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Aminosugar motifs via an allene aziridination strategy

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ABSTRACT

Aminosugar motifs occur in many biologically active natural products and pharmaceuticals; however, stereocontrolled access to diverse structures with minimal use of protecting groups and oxidation state changes is challenging. This paper describes a chemo-, regio-, and stereoselective approach to aminosugar motifs that utilizes an allene aziridination strategy to rapidly install three of the contiguous heteroatom-bearing carbons with stereochemical flexibility.

1. Introduction

Aminosugars are components of a variety of biologically active and important compounds, including mono- and polysaccharides, glycolipids, nucleotides, anthracycline antitumor agents, and antibiotics.[1] Neuraminic acid, glucosamine, and galactosamine (Fig. 1) are among the most common examples of aminosugars found in nature, but there is also significant interest in the synthesis of unnatural aminosugars.[2] Indeed, modular approaches to construct libraries of such compounds for incorporation into glycoconjugates are highly desirable, as glycodiversification has been successful for exploring important problems in the areas of chemistry, biology, and medicine.[3]

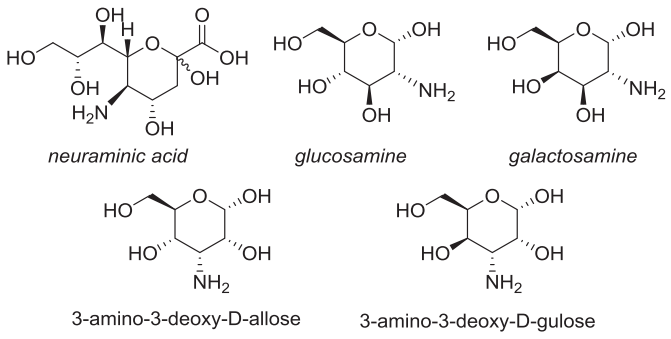

Fig. 1. Examples of aminosugars.

The broad interest in aminosugars has led to the development of several approaches for the synthesis of these classes of molecules. The most common methods employ sugars as starting materials, particularly glucose, mannose and galactose.[4] The advantages of utilizing substrates from the chiral pool are the intrinsic chirality and the ready availability of sugars. However, the two major challenges associated with using carbohydrate-based substrates are the need to protect the amino and hydroxyl groups and the difficulty of inverting stereocenters at will. While a more diverse range of aminosugars can be obtained via the oxidation of stereodefined and enantioenriched allylic alcohols/amines, multiple starting materials must be employed and issues with poor reactivity, regio- and stereoselectivity often arise.[5]

Our group has been engaged in developing allene aziridination as a strategy for synthesizing aminated stereotriads,[7] and we felt that aminosugars would be a challenging target on which to test the scope of our methodology. The hope was that the allene functionality could be utilized to flexibly install three contiguous heteroatom-bearing stereocenters within the aminosugar core. In addition, we aimed to control the relative stereochemistries of the three adjacent stereocenters, with the added benefit of setting the absolute stereochemistry via axial-to-central chirality transfer.[6]

2. Results and discussion

Our strategy for the synthesis of a simple aminosugar motif is shown in Scheme 1. Treatment of the homoallenic sulfamate **1** with

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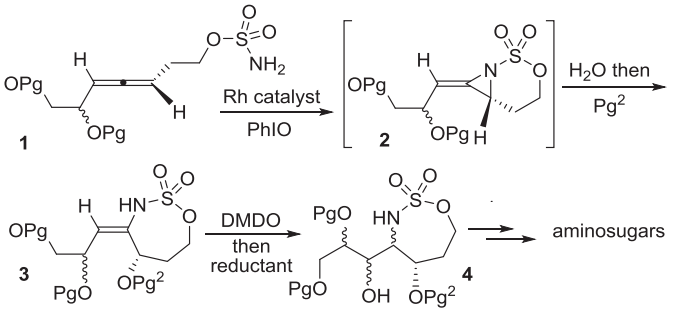
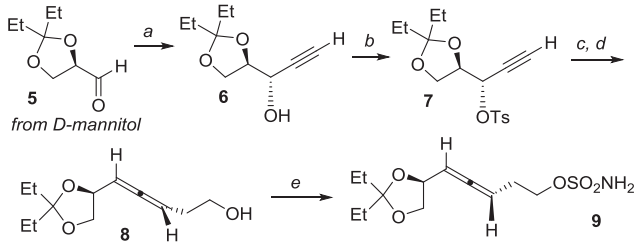
a Rh catalyst leads to an intermediate (*E*)-bicyclic methylene aziridine **2**. Ring-opening of **2** with water, followed by protection of the resulting alcohol, would yield enesulfamate **3**. We have previously demonstrated that treatment of simple enesulfamates with dimethyldioxirane (DMDO) and a reductant leads to 2-amino-1,3-diol motifs;[7c] the successful application of this strategy to **3** would generate stereotetrad **4** as a direct precursor to aminosugar products. However, the use of homoallenic sulfamate **1** presented an additional challenge, since the effect of the vicinal diol on the stereo- and regiochemical outcome of the allene oxidation was not clear. In particular, the stability of the sensitive methylene aziridine motif **2** in the presence of other potentially nucleophilic heteroatoms was unknown.



Scheme 1. Allene aziridination strategy in aminosugar synthesis.

The substrate for our initial studies was easily prepared from the enantioenriched aldehyde **5** (Scheme 2).[8] Protection of the 1,2-diol as the diethylketal **5** was necessary for reasons that will be discussed in relation to Schemes 3 and 4 (vide infra). Addition of a Ti acetylide to aldehyde **5** gave **6** in a dr of ca. 5:1.[9] The propargyl alcohol was converted to the tosylate **7**, treated with an organocopper reagent and reduced to yield the allenic alcohol **8**.[10] Finally, sulfamoylation of the alcohol gave the key building block **9** for our aminosugar synthesis. This sequence of reactions could be run on multi-gram scales with reproducible yields.

