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Sulfamate-Tethered *Aza*-Wacker Cyclization Strategy for the Syntheses of 2-Amino-2-deoxyhexoses: Preparation of Orthogonally Protected D-Galactosamines

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Abstract

We present a new strategy for the assembly of protected D-galactosamine synthons. Our route uses a sulfamate-tethered *aza*-Wacker cyclization as a key step and commences from D-erythrono-1,4-lactone. This stands in contrast to most literature syntheses of 2-amino-2-deoxyhexose derivatives, as these generally employ glycals or hexoses as starting materials. This strategy may serve as a template for the assembly of many other 2-amino-2-deoxyhexoses with protection patterns difficult to access by conventional methods.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02346.

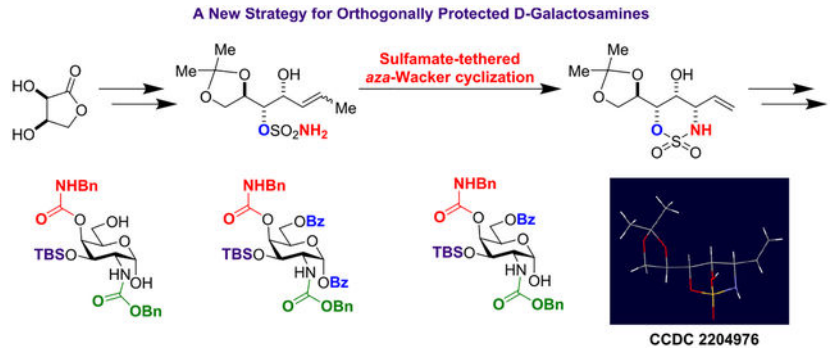
Includes additional experimental details such as structural reasoning, X-ray crystallographic data, and NMR spectra (PDF)

Accession Codes

CCDC 2204976 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c02346

The authors declare no competing financial interest.



INTRODUCTION

D-Galactosamine (Figure 1) is one of the 2-amino-2-deoxyhexose monosaccharides, which are important components of polysaccharides and glycoproteins.[1] D-Galactosamine itself is biologically active and is a known hepatotoxin; for this reason, D-galactosamine is used as a reagent to induce hepatitis in animal models.[2] *N*-Acetyl-D-galactosamine is an essential component of chondroitin sulfate, a glycosaminoglycan that is abundant in cartilage.[3] D-Galactosamine derivatives are also found in blood group antigens, antifreeze glycoproteins, and glycosphingolipids.[1,4]

D-Galactosamine and *N*-acetyl-D-galactosamine are obtainable from hydrolysis of chondroitin sulfates,[5] but differentially protected derivatives require total syntheses. To date, almost all orthogonally protected D-galactosamines have been prepared using "heterocycle → heterocycle" approaches (Scheme 1A) with either glycals[6–8] or other hexoses[9–14] as starting materials.[15] Diverse alkene functionalization reactions have been employed for the transformation of glycals into D-galactosamine derivatives.[16–23] A variety of nucleophilic substitution protocols have been developed for the conversion of D-glucosamines into D-galactosamines.[24–30] Kulkarni and Emmadi have employed D-mannose as a starting material for D-galactosamine thioglycosides.[31,32]

We envisioned an alternate strategy for the preparation of an orthogonally protected D-galactosamine (Scheme 1B). Our laboratory has a programmatic focus on the development of tethered *aza*-Wacker technology for complex molecule synthesis.[33–36] In general, both classical[37–39] and tethered *aza*-Wacker cyclization reactions[40,41] have been underemployed as key steps in total syntheses. We thus imagined preparing new, orthogonally protected D-galactosamines using our laboratory's sulfamate-tethered *aza*-Wacker cyclization as a key step. Success with such a synthesis would allow access to interesting D-galactosamine synthons, but, more importantly, could represent a unique and potentially general strategy for the assembly of a variety of 2-amino-2-deoxyhexose monosaccharides.

RESULTS AND DISCUSSION

Our retrosynthetic analysis of an orthogonally protected D-galactosamine is shown in Scheme 2. Late-stage hemi-acetalization of **B** would form target **A**. Aldehyde **B** would be synthesized from intermediate **C** by oxidative alkene cleavage and oxathiazinane

ring-opening. Sulfamate **D**, obtained from sulfamoylation of **E**, would be converted into oxathiazinane **C** using our laboratory's sulfamate-tethered *aza*-Wacker cyclization reaction. We envisioned that **E** would be accessible from intermediate **F** using a Grignard addition/ketone reduction sequence.

Our synthesis commenced with ring-opening of D-eryth-rono-1,4-lactone (**1**) with morpholine followed by ketalization with 2,2-dimethoxypropane and 10-CSA (Scheme 3).[42] Protection of the secondary alcohol into its corresponding TBS ether proceeded smoothly with TBSOTf/2,6-lutidine to furnish **3**. Subsequent addition of propenyl magnesium bromide (commercially available as a cis/trans mixture or freshly prepared from 1-bromo-1-propene and magnesium) formed enone **4**. While the reaction did not go to completion even with 3 equivalents of the Grignard reagent, the overall mass balance was satisfactory, and starting material **3** could be recovered and recycled. Luche reduction with $NaBH_4/CeCl_3$ $7H_2O$ formed allylic alcohol **5** with excellent chemoselectivity and diastereocontrol (dr > 20:1). The allylic alcohol was transformed into its corresponding benzoate ester **6** using benzoyl chloride/TMEDA. The TBS group was cleaved with TBAF/THF, and the resulting alcohol was sulfamoylated with $ClSO_2NH_2$ (prepared in situ by the addition of HCO_2H to $ClSO_2NCO$[43]) in a mixture of CH_3CN/DMA.

Sulfamate **8** was then subjected to one of the protocols that our laboratory has previously developed for *aza*-Wacker cyclizations[35] (Scheme 4). When **8** was heated to 55 °C with a mixture of $Pd(OAc)_2$ and $Cu(OAc)_2$ under 1 atm of O_2 in CH_3CN, the mass balance of the reaction was poor, and no desired product was observed. Several investigators have established that Pd(II) salts catalyze efficient [3,3]-sigmatropic rearrangements of allylic esters.[44–48] We know from our own experience that allylic sulfamates are generally very unstable; thus, we hypothesized that a Pd(II)-catalyzed [3,3]-sigma-tropic rearrangement was a likely pathway leading to unproductive consumption of **8**.

The benzoate ester was hydrolyzed using K_2CO_3/MeOH to form **9** (Scheme 5). We were pleased to see that when **9** was heated with $Pd(OAc)_2$ (15 mol %) and 1 equiv of $Cu(OAc)_2$ under 1 atm of O_2 in CH_3CN, cyclized product **10** formed in a 32% yield (Scheme 5, entry 1) and as a single diastereomer. A crystal structure of **10** allowed us to assign product identity and stereochemistry unambiguously (CCDC 2204976). The reaction yield was similar with 15 mol % of $Pd_2(dba)_3$ (Scheme 5, entry 2), but we observed a much better result upon switching to $PdCl_2(nbd)$ and $Pd(PhCN)_2Cl_2$ (Scheme 5, entries 3 and 4). Switching solvents from CH_3CN to dioxane or to DMA (Scheme 5, entries 5 and 6) was deleterious, but reaction performance was reasonable in DMSO (Scheme 5, entry 7). The Yu laboratory has shown that mono-protected amino acid (MPAA) ligands are excellent in promoting Pd(II)–Pd(0) catalytic cycles in C–H functionalization reactions.[49–51] *Aza*-Wacker cyclization reactions also proceed via a Pd(II)–Pd(0) redox manifold, and we thus hypothesized that an MPAA ligand may boost reaction performance. In line with this idea, we were pleased to see a 15% boost in yield when 1 equiv of Fmoc-Gly-OH and 4 Å molecular sieves were added to the reaction mixture (Scheme 5, entry 9).

Moving forward, the secondary alcohol was transformed into the corresponding TBS ether using TBSOTf/2,6-lutidine (Scheme 6). We[34] and others[43,52,53] have established

that activated oxathiazinane heterocycles are excellent synthons for ring-opening with a variety of nucleophiles. Accordingly, a Cbz group was appended to oxathiazinane **11** using benzyl chloroformate and TMEDA, and ring-opening was effected by heating **12** with KOAc in DMSO to form linear intermediate **13**. Many biologically active natural products contain carbamoylated hexose components.[54] Thus, in our D-galactosamine synthons, we planned that one of the OH-protecting groups would be a carbamate. Accordingly, the acetate of **13** was hydrolyzed using K_2CO_3 in MeOH, and alcohol **14** was converted into benzyl carbamate **15** by heating with benzyl isocyanate in toluene. Dihydroxylation of **15** proceeded smoothly with 10 mol % $K_2OsO_4{\cdot}2H_2O$ and stoichiometric NMO. Cleavage with $NaIO_4$ formed an aldehyde that was unstable to purification and thus was immediately subjected to hemiacetalization with TsOH. Based on the coupling constant of the anomeric proton (~2 Hz), we conclude that cyclization selectively furnished the alpha anomer. The free alcohols of pyranose **17** were converted into their benzoate esters using benzoyl chloride and TMEDA. The anomeric benzoate could be selectively deprotected using $MeNH_2$ in THF.[55] Overall, **17**, **18**, and **19** represent new D-galactosamine synthons.

