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Heptanosides from Galactose-Derived Oxepenes via Stereoselective Addition Reactions

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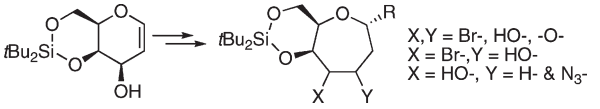

Addition reactions to a 3,4-anhydroheptanose gave heptanoside analogues of carbohydrate derivatives in good to excellent stereochemical purity. Characterization of the products by ^{1}H and ^{13}C NMR, COSY, HSQC-DEPT, HMBC, 1D TOCSY, and NOE experiments were performed to obtain the stereochemistry of addition. The 3,4-anhydroheptanose used in this study is obtained from the ring-expansion of a cyclopropanated galactal and thus demonstrates the synthetic utility of heptanose synthesis via cyclopropanated carbohydrates.

Introduction

Heptanoses are seven-membered ring sugars that are increasingly becoming important in a biological setting.[1,2] Examples include protein-binding studies[3,4] and heptanose-based nucleic acids for oligonucleotide synthesis.[5,6] By necessity, the synthesis of heptanoses is also gaining attention, and many new strategies for their construction have arisen. These strategies, among others,[1,7−11] include ring-closing metathesis (RCM)[12] followed by addition to the resulting alkene and ring-expansion of cyclopropanated pyranosides.[13] Over a decade ago, we reported on the ring-expansion of cyclopropanated sugars to give oxepenes **2**,[13−17] Scheme 1, and since then this methodology has been elaborated and expanded upon in very perceptive methods.[18−21] In both the RCM and ring-expansion methods, the formation of an alkene moiety occurs that must be further elaborated to fully develop the heptanose sugar. In the report by Damha,[5] who used our ring-expansion for the initial synthesis of heptanose nucleic acids, a straightforward hydrogenation over Pd/C was performed, thus alleviating any issues with the stereochemistry of addition. However, the conversion of oxepenes to heptanoses involving other reagents must involve a controlled addition in which the stereochemistry of addition can be ascertained. Peczuh[1] has addressed the addition to seven-membered-ring cyclic enol ethers (1,2-anhydroheptanoses), but no studies have been reported on the addition to oxepenes of type **2**. Herein, we report on a series of addition reactions and stereochemical outcomes and conformations of the products. From these studies, an

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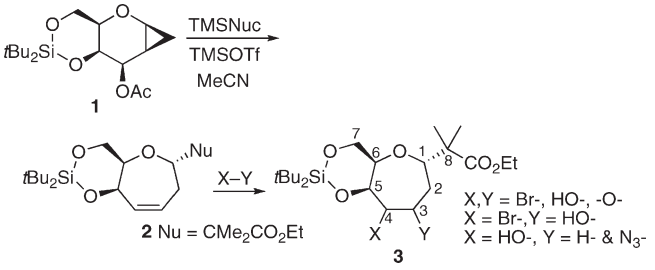
SCHEME 1. Ring-Expansion and Addition Reaction of Cyclopropanated Carbohydrates



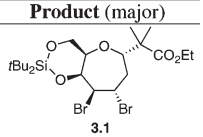
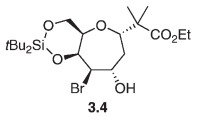
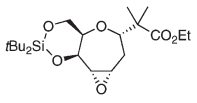
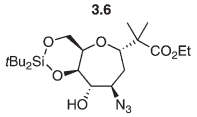
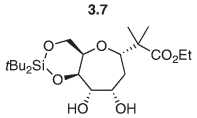
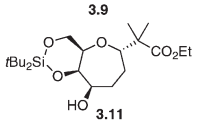
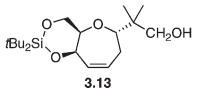
excellent method has been established for a route to heptanose sugars **3**.

