Si^+$ $[M+Na]^+$: 858.4947, found: 858.4940.

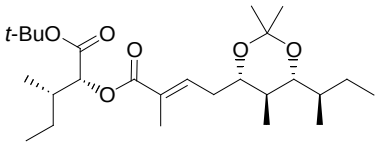
Analytical data for compound **2b**: $[\alpha]_D^{20}$ = + 24.3 (*c* 1.9, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) existed as rotational conformers: δ 7.29-7.09 (m, 5H), 7.02 (t, *J* = 6.9 Hz, 1H), 5.88-5.68 (m, 1H), 5.15 (dd, *J* = 14.9, 7.4 Hz, 1H), 5.03-4.87 (m, 2H), 4.44-4.25 (m, 1H), 4.21-4.05 (m, 1H), 4.05-3.92 (m, 1H), 3.18-2.92 (m, 10H), 2.92-2.84 (m, 1H), 2.31 (s, 2H), 2.18-2.04 (m, 1H), 2.03-1.95 (m, 1H), 1.91-1.78 (m, 4H), 1.76-1.69 (m, 1H), 1.52-1.15 (m, 25H), 1.02-0.75 (m, 30H), 0.63 (q,*J* = 8.0 Hz, 6H) ppm; ^{13}C NMR (125 MHz, MeOD) existed as rotational conformers: δ 173.8, 172.3, 171.7, 170.9, 169.2, 169.0, 167.8, 156.0, 142.2, 136.9, 129.3, 129.0, 128.6, 127.9, 127.2, 126.2, 124.2, 119.4, 105.0, 81.6, 79.0, 78.0, 75.2, 75.1, 71.1, 67.9, 54.6, 52.8, 52.6, 51.2, 41.4, 38.0, 36.8, 36.7, 36.2, 35.8, 34.8, 34.7, 30.6, 30.5, 30.2, 29.7, 29.3, 27.3, 27.0, 26.7, 26.4, 26.3, 25.9, 25.1, 15.8, 13.8, 13.6, 13.5, 11.5,

11.5, 10.9, 10.8, 10.6, 8.8, 6.0, 4.7 ppm; HRMS (ESI) *m/z* calculated for $C_{60}H_{103}N_5NaO_{13}Si^+$ $[M+Na]^+$: 1152.7214, found: 1152.7215.

Analytical data for lagunamide A **1b**: $[\alpha]_D^{20}$ = – 17.8 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, MeOD): δ 7.37 (d, *J* = 10.3 Hz, 1H), 7.21-7.14 (m, 5H), 5.47 (dd, *J* = 10.3, 5.0 Hz, 1H), 5.19 (dd, *J* = 9.5, 4.0 Hz, 1H), 4.92-4.89 (m, 2H), 4.66-4.48 (m, 1H), 4.22 (d, *J* = 18.2 Hz, 1H), 3.95 (q, *J* = 6.9 Hz, 1H), 3.89-3.81 (m, 1H), 3.57 (d, *J* = 18.2 Hz, 1H), 3.26 (s, 3H), 3.06 (s, 3H), 3.05-3.01 (m, 1H), 2.95 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.90 (s, 3H), 2.25 (dd, *J* = 25.1, 10.5 Hz, 1H), 2.15 (br, s, 1H), 2.08-2.03 (m, 1H), 1.91 (s, 3H), 1.91-1.87 (m, 1H),1.87-1.82 (m, 1H), 1.69 (d, *J* = 7.2 Hz, 1H), 1.63-1.45 (m, 3H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.41-1.22 (m, 3H), 1.14 (dd, *J* = 14.1, 6.9 Hz, 1H), 1.06 (t, *J* = 7.4 Hz, 3H), 1.00-0.86 (m, 21H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 173.8, 172.0, 171.9, 171.7, 171.4, 170.5, 169.3, 145.8, 137.4, 129.6, 128.0, 127.5, 126.3, 77.9, 76.7, 70.3, 58.8, 54.0, 52.6, 51.7, 45.2, 40.4, 37.9, 37.5, 37.2, 35.6, 35.4, 34.8, 29.5, 29.5, 27.2, 26.7, 26.3, 14.7, 13.5, 13.2, 12.9, 11.7, 11.4, 11.3, 10.8, 10.3, 8.9 ppm; HRMS (ESI) *m/z* calculated for $C_{45}H_{71}N_5NaO_{10}^+$ $[M+Na]^+$: 864.5093, found: 864.5091.