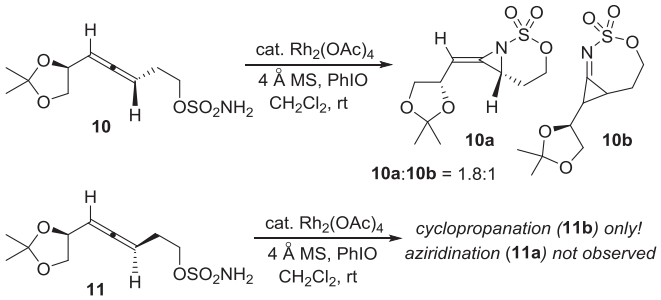


a) TMSCCH, *n*BuLi, 0 °C, THF then Ti(O^{i}Pr)$_3$Cl, -78 °C then **5**, -78 °C to 0 °C, then K_2CO_3/MeOH, 96%, 4.6:1 *dr*. *b*) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 85%. *c*) LDA, EtOAc, CuI, THF, -78 °C. *d*) LAH, THF, 0 °C, 53% over two steps. *e*) CSI, HO_2CH, py, CH_2Cl_2, 0 °C to rt, 93%.

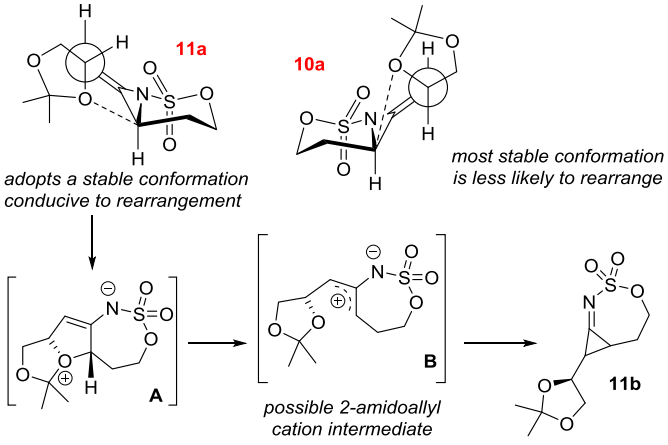
Scheme 2. Synthesis of homoallenic sulfamate **9**.

Our initial attempts to carry out allene aziridination on the dimethylketal-substituted allene **10** (generated in a manner analogous to that shown in Scheme 2) were fraught with unexpected difficulties. Treatment of **10** with $Rh_2(OAc)_4$ and PhIO gave some of the desired (*E*)-methylene aziridine **10a**, along with an undesired side-product identified as the cyclopropane **10b**.[11]

Interestingly, the diastereomeric allene **11** (Scheme 3), prepared by an alternative protocol,[12] gave only the cyclopropane **11b** upon treatment with $Rh_2(OAc)_4$, suggesting that the relative stereochemistry between the allenic hydroxyl group and the allene is



Scheme 3. Preventing competing cyclopropane formation.

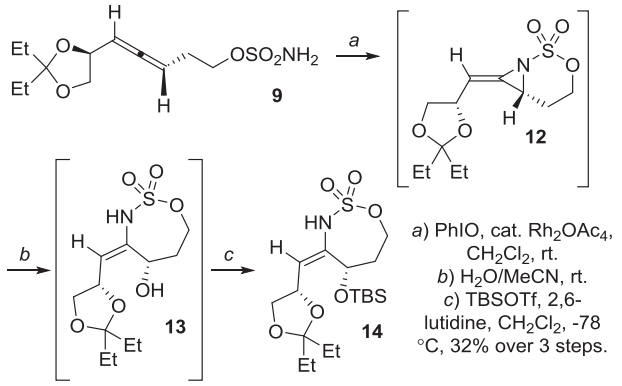


Scheme 4. Rationale for cyclopropylimine formation.

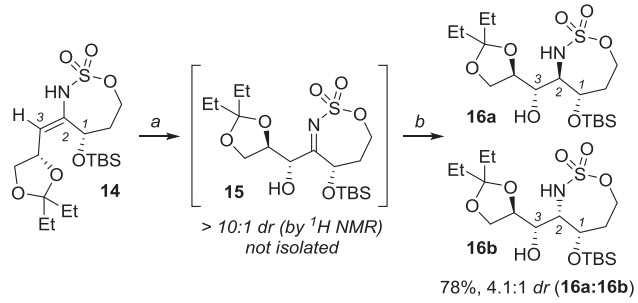
important to the successful isolation of the methylene aziridine. We hypothesize that rearrangement occurs when the proximal oxygen of the dimethylketal is aligned in such a fashion that it can readily ring-open the sensitive bicyclic methylene aziridine (Scheme 4). In **11a**, the oxygen attacks the methylene aziridine, leading to an intermediate that could be represented as either **A** or **B**. This reactive intermediate undergoes ring closure to generate the cyclopropane **11b**. In contrast, **10a** cannot easily adopt a conformation that permits nucleophilic attack on the methylene aziridine, due to unfavorable steric interactions that would occur between the dimethylketal and the six-membered ring of the bicyclic methylene aziridine. Consequently, less rearrangement of **10a** occurs, although some of the cyclopropane **10b** is still observed.

Ultimately, we found that replacing the dimethylketal with a diethylketal, as in **9**, minimized the production of the cyclopropane due to the increased steric bulk of this protecting group. With the methylene aziridine accessible in good selectivity from this substrate, a facile ring-opening was carried out by the addition of water under neutral conditions, followed by a TBS protection of the alcohol (Scheme 5). Presumably, the considerable ring strain of this intermediate permits ring-opening without the need for exogenous Lewis acid additives.[13]

To generate the core of the aminosugar backbone, the DMDO oxidation/imine reduction sequence was carried out on enesulfamate **14**. The use of DMDO in CH_2Cl_2 gave the sensitive α-hydroxyimine intermediate **15** in greater than 10:1 dr, followed immediately by reduction with $Zn(BH_4)_2$ to yield the stereotetrad **16** as a 4:1 mixture of easily separable diastereomers (Scheme 6). The stereochemical outcome of the DMDO oxidation was inferred from our previous work,[7c] while the relationship between the C1-OTBS and C2-amine groups was inferred by analysis of ^{1}H NMR coupling constants between the C1 and C2 protons.[14] The *anti* relationship between the C2-amine and C3-hydroxyl agrees with



Scheme 5. Synthesis of enesulfamate **14**.

