Glycosamino Acids: New Building Blocks for Combinatorial Synthesis

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Abstract: In order to produce inexpensive, chemically diverse carbohydrate building blocks more amenable for use in combinatorial organic synthesis, amine and carboxylic acid functional groups were incorporated into several monosaccharides. A series of 12 new glycosamino acids was prepared from commercially available starting materials. Conventional peptide synthesis solution coupling techniques were used to ligate glycosamino acids, producing oligomeric "glycotides". Finally, a library of glycotides was produced by coupling of a glycosamino acid mixture to a rigid template.

Introduction

Combinatorial chemistry has the potential to become an important tool in the pharmaceutical industry for generating lead compounds with desirable biological activities and for optimizing these compounds.[1] The ideal monomeric building blocks for an oligomeric combinatorial library would be structurally diverse yet conformationally restrained, synthetically accessible, and easily converted to a series of congeners for the purposes of lead optimization. Carbohydrates, in addition to possessing the aforementioned qualities, contain a higher level of functional group diversity per unit mass than other biopolymeric building blocks.[2] Nature has taken advantage of these properties to assemble heparin, a polysaccharide library with a wide variety of distinct biological activities.[3]

In contrast to the efficient biosynthetic polymerization of heparin, the assembly of synthetic polysaccharide libraries is difficult. In spite of significant recent advances using chemical[4] and enzymatic[5] techniques, solid phase carbohydrate synthesis has not become routine. Even if all synthetic obstacles could be overcome, an oligosaccharide library may not produce drug candidates due to the low bioavailabilities (*e.g.*, susceptibility to glycosidases, poor cellular uptake) of its components.[6]

To circumvent the synthetic problems associated with carbohydrate libraries, we chose to modify monosaccharide building blocks by incorporating into them amine and carboxylic acid functional groups, affording glycosamino acids. These synthetic monomers can be ligated using the well-developed chemistry of peptide synthesis.[7] The resultant oligomers ("glycotides") may be useful drug candidates, since they would not be susceptible to glycosidases and may not be recognized by proteases due to the altered backbone relative to natural peptide substrates. Functional group modifications, in particular hydroxyl protection, could increase the lipophilicity of the molecules and render them more likely to permeate cell membranes. We report herein the synthesis of 12 protected glycosamino acids and their oligomerization to form two glycotide oligomers and a small glycotide library.

Results and Discussion

Glycosamino acids occur naturally (*e.g.*, sialic acid), and synthetic congeners have been utilized as peptidomimetics,[8] glycosidase inhibitors,[9] and starting materials in polymer[10] and natural product syntheses.[11] We have synthesized 12 glycosamino acid precursors, protected as azido esters, starting from five different commercially available monosaccharides (Figure 1). In each case, the latent amino group was incorporated by displacement of a primary or secondary sulfonate ester with an azide nucleophile. The carboxyl group was introduced using one of three reactions: (1) Wittig reaction of methyl(triphenylphosphoranylidene) acetate with either a furanose hemiacetal to form the C-glycosides **1**, **2**, **3**, and **4** or with a 3-ketofuranose (followed by thiolate Michael addition) to afford **8** and **9**; (2) oxidative cleavage of a C-allyl glycoside (**5**, **6**, **7**, **11**, **12**); and (3) oxidation of a primary alcohol (**10**). Monomer syntheses ranged from 4 to 11 steps, starting with inexpensive commercially available materials and proceeding in unoptimized overall yields ranging from 5 to 50%.

Monomer syntheses were designed to maximize efficiency by diverging from a common starting material. This principle

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(6) Cellular uptake may not be a significant problem, since many natural carbohydrate ligands, of the type which could be mimicked by glycotides, have extracellular targets.

(7) (a) Bodanszky, A.; Bodanszky, M.; Chandramouli, N.; Kwei, J. Z.; Marinez, J.; Tolle, J. C. *J. Org. Chem.* **1980**, *45*, 72−76. (b) Kent, S. B. H. *Ann. Rev. Biochem.* **1988**, *57*, 957−989.

(8) Graf von Roedern, E.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 687−689.

(9) Gurjar, M. K.; Mainkar, A. S.; Syamala, M. *Tetrahedron: Asymmetry* **1993**, *4*, 2343−2346.

