Supporting Information

Formal Synthesis of Kanamienamide

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General Information

All reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry nitrogen or argon. Oxygen and/or moisture sensitive solids and liquids were transferred appropriately. Concentration of solutions *in vacuo* was accomplished using a rotary evaporator fitted with a water aspirator. Residual solvents were removed under high vacuum (0.1-0.2 mm Hg). All reaction solvents were purified before use: Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone. Toluene was distilled over molten sodium metal. Dichloromethane, dimethylformamide, diethylamine, triethylamine and diisopropylethylamine were distilled from CaH$_2$. Methanol was distilled from Mg/I$_2$. Flash column chromatography was performed using the indicated solvents on E. Qingdao silica gel 60 (230-400 mesh ASTM). TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2 mm). Compounds were visualized with UV light, iodine, *p*-anisaldehyde stain, ceric ammonium molybdate stain, or phosphomolybdic acid in EtOH. NMR spectra were recorded on Bruker DPX 300 MHz, Avance 400 MHz or AV 500 MHz spectrometers. Chemical shifts were reported in parts per million (ppm), relative to either a tetramethylsilane (TMS) internal standard or the signals due to the solvent. The following abbreviations are used to describe spin multiplicity: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *qn* = quintet, *m* = multiplet, *br* = broad, *dd* = doublet of doublets, *dt* = doublet of triplets, *dq* = doublet of quartets, *ddd* = doublet of doublet of doublets; other combinations are derived from those listed above. AB quartet relationships are noted, but listed as a pair of doublets. Coupling constants (*J*) are reported in Hertz. $^{13}$C NMR spectra were completely heterodecoupled and measured at 125, 100, or 75 MHz. Residual chloroform (δ$_C$ 77.16 ppm) was used as internal reference for spectra measured in this solvent. Low- and high-resolution EI and ESI mass spectra were obtained using an AB QSTAR Elite mass spectrometer. Optical rotations were recorded on a Rudolph AutoPol-I polarimeter at 589 nm, 100 mm cell or 50 mm cell at 20 °C.
Synthesis of Compound 10.

To a stirred mixture of LiCl (1.0 g, 23.6 mmol) and DIPEA (3.5 mL, 20.1 mmol) in MeCN (50 mL) at 0 °C was added dropwise a solution of phosphonate ester 6 (5.0 g, 14.1 mmol) in MeCN (5 mL) under nitrogen. The mixture was stirred for 15 min, then a solution of aldehyde 9 (1.9 g, 9.4 mmol) in MeCN (5 mL) was added. The reaction mixture was slowly warmed to room temperature and then stirred for additional 24 h. The reaction mixture was quenched with saturated aqueous solution of NH₄Cl (20 mL) and then extracted with Et₂O (3 × 100 mL). The combined organic extracts were washed with brine (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:9) to give rise to the desired product 10 (3.1 g, 82%) as a colorless oil.

\[ \alpha ]_D^{20} = -47.5 (c = 1.0, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.36 – 7.13 (m, 7H), 4.73 (ddt, J = 9.4, 7.6, 3.2 Hz, 1H), 4.26 – 4.11 (m, 2H), 3.63 – 3.53 (m, 2H), 3.32 (dd, J = 13.4, 3.4 Hz, 1H), 2.79 (13.4, 9.5 Hz, 1H), 2.68 – 2.55 (m, 1H), 1.0 (d, J = 6.7 Hz, 3H), 0.90 (s, 9H), 0.08 – 0.04 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 165.2, 154.0, 153.5, 135.6, 129.6, 129.1, 127.4, 120.1, 67.1, 66.2, 55.4, 39.8, 38.1, 26.1, 18.5, 15.8, -5.2; HRMS (ESI) Calcd. for C₂₂H₃₃NO₄Si Na⁺ [M+Na⁺]: 426.2071, Found: 426.2070.

Synthesis of Compound 11.

To a solution of compound 10 (730 mg, 1.8 mmol) in ethyl acetate (45 mL) was added Pd/C (0.1 g, 10% Pd on charcoal). The reaction flask was evacuated and purged with hydrogen three times, and then stirred under a hydrogen atmosphere at ambient temperature for 6 h. The mixture was filtered through a pad of Celite to remove catalyst and eluted with ethyl acetate (15 mL). The filtrate was concentrated under reduced pressure to afford the corresponding saturated product as an oil, which was pure enough to use in the next step.