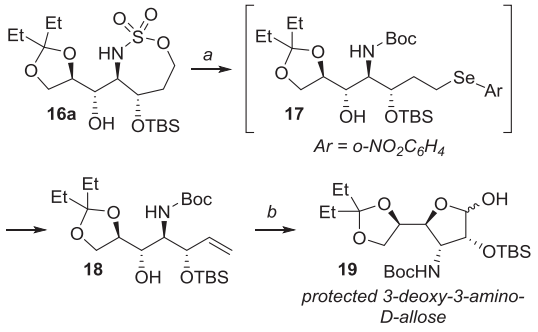


a) 2.5 equiv DMDO, 4 Å MS, CH_2Cl_2, 0 °C. *b*) 1 equiv. $Zn(BH_4)_2$, CH_2Cl_2, -78 °C.

Scheme 6. Synthesis of aminosugar precursors **16a** and **16b**.

related findings in the $Zn(BH_4)_2$-mediated reduction of α-hydroxy ketones.[15]

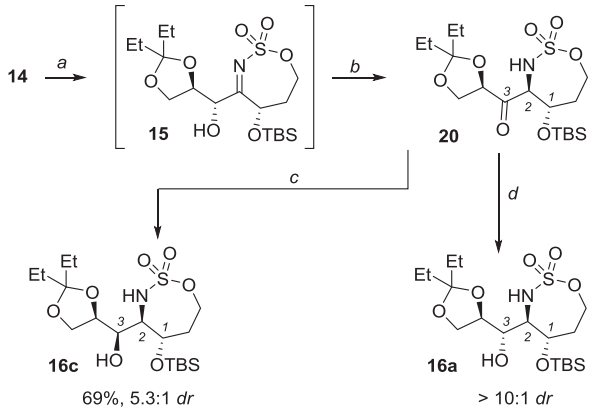
Compound **16a** could be easily converted in two steps to an aminosugar motif (Scheme 7). A one-pot removal of the sulfamoyl group was achieved through *N*-Boc protection and subsequent nucleophilic displacement using an aryl selenide to give **17**.[16] Addition of peroxide to **17** promoted a facile, in situ selenoxide elimination and the resulting olefin was cleaved via ozonolysis to give a protected derivative of 3-deoxy-3-amino-D-allose **19**.



a) Boc_2O, Et_3N, DMAP, CH_2Cl_2 then o-$NO_2C_6H_4SeCN$, $NaBH_4$ then dilute HCl, H_2O_2/THF, rt, 58%. *b*) O_3, then Me_2S, -78 °C to rt, 73%.

Scheme 7. Transformation of **16** to protected aminosugar **19**.

The possibility for accessing multiple aminosugar stereoisomers using allene aziridination as a key step was investigated. Both the enesulfamate oxidation and imine reduction steps proved to be highly substrate controlled in their stereochemical preference; therefore, an alternative approach involving the isomerization of the α-hydroxy imine 15 to an α-aminoketone of the form 20 was employed (Scheme 8). Such isomerizations of α-hydroxy ketones and imines are known to be catalyzed by a variety of Lewis and Brønsted acids,[17] and we found that $Al(O^tBu)_3$ catalyzed this transformation with good transfer of the imine stereochemistry. The stereochemical configuration of **20** was inferred from ^1H NMR coupling between the C1 and C2 hydrogens, analogous to **16a** and **16b**. Reduction of **20** with $LiBEt_3H$ resulted in a second O/N/O diastereomer **16c** with the stereochemical configuration of 3-amino-3-deoxy-D-gulose. Reduction with DIBAL-H provided the already accessible diastereomer **16a**.



a) 2.5 equiv DMDO, 4Å MS, CH_2Cl_2, 0 °C. *b*) 1 equiv $Al(O^tBu)_3$, $(CH_2Cl)_2$, 45 °C, 27%. *c*) 5 equiv $LiBEt_3H$, Et_2O, -78 to 0 °C. *d*) 4 equiv DIBAL-H, THF, 0 °C.

Scheme 8. Synthesis of an alternative stereoisomer **16c**.

3. Conclusions

In conclusion, we have demonstrated that allene aziridination is a viable approach toward the synthesis of aminosugar motifs. Aziridination of a stereodefined allene derived from D-mannitol delivered a strained, bicyclic methylene aziridine that could be rapidly elaborated in a regio-, chemo-, and stereoselective manner to two different stereoisomeric 2-amino-1,3-diol aminosugar cores. Current efforts are focused on exploring ways to obtain all four possible diastereomeric aminosugar motifs from the same allene precursor and introducing other heteroatoms to gain access to novel aminosugars for biological testing.

4. Experimental section

4.1. General

All glassware was either oven-dried overnight at 130 °C or flame-dried under a stream of dry nitrogen prior to use. Unless otherwise specified, reagents were used as obtained from the vendor without further purification. Tetrahydrofuran and diethyl ether were freshly distilled from purple Na/benzophenone ketyl. Dichloromethane, acetonitrile, and toluene were dried over CaH_2 and freshly distilled prior to use. All other solvents were purified in accordance with 'Purification of Laboratory Chemicals'.[18] Air- and moisture-sensitive reactions were performed using standard Schlenk techniques under an atmosphere of nitrogen. Analytical thin layer chromatography (TLC) was performed utilizing precoated silica gel 60 F_{254} plates containing a fluorescent indicator, while preparative chromatography was performed using SilicaFlash P60 silica gel (230–400 mesh) via Still's method.[19] Unless otherwise stated, the mobile phases for column chromatography were

mixtures of hexanes/ethyl acetate. Columns were typically run using a gradient method, beginning with 100% hexanes and gradually increasing the polarity using ethyl acetate. Various stains were used to visualize reaction products, including *p*-anisaldehyde, $KMnO_4$, ceric ammonium molybdate (CAM stain), and iodine powder. ^1H NMR and ^{13}C NMR spectra were obtained using Bruker-300, Varian-300, Varian Inova-500, or Varian Unity-500 spectrometers. For ^1H NMR, chemical shifts are reported relative to residual protiated solvent peaks (δ 7.26, 2.49, 7.15, and 7.09 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6, and $CD_3C_6D_5$, respectively). ^{13}C NMR spectra were measured at either 125 MHz or 75 MHz on the same instruments noted above for recording ^1H NMR spectra. Chemical shifts were again reported in accordance to residual protiated solvent peaks (δ 77.0, 39.5, 128.0, and 137.9 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6, and $CD_3C_6D_5$, respectively). Accurate mass measurements were acquired at the University of Wisconsin-Madison using a Micromass LCT (electrospray ionization, time-of flight analyzer or electron impact methods). The NMR and mass spectrometry facilities are funded by the NSF (CHE-9974839, CHE-9304546, CHE-9208463, CHE-9629688) and the University of Wisconsin, as well as the NIH (RR08389-01).