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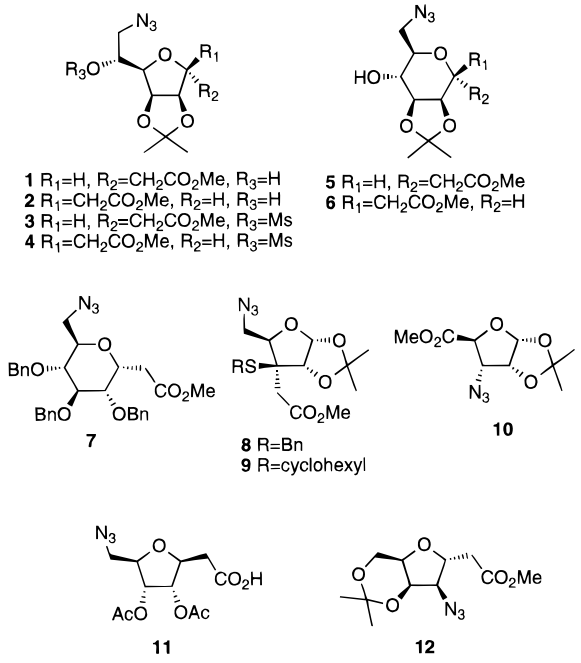
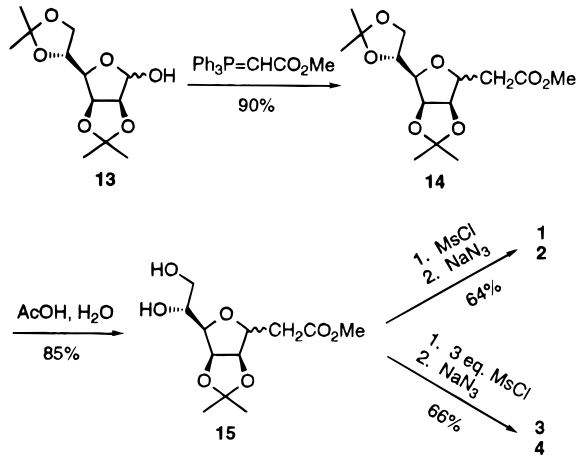


Figure 1. Glycosamino acid precursors discussed herein.[9]

Scheme 1. Divergent Synthesis of Glycosamino Acid Precursors **1**, **2**, **3**, and **4**[a]



[a] Details are included in the Experimental Section.

is exemplified by the synthesis of compounds **1**−**4** (Scheme 1). A Wittig reaction on the commercially available 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**13**), followed by cyclization *via* intramolecular Michael addition, provided **14**[12] as an anomeric mixture. Selective hydrolysis of the 5,6-acetonide produced the anomeric diols **15**, which served as the branching point in the synthesis. Selective mesylation of the primary alcohol, followed by treatment with sodium azide, provided the azido esters **1** and **2** (49% combined overall yield from **13**).[13] Dimesylation of **15**, followed by selective displacement of the primary mesylate with sodium azide, afforded the base-stable[14] monomesylates **3** and **4** (50% combined overall yield).[13] Conversion of azido esters **1**−**4** to the corresponding *tert*-butyl carbamate(BOC)-protected acids for use in solid-phase synthesis (not discussed herein) was achieved using a one-pot procedure (azide hydrogenation and carbamate formation followed by ester hydrolysis).[15] The base-sensitive fluorenyl methyl carbamate (FMOC)-protected acids, which would be preferred for solid-phase syntheses involving acid-sensitive monomers, such as the acetonides **1**−**6**, **8**−**10**, and **12**, could be produced by an analogous procedure.

Glycosamino acids **5** and **6** were prepared from peracetylated mannose (Scheme 2). The allyl glycoside was generated as an anomeric mixture **18**, which was taken through a series of transformations to install the azido group at C-6, followed by oxidative cleavage of the allyl group and separation of anomers **5** and **6** (Scheme 2).

Glycosamino acid **7** was prepared from 1,6-β-D-anhydroglucose in a six step sequence (Scheme 3), the key step being a stereospecific allylation (**22** to **23**). The azide was introduced by displacement of the primary *C-6* mesylate (**23** to **24**), and the carboxyl group was introduced by oxidative cleavage of the allyl group (**24** to **7**).

Glycosamino acids **8** and **9** were prepared by the stereospecific Michael addition (directed by the isopropylidene ketal) of thiolates to the α,β-unsaturated azido ester **27b**, which was produced from 1,2-*O*-isopropylidene-α-D-xylofuranose (Scheme 4). Compound **10** was produced from the identical starting material (Scheme 5). In this route, the azide was introduced by displacement of the C-3 secondary triflate (**28** to **29**) and the carboxyl group was introduced by oxidation of a primary alcohol (**29** to **10**).

Glycosamino acid **11** was synthesized from peracetylated ribose, starting with a nonspecific allylation to generate a mixture of anomers, **30a** and **30b**. Compound **30b** was elaborated into **11** by a simple five-step sequence (Scheme 6). Finally, glycosamino acid **12** was generated from peracetylated xylose by a similar sequence (Scheme 7).