Results and Discussion

Peczuh and co-workers used modeling studies and experimental observations and reported that the underlying forces determining the preferred conformations of furanose and pyranose rings can generally be extended to the heptanoses.[1] Thus, the compounds formed by addition to the alkene moiety of the ring-expanded products are in effect heptanose analogues of carbohydrate derivatives. Seven-membered rings are known to exist in four principle conformers[22] with the predominant form in solution being the twist-chair (see Figure 1 below), which accounts for ~80% of the conformations of compounds with this type of structure.[1] We were able to confirm this with our system as well, and the following drawings in Figure 1 are all illustrated in the twist-chair conformation. NOE enhancements and vicinal $^1H-^1H$ coupling constants were used to determine relative stereochemistry of the reaction products obtained. Based on the Karplus relationship and typical values observed in hexoses, large couplings (8−14 Hz) were assumed to be due to 1,2-diaxial arrangements while axial−equatorial and equatorial-equatorial arrangements assigned to the smaller couplings (1−7 Hz, with 2−3 Hz being more typical).[23] Oxepene **2** (Nuc = CMe_2CO_2Et) was chosen as the substrate for this study as it is synthesized in high yield and in a stereochemically pure form, with the stereochemistry at C-1 established using NOE data between a *gem*-dimethyl and the proton on C-6.[17] The reactions investigated were bromination, bromohydrin formation, epoxidation, dihydroxylation, and hydroboration. These reactions were chosen as they provide an established set of transformations to probe the reactivity and stereochemistry, and also elaborate the oxepane ring toward more useful heptanose sugars. To aid in the following discussions, the numbering system in structure **3**, Scheme 1, is used throughout and the usual carbohydrate terminology of α and β faces is employed where H1 is on the β face.

Halogen Addition. Addition of bromine to a solution of oxepane **2** in $CHCl_3$ at ambient temperature gave two isomers in 90% overall yield in a 2:1 ratio (entry one, Table 1). Both isomers could be separated and purified by column chromatography. Mass spectrometry of both revealed the presence of two bromine atoms in each isomer,

TABLE 1. Functionalization of 2

Entry	Conditions	Yield[a]	ds[b]	Product (major)
1	Br_2, $CHCl_3$, rt, 1h	90%	2:1	 **3.1**
2	NBS THF/H_2O 1:1, rt, 1h	77%	5:1	 **3.4**
3	mCPBA CH_2Cl_2, rt, 24h	83%	>100:1	 **3.6**
4	**3.6**, NaN_3,NH_4Cl, MeOH/H_2O 8:1 reflux, rt, 24h	63%	>100:1	 **3.7**
5	OsO_4, NMO, Et_2O/H_2O 1:1, rt, 2h	59%	>100:1	 **3.9**
6	BH_3·DMS, THF, 0 °C then NaOH, H_2O_2	40%	>100:1	 **3.11**
7	DIBAL, CH_2Cl_2, -78 °C, 24h	54%	-	 **3.13**

[a]Isolated yield. [b]Determined on the crude reaction mixture by fused silica capillary gas chromatography.

while NMR indicated the absence of the alkene. The ^1H NMR was congested between δ_H 4 and 5 ppm, making it difficult to distinguish individual signals. However, the spectral data set of the minor isomer showed better resolution in the ^1H NMR enabling its assignment.

The structure of the minor isomer, oxepane **3.2**, was assigned by ^1H, ^{13}C NMR, COSY, HSQC-DEPT, HMBC, 1D TOCSY, and NOE experiments. As with all products formed in this study, the presence of the *gem*-dimethyl ester group was confirmed by ^1H resonances consistent with two methyls (δ_H 1.19 and 1.15) and an ethyl group (δ_H 4.60 and δ_H 1.30). Similarly observed were ^{13}C resonances consistent with a carbonyl group (δ_C 176.0) and a quaternary carbon (δ_C 47.5). ^1H resonances also confirmed the presence of the di-*tert*-butylsilyl protecting group (δ_H 1.18, 18H). The HSQC-DEPT experiment, as well as establishing direct hydrogen−carbon connectivity, revealed the presence on the main ring of three oxymethines, two methines, an oxymethylene, and a methylene, which COSY correlations confirmed were all part of the same ^1H spin system. An HMBC correlation from the *gem*-dimethyl quaternary carbon was observed to the C-1 oxymethine (δ_H 4.41, δ_C 78.8). The connectivity of the ^1H spin system was then constructed from a series of COSY and TOCSY correlations from the C-1 oxymethine proton to a methylene (C-2: δ_H 2.80 and 1.97, δ_C 28.0) to a methine (C-3: δ_H 4.70, δ_C 48.5) to a second methine (C-4: δ_H 4.74, δ_C 57.6) to an oxymethine (C-5: δ_H 4.64, δ_C 79.8) to a second oxymethine (C-6: δ_H 4.07, δ_C 66.9) and finally to an oxymethylene (C-7: δ_H 4.22 and 4.12, δ_C 70.4). The conformation and relative stereochemistry