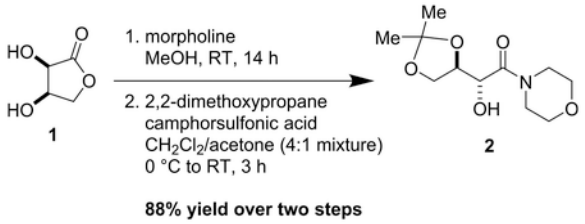
In summary, we present a new strategy for the assembly of protected D-galactosamine molecules, which we envision may be employed as synthetic intermediates for various applications. Our route uses a sulfamate-tethered *aza*-Wacker cyclization as a key step and commences from D-erythrono-1,4-lactone. This stands in contrast to most literature syntheses of 2-amino-2-deoxyhexose derivatives, which generally employ glycals or hexoses as starting materials. While we have focused specifically on D-galactosamine synthons, we hope that this strategy may be employed in the syntheses of many other 2-amino-2-deoxyhexoses.

EXPERIMENTAL SECTION

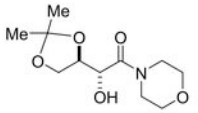
General Considerations.

All reagents were obtained commercially unless otherwise noted. Solvents were purified by passage under 10 psi N_2 through activated alumina columns. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR Spectrometer; data are reported in frequency of absorption (cm^{-1}). ^1H NMR spectra were recorded at 400, 500, or 600 MHz. Data are recorded as: chemical shift in ppm referenced internally using residual solvent peaks, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances), integration, coupling constant (Hz). ^{13}C NMR spectra were recorded at 101 MHz or at 126 MHz. Exact mass spectra were recorded using an electrospray ion source (ESI) either in positive mode or negative mode and with a time-of-flight (TOF) analyzer on a Waters LCT PremierTM mass spectrometer and are given in *m*/*z*. TLC was performed on precoated glass plates (Merck) and visualized either with a UV lamp (254 nm) or by dipping into a solution of $KMnO_4{-}K_2CO_3$ in water followed by heating. Flash chromatography was performed on silica gel (230–400 mesh) or Florisil (60–100 mesh). Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. Compound **1** is commercially available and was purchased from Biosynth International, Inc. Note: NEt_3-treated silica gel was used for column purification of compounds 6, 9, 12, 13, 14, 15, and 16. For these compounds,

prior to purification, a column of normal silica gel was thoroughly flushed with 1% NEt_3 in hexanes.

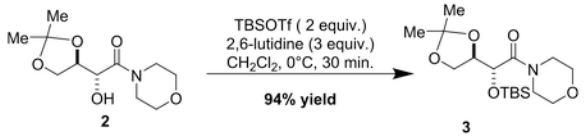


A 250 mL round-bottom flask was charged with a stir bar, **1** (10 g, 84.7 mmol, 1 equiv), and MeOH (100 mL). Subsequently, morpholine (8.0 mL, 8.08 g, 92.8 mmol, 1.1 equiv) was added at room temperature, and the reaction mixture was stirred for 14 h. Following this time, the reaction was concentrated under reduced pressure using toluene as an azeotrope (50 mL × 3) to remove excess morpholine. Then, CH_2Cl_2 (100 mL) and acetone (25 mL) were added to the crude product, and the mixture was cooled to 0 °C using an ice-water bath. 2,2-Dimethoxypropane (20.2 mL, 17.2 g, 165 mmol, 2 equiv) and camphorsulfonic acid (6.6 g, 28 mmol, 0.33 equiv) were added sequentially. The reaction mixture was warmed to room temperature over a period of 3 h. Following this time, the reaction was quenched by the addition of Et_3N (8.0 mL) and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–50% EtOAc/hexanes on silica gel to yield **2** (white solid, 18.2 g, 74.2 mmol, 88% yield).



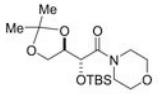
(*R*)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxy-1-morpholinoethan-1-one

Compound 2.—^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (d, J = 7.9 Hz, 1H), 4.19 (dd, J = 8.5, 6.1 Hz, 1H), 4.06−3.95 (m, 2H), 3.95−3.88 (m, 1H), 3.80−3.61 (m, 5H), 3.53−3.41 (m, 2H), 1.41 (s, 3H), 1.32 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.1, 110.0, 77.5, 69.0, 67.8, 66.8, 66.7, 46.2, 43.2, 26.3, 24.9. IR (ν_{max}) 3500, 2986, 1644, 1373, 1270, 1067 cm^{-1}. $[\alpha]_D^{23.7}$ = −36.42 (c 0.98, CH_3Cl). HRMS (ESI) m/z = [M + Na^+] calcd mass for $C_{11}H_{19}NO_5Na^+$ 268.1155. Found 268.1137 (6.7 ppm error).



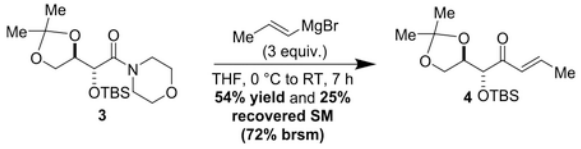
A 250 mL round-bottom flask was charged with a stir bar, **2** (11.4 g, 46.5 mmol, 1 equiv), and CH_2Cl_2 (80 mL). The reaction flask was cooled to 0 °C using an ice-water bath. 2,6-Lutidine (16.3 mL, 15.1 g, 140 mmol, 3 equiv) and TBSOTf (21.4 mL, 24.6 g, 93.0 mmol, 2 equiv) were sequentially added dropwise. The reaction mixture was stirred at 0 °C for 30 min. The reaction was then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (100 mL), and the mixture was transferred to a separatory funnel. The aqueous

layer was extracted with CH_2Cl_2 (2 × 80 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–20% EtOAc/hexanes on silica gel to yield **3** (colorless oil, 15.7 g, 43.7 mmol, 94% yield).



(*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-morpholinoethan-1-one

Compound 3.—^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (d, J = 7.0 Hz, 1H), 4.21 (dt, J = 7.0, 6.0 Hz, 1H), 4.06 (dd, J = 8.6, 6.2 Hz, 1H), 3.90 (dd, J = 8.6, 5.9 Hz, 1H), 3.80−3.50 (m, 8H), 1.39 (s, 3H), 1.30 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.4, 109.9, 77.3, 73.6, 67.1, 67.0, 66.8, 46.1, 42.7, 26.6, 25.7, 25.2, 18.2, −4.4, −5.1. IR (ν_{max}) 2929, 1658, 1253, 1116 cm^{-1}. $[\alpha]_D^{24.7}$ = +7.75 (c 0.92, CH_3Cl). HRMS (ESI) m/z = [M + Na^+] calcd mass for $C_{17}H_{33}NO_5SiNa^+$ 382.2020. Found 382.1993 (7.1 ppm error).



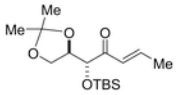
Note: Commercially available 1-propenyl magnesium bromide solution (sold as a cis/trans mixture) can also be used for this reaction and gives a similar yield. Subsequent steps are also not affected using products that are mixtures of geometric isomers.

Preparation of *trans*-1-propenyl magnesium bromide solution (this procedure can also be used for the preparation of *cis*-1-propenyl magnesium bromide solution): a 500 mL two-neck oven-dried round-bottom flask was charged with a stir bar, Mg turnings (2.88 g, 118 mmol, 1.2 equiv), I_2 (0.254 g, 1 mmol, 0.01 equiv), and THF (200 mL). A reflux condenser was attached to one neck of the flask. *Trans*-1-bromo-1-propene (8.5 mL, 12.0 g, 99 mmol, 1 equiv) was added to the flask dropwise at room temperature, and the heterogeneous mixture was heated to 60 °C for 3 h using an oil bath. Following this time, the reaction was cooled to room temperature and stirred for an additional 12 h.

Note: The following reaction was performed in two separate batches of 6 g each. The yield is reported for both batches combined.

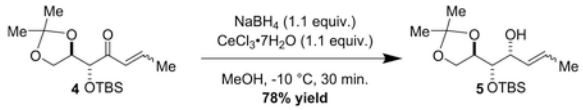
A 250 mL round-bottom flask was charged with a stir bar, compound **3** (6 g, 16.7 mmol, 1 equiv), and THF (40 mL) and cooled to 0 °C using an ice-water bath. Subsequently, the freshly prepared Grignard solution (~0.5 M concentration, 100 mL, ~50 mmol, ~3 equiv) was added dropwise. The reaction mixture was warmed to room temperature over a period of 7 h. Following this time, the reaction was cooled to 0 °C using an ice-water bath and quenched by slow addition of a saturated aqueous solution of NH_4Cl (100 mL). The mixture was transferred to a separatory funnel and further diluted with water (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The organic layers were collected, dried over

Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–10% EtOAc/hexanes on silica gel to yield **4**. Over two batches: (colorless oil, 5.7 g, 18.1 mmol, 54% yield) and recovered starting material: 3 g (25%).

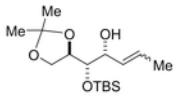


(*R*,*E*)-1-((*tert*-butyldimethylsilyl)oxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-en-2-one

Compound 4.—^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dq, J = 15.6, 6.9 Hz, 1H), 6.53 (dq, J = 15.6, 1.7 Hz, 1H), 4.24−4.15 (m, 2H), 3.94 (qdd, J = 8.3, 4.3, 1.5 Hz, 2H), 1.92 (dd, J = 6.9, 1.7 Hz, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 198.7, 144.8, 126.9, 109.8, 78.3, 77.3, 65.8, 26.6, 25.8, 25.5, 18.6, 18.3, −4.6, −4.7. IR (ν_{max}) 2931, 1692, 1632, 1253, 1076 cm^{-1}. HRMS (ESI) m/z = [M + Na$^+$] calcd mass for $C_{16}H_{30}O_4SiNa^+$ 337.1806. Found 337.1811 (1.5 ppm error).