Assembly of glycosamino acid units into oligoglycotides such as **16** and **17** (Figure 2) was accomplished using solution-phase peptide synthesis methods. The amino terminus was deprotected by hydrogenation (10% Pd on carbon) of the azide, while the carboxylic acid was liberated by ester hydrolysis. The β-glycoside **4** was saponified (providing **4c**, **c** designates free acid), while the α-glycoside **3** was hydrogenated (**3n** designates free amine), and equimolar amounts of the amine and acid components were coupled (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and triethylamine in methylene chloride) to produce a diglycotide **36** (Figure 2) in 28% yield. Hydrogenation of the diglycotide azide, followed by coupling of the resultant amine to carboxylic acid **11**, afforded triglycotide **16** in 44% yield. Hydrogenation of **12** followed by coupling to **4c** provided diglycotide **17** in 67% yield.

In addition to linear glycotide oligomers, a branched, template-directed glycotide library[16] was assembled using 1,3,5-benzenetricarboxylic acid chloride as the template. A preliminary, small-scale experiment using *ca.* 4 molar equiv of the single monomer **2** produced, after azide hydrogenation followed by addition of the acid chloride, the desired trifunctional product **37** (Figure 2) with a purity (after extraction, without chromatography) of ≥90%, as estimated by ^{1}H NMR and HPLC (two minor impurity peaks were visible).[17] A library was produced

(12) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602−4613.

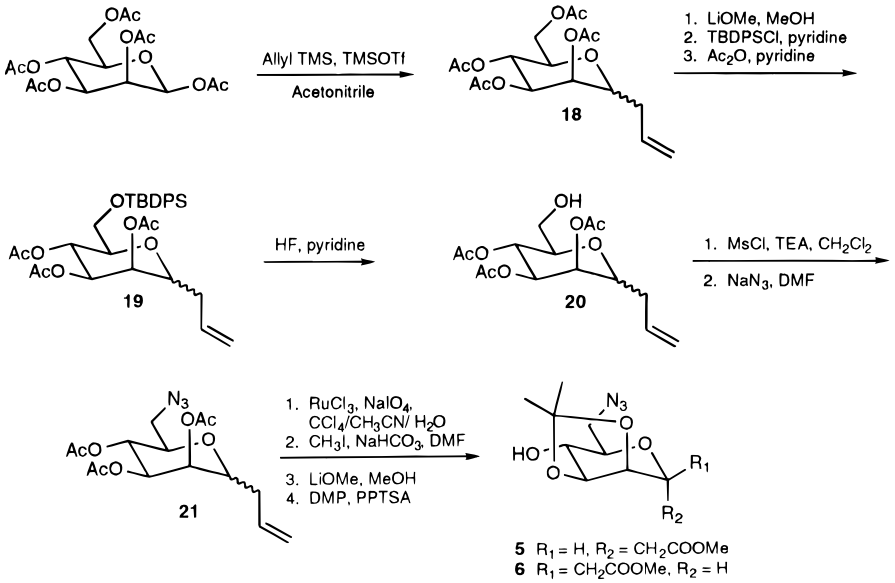
(13) The pairs of anomeric azido esters **1** and **2** and **3** and **4** were separated using flash chromatography on silica gel.

(14) The azido ester mesylates **3** and **4** were stable to diazabicycloundecene (1 equiv) in toluene at room temperature or NaOMe (1 equiv) in methanol at room temperature.

(15) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837−838.

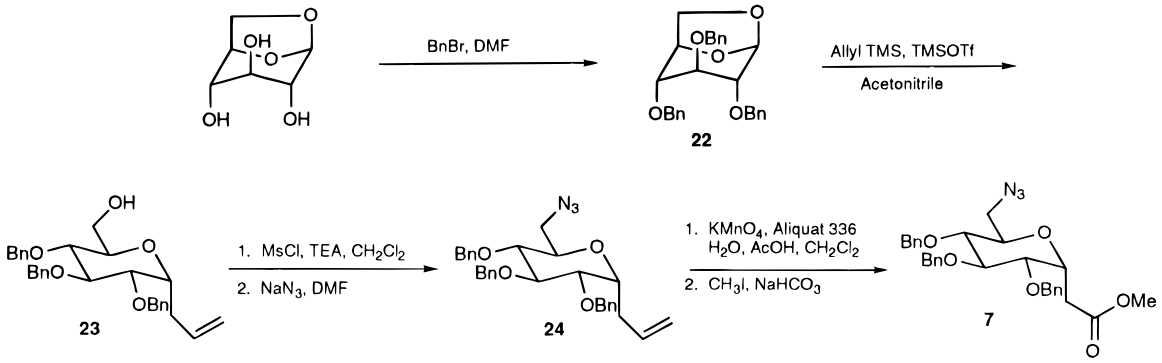
(16) (a) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217−9218. (b) Carell, T.; Wintner, E. A.; Bashir-Hashemi, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2059−2061. (c) Patek, M.; Drake, B.; Lebl, M. *Tetrahedron Lett.* **1994**, *35*, 9169−9172.