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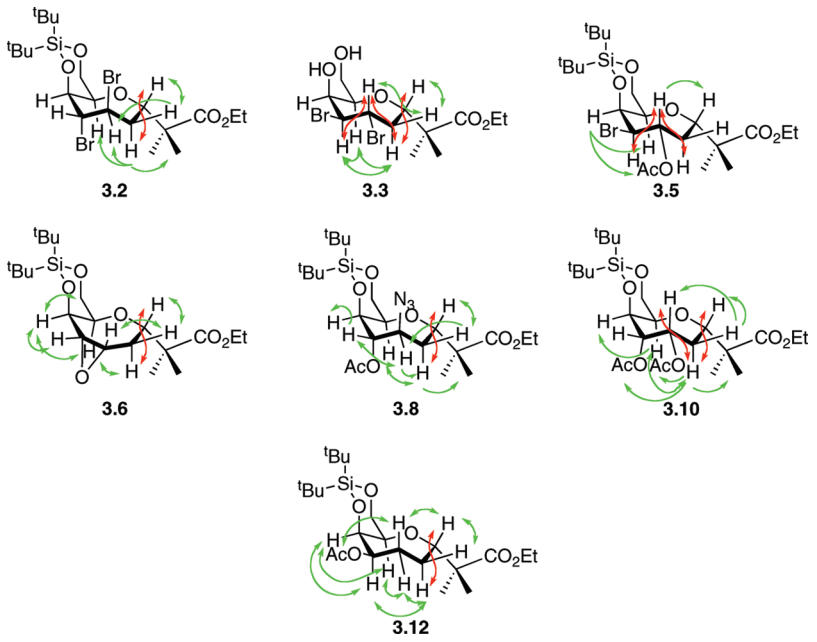

FIGURE 1. NOE enhancement experiments in green and ^{1}H axial−axial couplings in red.

around the oxepane ring were established from an analysis of NOE enhancements and ^{1}H−^{1}H coupling constants (Figure 1, **3.2**).

H-1 on the β face of the molecule has a large coupling constant of 12.0 Hz shared with one of the protons at H-2 (δ_H 2.80) indicating the *anti*-relationship of these two protons and establishing this methylene proton's position on the α face of the ring. Clear NOE enhancements were observed from H-2α to H-6 and H-3, which assigns these protons on the same side of the ring (α). These relationships establish the bromine at C-3 as being on the β face. The second bromine at C-4 is in an *anti*-relationship with its partner at C-3 and must therefore be on the α face. Coupling constants for H-3, H-4, and H-5 were all <7 Hz assigning them in equatorial positions, consistent with axial bromines at C-3 and C-4. The 1,2-axial positioning of the C-3 and C-4 bromines is consistent with a stable twist-chair conformation of the oxepane ring, the presence of the large bulky α *gem*-dimethyl substituent at C-1, and the effect of the cyclic silyl-protecting group.

The major isomer from the reaction, oxepane **3.1**, was similarly assigned using ^{1}H, ^{13}C COSY, HSQC-DEPT, and HMBC; however, the ^{1}H NMR spectrum of this compound was particularly congested in the 4.2−4.0 ppm region and produced some uncertainty in our assignments. Therefore, isomer **3.1** was deprotected with TBAF to give diol **3.3** (the structure is shown in Figure 1; see the Supporting Information for NMR data), which resolved the overlapping signals. The connectivity of the ^{1}H spin system was constructed from a series of COSY correlations from the C-1 oxymethylene (δ_H 4.34, δ_C 78.9) to a methylene (C-2: δ_H 2.50 and 2.23, δ_C 39.7) to a methine (C-3: δ_H 4.51, δ_C 53.7) to a second methine (C-4: δ_H 4.25, δ_C 63.5) to an oxymethine (C-5; δ_H 4.43, δ_C 76.0) to a second oxymethine (C-6: δ_H 3.84, δ_C 74.9) and finally to an oxymethylene (C-7: δ_H 3.78 and 3.71, δ_C 65.4). Again, analysis of NOE enhancements and ^{1}H−^{1}H coupling constants gave the relative stereochemistry around the ring. H-1 has a large coupling constant of 10.5 Hz with H-2α (δ_H 2.23) verifying the *anti* relationship. H-2α displayed NOE enhancements to H-4 and H-6 and exhibited a large coupling constant of 12.2 Hz to the *anti* H-3 proton. Finally, a coupling constant of 10.7 Hz between H-4 and H-3 confirmed the axial position of H-4. This places both bromines equatorial, at C-3 α and at C-4 β, and confirms the structure of **3.1** and **3.2**.