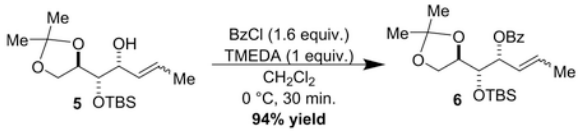


A 250 mL round-bottom flask was charged with a stir bar, **4** (5.6 g, 17.8 mmol, 1 equiv), and MeOH (40 mL). The reaction flask was cooled to −10 °C using a NaCl/ice-water bath. $CeCl_3{\cdot}7H_2O$ (7.3 g, 19.6 mmol, 1.1 equiv.) was added and, after 15 min, $NaBH_4$ (0.732 g, 19.3 mmol, 1.1 equiv) was added portion-wise. The reaction mixture was stirred at −10 °C for 30 min. Following this time, the reaction was quenched with a saturated aqueous solution of NH_4Cl (50 mL), and the MeOH was evaporated under reduced pressure. The aqueous mixture was then transferred to a separatory funnel and extracted with EtOAc (2 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–20% EtOAc/hexanes on silica gel to yield **5** (colorless oil, 4.4 g, 13.9 mmol, 78% yield).



(1*S*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-en-2-ol

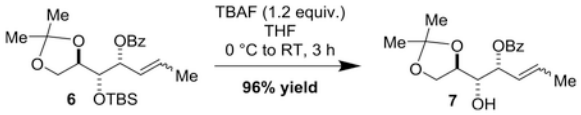
Compound 5.—^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81−5.69 (m, 1H), 5.53 (ddq, J = 15.3, 5.4, 1.6 Hz, 1H), 4.17−4.04 (m, 2H), 4.01 (dd, J = 8.1, 6.2 Hz, 1H), 3.81 (dd, J = 8.1, 6.9 Hz, 1H), 3.75 (dd, J = 6.2, 3.3 Hz, 1H), 1.73 (dt, J = 6.5, 1.4 Hz, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 130.9, 127.5, 109.1, 76.8, 75.0, 73.7, 66.8, 26.9, 26.1, 25.6, 18.4, 18.1, −3.9, −4.0. IR (ν_{max}) 3500, 2931, 1473, 1253 cm^{-1}. HRMS (ESI) m/z = [M + Na$^+$] calcd mass for $C_{16}H_{32}O_4SiNa^+$ 339.1962. Found 339.1985 (6.8 ppm error).



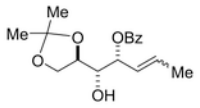
A 100 mL round-bottom flask was charged with a stir bar, **5** (4.3 g, 13.6 mmol, 1 equiv), and CH_2Cl_2 (30 mL). The reaction flask was cooled to 0 °C using an ice-water bath. TMEDA (2.0 mL, 1.55 g, 13.3 mmol, 1 equiv) was added followed by dropwise addition of benzoyl chloride (2.6 mL, 3.15 g, 22.4 mmol, 1.6 equiv). The reaction mixture was stirred at 0 °C for 0.5 h. Following this time, the reaction was quenched with a saturated aqueous solution of NH_4Cl (50 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–5% EtOAc/hexanes on NEt_3-treated silica gel to yield **6** (colorless oil, 5.4 g, 12.8 mmol, 94% yield).

(1*S*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-en-2-yl benzoate

Compound 6.—^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.01 (m, 2H), 7.56 (ddt, J = 7.9, 6.9, 1.4 Hz, 1H), 7.49−7.40 (m, 2H), 5.82 (dqd, J = 15.2, 6.5, 0.9 Hz, 1H), 5.54 (ddq, J = 15.0, 6.6, 1.5 Hz, 1H), 5.47 (ddt, J = 6.5, 4.1, 1.0 Hz, 1H), 4.22−4.14 (m, 1H), 4.14−4.08 (m, 1H), 3.94 (t, J = 7.6 Hz, 1H), 3.87 (dd, J = 7.8, 6.4 Hz, 1H), 1.72 (ddd, J = 6.5, 1.6, 1.0 Hz, 3H), 1.39 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.5, 133.1, 130.4, 129.9, 129.8, 128.5, 126.0, 108.3, 76.3, 75.7, 73.2, 65.0, 26.6, 25.9, 25.3, 18.2, 18.0, −4.0, −4.1. IR (ν_{max}) 2931, 1726, 1267 cm^{-1} HRMS (ESI) m/z = [M + Na$^+$] calcd mass for $C_{23}H_{36}O_5SiNa^+$ 443.2224. Found 443.2214 (2.3 ppm error).

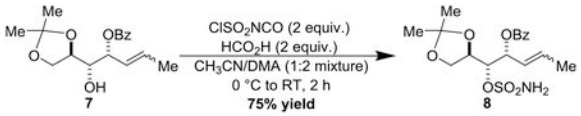


A 100 mL round-bottom flask was charged with a stir bar, **6** (5.3 g, 12.6 mmol, 1 equiv), and THF (25 mL). The reaction flask was cooled to 0 °C using an ice-water bath, and TBAF (1 M in THF, 15.2 mL, 15.2 mmol, 1.2 equiv) was added dropwise. The reaction mixture was warmed to room temperature over a period of 3 h. Following this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (30 mL) and water (20 mL). The mixture was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 80 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–5% EtOAc/hexanes on silica gel to yield **7** (colorless oil, 3.7 g, 12.1 mmol, 96% yield).



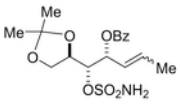
(1*S*,2*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-hydroxypent-3-en-2-yl benzoate

Compound 7.—^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08−8.01 (m, 2H), 7.57 (ddt, J = 7.9, 7.0, 1.3 Hz, 1H), 7.51−7.41 (m, 2H), 5.91 (dqd, J = 15.3, 6.5, 0.8 Hz, 1H), 5.65 (ddq, J = 15.1, 7.1, 1.6 Hz, 1H), 5.59 (ddt, J = 7.1, 3.9, 0.8 Hz, 1H), 4.12 (q, J = 6.1 Hz, 1H), 4.06 (dd, J = 8.3, 6.0 Hz, 1H), 3.99 (dd, J = 8.3, 6.3 Hz, 1H), 3.90 (dd, J = 5.8, 3.8 Hz, 1H), 1.78−1.71 (m, 3H), 1.43 (s, 3H), 1.33 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.6, 133.3, 131.5, 130.2, 129.8, 128.6, 125.9, 109.2, 75.9, 74.9, 73.5, 65.6, 26.8, 25.4, 18.0. IR (ν_{max}) 3471, 2929, 1715, 1270 cm^{-1}. HRMS (ESI) m/z = [M + Na^{+}] calcd mass for $C_{17}H_{22}O_5Na^{+}$ 329.1359. Found 329.1368 (2.7 ppm error).



Preparation of $ClSO_2NH_2$: a 50 mL oven-dried round-bottom flask was fitted with a balloon of N_2 gas and charged with a stir bar. $ClSO_2NCO$ (2.0 mL, 3.26 g, 23.0 mmol, 2 equiv) was added, and the flask was cooled to 0 °C using an ice-water bath. HCO_2H (0.9 mL, 1.10 g, 23.9 mmol, 2 equiv) was added dropwise (*Caution*: vigorous gas evolution upon addition). The mixture solidified into a white solid within 5 mi of addition. CH_3CN (12 mL) was added, and the reaction mixture was warmed to room temperature over a period of 5 h.

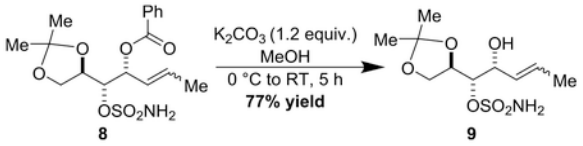
A separate 100 mL oven-dried round-bottom flask was fitted with a nitrogen balloon and charged with a stir bar, **7** (3.6 g, 11.75 mmol, 1 equiv), and DMA (25 mL). The reaction flask was cooled to 0 °C using an ice-water bath, and freshly prepared $ClSO_2NH_2$ (in 12 mL of CH_3CN) was added dropwise. The reaction mixture was warmed to room temperature over a period of 2 h. Following this time, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was transferred to a separatory funnel and further diluted with water (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–25% EtOAc/hexanes on silica gel to yield **8** (colorless oil, 3.4 g, 8.82 mmol, 75% yield).



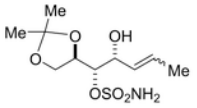
(1*S*,2*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-(sulfamoyloxy)pent-3-en-2-yl benzoate

Compound 8.—^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.01 (m, 2H), 7.62−7.54 (m, 1H), 7.49−7.41 (m, 2H), 5.98 (dq, J = 14.4, 6.6 Hz, 1H), 5.67−5.55 (m, 2H), 5.01 (dd, J = 4.7, 3.9 Hz, 1H), 4.97 (broad s, 2H), 4.31 (td, J = 6.8, 4.0 Hz, 1H), 4.06 (dd, J = 8.5, 7.0 Hz, 1H), 3.98 (dd, J = 8.5, 6.5 Hz, 1H), 1.76 (dd, J = 6.5, 1.4 Hz, 3H), 1.42 (s, 3H), 1.36−1.33 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.4, 133.6, 133.3, 129.9, 129.6, 128.7, 124.4, 109.4, 81.9, 74.6, 73.5, 64.8, 26.5, 25.2, 18.0. IR (ν_{max}) 3450, 2988, 1710, 1373,

1270 cm^{-1}. HRMS (ESI) *m*/*z*: [M + Na^+] calcd mass for $C_{17}H_{23}NO_7SNa^+$ 408.1087. Found 408.1092 (1.2 ppm error).

