Design and Synthesis of Conformationally Constrained Glycosylated Amino Acids

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To probe the conformational requirements of *O*-linked glycoproteins for binding to various enzymes and receptors, two conformationally constrained glycosylated amino acids, **2** and **3**, were designed. The analogues were found to represent two potential low energy conformations of the parent conjugate, **1**, by molecular modeling. A convergent synthesis of both **2** and **3** from D-galactose and L-methionine is presented.

Peptides that contain conformational constraints have allowed access to a wealth of data concerning the conformations of ligands that are bound by biological receptors and have been valuable in the development of pharmaceutical agents.[1] Additionally, conformationally constrained peptides are indispensable tools in elucidating principles that govern polypeptide secondary structure.[1] While the ground-state solution structures of small glycopeptide fragments are well studied,[2] little is known about the conformations that are recognized by enzymes and receptors. To probe this issue, several glycoconjugates that contain conformational constraints have been synthesized and evaluated, but in general, these concepts are not well developed.[3]

One prevalent class of glycoproteins consists of the O-linked group[4] and is characterized by the α-*N*-acetylgalactosaminyl (GalNAc) serine (or threonine) linkage as represented by the tumor-associated sialyl T antigen (Figure 1). This class is often found on the surfaces of cells in the circulatory and immune systems, among other locations. The sialyl T antigen is present on the surface of several metastatic tumor cell types and is a current target for cancer immunotherapy.[5] This report describes a strategy for constraining torsional angles about the bonds linking the peptide to the carbohydrate components within this class. The constrained glycopeptides have the potential to be useful tools in understanding the conformational requirements for binding to various receptors and enzymes.

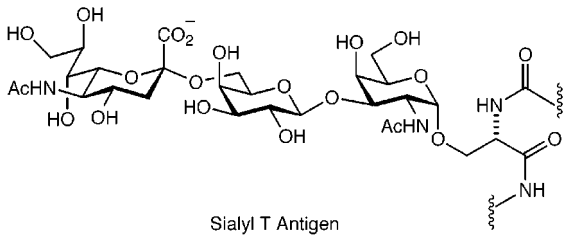

Figure 1.

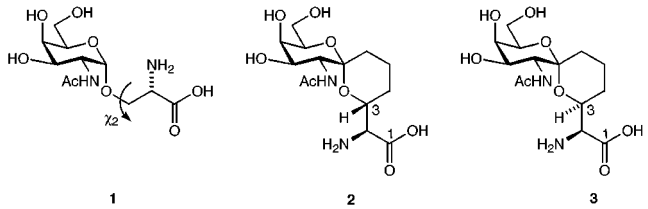

Figure 2.

In general, the conformation of the C1−O1 bond of the carbohydrate moiety of motifs such as **1** (Figure 2) is somewhat rigid and can be predicted by the anomeric and exo-anomeric effects.[6] The remaining bonds linking carbohydrate to peptide, specifically χ_2, in the serine/threonine side chain are more flexible. The targets chosen for this study are the glycosylated amino acids **2** and **3**, in which rotation about the torsional angle χ_2 is restricted by incorporation of the side chain into a small ring.[7] Incorporation of **2** and **3** into peptides and evaluation of the binding of the resulting constructs to receptors and enzymes whose parent ligands are the native glycopeptides will ideally provide valuable information about the conformations of the ligand that are selected for binding.

To determine if the proposed conformationally constrained analogues actually represent reasonable conformations of the native GalNAc-Ser, a molecular modeling analysis was performed. To avoid problems related to charge, the amine was capped with an acetyl group, and the carboxylate was cloaked as a methyl ester.

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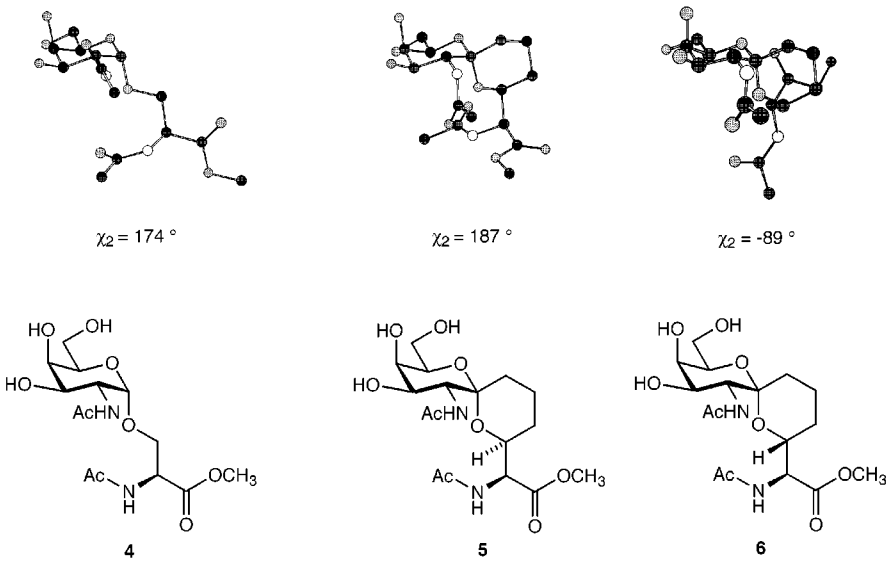
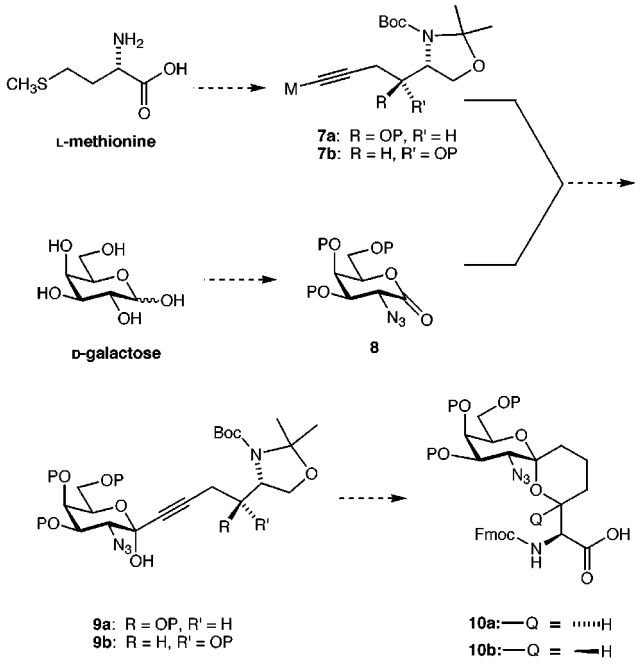


Figure 3.

Molecular modeling of **4**, **5**, and **6** (Figure 3) utilizing the AMBER force field, which included the carbohydrate potentials developed by Homans,[8] afforded low energy conformations, and χ_2 was measured for each compound. As expected, it was found that the lowest energy conformation of native GalNAc-Ser (**4**) contains an anti relationship between the anomeric carbon of the sugar and the α-carbon of the peptide backbone ($\chi_2 = 174°$). Although this protocol resulted in a single low energy conformation, structures with a gauche relationship ($\chi_2 \approx \pm 60°$) should also be considered as potential bound conformations. In actuality, compounds **5** and **6** contain torsional angles χ_2 187° and −89°, respectively. These results suggest that the analogue **2** is a good structural replacement for the anti conformation, while **3** approximates one of the two possible gauche conformations. Since these conformationally constrained glycopeptides represent potential low energy conformations of the parent glycopeptide, a synthesis of each one was undertaken.

The synthesis plan for **2** and **3**, which contain suitable protecting groups for peptide synthesis, is shown in Scheme 1. Since **2** and **3** differ by a single stereocenter, it was anticipated that both compounds could be constructed through independent but similar sequences. A convergent synthesis was devised, in which an L-methionine-derived alkyne would be joined with a D-galactose-derived lactone. Nonstereoselective introduction of a secondary alcohol stereocenter in an early intermediate derived from L-methionine would be followed by separation of the diastereomers to afford the acetylides **7a** and **7b** as key intermediates. The sugar component of **2** and **3** could be derived from the suitably protected 2-deoxy-2-azidogalactonolactone **8**, which in turn could arise from D-galactose. The C2-azide was chosen as a masked version of the acetamide due the stability of azides to carbon nucleophiles such as **7a** and **7b**. The key C-glycosylation step could be accomplished by addition of the acetylide **7a** or **7b** to the lactone **8** to afford **9a** and

Scheme 1



9b, respectively. Reduction of the alkyne and subsequent acid-induced spiroketalization would give **10a** and **10b** after protecting group adjustments. The spiroketalization was predicted to afford the product in which each ketal oxygen is axial to the opposing ring, according to stereoelectronic principles.[9]

The synthesis of **10a** and **10b** began with the olefin **11**, which was prepared in five steps from L-methionine.[10] Attempted epoxidation of the olefin under a variety of standard conditions (*m*-CPBA, *m*-CPBA + base, *tert*-butylhydroperoxide, Oxone−acetone, DCC−H_2O_2) was problematic, but fortunately, treatment of **11** with excess anhydrous dimethyldioxirane[11] afforded a 79:21 mixture of diastereomers **12a** and **12b** in 84% combined yield

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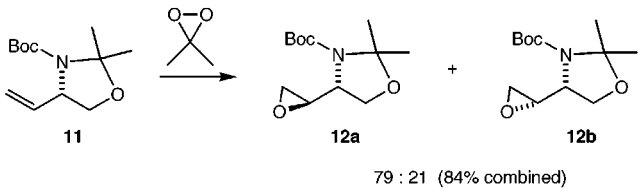
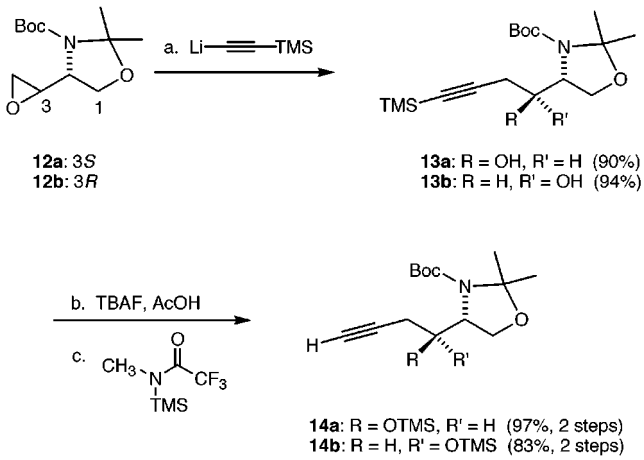
Scheme 2[a]



[a] Reagents and conditions: dimethyldioxirane, CH_2Cl_2, rt, 12 h.