Bromohydrin Formation. Reaction of oxepane **2** with NBS in water gave the bromohydrin **3.4** in a 77% yield as a 5:1 mixture with its minor isomer (entry 2, Table 1). The ^{1}H NMR of the major product was far too congested to allow complete structural assignment due to the presence of three methines and two oxymethines between δ_H 4.0 and 4.2 ppm. Therefore, **3.4** was acetylated to give oxepane **3.5** (Figure 1) and a much more resolved ^{1}H NMR that made it possible to assign the parent structure based on 1D and 2D NMR data. Signals in the ^{1}H and ^{13}C NMR confirmed the presence of the *gem*-dimethyl containing ester group and the di-*tert*-butyl silyl-protecting group. As the oxymethine at C-1 was obscured in the ^{1}H spectrum, the ^{1}H spin system was constructed from COSY correlations starting with the C-2 methylene (δ_H 1.96, δ_C 33.3). These protons couple to an oxymethine (C1: δ_H ~4.2, δ_C 78.0) and to a second oxymethine (C-3: δ_H 5.14, δ_C 58.7). H-3 couples to a methine (C-4: δ_H ~4.1, δ_C 58.7), which in turn couples to an oxymethine (C-5: δ_H 4.53, δ_C 74.3 ppm). These correlations confirm the substitution pattern as 3-hydroxy-4-bromo. H-3 was clearly identifiable as a result of the acetylation and appeared as a triplet of doublets with coupling constants of 10.4 and 1.6 Hz. The large coupling of 10.4 indicated the *anti* relationship with both H-2α and H-4, placing both the hydroxyl at C-3 and the bromine at C-4 in equatorial orientations. Furthermore, an NOE enhancement was observed from H-3 to H-1 confirming the position of H-3 on the β face. These relationships establish that for the major isomer, initial addition of bromine appears to be on the β face, contrary to the more sterically open α face. These results, and the formation of **3.1**,

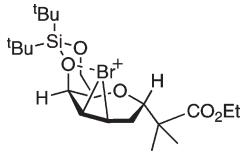

FIGURE 2. Bromonium formation via coordination to the C-5 oxygen.

can perhaps be rationalized by "halogen" bonding[24] via an O-5 coordination to the bromine, directing the bromine to the β face as shown in Figure 2.

Epoxidation. An epoxidation was then performed to determine the stereochemical outcome of an undirected reaction. Epoxidation of oxepane **2** with *m*-CPBA[25] gave only one product, **3.6**, in an 83% yield (entry 3, Table 1). The connectivity of the ^{1}H spin system was constructed from a series of COSY correlations from the C-1 oxymethine (δ_H 4.23, δ_C 78.3) to the C-2 methylene (δ_H 2.13 and 1.91, δ_C 27.1) to an oxymethine (C-3: δ_H 3.28, δ_C 55.6) to a second oxymethine (C-4: δ_H 3.05, δ_C 56.6) and finally to a third oxymethine (C-5: δ_H 4.60, δ_C 74.1). The conformation and relative stereochemistry were established starting with H-1, which has a large coupling constant of 12.5 Hz with H-2α (δ_H 1.91) confirming their *anti* relationship, and confirmed by an NOE enhancement of H-2α to H-6. The H-3 coupling constants of 8.5 and 4.7 Hz place it *syn* to H-4 and in an eclipsed relationship with H-2β (δ_H 2.14). Furthermore, NOE enhancements are observed from H-2β to both H-3 and H-1 placing these three protons all on the β face and thus the epoxide on the α face.

