

Supporting Information for

**A Practical, Component-Based Synthetic Route to
Methylthiolincosamine Permitting Facile Northern-Half
Diversification of Lincosamide Antibiotics**

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General Experimental Procedures.

All reactions were performed in oven- or flame-dried round-bottomed or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon (dried by passage through a column of Drierite calcium sulfate desiccant), unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless-steel cannula. When necessary (so noted), solutions were deoxygenated by three cycles of freezing (liquid nitrogen), evacuation, and thawing under static vacuum. Organic solutions were concentrated by rotary evaporation (house vacuum, ~60 Torr) at 23–30 °C. Flash-column chromatography was performed as described by Still et al.,¹ employing silica gel (60-Å pore size, 230–400 mesh, Agela Technologies, Chicago, IL; or RediSep silica cartridges, Teledyne Isco, Lincoln, NE). Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60-Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). In special cases (so noted), analytical TLC was performed with aminopropyl-modified silica gel (NH₂ silica gel, 60-Å pore size, Wako Chemicals USA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to iodine vapor (I₂), basic aqueous potassium permanganate solution (KMnO₄), acidic ethanolic *para*-anisaldehyde solution (PAA), acidic aqueous ceric ammonium molybdate solution (CAM), or ethanolic solution of phosphomolybdic acid (PMA) followed by brief heating on a hot plate as needed (~200 °C, ≤15 s).² In some cases, reaction monitoring was carried out by analytical liquid chromatography–mass spectrometry (LCMS), or by flow-injection analysis–high-resolution mass spectrometry (FIA-HRMS).

¹ Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

² Sanford, M. TLC stains. Umich.edu/~mssgroup/docs/TLCStains.pdf (accessed April 14, 2018).

Materials

Commercial reagents and solvents were used as received, unless mentioned otherwise. Dichloromethane, ethyl ether, tetrahydrofuran, 1,4-dioxane, *N,N*-dimethylformamide, toluene, and benzene were purified by passage through Al₂O₃ under argon, according to the method of Pangborn et al.³ 5'-(4-Fluorobutyl)azepine acid **35** and 1-(chloromethylene)pyridine-1-ium chloride (Vilsmeier reagent **33**) were prepared according to Lewis and co-workers.⁴ *Trans*-4-*n*-propyl-L-hygric acid hydrochloride (**41**) was prepared from lincomycin according to Herr and Slomp.⁵ Ethynyltriisopropylsilane, triethylphosphonoacetate, 1,8-diazabicyclo[4.5.0]undec-7-ene, (–)-diethyl-D-tartrate, *tert*-butylchlorodiphenylsilane, chlorotriisopropylsilane, imidazole, trimethyl phosphite, sodium triacetoxyborohydride, trifluoroacetic acid, 1-[2-(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione (Teoc-OSu), Oxone monopersulfate compound, hexamethyldisilazane, methyl trifluoroacetate, HATU, and 2,4,6-trimethylbenzenesulfonyl chloride were purchased from Oakwood Products, Inc. (Estill, SC, USA). Anhydrous cupric acetate and tungsten hexacarbonyl (99%, <0.3% molybdenum) were purchased from Strem Chemicals, Inc. (Newburyport, MA, USA). 4-(*tert*-Butylthio)phenylboronic acid was purchased from Alchem Pharmtech, Inc. (Monmouth Junction, NJ, USA). (4-Mercaptophenyl)(morpholino)methanone (**S29**) was prepared according to published procedures.⁶ 4-Pyridin-3-ylaniline (**S37**) was purchased from Maybridge Chemical

³ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

⁴ Lewis, J. G.; Anandan, S. K.; O'Dowd, H.; Gordeev, M. F.; Li, L. Lincomycin derivatives possessing antibacterial activity. US Patent 7,361,743 B2, April 22, 2008.

⁵ Herr, R. R.; Slomp, G. *J. Am. Chem. Soc.* **1967**, *89*, 2444–2447.

⁶ Ahlmark, M.; Din, B. D.; Kauppala, M.; Luiro, A.; Pajunen, T.; Pystynen, J.; Tiainen, E.; Vaismaa, M.; Messinger, J. Preparation of 2-substituted 4,5-dihydroxyisophthalonitriles and their analogs as inhibitors of catechol-*O*-methyltransferase for the treatment of Parkinson's disease. WO Patent 2013175053A1, May 23, 2013.

Company (Altrincham, UK). All other chemicals and reagents were purchased from Sigma-Aldrich Corporation (Natick, MA, USA).

Instrumentation

Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Mercury 400 (400 MHz/100 MHz), Varian Inova 500 (500 MHz/125 MHz), or Varian Inova 600 (600 MHz/150 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent (CHCl_3 , δ 7.26; CHD_2OD , δ 3.31; $\text{C}_6\text{D}_5\text{H}$, δ 7.16). Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent (CDCl_3 , δ 77.2; CD_3OD , δ 49.0; C_6D_6 , δ 128.1). Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublet of doublets, td = triplet of doublets, ABq = AB quartet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (J) in Hertz (Hz). Infrared transmittance (IR) spectra were obtained using a Bruker ALPHA FTIR spectrophotometer referenced to a polystyrene standard. Data are represented as follows: Frequency of absorption (cm^{-1}), and intensity (s = strong, m = medium, br = broad). Melting points were determined using a Thomas Scientific capillary melting point apparatus. High-resolution mass spectrometry (including FIA-HRMS reaction monitoring) was performed at the Harvard University Mass Spectrometry Facility using a Bruker micrOTOF-QII mass spectrometer. X-ray crystallographic analysis was performed at the Harvard University X-Ray Crystallographic Laboratory by Dr. Shao-Liang Zheng. High-performance liquid chromatography–mass spectrometry (LCMS) was performed using an Agilent Technologies 1260-series analytical HPLC system in tandem with an Agilent Technologies 6120

Quadrupole mass spectrometer; a Zorbax Eclipse Plus reverse-phase C₁₈ column (2.1 × 50 mm, 1.8 μm pore size, 600 bar rating; Agilent Technologies, Santa Clara, CA) was employed as stationary phase. LCMS samples were eluted at a flow rate of 650 μL/min, beginning with 5% acetonitrile–water containing 0.1% formic acid, grading linearly to 100% acetonitrile containing 0.1% formic acid over 3 minutes, followed by 100% acetonitrile containing 0.1% formic acid for 2 minutes (5 minutes total run time).

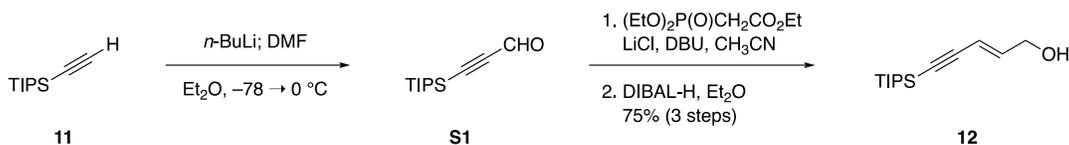
Antimicrobial Assays

The minimum inhibitory concentrations (MICs) for both test and control compounds were performed in accordance with guidelines of the Clinical Laboratory Standards Institute (CLSI)⁷ for broth microdilution susceptibility testing. Bacterial strains MMX 3028 (*S. pneumoniae*, cErmB genotype), MMX 3031 (*S. pneumoniae*, cMefA genotype), and MMX 946 (*S. pyogenes*, MLS_B phenotype) were purchased from Micromyx, LLC (Kalamazoo, MI, USA). Bacterial strains ATCC 29213 (*S. aureus*), BAA 977 (*S. aureus*, iErmA genotype), ATCC 49619 (*S. pneumoniae*), ATCC 19615 (*S. pyogenes*), ATCC 29212 (*E. faecalis*), ATCC 10031 (*K. pneumoniae*), ATCC 25922 (*E. coli*), ATCC 27853 (*P. aeruginosa*), and ATCC 49247 (*H. influenzae*) were purchased from the American Type Culture Collection (Manassas, VA, USA).

Compound Numbering. For clarity, intermediates that have not been assigned numbers in the preceding text are numbered sequentially in this section, beginning with **S1**.

⁷ Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Tenth Edition: Approved Standard M07-A10. CLSI, Wayne, PA, U.S.A., 2015.

Synthesis of Building Blocks 9 and 10



Enynol **12**.

Formylation of ethynyltriisopropylsilane was performed according to the procedure reported by Robles and McDonald.⁸ To a solution of ethynyltriisopropylsilane (**11**, 20.0 g, 110 mmol, 1 equiv) in ethyl ether (100 mL) was added *n*-butyllithium solution (2.12 M in hexane, 51.7 mL, 110 mmol, 1.00 equiv) slowly by cannula at 0 °C over approximately 15 min. The resulting solution was stirred at 0 °C for an additional 40 min. This lithium acetylide solution was then transferred via cannula over a period of 5–10 min to a 500-mL round-bottomed flask containing a mixture of *N,N*-dimethylformamide (25.5 mL, 329 mmol, 3.00 equiv) and ethyl ether (100 mL) chilled to $-78 \text{ }^\circ\text{C}$. A white suspension formed. The reaction mixture was stirred at $-78 \text{ }^\circ\text{C}$ for 1 h before warming to 0 °C, at which temperature the mixture became homogeneous. After 1 h of stirring at 0 °C, the mixture was transferred to an ice-cold aqueous sulfuric acid solution (5% v/v, 250 mL). The resulting biphasic mixture was stirred at 0 °C for 1 h, and then the layers were separated. The aqueous phase was extracted with ethyl ether ($3 \times 150 \text{ mL}$), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL). The washed organic solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to give 3-(triisopropylsilyl)propionaldehyde (**S1**) as a colorless oil that was used in the next step without further purification. The ^1H NMR data matched literature values.⁸

⁸ Robles, O.; McDonald, F. E. *Org. Lett.* **2008**, *10*, 1811–1814.

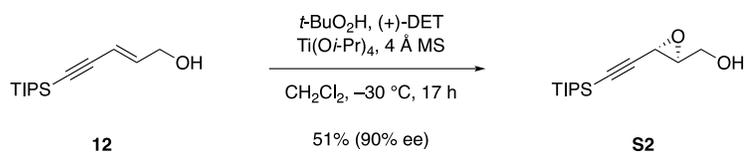
Horner–Wadsworth–Emmons olefination of the crude ynal formed in the preceding formylation reaction was performed according to the procedure reported by Bode and co-workers.⁹ An oven-dried 2-L round-bottomed flask was charged with lithium chloride (5.60 g, 132 mmol, 1.20 equiv), and the apparatus was flame-dried. Once cooled, the flask was charged with a magnetic stir bar and acetonitrile (1.3 L), and the resulting suspension was stirred at 23 °C for 10 min (lithium chloride does not fully dissolve). 3-(Triisopropylsilyl)propionaldehyde (**S1**, theoretically 110 mmol, 1 equiv) and triethyl phosphonoacetate (22.5 mL, 112 mmol, 1.02 equiv) were then added sequentially. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 16.6 mL, 110 mmol, 1.00 equiv) was added dropwise over 5 min, causing the mixture to warm to approximately 40 °C with concomitant transformation of the originally colorless reaction solution to an opaque, off-white suspension. Progress was monitored by TLC (20% dichloromethane–hexanes, UV+PAA); after 10 min, the reaction was judged to be complete. The mixture was concentrated by rotary evaporation to a volume of approximately 300 mL, and the concentrated mixture was transferred to a separatory funnel containing saturated aqueous ammonium chloride solution (400 mL) and ethyl ether (300 mL). The mixture was shaken, and the layers were separated. The aqueous phase was extracted with ethyl ether (3 × 300 mL); the combined organic layers were then washed sequentially with water (250 mL) and saturated aqueous sodium chloride solution (250 mL). The washed organic solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to give ethyl (*E*)-5-(triisopropylsilyl)pent-2-en-4-ynoate as a colorless oil that was used in the next step without further purification. The ¹H NMR data matched literature values.⁹

⁹ Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371.

Reduction of the crude ester formed in the preceding Horner–Wadsworth–Emmons olefination reaction was performed according to the procedure reported by Bressy and co-workers.¹⁰ To a rapidly stirred solution of crude ethyl (*E*)-5-(triisopropylsilyl)pent-2-en-4-ynoate (theoretically 110 mmol, 1 equiv) in ethyl ether (220 mL) was added diisobutyl aluminum hydride (1.0 M solution in hexane, 243 mL, 2.2 equiv) by cannula at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then at $0\text{ }^{\circ}\text{C}$ for 1.5 h. The reaction mixture was then transferred by wide-bore cannula to a 2-L round-bottomed flask containing a rapidly stirred aqueous Rochelle salt solution (potassium sodium tartrate, 0.80 M, 410 mL, 328 mmol, 3.0 equiv) pre-chilled to $0\text{ }^{\circ}\text{C}$. A cloudy slurry formed immediately upon aqueous quenching of the reaction mixture; after approximately 3 min of stirring at $0\text{ }^{\circ}\text{C}$, this suspension thickened to form a gel. Gas evolution was then observed, followed by gradual collapse of the gel to form a cloudy, light yellow emulsion. The mixture was stirred at $23\text{ }^{\circ}\text{C}$ overnight under an atmosphere of nitrogen gas, during which time the emulsion separated into a biphasic mixture. The layers were separated at the end of this period, and the aqueous phase was extracted with ethyl ether ($3 \times 200\text{ mL}$). The combined organic layers were then washed with saturated aqueous sodium chloride solution (200 mL), and the washed organic product solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to give a light-yellow oil. This residue was purified by flash-column chromatography (500 g silica gel, eluting with 5% ethyl acetate–hexanes initially, grading to 10% ethyl acetate–hexanes) to afford allylic alcohol **12** as a colorless oil (19.7 g, 75%, 3 steps). The ^1H NMR, ^{13}C NMR, FTIR, and HRMS data matched literature values.¹¹

¹⁰ Candy, M.; Tomas, L.; Parat, S.; Heran, V.; Bienaymé, H.; Pons, J.-M.; Bressy, C. *Chem. Eur. J.* **2012**, *18*, 14267–14271.

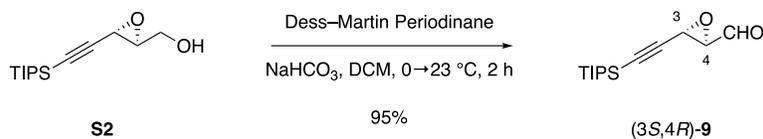
¹¹ Cho, J.; Lee, Y. M.; Kim, D.; Kim, S. *J. Org. Chem.* **2009**, *74*, 3900–3904.



Epoxyalcohol S2.

A 250-mL round-bottomed flask was charged with vacuum-oven-dried, powdered 4 Å molecular sieves (6.96 g). The flask was evacuated, and the contents were flame-dried. Once cooled, the flask was back-filled with argon gas. Dichloromethane (60 mL) and (+)-diethyl tartrate (5.27 mL, 30.7 mmol, 1.50 equiv) were added, followed by titanium tetra-*iso*-propoxide (7.68 mL, 26.2 mmol, 1.28 equiv). The resulting mixture was chilled to $-20\text{ }^\circ\text{C}$ and stirring was maintained at that temperature for 1 h to ensure thermal equilibration. A solution of allylic alcohol **12** (4.88 g, 20.5 mmol, 1 equiv) in dichloromethane (60 mL) was then added by syringe, and the mixture was stirred at $-20\text{ }^\circ\text{C}$ for 30 min. Next, a solution of *tert*-butyl hydroperoxide (5–6 M solution in decane, 11.2 mL, 60 mmol, 3 equiv) was added dropwise over 10 min at $-20\text{ }^\circ\text{C}$. After 17 h, TLC analysis (30 % ethyl acetate–hexanes, UV+KMnO₄) indicated that no olefin starting material remained. Ice-cold aqueous DL-tartaric acid solution (10% w/v, 120 mL) was added, and the resulting mixture was stirred at $-20\text{ }^\circ\text{C}$ for 30 min before it was allowed to warm to $23\text{ }^\circ\text{C}$ over 1 h. The warmed mixture was transferred to a separatory funnel containing dichloromethane (100 mL). The layers were gently shaken and were then separated. The aqueous phase was extracted with fresh dichloromethane ($3 \times 100\text{ mL}$). The combined extracts were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to give a cloudy, colorless oil. This material was purified by flash-column chromatography (120 g silica gel, eluting with 5% ethyl acetate–hexanes initially; grading to 20% ethyl acetate–hexanes) to provide epoxyalcohol **S2** as a colorless oil (2.63 g, 51%, 90% ee).

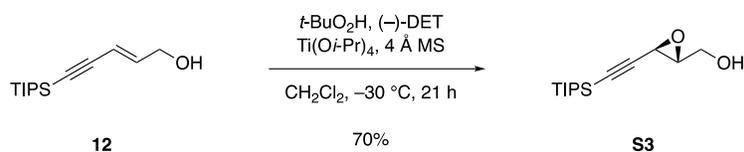
The TLC R_f , ^1H NMR, ^{13}C NMR, FTIR, and HRMS data matched those of the enantiomer, **S3**, catalogued below. Enantiomeric excess was determined by conversion of epoxyalcohol **S2** to the corresponding Mosher ester according to the same procedure described below for optical purity analysis of **S3**.



Epoxyaldehyde (3*S*,4*R*)-9.

Oxidation of alcohol **S2** was performed according to a procedure described by Fürstner and co-workers.¹² In a 100-mL round-bottomed flask, epoxyalcohol **S2** was dissolved in dichloromethane (6.64 mL). This solution was chilled to 0 °C before solid sodium bicarbonate (558 mg, 6.64 mmol, 10.0 equiv) was added. The resulting suspension was stirred at 0 °C for 30 min before Dess–Martin periodinane (423 mg, 0.996 mmol, 1.50 equiv) was added. The mixture was removed from the cooling bath and was allowed to warm to 23 °C gradually. After 2 h, TLC analysis (40% ethyl acetate–hexanes, PAA) indicated that no epoxyalcohol starting material remained. The mixture was again cooled to 0 °C before saturated aqueous sodium bicarbonate solution (3 mL) was added dropwise, followed by saturated aqueous sodium thiosulfate solution (3 mL). The mixture was stirred at 0 °C for 15 min before stirring was discontinued and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 6 mL). The combined organic extracts were washed sequentially with 1:1 saturated aqueous sodium bicarbonate–saturated aqueous sodium thiosulfate solution (10 mL), then with brine. The washed organic solution was dried over sodium sulfate, filtered, and concentrated to provide a milky oil. The crude residue was purified by flash-column chromatography (4 g silica gel, eluting with 5% ethyl acetate–hexanes initially; grading to 20% ethyl acetate–hexanes) to provide epoxyaldehyde (3*S*,4*R*)-**9** as a colorless oil (159 mg, 95%). The TLC R_f , ^1H NMR, ^{13}C NMR, FTIR, and HRMS data matched those of the enantiomer, (3*R*,4*S*)-**9**, catalogued below.

¹² Fürstner, A.; Flügge, S.; Larionov, O.; Takahashi, Y.; Kubota, T.; Kobayashi, J. *Chem. Eur. J.* **2009**, *15*, 4011–4029.

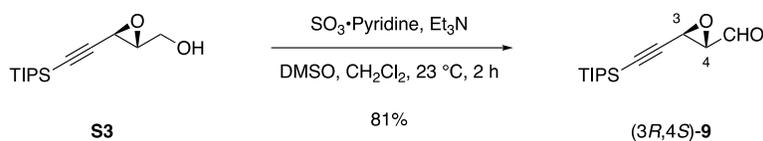


Epoxyalcohol S3.

Sharpless asymmetric epoxidation was performed according to a procedure adapted from the report of Kim and co-workers.^{11 11} A 1-L, 2-necked round-bottomed flask was oven-dried. Once cooled, the flask was charged with a magnetic stir bar and powdered 4-Å molecular sieves (20.0 g, Sigma-Aldrich, activated by heating overnight in a vacuum drying oven [200 °C, ~70 Torr]). A thermocouple probe was fitted to one neck of the flask, while the other neck was sealed with a rubber septum. Dichloromethane (229 mL) was added, and the resulting slurry was cooled to -30 °C in a CryoCool bath. (-)-Diethyl-D-tartrate (7.21 mL, 41.9 mmol, 0.500 equiv) was added. Titanium tetra-*iso*-propoxide (9.83 mL, 33.6 mmol, 0.400 equiv) was then added dropwise over 2 min, causing the internal temperature to rise to -26 °C briefly. The resulting mixture was stirred at -30 °C for 20 min, after which time a solution of allylic alcohol **12** (20.0 g, 84.0 mmol, 1 equiv) in dichloromethane (295 mL) was added slowly by cannula over 10 min. The mixture was incubated at -30 °C for 30 min. *tert*-Butylhydroperoxide solution (TBHP, ~5.5 M solution in decane, 30.5 mL, 170 mmol, 2.0 equiv) was finally added at a rate of 2.0 mL/min with a syringe pump, such that the internal temperature of the mixture did not rise above -28 °C. Stirring was maintained at -30 °C following the addition of TBHP, and progress was monitored by TLC (10% ethyl acetate-dichloromethane, UV+PAA). After 21 h, the reaction was judged to be complete. A solution comprising iron(II) sulfate heptahydrate (27 g, 97 mmol, 1.2 equiv), DL-tartaric acid (62 g, 0.41 mol, 4.9 equiv), and water (517 mL) was added to the reaction mixture, and the resulting biphasic mixture was stirred at 0 °C for 10 min at a moderate stir rate (350 rpm) The mixture was

then transferred to a separatory funnel where the layers were separated. The aqueous phase was extracted with ethyl ether (3×300 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (2×200 mL). The washed organic solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to give a slightly cloudy colorless oil. This residue was purified by flash-column chromatography (800 g silica gel, eluting with 5% ethyl acetate–hexanes initially, grading to 15% ethyl acetate–hexanes) to give epoxyalcohol **S3** as a colorless, viscous oil (14.9 g, 70%). The ^1H NMR, ^{13}C NMR, FTIR, and HRMS data matched reported values.¹¹

The enantiomeric excess was determined by conversion to the corresponding Mosher esters. In this procedure, a solution of epoxyalcohol **S3** (10 mg, 39 μmol , 1 equiv) in 4:1 dichloromethane–pyridine (200 μL) was treated with (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (8.8 μL , 47 μmol , 1.2 equiv) at 23 °C. The mixture was stirred at 23 °C for 30 min, at which point TLC analysis (50% ethyl acetate–hexanes, UV+KMnO₄) indicated complete consumption of starting material. The reaction mixture was concentrated, and the crude residue was subjected to ^1H NMR analysis (600 MHz, CDCl₃). Integration of the major methylene resonance at δ 4.60 (dd, $J = 12.3, 3.2$ Hz, 1H) relative to its minor diastereomeric counterpart at δ 4.66 (dd, $J = 12.5, 3.0$ Hz, 1H, derived from undesired (*2S,3S*)-product enantiomer) demonstrated an enantiomeric ratio of 94:6 (88% ee). Use of the enantiomeric (*S*)-Mosher acyl chloride reagent gave the same result.



Epoxyaldehyde (**3R,4S**)-**9**.

A solution of epoxyalcohol **S3** (14.9 g, 58.6 mmol, 1 equiv) in dichloromethane (468 mL) and anhydrous dimethyl sulfoxide (117 mL) was treated with triethylamine (65.3 mL, 468 mmol, 8.00 equiv). Sulfur trioxide–pyridine complex (37.3 g, 234 mmol, 4.00 equiv) was then added in three portions over 15 min at 23 °C. The resulting salmon-pink solution was stirred at 23 °C, and after 2 h, TLC analysis (30% ethyl acetate–hexanes, PAA) indicated complete consumption of starting material. The reaction mixture was transferred to a separatory funnel containing 1.2 L of 0.5 M copper(II) sulfate solution. The layers were shaken, then separated, and the aqueous phase was extracted with dichloromethane (3 × 300 mL). The combined organic layers were then washed with saturated aqueous sodium chloride solution (200 mL), and the washed organic product solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to give a brown oil. This residue was purified by flash-column chromatography (600 g silica gel, eluting with 5% ethyl acetate–hexanes initially, grading to 10% ethyl acetate–hexanes) to afford (**3R,4S**)-**9** as a colorless oil (12.0 g, 81%).

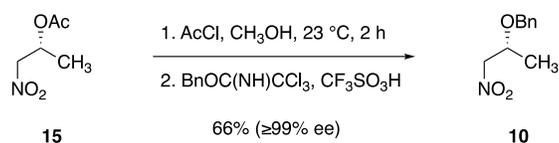
$R_f = 0.57$ (40% ethyl acetate–hexanes, KMnO_4).

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 9.02 (d, $J = 6.1$ Hz, 1H), 3.69 (d, $J = 1.8$ Hz, 1H), 3.54 (dd, $J = 6.1, 1.8$ Hz, 1H), 1.07 (s, 21H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 196.3, 99.9, 88.9, 60.5, 44.2, 18.6, 11.2.

FTIR (neat, cm^{-1}): 2944 (s), 2866 (s), 1733 (s), 1463 (m), 1411 (m), 1046 (m), 883 (m), 833 (m),
667 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{14}\text{H}_{24}\text{O}_2\text{Si}$, 252.1542; found 252.1540.



Nitro compound **10**.

Acetyl chloride (123 mL, 1.73 mol, 12.8 equiv) was added dropwise over 15 min to a solution of (*R*)-1-nitropropan-2-yl acetate (**15**, 20.0 g, 136 mmol, 1 equiv)¹³ in methanol (1.23 L) at 0 °C. Following the addition of acetyl chloride, the mixture was allowed to warm to 23 °C; progress was monitored by TLC (40% ethyl acetate–hexanes, KMnO₄). After 2 h, complete consumption of starting material was noted, and the mixture was concentrated by rotary evaporation to obtain (*R*)-1-nitropropan-2-ol as a faint yellow oil. Residual methanol present in the crude product was removed by azeotropic removal of benzene. The crude product thus obtained was used in the next step without further purification.

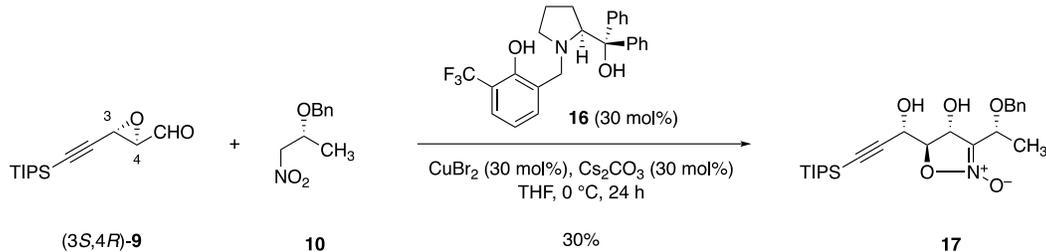
To a solution of (*R*)-1-nitropropan-2-ol (theoretically 136 mmol) in 1:2 dichloromethane–hexane (412 mL) was added benzyl 2,2,2-trichloroacetimidate (30.5 mL, 163 mmol, 1.20 equiv). Trifluoromethanesulfonic acid (1.21 mL, 13.6 mmol, 0.100 equiv) was then added dropwise over 30 min at 23 °C, causing a white precipitate to appear. After 5 h, TLC analysis (20% ethyl acetate–hexanes, UV+KMnO₄) indicated that all starting material had been consumed. The reaction mixture was filtered through a pad of Celite to remove the trichloroacetamide precipitate, and the filter pad was washed with hexanes (2 × 50 mL). The filtrate was concentrated to give a muddy brown slurry, which was purified by two sequential recrystallizations from 1% ethyl acetate–hexanes (200 mL) to give benzyl ether **10** as a brilliant white, fluffy powder (17.4 g, 66%, 2 steps).

¹³ Kitayama, T. *Tetrahedron* **1996**, 52, 6139–6148.

The ^1H NMR and melting-point data matched reported values.¹⁴ Enantiomeric excess was determined to be $\geq 99\%$ by chiral HPLC analysis using a chiral stationary-phase AD-H column using 2% isopropanol–hexanes as eluent at a flow rate of 1.0 mL/min, with detection at 300 nm. Major enantiomer $R_t = 14.7$ min, minor enantiomer $R_t = 11.7$ min.

¹⁴ Bartoli, G.; Marcantoni, E.; Petrini, M. *J. Chem. Soc. Chem. Commun.* **1991**, 793–794.

Synthesis of Isoxazoline *N*-oxides **17** and **18**



Isoxazoline *N*-oxide **17**.

A 4-mL glass vial was charged with a magnetic stir bar, nitro compound **10** (64 mg, 0.33 mmol, 1.7 equiv), copper(II) bromide (13 mg, 59 μ mol, 0.30 equiv), cesium carbonate (29mg, 89 μ mol, 0.45 equiv), and prolinol ligand **16** (25 mg, 59 μ mol, 0.30 equiv).¹⁵ This mixture was suspended in tetrahydrofuran (800 μ L), the vial was sealed with a PTFE-lined screw cap, and the mixture was stirred at 23 °C for 4 h; over this time, the mixture changed from dark black to cerulean blue. The mixture was then chilled to 0 °C before a solution of epoxyaldehyde (3*S*,4*R*)-**9** (50 mg, 0.20 mmol, 1 equiv) in tetrahydrofuran (100 μ L) was added. The mixture was warmed to 4 °C, and it was stirred at this temperature for 24 h, until TLC analysis (30% ethyl acetate–hexanes) showed complete consumption of aldehyde starting material. The mixture was neutralized with the addition of saturated aqueous ammonium chloride solution (1.0 mL). This mixture was then extracted with ethyl acetate (3 \times 2 mL); the combined organic extracts were dried over sodium sulfate, filtered, and concentrated to provide a dark green-black oil. This crude mixture was purified by flash-column chromatography (12 g silica gel, eluting with 10% ethyl acetate–hexanes initially, grading to 35% ethyl acetate–hexanes) to provide **17** as a white, crystalline solid (26 mg, 30%).

¹⁵ Xu, K.; Lai, G.; Zha, Z.; Pan, S.; Chen, H.; Wang, Z. *Chem. Eur. J.* **2012**, *18*, 12357–12362.

Crystals suitable for X-ray diffraction analysis were prepared by dissolving the product (20 mg) in dichloromethane (1 mL). This solution was passed through a cotton plug to remove any insoluble impurities, and the filtrate was collected in a 1-mL glass vial. This vial was placed within a 20-mL glass vial into which hexanes (~5 mL) had been introduced. The large vial was capped, and the assembly was allowed to stand at 23 °C; after 1 d, the hexanes in the large vial was removed by pipette, and fresh portion of hexanes (~5 mL) was introduced. The cap to the large vial was left slightly ajar to allow slow evaporation of solvent, and after 4 d of standing, needle-shaped crystals had formed.

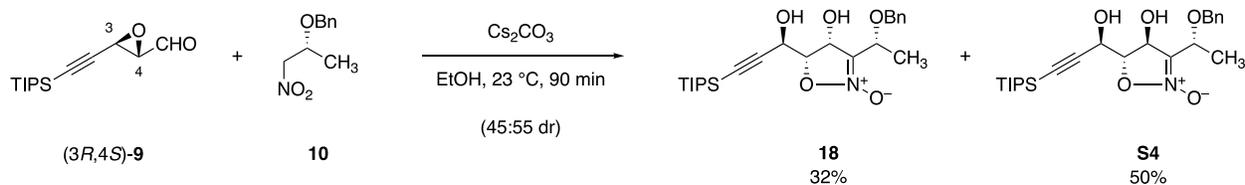
$R_f = 0.32$ (30% ethyl acetate–hexanes, UV+KMnO₄).

¹H NMR (500 MHz, CDCl₃) δ 7.35–7.29 (m, 5H), 5.60 (d, $J = 2.5$ Hz, 1H), 4.67 (d, $J = 3.0$ Hz, 1H), 4.60 (q, $J = 6.7$ Hz, 1H), 4.57 (d, $J = 11.2$ Hz, 1H), 4.45–4.43 (m, 2H), 1.52 (d, $J = 6.7$ Hz, 3H), 1.08 (s, 21H).

¹³C NMR (126 MHz, CDCl₃) δ 137.3, 128.7, 128.3, 128.2, 119.6, 102.2, 89.9, 84.6, 75.2, 72.1, 70.3, 62.6, 19.1, 18.7, 11.2.

FTIR (neat, cm⁻¹): 3386 (br), 2865 (m), 1636 (s), 1462 (m), 1366 (m), 1209 (m), 1088 (s), 882 (s), 676 (s).

HRMS (ESI+, m/z): [M+Na]⁺ calc'd for C₂₄H₃₇NO₅Si, 470.2333; found 470.2321.



Non-diastereoselective synthesis of isoxazoline *N*-oxides **18** and **S4**.

In a 20-mL glass vial fitted with a magnetic stir bar, nitro compound **10** (914 mg, 4.68 mmol, 1.20 equiv) was added to a solution of epoxyaldehyde (*3R,4S*)-**9** (985 mg, 3.90 mmol, 1 equiv) in ethanol (200 proof, 7.80 mL). The mixture was stirred at 23 °C for 5–10 min, until the nitro compound was fully dissolved, before cesium carbonate (254 mg, 780 μmol, 0.200 equiv) was added in a single portion. The mixture immediately turned canary yellow in color. Progress was monitored by ¹H-NMR analysis; after 90 min, an aliquot of the reaction mixture was concentrated, re-dissolved in CDCl₃ and analyzed by ¹H-NMR, revealing that no epoxy aldehyde starting material remained, and that cyclization of the intermediate nitroaldol adducts was complete. The stir bar was removed, and the reaction mixture was concentrated directly in vacuo to provide a viscous, yellow oil. This was purified by flash-column chromatography (80 g silica gel, eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes) to furnish, in order of elution, the undesired C5 epimer **S4** (866 mg, 50%) and the desired C5 epimer **18** (560 mg, 32%) as colorless oils.

Compound **18**:

$R_f = 0.61$ (50% ethyl acetate–hexanes, UV+KMnO₄).

¹H NMR (600 MHz, CDCl₃): δ 7.37–7.29 (m, 5H), 5.14 (app t, $J = 6.9$ Hz, 1H), 4.77 (app t, $J = 5.4$ Hz, 1H), 4.66 (d, $J = 12.1$ Hz, 1H), 4.63 (q, $J = 6.7$ Hz, 1H), 4.43 (d, $J = 12.2$ Hz, 1H),

3.92 (dd, $J = 6.7, 5.6$ Hz, 1H), 3.60 (d, $J = 7.2$ Hz, 1H), 3.35 (d, $J = 5.8$ Hz, 1H), 1.49 (d, $J = 6.7$ Hz, 3H), 1.09 (br s, 21H).

^{13}C NMR (150 MHz, CDCl_3) δ 162.6, 138.0, 128.7, 128.4, 127.9, 119.6, 103.2, 89.6, 79.4, 77.4, 77.2, 76.9, 74.7, 72.8, 70.8, 60.4, 19.1, 18.7, 11.2.

FTIR: 3380 (br), 2942 (s), 2865 (s), 1630 (s), 1463 (m), 1381 (m), 1083 (s), 883 (s), 678 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{37}\text{NO}_5\text{Si}$, 448.2514; found 448.2529.

Compound S4:

$R_f = 0.67$ (50% ethyl acetate–hexanes, UV+ KMnO_4).

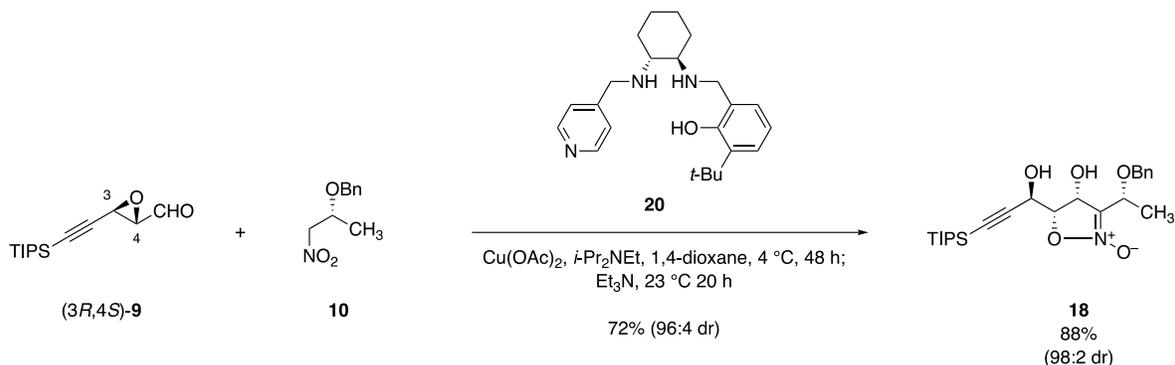
^1H NMR (500 MHz, CDCl_3) δ 7.38–7.29 (m, 5H), 5.47 (dd, $J = 3.6, 2.5$ Hz, 1H), 4.72–4.68 (m, 2H), 4.63 (d, $J = 11.5$ Hz, 1H), 4.59 (d, $J = 11.5$ Hz, 1H), 4.47 (app t, $J = 2.7$ Hz, 1H), 2.85 (d, $J = 5.5$ Hz, 1H), 2.83 (d, $J = 3.7$ Hz, 1H), 1.45 (d, $J = 6.6$ Hz, 3H), 1.08 (s, 21H).

^{13}C NMR (126 MHz, CDCl_3) δ 137.3, 128.8, 128.3, 128.2, 117.9, 102.0, 90.0, 84.1, 74.5, 72.0, 70.0, 63.0, 18.7, 17.7, 11.1.

FTIR (neat, cm^{-1}): 3395 (br), 2943 (s), 2866 (s), 1630 (s), 1463 (m), 1213 (m), 1089 (s), 833 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{37}\text{NO}_5\text{Si}$, 448.2514; found 448.2502.

Synthesis of Methylthiolincosamine (1)



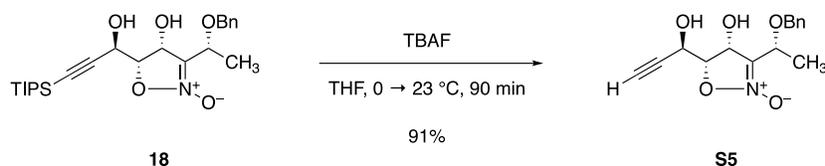
Diastereoselective synthesis of isoxazoline *N*-oxide **18**.

To a mixture of (*R,R*)-diaminocyclohexane ligand **20** (1.75 g, 47.5 mmol, 0.0100 equiv),¹⁶ and anhydrous copper(II) acetate (863 mg, 4.75 mmol, 0.0100 equiv) was added 1,4-dioxane (47.5 mL mL). The resulting dark forest-green solution was stirred at 23 °C for 30 min before *N,N*-diisopropylethylamine (830 μL , 4.75 mmol, 0.0100 equiv) was added. The catalyst mixture was then stirred an additional 10 min at 23 °C before cooling to 5–10 °C in an ice-water bath. Nitropropane **10** (12.1 g, 61.8 mmol, 1.30 equiv) was added in one portion, followed by the epoxyaldehyde (3*S*,4*R*)-**9** (12.0 g, 47.5 mmol, 1 equiv), which was added by cannula transfer (transfer was quantitated with 2 \times 2 mL 1,4-dioxane rinses). The mixture was then transferred to a 4 °C cold-room, where constant stirring was maintained at that temperature.¹⁷ Progress was monitored by NMR as follows: Aliquots of the reaction mixture (ca. 50 μL) were diluted with ethyl acetate (2 mL), and the diluted samples were washed with saturated aqueous ammonium chloride solution (1 mL). The washed samples were then dried by passage through a short plug of sodium sulfate (1 \times 2 cm), and the dried filtrate was concentrated. The green-brown residue thus

¹⁶ (a) Chougnat, A.; Zhang, G.; Liu, K.; Häussinger, D.; Kägi, A.; Allmendinger, T.; Woggon, W.-D. *Adv. Synth. Catal.* **2011**, 353, 1797–1806. (b) Zhang, G.; Yashima, E.; Woggon, W.-D. *Adv. Synth. Catal.* **2009**, 351, 1255–1262.

¹⁷ Although the melting point of pure 1,4-dioxane is 12 °C, freezing point depression prevents the solidification of the reaction mixture at these temperatures.

obtained was analyzed by ^1H NMR (CDCl_3), where consumption of epoxyaldehyde was gauged relative to the triisopropylsilyl signal (δ 1.15–1.00, 21H). After 48 h at 4 °C, conversion of aldehyde had reached $\geq 95\%$, and triethylamine (13.3 mL, 95.0 mmol, 2.00 equiv) was added to induce cyclization. The mixture was warmed to 23 °C and stirred for 20 h, whereupon aliquot NMR analysis (as above) showed the absence of epoxide methine resonances (ca. δ 3.45, 3.30), with concomitant formation of isoxazoline *N*-oxide products as a 98:2 diastereomeric mixture. The product mixture was poured into a separatory funnel containing 175 mL saturated aqueous ammonium chloride solution, and the resulting mixture was extracted with ethyl acetate (3×150 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL), and the washed organic phase was dried over sodium sulfate. The dried product solution was filtered, and the filtrate was concentrated to afford crude product as a dark brown oil. This residue was purified by flash-column chromatography (2.0 kg silica; eluting 10% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to afford the isoxazoline *N*-oxide **18** an amber-brown, viscous oil (16.4 g, 77%).



Propargylic alcohol **S5**.

A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 88 mL, 88 mmol, 2.5 equiv) was added via cannula over 5 min to a solution of alkynyl silane **18** (15.8 g, 35.3 mmol, 1 equiv) in tetrahydrofuran (118 mL) at 0 °C. The mixture was then warmed to 23 °C, and after 90 min of stirring at this temperature, TLC analysis (50% ethyl acetate–hexanes, UV+KMnO₄) indicated full conversion of starting material. The product solution was then poured into a separatory funnel containing 350 mL of water to which 35 mL of saturated aqueous sodium chloride solution had been added. The resulting biphasic mixture was extracted with ethyl acetate (3 × 150 mL). The organic layers were combined, and the organic solution was washed with saturated aqueous sodium chloride solution (100 mL). The washed product solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated to afford crude product as a light amber oil. This residue was purified by flash-column chromatography (500 g silica; eluting 35% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes) to provide **S5** as a sand-colored, powdery solid (9.38 g, 91%).

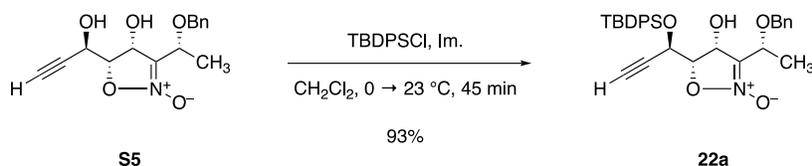
$R_f = 0.45$ (60% ethyl acetate–hexanes, UV+KMnO₄).

¹H NMR (600 MHz, CDCl₃): δ 7.37–7.29 (m, 5H), 5.22 (d, $J = 6.7$ Hz, 1H), 4.77 (dd, $J = 6.3, 2.3$ Hz, 1H), 4.61 (q, $J = 6.7$ Hz, 1H), 4.60 (d, $J = 12.2$ Hz, 1H), 4.45 (d, $J = 12.1$ Hz, 1H), 4.06 (app t, $J = 6.5$ Hz, 1H), 4.03 (br s, 1H), 2.59 (d, $J = 2.2$ Hz, 1H), 1.48 (d, $J = 6.7$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 137.6, 128.7, 128.4, 127.9, 120.0, 80.3, 79.3, 75.7, 73.9, 72.6, 70.5, 59.2, 18.9.

FTIR (neat, cm^{-1}): 3373 (br), 3284 (m), 1628 (s), 1377 (m), 1085 (s), 1046 (m), 699 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{15}\text{H}_{17}\text{NO}_5$, 314.0999; found 314.1009.



***tert*-Butyldiphenylsilyl ether 22a.**

A mixture of diol **S5** (9.38 g, 32.2 mmol, 1 equiv) and imidazole (6.58 g, 97.0 mmol, 3.00 equiv) was dissolved in dichloromethane (161 mL), and the resulting solution was cooled to 0 °C. *tert*-Butyl(chloro)diphenylsilane (12.4 mL, 48.3 mmol, 1.50 equiv) was then added in one portion, and the solution was warmed to 23 °C. Within 2–5 min of addition of the silyl chloride, a precipitate formed, imparting a cloudy appearance to the reaction mixture. Progress was monitored by TLC (60% ethyl acetate–hexanes, UV+KMnO₄), and after 45 min, full consumption of starting material was observed. The reaction mixture was quenched with the addition of 150 mL saturated aqueous sodium bicarbonate solution, and the mixture was stirred rapidly at 23 °C for 10 min. The biphasic mixture was then extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL). The organic solution was then dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated to give a peach-colored oil, which was purified by flash-column chromatography (700 g silica; eluting with hexanes initially, grading to 25% ethyl acetate–hexanes) to provide **22a** as a colorless, highly viscous oil (15.8 g, 93%).

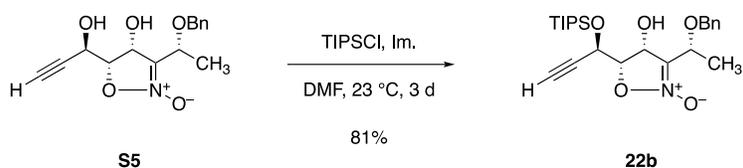
$R_f = 0.49$ (30% ethyl acetate–hexanes, UV+KMnO₄).

¹H NMR (500 MHz, CDCl₃): δ 7.75–7.68 (m, 4H), 7.49–7.44 (m, 2H), 7.43–7.28 (m, 9H), 5.17 (app t, $J = 7.6$ Hz, 1H), 4.72 (dd, $J = 4.6, 2.2$ Hz, 1H), 4.66 (q, $J = 6.8$ Hz, 1H), 4.64 (d, $J = 12.2$ Hz, 1H), 4.46 (d, $J = 12.1$ Hz, 1H), 4.02 (dd, $J = 6.9, 4.7$ Hz, 1H), 3.59 (d, $J = 8.3$ Hz, 1H), 2.45 (d, $J = 2.3$ Hz, 1H), 1.50 (d, $J = 6.8$ Hz, 3H), 1.09 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3): δ 138.1, 136.2, 136.1, 132.0, 131.4, 130.6, 130.4, 128.6, 128.2 (2 \times C), 127.9, 127.8, 118.9, 79.4, 78.9, 76.7, 74.6, 72.6, 70.7, 61.7, 26.9, 19.4, 19.2.

FTIR (neat, cm^{-1}): 3367 (br), 2932 (m), 2858 (m), 1632 (s), 1428 (m), 1112 (s), 1087 (s), 701 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{31}\text{H}_{35}\text{NO}_5\text{Si}$, 552.2177; found 552.2177.



Triisopropylsilyl ether **22b**.

To a solution of diol **S5** (329 mg, 1.13 mmol, 1 equiv) and imidazole (615 mg, 9.04 mmol, 8.00 equiv) in dimethylformamide (11.3 mL) was added triisopropylchlorosilane (718 μL , 3.39 mmol, 3.00 equiv) in one portion at 23 $^\circ\text{C}$. Reaction progress was monitored by TLC (80% ethyl acetate–hexanes, UV+KMnO₄). After 3 d, full consumption of starting material was observed, and water (25 mL) was added. The resulting mixture was extracted with ethyl ether (3 \times 25 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (25 mL). The washed organic solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash-column chromatography (24 g silica; eluting 5% ethyl acetate–hexanes, grading to 20% ethyl acetate–hexanes) to obtain **22b** as a bright white, crystalline solid (407 mg, 81%).

Crystals of **22b** suitable for X-ray analysis were prepared as follows: A 1-mL vial was charged with 20 mg of **22b**, and a minimum quantity of benzene (ca. 50 μL) was added to dissolve this material. The sample vial was then placed inside a larger, 20-mL scintillation vial filled with ca. 5 mL of hexanes, and the large vial was sealed with a screw cap. Slow diffusion of hexane into the solution of **22b** in benzene occurred over several days at 23 $^\circ\text{C}$, resulting in the growth of long, needle-shaped crystals. See Appendix A for X-ray crystal structure data.

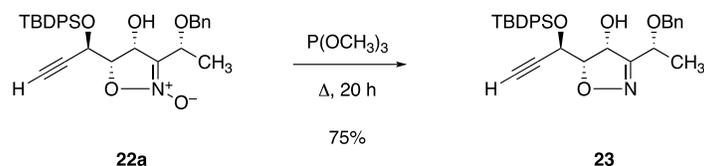
$R_f = 0.56$ (30% ethyl acetate–hexanes, UV+KMnO₄).

^1H NMR (600 MHz, CDCl_3) δ 7.38–7.28 (m, 5H), 5.21 (dd, $J = 8.1, 7.2$ Hz, 1H), 4.92 (dd, $J = 4.3, 2.3$ Hz, 1H), 4.65 (q, $J = 6.8$ Hz, 1H), 4.64 (d, $J = 12.2$ Hz, 1H), 4.45 (d, $J = 12.2$ Hz, 1H), 4.08 (d, $J = 8.2$ Hz, 1H), 4.04 (dd, $J = 7.2, 4.3$ Hz, 1H), 2.61 (d, $J = 2.2$ Hz, 1H), 1.50 (d, $J = 6.8$ Hz, 3H), 1.22–1.15 (m, 3H), 1.09 (app dd, $J = 7.4, 5.4$ Hz, 18H).

^{13}C NMR (151 MHz, CDCl_3) δ 140.2, 130.6, 130.2, 129.9, 120.9, 81.8, 80.6, 78.4, 76.9, 74.5, 72.7, 63.6, 21.1, 20.0, 19.9, 14.2.

FTIR (neat, cm^{-1}): 3345 (m), 3260 (m), 2939 (m), 2865 (m), 1639 (s), 1202 (m), 1115 (s), 873 (m), 816 (m), 733 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{37}\text{NO}_5\text{Si}$, 448.2514; found 448.2516.



Isoxazoline **23a**.

The procedure for isoxazoline *N*-oxide deoxygenation was adapted from the report of Marotta and coworkers.¹⁸ A 500-mL round-bottomed flask was charged with isoxazoline *N*-oxide **22a** (15.7 g, 29.6 mmol), and this substrate was dried by azeotropic removal of benzene. Once dried, the starting material was dissolved in trimethyl phosphite (119 mL; CAUTION: trimethyl phosphite is a highly malodorous, volatile substance. All operations up to and including the aqueous acid quench should be carried out in a well-ventilated fume hood.), and the flask was sealed. The mixture was heated to 100 °C in a pre-heated oil bath for 20 h, at which point TLC analysis (30% ethyl acetate–hexanes, UV+PAA) indicated full consumption of starting material. The solution was cooled to 23 °C, and the cooled product solution was transferred to a 2-L round-bottomed flask containing 500 mL of ethyl ether. The product solution was cooled to 5 °C in an ice-water bath, and the chilled mixture was treated very carefully with 1N aqueous hydrochloric acid solution (100 mL, added in 1-mL portions over 30 minutes). Care was taken not to allow the internal temperature of the mixture rise above 15 °C during the acidification procedure. The acidified mixture was transferred to a separatory funnel, where the layers were separated. The organic layer was washed with 1N aqueous hydrochloric acid solution (2 × 75 mL). The combined aqueous washes were extracted with fresh portions of ethyl ether (2 × 75 mL). The combined organic phases were then washed sequentially with half-saturated aqueous sodium chloride solution (50 mL), and saturated aqueous sodium chloride solution (50 mL). The organic layer was

¹⁸ Marotta, E.; Micheloni, L. M.; Scardovi, N.; Righi, P. *Org. Lett.* **2001**, *3*, 727–729.

then dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to afford crude product as a light-yellow oil. The crude material was purified by flash-column chromatography (700 g silica; eluting with 5% ethyl acetate–hexanes initially, grading to 25% ethyl acetate–hexanes) to furnish **23** as a light peach-colored, highly viscous oil (11.5 g, 75%).

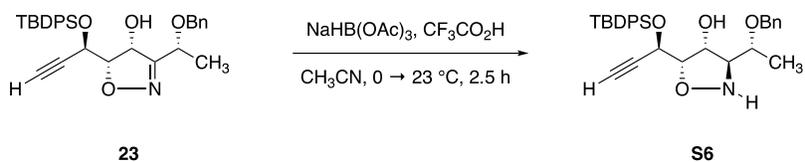
$R_f = 0.56$ (30% ethyl acetate–hexanes, UV+PAA).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.79–7.76 (m, 4H), 7.50–7.46 (m, 2H), 7.44–7.41 (m, 4H), 7.37–7.34 (m, 4H), 7.32–7.29 (m, 1H), 5.28 (app t, $J = 8.3$ Hz, 1H), 4.88 (dd, $J = 4.0, 2.3$ Hz, 1H), 4.58 (q, $J = 6.8$ Hz, 1H), 4.56 (d, $J = 12.3$ Hz, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.23 (d, $J = 8.2, 4.0$ Hz, 1H), 4.15 (d, $J = 8.6$ Hz, 1H), 2.48 (d, $J = 2.3$ Hz, 1H), 1.59 (d, $J = 6.8$ Hz, 3H), 1.10 (s, 9H).

$^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 161.3, 137.5, 136.3, 136.2, 132.1, 131.3, 130.5, 130.2, 128.5, 128.0, 127.9, 127.7, 83.4, 80.1, 76.0, 71.2, 70.9, 62.6, 26.9, 20.0, 19.4.

FTIR (neat, cm^{-1}): 3471 (br), 2932 (m), 2858 (m), 1428 (m), 1086 (s), 907 (m), 608 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{31}\text{H}_{35}\text{NO}_4\text{Si}$, 514.2408; found 514.2424.



Isoxazolidine S6.

The procedure for isoxazoline reduction was adapted from the report of Bauder.¹⁹ A mixture of isoxazoline **23** (11.4 g, 22.1 mmol, 1 equiv) and sodium triacetoxyborohydride (23.4 g, 110 mmol, 5.00 equiv) was suspended in anhydrous acetonitrile (184 mL). The resulting milky-white suspension was cooled to 0 °C in an ice-water bath with constant stirring, and to the cooled suspension was added trifluoroacetic acid (170 mL, 2.21 mol, 100 equiv) over 10 min via an oven-dried pressure-equalizing addition funnel. Addition of trifluoroacetic acid caused the suspension to resolve into a colorless solution; following this addition, the ice-water bath was removed, and the reaction solution was allowed to warm to 23 °C. Progress was monitored by TLC (30% ethyl acetate–hexanes, UV+PAA), and after 2.5 h, starting material was fully consumed. The mixture was cooled to 0 °C, and was then transferred via cannula to a stirred, ice-cold mixture of dichloromethane (300 mL) and 2N aqueous sodium hydroxide solution (1.10 L, 2.21 mol). The resulting biphasic mixture was stirred rapidly for 10 min. Additional sodium hydroxide solution was added as necessary, until the aqueous phase attained pH > 8. The mixture was then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 300 mL), and the combined organic extracts were washed with brine (300 mL). The washed organic layer was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to afford crude isoxazolidine product as a colorless oil. This material was used in the next step without further purification.

¹⁹ Bauder, C. *Org. Biomol. Chem.* **2008**, *6*, 2952–2960.

For characterization purposes, a small quantity (ca. 25 mg) of crude residue was purified by HPLC (eluting with 0.1% trifluoroacetic acid–25% acetonitrile–water, grading to 0.1% trifluoroacetic acid–95% acetonitrile–water over 45 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 254 nm; product $R_t = 33.5$ min). The trifluoroacetic acid salt thus obtained (**S6** • CF₃CO₂H) exhibited the following spectral properties:

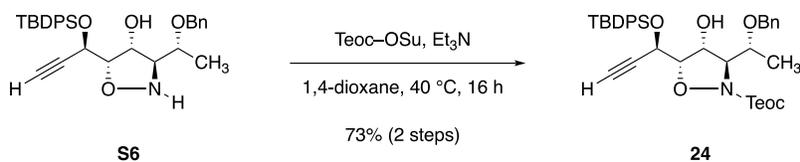
¹H NMR (600 MHz, CDCl₃) δ 7.76–7.69 (m, 4H), 7.48–7.43 (m, 2H), 7.42–7.28 (m, 9H), 4.91 (dd, $J = 5.1, 2.8$ Hz, 1H), 4.74 (dd, $J = 4.9, 2.2$ Hz, 1H), 4.66 (d, $J = 11.5$ Hz, 1H), 4.40 (d, $J = 11.6$ Hz, 1H), 3.98 (app t, $J = 5.0$ Hz, 1H), 3.81 (m, 1H), 3.51 (app t, $J = 3.3$ Hz, 1H), 2.40 (d, $J = 2.2$ Hz, 1H), 1.39 (d, $J = 6.2$ Hz, 3H), 1.09 (s, 9H).

¹³C NMR (126 MHz, CDCl₃): δ 137.6, 136.2, 136.1, 132.2, 131.7, 130.5, 130.3, 128.8, 128.2, 128.1, 128.0, 127.7, 86.1, 80.4, 76.1, 75.4, 73.9, 70.9, 70.7, 62.1, 26.9, 19.4, 16.7.

Trifluoroacetate carbons were not resolved due to ¹⁹F nuclear coupling.

FTIR (neat, cm⁻¹): 3302 (br), 2932 (m), 2859 (m), 1671 (s), 1428 (m), 1199 (m), 1113 (s), 701 (s).

HRMS (ESI+, m/z): [M+Na]⁺ calc'd for C₃₁H₃₇NO₄Si, 538.2384; found 538.2385.



Alkynol **24**.

