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Stereoselective Synthesis of Conformationally Constrained Glycosylated Amino Acids Using an Enzyme-Catalyzed Desymmetrization

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As part of an effort to probe the mechanism by which glycosyltransferases recognize glycoproteins and assemble the core structures of *O*-linked oligosaccharides, constrained glycopeptides, compounds **2** and **3**, based on the α-*N*-acetylgalactosaminyl serine substructure **1**, were designed. In this paper we describe a stereoselective preparation of protected versions of these compounds. A pig liver esterase-catalyzed enzymatic desymmetrization of a diacetate substrate, **10**, was employed as a key component in the synthesis.

1. Introduction

Glycosylation is a ubiquitous posttranslational modification of proteins and is associated with a number of processes both within cells and at cell surfaces. These include protein transport, cell adhesion, and signal transduction.[1] Aberrant glycosylation of cellular proteins and glycolipids is associated with various diseases, including cancerous and inflammatory conditions.[2] Therefore, an understanding on a molecular level of the structural features of glycoproteins that are recognized by various enzymes and receptors would be valuable in developing inhibitor-based strategies to control carbohydrate-mediated cellular processes. This fundamental understanding could, in turn, lead to new therapeutic strategies for conditions that are characterized by abnormal glycosylation.

The concept of aberrant glycosylation of proteins is exemplified by the presence of large quantities of the Thomsen−Freidenreich antigen (T antigen; Figure 1) on the surface of many types of tumor cells, specifically highly metastatic cells.[3] The T antigen lacking any additional sugar units is often referred to as Core 1 and represents the *O*-linked oligosaccharides,[1] a common class of glycoproteins. The foundation of Core 1 is comprised of the prevalent α-*N*-acetylgalactosaminyl serine glycoconjugate substructure **1** (Figure 2), and

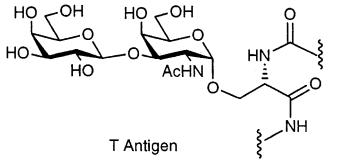

FIGURE 1. Thomsen−Freidenreich antigen.

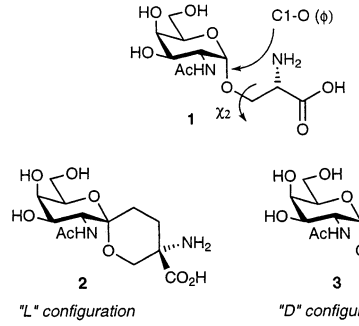

FIGURE 2. α-*N*-Acetylgalactosaminyl serine glycoconjugate substructure and corresponding constrained glycopeptide targets.

assembly of the Core 1 disaccharide from **1** is mediated by a *β*-1,3-galactosyltransferase (Core 1 GalTase) enzyme.[4] This particular transferase was chosen for detailed study in our group.

The ground-state conformations of small glycopeptides have been studied in some detail by NMR spectroscopy;[5] however, relatively little is known about the conformations that are recognized by various enzymes and receptors. The preferred torsional angle about the exocyclic

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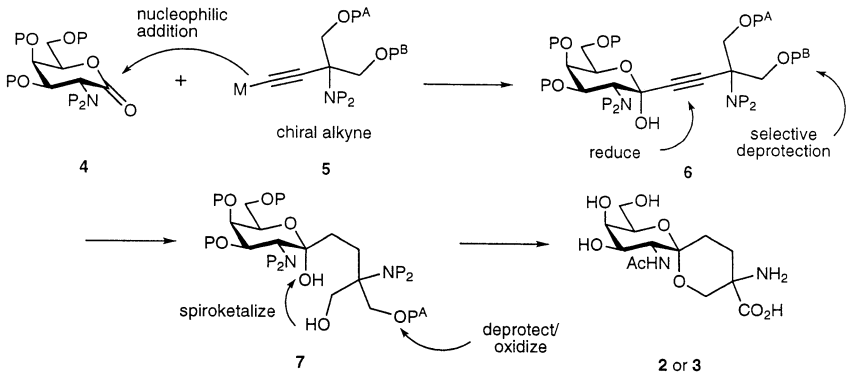
SCHEME 1. Selective Synthesis Strategy for Constrained Glycopeptides



C1−O bond (ϕ) of the carbohydrate moiety in the ground state is somewhat rigid, as predicted by the exoanomeric effect (Figure 2).[6] However, other torsional angles within the side chain, including χ_2, are somewhat more flexible, as illustrated in **1**. Significant research has gone into designing conformational constraints into various amino acid and peptide motifs to probe bioactive conformations.[7] However, conformationally restricted glycopeptides are relatively unexplored.[8]

In an effort to probe the mechanism by which glycosyltransferases recognize glycoproteins and assemble the core structures of *O*-linked oligosaccharides, a series of conformationally constrained glycopeptides was chosen for synthesis.[9] These targets were designed in an effort to represent the accessible low-energy conformations about χ_2 of the native structure **1**, and will ultimately be incorporated into peptides for evaluation as substrates for, or inhibitors of, Core 1 GalTase. Among those chosen was compound **2** in which the α-carbon (Cα) of the amino acid component of the structure is incorporated into a six-membered ring and exhibits the natural L-serine configuration. The χ_2 torsional angle is effectively constrained in one of the two possible gauche conformations, and the C1−O bond is locked into the low-energy exoanomeric orientation. The unnatural D-serine configuration could also be useful in our studies, and is represented by the similarly constrained analogue **3** (Figure 2).

Through our previous strategy,[10] fully protected versions of constrained glycopeptides **2** and **3** were successfully synthesized, albeit with low overall diastereoselectivity. In an effort to preferentially obtain one amino acid configuration over the other and to more readily secure the quantities of diastereomerically pure material necessary for biological evaluation and structural studies, a more selective synthesis was desired.

The first-generation synthesis strategy was designed to establish the desired anomeric orientation at the spiroketal center through a thermodynamic spiroketalization event.[11] Furthermore, it was predicted that diastereomeric preferences inherent within this same process would afford an excess of the natural L-serine configuration at Cα in a diastereotopic group-selective cyclization. Although the strategy was relatively successful in producing the correct stereochemistry at the spiroketal center, it failed to yield an excess of either the L- or D-serine configuration.[10]

Therefore, we pursued an alternate synthesis strategy (Scheme 1) in which a differentially protected chiral alkyne, **5**, representing the α,α-disubstituted α-amino acid component of the target glycopeptide, would undergo a nucleophilic addition to the carbohydrate lactone **4**.[9,10] Selective deprotection of the resulting product **6** followed by reduction of the internal alkyne would provide the spiroketal precursor **7**. This method has the advantage of setting the configuration at Cα prior to ring closure, and circumvents any dependence on the spiroketalization process itself to provide diastereoselection at the amino acid stereocenter. Selective thermodynamic spiroketalization of the free primary hydroxyl group in **7** should accomplish the original goal of installing the correct anomeric configuration. Deprotection and subsequent oxidation of the other hydroxyl group in **7** followed by further manipulations should provide either **2** or **3**, selectively, depending on the stereochemical configuration of **5**. The successful implementation of this second-generation route is reported here.

The stereoselective construction of α,α-disubstituted α-amino acids has attracted a great deal of attention in the synthesis community for some time, and numerous

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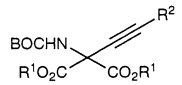
elegant methods have been developed.[12] This attention is undoubtedly due to inherent structural challenges of these compounds as well as their notable effects on biological activity.[13] These quaternary amino acids have been utilized in studies of enzyme mechanisms[14] and as enzyme inhibitors[15] and have been found to exert a strong influence on the conformation of peptides into which they are incorporated.[16] Many of these compounds are naturally occurring, including a number that are present as substructures of natural products. Specifically, the α-substituted serine unit, a structural feature embedded in our targets, has been investigated in the design of peptides[12b] and is contained within natural products such as myriocin, (+)-lactacystin, (+)-conagenin, and sphingofungin E.[17]

Traditionally, α-substituted serines were prepared through a number of standard methods including rearrangements of chiral trichloroacetimidates,[17b,18] alkylation of chiral enolates,[19] and ring-opening of chiral aziridines.[20] Additionally, several enzymatic resolution strategies have been developed to produce α,α-disubstituted amino acids in enantiomerically pure form from racemic mixtures.[12b] However, to our knowledge only one type of enzyme-catalyzed desymmetrization strategy for constructing these compounds has been reported.[17a,21] This strategy, based on the hydrolytic enzymatic desymmetrization of α-alkyl aminomalonate derivatives, was first utilized by Fukuyama and co-workers in their total synthesis of (−)-tantazole B.[21] Fukuyama's method was subsequently employed in a recent effort by Nagao and co-workers.[17a] The latter study detailed a synthesis of α-substituted serines based on the enantioselective enzymatic hydrolysis of a series of diethyl α-alkyl-α-(benzyloxycarbonylamino)malonates using pig liver esterase (PLE) or rabbit liver esterase (RLE).[17a]

The important role of enzymes in organic synthesis is well-documented,[22,23] and the advantages include minimal byproducts and mild reaction conditions. In light of the study by Nagao and co-workers, we determined that a similar enzymatic desymmetrization would be appropriate for the synthesis of our chiral nucleophilic addition precursor **5**. The mild nature of the procedure would tolerate sensitive protecting groups, and enantioselectivities were predicted to be relatively high on the basis of similarities between our substrates and those in the work reported earlier.[17a]



8

R^1 = Me, Et
R^2 = H, TMS

FIGURE 3. Dialkyl malonate PLE desymmetrization substrates.