Scheme 3[a]



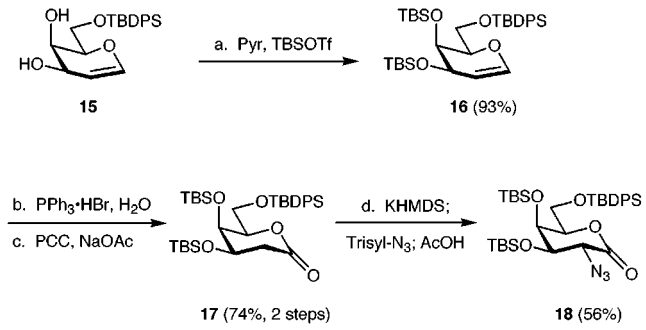
[a] Reagents and conditions: (a) trimethylsilylacetylene, *n*-BuLi, THF, 0 °C, 20 min; **12a** or **12b**, $BF_3{\cdot}Et_2O$, −78 °C, 1 h; (b) TBAF, AcOH, THF, rt, 30 min; (c) MSTFA, CH_3CN, rt, 12 h.

(Scheme 2). The structure of the major diastereomer was assigned as **12a** by comparison of its spectral data with that previously reported for the same compound,[12] and the structure of the minor diastereomer **12b** was confirmed by X-ray crystallographic analysis (see the Supporting Information).

Since the newly formed stereocenter corresponds to C-3 of **10a** and **10b**, both **12a** and **12b** could be productively utilized. The diastereomeric epoxides were separated chromatographically, and carried through the sequence separately (Scheme 3). Opening of the epoxides with the lithium trimethylsilylacetylide afforded secondary alcohols **13a** (90%) and **13b** (94%). The acetylenic silyl group was removed with fluoride, and the secondary alcohol was protected as a silyl ether. While more standard alcohol silylation conditions (TMSCl, amine base) failed, and silylation with TMSOTf was accompanied by migration of the acetonide, simply stirring the secondary alcohols with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA), either neat or in CH_3CN, afforded the alkynes **14a** and **14b** in excellent yields (100% and 91%, respectively).

The lactone **18** was prepared as described in Scheme 4. A key aspect of the synthesis was the choice of protecting groups for the sugar hydroxyls. The protecting groups were required to be stable to both acetylide addition as well as the acidic conditions necessary for spiroketalization. Therefore, silyl groups were chosen, with a more acid stable *tert*-butyldiphenylsilyl (TBDPS) group on the primary C6 alcohol. D-Galactal was selec-

Scheme 4[a]



[a] Reagents and conditions: (a) TBSOTf, pyr, 0 °C to rt, 24 h; (c) $PPh_3{\cdot}HBr$, THF, H_2O, rt, 6 h; (d) PCC, NaOAc, CH_2Cl_2, rt, 2 h; (e) KHMDS, THF, −78 °C, 45 min; Trisyl-N_3, −96 °C, 5 min; AcOH, −96 °C to rt, 1 h.

tively silylated with TBDPSCl in pyridine according to a published procedure to give **15**,[13] and the remaining C3 and C4 hydroxyl groups were protected as *tert*-butyldimethylsilyl (TBS) ethers to afford **16**. When the glycal **16** was exposed to the standard azidonitration conditions developed by Lemieux (ceric ammonium nitrate, sodium azide) to introduce the C2 azide,[14] the intermediate glycosyl nitrate was found to decompose rapidly. A more successful alternative was developed in which glycal **16** was hydrated using a modification of the procedure developed by Falck and co-workers,[15] and the resulting hemiacetal was oxidized with PCC to give the lactone **17** in 74% for two steps. The 2-azido functional group was installed by sequential enolization of **17** with KHMDS, trapping with 2,4,6-triisopropylphenylsulfonyl azide (Trisyl-N_3), and quenching with acetic acid to afford the azidolactone **18** in 56% yield.[16] It is worth noting that although similar 2-azidolactones are reported to be unstable,[16] compound **18** could be chromatographed on neutral silica gel and stored at 0 °C for several months with no noticeable decomposition.

At this stage, it was necessary to form the C-glycoside by addition of the acetylide anions derived from **14a** and **14b** to the lactone **18**. Deprotonation of alkynes **14a** and **14b** with *n*-BuLi and addition to the lactone **18** in the presence of TMEDA at −78 °C gave the hemiketal products **19a** and **19b** in 77% and 62% respectively (Scheme 5).[17] If the reaction was carried out in the absence of TMEDA, the trimethylsilyl group in **14** was cleaved, and no addition of the acetylide to the lactone occurred. The alkyne in **19a** or **19b** could be exhaustively hydrogenated with Pd/C in methanol to provide the corresponding alkane, but there were a few problematic issues associated with the latter intermediate. Under these hydrogenation conditions, the trimethylsilyl group was also removed. But when the resulting secondary alcohol was treated with a variety of acids to induce spiroketalization, under no conditions was the desired spiroketal observed.

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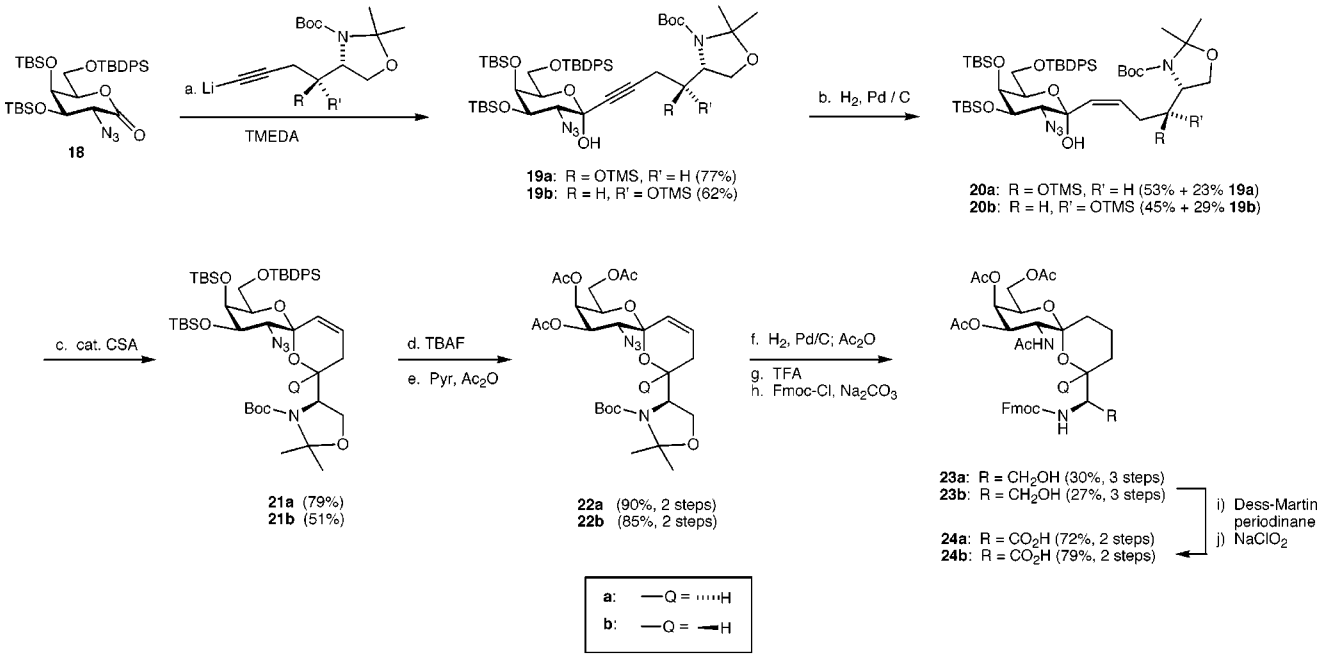
(17) Compounds **19a**, **19b**, **20a**, and **20b** each exist as a complex mixture, presumably of anomers, the open-chain ketone, and rotamers. As such, the ratio of anomers could not be determined.

Scheme 5[a]



[a] Reagents and conditions: (a) **14a** or **14b**, *n*-BuLi, TMEDA, THF, −78 °C, 1.5 h; **18**, THF, −78 °C, 30 min; (b) 10% Pd/C, H_2, ethyl acetate/MeOH, rt, 24−48 h; (c) CSA, CH_2Cl_2, rt, 20 h; (d) TBAF, THF, rt, 2 h; (e) Ac_2O, Pyr, rt, 10 h; (f) 10% Pd/C, H_2, MeOH, Ac_2O, rt, 20 h; (g) TFA, CH_2Cl_2, rt, 3 h; (h) Na_2CO_3, FmocCl, MeOH, rt, 30 min; (i) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 30 min; (j) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, rt, 30 min.