Amino substitutents are an integral part of carbohydrates, the ring-opening of the epoxide in **3.6** in a regioselective manner was deemed important. Treatment of epoxide **3.6** with sodium azide and ammonium chloride in a mixture of 8:1 MeOH/H_2O gave **3.7** as a single product in 63% yield (entry 4, Table 1). The ^{1}H NMR spectrum was very congested, with four methines and two oxymethylenes between δ_H 4.2 and 4.0, which made it very difficult to assign the stereochemistry. Acetylation of **3.7** gave **3.8** and resolved most of the ring protons making assignment of the stereochemistry possible. As the oxymethine proton on C-1 was obscured in the ^{1}H spectrum, connectivity of the ^{1}H spin system was constructed from a series of COSY correlations from the C-2 methylene (δ_H 2.17 and 1.75, δ_C 26.7) to an oxymethine (C-1: δ_H 4.15, δ_C 76.7) and to a methine (C-3: δ_H 3.95, δ_C 58.8). H-3 correlates to the C-4 oxymethine bearing the acetate group (δ_H 5.33, δ_C 73.7) to a second oxymethine (C-5: δ_H 4.25, δ_C 75.9). This assigns the regioselectivity of the azide addition to C-3. The conformation and relative stereochemistry around the oxepane ring were established from an analysis of NOE and NOESY enhancements and ^{1}H$-^1$H coupling constants. A clear NOE enhancement was observed from H-6 to H-2α (δ_H 2.17) assigning this proton to the same face. H-2α has coupling constants of 12.8 and 3.4 Hz to H-1 and H-3, respectively, thus confirming the equatorial position of H-3. H-3 also displayed NOE enhancements to H-2α, H-2β, and H-4, which places this proton in a *syn* orientation to these three protons. The coupling constants of H-4 and H-5 are <6.5 Hz, which places them in equatorial positions as well and it would appear that azide attack occurs at the least sterically hindered carbon to give **3.7**.

Dihydroxylation. Reaction of oxepane **2** with osmium tetraoxide produced a single product, diol **3.9**, in a 59% yield (entry 5, Table 1). Again, the ^{1}H NMR was too congested to allow detailed assignment, as the signals for the four methines and two oxymethylenes were all in the δ_H 3.9$-$4.15 region. Acetylation of diol **3.9** gave **3.10** in a decent 79% yield and allowed for successful stereochemical assignment. Connectivity of the ^{1}H spin system was then constructed from a series of COSY correlations from the C-2 methylene (δ_H 2.49, 1.67, δ_C 27.0), which coupled to an oxymethine (C-1: δ_H 4.15, δ_C 78.5) and a second oxymethine (C-3: δ_H 5.19, δ_C 70.6). C-3 was shown to couple to an oxymethine (C-4: δ_H 5.24, δ_C 74.0) which coupled to a second oxymethine (C-5: δ_H 3.99, δ_C 73.5). A clear NOE enhancement was observed from H-6 to H-2α (δ_H 2.49) assigning these protons to the same face. NOE enhancements were also observed from H-2α to the *gem*-dimethyls and both acetates indicating that these groups were also on the α face. H-2α appears as a triplet of doublets with a large coupling constant of 10.5 Hz, indicating an *anti* relationship to both H-1 and H-3, and placing these protons *axial* and on the β face. By necessity, the acetylated hydroxyl at C-3 must be in an equatorial orientation and since the dihydroxylation produces a *cis* diol the oxygen at C-4 must be axial. This is confirmed by a coupling constant between H-3 and H-4 of 1.7 Hz, which places H-4 in an equatorial orientation to the axial proton at H-3. This is the expected product due to steric factors influencing the initial addition of the osmium tetraoxide to the alkene. Models suggested that the most likely conformation of this oxidation product in solution is again twist-chair.

Hydroboration. Attempts were next made to convert the alkene to an alcohol using Brown's hydroboration conditions. Reacting oxepane **2** in THF with 9-BBN at 0 °C followed by addition of NaOH and H_2O_2, then warming to ambient temperature for 12 h, returned only starting material despite repeated attempts. Repeating the reaction with $BH_3\cdot$DMS as the hydroboration reagent gave one product, **3.11**, in 40% yield along with 26% of starting material (entry 6, Table 1). ^{1}H NMR again gave a very congested spectrum with four methine and two oxymethylene signals between δ_H 3.9 and 4.2 ppm but also indicated the expected presence of two unsubstituted methylenes. Acetylation of the alcohol gave **3.12**, again dispersing the ^{1}H signals allowing assignment of the structure. Connectivity of the ^{1}H spin system was then constructed from a series of COSY correlations from the C-1 oxymethine (δ_H 3.89, δ_C 82.4) to a methylene (C-2: δ_H 2.00 and 1.51, δ_C 19.7) to a second methylene (C-3: δ_H 1.92, δ_C 25.5) to an oxymethine (C-4: δ_H 4.96, δ_C 73.3) to a second oxymethine (C-5: δ_H 4.10, δ_C 75.7). The COSY data revealed that two unsubstituted methylenes are next to each other, suggesting that the hydroxylation has occurred at the C-4 position rather than the C-3 position. The H-1 proton of acetate 3.12 has a large coupling constant of 12.5 Hz with H-2α (δ_H 2.00) placing it axial in an *anti* relationship. H-2α shows clear NOE enhancements to H-3α and H-4 placing the acetylated hydroxyl at C-4 on the β-face, which was confirmed by a weak NOE of the acetyl methyl protons to H-3β.