4.2. Preparation of homoallenic alcohol 8 from 5

*4.2.1. (S)-1-((R)-2,2-Diethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (**6**).* A 2 L round-bottomed flask was charged with 450 mL dry ether. A portion of 25.7 mL ethynyl trimethylsilane (180 mmol, 1.1 equiv) was added and the flask was cooled to 0 °C. A solution of 72.1 mL ^{n}BuLi (2.5 M in hexanes, 180 mmol, 1.1 equiv) was added dropwise, the mixture stirred for 10 min and then cooled to −78 °C. After stirring for 30 min, 43.1 mL (^{i}PrO)$_3$TiCl (180 mmol, 1.1 equiv) in 180 mL dry ether was added to the reaction vessel. The solution was stirred for 30 min and 25.9 g aldehyde **5** (164 mmol, 1.0 equiv) in 180 mL ether was added over a period of 10 min. The reaction mixture was stirred at −78 °C for 1 h, and then warmed to 0 °C for 2 h. A solution of 650 mL of saturated Rochelle's salt was added and the phases separated. The aqueous phase was extracted with EtOAc (3×400 mL) and the combined organic fractions were washed with brine. After drying with Na_2SO_4 and removing the volatiles under reduced pressure, the crude oil was treated with 500 mL of MeOH saturated with K_2CO_3 for 20 min. The mixture was concentrated to 200 mL, diluted with 400 mL H_2O, and extracted with EtOAc (4×200 mL). The volatiles were removed under reduced pressure to provide a yellow oil of sufficient purity for the subsequent step (28.95 g, 157 mmol, 96%, dr=5.25:1). ^1H NMR (500 MHz, $CDCl_3$) δ 4.51 (td, *J*=4.5, 2.3 Hz, 1H), 4.24 (td, *J*=6.7, 4.5 Hz, 1H), 4.11 (dd, *J*=8.4, 6.7 Hz, 1H), 4.01 (dd, *J*=8.4, 6.8 Hz, 1H), 2.48 (d, *J*=2.3 Hz, 1H), 2.31 (d, *J*=4.5 Hz, 1H), 1.68−1.76 (m, 2H), 1.65 (q, *J*=7.5 Hz, 2H), 0.94 (t, *J*=7.5 Hz, 3H), 0.90 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 114.0, 81.0, 77.8, 74.5, 65.5, 62.3, 29.3, 28.8, 8.2, 8.0. HRMS *m*/*z* $[M+H]^+$ predicted, 185.1173; observed, 185.1166.

*4.2.2. (S)-1-((R)-2,2-Diethyl-1,3-dioxolan-4-yl)prop-2-ynyl 4-methylbenzenesulfonate (**7**).* The propargyl alcohol **6** (28.9 g, 157.1 mmol, 1.0 equiv) was dissolved in 320 mL CH_2Cl_2. DMAP (0.96 g, 7.86 mmol, 0.05 equiv) and 24.1 mL triethylamine (173 mmol, 1.10 equiv) were added, followed by TsCl (30.0 g, 157.1 mmol, 1.0 equiv). The solution was stirred at rt for 2 h, then diluted with water (300 mL) and extracted with CH_2Cl_2 (3×150 mL). The combined organic fractions were washed with brine, dried with Na_2SO_4, and concentrated by rotary evaporation. The crude residue was purified by column chromatography (%−40% EtOAc in hexanes) to give **7** as a pale yellow oil (49.8 g, 147.3 mmol, 94%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.5 Hz, 2H), 7.34 (d, *J*=8.5 Hz, 2H), 5.07 (dd, *J*=5.6, 2.2 Hz, 1H), 4.26 (app q, *J*=6.1 Hz, 1H), 4.09 (dd, *J*=8.8, 6.4 Hz, 1H), 3.92 (dd, *J*=8.8, 5.9 Hz, 1H), 2.45 (s, 3H), 2.42 (d, *J*=2.2 Hz, 1H), 1.55−1.72 (m, 4H), 0.88 (t, *J*=7.5 Hz, 3H), 0.87 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 145.1, 133.5, 129.7, 128.2, 114.8, 77.3, 76.5, 76.4, 69.8, 65.9, 29.3, 28.7, 21.7, 8.0, 8.0. HRMS *m*/*z* $[M+H]^+$ predicted, 339.1261; observed, 339.1263.