Scheme 2. Synthetic Route to Glycosamino Acids **5** and **6**[a]



[a] Details are included in the Experimental Section.

Scheme 3. Synthetic Route to Glycosamino Acid **7**[a]



[a] Details are included in the Experimental Section.

by hydrogenation of 4 equiv of **4**, 4 equiv of **5**, and 2 equiv of **8** (at short reaction times, the azide reduction was complete and the *S*-benzyl group in **8** was not hydrogenated), followed by reaction of the amines with the template to produce a (theoretical) ten component library, nine of which were clearly observed by fast-atom bombardment mass spectrometry of the mixture.[17] The symmetrical compound containing three groups derived from **8** ligated to the template was not expected to be produced in significant amounts due to the experimental stoichiometry and was not detected.

Conclusions

This paper reports 12 new glycosamino acids, a new family of building blocks for combinatorial synthesis. The compounds can be accessed by simple synthetic routes starting with inexpensive starting materials. They can be further functionalized (acylation of alcohols, etc.) to enlarge the family. These monomers can be ligated using known chemistry to afford glycotides. Although solution-phase methods have been used, solid-phase approaches to glycotide synthesis should be developed in order to obtain large libraries that will be useful in an industrial setting. Solid-phase methodology will facilitate synthesis and characterization of library components by making glycotide production more amenable to spatially addressable[18,19] or encoding[20] approaches to combinatorial synthesis. Undoubtedly, the requirement for preliminary monomer synthesis reduces the appeal of glycotide libraries relative to libraries that can be readily assembled using commercially available monomers. However, this is a small cost to pay for a combinatorial library significantly different from any in existence. A library of glycotides would provide a convenient mechanism to access the tremendous structural diversity of carbohydrates without the synthetic difficulties and uncertain bioavailabilities associated with natural carbohydrates. In addition, carbohydrate pharmacophores can be easily incorporated into a directed library using these monomers. Finally, the general approach of modifying monosaccharides for convenient oligomerization could be expanded to include ligation by urea[21] or carbamate[22] formation.[23]

(17) The compound library eluted on RP-HPLC (C18, 300 Å) from 20 to 55 min in CH_3CN/H_2O/0.1% TFA using the following gradient: % CH_3CN at time $t = 20 + 0.9(t-5)$ through $t = 50$ min; % $CH_3CN = 60.5 + 2.5(t-50)$ after $t = 50$ min. Eleven clearly resolved peaks were visible, two of which constituted less than 2% of the total. These peaks may correspond to the nine compounds detected by mass spectrometry and trace impurities.