2. Results and Discussion

Several dialkyl α-alkynyl-α-(*tert*-butoxycarbonylamino)-malonates of the general structure **8** (Figure 3) were constructed.[24] Unfortunately, subjection of these substrates **8** to PLE under a variety of reaction conditions failed to yield any of the desired desymmetrized hydrolysis products. Only starting material and traces of unidentified byproducts were recovered from these reactions.

These unanticipated results prompted us to refocus our efforts on obtaining and desymmetrizing a diacetate substrate bearing functionality similar to that in **8**. Like diesters, diacetates are known to be effective precursors for PLE desymmetrization protocols.[22] Furthermore, such compounds should be readily available through chemistry developed in our first-generation synthesis.[10] The enantioenriched alcohol product would be presumably more convenient to purify than the corresponding carboxylic acid afforded by an ester hydrolysis, and should be more readily amenable to protecting group installation as well.

We were delighted to find that the configuration of the amino acid component **5** could indeed be established through a PLE-catalyzed enzymatic desymmetrization of the symmetric diacetate **9** (Scheme 2). Diacetate **9** was obtained from acetylation of the diol **11**, which was an intermediate in the first-generation synthesis strategy.[10] Employing acetonitrile as a cosolvent, the monoacetate **10** was routinely produced in good yield with enantiomeric excesses of 80% as measured by chiral GC. The overhydrolyzed product **11** was easily recovered and recycled. The highlights of these studies are detailed in the abbreviated table in Scheme 2.

The stereochemistry of **10** could not be assigned unambiguously at this point. However, this information was later determined through subsequent transformations (see below), and the major enantiomer was found

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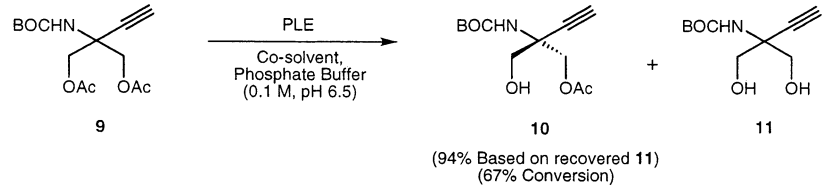
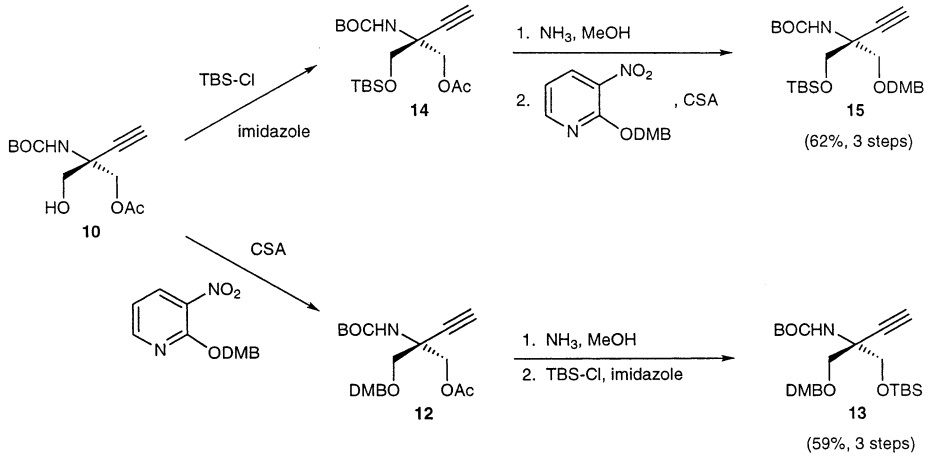
SCHEME 2. Successful Desymmetrization of 9



Temp	Co-solvent (%)	Time (h)	10:11	Selectivity (%ee)
RT	Acetone (10)	21	1:4.5	66-74
RT	Acetone (20)	10	1.7:1	62
RT	THF (10)	8	1.1:1	62
RT	Dioxane (10)	2	1.9:1	62
RT	**Acetonitrile (10-15)**	**3**	**2:1**	**76-80**

SCHEME 3. Divergent Synthesis of 13 and 15



to possess the (*S*)-configuration shown in Scheme 2. It is typically more difficult to predict the stereoselectivities of enzyme-catalyzed transformations of acyclic substrates such as **9** than of their cyclic counterparts due to the greater conformational mobilities of open-chain compounds in the relevant active sites.[25] This stereochemical outcome was, however, in agreement with a study conducted by Norin and co-workers concerning the desymmetrization of a series of acyclic malonates.[26] Regardless, a judicious protecting group installation strategy in the construction of the nucleophilic addition precursor **5** would eventually provide selective access to either configuration at Cα independent of the desymmetrization outcome.

The synthesis of the nucleophilic amino acid which would ultimately bear the D-serine configuration commenced with the protection of the free hydroxyl group of the enantiomerically enriched alkyne **10** as the 3,4-dimethoxybenzyl (DMB) ether to give compound **12** (Scheme 3). Previous attempts to incorporate the more standard 4-methoxybenzyl (PMB) protecting group into our synthesis were unsuccessful due to difficulties associated with installation and later removal of this group. The relatively mild, acid-catalyzed protection employed a modification of a recent protocol by Mukaiyama and co-workers.[27] Conditions for this transformation were optimized in an effort to avoid significant racemization of **10** through acetate migration. A racemization of a similar substrate was documented recently.[28] Removal of the acetate protecting group of **12** under mild conditions followed by silyl protection of the resulting free hydroxyl group gave the appropriately protected alkyne **13** in good yield.

Alternatively, the benzyl and silyl protecting groups were successfully installed in reverse order to provide the enantiomer of **13**, compound **15**, which would ultimately bear the L-serine configuration. Initial protection of the free primary hydroxyl group in **10** provided the silyl ether **14**. The acetate protecting group on **14** was then removed under mild conditions in an effort to avoid silyl migration. Subsequent protection of the resulting free primary hydroxyl group as the DMB ether gave **15** in good yield (Scheme 3). Enantiomeric ratios of both **13** and **15** were determined by ^{1}H NMR analysis of their respective diastereomeric (*R*)-MTPA esters,[29] and were found to be ca. 9:1 in each case. The MTPA esters were prepared by esterification of the free primary hydroxyl groups afforded by desilylation of **13** and **15**. This important analysis verified the successful suppression of any racemization pathways.

Following the successful preparation of **13** and **15**, we were positioned to execute a convergent coupling between