Synthetic route and data for lagunamide A **1c**:

Homoallylic alcohol **25** was prepared from the known intermediate **20**. The corresponding crotylation reaction employed (+)-Ipc_2BOMe and (*E*)-but-2-ene as reagents. The stereochemistry of **25** and its diastereomer **25.1** was confirmed by examining the spectral properties of the corresponding acetonides **22c** and **22**, respectively. Acetonide **22c** was converted into **1c** according to procedures for the preparation of the lagunamide A **1** as illustrated in Schemes 4-6. Analytical data for key intermediates were listed below:



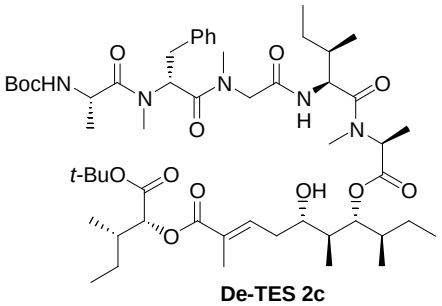
Analytical data for above acetonide: $[\alpha]_D^{20}$ = + 1.6 (*c* 1.9, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (t, *J* = 6.8 Hz, 1H), 4.93 (d, *J* = 3.2 Hz, 1H), 3.62-3.56 (m, 1H), 3.36 (dd, *J* = 10.3, 1.5 Hz, 1H), 2.51-2.46 (m, 1H), 2.38-2.26 (m, 1H), 2.02-1.98 (m, 1H), 1.86 (s, 3H), 1.63-1.55 (m, 1H), 1.55-1.49 (m, 1H), 1.49-1.40 (m, 3H), 1.46 (s, 9H), 1.37(s, 3H), 1.32 (s, 3H), 1.21-1.14 (m, 1H), 0.99 (t, *J* = 5.9 Hz, 3H), 0.96-0.90 (m, 6H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 167.4, 140.0, 128.2, 97.9, 81.6, 78.4,75.0, 73.8, 36.8, 35.2, 35.0, 32.7, 30.0,

28.0, 26.3, 21.7, 19.4, 16.5, 14.2, 12.5, 12.3, 12.0, 11.7 ppm; HRMS (ESI) *m/z* calculated for $C_{26}H_{46}NaO_6^+$ $[M+Na]^+$: 477.3187, found: 477.3187.

Analytical data for compound **18c**: $[\alpha]_D^{20}$ = – 6.3 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (t, *J* = 7.0 Hz, 1H), 4.94 (d, *J* = 3.4 Hz, 1H), 3.84-3.80 (m, 1H), 3.49-3.43 (m, 1H), 2.55-2.44 (m, 1H),2.44-2.32 (m, 1H), 2.04-1.93 (m, 1H), 1.93-1.89 (m, 1H), 1.89 (s, 3H), 1.81-1.78 (m, 1H), 1.64-1.53 (m, 1H), 1.46 (s, 9H), 1.36-1.19 (m, 2H), 1.15-1.09 (m, 1H), 1.04-0.86 (m, 12H), 0.84-0.71 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 167.4, 139.6, 129.3, 81.8, 81.5, 75.5, 75.2, 40.7, 37.2, 36.8, 34.4, 28.0, 26.2, 21.4, 16.6, 14.3, 13.4, 12.7, 12.1, 11.7 ppm; HRMS (ESI) *m/z* calculated for $C_{23}H_{42}NaO_6^+$ $[M+Na]^+$: 437.2874, found: 437.2874.