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These correlations are consistent with the proposed conformation in solution being a twist-chair. This was a somewhat surprising result as we expected boration to occur on the opposite carbon of the starting alkene and the opposite face;[26] however, it again appears that complexation of the boron reagent to the C-5 oxygen is occurring, and this directing affect is overriding any steric conditions to produce the observed selectivity.

Finally, reduction of the ester (entry 7) was performed to ascertain the propensity for formation of the aldehyde. In this endeavor, we were unable to obtain any aldehyde, and only alcohol **3.13** was obtained.

Conclusion

All the reactions in this work led to either the formation of a single product or a mixture of easily separable isomers with the only exception to this being the products of the bromohydrin addition. The reactions all demonstrate good to high diastereo- and regioselectivity using common reagents, and it is relatively easy to predict the stereochemistry of the resulting heptanose. Information was also obtained regarding the conformation of the oxepane in solution. The preferred conformation adopted in solution was that of the twist-chair, with none of the other possible conformers observed. This is in line with other conformations reported for seven-membered rings.[1] The modest yields observed in entries 4−7 are most likely due to loss of the silyl protecting group during the reaction to produce the diol. Subsequently, we have learned that reagents such as NH_4Cl, osmium, and select boranes do lead to deprotection of silyl groups.[27−29] Thus, these results demonstrate the synthetic utility of the oxepane moiety as a precursor to heptanoses, and future modifications to select conditions will target improved yields.

Experimental Section

(1*R*,7*R*)-3-(Ethyl 2-methyl-2-propanoate)-9,9-di-*tert*-butyl-2,8,10-trioxa-9-silabicyclo[5.4.0]-5,6-dibromoundecane (3.1). A solution of oxepane **2** (101 mg, 0.253 mmol) in $CHCl_3$ (1 mL) at ambient temperature was treated with bromine (19 μL, 0.38 mmol, 1.5 equiv) and then stirred for 30 min. The mixture was poured into Et_2O (20 mL) and washed with H_2O (2 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. Flash chromatography on silica with 9:1 hexanes/EtOAc provided 84.9 mg of **3.1** and 42.5 mg of **3.2** (90% overall yield). Major fraction **3.1**: ^{1}H NMR δ_H = 4.64 (d, J = 3.2 Hz, 1H, H-5), 4.45 (td, J = 11.0, 1.7 Hz, 1H, H-3), 4.23−4.0 (m, 6H, H-1, H-4, H-7, −OCH_2Me), 3.85 (s, 1H, H-6), 2.57 (dt, J = 15.4, 2.2 Hz, 1H, H-2), 2.35 (dt, J = 15.4, 11.5 Hz, 1H, H-2), 1.27 (t, J = 7.1 Hz, 3H, −OCH_2Me), 1.19 (s, 3H, H-9), 1.15 (s, 3H, H-10), 1.08 (s, 18H, *t*Bu); ^{13}C NMR δ_C = 175.8 (C-11), 79.2 (C-1), 75.9 (C-5), 71.9 (C-6), 70.4 (C-7), 62.8 (C-4), 60.7 (−OCH_2Me), 52.9 (C-3), 47.9 (C-8), 38.6 (C-2), 27.6 (-*t*Bu), 23.5 (C-9), 20.9 (C-10), 20.6 (Si−C), 14.1 (−OCH$_2$*Me*); IR (neat) 2935, 2859, 1723 cm^{-1}. Minor product **3.2**: ^{1}H NMR δ_H = 4.74 (t, J = 2.8 Hz, 1H, H-4), 4.70 (d, J = 6.5 Hz, 1H, H-3), 4.64 (d, J = 1.5 Hz, 1H, H-5), 4.60 (dd, J = 10.7, 7.0 Hz, 1H, −OCH_2Me), 4.41 (dd, J = 12.0, 3.7 Hz, 1H, H-1), 4.22 (dd, J = 11.4, 1.9 Hz, 1H, H-7), 4.18 (dd, J = 10.7, 7.0 Hz, 1H, −OCH_2Me), 4.12 (dd, J = 11.4, 1.9 Hz, 1H, H-7), 4.07 (m, 1H, H-6), 2.80 (ddd, 1H, J = 15.6, 12.2, 1.2 Hz, H-2), 1.97 (dt, 1H, J = 16.6, 1.2 Hz, H-2), 1.30 (t, 3H, J = 7.1 Hz, −OCH$_2$*Me*), 1.25 (s, 3H, H-9), 1.24 (s, 3H, H-10), 1.09 (s, 9H, *t*Bu), 1.04 (s, 9H, *t*Bu); ^{13}C NMR δ_C = 176 (C-11), 79.8 (C-5), 78.9 (C-1), 70.4 (C-7), 66.9 (C-6), 60.7 (−OCH_2Me), 57.6 (C-4), 48.6 (C-3), 47.5 (C-8), 28.0 (C-2), 27.6 (-*t*Bu), 27.3 (-*t*Bu), 22.5 (C-10), 22.3 (C-9), 20.9 (Si−C), 14.1 (−OCH$_2$Me); IR (neat) 2935, 2859, 1722, 1472, 1389, 1365, 1265, 1105, 899, 825, 737 cm^{-1}; ES HRMS m/z calcd for $C_{21}H_{38}Br_2O_5Si$ + H (**3.1**) 557.0928, found 557.0934.