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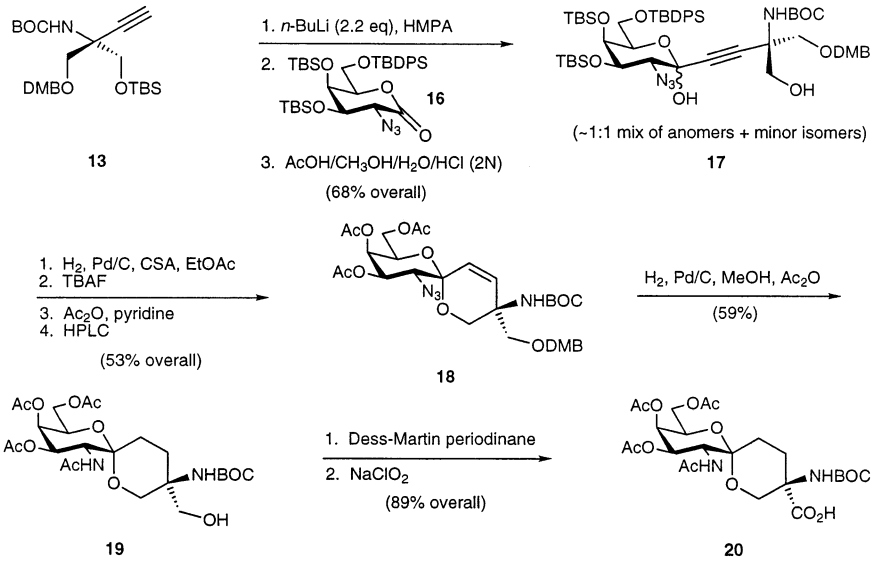
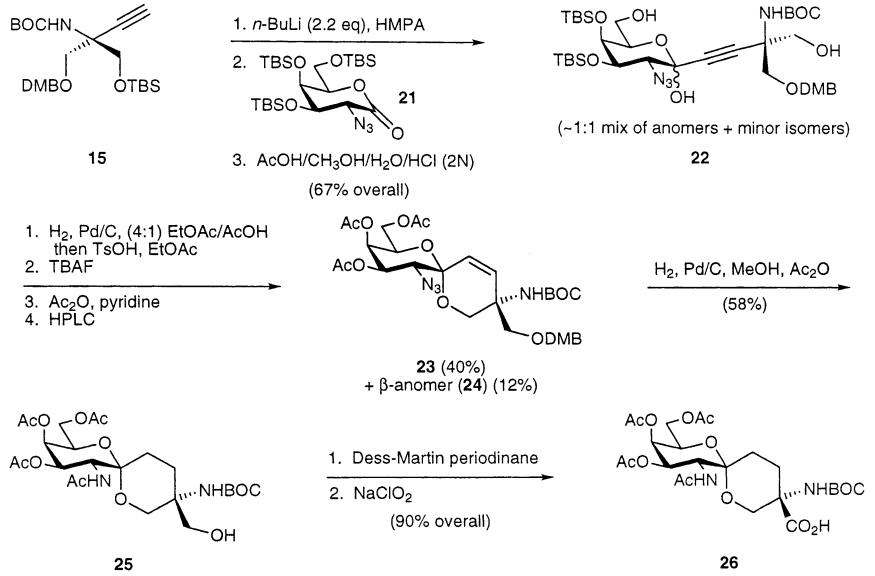
SCHEME 4. Synthesis of the Constrained Glycopeptide Bearing the D-Configuration

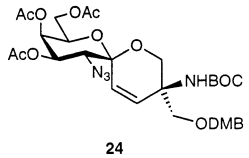


SCHEME 5. Synthesis of the Constrained Glycopeptide Bearing the L-Configuration



the respective amino acid and carbohydrate components of our targets. The incorporation of the D-serine configuration was accomplished in good overall yields without significant difficulties. Addition of a 3-fold excess of the dianion of **13** to the lactone **16**[9] afforded a hemiketal intermediate (Scheme 4). However, removal of unreacted **13** at this point using conventional chromatography was only partially successful. Therefore, the product mixture including unreacted **13** was subjected to acidic deprotection conditions to produce **17**. Then, desilylated **13** could be easily removed by chromatography and recycled. All intermediates following the acetylide addition and prior to the spiroketal were comprised of two major diastereomers, which were presumed to be anomers at C1 of the sugar. Partial reduction of the alkyne group of **17** to the *cis*-alkene and acid-catalyzed spiroketalization were performed in a one-pot reaction to give one major product, confirming an excess of one configuration at Cα. Removal of the silyl protecting groups followed by peracetylation afforded **18** in good overall yield and purity. Reduction of the azide and olefin functional groups in **18** occurred with unexpected simultaneous removal of the dimethoxybenzyl group to provide the acetamide **19**. A two-step oxidation sequence then provided the desired acid **20** in excellent yield and purity.

To selectively obtain the L-serine configuration, experiments were conducted to incorporate **15** through the usual acetylide addition to **16**. The addition as well as the subsequent removal of the primary TBS protecting group were successful, and two major anomers were again observed, each of which, as before, consisted of one major configuration at Cα. Unfortunately, attempts to carry out the ensuing spiroketalization led to complicated product mixtures. ^{1}H NMR analysis of these mixtures suggested that the *tert*-butylcarbamate (BOC) protecting group was lost in the majority of products. Our previous strategy entailed the successful spiroketalization of a similar compound which lacked the DMB group.[10] Therefore, we hypothesized that the DMB protecting group was adversely affecting the spiroketalization in this instance. The loss of the BOC protecting group was possibly facilitated by the relief of unfavor-



24

FIGURE 4. β-Anomer **24**.

able steric interactions with the *tert*-butyldiphenylsilyl (TBDPS) protecting group at O6 of the sugar. The notion seemed reasonable since molecular models of this spiroketal suggested that these two large protecting groups would be in close proximity to each other. This same interaction would not be present in a spiroketal bearing the D-serine configuration. Options to replace the DMB protecting group with smaller groups, as well as alternative reaction conditions for the spiroketalization, were explored, but were found to have little effect on the outcome of the reaction. Therefore, an alternate protecting group pattern was developed in which no unfavorable interactions between these positions would be present. To be specific, a protecting group that could be removed prior to spiroketalization was installed on O6 of the carbohydrate component.

The revised route commenced with the addition of a 3-fold excess of the dianion of **15** to the modified lactone **21**,[9,30] affording a hemiketal intermediate (Scheme 5). The ensuing deprotection was executed on this intermediate, which was contaminated with unreacted **15**. The mixture was subjected to acidic conditions as before to successfully liberate the two desired primary hydroxyl groups and give **22**. Desilylated **15** was removed and recycled at this point. The intermediate **22**, which now lacked an O6 protecting group on the sugar, was subjected to the one-pot hydrogenation/spiroketalization reaction conditions employed for **17**. Although the desired spiroketal was produced, yields were low, and significant amounts of byproducts which lacked the DMB protecting group were also obtained. More successful conditions involved initial hydrogenation of **22** in the presence of a mild acid to give the intermediate *cis*-alkene. The catalyst was then removed, and the mixture was treated with a stronger acid to induce spiroketalization. Protecting group manipulations as before gave compound **23** and the β-anomer **24** (see Figure 4) in good combined overall yield. The stereochemistry of **24** was verified through NOESY experiments. Attempts to equilibrate the β-anomer to the α-anomer at any point after the cyclization were unsuccessful. Reduction of **23** under the usual conditions gave compound **25**. Oxidation of the primary alcohol provided the carboxylic acid **26**. The structures of both **20** and **26** were confirmed by conversion to their corresponding methyl esters, whose structures were previously established.[10]

3. Conclusion

In conclusion, stereoselective syntheses of protected versions of two constrained glycopeptides, **2** and **3**, were developed. A PLE-catalyzed enzymatic desymmetrization of the diacetate **10** was employed as a key component in the synthesis. This route enables production of quantities of material necessary for incorporation into peptides and for subsequent biological evaluation and structural studies.

4. Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra are reported in parts per million (δ) relative to the peaks for $CHCl_3$ (7.24 and 77.23 ppm, respectively) or CD_3OD (3.31 and 49.15 ppm, respectively) as the internal standard.

(1,1-Bis(acetoxymethyl)prop-2-ynyl)carbamic Acid *tert*-Butyl Ester (9). Diol **11**[10] (2.850 g, 13.24 mmol, 1.0 equiv) was dissolved in 30 mL of a 2:1 pyridine/Ac_2O solution at rt, and DMAP (81 mg, 0.66 mmol, 0.05 equiv) was added in one portion. The resulting mixture was stirred for 12 h and was then concentrated on a high-vacuum (0.1 Torr) rotary evaporator to give a dark orange oil. The oil was chromatographed on silica gel (3:1 hexanes/EtOAc) to give **9** as a powdery white solid (3.708 g, 12.40 mmol, 94%) after drying under high vacuum (0.1 Torr) for several days. IR (thin film): 3283, 2978, 1748 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.97 (s, 1H), 4.38 (AB, J = 11.1 Hz, $\Delta\nu$ = 11.1 Hz, 4H), 2.39 (s, 1H), 2.09 (s, 6H) 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 154.1, 81.1, 80.0, 73.5, 64.9, 53.4, 28.5, 21.0. TLC (SiO_2, 50% EtOAc/ hexanes): R_f = 0.65. Mp: 73−75 °C. HRMS (*m*/*z*): calcd for $C_{14}H_{21}NO_6$ $(M + H)^+$ 300.1447, found 300.1438. Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 55.99; H, 6.82; N, 4.78.