In the optimal sequence, the alkyne was selectively reduced to a *cis*-olefin by changing the hydrogenation solvent to ethyl acetate/methanol (4:1 to 2:1) mixtures. Using these solvent mixtures, the reaction rate was substantially reduced, and hydrogenation was effectively controlled to afford the desired olefin with no loss of the trimethylsilyl group. To avoid reduction of the azide, the reaction was interrupted before complete consumption of the alkyne to give the desired olefins **20a** (53%) and **20b** (45%) along with the starting alkynes **19a** (23%) and **19b** (29%), respectively. The olefin was then separated chromatographically, and the starting material was recycled through the reaction conditions. With the *cis*-olefin present, spiroketalization of **20a** and **20b** occurred readily in the presence of catalytic camphorsulfonic acid (CSA) to afford a single diastereomer of **21a** or **21b** (79% and 51%, respectively).

It was next necessary to reduce both the olefin and the azide. These two operations could be accomplished in a single step by hydrogenation. However, reduction of the azide was slowed by the bulky silyl protecting groups on the sugar. Since silyl groups would not be ideally compatible with peptide synthesis, they were removed with fluoride and replaced with acetate groups to give the triacetates **22a** (90%, two steps) and **22b** (85%, two steps). The structures of the triacetates **22a** and **22b** were unambiguously established by X-ray crystallography (see the Supporting Information), which clearly shows the desired configuration at the spiroketal carbon. Reduction of the olefin and the azide was then successfully accomplished by hydrogenation of **22a** and **22b** with 10% Pd/C in methanol in the presence of acetic anhydride to afford the corresponding acetamides in 45% yield. The low yield was attributed to the production of a byproduct whose structure has not yet been determined.

To prepare for Fmoc-based peptide synthesis, the acetonide and *tert*-butoxycarbonyl (Boc) groups were removed under standard conditions and the resulting amine was reprotected with an Fmoc group in a one-pot procedure. The amino alcohols **23a** and **23b** were produced in 67% and 73% yield, respectively, using this one-pot sequence. Dess−Martin oxidation[18] followed by sodium chlorite oxidation[19] gave the amino acids **24a** (72%, two steps) and **24b** (79%, two steps), which are suitably protected for Fmoc-based solid-phase peptide synthesis.

In summary, two conformationally constrained glycoconjugate analogues **2** and **3** were proposed and shown to be reasonable conformational replacements for accessible low energy conformations of the native glycosylated amino acid by molecular modeling. These analogues were synthesized in a convergent manner from L-methionine and D-galactose. The synthesis included addition of an acetylide anion to galactonolactone, followed by a stereoselective spiroketalization. Analysis of the structural ramifications of incorporating these units into peptides and analysis of the binding properties of these constrained glycopeptides to protein targets are subjects of ongoing research in this laboratory.

Experimental Section

(4*R*,1′*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-oxiranyloxazolidine (12a) and (4*R*,1′*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-oxiranyloxazolidine (12b). Dimethyldioxirane[11] (84 mL, 0.097 M in acetone, 8.1 mmol) was added by addition funnel to a solution of olefin **11**[10] (1.2 g, 5.4 mmol) in CH_2Cl_2 (30 mL) over 1 h. The reaction was protected from light by wrapping in aluminum foil and allowed to stir at room temperature overnight. The solvents were removed under reduced pressure, and the resulting oil was suspended in Et_2O. The layers were separated, and the organic layer was dried

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over Na_2SO_4, filtered, and concentrated. The crude epoxides were separated by flash chromatography (SiO_2, 6:1 hexanes/EtOAc) to afford **12a** as a colorless oil (856 mg, 3.52 mmol, 65%) and **12b** as a white solid (248 mg, 1.02 mmol, 19%), each as a mixture of rotamers. **12a**: R_f 0.57 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ −14.1 (*c* 0.93, $CHCl_3$); IR (thin film) 2981, 2934, 1698, cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 120 °C) δ 3.91 (ABX, J_{ax} = 6.1 Hz, J_{bx} = 3.9 Hz, $\Delta\nu$ = 21.0 Hz, 2H), 3.61 (dt, *J* = 2.4 Hz, 6.3 Hz, 1H), 3.00 (ddd, *J* = 2.4, 3,9, 6.6 Hz, 1H), 2.83 (dd, *J* = 4.2, 5.1 Hz, 1H), 2.65 (dd, *J* = 2.7, 5.1 Hz, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 152.2, 151.7, 94.3, 93.7, 80.3, 80.0, 66.0, 65.4, 59.2, 58.9, 52.2, 51.9, 48.2, 48.1, 28.3, 28.2, 27.4, 26.5, 24.2, 23.0; HRMS *m/z* (CI) calcd for $C_{12}H_{22}NO_4$ [M + H]$^+$ 244.1549, found 244.1564. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.68; H, 8.32; N, 6.10. **12b**: R_f 0.51 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +52.1° (*c* 1.00, $CHCl_3$); IR (thin film) 3059, 2980, 2935, 1698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 140 °C) δ 4.07 (m, 1H), 3.92 (dd, *J* = 6.3, 9.3 Hz, 1H), 3.73 (dd, *J* =2.1, 9.3 Hz, 1H), 3.11 (m, 1H), 2.70 (t, *J* = 4.5 Hz, 1H), 2.50 (m), 1.51 (s, 3H), 1.49 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 153.2, 152.4, 94.8, 94.4, 81.3, 80.8, 63.8, 63.7, 57.1, 51.7, 44.8, 29.1, 27.7, 27.1, 25.0, 23.9; HRMS *m/z* (CI) calcd for $C_{12}H_{22}NO_4$ [M + H]$^+$ 244.1549, found 244.1552. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.93; H, 8.60; N, 5.90.

(1*S*,4′*R*)-1-(3′-*tert*-Butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-1-hydroxy-4-trimethylsilylbut-3-yne (13a). *n*-BuLi (21.2 mL, 1.6 M in hexanes, 34 mmol) was added to a 0 °C solution of trimethylsilylacetylene (4.8 mL, 34 mmol) in THF (65 mL). The resulting pale yellow solution was stirred for 20 min. The solution was then cooled to −78 °C and added by cannula to a −78 °C solution of epoxide **12a** (5.5 g, 23 mmol) in THF (225 mL). $BF_3{\cdot}OEt_2$ (8.3 mL, 68 mmol) was added, and the reaction mixture was stirred for 1 h, at which time Et_3N (17 mL) was added. The solution was stirred for an additional 20 min at −78 °C before warming to room temperature. The reaction mixture was concentrated, and flash chromatography of the crude product (SiO_2, 3:1 hexanes/EtOAc) afforded **13a** as a colorless oil and as a mixture of rotamers (6.9 g, 20 mmol, 90%): R_f 0.52 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +8.5 (*c* 1.04, $CHCl_3$); IR (thin film) 3466, 2977, 2176, 1701 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 45 °C) δ 5.07 (br s,1H), 3.99 (d, *J* = 7.2 Hz, 1H), 3.8 (m, 3H), 2.35 (m, 2H), 1.48 (s, 3H), 1.43 (s, 12H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 153.6, 151.7, 103.7, 102.7, 94.0, 87.0, 86.3, 80.7, 80.0, 71.0, 70.0, 64.4, 63.9, 61.3, 60.2, 28.1, 26.7, 25.9, 25.1, 24.0, 22.6, −0.2.; LRMS *m/z* (CI) calcd for $C_{17}H_{32}NO_4Si$ [M + H]$^+$ 342, found 342; HRMS *m/z* (EI) calcd for $C_{16}H_{28}NO_4Si$ [M − CH_3]$^+$ 326.1788, found 326.1794. Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 59.82; H, 8.75; N, 3.99.

(1*R*,4′*R*)-1-(3′-*tert*-Butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-1-hydroxy-4-trimethylsilylbut-3-yne (13b). Compound **13b** was prepared as described for **13a** starting from *n*-BuLi (6.3 mL, 1.45 M in hexanes, 9.2 mmol) and trimethylsilylacetylene (1.3 mL, 9.2 mmol) in THF (20 mL), **12b** (1.5 g, 6.2 mmol) in THF (60 mL), and $BF_3{\cdot}OEt_2$ (2.3 mL, 18.4 mmol). Flash chromatography of the crude product (SiO_2, 6:1 hexanes/EtOAc) afforded **13b** as a colorless oil and as a mixture of rotamers (2.0 g, 5.8 mmol, 90%): R_f 0.52 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +13.4 (*c* 1.06, $CHCl_3$); IR (thin film) 3475, 2977, 2176, 1701 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 60 °C) δ 4.98 (app d, 1H), 3.97 (m, 2H), 3.87 (m, 2H), 2.32 (ABX, J_{ax} = 4.5 Hz, J_{bx} = 7.2 Hz, $\Delta\nu$ = 46.1 Hz, 2H), 1.53 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 154.8, 102.9, 93.9, 87.4, 81.2, 71.6, 64.5, 61.3, 28.3, 27.0, 26.1, 24.1, 0.0; LRMS *m/z* (ESI) calcd for $C_{17}H_{32}NO_4Si$ [M + H]$^+$ 342, found 342; HRMS *m/z* (EI) calcd for $C_{16}H_{28}NO_4Si$ [M − CH_3]$^+$ 326.1788, found 326.1780. Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 60.15; H, 8.82; N, 4.02.