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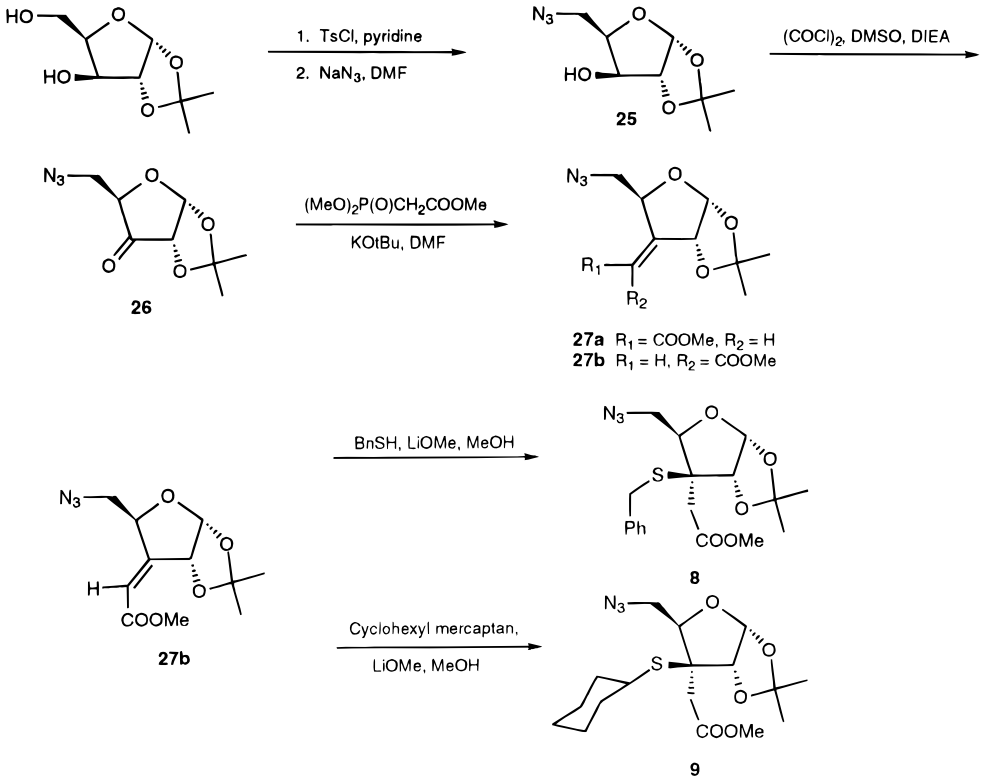
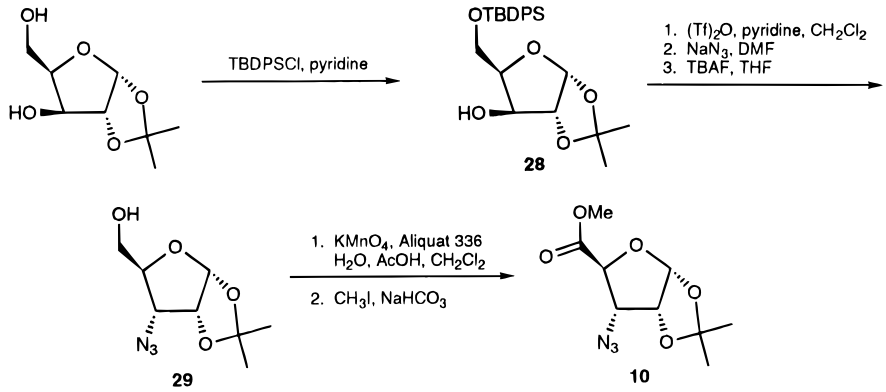
(21) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055−4058.

Scheme 4. Synthetic Route to Glycosamino Acids **8** and **9**[a]



[a] Details are included in the Experimental Section.

Scheme 5. Synthetic Route to Glycosamino Acid **10**[a]



[a] Details are included in the Experimental Section.

Experimental Section

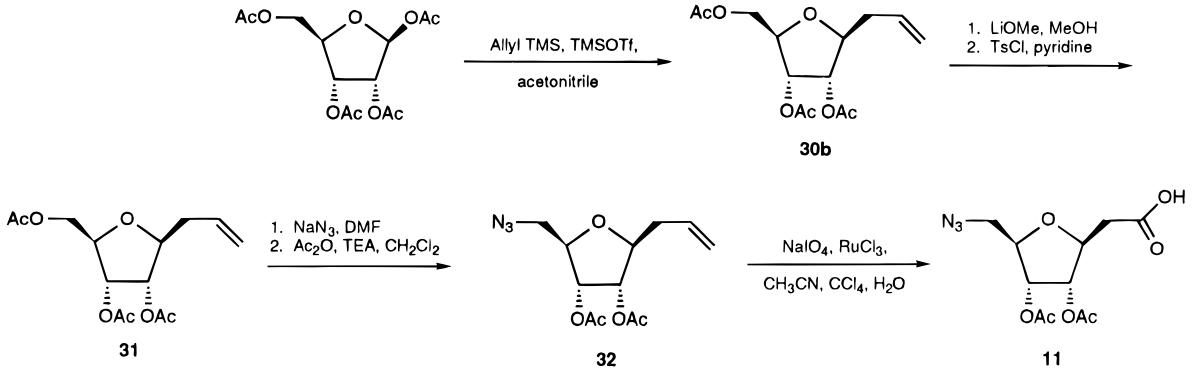
General Methods. All air-sensitive reactions were performed under an atmosphere of argon. Unless otherwise noted, materials were obtained from commercial sources and used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), triethylamine, and pyridine were distilled from calcium hydride. Other solvents were HPLC grade or commercially distilled. DOWEX 50 × 8−200 was used as a cation exchange resin. Analytical thin-layer chromatography was performed on EM Science (E. Merck) silica gel 60 F-254 and Analtech silica gel GF (250 microns). TLC staining of sugars was normally accomplished by spraying with a naphthoresorcinol stain (0.2 g of naphthoresorcinol, 100 mL of ethanol, and 4 mL of concentrated sulfuric acid). Improved detection of sugar amines or sugar amides was achieved by increasing the concentration of sulfuric acid to 5% and removing the naphthoresorcinol. Errors in R_f values are ±0.1. Chromatographic purifications were performed with EM Science 230−400 mesh silica gel or Baker silica gel (40 μm av particle diameter), unless otherwise noted. Reversed phase HPLC was performed on C18 columns (300 Å). ^{1}H and ^{13}C spectra were acquired using a Varian XL-300 or Varian UN-300 spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane ($\delta = 0$) for proton spectra and relative to internal $CDCl_3$ (77.0) for carbon spectra. ^{1}H NMR are tabulated in the following order: multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in Hertz. Infrared spectra were recorded on a Perkin Elmer 1600 Series FTIR. All mass spectra were obtained in the FAB mode.