A 200-mL round-bottomed flask was charged with isoxazolidine **S6** (crude product from the preceding directed reduction step, theoretically 22.1 mmol). The starting material was dissolved in 1,4-dioxane (55 mL) and to the resulting solution, triethylamine (15.4 mL, 110 mmol, 5.00 equiv) and *N*-[2-(trimethylsilyl)ethoxycarbonyloxy]succinimide (Teoc-OSu, 8.59 g, 33.1 mmol, 1.50 equiv) were added sequentially. The reaction mixture was heated to 40 °C, and consumption of starting material was monitored by LCMS. After 16 h, the reaction was judged to be complete. The reaction mixture was then diluted in 450 mL of ethyl acetate, and the diluted product solution was washed with saturated aqueous ammonium chloride solution (3 × 50 mL). The combined aqueous washes were extracted with a portion of fresh ethyl acetate (100 mL), and the combined organic layers were then washed with saturated aqueous sodium chloride solution (50 mL). The washed organic product solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to give a viscous orange oil. This material was purified by flash-column chromatography (1.00 kg silica gel, eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes) to provide **24** as a highly viscous, colorless oil (10.6 g, 73%, 2 steps).

$R_f = 0.43$ (20% ethyl acetate–hexanes, UV+KMnO₄).

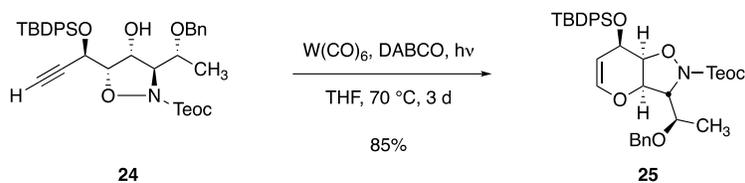
¹H NMR (600 MHz, CDCl₃): δ 7.78–7.74 (m, 4H), 7.48–7.44 (m, 2H), 7.42–7.36 (m, 4H), 7.35–7.27 (m, 5H), 4.90 (app t, *J* = 3.8 Hz, 1H), 4.79 (dd, *J* = 6.2, 2.2 Hz, 1H), 4.67 (d, *J* = 11.8

Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.25–4.12 (m, 4H), 3.65 (app p, J = 6.3 Hz, 1H), 3.31 (d, J = 3.9 Hz, 1H), 2.36 (d, J = 2.2 Hz, 1H), 1.33 (d, J = 6.2 Hz, 3H), 1.10 (s, 9H), 1.05–0.94 (m, 2H), 0.04 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3): δ 158.2, 138.3, 136.3, 136.0, 130.3, 130.2, 128.5, 127.9 (2 \times C), 127.8, 127.6, 83.9, 81.2, 75.7, 74.7, 74.1, 73.5, 71.4, 64.9, 62.1, 26.9, 19.4, 17.7, 17.0, 1.4.

FTIR (neat, cm^{-1}): 3463 (br), 2954 (m), 2858 (m), 1702 (m), 1325 (m), 1112 (s), 1064 (s), 838 (s), 700 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{37}\text{H}_{49}\text{NO}_6\text{Si}_2$, 660.3171; found 660.3161.



Glycal **25**.

The procedure for tungsten-catalyzed cycloisomerization was adapted from the reports of McDonald and Koo.²⁰ In a 200-mL round-bottomed flask, alkyne **24** (4.17 g, 6.32 mmol, 1 equiv) was dried by azeotropic removal of benzene under vacuum. The flask was back-filled with argon, and tungsten hexacarbonyl (556 mg, 1.58 mmol, 0.250 equiv),²¹ 1,4-diazabicyclo[2.2.2]octane (DABCO, 1.42 g, 12.6 mmol, 2.00 equiv), and degassed, anhydrous tetrahydrofuran (63.2 mL) were then added sequentially (CAUTION: tungsten hexacarbonyl is a volatile source of metal and of carbon monoxide. Manipulations of this reagent should be conducted within a well-ventilated fume hood.). The flask was fitted with an oven-dried reflux condenser, and the apparatus was transferred to a pre-heated oil bath ($70\text{ }^\circ\text{C}$) positioned inside a photochemistry safety cabinet. A positive pressure of dry argon was maintained via tubing connected to an argon-filled balloon placed outside of the lightbox. The reaction mixture was refluxed with constant UV irradiation from an adjacent 200-Watt mercury-vapor bulb filtered through a water-cooled Pyrex glass jacket (CAUTION: Exposure to high-intensity UV light can cause irreversible vision loss. Never open the safety cabinet when the UV lamp is on.). Progress was monitored by TLC (20% ethyl acetate–hexanes, UV+KMnO₄). After 3 d, full consumption of the alkyne substrate was achieved, and the crude product mixture was concentrated under a stream of dry nitrogen. The canary-yellow residue

²⁰ Koo, B.-S.; McDonald, F. E. *Org. Lett.* **2007**, *9*, 1737–1740.

²¹ Tungsten hexacarbonyl purchased from Strem (99%, <0.3% molybdenum) gave moderately higher yields than precatalyst purchased from Sigma-Aldrich (97%), likely due to the presence of molybdenum hexacarbonyl as a major impurity in the latter sample.

was purified by flash-column chromatography (eluting with hexanes initially, grading to 20% ethyl acetate–hexanes) to provide **25** as a viscous, colorless oil (3.53 g, 85%).

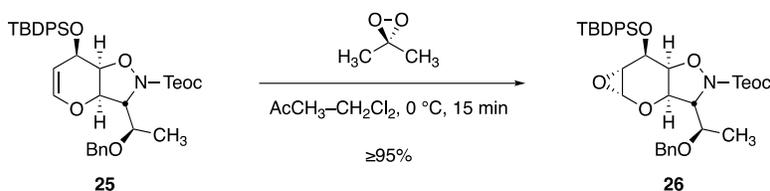
$R_f = 0.65$ (20% ethyl acetate–hexanes, UV+KMnO₄)

¹H NMR (500 MHz, CDCl₃): 7.77–7.74 (m, 2H), 7.70–7.67 (m, 2H), 7.44–7.38 (m, 2H), 7.37–7.31 (m, 4H), 7.27–7.23 (m, 3H), 7.22–7.19 (m, 2H), 6.10 (dd, $J = 6.4, 2.3$ Hz, 1H), 4.67 (app dt, $J = 6.5, 1.9$ Hz, 1H), 4.62 (d, $J = 2.9$ Hz, 1H), 4.56–4.51 (m, 2H), 4.36 (d, $J = 11.7$ Hz, 1H), 4.36–4.31 (m, 1H), 4.24 (td, $J = 10.4, 6.9$ Hz, 1H), 4.20 (app dt, $J = 4.6, 2.3$ Hz, 1H), 4.10 (d, $J = 5.1$ Hz, 1H), 3.72 (app p, $J = 6.2$ Hz, 1H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.08 (s, 9H), 0.07 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 157.1, 141.8, 138.2, 136.0 (2 \times C), 133.8, 133.6, 129.9 (2 \times C), 128.5, 127.9, 127.8 (3 \times C), 102.0, 77.5, 77.3, 73.6, 72.4, 71.9, 64.8, 63.0, 27.0, 19.4, 17.8, 17.2, 1.2.

FTIR (neat, cm⁻¹): 2954 (m), 2858 (m), 1703 (m), 1328 (m), 1112 (s), 1066 (s), 838 (m), 702 (s).

HRMS (ESI+, m/z): [M+H]⁺ calc'd for C₃₇H₄₉NO₆Si₂, 660.3171; found 660.3164.



Glycal epoxide **26**.

A solution of dimethyldioxirane in acetone was prepared, and its concentration was assayed according to the procedure of Murray and Singh.²² A solution of glycal **25** (1.45 g, 2.20 μmol , 1 equiv) in dichloromethane (22.0 mL) was cooled to 0 °C, whereupon dimethyldioxirane solution (0.0997 M, 26.4 mL, 2.64 μmol , 1.20 equiv) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 15 min, at which point TLC analysis (20% ethyl acetate–hexanes, UV+PAA) indicated full consumption of starting material. The mixture was then concentrated under a stream of dry argon, and the residue was dried by azeotropic removal of benzene to afford glycal epoxide **26** as a colorless oil that was suitable for use without further purification (quantitative yield, $\geq 95\%$ purity by NMR).

$R_f = 0.56$ (NH_2 silica gel,²³ 2% methanol–20% ethyl acetate–hexanes, UV+CAM).

$^1\text{H NMR}$ (500 MHz, C_6D_6) δ 7.89–7.83 (m, 2H), 7.77–7.71 (m, 2H), 7.21–7.09 (m, 7H), 7.08–7.00 (m, 4H), 4.66 (dd, $J = 2.6, 1.0$ Hz, 1H), 4.42 (d, $J = 5.1$ Hz, 1H), 4.34–4.21 (m, 4H), 4.21 (d, $J = 11.8$ Hz, 1H), 4.12–4.08 (m, 1H), 4.05 (d, $J = 11.8$ Hz, 1H), 3.56 (app p, $J = 6.2$ Hz, 1H), 2.97–2.92 (m, 1H), 1.19 (d, $J = 0.7$ Hz, 9H), 0.95 (d, $J = 6.4$ Hz, 3H), 0.91 (ddd, $J = 9.4, 6.7, 3.9$ Hz, 2H), -0.11 (d, $J = 0.7$ Hz, 9H).

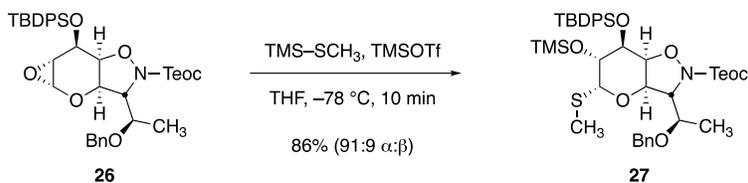
²² Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.

²³ Note: The acid-sensitive product is unstable toward chromatography using standard silica gel.

^{13}C NMR (125 MHz, C_6D_6) δ 157.95, 138.78, 136.31, 136.13, 133.68, 133.47, 130.36, 130.34, 128.59, 128.35, 128.31, 128.25, 128.20, 128.06, 127.87, 127.75, 77.12, 74.25, 74.12, 73.79, 73.33, 71.60, 67.08, 64.65, 51.67, 27.12, 19.63, 17.74, 16.79, -1.45.

FTIR (neat, cm^{-1}): 2953 (m), 2858 (m), 1703 (m), 1249 (m), 1112 (s), 837 (s), 701 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{37}\text{H}_{49}\text{NO}_7\text{Si}_2$, 676.3120; found 676.3118.



Thioglycoside **27**.

A 10-mL round-bottomed flask was charged with a magnetic stir bar and glycal epoxide **26** (103 mg, 152 μ mol, 1 equiv). This starting material was dried by azeotropic removal of benzene before it was dissolved in tetrahydrofuran (760 μ L). The solution was chilled to -78 °C before trimethyl(methylthio)silane (65.7 μ L, 456 μ mol, 3.00 equiv) was added. Trimethylsilyl trifluoromethanesulfonate (5.49 μ L, 30.4 μ mol, 0.200 equiv) was then added dropwise at -78 °C, and stirring was maintained at that temperature. Progress was monitored by TLC (NH₂ silica gel, 2% methanol–20% ethyl acetate–hexanes, UV+CAM), and after 10 min, the reaction was judged to be complete. The mixture was neutralized with the addition of 5% v/v triethylamine–dichloromethane (500 μ L), and the quenched reaction mixture was concentrated in vacuo. Crude ¹H-NMR analysis revealed a 91:9 mixture of anomers; this mixture was subjected to flash-column chromatography (12 g silica gel, eluting with hexanes initially, grading to 20% ethyl acetate–hexanes) to provide the product as a colorless oil (105 mg, 86%).

R_f = 0.40 (20% ethyl acetate–hexanes, UV+PMA).

¹H NMR (500 MHz, CDCl₃) δ 7.88–7.86 (m, 2H), 7.82–7.80 (m, 2H), 7.44–7.34 (m, 6H), 7.27–7.22 (m, 3 H), 7.13–7.11 (m, 2H), 5.08 (d, J = 4.9 Hz, 1H), 4.52 (d, J = 2.2 Hz, 1H), 4.42 (d, J = 11.8 Hz, 1H), 4.41 (dd, J = 9.1, 5.1 Hz), 4.33 (app t, J = 8.5 Hz, 2H), 4.19 (dd, J = 9.5, 3.8 Hz, 1H), 4.17 (d, J = 11.6 Hz, 1H), 4.02 (d, J = 6.6 Hz, 1H), 3.70 (dd, J = 3.8, 2.3

Hz, 1H), 3.31 (app p, $J = 6.2$ Hz, 1H), 1.97 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.11 (s, 9H), 0.20 (s, 9H), 0.11 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 158.2, 138.0, 136.2, 136.1, 134.5, 133.3, 129.8, 129.6, 128.4, 127.7 ($2 \times \text{C}$), 127.6, 127.5, 87.3, 79.6, 73.3, 73.1, 71.6 ($2 \times \text{C}$), 70.2, 69.8, 64.7, 27.1, 19.4, 17.8, 17.2, 12.7, 0.4, -1.3 .

IR (neat, cm^{-1}): 1703 (m), 1325 (m), 1105 (m), 1063 (m), 837 (s), 731 (s), 699 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{41}\text{H}_{61}\text{NO}_7\text{SSi}_3$, 818.3369; found 818.3356.

water initially, grading to 0.1% trifluoroacetic acid–80% acetonitrile–water over 30 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 254 nm and by ESI+ selected ion monitoring [$m/z = 342$]; $R_t = 14.8$ min) to provide the product as the corresponding hydrotrifluoroacetate salt, which featured sharper NMR peaks.

$R_f = 0.31$ (free base, 1% ammonium hydroxide–10% methanol–dichloromethane, UV+PAA).

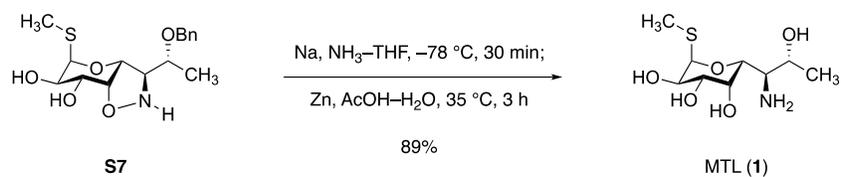
^1H NMR (free base, 600 MHz, CDCl_3) δ 7.37–7.35 (m, 2H), 7.32–7.28 (m, 2H), 5.24 (d, $J = 4.9$ Hz, 1H), 4.87 (br, 1H), 4.66 (d, $J = 11.7$ Hz, 1H), 4.35 (d, $J = 11.6$ Hz, 1H), 4.11 (br, 1H), 3.95 (br, 1H), 3.91 (dd, $J = 4.4, 2.8$ Hz, 1H), 3.55 (br, 1H), 3.36 (br, 1H), 3.17 (br, 1H), 3.03 (br, 1H), 2.15 (s, 3H), 1.32 (d, $J = 6.2$ Hz, 3H).

^1H NMR (hydrotrifluoroacetate salt, 500 MHz, CD_3OD) δ 7.38–7.34 (m, 4H), 7.31–7.29 (m, 1H), 5.26 (d, $J = 5.0$ Hz, 1H), 5.06 (d, $J = 2.2$ Hz, 1H), 4.69 (d, $J = 11.1$ Hz, 1H), 4.56 (dd, $J = 4.1, 2.3$ Hz, 1H), 4.49 (d, $J = 11.1$ Hz, 1H), 4.09 (dd, $J = 10.0, 5.0$ Hz, 1H), 3.99–3.97 (m, 2H), 3.93 (dd, $J = 9.9, 4.0$ Hz, 1H), 2.12 (s, 3H), 1.39 (d, $J = 5.8$ Hz, 3H).

^{13}C NMR (hydrotrifluoroacetate salt, 126 MHz, CD_3OD) δ 139.1, 129.5, 128.9 ($2 \times \text{C}$), 88.8, 85.6, 75.0, 73.1, 72.8, 72.1, 69.0, 68.7, 16.6, 13.1.

FTIR (neat, cm^{-1}): 3317 (br, w), 1668 (s), 1433 (w), 1197 (s), 1142 (s), 1093 (s), 699 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{16}\text{H}_{23}\text{NO}_5\text{S}$, 342.1370; found 342.1365.



Completion of the synthesis of methylthiolincosamine (1).

A flame-dried 2–5-mL glass microwave reaction vial was fitted with a magnetic stir bar and was sealed with a rubber septum. The septum was pierced with a 20-gauge needle to supply dry argon gas, and a second needle was used to vent the apparatus; under a steady stream of argon to exclude air and moisture, the empty apparatus was chilled to $-78\text{ }^\circ\text{C}$. The chilled flask was then slowly charged with anhydrous ammonia gas (supplied via a 22-gauge needle). After approximately 2 mL of liquid ammonia was condensed in this fashion, the needle supplying ammonia gas was removed, and a small piece of sodium metal (approximately 1 mm^3) was added. The mixture attained a deep blue color, and was stirred at $-78\text{ }^\circ\text{C}$ for 5 min. After this time, a solution of isoxazolidine **S7** (40.0 mg, $117\text{ }\mu\text{mol}$, 1 equiv) in tetrahydrofuran ($500\text{ }\mu\text{L}$) was introduced dropwise via syringe. During this addition, the blue coloration of the reaction mixture disappeared, signaling that the initial portion of sodium metal was fully consumed; additional 1-mm^3 pieces of sodium were added until a deep-blue color persisted. The mixture was then stirred at $-78\text{ }^\circ\text{C}$ for 30 min, until LCMS analysis indicated that *O*-debenzylation was complete (*N*-*O* bond cleavage stalls in the course of this reaction, leaving a roughly 50:50 mixture of fully reduced product and *O*-debenzylated isoxazolidine intermediate even after prolonged exposure to dissolving-metal conditions). Solid ammonium chloride was added portionwise in order to quench excess reductant, until a colorless mixture was obtained; the apparatus was then allowed to warm to $23\text{ }^\circ\text{C}$ in order to allow the ammonia co-solvent to evaporate. The mixture was then dried in vacuo to provide a white solid residue.

This residue was re-dissolved in 50% v/v acetic acid–water (1.0 mL), zinc powder (30.6 mg, 469 μ mol, 4.00 equiv) was added, and the mixture was heated to 35 °C with stirring, in order to quantitate *N*–*O* bond cleavage of intermediate isoxazolidine compound. After 3 h, LCMS analysis revealed that no isoxazolidine remained, and the mixture was filtered through a pad of Celite in order to remove any residual zinc metal. The filtrate was concentrated, and residual acetic acid and water were removed by repeated azeotropic concentration from 50% v/v methanol–toluene. The dried residue, containing the aminotetraol as its hydroacetate salt, along with zinc acetate and ammonium acetate, was dissolved in methanol (5.0 mL), and Amberlyst A26 ion-exchange resin (hydroxide form, 1.0 g) was added. The mixture was stirred at 23 °C for 1 h before the ion-exchange beads were removed by filtration. The filtrate was concentrated to provide crude product in its free-base form. This residue was purified by flash-column chromatography (4.0 g silica gel, eluting with 1% ammonium hydroxide–10% methanol–dichloromethane initially, grading to 10% ammonium hydroxide–40% methanol–dichloromethane) to provide methylthiolincosamine (**1**) as a brilliant white solid (26.4 mg, 89%).

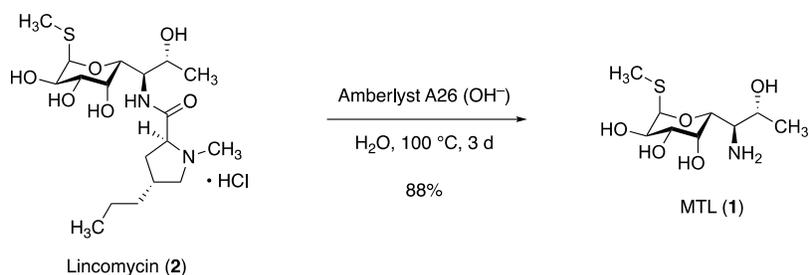
$R_f = 0.42$ (10% ammonium hydroxide–40% methanol–dichloromethane, PAA).

$^1\text{H NMR}$ (500 MHz, D_2O) δ 5.17 (d, $J = 5.8$ Hz, 1H), 3.97–3.93 (m, 3H), 3.82 (d, $J = 9.6$ Hz, 1H), 3.50 (dd, $J = 10.4, 3.3$ Hz, 1H), 3.01 (dd, $J = 9.6, 3.6$ Hz, 1H), 1.97 (s, 3H), 0.99 (d, $J = 6.4$ Hz, 3H).

$^{13}\text{C NMR}$ (126 MHz, D_2O) δ 88.0, 71.3, 70.4, 68.3, 67.7, 67.1, 53.6, 14.2, 12.9.

FTIR (neat, cm^{-1}): 3280 (br), 2904 (m), 1385 (m), 1076 (m), 1041 (s), 866 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_9\text{H}_{19}\text{NO}_5\text{S}$, 254.1057; found 254.1055.



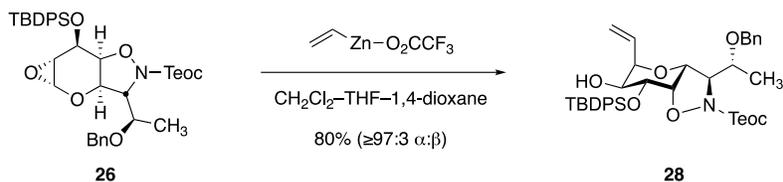
Semisynthetic preparation of methylthiolincosamine (1).

Based on the original report of Schroeder, Bannister, and Hoeksema,²⁴ an improved procedure for the preparation of methylthiolincosamine (1) from lincomycin (2) avoiding the use of the hazardous reagent hydrazine was developed. In a 250-mL round-bottomed flask, lincomycin hydrochloride (2 • HCl, 1.58 g, 3.57 mmol, 1 equiv), Amberlyst A26 ion-exchange resin (hydroxide form, 15.8 g), and water (71.3 mL) were combined. The flask was fitted with a reflux condenser, and the mixture was heated to reflux for 3 d, at which point LCMS analysis indicated that hydrolysis was complete. The mixture was allowed to cool to ambient temperature before the ion-exchange beads were removed by filtration. The filtrate was concentrated directly to afford pure methylthiolincosamine (MTL, 1) free base as a brilliant white solid (795 mg, 88%).

The TLC R_f , $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and HRMS data were identical to those of the synthetic sample prepared by the route described above.

²⁴ Schroeder, W.; Bannister, B.; Hoeksema, H. *J. Am. Chem. Soc.* **1967**, *89*, 2448–2453.

Synthesis of C-Glycosides 29, 30, and 31



Vinyl glycoside **28**.

An oven-dried 100-mL round-bottom flask was charged with a stir bar and divinylzinc solution (0.15 M solution in tetrahydrofuran–dioxane, 21.7 mL, 3.3 mmol, 2.3 equiv; prepared according to the method of Brubaker and Myers;²⁵ titrated according to the method of Krasovskiy and Knochel²⁶). This solution was chilled to 0 °C, and trifluoroacetic acid (250 μL , 3.3 mmol, 2.3 equiv) was then added dropwise. The resulting solution was stirred for 30 min at 0 °C prior to use.

In a separate 100-mL round-bottom flask, epoxide **26** (954 mg, 1.41 mmol, 1 equiv) was dried by azeotropic removal of benzene. The dried epoxide was dissolved in anhydrous dichloromethane (14.1 mL), and the resulting solution was chilled to 0 °C. This epoxide solution was then transferred by cannula to the flask containing freshly prepared vinylzinc trifluoroacetate, also at 0 °C. The resulting solution was stirred at 0 °C for 4 h, at which point TLC analysis (NH_2 silica gel, 20% ethyl acetate–hexanes + 2% methanol, UV+CAM) indicated full consumption of epoxide starting material. The reaction was quenched with the addition of 35 mL of saturated aqueous ammonium chloride solution, and the resulting biphasic mixture was stirred for 10 min. The layers were then separated, and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride

²⁵ Brubaker, J. D.; Myers, A. G. *Org. Lett.* **2007**, *9*, 3523–3525.

²⁶ Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890–891.

solution, and the washed organic product solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford crude product as a faint yellow oil. The product was purified by flash-column chromatography (40 g silica, eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes) to provide **28** as a colorless oil (846 mg, 1.20 mmol, 85%).

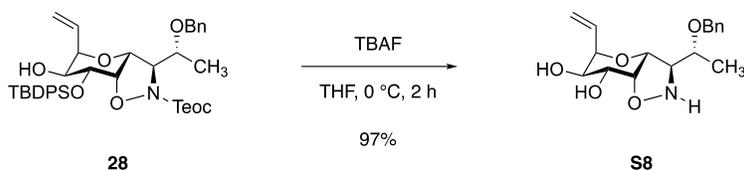
$R_f = 0.47$ (20% ethyl acetate–hexanes, UV+KMnO₄).

¹H NMR (600 MHz, C₆D₆) δ 7.96–7.94 (m, 2H), 7.83–7.79 (m, 2H), 7.22–7.19 (m, 2H), 7.18–7.16 (m, 1H), 7.15–7.11 (m, 4H), 7.07–7.00 (m, 4H). 5.74 (ddd, $J = 17.6, 11.0, 4.1$ Hz, 1H), 5.20 (app dt, $J = 17.6, 2.1$ Hz, 1H), 4.95 (app dt, $J = 11.1, 2.1$ Hz, 1H), 4.57 (app dt, $J = 9.7, 5.0$ Hz, 1H), 4.53 (d, $J = 2.4$ Hz, 1H), 4.50 (app ddt, $J = 6.1, 4.3, 2.2$ Hz, 1H), 4.40 (d, $J = 5.4$ Hz, 1H), 4.33 (app td, $J = 10.3, 6.5$ Hz, 1H), 4.30–4.25 (m, 2H), 4.23 (app t, $J = 3.0$ Hz, 1H), 4.09 (d, $J = 11.8$ Hz, 1H), 4.01 (dd, $J = 9.7, 3.6$ Hz, 1H), 3.60 (app qn, $J = 6.2$ Hz, 1H), 1.71 (d, $J = 4.2$ Hz, 1H), 1.18 (s, 9H), 1.07 (d, $J = 6.3$ Hz, 3H), 0.97–0.91 (m, 2H), –0.09 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 157.9, 138.1, 136.2, 135.8, 133.5, 133.3, 130.8, 130.1, 128.5, 128.0, 127.9, 127.8, 127.8, 119.2, 80.2, 76.3, 74.6, 73.2, 72.5, 71.7, 71.1, 68.7, 64.8, 27.1, 19.5, 17.7, 17.3, –1.2. Overlap of a single pair of phenyl carbon resonances accounts for the observation of only 11 unique phenyl-derived signals.

FTIR (neat, cm⁻¹): 3473 (br), 2953 (m), 2931 (m), 2895 (m), 2858 (m), 1702 (m), 1427 (m), 1250 (m), 1112 (s), 1082 (s), 838 (m), 702 (s).

HRMS (ESI+, m/z): [M+H]⁺ calc'd for C₃₉H₅₃NO₇Si₂, 704.3433; found 704.3418



Isoxazolidine diol **S8**.

In a 10-mL round-bottomed flask, isoxazolidine **28** (150 mg, 213 μmol , 1 equiv) was dissolved in tetrahydrofuran (2.13 mL). The resulting solution was chilled to 0 °C before it was treated with tetra-*n*-butylammonium fluoride solution (1.0 M in tetrahydrofuran, 640 μL , 3.0 equiv). While cleavage of the 2-(trimethylsilyl)ethyl carbamoyl protecting group is rapid, the *tert*-butyldiphenylsilyl ether group is less labile. After 2 h of stirring at 0 °C, LCMS analysis showed that global desilylation was complete and the reaction mixture was treated with saturated aqueous sodium bicarbonate solution (2 mL) and saturated aqueous sodium chloride solution (5 mL). This mixture was extracted with dichloromethane (3×10 mL), and the combined extracts were dried directly over sodium sulfate. The dried solution was then filtered, the filtrate was concentrated, and the crude residue was purified by flash-column chromatography (12 g silica gel, eluting with dichloromethane initially, grading to 10% methanol–dichloromethane) to furnish isoxazolidine diol product as a viscous, colorless oil (66.4 mg, 97%).

In its free-base form, this product displayed substantial ^1H - and ^{13}C -NMR peak broadening, likely owing to a nitrogen inversion process occurring on the NMR timescale. Thus, for NMR characterization purposes, the product was converted to its hydrochloride salt form by treating an ice-cold solution of free base (61 mg, 190 μmol , 1 equiv) in methanol (5.0 mL) with hydrogen chloride solution (4.0 M in 1,4-dioxane, 190 μL , 760 μmol , 4.0 equiv). The mixture was then concentrated *in vacuo* to provide the hydrochloride salt **S8** • HCl as a white solid.

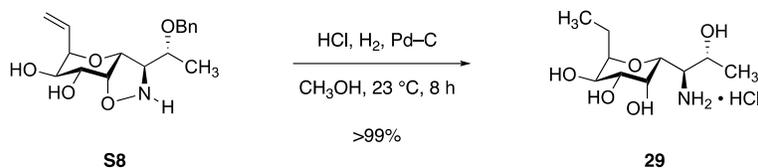
$R_f = 0.40$ (free base, 10% methanol–dichloromethane, I_2).

^1H NMR (hydrochloride salt, 500 MHz, CD_3OD) δ 7.39–7.33 (m, 4H), 7.30–7.27 (m, 1H), 6.09 (ddd, $J = 17.4, 10.8, 5.2$ Hz, 1H), 5.43 (app dt, $J = 17.4, 1.9$ Hz, 1H), 5.40 (app dt, $J = 10.1, 1.8$ Hz, 1H), 5.01 (dd, $J = 3.4, 2.1$ Hz, 1H), 4.71–4.70 (m, 1H), 4.67 (d, $J = 11.1$ Hz, 1H), 4.57–4.55 (m, 1H), 4.53 (d, $J = 11.1$ Hz, 1H), 4.14 (app t, $J = 2.5$ Hz, 1H), 4.09 (qd, $J = 6.2, 3.0$ Hz, 1H), 3.96–3.95 (m, 2H), 1.40 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (hydrochloride salt, 126 MHz, CD_3OD) δ 139.1, 132.7, 129.4, 128.8 ($2 \times \text{C}$), 119.8, 84.1, 76.8, 75.3, 72.5, 72.0, 71.4, 69.2, 68.5, 16.1.

FTIR (hydrochloride salt, neat, cm^{-1}): 3390 (br), 2895 (m), 1454 (m), 1087 (s), 698 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{17}\text{H}_{23}\text{NO}_5$, 322.1649; found 322.1658.



Aminotetraol **29**.

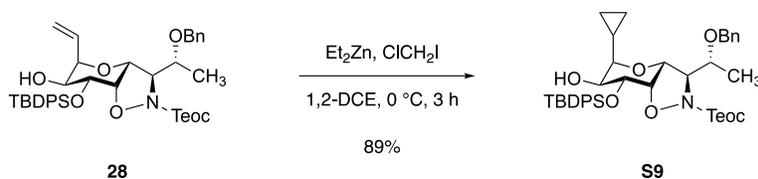
In a 10-mL round-bottomed flask, isoxazolidine **8** (67.6 mg, 0.189 mmol, 1 equiv) was dissolved in methanol (1.00 mL), and the solution was treated with hydrogen chloride solution (4.0 M in 1,4-dioxane, 190 μ L, 4.0 equiv). The mixture was then concentrated to dryness to provide the hydrochloride salt of the starting material; this salt was dissolved in methanol (1.89 mL), and the solution was treated with palladium on carbon (10% w/w, 20 mg). The headspace of the flask was replaced with hydrogen gas, and the black suspension was stirred at 23 $^\circ$ C for 8 h, whereupon LCMS analysis revealed that olefin saturation, isoxazolidine hydrogenation, and debenzoylation were all complete. The mixture was filtered through a pad of Celite to remove the catalyst, and the filter cake was washed with fresh methanol (3 \times 1 mL). The filtrate was concentrated to afford **29** \cdot HCl as a white foaming solid (54.3 mg, 106%).

^1H NMR (600 MHz, CD_3OD) δ 4.20 (app t, $J = 2.9$ Hz, 1H), 4.13 (app p, $J = 6.2$ Hz, 1H), 3.94–3.91 (m, 2H), 3.87 (td, $J = 7.0, 4.6$ Hz, 1H), 3.77 (dd, $J = 8.2, 3.1$ Hz, 1H), 3.63 (app t, $J = 6.4$ Hz, 1H), 1.64 (app p, $J = 7.3$ Hz, 2H), 1.29 (d, $J = 6.4$ Hz, 3H), 0.96 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 77.2, 71.5, 69.9, 69.7, 68.7, 65.5, 58.5, 19.7, 18.7, 10.9.

FTIR (neat, cm^{-1}): 3333 (br), 2968 (m), 2936 (m), 1503 (m), 1070 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{10}\text{H}_{21}\text{NO}_5$, 236.1492; found 236.1488.



Cyclopropyl glycoside **S9**.

Cyclopropanation was performed using the method described by Denmark and Edwards.²⁷ In a 2–5-mL glass microwave vial fitted with a magnetic stir bar, a solution of diethylzinc (43.9 μL , 0.426 mmol, 3.00 equiv) in 1,2-dichloroethane (800 μL) was chilled to 0 $^\circ\text{C}$. Chloriodomethane (61.9 μL , 0.852 mmol, 6.00 equiv) was then added dropwise to this solution, and the mixture was stirred at 0 $^\circ\text{C}$ for 5 min before a solution of olefin **28** (100 mg, 0.142 mmol, 1 equiv) in 1,2-dichloroethane (100 μL) was added by cannula. The reaction mixture was stirred at 0 $^\circ\text{C}$ for 3 h, whereupon TLC analysis (30% ethyl acetate–hexanes, UV+CAM) showed complete consumption of starting material. Excess Simmons–Smith reagent was quenched with the addition of saturated aqueous ammonium chloride solution (2 mL), and the resulting biphasic mixture was extracted with dichloromethane ($3 \times 10\text{ mL}$). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL), dried over sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash-column chromatography (12 g silica gel, eluting with 20% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes) to furnish **S9** as a colorless oil (90.9 mg, 89%).

$R_f = 0.64$ (30% ethyl acetate–hexanes, UV+CAM).

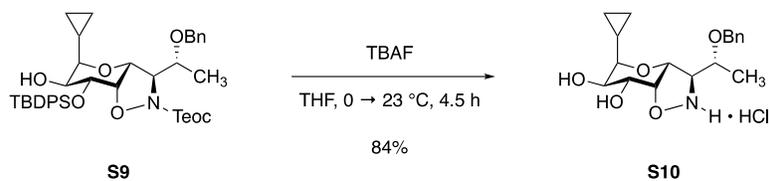
²⁷ Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974–6981.

^1H NMR (600 MHz, CDCl_3) δ 7.83–7.81 (m, 2H), 7.72–7.71 (m, 2H), 7.44–7.40 (m, 2H), 7.38–7.34 (m, 4H), 7.22–7.21 (m, 3H), 7.16–7.14 (m, 2H), 4.51 (d, $J = 11.5$ Hz, 1H), 4.41 (d, $J = 2.0$ Hz, 1H), 4.31 (d, $J = 11.7$ Hz, 1H), 4.30–4.26 (m, 2H), 4.20 (app dtd, $J = 7.6, 5.0, 2.5$ Hz, 1H), 4.02–4.00 (m, 2H), 3.95 (d, $J = 5.3$ Hz, 1H), 3.62 (app p, $J = 6.2$ Hz, 1H), 3.03 (dd, $J = 9.6, 5.4$ Hz, 1H), 1.75 (d, $J = 4.8$ Hz, 1H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.11 (s, 9H), 1.09–1.06 (m, 2H), 0.61–0.52 (m, 2H), 0.40 (tt, $J = 9.7, 3.9$ Hz, 1H), 0.25 (ddt, $J = 16.1, 9.2, 4.6$ Hz, 2H), 0.08 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 157.6, 138.2, 136.3, 135.9, 133.7, 133.5, 130.0, 128.5, 128.0, 127.8, 81.5, 79.9, 75.1, 73.4, 72.2, 71.9, 71.7, 70.2, 64.7, 27.1, 19.6, 17.7, 17.3, 7.4, 4.9, 1.7, –1.2. Overlapping pairs of phenyl carbon resonances are believed to account for the observation of only 9 unique phenyl-derived signals.

FTIR (neat, cm^{-1}): 2953 (m), 2931 (m), 2857 (m), 1698 (m), 1428 (m), 1333 (m), 1250 (m), 1113 (s), 1081 (s), 839 (m), 702 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{40}\text{H}_{55}\text{NO}_7\text{Si}_2$, 718.3590; found 718.3569.



Isoxazolidine diol **S10**.

To an ice-cold solution of **S9** (88 mg, 0.12 mmol, 1 equiv) in tetrahydrofuran (1.2 mL) was added tetra-*n*-butylammonium fluoride solution (1.0 M in tetrahydrofuran, 370 μ L, 370 μ mol, 3.0 equiv). The mixture was warmed to 23 $^\circ$ C, and desilylation was monitored by LCMS. While cleavage of the (trimethylsilyl)ethyl carbamate group was rapid (~30 min), the *tert*-butyldiphenylsilyl ether linkage underwent more sluggish deprotection. After 4.5 h, the reaction was complete, and the mixture was diluted with saturated aqueous sodium bicarbonate solution. The mixture was then extracted with dichloromethane (4 \times 10 mL), the combined extracts were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. This crude residue was purified by flash-column chromatography (4 g silica gel, eluting with dichloromethane initially, grading to 10% methanol–dichloromethane) to furnish the product in its free-base form. This material was then converted to its hydrochloride salt by dissolving it in methanol (3 mL), treating the resulting solution with hydrogen chloride solution (4.0 M in 1,4-dioxane, 120 μ L, 0.49 mmol, 4.0 equiv), and concentrating the acidified solution to dryness. This gave the product (**S10** \cdot HCl, 39 mg, 84%) as a light sand-colored solid.

R_f = 0.37 (free base, 10% methanol–dichloromethane, I_2).

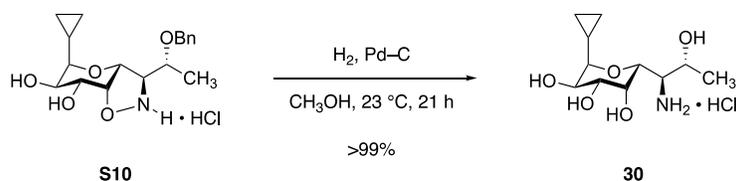
^1H NMR (hydrochloride salt, 600 MHz, CDCl_3) δ 7.40 (d, J = 7.0 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.3 Hz, 1H), 5.05 (app t, J = 3.7 Hz, 1H), 4.74 (app t, J = 4.1 Hz, 1H), 4.68 (d, J = 11.1 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.17 (dd, J = 7.7, 4.1 Hz, 1H), 4.11–

4.07 (m, 2H), 3.88 (dd, $J = 7.7, 3.7$ Hz, 1H), 3.14 (dd, $J = 9.8, 3.7$ Hz, 1H), 1.41 (d, $J = 6.0$ Hz, 1H), 1.15 (app tp, $J = 8.6, 4.6$ Hz, 1H), 0.65 (app tt, $J = 8.3, 4.3$ Hz, 1H), 0.58 (app tt, $J = 9.1, 4.1$ Hz, 1H), 0.36–0.28 (m, 2H).

^{13}C NMR (hydrochloride salt, 100 MHz, CDCl_3) δ 139.2, 129.4, 128.8, 128.7, 82.2, 80.2, 75.6, 72.2, 71.9, 70.4, 69.2, 68.8, 15.9, 9.6, 4.7, 3.0.

FTIR (hydrochloride salt, neat, cm^{-1}): 3347 (br), 2932 (w), 1454 (w), 1339 (w), 1127 (m), 1085 (s), 1026 (m), 677 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{18}\text{H}_{25}\text{NO}_5$, 336.1805; found 336.1820.



Aminotetraol **30**.

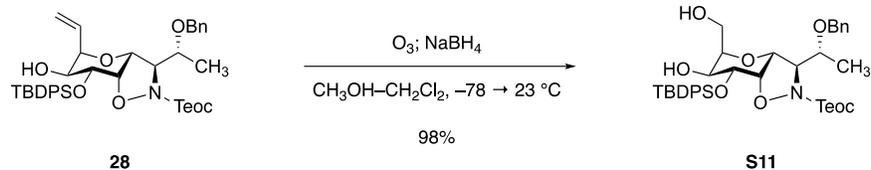
A 2–5-mL glass microwave vial was charged with a magnetic stir bar, isoxazolidine salt **S10** • HCl (38 mg, 0.10 mmol, 1 equiv), methanol (1.0 mL) and palladium on carbon (10% w/w, 11 mg). The headspace above the reaction mixture was flushed with hydrogen gas, and the mixture was stirred at 23 °C under a balloonful of hydrogen gas. After 21 h, LCMS analysis indicated that isoxazolidine hydrogenolysis and *O*-debenzylation were complete; the mixture was filtered through a Celite pad, and the filter cake was rinsed with methanol (3 × 1 mL). The filtrate was concentrated to afford analytically pure product (**30**) as a white solid (32 mg, 111%).

^1H NMR (600 MHz, CD_3OD) δ 4.18 (app t, $J = 2.3$ Hz, 1H), 4.12 (app p, $J = 6.3$ Hz, 1H), 4.06 (dd, $J = 7.4, 2.4$ Hz, 1H), 3.96 (dd, $J = 8.7, 5.0$ Hz, 1H), 3.89 (dd, $J = 8.7, 3.2$ Hz, 1H), 3.55 (app t, $J = 6.4$ Hz, 1H), 3.11 (dd, $J = 9.9, 5.0$ Hz, 1H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.15 (app ddq, $J = 12.9, 9.3, 4.8$ Hz, 1H), 0.71 (tdd, $J = 8.5, 5.9, 4.4$ Hz, 1H), 0.53 (app tt, $J = 9.1, 5.3$ Hz, 1H), 0.35 (dq, $J = 9.7, 4.8$ Hz, 1H), 0.29 (dq, $J = 9.6, 4.9$ Hz, 1H).

^{13}C NMR (100 MHz, CD_3OD) δ 82.0, 71.9, 70.5, 69.9 (2 × C), 65.6, 58.2, 18.4, 93, 5.9, 2.6.

FTIR (neat, cm^{-1}): 3350 (br), 2925 (m), 1620 (w), 1510 (m), 1094 (s), 1072 (s), 1002 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{11}\text{H}_{21}\text{NO}_5$, 248.1492; found 248.1498.



Hydroxymethyl glycoside **S11**.

A solution of **28** (654 mg, 0.929 mmol, 1 equiv) in 50% v/v dichloromethane–methanol (18.6 mL) was chilled to $-78 \text{ }^\circ\text{C}$. A mixture of ozone and dioxygen from an ozone generator was bubbled gently through the reaction solution, until an azure color appeared and persisted for 15 seconds, signaling saturation of the solution with ozone gas with concomitant disappearance of starting material. Ozone bubbling was then discontinued, and nitrogen gas was bubbled through the solution for 5 minutes in order to flush the solution of residual ozone. The resulting colorless solution was treated with sodium borohydride (351 mg, 9.29 mmol, 10.0 equiv) at $-78 \text{ }^\circ\text{C}$, and the mixture was subsequently allowed to warm to $23 \text{ }^\circ\text{C}$ with constant stirring (Note: gas evolution occurs upon warming, and the reaction flask should be adequately vented to avoid overpressurization). After stirring for 1 h at $23 \text{ }^\circ\text{C}$, the mixture was carefully treated with 30 mL of half-saturated aqueous sodium chloride solution (Caution: gas evolution!). The resulting mixture was stirred for 5 minutes, or until gas evolution ceased; and the mixture was then extracted with ethyl acetate ($3 \times 20 \text{ mL}$). The combined organic extracts were washed with saturated aqueous sodium chloride solution, the washed solution was dried over sodium sulfate, and the dried solution was concentrated to afford **S11** as a brilliant white solid (644 mg, 98%). This material was suitable for use without further purification.

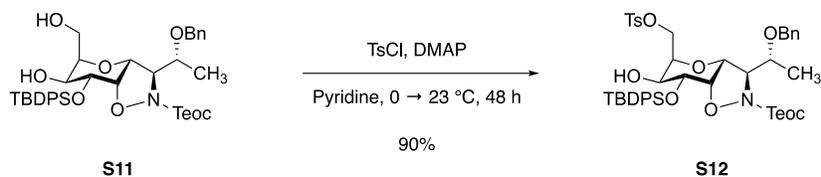
$R_f = 0.34$ (40% ethyl acetate–hexanes, UV+CAM).

^1H NMR (500 MHz, CDCl_3) δ 7.78–7.75 (m, 2H), 7.69–7.66 (m, 2H), 7.46–7.41 (m, 2H), 7.40–7.35 (m, 4H), 7.25–7.22 (m, 3H), 7.17–7.13 (m, 2H), 4.51 (d, $J = 11.6$ Hz, 1H), 4.39 (d, $J = 3.1$ Hz, 1H), 4.35–4.26 (m, 4H), 4.03 (t, $J = 3.3$ Hz, 1H), 4.00 (app q, $J = 5.9$ Hz, 1H), 3.95 (d, $J = 5.2$ Hz, 1H), 3.92 (dd, $J = 8.8, 3.3$ Hz, 1H), 3.67 (dd, $J = 11.9, 4.7$ Hz, 1H), 3.61 (app tt, $J = 11.8, 6.7$ Hz, 2H), 2.06 (s, 1H), 1.89 (s, 1H), 1.24 (d, $J = 6.4$ Hz, 3H), 1.09 (s, 9H), 1.07 (m, 2H), 0.08 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 157.4, 138.1, 136.2, 135.8, 133.4, 133.1, 130.2, 130.2, 128.5, 128.1, 128.0, 127.9, 127.9, 79.6, 76.2, 75.4, 73.2, 72.0, 71.9, 71.8, 70.2, 64.9, 59.9, 27.1, 19.5, 17.7, 17.3, –1.2.

FTIR (neat, cm^{-1}): 3452 (br), 2953 (m), 2933 (m), 2857 (m), 1703 (m), 1428 (m), 1250 (m), 1112 (s), 1085 (m), 359 (m), 838 (m), 702 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{38}\text{H}_{53}\text{NO}_8\text{Si}_2$, 708.3382; found 708.3366.



***para*-Toluenesulfonate ester **S12**.**

A flame-dried 25-mL round-bottomed flask was charged with diol **S11** (1.05 g, 1.48 mmol, 1 equiv), and this starting material was dried by azeotropic removal of benzene. Anhydrous pyridine (5.0 mL) was then added, and the resulting solution was chilled to 0 °C. Solid *p*-toluenesulfonyl chloride (481 mg, 2.52 mmol, 1.70 equiv) was added to the ice-cold solution, causing a golden yellow color to evolve. 4-Dimethylaminopyridine (DMAP, 9.1 mg, 74 μmol, 0.050 equiv) was then added, and the resulting solution was stirred at 0 °C for 5 minutes; the cooling bath was then removed, and the mixture was allowed to warm to 23 °C with constant stirring. The golden color dissipated within 30 minutes, leaving a colorless solution. Progress was monitored by TLC (60% ethyl acetate–hexanes, UV+CAM), and after 48 h, the reaction was judged to be complete. The mixture was concentrated *in vacuo*, and the residue was purified by flash-column chromatography (80 g silica, eluting with 10% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to give **S12** as a white foaming solid (1.15 g, 90%).

$R_f = 0.49$ (30% ethyl acetate–hexanes, UV+CAM).

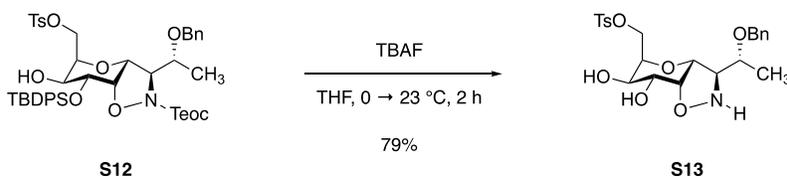
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.75–7.72 (m, 2H), 7.68–7.64 (m, 4H), 7.46–7.41 (m, 2H), 7.39–7.34 (m, 4H), 7.26–7.22 (m, 3H), 7.19–7.16 (m, 2H), 4.51 (d, $J = 11.7$ Hz, 1H), 4.44 (d, $J = 2.8$ Hz, 1H), 4.30 (d, $J = 11.8$ Hz, 1H), 4.28–4.24 (m, 3H), 4.10–4.00 (m, 3H), 3.96 (t, $J = 3.2$ Hz, 1H), 3.93 (d, $J = 5.4$ Hz, 1H), 3.83 (dd, $J = 9.2, 3.4$ Hz, 1H), 3.57 (app p, $J = 6.2$

Hz, 1H), 2.41 (s, 3H), 1.86 (d, $J = 3.7$ Hz, 1H), 1.22 (d, $J = 6.3$ Hz, 3H), 1.07 (s, 9H), 1.07–1.03 (m, 2H), 0.07 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 157.5, 144.9, 138.2, 136.1, 135.7, 133.4, 133.0, 132.9, 130.2, 129.9, 128.5, 128.2, 128.0, 127.9, 127.8, 79.4, 77.4, 77.2, 76.9, 76.0, 73.9, 73.0, 72.2, 71.7, 71.5, 68.5, 66.0, 64.8, 27.0, 21.8, 19.5, 17.7, 17.1, –1.3, –1.5.

FTIR (neat, cm^{-1}): 2954 (m), 2931 (m), 2896 (m), 2858 (m), 1707 (m), 1362 (m), 1177 (s), 1098 (s), 837 (s), 703 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{45}\text{H}_{59}\text{NO}_{10}\text{SSi}_2$, 884.3290; found 884.3262.



Isoxazolidine diol **S13**.

In a 100-mL round-bottomed flask, a solution of carbamate **S12** (1.15 g, 1.34 mmol, 1 equiv) in tetrahydrofuran (13.4 mL) was chilled to 0 °C was treated with tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 4.0 mL, 4.0 mmol, 3.0 equiv). Following the addition of TBAF, the ice-water cooling bath was removed, and the reaction solution was allowed to warm to 23 °C. Progress was monitored by LCMS; cleavage of the (trimethylsilyl)ethyl carbamate was observed within 15 minutes, while cleavage of the *tert*-butyldiphenylsilyl ether was comparatively slower. After 2 hours, the reaction was judged to be complete, and 20 mL of saturated aqueous sodium bicarbonate solution was added. The resulting mixture was extracted with dichloromethane (4 × 15 mL), and the combined organic layers were dried over sodium sulfate. The dried product solution was filtered, and the filtrate was concentrated to afford a colorless oil. This material was purified by flash-column chromatography (40 g silica, eluting with 1% methanol–dichloromethane initially, grading to 10% methanol–dichloromethane) to give **S13** as a white foaming solid (508 mg, 79%).

$R_f = 0.52$ (10% methanol–dichloromethane, UV+CAM).

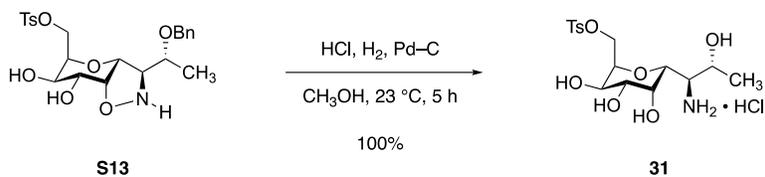
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.76 (d, $J = 8.3$ Hz, 2H), 7.34–7.30 (m, 2H), 7.29–7.25 (m, 5H), 4.70 (dd, $J = 4.1, 2.1$ Hz, 1H), 4.61 (d, $J = 11.6$ Hz, 1H), 4.32 (d, $J = 11.7$ Hz, 1H), 4.26–4.21 (m, 2H), 4.18 (app dt, $J = 6.9, 5.0$ Hz, 1H), 3.97 (dd, $J = 8.4, 5.3$ Hz, 1H), 3.88 (app

t, $J = 4.0$ Hz, 1H), 3.79 (dd, $J = 8.4, 3.8$ Hz, 1H), 3.57 (br s, 1H), 3.23 (dd, $J = 3.9, 2.1$ Hz, 1H), 2.39 (s, 3H), 1.27 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 144.9, 138.0, 132.9, 130.0, 128.6, 128.0, 128.0, 127.8, 81.7 (br), 78.4, 72.9, 71.9, 70.9, 70.6, 70.1, 69.1, 67.2, 21.7, 16.9.

FTIR (neat, cm^{-1}): 3378 (br), 2929 (w), 1453 (w), 1356 (m), 1174 (s), 1071 (s), 974 (m), 732 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{29}\text{NO}_8\text{S}$, 480.1687; found 480.1711.



Aminotetraol **31**.

In a 25-mL round-bottomed flask, a solution of isoxazolidine **S13** (368 mg, 767 μmol , 1 equiv) in methanol (8.00 mL) was cooled to 0 $^\circ\text{C}$ and was treated with hydrogen chloride solution (4.0 M in 1,4-dioxane, 770 μL , 3.1 mmol, 4.0 equiv). This solution was immediately concentrated to dryness, and the white residue obtained was re-dissolved in fresh methanol (7.67 mL). This solution was treated with palladium on carbon (10% w/w, 82.0 mg), the headspace of the flask was flushed with nitrogen gas, and the apparatus was fitted with a 3-way stopcock to which one arm was affixed to a high-vacuum line, and the other was affixed to a hydrogen gas-filled balloon. The headspace of the flask was replaced by briefly evacuating, then back-filling the flask with hydrogen gas using the stopcock (3 evacuation–backfill cycles), and the black suspension was stirred at 23 $^\circ\text{C}$ under 1 atm of hydrogen gas. After 5 h, LCMS analysis indicated that isoxazolidine ring and benzyl ether hydrogenolysis were complete, and the headspace of the flask was flushed with nitrogen gas. The reaction mixture was filtered through a Celite pad, and the filter cake was rinsed with methanol ($2 \times 3\text{ mL}$). The filtrate was concentrated to give the product (**31**) as a dull white crystalline solid (327 mg, 100%). This material was suitable for use in subsequent transformations without further purification.

Crystals suitable for X-ray analysis were prepared as follows: In a 1-mL glass sample vial, **31** \cdot HCl (3 mg) was deposited, and this material was dissolved in approximately 200 μL of 190-proof ethanol. The vial containing the ethanolic solution was then placed inside a 20-mL scintillation vial containing approximately 3 mL of acetonitrile. The large vial was capped, and

the assembly was allowed to stand undisturbed at 23 °C. After 2 days, needle-shaped crystals had formed.

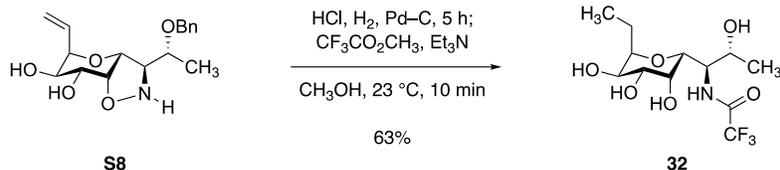
^1H NMR (600 MHz, CD_3OD) δ 7.80 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 4.35 (dd, $J = 11.7, 9.6$ Hz, 1H), 4.24–4.21 (m, 2H), 4.18 (app s, 1H), 4.09 (app p, $J = 6.3$ Hz, 1H), 3.99 (dd, $J = 7.1, 2.8$ Hz, 1H), 3.95 (dd, $J = 8.3, 5.0$ Hz, 1H), 3.66 (dd, $J = 8.3, 3.0$ Hz, 1H), 3.56 (app t, $J = 6.4$ Hz, 1H), 2.46 (s, 3H), 1.26 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 146.7, 134.3, 131.2, 129.0, 74.0, 71.7, 69.8, 69.5, 68.7, 68.1, 65.5, 58.1, 21.6, 18.7.

FTIR (neat, cm^{-1}): 3345 (br), 2927 (br), 1598 (w), 1495 (w), 1356 (m), 1190(m), 1175 (s), 1080 (s), 976 (m), 554 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{16}\text{H}_{25}\text{NO}_8\text{S}$, 414.1193; found 414.1203.

Synthesis of the Fully Synthetic Lincosamide 37



Trifluoroacetamide 32.

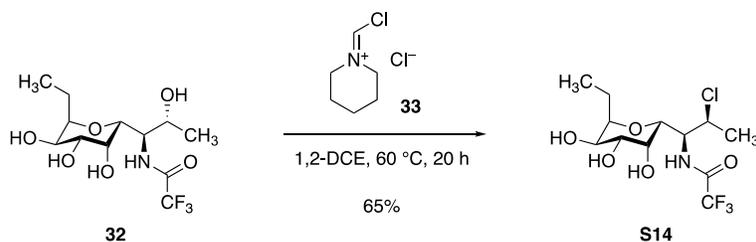
In a 10-mL glass microwave vial, an ice-cold solution of isoxazolidine **S8** (66 mg, 0.21 mmol, 1 equiv) in methanol (2.1 mL) was treated with hydrogen chloride solution (4.0 M in 1,4-dioxane, 210 μ L, 0.82 mmol, 4.0 equiv). This mixture was immediately concentrated to dryness to provide the hydrochloride salt of the starting material, which was re-dissolved in methanol (2.1 mL). This solution was then treated with palladium on carbon (10% w/w, 22 mg), the headspace of the reaction flask was replaced with hydrogen gas, and the black suspension was stirred under hydrogen gas (1 atm) at 23 $^{\circ}$ C for 5 h, at which point LCMS analysis indicated that olefin saturation, isoxazolidine hydrogenolysis, and debenzylation were all complete. Triethylamine (140 μ L, 1.0 mmol, 5.0 equiv) was added to basify the reaction mixture, and methyl trifluoroacetate (100 μ L, 1.0 mmol, 5.0 equiv) was added to protect the primary amine that had been generated in the hydrogenolytic operation. After 10 min of stirring at 23 $^{\circ}$ C, LCMS analysis indicated that trifluoroacetylation was complete, and the mixture was filtered through a pad of Celite to remove the heterogeneous catalyst. The filter cake was rinsed with methanol (3×1 mL), and the filtrate was concentrated *in vacuo* to give a white solid containing crude product contaminated with triethylamine hydrochloride. The latter was removed as follows: the crude product mixture was partitioned between ethyl acetate (15 mL) and saturated aqueous sodium chloride solution (15 mL). The layers were shaken, then separated. The organic layer was washed with a fresh portion of saturated aqueous sodium chloride solution. These combined aqueous washes were then themselves extracted with fresh ethyl acetate (2×10 mL), and the combined organic extracts (35

mL in total) were dried over sodium sulfate. The dried product solution was filtered, and the filtrate was concentrated to give pure trifluoroacetamide **32** as a white solid (43 mg, 63%).