(*S*)-(1-Acetoxymethyl-1-hydroxymethylprop-2-ynyl)-carbamic Acid *tert*-Butyl Ester (10). Three separate reactions were individually and simultaneously prepared in the following manner. A 100 mL round-bottomed flask was loaded with 37 mL of phosphate buffer (pH 6.5, 0.1 M) followed by 4.6 mL of CH_3CN. To this stirring mixture at rt was added PLE (lyophilized powder (20 units/mg of solid), 67 mg) followed by **9** (300 mg, 1.0 mmol). The three solutions were each stirred for 3 h, then saturated with excess NaCl(s), and allowed to stir for an additional 5 min. The three resulting mixtures were combined upon filtration through Celite with EtOAc washings. The biphasic filtrate was concentrated on a high-vacuum (0.1 Torr) rotary evaporator with toluene azeotropes as necessary to remove excess water, and the resulting residue was dissolved in acetone. This mixture of product and insoluble inorganic salts was filtered, with additional acetone washings as necessary, and the resulting organic filtrate was concentrated to give an oil. The oil was chromatographed on silica gel (1:1 hexane/EtOAc and then EtOAc) to give **10** as a clear oil (516 mg, 2.02 mmol, 67% conversion, 94% yield based on recovered **11**). Compound **10** was determined to be a 9:1 ratio of enantiomers in favor of the (*S*)-configuration by chiral GC (Beta Dex 120). $[\alpha]^{28}_D$: +8.06 (*c* 3.00, $CHCl_3$). IR (thin film): 3290, 2978, 1719 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10 (s, 1H), 4.37 (AB, J = 11.3 Hz, $\Delta\nu$ = 11.2 Hz, 2H), 3.80 (s, 2H), 2.42 (s, 1H), 2.11 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 154.9, 80.9, 80.8, 73.6, 65.5, 64.6, 55.2, 28.4, 20.9. TLC (SiO_2, 50% EtOAc/ hexanes): R_f = 0.41. HRMS (*m*/*z*): calcd for $C_{12}H_{19}NO_5$ $(M + H)^+$ 258.1341, found 258.1347. Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.35; H, 7.20; N, 5.32.

2-(3,4-Dimethoxybenzyloxy)-3-nitropyridine. In a modified literature procedure,[27] KOH (2.832 g, 50.50 mmol, 12.0 equiv) and K_2CO_3 (1.744 g, 12.62 mmol, 3.0 equiv) were dissolved in 60 mL of toluene. 3,4-Dimethoxybenzyl alcohol (3.184 g, 18.93 mmol, 4.5 equiv) in 20 mL of toluene was then added rapidly by syringe to the stirring mixture, followed by 2-chloro-3-nitropyridine (2.000 g, 12.62 mmol, 3.0 equiv). After the resulting mixture was stirred for 2 min, tris(3,6-dioxaheptylamine) (0.40 mL, 1.26 mmol, 0.3 equiv) was added dropwise, and the resulting brown solution was stirred for 3 h. The reaction mixture was then immediately filtered through Celite with toluene washings as necessary. The filtrate was

(30) (a) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, *4*, 945. (b) Rollin, P.; Sinay, P. *Carbohydr. Res.* **1981**, *98*, 139. (c) Mlynarski, J.; Banaszek, A. *Tetrahedron* **1999**, *55*, 2785.

subsequently concentrated on a high-vacuum (0.1 Torr) rotary evaporator, and the crude yellow oil was chromatographed on silica gel (3:1 and then 1:1 hexanes/EtOAc) to give a yellow solid which was recrystallized in hexanes/benzene. The product was isolated as yellow, needlelike crystals (2.565 g, 8.84 mmol, 70%). IR (thin film): 3080, 2831, 1600 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (dd, J = 4.8, 1.8 Hz, 1H), 8.26 (dd, J = 7.9, 1.8 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.04−7.00 (m, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.50 (s, 2H), 3.89 (s, 3H) 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 151.8, 149.2, 149.0, 135.3, 134.4, 128.7, 120.5, 116.9, 111.2, 111.1, 69.0, 56.1, 56.0. TLC (SiO_2, 25% EtOAc/hexanes): R_f = 0.16. Mp: 90−92 °C. HRMS (m/z): calcd for $C_{14}H_{14}N_2O_5$ 290.0903, found 290.0894. Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.32; H, 4.89; N, 9.78.

(*S*)-[1-(*tert*-Butyldimethylsilanyloxymethyl)-1-(3,4-dimethoxybenzyloxymethyl)prop-2-ynyl]carbamic Acid *tert*-Butyl Ester (13). Monoacetate **10** (9:1 ratio of enantiomers, 777 mg, 3.02 mmol, 1.0 equiv) was dissolved in 25 mL of CH_2Cl_2 at rt. To this mixture was added 2-(3,4-dimethoxybenzyloxy)-3-nitropyridine (435 mg, 1.51 mmol, 0.5 equiv) followed by a solution of camphorsulfonic acid (17 mg, 0.08 mmol, 0.025 equiv) in 1 mL of CH_2Cl_2, and the resulting mixture was stirred for 1.5 h at rt. The above additions of 2-(3,4-dimethoxybenzyloxy)-3-nitropyridine (435 mg, 1.51 mmol, 0.5 equiv) followed by a solution of camphorsulfonic acid (17 mg, 0.08 mmol, 0.025 equiv) in 1 mL of CH_2Cl_2 were then repeated. Shortly after this second addition, a white precipitate formed. After 1.5 h, the addition/stirring sequence was repeated. Upon completion of the final 1.5 h stirring period, additional camphorsulfonic acid (17 mg, 0.08 mmol, 0.025 equiv) in 1 mL of CH_2Cl_2 was added to ensure complete reaction, and the mixture was stirred for an additional 12 h. The mixture was diluted with 50 mL of CH_2Cl_2 and quenched with 25 mL of saturated aq NH_4Cl. The phases were separated, and the aq phase was extracted with 2 × 50 mL of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give a crude yellow oil. This crude oil was chromatographed on silica gel (3:1 hexanes/EtOAc) to give the product as a clear oil. TLC (SiO_2, 25% EtOAc/hexanes): $R_f \approx$ 0.30. This product was subsequently dissolved in 8 mL of a solution of ammonia in MeOH (1 M), and the resulting solution was stirred at rt for 12 h. The reaction mixture was then concentrated to give the crude product (800 mg, 2.18 mmol), which was redissolved in 15 mL of DMF at rt. Imidazole (592 mg, 8.72 mmol, 4.0 equiv) and *tert*-butyldimethylchlorosilane (1.314 g, 8.72 mmol, 4.0 equiv) were then successively added to the solution, and the resulting mixture was heated to 45 °C and stirred for 12 h. The reaction mixture was then cooled to rt and concentrated on a high-vacuum (0.1 Torr) rotary evaporator. The residue was dissolved in a mixture of 50 mL of EtOAc and 25 mL of saturated aq NH_4Cl. The phases were separated, and the aq phase was extracted with 2 × 50 mL of EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give a crude product. This product was chromatographed on silica gel (3:1 hexanes/EtOAc) to give **13** as a clear oil (840 mg, 1.75 mmol, 59% from **10**). Compound **13** was determined to be a 9:1 ratio of enantiomers in favor of the (*S*)-configuration through derivatization to the corresponding Mosher's esters.[29] $[\alpha]^{28}_D$: +2.98 (*c* 2.00, $CHCl_3$).