(1*S*,4′*R*)-1-(3′-*tert*-Butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-1-trimethylsilyloxybut-3-yne (14a). TBAF (44 mL, 1.0 M solution in THF, 44 mmol) and acetic acid (1.3 mL, 22 mmol) were added sequentially to a solution of **13a** (6.8 g, 20 mmol) in THF (200 mL). The reaction mixture was stirred at room temperature for 30 min. H_2O and EtOAc were added, the phases were separated, and the organic phase was washed with brine. The combined aqueous phases were extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (SiO_2, 3:1 hexanes/EtOAc) to afford the pure desilylated alkyne, (1*S*,4′*R*)-1-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-1-hydroxybut-3-yne**,** as a colorless oil and as a mixture of rotamers (5.2 g, 19 mmol, 97%): R_f 0.33 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +7.5 (*c* 1.84, $CHCl_3$); IR (thin film) 3462, 2979, 2936, 2120, 1694 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 90 °C) δ 3.8−4.0 (m, 4H), 2.57 (t, *J* = 2.3 Hz, 1H), 2.29 (m, 2H), 1.50 (s, 3H), 1.45 (s, 12 H); ^{13}C NMR (125 Hz, $CDCl_3$, mixture of rotamers) δ 154.0, 94.3, 81.2, 80.5, 71.5, 70.6, 70.1, 64.6, 64.0, 61.3, 60.1, 28.3, 26.6, 23.9, 23.5; LRMS *m/z* (CI) calcd for $C_{14}H_{24}NO_4$ [M + H]$^+$ 270, found 270; HRMS *m/z* (EI) calcd for $C_{13}H_{20}NO_4$ [M − CH_3]$^+$ 254.1392, found 254.1384.

N-Methyl-*N*-(trimethylsilyl)trifluoroacetamide (6.00 mL, 32.2 mmol) was added to a solution of the secondary alcohol prepared above (5.76 g, 21.4 mmol) in CH_3CN (50 mL). The resulting solution was stirred at room temperature for 12 h. Rotary evaporation followed by coevaporation with toluene under low pressure (0.1 Torr) afforded crude **14a**. Flash chromatography (SiO_2, 6:1 hexanes/EtOAc) afforded pure **14a** as a colorless oil and as a mixture of rotamers (7.31 g, 21.4 mmol, 100%): R_f 0.77 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +31.4 (*c* 1.54, $CHCl_3$); IR (thin film) 2975, 2121, 1696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 120 °C) δ 4.27 (ddd, *J* = 3.0, 6.3, 6.3 Hz, 1H), 4.01 (dd, *J* = 2.6, 7.4 Hz, 1H), 3.9 (m, 2H), 2.63 (m, 1H), 2.31 (m, 2H), 1.49 (s, 3H), 1.47 (s, 9H), 1.45 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 94.5, 93.8, 80.7, 80.0, 70.5, 68.5, 63.2, 62.6, 60.7, 60.3, 28.4, 26.6, 26.3, 25.4, 24.9, 23.3, 0.23; LRMS *m/z* (EI) calcd for $C_{17}H_{31}NO_4Si$ [M + H]$^+$ 342, found 342; HRMS *m/z* (EI) calcd for $C_{16}H_{28}NO_4Si$ [M − CH_3]$^+$ 326.1788, found 326.1777. Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 59.85; H, 8.81; N, 4.25.

(1*R*,4′*R*)-1-(3′-*tert*-Butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-1-trimethylsilyloxybut-3-yne (14b). Compound **14b** was prepared as described for **14a** starting with TBAF (12.5 mL, 1.0 M solution in THF, 12.5 mmol), acetic acid (0.35 mL, 6.2 mmol), and **13b** (1.94 g, 5.67 mmol) in THF (50 mL). The crude product was purified by flash chromatography (SiO_2, 3:1 hexanes/EtOAc) to afford the pure desilylated alkyne, (1*R*,4′*R*)-1-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-1-hydroxybut-3-yne, as a colorless oil and a mixture of rotamers (1.4 g, 5.2 mmol, 91%): R_f 0.34 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +6.2 (*c* 1.30, $CHCl_3$); IR (thin film) 3463, 2979, 2120, 1697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 60 °C) δ 5.01 (d, *J* = 5.4 Hz, 1H), 3.8−4.0 (m, 4H), 2.62 (t, *J* = 2.6 Hz, 1H), 2.24 (ABXY, J_{ax} = 2.9 Hz, J_{ay} = 2.9 Hz, J_{bx} = 7.4 Hz, J_{by} = 2.7 Hz, $\Delta\nu$ = 46.5 Hz, 2H), 1.52 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 154.7, 94.0, 81.2, 80.4, 70.8, 64.3, 61.0, 28.2, 27.0, 24.3, 24.0; LRMS *m/z* (EI) calcd for $C_{14}H_{24}NO_4$ [M + H]$^+$ 270.2, found 270.2; HRMS *m/z* (EI) calcd for $C_{14}H_{23}NO_4$ [M]$^+$ 269.1627, found 269.1624. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.71; H, 8.48; N, 4.80.

Compound **14b** was prepared from *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (1.60 mL, 8.63 mmol) and the secondary alcohol prepared above (2.00 g, 7.43 mmol) in CH_3CN (20 mL). Flash chromatography (SiO_2, 6:1 hexanes/EtOAc) afforded pure **14b** as a colorless oil and a mixture of rotamers (2.33 g, 6.82 mmol, 92%): R_f 0.83 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +15.6 (*c* 1.12, $CHCl_3$); IR (thin film) 2977, 2122, 1704 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 90 °C) δ 4.22 (m, 1H), 3.99 (d, *J* = 8.3 Hz, 1H), 3.9 (m, 2H), 2.60 (t, *J* = 2.7 Hz, 1H), 2.27 (ABXY, J_{ax} = 3.2 Hz, J_{ay} = 3.1 Hz, J_{bx} = 8.4 Hz, J_{by} = 2.6 Hz, $\Delta\nu$ = 54.5 Hz, 2H), 1.53 (s, 3H), 1.46 (s, 9H), 1.41 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 152.8, 152.2, 94.9, 94.1, 82.8, 82.7, 80.2, 70.1, 69.5, 69.3, 69.2, 63.1, 62.8, 60.7, 60.2, 28.6, 28.4, 26.8, 25.9, 23.8, 22.4, 22.1,

22.0, 0.4; LRMS *m/z* (ESI) calcd for $C_{17}H_{32}NO_4Si$ $[M + H]^+$ 342, found 342; HRMS *m/z* (ESI) calcd for $C_{17}H_{31}NO_4SiNa$ $[M + Na]^+$ 364.1920, found 364.1928. Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 60.12; H, 8.89; N, 4.04.

1,5-Anhydro-3,4-di-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*lyxo*-hex-1-enopyranose (16). TBSOTf (12.4 mL, 54.0 mmol) was added dropwise to a 0 °C solution of **15**[12] (7.0 g, 18 mmol) in anhyd pyridine (100 mL). The resulting solution was stirred for 30 min at 0 °C and then for 24 h at room temperature. The pyridine was removed by coevaporation with toluene under reduced pressure (ca. 0.1 Torr). The resulting syrup was dissolved in CH_2Cl_2 (150 mL), washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (SiO_2, 10:1 hexanes:Et_2O) to afford pure **16** as an amorphous solid (10.5 g, 17.1 mmol, 93%): R_f 0.83 (SiO_2, 20:1 hexanes/EtOAc); $[\alpha]^{20}_D$ −9.75 (*c* 1.11, $CHCl_3$); IR (thin film) 2956, 2929, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.3−7.4 (m, 6H), 6.10 (d, J = 6.2 Hz, 1H), 4.55 (t, J = 5.0 Hz, 1H), 4.02 (t, J = 3.7 Hz, 1H), 4.0 (m, 3H), 3.93 (dd, J = 2.7, 11.2 Hz, 1H) 1.05 (s, 9H), 0.85 (s, 9H), 0.72 (s, 9H), 0.06 (s, 6H), −0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 135.64, 135.59, 134.0, 129.43, 129.40 127.6, 127.5, 101.4, 79.5, 68.7, 65.0, 61.7, 26.9, 26.0, 25.9, 25.8, 19.3, 18.2, 18.1, −4.16, −4.52, −4.84, −4.94; LRMS *m/z* (CI) calcd for $C_{33}H_{55}O_4Si_3$ $[M - H]^+$ 611, found 611; HRMS *m/z* (EI) calcd for $C_{30}H_{47}O_4Si_3$ $[M - t\text{-Bu}]^+$ 555.2782, found 555.2755.

3,4-Di-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-galactono-1,5-lactone (17). PPh_3·HBr (494 mg, 1.44 mmol) was added to a solution of **16** (8.8 g, 14 mmol) in THF (300 mL) and H_2O (6.0 mL). The reaction mixture was stirred for 6 h at room temperature. Aqueous saturated $NaHCO_3$ and CH_2Cl_2 were added, and the phases were separated. The organic phase was washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (SiO_2, 10:1 hexanes/EtOAc) to afford 3,4-di-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-galactopyranose as a glass and a mixture of diastereomers (7.3 g, 12 mmol, 80%): R_f 0.36 (SiO_2, 5:1 hexanes/EtOAc); IR (thin film) 3440, 2928, 2857 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.6 (m, 4H), 7.4 (m, 2H), 7.3 (m, 4H), 5.2 (s, 1H), 4.57 (d, J = 9.3 Hz, 0.2H), 4.02 (d, J = 10.1 Hz, 0.8H), 3.6−3.9 (m, 4.8H), 3.2 (app. t, 0.2H), 2.01 (ddd, J = 3.2, 3.2, 12.1 Hz, 1H), 1.75−1.90 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.82 (s, 9H), 0.09 (s, 1H), 0.08 (s, 5H), 0.06 (s, 2H), 0.02 (s, 1H), 0.01 (s, 2H), −0.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 133.8, 133.7, 129.6, 127.6, 94.4, 92.5, 76.2, 72.8, 71.4, 70.4, 68.9, 67.9, 63.8, 63.1, 26.9, 26.2, 26.1, 18.5, 18.5, −3.8, −4.4, −4.7, −4.9; HRMS *m/z* (EI) calcd for $C_{34}H_{57}O_5Si_3$ $[M - H]^+$ 629.3514, found 629.3478.