^1H NMR (500 MHz, CD_3OD) δ 4.20 (app t, $J = 7.0$ Hz, 1H), 4.10 (qd, $J = 7.1, 1.7$ Hz, 1H), 4.01–3.96 (m, 2H), 3.88–3.82 (m, 2H), 1.70–1.60 (m, 2H), 1.17 (dd, $J = 6.4, 1.7$ Hz, 3H), 0.96 (t, $J = 6.8$ Hz, 3H).

^{19}F NMR (471 MHz, CD_3OD) δ –77.51 (s, 3F).

MS (ESI–, m/z): $[\text{M} - \text{H}]^-$ calc'd for $\text{C}_{12}\text{H}_{20}\text{F}_3\text{NO}_6$, 330.1; found 330.1.



Chloro compound S14.

In a 2–5-mL glass microwave vial, an ice-cold heterogeneous mixture of tetraol **S32** (44 mg, 0.13 mmol, 1 equiv) and 1,2-dichloroethane (2.2 mL) was treated with 1-(chloromethylene)pyridin-1-ium chloride (**33**, 130 mg, 0.80 mmol, 6.0 equiv). The vial was sealed, and the mixture was stirred at 0 °C for 15 min, during which time the originally light-yellow suspension clarified to form a light-yellow solution. The mixture was then heated to 60 °C for 21 h, at which point LCMS analysis showed that deoxychlorination was complete, as evidenced by the disappearance of (oligo)formylated starting material congeners (ESI⁻, [M-H]⁻ *m/z* = 358, 386, 414). The mixture was chilled to 0 °C, and excess Vilsmeier reagent was quenched with the addition of aqueous sodium hydroxide solution (0.50 M, 1.60 mL, 0.80 mmol, 6.0 equiv). The resulting aqueous layer was still acidic, so additional sodium hydroxide solution (0.50 M) was added to achieve (and maintain) pH ~10. The biphasic mixture was warmed to 23 °C with rapid stirring, and saponification of pendant formyl groups was monitored by LCMS. After 18 h, deformylation was complete. The layers were separated, and the aqueous phase was then treated with sodium chloride to the point of saturation, in order to diminish the product's solubility in that medium. The resulting aqueous mixture was then extracted with dichloromethane (5 × 2 mL), until no product could be detected in the aqueous phase by LCMS. The combined organic extracts were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude residue thus obtained was purified by flash-column chromatography (4 g silica gel, eluting

with dichloromethane initially, grading to 7% methanol–dichloromethane) to provide **S14** as a white solid (30 mg, 65%).

$R_f = 0.31$ (10% methanol–dichloromethane, CAM).

$^1\text{H NMR}$ (500 MHz, CD_3OD) δ 4.63 (qd, $J = 6.9, 1.7$ Hz, 1H), 4.50 (dd, $J = 9.8, 1.6$ Hz, 1H), 3.97 (dd, $J = 10.1, 6.3$ Hz, 1H), 3.87–3.83 (m, 2H), 3.77 (dd, $J = 3.3, 1.3$ Hz, 1H), 3.56 (dd, $J = 10.2, 3.3$ Hz, 1H), 1.73–1.62 (m, 2H), 1.44 (d, $J = 6.9$ Hz, 3H), 1.02 (t, $J = 7.4$ Hz, 3H).

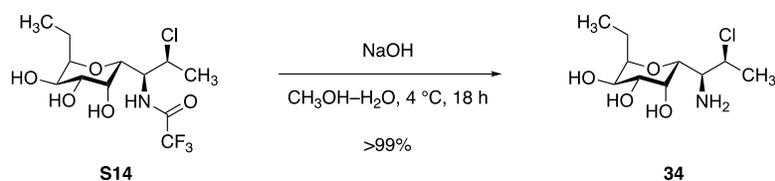
$^{13}\text{C NMR}$ (126 MHz, CD_3OD) δ 80.5, 71.9, 70.0, 69.9, 69.5, 58.9, 55.3, 23.1, 17.5, 11.2.

Trifluoroacetamide carbons were not resolved due to ^{19}F nuclear coupling.

$^{19}\text{F NMR}$ (471 MHz, CD_3OD) δ –76.74 (s, 3F).

FTIR (neat, cm^{-1}): 3365 (br), 2938 (w), 1712 (s), 1545 (w), 1212 (m), 1160 (s), 1079 (s), 963 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{12}\text{H}_{19}\text{ClF}_3\text{NO}_5$, 350.0977; found 350.0981.



Aminotriol **34**.

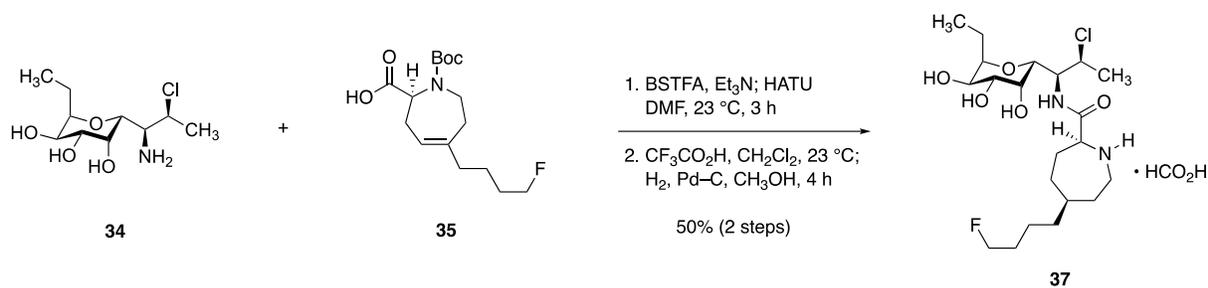
In a 4-mL glass vial, trifluoroacetamide **S14** (30 mg, 86 μmol , 1 equiv) was dissolved in methanol (50 μL). To this solution was then added ice-cold aqueous sodium hydroxide solution (1.0 M, 450 μL). Vigorous stirring was maintained, and the mixture was held at 4 $^\circ\text{C}$ for 18 h, at which point LCMS analysis indicated that no starting material remained. The mixture was diluted with 400 μL of ice-cold water, and the white suspension was filtered. This filter cake was washed with 300 μL of ice-cold water before being dried *in vacuo* to provide a crop of pure crystalline product (13 mg, 60%). The filtrate, containing additional aminotriol product, was acidified with the addition of aqueous hydrogen chloride solution (1.0 M, 500 μL) before it was concentrated to dryness to provide crude product as its hydrochloride salt, contaminated with sodium chloride. This solid was suspended in ethanol (190 proof, 1.0 mL), and the supernatant (containing **S34** • HCl) was transferred to a vial containing Amberlyst A26 resin (hydroxide form, 300 mg). This mixture was stirred at 0 $^\circ\text{C}$ for 30 min before the ion-exchange beads were removed by filtration. The filtrate was concentrated to provide additional product (11 mg, estimated 80% pure by ^1H NMR, ~40%).

^1H NMR (500 MHz, CD_3OD) δ 4.62 (q, $J = 6.7$ Hz, 1H), 4.08 (app t, $J = 2.6$ Hz, 1H), 3.91 (dd, $J = 9.4, 5.7$ Hz, 1H), 3.78 (app q, $J = 6.8$ Hz, 1H), 3.63 (dd, $J = 9.4, 3.4$ Hz, 1H), 3.48 (dd, $J = 9.3, 1.9$ Hz, 1H), 3.10 (d, $J = 9.2$ Hz, 1H), 1.63 (app p, $J = 7.4$ Hz, 2H), 1.56 (d, $J = 6.9$ Hz, 3H), 0.99 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 79.0, 72.9, 72.1, 70.2, 69.9, 61.0, 56.5, 22.7, 18.3, 11.1.

FTIR (neat, cm^{-1}): 3300 (br), 2929 (w), 2464 (w), 1620 (w), 1076 (s), 963 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{10}\text{H}_{20}\text{ClNO}_4$, 254.1154; found 254.1154.



Synthetic lincosamide **37**.

A solution of aminotriol **34** (12.9 mg, 51.0 μ mol, 1 equiv) in *N,N*-dimethylformamide (254 μ L) was treated sequentially with triethylamine (22.7 μ L, 163 μ mol, 3.20 equiv) and *N,O*-bis(trimethylsilyl)trifluoroacetamide (20.5 μ L, 76.0 μ mol, 1.50 equiv) at 23 °C. The mixture was stirred for 1 h to ensure complete *O*-silylation before a solution of azepine acid **35** (17.6 mg, 56.0 μ mol, 1.10 equiv)⁴ in *N,N*-dimethylformamide (200 μ L) was added. The reaction mixture was then treated with HATU (25.1 mg, 66.0 μ mol, 1.30 equiv), and the lemon-yellow mixture was stirred at 23 °C for 3 h. After this time, the reaction mixture was diluted with ethyl acetate (20 mL) and the diluted organic solution was washed sequentially with 10-mL portions of 10% w/v aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution. The washed organic layer was then dried over sodium sulfate, filtered, and concentrated. The dried residue was transferred to a 4-mL glass vial, where it was re-dissolved in 33% v/v trifluoroacetic acid–dichloromethane (300 μ L). Deprotection was monitored by LCMS, and after 15 min global trimethylsilyl and Boc removal was complete. The mixture was concentrated to dryness, and the residue was re-dissolved in methanol (300 mL). Palladium on carbon (10% w/w, 20 mg) was added, the headspace above the black suspension was replaced with hydrogen gas, and the mixture was stirred at 23 °C for 4 h, resulting in complete hydrogenation of the azepine, as indicated by LCMS. The mixture was filtered through a pad of Celite to remove the heterogeneous catalyst, and the filter cake was rinsed with methanol (3 \times 1 mL). The filtrate

was concentrated to give a brown film, which was subjected to preparative HPLC-MS on a Waters SunFire Prep C₁₈ column (5 μm, 250 × 19 mm; eluting with 0.1% formic acid–5% acetonitrile–water initially, grading to 0.1% formic acid–40% acetonitrile–water over 40 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 210 nm and ESI+ selected ion monitoring [*m/z* = 453]) to provide the product (**37** • HCO₂H, 3.0 mg, 50%, 2 steps) as a white solid.

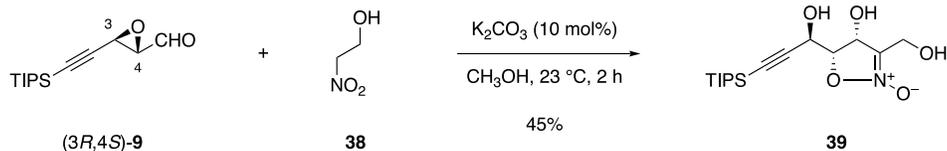
¹H NMR (600 MHz, CD₃OD) δ 8.42 (s, 1H), 4.64 (q, *J* = 6.8 Hz, 1H), 4.42 (dt, *J* = 47.5, 6.0 Hz, 2H), 4.41 (d, *J* = 9.7 Hz, 1H), 4.10 (app t, *J* = 5.6 Hz, 1H), 3.96 (dd, *J* = 10.1, 6.3 Hz, 1H), 3.85 (ddd, *J* = 10.1, 6.2, 3.2 Hz, 1H), 3.80 (app s, 1H), 3.68 (d, *J* = 9.7 Hz, 1H), 3.57 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.44 (dd, *J* = 13.3, 4.5 Hz, 1H), 3.13 (app t, *J* = 12.5 Hz, 1H), 2.25–2.14 (m, 2H), 2.02 (br d, *J* = 14.9 Hz, 1H), 1.94 (ddd, *J* = 14.8, 8.2, 4.0 Hz, 1H), 1.72–1.61 (m, 5H), 1.61–1.53 (m, 1H), 1.47–1.42 (m, 3H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.37–1.33 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (126 MHz, CD₃OD) δ 171.6, 84.7 (d, *J* = 163.7 Hz), 80.4, 71.8, 70.6, 69.9, 69.6, 60.5, 59.3, 55.0, 45.6, 38.9, 37.4, 33.3, 31.6 (d, *J* = 19.6 Hz), 30.7, 29.1, 23.8 (d, *J* = 5.1 Hz, 1H), 23.2, 17.4, 11.2.

FTIR (neat, cm⁻¹): 3266 (br), 2934 (m), 1672 (m), 1590 (s), 1459 (m), 1378 (m), 1346 (m), 1084 (m).

HRMS (ESI+, *m/z*): [M+H]⁺ calc'd for C₂₁H₃₈ClFN₂O₅, 453.2526; found 453.2526.

Synthesis of 8-Norlincomycin (42)



Isoxazoline *N*-oxide **39**.

In a 100-mL round-bottomed flask, epoxyaldehyde **(3*R*,4*S*)-9** (4.93 g, 19.5 mmol, 1 equiv) was dissolved in methanol (39.1 mL). To this solution were added nitroethanol (2.80 mL, 39.1 mmol, 2.0 equiv) and potassium carbonate (270 mg, 1.95 mmol, 0.100 equiv). After stirring for 2 h at 23 °C, TLC analysis (60% ethyl acetate–hexanes, CAM) showed complete consumption of epoxyaldehyde starting material, as well as the disappearance of intermediate, linear, mid-polar nitroaldol adducts (*R_f*'s 0.63–0.77, 60% ethyl acetate–hexanes, CAM). The mixture was concentrated *in vacuo*, and crude ¹H-NMR analysis of the residue revealed a 62:38 diastereomeric ratio favoring the desired C5 epimer. This crude mixture was subjected to flash-column chromatographic separation (700 g silica gel, eluting with 50% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes) to afford isoxazoline *N*-oxide **39** as a brilliant white powder (3.00 g, 45%).

Melting point: 55–57 °C.

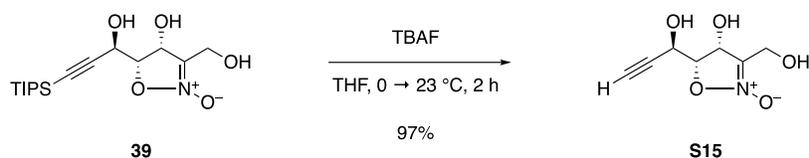
R_f = 0.38 (ethyl acetate, CAM).

¹H NMR (500 MHz, CDCl₃) δ 5.51 (app t, *J* = 6.9 Hz, 1H), 4.89 (dd, *J* = 6.6, 5.0 Hz, 1H), 4.67 (dd, *J* = 7.4, 5.0 Hz, 1H), 4.56–4.53 (m, 2H), 3.42 (d, *J* = 6.6 Hz, 1H), 2.97 (d, *J* = 6.7 Hz, 1H), 2.42 (t, *J* = 6.3 Hz, 1H), 1.09–1.08 (m, 21H).

¹³C NMR (126 MHz, CDCl₃) δ 118.7, 103.0, 89.8, 79.7, 74.8, 60.6, 55.2, 18.7, 11.2.

FTIR (neat, cm^{-1}): 3357 (br), 2942 (s), 2865 (s), 1639 (s), 1463 (m), 1014 (s), 883 (s), 677 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{16}\text{H}_{29}\text{NO}_5\text{Si}$, 366.1707; found 366.1703.



Triol S15.

To a solution of isoxazoline *N*-oxide **39** (4.70 g, 13.7 mmol, 1 equiv) in tetrahydrofuran (137 mL) was added tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 32.8 mL, 32.8 mmol, 2.40 equiv) dropwise at 0 °C. The resulting colorless solution was immediately warmed to 23 °C, and after 2 h of stirring at that temperature, TLC analysis (5% methanol–ethyl acetate, CAM) indicated complete consumption of starting material. The mixture was loaded directly onto a column of silica gel (500 g) pre-equilibrated with ethyl acetate. The product was eluted with 5% methanol–ethyl acetate, and product-containing fractions were pooled. The pooled fractions were concentrated to give **S15** as a buff white solid (221 mg, 97%).

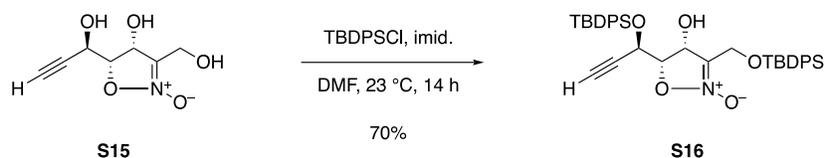
$R_f = 0.32$ (5% methanol–ethyl acetate, CAM).

$^1\text{H NMR}$ (500 MHz, CD_3OD) δ 5.25 (d, $J = 6.3$ Hz, 1H), 4.73 (dd, $J = 8.1, 2.2$ Hz, 1H), 4.45 (dd, $J = 6.3, 8.1$ Hz, 1H), 4.43 (d, $J = 14.6$ Hz, 1H), 4.33 (d, $J = 14.1$ Hz, 1H), 2.91 (d, $J = 2.2$ Hz, 1H).

$^{13}\text{C NMR}$ (126 MHz, CD_3OD) δ 120.8, 82.9, 81.9, 75.4, 75.4, 73.5, 73.5, 58.8, 55.1.

FTIR (neat, cm^{-1}): 3279 (br), 2933 (w), 1639 (s), 1293 (m), 1092 (m), 1044 (m), 1019 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_7\text{H}_9\text{NO}_5$, 210.0373; found 210.0370.



Bis-silyl ether **S16**.

To a solution of triol **S15** (2.35 g, 12.6 mmol, 1 equiv) and imidazole (4.27 g, 62.8 mmol, 8.00 equiv) in *N,N*-dimethylformamide (62.8 mL) was added *tert*-butyl(chloro)diphenylsilane (7.26 mL, 28.3 mmol, 4.00 equiv) dropwise at 0 °C. The mixture was then warmed to 23 °C. Silylation of the primary alcohol was fast (generally complete within 5 min), while silylation of the propargylic alcohol was substantially slower. After 14 h of stirring at 23 °C, TLC analysis (60% ethyl acetate–hexanes, UV+KMnO₄) showed complete consumption of the mono-silylated intermediate ($R_f = 0.61$). Excess chlorosilane reagent was quenched with the addition of saturated aqueous ammonium chloride (100 mL), and the resulting mixture was stirred rapidly at 23 °C for 10 min. The mixture was then extracted with 20% ethyl acetate–hexanes (4 × 100 mL); the organic extracts were then combined, washed with saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, filtered, and concentrated to give a light golden-amber oil. This residue was purified by flash-column chromatography (500 g silica gel, eluting with hexanes initially, grading to 20% ethyl acetate–hexanes) to provide **S16** as a white, foaming, amorphous solid (5.87 g, 70%).

$R_f = 0.39$ (20% ethyl acetate–hexanes, UV+KMnO₄).

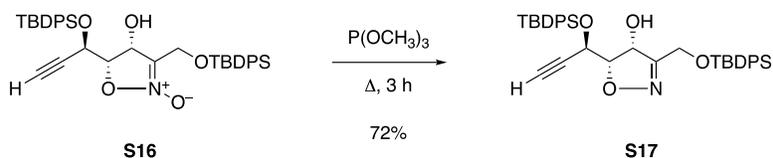
¹H NMR (500 MHz, CDCl₃) δ 7.80–7.78 (m, 2H), 7.76–7.71 (m, 6H), 7.51–7.46 (m, 4H), 7.45–7.40 (m, 8H), 5.34 (app t, $J = 7.7$ Hz, 1H), 4.81 (dd, $J = 5.1, 2.3$ Hz, 1H), 4.64 (d, $J = 13.7$

Hz, 1H), 4.57 (d, $J = 13.8$ Hz, 1H), 4.46 (dd, $J = 7.2, 5.1$ Hz, 1H), 3.38 (d, $J = 8.1$ Hz, 1H), 2.47 (d, $J = 2.3$ Hz, 1H), 1.12 (s, 18 H).

^{13}C NMR (126 MHz, CDCl_3) δ 136.2, 136.0, 135.6 (2 \times C), 132.6, 132.5, 132.1, 131.6, 130.5, 130.3, 130.2 (2 \times C), 128.1 (2 \times C), 128.0, 127.7, 116.9, 79.8, 79.2, 76.5, 74.3, 61.8, 57.0, 26.9 (2 \times C), 19.4, 19.3.

FTIR (neat, cm^{-1}): 2931 (w), 2858 (w), 1644 (m), 1427 (m), 1105 (s), 1082 (s), 699 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{39}\text{H}_{45}\text{NO}_5\text{Si}_2$, 664.2909; found 664.2900.



Isoxazoline **S17**.

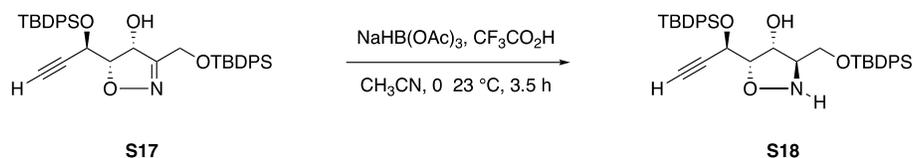
In a 100-mL round-bottomed flask, isoxazoline *N*-oxide **S16** (2.50 g, 3.77 mmol, 1 equiv) was dried by azeotropic removal of benzene. The dried starting material was then dissolved in trimethyl phosphite (15.1 mL), the flask was fitted with an oven-dried reflux condenser, and the reaction solution was heated to 100 °C in a pre-heated oil bath. After 3 h, TLC analysis (20% ethyl acetate–hexanes, PAA) showed complete consumption of starting material. The mixture was cooled to 0 °C and diluted in ethyl ether (200 mL); the organic product solution was then washed sequentially with 0.1 M aqueous HCl solution (2 × 40 mL) and saturated aqueous sodium chloride solution (50 mL). The washed organic solution was dried over sodium sulfate, filtered, and concentrated to give a light yellow foaming solid. This residue was purified by flash-column chromatography (220 g silica gel, eluting with hexanes initially, grading to 20% ethyl acetate–hexanes) to provide **S17** as a white, foaming, amorphous solid (1.76 g, 72%).

$R_f = 0.47$ (20% ethyl acetate–hexanes, UV+KMnO₄)

¹H NMR (600 MHz, CDCl₃) δ 7.78–7.76 (m, 2H), 7.74–7.71 (m, 4H), 7.70–7.68 (m, 2H), 7.48–7.44 (m, 4H), 7.42–7.39 (m, 8H), 5.43 (app t, $J = 8.8$ Hz, 1H), 4.85 (dd, $J = 4.0, 2.4$ Hz, 1H), 4.60 (d, $J = 13.1$ Hz, 1H), 4.56 (d, $J = 12.9$ Hz, 1H), 4.39 (dd, $J = 8.5, 3.9$ Hz, 1H), 3.90 (d, $J = 9.0$ Hz, 1H), 2.48 (d, $J = 2.3$ Hz, 1H), 1.08 (s, 9H), 1.06 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 159.9, 136.3 (2 \times C), 135.8, 135.7, 132.8 (2 \times C), 132.2, 131.5, 130.5, 130.2, 130.1 (2 \times C), 128.0, 128.0 (3 \times C), 127.7, 83.1, 80.4, 77.2, 76.0, 63.0, 57.5, 26.9 (2 \times C), 19.4 (2 \times C).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{39}\text{H}_{45}\text{NO}_4\text{Si}_2$, 648.2960; found 648.2957.



Isoxazolidine **S18**.

To a rapidly stirred, ice-cold suspension of isoxazoline **S17** (2.00 g, 3.09 mmol, 1 equiv) and sodium triacetoxyborohydride (3.27 mg, 15.4 mmol, 5.00 equiv) in acetonitrile (25.7 mL) was added trifluoroacetic acid (23.8 mL, 309 mmol, 100 equiv) dropwise over 2 min. The mixture was then warmed to 23 °C, and over the course of 1.5 h, the originally opaque white suspension gradually clarified, giving a light yellow, homogeneous solution. After 3.5, TLC analysis (20% ethyl acetate–hexanes, PAA) showed full consumption of isoxazoline starting material. The reaction mixture was transferred by cannula to a rapidly stirred, ice-cold biphasic mixture of aqueous sodium hydroxide solution (2.0 M, 155 mL, 309 mmol) and dichloromethane (155 mL). Additional 2.0 M aqueous sodium hydroxide solution was added as necessary to achieve $\text{pH} \geq 8.0$, and rapid stirring was maintained for 10 min. The layers were then separated, and the aqueous layer was extracted with dichloromethane (3×75 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated to give isoxazolidine **S18** as a foaming, dull-white solid that was used in the next step without further purification.

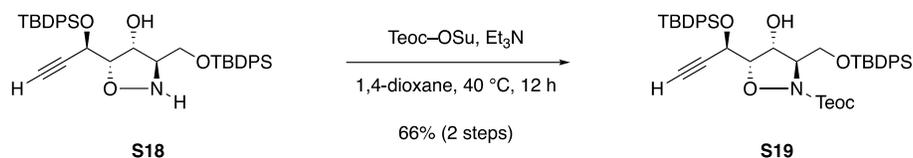
For characterization purposes, a small quantity (ca. 25 mg) of crude residue was purified by HPLC on a Waters SunFire Prep C₁₈ column (5 μm , 250 \times 19 mm; eluting with 0.1% formic acid–25% acetonitrile–water initially, grading to 0.1% formic acid–95% acetonitrile–water over 20 min, then holding at 0.1% formic acid–95% acetonitrile–water for 20 min with a flow rate of 15 mL/min; monitored by UV absorbance at 254 nm; $R_t = 31.9$ min) to give analytically pure sample with the following spectroscopic properties:

^1H NMR (500 MHz, CDCl_3) δ 7.80–7.72 (m, 4H), 7.67–7.61 (m, 4H), 7.50–7.36 (m, 12H), 4.90 (dd, $J = 5.3, 2.9$ Hz, 1H), 4.77 (dd, $J = 4.8, 2.2$ Hz, 1H), 3.94–3.88 (m, 2H), 3.71 (dd, $J = 11.0, 5.6$ Hz, 1H), 3.43 (dt, $J = 6.4, 3.6$ Hz, 1H), 2.44 (d, $J = 2.2$ Hz, 1H), 1.11 (s, 9H), 1.08 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 136.3, 136.1, 135.7, 135.6, 132.9 ($2 \times \text{C}$), 132.3, 132.0, 130.4, 130.3, 130.1 ($2 \times \text{C}$), 128.0 ($3 \times \text{C}$), 127.8, 127.7, 81.1, 77.7, 75.8, 70.9, 63.1, 61.0, 27.0 ($2 \times \text{C}$), 19.4 ($2 \times \text{C}$).

FTIR (neat, cm^{-1}): 3288 (w), 2931 (m), 2858 (m), 1428 (m), 1112 (s), 701 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{39}\text{H}_{47}\text{NO}_4\text{Si}_2$, 650.3116; found 650.3119.



Carbamate **S19**.

A solution of isoxazolidine **S18** (theoretically 3.09 mmol, 1 equiv) and *N*-[2-(trimethylsilyl)ethoxycarbonyloxy]succinimide (Teoc-OSu, 1.20 mg, 4.64 mmol, 1.50 equiv) in 1,4-dioxane (7.73 mL) was treated with triethylamine (2.15 mL, 15.5 mmol, 5.00 equiv) at 23 °C, and the resulting solution was warmed to 40 °C. After 12 h of stirring at this temperature, LCMS analysis showed full consumption of starting material, and the reaction mixture was diluted with ethyl acetate (200 mL). The resulting product solution was washed sequentially with saturated aqueous ammonium chloride solution (2 × 40 mL) and saturated sodium chloride solution (40 mL). The washed solution was then dried over sodium sulfate, filtered, and concentrated to provide a foaming, gummy oil. This crude residue was purified by flash-column chromatography (120 g silica gel, eluting with hexanes initially, grading to 15% ethyl acetate–hexanes) to furnish the product (**S19**) as a crispy, white amorphous solid (1.61 g, 66%, 2 steps).

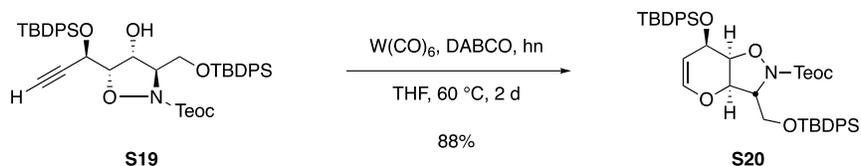
$R_f = 0.48$ (20% ethyl acetate–hexanes, UV+KMnO₄).

¹H NMR (500 MHz, CDCl₃) δ 7.83–7.80 (m, 4H), 7.71–7.67 (m, 4H), 7.51–7.38 (m, 8H), 4.96 (app t, $J = 3.8$ Hz, 1H), 4.87 (dd, $J = 5.6, 2.3$ Hz, 1H), 4.34 (dd, $J = 6.6, 4.1$ Hz, 1H), 4.27 (dd, $J = 5.6, 3.6$ Hz), 4.26–4.14 (m, 2H), 3.90 (dd, $J = 10.8, 4.1$ Hz, 1H), 3.73 (dd, $J = 10.8, 6.6$ Hz, 1H), 3.61 (d, $J = 3.8$ Hz, 1H), 2.42 (d, $J = 2.2$ Hz, 1H), 1.14 (s, 9H), 1.10 (s, 9H), 1.02–0.98 (m, 1H), 0.93–0.89 (m, 1H), 0.06 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 157.1, 136.3, 136.1, 135.7 ($2 \times \text{C}$), 133.0 ($2 \times \text{C}$), 132.3, 131.9, 130.3, 130.2, 130.0, 129.9, 128.0, 127.9 ($2 \times \text{C}$), 127.7, 83.2, 80.8, 75.9, 70.2, 64.8, 62.9, 62.1, 26.9 ($2 \times \text{C}$), 19.4 ($2 \times \text{C}$), 17.7, -1.4.

IR (neat, cm^{-1}): 2954 (2), 2858 (w), 1702 (w), 1427 (m), 1104 (s), 837 (m), 731 (s), 699 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{45}\text{H}_{59}\text{NO}_6\text{Si}_3$, 794.3723; found 794.3720.



Glycal **S20**.

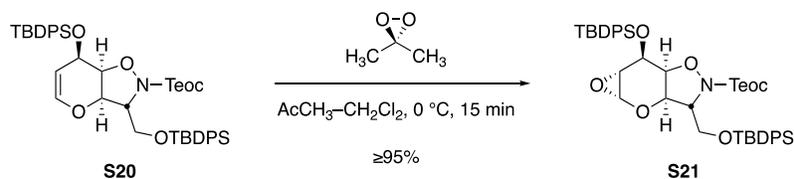
In a 100-mL borosilicate glass microwave reaction vial, alkynol **S19** (1.60 g, 2.02 mmol, 1 equiv) was dried by azeotropic removal of benzene. To the dried starting material was added tungsten hexacarbonyl (177 mg, 0.504 mmol, 0.250 equiv; CAUTION: tungsten hexacarbonyl is a volatile source of metal and of carbon monoxide. Manipulations of this reagent should be conducted within a well-ventilated fume hood.) and 1,4-diazabicyclo[2.2.2]octane (452 mg, 4.03 mmol, 2.00 equiv). The vial was flushed with dry argon gas, and then anhydrous, degassed tetrahydrofuran (20.2 mL) was added at 23 °C. The resulting colorless solution attained a vibrant fluorescent yellow color within 3 minutes. The vial was sealed and was transferred to a pre-heated oil bath (60 °C) positioned inside a photochemistry safety cabinet. The reaction mixture was heated with constant UV irradiation from an adjacent 200-Watt mercury-vapor bulb filtered through a water-cooled Pyrex glass jacket (CAUTION: exposure to high-intensity UV light can cause irreversible vision loss. Never open the safety cabinet when the UV lamp is on). Progress was monitored by TLC (20% ethyl acetate–hexanes, UV+KMnO₄). After 2 d, full consumption of alkynol substrate was achieved, and the crude product mixture was concentrated to dryness *in vacuo*. The goldenrod-colored, oily residue was purified by flash-column chromatography (120 g silica gel, eluting with hexanes initially, grading to 15% ethyl acetate–hexanes) to provide glycal **S20** as a viscous, colorless oil (1.40 g, 88%).

^1H NMR (500 MHz, C_6D_6) δ 7.93–7.91 (m, 2H), 7.88–7.85 (m, 2H), 7.70–7.65 (m, 4H), 7.28–7.18 (m, 12H), 5.98 (dd, $J = 6.5, 2.2$ Hz, 1H), 4.69 (app dt, $J = 6.5, 1.9$ Hz, 1H), 4.64 (dd, $J = 7.0, 4.1$ Hz, 1H), 4.61 (app dt, $J = 4.4, 2.1$ Hz), 4.32–4.26 (m, 2H), 4.24–4.17 (m, 2H), 3.85 (dd, $J = 10.9, 4.1$ Hz, 1H), 3.69 (dd, $J = 10.8, 7.0$ Hz, 1H), 1.22 (s, 9H), 1.10 (s, 9H), 0.91 (t, $J = 8.3$ Hz, 2H), -0.07 (s, 9H).

^{13}C NMR (126 MHz, C_6D_6) δ 157.3, 142.0, 136.3 ($2 \times \text{C}$), 136.0 ($2 \times \text{C}$), 134.2 ($2 \times \text{C}$), 133.5, 133.4, 130.2 ($4 \times \text{C}$), 128.4, 128.2 ($2 \times \text{C}$), 128.1, 102.1, 78.9, 76.9, 69.3, 64.5, 63.6, 63.3, 27.1 ($2 \times \text{C}$), 19.6, 19.4, 17.7, -1.4 .

IR (neat, cm^{-1}): 2954 (m), 2931 (m), 2857 (m), 1702 (m), 1427 (m), 1111 (s), 1066 (s), 837 (m), 701 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{45}\text{H}_{59}\text{NO}_6\text{Si}_3$, 794.3723; found 794.3696.



Glycal epoxide **S21**.

A solution of dimethyldioxirane in acetone was prepared, and its concentration was assayed according to the procedures of Murray and Singh.²² A solution of glycal **S20** (920 mg, 1.16 mmol, 1 equiv) in dichloromethane (11.6 μL) was cooled to 0 $^\circ\text{C}$, whereupon dimethyldioxirane solution (0.0775 M, 17.9 mL, 1.39 μmol , 1.20 equiv) was added dropwise over 3 min. The reaction mixture was stirred at 0 $^\circ\text{C}$ for 15 min, at which point TLC analysis (NH_2 silica gel, 20% ethyl acetate–hexanes, UV+PAA) indicated full consumption of starting material. The mixture was then concentrated under a stream of dry argon, and the residue was dried by azeotropic removal of benzene to afford glycal epoxide **S21** as a colorless oil that was suitable for use without further purification (quantitative yield, $\geq 95\%$ purity by NMR).

$R_f = 0.63$ (NH_2 silica gel, 20% ethyl acetate–hexanes + 2% methanol, UV+CAM).

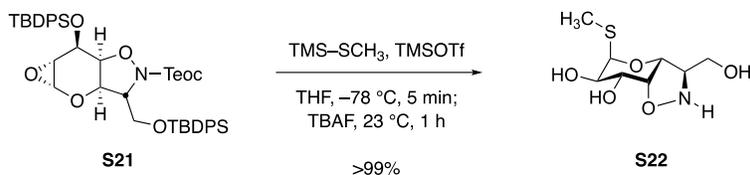
$^1\text{H NMR}$ (500 MHz, C_6D_6) δ 7.89–7.86 (m, 2H), 7.80–7.76 (m, 2H), 7.65–7.59 (m, 4H), 7.22–7.13 (m, 12H), 4.65 (app dt, $J = 2.3, 1.1$ Hz, 1H), 4.61 (dd, $J = 7.1, 4.3$ Hz, 1H), 4.31 (d, $J = 5.1$ Hz, 1H), 4.28–4.17 (m, 2H), 4.12 (d, $J = 2.0$, 1H), 3.88 (d, $J = 4.9$ Hz, 1H), 3.74 (dd, $J = 10.9, 4.3$ Hz, 1H), 3.53 (dd, $J = 10.8, 7.2$ Hz, 1H), 2.94 (app t, $J = 1.1$ Hz, 1H), 1.19 (s, 9H), 1.04 (s, 9H), 0.88 (t, $J = 8.3$ Hz, 2H), -0.11 (s, 9H).

$^{13}\text{C NMR}$ (126 MHz, C_6D_6) δ 157.2, 136.2, 136.1, 135.9 (2 \times C), 133.4 (2 \times C), 133.3, 133.2, 130.3 (2 \times C), 130.1, 128.3, 128.2, 128.1, 77.1, 74.7, 73.2, 69.4, 66.9, 64.5, 63.3, 51.6, 27.0, 19.6, 19.3, 17.6, -1.5 . Two phenyl carbons are not observed: one is believed to be

obfuscated by the solvent signal, and the other is believed to coincide with another resonance (δ 130.1).

IR (neat, cm^{-1}): 2954 (m), 2931 (m), 2858 (m), 1703 (m), 1427 (m), 1249 (m), 1111 (s), 822 (s), 700 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{45}\text{H}_{59}\text{NO}_7\text{Si}_3$, 810.3672; found 810.3667.



Isoxazolidine triol **S22**.

In a 25-mL round-bottomed flask fitted with a magnetic stir bar, glycal epoxide **S21** (321 mg, 396 μmol , 1 equiv) was dried by azeotropic removal of benzene. Once dried, the starting material was dissolved in tetrahydrofuran (3.96 mL), and the resulting solution was chilled to -78 $^\circ\text{C}$. Once cooled, (methylthio)trimethylsilane (169 μL , 1.19 mmol, 3.00 equiv) was added; next, trimethylsilyl trifluoromethanesulfonate (14.3 μL , 79.0 μmol , 0.200 equiv) was added dropwise. After 5 min, TLC analysis (NH_2 silica gel, 2% methanol–20% ethyl acetate–hexanes, UV+CAM) showed complete conversion of starting material to a slightly more polar product. At this point the reaction was quenched with the addition of tetra-*n*-butylammonium fluoride solution (1.0 M in tetrahydrofuran, 2.8 mL, 2.8 mmol, 7.0 equiv), and the mixture was warmed to 23 $^\circ\text{C}$. After 1 h of stirring at 23 $^\circ\text{C}$, LCMS analysis showed that global desilylation was complete. The mixture was loaded directly onto a column of silica gel (20 g) that had been pre-equilibrated with ethyl acetate; the column was eluted first with ethyl acetate (300 mL), then with 5% methanol–ethyl acetate (300 mL), and finally with 10% methanol–ethyl acetate (600 mL). Fractions containing product were identified by TLC (10% methanol–ethyl acetate, PAA), and these fractions were pooled and concentrated to afford isoxazolidine triol **S22** (103 mg, 110%) that was sufficiently pure for use in the subsequent *N*–*O* bond cleavage reaction.

For characterization purposes, a small quantity (ca. 20 mg) of this product was subjected to preparative HPLC (with a flow rate of 15 mL/min, eluting with 0.1% trifluoroacetic acid–1% acetonitrile–water for 2 min, then grading to 0.1% trifluoroacetic acid–20% acetonitrile–water

over 18 min; monitored by UV absorbance at 210 nm; product $R_t = 8.75$ min) to give the trifluoroacetic acid salt of **S22** • CF₃CO₂H in pure form.

$R_f = 0.06$ (free base, 10% methanol–ethyl acetate, PAA).

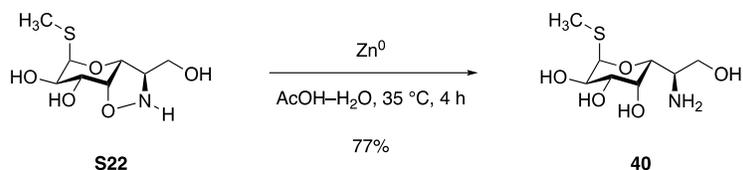
¹H NMR (hydrotrifluoroacetate salt, 500 MHz, CD₃OD) δ 5.27 (d, $J = 5.0$ Hz, 1H), 4.98 (d, $J = 2.0$ Hz, 1H), 4.71 (dd, $J = 3.8, 2.1$ Hz, 1H), 4.12 (dd, $J = 10.1, 5.1$ Hz, 1H), 4.10 (app t, $J = 5.5$ Hz, 1H), 3.99 (dd, $J = 10.0, 3.8$ Hz, 1H), 3.87 (dd, $J = 12.0, 4.8$ Hz, 1H), 3.83 (dd, $J = 12.0, 6.0$ Hz, 1H), 2.14 (s, 3H).

¹³C NMR (hydrotrifluoroacetate salt, 100 MHz, CD₃OD) δ 89.0, 85.4, 76.1, 70.1, 69.0, 68.6, 59.0, 13.1.

¹⁹F NMR (hydrotrifluoroacetate salt, 471 MHz, CD₃OD) δ -77.3 (s, 3F).

IR (hydrotrifluoroacetate salt, neat, cm⁻¹): 3349 (br), 1672 (s), 1434 (w), 1199 (s), 1139 (m), 1095 (m), 1051 (m).

HRMS (ESI+, m/z): [M+H]⁺ calc'd for C₈H₁₅NO₅S 238.0744; found 238.0739.



Methylthio-8-norlincosamine (**40**).

To a solution of isoxazolidine triol **S22** (234 mg, 986 μmol , 1 equiv) in 50% v/v acetic acid–water (9.86 mL) was added activated zinc powder (258 mg, 3.94 mmol, 4.00 equiv). The mixture was heated to 35 $^\circ\text{C}$ with stirring, and after 4 h, LCMS showed complete conversion of starting material to aminotetraol product. The mixture was cooled before it was filtered through a Celite pad. The filter cake was washed with methanol (3×5 mL), and the combined filtrates were concentrated to dryness. Residual acetic acid was removed by repeated concentration from 50% v/v methanol–toluene. Once dried, the crude residue, containing the hydroacetate salt of the desired product as well as zinc acetate as a major impurity, was dissolved in methanol (20 mL) and was treated with Amberlyst A26 resin (hydroxide form, 4.00 g). After stirring the mixture at 23 $^\circ\text{C}$ for 1 h, the ion-exchange beads were removed by filtration, and the filtrate was concentrated to give a white solid. This crude residue was finally purified by flash-column chromatography (25 silica gel, eluting with 1% ammonium hydroxide–10% methanol–dichloromethane initially, grading to 10% ammonium hydroxide–40% methanol–dichloromethane) to provide methylthio-8-norlincosamine (**40**) as a white solid (182 mg, 77%).

$R_f = 0.30$ (10% ammonium hydroxide–40% methanol–dichloromethane, ninhydrin).²⁸

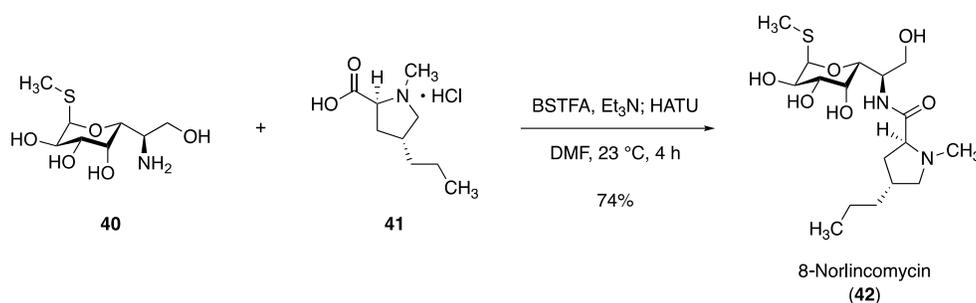
²⁸ Note: Prior to staining with ninhydrin, TLC plates must be heated thoroughly (~ 200 $^\circ\text{C}$, 30 s) to drive off residual ammonia, which interferes with proper staining.

^1H NMR (400 MHz, D_2O) δ 5.17 (d, $J = 5.7$ Hz, 1H), 3.95–3.92 (m, 2H), 3.84 (d, $J = 9.2$ Hz, 1H), 3.63 (dd, $J = 11.0, 2.5$ Hz, 1H), 3.54 (dd, $J = 10.2, 2.9$ Hz, 1H), 3.38 (dd, $J = 11.2, 6.1$ Hz, 1H), 2.91 (ddd, $J = 9.0, 6.1, 3.2$ Hz, 1H), 1.92 (s, 3H).

^{13}C NMR (100 MHz, D_2O) 87.0, 70.5, 70.3, 68.2, 67.8, 63.0, 50.6, 12.0.

FTIR (neat, cm^{-1}): 2939 (s), 2865 (m), 1711 (s), 1464 (m), 1434 (m), 1125 (m), 1036 (m), 756 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_8\text{H}_{17}\text{NO}_5\text{S}$, 240.0900; found 240.0899.



8-Norlincomycin (3.5).

In a 2–5-mL glass microwave vial fitted with a magnetic stir bar, methylthio-8-norlincomosamine (**40**, 100 mg, 418 μ mol, 1 equiv) was dissolved in *N,N*-dimethylformamide (2.09 mL). Triethylamine (262 μ L, 1.88 mmol, 4.50 equiv) and *N,O*-bis(trimethylsilyl)trifluoroacetamide (224 μ L, 836 μ mol, 2.00 equiv) were added next, and the solution was stirred at 23 °C for 1 h to ensure complete *O*-silylation. After this period, *trans*-4-*n*-propyl-L-hygric acid hydrochloride (**41**) (104 mg, 501 μ mol, 1.20 equiv) and HATU (222 mg, 585 μ mol, 1.40 equiv) were added, causing the reaction mixture to attain a canary yellow hue. Following 4 h of stirring at 23 °C, LCMS analysis showed complete conversion of aminotetraol starting material and its (oligo)silylated congeners to amide products. The reaction mixture was consequently diluted with ethyl acetate (25 mL) and the diluted solution was washed with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 \times 10 mL), and the combined organic layers were then washed with saturated aqueous sodium chloride solution (15 mL). The washed organic solution was dried over sodium sulfate, filtered, and concentrated; and the residue thus obtained was re-dissolved in 50% v/v methanol–acetic acid. This colorless solution was stirred at 40 °C for 24 h to ensure complete desilylation before it was concentrated to dryness *in vacuo*. Residual acetic acid was removed by repeated concentration of the mixture from 50% v/v methanol–toluene. Once thoroughly dried, the crude residue was treated

with methanol (10 mL) and Amberlyst A26 resin (hydroxide form, 2.00 g). The resulting mixture was stirred at 23 °C for 1 h before the ion-exchange beads were removed by filtration and the filtrate was concentrated. This light amber-colored oily residue was purified by flash-column chromatography (18 g silica gel, eluting with 0.5% ammonium hydroxide–5% methanol–dichloromethane initially; grading to 1% ammonium hydroxide–10% methanol–dichloromethane) to furnish 8-norlincomycin (**42**) as a light yellow, foaming solid (121 mg, 74%).

$R_f = 0.23$ (1% ammonium hydroxide–10% methanol–dichloromethane, PMA or I₂).

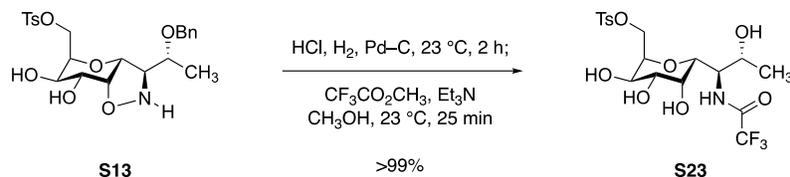
¹H NMR (500 MHz, CD₃OD) δ 5.29 (d, $J = 5.6$ Hz, 1H), 4.17 (d, $J = 8.9$ Hz, 1H), 4.12–4.08 (m, 2H), 3.78 (app dt, $J = 6.6, 5.1$ Hz, 2H), 3.72 (dd, $J = 10.7, 4.2$ Hz, 1H), 3.63 (dd, $J = 10.1, 3.4$ Hz, 1H), 3.21 (dd, $J = 8.7, 6.0$ Hz, 1H), 2.95 (dd, $J = 10.6, 4.8$ Hz, 1H), 2.37 (s, 3H), 2.19–2.15 (m, 1H), 2.08 (s, 3H), 2.05 (dd, $J = 10.1, 8.8$ Hz, 1H), 1.99 (ddd, $J = 13.0, 8.2, 4.8$ Hz, 1H), 1.84 (app dt, $J = 12.9, 10.3$ Hz, 1H), 1.36–1.31 (m, 4H), 0.92 (t, $J = 6.5$ Hz, 3H).

¹³C NMR (126 MHz, CD₃OD) δ 178.2, 89.0, 71.9, 70.4, 69.8 (2 \times C), 69.5, 63.8, 61.5, 51.9, 41.9, 38.9, 38.6, 37.0, 22.6, 14.6, 12.8.

FTIR (neat, cm⁻¹): 3333 (br), 2920 (s), 2787 (m), 1644 (s), 1525 (s), 1080 (s).

HRMS (ESI+, m/z): [M+H]⁺ calc'd for C₁₇H₃₂N₂O₆S, 393.2054; found 393.2050.

Synthesis of Fully Synthetic Lincosamide Analogs 43–50



***N*-Trifluoroacetamido tetraol S23.**

A 50-mL round-bottomed flask was charged with isoxazolidine **13** (508 mg, 1.06 mmol, 1 equiv). Methanol (10.6 mL) was added, the resulting solution was chilled to 0 °C, and the stirred solution was treated with hydrogen chloride (1.06 mL, 4 M solution in dioxane, 4.24 mmol, 4.00 equiv). The mixture was then concentrated *in vacuo* to remove methanol, dioxane, and excess hydrogen chloride; and the dried residue (**S13** • HCl) was re-dissolved in methanol (10.6 mL). To this solution was added 10% w/w palladium on carbon (113 mg). The reaction flask was fitted with a 3-way stopcock to which a hydrogen-filled balloon had been affixed. The headspace in the flask was replaced with hydrogen gas by three evacuation–backfilling cycles, and the black reaction mixture was stirred at 23 °C. After 2 h, LCMS analysis indicated that isoxazolidine hydrogenolysis and *O*-debenzylation were complete. At this point, triethylamine (738 μL, 5.30 mmol, 5.00 equiv) and methyl trifluoroacetate (533 μL, 5.30 mmol, 5.00 equiv) were added sequentially. After an additional 25 min, LCMS analysis demonstrated complete conversion of the primary amine intermediate to the corresponding trifluoroacetamide. The reaction mixture was filtered through a pad of Celite to remove catalyst, and the filtrate was concentrated to give product alongside triethylamine hydrochloride. In order to remove the latter, the crude residue was suspended in ethyl acetate (30 mL), and the organic solution was washed with saturated aqueous sodium chloride solution (3 × 10 mL). The combined aqueous washes were extracted with ethyl

acetate (2×10 mL), and these extracts were washed with a fresh portion of saturated aqueous sodium chloride solution (10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to give the product (**S23**) as a white solid (529 mg, 102%). This material was sufficiently pure ($\geq 90\%$, based on ^1H NMR analysis) for use without further purification. An analytically pure sample (~ 25 mg) was prepared by flash-column chromatography (4.5 g silica gel, eluting with 3% methanol–dichloromethane initially, grading to 10% methanol–dichloromethane).

$R_f = 0.27$ (10% methanol–dichloromethane, UV+PMA).

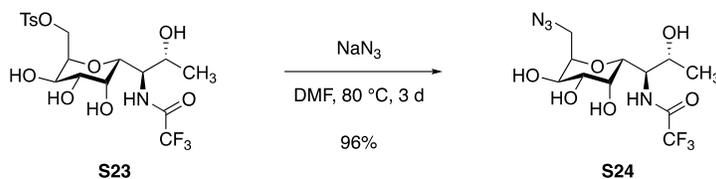
^1H NMR (600 MHz, CD_3OD) δ 7.81 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 8.1$ Hz, 2H), 4.41 (dd, $J = 11.4, 9.6$ Hz, 1H), 4.28 (dd, $J = 11.4, 2.8$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 1H), 4.18 (ddd, $J = 9.5, 7.0, 2.9$ Hz, 1H), 3.98–3.95 (m, 2H), 3.87 (dd, $J = 7.2, 1.4$ Hz, 1H), 3.48 (dd, $J = 10.1, 3.2$ Hz, 1H), 2.46 (s, 3H), 1.15 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 146.6, 134.3, 131.2, 129.0, 76.1, 72.0, 70.9, 70.5, 68.2, 68.1, 66.6, 57.1, 21.6, 19.1. Trifluoroacetamide carbons were not resolved due to ^{19}F nuclear coupling.

^{19}F NMR (376 MHz, CD_3OD) δ -77.44 (s, 3F).

FTIR (neat, cm^{-1}): 3381 (br), 2519 (br), 1710 (s), 1353 (m), 1175 (s), 1080 (m), 973 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{18}\text{H}_{24}\text{F}_3\text{NO}_9\text{S}$, 488.1197; found 488.1192.



Azidomethyl glycoside **S24**.

An oven-dried 20-mL microwave vial was charged with a stir bar and **S23** (400 mg, 821 μmol , 1 equiv), and this material was dried by azeotropic removal of benzene. Sodium azide (533 mg, 8.21 mmol, 10.0 equiv) and anhydrous *N,N*-dimethylformamide (4.10 mL) were then added, and the vial was sealed. The mixture was heated to 80 $^\circ\text{C}$ with rapid stirring. After 3 days, LCMS analysis indicated complete consumption of starting material; at this time the mixture was cooled, and the cooled reaction mixture was diluted with water (5 mL) and saturated aqueous sodium chloride solution (35 mL). This mixture was extracted with ethyl acetate (4 \times 20 mL). The combined organic extracts were dried over sodium sulfate, the dried product solution was filtered, and the filtrate was concentrated to give a light brown oil. In order to remove residual *N,N*-dimethylformamide, the crude residue was concentrated repeatedly from 10% methanol–toluene, affording **S24** as a dull brown solid (281 mg, 96%). This material could be used in subsequent steps without further purification; an analytically pure sample (~20 mg) was prepared by flash-column chromatography (10 g silica gel, eluting with 5% methanol–dichloromethane initially, grading to 10% methanol–dichloromethane), affording a brilliant white crystalline solid.

Melting point: 140–143 $^\circ\text{C}$.

R_f = 0.12 (10% methanol–dichloromethane, PMA).

^1H NMR (600 MHz, CD_3OD) δ 4.26 (app t, $J = 6.9$ Hz, 1H), 4.18 (ddd, $J = 10.1, 6.5, 3.1$ Hz, 1H), 4.05–3.97 (m, 4H), 3.71 (dd, $J = 13.8, 10.5$ Hz, 1H), 3.56 (dd, $J = 9.9, 3.3$ Hz, 1H), 3.45 (dd, $J = 13.8, 3.1$ Hz 1H), 1.19 (d, $J = 6.4$ Hz, 3H).

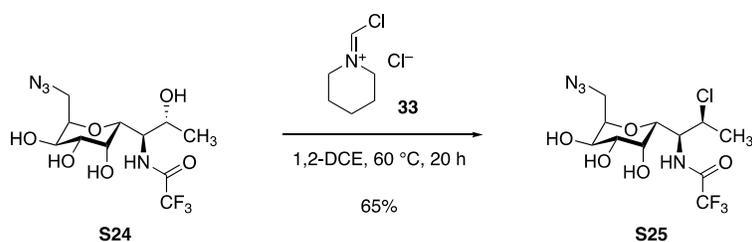
^{13}C NMR (100 MHz, CD_3OD) δ 77.3, 71.8, 70.8, 70.3, 68.6, 68.2, 57.5, 47.3, 19.4.

Trifluoroacetamide carbons were not resolved due to ^{19}F nuclear coupling.

^{19}F NMR (471 MHz, CD_3OD) δ -77.56 (s, 3F).

FTIR (neat, cm^{-1}): 3319 (br), 2933 (w), 2105 (s), 1710 (s), 1556 (m), 1282 (m), 1214 (s), 1183 (s), 1159 (s), 1073 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{11}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_6$, 359.1173; found 359.1180.



Chloro compound S25.

A flame-dried 20-mL microwave vial was charged with azidotetraol **S24** (250 mg, 698 μmol , 1 equiv), and this starting material was dried by azeotropic removal of benzene. The dried residue was suspended in 1,2-dichloroethane (11.6 mL), and the resulting suspension was cooled to 0 °C. Chloromethylenepipiridinium chloride (**33**, 704 mg, 4.19 mmol, 6.00 equiv) was added in one portion, and the mixture was stirred rapidly at 0 °C. After 15 min, the originally light yellow suspension had clarified, forming a yellow homogeneous solution. The reaction mixture was then heated to 60 °C, and over the course of 2 h the solution attained an intense sunset orange color. After 20 h, LCMS analysis indicated that deoxychlorination was complete (evidenced by the disappearance of starting material and its mono- and di-formylated congeners; ESI- m/z = 357, 385, and 413, respectively). The reaction mixture was cooled to 23 °C, and the cooled solution was transferred by cannula to a rapidly stirred, ice-cold sodium hydroxide solution (8.38 mL, 0.5 M, 4.19 mmol, 6.00 equiv). In order to saponify the formyl esters formed upon workup, the biphasic mixture was treated with additional 0.5 M sodium hydroxide solution until the aqueous phase achieved pH = 11; the mixture was then warmed to 23 °C with constant vigorous stirring, and additional sodium hydroxide solution was added periodically to maintain pH = 11. After 24 h, deformylation was complete by LCMS analysis. The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous phase was then treated with solid sodium chloride until saturation was achieved, and the resulting aqueous solution was extracted with

dichloromethane (5×7 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to give a brown oil. This residue was purified by flash-column chromatography (12 g silica, eluting with dichloromethane initially, grading to 8% methanol–dichloromethane) to give **S25** as a brilliant white solid (170 mg, 65%).