Analytical data for compound **19c**: $[\alpha]_D^{20}$ = – 1.5 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD): δ 6.99 (t, *J* = 6.5 Hz, 1H), 4.88 (d, *J* = 3.4 Hz, 1H), 4.34-4.29 (m, 1H), 3.24 (dd, *J* = 9.7, 2.3 Hz, 1H), 2.39-2.33 (m, 2H), 2.05-1.96 (m, 1H), 1.96-1.92 (m, 1H), 1.88 (s, 3H), 1.55-1.42 (m, 2H), 1.47 (s, 9H), 1.42-1.27 (m, 2H), 1.20-1.06 (m, 1H), 1.06-0.90 (m, 21H), 0.90-0.80 (m, 3H), 0.71-0.56 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 169.4, 167.7, 142.1, 127.9, 81.7, 77.5, 75.1, 72.0, 42.3, 37.0, 36.7, 30.6, 26.9, 25.9, 21.2, 15.9, 13.5, 11.4, 11.2, 10.6, 9.3, 6.0, 4.7 ppm; HRMS (ESI) *m/z* calculated for $C_{29}H_{56}NaO_6Si^+$ $[M+Na]^+$: 551.3738, found: 551.3732.

Analytical data for compound **4c**: $[\alpha]_D^{20}$ = – 31.3 (*c* 0.9,CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD): δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.67-7.51 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 6.89-6.81 (m, 1H), 4.79-4.63 (m, 1H), 4.49-4.37 (m, 1H),4.31-4.20 (m, 1H), 3.89-3.73 (m, 1H), 2.84 (s, 3H), 2.38-2.22 (m, 2H), 2.15-2.08 (m, 1H), 1.97-1.90 (m, 1H), 1.81 (s, 3H), 1.79-1.63 (m, 1H),1.54-1.48 (m, 1H), 1.50-1.36 (m, 13H), 1.36-1.20 (m, 3H), 1.15-1.06 (m, 1H), 1.01-0.76 (m, 26H), 0.68-0.47 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 172.1, 169.3, 167.6, 156.7, 143.9, 141.3, 128.2, 127.4, 126.8, 124.7, 119.6, 81.6, 80.3, 75.1, 71.1, 67.6, 54.6, 41.0, 36.7, 36.2, 35.8, 30.6, 29.6, 25.8, 22.0, 15.4, 14.0, 13.5, 11.6, 11.5, 10.8, 10.7, 10.5, 6.0, 4.7 ppm; HRMS (ESI) *m/z* calculated for $C_{48}H_{73}NNaO_9Si^+$ $[M+Na]^+$: 858.4947, found: 858.4946.



De-TES 2c

Preparation of compound **2c** was conduced according to procedures described for **2**. Due to the acidity of the silica gel employed for column chromatographic purification, the TES protecting group of **2c** was cleaved to give **De-TES 2c** as the isolated product. Analytical data for compound **De-TES 2c**: $[\alpha]_D^{20}$ = + 4.7 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) existed as rotational conformers: δ 7.27-7.10 (m, 5H), 7.09-6.90 (m, 1H), 5.88-5.66 (m, 1H), 5.07-4.98 (m, 1H), 4.79-4.68 (m, 1H), 4.43-4.21 (m, 1H), 4.17-4.03 (m, 1H), 3.80-3.64 (m, 1H), 3.19-3.07 (m, 3H), 3.07-2.98 (m, 6H), 2.98-2.92 (m, 1H), 2.87-2.72 (m, 1H), 2.46-2.35 (m, 1H), 2.30-2.18 (m, 1H), 2.18-2.09 (m, 1H), 2.04-1.93 (m, 1H), 1.92-1.85 (m, 1H),1.88 (s, 3H), 1.82-1.67 (m, 1H), 1.65-1.56 (m, 1H), 1.50-1.20 (m, 26H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.03-0.84 (m, 20H), 0.84-0.69 (m, 3H) ppm; ^{13}C NMR (100 MHz, MeOD) existed as rotational conformers: δ 173.8, 172.2, 171.7, 170.9, 169.4, 167.8, 156.0, 141.7,