NaOAc (5.7 g, 70 mmol) was added to a solution of the galactopyranose prepared above (7.3 g, 12 mmol) in CH_2Cl_2 (200 mL). Molecular sieves (4 Å) and PCC (3.0 g, 14 mmol) were added, and the reaction mixture was stirred for 1 h at room temperature. Additional PCC (3.3 g, 15 mmol) was added, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was filtered through SiO_2 with hexanes/EtOAc (5:1). Concentration afforded pure **17** as a white solid (6.7 g, 11 mmol, 92%): R_f 0.47 (SiO_2, 5:1 hexanes/EtOAc); mp 94−95 °C; $[\alpha]^{20}_D$ −2.2 (*c* 1.11, $CHCl_3$); IR (thin film) 2956, 2930, 1742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.35−7.45 (m, 6H), 4.16 (s, 1H), 4.00 (t, J = 6.9 Hz, 1H), 3.95 (ddd, J = 1.8, 6.6, 10.0 Hz, 1H), 3.88 (dd, J = 8.0, 10.3 Hz, 1H), 3.78 (dd, J = 5.8, 10.4 Hz, 1H), 2.74 (dd, J = 10.9, 17.7 Hz, 1H), 2.61 (dd, J = 6.5, 17.7 Hz, 1H), 1.06 (s, 9H), 0.91 (s, 9H), 0.83 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 135.5, 133.1, 132.9, 130.0, 129.9, 127.82, 127.75, 80.0, 68.9, 68.2, 61.7, 35.5, 26.8, 26.0, 25.9, 19.1, 18.39, 18.35, −4.0, −4.6, −4.8, −5.1; LRMS *m/z* (CI) calcd for $C_{34}H_{56}O_5Si_3$ $[M]^+$ 628, found 628; HRMS *m/z* (EI) calcd for $C_{33}H_{53}O_5Si_3$ $[M - CH_3]^+$ 613.3201, found 613.3177. Anal. Calcd for $C_{34}H_{56}O_5Si_3$: C, 64.42; H, 8.97. Found: C, 64.42; H, 8.80.

2-Azido-3,4-di-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-galactono-1,5-lactone (18). KHMDS (23.4 mL, 0.50 M in toluene, 12 mmol) was added to a −78 °C solution of lactone **17** (6.7 g, 11 mmol) in THF (100 mL). The reaction mixture was stirred for 45 min at −78 °C and then cooled to −96 °C. Trisyl azide (3.3 g, 11 mmol) was dissolved in THF (35 mL), cooled to −96 °C, and added by cannula to the solution of the lactone enolate. The resulting yellow mixture was stirred for 5 min at −96 °C. AcOH (1 mL) was added, and the solution became bright yellow. The reaction mixture was allowed to warm to room temperature over 1 h at which time the color had dissipated. The solution was concentrated under vacuum, and the crude product was purified by flash chromatography (SiO_2 pH 7.0, 20:1 hexanes/EtOAc) to afford pure **18** as a white solid (4.0 g, 57 mmol, 56%): R_f 0.71 (SiO_2, 8:1 hexanes/EtOAc); mp 84−86 °C; $[\alpha]^{20}_D$ +56.9 (*c* 1.36, $CHCl_3$); IR (thin film) 2953, 2891, 2114, 1747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.6 (m, 4H), 7.5 (m, 2H), 7.4 (m, 4H), 4.22 (d, J = 9.5 Hz, 1H), 4.21 (s, 1H), 3.98 (dd, J = 6.4, 7.7 Hz, 1H), 3.84 (dd, J = 8.2, 10.4 Hz, 1H), 3.76 (dd, J = 5.9, 10.4 Hz, 1H), 3.68 (dd, J = 1.6, 9.9 Hz, 1H), 1.05 (s, 9H), 0.94 (s, 9H), 0.83 (s, 9H), 0.17 (s, 3H), 0.164 (s, 3H), 0.161 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 135.5, 132.8, 132.7, 130.1, 130.0, 127.9, 127.8, 79.8, 73.4, 69.4, 63.4, 61.2, 26.8, 26.0, 25.9, 19.1, 18.40, 18.35, −3.8, −4.1, −4.7, −5.1; HRMS *m/z* (FAB) calcd for $C_{34}H_{56}N_3O_5Si_3$ $[M + H]^+$ 670.3528, found 670.3539.

(4′*S*,4″*R*)-2-Azido-1-*C*-[4′-(3″-*tert*-butoxycarbonyl-2″,2″-dimethyloxazolidin-4″-yl)-4′-trimethylsilyloxy-1′-butynyl]-3,4-di-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α,β-D-galactopyranose (19a). TMEDA (2.40 mL, 15.6 mmol) was added to a solution of **14a** (2.7 g, 7.8 mmol) in THF (80 mL). The solution was cooled to −78 °C, *n*-BuLi (5.0 mL, 7.8 mmol, 1.53 M in hexanes) was added, and the resulting solution was stirred for 1.5 h. The lactone **18** (3.5 g, 5.2 mmol) was dissolved in THF (40 mL) and added to the acetylide solution. The reaction mixture was stirred for 30 min, at which time TLC analysis indicated complete disappearance of the lactone. Saturated aq NH_4Cl was added, and the reaction mixture was allowed to warm to room temperature. EtOAc was added, and the phases were separated. The organic layer was washed with H_2O and brine. The combined aq layers were extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, 10:1 hexanes/EtOAc) afforded pure **19a** as an amorphous solid and as mixture of diastereomers and rotamers (4.0 g, 4.0 mmol, 77%): R_f 0.39 (SiO_2, 8:1 hexanes/EtOAc); IR (thin film) 3416, 2953, 2892, 2218, 1688 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 120 °C) δ 7.6 (m, 4H), 7.4 (m, 6H), 3.6−4.1 (m, 10H), 2.42 (m, 2H), 1.2−1.6 (m, 15H), 0.8−1.1 (m, 27H), 0.05−0.18 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.6, 133.8, 133.7, 129.5, 127.6, 127.5, 94.0, 93.7, 80.9, 80.3, 79.7, 74.2, 73.8, 69.0, 64.2, 62.9, 61.1, 60.4, 34.6, 31.6, 28.4, 27.0, 26.0, 25.9, 22.6, 19.2, 18.3, 18.2, 14.2, 14.1 0.3, −4.1, −4.4, −4.7, −4.8; MS *m/z* (FAB) calcd for $C_{51}H_{90}N_5O_9Si_4$ $[M + NH_4]^+$ 1029, found 1029.

(4′*R*,4″*R*)-2-Azido-1-*C*-[4′-(3″-*tert*-butoxycarbonyl-2″,2″-dimethyloxazolidin-4″-yl)-4′-trimethylsilyloxy-1′-butynyl]-3,4-di-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α,β-D-galactopyranose (19b). Compound **19b** was prepared as described for **19a** starting with TMEDA (0.45 mL, 3.0 mmol), **14a** (500 mg, 1.5 mmol) in THF (15 mL), *n*-BuLi (1.0 mL, 1.5 mmol, 1.45 M in hexanes), and the lactone **18** (670 mg, 1.0 mmol) in THF (1.0 mL). Flash chromatography (SiO_2, 10:1 hexanes/EtOAc) afforded pure **19b** as an amorphous solid and as a mixture of diastereomers and rotamers (623 mg, 0.62 mmol, 62%): R_f 0.58 (SiO_2, 5:1 hexanes/EtOAc); IR (thin film) 2930, 2857, 2218, 2113, 1704 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.61 (m, 4H), 7.41 (m, 6H), 6.92 (m, 1H), 3.6−4.4 (m, 10H) 2.2−2.7 (m), 1.4−1.5 (m, 15H), 0.8−1.0 (m, 27H), −0.03−0.2 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 153.0, 152.8, 135.7, 135.6, 133.4, 129.8, 129.7, 127.7, 127.6, 95.4, 94.7, 94.2, 91.7, 83.1, 80.8, 80.6, 80.4, 79.8, 73.6, 72.4, 71.4, 70.9, 68.8, 66.3, 62.8, 61.6, 60.6, 59.9, 28.6, 28.4, 26.9, 26.8, 26.3, 26.2, 26.13, 26.11, 26.0, 25.9, 25.7,

22.5, 22.0, 19.1, 18.6, 18.5, 0.35, 0.28, 0.19, 0.09, −3.3, −3.8, −3.9, −4.5, −4.6, −4.7; HRMS *m*/*z* (FAB) calcd for $C_{51}H_{86}N_4O_9Si_4Na$ [M + Na]$^+$ 1033.537, found 1033.534.