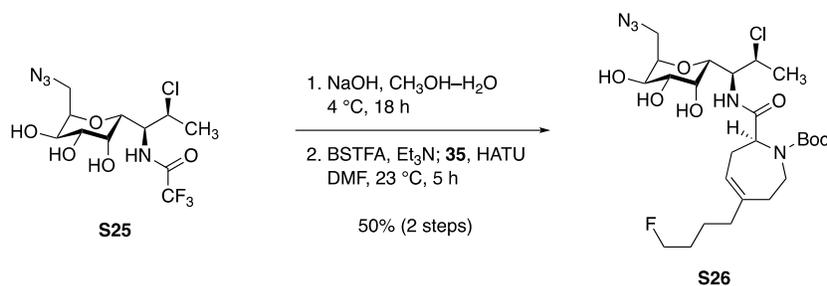
$R_f = 0.23$ (10% methanol–dichloromethane PMA).

$^1\text{H NMR}$ (600 MHz, CD_3OD) δ 4.64 (qd, $J = 6.8, 1.9$ Hz, 1H), 4.51 (dd, $J = 9.6, 1.8$ Hz, 1H), 4.15 (ddd, $J = 9.6, 6.5, 3.1$ Hz, 1H), 4.01 (dd, $J = 9.9, 6.6$ Hz, 1H), 3.97 (dd, $J = 9.5, 1.4$ Hz, 1H), 3.82 (dd, $J = 3.3, 1.3$ Hz, 1H), 3.66 (dd, $J = 13.8, 9.4$ Hz, 1H), 3.60 (dd, $J = 13.8, 3.2$ Hz, 1H), 3.53 (dd, $J = 9.9, 3.2$ Hz, 1H), 1.44 (d, $J = 6.8$ Hz, 3H).

$^{13}\text{C NMR}$ (126 MHz, CD_3OD) δ 159.3 (q, $J = 37.4$ Hz), 117.5 (q, $J = 286.8$ Hz), 77.1, 72.2, 71.3, 69.5, 68.6, 58.8, 55.1, 47.5, 22.8.

FTIR (neat, cm^{-1}): 3384 (br), 2106 (s), 1716 (s), 1545 (m), 1289 (m), 1217 (s), 1176 (s), 1165 (s), 1078 (s).

HRMS (ESI⁻, m/z): $[\text{M}-\text{H}]^-$ calc'd for $\text{C}_{11}\text{H}_{16}\text{ClF}_3\text{N}_4\text{O}_5$, 375.0689; found 375.0692.



Protected lincosamide **S26**.

In a 10-mL round-bottomed flask, trifluoroacetamide **S25** (170 mg, 451 μ mol, 1 equiv) was dissolved in a minimal quantity of methanol (500 μ L). This solution was chilled to 0 °C before it was treated with ice-cold aqueous sodium hydroxide solution (1.00 M, 2.26 mL, 2.26 mmol, 5.0 equiv). The mixture was stirred at 4 °C for 18 h, at which point LCMS analysis showed that no starting material remained. The mixture was acidified with the addition of aqueous hydrogen chloride solution (1.0 M), until the pH < 2 was attained. The acidified mixture was then concentrated to dryness to give a light-yellow residue comprising deacylated product, sodium chloride, and sodium trifluoroacetate. This mixture was suspended in ethanol (190 proof, 5 mL), and the suspension was filtered. The solids were rinsed with fresh ethanol (190 proof, 2 \times 2 mL), and the combined filtrates were concentrated. This residue was then re-dissolved in methanol (10 mL), the solution was cooled to 0 °C, and the mixture was treated with Amberlyst A26 resin (hydroxide form, 2.0 g). After stirring for 1 h at 0 °C, the ion-exchange beads were removed by filtration, and the filtrate was concentrated to provide aminotriol intermediate (132 mg, 104%).

A portion of this crude aminotriol (100 mg, 360 μ mol, 1 equiv) transferred to a 2–5-mL glass microwave vial containing a magnetic stir bar, where it was dissolved in *N,N*-dimethylformamide (1.78 mL). This solution was chilled to 0 °C, triethylamine (169 μ L, 1.21 mmol, 3.40 equiv) and *N,O*-bis(trimethylsilyl)trifluoroacetamide (143 μ L, 534 μ mol, 1.50 equiv)

were added, and the mixture was warmed immediately back to 23 °C. After 1 h of stirring at this temperature, the mixture was transferred via cannula to a separate 4-mL glass vial (fitted with a magnetic stir bar and silicone septum screw cap) containing azepine acid **35** (135 mg, 427 μmol, 1.20 equiv).⁴ The mixture was then treated with HATU (176 mg, 463 μmol, 1.30 equiv), causing the dull brown solution to turn the color of chartreuse. After 5 h, the mixture was diluted with ethyl acetate (40 mL), and the diluted solution was washed sequentially with 10% w/v aqueous citric acid solution (2 × 10 mL), saturated aqueous sodium bicarbonate solution (2 × 10 mL), and saturated aqueous sodium chloride solution (10 mL). The product solution was then dried over sodium sulfate, filtered, and concentrated; the residue obtained was re-dissolved in 50% v/v acetic acid–methanol (8 mL), and the resulting solution was stirred at 40 °C overnight in order to effect global desilylation. The mixture was then diluted with toluene (10 mL) and the diluted solution was concentrated. The dried residue was purified by flash-column chromatography (24 g silica gel, eluting with dichloromethane initially, grading to 10% methanol–dichloromethane) to provide **S26** as white solid (98.2 mg, 50%, 2 steps).

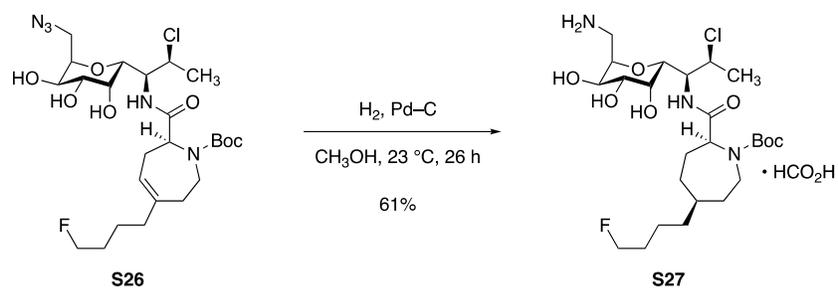
$R_f = 0.16$ (10% methanol–dichloromethane, PMA)

¹H NMR (600 MHz, CD₃OD) δ 5.53–5.48 (m, 1H), 4.70–4.63 (m, 1H), 4.53 (dd, $J = 12.0, 4.1$ Hz, 1H), 4.41 (dt, $J = 47.5, 5.9$ Hz, 2H), 4.30 (d, $J = 9.5$ Hz, 1H), 4.14 (ddd, $J = 9.6, 6.7, 3.2$ Hz, 1H), 4.03–3.98 (m, 1H), 3.90–3.85 (m, 1H), 3.83 (dd, $J = 4.8, 3.8$ Hz, 1H), 3.80–3.73 (m, 2H), 3.67–3.57 (m, 2H), 3.54 (dd, $J = 10.0, 3.2$ Hz, 1H), 2.83–2.74 (m, 1H), 2.51–2.38 (m, 2H), 2.34–2.30 (d, $J = 17.8$ Hz, 1H), 2.01 (app t, $J = 7.6$ Hz, 2H), 1.69–1.58 (m, 2H), 1.54–1.44 (m, 14H).

^{13}C NMR (126 MHz, CD_3OD) δ 175.9, 157.8, 142.8, 120.2, 111.4, 84.7 (d, $J = 163.8$ Hz), 81.9, 77.2, 72.5, 72.1, 69.6, 68.9, 62.9, 59.4, 54.4, 47.7, 41.8, 39.5, 35.4, 31.0 (d, $J = 19.8$ Hz), 28.8, 24.8 (d, $J = 4.3$ Hz), 22.8.

FTIR (neat, cm^{-1}): 3395 (br), 2972 (m), 2935 (m), 2101 (s), 1663 (s), 1445 (m), 1413 (m), 1393 (m), 1368 (m), 1253 (m), 1163 (s), 1084 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{41}\text{ClFN}_5\text{O}_7$, 578.2751; found 578.2738.



Aminomethyl protected lincosamide **S27**.

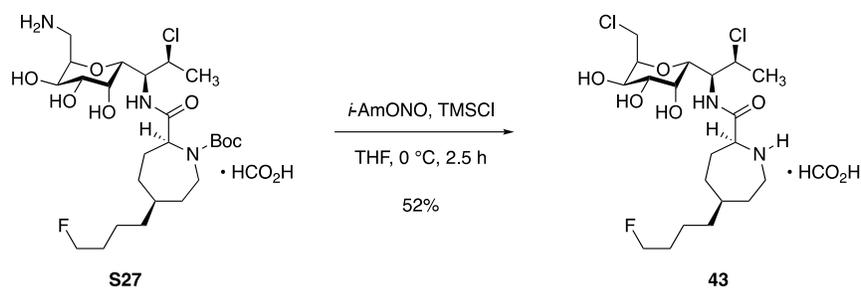
To a 1-dram vial containing azidetriol **S26** (40.0 mg, 69.0 μmol , 1 equiv) was added methanol (690 μL) and palladium on carbon (10% w/w, 4.0 mg). The vial was fitted with a rubber septum and the headspace above the reaction mixture was flushed with hydrogen gas. The black heterogeneous reaction mixture was stirred at 23 $^{\circ}\text{C}$ under an atmosphere of hydrogen gas supplied by a balloon. After 26 h, complete consumption of starting material was noted by LCMS analysis, and the reaction mixture was filtered through a pad of Celite (1 \times 1 cm) to remove catalyst. The filter pad was rinsed with methanol (3 \times 2 mL), and the filtrate was concentrated to give a colorless oil. The residue was purified by preparative HPLC on a Waters SunFire Prep C₁₈ column (5 μm , 250 \times 19 mm; eluting with 0.1% formic acid–5% acetonitrile–water initially, grading to 0.1% formic acid–25% acetonitrile–water over 10 min, then grading to 0.1% formic acid–55% acetonitrile–water over the next 30 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 210 nm) to provide **S27** as a brilliant white solid (25.4 mg, 61%).

^1H NMR (65:35 mixture of rotamers, asterisk [*] denotes minor rotamer peaks that could be resolved, 500 MHz, CD₃OD) δ 8.49 (br, 1H), 4.73 (q, $J = 6.5$ Hz, 1H), 4.51 (dd, $J = 12.6$, 5.8 Hz, 1H),* 4.47–4.35 (m, 4H). 4.22 (app dq, $J = 6.1$, 4.2 Hz, 1H), 4.08 (dd, $J = 9.4$, 6.4 Hz, 1H),* 4.05 (dd, $J = 9.5$, 6.3 Hz, 1H), 3.97–3.86 (m, 2H), 3.68 (d, $J = 9.5$ Hz, 1H), 3.66

(d, $J = 9.7$ Hz, 1H),* 3.54 (dd, $J = 9.5, 3.2$ Hz, 1H), 3.36 (app dt, $J = 13.5, 4.1$ Hz, 1H), 3.21 (ddd, $J = 13.3, 9.0, 3.1$ Hz, 1H), 3.11 (dd, $J = 15.1, 11.7$ Hz, 1H), 3.05 (dd, $J = 14.7, 12.0$ Hz, 1H),* 2.37–2.25 (m, 1H), 1.99–1.95 (m, 1H), 1.88–1.60 (m, 4H), 1.48 (s, 9H), 1.46–1.37 (m, 3H), 1.31–1.26 (m, 2H), 1.21–1.07 (m, 2H).

FTIR (neat, cm^{-1}): 3269 (br), 2967 (m), 2929 (m), 1655 (s), 1586 (s), 1406 (m), 1395 (m), 1367 (m), 1347 (m), 1248 (m), 1161 (s), 1082 (m), 776 (w).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{45}\text{ClFN}_3\text{O}_7$, 554.3003; found 554.3005.



Synthetic lincosamide 43.

A nitrosyl chloride solution (1.08 M) was prepared according to the method described by Weiß and Wagner.²⁹ A solution of isoamyl nitrite (501 μL , 3.73 mmol) in tetrahydrofuran (2.50 mL) was cooled to 0 $^\circ\text{C}$ and was treated with chlorotrimethylsilane (475 μL , 3.73 mmol). The resulting solution was stirred at 0 $^\circ\text{C}$ for 1.5 h prior to use.

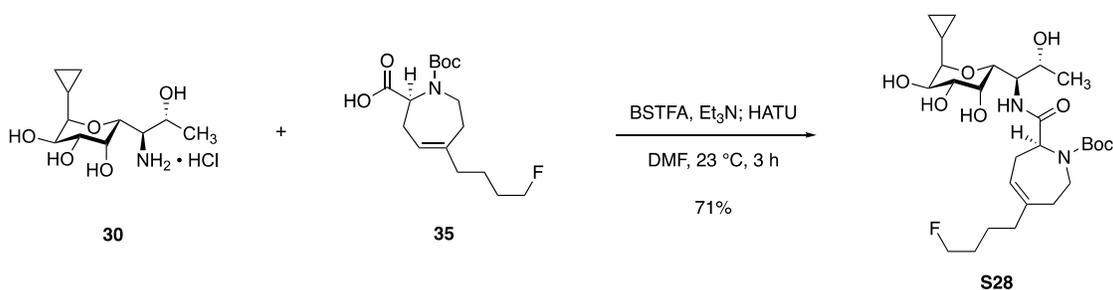
In a 1-mL vial, aminotriol **S27** (5.0 mg, 9.0 μmol) was dried by azeotropic removal of benzene. The dried starting material was then dissolved in tetrahydrofuran (100 μL), and the resulting solution was cooled to 0 $^\circ\text{C}$ with stirring. Nitrosyl chloride solution (1.08 M, 100 μL , 108 μmol , 12.0 equiv) was then added, and the resulting solution was stirred at 0 $^\circ\text{C}$. After 2.5 h, LCMS analysis indicated no starting material remained; the reaction mixture was concentrated under a stream of nitrogen. The dried residue was re-dissolved in 33% trifluoroacetic acid–dichloromethane, and the resulting solution was stirred at 23 $^\circ\text{C}$ for 30 min, at which point LCMS analysis indicated that Boc removal was complete. Toluene (1 mL) was added, and the resulting mixture was concentrated to dryness. The residue was purified by preparative HPLC on a Waters SunFire Prep C₁₈ column (5 μm , 250 \times 19 mm; eluting with 1% formic acid–5% acetonitrile–water initially, grading to 0.1% formic acid–50% acetonitrile–water over 40 min, with a flow rate of 15

²⁹ Weiß, R.; Wagner, K.-G. *Chem. Ber.* **1984**, *117*, 1973–1976.

mL/min; monitored by UV absorbance at 210 nm) to afford **43** • HCO₂H as a white solid (2.2 mg, 52%).

¹H NMR (600 MHz, CD₃OD) δ 4.69 (q, *J* = 7.0 Hz, 1H), 4.43 (dt, *J* = 47.5, 6.0 Hz, 2H), 4.40 (m, 1H), 4.17 (app dt, *J* = 8.9, 5.8 Hz, 1H), 4.03 (dd, *J* = 10.0, 6.5 Hz, 1H), 4.00 (dd, *J* = 10.1, 2.6 Hz, 1H), 3.85 (m, 2.0 H), 3.81 (d, *J* = 3.2 Hz, 1H), 3.76 (d, *J* = 9.7 Hz, 1H), 3.54 (d, *J* = 10.0, 3.2 Hz, 1H), 3.36 (ddd, *J* = 14.0, 6.2, 3.1 Hz, 1H), 2.32 (m, 1H), 2.04 (m, 2H), 1.93 (m, 1H), 1.73–1.52 (m, 4H), 1.49–1.45 (m, 2H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.42–1.36 (m, 3H). One methylene proton corresponding to the ζ position of the azepane is obfuscated by CHD₂OD signal.

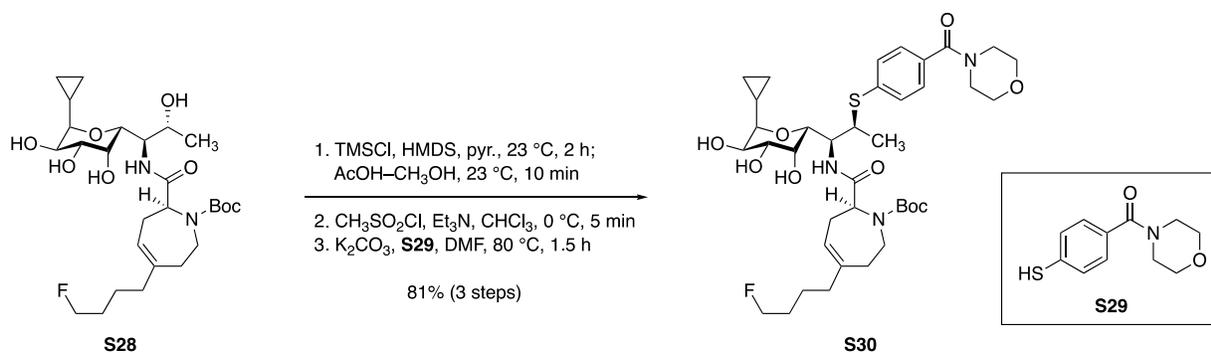
HRMS (ESI+, *m/z*): [M+H]⁺ calc'd for C₂₀H₃₅Cl₂FN₂O₅, 473.1980; found 473.1983.



Protected lincosamide **S28**.

In a 4-mL glass vial fitted with a magnetic stir bar and silicone septum screw cap, an ice-cold solution of aminotetraol hydrochloride salt **30** • HCl (32 mg, 0.11 mmol) and triethylamine (66 μ L, 0.47 mmol, 4.2 equiv) in *N,N*-dimethylformamide (564 μ L) was treated with *N,O*-bis(trimethylsilyl)trifluoroacetamide (61 μ L, 0.23 mmol, 2.0 equiv). The mixture was warmed to 23 °C and was stirred at that temperature for 1 h to ensure complete *O*-silylation before it was transferred via cannula to a separate 4-mL glass vial (fitted with a magnetic stir bar and silicone septum screw cap) containing azepine acid **35** (39 mg, 0.12 mmol, 1.1 equiv).⁴ The resulting mixture was then treated with HATU (56 mg, 0.15 mmol, 1.3 equiv), and the yellow solution was stirred at 23 °C. After 3 h, this solution was diluted with ethyl acetate (20 mL), and the organic solution was washed sequentially with 10-mL portions of 10% w/v aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution. The washed organic product solution was then dried over sodium sulfate, filtered, and concentrated to give a residue that was re-dissolved in 50% v/v acetic acid–methanol (4 mL). This solution was stirred at 40 °C overnight to effect global desilylation, the desilylated mixture was diluted with toluene (4 mL), and the diluted mixture was concentrated to dryness *in vacuo*. The residue thus obtained was purified by flash-column chromatography (12 g silica gel, eluting with dichloromethane initially, grading to 10% methanol–dichloromethane) to provide **S28** as a white solid (44 mg, 71%).

^1H NMR (60:40 mixture of rotamers, asterisk [*] denotes minor rotamer signals that could be resolved, 600 MHz, CD_3OD) δ 7.97 (d, $J = 8.9$ Hz, 1H),* 7.83 (d, $J = 9.3$ Hz, 1H), 5.50–5.46 (m, 1H), 4.48 (dd, $J = 12.3, 4.5$ Hz, 1H), 4.40 (app dq, $J = 47.5, 6.3$ Hz, 2H), 4.12–4.07 (m, 1H), 4.07–4.02 (m, 1H), 4.01–4.91 (m, 3H), 3.88 (d, $J = 8.1$ Hz, 1H), 3.86–3.80 (m, 1H), 3.78–3.74 (m, 1H), 3.71–3.64 (m, 1H), 3.07 (dd, $J = 9.8, 6.8$ Hz, 1H), 2.74 (app q, $J = 15.5$ Hz, 1H), 2.49–2.37 (m, 2H), 2.32 (br s, 1H), 2.29 (br s, 1H),* 1.99 (app q, $J = 7.2$ Hz, 1H), 1.67–1.57 (m, 2H), 1.52–1.48 (m, 2H), 1.48 (s, 9H), 1.45 (s, 9H),* 1.22 (d, $J = 6.3$ Hz, 3H), 1.19 (d, $J = 6.4$ Hz, 3H),* 1.15–1.09 (m, 1H), 0.74 (tdd, $J = 8.5, 6.0, 4.4$ Hz, 1H), 0.50 (tq, $J = 9.2, 4.9$ Hz, 1H), 0.37 (dq, $J = 9.8, 4.9$ Hz, 1H), 0.27 (dq, $J = 10.0, 5.1$ Hz, 1H).



Protected lincosamide **S30**.

In a 1-mL glass vial fitted with a magnetic stir bar, an ice-cold solution of tetraol **S28** (20.3 mg, 37.3 μ mol, 1 equiv) in pyridine (62.1 μ L) was treated sequentially with hexamethyldisilazane (44.8 μ L, 214 μ mol, 5.74 equiv) and chlorotrimethylsilane (12.1 μ L, 94.3 μ mol, 2.53 equiv). The cooling bath was then removed, and the milky white suspension was stirred at 23 °C for 2 h before it was concentrated to dryness. The dried residue was partitioned between water (10 mL) and 50% v/v ethyl acetate–hexanes (10 mL); the biphasic mixture was shaken vigorously until the layers were clear, and then the layers were separated. The organic layer was washed with a fresh portion of water (5 mL). The washed organic solution was dried over sodium sulfate, filtered, and concentrated to give 2,3,4,7-tetrakis-*O*-trimethylsilylated intermediate as a colorless oil. This material was dissolved in methanol (500 μ L), and 80% v/v acetic acid–water (75 μ L) was added. Desilylation was monitored by TLC, and after 1.5 h, complete disappearance of starting material ($R_f = 0.50$, 20% ethyl acetate–hexanes, CAM) was observed. The mixture was neutralized with the addition of saturated aqueous sodium bicarbonate solution (200 μ L), and the basified mixture was concentrated to dryness. The dried residue was partitioned between water (10 mL) and 50% ethyl ether–hexanes (10 mL), the biphasic mixture was agitated, and the layers were separated. The organic product solution was then washed with a fresh portion of water (5 mL), dried over sodium

sulfate, filtered, and concentrated to give 2,3,4,-tris-*O*-trimethylsilylated intermediate as a colorless oil.

This material was transferred to a clean 1-mL glass vial containing a magnetic stir bar, where it was dissolved in chloroform (123 μ L). The solution was chilled to 0 $^{\circ}$ C before triethylamine (12.8 μ L, 92.0 μ mol, 2.50 equiv) and methanesulfonyl chloride (5.73 μ L, 73.6 μ mol, 2.00 equiv) were added sequentially by micropipette. After 5 min of stirring at 0 $^{\circ}$ C, TLC analysis (40% ethyl acetate–hexanes, CAM) indicated that no 2,3,4,-tris-*O*-trimethylsilylated intermediate remained. The reaction mixture was diluted with dichloromethane (5 mL), and the mixture was washed with saturated aqueous sodium bicarbonate solution (2 \times 2 mL). The washed product solution was then dried over sodium sulfate, filtered, and concentrated to give 2,3,4-tris-*O*-trimethylsilyl-7-*O*-methanesulfonyl intermediate as a foaming, off-white solid.

Finally, in a 1-mL glass vial, methanesulfonate ester intermediate (25.6 mg, 30.5 μ mol, 1 equiv), (4-mercaptophenyl)(morpholino)methanone (**S29**, 13.6 mg, 61.0 μ mol, 2.00 equiv),³⁰ and potassium carbonate (12.7 mg, 91.5 μ mol, 3.00 equiv) were suspended in *N,N*-dimethylformamide (76.0 μ L). This mixture was heated to 80 $^{\circ}$ C for 1.5 h, whereupon TLC analysis (40% ethyl acetate–hexanes, UV+PAA) showed that no sulfonate ester intermediate remained. The reaction mixture was diluted with ethyl acetate (5 mL), the diluted solution was washed with water (2 \times 1 mL), and the washed solution was concentrated. The residue was re-dissolved in 50% v/v acetic acid–methanol (2 mL), and the resulting solution was stirred at 40 $^{\circ}$ C overnight in order to effect global desilylation. The desilylated product mixture was concentrated to dryness, and the dried residue was subjected to flash-column chromatography (4 g silica gel, eluting with

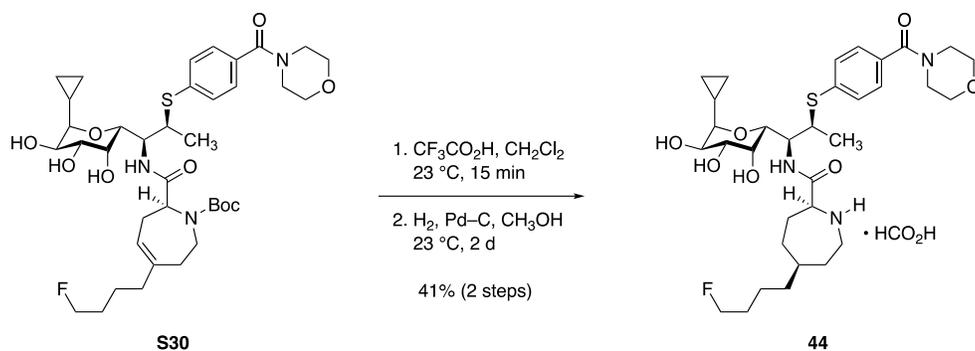
³⁰ Ahlmark, M.; Din Belle, D.; Kauppala, M.; Luiro, A.; Pajunen, T.; Pystynen, J.; Tianen, E.; Vaismaa, M.; Messinger, J. WO patent 2013/175053 A1, November 28, 2013.

dichloromethane initially, grading to 10% methanol–dichloromethane) to furnish **S30** as a colorless oil (18.2 mg, 69% overall).

$R_f = 0.26$ (10% methanol–dichloromethane, UV+PAA).

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.44 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 6.68 (d, $J = 9.2$ Hz, 1H), 5.44 (app t, $J = 6.8$ Hz, 1H), 4.55 (dd, $J = 11.5, 3.5$ Hz, 1H), 4.43 (dt, $J = 47.3, 6.0$ Hz, 2H), 4.19 (app td, $J = 9.6, 2.2$ Hz, 1H), 4.14–4.07 (m, 1H), 4.01 (dd, $J = 9.6, 6.0$ Hz, 1H), 3.88–3.77 (m, 3H), 3.76–3.76 (m, 7H), 3.20 (dd, $J = 9.6, 6.2$ Hz, 1H), 2.81–2.77 (br, 1H), 2.76–2.49 (br, 1H), 2.48–2.35 (br, 1H), 2.34–2.26 (m, 1H), 2.02–1.95 (m, 2H), 1.70–1.59 (m, 2H), 1.54–1.41 (m, 11H), 1.29–1.23 (m, 3H), 1.03–0.96 (br, 1H), 0.74–0.67 (br, 1H), 0.42–0.28 (br, 2H), 0.26–0.15 (br, 1H).

MS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{38}\text{H}_{56}\text{FN}_3\text{O}_9\text{S}$, 750.4; found 750.4.



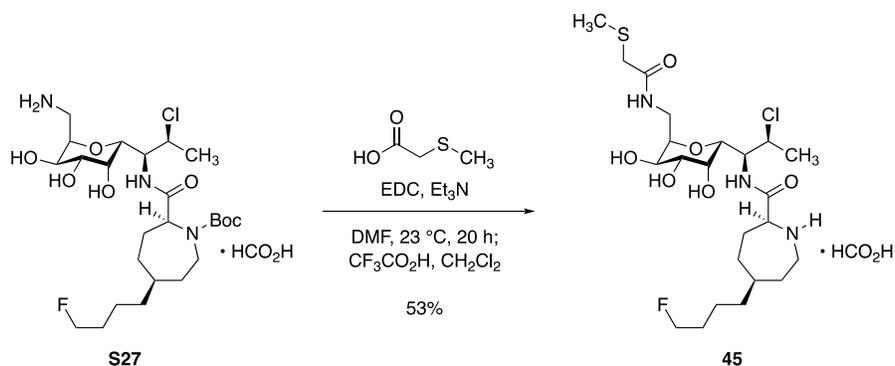
Synthetic lincosamide 44.

In a 4-mL glass vial fitted with a magnetic stir bar and silicone septum screw-cap, azepine **S30** (18.2 mg, 24.3 μmol , 1 equiv) was dissolved in 33% v/v trifluoroacetic acid–dichloromethane (450 μL), and the resulting solution was stirred at 23 $^\circ\text{C}$. After 15 min, LCMS analysis indicated that Boc removal was complete; toluene (1 mL) was added, and the mixture was concentrated to dryness. The residue was then re-dissolved in methanol (500 μL), palladium on carbon (10% w/w, 20 mg) was added, the headspace above the reaction mixture was replaced with hydrogen gas, and the mixture was stirred at 23 $^\circ\text{C}$ under a balloonful of hydrogen gas. After 2 d, LCMS showed that azepine hydrogenation was $\sim 75\%$ complete, and the mixture was filtered through a Celite pad to remove the heterogeneous catalyst. The filter cake was rinsed with methanol ($3 \times 1 \text{ mL}$), and the filtrate was concentrated to give a colorless oil. This residue was purified by preparative HPLC on a Waters SunFire Prep C₁₈ column (5 μm , 250 \times 19 mm; eluting with 0.1% formic acid–10% acetonitrile–water initially, grading to 0.1% formic acid–50% acetonitrile–water over 30 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 254 nm) to provide **44** \cdot HCO₂H (6.9 mg, 41%) as a white solid.

¹H NMR (600 MHz, CD₃OD) δ 8.38 (br, 1H), 7.47 (d, $J = 8.4 \text{ Hz}$, 2H), 7.40 (d, $J = 8.3 \text{ Hz}$, 2H), 4.54 (dd, $J = 9.8, 2.3 \text{ Hz}$, 1H), 4.42 (dt, $J = 47.5, 6.0 \text{ Hz}$, 2H), 4.12–4.08 (m, 2H), 4.00 (qd,

$J = 6.8, 2.2$ Hz, 1H), 3.97 (dd, $J = 10.1, 6.1$ Hz, 1H), 3.88 (d, $J = 3.3$ Hz, 1H), 3.77 (dd, $J = 10.2, 3.3$ Hz, 1H), 3.76–3.69 (br, 4H), 3.68–3.60 (br, 2H), 3.57–3.48 (br, 2H), 3.45 (dd, $J = 13.5, 4.3$ Hz, 1H), 3.14 (app t, $J = 12.6$ Hz, 3.06 (dd, $J = 10.1, 6.1$ Hz, 1H), 2.27–2.16 (m, 2H), 2.06–2.00 (m, 1H), 1.96–1.91 (m, 1H), 1.72–1.55 (m, 4H), 1.48–1.41 (m, 3H), 1.38 (d, $J = 6.9$ Hz, 3H), 1.37–1.33 (m, 2H), 1.07 (tdd, $J = 12.9, 6.6, 4.0$ Hz, 1H), 0.64–0.59 (m, 1H), 0.28 (dq, $J = 9.5, 4.8$ Hz, 1H), 0.10 (tt, $J = 8.5, 5.1$ Hz, 1H), 0.04 (ddd, $J = 11.0, 9.3, 5.1$ Hz, 1H).

HRMS (ESI+, m/z): $[M+H]^+$ calc'd for $C_{33}H_{50}FN_3O_7S$, 652.3426; found 652.3443.



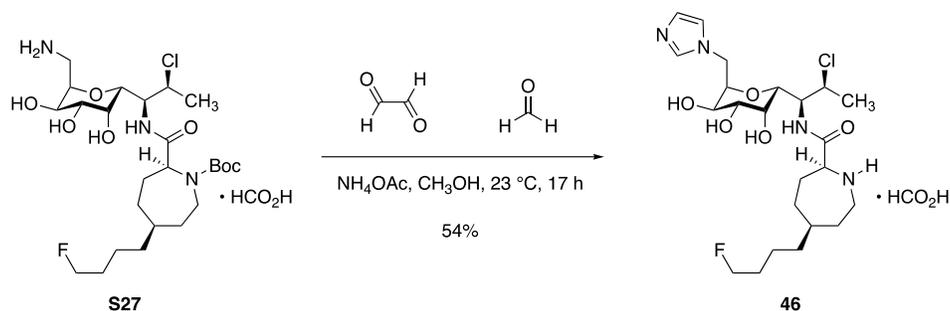
Synthetic lincosamide 45.

A 1-mL vial was charged sequentially with aminotriol **S27** (5.0 mg, 8.3 μmol , 1 equiv), *N,N*-dimethylformamide (83 μL), triethylamine (3.5 μL , 25 μmol , 3.0 equiv), and 2-(methylthio)acetic acid (1.1 μL , 10 μmol , 1.2 equiv). *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC, 1.8 mg, 9.2 μmol , 1.1 equiv) was then added. The resulting solution was stirred at 23 $^{\circ}\text{C}$ for 1 h, at which time additional triethylamine (6.0 μL , 43 μmol , 5.2 equiv) and 2-(methylthio)acetic acid (1.1 μL , 10 μmol , 1.2 equiv) were added. After 19 h, LCMS analysis showed no starting material remained. Methanol (200 μL) and toluene (200 μL) were added, and the resulting solution was concentrated to dryness. The residue was then re-dissolved in 33% trifluoroacetic acid–dichloromethane (200 μL), and after 30 min of stirring at 23 $^{\circ}\text{C}$, LCMS analysis indicated that Boc removal was complete. Toluene (300 μL) was added, and the resulting solution was concentrated to dryness. The crude residue was purified by preparative HPLC on a Waters SunFire Prep C₁₈ column (5 μm 250 \times 19 mm, eluting with 0.1% formic acid–5% acetonitrile–water, grading to 0.1% formic acid–50% acetonitrile–water over 30 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 210 nm) to afford **45** \cdot HCO₂H (2.6 mg, 53%) as a white solid.

45 • HCO₂H:

¹H NMR (600 MHz, CD₃OD) δ 4.70 (q, *J* = 6.3 Hz, 1H), 4.47–4.43 (m, 1H), 4.42 (dd, *J* = 47.4, 5.9 Hz, 2H), 4.17 (ddd, *J* = 10.5, 6.4, 4.0 Hz, 1H), 4.06–3.99 (m, 2H), 3.82 (d, *J* = 3.3 Hz, 1H), 3.70 (d, *J* = 9.6 Hz, 1H), 3.65–3.53 (m, 3H), 3.37 (ddd, *J* = 13.9, 6.3, 3.2 Hz, 1H), 3.20 (app q, *J* = 15.1 Hz, 2H), 2.37–2.30 (m, 1H), 2.15 (s, 3H), 2.09–2.02 (m, 2H), 1.93 (app q, *J* = 12.6 Hz, 1H), 1.74–1.53 (m, 4H), 1.50–1.45 (m, 2H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.43–1.34 (m, 3H). One methylene proton corresponding to the ζ position of the azepane is obfuscated by CHD₂OD signal.

HRMS (ESI+, *m/z*): [M+H]⁺ calc'd for C₂₃H₄₁ClFN₃O₆S, 542.2461; found 542.2451.



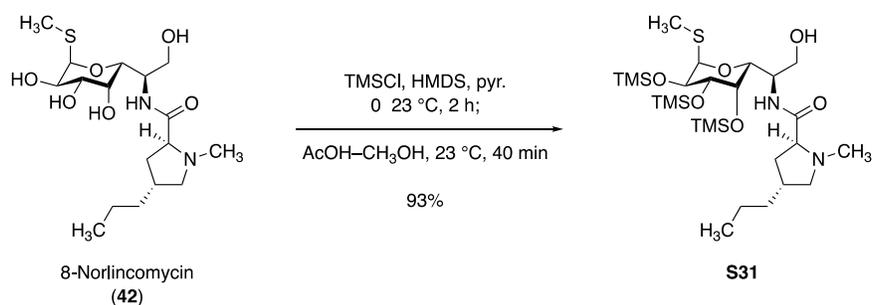
Synthetic lincosamide 46.

To a 1-mL vial, aminotriol **S27** (5.0 mg, 9.02 μmol , 1 equiv), methanol (180 μL), ammonium acetate (2.1 mg, 27 μmol , 3.0 equiv), glyoxal (40% w/w aqueous solution, 3.9 μL , 27 μmol , 3.0 equiv), and formalin (37% w/w, 2.0 μL , 27 μmol , 3.0 equiv) were added sequentially. The mixture was stirred at 23 $^\circ\text{C}$. After 3 h, additional glyoxal (3.9 μL , 3.0 equiv) and formalin (2.0 μL , 3.0 equiv) were added. After an additional 14 h, no starting material remained by LCMS, and the mixture was diluted with benzene (300 μL). The mixture was concentrated, and the dried residue was re-dissolved in 33% trifluoroacetic acid–dichloromethane (200 μL). After 30 min of stirring at 23 $^\circ\text{C}$, LCMS analysis indicated that Boc removal was complete. Toluene (500 μL) was added, and the mixture was concentrated. The dried residue was purified by preparative HPLC on a Waters SunFire Prep C₁₈ column (5 μm , 250 \times 19 mm; eluting with 0.1% formic acid–5% acetonitrile–water initially, grading to 1% formic acid–50% acetonitrile–water over 40 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 210 nm) to afford **46** \cdot HCO₂H as a white solid (2.9 mg, 54%).

¹H NMR (600 MHz, CD₃OD) δ 8.78 (s, 1H), 8.10 (br, 1H), 7.65 (s, 1H), 7.51 (s, 1H), 4.66–4.52 (m, 3H), 4.47–4.44 (m, 1H), 4.43 (dd, $J = 47.2, 6.0$ Hz, 2H), 4.25 (app q, $J = 6.6$ Hz, 1H), 4.14 (dd, $J = 9.7, 6.3$ Hz, 1H), 4.10–4.05 (m, 1H), 3.92–3.89 (m, 1H), 3.84 (d, $J = 9.6$ Hz,

1H), 3.67 (dd, $J = 9.9, 3.0$ Hz, 1H), 3.38 (ddd, $J = 14.3, 6.2, 3.3$ Hz, 1H), 2.33 (dd, $J = 14.8, 6.3$ Hz, 1H), 2.09–2.02 (m, 2H), 1.92 (app q, $J = 12.2$ Hz, 1H), 1.74–1.53 (m, 4H), 1.50–1.38 (m, 5H), 1.37 (d, $J = 7.0$ Hz, 3H). One methylene proton corresponding to the ζ position of the azepane is obfuscated by CHD₂OD signal.

HRMS (ESI+, m/z): [M+H]⁺ calc'd for C₂₃H₃₈ClFN₄O₅, 505.2588; found 505.2590.



Alcohol S31.

In a 2–5-mL glass microwave vial, an ice-cold solution of 8-norlincomycin (**42**, 90.0 mg, 229 μmol , 1 equiv) in pyridine (382 μL) was treated sequentially with hexamethyldisilazane (121 μL , 578 μmol , 2.52 equiv) and chlorotrimethylsilane (168 μL , 1.31 mmol, 5.72 equiv). Following the addition of these reagents, the mixture was warmed to 23 $^{\circ}\text{C}$, and stirring was maintained for 2 h. The mixture was then concentrated to dryness *in vacuo*, and the residue was partitioned between hexanes (10 mL) and water (10 mL). The layers were separated, and the aqueous phase was extracted with additional hexanes (3 \times 5 mL). The combined organic extracts were then dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to afford crude, persilylated 8-norlincomycin as a brilliant white solid. This material was then suspended in methanol (887 μL), and 80% v/v acetic acid–water (133 μL) was added to the suspension, causing the mixture to become a homogeneous, colorless solution. Desilylation was monitored by TLC (40% ethyl acetate–hexanes, CAM; persilylated intermediate $R_f = 0.64$; alcohol product $R_f = 0.16$), and after 40 min of stirring at 23 $^{\circ}\text{C}$, the reaction was judged to be complete. The reaction mixture was transferred to a separatory funnel containing hexanes (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The mixture was shaken vigorously, and the layers were separated. The aqueous layer was extracted with fresh hexanes (3 \times 5 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic

solution was then dried over sodium sulfate, filtered, and concentrated to provide 2,3,4-tris-*O*-trimethylsilyl-8-norlincomycin (**S31**) as a white, foaming, amorphous solid (115 mg, 93%).

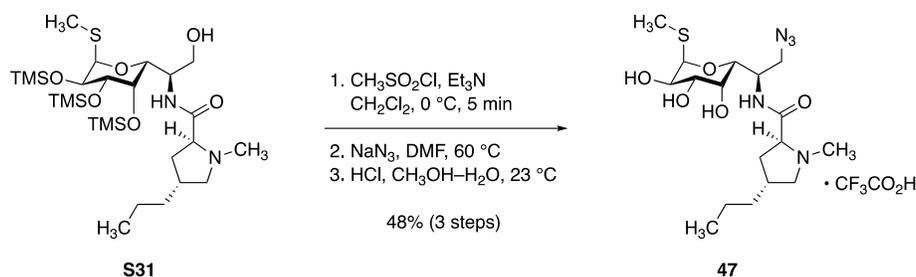
$R_f = 0.16$ (40% ethyl acetate–hexanes, CAM).

$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.73 (d, $J = 8.8$ Hz, 1H), 5.22 (d, $J = 5.6$ Hz, 1H), 4.17–4.11 (m, 3H), 3.92 (br d, $J = 11.0$ Hz, 1H), 3.81 (d, $J = 2.6$ Hz, 1H), 3.70 (br d, $J = 10.8$ Hz, 1H), 3.66 (dd, $J = 9.4, 2.6$ Hz, 1H), 3.16–3.12 (m, 1H), 2.94 (dd, $J = 10.8, 4.2$ Hz, 1H), 2.57 (br, 1H), 2.34 (s, 3H), 2.07 (s, 3H), 2.04–2.02 (m, 2H), 1.97–1.93 (m, 1H), 1.85–1.80 (m, 1H), 1.30–1.24 (m, 4H), 0.87 (t, $J = 6.7$ Hz, 3H), 0.17 (s, 9H), 0.12 (s, 9H), 0.11 (s, 9H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 174.8, 88.3, 72.6 ($2 \times \text{C}$), 70.9, 69.0, 68.9, 62.9, 62.8, 50.0, 42.0, 38.3, 37.8, 35.8, 21.7, 14.4, 12.7, 0.9, 0.5, 0.3.

FTIR (neat, cm^{-1}): 2957 (m), 1659 (m), 1518 (m), 1250 (m), 1132 (m), 1070 (m), 893 (s), 839 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{26}\text{H}_{56}\text{N}_2\text{O}_6\text{SSi}_3$, 609.3240; found 609.3259.



Synthetic lincosamide 47.

In a 1-mL glass vial fitted with a magnetic stir bar and a PTFE-lined screw cap, 2,3,4-tris-*O*-trimethylsilyl-8-norlincomycin (**S31**, 20 mg, 33 μmol , 1 equiv) was dissolved in chloroform (160 μL). Triethylamine (11 μL , 82 μmol , 2.5 equiv) was added, the vial was sealed, and the solution was chilled to 0 $^\circ\text{C}$. Methanesulfonyl chloride (5.1 μL , 66 μmol , 2.0 equiv) was then added, the vial re-sealed, and the mixture stirred at 0 $^\circ\text{C}$ for 5 min, whereupon TLC analysis (10% methanol–dichloromethane, PAA) revealed that all of the starting material had been consumed. The reaction mixture was diluted with dichloromethane (1 mL), and the diluted mixture was transferred to a separatory funnel containing hexanes (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The biphasic mixture was shaken vigorously for 1 min before the layers were separated; the aqueous layer was extracted with fresh hexanes ($2 \times 5 \text{ mL}$), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (5 mL). The washed organic solution was dried over sodium sulfate, filtered, and concentrated to give crude methanesulfonate ester intermediate as a white solid. This material was transferred to a 4-mL glass vial and was dried by azeotropic removal of benzene before sodium azide (21 mg, 330 μmol , 10 equiv) and *N,N*-dimethylformamide (330 μL) were added. The vial was sealed with a PTFE-lined screw cap, and the reaction mixture was heated to 60 $^\circ\text{C}$ in a pre-heated oil bath. After 18 h, LCMS analysis showed that all the intermediate sulfonate ester had been consumed, and the product mixture was transferred to a separatory funnel containing 50% v/v saturated aqueous

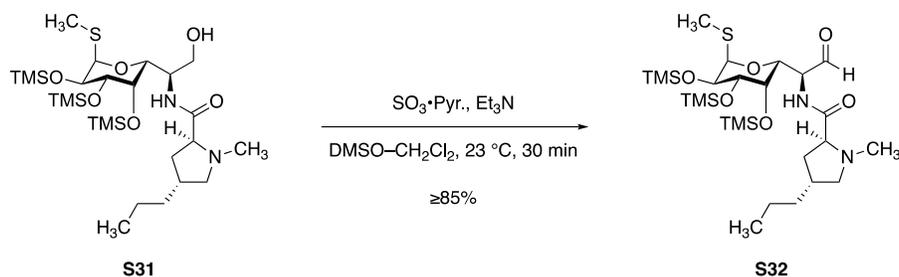
sodium bicarbonate solution–saturated aqueous sodium chloride solution (10 mL). This mixture was then extracted with ethyl acetate (4 × 5 mL), the combined organic extracts were dried over sodium sulfate, the dried product solution was filtered, and the filtrate was concentrated. The residue thus obtained was then re-dissolved in 50% v/v methanol–1N aqueous hydrogen chloride solution; after 30 min of stirring this mixture, LCMS analysis showed that global desilylation was complete, and the mixture was passed through a 0.2- μ m PTFE filter. The filtrate was concentrated, and the crude residue was subjected to preparative HPLC on a Waters SunFire Prep C₁₈ column (5 μ m, 250 × 19 mm; eluting with 0.1% trifluoroacetic acid–water, grading to 0.1% trifluoroacetic acid–40% acetonitrile–water over 40 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 210 nm; R_t = 28.6 min) to provide azide analog **47** • CF₃CO₂H as a white solid (8.4 mg, 48%).

¹H NMR (600 MHz, CD₃OD) δ 5.29 (d, *J* = 5.7 Hz, 1H), 4.42 (ddd, *J* = 9.3, 5.8, 3.3 Hz, 1H), 4.22 (dd, *J* = 9.5, 1.3 Hz, 1H), 4.18 (dd, *J* = 9.7, 6.6 Hz, 1H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1H), 3.85 (dd, *J* = 3.4, 1.3 Hz, 1H), 3.77 (dd, *J* = 11.1, 6.8 Hz, 1H), 3.69 (dd, *J* = 12.7, 3.4 Hz, 1H), 3.59 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.53 (dd, *J* = 12.7, 5.9 Hz, 1H), 2.94 (s, 3H), 2.89 (app t, *J* = 11.0 Hz, 1H), 2.39–2.32 (m, 1H), 2.29–2.24 (m, 2H), 2.10 (s, 3H), 1.52–1.45 (m, 2H), 1.39–1.34 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CD₃OD) δ 169.0, 89.5, 72.0, 69.9, 69.8, 69.6, 69.4, 62.3, 52.7, 50.8, 41.1, 38.0, 36.4, 35.7, 22.1, 14.2, 13.1.

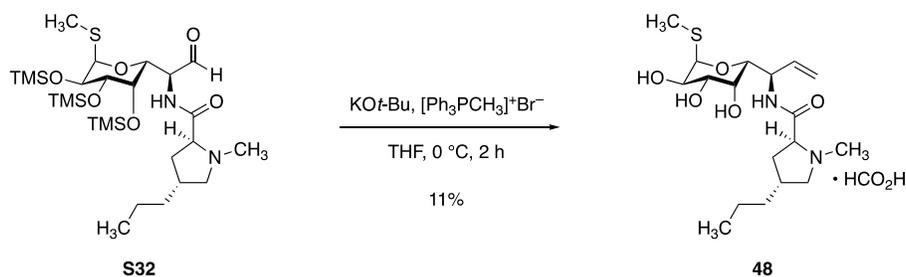
FTIR (neat, cm⁻¹): 3367 (br), 2927 (w), 2105 (s), 1671 (s), 1453 (m), 1202 (s), 1136 (m).

HRMS (ESI+, *m/z*): [M+H]⁺ calc'd for C₁₇H₃₁N₅O₅S, 418.2119; found 418.2132.



Aldehyde **S32**.

To a solution of 2,3,4-tris-*O*-trimethylsilyl-8-norlincomycin (**S31**, 50 mg, 82 μmol , 1 equiv) in dichloromethane (660 μL) and dimethyl sulfoxide (160 μL) were added triethylamine (92 μL , 660 μmol , 8.0 equiv) and sulfur trioxide–pyridine complex (52 mg, 330 μmol , 4.0 equiv) at 23 $^\circ\text{C}$. After 15 min, TLC analysis (10% methanol–dichloromethane, PAA) showed that reaction progress had stalled, and additional portions of triethylamine (92 μL , 660 μmol , 8.0 equiv) and sulfur trioxide–pyridine complex (52 mg, 330 μmol , 4.0 equiv) were added. After an additional 15 min of stirring at 23 $^\circ\text{C}$, TLC analysis showed the reaction was complete. The mixture was diluted with dichloromethane (10 mL), and the diluted solution was transferred to a separatory funnel containing saturated aqueous sodium bicarbonate solution (10 mL). The layers were shaken vigorously, then separated, and the aqueous phase was extracted with fresh portions of dichloromethane (3×5 mL). The combined organic extracts were then washed with saturated aqueous sodium chloride solution (10 mL) before being dried over sodium sulfate, filtered, and concentrated to provide crude aldehyde **S32** as a dull white solid. This material was unstable toward column chromatography, and thus an analytically pure sample could not be obtained; instead, purity of $\geq 85\%$ was assumed based on crude ^1H NMR analysis (CDCl_3), and this material was used directly in subsequent transformations, after which 2-step yields were determined.



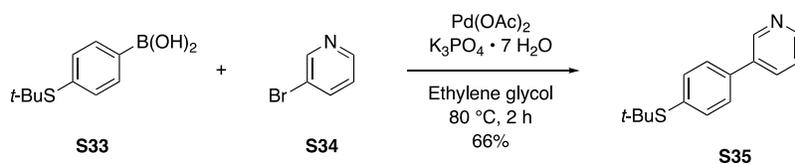
Synthetic lincosamide 48.

An oven-dried 4-mL glass vial was charged with a magnetic stir bar, methyltriphenylphosponium bromide (16 mg, 46 μmol , 1.4 equiv), and tetrahydrofuran (330 μL). The vial was sealed with a silicone septum-lined screw cap, and the mixture was chilled to 0 $^\circ\text{C}$ before potassium *tert*-butoxide solution (1.0 M in tetrahydrofuran, 40 μL , 40 μmol , 1.2 equiv) was added. Upon treatment with alkoxide base, the heterogeneous mixture immediately attained a vibrant, highlighter-yellow color. This mixture was stirred at 0 $^\circ\text{C}$ for 30 min before a solution of aldehyde **3.83** (theoretically 20 mg, 33 μmol , 1 equiv) in tetrahydrofuran (330 μL) was added by cannula, causing the yellow color to disappear. After 5 min of stirring at 0 $^\circ\text{C}$, TLC analysis (7% methanol–dichloromethane, PAA) revealed that no starting material remained, and excess Wittig reagent was quenched with the addition of acetone (150 μL). The product mixture was diluted with hexanes (15 mL), dried over sodium sulfate, filtered, and concentrated to give a white film that was re-dissolved in 50% v/v methanol–1N aqueous hydrogen chloride solution (1.5 mL). This mixture was stirred at 23 $^\circ\text{C}$ for 1 h, at which point LCMS analysis indicated that global desilylation was complete. The mixture was passed through a 0.2- μm PTFE filter, the filtrate was concentrated, and the crude residue was purified by preparative HPLC-MS on a Waters SunFire Prep C₁₈ column (5 μm , 250 \times 19 mm; eluting with 0.1% formic acid–water, grading to 0.1% formic acid–35% acetonitrile–water over 40 min, with a flow rate of 15 mL/min; monitored by

UV absorbance at 210 nm and ESI+ selected ion monitoring [$m/z = 389$]; $R_t = 18.9$ min) to provide vinyl analog **48** • HCO₂H as a white solid (1.5 mg, 11%, 2 steps).

¹H NMR (600 MHz, CD₃OD) δ 8.37 (s, 1H), 6.01 (ddd, $J = 17.3, 10.5, 5.5$ Hz, 1H), 5.28 (d, $J = 5.6$ Hz, 1H), 5.23 (app dt, $J = 17.3, 1.5$ Hz, 1H), 5.21 (app dt, $J = 10.4, 1.4$ Hz, 1H), 4.71 (app ddt, $J = 8.5, 5.5, 1.6$ Hz, 1H), 4.11 (dd, $J = 10.1, 5.7$ Hz, 1H), 4.09 (dd, $J = 8.2, 0.8$ Hz, 1H), 3.88 (dd, $J = 3.5, 1.3$ Hz, 1H), 3.59 (dd, $J = 10.1, 3.3$ Hz, 1H), 3.44–3.41 (m, 1H), 2.59 (s, 3H), 2.38 (app t, $J = 10.0$ Hz, 1H), 2.30–2.23 (m, 1H), 2.08 (ddd, $J = 13.5, 8.3, 5.4$ Hz, 1H), 2.04 (s, 3H), 2.01–1.95 (m, 1H), 1.42–1.32 (m, 4H), 0.94 (t, $J = 7.1$ Hz, 3H).

HRMS (ESI+, m/z): [M+H]⁺ calc'd for C₁₈H₃₂N₂O₅S, 389.2105; found 389.2111.



***tert*-Butane sulfide S35.**

Ligand-free Suzuki coupling was performed according to the method of Liu, Han, Song, and Qiu.³¹ Taking no special precautions to exclude air or moisture, a 300-mL round-bottomed flask was charged with a magnetic stir bar, (4-(*tert*-butylthio)phenyl)boronic acid (**S33**, 4.79 g, 22.8 mmol, 1.20 equiv), potassium phosphate heptahydrate (12.9 g, 38.0 mmol, 2.00 equiv), palladium(II) acetate (43.0 mg, 0.190 mmol, 0.0100 equiv), and ethylene glycol (146 mL). 3-Bromopyridine (**S34**, 1.83 mL, 19.0 mmol, 1 equiv) was added last, stirring was initiated, and the reaction mixture was heated to 80 °C (open to the atmosphere) in a pre-heated oil bath. Within 30 min, the suspension had clarified, forming an amber-brown homogeneous solution; and after 1 h, the mixture became a light tan, turbid suspension. After 2 h of stirring at 80 °C, TLC analysis (60% ethyl acetate–hexanes, UV) showed that no starting material remained. The mixture was cooled to 23 °C and was then poured into a separatory funnel containing saturated aqueous sodium chloride solution (250 mL). The aqueous suspension was extracted with ethyl ether (4 × 50 mL), and the combined organic extracts were washed with a fresh portion of saturated aqueous sodium chloride solution (50 mL). The washed organic product solution was then dried over sodium sulfate, filtered, and concentrated to give a milky, light yellow oil that was purified by flash-column chromatography (120 g silica gel, eluting with 10% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes) to provide the product as a brilliant white, fluffy powder (3.04 g, 66%).

³¹ Liu, C.; Han, N.; Song, X.; Qiu, J. *Eur. J. Org. Chem.* **2010**, 5548–5551.

Melting point: 55–57 °C.

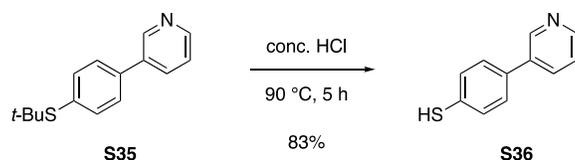
$R_f = 0.37$ (60% ethyl acetate–hexanes, UV).

$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.86 (d, $J = 1.7$ Hz, 1H), 8.61 (dd, $J = 4.7, 1.6$ Hz, 1H), 7.88 (ddd, $J = 7.9, 2.4, 1.6$ Hz, 1H), 7.64 (d, $J = 8.3$ Hz, 2H), 7.55 (d, $J = 8.2$ Hz, 2H), 7.38 (ddd, $J = 7.8, 4.8, 0.9$ Hz, 1H), 1.33 (s, 9H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 148.9, 148.4, 138.2 ($2 \times \text{C}$), 136.0, 134.4, 133.0, 127.2, 123.7, 46.4, 31.1.

FTIR (neat, cm^{-1}): 2960 (s), 1573 (w), 1471 (s), 1363 (s), 1168 (m), 1001 (m), 800 (s), 711 (s), 561 (m).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{15}\text{H}_{17}\text{NS}$, 244.1154; found 244.1167.



Biaryl thiol 2.39b.

In a 500-mL round-bottomed flask containing a magnetic stir bar, *tert*-butanesulfide **S35** (3.00 g, 12.3 mmol, 1 equiv) and concentrated hydrochloric acid (38% w/w in water, 123 mL) were combined. The headspace was flushed with argon, and the mixture was heated to 90 °C with constant stirring; the starting material gradually dissolved upon warming. After 5 h, LCMS analysis showed that no starting material remained, and the reaction mixture was cooled to 0 °C. The chilled solution was basified with the careful addition of aqueous 6N sodium hydroxide solution, until pH = 8 was achieved. The aqueous mixture was then extracted with ethyl ether (4 × 75 mL), the combined extracts were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to give a colorless oil. This crude residue was finally purified by flash-column chromatography (80 g silica gel, eluting with 20% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes) to provide arenethiol product as a light yellow solid (1.92 g, 83%).

Melting point: 42–44 °C.

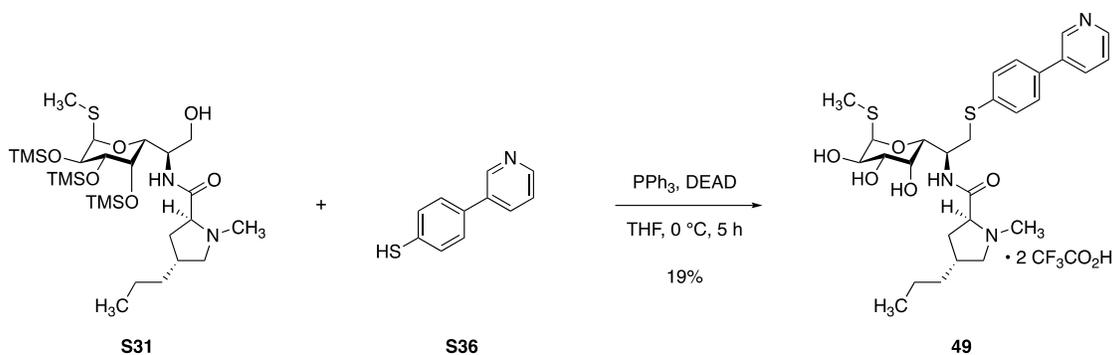
R_f = 0.23 (60% ethyl acetate–hexanes, UV).