Ester 14. Acetonitrile (60 mL) was added to a mixture of diisopropylidene **13** (1.252 g, 4.81 mmol) and methyl(triphenylphosphoranylidene)acetate (3.31 g, 9.90 mmol), and the resulting solution was heated to reflux under argon. After refluxing 14 h, the solution was concentrated to a small volume, then taken up in 40 mL EtOAc,

(22) Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303−1305.

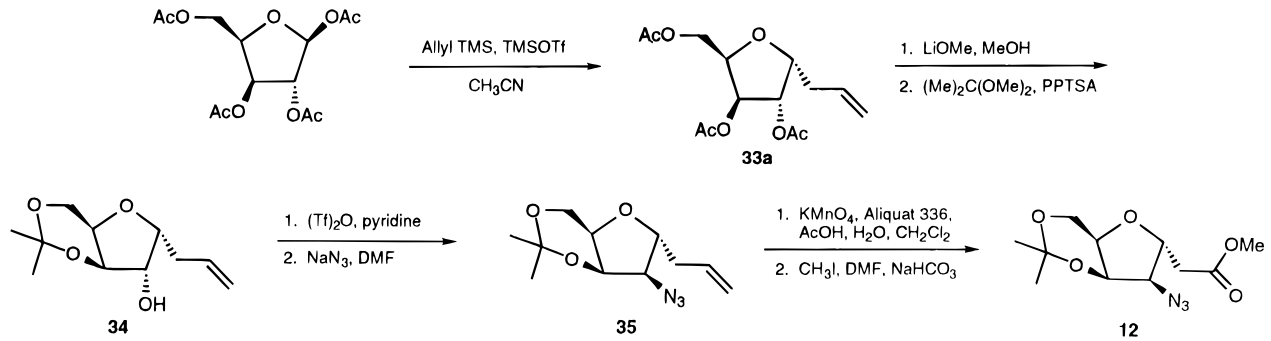
(23) During the review and revision of this manuscript, a communication appeared which reports an alternative approach to peptide-saccharide hybrids: Wessel, H. P.; Mitchell, C. M.; Lobato, C. M.; Schmid, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2712−13.

Scheme 6. Synthetic Route to Glycosamino Acid **11**[a]



[a] Details are included in the Experimental Section.

Scheme 7. Synthetic Route to Glycosamino Acid **12**[a]



[a] Details are included in the Experimental Section.

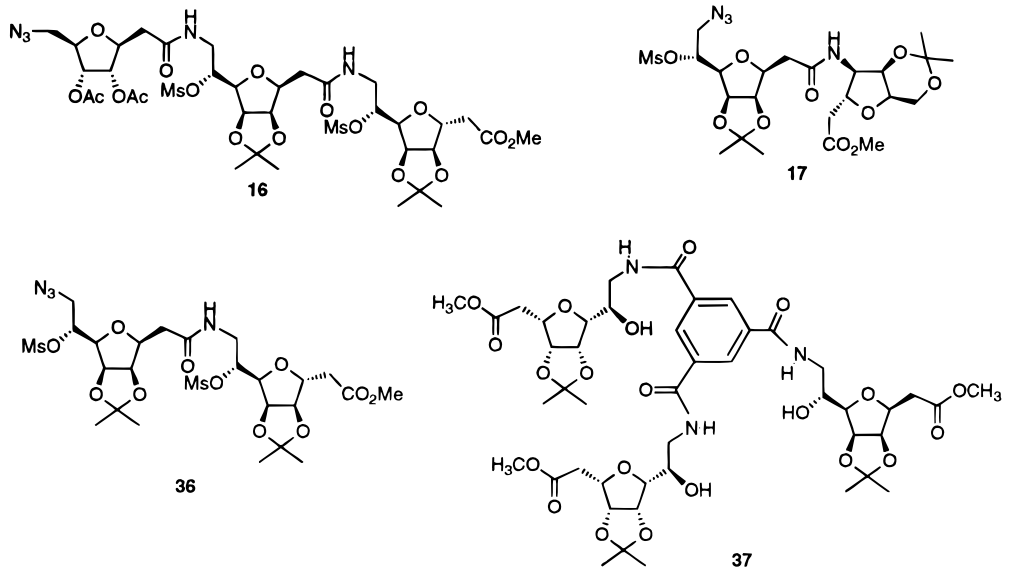


Figure 2. Four glycotides, synthesized by solution peptide coupling methods and described herein. Details are included in the Experimental Section.