To a solution of above product in dry THF (20 mL), NaHMDS (1.9 mL, 1.9 mmol, 1M in THF) was added dropwise at -78 °C. After being stirred at -78 °C for 30 min, MeI (0.18 mL, 2.9 mmol) was added and the mixture was stirred for an additional 2 h at -78 °C. The reaction mixture was quenched with saturated aqueous solution of NH₄Cl (25 mL), warmed to room temperature and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:9) to afford the desired product 11 (668 mg, 88% for 2 steps) as a
light yellow oil.

\[ \alpha \]D^20 = -72.6 (c = 1.0, CHCl_3); 1H NMR (500 MHz, CDCl_3) \( \delta \) 7.38 – 7.19 (m, 5H), 4.67 (ddt, \( J = 10.4, 6.9, 3.2 \) Hz, 1H), 4.25 – 4.13 (m, 2H), 3.89 – 3.77 (m, 1H), 3.50 – 3.34 (m, 2H), 3.27 (dd, \( J = 13.3, 3.4 \) Hz, 1H), 2.77 (dd, \( J = 13.3, 9.6 \) Hz, 1H), 1.72 – 1.60 (m, 1H), 1.58 – 1.50 (m, 2H), 1.21 (d, \( J = 6.8 \) Hz, 3H), 0.90 (d, \( J = 6.6 \) Hz, 3H), 0.89 (s, 9H), 0.10 – 0.01 (m, 6H); 13C NMR (125 MHz, CDCl_3) \( \delta \) 177.7, 153.1, 135.5, 129.6, 129.1, 127.5, 68.5, 66.1, 55.5, 38.1, 36.9, 35.6, 33.8, 26.1, 18.5, 17.5, 16.8, -5.2; HRMS (ESI) Calcd. for C_{23}H_{37}NO_4SiNa \([M+Na]^+\): 442.2384, Found: 442.2385.

Synthesis of Compound 12.

To a solution of compound 11 (1.1 g, 2.6 mmol) in MeOH (60 ml) at 0 °C was added D-camphorsulfonic acid (36 mg, 0.15 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 2 h and then poured over a saturated aqueous solution of NaHCO_3 (20 mL) and extracted with ethyl acetate (2 \( \times \) 200 mL). The combined organic layers were washed successively with a saturated aqueous solution of NH_4Cl (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:2) to afford the desired product 12 (738 mg, 92%) as a colorless oil.

\[ \alpha \]D^20 = -69.5 (c = 1.0, CHCl_3); 1H NMR (400 MHz, CDCl_3) \( \delta \) 7.37 – 7.17 (m, 5H), 4.67 (ddt, \( J = 9.5, 7.5, 3.2 \) Hz, 1H), 4.25 – 4.12 (m, 2H), 3.92 – 3.77 (m, 1H), 3.48 – 3.41 (m, 2H), 3.25 (dd, \( J = 13.4, 3.4 \) Hz, 1H), 2.77 (dd, \( J = 13.3, 9.5 \) Hz, 1H), 1.78 – 1.60 (m, 2H), 1.49 (ddd, \( J = 13.1, 7.3, 5.5 \) Hz, 1H), 1.21 (d, \( J = 6.8 \) Hz, 3H), 0.93 (d, \( J = 6.5 \) Hz, 3H); 13C NMR (100 MHz, CDCl_3) \( \delta \) 177.6, 153.2, 135.4, 129.5, 129.0, 127.4, 68.2, 66.2, 55.5, 38.0, 36.8, 35.3, 33.6, 17.7, 16.6; HRMS (ESI) Calcd. for C_{17}H_{23}NO_4Na \([M+Na]^+\): 328.1519, Found: 328.1521.


To a stirred solution of compound 12 (800 mg, 2.6 mmol) and NaHCO_3 (420 mg, 5.0 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (1.3 g, 3.1 mmol). The reaction mixture was stirred at room temperature for 1 h before an aqueous solution of Na_2S_2O_3 (5 mL, 10 mmol, 2.0 M) was added. The reaction mixture was extracted with ethyl acetate (50 mL), the organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced
pressure to afford the corresponding aldehyde as a colorless oil, which was used in the next step without further purification.