^1H NMR (600 MHz, CDCl_3) δ 8.79 (d, J = 2.4 Hz, 1H), 8.56 (dd, J = 4.8, 1.6 Hz, 1H), 7.79 (dt, J = 7.9, 2.0 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.32 (dd, J = 7.9, 4.9 Hz, 1H), 3.55 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 148.5, 148.0, 135.8, 135.1, 134.0, 131.4, 129.8, 127.7, 123.6.

FTIR (neat, cm^{-1}): 3027 (m), 2398 (br), 1903 (w), 1597 (m), 1468 (s), 1423 (m), 1393 (m), 1185 (m), 1103 (s), 1000 (s), 794 (s), 708 (s), 547 (s).

HRMS (ESI+, m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{11}\text{H}_9\text{NS}$, 188.0528; found 188.0526.

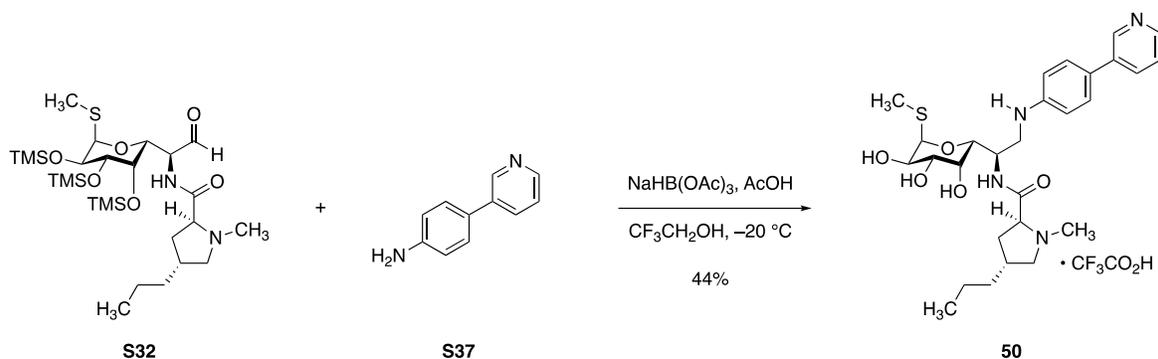


Synthetic lincosamide **49**.

In a 1-mL glass vial, 2,3,4-tris-*O*-trimethylsilyl-8-norlincomycin (**S31**, 20 mg, 33 μ mol, 1 equiv) and triphenylphosphine (17 mg, 66 μ mol, 2.0 equiv) were dissolved in tetrahydrofuran (660 μ L), and the resulting solution was chilled to 0 $^{\circ}$ C. With constant stirring, diethyl azodicarboxylate solution (40% w/w in toluene, 30 μ L, 66 μ mol, 2.0 equiv) was added dropwise, and the mixture was stirred at 0 $^{\circ}$ C for 5 min, during which time the original orange color of the azodicarboxylate reagent faded to afford a colorless reaction mixture. 4-(Pyridin-3-yl)benzenethiol (**S36**, 15 mg, 82 μ mol, 2.5 equiv) was added next, resulting in a flash of yellow-orange color that then disappeared. Progress was monitored by LCMS, and after 5 h, the reaction was judged to be complete. The mixture was concentrated to dryness under a stream of nitrogen, and the residue was then re-dissolved in 50% v/v methanol–1N aqueous hydrogen chloride solution (800 μ L). After 30 min of stirring at 23 $^{\circ}$ C, LCMS analysis showed that global desilylation was complete, and the mixture was passed through a 0.2- μ m PTFE filter. The filtrate was concentrated, and the crude residue was subjected to preparative HPLC on a Waters SunFire Prep C₁₈ column (5 μ m, 250 \times 19 mm; eluting with 0.1% trifluoroacetic acid–water, grading to 0.1% trifluoroacetic acid–40% acetonitrile–water over 40 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 254 nm; R_t = 27.8 min) to provide arenesulfide analog **49** \cdot 2 CF₃CO₂H as a white solid (4.8 mg, 19%).

^1H NMR (600 MHz, CD_3OD) δ 9.09 (s, 1H), 8.75 (d, $J = 4.9$ Hz, 1H), 8.70 (d, $J = 8.2$ Hz, 1H), 8.00 (dd, $J = 8.2, 5.4$ Hz, 1H), 7.75 (d, $J = 8.5$ Hz, 2H), 7.54 (d, $J = 8.5$ Hz, 2H), 5.33 (d, $J = 5.6$ Hz, 1H), 4.50 (app td, $J = 9.0, 3.4$ Hz, 1H), 4.24 (dd, $J = 8.8, 1.3$ Hz, 1H), 4.16 (dd, $J = 9.8, 6.3$ Hz, 1H), 4.11 (dd, $J = 10.1, 5.6$ Hz, 1H), 3.90 (dd, $J = 3.4, 1.2$ Hz, 1H), 3.74 (dd, $J = 11.1, 6.8$ Hz, 1H), 3.70 (dd, $J = 14.0, 3.5$ Hz, 1H), 3.60 (dd, $J = 10.1, 3.3$ Hz, 1H), 3.14 (dd, $J = 14.0, 9.2$ Hz, 1H), 2.92 (s, 3H), 2.86 (app t, $J = 11.1$ Hz, 1H), 2.34–2.26 (m, 1H), 2.22–2.15 (m, 2H), 2.11 (s, 3H), 1.46–1.39 (m, 2H), 1.33–1.28 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H).

HRMS (ESI+, m/z): $[\text{M}+2\text{H}]^{2+}$ calc'd for $\text{C}_{28}\text{H}_{39}\text{N}_3\text{O}_5\text{S}_2$, 281.6238; found 281.6238.



Synthetic lincosamide **50**.

A 4-mL glass vial fitted with a PTFE-lined screw cap was charged with a magnetic stir bar, aldehyde **S32** (theoretically 10 mg, 16 μmol , 1 equiv), 2,2,2-trifluoroethanol (330 μL), and powdered, activated 4 \AA molecular sieves (10 mg). The suspension was chilled to $-20\text{ }^\circ\text{C}$ in an acetone bath, whereupon acetic acid (5.7 μL , 99 μmol , 6.0 equiv) was added. 4-(Pyridin-3-yl)aniline (**S37**, 8.4 mg, 49 μmol , 3.0 equiv) was added next, causing the mixture to turn tennis-ball yellow; and the mixture was stirred at $-20\text{ }^\circ\text{C}$ for 15 min before the mixture was treated with sodium triacetoxyborohydride (10 mg, 49 μmol , 3.0 equiv). After 30 min, LCMS analysis showed complete consumption of aldehyde starting material and imine intermediate. The mixture was warmed to $23\text{ }^\circ\text{C}$ and was concentrated to dryness before being re-suspended in 50% v/v methanol–1N aqueous hydrogen chloride solution. After 5 min of stirring at $23\text{ }^\circ\text{C}$, LCMS analysis showed that global desilylation was complete, and the yellow mixture was filtered through a 0.2- μm PTFE filter. The filtrate was concentrated, and the crude residue was purified by preparative HPLC on a Waters SunFire Prep C₁₈ column (5 μm , 250 \times 19 mm; eluting with 0.1% trifluoroacetic acid–water, grading to 0.1% trifluoroacetic acid–50% acetonitrile–water over 40 min, with a flow rate of 15 mL/min; monitored by UV absorbance at 280 nm; $R_t = 22.2$ min) to provide (pyridyl)aniline analog **50** \cdot CF₃CO₂H as a white solid (5.6 mg, 44%, 2 steps).

^1H (500 MHz, CD_3OD) δ 9.03 (d, $J = 2.1$ Hz, 1H), 8.77 (ddd, $J = 8.4, 2.3, 1.3$ Hz, 1H), 8.62 (dd, $J = 5.6, 1.1$ Hz, 1H), 8.03 (dd, $J = 8.3, 5.6$ Hz, 1H), 7.63 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 5.35 (d, $J = 5.6$ Hz, 1H), 4.50 (app td, $J = 9.1, 3.9$ Hz, 1H), 4.25 (d, $J = 8.9$ Hz, 1H), 4.16–4.11 (m, 2H), 3.91 (dd, $J = 3.3, 1.1$ Hz, 1H), 3.72–3.66 (m, 2H), 3.62 (dd, $J = 10.1, 3.3$ Hz, 1H), 3.37 (dd, $J = 14.1, 9.3$ Hz, 1H), 2.91 (s, 3H), 2.83 (app t, $J = 11.0$ Hz, 1H), 2.23–2.16 (m, 1H), 2.09 (s, 3H), 2.09–2.00 (m, 2H), 1.43–1.30 (m, 2H), 1.27–1.19 (m, 2H), 0.84 (t, $J = 7.2$ Hz, 3H).

HRMS (ESI+, m/z): $[\text{M}+2\text{H}]^{2+}$ calc'd for $\text{C}_{28}\text{H}_{40}\text{N}_4\text{O}_5\text{S}$, 273.1432; found 273.1432.

Catalog of X-ray Crystal Structures

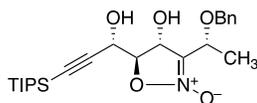
X-Ray Crystallography: Data were collected from a crystal mounted on a diffractometer at 100 K. The intensities of the reflections were collected using a Bruker APEX II DUO CCD diffractometer (CuK α radiation, $\lambda=1.54178$ Å) equipped with an Oxford Cryosystems nitrogen-flow apparatus. The collection method involved 1.0° scans in ω at -30°, -55°, -80°, 30°, 55°, 80° and 115° in 2θ . Data integration down to 0.84-Å resolution was carried out using SAINT V8.34 C with reflection spot size optimization. Absorption corrections were made with the program SADABS.³² The structure was solved by the intrinsic-phasing method and was refined against F^2 by least-squares using SHELXT-2014 and SHELXL-2014³³ through the OLEX 2 interface. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at idealized positions and were refined using a riding model. Crystal data as well as details of data collection and refinement are summarized in Tables S1, S4, and S7; geometric parameters are shown in Tables S2, S5, and S8; and hydrogen-bond geometric parameters are listed in Tables S3, S6, and S9. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.³⁴

³² Bruker AXS APEX3, Bruker AXS, Madison, Wisconsin, 2015.

³³ Sheldrick, G. M. *Acta Cryst.* **2015**, *A71*, 3–8. Sheldrick, G. M. *Acta Cryst.* **2015**, *C21*, 3–8.

³⁴ Accelrys DS Visualizer v2.0.1, Accelrys Software, Inc., 2007.

Crystallographic Data for Compound 17



17

Table S1. Experimental details

CCDC Deposition Number 2072279	
Chemical formula	C ₂₄ H ₃₇ NO ₅ Si
<i>M_r</i>	447.63
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	11.7798 (16), 6.7133 (10), 19.712 (3)
β (°)	103.006 (7)
<i>V</i> (Å ³)	1518.8 (4)
<i>Z</i>	2
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	0.90
Crystal size (mm)	0.12 × 0.01 × 0.01
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer
Absorption correction	Multi-scan <i>SADABS</i>
<i>T_{min}</i> , <i>T_{max}</i>	0.683, 0.864
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	22195, 4853, 3617
<i>R_{int}</i>	0.109
(sin θ/λ) _{max} (Å ⁻¹)	0.596
Refinement	
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.084, 0.231, 1.04
No. of reflections	4853
No. of parameters	314
No. of restraints	85
H-atom treatment	H-atom parameters constrained

Table S1 (Continued)

$\Delta\rho_{\max}, \Delta\rho_{\min}$ ($e \text{ \AA}^{-3}$)	0.49, -0.26
Absolute structure	Flack x determined using 1118 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.05 (5)

Computer programs: *APEX3* v2015.5.2 (Bruker-AXS, 2015), *SAINT* 8.34C (Bruker-AXS, 2014), *SHELXT2014* (Sheldrick, 2015), *SHELXL2014* (Sheldrick, 2015), Bruker *SHELXTL* (Sheldrick, 2015).

Table S2. Geometric parameters (\AA , $^\circ$)

C1—C6	1.361 (10)	C20—H20A	0.9800
C1—C2	1.385 (10)	C20—H20B	0.9800
C1—H1	0.9500	C20—H20C	0.9800
C2—C3	1.374 (13)	C21—H21A	0.9800
C2—H2	0.9500	C21—H21B	0.9800
C3—C4	1.392 (14)	C21—H21C	0.9800
C3—H3	0.9500	C22—C24	1.50 (2)
C4—C5	1.370 (10)	C22—C23	1.57 (2)
C4—H4	0.9500	C22—H22	1.0000
C5—C6	1.392 (11)	C23—H23A	0.9800
C5—H5	0.9500	C23—H23B	0.9800
C6—C7	1.506 (8)	C23—H23C	0.9800
C7—O1	1.430 (9)	C24—H24A	0.9800
C7—H7A	0.9900	C24—H24B	0.9800
C7—H7B	0.9900	C24—H24C	0.9800
C8—O1	1.416 (7)	C14A—C15A	1.248 (19)
C8—C10	1.495 (9)	C15A—Si1A	1.90 (2)
C8—C9	1.510 (10)	Si1A—C16A	1.82 (2)
C8—H8	1.0000	Si1A—C22A	1.94 (2)
C9—H9A	0.9800	Si1A—C19A	1.96 (3)
C9—H9B	0.9800	C16A—C18A	1.53 (3)
C9—H9C	0.9800	C16A—C17A	1.61 (3)
C10—N1	1.312 (8)	C16A—H16A	1.0000
C10—C11	1.504 (9)	C17A—H17D	0.9800

Table S2 (Continued)

C11—O4	1.413 (8)	C17A—H17E	0.9800
C11—C12	1.555 (9)	C17A—H17F	0.9800
C11—H11	1.0000	C18A—H18D	0.9800
C12—O2	1.451 (7)	C18A—H18E	0.9800
C12—C13	1.510 (9)	C18A—H18F	0.9800
C12—H12	1.0000	C19A—C20A	1.36 (3)
C13—O5	1.422 (8)	C19A—C21A	1.47 (3)
C13—C14A	1.475 (9)	C19A—H19A	1.0000
C13—C14	1.475 (9)	C20A—H20D	0.9800
C13—H13	1.0000	C20A—H20E	0.9800
C13—H13A	1.0000	C20A—H20F	0.9800
C14—C15	1.199 (12)	C21A—H21D	0.9800
C15—Si1	1.851 (13)	C21A—H21E	0.9800
Si1—C16	1.854 (12)	C21A—H21F	0.9800
Si1—C19	1.881 (16)	C22A—C24A	1.49 (3)
Si1—C22	1.931 (17)	C22A—C23A	1.59 (3)
C16—C18	1.560 (17)	C22A—H22A	1.0000
C16—C17	1.61 (2)	C23A—H23D	0.9800
C16—H16	1.0000	C23A—H23E	0.9800
C17—H17A	0.9800	C23A—H23F	0.9800
C17—H17B	0.9800	C24A—H24D	0.9800
C17—H17C	0.9800	C24A—H24E	0.9800
C18—H18A	0.9800	C24A—H24F	0.9800
C18—H18B	0.9800	N1—O3	1.261 (7)
C18—H18C	0.9800	N1—O2	1.424 (7)
C19—C20	1.36 (2)	O4—H4A	0.8400
C19—C21	1.50 (2)	O5—H5A	0.8400
C19—H19	1.0000		
C6—C1—C2	122.8 (8)	C19—C20—H20C	109.5
C6—C1—H1	118.6	H20A—C20—H20C	109.5
C2—C1—H1	118.6	H20B—C20—H20C	109.5
C3—C2—C1	117.8 (7)	C19—C21—H21A	109.5
C3—C2—H2	121.1	C19—C21—H21B	109.5
C1—C2—H2	121.1	H21A—C21—H21B	109.5

C2—C3—C4	121.5 (7)	C19—C21—H21C	109.5
C2—C3—H3	119.2	H21A—C21—H21C	109.5
C4—C3—H3	119.2	H21B—C21—H21C	109.5
C5—C4—C3	118.3 (9)	C24—C22—C23	111.7 (18)
C5—C4—H4	120.9	C24—C22—Si1	116.5 (14)
C3—C4—H4	120.9	C23—C22—Si1	106.8 (13)
C4—C5—C6	121.9 (8)	C24—C22—H22	107.1
C4—C5—H5	119.1	C23—C22—H22	107.1
C6—C5—H5	119.1	Si1—C22—H22	107.1
C1—C6—C5	117.7 (6)	C22—C23—H23A	109.5
C1—C6—C7	123.6 (7)	C22—C23—H23B	109.5
C5—C6—C7	118.6 (6)	H23A—C23—H23B	109.5
O1—C7—C6	108.4 (5)	C22—C23—H23C	109.5
O1—C7—H7A	110.0	H23A—C23—H23C	109.5
C6—C7—H7A	110.0	H23B—C23—H23C	109.5
O1—C7—H7B	110.0	C22—C24—H24A	109.5
C6—C7—H7B	110.0	C22—C24—H24B	109.5
H7A—C7—H7B	108.4	H24A—C24—H24B	109.5
O1—C8—C10	111.2 (6)	C22—C24—H24C	109.5
O1—C8—C9	106.4 (5)	H24A—C24—H24C	109.5
C10—C8—C9	113.4 (6)	H24B—C24—H24C	109.5
O1—C8—H8	108.6	C15A—C14A—C13	170 (4)
C10—C8—H8	108.6	C14A—C15A—Si1A	172 (7)
C9—C8—H8	108.6	C16A—Si1A—C15A	110 (2)
C8—C9—H9A	109.5	C16A—Si1A—C22A	125.3 (15)
C8—C9—H9B	109.5	C15A—Si1A—C22A	109 (3)
H9A—C9—H9B	109.5	C16A—Si1A—C19A	112.3 (16)
C8—C9—H9C	109.5	C15A—Si1A—C19A	106 (3)
H9A—C9—H9C	109.5	C22A—Si1A—C19A	90.8 (17)
H9B—C9—H9C	109.5	C18A—C16A—C17A	115 (2)
N1—C10—C8	121.0 (6)	C18A—C16A—Si1A	102 (2)
N1—C10—C11	109.4 (5)	C17A—C16A—Si1A	113 (2)
C8—C10—C11	129.6 (5)	C18A—C16A—H16A	108.7
O4—C11—C10	113.5 (5)	C17A—C16A—H16A	108.7
O4—C11—C12	113.2 (5)	Si1A—C16A—H16A	108.7
C10—C11—C12	103.2 (5)	C16A—C17A—H17D	109.5
O4—C11—H11	108.9	C16A—C17A—H17E	109.5

Table S2 (Continued)

C10—C11—H11	108.9	H17D—C17A—H17E	109.5
C12—C11—H11	108.9	C16A—C17A—H17F	109.5
O2—C12—C13	108.6 (5)	H17D—C17A—H17F	109.5
O2—C12—C11	105.6 (5)	H17E—C17A—H17F	109.5
C13—C12—C11	114.4 (5)	C16A—C18A—H18D	109.5
O2—C12—H12	109.3	C16A—C18A—H18E	109.5
C13—C12—H12	109.3	H18D—C18A—H18E	109.5
C11—C12—H12	109.3	C16A—C18A—H18F	109.5
O5—C13—C14A	111.8 (5)	H18D—C18A—H18F	109.5
O5—C13—C14	111.8 (5)	H18E—C18A—H18F	109.5
O5—C13—C12	109.5 (5)	C20A—C19A—C21A	111 (3)
C14A—C13—C12	108.9 (6)	C20A—C19A—Si1A	110 (3)
C14—C13—C12	108.9 (6)	C21A—C19A—Si1A	114 (3)
O5—C13—H13	108.9	C20A—C19A—H19A	106.9
C14—C13—H13	108.9	C21A—C19A—H19A	106.9
C12—C13—H13	108.9	Si1A—C19A—H19A	106.9
O5—C13—H13A	108.9	C19A—C20A—H20D	109.5
C14A—C13—H13A	108.9	C19A—C20A—H20E	109.5
C12—C13—H13A	108.9	H20D—C20A—H20E	109.5
C15—C14—C13	173.3 (17)	C19A—C20A—H20F	109.5
C14—C15—Si1	168 (3)	H20D—C20A—H20F	109.5
C15—Si1—C16	104.6 (11)	H20E—C20A—H20F	109.5
C15—Si1—C19	108.3 (14)	C19A—C21A—H21D	109.5
C16—Si1—C19	111.1 (8)	C19A—C21A—H21E	109.5
C15—Si1—C22	103.5 (9)	H21D—C21A—H21E	109.5
C16—Si1—C22	111.5 (7)	C19A—C21A—H21F	109.5
C19—Si1—C22	116.8 (9)	H21D—C21A—H21F	109.5
C18—C16—C17	111.7 (13)	H21E—C21A—H21F	109.5
C18—C16—Si1	109.4 (8)	C24A—C22A—C23A	112 (3)
C17—C16—Si1	114.1 (12)	C24A—C22A—Si1A	114 (3)
C18—C16—H16	107.1	C23A—C22A—Si1A	104 (2)
C17—C16—H16	107.1	C24A—C22A—H22A	108.8
Si1—C16—H16	107.1	C23A—C22A—H22A	108.8
C16—C17—H17A	109.5	Si1A—C22A—H22A	108.8
C16—C17—H17B	109.5	C22A—C23A—H23D	109.5

Table S2 (Continued)

H17A—C17—H17B	109.5	C22A—C23A—H23E	109.5
C16—C17—H17C	109.5	H23D—C23A—H23E	109.5
H17A—C17—H17C	109.5	C22A—C23A—H23F	109.5
H17B—C17—H17C	109.5	H23D—C23A—H23F	109.5
C16—C18—H18A	109.5	H23E—C23A—H23F	109.5
C16—C18—H18B	109.5	C22A—C24A—H24D	109.5
H18A—C18—H18B	109.5	C22A—C24A—H24E	109.5
C16—C18—H18C	109.5	H24D—C24A—H24E	109.5
H18A—C18—H18C	109.5	C22A—C24A—H24F	109.5
H18B—C18—H18C	109.5	H24D—C24A—H24F	109.5
C20—C19—C21	109.7 (19)	H24E—C24A—H24F	109.5
C20—C19—Si1	116.0 (15)	O3—N1—C10	131.2 (6)
C21—C19—Si1	111.6 (15)	O3—N1—O2	114.7 (4)
C20—C19—H19	106.3	C10—N1—O2	114.1 (5)
C21—C19—H19	106.3	C8—O1—C7	113.6 (5)
Si1—C19—H19	106.3	N1—O2—C12	107.2 (4)
C19—C20—H20A	109.5	C11—O4—H4A	109.5
C19—C20—H20B	109.5	C13—O5—H5A	109.5
H20A—C20—H20B	109.5		
C6—C1—C2—C3	-0.4 (13)	C15—Si1—C16—C18	64.9 (15)
C1—C2—C3—C4	0.8 (13)	C19—Si1—C16—C18	-178.5 (10)
C2—C3—C4—C5	-0.5 (14)	C22—Si1—C16—C18	-46.4 (12)
C3—C4—C5—C6	0.0 (13)	C15—Si1—C16—C17	-61.1 (16)
C2—C1—C6—C5	-0.1 (12)	C19—Si1—C16—C17	55.5 (14)
C2—C1—C6—C7	179.2 (8)	C22—Si1—C16—C17	-172.4 (12)
C4—C5—C6—C1	0.3 (12)	C15—Si1—C19—C20	37 (2)
C4—C5—C6—C7	-179.0 (8)	C16—Si1—C19—C20	-77.8 (18)
C1—C6—C7—O1	-12.5 (9)	C22—Si1—C19—C20	152.8 (17)
C5—C6—C7—O1	166.8 (7)	C15—Si1—C19—C21	163.2 (17)
O1—C8—C10—N1	-114.6 (6)	C16—Si1—C19—C21	48.9 (19)
C9—C8—C10—N1	125.6 (7)	C22—Si1—C19—C21	-80.5 (18)
O1—C8—C10—C11	63.3 (9)	O5—C13—C14A—C15A	79 (28)
C9—C8—C10—C11	-56.4 (9)	C12—C13—C14A—C15A	-42 (28)
N1—C10—C11—O4	-117.9 (6)	C15A—Si1A—C16A—C18A	39 (4)

Table S2 (Continued)

C8—C10—C11—O4	64.0 (8)	C22A—Si1A—C16A—C18A	-95 (3)
N1—C10—C11—C12	4.9 (7)	C19A—Si1A—C16A—C18A	157 (2)
C8—C10—C11—C12	-173.2 (6)	C15A—Si1A—C16A—C17A	163 (4)
O4—C11—C12—O2	116.0 (5)	C22A—Si1A—C16A—C17A	29 (3)
C10—C11—C12—O2	-7.1 (6)	C19A—Si1A—C16A—C17A	-79 (2)
O4—C11—C12—C13	-124.6 (6)	C8—C10—N1—O3	-0.7 (11)
C10—C11—C12—C13	112.3 (6)	C11—C10—N1—O3	-179.0 (6)
O2—C12—C13—O5	67.1 (6)	C8—C10—N1—O2	177.5 (5)
C11—C12—C13—O5	-50.6 (7)	C11—C10—N1—O2	-0.9 (7)
O2—C12—C13—C14A	-170.4 (5)	C10—C8—O1—C7	65.1 (7)
C11—C12—C13—C14A	71.9 (7)	C9—C8—O1—C7	-171.1 (6)
O2—C12—C13—C14	-170.4 (5)	C6—C7—O1—C8	172.2 (5)
C11—C12—C13—C14	71.9 (7)	O3—N1—O2—C12	174.4 (5)
C14—C15—Si1—C16	-15 (11)	C10—N1—O2—C12	-4.0 (7)
C14—C15—Si1—C19	-134 (11)	C13—C12—O2—N1	-116.4 (5)
C14—C15—Si1—C22	102 (10)	C11—C12—O2—N1	6.8 (6)

Table S3. Hydrogen-bond parameters

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
O4—H4A \cdots O3 ⁱ	0.84	2.43	2.727 (6)	101.5
O5—H5A \cdots O2	0.84	2.46	2.871 (6)	111.1

Symmetry code(s): (i) $-x+1, y-1/2, -z+1$.

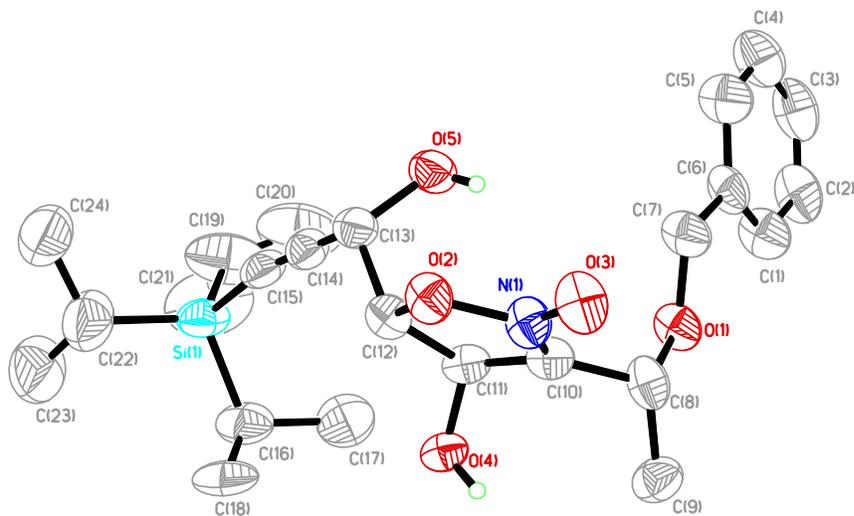


Figure S1. Perspective views showing 50% probability displacement

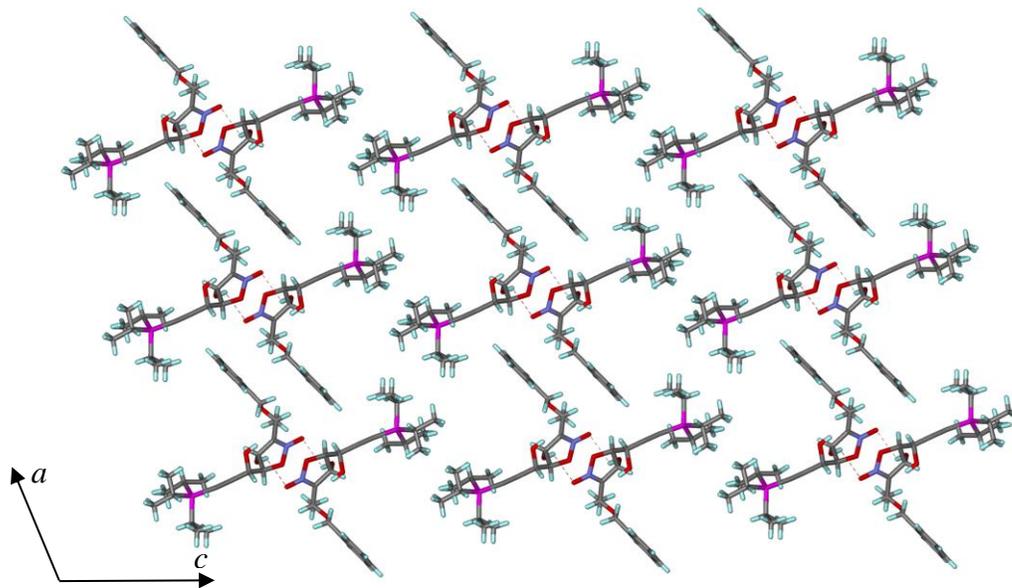
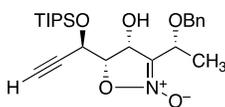


Figure S2. Three-dimensional supramolecular architecture viewed along the *b*-axis direction.

Crystallographic Data for Compound 22b



22b

Table S4. Experimental details

CCDC Deposition Number 2072280	
Chemical formula	C ₂₄ H ₃₇ NO ₅ Si
<i>M_r</i>	447.63
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	10.4700 (7), 6.9042 (4), 17.1454 (10)
β (°)	92.914 (5)
<i>V</i> (Å ³)	1237.79 (13)
<i>Z</i>	2
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	1.11
Crystal size (mm)	0.16 × 0.08 × 0.01
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer
Absorption correction	Multi-scan <i>SADABS</i>
<i>T_{min}</i> , <i>T_{max}</i>	0.688, 0.864
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	16287, 3956, 3393
<i>R_{int}</i>	0.081
(sin θ/λ) _{max} (Å ⁻¹)	0.596
Refinement	
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.055, 0.143, 1.10
No. of reflections	3956
No. of parameters	291
No. of restraints	1

Table S4 (Continued)

H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}, \Delta\rho_{\min}$ (e Å ⁻³)	0.32, -0.41
Absolute structure	Flack x determined using 1252 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.01 (5)

Computer programs: *APEX3* v2015.5.2 (Bruker-AXS, 2015), *SAINT* 8.34C (Bruker-AXS, 2014), *SHELXT2014* (Sheldrick, 2015), *SHELXL2014* (Sheldrick, 2015), Bruker *SHELXTL* (Sheldrick, 2015).

Table S5. Geometric parameters (Å, °)

C1—C2	1.184 (7)	C16—C17	1.534 (8)
C1—H1	0.9500	C16—C18	1.535 (7)
C2—C3	1.480 (7)	C16—Si1	1.885 (5)
C3—O1	1.419 (5)	C16—H16	1.0000
C3—C4	1.529 (6)	C17—H17A	0.9800
C3—H3	1.0000	C17—H17B	0.9800
C4—O4	1.454 (5)	C17—H17C	0.9800
C4—C5	1.537 (6)	C18—H18A	0.9800
C4—H4	1.0000	C18—H18B	0.9800
C5—O2	1.410 (6)	C18—H18C	0.9800
C5—C6	1.495 (6)	C19—C21	1.538 (7)
C5—H5	1.0000	C19—C20	1.542 (7)
C6—N1	1.300 (6)	C19—Si1	1.882 (6)
C6—C7	1.505 (6)	C19—H19	1.0000
C7—O3	1.426 (6)	C20—H20A	0.9800
C7—C15	1.516 (7)	C20—H20B	0.9800
C7—H7	1.0000	C20—H20C	0.9800
C8—O3	1.435 (6)	C21—H21A	0.9800
C8—C9	1.508 (7)	C21—H21B	0.9800
C8—H8A	0.9900	C21—H21C	0.9800
C8—H8B	0.9900	C22—C23	1.525 (7)
C9—C10	1.379 (8)	C22—C24	1.532 (7)

Table S5 (Continued)

C9—C14	1.392 (8)	C22—Si1	1.880 (5)
C10—C11	1.396 (7)	C22—H22	1.0000
C10—H10	0.9500	C23—H23A	0.9800
C11—C12	1.371 (9)	C23—H23B	0.9800
C11—H11	0.9500	C23—H23C	0.9800
C12—C13	1.385 (9)	C24—H24A	0.9800
C12—H12	0.9500	C24—H24B	0.9800
C13—C14	1.403 (8)	C24—H24C	0.9800
C13—H13	0.9500	N1—O5	1.259 (5)
C14—H14	0.9500	N1—O4	1.435 (4)
C15—H15A	0.9800	O1—Si1	1.672 (3)
C15—H15B	0.9800	O2—H2	0.84 (8)
C15—H15C	0.9800		
C2—C1—H1	180.0	C18—C16—H16	106.3
C1—C2—C3	176.0 (5)	Si1—C16—H16	106.3
O1—C3—C2	112.5 (3)	C16—C17—H17A	109.5
O1—C3—C4	105.6 (4)	C16—C17—H17B	109.5
C2—C3—C4	109.9 (4)	H17A—C17—H17B	109.5
O1—C3—H3	109.6	C16—C17—H17C	109.5
C2—C3—H3	109.6	H17A—C17—H17C	109.5
C4—C3—H3	109.6	H17B—C17—H17C	109.5
O4—C4—C3	107.5 (4)	C16—C18—H18A	109.5
O4—C4—C5	105.5 (3)	C16—C18—H18B	109.5
C3—C4—C5	115.0 (4)	H18A—C18—H18B	109.5
O4—C4—H4	109.6	C16—C18—H18C	109.5
C3—C4—H4	109.6	H18A—C18—H18C	109.5
C5—C4—H4	109.6	H18B—C18—H18C	109.5
O2—C5—C6	110.1 (4)	C21—C19—C20	110.6 (4)
O2—C5—C4	117.0 (4)	C21—C19—Si1	116.6 (4)
C6—C5—C4	99.9 (4)	C20—C19—Si1	113.9 (4)
O2—C5—H5	109.8	C21—C19—H19	104.8
C6—C5—H5	109.8	C20—C19—H19	104.8
C4—C5—H5	109.8	Si1—C19—H19	104.8
N1—C6—C5	110.2 (4)	C19—C20—H20A	109.5

Table S5 (Continued)

N1—C6—C7	121.0 (4)	C19—C20—H20B	109.5
C5—C6—C7	128.5 (4)	H20A—C20—H20B	109.5
O3—C7—C6	108.6 (4)	C19—C20—H20C	109.5
O3—C7—C15	107.1 (4)	H20A—C20—H20C	109.5
C6—C7—C15	112.0 (4)	H20B—C20—H20C	109.5
O3—C7—H7	109.7	C19—C21—H21A	109.5
C6—C7—H7	109.7	C19—C21—H21B	109.5
C15—C7—H7	109.7	H21A—C21—H21B	109.5
O3—C8—C9	109.9 (4)	C19—C21—H21C	109.5
O3—C8—H8A	109.7	H21A—C21—H21C	109.5
C9—C8—H8A	109.7	H21B—C21—H21C	109.5
O3—C8—H8B	109.7	C23—C22—C24	109.9 (4)
C9—C8—H8B	109.7	C23—C22—Si1	113.2 (4)
H8A—C8—H8B	108.2	C24—C22—Si1	113.9 (3)
C10—C9—C14	119.5 (5)	C23—C22—H22	106.4
C10—C9—C8	122.0 (5)	C24—C22—H22	106.4
C14—C9—C8	118.3 (5)	Si1—C22—H22	106.4
C9—C10—C11	120.4 (6)	C22—C23—H23A	109.5
C9—C10—H10	119.8	C22—C23—H23B	109.5
C11—C10—H10	119.8	H23A—C23—H23B	109.5
C12—C11—C10	120.3 (6)	C22—C23—H23C	109.5
C12—C11—H11	119.9	H23A—C23—H23C	109.5
C10—C11—H11	119.9	H23B—C23—H23C	109.5
C11—C12—C13	120.1 (5)	C22—C24—H24A	109.5
C11—C12—H12	119.9	C22—C24—H24B	109.5
C13—C12—H12	119.9	H24A—C24—H24B	109.5
C12—C13—C14	119.8 (6)	C22—C24—H24C	109.5
C12—C13—H13	120.1	H24A—C24—H24C	109.5
C14—C13—H13	120.1	H24B—C24—H24C	109.5
C9—C14—C13	119.9 (6)	O5—N1—C6	132.6 (4)
C9—C14—H14	120.1	O5—N1—O4	114.4 (3)
C13—C14—H14	120.1	C6—N1—O4	112.9 (4)
C7—C15—H15A	109.5	C3—O1—Si1	127.9 (3)
C7—C15—H15B	109.5	C5—O2—H2	117 (6)
H15A—C15—H15B	109.5	C7—O3—C8	113.0 (4)

Table S5 (Continued)

C7—C15—H15C	109.5	N1—O4—C4	104.0 (3)
H15A—C15—H15C	109.5	O1—Si1—C22	103.0 (2)
H15B—C15—H15C	109.5	O1—Si1—C19	114.1 (2)
C17—C16—C18	109.8 (4)	C22—Si1—C19	113.2 (2)
C17—C16—Si1	112.5 (3)	O1—Si1—C16	107.2 (2)
C18—C16—Si1	115.0 (4)	C22—Si1—C16	110.3 (2)
C17—C16—H16	106.3	C19—Si1—C16	108.7 (2)
O1—C3—C4—O4	179.1 (3)	C2—C3—O1—Si1	-84.3 (5)
C2—C3—C4—O4	57.6 (5)	C4—C3—O1—Si1	155.9 (3)
O1—C3—C4—C5	-63.8 (5)	C6—C7—O3—C8	73.1 (5)
C2—C3—C4—C5	174.7 (4)	C15—C7—O3—C8	-165.7 (4)
O4—C4—C5—O2	91.9 (5)	C9—C8—O3—C7	-156.6 (4)
C3—C4—C5—O2	-26.3 (6)	O5—N1—O4—C4	170.6 (4)
O4—C4—C5—C6	-26.8 (5)	C6—N1—O4—C4	-12.0 (5)
C3—C4—C5—C6	-145.0 (4)	C3—C4—O4—N1	147.5 (3)
O2—C5—C6—N1	-103.3 (5)	C5—C4—O4—N1	24.3 (5)
C4—C5—C6—N1	20.4 (5)	C3—O1—Si1—C22	-149.6 (3)
O2—C5—C6—C7	69.8 (6)	C3—O1—Si1—C19	-26.4 (4)
C4—C5—C6—C7	-166.5 (5)	C3—O1—Si1—C16	94.0 (4)
N1—C6—C7—O3	-162.7 (5)	C23—C22—Si1—O1	170.0 (4)
C5—C6—C7—O3	24.8 (7)	C24—C22—Si1—O1	43.5 (4)
N1—C6—C7—C15	79.2 (6)	C23—C22—Si1—C19	46.3 (5)
C5—C6—C7—C15	-93.3 (6)	C24—C22—Si1—C19	-80.2 (4)
O3—C8—C9—C10	26.4 (6)	C23—C22—Si1—C16	-75.8 (5)
O3—C8—C9—C14	-158.1 (4)	C24—C22—Si1—C16	157.7 (4)
C14—C9—C10—C11	0.3 (7)	C21—C19—Si1—O1	-67.6 (4)
C8—C9—C10—C11	175.7 (5)	C20—C19—Si1—O1	63.1 (4)
C9—C10—C11—C12	-1.3 (8)	C21—C19—Si1—C22	49.8 (4)
C10—C11—C12—C13	1.4 (9)	C20—C19—Si1—C22	-179.5 (3)
C11—C12—C13—C14	-0.6 (8)	C21—C19—Si1—C16	172.8 (4)
C10—C9—C14—C13	0.5 (7)	C20—C19—Si1—C16	-56.5 (4)
C8—C9—C14—C13	-175.1 (5)	C17—C16—Si1—O1	64.1 (4)
C12—C13—C14—C9	-0.3 (8)	C18—C16—Si1—O1	-169.2 (4)
C5—C6—N1—O5	170.6 (5)	C17—C16—Si1—C22	-47.4 (5)

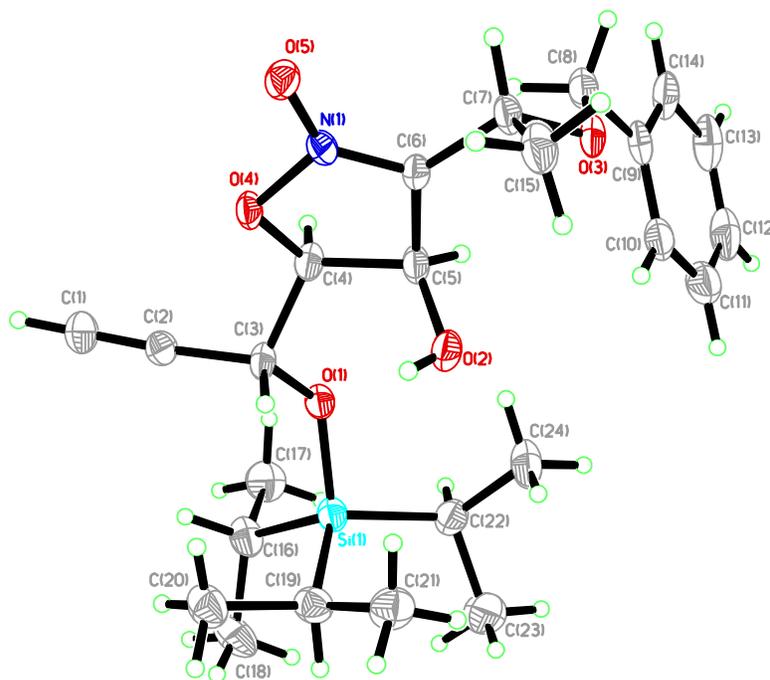
Table S5 (Continued)

C7—C6—N1—O5	-3.1 (9)	C18—C16—Si1—C22	79.3 (5)
C5—C6—N1—O4	-6.2 (6)	C17—C16—Si1—C19	-172.1 (4)
C7—C6—N1—O4	-179.9 (4)	C18—C16—Si1—C19	-45.4 (5)

Table S6. Hydrogen-bond parameters

$D-H\cdots A$	$D-H$ (Å)	$H\cdots A$ (Å)	$D\cdots A$ (Å)	$D-H\cdots A$ (°)
O2—H2 \cdots O5 ⁱ	0.84 (8)	1.97 (8)	2.798 (5)	167 (8)

Symmetry code(s): (i) $-x+1, y-1/2, -z+1$.

**Figure S3.** Perspective views showing 50% probability displacement

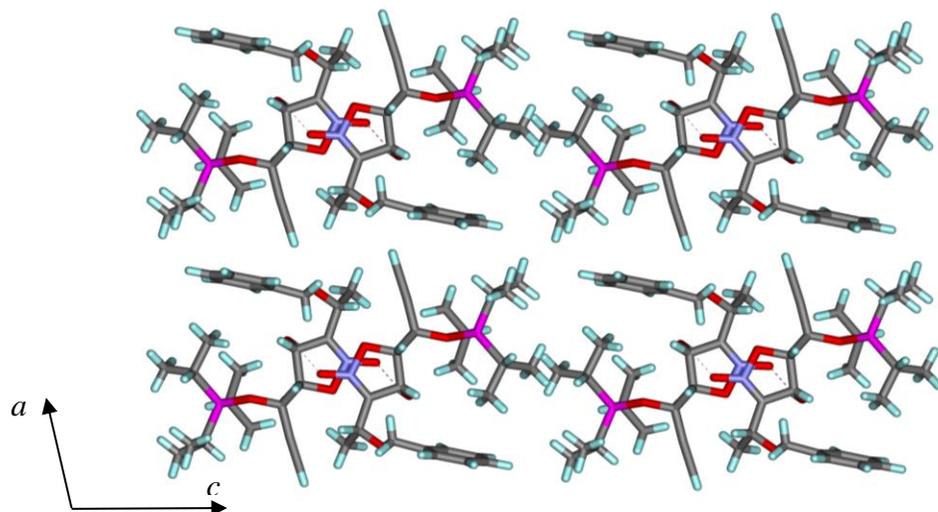
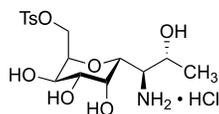


Figure S4. Three-dimensional supramolecular architecture viewed along the *b*-axis direction.

Crystallographic Data for Compound 31



31

Table S7. Experimental details

CCDC Deposition Number 2072281	
Chemical formula	C ₁₆ H ₂₆ ClNO ₈ S
<i>M_r</i>	427.89
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	6.0507 (3), 9.9307 (4), 16.3874 (7)
β (°)	97.2807 (15)
<i>V</i> (Å ³)	976.74 (8)
<i>Z</i>	2
Radiation type	Mo <i>K</i> α
μ (mm ⁻¹)	0.35
Crystal size (mm)	0.20 × 0.12 × 0.06
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan <i>SADABS</i>
<i>T_{min}</i> , <i>T_{max}</i>	0.806, 0.862
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	7929, 4202, 3942
<i>R_{int}</i>	0.020
(sin θ/λ) _{max} (Å ⁻¹)	0.641
Refinement	
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.032, 0.067, 1.08
No. of reflections	4202
No. of parameters	274
No. of restraints	1

Table S7 (Continued)

H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}, \Delta\rho_{\min}$ (e Å ⁻³)	0.22, -0.29
Absolute structure	Flack x determined using 1719 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.02 (2)

Computer programs: *APEX3* v2016.1-0 (Bruker-AXS, 2016), *SAINT* 8.37A (Bruker-AXS, 2016), *SHELXT2014* (Sheldrick, 2015), *SHELXL2014* (Sheldrick, 2015), Bruker *SHELXTL* (Sheldrick, 2015).

Table S8. Geometric parameters (Å, °)

S1—O8	1.428 (2)	C4—C5	1.524 (4)
S1—O7	1.434 (2)	C4—H4A	1.0000
S1—O6	1.578 (2)	C5—C6	1.531 (4)
S1—C10	1.747 (3)	C5—H5A	1.0000
O1—C2	1.428 (3)	C6—C7	1.506 (4)
O1—H1	0.72 (4)	C6—H6	1.0000
O2—C8	1.435 (3)	C7—C8	1.524 (4)
O2—C4	1.435 (3)	C7—H7	1.0000
O3—C5	1.432 (3)	C8—C9	1.525 (4)
O3—H3	0.74 (4)	C8—H8	1.0000
O4—C6	1.430 (3)	C9—H9A	0.9900
O4—H4	0.76 (4)	C9—H9B	0.9900
O5—C7	1.431 (3)	C10—C11	1.387 (4)
O5—H5	0.73 (4)	C10—C15	1.394 (4)
O6—C9	1.471 (3)	C11—C12	1.387 (4)
N1—C3	1.491 (4)	C11—H11	0.9500
N1—H1A	0.84 (4)	C12—C13	1.387 (5)
N1—H1B	0.91 (4)	C12—H12	0.9500
N1—H1C	0.90 (4)	C13—C14	1.391 (5)
C1—C2	1.513 (4)	C13—C16	1.505 (4)
C1—H1D	0.9800	C14—C15	1.383 (4)

Table S8 (Continued)

C1—H1E	0.9800	C14—H14	0.9500
C1—H1F	0.9800	C15—H15	0.9500
C2—C3	1.525 (4)	C16—H16A	0.9800
C2—H2	1.0000	C16—H16B	0.9800
C3—C4	1.530 (4)	C16—H16C	0.9800
C3—H3A	1.0000		
O8—S1—O7	119.62 (15)	O4—C6—C7	110.6 (2)
O8—S1—O6	103.82 (12)	O4—C6—C5	107.8 (2)
O7—S1—O6	108.86 (12)	C7—C6—C5	111.2 (2)
O8—S1—C10	110.90 (14)	O4—C6—H6	109.1
O7—S1—C10	109.04 (15)	C7—C6—H6	109.1
O6—S1—C10	103.23 (12)	C5—C6—H6	109.1
C2—O1—H1	108 (3)	O5—C7—C6	108.3 (2)
C8—O2—C4	115.4 (2)	O5—C7—C8	111.0 (2)
C5—O3—H3	106 (3)	C6—C7—C8	111.7 (2)
C6—O4—H4	106 (3)	O5—C7—H7	108.6
C7—O5—H5	105 (3)	C6—C7—H7	108.6
C9—O6—S1	117.63 (16)	C8—C7—H7	108.6
C3—N1—H1A	110 (2)	O2—C8—C7	110.2 (2)
C3—N1—H1B	112 (2)	O2—C8—C9	111.7 (2)
H1A—N1—H1B	106 (3)	C7—C8—C9	113.3 (2)
C3—N1—H1C	114 (2)	O2—C8—H8	107.1
H1A—N1—H1C	109 (3)	C7—C8—H8	107.1
H1B—N1—H1C	107 (3)	C9—C8—H8	107.1
C2—C1—H1D	109.5	O6—C9—C8	106.3 (2)
C2—C1—H1E	109.5	O6—C9—H9A	110.5
H1D—C1—H1E	109.5	C8—C9—H9A	110.5
C2—C1—H1F	109.5	O6—C9—H9B	110.5
H1D—C1—H1F	109.5	C8—C9—H9B	110.5
H1E—C1—H1F	109.5	H9A—C9—H9B	108.7
O1—C2—C1	111.3 (2)	C11—C10—C15	120.1 (3)
O1—C2—C3	107.6 (2)	C11—C10—S1	120.1 (2)
C1—C2—C3	113.5 (2)	C15—C10—S1	119.6 (2)
O1—C2—H2	108.1	C12—C11—C10	119.5 (3)

Table S8 (Continued)

C1—C2—H2	108.1	C12—C11—H11	120.3
C3—C2—H2	108.1	C10—C11—H11	120.3
N1—C3—C2	108.6 (2)	C11—C12—C13	121.3 (3)
N1—C3—C4	109.8 (2)	C11—C12—H12	119.3
C2—C3—C4	117.2 (2)	C13—C12—H12	119.3
N1—C3—H3A	106.9	C12—C13—C14	118.2 (3)
C2—C3—H3A	106.9	C12—C13—C16	120.7 (3)
C4—C3—H3A	106.9	C14—C13—C16	121.1 (3)
O2—C4—C5	112.1 (2)	C15—C14—C13	121.5 (3)
O2—C4—C3	102.8 (2)	C15—C14—H14	119.3
C5—C4—C3	117.1 (2)	C13—C14—H14	119.3
O2—C4—H4A	108.1	C14—C15—C10	119.2 (3)
C5—C4—H4A	108.1	C14—C15—H15	120.4
C3—C4—H4A	108.1	C10—C15—H15	120.4
O3—C5—C4	110.1 (2)	C13—C16—H16A	109.5
O3—C5—C6	109.8 (2)	C13—C16—H16B	109.5
C4—C5—C6	108.0 (2)	H16A—C16—H16B	109.5
O3—C5—H5A	109.6	C13—C16—H16C	109.5
C4—C5—H5A	109.6	H16A—C16—H16C	109.5
C6—C5—H5A	109.6	H16B—C16—H16C	109.5
O8—S1—O6—C9	-176.1 (2)	C4—O2—C8—C7	-54.4 (3)
O7—S1—O6—C9	-47.6 (2)	C4—O2—C8—C9	72.5 (3)
C10—S1—O6—C9	68.1 (2)	O5—C7—C8—O2	173.5 (2)
O1—C2—C3—N1	-53.8 (3)	C6—C7—C8—O2	52.5 (3)
C1—C2—C3—N1	-177.4 (2)	O5—C7—C8—C9	47.5 (3)
O1—C2—C3—C4	71.3 (3)	C6—C7—C8—C9	-73.5 (3)
C1—C2—C3—C4	-52.3 (3)	S1—O6—C9—C8	134.41 (19)
C8—O2—C4—C5	57.4 (3)	O2—C8—C9—O6	59.8 (3)
C8—O2—C4—C3	-175.9 (2)	C7—C8—C9—O6	-175.1 (2)
N1—C3—C4—O2	-55.1 (3)	O8—S1—C10—C11	156.8 (2)
C2—C3—C4—O2	-179.6 (2)	O7—S1—C10—C11	23.1 (3)
N1—C3—C4—C5	68.3 (3)	O6—S1—C10—C11	-92.5 (2)
C2—C3—C4—C5	-56.1 (3)	O8—S1—C10—C15	-27.4 (3)
O2—C4—C5—O3	64.8 (3)	O7—S1—C10—C15	-161.2 (2)

Table S8 (Continued)

C3—C4—C5—O3	-53.7 (3)	O6—S1—C10—C15	83.2 (2)
O2—C4—C5—C6	-55.1 (3)	C15—C10—C11—C12	-2.8 (4)
C3—C4—C5—C6	-173.6 (2)	S1—C10—C11—C12	172.9 (2)
O3—C5—C6—O4	56.1 (3)	C10—C11—C12—C13	-0.2 (4)
C4—C5—C6—O4	176.1 (2)	C11—C12—C13—C14	3.9 (4)
O3—C5—C6—C7	-65.3 (3)	C11—C12—C13—C16	-175.8 (3)
C4—C5—C6—C7	54.7 (3)	C12—C13—C14—C15	-4.7 (4)
O4—C6—C7—O5	62.9 (3)	C16—C13—C14—C15	175.0 (3)
C5—C6—C7—O5	-177.4 (2)	C13—C14—C15—C10	1.7 (4)
O4—C6—C7—C8	-174.6 (2)	C11—C10—C15—C14	2.1 (4)
C5—C6—C7—C8	-54.8 (3)	S1—C10—C15—C14	-173.7 (2)

Table S9. Hydrogen-bond parameters

<i>D</i> —H... <i>A</i>	<i>D</i> —H (Å)	H... <i>A</i> (Å)	<i>D</i> ... <i>A</i> (Å)	<i>D</i> —H... <i>A</i> (°)
O4—H4...O5	0.76 (4)	2.55 (4)	2.832 (3)	104 (4)
N1—H1B...O1	0.91 (4)	2.31 (4)	2.737 (3)	108 (3)
N1—H1C...O2	0.90 (4)	2.29 (4)	2.686 (3)	107 (3)
N1—H1B...O3	0.91 (4)	2.43 (3)	2.789 (3)	104 (2)
O1—H1...Cl1 ⁱ	0.72 (4)	2.47 (4)	3.155 (2)	160 (4)
O3—H3...Cl1 ⁱⁱ	0.74 (4)	2.45 (4)	3.176 (2)	170 (5)
O5—H5...Cl1 ⁱⁱⁱ	0.73 (4)	2.38 (4)	3.108 (3)	172 (4)
N1—H1A...Cl1 ^{iv}	0.84 (4)	2.36 (4)	3.191 (3)	168 (3)
N1—H1B...O4 ⁱ	0.91 (4)	2.23 (4)	2.847 (3)	125 (3)

Symmetry code(s): (i) $-x-1, y+1/2, -z$; (ii) $x-1, y, z$; (iii) $-x, y-1/2, -z$; (iv) $-x, y+1/2, -z$.