and washed with water (1 × 30 mL) and brine (1 × 30 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resultant syrup was purified by flash chromatography (hexane/ethyl acetate = 4:1) to give **14** as a mixture of anomers (1.37 g, 4.32 mmol) in 90% yield. Physical data for **14** matched literature values.[12]

Diol 15. Water (280 μL) was added to a solution of the diacetonide **14** (176 mg, 0.556 mmol) in glacial acetic acid (2 mL). Stirring was commenced and proceeded for 16 h at room temperature, at which time TLC (hexane/EtOAc, 1:1) indicated the absence of **14**. The solution was concentrated under reduced pressure to a syrup, which solidified upon standing. The white solid was dissolved in CH_2Cl_2 and filtered through a plug of silica gel (CH_2Cl_2/acetone = 8:1, then 1.5:1). The solvent was removed *in vacuo* to give **15** (131 mg, 0.474 mmol) as a mixture of anomers in 85% yield. R_f = 0.2 (dichloromethane/acetone = 3:1); IR (film) 3441, 2986, 2939, 2878, 1738, 1209, 1088 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (dd, 0.5H, J = 6.1, 4.0), 4.84 (dd, 0.5H, J = 6.2, 3.7), 4.76 (dd, 0.5H, J = 6.2, 3.7), 4.63 (dd, 0.5H, J = 6.2, 1.0), 4.49 (dd, 0.5H, J = 7.5, 7.2), 3.76−4.01 (m, 3H), 3.70 (s, 3H), 3.66−3.72 (m, 1H), 3.53 (dd, 0.5H, J = 7.2, 3.8), 3.13−3.17 (m, 1H), 2.63−2.85 (m, 2H), 2.45−2.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 170.7, 113.0, 112.5, 84.6, 84.6, 81.2, 81.2, 80.8, 80.5, 79.8, 77.5, 70.2, 69.9, 64.4, 64.3, 51.9, 51.7, 36.2, 33.2, 26.1, 25.8, 24.8, 24.7; FABMS: 277 (M + H)$^+$.

Azides 1 and 2. A 0 °C solution of the diol **15** (1.29 g, 4.67 mmol) in pyridine (14 mL) was treated with methanesulfonyl chloride (390 μL, 5.04 mmol). After warming to room temperature and stirring for 18 hours, DMAP (5 mg) was added to the reaction flask. Stirring was continued for an additional 4 h, at which point only a trace of starting material remained and a small amount of the dimesylate impurity had

formed. Methanol (3 mL) was added to destroy excess methanesulfonyl chloride. The resulting solution was concentrated under reduced pressure to afford an oil, which was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were washed successively with 1 M HCl (1 × 25 mL), saturated sodium bicarbonate (1 × 20 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to an oil. Purification by flash chromatography (hexane/EtOAc = 1.3:1) provided the monomesylate (1.25 g, 3.54 mmol) as an oil in 76% yield. It is important to remove the dimesylate impurities before proceeding to the next step. Sodium azide (750 mg, 11.6 mmol) was added to a solution of the monomesylate product (779 mg, 2.20 mmol) in DMF (15 mL). The resulting suspension was stirred for 8 h in an oil bath heated to 70 °C. The suspension was cooled to room temperature, and water (30 mL) was added, producing a homogeneous solution. This solution was extracted with ether (2 × 30 mL), and the pooled organic extracts were washed with brine (1 × 30 mL) and dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography (ether/petroleum ether = 1.3:1) provided the glycosazido esters **1** and **2** (555.9 mg, 1.84 mmol) as a mixture of anomers in 84% yield. Purification on fine silica gel (EM Science, silica gel 60) was required to completely resolve the anomers. (**1**, α anomer) $R_f = 0.48$ (hexane/ethyl acetate = 1:1); IR (film) 3474 (br), 2990, 2940, 2103, 1737, 1438, 1382, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (dd, 1H, J = 6.0, 4.1), 4.67 (dd, 1H, J = 6.0, 1.0), 4.47−4.52 (m, 1H), 4.03−4.12 (m, 1H), 3.83 (dd, 1H, J = 8.3, 4.1), 3.71 (s, 3H), 3.54 (dd, 1H, J = 12.9, 2.7), 3.42 (dd, J = 12.9, 6.3), 2.75−2.80 (m, 1H), 2.44−2.58 (m, 2H), 1.51 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 113.2, 84.7, 81.0, 80.5, 79.9, 69.7, 54.1, 51.9, 36.2, 26.1, 24.7; HRMS Calcd for $C_{12}H_{19}N_3O_6$ $(M + H)^+$: 302.1352; found: 302.1349. (**2**, β anomer) $R_f = 0.5$ (hexane/ethyl acetate = 1:1); IR (film) 3481 (br), 2987, 2934, 2097, 1734, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (dd, 1H, J = 6.1, 3.7), 4.77 (dd, 1H, J = 6.1, 3.3), 4.05−4.13 (m, 1H), 3.93−3.99 (m, 1H), 3.70 (s, 3H), 3.55 (dd, 1H, J = 12.8, 3.3), 3.50 (dd, J = 8.2, 3.7), 3.42 (dd, 1H, J =12.8, 6.5), 2.68−2.85 (m, 2H), 2.63−2.68 (m, 1H), 1.48 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 112.8, 81.0, 80.9, 80.9, 77.6, 69.4, 54.4, 51.8, 33.3, 25.8, 24.7; HRMS Calcd for $C_{12}H_{19}N_3O_6$ $(M + H)^+$: 302.1352; found: 302.1349.