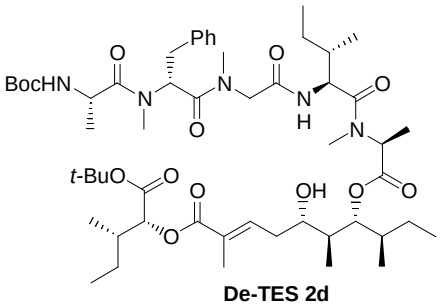
136.8, 129.3, 128.5, 127.9, 126.8, 126.2, 120.6, 119.2, 106.8, 81.8, 80.2, 78.9, 75.1, 69.8, 54.6, 53.5, 52.5, 51.1, 46.4, 40.8, 36.8, 36.7, 35.7, 34.6, 31.5, 30.6, 29.6, 27.3, 26.9, 26.1, 25.8, 22.1, 15.7, 15.3, 13.4, 13.4, 11.4, 10.8, 10.6, 10.2, 9.2 ppm; HRMS (ESI) *m/z* calculated for $C_{54}H_{89}N_5NaO_{13}^+$ $[M+Na]^+$: 1038.6349, found: 1038.6301.

1c was prepared from **De-TES 2c** according to the procedure employed for the synthesis of **1** from intermediate **2**. Analytical data for compound **1c**: $[\alpha]_D^{20} = -7.1$ (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, MeOD): δ 7.35 (d, *J* = 8.1 Hz, 1H), 7.25-7.14 (m, 5H), 5.47 (dd, *J* = 10.3, 5.2 Hz, 1H), 5.18 (d, *J* = 4.0 Hz, 1H), 4.61-4.51 (m, 3H), 4.22 (d, *J* = 18.3 Hz, 1H), 3.94 (q, *J* = 6.8 Hz, 1H), 3.83 (d, *J* = 9.2 Hz, 1H), 3.57 (d, *J* = 18.2 Hz, 1H), 3.26 (s, 3H), 3.05-3.02 (m, 1H), 3.04 (s, 3H), 3.02-2.92 (m, 1H), 2.88 (s, 3H), 2.31-2.21 (m, 1H), 2.21-2.12 (m, 1H), 2.05 (brd, 1H), 1.91 (s, 3H), 1.88 (d, *J* = 10.9 Hz, 1H), 1.81 (d, *J* = 6.8 Hz, 1H), 1.76 (brs, 1H), 1.66-1.45 (m, 4H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.38-1.27 (m, 2H), 1.25-1.12 (m, 1H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.00-0.83 (m, 21H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 173.5, 171.8, 171.6, 171.4, 171.1, 170.1, 169.0, 145.4, 137.1, 129.2, 127.7, 127.3, 126.0, 79.8, 76.4, 70.1, 58.7, 53.7, 52.2, 51.4,44.9, 40.0, 37.6, 37.2, 36.5, 35.4, 35.1, 34.5, 29.3, 29.2, 26.4, 26.0, 21.9, 15.6, 14.4, 13.2, 12.9, 12.6, 11.0, 11.0, 10.9, 10.5, 8.6 ppm; HRMS (ESI) *m/z* calculated for $C_{45}H_{71}N_5NaO_{10}^+$ $[M+Na]^+$: 864.5093, found: 864.5023.

Synthetic routes and data for **1d** and **1e**:

Tetrapeptide **3.1** was prepared by replacing L-*allo*-isoleucine with L-isoleucine, according to procedures for construction of **3**. After saponification, the corresponding acid was coupled with intermediates **4b** and **4c** to afford linear precursors **2d** and **2e**, respectively. Following procedures for the synthesis of **1**, the linear precursors **2d** and **2e** were converted into the corresponding final products **1d** and **1e**, respectively.

Analytical data for compound **3.1**: $[\alpha]_D^{20}$ = + 47.4 (*c* 3.2,CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.07 (m, 5H), 6.63 (d, *J* = 8.6 Hz, 1H), 5.82-5.53 (m, 1H), 5.33 (d, *J* = 8.0 Hz, 1H), 4.56-4.50 (m, 1H), 4.48-4.33 (m, 1H), 4.10 (d, *J* = 15.5 Hz, 1H), 3.86 (d, *J* = 15.5 Hz, 1H), 3.69 (s, 3H), 3.18-3.08 (m, 1H), 3.06-3.01 (m, 1H), 3.01 (s, 3H), 3.00 (s, 3H), 1.91-1.82 (m, 1H), 1.53-1.30 (m, 10H), 1.21-1.06 (m, 1H), 0.99-0.69 (m, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 172.1, 171.1, 168.1, 155.2, 136.4, 129.3, 129.1, 128.4, 126.8, 79.4,56.3, 53.9, 52.5, 52.0, 46.6, 37.7, 36.5, 35.3, 30.4, 28.3, 25.1, 17.7, 15.4, 11.5 ppm; HRMS (ESI) *m/z* calculated for $C_{28}H_{44}N_4NaO_7^+$ $[M+Na]^+$: 549.3283, found: 549.3284.