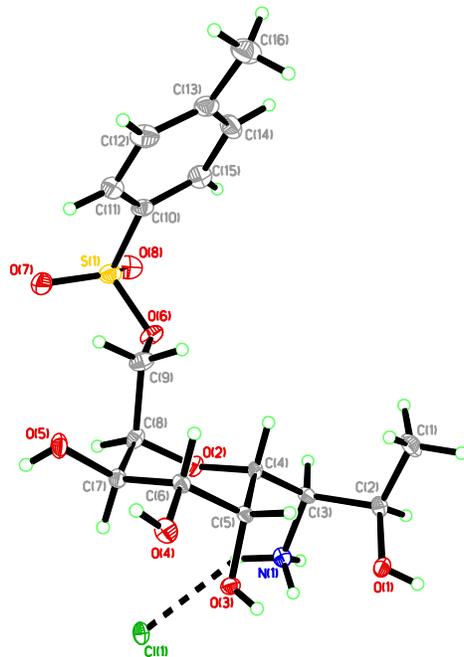


Figure S5. Perspective views showing 50% probability displacement

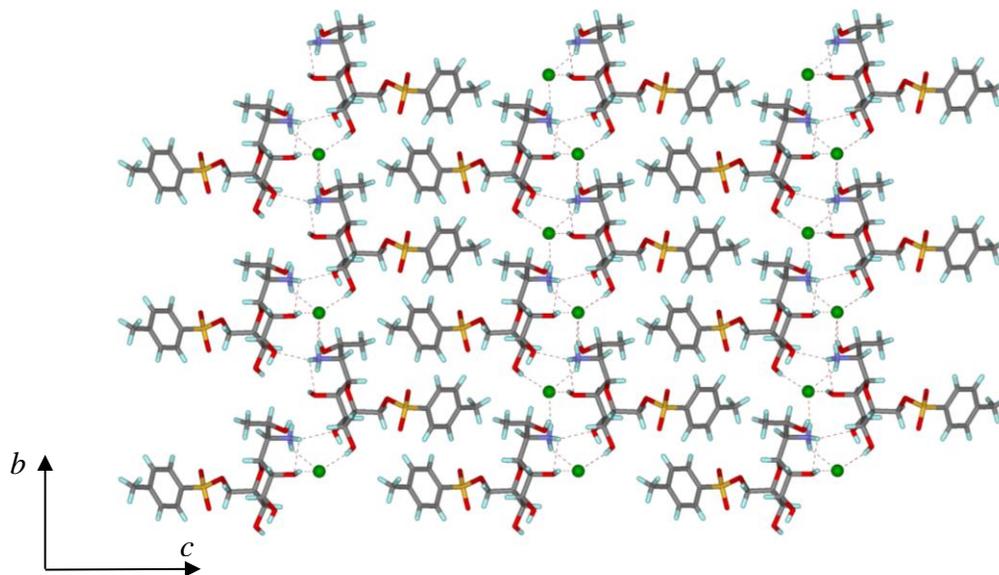
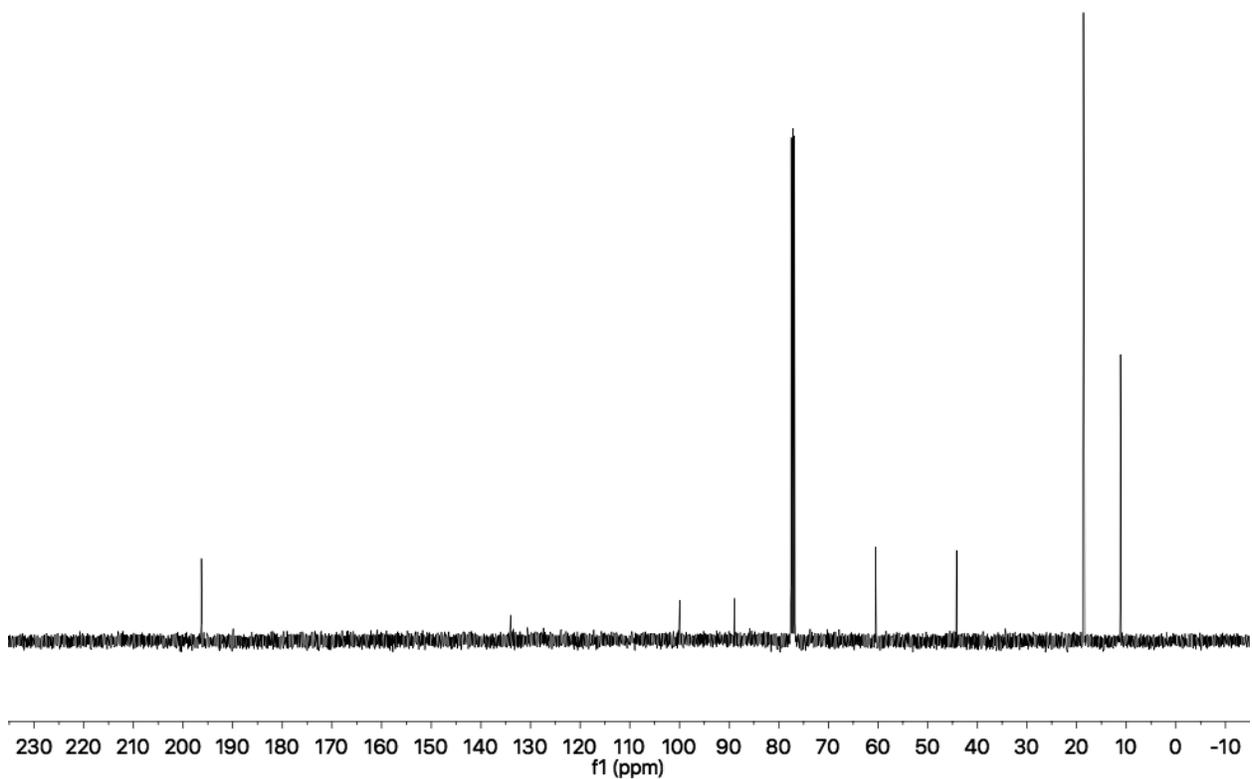
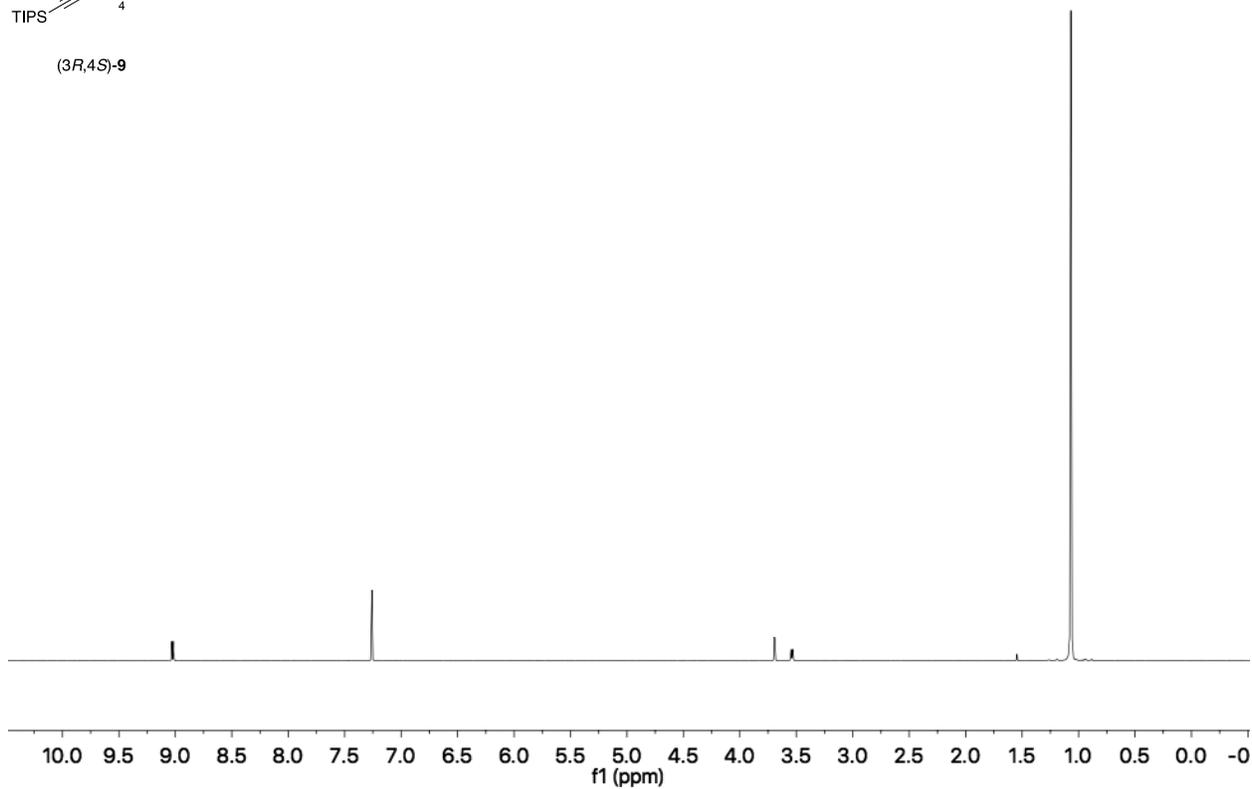
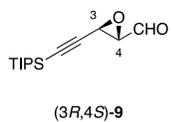
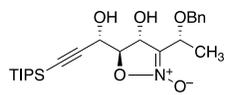


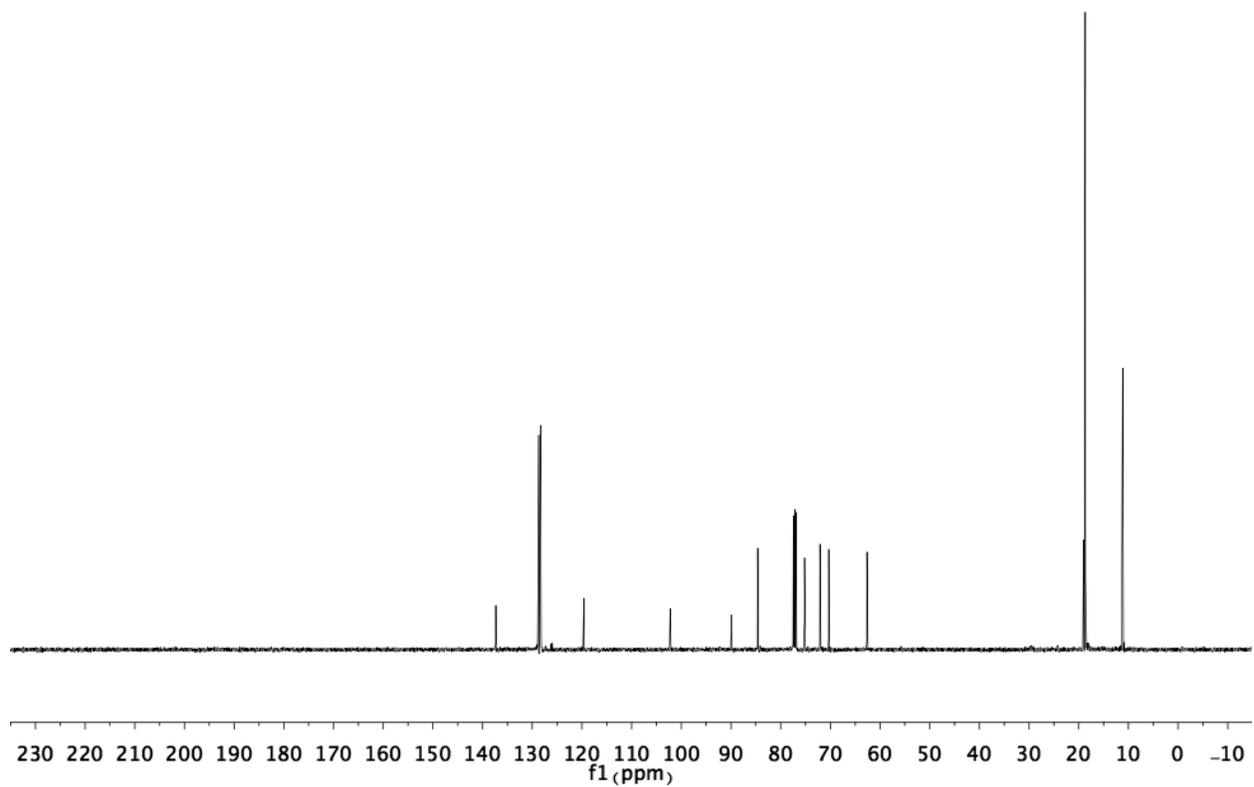
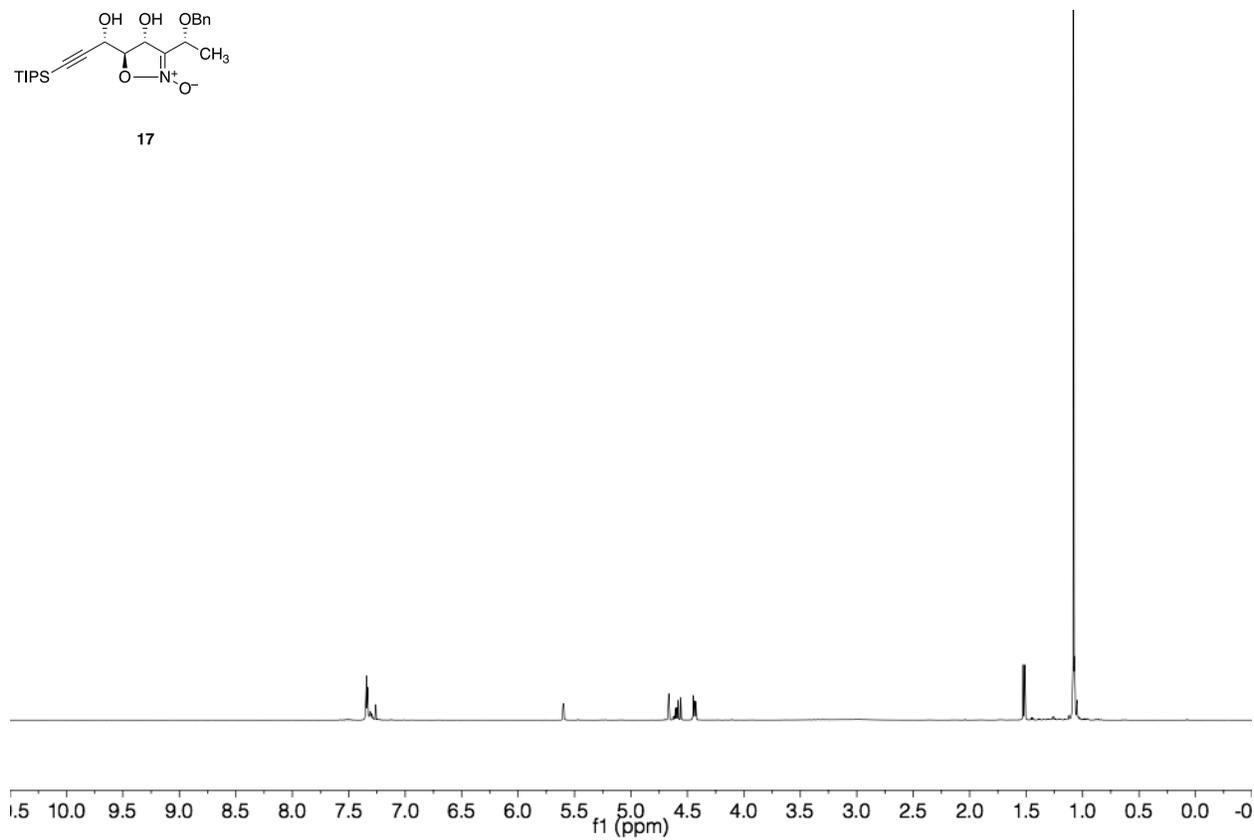
Figure S6. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

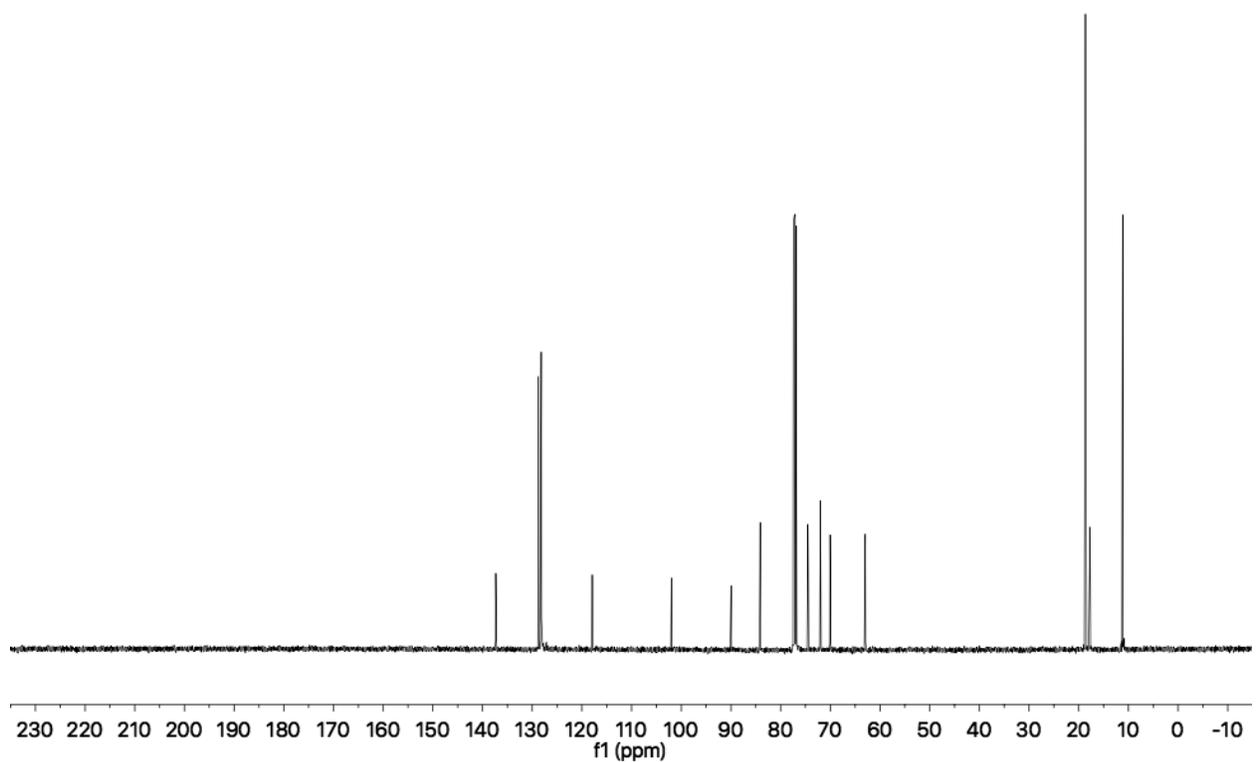
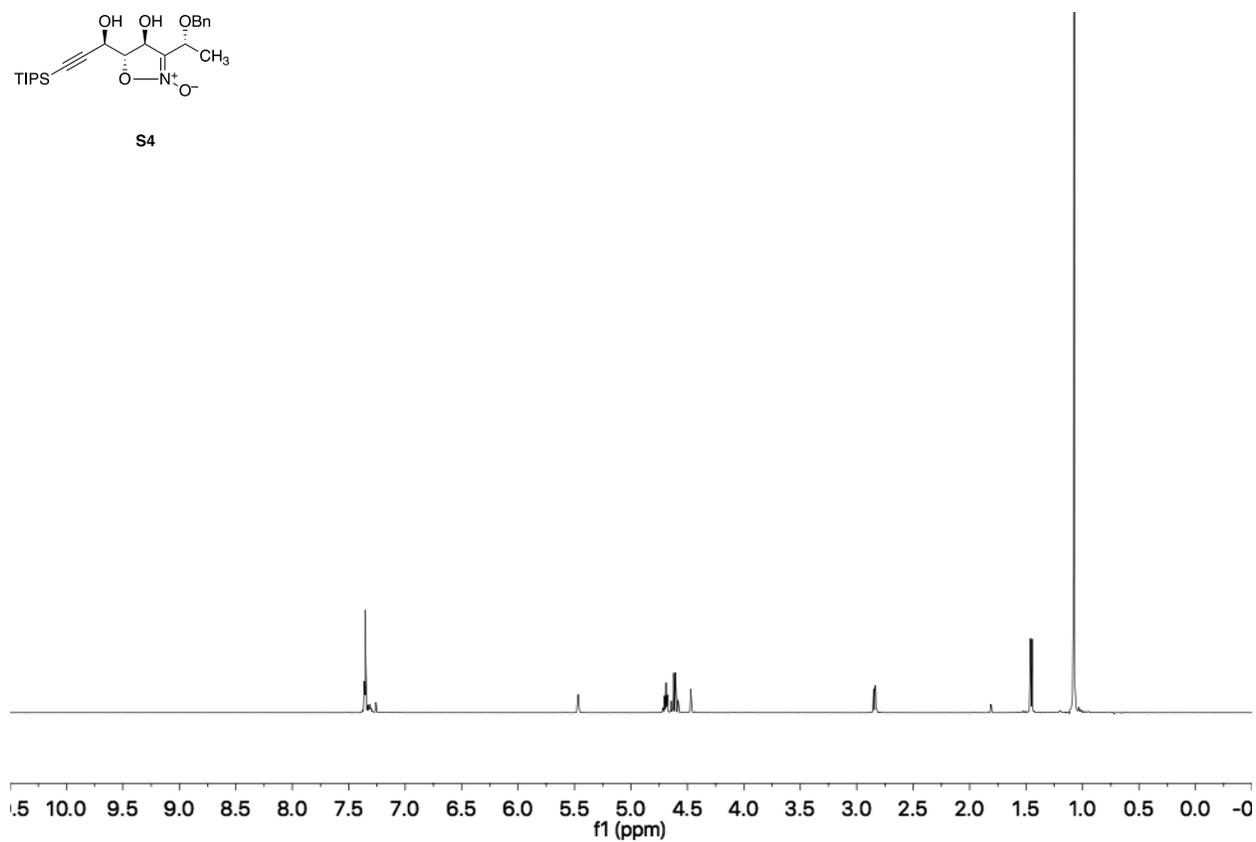
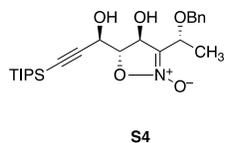
Catalog of NMR Spectra

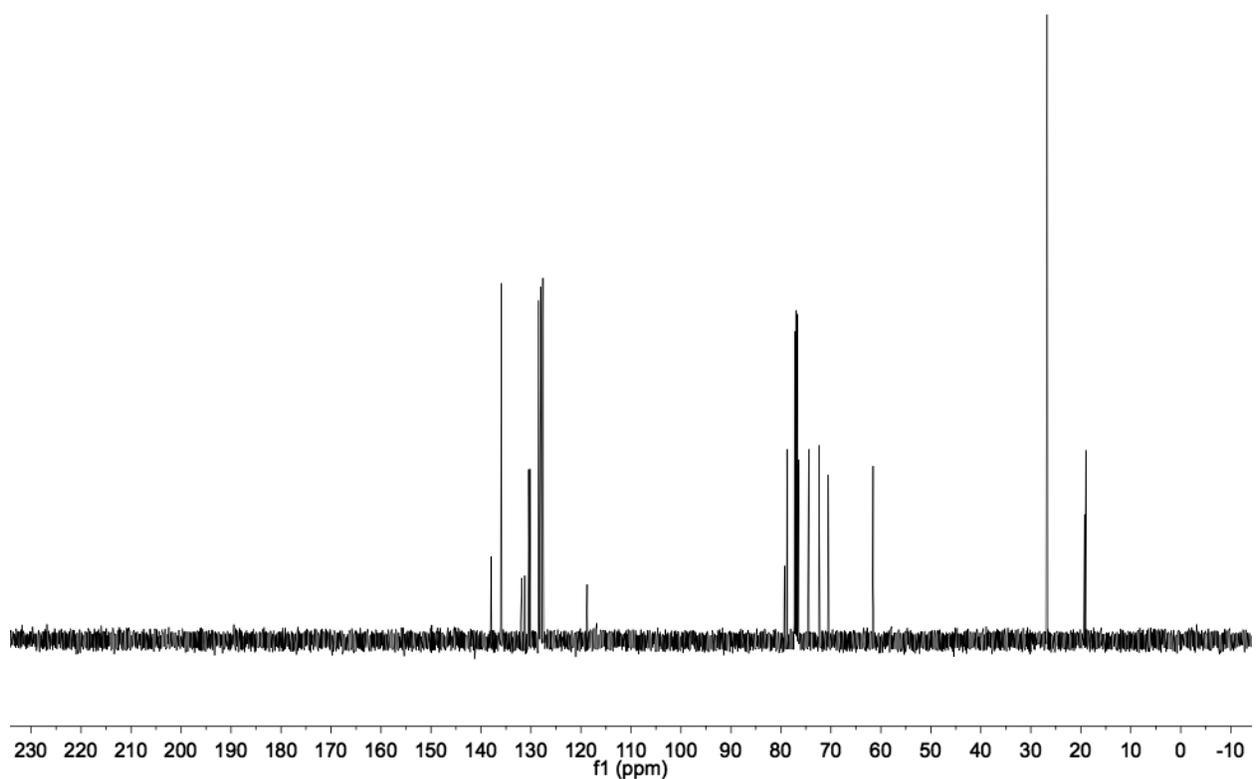
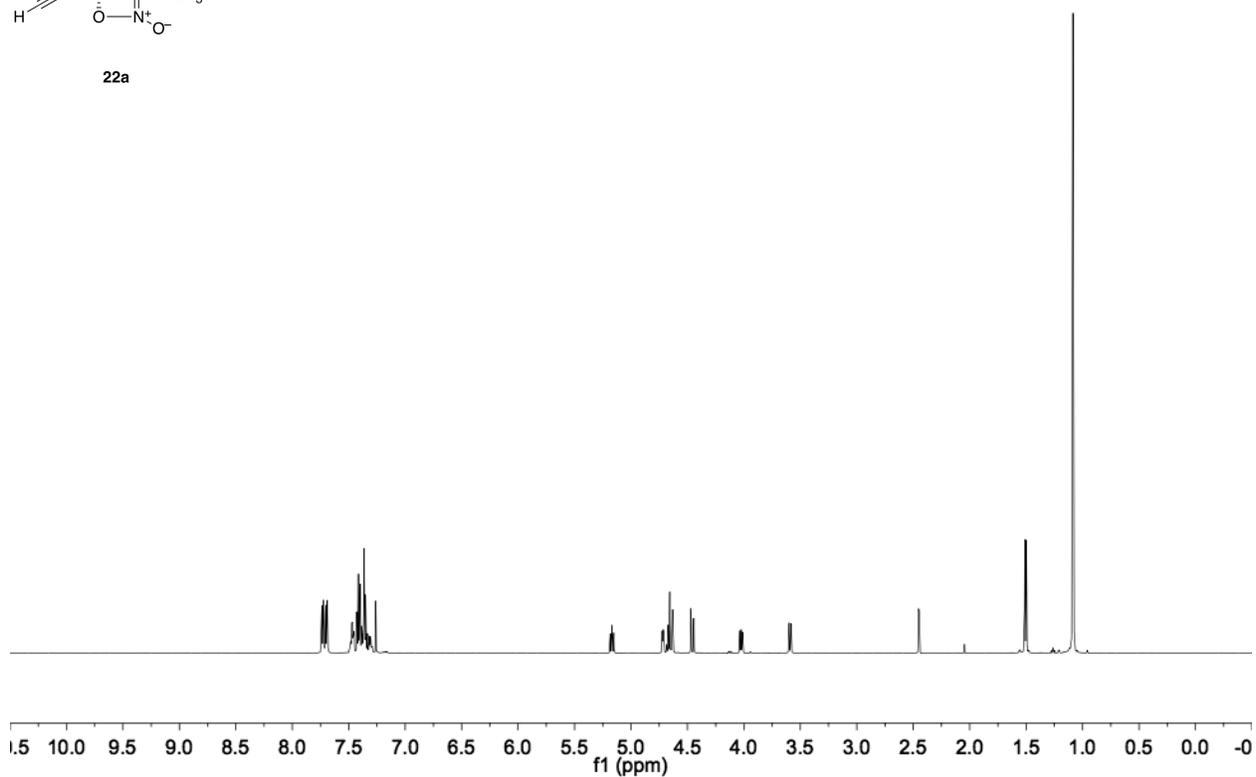
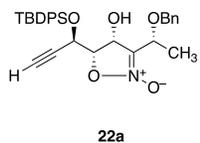


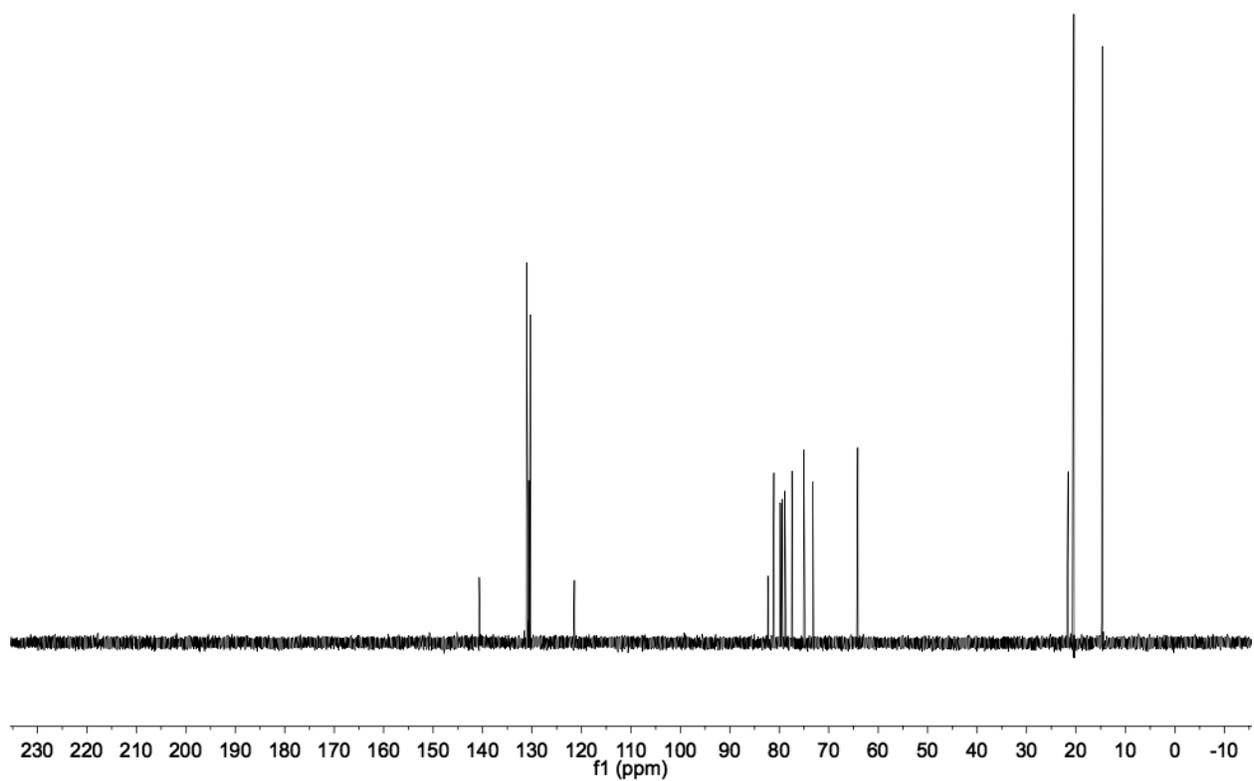
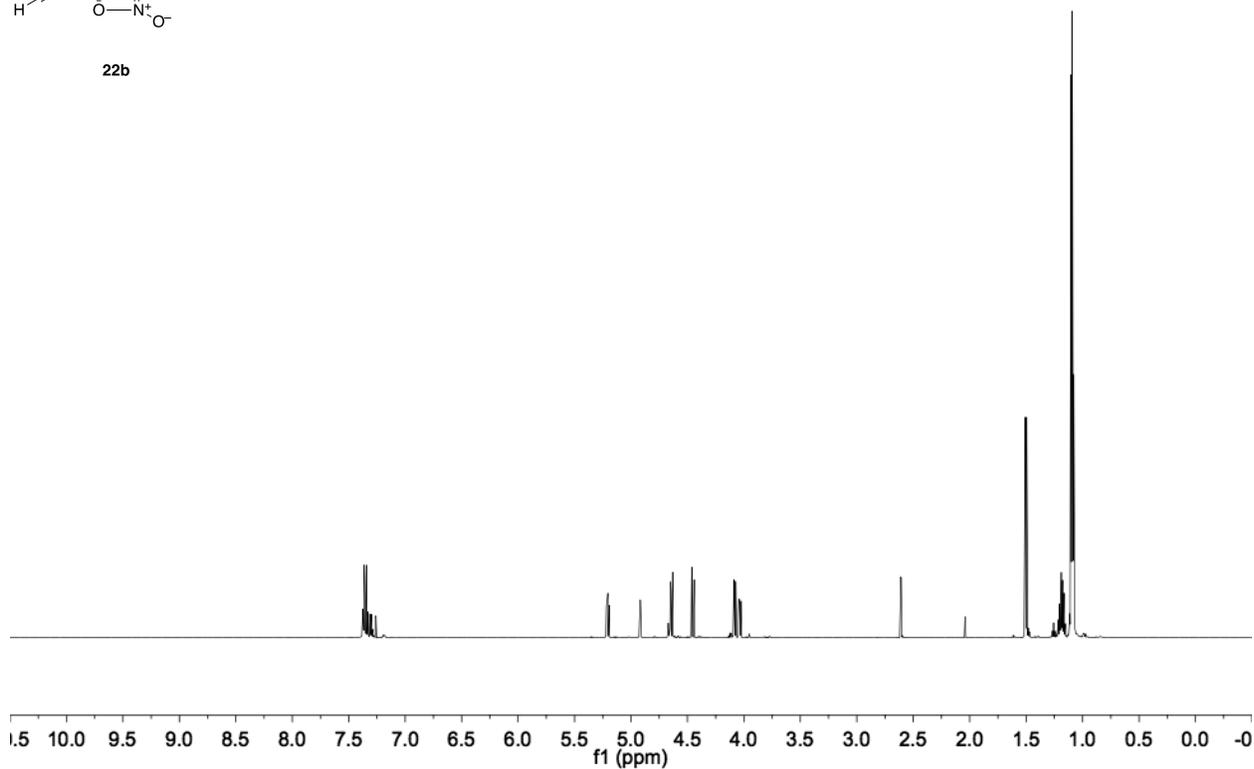
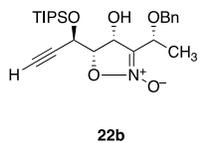


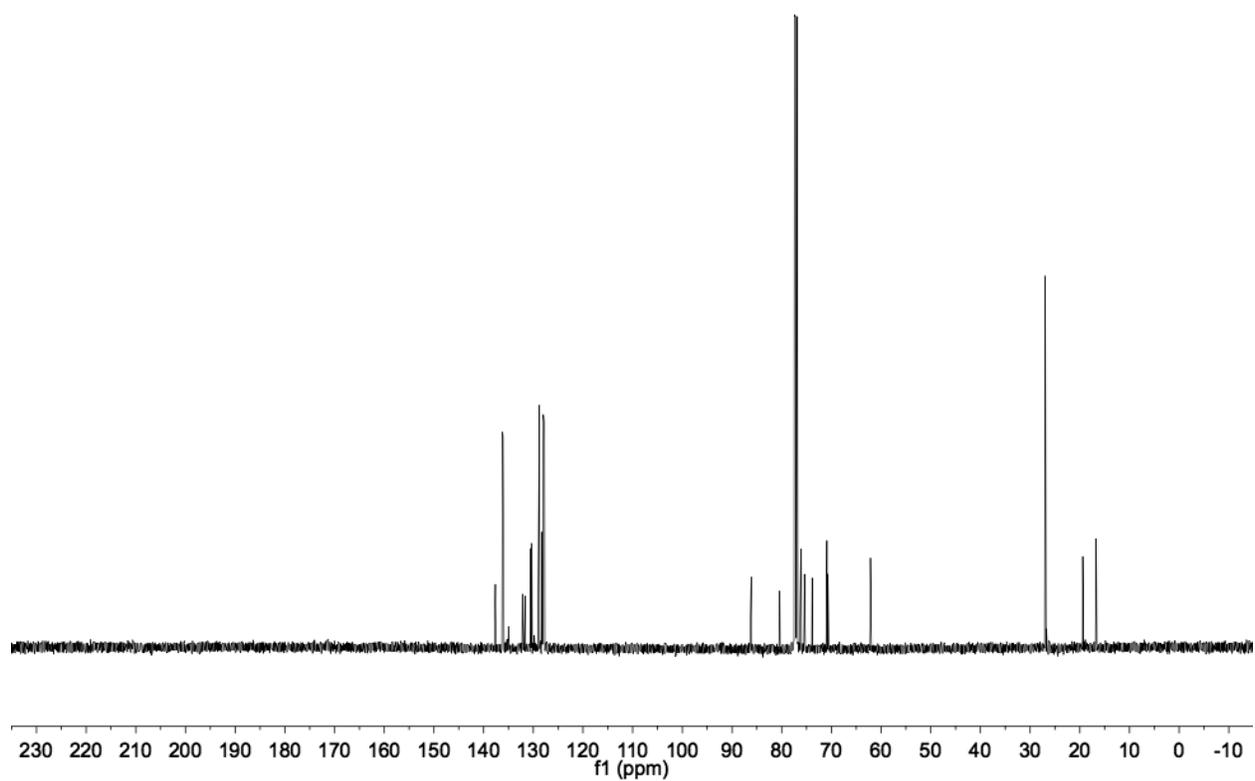
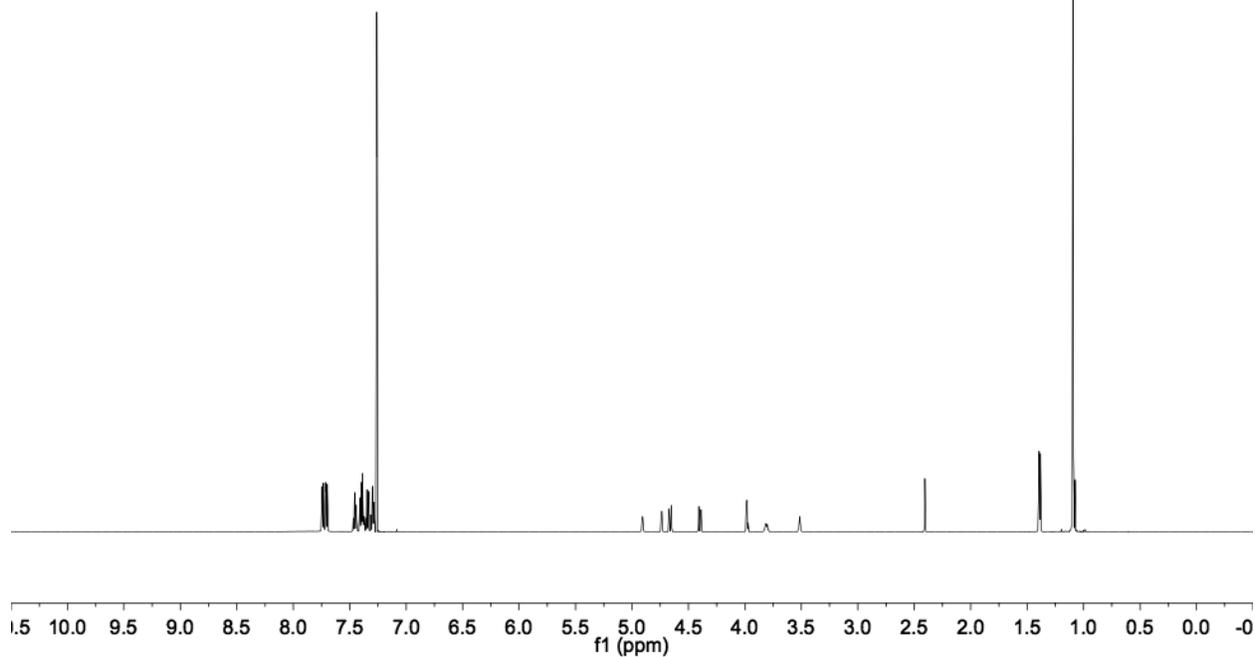
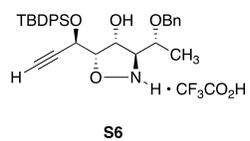
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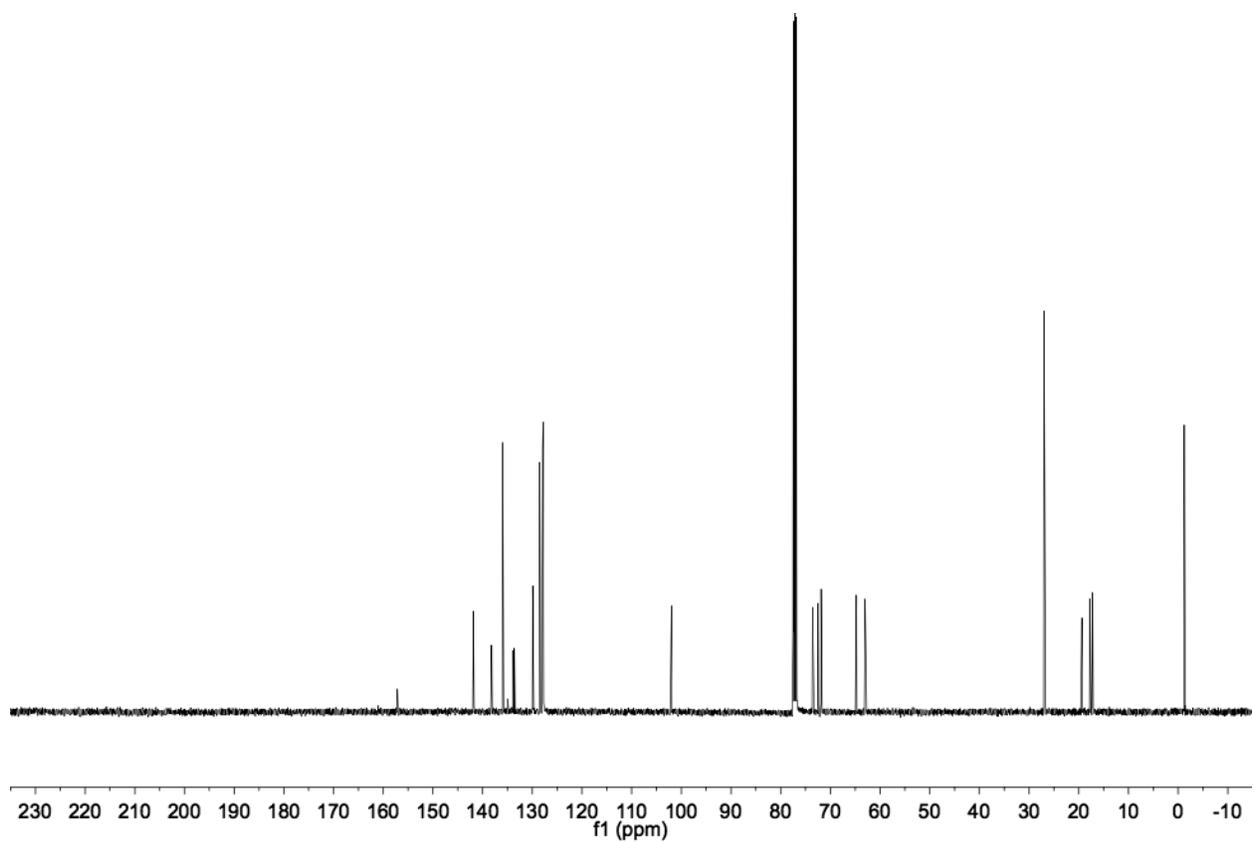
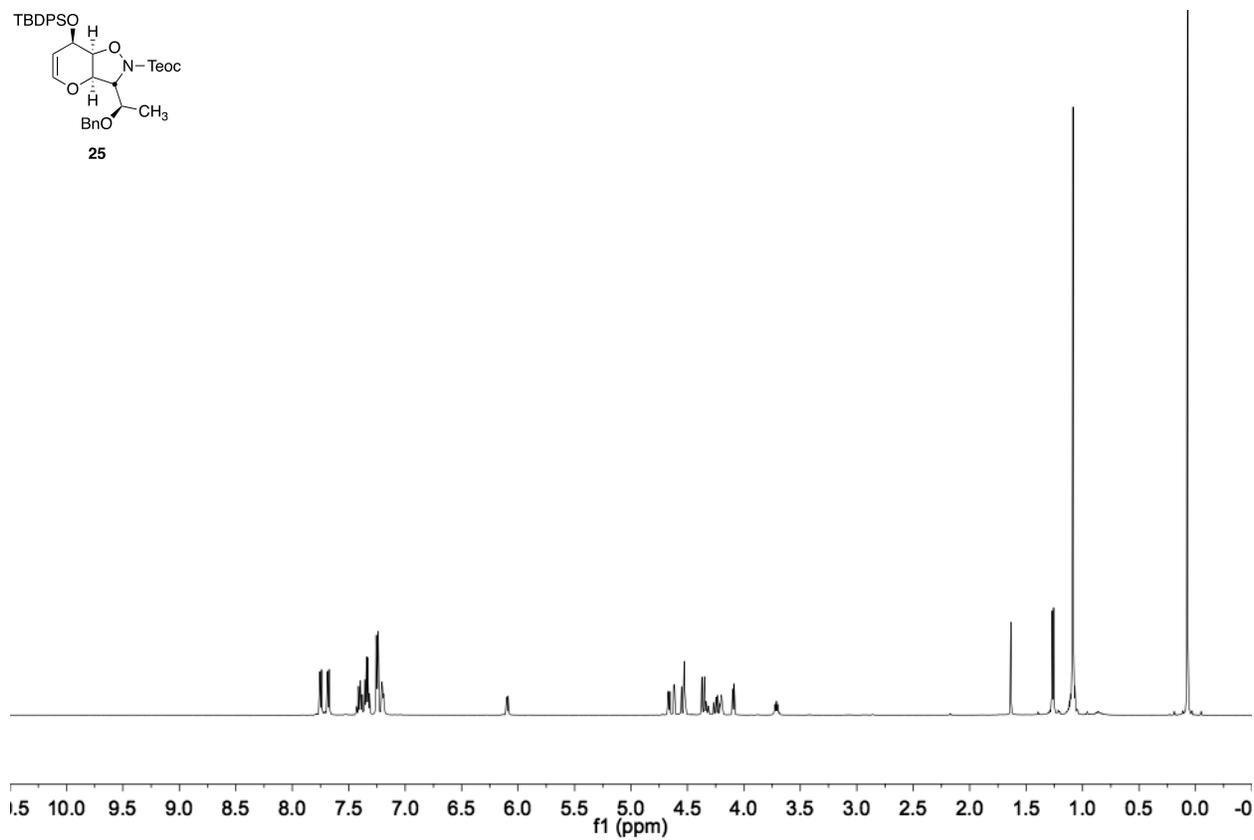
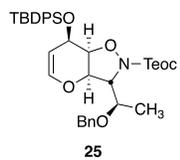


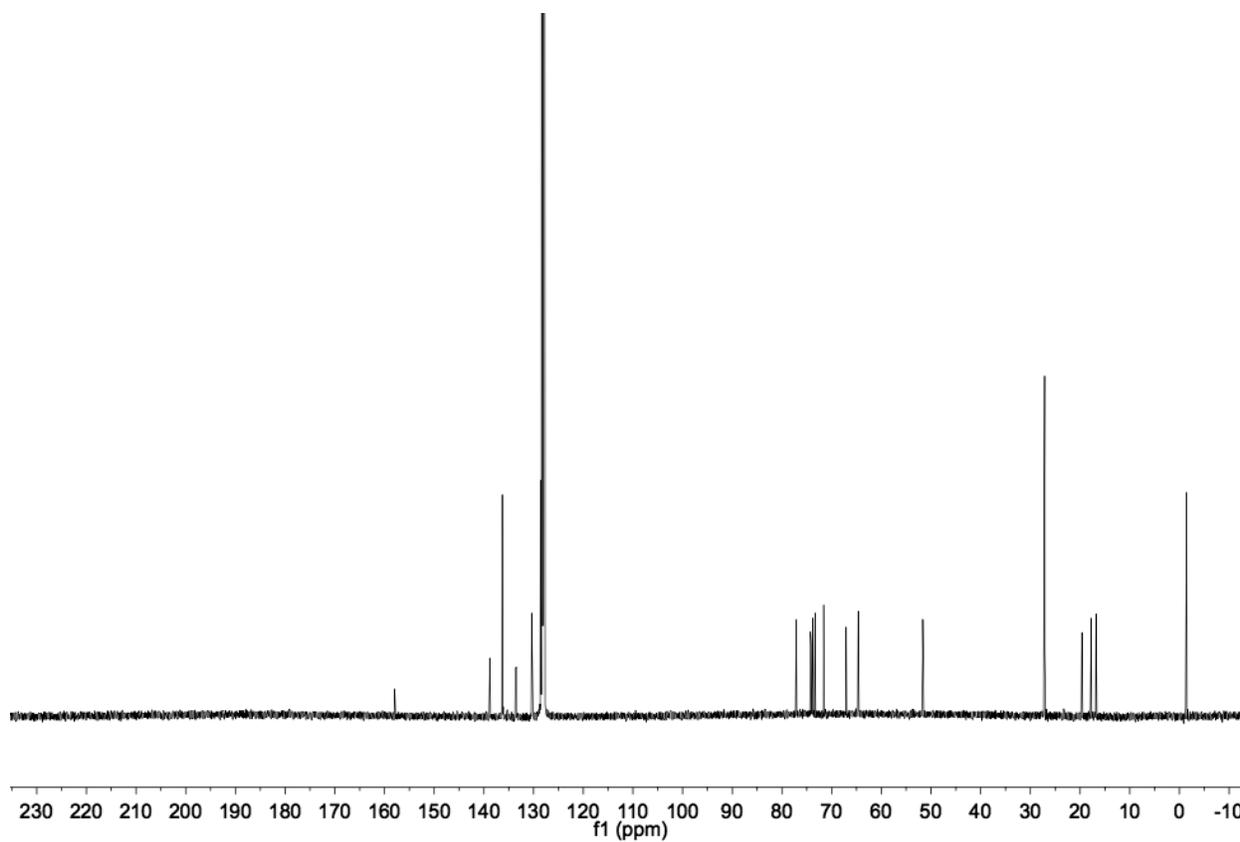
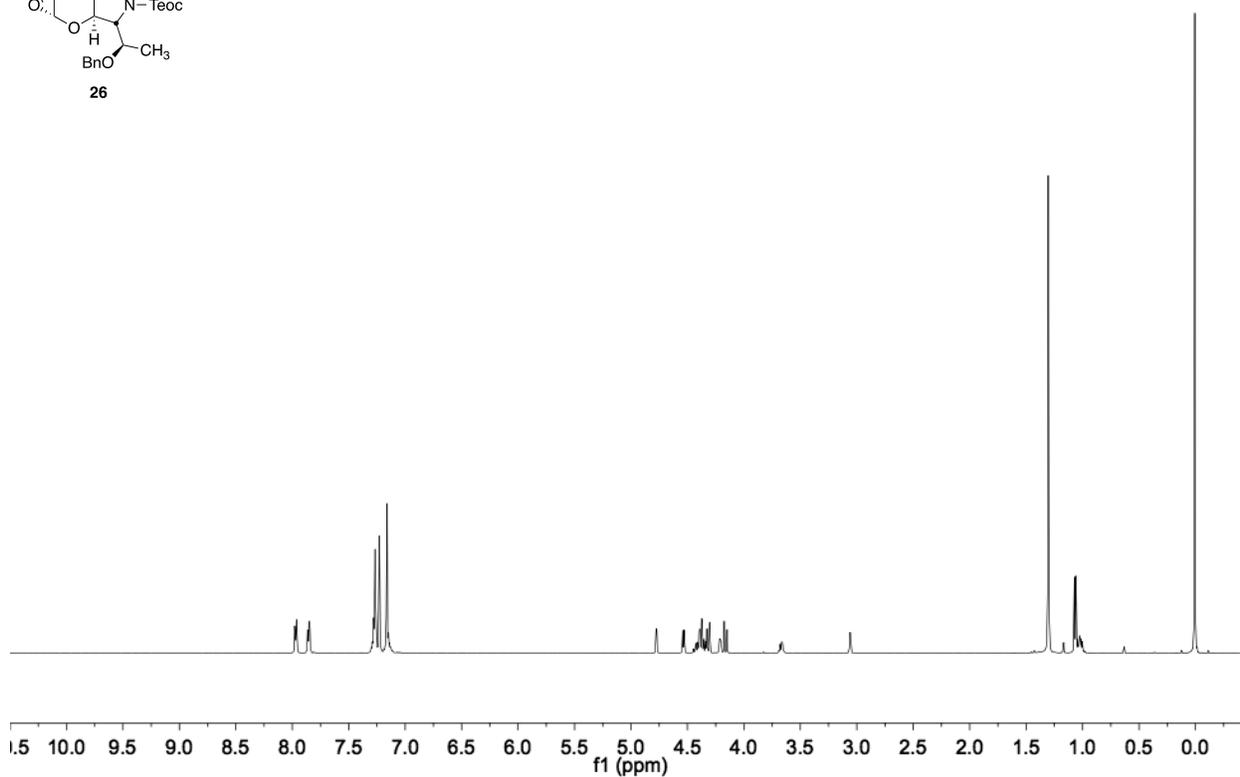
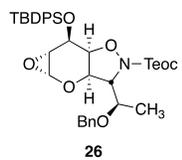


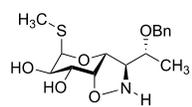




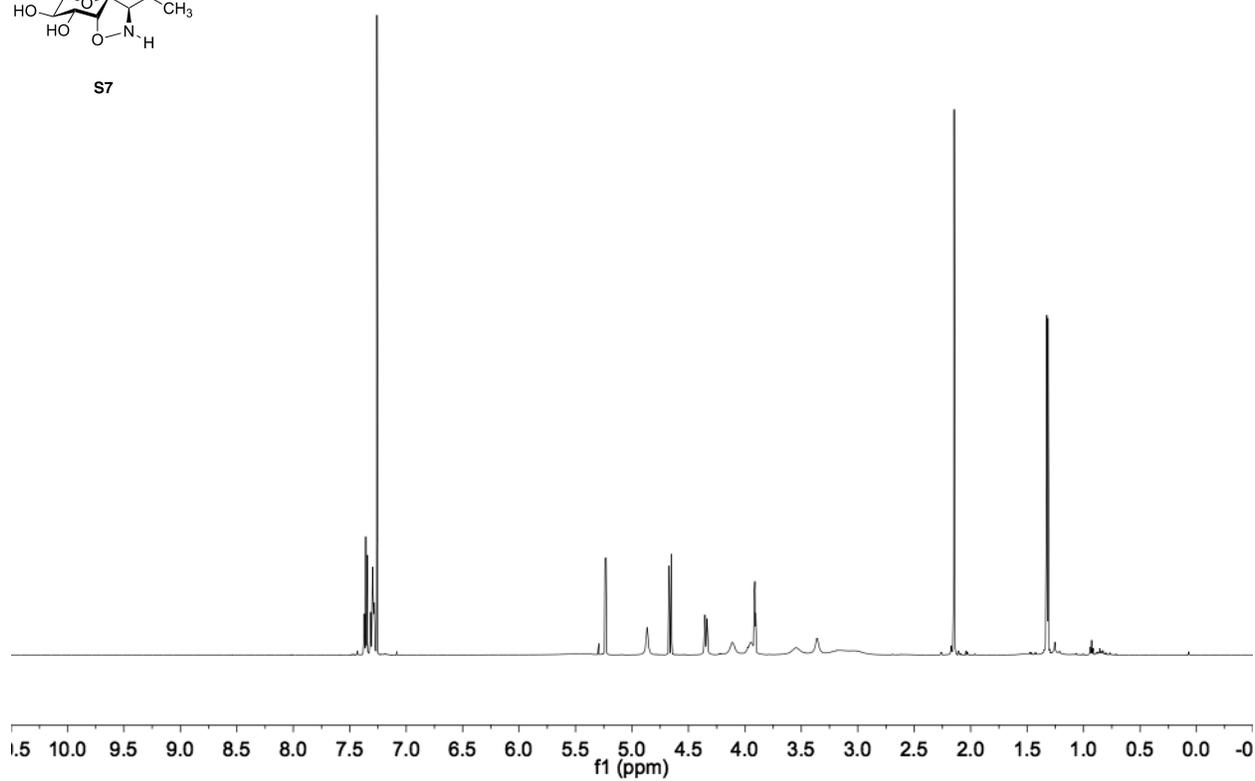


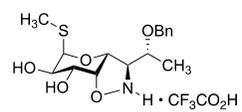




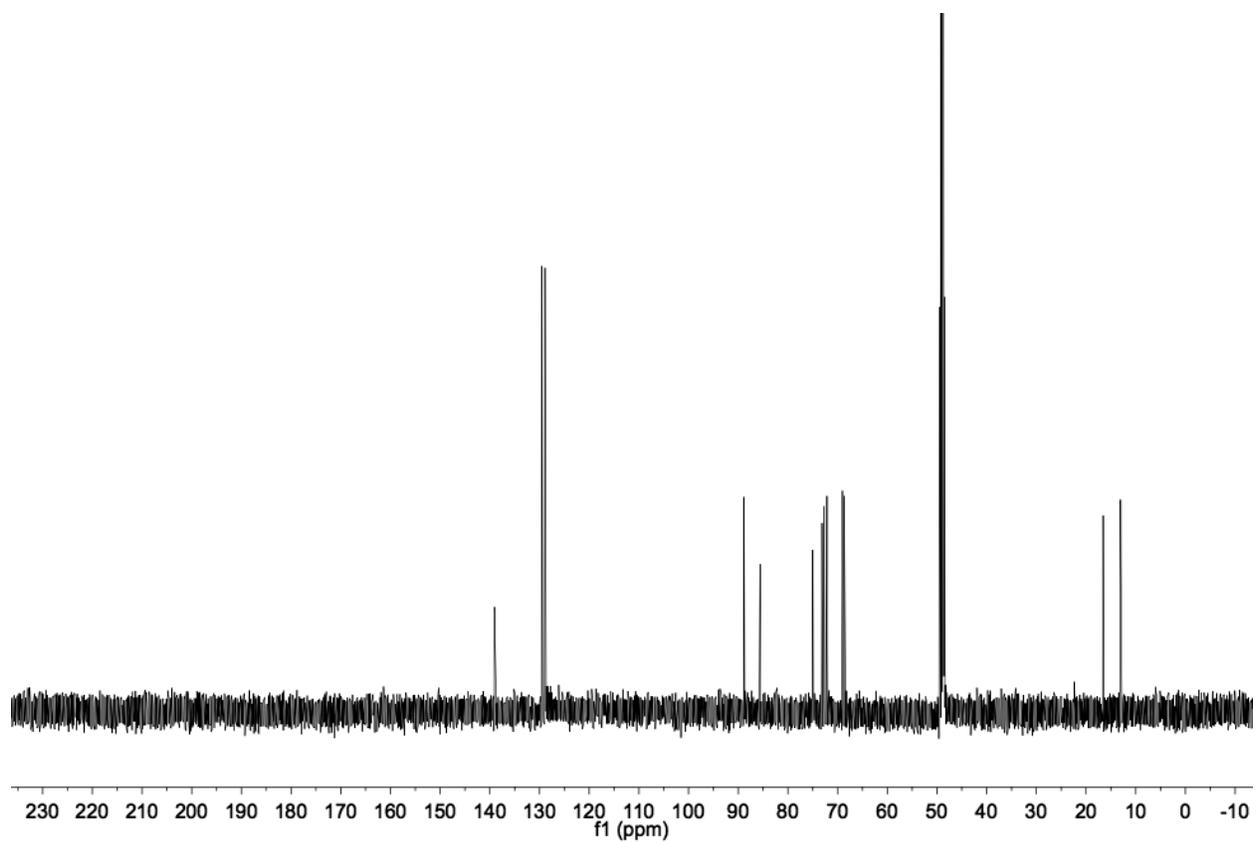
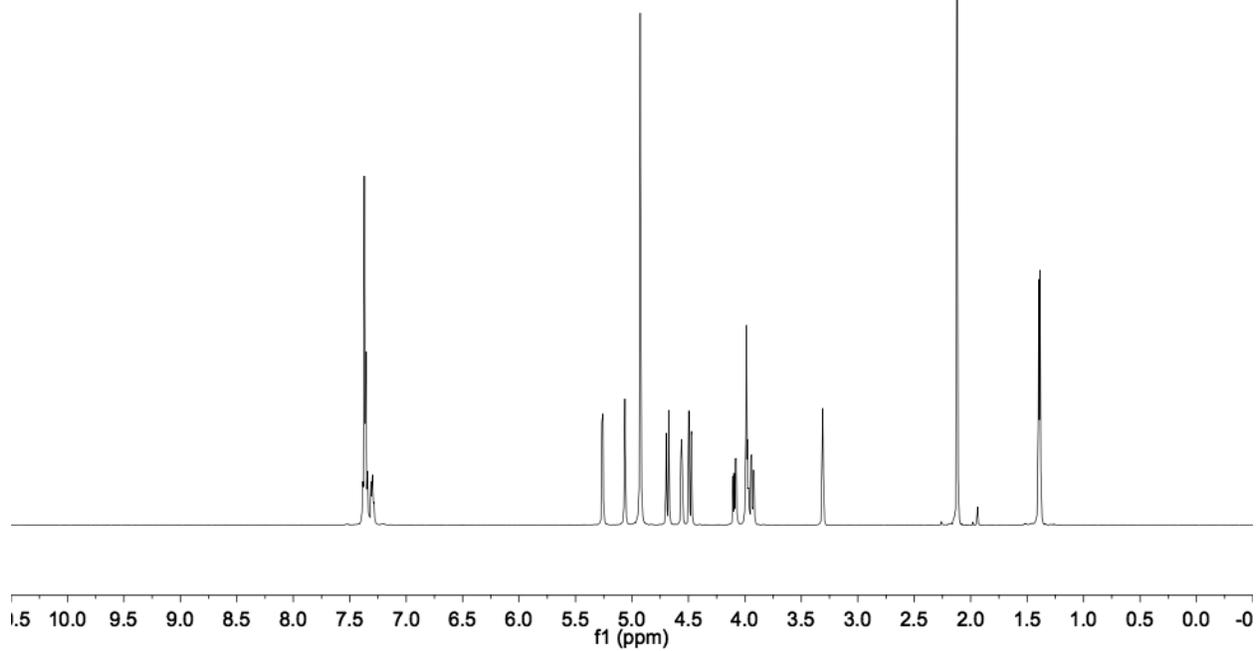