*4.2.3. (P)-5-((S)-2,2-Diethyl-1,3-dioxolan-4-yl)penta-3,4-dien-1-ol (**8**).* Diisopropylamine (20.6 mL, 147 mmol, 1.0 equiv) was placed in a 2 L round-bottomed flask and 600 mL of dry THF was added under a stream of nitrogen. The flask was cooled to −78 °C and 58.9 mL ^{n}BuLi (2.5 M in hexanes, 147 mmol, 1.0 equiv) was added dropwise. The solution was stirred for 15 min at −78 °C and 20 min at 0 °C before the reaction mixture was recooled to −78 °C. EtOAc (14.4 mL, 147 mmol, 1.0 equiv) in 90 mL THF was added dropwise and the solution stirred for 30 min. CuI (28.0 g, 147.3 mmol, 1.0 equiv) was added under nitrogen and the resulting tan slurry was stirred for 75 min. The tosylate **7** (49.8 g, 147.3 mmol, 1.0 equiv) dissolved in 60 mL of dry THF was added and the slurry stirred for 15 min. The cold bath was removed and the green solution stirred until it turned yellow (about 7 min). The reaction was quenched with 1 L of saturated aqueous NH_4Cl and the mixture extracted with EtOAc (4×250 mL). The combined organic fractions were dried with Na_2SO_4 and the volatiles removed under reduced pressure to yield a crude brown oil (Note: The product ester can be purified at this point, however it is usually more convenient to immediately reduce the compound to avoid undesired isomerization of the homoallenic ester.). The brown oil was dissolved in 50 mL dry THF and slowly added to a stirring suspension of $LiAlH_4$ (10.4 g, 274.0 mmol, 1.9 equiv) in 550 mL dry THF at 0 °C. After stirring for 20 min, the hydride was carefully quenched using a typical Fieser workup. The reaction mixture was filtered, the volatiles removed and the crude residue purified by column chromatography (8−40% EtOAc in hexanes) to yield 16.6 g of **8** as a pale brown oil (78.06 mmol, 53%). ^1H NMR (500.0 MHz, $CDCl_3$) δ 5.30 (qd, *J*=6.5, 1.6 Hz, 1H), 5.23 (tt, *J*=7.0, 2.9 Hz, 1H), 4.57 (dddd, *J*=8.0, 7.0, 6.2, 1.6 Hz, 1H), 4.13 (dd, *J*=8.0, 6.2 Hz, 1H), 3.71−3.76 (m, 2H), 3.64 (app t, *J*=8.0 Hz, 1H), 2.31 (m, 2H), 1.79 (br s, 1H), 1.67 (q, *J*=7.5 Hz, 2H), 1.64 (q, *J*=7.5 Hz, 2H), 0.92 (t, *J*=7.5 Hz, 3H), 0.91 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 205.4, 113.5, 91.0, 89.8, 74.8, 70.0, 61.6, 31.7, 29.9, 29.6, 8.1, 8.1. HRMS *m*/*z* $[M+NH_4]^+$ predicted, 230.1751; observed, 230.1744.

4.3. General preparation of homoallenic sulfamates

Chlorosulfonyl isocyanate (1.5 equiv) was placed in a round-bottomed flask equipped with a drying tube and cooled to 0 °C. Formic acid (1.5 equiv) was added dropwise (caution: vigorous gas evolution), resulting in solidification of the mixture after 5 min. CH_2Cl_2 (1.9 M in formic acid) was added and the mixture allowed to stir at rt overnight. The solution was cooled to 0 °C and a mixture of the alcohol (1.0 equiv), pyridine (1.5 equiv), and CH_2Cl_2 (1.4 M in alcohol) was added dropwise. The reaction mixture was stirred at rt for 50 min before it was quenched with EtOAc and H_2O. Additional EtOAc and H_2O were added and the phases separated. The aqueous phase was extracted once with EtOAc, the combined organic fractions washed twice with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by column chromatography (40−50% EtOAc in hexanes).

*4.3.1. (P)-5-((S)-2,2-Diethyl-1,3-dioxolan-4-yl)penta-3,4-dienyl sulfamate (**9**).* The alcohol (13.0 g, 61.4 mmol) **8** yielded **9** as a pale amber oil using the general procedure described above (16.7 g, 57.5 mmol, 93%). ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (br s, 2H), 5.32 (app q, *J*=5.4 Hz, 1H), 5.21 (ddt, *J*=7.5, 5.4, 3.5 Hz, 1H), 4.61 (ddd, *J*=8.0, 7.5, 6.3 Hz), 4.31 (m, 2H), 4.17 (dd, *J*=8.4, 6.3 Hz, 1H), 3.65 (dd, *J*=8.4, 8.0 Hz, 1H), 2.40−2.55 (m, 2H), 1.66 (2 q, *J*=7.5 Hz, 4H), 0.91 (t, *J*=7.5 Hz, 3H), 0.90 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$)

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δ 206.0, 113.8, 92.1, 88.7, 75.6, 69.8, 68.4, 29.8, 29.5, 26.6, 8.0, 8.0. HRMS *m*/*z* $[M+H]^+$ predicted, 292.1214; observed, 292.1210.

*4.3.2. (P)-5-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)penta-3,4-dienyl sulfamate (**10**).* The alcohol (1.34 g, 7.28 mmol, 1.0 equiv) yielded **10** as a pale yellow oil (1.12 g, 4.25 mmol, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (br s, 2H), 5.32 (app q, *J*=5.9 Hz, 1H), 5.23 (ddt, *J*=8.5, 5.9, 3.5 Hz, 1H), 4.61 (ddd, *J*=8.5, 7.2, 6.2 Hz, 1H), 4.30 (m, 2H), 4.15 (dd, *J*=8.5, 6.2 Hz, 1H), 3.69 (dd, *J*=8.5, 7.2 Hz, 1H), 2.45–2.52 (m, 2H), 1.43 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 205.9, 109.6, 92.1, 88.7, 75.2, 69.3, 68.5, 26.7, 26.7, 25.7. HRMS *m*/*z* $[M+H]^+$ predicted, 264.0901; observed, 264.0896.

*4.3.3. (M)-5-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)penta-3,4-dienyl sulfamate (**11**).* The alcohol (0.63 g, 3.44 mmol) yielded **11** as a pale yellow oil (0.60 g, 2.29 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30–5.38 (m, 2H), 5.09 (br s, 2H), 4.61 (qd, *J*=6.0, 2.3 Hz, 1H), 4.23–4.33 (m, 2H), 4.11 (dd, *J*=8.3, 6.0 Hz, 1H), 3.82 (dd, *J*=8.3, 6.3 Hz, 1H), 2.41–2.54 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 204.6, 109.7, 92.6, 89.0, 73.7, 69.3, 68.9, 27.8, 26.7, 25.7. HRMS *m*/*z* $[M+NH_4]^+$ predicted, 281.1166; observed, 281.1169.