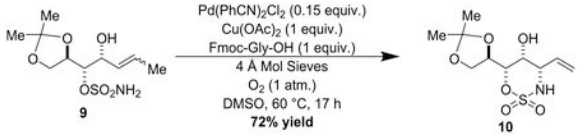


A 100 mL round-bottom flask was charged with a stir bar, **8** (3.4 g, 8.8 mmol, 1 equiv), and MeOH (20 mL). The reaction flask was cooled to 0 °C using an ice-water bath, and K_2CO_3 (1.5 g, 10.9 mmol, 1.2 equiv) was added in one bolus. The reaction mixture was warmed to room temperature over a period of 5 h. Then, the reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL), and the methanol was removed under reduced pressure. The mixture was transferred to a separatory funnel, further diluted with water (20 mL), and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were collected, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–35% EtOAc/hexanes on NEt_3-treated silica gel to yield **9** (colorless oil, 1.9 g, 6.8 mmol, 77% yield).



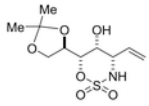
(1*S*,2*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypent-3-en-1-yl sulfamate

Compound 9.—^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (dqd, *J* = 15.3, 6.5, 1.1 Hz, 1H), 5.57 (ddq, *J* = 15.3, 7.0, 1.6 Hz, 1H), 5.19 (s, 2H), 4.70 (dd, *J* = 5.3, 4.5 Hz, 1H), 4.29 (qd, *J* = 6.7, 2.8 Hz, 2H), 4.08−3.90 (m, 2H), 2.57 (broad s, 1H), 1.76 (ddd, *J* = 6.5, 1.7, 0.8 Hz, 3H), 1.48−1.42 (s, 3H), 1.40−1.34 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 130.8, 128.3, 109.7, 83.8, 74.6, 72.4, 65.1, 26.4, 25.3, 17.9. IR (ν_{max}) 3500, 2930, 1373, 1216 cm^{-1}. HRMS (ESI) *m*/*z* = [M + Na^+] calcd mass for $C_{10}H_{19}NO_6SNa^+$ 304.0825. Found 304.0845 (6.6 ppm error).



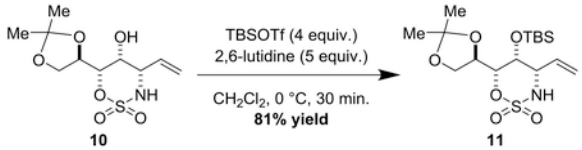
A 250 mL round-bottom flask was charged with a stir bar, **9** (1.4 g, 4.98 mmol, 1 equiv), $Pd(PhCN)_2Cl_2$ (0.282 g, 0.73 mmol, 0.15 equiv), $Cu(OAc)_2$ (0.890 g, 4.9 mmol, 1 equiv), Fmoc-Gly-OH (1.4 g, 4.7 mmol, 1 equiv), molecular sieves (4 Å, 725 mg (5 mg mL^{-1} of solvent)), and DMSO (145 mL, final concentration: 0.034 M). The reaction vessel was evacuated and backfilled with O_2 gas three times. Then, it was submerged in an oil bath preheated to 60 °C and kept at this temperature under a balloon of O_2 (~1 atm) for 17 h. Following this time, the reaction mixture was filtered through a pad of silica gel. The filter cake was further washed with EtOAc. The filtrate was diluted with H_2O (500 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 200 mL). The organic layers were collected, dried over Na_2SO_4, and

concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–35% EtOAc/hexanes on silica gel to yield **10** (crystalline solid, 1.0 g, 3.58 mmol, 72% yield).

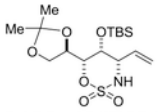


(4*S*,5*R*,6*S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-hydroxy-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide

Compound 10.—^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, J = 17.3, 10.7, 4.7 Hz, 1H), 5.46 (dd, J = 5.8, 1.8 Hz, 1H), 5.43 (d, J = 1.8 Hz, 1H), 4.80 (d, J = 11.3 Hz, 1H), 4.54 (dd, J = 7.9, 1.2 Hz, 1H), 4.46−4.38 (m, 2H), 4.18 (dd, J = 9.2, 6.2 Hz, 1H), 4.05 (dd, J = 9.2, 4.3 Hz, 1H), 3.93 (dt, J = 4.6, 1.4 Hz, 1H), 2.71 (d, J = 4.6 Hz, 1H), 1.46 (s, 3H), 1.39 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 132.2, 119.1, 110.5, 84.8, 72.9, 66.7, 62.7, 60.9, 26.9, 25.0. IR (ν_{max}) 3548, 2937, 1370, 1190 cm^{-1}. HRMS (ESI) m/z = [M − H] calcd mass for $C_{10}H_{16}NO_6S^-$ 278.0704. Found 278.0685 (6.8 ppm error).

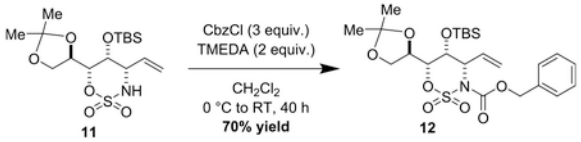


A 50 mL round-bottom flask was charged with a stir bar, **10** (0.824 g, 2.95 mmol, 1 equiv), and CH_2Cl_2 (15 mL). The reaction flask was cooled to 0 °C using an ice-water bath. 2,6-Lutidine (1.72 mL, 1.59 g, 14.8 mmol, 5 equiv) and TBSOTf (2.8 mL, 3.22 g, 12.2 mmol, 4 equiv) were sequentially added dropwise. The reaction mixture was stirred at 0 °C for 30 min. The reaction was then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (15 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–15% EtOAc/hexanes on silica gel to yield compound **11** (colorless oil, 0.937 g, 2.38 mmol, 81% yield).

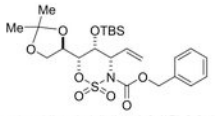


(4*S*,5*R*,6*R*)-5-(((*tert*-butyldimethylsilyl)oxy)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide

Compound 11.—^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.2, 10.7, 4.1 Hz, 1H), 5.41−5.29 (m, 2H), 4.44−4.31 (m, 3H), 4.22−4.14 (m, 2H), 4.01−3.96 (m, 1H), 3.90 (t, J = 1.0 Hz, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.18 (s, 3H), 0.09 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 133.5, 118.2, 110.4, 86.5, 71.2, 67.3, 64.5, 61.9, 26.9, 26.3, 25.1, 18.6, −3.6, −4.2. IR (ν_{max}) 3271, 2931, 1373, 1196 cm^{-1}. $[\alpha]_D^{26.0}$ = −20.55 (c 0.85, CH_3Cl). HRMS (ESI) m/z = [M − H] calculated mass for $C_{16}H_{30}NO_6SSi^-$ 392.1569. Found 392.1561 (2.0 ppm error).

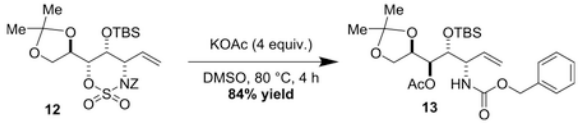


A 100 mL round-bottom flask was charged with a stir bar, **11** (920 mg, 2.33 mmol, 1 equiv), and CH_2Cl_2 (25 mL). The reaction flask was cooled to 0 °C using an ice-water bath. Sequentially, TMEDA (0.7 mL, 0.55 g, 4.7 mmol, 2 equiv) and CbzCl (1.0 mL, 1.2 g, 7.03 mmol, 3 equiv) were added dropwise. The reaction mixture was warmed to room temperature over a period of 40 h. Subsequently, the reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–20% EtOAc/hexanes on NEt_3-treated silica gel to yield **12** (colorless oil, 860 mg, 1.63 mmol, 70% yield).

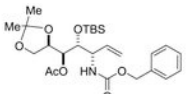


benzyl (4*S*,5*R*,6*R*)-5-((*tert*-butyldimethylsilyl)oxy)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-vinyl-1,2,3-oxathiazinane-3-carboxylate 2,2-dioxide

Compound 12.—^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.29 (m, 5H), 6.15 (ddd, J = 17.1, 10.5, 7.8 Hz, 1H), 5.41−5.27 (m, 4H), 5.19 (tt, J = 7.6, 1.2 Hz, 1H), 4.80 (dd, J = 6.7, 5.8 Hz, 1H), 4.60 (dd, J = 7.4, 5.8 Hz, 1H), 4.43 (td, J = 6.6, 5.6 Hz, 1H), 4.13 (dd, J = 9.1, 6.4 Hz, 1H), 4.02 (dd, J = 9.0, 5.7 Hz, 1H), 1.43−1.38 (m, 3H), 1.37−1.31 (m, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). 3C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.7, 134.6, 131.8, 128.7, 128.6, 127.8, 121.2, 110.1, 85.3, 72.1, 69.8, 67.7, 66.1, 63.6, 26.6, 25.8, 25.3, 18.1, −4.4, −4.9. IR (ν_{max}) 2971, 1704, 1284, 1190 cm^{-1}. $[\alpha]_D^{26.0}$ = −10.8 (c 1.30, CH_3Cl). HRMS (ESI) m/z = [M − H] calcd mass for $C_{24}H_{36}NO_8SSi^-$ 526.1936. Found 526.1925 (2.1 ppm error).