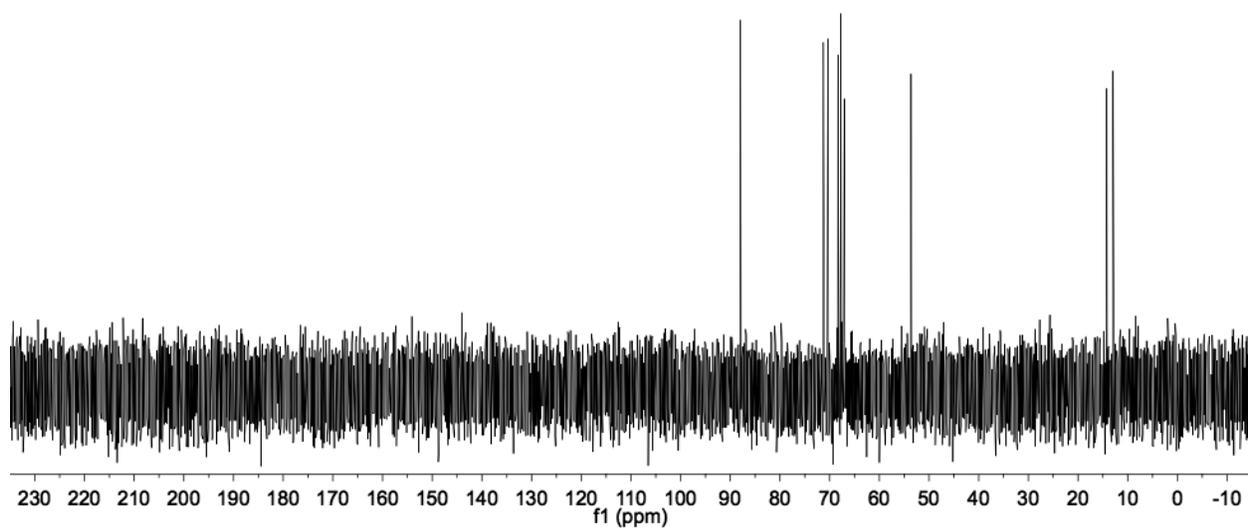
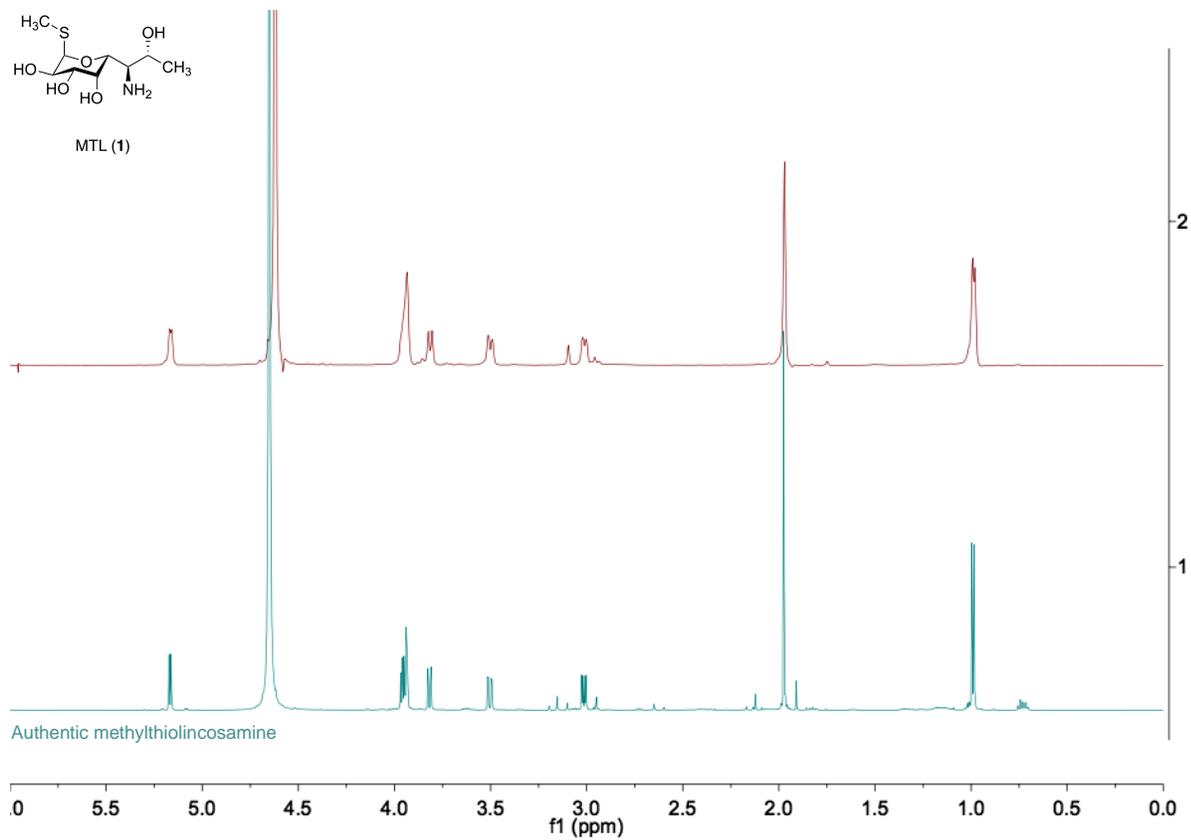
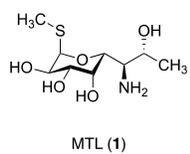
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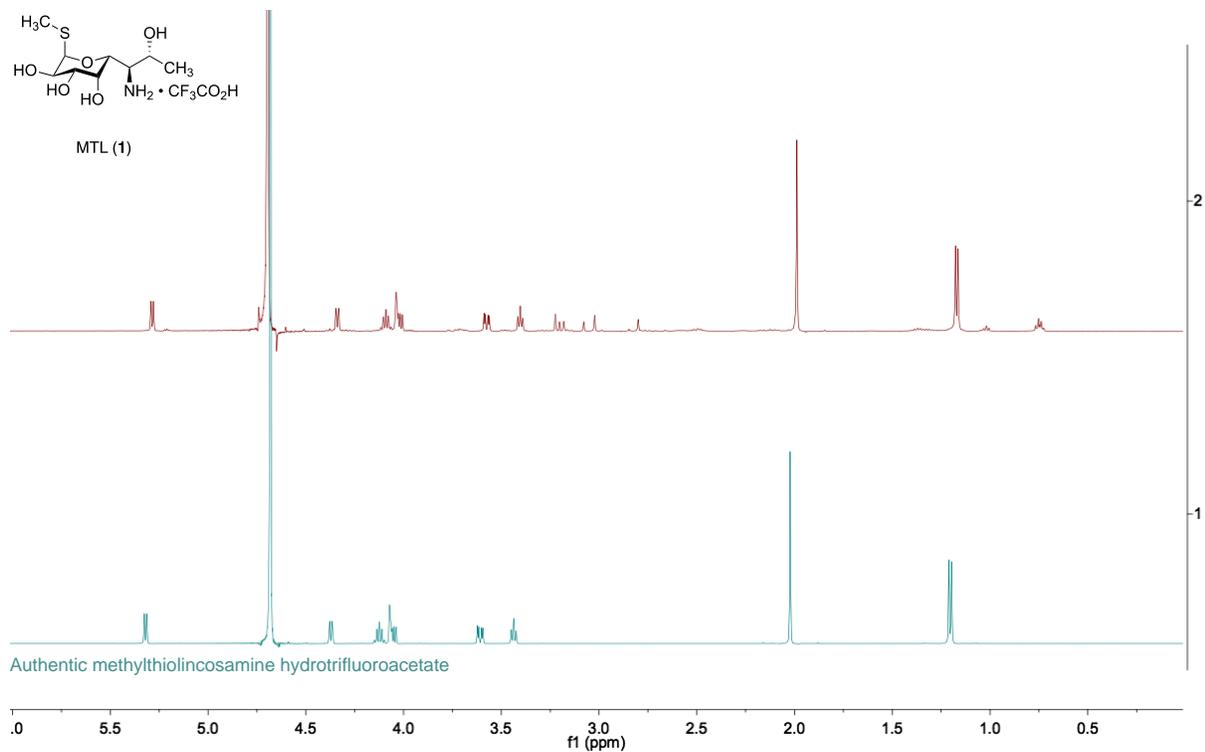


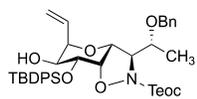


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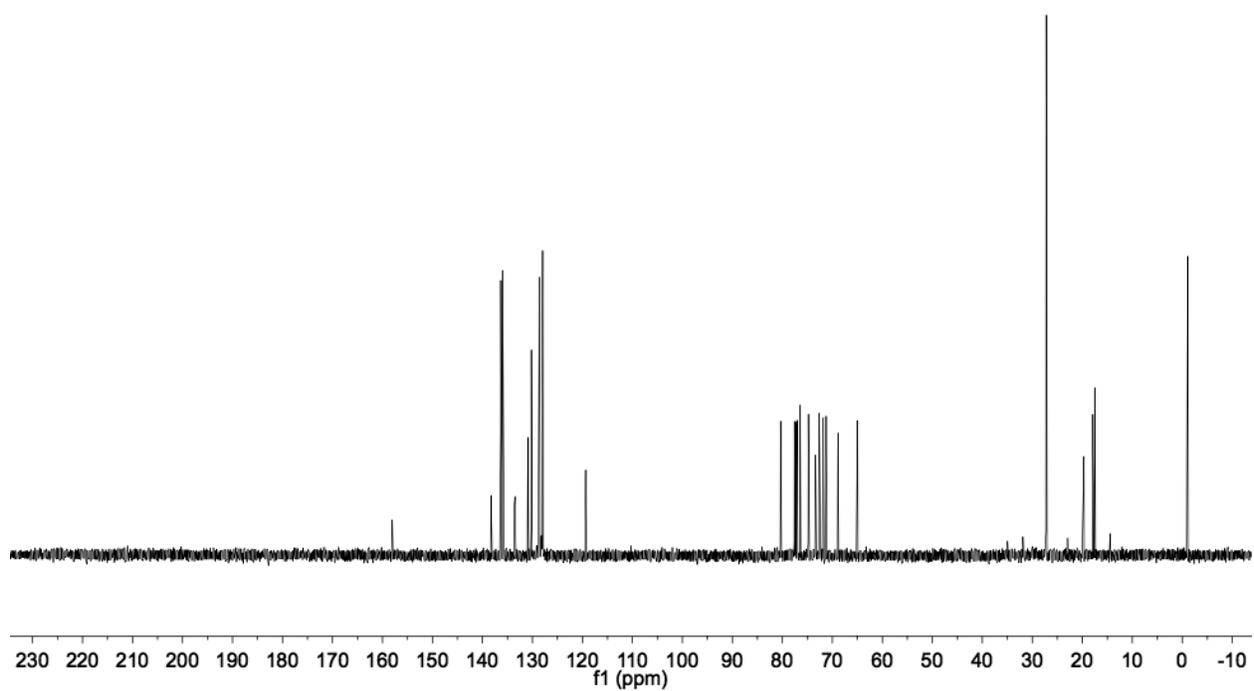
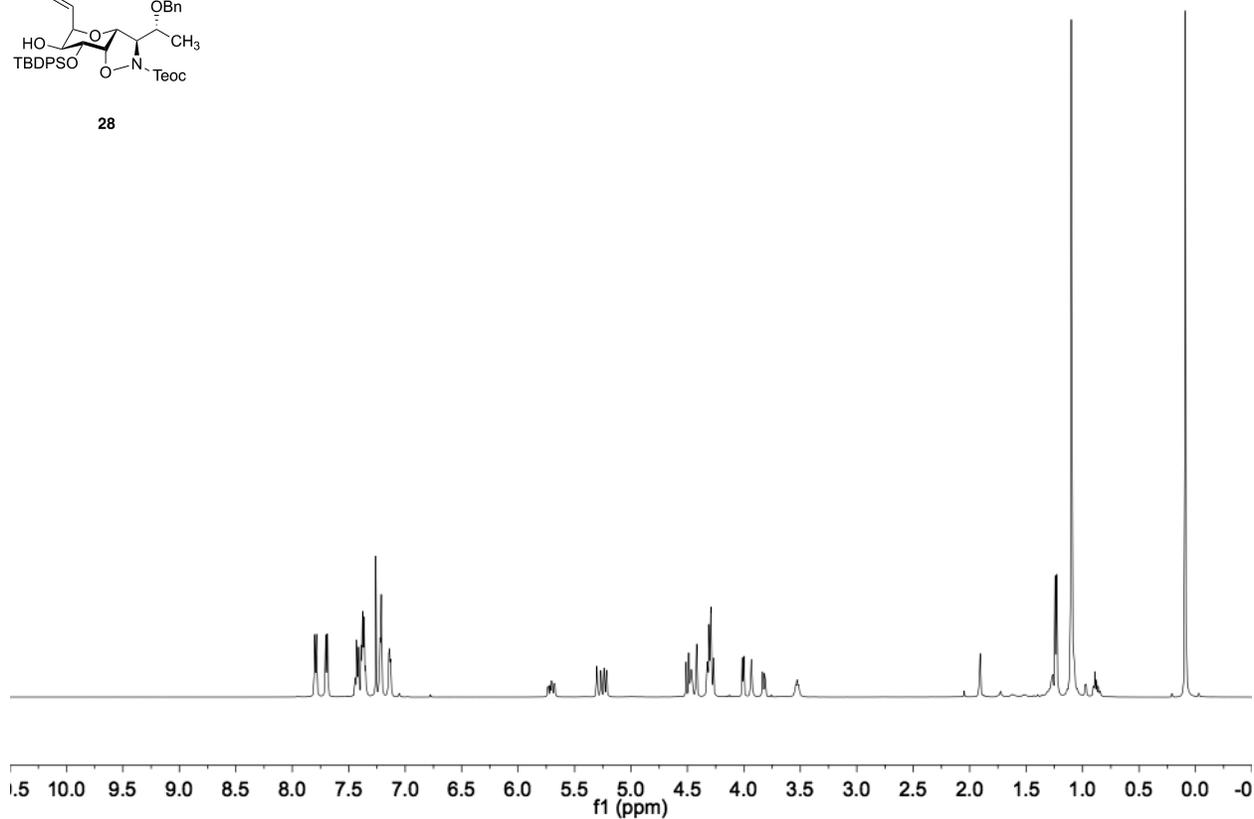


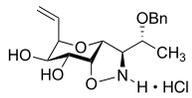




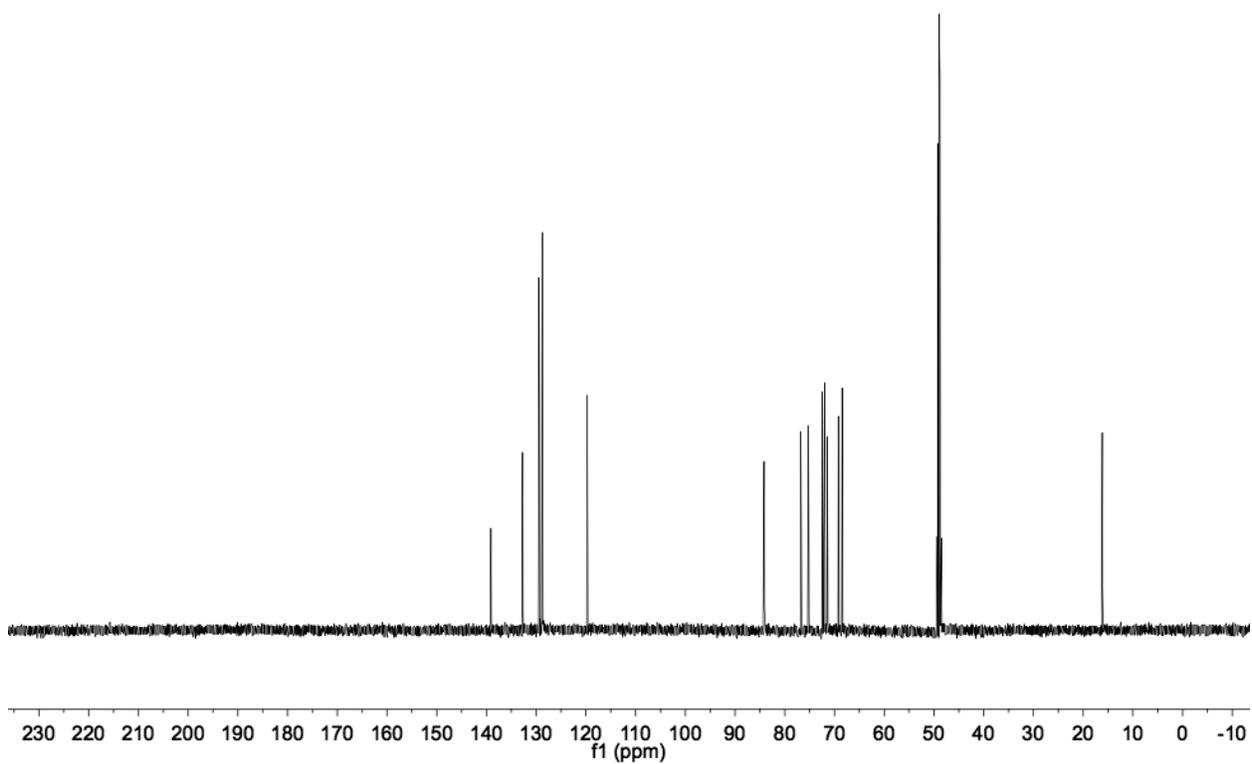
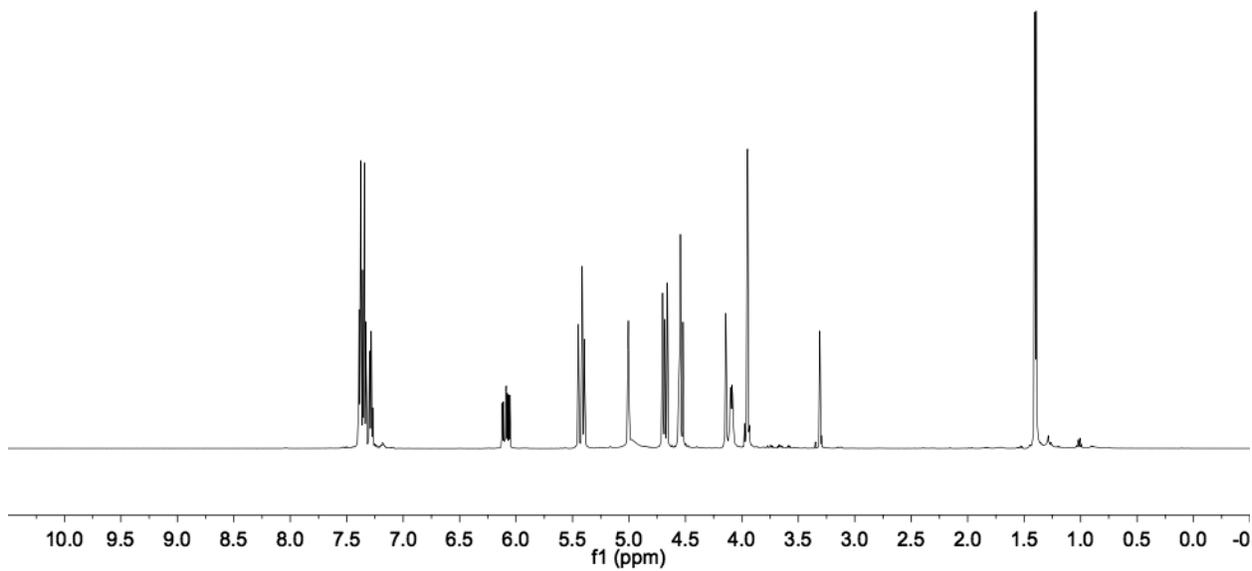


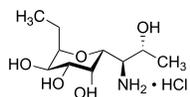
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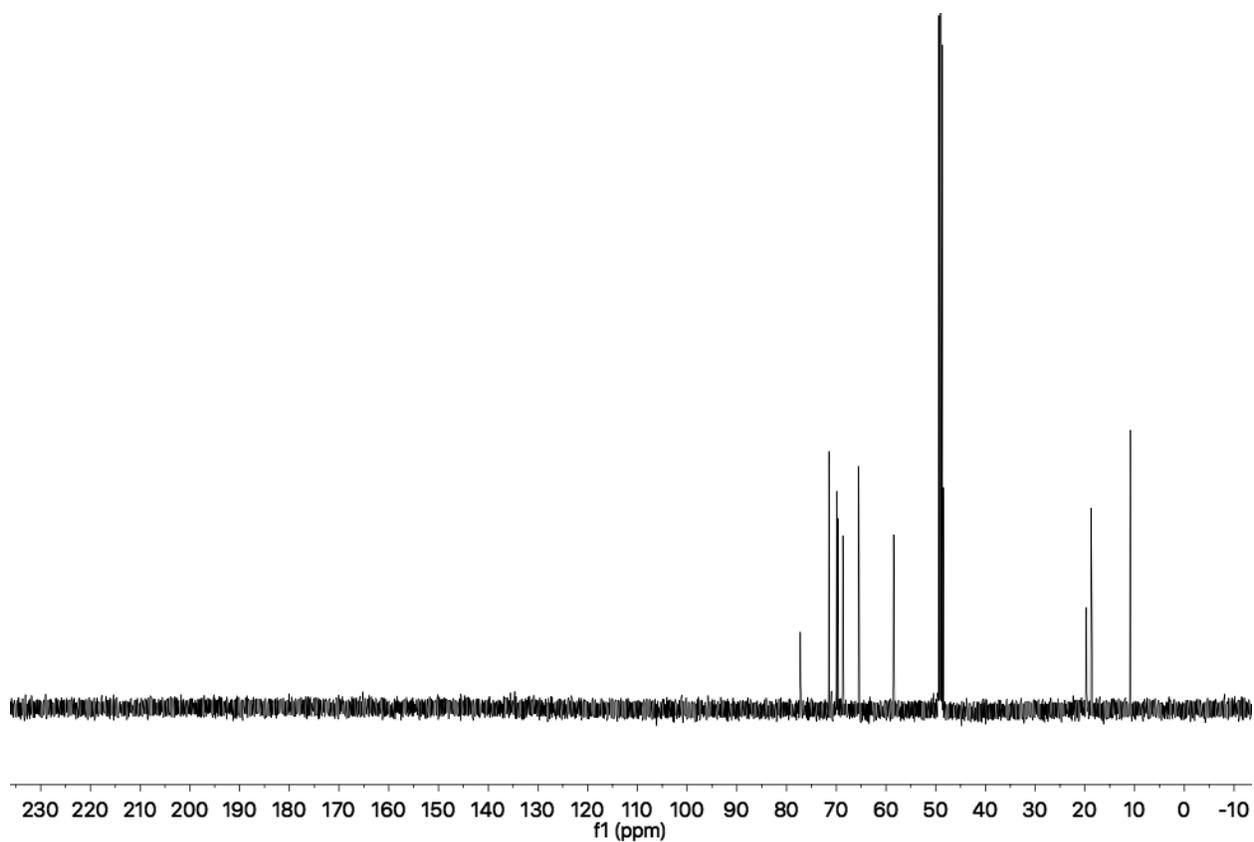
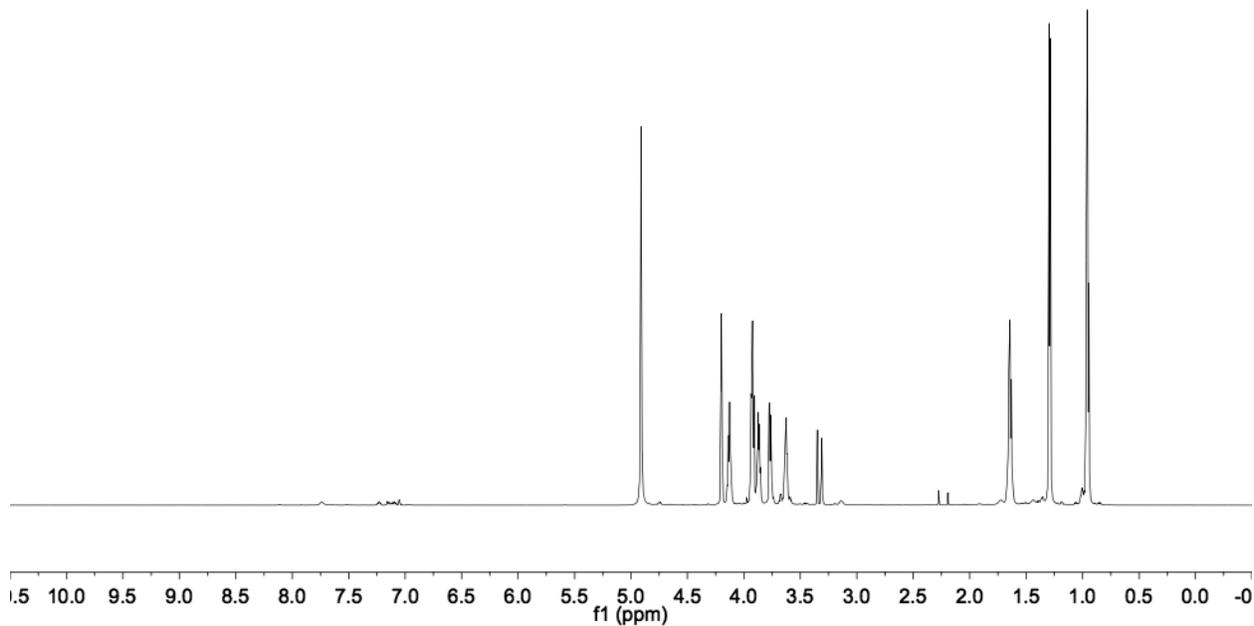


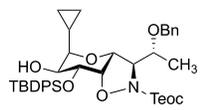
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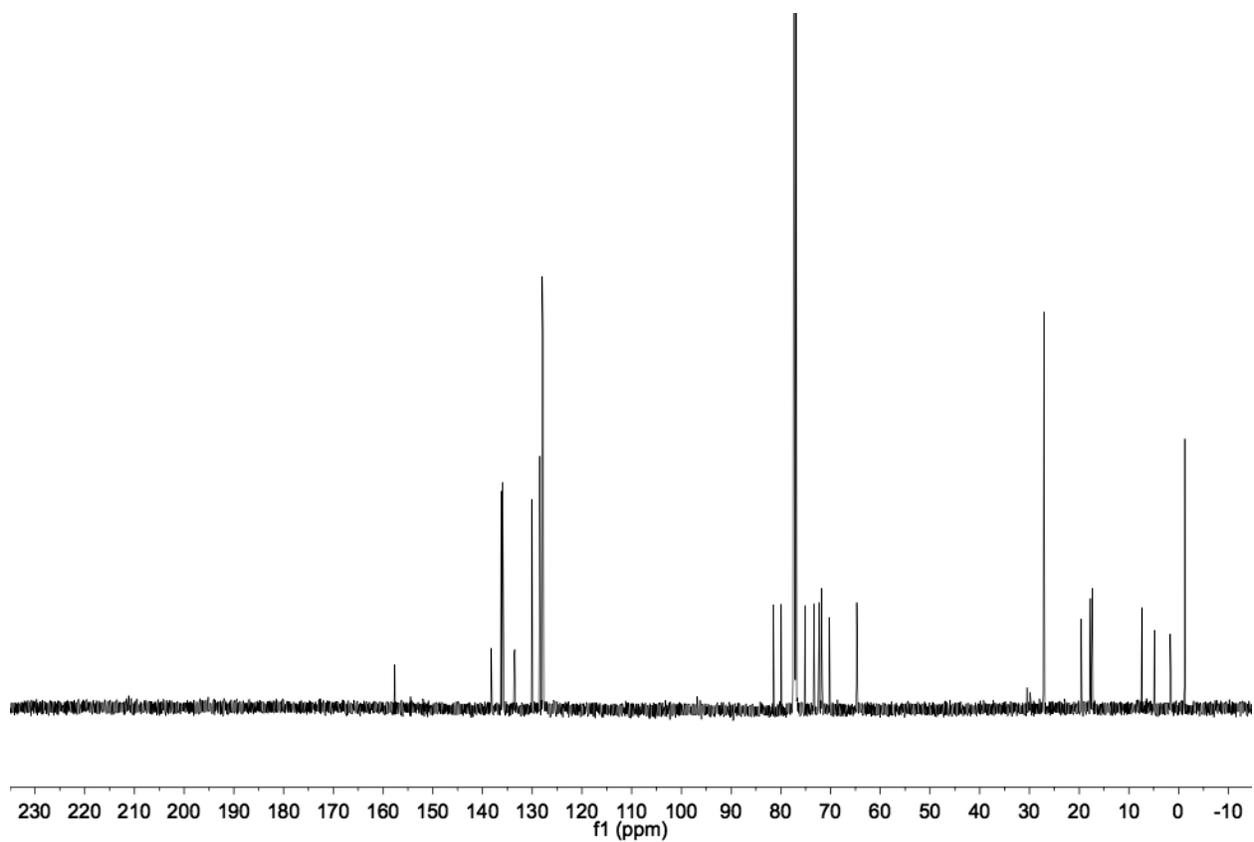
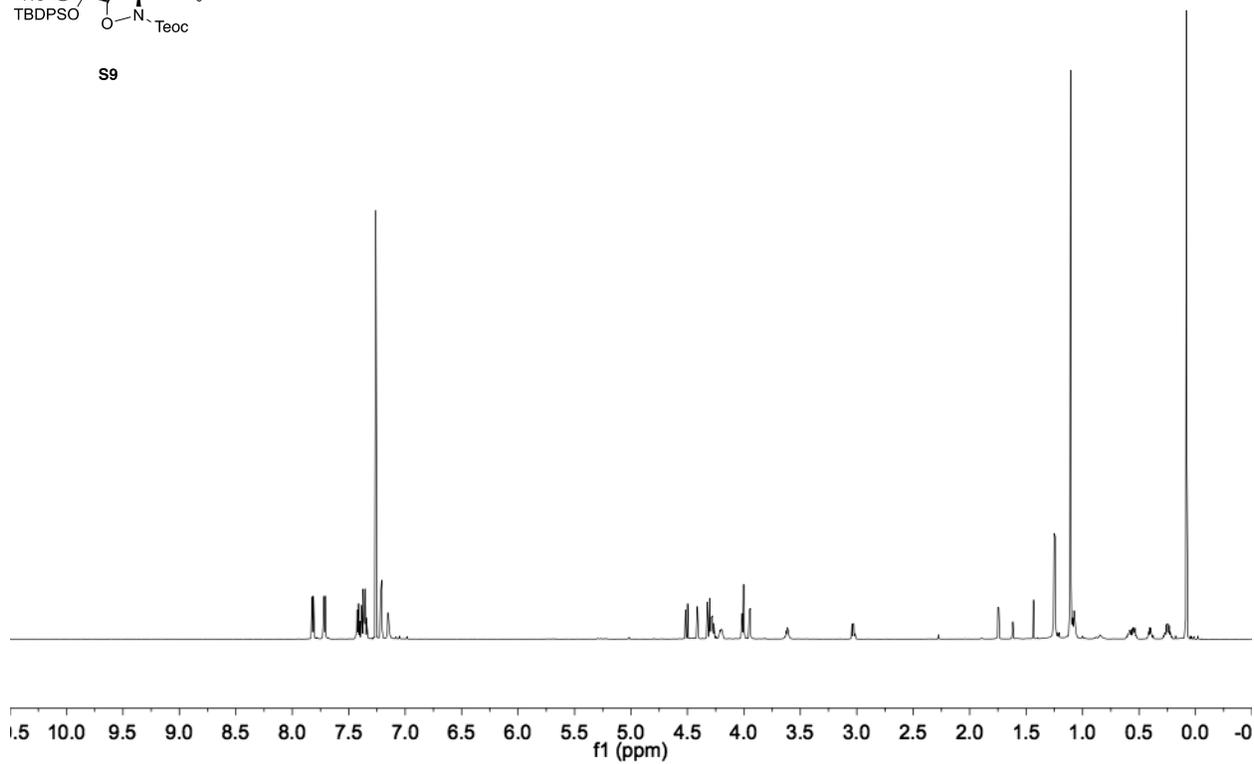


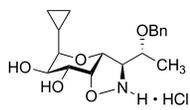
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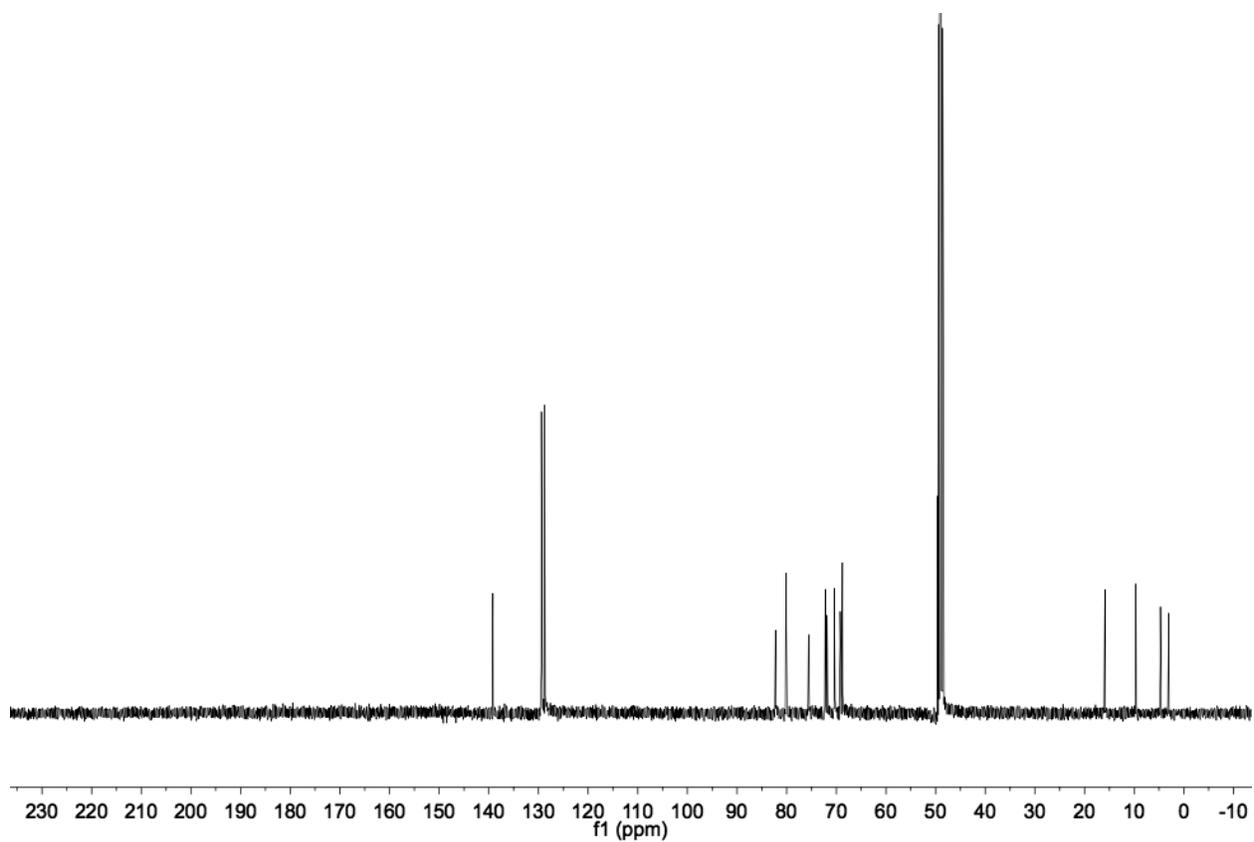
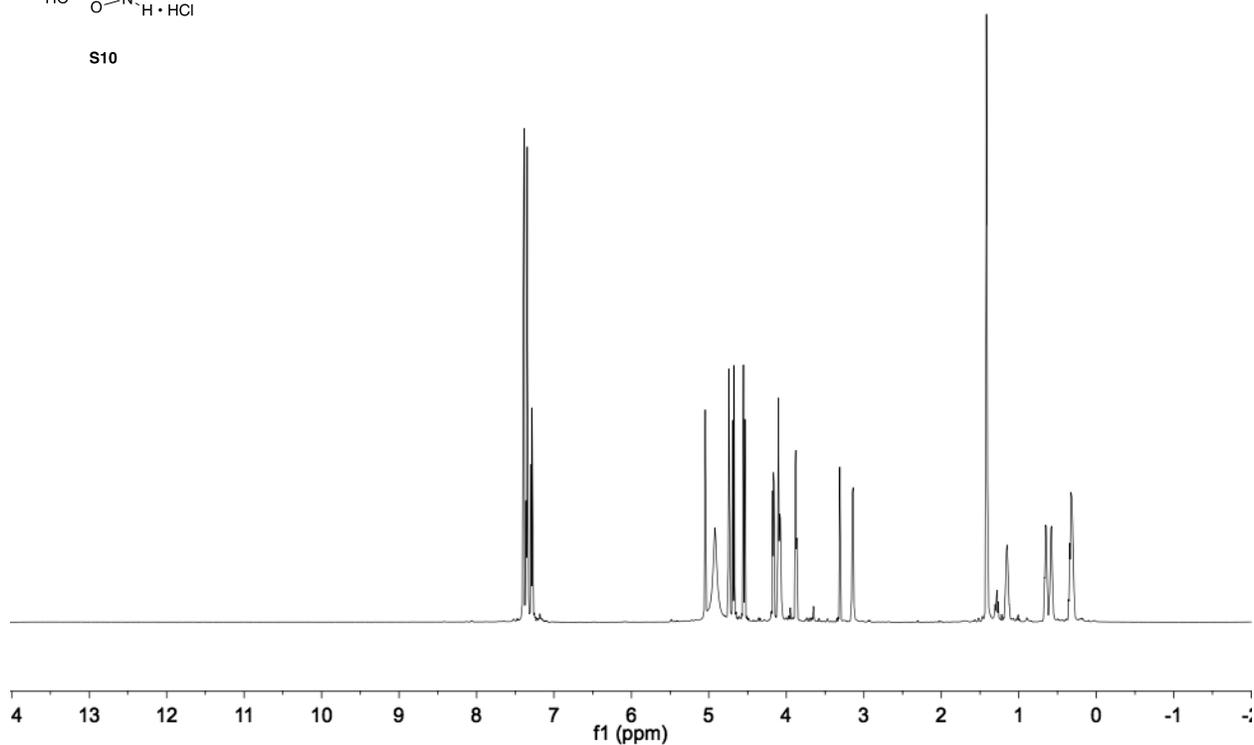


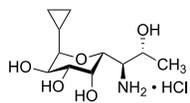
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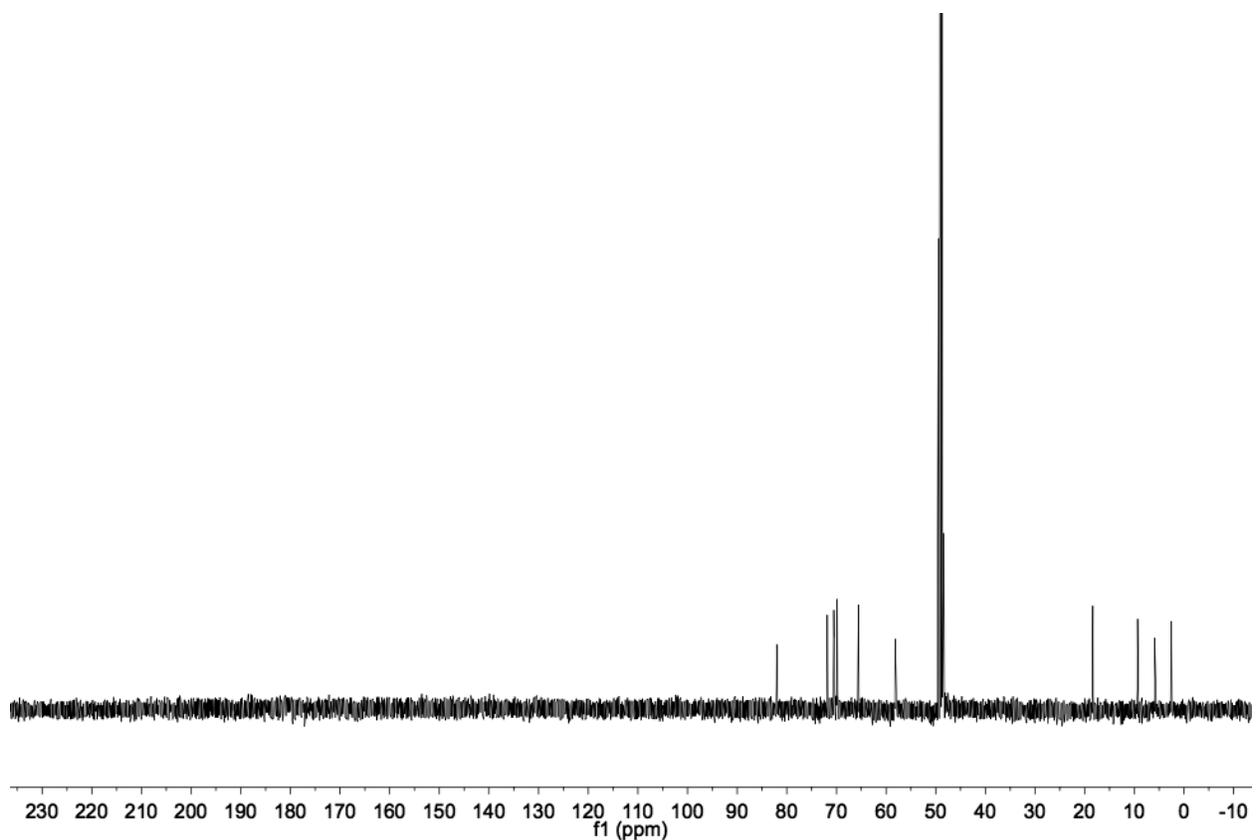
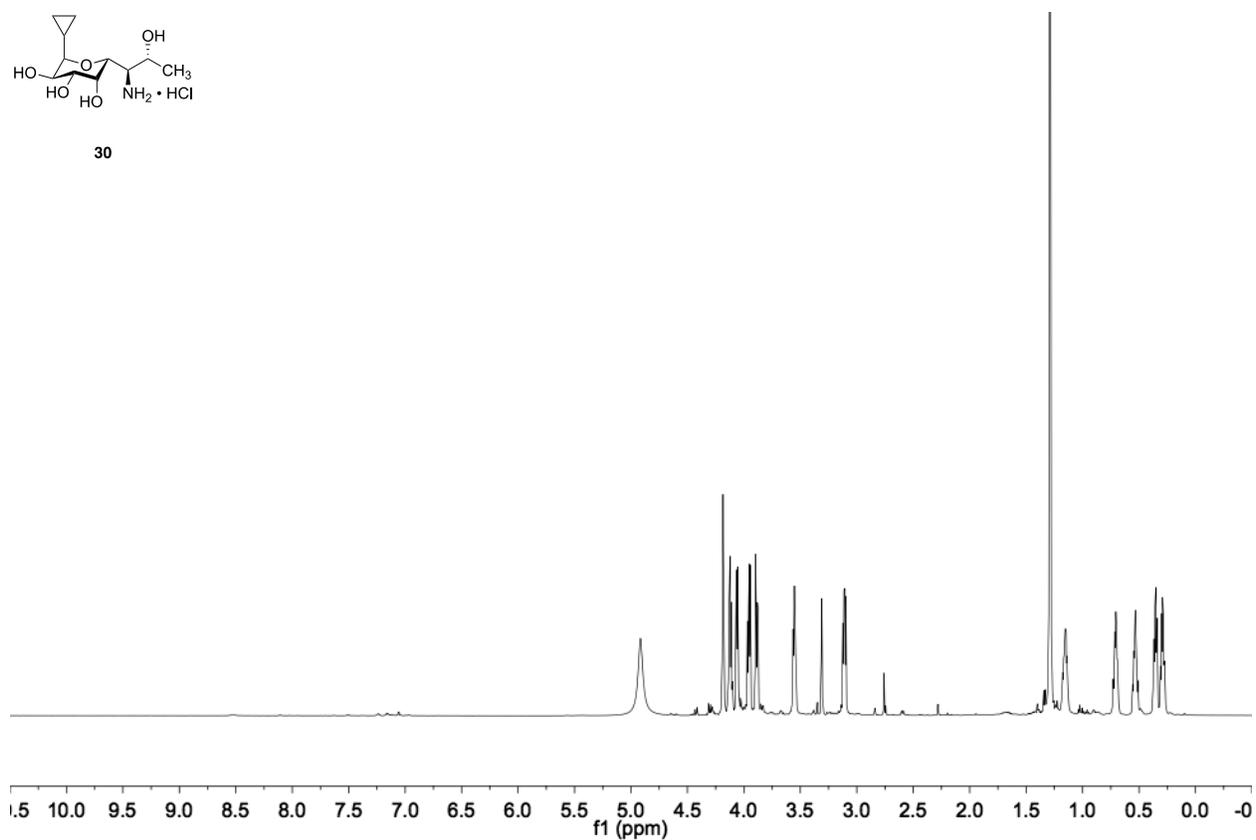


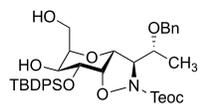
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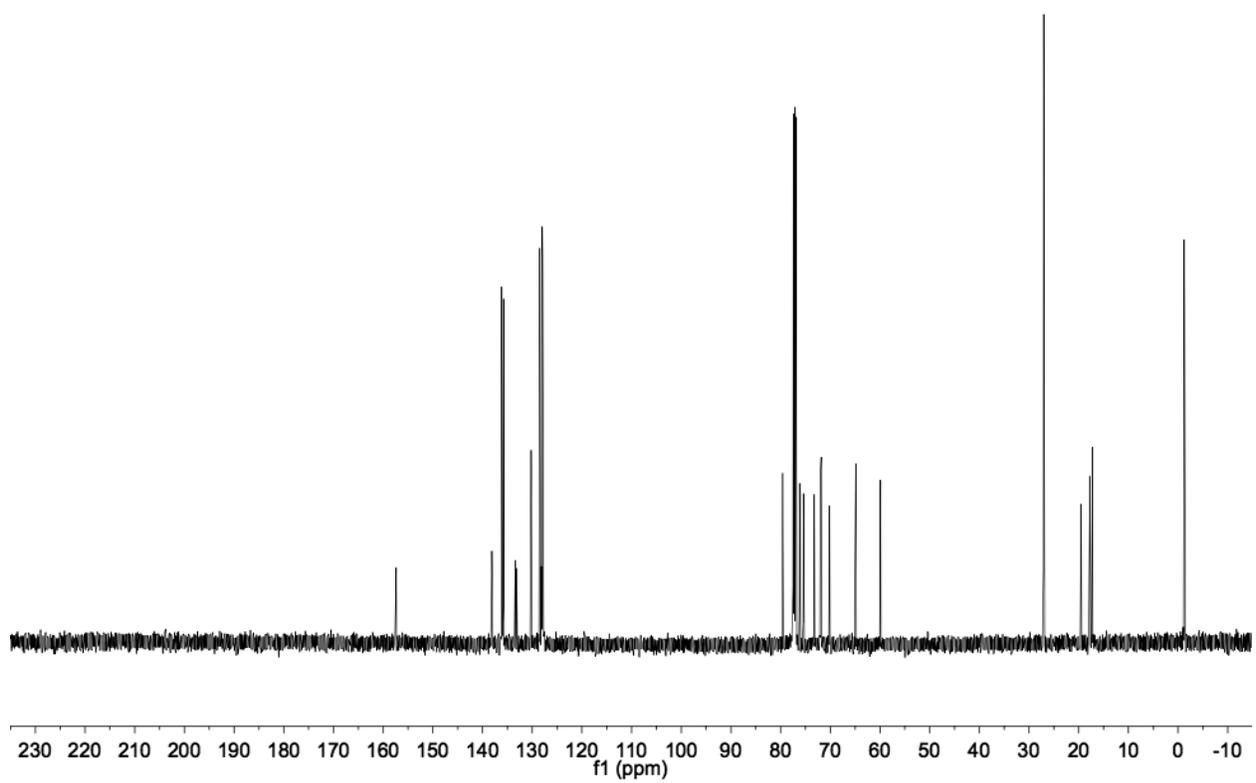
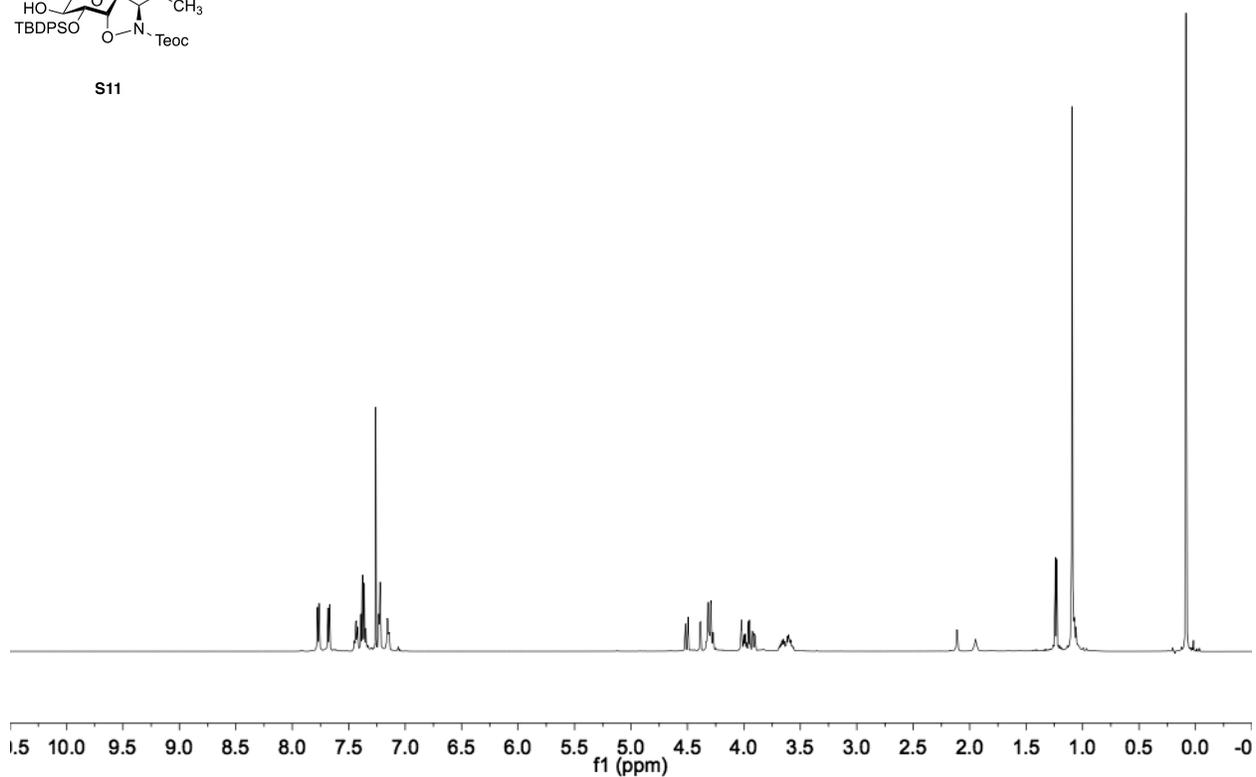


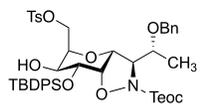
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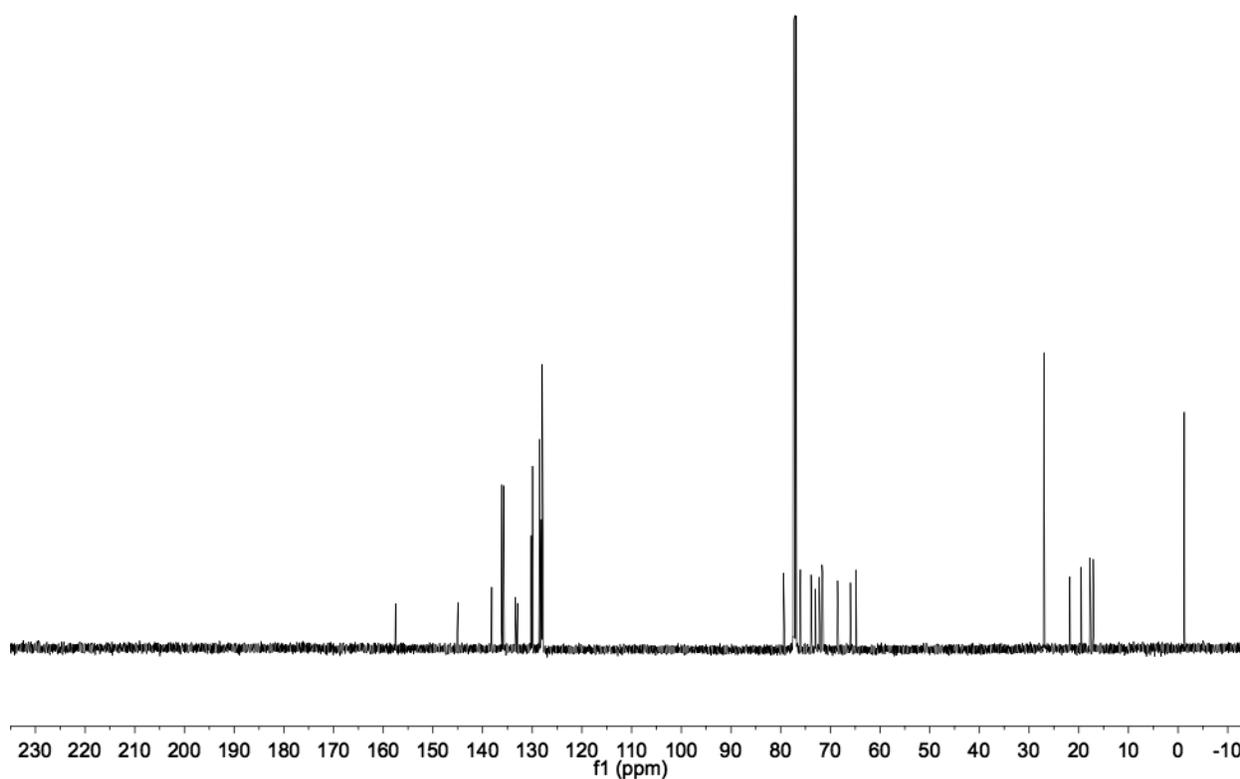
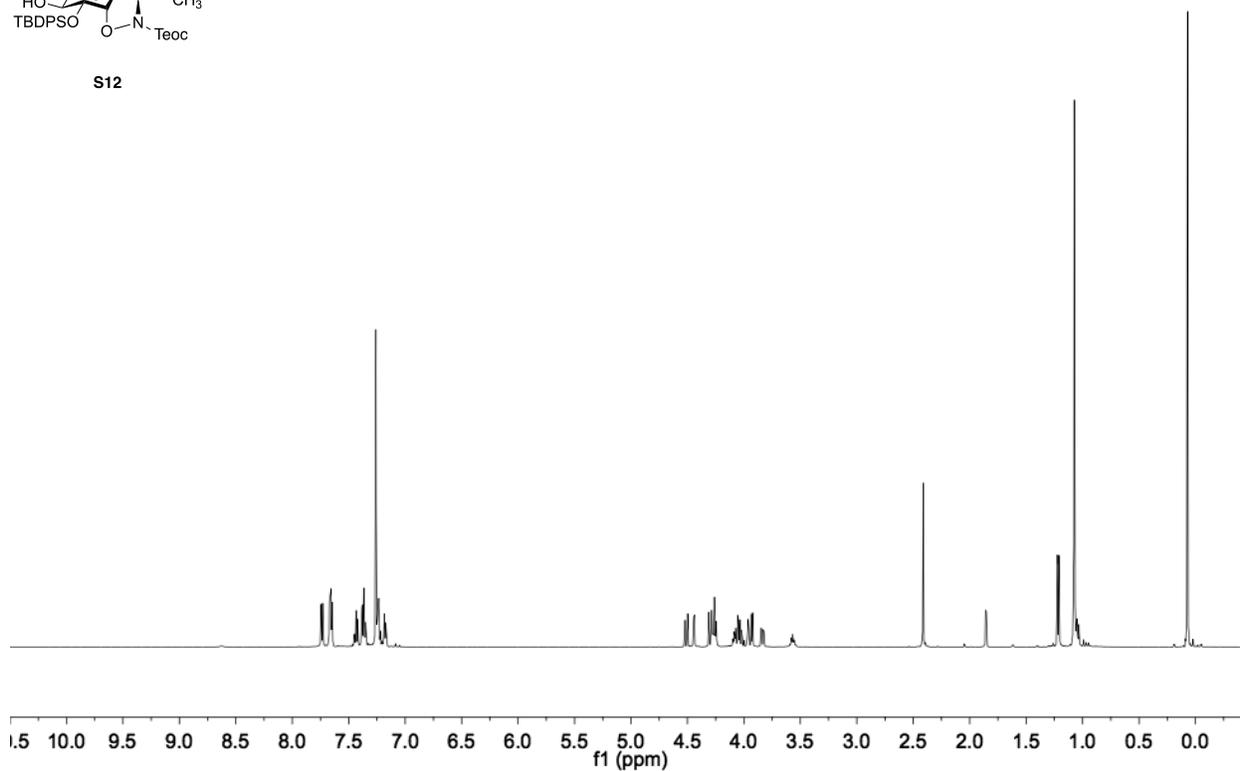


