Supporting Information
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General Remarks: Nuclear magnetic resonance (¹H NMR (400 MHz), ¹³C NMR (100 MHz)) spectra were determined on a JEOL-ECS400 instrument. Chemical shifts for ¹H NMR are reported in parts per million downfields from tetramethylsilane (δ) as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ¹³C NMR were reported in ppm relative to the center line of a triplet at 77.0 ppm for deuteriochloroform. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm⁻¹). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-T100LP AccuTOF LC-plus either in positive electrospray ionization (ESI) method, using PEG as the internal standard. Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F₂₅₄. Preparative TLC separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F₂₅₄ unless otherwise noted. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (spherical, 40-100 mesh) unless otherwise noted. Reagents were commercial grades and were used without any purification. Dehydrated tetrahydrofuran, diethyl ether, toluene, and dichloromethane were purchased from Kanto Chemicals Co., Inc., and were purified using a Glass Contour Solvent System. Dehydrated benzene and N,N-dimethylformamide were purchased from Kanto Chemicals Co., Inc. and stored over activated MS4A*. Dehydrated methanol, ethanol and acetonitrile were also purchased from Kanto Chemicals Co., Inc. and stored over activated MS3A*. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Benzyl 4-((tert-butyldimethylsilyloxy)butyl)-2-oxotetrahydrofuran-3-carboxylate (8)

To a stirred solution of cupper iodide (4.2 g, 22 mmol) in tetrahydrofuran (100 mL) was added a solution of Grignard reagent 7 (0.5 M in THF 440 mL, 220 mmol) dropwise at −40 °C. After stirring for 40 minutes, a solution of 6 (25.4 g, 110 mmol) in tetrahydrofuran (500 mL) was added to the reaction mixture. After stirring for 1 h, the reaction mixture was warmed to 0 °C. The reaction was quenched with saturated aqueous ammonium chloride. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, filtered

* Molecular sieves were “activated” in the following manner: A round-bottom flask containing molecular sieves was heated in a regular microwave for 1.5-2.0 minute and the flask was immediately evacuated. When cooled to room temperature, the flask was backfilled with argon. The above procedure was repeated three times.
and concentrated in reduced pressure. The residual oil was roughly purified by flash column chromatography (5% hexane/ethyl acetate then 10%) to afford 8 as a colorless oil. The residue was used in the next step without further purification. The spectroscopic data for 8 were collected after purification by preparative TLC (20% ethyl acetate/hexane). IR (neat, cm⁻¹): 2930, 2857, 1783, 1460, 1387, 1255; ¹H-NMR (CDCl₃): δ 7.37-7.33 (m, 5H), 5.22 (s, 2H), 4.48 (t, J=8.5 Hz, 1H), 3.88 (t, J=8.5 Hz, 1H), 3.55 (t, J=6.4 Hz, 2H), 3.27 (d, J=9.2 Hz, 1H), 2.96 (m, 1H), 1.58-1.44 (m, 4H), 1.34-1.26 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ¹³C-NMR (CDCl₃): δ 171.8 (C), 167.5 (C), 135.0 (C), 128.5 (CH), 128.4 (CH), 128.1 (CH), 71.9 (CH₂), 67.6 (CH₂), 62.4 (CH₂), 52.5 (C), 40.2 (CH), 32.3 (CH₃), 32.0 (CH₃), 25.8 (CH₃), 23.3 (CH₂), 18.2 (C), −5.4 (CH₃); HRMS (ESI+) 429.2064 (calcd for C₂₂H₃₄NaO₅Si 429.2073).

(3S*,4R*)-Benzyl 4-(((tert-butyldimethylsilyl)oxy)butyl)-3-(3-methoxy-3-oxopropyl)-2-oxotetrahydrofuran-3-carboxylate (9)

To a stirred solution of 8 (110 mmol) and potassium carbonate (22.8 g, 165 mmol) in N,N-dimethylformamide (300 mL) was added methyl acrylate (12.0 mL, 132 mmol) dropwise at rt. Then the reaction mixture was warmed to 50 °C and stirred for 1.5 hours. After the reaction mixture was cooled to rt, the reaction was quenched with water. The solution was partitioned between diethyl ether and water. The aqueous phase was extracted twice with diethyl ether. The combined organic extracts were washed three time with brine, dried over magnesium sulfate, filtered and concentrated in reduced pressure. The residue was used in the next step without further purification.