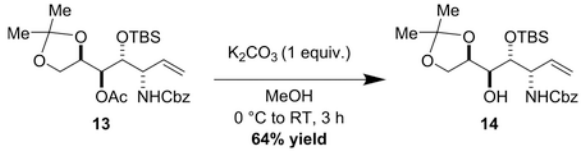


A 50 mL round-bottom flask was charged with a stir bar, **12** (0.820 g, 1.55 mmol, 1 equiv), DMSO (20 mL), and KOAc (0.610 g, 6.21 mmol, 4 equiv). The reaction vessel was then submerged in an oil bath preheated to 80 °C and kept at this temperature under a balloon of N_2 (~1 atm) for 4 h. Following this time, the reaction was cooled to room temperature, diluted with water (80 mL), and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–20% EtOAc/hexanes on NEt_3-treated silica gel to yield **13** (colorless oil, 0.661 g, 1.30 mmol, 84% yield).

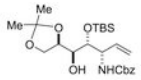


(1*S*,2*R*,3*S*)-3-{((benzyloxy)carbonyl)amino)-2-{(*tert*-butyldimethylsilyl)oxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-1-yl acetate

Compound 13.—^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.29 (m, 5H), 5.81 (ddd, J = 17.2, 10.4, 4.5 Hz, 1H), 5.28−5.17 (m, 2H), 5.08 (dd, J = 11.4, 7.1 Hz, 3H), 4.87 (dd, J = 8.6, 1.9 Hz, 1H), 4.44 (ddt, J = 10.8, 3.9, 1.8 Hz, 1H), 4.35 (td, J = 6.6, 1.9 Hz, 1H), 4.13 (dd, J = 8.6, 1.7 Hz, 1H), 3.98 (dd, J = 8.7, 6.8 Hz, 1H), 3.67 (dd, J = 8.7, 6.4 Hz, 1H), 2.10 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6, 156.0, 136.7, 136.6, 128.6, 128.4, 128.2, 116.2, 109.4, 73.6, 72.9, 71.5, 67.0, 65.7, 54.2, 26.2, 25.6, 21.1, 18.3, −3.3, −4.4. IR (ν_{max}) 3448, 2954, 1747, 1730, 1504, 1224 cm^{-1}. $[\alpha]_D^{26.6}$ = −24.89 (*c* 1.30, CH_3Cl). HRMS (ESI) m/z = [M + Na$^+$] calcd mass for $C_{26}H_{41}NO_7SiNa^+$ 530.2545. Found 530.2546 (0.2 ppm error).

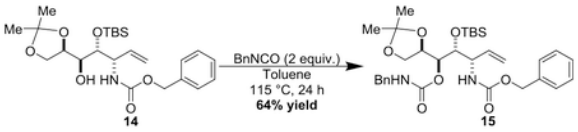


A 100 mL round-bottom flask was charged with a stir bar, **13** (0.65 g, 1.28 mmol, 1 equiv), and MeOH (6 mL). The reaction flask was cooled to 0 °C using an ice-water bath, and K_2CO_3 (0.177 g, 1.28 mmol, 1.0 equiv) was added in one portion. The reaction mixture was warmed to room temperature over a period of 3 h. Following this time, the reaction was quenched with a saturated aqueous solution of NH_4Cl (15 mL), further diluted with water (20 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–20% EtOAc/hexanes on NEt_3-treated silica gel to yield **14** (colorless oil, 0.381 g, 0.818 mmol, 64% yield).

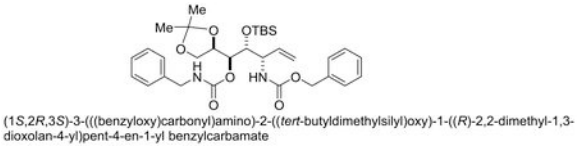


benzyl ((3*S*,4*R*,5*S*)-4-{(*tert*-butyldimethylsilyl)oxy)-5-{(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-hydroxypent-1-en-3-yl)carbamate

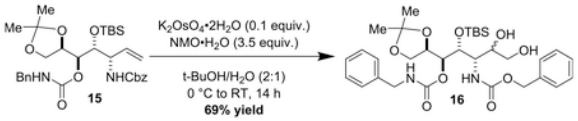
Compound 14.—^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.28 (m, 5H), 5.94 (ddd, J = 17.3, 10.5, 4.4 Hz, 1H), 5.60 (d, J = 9.8 Hz, 1H), 5.31−5.20 (m, 2H), 5.19−5.05 (m, 2H), 4.61 (dtd, J = 10.6, 6.2, 5.3, 3.1 Hz, 1H), 4.30 (td, J = 7.0, 2.2 Hz, 1H), 4.00 (dd, J = 8.0, 6.7 Hz, 1H), 3.87 (t, J = 7.6 Hz, 1H), 3.72 (dd, J = 9.1, 2.5 Hz, 1H), 3.38 (t, J = 7.6 Hz, 1H), 2.49 (d, J = 8.1 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.2, 136.6, 135.2, 128.6, 128.3, 128.2, 116.0, 109.4, 74.3, 74.1, 70.9, 67.0, 66.2, 55.8, 26.5, 26.0, 25.2, 18.1, −3.8, −4.6. IR (ν_{max}) 3434, 2931, 1724, 1504, 1258 cm^{-1}. $[\alpha]_D^{26.3}$ = −58.15 (*c* 1.00, CH_3Cl). HRMS (ESI) m/z = [M + Na$^+$] calcd mass for $C_{24}H_{39}NO_6SiNa^+$ 488.2439. Found 488.2438 (0.2 ppm error).



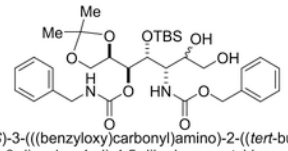
A 50 mL round-bottom flask was charged with a stir bar, **14** (0.370 g, 0.795 mmol, 1 equiv), toluene (6 mL), and benzyl isocyanate (0.2 mL, 0.216 g, 1.62 mmol, 2 equiv). The reaction vessel was then submerged into an oil bath preheated to 115 °C and kept at this temperature under a balloon of N_2 (~1 atm) for 24 h. Subsequently, the reaction was cooled to room temperature, and the solvent was removed under reduced pressure. The resulting residue was purified using a gradient of 0–20% EtOAc/hexanes on NEt_3-treated silica gel to yield **15** (colorless oil, 0.302 g, 0.504 mmol, 64% yield).



Compound 15.—^{1}H NMR (400 MHz, chloroform-*d*) δ 7.47−7.27 (m, 10H), 5.85 (ddd, J = 17.2, 10.3, 4.6 Hz, 1H), 5.27−5.15 (m, 3H), 5.10 (s, 2H), 5.01 (t, J = 5.9 Hz, 1H), 4.89−4.79 (m, 1H), 4.50 (d, J = 8.1 Hz, 1H), 4.43−4.24 (m, 3H), 4.14−3.94 (m, 2H), 3.79 (dd, J = 8.6, 6.8 Hz, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 0.88 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.0, 155.9, 138.3, 136.8, 136.3, 128.7, 128.6, 128.3, 128.2, 127.6, 127.5, 116.2, 109.3, 74.1, 73.0, 72.5, 66.9, 65.7, 54.7, 45.4, 26.3, 26.1, 25.6, 18.3, −3.5, −4.5. IR (ν_{max}) 3340, 2931, 1738, 1654, 1415 cm^{-1}. [α] $^{26.7}_D$ = −8.02 (c 1.40, CH_3Cl). HRMS (ESI) m/z = [M + Na$^+$] calcd mass for $C_{32}H_{46}N_2O_7SiNa^+$ 621.2966. Found 621.2987 (3.4 ppm error).

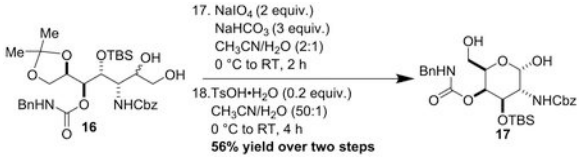


A 50 mL round-bottom flask was charged with a stir bar, **15** (0.25 g, 0.417 mmol, 1 equiv), and ^{t}BuOH/H_2O (2:1 mixture, 4 mL total volume). The reaction flask was cooled to 0 °C using an ice-water bath. $K_2OsO_4{\cdot}2H_2O$ (16 mg, 0.043 mmol, 0.1 equiv) and $NMO{\cdot}H_2O$ (195 mg, 1.44 mmol, 3.5 equiv) were added sequentially. The reaction mixture was warmed to room temperature over a period of 14 h. Following this time, it was quenched with a saturated, aqueous solution of Na_2SO_3 (20 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 15 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–60% EtOAc/hexanes on NEt_3-treated silica gel to yield **16** (colorless oil, 0.181 g, 0.286 mmol, 69% yield).



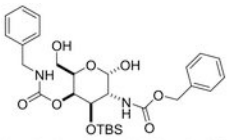
(1*S*,2*R*,3*S*)-3-(((benzyloxy)carbonyl)amino)-2-(((*tert*-butyldimethylsilyl)oxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,5-dihydroxypentyl benzylcarbamate

Compound 16.—^{1}H NMR (500 MHz, CD_3OD) δ 7.41−7.18 (m, 10H), 5.12−5.00 (m, 2H), 4.78 (ddd, J = 10.3, 7.4, 2.8 Hz, 1H), 4.51 (dd, J = 7.5, 1.2 Hz, 1H), 4.41 (td, J = 6.7, 2.7 Hz, 1H), 4.31−4.21 (m, 2H), 4.07−3.98 (m, 1H), 3.81−3.72 (m, 2H), 3.62 (dtd, J = 9.4, 4.6, 2.3 Hz, 1H), 3.57−3.49 (m, 2H), 1.38 (s, 3H), 1.34 (s, 3H), 0.92 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD) δ 158.7, 158.3, 140.4, 138.0, 129.5, 129.4, 129.2, 129.1, 128.2, 128.0, 110.6, 75.5, 74.1, 71.9, 70.3, 68.1, 66.5, 65.2, 53.7, 45.6, 26.7, 26.4, 25.9, 19.2, −4.0, −4.3. IR (ν_{max}) 3446, 2929, 1701, 1427, 1253 cm^{-1}. HRMS (ESI) m/z = [M + Na^{+}] calcd mass for $C_{32}H_{48}N_2O_9SiNa^{+}$ 655.3021. Found 655.3051 (4.6 ppm error).