To a stirred mixture of LiCl (210 mg, 5.0 mmol) and DIPEA (0.86 mL, 5.1 mmol) in MeCN (50 mL) at 0 °C, was added a solution of phosphonate ester 7 (1.2 g, 3.8 mmol) in MeCN (5 mL). The mixture was stirred for 15 min, then was added a solution of the aldehyde in MeCN (5 mL). The reaction mixture was slowly warmed to room temperature, stirred under nitrogen for 24 h, then quenched with saturated aqueous solution of NH₄Cl (20 mL) and extracted with Et₂O (3 × 100 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:4) to give rise to the desired product 4 (1.05 g, 82% for 2 steps) as a colorless oil.

\[ \alpha \]D²⁰ = -91.7 (c = 1.0, CH₂Cl₂); 1H NMR (500 MHz, CDCl₃) δ 7.36 – 7.16 (m, 10H), 6.64 (dd, J = 15.9, 8.1 Hz, 1H), 5.96 (dd, J = 15.9, 1.1 Hz, 1H), 4.63 (ddt, J = 9.6, 7.7, 3.1 Hz, 1H), 4.49 (s, 2H), 4.23 – 4.11 (m, 2H), 3.80 – 3.70 (m, 1H), 3.48 (t, J = 6.2 Hz, 2H), 2.76 (dd, J = 13.4, 3.4 Hz, 1H), 2.55 (t, J = 7.2 Hz, 2H), 2.43 – 2.32 (m, 1H), 1.93 (ddd, J = 13.6, 8.5, 6.2 Hz, 1H), 1.74 – 1.58 (m, 4H), 1.47 (ddd, J = 13.7, 8.1, 5.9 Hz, 1H), 1.21 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H); 13C NMR (125 MHz, CDCl₃) δ 200.5, 176.7, 152.9, 151.3, 138.7, 135.2, 129.4, 129.1, 128.9, 128.3, 127.6, 127.5, 127.4, 127.3, 127.2, 72.9, 70.1, 66.1, 55.3, 39.6, 39.3, 37.9, 35.6, 34.8, 29.3, 21.0, 19.5, 18.0; HRMS (ESI) Calcd. for C₃₀H₃₈N₂O₅ [M+H]+: 492.2744, Found: 492.2735.

Synthesis of Compound SI-1.

To a solution of BH₃·THF (2.0 mL, 2.0 mmol, 1.0 M in THF) and (R)-2-methyl-CBS-oxazaborolidine (0.15 mL, 0.15 mmol, 1.0 M in toluene) in THF (10 mL) at -25 °C was slowly added a solution of compound 4 (480 mg, 0.98 mmol) in THF (2.5 mL). The reaction mixture was stirred at -25 °C for 1 h, and then quenched with MeOH (0.5 mL). The mixture was diluted with ethyl acetate (50 mL), washed with saturated aqueous solution of NH₄Cl (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:3) to afford the desired product SI-1 (430 mg, 89% with 10:1 diastereomeric ratio) as a colorless oil.

\[ \alpha \]D²⁰ = -54.8 (c = 1.0, CH₂Cl₂); 1H NMR (400 MHz, CDCl₃) δ 7.43 – 7.16 (m, 10H), 5.39 (dd, J = 15.3, 8.6 Hz, 1H), 5.27 (dd, J = 15.3, 7.3 Hz, 1H), 4.69 (ddt, J = 9.7, 7.7, 3.0 Hz, 1H), 4.48 (s, 2H), 4.21 (dd, J = 9.1, 7.6 Hz, 1H), 4.14 (dd, J = 9.1, 2.7 Hz, 1H), 4.04 – 3.92 (m, 1H), 3.93 – 3.81 (m, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.24 (dd, J = 13.3, 3.4 Hz, 1H), 2.75 (dd, J = 13.3, 9.6 Hz, 1H), 2.19 – 2.07 (m, 1H), 1.97 – 1.83 (m, 2H), 1.65 – 1.58 (m, 2H), 1.58 – 1.49 (m, 1H), 1.49 – 1.37 (m, 2H), 1.37 – 1.25 (m, 2H), 1.20 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl₃) δ 177.4, 153.5, 138.8, 137.3, 135.4, 132.7, 129.6, 129.1, 128.5, 127.7, 127.6, 127.5, 73.1, 73.0, 70.4, 66.2, 55.5, 40.6, 38.1,