(*R*)-[1-(*tert*-Butyldimethylsilanyloxymethyl)-1-(3,4-dimethoxybenzyloxymethyl)prop-2-ynyl]carbamic Acid *tert*-Butyl Ester (15). Monoacetate **10** (9:1 ratio of enantiomers, 850 mg, 3.30 mmol, 1.0 equiv) was dissolved in 22 mL of DMF at rt. Imidazole (446 mg, 6.60 mmol, 2.0 equiv) and *tert*-butyldimethylchlorosilane (988 mg, 6.60 mmol, 2.0 equiv) were then sucessively added to the solution, and the resulting mixture was heated to 45 °C and stirred for 12 h. The reaction mixture was then cooled to rt and concentrated on a high-vacuum (0.1 Torr) rotary evaporator. The resulting residue was dissolved in a mixture of 50 mL of EtOAc and 25 mL of saturated aq NH_4Cl. The phases were separated, and the aq phase was extracted with 2 × 50 mL of EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give a crude oil. This product was subsequently dissolved in 8 mL of a solution of ammonia in MeOH (1 M), and the resulting solution was stirred at rt for 12 h. The reaction mixture was then concentrated to give a crude oil which was chromatographed on silica gel (3:1 hexanes/EtOAc) to give the product as a clear oil (948 mg, 2.86 mmol). TLC (SiO_2, 25% EtOAc/hexanes): $R_f \approx$ 0.35. This product was subsequently dissolved in 19 mL of CH_2Cl_2. To this mixture was added 2-(3,4-dimethoxybenzyloxy)-3-nitropyridine (332 mg, 1.14 mmol, 0.4 equiv) followed by camphorsulfonic acid (17 mg, 0.07 mmol, 0.025 equiv), and the resulting mixture was stirred for 1 h at rt. At this time, the above additions of 2-(3,4-dimethoxybenzyloxy)-3-nitropyridine (332 mg, 1.14 mmol, 0.4 equiv) followed by camphorsulfonic acid (17 mg, 0.07 mmol, 0.025 equiv) were repeated. Shortly after this second addition, a white precipitate formed. After 1 h, the addition/stirring sequence was repeated three more times as above. Upon completion of the final 1 h stirring period, additional camphorsulfonic acid (17 mg, 0.07 mmol, 0.025 equiv) was added to ensure complete reaction, and the mixture was stirred for an additional 12 h. The mixture was diluted with 50 mL of CH_2Cl_2 and quenched wth 25 mL of saturated aq NH_4Cl. The phases were separated, and the aq phase was extracted with 2 × 50 mL of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give a crude yellow oil. This oil was chromatographed on silica gel (3:1 hexanes/EtOAc) to give **15** as a clear oil (970 mg, 2.02 mmol, 62% from **10**). Compound **15** was determined to be a 9:1 ratio of enantiomers in favor of the (*R*)-configuration through derivatization to the corresponding Mosher's esters.[29] $[\alpha]^{28}_D$: −1.97 (*c* 2.00, $CHCl_3$). IR (thin film): 3437, 2951, 2854, 1724 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.88−6.79 (m, 3H), 5.02 (s, 1H), 4.53 (s, 2H), 3.87−3.78 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.74 (d, J = 9.3 Hz, 1H), 3.59 (d, J = 9.3 Hz, 1H), 2.33 (s, 1H), 1.41 (s, 9H) 0.85 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 149.2, 148.8, 130.6, 120.6, 111.2, 110.0, 82.7, 80.0, 73.6, 72.0, 71.0, 64.8, 56.1, 56.0, 55.0, 28.6, 26.0, 18.4, −5.1, −5.2. TLC (SiO_2, 25% EtOAc/hexanes): R_f = 0.37. HRMS (m/z): calcd for $C_{25}H_{41}NO_6Si$ $(M + H)^+$ 480.2781, found 480.2758. Anal. Calcd for $C_{25}H_{41}NO_6Si$: C, 62.60; H, 8.62; N, 2.92. Found: C, 62.93; H, 8.53; N, 2.99.

(*R*)-MTPA Derivative of 15. All (*R*)-MTPA derivatives were prepared according to published procedures.[29] Products were purified by silica gel column chromatography (3:1 hexanes/EtOAc) to give quantitatively the (*R*)-MTPA esters of **13** and **15**. ^1H NMR analysis indicated a 9:1 ratio of diastereomers on the basis of integration of the alkyne protons. The minor diastereomer of the MTPA ester of **13** was identical to the major diastereomer produced from the derivatization of **15** and vice versa. ^1H NMR (500 MHz, $CDCl_3$): δ 7.57−7.48 (m, 2H), 7.41−7.32 (m, 3H), 6.84−6.76 (m, 3H), 4.99 (s, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.56 (d, J = 10.5 Hz, 1H), 4.41 (AB, J = 11.7 Hz, $\Delta\nu$ = 16.5 Hz, 2H), 3.86 (s, 6H), 3.55 (s, 2H), 3.50 (s, 3H), 2.37 (s, 1H), 1.41 (s, 9H). MS (m/z): calcd for $C_{29}H_{34}NO_8F_3$ $(M + Na)^+$ 604, found 604.

(*R*)-MTPA Derivative of 13. ^1H NMR analysis of the product indicated a 9:1 ratio of diastereomers. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52−7.47 (m, 2H), 7.41−7.32 (m, 3H), 6.85−6.78 (m, 3H), 4.98 (s, 1H), 4.66 (AB, J = 10.5 Hz, $\Delta\nu$ = 14.3 Hz, 2H), 4.46 (s, 2H), 3.86 (s, 6H), 3.59 (AB, J = 9.5 Hz, $\Delta\nu$ = 15.8 Hz, 2H), 3.48 (s, 3H), 2.34 (s, 1H), 1.40 (s, 9H). MS (m/z): calcd for $C_{29}H_{34}NO_8F_3$ $(M + Na)^+$ 604, found 604.

Compound 17. To a solution of **13** (1.167 g, 2.44 mmol, 3.0 equiv) in 24.4 mL of anhydrous THF at rt was added hexamethylphosphoramide (1.70 mL, 9.74 mmol, 12.0 equiv). The mixture was cooled to −78 °C, and *n*-butyllithium (1.52 M in hexanes, 3.36 mL, 5.12 mmol, 6.3 equiv) was added slowly. The resulting pale yellow mixture was stirred for 1.5 h at −78 °C, after which a solution of **16**[9] (543 mg, 0.81 mmol, 1.0 equiv) in 8.1 mL of anhydrous THF was added slowly by cannula.

The mixture was stirred for an additional 25 min at −78 °C and was then quenched with 1 mL of H_2O, followed by 1 mL of saturated aq NH_4Cl. The heterogeneous mixture was warmed to rt and was then diluted with 50 mL of EtOAc and an additional 35 mL of saturated aq NH_4Cl. The phases were separated, and the aq phase was extracted with 2 × 50 mL of EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The concentrated solution was chromatographed on silica gel (9:1 and then 3:1 hexanes/EtOAc) to give a mixture of unreacted **13** and addition product. TLC (products) (SiO_2, 25% EtOAc/ hexanes): R_f values ∼0.44−0.50. This mixture of **13** and the addition products could be quantitatively separated by HPLC if desired, but was typically carried on without purification.

The above mixture was dissolved in 20 mL of an 8:1:1 AcOH/H_2O/MeOH solution. Two drops of aqueous HCl solution (2 N) was then added to the mixture, and the resulting solution was stirred for 2 h at rt. The reaction was then diluted with excess toluene, and the resulting biphasic mixture was concentrated on a high-vacuum (0.1 Torr) rotary evaporator at a temperature not exceeding 30 °C. The resulting crude oil was immediately chromatographed on silica gel (3:1 and then 1:1 hexanes/EtOAc) to give **17** as a foam (574 mg, 0.56 mmol, 68% from **16**). Desilylated **13** was recovered as a clear oil (547 mg, 1.49 mmol). Compound **17** was isolated as an inseparable mixture comprised of a major product bearing the D-configuration at Cα, observed to be a 1:1 mixture of anomers, and a minor product believed to be an anomeric mixture of the L-configuration at Cα, as determined by ^{1}H NMR. $[\alpha]^{28}_D$: +22.5 (*c* 2.25, $CHCl_3$). IR (thin film): 3417, 2955, 2854, 2109, 1713 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65−7.57 (m, 4H), 7.42−7.31 (m, 6H), 6.86−6.76 (m, 3H), 5.34−5.23 (m, 1H), 4.52−4.42 (m, 2H), 4.08−3.57 (m, 17H), 1.43−1.35 (s (minor), δ 1.40; s (major), δ 1.382; s (major), δ 1.377; s (minor), δ 1.368; s (minor), δ 1.365; total 9H), 1.07−1.00 (s (minor), δ 1.06; s (major), δ 1.03; s (major), δ 1.02; total 9H), 0.97−0.76 (s (major), δ 0.943; s (minor), δ 0.935; s (major), δ 0.93; s (minor), δ 0.90; s (minor), δ 0.89; s (major), δ 0.81; s (major), δ 0.80; s (minor), δ 0.782; s (minor), δ 0.780; total 18H), 0.19−0.10 (s (minor), δ 0.17; s (major), δ 0.16; s (major), δ 0.15; s (major), δ 0.14; s (major), δ 0.13; s (major), δ 0.11; s (minor), δ 0.10; s (minor), δ 0.09; s (minor), δ 0.07; s (major), δ 0.03; s (minor), δ 0.02; s (major), δ −0.01; s (minor), δ −0.016; s (minor), δ −0.019; s (minor), δ −0.08; total 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 154.9, 149.3, 149.2, 149.1, 149.0, 135.9, 135.8, 135.7, 133.7, 133.6, 133.5, 133.4, 130.1, 130.0, 129.9, 129.8, 127.9, 127.8, 127.7, 120.8, 120.7, 111.3, 111.2, 111.1, 94.8, 92.3, 84.8, 82.2, 80.7, 76.0, 73.9, 73.8, 73.6, 73.4, 72.4, 72.2, 71.5, 71.1, 70.9, 67.8, 67.2, 66.7, 63.0, 62.3, 56.1, 55.1, 29.9, 28.5, 28.4, 27.1, 27.0, 26.6, 26.5, 26.4, 26.3, 19.4, 19.3, 18.7, 18.6, 13.9, −3.4, −3.5, −3.7, −3.8, −4.3, −4.4, −4.5, −4.6. TLC (SiO_2, 25% EtOAc/ hexanes): R_f = 0.13. MS (*m*/*z*): calcd for $C_{53}H_{82}N_4O_{11}Si_3$ $(M + Na)^+$ 1057, found 1057.