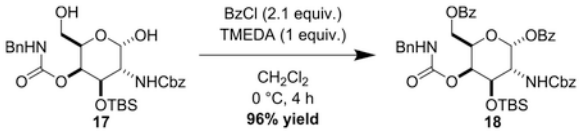
A 50 mL round-bottom flask was charged with a stir bar, **16** (0.170 g, 0.27 mmol, 1 equiv), and CH_3CN/H_2O (2:1 mixture; 6 mL total volume). The reaction flask was cooled to 0 °C using an ice-water bath. $NaIO_4$ (0.115 g, 0.54 mmol, 2 equiv) and $NaHCO_3$ (0.068 g, 0.81 mmol, 3 equiv) were added sequentially. The reaction mixture was warmed to room temperature over a period of 2 h. Following this time, the reaction mixture was filtered through a sintered glass funnel, and the filtrate was transferred to a separatory funnel with 20 mL of H_2O. The aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was used in the next step without further purification.

A 50 mL round-bottom flask was charged with a stir bar, aldehyde starting material, and CH_3CN/H_2O (50:1 mixture, 4 mL total volume). The reaction flask was cooled to 0 °C using an ice-water bath, and *p*-TsOH·H_2O (10 mg, 0.053 mmol, 0.2 equiv) was added. The reaction mixture was warmed to room temperature over a period of 4 h. Following this time, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 ×10 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 50–100% EtOAc/hexanes on silica gel to yield **17** (colorless oil, 0.084 g, 0.150 mmol, 56% yield over two steps).

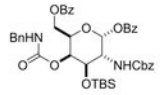


(2*R*,3*S*,4*R*,5*R*,6*S*)-5-(((benzyloxy)carbonyl)amino)-4-(((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-2-(hydroxymethyl)tetrahydro-2*H*-pyran-3-yl benzylcarbamate

Compound 17.—^{1}H NMR (500 MHz, CD_3OD) δ 7.46−7.17 (m, 10H), 5.10−5.09 (m, 1H), 5.06 (broad s, 3H), 4.33−4.21 (m, 2H), 4.15 (t, J = 6.4 Hz, 1H), 4.04−3.98 (m, 2H), 3.59−3.50 (m, 2H), 0.80 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD) δ 159.1, 158.6, 140.4, 138.1, 129.46, 129.45, 129.1, 129.0, 128.4, 128.1, 93.7, 73.2, 71.1, 69.7, 67.6, 62.2, 54.1, 45.5, 26.2, 18.7, −4.5, −4.8. IR (ν_{max}) 3412, 2951, 1715, 1521, 1253 cm^{-1}. HRMS (ESI) m/z = [M + Na^{+}] calcd mass for $C_{28}H_{40}N_2O_8SiNa^{+}$ 583.2446. Found 583.2472 (4.8 ppm error).

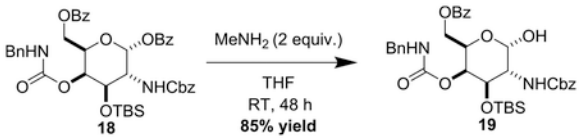


A 25 mL round-bottom flask was charged with a stir bar, **17** (0.028 g, 0.050 mmol, 1 equiv), and CH_2Cl_2 (2 mL). The reaction flask was cooled to 0 °C using an ice-water bath. Subsequently, TMEDA (7 μL, 6 mg, 0.049 mmol, 1 equiv) followed by BzCl (13 μL, 15 mg, 0.107 mmol, 2.1 equiv) were added dropwise. The reaction mixture was stirred at 0 °C for 4 h. Following this time, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified using a gradient of 0–5% EtOAc/hexanes on silica gel to yield **18** (colorless oil, 0.037 g, 0.048 mmol, 96% yield).

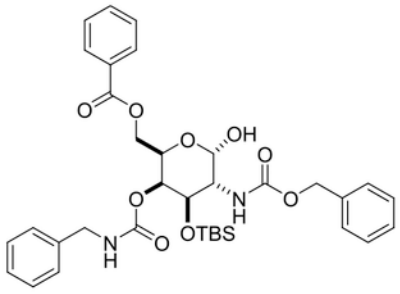


((2*R*,3*S*,4*R*,5*R*,6*R*)-6-(benzoyloxy)-3-((benzylcarbamoyl)oxy)-5-(((benzyloxy)carbonyl)amino)-4-(((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl benzoate

Compound 18.—^{1}H NMR (500 MHz, CD_3OD) δ 8.14−8.07 (m, 2H), 7.91−7.83 (m, 2H), 7.68−7.58 (m, 1H), 7.58−7.46 (m, 3H), 7.44−7.18 (m, 12H), 6.41 (d, J = 3.8 Hz, 1H), 5.35 (d, J = 3.5 Hz, 1H), 5.11−5.01 (m, 2H), 4.52 (dd, J = 7.4, 4.5 Hz, 1H), 4.43−4.32 (m, 3H), 4.26 (td, J = 5.7, 3.4 Hz, 3H), 0.82 (s, 9H), 0.16 (s, 3H), 0.10 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD) δ 164.6, 163.7, 156.0, 155.4, 137.3, 135.1, 131.8, 131.3, 128.1, 127.6, 126.7, 126.6, 126.5, 126.4, 126.1, 125.5, 125.4, 125.1, 91.1, 69.4, 68.5, 66.7, 64.9, 61.8, 50.1, 42.6, 23.2, 15.8, −7.3, −7.6. IR (ν_{max}) 2929, 1724, 1453, 1260 cm^{-1}. HRMS (ESI) m/z = [M + Na^{+}] calcd mass for $C_{42}H_{48}N_2O_{10}SiNa^{+}$ 791.2970. Found 791.2997 (3.4 ppm error).



A 25 mL round-bottom flask was charged with a stir bar, **18** (0.03 g, 0.039 mmol, 1 equiv), and THF (6 mL). $MeNH_2$ (2.0 M solution in THF, 0.039 mL, 0.078 mmol, 2 equiv) was added at room temperature. The reaction mixture was stirred for 48 h. Following this time, the solvent was removed under reduced pressure. The resulting residue was purified using a gradient of 0–20% EtOAc/hexanes on silica gel to yield **19** (colorless oil, 0.022 g, 0.033 mmol, 85% yield).



((2*R*,3*S*,4*R*,5*R*,6*S*)-3-((benzylcarbamoyl)oxy)-5-(((benzyloxy)carbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-6-hydroxytetrahydro-2*H*-pyran-2-yl)methyl benzoate