The spectroscopic data for 9 were collected after purification by preparative TLC (20% ethyl acetate/hexane). IR (neat, cm⁻¹): 2951, 2931, 2857, 1779, 1741, 1254, 1175, 1097; ¹H-NMR (CDCl₃): δ 7.37-7.32 (m, 5H), 5.27 (d, J=12.2 Hz, 1H), 5.12 (d, J=12.2 Hz, 1H), 4.37 (t, J=8.5 Hz, 1H), 3.89 (dd, J=10.5 Hz, 8.5 Hz, 1H), 3.66 (s, 3H), 3.51 (t, J=6.2 Hz, 2H), 2.75 (ddd, J=16.3 Hz, 10.8 Hz, 5.3 Hz, 1H), 2.47-2.31 (m, 3H), 2.09 (ddd, J=15.6 Hz, 10.6 Hz, 5.3 Hz, 1H), 1.48-1.17 (m, 6H), 0.87 (s, 9H), 0.02 (s, 6H); ¹³C-NMR (CDCl₃): δ 175.0 (C), 173.2 (C), 167.9 (C), 134.7 (CH), 128.7 (C), 128.6 (CH), 70.8 (CH₂), 67.5 (CH₂), 62.4 (CH₂), 56.2 (C), 51.7 (CH₃), 44.9 (CH), 32.5 (CH₂), 28.7 (CH₂), 27.8 (CH₂), 27.7 (CH₂), 25.9 (CH₃), 23.6 (CH₃), 18.3 (C), −5.4 (CH₃); HRMS (ESI+) 515.2431 (calcd for C₂₆H₄₀NaO₇Si 515.2441).
(3S’,4R’)-Benzy1 4-(4-hydroxybutyl)-3-(3-methoxy-3-oxopropyl)-2-oxotetrahydrofuran-3-carboxylate (S1)

To a stirred solution of 9 (110 mmol) in tetrahydrofuran (300 mL) was added tetra-n-butyrammonium fluoride (1.0 M, 165 mL, 165 mmol) at rt. After stirring for 40 min, the reaction was quenched with water. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated in reduced pressure. The residue was used in the next step without further purification. The spectroscopic data for S1 were collected after purification by preparative TLC (67% ethyl acetate/hexane). IR (neat, cm⁻¹): 3534, 2939, 2862, 1770, 1731, 1455, 1376; ¹H-NMR (CDCl₃): δ 7.38-7.30 (m, 5H), 5.30 (d, J=12.1 Hz, 1H), 5.13 (d, J=12.1 Hz, 1H), 4.39 (t,J=8.9 Hz, 1H), 3.91 (t, J=8.9 Hz, 1H), 3.68 (s, 3H), 3.54 (t, J=6.0 Hz, 2H), 2.75 (ddd, J=16.2 Hz, 10.4 Hz, 5.4 Hz, 1H), 2.48-2.33 (m, 3H), 2.11 (ddd, J=14.4 Hz, 10.4 Hz, 4.5 Hz, 1H), 1.48-1.22 (m, 6H), 1.00-0.88 (m, 1H); ¹³C-NMR (CDCl₃): δ 174.9 (C), 173.3 (C), 167.9 (C), 134.7 (CH), 128.7 (CH), 128.7 (CH), 70.8 (CH₂), 67.6 (CH₂), 62.0 (CH₂), 56.2 (C), 51.8 (CH₃), 44.8 (CH), 32.2 (CH₂), 28.7 (CH₃), 27.7 (CH₂), 27.7 (CH₂), 23.5 (CH₂); HRMS (ESI+) 401.1580 (calcd for C₂₆H₃₆NaO₇ 401.1576).

(3S’,4R’)-Benzy1 4-((tert-butyldiphenylsilyl)oxy)butyl)-3-(3-methoxy-3-oxopropyl)-2-oxotetrahydrofuran-3-carboxylate (10)

