SUPPORTING INFORMATION

for

Polyketide Intermediate Mimics as Probes for Revealing Cryptic Stereochemistry of Ketoreductase Domains

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Supplementary Table 1. LC-MS/MS retention times for standards 18–25.

| Standards | Structure | Transition m/z | Retention time (min) |
|-----------|-----------|----------------|----------------------|
| 18        | ![Structure of Standard 18](image) | 314→198 | 4.24 |
| 20        | ![Structure of Standard 20](image) | 314→198 | 4.69 |
| 22/24     | ![Structure of Standards 22/24](image) | 292→216 | 3.99, 4.23 |
| 19        | ![Structure of Standard 19](image) | 328→212 | 5.97, 6.22 |
| 21        | ![Structure of Standard 21](image) | 328→212 | 5.87, 6.93 |
| 23/25     | ![Structure of Standards 23/25](image) | 306→230 | 5.68, 5.83 |
Supplementary Figure 4. LC-MS/MS analysis for enzymatic products of substrate 13 by PikKR2-DH2 didomain; red trace represents MRM (m/z 306→230); blue trace represents MRM (m/z 328→212); the relative enzymatic product ratio of (23 or 25):21 is 1:18.
Supplementary Figure 5. Michaelis-Menton curves of substrates 12, 13, 63, 64 and NADPH.

Supplementary Figure 6. Chiral HPLC trace of enzymatic products of diketide substrate 63 by PikKR2.
**General biology procedures.** All chemical reagents were purchased from Sigma-Aldrich and were used directly without further purification. *E. coli* BL21(DE3) cells were from New England BioLabs. IPTG was acquired through Gold Biotechnology. His60 Ni Superflow resin was purchased from Clontech Laboratories, Inc. OD$_{600}$ were measured on an Eppendorf BioPhotometer. Gel filtration purification was performed on HiLoad 16/600 Superdex 75 pg column (GE). The protein mass spectra data was obtained by QSTAR XL (AB Sciex) mass spectrometer. NADPH consumption was detected by SpectraMax M5e (Molecular Devices) microplate reader. LC–MS/MS was conducted with AB Sciex QTRAP 5500 mass spectrometer and Shimadzu LC system.

**Cloning.** The PikKR2 domain was cloned from the cosmid pLZ51 using ligation independent cloning (LIC)-compatible forward: 5’-TACTTCCAATCCAATGCCAGCCGCCTCGGCGGGG-3’; and reverse: 5’- TTATCCACTTCCAATGCTACGGCCGGGCCCGG-3’ primers (LIC-overhangs shown in **bold**; inserted stop codon **underlined**). The resulting insert was cloned into pMCSG7 vector using a LIC-qualified T4 DNA polymerase (Novagen). The resulting LIC-cloning reaction was directly transform into a chemically competent *E. coli* cell line (XL1Blue). The PikKR2-containing plasmid was isolated from a single colony grown overnight.

**Protein expression and purification.** Competent *E. coli* BL21 (DE3) cells were transformed with pMCSG7. The cells were grown in Terrific Broth (TB) media with 100 µg/mL ampicillin at 37 °C to an OD$_{600}$ of 1.6. The cultures were cooled to 20 °C and 200 µM IPTG was added to induce protein expression. After overnight expression, cells were harvested by centrifugation at 6000g and 4 °C for 10 min, and the resulting cell pellet was frozen (−80 °C, 10 min). The frozen pellet was resuspended in lysis buffer (50 mM HEPES, 300 mM NaCl, 10 mM imidazole, pH 8) and lysed by sonication. The lysate was clarified by centrifuging at 50000g and 4 °C for 10 min.
The cleared lysate was incubated with His-60 Ni superflow resin (2 mL) at 4 °C for 1 h and then loaded onto a gravity column. The column was washed with 14 mL of wash buffer (10 mM imidazole, 50 mM HEPES, 300 mM NaCl, pH 8.0) and eluted with 2.5 mL elution buffer (500 mM imidazole, 50 mM HEPES, 300 mM NaCl, pH 8.0). The protein was further purified via size exclusion chromatography on a Superdex 200 gel filtration column eluting at 0.5 mL min⁻¹ with 50 mM sodium phosphate (pH 7.1) and 150 mM NaCl. Purified PikKR2 was pooled and concentrated to afford 45 mg of purified enzyme per liter of culture that was greater than 95% pure as judged by SDS-PAGE. For long-term storage, the protein was transferred to storage buffer (20 mM Tris, 150 mM NaCl, 10% (v/v) glycerol, pH 7.5). The enzyme was stored at –80 °C and was stable for at least 6 months. The protein concentration was determined using the Bio-Rad protein assay kit, with bovine serum albumin as the standard. The native molecular weight and oligomeric state was estimated using gel filtration on a column calibrated with Gel Filtration Calibration Kit LMW (GE Healthcare) molecular-weight markers. Exact molecular weight of the purified monomeric protein was measured by ESI mass spectrometry.

**NADPH consumption kinetic assay.** PikKR2 activity was measured spectrophotometrically under initial velocity conditions via detection of NADPH consumption at 340 nm (λ_340 = 6220 M⁻¹ cm⁻¹). Each reaction contained PikKR2 (5 µM), NADPH (0.5 mM), sodium phosphate buffer (100 mM, pH 7.2) and substrates (10, 11, 63 and 64) at variable concentrations (0–40 mM) in a total volume of 100 µL. Substrates were dissolved in DMSO and the final concentration of DMSO was kept constant at 5% (v/v). The enzyme was incubated with NADPH at 25 °C for 15 min before the addition of substrates. The UV absorbance at 340 nm was monitored for 5 min at 15 s intervals. Kinetic parameters for NADPH were determined in a similar manner by pre-incubation with substrate 63 (40 mM), followed by addition of various NADPH concentrations
(0–500 µM). Each reaction was performed in triplicate. Apparent steady-state kinetic parameters were determined by fitting the normalized $v_0$ vs $[S]$ plots to the Michaelis–Menten equation by nonlinear regression analysis using GraphPad Prism 5.0.

**Kinetic assay and analysis of PikKR2 reaction products by LC-MS/MS.** Substrates 12 and 13 (1 mM) were incubated with PikKR2 (5 µM), NADPH (2 mM) and sodium phosphate buffer (100 mM, pH 7.2) in a total volume of 100 µL at 25 °C for 12 h. The reaction was quenched with 100 µL MeCN. Following centrifugation, the supernatant was diluted to 100-fold in 1:1 MeCN–100 mM sodium phosphate buffer and analyzed by LC-MS/MS employing a Kinetix reverse-phase C$_{18}$ column (50 mm × 2.1 mm, 2.6 µm, Phenomenex) operated at 0.4 mL min$^{-1}$ with a gradient between mobile phase A (15 mM ammonium acetate in H$_2$O) and mobile phase B (MeCN or MeOH). For optimal resolution, MeCN was chosen as the mobile phase B for 1-carbon-linker mimics 18, 20 and 22/24 while MeOH gave better separation for 2-carbon-linker mimics 19, 21 and 23/25. The gradient program was 0 min, 5% B; 2 min, 5% B; 7 min, 55% B; 8 min, 95% B; 9 min, 95% B; 9.5 min, 5% B, 12 min, 5% B. Retention times were obtained and compared to that of synthetic standards.

In order to carry out kinetic analysis, the enzymatic reactions were carried out in a total volume of 20 µL under initial velocity conditions containing PikKR2 (5 µM), NADPH (0.5 mM), sodium phosphate buffer (100 mM, pH 7.2) and substrates at variable concentrations (0–8 mM). Each reaction was incubated 25 °C for 12 min then quenched by addition of 20 µL MeCN containing an internal standard. Following centrifugation, the supernatant was diluted to 10-fold in precipitated 1:1 MeCN–sodium phosphate reaction buffer and quantified by LC-MS/MS system as described above. Synthetic standards were diluted in reaction buffer and processed as previously mentioned. Standards at varying concentrations were injected with a fixed
concentration of an internal standard to generate the standard curves. For the observed product 20, compound 19 was used as the internal standard. For the observed product 21, compound 18 was used as the internal standard. The amount of enzymatic products was calculated by plotting the area ratio into the standard curve and converted to initial velocity. The apparent steady-state kinetic parameters were determined as described for the NADPH consumption kinetic assay.

**PikKR products isolation and separation by chiral HPLC.** Substrates 63 (5 mM) was incubated with PikKR2 (25 µM), NADPH (10 mM) and sodium phosphate buffer (100 mM, pH 7.2) in a total volume of 500 µL at 25 °C for 12 h. The reaction was extracted with 5 × 500 µL EtOAc and then concentrated. The extract was dissolved in EtOH (500 µL) and injected to normal-phase HPLC using a ChiralCel OD column (250 × 4.6 mm). An isocratic elution (6: 94 EtOH: hexanes) at a flow rate of 0.8 mL min⁻¹ with monitoring at 235 nm was used to afford separation of the enantiomers.

**Product inhibition.** Product 21 (0–0.5 mM) was preincubated with PikKR2 (5 µM) in the reaction buffer described before for 10 min. Cofactor NADPH (2 mM) and substrates 13 (1 mM) were added and incubated at 25 °C for 12 h. The reaction mixture was quenched, diluted and analyzed by LC-MS/MS as described before. The amount of enzymatic product formation was calculated by subtracting the amount of the preincubated product.

**General chemistry procedures.** All commercial reagents were used as provided unless otherwise indicated. THF and CH₂Cl₂ were purified by passage through alumina columns. All reactions were performed under an inert atmosphere of dry N₂ in oven-dried (150 ºC) glassware. Flash chromatography was conducted on silica gel (230–400 mesh) using the indicated solvent systems. TLC was performed on 250 µm, F₂₅₄ silica gel plates, and were visualized by UV and
p-anisaldehyde stain. Optical rotations were determined on a Rudolph Autopol III polarimeter using the sodium D line (\( \lambda = 589 \) nm) at the temperature indicated and are reported as follows: \([\alpha]_{D}^{\text{temp}}\), concentration (\( c = \text{g/100 mL} \)), and solvent. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker 400 spectrometer at 400 Hz for \(^1\)H NMR and at 100 Hz for \(^{13}\)C NMR. Chemical shifts are reports in ppm from an internal standard of residual CHCl\(_3\) (7.26 ppm for \(^1\)H NMR and 77.00 for \(^{13}\)C NMR) or H\(_2\)O (4.80 ppm for \(^1\)H NMR). Proton chemical data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. High resolution mass spectra were obtained on a Bruker BioTOF II ESI-TOF/MS using either PEG or PPG standards as high resolution calibrants.

\((3S,4R,5R)-3\)-Hydroxy-1-\([(R)-4\text{-isopropyl-2-thioxothiazolidin-3-yl}]-4\text{-methyl-5-}\)

\([(\text{triisopropylsilyl})\text{oxy}]\text{heptan-1-one (28).} \) To a solution of thiazolidinethione 26 (574 mg, 2.82 mmol, 1.60 equiv) in CH\(_2\)Cl\(_2\) (10 mL) at –40 °C was added TiCl\(_4\) (0.33 mL, 3.0 mmol, 1.7 equiv). After stirring at –40 °C or 30 min, \(\text{i-Pr}_2\text{NEt (0.52 mL, 3.0 mmol, 1.7 equiv) was added and stirred at –40 °C for 2 h. The reaction mixture was cooled to –78 °C and then aldehyde 27 (481 mg, 1.77 mmol, 1.00 equiv) was added, followed by rinsing with CH\(_2\)Cl\(_2\) (3 \(\times\) 0.5 mL). After stirring at –78 °C for 110 min, the reaction was quenched by addition of saturated aqueous NH\(_4\)Cl (20 mL). The layers were separated and the aqueous layer was extracted with saturated aqueous NH\(_4\)Cl (20 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound (748 mg, 89%) as a yellow oil. \(R_f = 0.38\) (20% EtOAc/hexanes); \([\alpha]_{D}^{22} = –247.0\) (c 0.42, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 5.18\) (t, \(J = 7.1\) Hz, 1H), 4.45–4.37 (m, 1H), 4.02–3.92 (m, 1H), 3.55–3.43 (m, 2H), 3.37 (dd, \(J = 17.3, 9.0\) Hz, 1H), 3.28 (d, \(J = 1.5\) Hz, 1H), 3.00 (d, \(J = 11.5\) Hz, 1H), 2.37 (dq, \(J = 13.6, 6.8\) Hz, 1H), 1.72–1.58 (m, 3H), 1.14–1.00 (m, 24H),
0.96 (dt, J = 6.8, 4.9 Hz, 6H), 0.82 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 202.9, 172.2, 78.7, 71.5, 71.3, 44.1, 39.4, 30.6, 27.4, 19.0, 18.2, 17.8, 13.3, 10.0, 6.2; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{23}$H$_{45}$NNaO$_3$S$_2$Na 498.2502; Found 498.2512.