To a solution of compound SI-1 (612 mg, 1.2 mmol) in MeOH (30 mL) and TEA (250 µL, 1.8 mmol) was added a catalytic amount of Pd/C (300 mg, 10% Pd on charcoal). The reaction flask was evacuated and purged with hydrogen three times. The reaction mixture was stirred under a hydrogen atmosphere at ambient temperature for 1 h. The flask was then evacuated and purged with nitrogen and the catalyst was removed by filtration through Celite and eluted with ethyl acetate (200 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:4) to give rise to the desired product 13 (560 mg, 91%) as a colorless oil.

\[\alpha\]_D^20 = -65.8 (c = 1.0, CH₂Cl₂); ^1H NMR (500 MHz, CDCl₃) δ 7.36 – 7.17 (m, 10H), 4.66 (ddt, J = 9.6, 7.6, 3.0 Hz, 1H), 4.50 (s, 2H), 4.24 – 4.12 (m, 2H), 3.90 – 3.79 (m, 1H), 3.58 – 3.51 (m, 1H), 3.48 (t, J = 6.5 Hz, 2H), 3.26 (dd, J = 13.3, 3.3 Hz, 1H), 2.76 (dd, J = 13.4, 9.6 Hz, 1H), 1.66 – 1.60 (m, 2H), 1.60 – 1.53 (m, 1H), 1.53 – 1.37 (m, 9H), 1.37 – 1.31 (m, 1H), 1.19 (d, J = 6.8 Hz, 3H), 1.17 – 1.09 (m, 1H), 0.90 (d, J = 6.1 Hz, 3H); ^13C NMR (125 MHz, CDCl₃) δ 177.8, 153.2, 138.8, 135.5, 129.6, 129.1, 128.5, 127.8, 127.7, 127.5, 73.1, 72.3, 70.5, 66.2, 55.6, 40.5, 38.1, 37.4, 35.5, 35.0, 33.3, 30.9, 29.9, 22.5, 19.6, 17.4; HRMS (ESI) Calcd. for C₃₀H₄₁NO₅Na⁺ [M+Na]⁺: 518.2877, Found: 518.2877.

Synthesis of Compound 3-a.

To a solution of 13 (59 mg, 0.12 mmol) and 5a (65 mg, 0.26 mmol) in CH₂Cl₂ (10 mL) was added sequentially TEA (0.21 mL, 1.5 mmol), TCBC (0.11 mL, 0.7 mmol) and DMAP (180 mg, 1.5 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 24 h, and then quenched with saturated aqueous solution of NH₄Cl (5 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:4) to give rise to the desired product 3a (78 mg, 90%) as a colorless oil.
Synthesis of Compound 14a via the Macrolactamization of 3a.

To an ice cooled solution of 3a (171 mg, 0.24 mmol) in 6 mL of a 2:1 mixture of THF:H$_2$O was added 30% solution of H$_2$O$_2$ (0.24 mL, 2.4 mmol), followed by addition of LiOH·H$_2$O (40 mg, 0.9 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then an aqueous solution of Na$_2$S$_2$O$_8$ (3 mL, 10 mmol, 2.0 M) was added. After being stirred for 5 min, the mixture was acidified to pH 2 with an aqueous solution of NaHSO$_4$ (1 M) and extracted with Et$_2$O (2 × 20 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered through a short pad of silica gel and concentrated under reduced pressure to give rise to the acid as a colorless oil which was directly used in next step.

To a solution of HCl in dioxane (10 mL, 20 mmol, 2.0 M) was added the above acid. The reaction mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure to afford a viscous oil, which was used in the next step without further purification.