To a stirred solution of S1 (110 mmol) and imidazole (11.2 g, 165 mmol) in N,N-dimethylformamide (300 mL) was added tert-butyldiphenylchlorosilane (33.9 mL, 132 mmol) at rt. After stirring for 50 min, the reaction was quenched with saturated aqueous sodium hydrogen carbonate. The solution was partitioned between diethyl ether and water. The aqueous phase was extracted twice with diethyl ether. The combined organic extracts were washed three times with brine, dried over magnesium sulfate, filtered and concentrated in reduced pressure. The residue was purified by flash column chromatography (10% ethyl acetate/hexane, then 20%) to afford 10 (27.7 g, 44.9 mmol, 41%, 4 steps) as a colorless oil. IR (neat, cm⁻¹): 2932, 2857, 1777, 1739, 1428, 1174, 1109; ¹H-NMR (CDCl₃): δ 7.64 (dd, J=6.6 Hz, 1.2 Hz, 4H), 7.46-7.37 (m, 6H), 3.44 (m, 5H), 5.26 (d, J=12.1 Hz, 1H), 5.12 (d, J=12.1 Hz, 1H), 4.34 (t, J=8.6 Hz, 1H), 3.88 (dd, J=10.0 Hz, 8.6 Hz, 1H), 3.67 (s, 3H), 3.58 (t, J=6.1 Hz, 2H), 2.33 (s, 3H), 1.48-1.12 (m, 6H), 1.00-0.88 (m, 1H); ¹³C-NMR (CDCl₃): δ 174.9 (C), 173.3 (C), 167.9 (C), 134.7 (CH), 128.7 (CH), 128.7 (CH), 70.8 (CH₂), 67.6 (CH₂), 62.0 (CH₂), 56.2 (C), 51.8 (CH₃), 44.8 (CH), 32.2 (CH₂), 28.7 (CH₃), 27.7 (CH₂), 27.7 (CH₂), 23.5 (CH₂); HRMS (ESI+) 401.1580 (calcd for C₂₆H₃₆NaO₇ 401.1576).
2.77 (ddd, J=16.3 Hz, 10.8 Hz, 5.1 Hz, 1H), 2.48-2.31 (m, 3H), 2.10 (ddd, J=14.6 Hz, 9.9 Hz, 5.1 Hz, 1H), 1.49-1.20 (m, 5H), 1.05 (s, 9H), 0.92 (m, 1H); \(^{13}C\)-NMR (CDCl\(_3\)): \(\delta\) 174.9 (C), 173.2 (C), 167.9 (C), 135.5 (CH), 134.7 (C), 133.8 (C), 129.6 (CH), 128.7 (CH), 128.7 (CH), 128.6 (CH), 127.6 (CH), 70.8 (CH\(_2\)), 67.5 (CH\(_2\)), 63.2 (CH\(_2\)), 56.2 (C), 51.7 (CH\(_2\)), 44.9 (CH), 32.3 (CH\(_2\)), 28.7 (CH\(_2\)), 27.8 (CH\(_2\)), 27.8 (CH\(_2\)), 26.8 (CH\(_3\)), 23.5 (CH\(_3\)), 19.2 (C); HRMS (ESI+) 639.2735 (calcld for C\(_{36}\)H\(_{44}\)NaO\(_7\)Si 639.2754).

\((3R',4R')-4-(4-((\text{tert-Butyldiphenylsilyl})oxy)butyl)-3-(3-methoxy-3-oxopropyl)-2-oxotetrahydrofuran-3-carboxylic acid (S2)\)

![Diagram of S2](image)

To a stirred solution of 10 (10.2 g, 16.5 mmol) in ethanol (50 mL) was added palladium on charcoal (10%, wet, 3.5 g, 1.7 mmol). The suspension was stirred for 3 h at rt under an atmosphere of hydrogen. The mixture was filtered through a thin pad of Celite and the filtrate was concentrated under reduced pressure. The residue was used in the next step without further purification. The spectroscopic data for S2 were collected after purification by preparative TLC (ethyl acetate). IR (neat, cm\(^{-1}\)): 3100, 2932, 2857, 1777, 1740, 1428, 1356, 1176, 1110, 1025; \(^1H\)-NMR (CDCl\(_3\)): \(\delta\) 8.47 (br, 1H), 7.65 (dd, \(J=7.6\) Hz, 1.4 Hz, 4H), 7.44-7.36 (m, 6H), 4.41 (t, \(J=8.9\) Hz, 1H), 4.03 (t, \(J=8.9\) Hz, 1H), 3.67 (m, 5H), 2.77 (ddd, \(J=16.4\) Hz, 10.4 Hz, 5.3 Hz, 1H), 2.51-2.43 (m, 2H), 2.32 (ddd, \(J=14.8\) Hz, 10.0 Hz, 5.3 Hz, 1H), 2.10 (ddd, \(J=14.8\) Hz, 10.4 Hz, 5.1 Hz, 1H), 1.63-1.48 (m, 3H), 1.42-1.24 (m, 3H), 1.04 (s, 9H); \(^{13}C\)-NMR (CDCl\(_3\)): \(\delta\) 174.9 (C), 173.3 (C), 172.6 (C), 135.5 (CH), 133.7 (C), 129.6 (CH), 127.6 (CH), 70.8 (CH\(_2\)), 63.3 (CH\(_2\)), 56.3 (C), 51.9 (CH\(_3\)), 44.6 (CH), 32.3 (CH\(_2\)), 28.8 (CH\(_2\)), 27.9 (CH\(_2\)), 27.5 (CH\(_3\)), 26.8 (CH\(_3\)), 23.7 (CH\(_3\)), 19.2 (C); HRMS (ESI–) 525.2285 (calcld for C\(_{29}\)H\(_{37}\)O\(_7\)Si 525.2309).