$N$-{2-[2-Nitrophenyl)sulfonamido]ethyl}acetamide (64). To a solution of $N$-(2-aminooethyl)acetamide (63) (90%, 0.53 mL, 5.0 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (50 mL) at room temperature was added Et$_3$N (1.05 mL, 7.50 mmol, 1.50 equiv) and 2-nitrobenzenesulfonyl chloride (1.44 g, 6.50 mmol, 1.30 equiv). After stirring at room temperature for 20 min, the reaction was quenched by addition of saturated aqueous NH$_4$Cl (50 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH$_2$Cl$_2$) afforded the title compound (1.43 g, 99%) as a colorless wax. $R_f$ = 0.24 (5% MeOH/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 500 MHz) δ 8.16–8.09 (m, 1H), 7.90–7.85 (m, 1H), 7.80–7.72 (m, 2H), 5.95 (s, 1H), 5.72 (t, J = 5.9 Hz, 1H), 3.42 (q, J = 5.7 Hz, 2H), 3.25 (q, J = 5.8 Hz, 2H), 1.99 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 171.1, 148.0, 133.8, 133.3, 132.9, 131.0, 125.4, 43.4, 39.5, 23.1; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{10}$H$_{13}$N$_3$NaO$_5$S$_2$Na 310.0468; Found 310.0472.

$N$-{2-[(N-Methyl-2-nitrophenyl)sulfonamido]ethyl}acetamide (65). To a solution of sulfonamide 64 (184 mg, 0.640 mmol, 1.00 equiv) in MeCN (6.4 mL) at room temperature was added Cs$_2$CO$_3$ (229 mg, 0.704 mmol, 1.10 equiv). After stirring at room temperature for 15 min, MeI (120 µL, 1.92 mmol, 3.00 equiv) was added. The reaction mixture was stirred at room temperature for an additional 1 h, and quenched by addition of H$_2$O (10 mL). The layers were separated, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL), and the combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. Purification by
flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (183 mg, 95%) as a colorless oil. Rᵣ = 0.31 (5% MeOH/CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 8.03–7.95 (m, 1H), 7.77–7.67 (m, 2H), 7.67–7.60 (m, 1H), 5.96 (s, 1H), 3.47 (q, J = 5.8 Hz, 2H), 3.38 (t, J = 5.7 Hz, 2H), 2.93 (s, 3H), 1.96 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.7, 148.1, 133.7, 132.0, 131.7, 131.0, 124.2, 49.1, 36.8, 34.7, 23.1; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₁H₁₅N₃NaO₅NaS 324.0625; Found 324.0622.

N-[2-(Methylamino)ethyl]acetamide (30). To a solution of N-methylsulphonamide 65 (151 mg, 0.500 mmol, 1.0 equiv) in MeCN (5 mL) at room temperature was added Cs₂CO₃ (326 mg, 1.00 mmol, 2.00 equiv), followed by PhSH (51 µL, 0.50 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 5.5 h until no starting material was observed by TLC (5% MeOH/CH₂Cl₂). The resulting solution of the title compound was used as such for the next reaction.

(3S,4R,5S)-N-(2-Acetamidoethyl)-3-hydroxy-4-methyl-5-
[(triisopropylsilyl)oxy]heptanamide (31). To a solution of thiazolidinethione 28 (230 mg, 0.483 mmol, 1.00 equiv) in CH₂Cl₂ (3.5 mL) at room temperature was added N-(2-aminoethyl)acetamide (29) (90%, 67 µL, 0.63 mmol, 1.3 equiv), and the reaction mixture immediately turned colorless. After stirring at room temperature for 5 min, the reaction was quenched by addition of saturated aqueous NH₄Cl (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (184 mg, 92%) as a white wax. Rᵣ = 0.26 (5% MeOH/CH₂Cl₂); [α]D²² = –14.8 (c 0.80, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 6.78 (s, 1H), 6.38 (s, 1H), 4.21 (d, J = 9.9 Hz, 1H), 4.04–3.97 (m, 1H), 3.96 (s, 1H), 3.52–3.28 (m, 4H), 2.49 (dd, J = 14.8, 10.1 Hz, 1H), 2.24 (d, J = 14.7
Hz, 1H), 1.96 (s, 3H), 1.68–1.57 (m, 3H), 1.18 (s, 21H), 0.92 (d, J = 7.0 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); 13C NMR (CDCl3, 100 MHz) δ 173.6, 170.8, 79.9, 72.9, 42.4, 40.5, 39.4, 39.2, 27.3, 23.2, 18.2, 13.4, 10.0, 5.1; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for C21H44N2NaO4SiNa 439.2963; Found 439.2963.

(3S,4R,5R)-N-(2-Acetamidoethyl)-3-hydroxy-N,4-dimethyl-5-
[(triisopropylsilyl)oxy]heptanamide (32). To a solution of thiazolidinethione 28 (50 mg, 0.11 mmol, 1.0 equiv) in CH2Cl2 (2 mL) at room temperature was added N-methylamine 30 (0.1 M in MeCN, 1.3 mL, 0.13 mmol, 1.2 equiv) dropwise and the yellow color of the reaction mixture immediately faded. The reaction was stirred at room temperature for 1 h and quenched by addition of saturated aqueous NH4Cl (5 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na2SO4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH2Cl2) afforded the title compound (33 mg, 73%) as a colorless oil. Rf = 0.22 (5% MeOH/CH2Cl2); [α]22 D = –22.3 (c 0.88, CHCl3); 1H NMR (CDCl3, 400 MHz, approximately 3:1 mixture of rotamers where the integrations have been normalized) δ 6.60 (s, 0.25H), 6.33 (s, 0.75H), 4.41 (d, J = 9.7 Hz, 0.25H), 4.27–4.17 (m, 0.75H), 4.06–3.98 (m, 0.25H), 3.97–3.90 (m, 1H), 3.87 (s, 0.75H), 3.80–3.70 (m, 0.25H), 3.64–3.55 (m, 0.75H), 3.54–3.44 (m, 1H), 3.44–3.31 (m, 2H), 3.04 (s, 2.25H), 2.94 (s, 0.75H), 2.79 (dd, J = 14.5, 9.8 Hz, 0.25H), 2.56 (dd, J = 15.7, 8.8 Hz, 0.75H), 2.45 (dd, J = 15.7, 3.8 Hz, 0.75H), 2.22 (dd, J = 14.5, 1.9 Hz, 0.25H), 1.96–1.89 (m, 3H), 1.74–1.67 (m, 1H), 1.67–1.55 (m, 2H), 1.07 (s, 21H), 0.99–0.92 (m, 3H), 0.87–0.79 (m, 3H); 13C NMR (CDCl3, 100 MHz) δ Major rotamer: 174.1, 170.6, 78.0, 71.3, 46.9, 40.1, 38.4, 38.3, 36.0, 27.16, 23.2, 18.3, 13.3, 10.1, 7.4; Minor
rotamer: 172.2, 170.6, 79.5, 73.6, 48.5, 39.4, 38.2, 37.4, 33.0, 27.23, 22.9, 18.1, 13.4, 10.0, 6.0;
HRMS (ESI-TOF) m/z: [M + Na]^+ Calcd for C_{22}H_{46}N_{2}NaO_{4}SiNa 453.3119; Found 453.3110.

(4S,5R)-N-(2-Acetamidoethyl)-4-methyl-3-oxo-5-[(triisopropylsilyl)oxy]heptanamide (33). To a solution of amide 31 (31 mg, 0.074 mmol, 1.0 equiv) in CH_{2}Cl_{2} (2 mL) at room temperature was added 4-methylmorpholine N-oxide (13 mg, 0.11 mmol, 1.5 equiv) and 4 Å molecular sieves (37 mg), followed by the addition of TPAP (1.3 mg, 0.0037 mmol, 5%). The reaction mixture was stirred at room temperature for 2 h, and then MeCN (0.2 mL) was added. After stirring for an additional 3.5 h, the reaction was concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH_{2}Cl_{2}) afforded the title compound (15 mg, 48%) as a colorless oil. \( R_f = 0.32 \) (5% MeOH/CH_{2}Cl_{2}); \([\alpha]^2_{D} = 23.2 \ (c 0.50, \text{CHCl}_3)\); \(^{1}\text{H} \text{NMR (CDCl}_{3}, 400 \text{MHz}) \delta 7.43 \ (s, 1\text{H}), 6.34 \ (s, 1\text{H}), 4.21–4.02 \ (m, 1\text{H}), 3.66–3.32 \ (m, 6\text{H}), 2.84–2.67 \ (m, 1\text{H}), 1.97 \ (s, 3\text{H}), 1.66–1.46 \ (m, 2\text{H}), 1.10 \ (d, J = 6.9 \text{ Hz}, 3\text{H}), 1.05 \ (s, 21\text{H}), 0.87 \ (t, J = 7.4 \text{ Hz}, 3\text{H}); \(^{13}\text{C} \text{NMR (CDCl}_{3}, 100 \text{MHz}) \delta 209.4, 170.8, 167.4, 74.8, 51.6, 47.8, 40.4, 39.6, 27.6, 23.2, 18.2, 12.9, 9.94, 9.85; \) HRMS (ESI-TOF) m/z: [M + Na]^+ Calcd for C_{21}H_{42}N_{2}NaO_{4}SiNa 437.2806; Found 437.2805.

(4S,5R)-N-(2-Acetamidoethyl)-N,4-dimethyl-3-oxo-5-[(triisopropylsilyl)oxy]heptanamide (34). To a solution of N-methylamide 32 (33 mg, 0.077 mmol, 1.0 equiv) in CH_{2}Cl_{2} (1 mL) at room temperature was added 4-methylmorpholine N-oxide (13 mg, 0.12 mmol, 1.5 equiv) and 4 Å molecular sieves (39 mg), followed by the addition of TPAP (2.7 mg, 0.0077 mmol, 10%). The reaction mixture was stirred at room temperature for 1 h until no starting material was observed by TLC (5% MeOH/CH_{2}Cl_{2}). The reaction was concentrated under reduced pressure, and purification by flash chromatography (5% MeOH/CH_{2}Cl_{2}) afforded the title compound (25 mg, 76%) as a colorless oil. \( R_f = 0.30 \) (5% MeOH/CH_{2}Cl_{2}); \([\alpha]^2_{D} = 21.3 \ (c 0.60, \text{CHCl}_3)\); \(^{1}\text{H}
NMR (CDCl₃, 400 MHz, approximately 13:3:4 mixture of major rotamer:minor rotamer:enol where the integrations have been normalized) δ 14.56 (s, 0.2H), 6.42 (s, 1H), 5.15 (s, 0.2H), 4.18–4.04 (m, 1H), 3.83–3.66 (m, 1.6H), 3.65–3.36 (m, 4H), 3.01–2.92 (m, 3H), 2.92–2.88 (m, 0.15H), 2.88–2.81 (m, 0.65H), 2.43–2.36 (m, 0.2H), 2.00 (s, 0.45H), 1.96 (s, 1.95H), 1.93 (s, 0.6H), 1.66–1.43 (m, 2H), 1.16–1.10 (m, 3H), 1.09–1.01 (m, 21H), 0.94–0.84 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz, major rotamer) δ 207.1, 170.9, 168.8, 75.3, 51.5, 49.1, 46.8, 37.6, 36.4, 27.5, 23.2, 18.2, 12.9, 11.1, 10.1; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₂₂H₄₄N₂NaO₄SiNa 451.2963; Found 451.2955.