4.4. Aziridination of 10

The sulfamate **10** (0.0850 g, 0.323 mmol, 1.0 equiv) was dissolved in 3 mL dry CH_2Cl_2. $Rh_2(OAc)_4$ (0.0029 g, 0.0065 mmol, 2 mol %) was added with 0.0850 g powdered 4 Å molecular sieves and the solution stirred for 5 min prior to the addition of 0.0850 g PhIO (0.387 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h, filtered through Celite, and concentrated by rotary evaporation. ^{1}H NMR analysis of the crude mixture showed **10a** and **10b**. A mesitylene standard could be used to quantify the amounts of the materials. Compound **10a** gives a distinct doublet at 5.88 ppm in the ^{1}H NMR spectrum, but was too sensitive to isolate and characterize. However, silica gel chromatography yielded a water-opened enesulfamate of **10a**. The cyclopropane **10b** was also sensitive, but small amounts could be isolated by chromatography (15–75% EtOAc/hexane) for characterization.

*4.4.1. (4E,5S)-4-{[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]methylidene}-1,2,3-oxathiazepan-5-ol 2,2-dioxide (water-opened **10a**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (br s, 1H), 5.77 (d, *J*=8.6 Hz, 1H), 5.03 (t, *J*=3.5 Hz, 1H), 4.65–4.80 (m, 2H), 4.21 (dt, *J*=12.8, 3.6 Hz, 1H), 4.12 (dd, *J*=8.7, 6.7 Hz, 1H), 3.69 (dd, *J*=8.3, 7.5 Hz, 1H), 2.60 (br s, 1H), 2.08–2.12 (m, 2H), 1.43 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.0, 127.1, 110.1, 70.8, 69.2, 64.9, 64.1, 36.8, 26.6, 25.8. HRMS *m*/*z* $[M-H]^-$ predicted, 278.0703; observed, 278.0696.

*4.4.2. 8-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-oxa-3-thia-2-azabicyclo[5.1.0]oct-1-ene 3,3-dioxide (**10b**).* ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 5.10 (dd, *J*=6.3, 3.6 Hz, 1H), 4.97 (dd, *J*=12.0, 3.7 Hz, 1H), 4.64 (td, *J*=12.2, 3.6 Hz, 1H), 4.51 (ddd, *J*=12.2, 5.5, 1.9 Hz, 1H), 4.12 (d, *J*=11.0 Hz, 1H), 3.99 (dd, *J*=11.0, 3.6 Hz, 1H), 3.16 (d, *J*=6.3 Hz, 1H), 2.34 (dtd, *J*=14.5, 12.2, 5.5 Hz, 1H), 2.17 (dtd, *J*=14.5, 3.6, 1.9 Hz, 1H), 1.36 (s, 3H), 1.33 (s, 3H). ^{13}C NMR: (125.7 MHz, CDCl3) δ 194.1, 85.7, 84.6, 80.3, 72.1, 68.9, 60.5, 30.4, 27.8, 24.6. HRMS *m*/*z* $[M+NH_4+H_2O]^+$ predicted, 297.1115; observed, 297.1112.

4.5. Preparation of 19 from 9

*4.5.1. (4E,5S)-4-{[(4S)-2,2-Diethyl-1,3-dioxolan-4-yl]methyl-idene}-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,2,3-oxathiazepane 2,2-dioxide (**14**).* The sulfamate **9** (0.50 g, 1.72 mmol, 1.0 equiv) was dissolved in 12 mL dry CH_2Cl_2. $Rh_2(OAc)_4$ (0.0150 g, 0.034 mmol, 2 mol %) was added and the solution stirred for 5 min prior to the addition of 0.453 g PhIO (2.06 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h, filtered through Celite, and concentrated by rotary evaporation. The crude methylene aziridine was treated with 0.150 mL H_2O (8.58 mmol, 5.00 equiv) in 4.3 mL CH_3CN, stirred for 2 h, and diluted with 30 mL CH_2Cl_2. The mixture was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude enesulfamate **13** was dissolved in 6 mL dry CH_2Cl_2 and cooled to 0 °C. A portion of 2,6-lutidine (0.200 mL, 1.72 mmol, 1.0 equiv) and 0.395 mL TBSOTf (1.72 mmol, 1.0 equiv) were added successively, the mixture stirred for 30 min, quenched with water, and extracted with CH_2Cl_2. Final purification was accomplished by column chromatography (2–10% EtOAc in hexanes) to give 0.235 g **14** (0.557 mmol, 32%) as a pale yellow oil that solidified upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (br s, 1H), 5.77 (d, *J*=8.8 Hz, 1H), 4.96 (t, *J*=3.0 Hz, 1H), 4.70 (t, *J*=13.0 Hz, 1H), 4.68 (dd, *J*=14.6, 8.3 Hz, 1H), 4.18 (dt, *J*=13.0, 3.0 Hz, 1H), 4.08 (dd, *J*=8.3, 6.1 Hz, 1H), 3.62(t, *J*=8.3 Hz, 1H), 2.05 (ddt, *J*=15.0, 12.2, 3.0 Hz, 1H), 1.89 (dt, *J*=15.0, 3.2 Hz, 1H), 1.66 (qd, *J*=7.5, 1.3 Hz, 2H), 1.65 (q, *J*=7.5 Hz, 2H), 0.92–0.89 (m, 15H), 0.13 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 135.7, 126.2, 113.9, 71.1, 69.5, 64.9, 64.6, 38.3, 29.9, 29.5, 25.7, 18.1, 8.11, 8.08, −5.0, −5.1. HRMS *m*/*z* $[M+NH_4]^+$ predicted, 439.2293; observed, 439.2297.