(4′*S*,4″*R*)-2-Azido-1-*C*-[4′-(3″-*tert*-butoxycarbonyl-2″,2″-dimethyloxazolidin-4″-yl)-4′-trimethylsilyloxy-1′-*Z*-butenyl]-3,4-di-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α,β-D-galactopyranose (20a). Pd/C (10%, 200 mg) was added to a solution of **19a** (3.0 g, 3.0 mmol) in EtOAc (30 mL). The flask was evacuated (ca. 20 Torr), refilled with H_2 three times, and then stirred under H_2 (690 Torr) for 72 h. The reaction mixture was filtered through Celite, concentrated, and purified by flash chromatography (SiO_2, 10:1 hexanes/EtOAc) to afford **20a** as an amorphous as a mixture of anomers, the hydroxy ketone, and rotamers solid (1.6 g, 1.6 mmol, 53%) and **19a** (0.71 g, 0.71 mmol, 23%): R_f 0.56 (SiO_2, 5:1 hexanes/EtOAc); IR (thin film) 3350, 2958, 2858, 2109, 1695 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.6 (m, 4H), 7.4 (m, 6H), 6.17 (s, 1H), 5.52 (br s, 2H), 4.0−4.2 (m, 2H), 3.8−4.0 (m, 3H), 3.7 (m, 1H), 3.64 (dd, J = 5.4, 9.3 Hz, 1H), 3.55 (d, J = 9.9 Hz, 1H), 2.7 (m, 1H), 2.25 (m, 1H), 1.45 (s, 3H), 1.42 (s, 9H), 1.37 (s, 3H), 1.05 (s, 9H), 0.97 (s, 9H), 0.88 (s, 9H), 0.05−0.18 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 153.4, 152.4, 148.4, 135.6, 135.5, 134.6, 133.6, 133.5, 129.8, 129.6, 127.7, 127.6, 97.5, 94.3, 80.4, 80.1, 72.2, 71.9, 71.4, 68.8, 68.1, 65.9, 64.8, 64.5, 62.6, 62.0, 61.8, 60.8, 32.2, 28.4, 26.9, 26.3, 26.1, 22.6, 19.2, 18.6, 18.5, 14.1, 0.7, −3.5, −4.0, −4.6, −4.7; MS *m*/*z* (ESI) calcd for $C_{51}H_{88}N_4O_9Si_4Na$ [M + Na]$^+$ 1035, found 1035.

(4′*R*,4″*R*)-2-Azido-1-*C*-[4′-(3″-*tert*-butoxycarbonyl-2″,2″-dimethyloxazolidin-4″-yl)-4′-trimethylsilyloxy-1′-*Z*-butenyl]-3,4-di-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α,β-D-galactopyranose (20b). Compound **20b** was prepared as described for **20a** starting with 10% Pd/C (38 mg) and **19b** (0.5 g, 0.5 mmol) in EtOAc/methanol (4:1, 15 mL). The reaction leading to **20b** was carried out for 48 h and purified by flash chromatography (SiO_2,10:1 hexanes/EtOAc) to afford **20b** as an amorphous solid as a mixture of anomers, the hydroxy ketone, and rotamers (225 mg, 0.222 mmol, 45%) and **19b** (146 mg, 0.144 mmol, 29%): R_f 0.53 (SiO_2, 5:1 hexanes/EtOAc); IR (thin film) 3348, 2956, 2931, 2858, 2108, 1704, 1694 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ 7.6 (m, 4H), 7.4 (m, 6H), 6.4 (m, 1H), 5.5 (m, 1H), 5.05 (m, 1H), 4.7 (m, 1H), 3.7−4.1 (m, 7H), 3.5 (m, 3H), 2.6 (m, 1H), 2.4 (m, 1H), 1.4 (m, 15H), 0.82−1.0 (m, 27H), 0.04−0.16 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 195.9, 152.7, 152.1, 135.6, 135.5, 134.0, 133.6, 131.9, 131.4, 129.7, 129.6, 127.7, 127.6, 127.5, 96.4, 96.2, 94.9, 94.1, 80.2, 73.9, 72.7, 72.2, 72.1, 71.1, 70.7, 70.1, 69.6, 68.1, 66.6, 65.1, 64.7, 63.1, 62.8, 61.9, 61.8, 61.1, 60.8, 60.5, 60.4, 59.7, 34.6, 32.4, 32.0, 31.6, 29.5, 28.7, 28.4, 26.9, 26.3, 26.1, 25.8, 25.5, 25.3, 24.0, 22.6, 19.5, 19.2, 18.6, 18.5, 18.4, 14.1, 0.43, 0.11, −3.4, −3.7, −3.8, −4.0, −4.2, −4.5, −4.7; MS *m*/*z* (FAB) calcd for $C_{51}H_{88}N_4O_9Si_4Na$ [M + Na]$^+$ 1035.553, found 1035.550.

(2*R*,3*S*,4*R*,5*R*,6*S*,8*S*,4′*R*)-5-Azido-8-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-3,4-di-*tert*-butyldimethylsilyloxy-2-*tert*-butyldiphenylsilyloxymethyl-1,7-dioxaspiro[5.5]undec-10-ene (21a). CSA (4.0 mg, 0.017 mmol, 5 mol %) was added to a solution of **20a** (346 mg, 0.342 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred at room temperature for 20 h. Saturated aqueous $NaHCO_3$ and EtOAc were added, and the phases were separated. The organic phase was washed with brine. The combined aqueous phases were extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (SiO_2, 5:1 hexanes/EtOAc) to afford **21a** as an amorphous solid and a mixture of rotamers (248 mg, 0.269 mmol, 79%): R_f 0.65 (SiO_2, 5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +64.2 (*c* 1.2, $CHCl_3$); IR (thin film) 2955, 2887, 2108, 1702 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ 7.6 (m, 4H), 7.4 (m, 6H), 6.18 (ddd, J = 1.8, 6.0, 9.9 Hz, 1H), 5.60 (dd, J = 1.8, 9.9 Hz, 1H), 4.1 (m, 2H), 4.05 (m, 1H), 4.01 (t, J = 6.3 Hz, 1H), 3.9 (m, 3H), 3.75 (m, 2H), 3.59 (d, J = 9.9 Hz, 1H), 2.2 (m, 1H), 2.0 (m, 1H), 1.49 (s, 3H), 1.48 (s, 3H), 1.43 (s, 9H), 1.05 (s, 9H), 0.98 (s, 9H), 0.79 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.12 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 135.6, 133.6, 133.3, 130.9, 130.5, 130.1, 129.6, 127.7, 127.6, 127.1, 126.7, 97.1, 94.0, 93.6, 80.2, 73.6, 71.7, 69.4, 65.0, 64.8, 64.7, 63.1, 62.6, 60.3, 28.4, 27.5, 26.9, 26.2, 25.9, 24.4, 22.8, 19.2, 18.6, 18.5, −3.4, −4.0, −4.8, −4.9. MS *m*/*z* (ESI) calcd for $C_{48}H_{78}N_4O_8Si_3Na$ [M + Na]$^+$ 945.5025, found 945.5007.

(2*R*,3*S*,4*R*,5*R*,6*S*,8*R*,4′*R*)-5-Azido-8-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-3,4-di-*tert*-butyldimethylsilyloxy-2-*tert*-butyldiphenylsilyloxymethyl-1,7-dioxaspiro[5.5]undec-10-ene (21b). Compound **21b** was prepared as described for **21a**, starting with CSA (18.0 mg, 0.076 mmol, 20 mol %) and **20b** (382 mg, 0.377 mmol) in CH_2Cl_2 (6 mL). The reaction leading to **21b** was carried out for 10 h. The crude product was purified by flash chromatography (SiO_2, 5:1 hexanes/EtOAc) to afford **21b** as an amorphous solid and as a mixture of rotamers (178 mg, 0.269 mmol, 51%): R_f 0.56 (SiO_2, 5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +17.1 (*c* 1.80, $CHCl_3$); IR (thin film) 2930, 2858, 2110, 1703 cm^{-1},^{1}H NMR (300 MHz, DMSO-d_6, 75 °C, mixture of rotamers) δ 7.6 (m, 4H), 7.4 (m, 6H), 6.0−6.3 (m, 1H), 5.6 (d, J = 10.3 Hz, 1H), 4.4 (m, 1H), 3.9−4.1 (m, 5H), 3.5−3.8 (m, 4H), 2.0 (m, 2H), 1.3−1.5 (m, 15H), 1.0 (s, 9H), 0.8−0.9 (m, 12H), −0.07−0.2 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 152.1, 135.5, 133.4, 130.7, 129.7, 127.7, 127.1, 96.1, 94.1, 80.1, 73.3, 72.6, 72.1, 71.2, 67.0, 64.9, 63.7, 62.2, 59.4, 34.7, 31.6, 28.4, 26.9, 26.3, 26.0, 25.3, 23.2, 22.6, 19.2, 18.5, 14.1, −3.6, −3.9, −4.6, −4.7; HRMS *m*/*z* (FAB) calcd for $C_{48}H_{78}N_4O_8Si_3Na$ [M + Na]$^+$ 945.5025, found 945.5007.

(2*R*,3*S*,4*R*,5*R*,6*S*,8*S*,4′*R*)-2-Acetoxymethyl-5-azido-8-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-3,4-diacetoxy-1,7-dioxaspiro[5.5]undec-10-ene (22a). TBAF (2.8 mL, 2.8 mmol, 1.0 M in THF) was added to a solution of **21a** (794 mg, 0.860 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 2 h. H_2O (5 mL) and EtOAc (30 mL) were added, and the phases were separated. The organic layer was washed with brine. The combined aqueous layers were extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, EtOAc) afforded the pure triol (2*R*,3*R*,4*R*,5*R*,6*S*,8*S*,4′*R*)-5-azido-8-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-3,4-dihydroxy-2-hydroxymethyl-1,7-dioxaspiro[5.5]undec-10-ene as a colorless oil and as a mixture of rotamers (352 mg, 0.772 mmol, 90%): R_f 0.38 (SiO_2, EtOAc); $[\alpha]^{20}_D$ +90.6 (*c* 1.01, $CHCl_3$); IR (thin film) 3419, 2977, 2866, 2109, 1701 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 105 °C) δ 6.06 (m, 1H), 5.56 (m, 1H), 4.06 (m, 2H), 3.9 (m, 4H), 3.76 (dd, J = 6.7, 13.5 Hz, 1H), 3.57 (dd, J = 6.9, 10.5 Hz, 1H), 3.44 (dd, J = 5.6, 10.5 Hz, 1H), 3.29 (d, J = 10.5 Hz, 1H), 1.9−2.1 (m, 2H), 1.48 (s, 3H), 1.44 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 152.9, 152.2, 130.6, 130.3, 126.4, 97.4, 94.2, 93.9, 80.6, 80.4, 70.4, 70.0, 69.6, 68.7, 68.3, 67.6, 64.1, 63.3, 62.4, 61.9, 59.7, 28.2, 27.0, 24.4, 22.8; HRMS *m*/*z* (ESI) calcd for $C_{20}H_{32}N_4O_8Na$ [M + Na]$^+$ 479.2118, found 479.2125.