(4S,5R)-N-(2-Acetamidoethyl)-5-hydroxy-4-methyl-3-oxoheptanamide (10). To a solution of silyl ether 33 (14 mg, 0.034 mmol, 1.0 equiv) in MeCN (0.5 mL) at 0 °C was added a solution of 48% HF in MeCN (2 mL, 11:89). The reaction mixture was allowed to warm up to room temperature and stirred at room temperature for 10 h. The reaction mixture was cooled in an ice bath and quenched by addition of saturated aqueous NaHCO₃ until pH 7 was obtained. The mixture was extracted with n-butanol (3 × 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% MeOH/CH₂Cl₂) afforded the title compound (6.4 mg, 74%) as a colorless oil. Rƒ = 0.19 (10% MeOH/CH₂Cl₂); [α]D²¹ = 7.7 (c 0.32, CHCl₃); ¹H NMR (CDCl₃, 400 MHz, approximately 3:1 mixture of rotamers where the integrations have been normalized) δ 7.22 (s, 1H), 6.39 (s, 0.25H), 6.30 (s, 0.75H), 3.96 (s, 0.75H), 3.58 (s, 0.25H), 3.59–3.31 (m, 6H), 3.09 (s, 1H), 2.79–2.63 (m, 1H), 1.98 (s, 3H), 1.71–1.37 (m, 2H), 1.11 (d, J = 6.6 Hz, 2.25H), 1.07 (d, J = 6.7 Hz, 0.75H), 1.02–0.93 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ Major rotamer: 209.6, 171.6, 167.25, 72.6, 51.9, 48.4, 40.0, 39.62, 27.2, 23.17, 10.6, 8.6; Minor rotamer: 210.5, 171.5,
(4S,5R)-N-(2-Azetamidoethyl)-5-hydroxy-N,4-dimethyl-3-oxoheptanamide (11). To a solution of silyl ether 34 (25 mg, 0.058 mmol, 1.0 equiv) in MeCN (1.0 mL) at 0 °C was added a solution of 48% HF in MeCN (3 mL, 11:89). The reaction mixture was allowed to warm up to room temperature and stirred at room temperature for 11.5 h until all the starting material was consumed by TLC (5% MeOH/CH₂Cl₂). The reaction mixture was quenched by addition of saturated aqueous NaHCO₃ until pH 7, then extracted with n-butanol (3 × 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% MeOH/CH₂Cl₂) afforded the title compound (12 mg, 75%) as a colorless oil. Rᶠ = 0.33 (10% MeOH/CH₂Cl₂); [α]₂¹⁰ = 22.6 (c 0.31, CHCl₃); ¹H NMR (CDCl₃, 400 MHz, approximately 13:3:4 mixture of major rotamer:minor rotamer:enol where the integrations have been normalized) δ 14.90 (s, 0.2H), 6.50 (s, 0.35H), 6.37 (s, 0.65H), 5.13 (s, 0.2H), 4.03–3.87 (m, 0.8H), 3.86–3.61 (m, 1.8H), 3.59–3.31 (m, 4H), 3.03–2.92 (m, 3H), 2.79–2.66 (m, 0.8H), 2.33–2.27 (m, 0.2H), 2.00–1.89 (m, 3H), 1.58–1.36 (m, 2H), 1.19–1.05 (m, 3H), 0.96 (t, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz, major rotamer) δ 208.4, 170.9, 168.9, 72.9, 51.4, 47.7, 46.9, 37.5, 36.5, 26.9, 23.2, 10.5, 9.1; HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for C₁₂H₂₂N₂NaO₄SiNa 281.1472; Found 281.1471.

(3S,4S,5R)-N-(2-Azetamidoethyl)-3,5-dihydroxy-4-methylheptanamide (66). To a solution of silyl ether 31 (39 mg, 0.094 mmol, 1.0 equiv) in MeCN (1 mL) at 0 °C was added a solution of 48% HF in MeCN (5 mL, 11:89). After stirring at 0 °C for 5 h, the reaction mixture was cooled in an ice bath and quenched by the addition of saturated aqueous NaHCO₃ until pH 7. The mixture was extracted with n-butanol (3 × 10 mL), and the combined organic layers were dried
(Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% MeOH/CH₂Cl₂) afforded the title compound (23 mg, 96%) as a colorless wax. Rₓ = 0.16 (10% MeOH/CH₂Cl₂); [α]D²¹ = −9.8 (c 0.50, CHCl₃); ¹H NMR (D₂O, 400 MHz) δ 4.20–4.09 (m, 1H), 3.74–3.61 (m, 1H), 3.43–3.25 (m, 4H), 2.59–2.38 (m, 2H), 2.00 (s, 3H), 1.66–1.48 (m, 3H), 1.03–0.86 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 173.6, 171.6, 77.7, 73.5, 41.3, 40.6, 39.83, 39.77, 27.8, 23.1, 10.4, 5.1; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₂H₂₄N₂O₄SiNa 283.1628; Found 283.1635.

**N-(2-Acetamidoethyl)-2-[(4S,5S,6R)-6-ethyl-2,2,5-trimethyl-1,3-dioxan-4-yl]acetamide (67).**

To a solution of diol 66 (19 mg, 0.073 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL) at room temperature was added 2,2-dimethoxypropane (0.18 mL, 1.5 mmol, 20 equiv) and a catalytic amount of PPTS. The reaction mixture was stirred at room temperature for 2 h and then quenched by addition of saturated aqueous NaHCO₃ (5 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (16 mg, 73%) as colorless oil. Rₓ = 0.34 (5% MeOH/CH₂Cl₂); [α]D²² = −9.4 (c 0.50, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 6.62 (s, 1H), 6.38 (s, 1H), 4.30 (d, J = 9.2 Hz, 1H), 3.78 (t, J = 6.7 Hz, 1H), 3.45–3.25 (m, 4H), 2.45 (dd, J = 14.8, 9.7 Hz, 1H), 2.17 (d, J = 14.8 Hz, 1H), 1.97 (s, 3H), 1.59–1.46 (m, 1H), 1.43 (s, 3H), 1.41–1.35 (m, 4H), 0.87 (t, J = 7.4 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 172.8, 170.9, 99.2, 74.6, 70.6, 40.7 (ovlp, 2C), 39.4, 34.5, 30.0, 25.4, 23.2, 19.7, 9.6, 4.8; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₅H₂₈N₂NaO₄SiNa 323.1941; Found 323.1945.

**(2S,3R)-1-[(R)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-[(triethylsilyl)oxy]-2-methylpentan-1-one (36).** To a solution of alcohol 35 (702 mg, 2.17 mmol, 1.00 equiv) in CH₂Cl₂ (30 mL) at
0 °C was added i-Pr₂NEt (0.68 mL, 3.9 mmol, 1.8 equiv) and TESOTf (0.74 mL, 3.3 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 100 min. The reaction was quenched by the addition of saturated aqueous NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl (40 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound (928 mg, 98%) as a yellow oil. 

Rᶠ = 0.57 (20% EtOAc/hexanes); [α]_D²² = −106.3 (c 1.0, CHCl₃); 

¹H NMR (CDCl₃, 400 MHz) δ 7.37–7.26 (m, 5H), 5.40–5.31 (m, 1H), 4.72 (p, J = 6.8 Hz, 1H), 4.16 (q, J = 5.5 Hz, 1H), 3.33 (dd, J = 11.5, 7.2 Hz, 1H), 3.21 (dd, J = 13.1, 3.7 Hz, 1H), 3.03 (dd, J = 13.0, 10.7 Hz, 1H), 2.86 (dd, J = 11.6, 0.9 Hz, 1H), 1.64–1.53 (m, 2H), 1.21 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.9 Hz, 9H), 0.92 (t, J = 7.4 Hz, 3H), 0.63 (q, J = 8.0 Hz, 6H); 

¹³C NMR (CDCl₃, 100 MHz) δ 201.0, 176.9, 136.6, 129.4, 128.9, 127.2, 74.0, 69.1, 43.4, 37.1, 31.6, 28.4, 14.0, 9.6, 7.0, 5.3; HRMS (ESI-TOF) m/z: [M + Na]⁺ 

Calcd for C₂₂H₃₅NNaO₂S₂SiNa 460.1771; Found 460.1766.

(2S,3R)-2-Methyl-3-[(triethylsilyl)oxy]pentanal (37). To a solution of thiazolidinethione 36 (928 mg, 2.12 mmol, 1.00 equiv) in CH₂Cl₂ (50 mL) at −78 °C was added i-Bu₂AlH (1.2 M in PhMe, 2.83 mL, 3.39 mmol, 1.60 equiv). The reaction mixture was stirred at −78 °C until the bright yellow color faded (<5 min), then immediately quenched by addition of saturated aqueous sodium potassium tartrate (40 mL). The reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The layers were separated and aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl (80 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was dissolved in hexanes (4 mL) and purified by flash chromatography (10% EtOAc/hexanes) to
afford the title compound (419 mg, 86%) as a colorless oil. $R_f = 0.47$ (10% EtOAc/hexanes); $[\alpha]^2_{D} = 53.7$ (c 1.1, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 9.75 (s, 1H); 4.05 (dt, $J = 6.5$, 3.8 Hz, 1H), 2.49–2.37 (m, 1H), 1.60–1.43 (m, 2H), 0.93 (t, $J = 7.9$ Hz, 9H), 0.88 (t, $J = 7.4$ Hz, 3H), 0.57 (q, $J = 7.6$ Hz, 6H); $^13$C NMR (CDCl$_3$, 100 MHz) $\delta$ 205.3, 73.4, 50.9, 27.5, 10.1, 7.5, 6.8, 5.1; HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ Calcd for C$_9$H$_{20}$NaO$_2$SiNa 253.1594; Found 253.1605.

(3R,4R,5R)-3-Hydroxy-N-methoxy-N,4-dimethyl-5-[(triethylsilyl)oxy]heptanamide (38) and (3S,4R,5R)-3-hydroxy-N-methoxy-N,4-dimethyl-5-[(triethylsilyl)oxy]heptanamide (39). To a solution of distilled $i$-Pr$_2$NH (0.36 mL, 2.6 mmol, 1.4 equiv) in THF (30 mL) at $-78 ^\circ$C was added $n$-BuLi (2.2 M in THF, 1.1 mL, 2.4 mmol, 1.3 equiv). After stirring at $-78 ^\circ$C for 30 min, $N$-methoxy-$N$-methylacetamide (0.25 mL, 2.4 mmol, 1.3 equiv) was added. The reaction mixture was stirred at $-78 ^\circ$C for an additional 30 min, followed by the addition of a solution of aldehyde 37 (419 mg, 1.82 mmol, 1.00 equiv) in THF (0.5 mL) in a dropwise fashion with the aid of THF (2 $\times$ 0.5 mL). The reaction mixture was stirred at $-78 ^\circ$C for and additional 3 h, then quenched by the addition of saturated aqueous NH$_4$Cl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (50% EtOAc/hexanes) to afford the title compounds 38 (334 mg, 55%) and 39 (140 mg, 23%) as colorless oils (total yield = 78%, dr = 7: 3). Compound 38: $R_f = 0.42$ (50% EtOAc/hexanes); $[\alpha]^2_{D} = 36.8$ (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 4.14 (s, 1H), 4.00 (dt, $J = 9.0$, 2.6 Hz, 1H), 3.93 (dt, $J = 6.7$, 2.1 Hz, 1H), 3.69 (s, 3H), 3.18 (s, 3H), 2.65 (d, $J = 15.7$ Hz, 1H), 2.51 (dd, $J = 15.6$, 9.3 Hz, 1H), 1.72–1.63 (m, 1H), 1.59–1.45 (m, 2H), 0.95 (t, $J = 7.9$ Hz, 9H), 0.86 (t, $J = 7.4$ Hz, 3H), 0.80 (d, $J = 7.0$ Hz, 3H), 0.61 (q, $J = 7.9$ Hz, 6H); $^13$C NMR (CDCl$_3$, 100 MHz) $\delta$
173.7, 75.0, 70.0, 61.2, 41.8, 36.9, 31.9, 26.6, 10.6, 10.5, 6.9, 5.1; HRMS (ESI-TOF) m/z: [M + Na]^+ Calcd for C_{16}H_{35}NNaO_{4}SiNa 356.2228; Found 356.2223. Compound 39: \( R_f = 0.32 \) (50% EtOAc/hexanes); \([\alpha]_{D}^{22} = -32.4 \) (c 1.0, CHCl_3); \(^1\)H NMR (CDCl_3, 400 MHz) \( \delta 4.23-4.16 \) (m, 1H), 3.83–3.77 (m, 1H), 3.67 (d, \( J = 1.5 \) Hz, 1H), 2.68–2.58 (m, 2H), 1.67 (tq, \( J = 7.0, 3.7 \) Hz, 1H), 1.59–1.50 (m, 2H), 0.95 (t, \( J = 8.0 \) Hz, 9H), 0.94 (d, \( J = 7.0 \) Hz, 3H), 0.84 (t, \( J = 7.4 \) Hz, 3H), 0.61 (q, \( J = 7.9 \) Hz, 6H); \(^{13}\)C NMR (CDCl_3, 100 MHz) \( \delta 173.5, 77.2, 70.2, 61.1, 40.3, 36.7, 31.7, 26.8, 9.8, 7.7, 6.8, 5.2; \) HRMS (ESI-TOF) m/z: [M + Na]^+ Calcd for C_{16}H_{35}NNaO_{4}SiNa 356.2228; Found 356.2223.