De-TES 2d

Preparation of compound **2d** was conduced according to procedures described for **2**. Due to the acidity of the silica gel employed for column chromatographic purification, the TES protecting group was cleaved to give **De-TES 2d** as the isolated product. Analytical data for compound **De-TES 2d**:

Analytical data for compound **De-TES 2d**: $[\alpha]_D^{20}$ = + 11.4 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) existed as rotational conformers: δ 7.35-7.10 (m, 5H), 7.04-6.87 (m, 1H), 5.88-5.72 (m, 1H), 4.99 (d, *J* = 7.6 Hz, 2H), 4.43-4.32 (m, 2H),4.18-3.92 (m, 1H), 3.80-3.68 (m, 1H), 3.21-2.76 (m, 11H), 2.45-2.39 (m, 1H), 2.29-2.18 (m, 1H), 2.18-2.09 (m, 1H), 2.01-1.92(m, 1H), 1.92-1.84 (m, 4H), 1.84-1.77 (m, 1H), 1.55-1.32 (m, 27H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.95-0.78 (m, 21H) ppm; ^{13}C NMR (125 MHz, MeOD) existed as rotational conformers: δ 172.5, 171.5, 170.8, 169.5, 168.9, 167.8, 156.0, 141.5, 137.0, 129.3, 128.6, 128.0, 127.9, 127.7, 126.3, 81.8, 80.3, 75.2, 70.0, 53.0, 46.5, 40.9, 37.5, 37.1, 37.0, 36.7, 35.8, 35.5, 34.6, 31.6, 30.7, 30.3, 29.8, 29.7, 29.3, 27.3, 27.0, 25.9, 22.2, 15.3, 14.6, 13.6, 13.5, 11.5, 10.7, 10.6, 8.3 ppm; HRMS (ESI) *m/z* calculated for $C_{54}H_{89}N_5NaO_{13}^+$ $[M+Na]^+$: 1038.6349, found: 1038.6341.

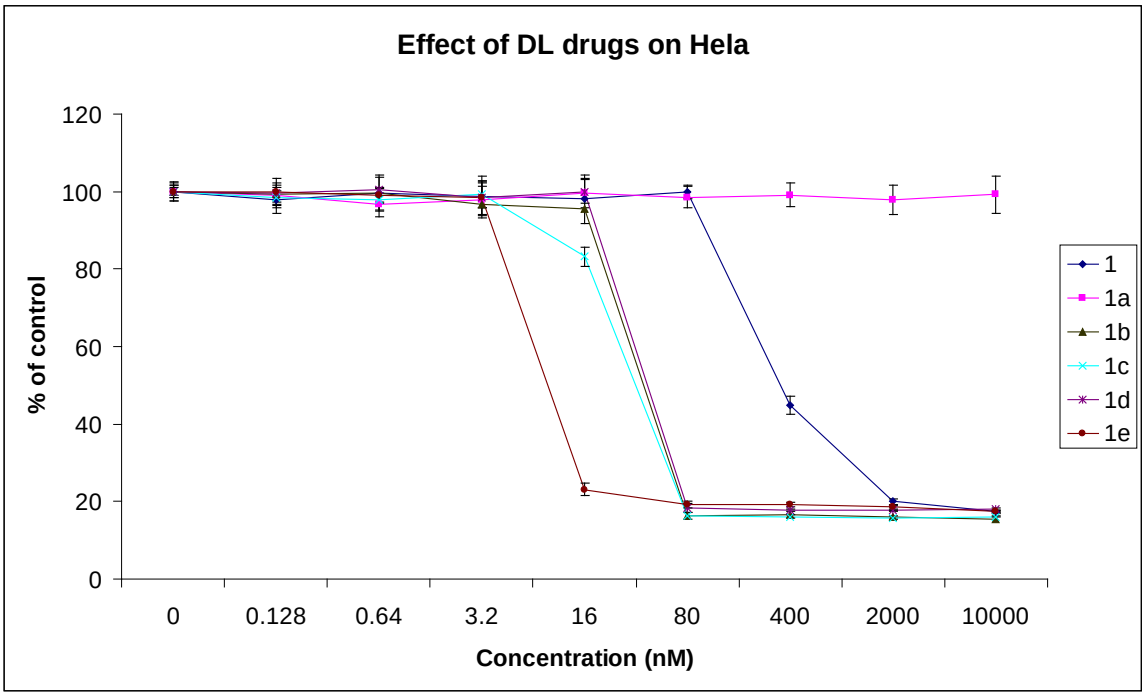
Analytical data for compound **2e**: $[\alpha]_D^{20}$ = + 13.8 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) existed as rotational conformers: δ 7.30-7.10 (m, 5H), 7.01-6.87 (m, 1H), 5.88-5.72 (m, 1H), 5.21 (d, *J* = 7.4 Hz, 1H), 5.03-4.90 (m, 3H), 4.47-4.24 (m, 1H), 4.16-4.02 (m, 1H), 3.92-3.87 (m, 1H),