(1*R*,7*R*)-3-(Ethyl 2-methyl-2-propanoate)-9,9-di-*tert*-butyl-2,8,10-trioxa-9-silabicyclo[5.4.0]-5(*R*),6(*S*)-epoxyundecane (3.6). To a solution of oxepane **2** (230 mg, 0.577 mmol) in CH_2Cl_2 (10 mL) at ambient temperature was added 75% *m*-CPBA (1.78 mg, 0.75 mmol, 1.5 equiv) and the reaction stirred overnight. The resulting mixture was poured into Et_2O (20 mL) and washed with H_2O (3 × 20 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica with 9:1 hexanes/EtOAc gave 198 mg of **3.6** as a colorless oil (83%): ^{1}H NMR: δ_H = 4.60 (s, 1H, H-5), 4.23 (dd, J = 12.5, 1.9 Hz, 1H, H-1), 4.16 (q, J = 7.0 Hz, 2H, −OCH_2Me), 4.14 (s, 2H, H-7), 3.58 (s, 1H, H-6), 3.28 (dt, J = 8.5, 4.5 Hz, 1H, H-3), 3.05 (dd, J = 4.1, 1.2 Hz, 1H, H-4), 2.14 (ddd, J = 15.9, 7.8, 1.9 Hz, 1H, H-2), 1.91 (ddd, J = 15.9, 12.4, 5.1 Hz, 1H, H-2), 1.24 (t, J = 7.2 Hz, 3H, −OCH$_2$*Me*), 1.15 (s, 3H, H-9), 1.08 (s, 3H, H-10), 1.03 (s, 18H, *t*Bu). ^{13}C NMR: $_C$ = 176.2 (C-11), 78.3 (C-1), 74.1 (C-5), 69.2 (C-7), 68.0 (C-6), 60.5 (−OCH_2Me), 56.6 (C-4), 55.6 (C-3), 47.7 (C-8), 27.6 (-*t*Bu), 27.3 (-*t*Bu), 27.1 (C-2), 23.3 (C−Si), 22.5 (C-9), 22.4 (Si−C), 20.0 (C-10), 14.2 (−OCH$_2$*Me*); IR (neat) 3405 2934, 2859, 1721, 1472, 1365, 1101, 827, 738 cm^{-1}; HRMS m/z calcd for $C_{21}H_{38}O_6Si$ + Na 437.2335, found 437.2333.