*4.5.2. (4S,5S)-4-[(S)-[(4R)-2,2-Diethyl-1,3-dioxolan-4-yl]-(hydroxyl)methyl]-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,2,3-oxathiazepane 2,2-dioxide (**16a**).* The enesulfamate **14** (52.1 mg, 0.123 mmol, 1 equiv) was added to a 2 mL screw-cap flask, along with 50 mg 4 Å powdered molecular sieves. The flask was cooled to 0 °C in an ice bath, and DMDO (1.35 mL of a 0.22 M solution in CH_2Cl_2, 0.297 mmol, 2.4 equiv) was added. The solution was stirred for 2 h at 0 °C, at which point TLC (30% EtOAc/hexanes, CAM stain) indicated completion. The solution was concentrated under reduced pressure, and fresh CH_2Cl_2 (1.2 mL) was added. The solution was cooled to −78 °C and $Zn(BH_4)_2$ (0.240 mL of a 0.5 M solution in THF, 0.120 mmol, 1 equiv) was added in one portion. The reaction mixture was stirred for 2 h, and then quenched by the addition of saturated NH_4Cl solution. The mixture was extracted twice with CH_2Cl_2, and the combined organic layers were washed with brine and dried over Na_2SO_4. The resulting crude oil was purified by column chromatography (10–25% EtOAc/hexane) to give 32.0 mg of **16a** in addition to 10.5 mg of two minor diastereomers in a 3:1 ratio (favoring **16b**). Combined, this equates to a 78% yield and 4.1:1:0.33 dr. The third diastereomer is not mentioned in this report due to its very low yield of formation. Major diastereomer (**16a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (d, *J*=4.7 Hz, 1H), 4.51 (ddd, *J*=12.5, 9.1, 1.4 Hz, 1H), 4.37 (q, *J*=6.6 Hz, 1H), 4.26 (dds, *J*=12.6, 6.6, 2.2 Hz, 1H), 4.23 (td, *J*=6.0, 3.0 Hz, 1H), 3.87 (t, *J*=7.5 Hz, 1H), 3.19 (dt, *J*=7.5, 5.2 Hz, 1H), 2.90 (d, *J*=2.3 Hz, 1H), 2.34 (ddt, *J*=15.6, 9.3, 2.6 Hz, 1H), 1.95 (dtd, *J*=15.6, 6.6, 1.2 Hz, 1H), 1.66 (m, 4H), 0.91 (m, 15H), 0.12 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 113.6, 75.9, 70.7, 70.7, 66.2, 65.5, 61.1, 35.4, 29.4, 28.8, 25.7, 17.9, 8.2, 8.0, −4.5, −4.9. HRMS *m*/*z* $[M+NH_4]^+$ predicted, 457.2399; observed, 457.2404. Minor diastereomer (**16b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (d, *J*=10.5 Hz, 1H), 4.61 (t, *J*=12.4 Hz, 1H), 4.39 (t, *J*=2.9 Hz, 1H), 4.19 (dt, *J*=13.0, 3.2 Hz, 1H), 4.17 (dd, *J*=8.4, 6.1 Hz, 1H), 4.03 (app q, *J*=6.9 Hz, 1H), 3.87 (app t, *J*=7.9 Hz, 1H), 3.61 (m, 2H), 2.43 (d, *J*=2.3 Hz, 1H), 2.21 (ddt, *J*=15.6, 12.0, 2.7 Hz, 1H), 1.91 (dt, *J*=15.6, 3.7 Hz, 1H), 1.63 (m, 4H), 0.93 (s, 9H), 0.90 (t, *J*=7.5 Hz, 3H), 0.89 (t, *J*=7.5 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 113.3, 76.2, 73.9, 70.6, 67.5, 64.3, 57.7, 36.9, 29.6, 29.1, 25.8, 17.9, 8.2, 8.1, −4.1, −4.8. HRMS *m*/*z* $[M+H]^+$ predicted, 440.2133; observed, 440.2137.

*4.5.3. tert-Butyl{(1S,2S,3S)-1-[(4R)-2,2-diethyl-1,3-dioxolan-4-yl]-1-hydroxy-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]pent-4-en-2-yl}carbamate (**18**).* The triad **16a** (0.0650 g, 0.148 mmol, 1.0 equiv) was

dissolved in 1.5 mL CH_2Cl_2. The solution was cooled to 0 °C and 2.0 mg DMAP (0.0148 mmol, 0.1 equiv), 0.0230 mL triethylamine (0.163 mmol, 1.1 equiv), and 0.0356 g Boc_2O (0.163 mmol, 1.10 equiv) were added successively. After stirring for 40 min, the solution was diluted with 5 mL ether and passed through a short plug of silica. The solids were rinsed with ether (2×3 mL) and the filtrate concentrated. The residue was dissolved in 3 mL of 1:1 EtOH/CH_2Cl_2. Meanwhile, 0.0370 g *o*-nitrophenyl selenocyanate (0.163 mmol, 1.10 equiv) in 1 mL EtOH was cautiously treated with 6.70 mg $NaBH_4$ (0.177 mmol, 1.2 equiv), and stirred for 20 min. The solution containing the Boc-protected triad was added to the selenide, and the reaction mixture stirred at rt for 4 h. The reaction mixture was diluted with 10 mL CH_2Cl_2 and quenched with 10 mL 0.1 M HCl. The product was extracted into CH_2Cl_2, the combined organics were washed with aqueous $NaHCO_3$ and the volatiles removed under reduced pressure. The crude residue was dissolved in 1.5 mL THF and 0.152 mL 30% by weight H_2O_2 (1.48 mmol, 10.0 equiv) and stirred at rt overnight. The solution was diluted with CH_2Cl_2, washed with aqueous $Na_2S_2O_8$, and concentrated. Chromatography (6–30% EtOAc in hexanes) gave **18** as a colorless oil (0.0392 g, 0.0853 mmol, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (ddd, J=16.2, 10.6, 4.6 Hz, 1H), 5.38 (d, J=16.2 Hz, 1H), 5.23 (d, J=10.6 Hz, 1H), 4.85 (d, J=7.6 Hz, 1H), 4.61 (s, 1H), 4.19 (app q, J=6.4 Hz, 1H), 4.12 (app t, J=6.4 Hz, 1H), 3.87 (t, J=7.7 Hz, 1H), 3.72 (m, 2H), 3.03 (d, J=3.2 Hz, 1H), 1.55–1.73 (m, 4H), 1.43 (s, 9H), 0.91 (m, 12H), 0.88 (t, J=7.2 Hz, 3H), 0.09 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 155.9, 137.2, 116.3, 112.9, 79.5, 76.4, 73.8, 73.3, 66.6, 56.1, 29.4, 28.8, 28.3, 25.8, 18.1, 8.3, 8.0, −4.7, −5.1. HRMS m/z $[M+H]^+$ predicted, 460.3089; observed, 460.3098.