\((4R,5R,6R)-1\)-Chloro-4-hydroxy-5-methyl-6-[(triethylsilyl)oxy]octan-2-one (40). To a solution of Weinreb amide 38 (144 mg, 0.432 mmol, 1.00 equiv) in THF (25 mL) at −78 °C was added ClCH_2I (0.19 mL, 2.6 mmol, 6.0 equiv) and MeLi (1.6 M in Et_2O, 1.1 mL, 1.7 mmol, 4.0 equiv) dropwise. After stirring at −78 °C for 3 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (20 mL). The reaction mixture was allowed to warm up to room temperature and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (20 ml), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound (81 mg, 58%) as a colorless oil. \( R_f = 0.62 \) (30% EtOAc/hexanes); \([\alpha]_{D}^{22} = 40.4 \) (c 1.0, CHCl_3); \(^1\)H NMR (CDCl_3, 400 MHz) \( \delta 4.36 \) (s, 1H), 4.22 (s, 2H), 4.07 (t, \( J = 8.7 \) Hz, 1H), 3.74 (dt, \( J = 6.3, 2.4 \) Hz, 1H), 2.70 (dd, \( J = 14.6, 3.1 \) Hz, 1H), 2.60 (dd, \( J = 14.6, 8.5 \) Hz, 1H), 1.80–1.67 (m, 1H), 1.53 (p, \( J = 7.1 \) Hz, 2H), 0.95 (t, \( J = 7.8 \) Hz, 9H), 0.91 (t, \( J = 7.4 \) Hz, 3H), 0.79 (d, \( J = 7.1 \) Hz, 3H), 0.61 (q, \( J = 8.2 \) Hz, 6H); \(^{13}\)C NMR (CDCl_3, 100 MHz) \( \delta 202.2, 78.2, 71.1, 49.6, 45.8, 42.3, 24.7, 12.7, 11.0, 6.8, 5.0; \) HRMS (ESI-TOF) m/z: [M + Na]^+ Calcd for C_{15}H_{31}ClNaO_{3}SiNa 345.1623; Found 345.1621.
(5S,6R)-1-Chloro-5-methyl-6-[(triethylsilyl)oxy]octan-2,4-dione (41). To a solution of alcohol 40 (79 mg, 0.24 mmol, 1.0 equiv) in EtOAc (5 mL) was added IBX (45%, 457 mg, 0.734 mmol, 3.00 equiv). After heating at reflux for 3.5 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (62 mg, 79%) as an orange oil. $R_f = 0.62$ (20% EtOAc/hexanes); $[\alpha]_D^{22} = 12.3$ (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 15.15 (s, 1H), 5.88 (s, 1H), 4.04 (s, 2H), 3.90 (q, $J = 5.7$ Hz, 1H), 2.57–2.43 (m, 1H), 1.60–1.43 (m, 2H), 1.14 (d, $J = 6.9$ Hz, 3H), 0.94 (t, $J = 7.9$ Hz, 9H), 0.89 (t, $J = 7.4$ Hz, 3H), 0.57 (q, $J = 7.6$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 196.2, 188.2, 97.7, 74.8, 46.6, 44.6, 28.0, 11.8, 9.5, 6.9, 5.1; HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ Calcd for C$_{15}$H$_{29}$ClNaO$_3$SiNa 343.1467; Found 343.1463.

(5S,6R)-5-Methyl-1-[N-(2-acetamidoethyl)thio]-6-[(triethylsilyl)oxy]octan-2,4-dione (42). To a solution of chloromethyl ketone 41 (66 mg, 0.21 mmol, 1.0 equiv) in THF (5 mL) was added N-acetylcysteamine (24 µL, 0.23 mmol, 1.1 equiv) and a catalytic amount of Cs$_2$CO$_3$ at room temperature. The reaction mixture was stirred at room temperature for 7.5 h. The reaction was quenched by the addition of saturated aqueous NH$_4$Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure to afford the title compound (76 mg) as a crude product. Due to its instability, the crude product was submitted to the next reaction without further purification. An analytically pure sample was obtained by purification by flash chromatography (5% MeOH/EtOAc) to afford the pure title compound as a light yellow oil. $R_f = 0.54$ (5% MeOH/CH$_2$Cl$_2$); $[\alpha]_D^{22} = 6.0$ (c 0.15, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz, approximately 7:1 mixture of enol:ketone forms where the integrations have been normalized) $\delta$ 15.26 (s, 0.88H), 6.02 (s, 1H), 5.69 (s, 0.88H), 3.92–3.84
(m, 1H), 3.51–3.39 (m, 2H), 3.36 (s, 0.25H), 3.24 (s, 1.75H), 2.73 (t, $J = 6.2$ Hz, 1.75H), 2.65 (t, $J = 6.2$ Hz, 0.25H), 2.54–2.40 (m, 1H), 1.99 (s, 3H), 1.59–1.42 (m, 2H), 1.13 (d, $J = 6.9$ Hz, 2.62H), 1.07 (d, $J = 5.4$ Hz, 0.38H), 0.98–0.86 (m, 12H), 0.68–0.50 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz, enol form) $\delta$ 194.9, 192.0, 170.1, 99.0, 74.7, 46.3, 38.2, 37.8, 32.5, 28.0, 23.3, 12.0, 9.5, 7.0, 5.1; HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ Calcd for C$_{19}$H$_{37}$NNaO$_4$SiNa 426.2105; Found 426.2100.

(5S,6R)-6-Hydroxy-5-methyl-1-[N-(2-acetamidoethyl)thio]octane-2,4-dione (12). To a solution of crude silyl ether 42 (21 mg, 0.052 mmol, 1.0 equiv) in THF (4 mL) at 0 °C was added a solution of 70% HF•pyridine:pyridine:THF (1 mL, 1:2:8) in a dropwise fashion. The reaction mixture was stirred at 0 °C for 13 h until the starting material was consumed by TLC (5% MeOH/EtOAc). The reaction was cooled in an ice bath, quenched by addition of saturated aqueous NaHCO$_3$ to pH 7, and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in MeCN (1 mL), and purification by reverse-phase HPLC (Dynamax C$_{18}$, 10 × 250 mm, Varian) using a gradient elution (20–30% MeCN/H$_2$O at 0–15 min; 30–60% MeCN/H$_2$O at 15-28 min; 60–20% MeCN/H$_2$O at 28–40 min) at a flow rate of 3 mL/min monitoring at 254 nm afforded the title compound (10 mg, 30% over 2 steps) as a colorless oil. $R_f = 0.26$ (5% MeOH/EtOAc); Due to the instability of the compound an optical rotation could not be obtained; $^1$H NMR (CDCl$_3$, 400 MHz, approximately 8:5:7
mixture of A:B:C where the integrations have been normalized \( \delta \) 6.65–6.43 (m, 1H), 5.74 (s, 0.35H), 4.35–4.18 (m, 0.6H), 3.97–3.59 (m, 3.7H), 3.54–3.40 (m, 0.4H), 3.33 (d, \( J = 13.7 \) Hz, 0.25H), 3.26–3.05 (m, 1.4H), 3.04–2.86 (m, 1.4H), 2.82 (d, \( J = 14.4 \) Hz, 0.25H), 2.64–2.27 (m, 2H), 2.22–2.09 (m, 0.35H), 1.99 (s, 3H), 1.78–1.63 (m, 0.5H), 1.59–1.37 (m, 1.5H), 1.17 (d, \( J = 7.0 \) Hz, 1.2H), 1.14–1.08 (m, 1.8H), 1.04–0.91 (m, 3H); Due to the instability of the compound a \(^{13}\)C NMR could not be obtained; HRMS (ESI-TOF) \( \text{m/z} \): [M + Na]\(^{+}\) Calcd for C\(_{12}\)H\(_{23}\)NNaO\(_{4}\)SNa 312.1240; Found 312.1244.

\((5R,6R,7R)-5\)-Hydroxy-6-methyl-7-[(triethylsilyl)oxy]non-1-en-3-one (43). To a solution of tetravinyltin (0.12 mL, 0.68 mmol, 1.2 equiv) in THF (10 mL) at \(-78^\circ\)C was added MeLi (1.60 M in Et\(_2\)O, 1.43 mL, 2.28 mmol, 4.00 equiv). The reaction mixture was stirred at \(-78^\circ\)C for 30 min, followed by the addition of a solution of Weinreb amide 38 (190 mg, 0.570 mmol, 1.00 equiv) in THF (3 mL) in a dropwise fashion. After stirring at \(-78^\circ\)C for an additional 2.5 h, the reaction mixture was quenched by the addition of saturated aqueous NH\(_4\)Cl (10 mL) then warmed to room temperature and diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na\(_2\)SO\(_4\)), and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound (71 mg, 42%) as a colorless oil. \( R_f = 0.50 \) (20% EtOAc/hexanes); \( [\alpha]_D^{21} = 31.4 \) (c 0.80, CHCl\(_3\)). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 6.40 (dd, \( J = 17.6, 10.5 \) Hz, 1H), 6.24 (d, \( J = 17.6 \) Hz, 1H), 5.83 (d, \( J = 11.3 \) Hz, 1H), 4.14–4.06 (m, 1H), 4.02 (d, \( J = 2.8 \) Hz, 1H), 3.84 (dt, \( J = 6.9, 2.5 \) Hz, 1H), 2.77 (dd, \( J = 16.0, 3.4 \) Hz,1H), 2.68 (dd, \( J = 16.0, 8.4 \) Hz, 1H), 1.76–1.67 (m, 1H), 1.59–1.48 (m, 2H), 0.95 (t, \( J = 7.9 \) Hz, 9H), 0.88 (t, \( J = 7.4 \) Hz, 3H), 0.80 (d, \( J = 7.0 \) Hz, 3H), 0.61 (q, \( J = 7.9 \) Hz, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 200.8, 136.9, 128.5, 76.5, 70.4, 45.2,
41.9, 25.8, 11.5, 10.8, 6.8, 5.1; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C_{16}H_{32}NaO_{3}SiNa 323.2013; Found 323.2017.

(6S,7R)-6-Methyl-7-[(triethylsilyl)oxy]non-1-ene-3,5-dione (44). To a solution of alcohol 43 (65 mg, 0.22 mmol, 1.00 equiv) in EtOAc (5 mL) was added IBX (45%, 404 mg, 0.649 mmol, 3.00 equiv). The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (59 mg, 91%) as an orange oil. R_f = 0.69 (20% EtOAc/hexanes); [α]_D^{22} = 15.6 (c 0.50, CHCl₃); 1H NMR (CDCl₃, 400 MHz) δ 15.23 (s, 1H), 6.27 (d, J = 18.5 Hz, 1H), 6.14 (dd, J = 17.2, 10.3 Hz, 1H), 5.67 (d, J = 10.3 Hz, 1H), 5.62 (s, 1H), 3.90 (q, J = 5.7 Hz, 1H), 2.55 (p, J = 6.9 Hz, 1H), 1.57–1.44 (m, 2H), 1.13 (d, J = 7.0 Hz, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.89 (t, J = 7.4 Hz, 3H), 0.58 (q, J = 7.7 Hz, 6H); 13C NMR (CDCl₃, 100 MHz) δ 204.0, 176.3, 132.7, 125.1, 100.3, 75.1, 48.8, 28.1, 12.0, 9.5, 6.9, 5.1; HRMS (ESI-TOF) m/z: [2M – H]⁺ Calcd for C_{32}H_{59}O_{6}Si₂ 595.3856; Found 595.3837.

(6S,7R)-6-Methyl-1-[N-(2-acetamidoethyl)thio]-7-[(triethylsilyl)oxy]nonane-3,5-dione (45). To a solution of vinyl ketone 44 (37 mg, 0.12 mmol, 1.0 equiv) in THF (10 mL) was added N-acetylcysteamine (14 µL, 0.13 mmol, 1.1 equiv) and a catalytic amount of Cs₂CO₃ at room temperature. After stirring at room temperature for 2.5 h, the reaction was quenched by the addition of saturated aqueous NH₄Cl (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure to afford the crude title compound (52 mg) that was used without further purification due to its instability. An analytically pure sample was obtained by flash chromatography (5% MeOH/EtOAc) to afford the pure title compound as a light yellow oil. R_f = 0.34 (5% MeOH/CH₂Cl₂); [α]_D^{21} = 67.2 (c 0.25, CHCl₃); 1H
NMR (CDCl$_3$, 400 MHz, approximately 5:1 mixture of enol:ketone forms where the integrations have been normalized) δ 15.45 (s, 0.83H), 6.05 (s, 0.17H), 5.98 (s, 0.83H), 5.54 (s, 0.83H), 3.88 (q, $J = 5.6$ Hz, 0.83H), 3.72 (d, $J = 3.2$ Hz, 0.17H), 3.45 (q, $J = 6.1$ Hz, 2H), 2.87–2.73 (m, 2.34H), 2.68 (s, 2H), 2.60 (t, $J = 7.1$ Hz, 1.66H), 2.42 (p, $J = 6.8$ Hz, 1H), 1.99 (s, 3H), 1.57–1.41 (m, 2H), 1.11 (d, $J = 6.9$ Hz, 2.5H), 1.05 (d, $J = 7.0$ Hz, 0.5H), 0.93 (t, $J = 8.0$ Hz, 9H), 0.88 (t, $J = 7.4$ Hz, 3H), 0.65–0.53 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 194.7, 193.6, 170.1, 99.7, 74.8, 46.3, 39.0, 38.4, 32.1, 28.0, 26.8, 23.3, 12.0, 9.4, 6.9, 5.1; HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ Calcd for C$_{20}$H$_{39}$NNaO$_4$SSi 440.2261; Found 440.2264.