Methyl 3-((3R',4R')-3-(azidocarbonyl)-4-((\text{tert-butyldiphenylsilyl})oxy)butyl)-2-oxotetrahydrofuran-3-yl)propanoate (11)

![Diagram of 11](image)

To a stirred solution of S2 (16.5 mmol) and \(N,N\)-dimethylformamide (160 \(\mu\)L, 1.7 mmol) in dichloromethane (50 mL) was added oxalyl chloride (2.8 mL, 33 mmol) dropwise at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was concentrated at 0 °C under reduced pressure. The residue was dissolved in acetone (40 mL). To the solution was added sodium azide (3.2 g, 49.5 mmol) and water (10 mL) at 0 °C. Then the reaction mixture was warmed to rt and stirred for 2 h. The reaction was quenched with aqueous sodium hydrogen carbonate. The
solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated in reduced pressure. The residue was used in the next step without further purification. The spectroscopic data for 11 were collected after purification by preparative TLC (20% ethyl acetate/hexane). IR (neat, cm⁻¹): 3071, 2997, 2932, 2858, 2252, 2144, 1770, 1732, 1714, 1428; ¹H-NMR (CDCl₃): δ 7.65 (dd, J=6.4 Hz, 0.9 Hz, 4H), 7.45-7.37 (m, 6H), 4.42 (t, J=9.1 Hz, 1H), 4.03 (t, J=9.1 Hz, 1H), 3.68-3.64 (m, 5H), 2.74 (ddd, J=16.4 Hz, 10.6 Hz, 5.2 Hz, 1H), 2.50-2.39 (m, 2H), 2.34 (ddd, J=14.8 Hz, 10.6 Hz, 4.9 Hz, 1H), 2.10 (ddd, J=14.8 Hz, 10.3 Hz, 5.2 Hz, 1H), 1.63-1.48 (m, 3H), 1.42-1.23 (m, 3H), 1.05 (s, 9H); ¹³C-NMR (CDCl₃): δ 175.4 (C), 174.2 (C), 173.0 (C), 135.5 (CH), 133.8 (C), 129.6 (CH), 127.6 (CH), 70.8 (CH₂), 63.2 (CH₂), 57.7 (C), 51.8 (CH₃), 45.1 (CH), 32.3 (CH₂), 28.7 (CH₂), 27.9 (CH₂), 27.7 (CH₂), 26.8 (CH₃), 23.3 (CH₂), 19.1 (C); HRMS (ESI+) 574.2343 (calcd for C₂₉H₃₇N₃NaO₆Si 574.2349).

(5S,9R*)-9-(4-((tert-Butyldiphenylsilyl)oxy)butyl)-7-oxa-1-azaspiro[4.4]nonane-2,6-dione (12)

A solution of 11 (16.5 mmol) in tetrahydrofuran (1.5 L) was heated at reflux for 2 h. After the reaction mixture was cooled to rt, acetic acid (150 mL) and water (150 mL) were added to the reaction mixture at rt. Then the mixture was heated again at reflux for 1.5 h. The reaction mixture was cooled to 0 °C. The reaction was quenched with saturated aqueous sodium carbonate. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was purified by flash column chromatography (50% ethyl acetate/hexane, then 67%) to afford 12 (4.4 g, 9.4 mmol, 57%, 3 steps) as a white form. IR (neat, cm⁻¹): 3203, 2932, 2857, 1779, 1696, 1461, 1428; ¹H-NMR (CDCl₃): δ 8.11 (br, 1H), 7.65 (dd, J=7.8 Hz, 1.4 Hz, 4H), 7.44-7.36 (m, 6H), 4.38 (dd, J=9.2 Hz, 7.2 Hz, 1H), 4.05 (dd, J=9.2 Hz, 7.6 Hz, 1H), 3.67 (t, J=6.2 Hz, 2H), 2.64 (dt, J=16.5 Hz, 8.4 Hz, 1H), 2.46-2.31 (m, 2H), 2.29 (m, 1H), 2.03 (ddd, J=12.4 Hz, 9.2 Hz, 8.3 Hz, 1H), 1.65-1.30 (m, 6H), 1.05 (s, 9H); ¹³C-NMR (CDCl₃): δ 179.0 (C), 177.2 (C), 135.5 (CH), 133.8 (C), 129.6 (CH), 70.8 (CH₂), 63.2 (CH₂), 44.5 (CH), 32.2 (CH₂), 29.5 (CH₂), 29.1 (CH₃), 26.8 (CH₃), 26.1 (CH₂), 23.3 (CH₂), 19.1 (C); HRMS (ESI+) 488.2252 (calcd for C₂₇H₃₇NNaO₆Si 488.2233).
(5S,6S,9R\(^\ast\))-6-Allyl-9-((tert-butyldiphenylsilyl)oxy)butyl)-7-oxa-1-azaspiro[4.4]nonane-2,8-dione (14a)

To a stirred solution of 12 (4.2 g, 9.0 mmol) in dichloromethane (90 mL) was added diisobutylaluminum hydride (1.0 M, 27.0 mL, 27.0 mmol) dropwise at –78 °C. After stirring for 30 min at –78 °C, the reaction was quenched with methanol. Then the reaction mixture was warmed to 0 °C. To the mixture was added aqueous potassium sodium tartrate (30%). The reaction mixture was warmed to rt. The solution was partitioned between dichloromethane and water. The aqueous phase was extracted four times with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue containing hemiacetal was used in the next step without further purification.