Compound 19.—^{1}H NMR (500 MHz, CD_3OD) δ 8.04 (dt, J = 8.1, 1.2 Hz, 2H), 7.59 (tq, J = 7.0, 1.3 Hz, 1H), 7.49−7.42 (m, 2H), 7.39−7.17 (m, 10H), 5.25−5.21 (m, 1H), 5.15−5.13 (m, 1H), 5.06 (s, 2H), 4.54−4.46 (m, 1H), 4.42−4.33 (m, 2H), 4.30−4.20 (m, 2H), 4.09−4.03 (m, 2H), 0.81 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD) δ 167.7, 158.6, 140.3, 138.1, 134.2, 131.2, 130.7, 129.5, 129.45, 129.40, 129.1, 129.0, 128.3, 128.0, 93.8, 73.1, 69.5, 68.4, 67.6, 64.9, 54.0, 45.5, 26.2, 18.6, −4.5, −4.7. IR (ν_{max}) 3348, 2929, 1730, 1267 cm^{-1}. HRMS (ESI) m/z = [M + Na^+] calcd mass for $C_{35}H_{44}N_2O_9SiNa^+$ 687.2708. Found 687.2711 (0.4 ppm error).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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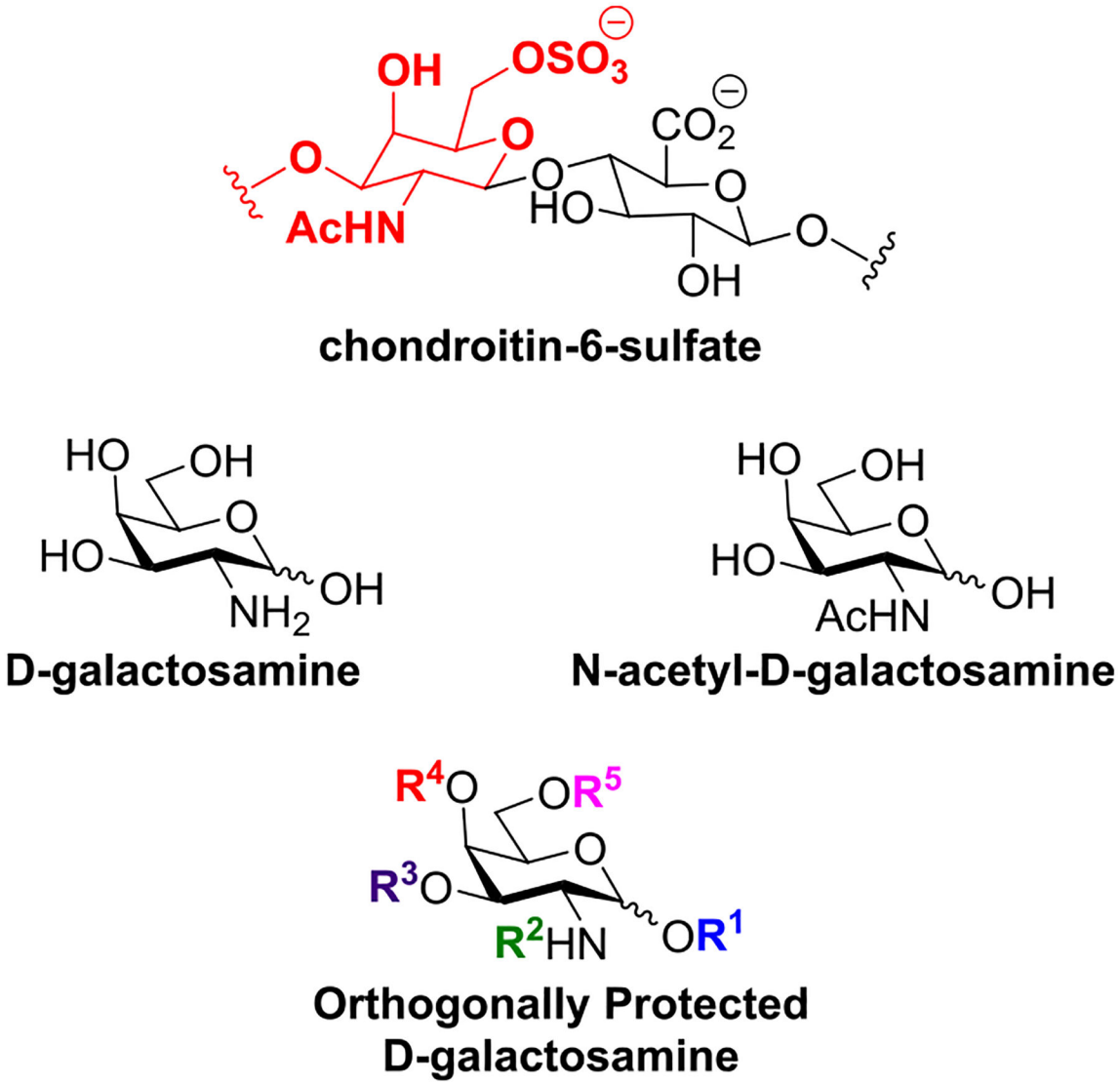
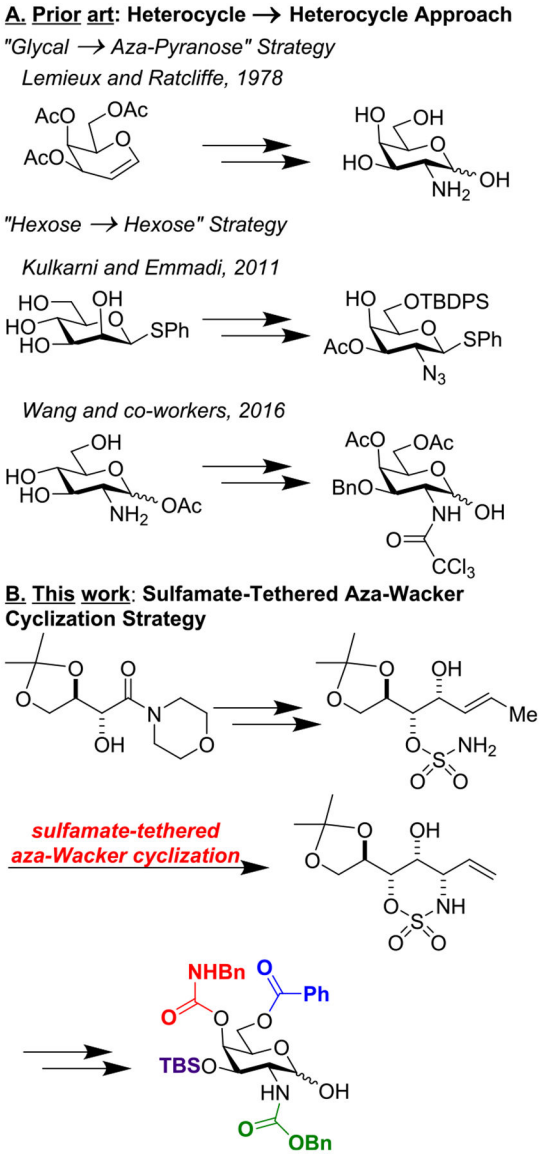


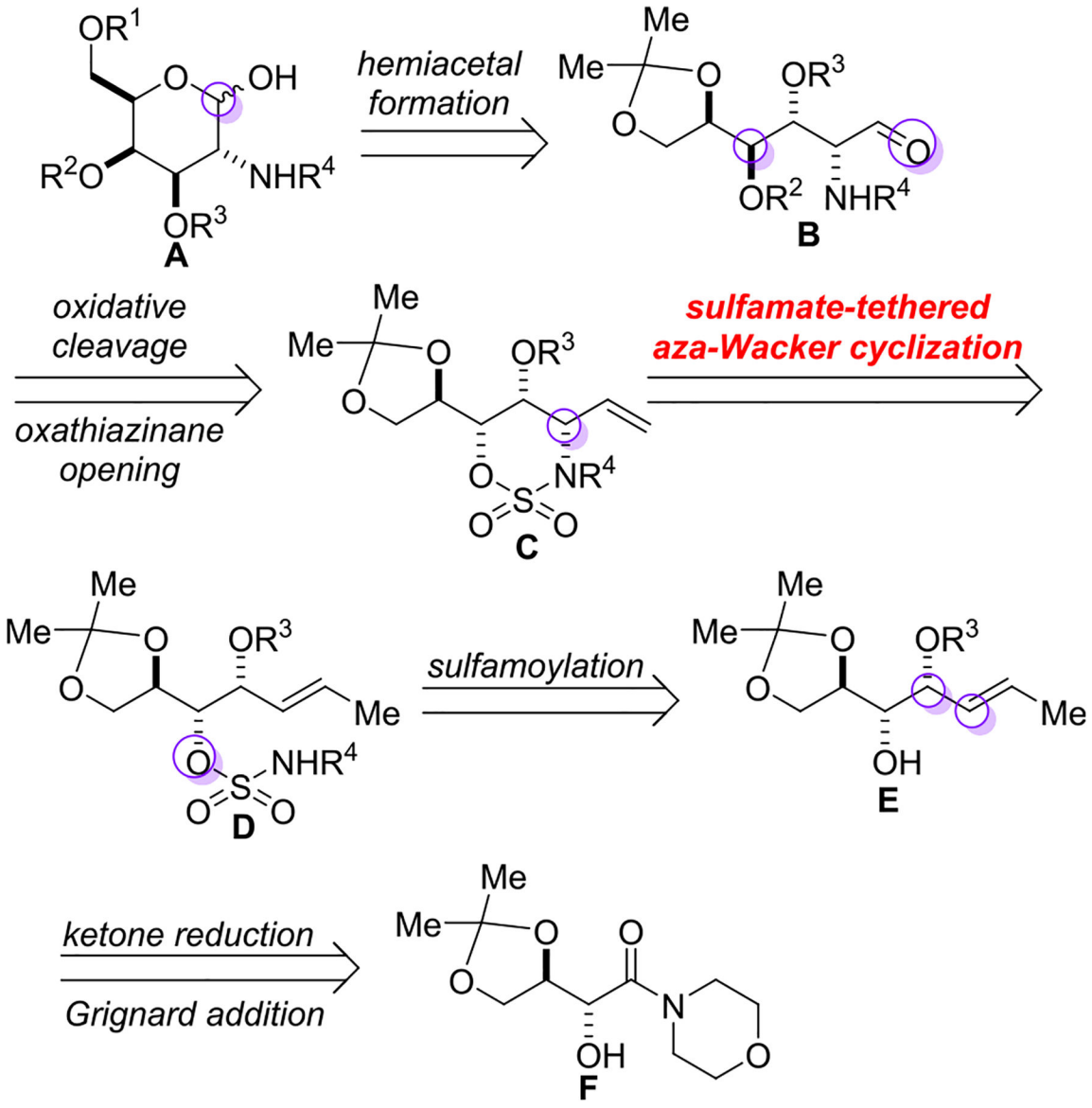
Figure 1.

D-Galactosamine and *N*-acetyl-D-galactosamine are available from hydrolysis of chondroitin sulfates, but orthogonally protected derivatives require de novo syntheses.