Pyridine (5 mL) and Ac_2O (5 mL) were added to the triol prepared above (352 mg, 0.772 mmol). The resulting solution was stirred overnight at room temperature. Co-distillation with toluene under high vacuum (2×, 0.1 Torr) gave crude **22a**, which was purified by flash chromatography (SiO_2, EtOAc) to afford **22a** as a white solid and as a mixture of rotamers (450 mg, 0.77 mmol, quant): R_f 0.24 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +118.7 (*c* 0.9, $CHCl_3$); IR (thin film) 2977, 2935, 2109, 1754, 1697 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ 6.22 (ddd, J = 2.1, 6.0, 10.2 Hz, 1H), 5.75 (ddd, J = 1.4, 2.6, 10.2 Hz, 1H), 5.3 (m, 2H), 4.28 (ddd, J = 1.2, 6.0, 6.0 Hz, 1H), 4.1 (m, 3H), 3.9 (m, 3H), 3.63 (d, J = 10.5 Hz, 1H), 2.2 (m, 1H), 2.12 (s, 3H), 2.05 (m, 1H), 2.00 (s, 3H), 1.98 (s, 3H), 1.55 (s, 3H), 1.49 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 170.3, 170.1, 169.7, 169.6, 152.9, 152.1, 131.5, 131.1, 125.5, 125.4, 97.6, 97.4, 94.2, 93.9, 80.4, 70.3, 69.7, 68.4, 67.4, 65.2, 63.7, 61.5, 60.8, 59.8, 59.7, 58.6, 31.5, 28.4, 28.2, 27.4, 27.2, 27.0, 26.7, 24.6, 24.4, 22.7, 22.6, 20.6, 20.5, 14.0; HRMS *m*/*z* (ESI) calcd for $C_{26}H_{38}N_4O_{11}Na$ [M + Na]$^+$ 605.2435, found 605.2433.

(2*R*,3*S*,4*R*,5*R*,6*S*,8*R*,4′*R*)-2-Acetoxymethyl-5-azido-8-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-3,4-diacetoxy-1,7-dioxaspiro[5.5]undec-10-ene (22b). Compound **22b** was prepared as described for **22a** starting with TBAF (1.0 mL, 1.0 mmol, 1.0 M in THF) and **21b** (183 mg, 0.198 mmol) THF (2.0 mL). Flash chromatography (SiO_2, EtOAc) afforded the pure triol (2*R*,3*R*,4*R*,5*R*,6*S*,8*R*,4′*R*)-5-azido-8-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-3,4-dihydroxy-2-hydroxymethyl-1,7-dioxaspiro[5.5]undec-10-ene as colorless oil and as a mixture of rotamers (78 mg, 0.17 mmol, 85%): R_f 0.25 (SiO_2, EtOAc); $[\alpha]^{20}_D$ +59.1 (*c* 1.20, $CHCl_3$); IR (thin film) 3402, 2926, 2854, 2110, 1697 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, 105 °C) δ 6.17 (ddd, J = 3.4, 5.7, 9.6 Hz, 1H), 5.61 (d, J = 9.8 Hz, 1H), 4.72 (m, 1H), 4.46 (m, 1H), 4.2 (m, 2H), 3.9−4.1 (m, 6H), 3.4−3.6 (m, 3H), 2.06 (m, 2H), 1.51 (s, 3H), 1.42 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 152.9, 152.2, 131.3, 130.9, 126.6, 126.5, 96.4, 96.1, 94.3, 93.8, 80.6, 80.3, 72.9, 72.7, 70.8, 70.1, 69.8, 69.5, 66.1, 65.9, 63.9, 63.7, 62.3, 60.4, 60.0, 59.1, 52.6, 29.6, 28.3, 27.1, 26.7, 26.0, 24.4, 22.5; HRMS *m*/*z* (FAB) calcd for calcd for $C_{20}H_{32}N_4O_8$ $[M]^+$ 457.2298, found 457.2317.

Compound **22b** was prepared starting with pyridine (51.5 mL), Ac_2O (1.5 mL) and the triol prepared above (42 mg, 0.092 mmol). Flash chromatography (SiO_2, EtOAc) afforded **22b** as a white solid and as a mixture of rotamers (57 mg, 0.097 mmol, quant): R_f 0.20 (SiO_2, 3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +44.9 (*c* 1.50, $CHCl_3$); IR (thin film) 2978, 2935, 2112, 1754, 1698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 105 °C) δ 6.33 (m, 1H), 5.80 (dt, J = 1.8, 10.2 Hz, 1H), 5.30 (m, 1H), 5.22 (dd, J = 3.6, 10.8 Hz, 1H), 4.43 (m, 2H), 3.8−4.1 (m, 6H), 2.15 (m, 5H), 1.99 (s, 3H), 1.97 (s, 3H), 1.53 (s, 3H), 1.46 (s, 9H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 170.3, 170.1, 170.0, 169.8, 152.8, 152.1, 132.4, 132.0, 131.8, 131.4, 125.9, 125.7, 96.3, 96.0, 94.3, 93.8, 80.4, 80.3, 74.4, 73.2, 70.3, 69.6, 67.6, 67.4, 63.9, 63.5, 63.2, 63.0, 61.8, 61.5, 60.7, 59.8, 58.9, 28.2, 27.1, 26.0, 24.7, 24.2, 23.3, 23.4, 20.6; HRMS *m*/*z* (FAB) calcd for $C_{26}H_{38}N_4O_{11}Na$ $[M + Na]^+$ 605.2435, found 605.2439.

(2*R*,3*S*,4*R*,5*R*,6*S*,8*S*,2′*R*)-5-Acetamido-2-acetoxymethyl-8-[2′-[(9*H*-fluoren-9-ylmethoxy)carbonyl]aminoethanol]-3,4-diacetoxy-1,7-dioxaspiro[5.5]undecane (23a). Ac_2O (0.1 mL) and 10% Pd/C (10 mg) were added to a solution of **22a** (100 mg, 0.17 mmol) in MeOH (2 mL). The reaction mixture was evacuated and refilled with H_2 three times and then stirred under a H_2 atmosphere for 20 h, filtered through Celite, and concentrated. Flash chromatography (SiO_2, EtOAc) of the crude product afforded (2*R*,3*S*,4*R*,5*R*,6*S*,8*S*,4′*R*)-5-acetamido-2-acetoxymethyl-8-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl)-3,4-diacetoxy-1,7-dioxaspiro[5.5]-undecane as a colorless oil (46 mg, 0.077 mmol, 45%): R_f 0.34 (SiO_2, EtOAc); $[\alpha]^{20}_D$ +91.8 (*c* 0.27, MeOH); IR (thin film) 2934, 1749, 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.8 (br d, 1H), 5.34 (d, J = 3.0 Hz, 1H), 5.15 (dd, J = 3.5, 11.0 Hz, 1H), 4.31 (t, J = 10.5 Hz, 1H), 4.1 (m, 3H), 3.9 (m, 4H), 2.13 (s, 3H), 2.03 (s, 6H), 1.96 (s, 3H). 1.95 (s, 3H), 1.6 (m, 12H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 170.8, 170.5, 170.3, 152.7, 99.1, 93.8, 80.5, 70.2, 69.5, 67.3, 67.0, 63.9, 62.0, 60.5, 51.2, 30.2, 28.3, 27.4, 27.0, 24.2, 23.5, 20.8, 20.7, 20.6, 17.7; HRMS *m*/*z* (EI) calcd for $C_{28}H_{44}N_2O_{12}$ $[M]^+$ 600.2894, found 600.2875.

TFA (42 μL, 0.55 mmol) was added to a stirred solution of the compound prepared above (33 mg, 0.055 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 3 h and concentrated under reduced pressure. The crude amino alcohol was dissolved in methanol, and Na_2CO_3 (58 mg, 0.55 mmol) was added followed by FmocCl (14 mg, 0.055 mmol). The resulting solution was stirred for 30 min. H_2O and EtOAc were added, and the phases were separated. The organic phase was washed with brine, and the combined aqueous phases were extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, EtOAc) afforded **23a** as a colorless oil (25 mg, 0.037 mmol, 67%): R_f 0.38 (SiO_2, 95:5 CH_2Cl_2/MeOH), $[\alpha]^{20}_D$ +60.7 (*c* 0.58, MeOH); IR (thin film) 3340, 2950, 1747, 1661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 7.4 Hz, 2H), 7.57 (d, J = 7.5 Hz, 2H), 7.38 (dd, J = 7.4, 7.5 Hz, 2H), 7.30 (dd, J = 7.4, 7.5 Hz, 2H), 5.60 (d, J = 10.3 Hz, 1H), 5.32 (d, J = 2.8 Hz), 5.28 (d, J = 8.7 Hz, 1H), 5.04 (dd, J = 2.9, 11.0 Hz, 1H), 4.46 (m, 1H), 4.41 (m, 1H), 4.32 (t, J = 10.5 Hz, 1H), 4.19 (t, J = 6.5 Hz, 1H), 4.1 (m, 4H), 3.9 (m, 1H), 3.7 (m, 3H), 2.14 (s, 3H), 2.01 (s, 3H), 1.96 (s, 6H), 1.6 (m, 6H); ^{13}C NMR (125 MHz) δ 171.2, 171.0, 170.5, 170.3, 156.4, 143.8, 143.7, 141.3, 127.7, 127.0, 124.9, 120.0, 99.4, 69.5, 67.2, 66.6, 66.4, 62.1, 60.9, 55.4, 51.1, 47.3, 29.9, 28.3, 26.8, 23.4, 20.8, 17.9; HRMS *m*/*z* (FAB) calcd for $C_{35}H_{42}N_2O_{12}$ $[M + H]^+$ 683.2816, found 683.2844.