(6S,7R)-7-Hydroxy-6-methyl-1-[N-(2-acetamidoethyl)thio]nonane-3,5-dione (13). To a solution of silyl ether 45 (52 mg, 0.12 mmol, 1.0 equiv) in THF (8 mL) at 0 °C was added a solution of 70% HF-pyridine:pyridine:THF (1:2:8, 4 mL) in a dropwise fashion. The reaction mixture was stirred at 0 °C for 8 h, cooled in an ice bath, then quenched by addition of saturated aqueous NaHCO$_3$ to adjust the mixture to pH 7. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The oily residue was dissolved in MeCN (1 mL) and purified by reverse-phase HPLC (Dynamax C$_{18}$, 10 × 250 mm, Varian). A gradient elution (20–30% MeCN/H$_2$O at 0–15 min; 30–60% MeCN/H$_2$O at 15-28 min; 60–20% MeCN/H$_2$O at 28–40 min) at a flowrate of 3 mL/min with monitoring at 254 nm afforded the
title compound (20 mg, 53% over 2 steps) as a colorless oil. \( R_f = 0.26 \) (5% MeOH/EtOAc); Due to the instability of the compound the optical rotation could not be obtained; \(^1\)H NMR (CDCl\(_3\), 400 MHz, approximately 12:5:3 mixture of A:B:C where the integrations have been normalized) 
\[ \delta \: s, 0.6H, 6.53–6.35 \: m, 0.4H, 5.94 \: s, 0.6H, 5.62 \: s, 0.25H, 5.57 \: s, 0.6H, 4.23–4.14 \: m, 0.25H, 3.95–3.88 \: m, 0.15H, 3.85–3.68 \: m, 1.7H, 3.44 \: q, J = 6.1 \: Hz, 1.2H, 3.13–2.95 \: m, 0.8H, 2.90–2.76 \: m, 2H, 2.73–2.57 \: m, 2.4H, 2.51–2.24 \: m, 1.8H, 2.03–1.95 \: m, 3H, 1.69–1.60 \: m, 0.5H, 1.56–1.42 \: m, 1.5H, 1.16 \: d, J = 7.0 \: Hz, 1.8H, 1.11 \: d, J = 7.0 \: Hz, 0.45H, 1.08 \: d, J = 7.1 \: Hz, 0.75H, 1.00–0.91 \: m, 2.55H, 0.90–0.85 \: m, 0.45H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, major isomer A) \[ \delta \: 197.3, 192.1, 170.2, 99.3, 73.8, 46.7, 38.5 \: (ovlp, 2C), 32.0, 27.3, 27.1, 23.3, 11.1, 10.4; \] HRMS (ESI-TOF) \[ m/z: [M + Na]^+ \] Calcd for C\(_{14}\)H\(_{25}\)NNaO\(_4\)S 326.1397; Found 326.1408.

(3R,4S,5R)-3,5-Dihydroxy-N-methoxy-N,4-dimethylheptanamide (68). To a solution of silyl ether 38 (68 mg, 0.20 mmol, 1.0 equiv) in THF (10 mL) at 0 °C was added TBAF (1.0 M in THF, 0.40 mL, 0.40 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 10 min and then quenched by addition of saturated aqueous NH\(_4\)Cl (10 mL). The reaction mixture was extracted with EtOAc (3 \times 10 mL), and the combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH\(_2\)Cl\(_2\)) afforded the title compound (37 mg, 83%) as a colorless oil. \( R_f = 0.39 \) (5% MeOH/CH\(_2\)Cl\(_2\)); \[ \alpha_{D}^{21} = 59.4 \: (c = 0.50, \text{CHCl}_3); \] \(^1\)H NMR (CDCl\(_3\), 400 MHz) \[ \delta \: 4.31 \: s, 1H, 4.08 \: ddd, J = 9.6, 6.2, 2.4 \: Hz, 1H, 3.84–3.77 \: m, 1H, 3.70 \: s, 3H, 3.20 \: (s, 3H), 3.16 \: (s, 1H), 2.72 \: (d, J = 16.4 \: Hz, 1H), 2.58 \: (dd, J = 16.7, 10.1 \: Hz, 1H), 1.69–1.60 \: (m, 1H), 1.60–1.50 \: (m, 1H), 1.47–1.36 \: (m, 1H), 0.97 \: (t, J = 7.5 \: Hz, 3H), 0.95 \: (d, J = 7.1 \: Hz, 7H); \]
$^{13}$C NMR (CDCl$_3$, 100 MHz) δ 173.9, 73.9, 72.0, 61.3, 41.4, 36.3, 31.9, 26.6, 11.3, 10.9; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{10}$H$_{21}$NNaO$_2$ 242.1363; Found 242.1360.

**(3S,4S,5R)-3,5-Dihydroxy-N-methoxy-N,4-dimethylheptanamide (69).** Identical reaction conditions for the synthesis of diol 68 were used, except for the use of silyl ether 39 (52 mg, 0.16 mmol, 1.0 equiv). Purification by flash chromatography (5% MeOH/CH$_2$Cl$_2$) afforded the title compound (28 mg, 82%) as a colorless oil. $R_f$ = 0.44 (5% MeOH/CH$_2$Cl$_2$); $[\alpha]_D^{22}$ = −49.6 (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) δ 4.30 (d, $J$ = 9.4 Hz, 1H), 4.13 (s, 1H), 3.81 (t, $J$ = 6.5 Hz, 1H), 3.70 (s, 3H), 3.30 (s, 1H), 3.20 (s, 3H), 2.69–2.51 (m, 2H), 1.65–1.49 (m, 2H), 1.48–1.36 (m, 1H), 0.95 (d, $J$ = 7.2 Hz, 3H), 0.93 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 173.9, 77.7, 73.0, 61.3, 40.3, 36.2, 31.9, 27.6, 10.5, 5.1; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{10}$H$_{21}$NNaO$_2$ 242.1363; Found 242.1360.

**2-[(4R,5S,6R)-6-Ethyl-2,2,5-trimethyl-1,3-dioxan-4-yl]-N-methoxy-N-methylacetamide (70).** To a solution of diol 68 (35 mg, 0.16 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (5 mL) at room temperature was added 2,2-dimethoxypropane (0.20 mL, 1.6 mmol, 10 equiv), followed by the addition of PPTS (8.0 mg, 0.032 mmol, 0.2 equiv). The reaction was stirred at room temperature for 20 h, then quenched with saturated aqueous NaHCO$_3$ (10 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL), and the combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (40% EtOAc/hexanes) afforded the title compound (28 mg, 68%) as a colorless oil. $R_f$ = 0.45 (40% EtOAc/hexanes); $[\alpha]_D^{21}$ = −11.3 (c 0.30, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) δ 3.83 (ddd, $J$ = 9.2, 8.3, 3.2 Hz, 1H), 3.74 (dt, $J$ = 8.8, 5.0 Hz, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 2.79 (dd, $J$ = 14.7, 9.4 Hz, 1H), 2.45 (dd, $J$ = 15.4, 3.2 Hz, 1H), 1.78–1.66 (m, 1H), 1.52–1.34 (m, 2H), 1.37 (s, 3H), 1.31 (s, 3H), 0.92 (t, $J$ = 7.3 Hz, 3H), 0.85 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR
(CDCl₃, 100 MHz) δ 172.0, 100.7, 71.2, 70.7, 61.2, 39.4, 37.0, 32.1, 24.8, 23.8, 23.5, 11.4, 10.6; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₃H₂₅NNaO₄ 282.1676; Found 282.1680.

2-[(4S,5S,6R)-6-Ethyl-2,2,5-trimethyl-1,3-dioxan-4-yl]-N-methoxy-N-methylacetamide (71). Identical reaction conditions for the synthesis of acetonide 70 were used, except for the use of diol 69 (27 mg, 0.12 mmol, 1.0 equiv). Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (25 mg, 78%) as a colorless oil. Rᵣ = 0.50 (5% MeOH/CH₂Cl₂); [α]²²D = 3.6 (c 0.80, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 4.47 (ddd, J = 7.7, 6.0, 2.2 Hz, 1H), 3.82 (ddd, J = 7.3, 6.9, 2.1 Hz, 1H), 3.70 (s, 3H), 3.18 (s, 3H), 2.75 (dd, J = 14.9, 6.0 Hz, 1H), 2.43 (dd, J = 15.8, 5.3 Hz, 1H), 1.58–1.48 (m, 2H), 1.45 (s, 3H), 1.42–1.33 (m, 1H), 1.37 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 171.9, 99.0, 74.6, 70.0, 61.3, 35.1, 33.8, 32.0, 29.9, 25.6, 19.7, 9.7, 4.9; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₃H₂₅NNaO₄ 282.1676; Found 282.1681.

(3R,4S,5R)-N-Methoxy-N,4-dimethyl-3,5-bis[(triethylsilyl)oxy]heptanamide (46). To a solution of alcohol 38 (494 mg, 1.48 mmol, 1.00 equiv) in CH₂Cl₂ (30 mL) at 0 °C was added i-Pr₂NEt (0.41 mL, 2.4 mmol, 1.6 equiv) and TESOTf (0.54 mL, 2.4 mmol, 1.6 equiv). After stirring at 0 °C for 70 min, the reaction mixture was quenched by the addition of saturated aqueous NaHCO₃ (20 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound (636 mg, 96%) as a colorless oil. Rᵣ = 0.63 (20% EtOAc/hexanes); [α]²¹D = 25.2 (c 0.50, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 4.30 (dt, J = 9.7, 3.0 Hz, 1H), 3.70 (s, 3H), 3.52 (q, J = 5.6 Hz, 1H), 3.17 (s, 3H), 2.79 (d, J = 13.9 Hz, 1H), 2.20 (dd, J = 14.9, 2.2 Hz, 1H), 1.84–1.75 (m, 1H), 1.60–1.50 (m, 2H), 1.50–1.40 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H).
0.98–0.85 (m, 24H), 0.63–0.54 (m, 12H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 173.1, 75.2, 71.2, 61.2, 42.9, 34.8, 32.0, 27.7, 8.9, 8.8, 7.0, 6.8, 5.4, 4.9; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{22}$H$_{49}$NaO$_4$Si$_2$ 470.3092; Found 470.3094.

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(3S,4S,5R)-N-Methoxy-N,4-dimethyl-3,5-bis[(triethylsilyl)oxy]heptanamide (47). Identical reaction conditions for the synthesis of silyl ether 46 were used, except for the use of alcohol 39 (403 mg, 1.21 mmol, 1.00 equiv). Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound 47 (434 mg, 80%) as a colorless oil. $R_f = 0.54$ (20% EtOAc/hexanes); $[^{22}]\alpha_D = -29.2$ (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) δ 4.29 (dt, $J = 8.3$, 4.4 Hz, 1H), 3.78 (q, $J = 5.6$ Hz, 1H), 3.67 (s, 3H), 3.16 (s, 3H), 2.69 (dd, $J = 15.2$, 7.7 Hz, 1H), 2.54 (dd, $J = 15.4$, 4.2 Hz, 1H), 1.71–1.62 (m, 1H), 1.59–1.49 (m, 2H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.92 (t, $J = 8.0$ Hz, 9H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.84 (t, $J = 7.4$ Hz, 3H), 0.59 (q, $J = 7.9$ Hz, 6H); 0.57 (q, $J = 7.9$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 173.0, 73.3, 70.6, 61.2, 42.0, 37.3, 32.0, 27.5, 10.1, 9.4, 7.0, 6.9, 5.4, 5.1; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{22}$H$_{49}$NaO$_4$Si$_2$ 470.3092; Found 470.3092.

(4R,5S,6R)-1-Chloro-5-methyl-4,6-bis[(triethylsilyl)oxy]octan-2-one (48). To a solution of Weinreb amide 46 (158 mg, 0.353 mmol, 1.00 equiv) in THF (10 mL) at −78 °C was added ClCH$_2$I (0.15 mL, 2.1 mmol, 6.0 equiv), followed by the addition of MeLi (1.6 M in Et$_2$O, 0.88 mL, 1.4 mmol, 4.0 equiv) in a dropwise fashion over 10 min. The reaction was stirred at −78 °C for 5 h, then quenched by the addition of saturated aqueous NH$_4$Cl (10 mL). The reaction mixture was allowed to warm to room temperature and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na$_2$SO$_4$), filtered, and concentrated. Purification by flash chromatography (5% EtOAc/hexanes) afforded the title compound (78 mg, 51%) as a light yellow oil. $R_f = 0.59$ (10% EtOAc/hexanes); $[^{23}]\alpha_D =$
45.0 (c 0.50, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 4.24 (dt, J = 9.7, 2.8 Hz, 1H), 4.14 (d, J = 1.6 Hz, 2H), 3.58–3.49 (m, 1H), 2.74 (dd, J = 15.1, 9.7 Hz, 1H), 2.52 (dd, J = 15.1, 2.2 Hz, 1H), 1.77 (tq, J = 7.0, 4.5 Hz, 1H), 1.58–1.47 (m, 2H), 0.94 (t, J = 7.9 Hz, 9H), 0.92 (t, J = 8.0 Hz, 9H), 0.89 (d, J = 6.6 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H), 0.57 (app. p, J = 8.0 Hz, 6H), 0.57 (q, J = 8.0 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 201.6, 75.3, 72.0, 50.0, 43.2, 42.4, 27.8, 9.3, 7.6, 7.0, 6.8, 5.4, 4.9; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₂₁H₄₅ClNaO₃Si₂ 459.2488; Found 437.2491.