3.15-3.12 (m, 4H), 3.04-2.98 (m, 6H), 2.94-2.87 (m, 1H), 2.32 (d, *J* = 7.3 Hz, 2H), 2.17-2.11 (m, 1H), 2.04-1.94 (m, 1H), 1.94-1.83 (m, 1H), 1.86 (d, *J* = 8.5 Hz, 3H), 1.77-1.63 (m, 1H), 1.57-1.25 (m, 24H), 1.24-1.10 (m, 2H), 1.08-0.85 (m, 27H), 0.81 (d, *J* = 7.1 Hz, 3H), 0.72-0.61 (m, 6H) ppm; ^{13}C NMR (125 MHz, MeOD) existed as rotational conformers: δ 173.9, 172.5, 171.6, 170.9, 169.2, 167.7, 156.1, 141.9, 141.8, 136.9, 129.3, 127.9, 126.3, 119.8, 81.7, 81.6, 79.0, 77.9, 77.8, 75.2, 71.2, 71.1, 54.6, 53.5, 52.7, 51.1, 46.4, 41.5, 41.4, 37.4, 36.9, 36.7, 36.2, 35.8, 34.7, 30.8, 30.4, 29.8, 29.7, 29.3, 27.3, 27.0, 27.0, 26.8, 26.7, 26.5, 26.1, 25.9, 24.1, 15.8, 14.7, 14.0, 13.8, 13.6, 13.5, 11.7, 11.5, 11.5, 10.9, 10.9, 10.7, 10.6, 10.0, 8.8, 6.0, 4.7, 4.7 ppm; HRMS (ESI) *m/z* calculated for $C_{60}H_{103}N_5NaO_{13}Si^+$ $[M+Na]^+$: 1152.7214, found: 1152.7211.