To a stirred solution of BOP-Cl (150 mg, 0.59 mmol), DIPEA (0.2 mL, 1.2 mmol) in CH$_2$Cl$_2$ (250 mL) was added a solution of the above viscous oil in CH$_2$Cl$_2$ (10 mL) via syringe pump over 10 h. The reaction mixture was stirred for additional 24 h, quenched with saturated aqueous solution of NH$_4$Cl (20 mL), then extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with saturated aqueous solution of NaHCO$_3$ (20 mL), brine (20 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:8) to give rise to the desired product 14a (35 mg, 33% for 3 steps) as a colorless oil.

$[\alpha]_{D}^{29}$ = -61.5 (c = 1.0, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.44 – 7.06 (m, 10H), 4.91 – 4.58 (m, 3H), 4.48 (s, 2H), 4.25 – 4.17 (m, 1H), 4.17 – 4.12 (m, 1H), 3.89 – 3.73 (m, 1H), 3.45 (t, $J$ = 6.5 Hz, 2H), 3.25 (dd, $J$ = 13.4, 3.3 Hz, 1H), 2.83 – 2.69 (m, 4H), 1.71 – 1.49 (m, 14H), 1.48 – 1.41 (m, 9H), 1.41 – 1.24 (m, 1H), 1.18 (d, $J$ = 6.8 Hz, 3H), 1.16 – 1.05 (m, 1H), 0.95 (d, $J$ = 6.5 Hz, 3H), 0.93 (d, $J$ = 6.2 Hz, 3H), 0.91 – 0.84 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 177.6, 155.8, 153.1, 138.8, 135.5, 129.6, 129.1, 128.5, 127.7, 127.6, 127.5, 80.2, 75.4, 73.0, 70.2, 66.2, 57.2, 56.3, 55.5, 40.4, 38.1, 35.5, 33.9, 33.0, 31.5, 30.5, 29.7, 28.5, 25.2, 24.8, 23.4, 22.1, 21.6, 21.3, 19.3, 17.3; HRMS (ESI) Calcd. for C$_{20}$H$_{35}$N$_{20}$O$_{10}$Na$^+$ [M+Na$^+$]: 745.4398, Found: 745.4402.

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Synthesis of Compound 3b.

To a solution of 13 (393 mg, 0.79 mmol) and 5b (0.46 g, 2.0 mmol) in CH2Cl2 (20 mL) was added sequentially TEA (0.8 mL, 5.7 mmol), TCBC (0.45 mL, 2.9 mmol) and DMAP (370 mg, 3.0 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 24 h, quenched with saturated aqueous solution of NH4Cl (10 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with saturated aqueous solution of NaHCO3 (20 mL), brine (20 mL), dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:4) to afford the desired product 3b (520 mg, 93%) as a colorless oil.

[α]D20 = -58.1 (c = 1.0, CH2Cl2); 1H NMR (500 MHz, CDCl3) δ 7.38 – 7.04 (m, 10H), 4.89 (d, J = 8.8 Hz, 1H), 4.87 – 4.82 (m, 1H), 4.66 (ddt, J = 9.6, 7.7, 3.0 Hz, 1H), 4.48 (s, 2H), 4.31 – 4.23 (m, 1H), 4.23 – 4.17 (m, 1H), 4.15 (dd, J = 9.1, 2.7 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.45 (t, J = 6.5 Hz, 2H), 3.25 (dd, J = 13.4, 3.3 Hz, 1H), 2.76 (dd, J = 13.4, 9.5 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.63 – 1.51 (m, 8H), 1.49 – 1.35 (m, 14H), 1.33 – 1.25 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H), 1.16 – 1.06 (m, 1H), 0.95 (d, J = 2.2 Hz, 3H), 0.94 (d, J = 2.3 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 177.6, 173.3, 155.5, 153.1, 138.7, 135.4, 129.5, 129.0, 128.4, 127.7, 127.7, 127.6, 79.7, 75.5, 73.0, 70.2, 66.1, 55.5, 52.5, 42.0, 40.3, 38.0, 35.5, 33.7, 32.9, 31.4, 30.5, 29.7, 28.4, 27.0, 24.9, 23.0, 22.1, 22.0, 19.3, 17.2; HRMS (ESI) Calcd. for C41H60N2O8Na+ [M+Na]+: 731.4242, Found: 731.4238.