To a stirred solution of the hemiacetal material (9.0 mmol) in tetrahydrofuran (90 mL) was added allylmagnesium chloride (2.0 M, 45 mL, 90 mmol) dropwise at rt. After stirring for 24 hours at rt, the reaction mixture was cooled to 0 °C. The reaction was quenched with saturated aqueous ammonium chloride at 0 °C. The solution was partitioned between dichloromethane and water. The aqueous phase was extracted four times with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue containing diol was used in the next step without further purification.

To a stirred mixture of the diol (9.0 mmol) and AZADO (274 mg, 1.8 mmol) in acetonitrile (90 mL) and phosphate buffer (10 mL, pH=6.8) was added (diacetoxy)iodobenzene (8.7 g, 27 mmol) at 0 °C. After stirring for 3 hours, the reaction was quenched with saturated aqueous sodium thiosulfate. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was purified by MPLC (ethyl acetate/hexane) to afford 14a (1.4 g, 2.8 mmol, 31%, 3 steps) as a white solid. mp 106.0-106.3 °C; IR (neat, cm\(^{-1}\)): 3218, 2932, 2857, 1777, 1697, 1427, 1109; \(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 7.65 (dd, \(J=7.8\) Hz, 0.9 Hz, 4H), 7.43-7.35 (m, 6H), 7.30 (br, 1H), 5.82 (dddd, \(J=17.0\) Hz, 9.8 Hz, 7.5 Hz, 6.0 Hz, 1H), 5.20 (dd, \(J=17.0\) Hz, 0.92 Hz, 1H), 5.14 (dd, \(J=9.8\) Hz, 0.92 Hz, 1H), 4.19 (dd, \(J=8.5\) Hz, 5.3 Hz, 1H), 3.67 (t, \(J=6.2\) Hz, 2H), 2.56-2.27 (m, 6H), 2.14-2.08 (m, 2H), 1.78-1.67 (m, 2H), 1.62-1.40 (m, 3H), 1.04 (s, 9H); \(^{13}\)C-NMR (CDCl\(_3\)): \(\delta\) 177.5 (C), 175.8 (C), 135.5 (CH), 133.8 (C), 132.1 (CH), 129.5 (CH), 127.6 (CH), 118.8 (CH\(_2\)), 85.1 (CH), 67.7 (C), 63.3 (CH\(_2\)), 50.1 (CH), 33.0 (CH\(_2\)), 32.4 (CH\(_2\)), 29.2 (CH\(_3\)), 27.1 (CH\(_3\)), 26.8 (CH\(_3\)), 24.1 (CH\(_2\)), 23.9 (CH\(_3\)), 19.1 (C); HRMS (ESI+) 528.2544 (calcd for C\(_{30}\)H\(_{39}\)NNaO\(_4\)Si 528.2546).
(5S,6S,9R')-6-Allyl-9-(4-hydroxybutyl)-7-oxa-1-azaspiro[4.4]nonane-2,8-dione (S3)

To a stirred solution of 14a (1.4 g, 2.8 mmol) in methanol (30 mL) was added acetyl chloride (2.0 mL, 28 mmol) dropwise at rt. After stirring for 30 min, the reaction was quenched with saturated aqueous sodium hydrogen carbonate. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted four times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was used in the next step without purification. The spectroscopic data for S3 were collected after purification by preparative TLC (67% acetone/hexane). IR (neat, cm⁻¹): 3296, 2937, 2865, 1769, 1694, 1424, 1341, 1281; ¹H-NMR (CDCl₃): δ 7.33 (br, 1H), 5.82 (dddd, J = 17.4 Hz, 10.2 Hz, 7.5 Hz, 6.2 Hz, 1H), 5.20 (d, J = 17.4 Hz, 1H), 5.14 (dd, J = 10.2 Hz, 1H), 4.24 (dd, J = 8.4 Hz, 5.2 Hz, 1H), 3.65 (t, J = 5.5 Hz, 2H), 2.56-2.31 (m, 6H), 2.26-2.11 (m, 2H), 1.82-1.72 (m, 2H), 1.65-1.45 (m, 4H); ¹³C-NMR (CDCl₃): δ 177.7 (C), 176.1 (C), 132.2 (CH), 118.8 (CH₂), 85.2 (CH), 67.8 (C), 61.9 (CH₂), 50.4 (CH), 33.0 (CH₂), 32.4 (CH₂), 29.2 (CH₂), 27.3 (CH₂), 24.1 (CH₂), 23.8 (CH₂); HRMS (ESI+) 290.1370 (calcd for C₁₄H₂₁NNaO₄ 290.1368).