(4S,5S,6R)-1-Chloro-5-methyl-4,6-bis[(triethylsilyl)oxy]octan-2-one (49). Identical reaction conditions for the synthesis of chloromethyl ketone 48 were used, except for the use of Weinreb amide 47 (135 mg, 0.301 mmol, 1.00 equiv). Purification by flash chromatography (5% EtOAc/hexanes) afforded the title compound (101 mg, 77%) as a light yellow oil. Rᵣ = 0.59 (10% EtOAc/hexanes); [α]₂⁰ = –41.6 (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 4.22 (ddd, J = 7.8, 5.6, 3.8 Hz, 1H), 4.11 (s, 2H), 3.85 (dt, J = 6.5, 3.3 Hz 1H), 2.84 (dd, J = 15.8, 7.7 Hz, 1H), 2.71 (dd, J = 15.8, 3.7 Hz, 1H), 1.69–1.60 (m, 1H), 1.59–1.47 (m, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.93 (t, J = 8.0 Hz, 9H), 0.84 (d, J = 7.0 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H), 0.60 (q, J = 7.9 Hz, 6H), 0.57 (q, J = 8.0 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 201.7, 72.8, 71.0, 49.8, 44.8, 41.5, 27.8, 9.84, 9.80, 7.0, 6.9, 5.5, 5.0; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₂₁H₄₅ClNaO₃Si₂ 459.2488; Found 437.2489.

(4R,5R,6R)-5-Methyl-1-[N-(2-acetamidoethyl)thio]-4,6-bis[(triethylsilyl)oxy]octan-2-one (50). To a solution of chloromethyl ketone 48 (78 mg, 0.18 mmol, 1.0 equiv) in THF (10 mL) was added N-acetylcysteamine (28 µL, 0.27 mmol, 1.5 equiv) and a catalytic amount of Cs₂CO₃ at room temperature. The reaction was stirred at room temperature for 38 h, then quenched by the addition of saturated aqueous NH₄Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with
saturated aqueous NaCl (40 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (84 mg, 90%) as a colorless oil. \( R_f = 0.35 \) (5% MeOH/CH₂Cl₂); \( [\alpha]_{D}^{20} = 33.9 \) (c 1.0, CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 6.23 (s, 1H), 4.23 (dt, \( J = 9.5, 2.4 \) Hz, 1H), 3.55–3.48 (m, 1H), 3.46–3.35 (m, 2H), 3.30 (dd, \( J = 15.0, 9.6 \) Hz, 1H), 2.79 (dd, \( J = 15.4, 4.3 \) Hz, 2H), 2.69–2.56 (m, 2H), 2.51 (dd, \( J = 15.4, 2.2 \) Hz, 1H), 1.99 (s, 3H), 1.80–1.70 (m, 1H), 1.57–1.43 (m, 2H), 0.96–0.82 (m, 24H), 0.55 (app. p, \( J = 7.8 \) Hz, 12H); \(^13\)C NMR (CDCl₃, 100 MHz) \( \delta \) 205.5, 170.1, 75.2, 71.8, 44.1, 42.5, 42.4, 38.1, 32.1, 27.7, 23.2, 9.2, 7.9, 7.0, 6.9, 5.4, 5.0; HRMS (ESI-TOF) \( m/z: [\text{M + Na}]^+ \) Calcd for C₂₆H₅₅NNaO₃SSi₂ 542.3126; Found 542.3119.

\((4S,5R,6R)-5\text{-Methyl}-1-[N-(2-acetamidoethyl)thio]-4,6\text{-bis[(triethylsilyl)oxy]}\text{octan-2-one} \) (51). Identical reaction conditions for the synthesis of thioether 50 were used, except for the use of chloromethyl ketone 49 (50 mg, 0.11 mmol, 1.0 equiv). Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (48 mg, 81%) as a colorless oil. \( R_f = 0.37 \) (5% MeOH/CH₂Cl₂); \( [\alpha]_{D}^{22} = -28.0 \) (c 1.0, CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 6.15 (s, 1H), 4.19 (q, \( J = 5.6 \) Hz, 1H), 3.82 (q, \( J = 6.2 \) Hz, 1H), 3.41 (p, \( J = 6.0 \) Hz, 2H), 3.29 (s, 2H), 2.80 (d, \( J = 5.7 \) Hz, 2H), 2.63 (t, \( J = 6.2 \) Hz, 2H), 2.00 (s, 3H), 1.66–1.59 (m, 1H), 1.56–1.48 (m, 2H), 0.96 (t, \( J = 7.9 \) Hz, 9H), 0.93 (t, \( J = 8.0 \) Hz, 9H), 0.84 (d, \( J = 6.9 \) Hz, 3H), 0.82 (t, \( J = 7.5 \) Hz, 3H), 0.60 (q, \( J = 7.9 \) Hz, 6H), 0.57 (q, \( J = 8.0 \) Hz, 6H); \(^13\)C NMR (CDCl₃, 100 MHz) \( \delta \) 205.4, 170.1, 72.8, 70.8, 45.9, 42.3, 41.4, 38.1, 32.1, 27.8, 23.2, 9.73, 9.67, 7.02, 6.95, 5.5, 5.1; HRMS (ESI-TOF) \( m/z: [\text{M + Na}]^+ \) Calcd for C₂₆H₅₅NNaO₃SSi₂ 542.3126; Found 542.3129.
(4R,5R,6R)-4,6-Dihydroxy-5-methyl-1-[N-(2-acetamidoethyl)thio]octan-2-one (18). To a solution of silyl ether 50 (44 mg, 0.085 mmol, 1.0 equiv) in THF (8 mL) at 0 °C was added a solution of 70% HF-pyridine:pyridine:THF (1:2:8, 4 mL). The reaction was stirred at 0 °C for 6 h, then quenched at 0 ºC by the addition of saturated aqueous NaHCO₃ until the mixture was pH 7. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/EtOAc) afforded the title compound (15 mg, 60%) as a colorless oil. Rₛ = 0.31 (5% MeOH/EtOAc); Due to the instability of the compound the optical rotation could not be obtained; ¹H NMR (CDCl₃, 400 MHz, approximately 17:2:1 mixture of A:B:C where the integrations have been normalized) δ 6.16 (s, 0.1H), 6.10 (s, 0.05H), 5.96 (s, 0.85H), 4.24 (dt, J = 11.7, 4.8 Hz, 0.85H), 4.08–3.98 (m, 0.1H), 3.90–3.86 (m, 0.05H), 3.86–3.76 (m, 1H), 3.62 (s, 0.85H), 3.56–3.34 (m, 2.35H), 2.95–2.84 (m, 1.8H), 2.76–2.65 (m, 1.2H), 2.53 (d, J = 14.1 Hz, 0.9H), 1.99 (s, 3H), 1.93–1.85 (m, 1H), 1.78 (dd, J = 12.4, 4.8 Hz, 1.7H), 1.68–1.46 (m, 1.95H), 1.46–1.31 (m, 1H), 1.11 (d, J = 7.2 Hz, 0.15H), 1.05 (t, J = 7.1 Hz, 0.15H), 0.98 – 0.93 (m, 0.6H), 0.88 (t, J = 7.4 Hz, 2.55H), 0.81 (d, J = 6.9 Hz, 2.55H); ¹³C NMR (CDCl₃, 100 MHz, major hemiketal A) δ 206.4, 170.2, 96.2, 73.2, 67.8, 43.5, 38.7, 37.1, 33.2, 25.1, 23.3, 10.4, 3.6; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₃H₂₅NNaO₄S 314.1397; Found 314.1399.
(4S,5R,6R)-4,6-Dihydroxy-5-methyl-1-\([N-(2-acetamidoethyl)thio]octan-2-one\) (20). Identical reaction conditions for the synthesis of diol 18 were used, except for the use of silyl ether 51 (48 mg, 0.092 mmol, 1.0 equiv). Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (21 mg, 78%) as a colorless oil. \(R_f = 0.24\) (5% MeOH/EtOAc); Due to the instability of the compound the optical rotation could not be obtained; \(^1\)H NMR (CDCl₃, 400 MHz) δ 5.95 (s, 1H), 4.45 (d, \(J = 1.7\) Hz, 1H), 4.20–4.12 (m, 1H), 3.94–3.85 (m, 1H), 3.61 (d, \(J = 7.9\) Hz, 1H), 3.56–3.40 (m, 2H), 2.91–2.82 (m, 2H), 2.78–2.69 (m, 1H), 2.54 (d, \(J = 14.1\) Hz, 1H), 2.00 (s, 3H), 1.92–1.85 (m, 1H), 1.81–1.71 (m, 2H), 1.52 (dq, \(J = 14.9, 7.5\) Hz, 1H), 1.39 (dq, \(J = 13.8, 7.1\) Hz, 1H), 0.91 (t, \(J = 7.4\) Hz, 3H), 0.84 (d, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (CDCl₃, 100 MHz) δ 170.3, 96.9, 71.2, 68.2, 43.0, 38.7, 36.6, 33.8, 33.3, 25.0, 23.3, 10.3, 10.2; HRMS (ESI-TOF) \(m/z\): [M + Na]⁺ Calcd for C₁₃H₂₅NNaO₄S 314.1397; Found 314.1390.

(2S,3R)-3-Hydroxy-\(N\)-methoxy-\(N\),2-dimethylpentanamide (72). To a solution of thiazolidinethione 35 (535 mg, 1.65 mmol, 1.00 equiv) in CH₂Cl₂ (5 mL) at room temperature was added \(N,O\)-dimethylhydroxylamine hydrochloride (968 mg, 9.92 mmol, 6.00 equiv) and imidazole (1.35 g, 19.9 mmol, 12.0 equiv), followed by the addition of DMAP (40 mg, 0.33 mmol, 0.20 equiv). The reaction was stirred at room temperature for 24 h until the yellow color disappeared, then quenched by the addition of water (20 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (214 mg, 74%) as colorless oil. \(R_f = 0.34\) (5% MeOH.CH₂Cl₂); \([\alpha]_{D}^{22} = 18.6\) (c 1.0, CHCl₃); \(^1\)H NMR (CDCl₃, 400 MHz) δ 3.77 (ddd, \(J = 7.9, 5.4, 2.6\) Hz, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 2.90 (s, 2H), 1.66–1.51 (m, 1H), 1.45–1.34 (m, 1H), 1.16 (d, \(J = 7.1\) Hz, 3H), 0.96 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (CDCl₃, 100 MHz) δ
178.1, 73.0, 61.4, 38.2, 31.7, 26.7, 10.2, 10.1; HRMS (ESI-TOF) m/z: [M + Na]^+ Calcd for C₈H₁₇NNaO₃ 198.1101; Found 198.1108.

(2S,3R)-N-Methoxy-N,2-dimethy-3-[(triethylsilyl)oxy]lpentanamide (52). To a solution of alcohol 72 (134 mg, 0.765 mmol, 1.00 equiv) in CH₂Cl₂ (10 mL) at 0 ºC was added i-Pr₂NEt (0.24 mL, 1.4 mmol, 1.8 equiv), followed by the addition of TESOTf (0.26 mL, 1.1 mmol, 1.5 equiv) in a dropwise fashion. The reaction was stirred at 0 ºC for 1 h, then quenched by the addition of saturated aqueous NaHCO₃ (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound (198 mg, 90%) as colorless oil. Rᶠ = 0.37 (20% EtOAc/hexanes); [α]²² CD = 4.5 (c 0.40, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 3.89 (dt, J = 8.5, 4.9 Hz, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.98 (s, 1H), 1.59–1.38 (m, 2H), 1.17 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.89 (t, J = 7.5 Hz, 3H), 0.63 (q, J = 7.9 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 74.7, 61.4, 40.5, 32.1, 28.5, 14.7, 8.8, 7.0, 5.2; HRMS (ESI-TOF) m/z: [M + Na]^+ Calcd for C₁₄H₃₁NNaO₃Si 312.1965; Found 312.1970.