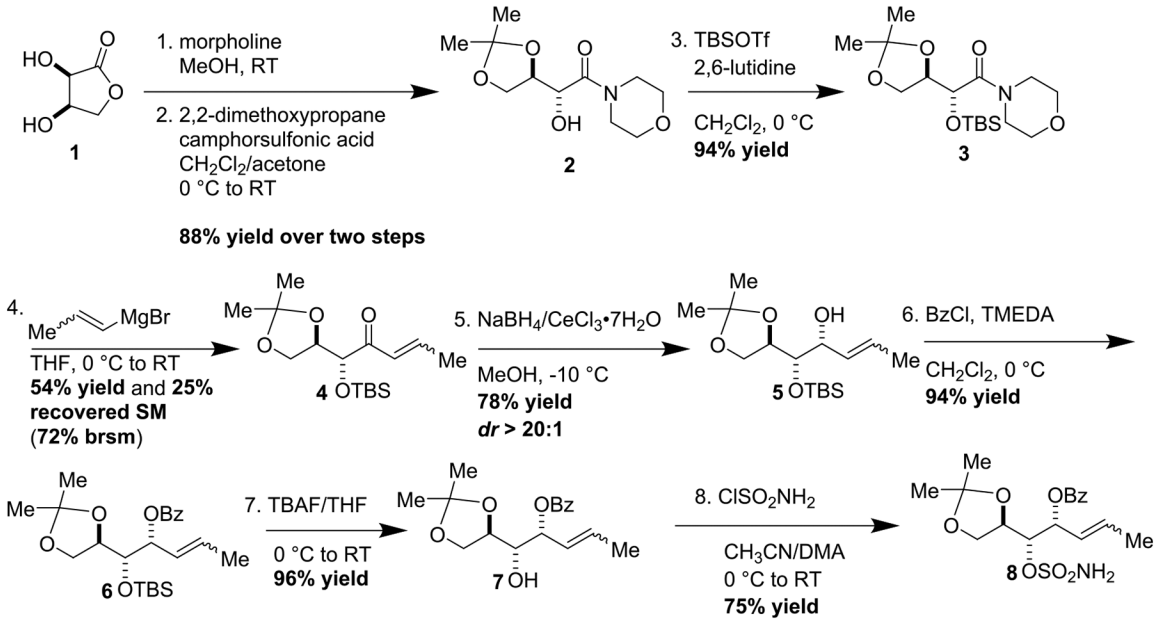
Scheme 1.

(A) Historically, Syntheses of D-Galactosamine and Protected Variants Have Commenced from Glycals or Other Pyranoses (Select Examples Shown); (B) Our Approach Uses a Different Chiron and a Sulfamate-Tethered *Aza*-Wacker Cyclization Strategy

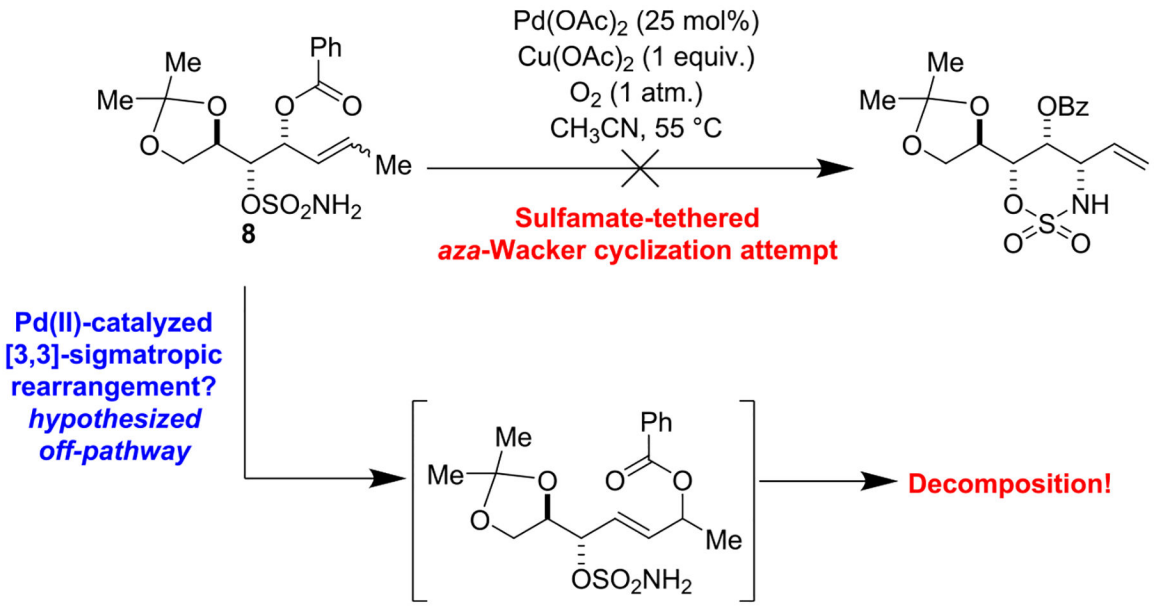


Scheme 2.

Retrosynthetic Analysis Incorporates a Sulfamate-Tethered *Aza*-Wacker Cyclization as a Key Step

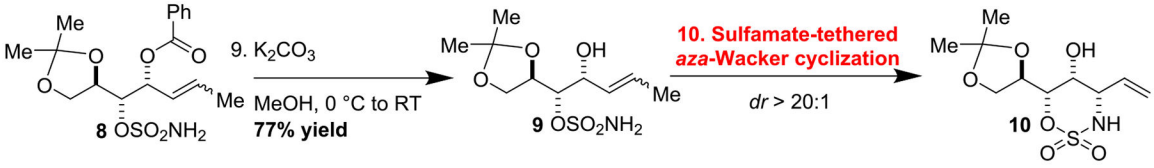


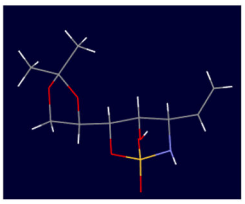
Scheme 3.
Opening Sequence of Reactions



Scheme 4.

Attempted Sulfamate-Tethered *Aza*-Wacker Cyclization with an Allylic Benzoate Present Fails, Presumably because of a Pd(II)-Catalyzed [3,3]-Sigmatropic Rearrangement





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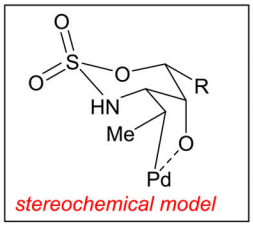
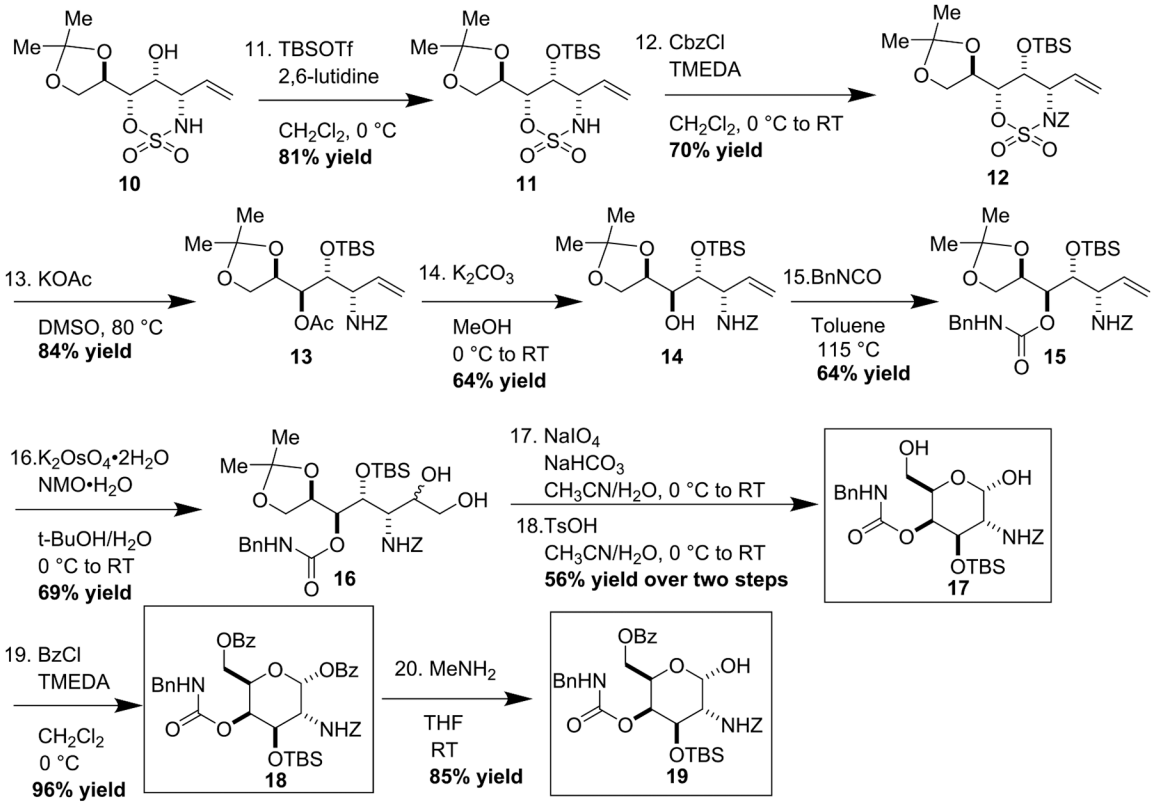


stereochemical model

Entry	Catalyst	Additional Parameters	Solvent	Yield
1	$Pd(OAc)_2$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.)	CH_3CN	32%
2	$Pd_2(dba)_3$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.)	CH_3CN	38%
3	$PdCl_2(nbd)$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.)	CH_3CN	55%
4	$Pd(PhCN)_2Cl_2$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.)	CH_3CN	59%
5	$Pd(PhCN)_2Cl_2$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.)	Dioxane	11%
6	$Pd(PhCN)_2Cl_2$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.)	DMA	18%
7	$Pd(PhCN)_2Cl_2$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.)	DMSO	55% (isolated)
8	$Pd(PhCN)_2Cl_2$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.) 4Å molecular sieves	DMSO	55% (isolated)
9	$Pd(PhCN)_2Cl_2$ (15%)	$Cu(OAc)_2$ (1 equiv.) O_2 (1 atm.) 4Å molecular sieves Fmoc-Gly-OH (1 equiv.)	DMSO	72% (isolated)

Scheme 5.
Optimization of the Sulfamate-Tethered *Aza*-Wacker Cyclization



Scheme 6.

Completion of Orthogonally Protected D-Galactosamines