4-((5S,6S,9R')-6-Allyl-2,8-dioxo-7-oxa-1-azaspiro[4.4]nonan-9-yl)butyl methanesulfonate (15a)

To a stirred solution of S3 (2.8 mmol) and triethylamine (1.2 mL, 8.4 mmol) in dichloromethane (30 mL) was added methanesulfonyl chloride (433 µL, 5.6 mmol) dropwise at 0 °C. After stirring for 30 min at 0 °C, the reaction was quenched with a saturated aqueous sodium hydrogen carbonate. The solution was partitioned between dichloromethane and water. The aqueous phase was extracted twice with dichloromethane. The combined organic extracts were washed, dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was purified by column chromatography (first, 50% ethyl acetate/hexane then 100%; second, 50% acetone/hexane) to afford 15a (662 mg, 1.9 mmol, 69%, 2 steps) as a white form. IR (neat, cm⁻¹): 3235, 3079, 1770, 1696, 1348, 1171, 985, 938; ¹H-NMR (CDCl₃): δ 7.25 (br, 1H), 5.82 (ddddd, J = 17.0 Hz, 10.3 Hz, 7.3 Hz, 6.3 Hz, 1H), 5.19 (d, J = 17.0 Hz, 1H), 5.15 (dd, J = 10.3 Hz, 1H), 4.28-4.23 (m, 3H), 3.03 (s, 3H), 2.52-2.30 (m, 5H), 2.25-2.15 (m, 2H), 1.96-1.47 (m, 6H); ¹³C-NMR (CDCl₃): δ 177.6 (C), 175.7 (C), 132.1 (CH), 116.9 (CH₂), 85.2

S7
(CH), 69.4 (CH), 67.8 (C), 50.3 (CH), 37.3 (CH₃), 33.0 (CH₂), 29.2 (CH₂), 29.0 (CH₂), 27.2 (CH₂), 23.7 (CH₂), 23.6 (CH₂); HRMS (ESI+) 368.1128 (calcd for C₁₅H₂₃NNaO₆S 368.1144).

4-(((5S,6S,9R)-6-(3-((tert-Butyldimethylsilyl)oxy)propyl)-2,8-dioxo-7-oxa-1-azaspiro[4.4]nonan-9-yl)butyl methanesulfonate (16a)

To a stirred solution of 15a (660 mg, 1.9 mmol) in tetrahydrofuran (10 mL) was added thexylborane (0.5 M, 11.5 mL, 5.7 mmol) dropwise at 0 °C. After stirring for 30 min at 0 °C, the reaction was quenched with aqueous hydrogen peroxide (30%, 650 µL, 19.1 mmol) and aqueous sodium hydroxide (5% w/w, 153 µL, 0.2 mmol) at 0 °C. After stirring for 30 min, saturated aqueous sodium thiosulfate was added to the mixture at 0 °C. The solution was partitioned between dichloromethane and water. The aqueous phase was extracted four times with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue containing an alcohol was used in the next step without further purification.

To a stirred solution of the alcohol (1.9 mmol) and imidazole (520 mg, 7.6 mmol) in dichloromethane was added tert-butylchlorodimethylsilane (864 mg, 5.7 mmol) at rt. After stirring for 1 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate. The solution was partitioned between dichloromethane and water. The aqueous phase was extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was purified by flash column chromatography (50% ethyl acetate/hexane then 100% ethyl acetate) to afford 16a (175 mg, 0.37 mmol, 19%, 2 steps) as a white solid. mp 113.6-113.8 °C; IR (neat, cm⁻¹): 3164, 3073, 2952, 2930, 2857, 1755, 1696, 1471, 1350, 1173, 1106; ¹H-NMR (CDCl₃): δ 6.20-6.15 (br, 1H), 4.28-4.21 (m, 3H), 3.71 (dt, J=10.6 Hz, 5.3 Hz, 1H), 3.63 (dt, J=10.6 Hz, 5.4 Hz, 1H), 3.03 (s, 3H), 2.51-2.38 (m, 3H), 2.27-2.12 (m, 2H), 1.89-1.45 (m, 10H), 0.88 (s, 9H), 0.04 (s, 6H); ¹³C-NMR (CDCl₃): δ 177.2 (C), 175.9 (C), 85.9 (CH), 69.3 (CH₂), 67.8 (C), 62.0 (CH₂), 50.3 (CH), 37.4 (CH₃), 29.2 (CH₂), 29.1 (CH₂), 29.0 (CH₃), 27.2 (CH₂), 25.9 (CH₃), 24.7 (CH₂), 23.8 (CH₂), 23.7 (CH₂), 18.2 (C), −5.3 (CH₃); HRMS (ESI+) 500.2092 (calcd for C₂₁Hₙ₉NNaO₇Si 500.2114).