Compound 18. To a solution of **17** (779 mg, 0.75 mmol, 1.0 equiv) in 53 mL of EtOAc was added 10% Pd/C (512 mg) followed by camphorsulfonic acid (175 mg, 0.75 mmol, 1.0 equiv). The flask was evacuated under aspirator vacuum and refilled with hydrogen three times, and then the mixture was stirred under hydrogen (1 atm) for 22 h. The mixture was then filtered through Celite and quenched with 2 mL of triethylamine. The solution was concentrated to give an oil, which was chromatographed on silica gel (3:1 hexanes/EtOAc) to give the product mixture as a clear foam (557 mg, 0.55 mmol). TLC (SiO_2, 50% EtOAc/hexanes): $R_f \approx 0.66$. This product was dissolved in 11 mL of THF, and tetrabutylammonium fluoride (1.0 M in hexanes, 2.74 mL, 2.74 mmol, 5.0 equiv) was added dropwise. The solution was stirred at rt for 12 h, after which the reaction mixture was chromatographed on silica gel (EtOAc and then 9:1 EtOAc/MeOH). The product was isolated as a clear foam. TLC (SiO_2, 90% EtOAc/MeOH): $R_f \approx 0.52$. The product mixture was taken up in 9 mL of a 2:1 pyridine/Ac_2O solution. A catalytic amount of DMAP was then added in one portion, and the mixture was stirred for 5 h at rt. The solution was concentrated on a high-vacuum (0.1 Torr) rotary evaporator, and the resulting oil was chromatographed on silica gel (1:1 hexane/EtOAc) to give the product mixture as a clear foam. The product was further purified by HPLC (silica gel, 1:1 hexanes/EtOAc). Compound **18** was isolated as a clear foam (273 mg, 0.40 mmol, 53% from **17**) in greater than 90% purity. $[\alpha]^{28}_D$: +31.5 (*c* 1.85, $CHCl_3$). IR (thin film): 2968, 2105, 1747, 1703 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86−6.76 (m, 3H), 6.42 (d, J = 10.1 Hz, 1H), 5.71 (d, J = 10.1 Hz, 1H), 5.43−5.33 (m, 1H), 5.38 (dd, J = 10.9, 3.4 Hz, 1H), 4.97 (s, 1H), 4.44 (AB, J = 11.8 Hz, $\Delta\nu$ = 10.8 Hz, 2H), 4.25 (t, J = 6.6 Hz, 1H), 4.15−4.00 (m, 2H), 3.97 (d, J = 11.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.79 (d, J = 11.5 Hz, 1H), 3.72−3.82 (m, 1H), 3.62 (d, J = 9.5 Hz, 1H), 3.48 (d, J = 10.9 Hz, 1H), 2.13 (s, 3H) 2.03 (s, 3H), 1.97 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.3, 170.0, 155.2, 149.1, 148.8, 134.0, 130.6, 127.0, 120.4, 111.1, 111.0, 96.6, 79.9, 73.7, 70.3, 68.6, 67.9, 67.6, 65.3, 61.6, 61.0, 56.1, 56.0, 51.4, 28.5, 20.8 (3H). TLC (SiO_2, 50% EtOAc/hexanes): R_f = 0.33. HRMS (*m*/*z*): calcd for $C_{31}H_{42}N_4O_{13}$ 678.2748, found 678.2771.

Compound 19. Compound **18** (182 mg, 0.27 mmol) was dissolved in 12 mL of a 20:1 EtOAc/Ac_2O solution, and 10% Pd/C (91 mg) was added to the mixture. The flask was evacuated under aspirator vacuum and refilled with hydrogen three times, and then the mixture was stirred under hydrogen (1 atm) for 6 h. The mixture was then filtered through Celite, and concentrated to give an oil. The oil was chromatographed on silica gel (EtOAc) to give **19** as a white foam (87 mg, 0.16 mmol, 59%). $[\alpha]^{28}_D$: +66.6 (*c* 0.70, $CHCl_3$). IR (thin film): 3397, 2968, 1741, 1654 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (s, 1H), 5.32 (d, J = 3.2 Hz, 1H), 5.15 (dd, J = 11.1, 3.4 Hz, 1H), 4.94 (s, 1H), 4.34 (t, J = 10.7 Hz, 1H), 4.12 (dd, J = 11.1, 7.1 Hz, 1H), 4.06 (dd, J = 11.3, 6.0 Hz, 1H), 4.03−3.98 (m, 1H), 3.71 (d, J = 10.9 Hz, 1H), 3.65 (d, J = 11.3 Hz, 1H), 3.56−3.46 (m, 1H), 3.50 (d, J = 11.7 Hz, 1H), 2.14 (s, 3H), 2.08−2.01 (m, 1H), 2.03 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.77 (dt, J = 15.3, 4.8 Hz, 1H), 1.72−1.60 (m, 3H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 170.7, 170.6, 170.5, 156.2, 98.9, 80.7, 69.1, 67.5, 67.4, 67.3, 65.4, 62.1, 54.1, 51.0, 28.6, 25.7, 23.4, 23.2, 21.0, 20.9 (2H). TLC (SiO_2, 100% EtOAc): R_f = 0.34. HRMS (*m*/*z*): calcd for $C_{24}H_{38}N_2O_{12}$ $(M + H)^+$ 547.2503, found 547.2489.

Compound 20. To a solution of **19** (58 mg, 0.11 mmol, 1.0 equiv) in 2.2 mL of CH_2Cl_2 at rt was added $NaHCO_3$ (68 mg) followed by Dess−Martin periodinane (90 mg, 0.21 mmol, 2.0 equiv). The reaction mixture was stirred for 9 h, after which it was quenched with 2 mL of a $Na_2S_2O_3$ solution (25 g of $Na_2S_2O_3$ per 100 mL). After being stirred for 15 min, the mixture was diluted with 15 mL of CH_2Cl_2 and 15 mL of H_2O. The phases were separated, and the aq phase was extracted with 2 × 10 mL of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The resulting product was dissolved in 3.5 mL of 4:1 *t*BuOH/H_2O. NaH_2PO_4 (31 mg, 0.22 mmol, 2.0 equiv), 2-methyl-2-butene (2.0 M in THF, 0.22 mL, 0.44 mmol, 4.2 equiv), and finally $NaClO_2$ (58 mg, 0.64 mmol, 6.0 equiv) were successively added, and the solution was stirred at rt for 12 h. The reaction mixture was then diluted with 15 mL of H_2O and 15 mL of EtOAc. The phases were separated, and the aq phase was extracted with 2 × 10 mL of EtOAc. The combined organic phases were washed with 10 mL of brine, dried (Na_2SO_4), filtered, and concentrated to give an oil. The oil was chromatographed on silica gel (EtOAc and then 95:5 EtOAc/AcOH) to give **20** as a white foam (53 mg, 0.09 mmol, 89%). $[\alpha]^{28}_D$: +80.7 (*c* 1.15, MeOH). IR (thin film): 3354, 2974, 1736, 1654 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 8.03 (d, J = 9.9 Hz, 1H), 7.12 (s, 1H), 5.39 (d, J = 3.4 Hz, 1H), 5.16 (dd, J = 11.1, 3.2 Hz, 1H), 4.32−4.23 (m, 1H), 4.22 (dd, J = 10.5, 7.5 Hz, 1H), 4.18−4.13 (m, 1H), 4.13−4.07 (m, 1H), 3.96 (AB, J = 11.3 Hz, $\Delta\nu$ = 30.7 Hz, 2H), 2.19 (dt, J = 13.7, 4.6 Hz, 1H), 2.15 (s, 3H), 2.08−1.86 (m, 2H), 2.05 (s, 3H) 2.00 (s, 3H), 1.93 (s, 3H), 1.55−1.47 (m,

1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ 174.4, 172.6, 171.1, 171.0, 170.7, 156.1, 98.1, 79.3, 69.4, 67.7, 67.4, 63.1, 62.2, 56.4, 50.7, 27.6, 25.4, 24.7, 21.5, 19.4 (2H), 19.3. TLC (SiO_2, EtOAc with 2% AcOH): R_f = 0.17. HRMS (*m*/*z*): calcd for $C_{24}H_{36}N_2O_{13}$ $(M + H)^+$ 561.2296, found 561.2294.