*4.5.4. tert-Butyl {(2S,3R,4R)-2-[(4R)-2,2-diethyl-1,3-dioxolan-4-yl]-5-hydroxy-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydrofuran-3-yl}carbamate (**19**).* The alkene **18** (0.0350 g, 0.0761 mmol, 1.0 equiv) was dissolved in 1.0 mL of 3:1 CH_2Cl_2/MeOH. The mixture was cooled to −78 °C and a stream of ozone was bubbled through the solution until a pale blue color persisted. Oxygen was then bubbled through the solution for 5 min prior to the addition of 0.056 mL Me_2S (0.761 mmol, 10.0 equiv). The solution was gradually warmed to rt over 1 h and then concentrated to afford a crude oil that was purified by column chromatography (5–25% EtOAc in hexanes) to give lactol **17** as a 1:1 mixture of anomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (t, J=4.0 Hz, 0.5H), 5.12 (s, 0.5H), 4.91 (d, J=7.0 Hz, 1H), 4.31 (m, 1H), 4.17 (m, 1H), 3.85–4.10 (m, 4H), 3.75 (br s, 0.5H), 3.46 (br s, 0.5H), 1.58–1.80 (m, 4H), 1.44 (s, 9H), 0.85–0.98 (m, 15H), 0.14 (s, 1.5H), 0.13 (s, 1.5H), 0.11 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 155.0 (2), 113.7, 113.5, 103.0, 96.9, 82.4, 80.9, 79.7, 76.6, 71.9 (2), 66.4 (2), 65.3 (2), 53.3, 52.2, 29.5, 29.4, 28.6, 28.4, 28.3 (2), 25.7 (2), 18.2, 18.2, 8.3, 8.2 (3), −4.8, −5.0, −5.2 (2).

4.6. Synthesis of alternate stereoisomer 16c from 14

*4.6.1. (4R)-2,2-Diethyl-1,3-dioxolan-4-yl][(4S,5S)-5-[(1,1-dimethylethyl)dimethylsilyl]oxy-2,2-dioxido-1,2,3-oxathiazepan-4-yl] methanone (**20**).* The enesulfamate **14** (101.1 mg, 0.240 mmol, 1 equiv) was added to a 10 mL round-bottomed flask, followed by 100 mg 4 Å powdered molecular sieves. The flask was cooled to 0 °C in an ice bath, and DMDO (2.70 mL of a 0.22 M solution in CH_2Cl_2, 0.594 mmol, 2.5 equiv) was added. The solution was stirred for 2 h at 0 °C, at which point TLC (30% EtOAc/hexanes, CAM stain) indicated completion. The solution was concentrated under reduced pressure and 1,2-dichloroethane (4.5 mL) was added to the residue, followed by $Al(O^tBu)_3$ (58.3 mg, 0.237 mmol, 1 equiv). The flask was fitted with an air condenser and heated to 50 °C for 4 h. The reaction was quenched by the addition of a saturated solution of Rochelle's salt and stirred for 30 min. The mixture was extracted twice with CH_2Cl_2, washed with brine, and dried over Na_2SO_4 to yield a crude oil. The residue was purified by column chromatography (5–25% EtOAc/hexane) to give 28.4 mg (0.0648 mmol, 27%) of the aminoketone **20** in a 17:1 dr and was used without further purification. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (d, J=10.5 Hz, 1H), 4.71 (dd, J=10.5, 9.2 Hz, 1H), 4.55 (dd, J=6.7, 6.2 Hz, 1H), 4.33 (dd, J=6.7, 3.4 Hz, 2H), 4.16 (d, J=3.4 Hz, 1H), 4.15 (d, J=2.4 Hz, 1H), 3.94 (td, J=9.1, 5.3 Hz, 1H), 2.17 (m, 2H), 1.68 (m, 4H), 0.94 (t, J=7.5 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), −0.04 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 206.8, 115.6, 80.5, 73.8, 66.6, 65.5, 57.9, 37.5, 29.2, 28.5, 25.5, 17.8, 8.2, 7.9, −4.5, −5.1. HRMS m/z $[M+NH_4]^+$ predicted, 455.2242; observed, 455.2243.

*4.6.2. (4S,5S)-4-[(R)-[(4R)-2,2-Diethyl-1,3-dioxolan-4-yl]-(hydroxy)methyl]-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,2,3-oxathiazepane 2,2-dioxide (**16c**).* The aminoketone **20** (10.0 mg, 0.0229 mmol, 1 equiv) was added to a 10 mL round-bottomed flask and 3 mL of Et_2O was added. The flask was cooled to −78 °C in a dry ice/acetone bath, and $LiBEt_3H$ (0.115 mL of a 1.0 M solution in THF, 0.115 mmol, 5 equiv) was added via syringe. The solution was stirred for 2 h, at which point the temperature of the bath had reached 0 °C. The solution was diluted with 20 mL Et_2O and washed twice with saturated NH_4Cl and once with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield a crude oil that was purified by column chromatography (0–30% EtOAc/hexane) to give 5.8 mg of the stereotetrad **16c** and 1.1 mg of **16a** as a separable minor diastereomer. Combined, this equates to 6.9 mg (0.0158 mmol, 69%) in a 5.3:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (d, J=10.1 Hz, 1H), 4.28 (m, 3H), 4.16 (dd, J=8.4, 6.5 Hz, 1H), 3.92 (m, 2H), 3.62 (dd, J=8.4, 5.6 Hz, 1H), 2.99 (td, J=9.7, 0.8 Hz, 1H), 2.62 (br s, 1H), 2.17 (m, 1H), 2.04 (m, 1H), 1.66 (q, J=7.4 Hz, 2H), 1.63 (q, J=7.5 Hz, 2H), 0.90 (t, J=7.5 Hz, 3H), 0.89 (t, J=7.4 Hz, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 113.9, 76.2, 70.0, 69.4, 67.0, 66.4, 57.9, 37.6, 29.4, 25.6, 17.8, 8.2, 7.7, −4.4, −5.2. HRMS m/z $[M+NH_4]^+$ predicted, 457.2399; observed, 457.2419.

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