![Chemical Structure of S4]

To a stirred solution of 16a (175 mg, 0.37 mmol) in tetrahydrofuran (4 mL) was added zirconocene chloride hydride (239 mg, 0.93 mmol) at –20 °C. After stirring for 30 min at –20 °C, the reaction mixture was warmed to 0 °C. Then the reaction was quenched with a saturated aqueous sodium hydrogen carbonate. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was used in the next step without further purification. The spectroscopic data for S4 were collected after purification by preparative TLC (50% ethyl acetate/hexane). IR (neat, cm⁻¹): 2953, 2929, 2857, 1771, 1626, 1352, 1173, 1099; ¹H-NMR (CDCl₃): δ 7.71 (s, 1H), 4.27-4.20 (m, 3H), 3.68 (td, J=10.9 Hz, 5.3 Hz, 1H), 3.57 (dt, J=10.9 Hz, 5.6 Hz, 1H), 3.00 (s, 3H), 2.70-2.62 (m, 2H), 2.54 (dd, J=7.8 Hz, 5.5 Hz, 1H), 1.91-1.18 (m, 12H), 0.87 (s, 9H), 0.03 (s, 6H); ¹³C-NMR (CDCl₃): δ 176.9 (C), 168.1 (CH), 85.6 (CH), 84.6 (C), 69.7 (CH₂), 62.3 (CH₂), 50.8 (CH), 37.3 (CH₂), 37.2 (CH₂), 29.3 (CH₂), 29.1 (CH₂), 26.0 (CH₂), 25.9 (CH₂), 24.4 (CH₂), 23.9 (CH₃), 23.7 (CH₃), 18.2 (C), -5.3 (CH₃); HRMS (ESI+) 484.2161 (calcld for C₂₁H₃₉NNaO₆Si 484.2165).


![Chemical Structure of 17a]

To a stirred solution of S4 (0.37 mmol) and acetic acid (42 µL, 0.74 mmol) in 1,2-dichloroethane (4 mL) was added sodium triacetoxyborohydride (157 mg, 0.74 mmol) at 0 °C. After stirring for 20 min at 0 °C, the reaction mixture was warmed to rt. Then the reaction was quenched with a saturated aqueous sodium hydrogen carbonate. The solution was partitioned between dichloromethane and water. The aqueous phase was extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was used in the next step without further purification. The spectroscopic data for 17a were collected after purification by preparative TLC (67% ethyl acetate/hexane). IR
(3S*,3aS*,11aR*)-3-((tert-Butyldimethylsilyl)oxy)propyl)octahydrofuro[3,4-b]pyrrolo[1,2-a]-azepin-1(3H)-one (18a)

To a stirred solution of 17a (0.37 mmol) in methanol (4 mL) was added triethylamine (154 µL, 1.1 mmol) at rt. Then the reaction was heated at reflux for 15 h. The reaction mixture was cooled to rt. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was purified by flash column chromatography (10% ethyl acetate/hexane then 20%) to afford 18a (80 mg, 0.22 mmol, 59%, 3 steps) as a colorless oil. IR (neat, cm⁻¹): 2928, 2856, 1768, 1254, 1198, 1179, 1100, 835, 775; ¹H-NMR (CDCl₃): δ 4.18 (dd, J=7.8 Hz, 4.6 Hz, 1H), 3.71 (dt, J=10.6 Hz, 5.4 Hz, 1H), 3.64 (dt, J=10.6 Hz, 5.5 Hz, 1H), 3.28 (dd, J=15.5 Hz, 8.5 Hz, 1H), 3.12 (dd, J=15.5 Hz, 1.8 Hz, 1H), 2.86-2.79 (m, 2H), 2.55 (dd, J=15.1 Hz, 11.0 Hz, 1H), 2.13-2.10 (m, 1H), 1.98-1.53 (m, 13H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C-NMR (CDCl₃): δ 177.6 (C), 90.0 (CH), 70.8 (C), 62.7 (CH₂), 51.8 (CH₂), 51.7 (CH), 48.4 (CH₂), 38.2 (CH₂), 29.6 (CH₂), 26.5 (CH₂), 25.9 (CH₃), 25.1 (CH₂), 24.1 (CH₂), 23.7 (CH₂), 23.1 (CH₂), 18.3 (C), –5.3 (CH₃); HRMS (ESI+) 390.2441 (calcd for C₂₀H₃₇NNaO₃Si 390.2440).