2-Azido-3,4,6-tri-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-galactono-1,5-lactone (21). Following a published procedure,[9] KHMDS (0.5 M in toluene, 4.9 mL, 2.4 mmol, 1.1 equiv) was added slowly to a solution of 3,4,6-tri-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-galactono-1,5-lactone[30] (1.135 g, 2.22 mmol, 1.0 equiv) in 22.2 mL of THF at −78 °C. The reaction mixture was stirred for 45 min at −78 °C and was then cooled to −96 °C. A solution of trisyl azide (756 mg, 2.44 mmol, 1.1 equiv) in 7.9 mL of THF at −78 °C was then added by cannula. The resulting pale yellow mixture was stirred for 5 min at −96 °C. AcOH (0.25 mL) was then added dropwise, and the solution subsequently became bright yellow. The reaction mixture warmed to rt over 1 h, after which the color somewhat dissipated. The reaction mixture was slowly warmed to 30 °C and stirred for an additional 20 min. After being cooled to rt, the solution was concentrated, and the residue was filtered through a short plug of silica gel (20:1 hexanes/EtOAc) to remove major impurities. The resulting clear oil was chromatographed on silica gel (40:1 and then 3:1 hexanes/EtOAc) to give **21** as a white crystalline solid (717 mg, 1.31 mmol, 59%) after drying under high vacuum (0.1 Torr) for several days. $[\alpha]^{28}_D$: +63.8 (*c* 2.05, $CHCl_3$). IR (thin film): 2925, 2849, 2116, 1747 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (d, J = 9.9 Hz, 1H), 4.15 (m, 1H), 4.10 (ddd, J = 8.3, 6.0, 0.8 Hz, 1H), 3.78−3.69 (m, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 80.3, 73.6, 69.4, 63.6, 60.2, 26.2, 26.1, 26.0, 18.7, 18.6, 18.3, −3.7, −3.9, −4.5, −4.9, −5.1, −5.2. TLC (SiO_2, 5% EtOAc/hexanes): R_f = 0.24. mp 58−60 °C. HRMS (*m*/*z*): calcd for $C_{24}H_{51}N_3O_5Si_3$ $(M + H)^+$ 546.3215, found 546.3239. Anal. Calcd for $C_{24}H_{51}N_3O_5Si_3$: C, 52.80; H, 9.42; N, 7.70. Found: C, 53.19; H, 9.10; N, 7.75.

Compound 22. To a solution of **15** (1.018 g, 2.05 mmol, 2.5 equiv) in 20.5 mL of anhydrous THF at rt was added hexamethylphosphoramide (1.42 mL, 8.19 mmol, 10.0 equiv). The mixture was then cooled to −78 °C, and *n*-butyllithium (1.52 M in hexanes, 2.83 mL, 4.30 mmol, 5.2 equiv) was added slowly. The resulting pale yellow mixture was stirred for 1.5 h at −78 °C, after which a solution of **21** (446 mg, 0.82 mmol, 1.0 equiv) in 8.2 mL of anhydrous THF was added slowly by cannula. The mixture was stirred for an additional 25 min at −78 °C and was then quenched with 1 mL of H_2O, followed by 1 mL of saturated aq NH_4Cl. The heterogeneous mixture was warmed to rt and was then diluted with 50 mL of EtOAc and an additional 35 mL of saturated aq NH_4Cl. The phases were separated, and the aq phase was extracted with 2 × 50 mL of EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The concentrated solution was chromatographed on silica gel (9:1 and then 3:1 hexanes/EtOAc) to give a mixture of unreacted **15** and the addition product. TLC (products) (SiO_2, 25% EtOAc/hexanes): R_f values ∼0.44−0.50. This mixture of **15** and the addition products could be quantitatively separated by HPLC if desired, but was typically carried on without further purification.

The above mixture was dissolved in 20 mL of an 8:1:1 AcOH/H_2O/MeOH solution. Two drops of aqueous HCl solution (2 N) was then added to the mixture, and the resulting solution was stirred for 2 h at rt. The reaction was then diluted with excess toluene, and the resulting biphasic mixture was concentrated on a high-vacuum (0.1 Torr) rotary evaporator at a temperature not exceeding 30 °C. The resulting oil was immediately chromatographed on silica gel (1:1 hexanes/EtOAc and then EtOAc) to give **22** as a foam (435 mg, 0.55 mmol, 67% from **21**). Desilylated **15** was recovered as a clear oil (413 mg, 1.12 mmol). Compound **22** was isolated as an inseparable mixture comprised of a major product bearing the L-configuration at Cα (1:1 mixture of anomers), as well as a minor product believed to be an anomeric mixture of the D-configuration at Cα by ^{1}H NMR. $[\alpha]^{28}_D$: +38.6 (*c* 1.45, $CHCl_3$). IR (thin film): 3430, 2952, 2105, 1638 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84−6.77 (m, 3H), 5.64−5.26 (s (major), δ 5.55; s (minor), δ 5.49; s (minor), δ 5.33; s (major), δ 5.30; total 1H), 4.56−4.41 (m, 2H), 4.20−3.40 (m, 19H), 1.43−1.34 (s (major), δ 1.40; s (minor), δ 1.39; s (major), δ 1.38; total 9H), 0.95−0.82 (s (major), δ 0.92; s (major), δ 0.91; s (minor), δ 0.90; s (major), δ 0.87; s (major), δ 0.86; s (minor), δ 0.85; total 18H), 0.16−0.01 (s (minor), δ 0.17; s (major), δ 0.16; s (minor), δ 0.15; s (minor), δ 0.14; s (minor), δ 0.13; s (major), δ 0.12; s (major), δ 0.106; s (minor), δ 0.099; s (major), δ 0.082; s (minor), δ 0.075; s (major), δ 0.04; s (minor), δ 0.03; s (major), δ 0.02; total 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 149.3, 149.2, 149.1, 149.0, 130.1, 129.9, 120.8, 120.7, 111.3, 111.0, 95.6, 95.1, 93.1, 92.1, 85.1, 82.4, 80.9, 80.6, 76.6, 76.4, 74.8, 73.9, 73.8, 73.3, 72.3, 72.2, 71.7, 71.6, 71.3, 71.0, 67.4, 66.4, 64.6, 64.2, 63.3, 62.9, 56.1, 56.0, 55.7, 55.2, 30.8, 28.7, 28.6, 28.5, 26.6, 26.5, 26.4, 26.3, 26.2, 26.1, 18.8, 18.7, 18.6, 13.9, −2.7, −3.2, −3.3, −3.4, −4.0, −4.1, −4.2, −4.3, −4.4, −4.5, −4.6. TLC (SiO_2, 50% EtOAc/hexanes): R_f = 0.16. HRMS (*m*/*z*): calcd for $C_{37}H_{64}N_4O_{11}Si_2$ 796.4110, found 796.4110.

Compounds 23 and 24. Compound **22** (198 mg, 0.25 mmol, 1.0 equiv) was dissolved in 20 mL of a 9:1 EtOAc/AcOH solution, and 10% Pd/C (15 mg) was added. The flask was evacuated under aspirator vacuum and refilled with hydrogen three times, and then the mixture was stirred under hydrogen (1 atm) for 5 h. The mixture was filtered through Celite, and the filtrate was concentrated on an aspirator pressure rotary evaporator followed by a high-vacuum (0.1 Torr) rotary evaporator. The resulting oil was dissolved in 20 mL of a *p*-toluenesulfonic acid monohydrate/EtOAc (1 mg/mL) solution, and the mixture was stirred for 12 h at rt. The reaction was quenched with 1 mL of triethylamine, and the solution was concentrated to give an oil. The oil was chromatographed on silica gel (1:1 and then hexanes/EtOAc) to give the product mixture as a clear foam (143 mg, 0.18 mmol). TLC (SiO_2, 50% EtOAc/ hexanes): R_f values ∼0.79−0.62. This product was dissolved in 4 mL of THF, and tetrabutylammonium fluoride (1.0 M in hexanes, 0.90 mL, 0.74 mmol, 4.0 equiv) was added dropwise. The solution was stirred at rt for 12 h, after which the mixture was chromatographed on silica gel (EtOAc and then 9:1 EtOAc/MeOH). The product was isolated as a clear foam. TLC (SiO_2, 90% EtOAc/MeOH): $R_f \approx$ 0.52. The product mixture was taken up in 6 mL of a 2:1 pyridine/Ac_2O solution. A catalytic amount of DMAP was then added in one portion, and the mixture was stirred for 5 h at rt. The solution was concentrated on a high-vacuum (0.1 Torr) rotary evaporator, and the resulting oil was chromatographed on silica gel (1:1 hexanes/EtOAc) to give the product mixture as a clear foam. The purified product was further purified by HPLC (silica gel, 1:1 hexanes/EtOAc). Compound **23** was isolated as a clear foam (67 mg, 0.10 mmol, 40% from **22**) in greater than 90% purity. Compound **24** was isolated as a clear foam (21 mg, 0.03 mmol, 12% from **22**) in greater than 90% purity.