Synthesis of Compound 14b.

To an ice cooled solution of 3b (225 mg, 0.3 mmol) in 7.5 mL of a 2:1 mixture of THF:H2O was added 30% solution of

H$_2$O$_2$ (0.4 mL, 4.0 mmol), followed by addition of LiOH·H$_2$O (50 mg, 1.2 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then an aqueous solution of Na$_2$S$_2$O$_3$ (5 mL, 10 mmol, 2 M) was added. After being stirred for 5 min, the mixture was acidified to pH 2 with an aqueous solution of NaHSO$_3$ (1 M), then extracted with Et$_2$O (2 × 20 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered through a short pad of silica gel and concentrated under reduced pressure to afford the corresponding acid as a colorless oil which was directly used in next step.

To a solution of HCl in dioxane (10 mL, 20 mmol, 2.0 M) was added the above acid. The reaction mixture was stirred at room temperature for 4 h, then concentrated under reduced pressure to give rise to a viscous oil, which was used in the next step without further purification.

To a stirred solution of BOP-Cl (230 mg, 0.9 mmol), DIPEA (0.2 mL, 1.2 mmol) in CH$_2$Cl$_2$ (300 mL) was added a solution of the above viscous oil in CH$_2$Cl$_2$ (10 mL) via syringe pump over 10 h. The reaction mixture was stirred for additional 24 h, quenched with saturated aqueous solution of NH$_4$Cl (20 mL), then extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with saturated aqueous solution of NaHCO$_3$ (20 mL), brine (20 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:8) to afford the desired product 14b (68 mg, 50% for 3 steps) as a colorless oil.

[α]$_D^2$ = -29.5 (c = 0.5, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$, rotamers present in NMR) δ 7.38 – 7.23 (m, 5H), 5.72 – 5.33 (m, 1H), 5.24 – 4.74 (m, 1H), 4.48 (s, 2H), 4.40 – 4.08 (m, 1H), 3.53 – 3.38 (m, 2H), 2.71 – 2.49 (m, 1H), 1.98 – 1.81 (m, 1H), 1.81 – 1.64 (m, 2H), 1.68 – 1.41 (m, 6H), 1.40 – 1.19 (m, 5H), 1.20 – 1.15 (m, 2H), 1.17 – 1.00 (m, 2H), 1.01 – 0.95 (m, 3H), 0.96 – 0.03 (m, 7H); $^{13}$C NMR (125 MHz, CDCl$_3$, rotamers present in NMR) δ 179.5, 177.3, 173.4, 171.9, 138.8, 138.8, 128.5, 128.5, 127.7, 127.7, 76.3, 73.1, 73.1, 70.3, 70.1, 54.9, 53.7, 42.4, 41.6, 39.9, 39.8, 39.2, 35.4, 34.5, 34.4, 34.3, 32.6, 32.1, 31.0, 31.0, 30.5, 29.8, 29.6, 25.4, 24.8, 23.2, 23.0, 22.9, 22.5, 22.3, 22.2, 21.2, 18.6, 15.6; HRMS (ESI) Calcd. for C$_{32}$H$_{42}$NO$_5$+ [M+H]$^+$: 432.3108; Found: 432.3109.

Synthesis of Compound 14a via N-Methylation of 14b.

To a solution of compound 14b (58 mg, 134 µmol) and MeI (200 µL, 320 µmol) in DMF (2.5 mL) under argon at 0 °C was added NaH (12 mg, 0.3 mmol, 60% dispersion in mineral oil). The reaction mixture was stirred at 0 °C for 10 min prior to being warmed to room temperature. The reaction mixture was stirred at room temperature for additional 1 h before quenching with saturated aqueous solution of NH$_4$Cl (5 mL), then extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:6) to afford the desired product 14a (53 mg, 89%) as a colorless oil.

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Synthesis of Compound 15.