(2*R*,3*S*,4*R*,5*R*,6*S*,8*R*,2′*R*)-5-Acetamido-2-acetoxymethyl-8-[2′-[(9H-fluoren-9-ylmethoxy)carbonyl]aminoethanol]-3,4-diacetoxy-1,7-dioxaspiro[5.5]undecane (23b). Compound **23b** was prepared as described for **23a** starting with Ac_2O (0.1 mL), 10% Pd/C (5 mg) and **22b** (56 mg, 0.096 mmol) in MeOH (1 mL). Flash chromatography (SiO_2, EtOAc) of the crude product afforded as a mixture of the **23b** with the corresponding olefin. The mixture was resubjected to hydrogenation for 12 h, filtered through Celite, and concentrated to afford (2*R*,3*R*,4*S*,5*R*,6*R*,8*R*,4′*R*)-5-acetamido-2-acetoxymethyl-8-(3′-*tert*-butoxycarbonyl-2′,2′-dimethyloxazolidin-4′-yl]-3,4-diacetoxy-1,7-dioxaspiro[5.5]undecane as a colorless oil (26 mg, 0.043 mmol, 45%): R_f 0.54 (SiO_2, EtOAc); $[\alpha]^{20}_D$ +23.8 (*c* 0.08, MeOH); IR (thin film) 3400 (br), 2975, 2949, 1747, 1693, 1681, 1667 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (d, J = 10.1 Hz, 1H), 5.30 (d, J = 2.2 Hz, 1H), 5.05 (dd, J = 2.8, 10.9 Hz, 1H), 4.30 (m, 2H), 3.88−4.12 (m, 6H), 2.13 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.6−1.8 (m, 6H), 1.51 (s, 3H), 1.47 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 170.9, 170.6, 170.5, 170.4, 153.0, 100.5, 93.8, 80.8, 72.6, 69.2, 67.6, 66.9, 63.2, 62.4, 59.8, 51.9, 28.4, 26.9, 26.6, 23.9, 23.4, 20.8, 20.7, 20.6, 20.1, 13.7; HRMS *m*/*z* (FAB) calcd for $C_{28}H_{44}N_2O_{12}Na$ $[M + H]^+$ 601.2973, found 601.2996.

Compound **23b** was prepared starting with TFA (23 μL, 0.30 mmol), the compound prepared above (19 mg, 0.032 mmol) in CH_2Cl_2 (0.5 mL), Na_2CO_3 (32 mg, 0.30 mmol), and FmocCl (8.0 mg, 0.03 mmol). Flash chromatography (SiO_2, EtOAc) afforded **23b** as a colorless oil (15 mg, 0.021 mmol, 73%): R_f 0.29 (SiO_2, 95:5 EtOAc:MeOH), $[\alpha]^{20}_D$ +32.8 (*c* 0.18, MeOH); IR (thin film) 3370, 2928, 1754, 1726, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 6.1 (d, J = 10.1 Hz, 1H), 5.32 (s, 1H), 5.18 (d, J = 6.7 Hz, 1H), 5.10 (dd, J = 3.0, 11.1 Hz, 1H), 4.45 (t, J = 6.0 Hz, 2H), 4.31 (m, 2H), 4.20 (t, J = 6.3 Hz, 2H), 4.11 (m, 1H), 4.03 (t, J = 7.5 Hz, 2H), 3.76 (m, 2H), 2.14 (s, 3H), 1.97 (s, 3H), 1.93 (s, 6H), 1.5−1.8 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 170.6, 170.5, 170.5, 156.8, 143.8, 143.7, 141.4, 127.8, 127.1, 125.0, 120.0, 100.6, 71.7, 69.3, 67.3, 66.9, 62.2, 62.0, 55.2, 52.1, 47.3, 29.7, 27.4, 23.2, 20.82, 20.79, 20.6, 13.52; MS (FAB) calcd for $C_{35}H_{42}N_2O_{12}$ $[M + H]^+$ 683.2816, found 683.2844.

(2*R*,3*S*,4*R*,5*R*,6*S*,8*S*,2′*R*)-5-Acetamido-2-acetoxymethyl-8-[2′-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2′-aminoacetic acid]-3,4-diacetoxy-1,7-dioxaspiro[5.5]undecane (24a). Dess−Martin periodinane (13.5 mg, 0.032 mmol) and $NaHCO_3$ (13.5 mg, 0.16 mmol) were added to a stirred solution of **23a** (20 mg, 0.029 mmol) in CH_2Cl_2 (1 mL). The resulting suspension was stirred for 1 h, at which time 10% aq $Na_2S_2O_3$ and EtOAc were added. The solution was stirred until clear (10 min), and the layers were separated. The aqueous phase was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The resulting solid was dissolved in EtOAc and filtered through a small plug of SiO_2. Concentration afforded the crude aldehyde, which was used without further purification. The aldehyde as prepared above was dissolved in *t*-BuOH/H_2O (4:1, 0.5 mL), and 2-methyl-2-butene (0.1 mL, 0.94 mmol), $NaClO_2$ (17 mg, 0.19 mmol), and NaH_2PO_4 (13 mg, 0.91 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 1 h, at which time H_2O and EtOAc were added. The phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. Chromatography (SiO_2, 95:5 EtOAc/HOAc) afforded pure **24a** as a yellow oil (15 mg, 0.021 mmol, 72%):

R_f 0.20 (SiO_2, 95:5 EtOAc/AcOH), $[\alpha]^{20}_D$ +49.8 (*c* 0.51, MeOH); IR (thin film) 3372, 2919, 1745, 1664 cm^{-}; ^1H NMR (500 MHz, CD_3OD) δ; 7.80 (d, J = 7.3 Hz, 2H), 7.67 (t, J = 7.6 Hz, 2H), 7.39 (t J = 7.4 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 5.38 (s, 1H), 5.09 (d, J = 11.3 Hz, 1H), 4.41 (t J = 7.4 Hz, 1H), 4.21 (m, 3H), 4.10 (m, 3H), 3.92 (t, J = 8.5 Hz), 2.13 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H), 1.5−1.7 (m, 6H). ^{13}C NMR (125 MHz, CD_3OD) δ 174.0, 172.3, 172.1, 158.5, 145.4, 145.3, 142.8, 129.0, 128.37, 126.35, 121.1, 101.0, 72.5, 70.7, 69.0, 68.4, 68.2, 63.2, 59.7, 52.3, 31.2, 27.9, 22.8, 20.8, 20.7, 20.7, 19.1; HRMS *m*/*z* (FAB) calcd for $C_{35}H_{41}N_2O_{13}$ $[M + H]^+$ 697.2609, found 697.2585.

(2*R*,3*S*,4*R*,5*R*,6*S*,8*R*,2′*R*)-5-Acetamido-2-acetoxymethyl-8-[2′-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2′-aminoacetic acid]-3,4-diacetoxy-1,7-dioxaspiro[5.5]undecane (24b). Compound **24b** was prepared as described for **24a** starting with Dess−Martin periodinane (10 mg, 0.023 mmol), $NaHCO_3$ (10 mg, 0.12 mmol), and **23b** (10.5 mg, 0.015 mmol) in CH_2Cl_2 (1 mL). Compound **24b** was prepared from the crude aldehyde prepared above, in *t*-BuOH/H_2O (4:1, 0.5 mL) with 2-methyl-2-butene (0.1 mL, 0.94 mmol), $NaClO_2$ (8.5 mg, 0.094 mmol), and NaH_2PO_4 (6.5 mg, 0.047 mmol). Flash chromatography (SiO_2, 95:5 EtOAc/HOAc) afforded **24b** as a yellow oil (8.2 mg, 0.012 mmol, 79%): R_f 0.25 (SiO_2, 95:5 EtOAc/AcOH), $[\alpha]^{20}_D$ +33.6 (*c* 0.45, MeOH); IR (thin film) 3200−3550 br, 2923, 1744, 1736 cm^{-1}, ^1H NMR (500 MHz, CD_3OD) δ 7.80 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 7.1, Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.1 Hz, 2H), 7.34 (m, 2H), 5.32 (d, J = 1.6 Hz, 1H), 5.18 (dd, J = 3.2, 11.2 Hz, 1H), 4.47 (m, 2H), 4.35 (m, 1H), 4.25 (m, 2H), 4.15 (m, 1H), 4.10 (m, 2H), 3.94 (dd, J = 6.9, 11.1 Hz, 1H), 2.12 (s, 3H), 1.99 (s, 6H), 1.96 (s, 3H), 1.5−1.7 (m, 6H). ^{13}C NMR (125 MHz, CD_3OD) δ 173.98, 172.38, 172.33, 172.01, 145.68, 145.52, 142.83, 129.08, 128.45, 126.32, 121.14, 101.49, 72.51, 70.60, 68.87, 68.80, 68.23, 63.01, 53.28, 30.67, 25.41, 22.74, 20.83, 20.71, 20.63, 15.00. HRMS *m*/*z* (FAB) calcd for $C_{35}H_{41}N_2O_{13}$ $[M + H]^+$ 697.2609, found 697.2633.

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Supporting Information Available: Complete X-ray crystallography data for compounds **12b**, **22a**, and **22b** and photocopies of selected ^1H and ^{13}C NMR spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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