(5S,6R)-5-Methyl-6-[(triethylsilyl)oxy]oct-1-en-4-one (53). To a solution of Weinreb amide 52 (69 mg, 0.24 mmol, 1.0 equiv) in THF (5 mL) at 0 ºC was added allylmagnesium bromide (1.0 M in Et₂O, 0.38 mL, 0.38 mmol, 1.6 equiv) dropwise. The reaction was stirred at 0 ºC for 15 min, then quenched by the addition of saturated aqueous NH₄Cl (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (58 mg, 91%) as a colorless oil. Rᶠ = 0.49 (10% EtOAc/hexanes); [α]²¹ CD = 42.3 (c 1.0,
CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 5.99–5.86 (m, 1H), 5.18–5.06 (m, 2H), 3.86 (q, J = 5.6 Hz, 1H), 3.33 (dd, J = 17.7, 6.4 Hz, 1H), 3.23 (dd, J = 17.1, 7.0 Hz, 1H), 2.71 (p, J = 6.6 Hz, 1H), 1.49 (tq, J = 13.4, 7.0 Hz, 1H), 1.36 (dp, J = 14.2, 7.1 Hz, 1H), 1.07 (d, J = 7.7 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.87 (t, J = 7.4 Hz, 3H), 0.61 (q, J = 8.0 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 211.2, 130.9, 118.9, 74.9, 50.8, 47.5, 27.5, 12.0, 9.9, 6.9, 5.2; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₅H₂₉NO₂Si 293.1907; Found 293.1913.

(3S,4R)-3-Methyl-1-(oxiran-2-yl)-4-[(triethylsilyl)oxy]hexan-2-one (54). To a solution of allyl ketone 53 (58 mg, 0.21 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) at room temperature was added m-CPBA (77%, 168 mg, 0.75 mmol, 3.5 equiv). The reaction mixture was stirred at room temperature for 14 h, then quenched by the addition of saturated aqueous Na₂HCO₃:Na₂S₂O₃ (1:1, 10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (47 mg, 77%, dr = 1:1) as a colorless oil. Rᵣ = 0.25 (10% EtOAc/hexanes); ¹H NMR (CDCl₃, 400 MHz) δ 3.90–3.80 (m, 1H), 3.31–3.22 (m, 1H), 2.92 (dd, J = 17.5, 5.7 Hz, 0.5H), 2.83 (t, J = 4.3 Hz, 1H), 2.75 (dd, J = 5.7, 2.3 Hz, 1H), 2.72–2.65 (m, 1H), 2.61 (dd, J = 17.5, 5.5 Hz, 0.5H), 2.50–2.44 (m, 1H), 1.49 (tq, J = 12.5, 7.0 Hz, 1H), 1.34 (tq, J = 14.2, 7.2 Hz, 1H), 1.06 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.87 (t, J = 7.4 Hz, 3H), 0.60 (q, J = 7.9 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 210.8, 210.7, 75.0, 74.9, 51.7, 51.5, 47.9, 47.8, 46.79, 46.78, 46.0, 45.7, 27.4, 27.3, 11.54, 11.48, 10.00, 9.96, 6.9, 5.1; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₅H₃₀NO₂Si 309.1856; Found 309.1858.

(5S,6R)-2-Hydroxy-5-methyl-1-[N-(2-acetamidoethyl)thio]-6-[(triethylsilyl)oxy]octan-4-one (55). To a solution of epoxide 54 (47 mg, 0.16 mmol, 1.0 equiv) in MeOH (3 mL) at 0 °C was
added *N*-acetylcysteamine (26 µL, 0.25 mmol, 1.5 equiv) and Na<sub>2</sub>CO<sub>3</sub> (19 mg, 0.18 mmol, 1.1 equiv). After stirring at 0 °C for 2 h, the reaction was quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), washed with saturated aqueous NaCl (10 mL), filtered, and concentrated under reduced pressure. Purification by flash chromatography (0–5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded the title compound (8.5 mg, 13%) as a colorless oil. *R*<sub>f</sub> = 0.30 (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.15 (s, 1H), 4.23–4.12 (m, 1H), 3.90–3.79 (m, 1H), 3.54–3.39 (m, 3H), 2.92–2.79 (m, 1H), 2.79–2.64 (m, 5H), 2.63–2.53 (m, 1H), 1.99 (s, 3H), 1.57–1.43 (m, 1H), 1.42–1.28 (m, 1H), 1.07 (app dd, *J* = 7.0, 4.6 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.61 (q, *J* = 8.0 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 214.2, 213.9, 170.1, 75.04, 75.00, 67.2, 67.1, 52.0, 51.8, 47.93, 47.88, 38.8, 38.3, 38.2, 32.74, 32.72, 27.29, 27.26, 23.24, 11.5, 11.4, 10.1, 10.0, 6.9, 5.1; HRMS (ESI-TOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>39</sub>NNaO<sub>4</sub>Si 428.2261; Found 428.2274.

**5S,6R)-2,6-Dihydroxy-5-methyl-1-[N-(2-acetamidoethyl)thio]octan-4-one (22/24).** To a solution of silyl ether 55 (8.5 mg, 0.021 mmol, 1.0 equiv) in THF (2 mL) at 0 °C was added a solution of 70% HF-pyridine:pyridine:THF (1:2:8, 1 mL). The reaction mixture was stirred at 0 °C for 5 h, then quenched by addition of saturated aqueous NaHCO<sub>3</sub> to adjust the mixture to pH 7. The layers were separated and the aqueous layer was extracted with n-butanol (3 × 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded the title compound (4.8 mg, 79%) as a colorless oil. *R*<sub>f</sub> = 0.38 (10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.10 (s, 1H), 4.27–4.15 (m, 1H), 3.99–3.85 (m, 1H), 3.61–3.39 (m, 3H), 2.86–2.56 (m, 8H), 1.99 (s, 3H), 1.61–1.35 (m, 2H), 1.12 (app t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H);
\[ ^{13}C \text{ NMR (CDCl}_3, 100 \text{ MHz}) \delta 215.1, 214.8, 170.4, 72.8, 72.5, 67.2, 67.0, 51.2, 50.9, 46.80, 46.77, 38.8, 38.5, 38.4, 32.60, 32.57, 27.1, 27.0, 23.3, 10.50, 10.47, 9.3, 9.1; \text{ HRMS (ESI-TOF) m/z: [M + Na]}^+ \text{ Calcd for C}_{13}H_{25}N\text{NaO}_4S 314.1397; \text{ Found 314.1389.} \]

\((5R,6S,7R)-6\text{-Methyl-5,7-bis[(triethylsilyl)oxy]non-1-en-3-one (56).}\) To a solution of tetravinyltin (41 µL, 0.22 mmol, 1.2 equiv) in THF (5 mL) at \(-78^\circ\text{C}\) was added MeLi (1.6 M in Et\(_2\)O, 0.46 mL, 0.74 mmol, 4.0 equiv). After stirring at \(-78^\circ\text{C}\) for 30 min, Weinreb amide 46 (83 mg, 0.19 mmol, 1.0 equiv) was added with the aid of THF (2 mL). The reaction mixture was stirred at \(-78^\circ\text{C}\) for 40 min, quenched by the addition of saturated aqueous NH\(_4\)Cl (10 mL), and allowed to warm up to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 \(\times\) 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na\(_2\)SO\(_4\)), and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (59 mg, 77%) as a colorless oil. \(R_f = 0.73\) (20% EtOAc/hexanes); [\(\alpha\)]\(_D\)\(^{21}\) = 34.0 (c 1.0, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 6.36\) (dd, \(J = 17.6, 10.5\) Hz, 1H), 6.20 (d, \(J = 17.6\) Hz, 1H), 5.80 (d, \(J = 10.5\) Hz, 1H), 4.33–4.27 (m, 1H), 3.56–3.50 (m, 1H), 2.86 (dd, \(J = 15.6, 9.3\) Hz, 1H), 2.49 (dd, \(J = 15.6, 2.2\) Hz, 1H), 1.82–1.72 (m, 1H), 1.58–1.47 (m, 1H), 0.97–0.83 (m, 24H), 0.57 (q, \(J = 7.8\) Hz, 6H), 0.54 (q, \(J = 7.8\) Hz, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta 200.1, 137.6, 128.0, 75.3, 71.1, 42.82, 42.77, 27.8, 9.2, 8.3, 7.0, 6.9, 5.4, 5.0; \text{ HRMS (ESI-TOF) m/z: [M + Na]}^+ \text{ Calcd for C}_{22}H_{46}N\text{O}_3\text{Si}_2 437.2878; \text{ Found 437.2881.} \)

\((5S,6S,7R)-6\text{-Methyl-5,7-bis[(triethylsilyl)oxy]non-1-en-3-one (57).}\) Identical reaction conditions for the synthesis of vinyl ketone 56 were used, except for the use of Weinreb amide 47 (62 µL, 0.34 mmol, 1.2 equiv). Purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (67 mg, 57%) as a colorless oil. \(R_f = 0.67\) (20% EtOAc/hexanes);
\[ \alpha \] = -37.6 (c 0.50, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 6.36 (dd, \( J = 17.6, 10.5 \) Hz, 1H), 6.20 (dd, \( J = 17.6, 1.0 \) Hz, 1H), 5.81 (dd, \( J = 10.5, 1.0 \) Hz, 1H), 4.30 (dt, \( J = 7.1, 4.7 \) Hz, 1H), 3.79 (q, \( J = 5.8 \) Hz, 1H), 2.84 (dd, \( J = 16.1, 7.2 \) Hz, 1H), 2.76 (dd, \( J = 16.1, 4.4 \) Hz, 1H), 1.69–1.60 (m, 1H), 1.59–1.49 (m, 2H), 0.96 (t, \( J = 7.9 \) Hz, 9H), 0.92 (t, \( J = 7.9 \) Hz, 9H), 0.87 (d, \( J = 7.0 \) Hz, 3H), 0.84 (t, \( J = 7.5 \) Hz, 3H), 0.60 (q, \( J = 7.8, 6 \) H), 0.56 (q, \( J = 8.0, 6 \) H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta \) 200.0, 137.5, 128.0, 73.3, 70.2, 45.1, 41.9, 27.5, 10.0, 9.5, 7.02, 6.95, 5.5, 5.1; HRMS (ESI-TOF) \textit{m/z}: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{22}H\textsubscript{46}NaO\textsubscript{3}Si\textsubscript{2} 437.2878; Found 437.2881.

\( (5R,6R,7R) \)-6-Methyl-1-[N-(2-acetamidoethyl)thio]-5,7-bis[(triethylsilyl)oxy]nonan-3-one (58). To a solution of vinyl ketone 56 (58 mg, 0.14 mmol, 1.0 equiv) in THF (10 mL) was added \textit{N}-acetylcysteamine (22 µL, 0.21 mmol, 1.5 equiv) and a catalytic amount of Cs\textsubscript{2}CO\textsubscript{3}. The reaction was stirred at room temperature for 2 h, then quenched by the addition of saturated aqueous NH\textsubscript{4}Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (40 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH\textsubscript{2}Cl\textsubscript{2}) afforded the title compound (70 mg, 93%) as a colorless oil. \( R_f = 0.33 \) (5% MeOH/CH\textsubscript{2}Cl\textsubscript{2}); [\( \alpha \)] = 29.6 (c 0.50, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 6.12 (s, 1H), 4.31–4.20 (m, 1H), 3.55–3.48 (m, 1H), 3.48–3.41 (m, 2H), 2.81–2.68 (m, 4H), 2.68–2.56 (m, 3H), 2.40 (dd, \( J = 15.5, 2.1 \) Hz, 1H), 2.00 (s, 3H), 1.73 (dq, \( J = 12.5, 7.1 \) Hz, 1H), 1.57–1.42 (m, 2H), 0.93 (t, \( J = 8.0 \) Hz, 9H), 0.90 (t, \( J = 8.0 \) Hz, 9H), 0.87 (d, \( J = 6.9 \) Hz, 3H), 0.84 (t, \( J = 7.4 \) Hz, 3H), 0.56 (app p, \( J = 8.0 \) Hz, 12H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta \) 208.3, 170.1, 175.2, 71.3, 46.1, 44.4, 42.5, 38.4, 32.3, 27.7, 25.0, 23.2, 9.2, 8.0, 7.0, 6.9, 5.4, 5.0; HRMS (ESI-TOF) \textit{m/z}: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{27}H\textsubscript{57}NNaO\textsubscript{3}SSi\textsubscript{2} 556.3283; Found 556.3291.
(5S,6R,7R)-6-Methyl-1-[N-(2-acetamidoethyl)thio]-5,7-bis[(triethylsilyl)oxy]nonan-3-one (59). Identical reaction conditions used for the synthesis of thioether 58 were used, except for the use of vinyl ketone 57 (66 mg, 0.16 mmol, 1.0 equiv). Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (78 mg, 92%) as a colorless oil. \( R_f = 0.28 \) (5% MeOH/CH₂Cl₂); \( [\alpha]_D^{21} = -22.5 \) (c 0.4, CHCl₃); \( ^1\text{H} \) NMR (CDCl₃, 400 MHz) \( \delta \) 6.08 (s, 1H), 4.22 (q, \( J = 5.5 \) Hz, 1H), 3.83–3.77 (m, 1H), 3.45 (q, \( J = 6.0 \) Hz, 2H), 2.79–2.61 (m, 8H), 2.00 (s, 3H), 1.66–1.57 (m, 1H), 1.56–1.48 (m, 2H), 0.94 (app dt, \( J = 14.5, 7.9 \) Hz, 18H), 0.84 (d, \( J = 7.7 \) Hz, 3H), 0.83 (t, \( J = 7.7 \) Hz, 3H), 0.57 (app dq, \( J = 12.7, 7.9 \) Hz, 12H); \( ^{13}\text{C} \) NMR (CDCl₃, 100 MHz) \( \delta \) 208.1, 170.1, 73.0, 70.2, 48.1, 44.2, 41.5, 38.3, 32.3, 27.7, 25.0, 23.3, 9.9, 9.6, 7.02, 6.96, 5.5, 5.1; HRMS (ESI-TOF) \( m/z \): [M + Na]⁺ Calcd for C₂₇H₅₇NO₃SSi₂ 556.3283; Found 556.3289.