(1*R*,7*R*)-3-(Ethyl 2-methyl-2-propanoate)-9,9-di-*tert*-butyl-2,8,10-trioxa-9-silabicyclo[5.4.0]-5(*S*)-azido-6(*R*)-undecanol (3.7). To a solution of epoxide **3.6** (108 mg, 0.261 mmol) in a mixture of 8:1 MeOH/H_2O (1 mL) was added NaN_3 (89 mg, 1.31 mmol, 5 equiv) and NH_4Cl (31 mg, 0.57 mmol, 2.2 equiv), and the mixture was heated at reflux overnight. The mixture was poured into Et_2O (30 mL), washed with H_2O (2 × 20 mL) and brine (1 × 20 mL), and dried over $MgSO_4$. Concentration in vacuo followed by flash chromatography on silica in 9:1 hexanes/EtOAc gave 76 mg of a colorless oil (63%): ^{1}H NMR δ_H = 4.25−3.95 (m, 8H, H-1, H-3, H-4, H-5, H-7, −OCH_2Me), 3.8 (m, 1H, H-6), 3.01 (s, 1H, H-OH), 2.05 (ddd, J = 15.9, 12.7, 3.6 Hz, 1H, H-2), 1.73 (ddd, J = 15.9, 5.2, 3.2 Hz, 1H, H-2), 1.27 (t, J = 7.1 Hz, 3H, -OCH$_2$Me), 1.18 (s, 3H, H-9), 1.16 (s, 3H, H-10), 1.04 (s, 9H, -*t*Bu), 1.02 (s, 9H, -*t*Bu); ^{13}C NMR δ_C = 175.9 (C-11), 76.9 (C-1), 74.5 (C-4), 69.7 (C-3), 64.6 (C-7), 61.5 (C-6), 60.7 (−OCH_2Me), 47.4 (C-8), 28.5 (C-2), 27.4 (*t*Bu), 27.2 (*t*Bu), 22.1(C-9), 21.9 (C-10), 21.6 (Si-C), 21.2 (Si-C), 14.1 (−OCH$_2$-*Me*); IR (neat) 3463, 2934, 2859, 2102, 1713, 1473 cm^{-1}.

General Acetylation Method. To the oxepane (1 equiv) in CH_2Cl_2 (1 mL) was added Ac_2O (2 equiv per hydroxyl), pyridine (3 equiv per hydroxyl), and a catalytic amount of DMAP. The reaction was stirred until complete as monitored by TLC, poured into Et_2O (10 mL), and washed with H_2O (3 × 10 mL). The mixture was dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography on silica gel with 25:1 hexanes/EtOAc to give the acetylated product.

(1*R*,7*R*)-3-(Ethyl 2-methyl-2-propanoate)-9,9-di-*tert*-butyl-2,8,10-trioxa-9-silabicyclo[5.4.0]-5(*S*)-azido-6(*R*)-*O*-acetylundecanol (3.8). Azido alcohol **3.7** was acetylated using the general procedure to give **3.8** as a clear oil in 70% yield: ^{1}H NMR δ_H = 5.33 (t, J = 6.2 Hz, 1H, H-4), 4.2−4.05 (m, 6H, H-1, H-5, H-7, −OCH_2Me), 3.95 (ddd, J = 6.6, 5.1, 3.4 Hz, 1H, H-3), 3.88 (dd,

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J = 6.6, 3.7 Hz, 1H, H-6), 2.17 (ddd, J = 15.7, 12.8, 3.4 Hz, 1H, H-2), 2.10 (s, 3H, Ac), 1.75 (ddd, J = 15.7, 3.7, 3.0, 1H, H-2) 1.24 (t, 3H, J 7.1 Hz, $-OCH_2Me$), 1.17 (s, 3H, H-9), 1.15 (s, 3H, H-10), 1.02 (s, 9H, -*t*Bu), 1.00 (s, 9H, -*t*Bu); ^{13}C NMR δ_C = 176.1 (C-11), 169.5 (Ac), 76.7 (C-1), 75.9 (C-5), 73.7 (C-4), 69.3 (C-6), 67.6 (C-7), 60.7 (-OCH_2Me), 58.8 (C-3), 47.8 (C-8), 27.5 (-*t*Bu), 27.1 (-*t*Bu), 26.7 (C-2), 22.9 (Si−C), 22.2 (C-9), 21.7 (C-10), 14.1 ($-OCH_2Me$); IR (neat) 2935, 2860, 2103, 1728, 1474 cm^{-1}; HRMS m/z calcd for $C_{23}H_{41}N_3O_7Si$ + Na 522.2611, found 522.2613.

Supporting Information Available: ^1H and ^{13}C NMR spectra for all compounds in addition to experimental data for compounds **3.3**−**3.5** and **3.9**−**3.13**. This material is available free of charge via the Internet at http://pubs.acs.org.