To a solution of compound 14a (30 mg, 67 µmol) in ethyl acetate (3 mL) was added Pd/C (50 mg, 10% Pd on charcoal). The reaction flask was evacuated and purged with hydrogen three times. The reaction mixture was stirred under a hydrogen atmosphere at ambient temperature for 2 h. The flask was then evacuated and purged with nitrogen three times and the catalyst was removed by filtration through Celite and eluted with ethyl acetate (15 mL). The filtrate was concentrated under reduced pressure to afford the desired product 15 (23 mg, 97%) as a colorless oil, which was pure enough and was directly used in next step.

\[[\alpha]D^20 = -33.7 \text{ (c = 1.0, CH}_2\text{Cl}_2); ^1H \text{ NMR (500 MHz, CDCl}_3 \delta 5.03 \text{ (dtd, } J = 10.7, 7.0, 5.3 \text{ Hz, 1H)}, 4.52 \text{ (dd, } J = 8.6, 6.9 \text{ Hz, 1H}), 3.61 \text{ (t, } J = 6.5 \text{ Hz, 2H}), 2.86 \text{ (s, 3H)}, 2.84 - 2.78 \text{ (m, 1H)}, 1.89 - 1.81 \text{ (m, 3H)}, 1.74 \text{ (t, } J = 11.4 \text{ Hz, 1H}), 1.66 - 1.50 \text{ (m, 6H)}, 1.40 - 1.27 \text{ (m, 3H)}, 1.12 - 1.07 \text{ (m, 6H)}, 1.06 - 1.00 \text{ (m, 1H)}, 0.97 \text{ (d, } J = 6.7 \text{ Hz, 3H}), 0.93 \text{ (d, } J = 6.5 \text{ Hz, 3H}), 0.85 \text{ (d, } J = 6.0 \text{ Hz, 3H}); ^13C \text{ NMR (125 MHz, CDCl}_3 \delta 179.0, 173.0, 77.3, 62.7, 58.5, 43.3, 38.4, 35.4, 34.3, 33.8, 32.6, 31.6, 30.8, 29.0, 24.9, 23.1, 22.4, 21.6, 20.9, 18.7; HRMS (ESI) Calcd. for C_{20}H_{38}NO_4 [M+H]^+: 356.2795, Found: 356.2796.\]

Synthesis of Compound 2.

To a stirred solution of compound 15 (23 mg, 65 µmol) and NaHCO_3 (25 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (42 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 0.5 h prior to addition of an aqueous solution of Na_2S_2O_3 (1 mL, 2 mmol, 2.0 M). The reaction mixture was extracted with ethyl acetate (30 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the aldehyde as colorless oil, which was used in the next step without further purification.

To an ice cooled suspension of (iodomethyl)-triphenylphosphonium iodide (160 mg, 0.3 mmol) in THF (5 mL), NaHMDS (0.14 mL, 0.28 mmol, 2.0 M in THF) was added. After 2 min, the reaction mixture was cooled to -78 °C, and a solution of the aldehyde in THF (5 mL) was added dropwise. The mixture was maintained at -78 °C for additional 4 h,
quenched with saturated aqueous solution of NH₄Cl (2 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:5) to afford the desired product 2 (20 mg, 65%) as a colorless oil.

[α]D²⁰ = -48.0 (c = 1.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.22 (dt, J = 7.4, 1.3 Hz, 1H), 6.16 – 6.09 (m, 1H), 5.09 – 5.00 (m, 1H), 4.53 (dd, J = 8.6, 6.8 Hz, 1H), 2.87 (s, 3H), 2.86 – 2.79 (m, 1H), 2.19 – 2.09 (m, 2H), 1.90 – 1.80 (m, 3H), 1.75 (t, J = 11.4 Hz, 1H), 1.67 – 1.52 (m, 3H), 1.44 – 1.37 (m, 2H), 1.37 – 1.29 (m, 1H), 1.17 – 1.07 (m, 3H), 1.09 (d, J = 6.7 Hz, 3H), 1.07 – 0.96 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 178.9, 173.0, 140.6, 83.2, 77.1, 58.6, 43.4, 38.5, 35.0, 34.5, 34.3, 33.8, 31.6, 30.8, 29.0, 24.9, 23.8, 23.4, 22.4, 21.0, 18.8; HRMS (ESI) Calcd. for C₂₁H₃₇NO₃I [M+H]+: 478.1813, Found: 478.1816.