1d was prepared from **De-TES 2d** according to the procedure employed for the synthesis of **1** from intermediate **2**. Analytical data for compound **1d**: $[\alpha]_D^{20}$ = – 13.3 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, MeOD): δ 7.30 (d, *J* = 7.6 Hz, 1H), 7.26-7.10 (m, 5H), 5.46 (dd, *J* = 10.3, 5.1 Hz, 1H), 5.05 (d, *J* = 6.3 Hz, 1H), 4.87 (d, *J* = 3.6 Hz, 2H), 4.51 (d, *J* = 7.0 Hz, 1H), 4.20 (d, *J* = 18.4 Hz, 1H), 3.94-3.91 (m, 1H), 3.75 (d, *J* = 9.7 Hz, 1H), 3.57 (d, *J* = 18.3 Hz, 1H), 3.30 (s, 3H), 3.08-3.01 (m, 1H), 3.04 (s, 3H), 2.96 (d, *J* = 5.0 Hz, 1H), 2.89 (s, 3H), 2.29-2.20 (m, 1H), 2.20-2.15 (m, 1H), 2.08-2.02 (m, 1H), 1.91 (s, 3H), 1.91-1.81 (m, 2H), 1.76 (br, s, 1H), 1.64 (br, s, 2H), 1.57-1.46 (m, 1H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.39-1.27 (m, 3H), 1.27-1.13 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.02-0.89 (m, 23H), 0.86 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 173.8, 172.0, 171.7, 171.7, 171.5, 170.2, 169.3, 145.5, 137.3, 129.6, 128.0, 127.6, 126.3, 80.1, 76.7, 70.5, 59.3, 54.0, 53.6, 51.6, 45.3, 40.2, 38.4, 37.5, 36.9, 36.5, 35.5, 34.8, 29.6, 29.4, 26.3, 23.7, 22.3, 15.9, 14.9, 14.6, 13.5, 12.8, 11.4, 11.2, 10.8, 10.5, 9.0 ppm; HRMS (ESI) *m/z* calculated for$C_{45}H_{71}N_5NaO_{10}^+$ $[M+Na]^+$: 864.5093, found: 864.5093.

Analytical data for compound **1e**: $[\alpha]_D^{20}$ = – 33.8 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, MeOD): δ 7.32 (brd, 1H), 7.26-7.14 (m, 5H), 5.46 (dd, *J* = 10.3, 5.2 Hz, 1H), 5.05 (d, *J* = 6.2 Hz, 1H), 4.92 (m, 1H), 4.84 (m, 1H), 4.52 (q, *J* = 6.9 Hz, 1H), 4.20 (d, *J* = 18.4 Hz, 1H), 3.95 (q, *J* = 6.8 Hz, 1H), 3.76 (brd, 1H), 3.57 (d, *J* = 18.3 Hz, 1H), 3.30 (s, 3H), 3.09-3.02 (m, 1H), 3.04 (s, 3H), 2.96 (dd, *J* = 12.1, 5.8 Hz, 1H), 2.89 (s, 3H), 2.28-2.20 (m, 1H), 2.20-2.11 (m, 1H), 2.09-2.05 (m, 1H), 1.94 (s, 3H), 1.90-1.80 (m, 2H), 1.77-1.60 (m, 2H), 1.60-1.45 (m, 1H), 1.43 (d, *J* = 7.5 Hz, 3H), 1.38-1.26 (m, 3H), 1.19-1.10 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.01-0.89 (m, 21H), 0.86 (d, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, MeOD): δ 173.8, 172.0, 171.7, 171.7, 171.4, 170.2, 169.3, 145.6, 137.4, 129.6, 128.0, 127.6, 126.3, 78.0, 76.7, 70.4, 59.2, 54.0, 53.7, 51.6, 45.3, 40.3, 38.4, 37.5, 37.3, 36.4, 35.5, 34.8, 29.5, 29.5, 27.2, 26.3, 23.7, 14.9, 14.7, 13.5, 12.8, 11.7, 11.4, 11.3, 10.7, 10.4, 9.0 ppm; HRMS (ESI) *m/z* calculated for $C_{45}H_{71}N_5NaO_{10}^+$ $[M+Na]^+$: 864.5093, found: 864.5057.

Cell proliferation assays We established cell proliferation assay using 3-(4,5-dimethylthiazol-2-yl)-5-(3 carboxymethoxy phenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay kit (Promega Corp., Madison WI). Hela cells were seeded into 96-well plate and incubated overnight, followed by washing cells with PBS twice, and then the compounds were added to cells in serial dilutions. The cells were then incubated for another 72h at 37^{o}C. MTS working solution was added into each well and incubated at 37^{o}C up to 2h, followed by measuring OD at 490nm using a microplate reader (Model 680, Bio-Rad) according to manufacturer's instruction.



		1	1b	1c	1d	1e
IC_{50}	nM	358.00	23.50	19.90	43.10	8.99
	ng/ml	301.46	19.79	16.76	36.29	7.57