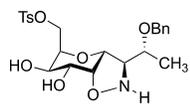
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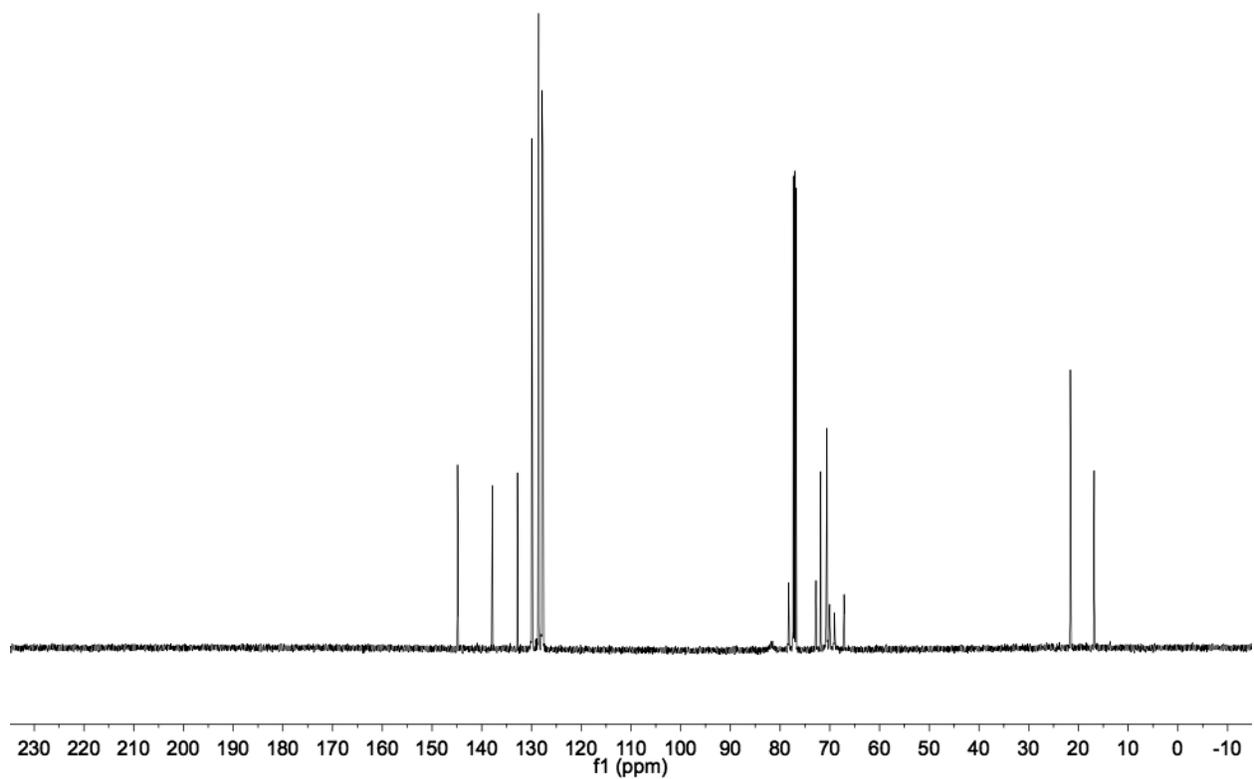
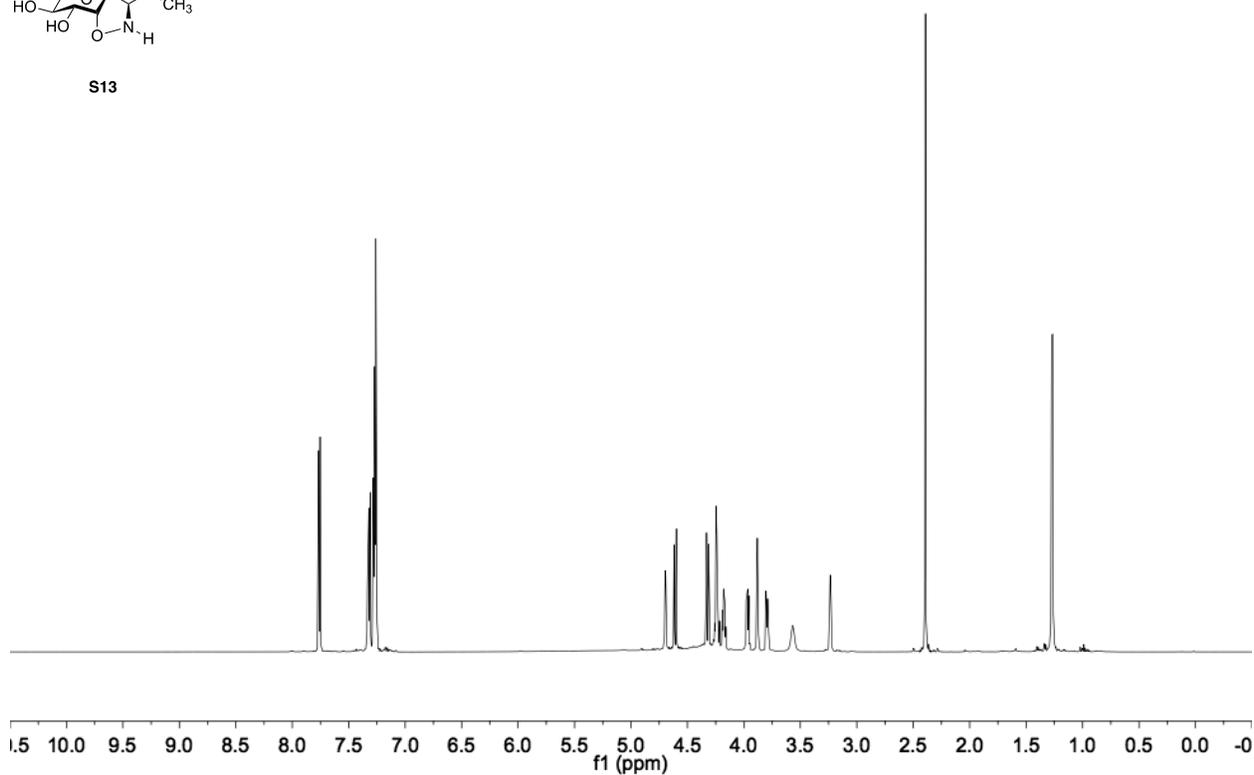


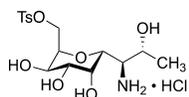
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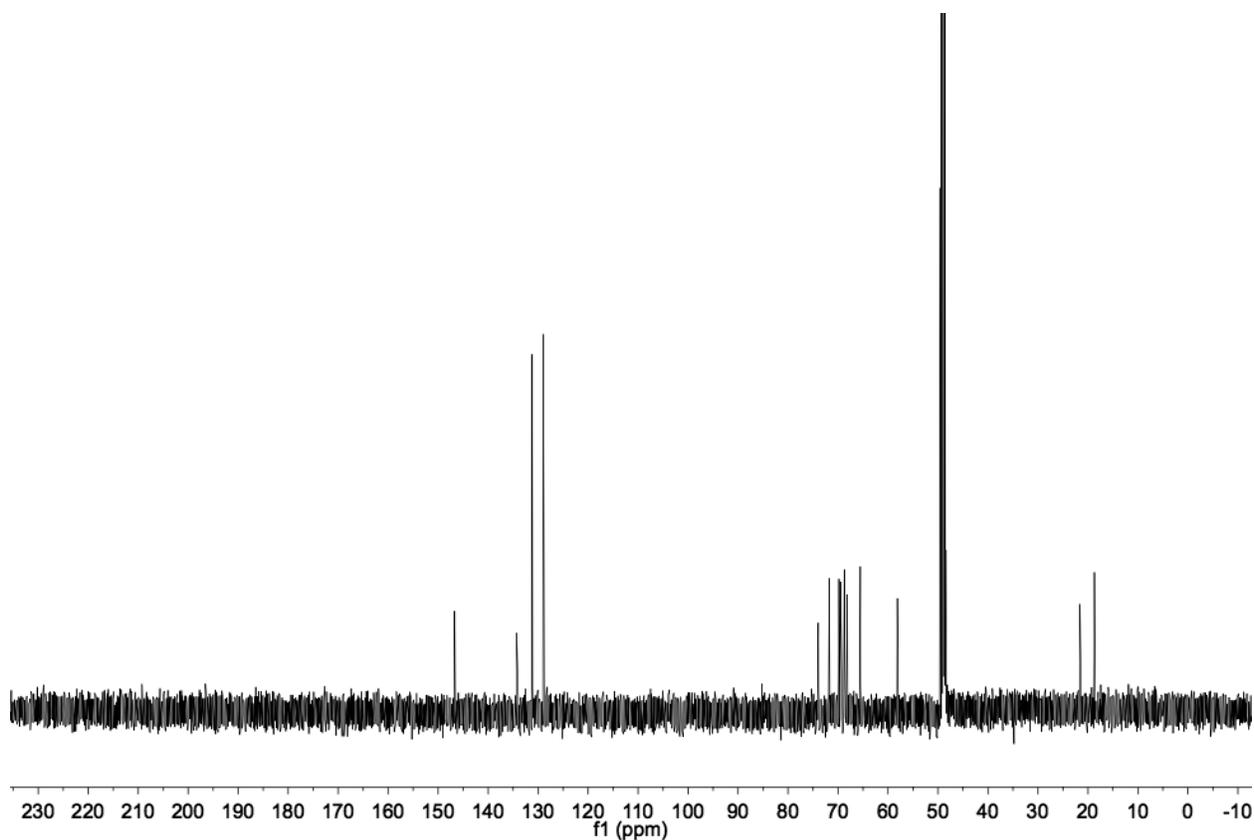
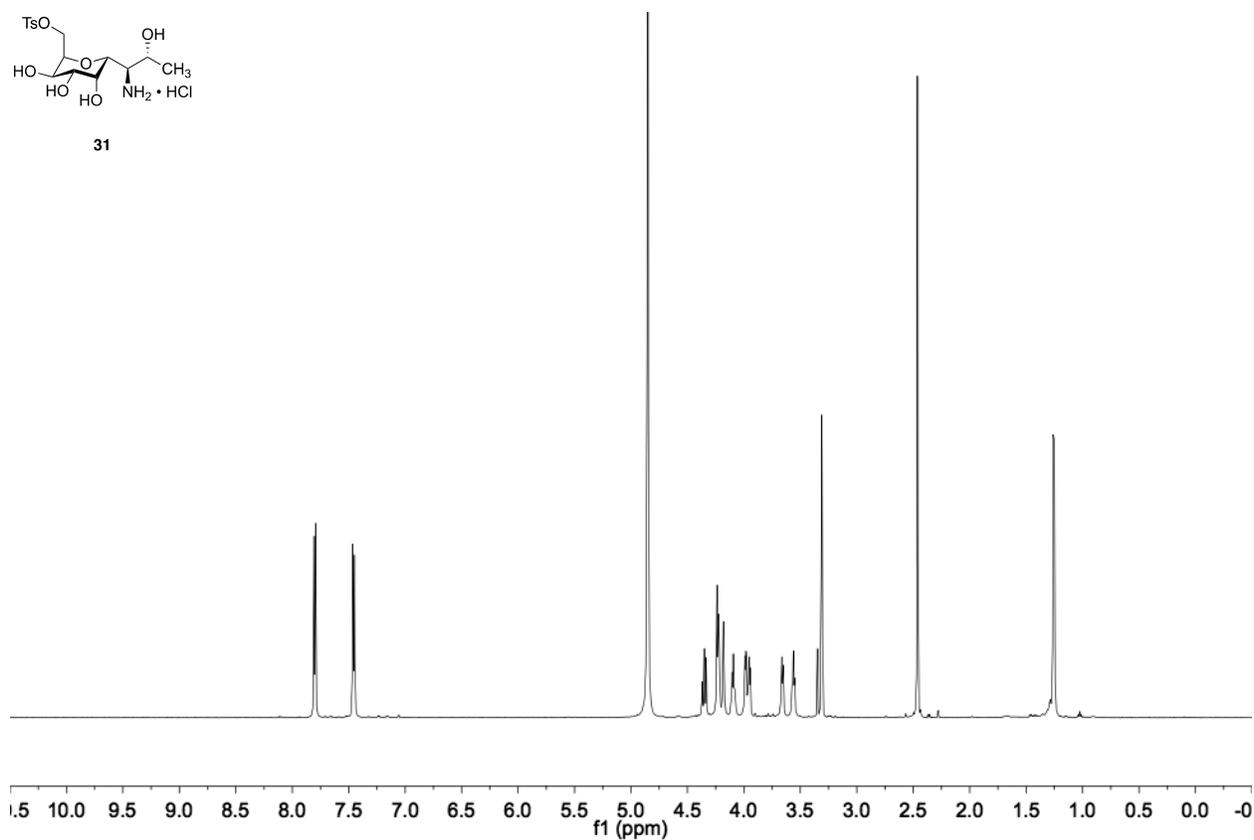


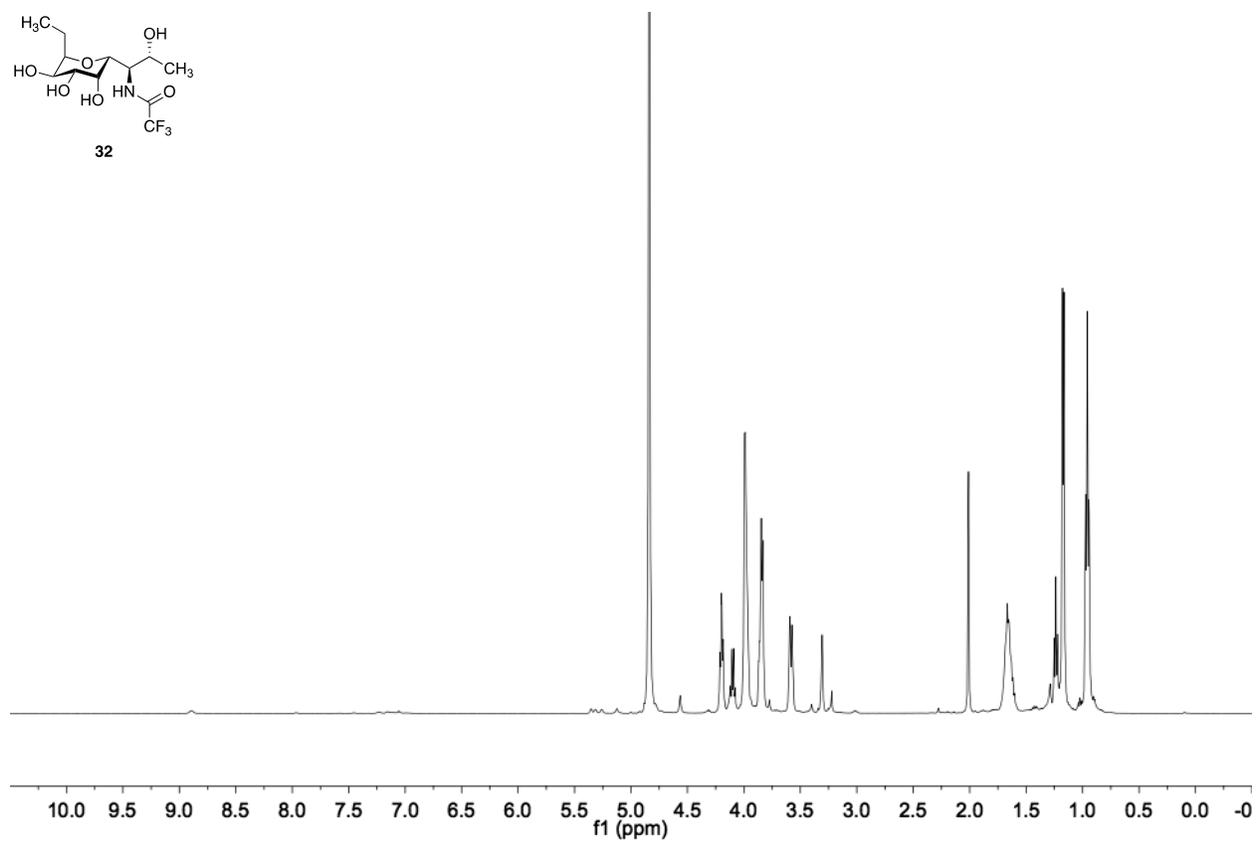
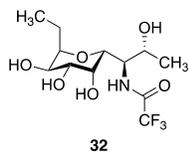
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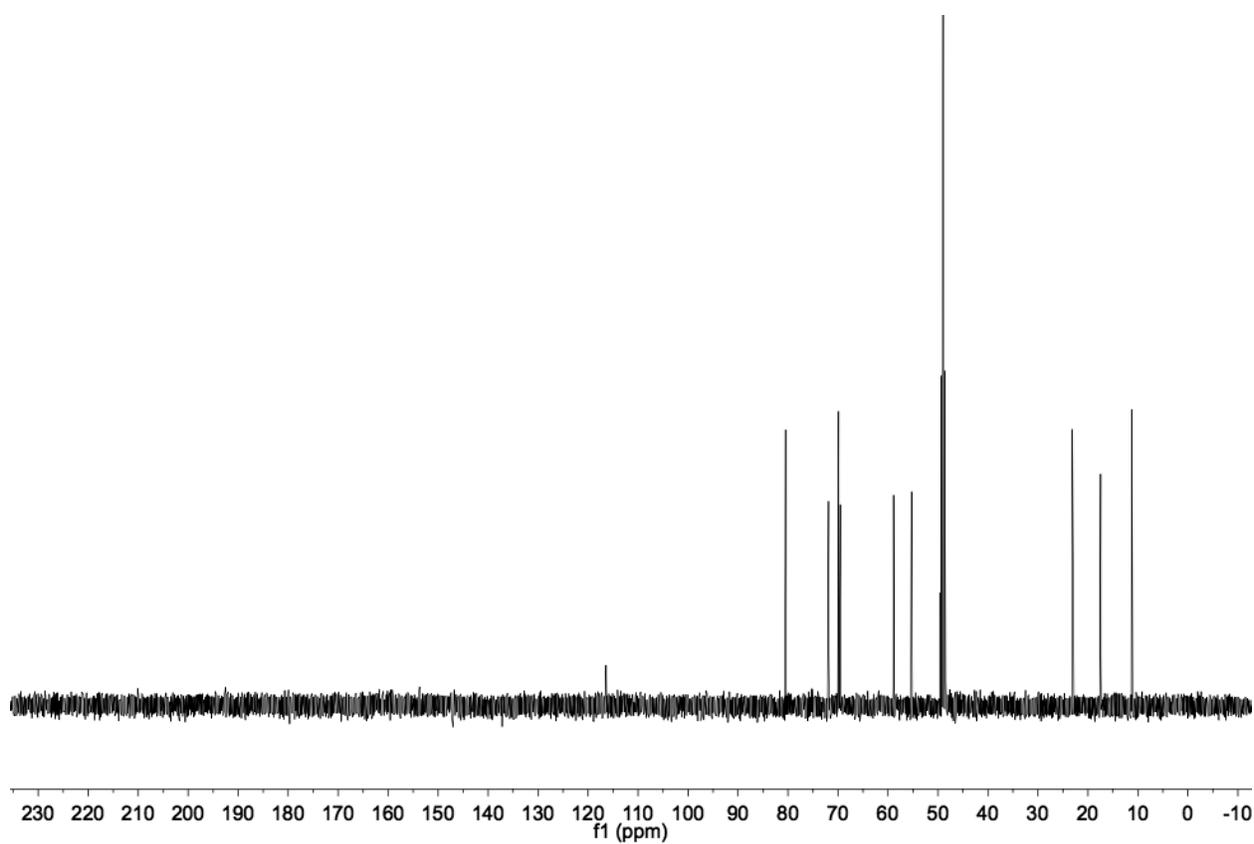
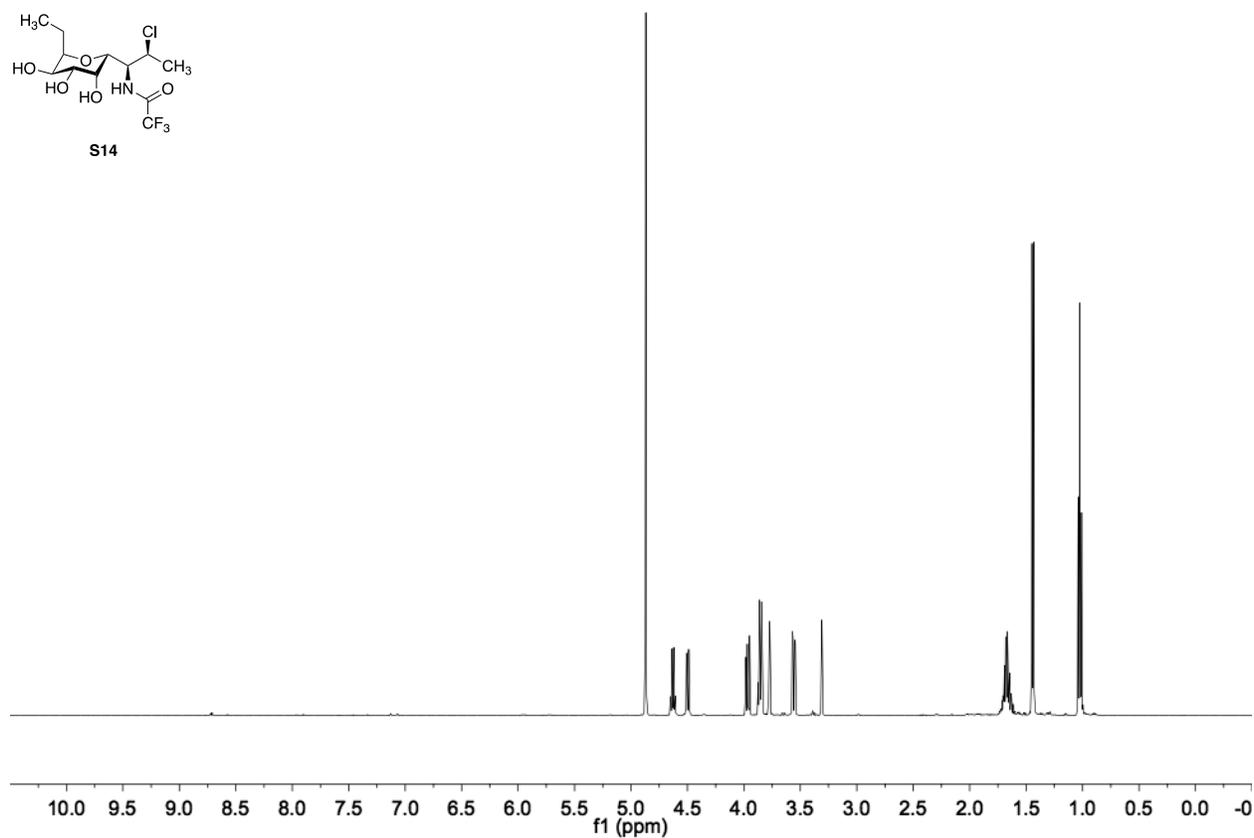
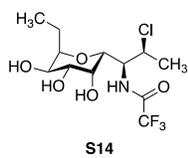


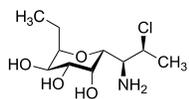


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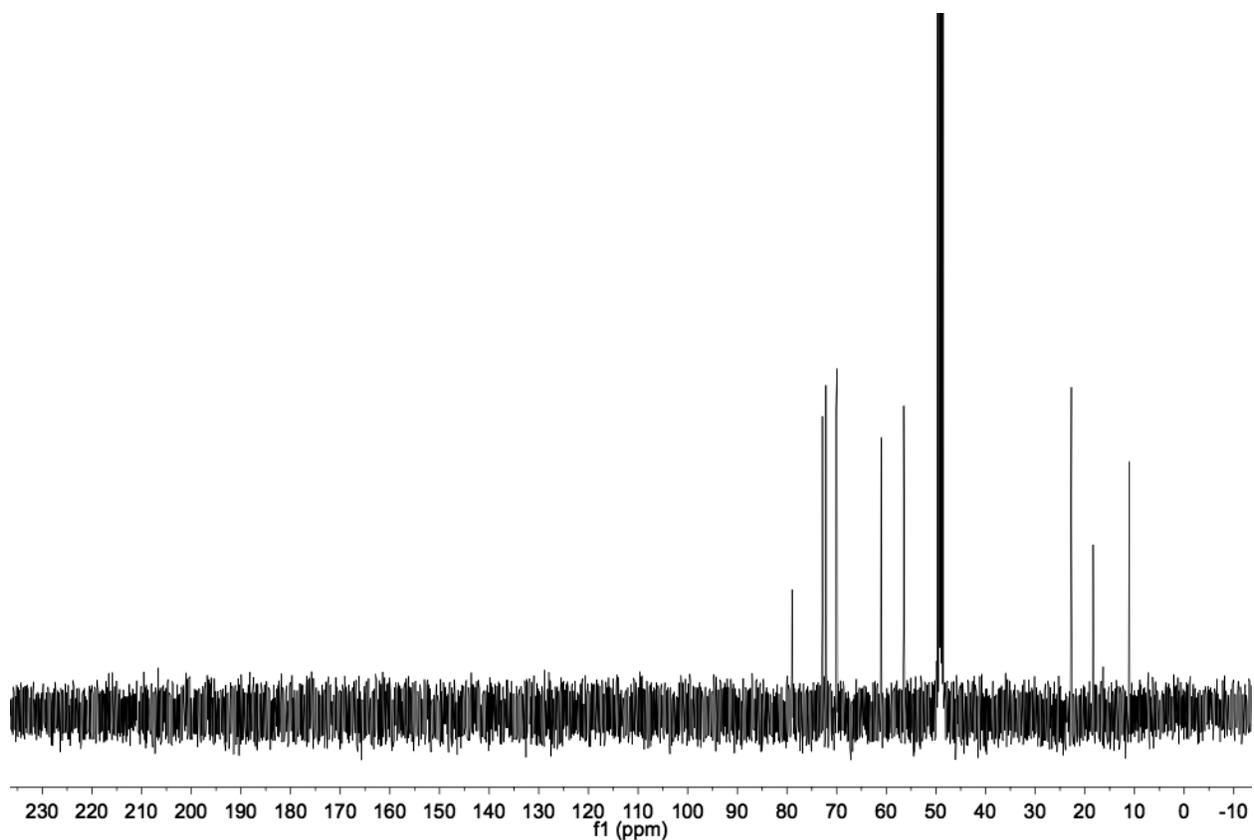
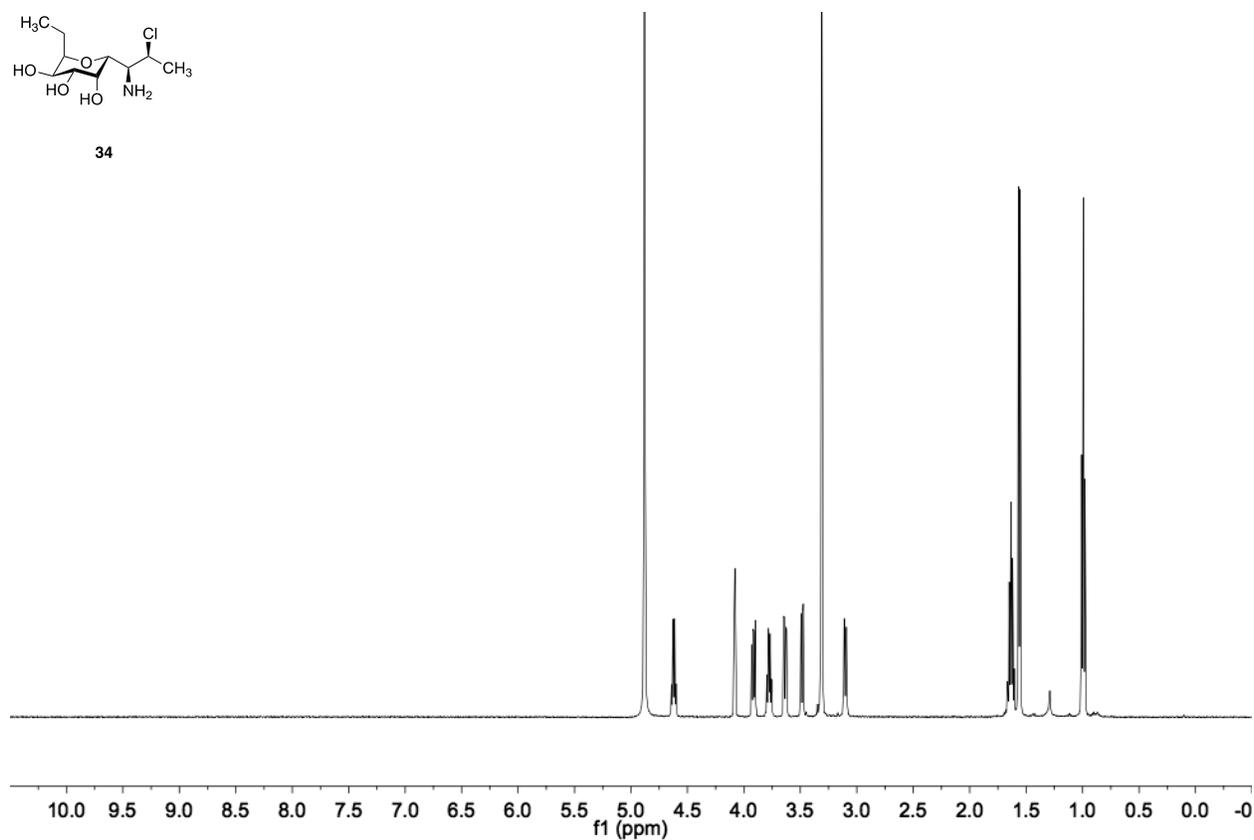


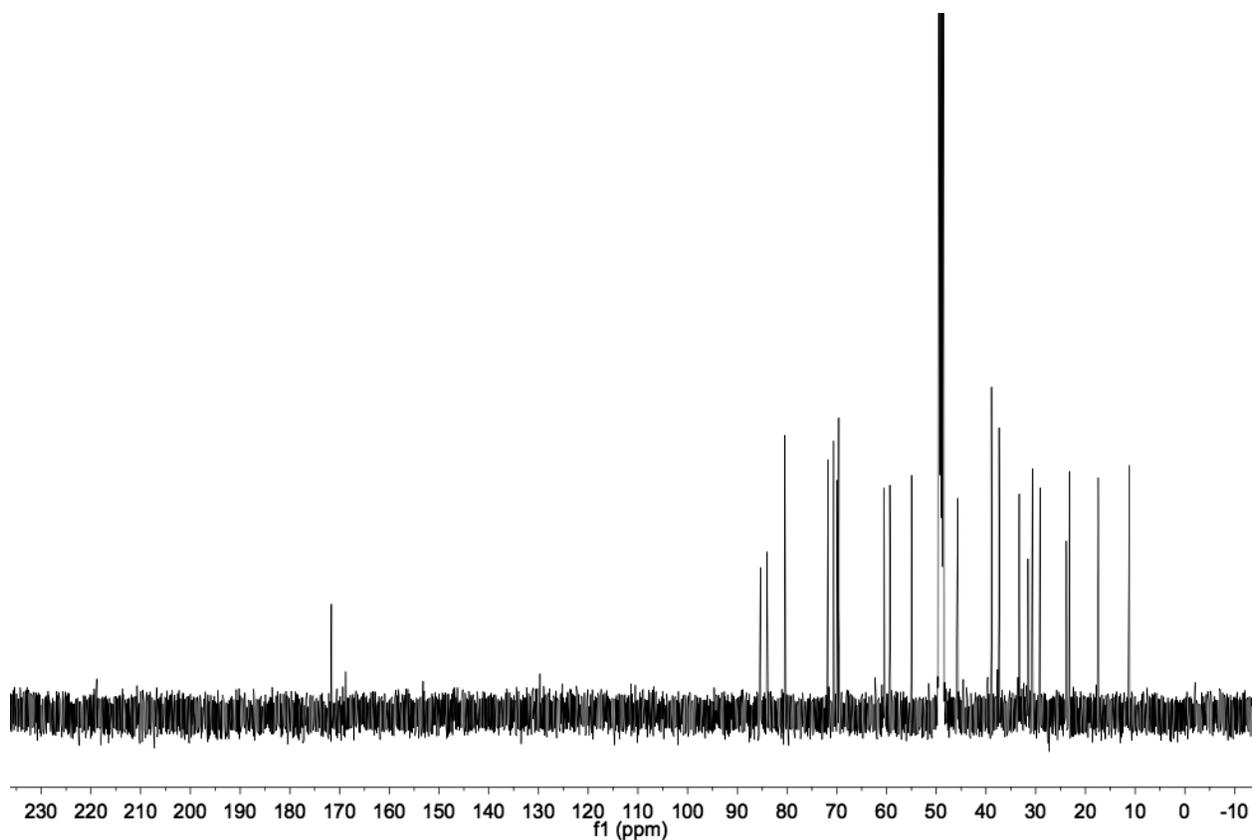
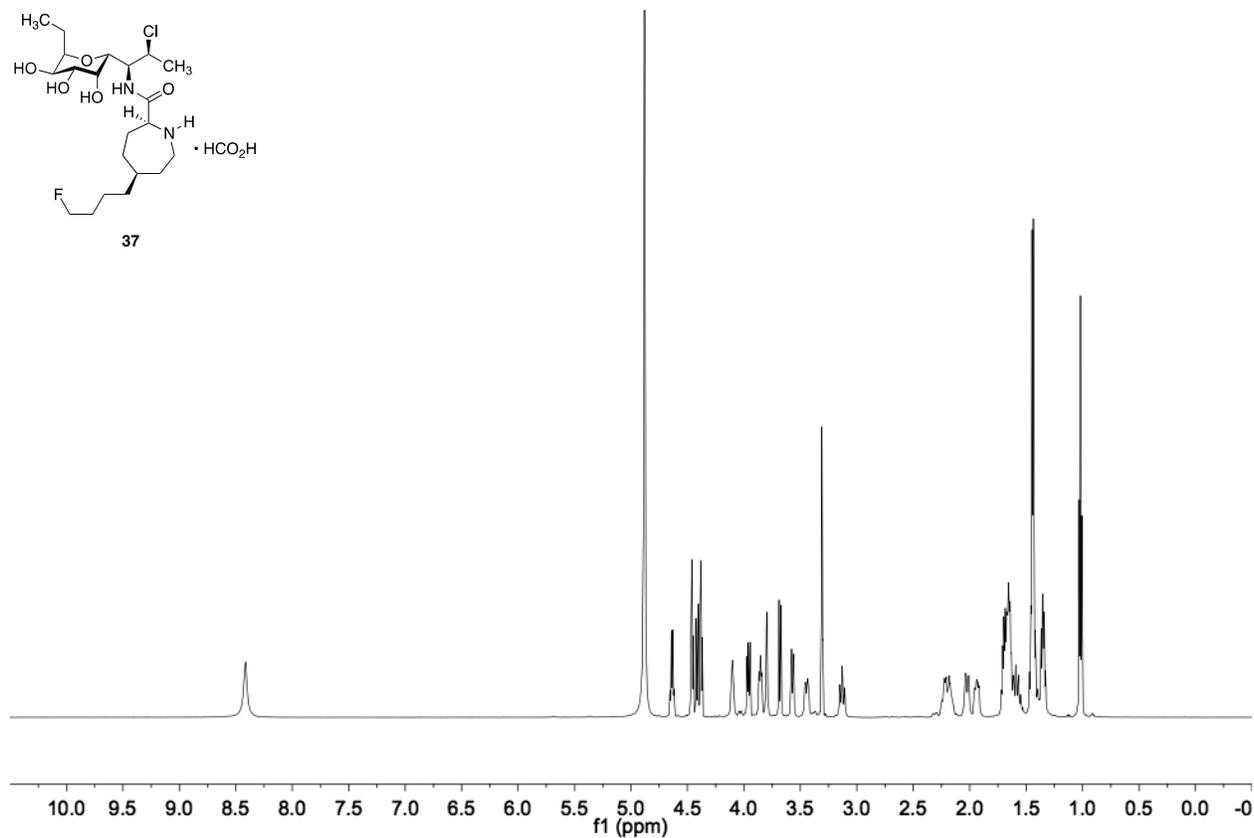
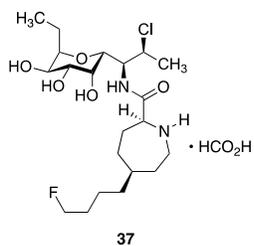


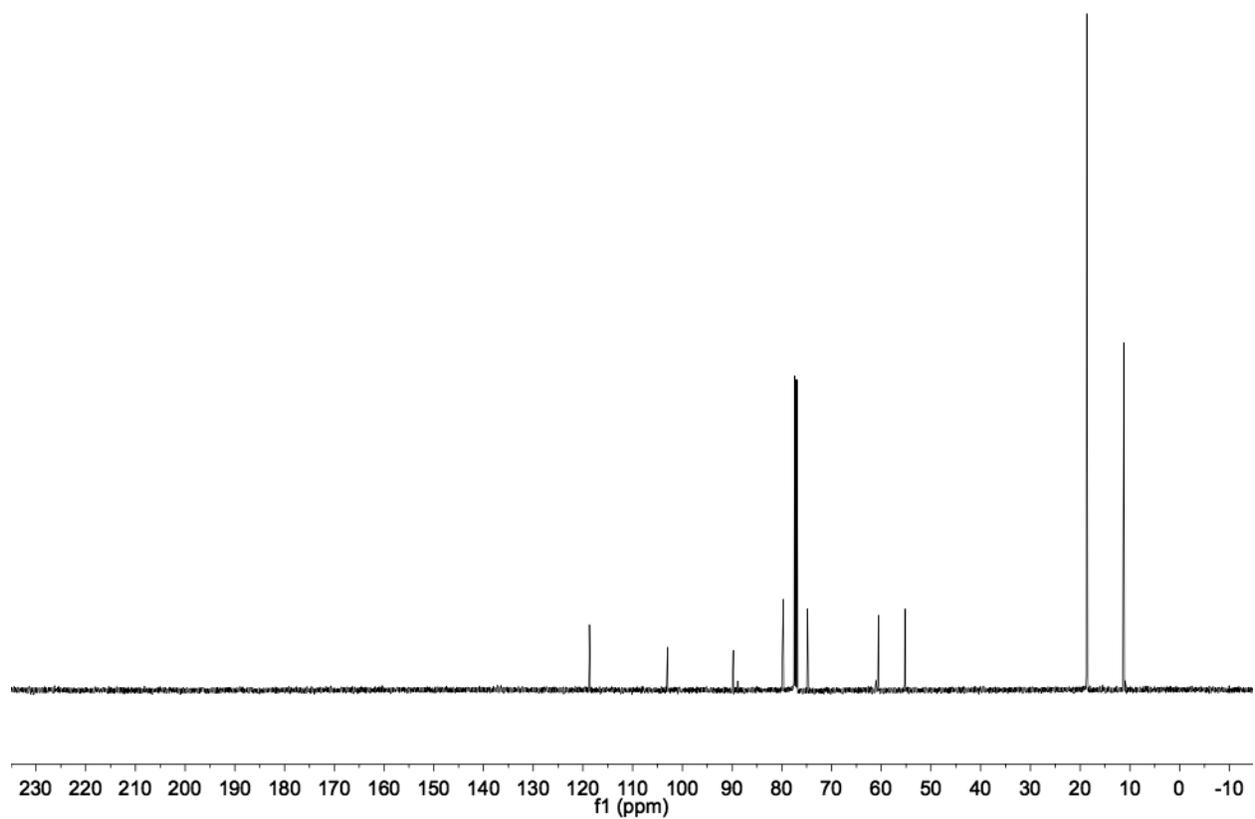
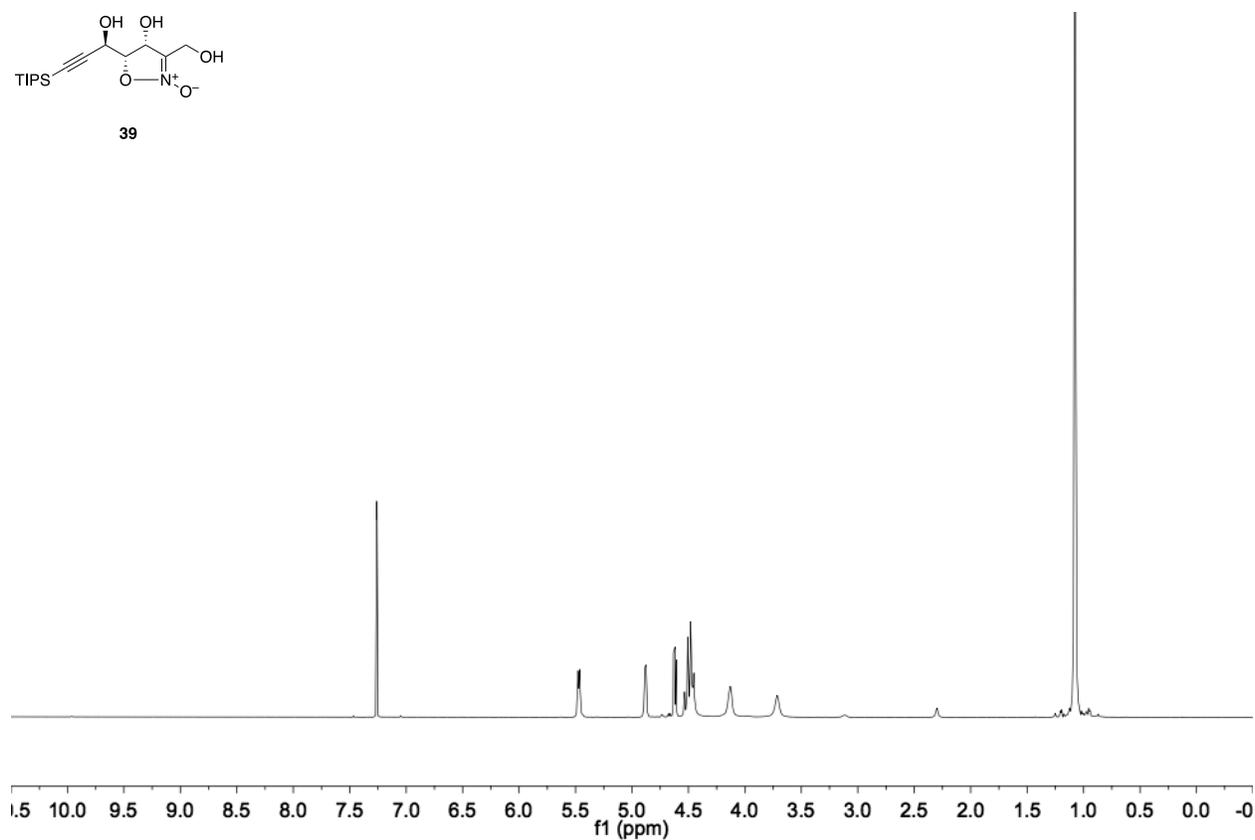
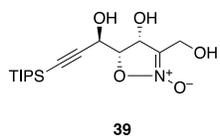


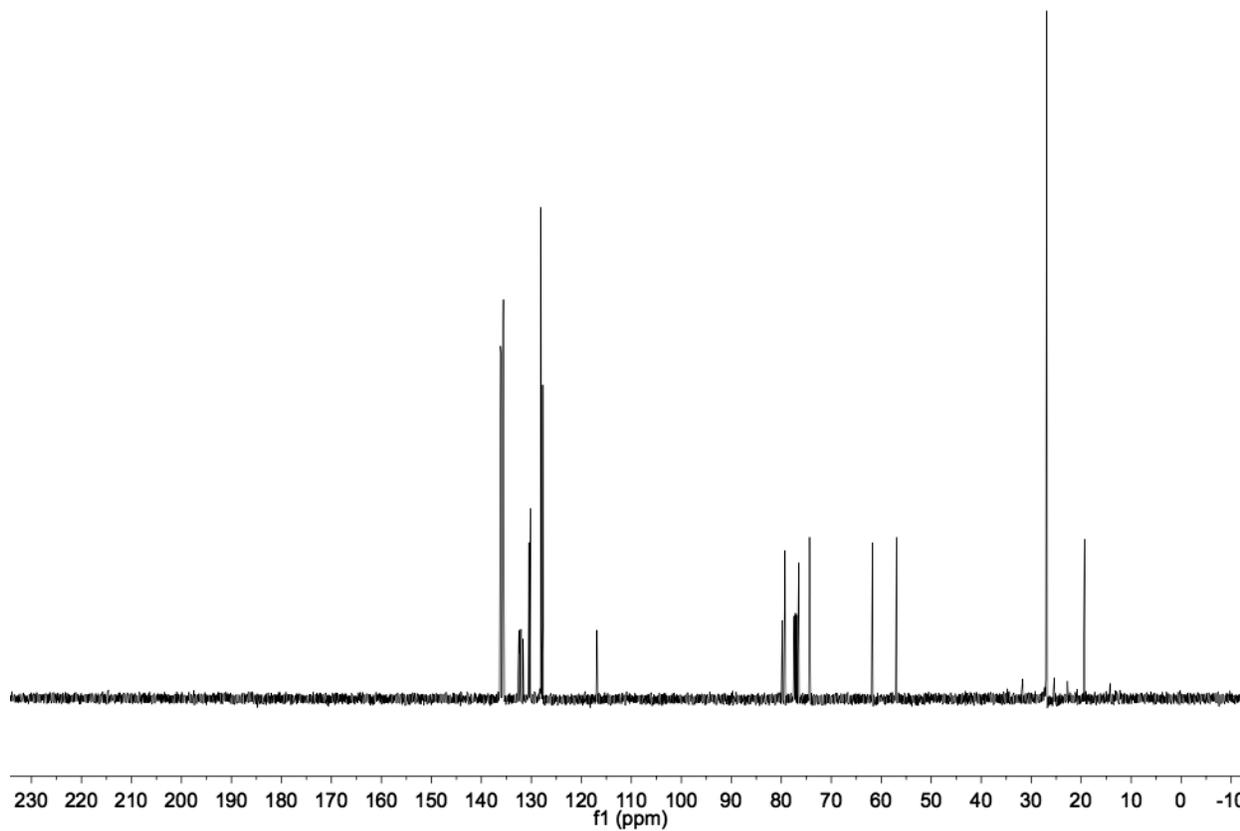
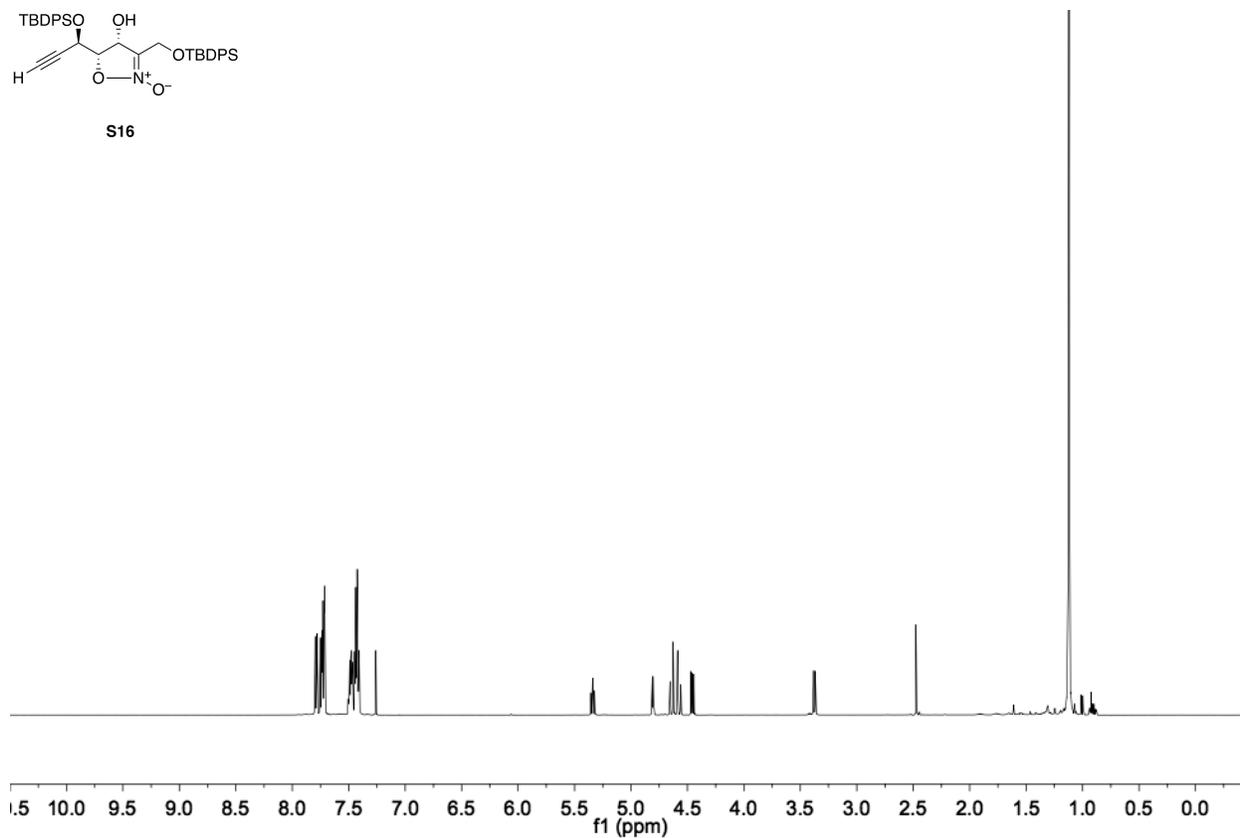
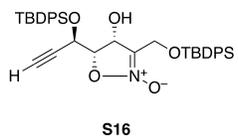


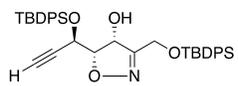
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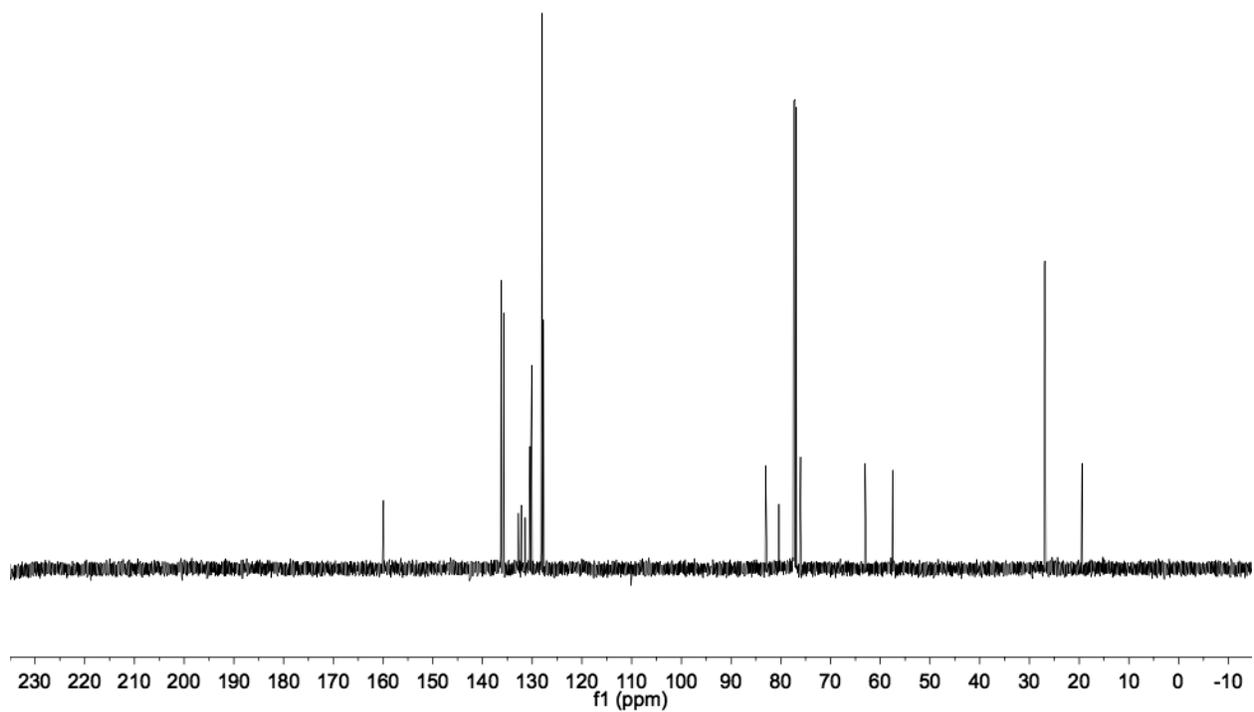
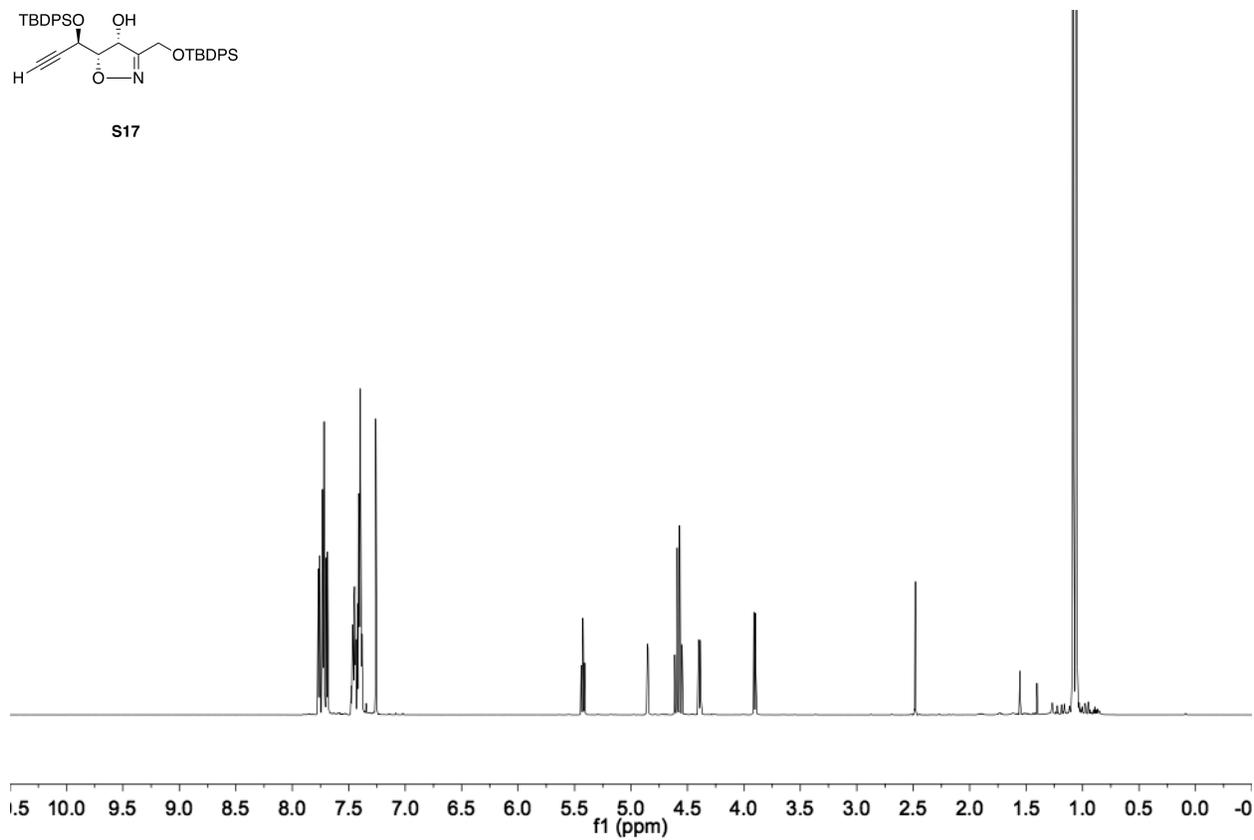


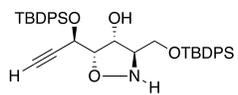






S17





S18