(3S*,3aS*,11aR*)-3-(3-Hydroxypropyl)octahydrofuro[3,4-b]pyrrolo[1,2-a]azepin-1(3H)-one (S5)
To a stirred solution of 18a (80 mg, 0.22 mmol) in methanol (2 mL) was added acetyl chloride (155 µL, 2.2 mmol) at 0 °C. After stirring for 15 min at 0 °C, the reaction was quenched with a saturated aqueous sodium hydrogen carbonate. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was used in the next step without further purification. The spectroscopic data for S5 were collected after purification by preparative TLC (50% ethyl acetate/hexane). IR (neat, cm⁻¹): 3438, 2926, 2868, 1762, 1446, 1322, 1202, 973; ¹H-NMR (CDCl₃): δ 4.20 (dd, J = 9.6 Hz, 3.2 Hz, 1H), 3.76-3.66 (m, 2H), 3.28 (td, J = 8.5 Hz, 6.8 Hz, 1H), 3.16-3.11 (m, 1H), 2.88-2.80 (m, 2H), 2.55 (dd, J = 15.4 Hz, 11.7 Hz, 1H), 2.18-1.50 (m, 13H), 1.40-1.30 (m, 2H); ¹³C-NMR (CDCl₃): δ 177.4 (C), 90.0 (CH), 70.8 (C), 62.7 (CH₂), 51.8 (CH₂), 51.7 (CH), 48.5 (CH₂), 38.2 (CH₂), 29.8 (CH₂), 26.6 (CH₂), 24.9 (CH₂), 24.1 (CH₂), 23.7 (CH₂), 23.1 (CH₂); HRMS (ESI⁺) 276.1563 (caled for C₁₄H₂₃NNaO₂ 276.1576).

(3S*)-3,4,5,6,8,9,10,11-octahydro-1H-3,7-propanofuro[3,4-e]azecin-1-one (21a)

To a stirred solution of S5 (0.22 mmol) and N,N,N′,N′-tetramethylethylenediamine (97 µL, 0.66 mmol) in dichloromethane (1 mL) was added methanesulfonyl chloride (34 µL, 0.44 mmol) at −78 °C. After stirring for 10 min at −78 °C, the reaction mixture was warmed to 0 °C. After stirring for 20 min at 0 °C, the reaction was quenched with a saturated aqueous sodium hydrogen carbonate. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue containing a mesylate was used in the next step without further purification. The mesylate (0.22 mmol) was dissolved in methanol (1 mL) at rt. Then the reaction mixture was warmed to 40 °C for 50 min. To the reaction mixture was added i-Pr₂NEt (115 µL, 0.66 mmol) at 40 °C. After stirring for 30 min, the reaction mixture was cooled to rt. The reaction was quenched with saturated aqueous sodium hydrogen carbonate. The solution was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated in reduced pressure. The residue was purified by preparative TLC (Merck HPTLC silica gel 60 NH₂F₂54, 33% ethyl acetate/hexane) to afford 21a (26 mg, 0.11 mmol, 51%, 3 steps) as a white solid. mp 149.0-149.1 °C; IR (neat, cm⁻¹): 2923, 2850, 2793, 1727, 1658, 1446, 1108, 1034, 990; ¹H-NMR (CDCl₃): δ 4.86 (br, 1H), 2.74 (td, J = 12.7 Hz, 3.6 Hz, 1H), 2.61 (td, J = 13.6 Hz, 4.4 Hz, 1H), 2.53-2.47 (m, 2H), 2.27 (dt, J = 14.7 Hz, 3.0 Hz, 1H), 2.25-1.75 (m, 7H), 1.72-1.65 (m, 2H), 1.56-1.45 (m, 3H), 1.28-1.23 (m, 3H); ¹³C-NMR (CDCl₃): δ 174.9 (C), 165.1 (C), 125.3 (C), 1108, 1034, 990; ¹H-NMR (CDCl₃): δ 4.86 (br, 1H), 2.74 (td, J = 12.7 Hz, 3.6 Hz, 1H), 2.61 (td, J = 13.6 Hz, 4.4 Hz, 1H), 2.53-2.47 (m, 2H), 2.27 (dt, J = 14.7 Hz, 3.0 Hz, 1H), 2.25-1.75 (m, 7H), 1.72-1.65 (m, 2H), 1.56-1.45 (m, 3H), 1.28-1.23 (m, 3H); ¹³C-NMR (CDCl₃): δ 174.9 (C), 165.1 (C), 1108, 1034, 990; ¹H-NMR (CDCl₃): δ 4.86 (br, 1H), 2.74 (td, J = 12.7 Hz, 3.6 Hz, 1H), 2.61 (td, J = 13.6 Hz, 4.4 Hz, 1H), 2.53-2.47 (m, 2H), 2.27 (dt, J = 14.7 Hz, 3.0 Hz, 1H), 2.25-1.75 (m, 7H), 1.72-1.65 (m, 2H), 1.56-1.45 (m, 3H), 1.28-1.23 (m, 3H); ¹³C-NMR (CDCl₃): δ 174.9 (C), 165.1 (C), 125.3 (C),
81.4 (CH), 57.2 (CH₂), 56.9 (CH₂), 50.4 (CH₂), 32.1 (CH₂), 30.3 (CH₂), 29.0 (CH₂), 27.2 (CH₂), 26.0 (CH₂), 24.6 (CH₂), 20.0 (CH₂); HRMS (ESI+) 236.1651 (calcd for C₁₄H₂₂N₉O₂ (M+H)* 236.1649).