![Chemical structure of (5S,6R,7R)-6-Methyl-1-[N-(2-acetamidoethyl)thio]-5,7-bis[(triethylsilyl)oxy]nonan-3-one](image)

(5R,6R,7R)-5,7-Dihydroxy-6-methyl-1-[N-(2-acetamidoethyl)thio]nonan-3-one (19). To a solution of silyl ether 58 (59 mg, 0.11 mmol, 1.0 equiv) in THF (10 mL) at 0 °C was added a solution of 70% HF-pyridine:pyridine:THF (1:2:8, 4 mL). The reaction was stirred at 0 °C for 6 h, then quenched by the addition of saturated aqueous NaHCO₃ to bring the reaction to pH 7, and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (40 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% MeOH/EtOAc) afforded the title compound (16 mg, 47%) as a colorless oil. \( R_f = 0.26 \) (10% MeOH/EtOAc); Due to the instability of the compound
the optical rotation could not be obtained; $^1$H NMR (CDCl$_3$, 400 MHz, approximately 6:6:1 mixture of A:B:C where the integrations have been normalized) δ 6.61 (s, 0.08H), 6.08 (s, 0.46H), 5.98 (s, 0.46H), 4.20 (dt, $J$ = 11.9, 4.8 Hz, 0.46H), 4.17–4.08 (m, 0.46H), 4.07–4.03 (m, 0.08H), 3.85–3.77 (m, 1H), 3.75–3.69 (m, 0.16H), 3.53–3.34 (m, 1.84H), 3.22–3.13 (m, 0.32H), 2.86–2.58 (m, 5.52H), 1.99 (app d, $J$ = 2.0 Hz, 3H), 1.95–1.84 (m, 1.38H), 1.81 (dd, $J$ = 4.8, 12.5 Hz, 0.46H), 1.65–1.34 (m, 3H), 1.09 (d, $J$ = 7.2 Hz, 0.24H), 1.05 (t, $J$ = 7.3 Hz, 0.24H), 0.98–0.87 (m, 4.14H), 0.80 (d, $J$ = 6.9 Hz, 1.38H); $^{13}$C NMR (CDCl$_3$, 100 MHz, major isomers A and B) δ 209.9, 170.4, 170.3, 97.5, 73.8, 72.9, 71.7, 67.6, 48.1, 43.4, 41.4, 41.3, 38.6, 38.3, 37.3, 37.2, 31.9, 31.5, 26.7, 25.2, 25.1, 25.0, 23.3, 23.2, 10.9, 10.8, 10.4, 3.6; HRMS (ESI-TOF) $m/z$: [M + Na]$^+$ Calcd for C$_{14}$H$_{27}$NNaO$_4$S 328.1553; Found 328.1561.

(55S,6R,7R)-5,7-Dihydroxy-6-methyl-1-[N-(2-acetamidoethyl)thio]nonan-3-one (21). Identical reaction conditions for the synthesis of diol 19 were used, except for the use of silyl ether 59 (76 mg, 0.14 mmol, 1.0 equiv). Purification by flash chromatography (5% MeOH/CH$_2$Cl$_2$) afforded the title compound (37 mg, 86%) as a colorless oil. $R_f$ = 0.42 (10% MeOH/EtOAc); Due to the instability of the compound the optical rotation could not be obtained; $^1$H NMR (CDCl$_3$, 400 MHz, 4:1 mixture of hemiketal A:ketone B where the integrations have been normalized) δ 5.92 (s, 1H), 4.67 (s, 0.8H), 4.34 (d, $J$ = 9.5 Hz, 0.2H), 4.18–4.07 (m, 0.8H), 3.98–3.88 (m, 0.8H), 3.83–3.76 (m, 0.2H), 3.56 (s, 0.2H), 3.52–3.37 (m, 2H), 3.32 (d, $J$ = 6.0 Hz, 0.8H), 2.84 (s, 0.2H), 2.80–2.59 (m, 4.6H), 2.52 (dd, $J$ = 16.9, 2.8 Hz, 0.2H), 1.99 (s, 3H), 1.91–1.83 (m, 1.6H),
1.82–1.66 (m, 2.6H), 1.62–1.47 (m, 1H), 1.47–1.32 (m, 1H), 0.97–0.89 (m, 3.5H), 0.84 (d, \( J = 7.1 \) Hz, 2.5H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, hemiketal form A) \( \delta \) 170.2, 97.3, 71.5, 67.6, 41.5, 38.2, 37.0, 34.2, 31.5, 25.1, 24.8, 23.3, 10.4, 10.2; HRMS (ESI-TOF) \( m/z \): [M + Na]^+ Calcd for C\(_{14}\)H\(_{27}\)NNaO\(_4\)S 328.1553; Found 328.1554.

**(3S,4R)-3-Methyl-4-[(triethylsilyl)oxy]hexan-2-one (60).** To a solution of Weinreb amide 52 (404 mg, 1.40 mmol, 1.00 equiv) in THF (20 mL) at 0 °C was added methylmagnesium bromide (3.0 M in Et\(_2\)O, 1.86 mL, 5.58 mmol, 4.00 equiv) dropwise. The reaction was stirred at 0 °C for 5 h, then quenched by the addition of saturated aqueous NH\(_4\)Cl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound (340 mg, 100%) as a colorless oil. \( R_f = 0.57 \) (20% EtOAc/hexanes); \([\alpha]\)^\(_{D}^{22} = 39.2 \) (c 1.0, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 3.88 (q, \( J = 5.7 \) Hz, 1H), 2.68–2.57 (m, 1H), 2.18 (s, 3H), 1.53–1.44 (m, 1H), 1.43–1.34 (m, 1H), 1.07 (d, \( J = 7.0 \) Hz, 3H), 0.96 (t, \( J = 7.9 \) Hz, 9H), 0.87 (t, \( J = 7.4 \) Hz, 3H), 0.60 (q, \( J = 8.0 \) Hz, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 211.8, 74.8, 51.7, 29.9, 27.5, 11.5, 9.9, 6.9, 5.1; HRMS (ESI-TOF) \( m/z \): [M + Na]^+ Calcd for C\(_{13}\)H\(_{28}\)NaO\(_2\)Si 267.1751; Found 267.1759.

**N-[2-[(3-Oxopropyl)thio]ethyl]acetamide (61).** To a solution of \( N \)-acetylcyctamine (73, 0.11 mL, 1.0 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (10 mL) at 0 °C was added Et\(_3\)N (28 \( \mu \)L, 0.20 mmol, 0.20 equiv), followed by the addition of acrolein (74, 67 \( \mu \)L, 1.0 mmol, 1.0 equiv). After stirring at 0 °C for 1 h, the reaction was quenched by the addition of saturated aqueous NH\(_4\)Cl (5 mL). The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried (Na\(_2\)SO\(_4\),
filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (149 mg, 85%) as colorless oil. $R_f = 0.24$ (5% MeOH/CH₂Cl₂); $^1$H NMR (CDCl₃, 400 MHz) δ 9.78 (s, 1H), 6.06 (s, 1H), 3.46 (q, $J = 6.1$ Hz, 2H), 2.86–2.74 (m, 4H), 2.69 (t, $J = 6.4$ Hz, 2H), 2.01 (s, 3H); $^{13}$C NMR (CDCl₃, 100 MHz) δ 200.2, 43.5, 38.4, 32.0, 23.8, 23.2; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C₇H₁₃NaNO₂S 198.0559; Found 198.0556.

(6S,7R)-3-Hydroxy-6-methyl-1-[N-(2-acetamidoethyl)thio]-7-[(triethylsilyl)oxy]nonan-5-one (62). To a solution of distilled i-Pr₂NH (0.19 mL, 1.4 mmol, 2.2 equiv) in THF (10 mL) at –78 °C was added n-BuLi (1.8 M in THF, 0.78 mL, 1.4 mmol, 2.2 equiv), followed by stirring at –78 °C for 30 min to prepare the LDA solution. To the LDA solution at –78 °C was added methyl ketone 60 (316 mg, 1.29 mmol, 2.10 equiv). After stirring at –78 °C for 30 min, aldehyde 61 (108 mg, 0.616 mmol, 1.00 equiv) was added with the aid of THF (3 × 0.5 mL), the reaction was stirred at –78 °C for an additional 3 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (15 mL) and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (118 mg, 46%, dr = 2:1) as a colorless oil. $R_f = 0.31$ (5% MeOH/CH₂Cl₂); $^1$H NMR (CDCl₃, 400 MHz) δ 5.97 (s, 1H), 4.22–4.09 (m, 1H), 3.89–3.78 (m, 1H), 3.51–3.39 (m, 2H), 3.36 (d, $J = 3.2$ Hz, 1H), 2.84–2.59 (m, 6.66H), 2.52 (dd, $J = 18.0, 9.1$ Hz, 0.34H), 1.99 (s, 3H), 1.80–1.70 (m, 1H), 1.68–1.58 (m, 1H), 1.55–1.43 (m, 1H), 1.42–1.29 (m, 1H), 1.06 (d, $J = 6.7$, 2H), 1.04 (d, $J = 7.0$, 1H), 0.95 (t, $J = 7.9$ Hz, 9H), 0.87 (t, $J = 7.4$ Hz, 3H), 0.60 (q, $J = 8.0$ Hz, 6H); $^{13}$C NMR (CDCl₃, 100 MHz) δ 214.9 (major), 214.6 (minor), 170.1, 75.0, 66.2 (major), 66.1 (minor), 51.9 (minor), 51.7 (major), 49.1

S51
(minor), 49.0 (major), 38.4, 36.0, 31.9, 27.7, 27.3, 23.3, 11.6 (minor), 11.4 (major), 10.1 (minor), 10.0 (major), 6.9, 5.1; HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₂₀H₄₁NNa₄S₄ 442.2418; Found 442.2425.

(6S,7R)-3,7-Dihydroxy-6-methyl-1-[N-(2-acetamidoethyl)thio]nonan-5-one (23/25). To a solution of silyl ether 62 (51 mg, 0.12 mmol, 1.0 equiv) in THF (6 mL) at 0 °C was added a solution of 70% HF-pyridine:pyridine:THF (1:2:8, 3 mL). The reaction was stirred at 0 °C for 12 h, then quenched by the addition of saturated aqueous NaHCO₃ to adjust the reaction to pH 7. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL) and n-butanol (3 × 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH₂Cl₂) afforded the title compound (32 mg, 86%) as a colorless oil. Rᶠ = 0.11 (5% MeOH/CH₂Cl₂); ^1H NMR (CDCl₃, 400 MHz) δ 6.22 (s, 1H), 4.24–4.14 (m, 1H), 3.90 (dt, J = 8.1, 4.6 Hz, 0.67H), 3.84 (dt, J = 8.1, 4.5 Hz, 0.33H), 3.50–3.34 (m, 2H), 3.10 (s, 2H), 2.78–2.53 (m, 7H), 1.98 (s, 3H), 1.82–1.71 (m, 1H), 1.71–1.61 (m, 1H), 1.55–1.45 (m, 1H), 1.45–1.34 (m, 1H), 1.10 (d, J = 8.0 Hz, 1H), 1.08 (d, J = 7.3 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^13C NMR (CDCl₃, 100 MHz) δ 215.7 (minor), 215.3 (major), 170.6, 72.8 (minor), 72.5 (major), 66.5 (major), 66.2 (minor), 51.1 (major), 50.8 (minor), 48.1 (minor), 48.0 (major), 38.5, 36.1 (major), 36.0 (minor), 31.7, 27.6, 27.04 (minor), 27.00 (major), 23.1, 10.47 (major), 10.45 (minor), 9.3 (minor), 9.1 (major); HRMS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₄H₂₇NNaO₄S 328.1553; Found 328.1559.
Me\(\text{NH}_{-}\text{S}-\text{OH}O\text{OTES}\text{Me Me}
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