Data for Compound 23. $[\alpha]^{28}_D$: +67.4 (*c* 3.75, $CHCl_3$). IR (thin film): 2968, 2105, 1747, 1714 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88−6.78 (m, 3H), 6.06 (s, 1H), 5.64 (s, 1H), 5.42−5.30 (m, 1H), 5.34 (dd, J = 10.9, 3.2 Hz, 1H), 5.04 (s, 1H), 4.45 (AB, J = 11.5 Hz, $\Delta\nu$ = 55.3 Hz, 2H), 4.22 (t, J = 6.8 Hz, 1H), 4.16−3.98 (m, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.76 (d, J = 10.3 Hz, 1H), 3.67 (d, J = 8.5 Hz, 1H), 3.55 (d, J = 10.9 Hz, 1H), 3.31 (d, J = 6.4 Hz, 1H), 2.11 (s, 3H) 2.02 (s, 3H), 1.99 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.3, 170.0, 154.2, 149.2, 149.0, 136.2, 130.1, 126.2, 120.8, 111.3, 111.0, 96.1, 79.8, 73.7, 70.4, 69.0, 67.7, 67.6, 61.8, 61.3, 60.7, 56.1, 56.0, 52.5, 28.4, 20.8 (3H). TLC (SiO_2, 50% EtOAc/hexanes): R_f = 0.38. HRMS (*m*/*z*): calcd for $C_{31}H_{42}N_4O_{13}$ 678.2748, found 678.2763.

Data for Compound 24. $[\alpha]^{28}_D$: +36.3 (*c* 0.95, $CHCl_3$). IR (thin film): 2974, 2110, 1747, 1703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85−6.77 (m, 3H), 6.50 (d, J = 10.2 Hz, 1H), 6.00

(d, J = 10.4 Hz, 1H), 5.39−5.33 (m, 1H), 4.95−4.87 (m, 2H), 4.45 (s, 2H), 4.11−4.01 (m, 4H), 3.98−3.91 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83−3.89 (m, 1H), 3.67 (AB, J = 9.5 Hz, $\Delta\nu$ = 36.0 Hz, 2H), 2.14 (s, 3H) 2.02 (s, 3H), 1.96 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.3, 170.0, 155.0, 149.2, 148.9, 135.2, 130.5, 122.0, 120.5, 111.1, 111.0, 97.6, 80.0, 73.7, 70.4, 69.7, 69.2, 66.6, 66.3, 63.4, 61.4, 56.1, 56.0, 51.7, 28.5, 20.9, 20.8, 20.7. TLC (SiO_2, 50% EtOAc/hexanes): R_f = 0.28. HRMS (m/z): calcd for $C_{31}H_{42}N_4O_{13}$ 678.2748, found 678.2750.

Compound 25. Compound **23** (114 mg, 0.17 mmol) was dissolved in 7 mL of a 20:1 EtOAc/Ac_2O solution, and 10% Pd/C (57 mg) was added to the mixture. The flask was evacuated under aspirator vacuum and refilled with hydrogen three times, and then the mixture was stirred under hydrogen (1 atm) for 12 h. A second portion of 10% Pd/C (28 mg) was added, and the stirring under hydrogen was continued for an additional 12 h. The mixture was then filtered through Celite, and concentrated to give an oil. The oil was chromatographed on silica gel (EtOAc and then 9:1 EtOAc/MeOH) to give **25** as a white foam (53 mg, 0.10 mmol, 58%). $[\alpha]^{28}_D$: +80.4 (c 0.85, $CHCl_3$). IR (thin film): 3430, 2974, 1747, 1643 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 5.86 (d, J = 10.1 Hz, 1H), 5.34 (dd, J = 3.2, 1.0 Hz, 1H), 5.12 (dd, J = 11.1, 3.4 Hz, 1H), 4.49 (s, 1H), 4.34 (t, J = 10.5 Hz, 1H), 4.15 (dd, J = 11.1, 6.6 Hz, 1H), 4.06 (dd, J = 11.1, 6.9 Hz, 1H), 4.03−3.96 (m, 2H), 3.85 (d, J = 11.7 Hz, 1H), 3.68 (d, J = 11.9 Hz, 1H), 3.38 (d, J = 10.9 Hz, 1H), 2.13 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.86−1.63 (m, 5H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 170.7, 170.6, 170.5, 156.1, 98.3, 80.9, 69.3, 67.4, 67.2, 63.6, 62.9, 61.8, 53.4, 50.7, 28.5, 27.1, 25.9, 23.5, 21.0, 20.9 (2H). TLC (SiO_2, 100% EtOAc): R_f = 0.20. HRMS (m/z): calcd for $C_{24}H_{38}N_2O_{12}$ $(M + H)^+$ 547.2503, found 547.2494.

Compound 26. To a solution of **25** (42 mg, 0.08 mmol, 1.0 equiv) in 1.5 mL of CH_2Cl_2 at rt was added $NaHCO_3$ (48 mg) followed by Dess−Martin periodinane (64 mg, 0.15 mmol, 2.0 equiv). The reaction mixture was stirred for 9 h, after which it was quenched with 1 mL of a $Na_2S_2O_3$ solution (25 g of $Na_2S_2O_3$ per 100 mL). After being stirred for 15 min, the mixture was diluted with 15 mL of CH_2Cl_2 and 15 mL of H_2O. The phases were separated, and the aq phase was extracted with 2 × 10 mL of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The resulting product was dissolved in 2.5 mL of 4:1 tBuOH/H_2O. NaH_2PO_4 (22 mg, 0.16 mmol, 2.0 equiv), 2-methyl-2-butene (2.0 M in THF, 0.16 mL, 0.32 mmol, 4.2 equiv), and finally $NaClO_2$ (41 mg, 0.46 mmol, 6.0 equiv) were successively added, and the solution was stirred at rt for 12 h. The reaction mixture was then diluted with 10 mL of H_2O and 15 mL of EtOAc. The phases were separated, and the aq phase was extracted with 2 × 10 mL of EtOAc. The combined organic phases were washed with 10 mL of brine, dried (Na_2SO_4), filtered, and concentrated to give a crude oil. The oil was chromatographed on silica gel (9:1 EtOAc/MeOH and then 90:8:2 EtOAc/MeOH/AcOH) to give **26** as a white foam (39 mg, 0.07 mmol, 90%). $[\alpha]^{28}_D$: +57.9 (c 1.05, MeOH). IR (thin film): 3424, 2979, 1736, 1643 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 7.89 (d, J = 8.9 Hz, 1H), 5.39 (d, J = 3.2 Hz, 1H), 5.16 (dd, J = 11.2, 3.3 Hz, 1H), 4.35 (d, J = 10.8 Hz, 1H), 4.30−4.08 (m, 4H), 3.46 (d, J = 11.0 Hz, 1H), 2.14 (s, 3H), 2.16−2.08 (m, 1H), 2.06 (s, 3H), 2.04−1.92 (m, 1H), 1.95 (s, 3H) 1.93 (s, 3H), 1.87 (dt, J = 13.5, 4.1 Hz, 1H), 1.64−1.55 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ 176.2, 174.1, 172.4, 172.3, 172.0, 157.2, 99.3, 80.8, 70.8, 69.0, 68.6, 65.8, 63.3, 56.3, 52.0, 28.8, 28.6, 27.7, 22.7, 20.8, 20.7, 20.6. TLC (SiO_2, 90:8:2 EtOAc/MeOH/AcOH): R_f = 0.09. HRMS (m/z): calcd for $C_{24}H_{36}N_2O_{13}$ $(M + H)^+$ 561.2296, found 561.2318.

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Supporting Information Available: ^{1}H and ^{13}C spectra for **9**, **10**, 2-(3,4-dimethoxybenzyloxy)-3-nitropyridine, **15**, the (*R*)-MTPA derivative of **15** (^{1}H only), the (*R*)-MTPA derivative of **13** (^{1}H only), and **17**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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