Azides 3 and 4. Methanesulfonyl chloride (400 μL, 5.17 mmol) was added to a 0 °C solution of **15** (374 mg, 1.35 mmol) and TEA (1.4 mL, 10.1 mmol) in CH_2Cl_2 (10 mL). The resulting suspension was stirred 48 h at room temperature, at which point methanol (1 mL) was added to destroy excess methanesulfonyl chloride. The solution was concentrated to an oil, which was dissolved in EtOAc (20 mL) and washed with saturated $NaHCO_3$ (2 × 15 mL) and brine (1 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated after addition of DMF (1 mL, to prevent bumping). The residual oil was taken up in DMF (8 mL) and treated with sodium azide (560 mg, 8.6 mmol). The resulting suspension was stirred for 14 h in an oil bath heated to 70 °C. The suspension was cooled to room temperature and dissolved in water (25 mL). This solution was extracted with ether (2 × 25 mL), and the pooled organic extracts were washed with brine (1 × 30 mL) and subsequently dried over sodium sulfate, filtered, and concentrated to an oil. Purification by flash chromatography (hexane/EtOAc = 3.1:1) gave the glycosazido esters **3** and **4** as an anomeric mixture in 66% yield (338 mg, 0.890 mmol). The anomers were resolved by repeated purifications on fine silica gel (EM Science, silica gel 60). (**3**, α anomer) $R_f = 0.65$ (hexane/EtOAc = 1:1); IR (film) 2988, 2941, 2110, 1738, 1439, 1360, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.91−4.96 (m, 1H), 4.82 (dd, 1H, J = 6.0, 3.7), 4.71 (dd, 1H, J = 6.0, 0.9) 4.49−4.53 (m, 1H), 4.14 (dd, 1H, J =7.6, 3.7), 3.89 (dd, 1H, J = 13.6, 2.6), 3.71 (s, 3H), 3.60 (dd, 1H, J =13.6, 4.3), 3.13 (s, 3H), 2.47−2.61 (m, 2H), 1.51 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 113.3, 84.8, 81.0, 80.2, 77.9, 77.7, 52.2, 52.0, 38.4, 36.0, 26.2, 24.9; HRMS Calcd for $C_{13}H_{21}N_3O_8S$ $(M + H)^+$: 380.1128; found: 380.1130. (**4**, β anomer) $R_f = 0.7$ (hexane/ethyl acetate = 1:1); IR (film) 2988, 2940, 2109, 1736, 1438, 1361, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.92−4.95 (m, 1H), 4.75−4.83 (m, 2H), 3.96−4.01 (m, 1H), 3.89 (dd, 1H, J = 13.4, 2.7), 3.82 (dd, 1H, J = 6.1, 3.5), 3.71 (s, 3H), 3.58 (dd, 1H, J = 13.4, 4.3), 3.13 (s, 3H), 2.68−2.84 (m, 2H), 1.48 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 112.9, 80.9, 80.0, 78.7, 77.9, 77.4, 52.3, 51.8, 38.4, 33.2, 25.8, 24.8; HRMS Calcd for $C_{13}H_{21}N_3O_8S$ $(M + H)^+$: 380.1128; found: 380.1130.

C-Glycoside 18. A solution of 1,2,3,4,6-penta-*O*-acetyl-β-D-mannopyranose (4.08 g, 10.5 mmol) and allyl TMS (4.93 mL, 31 mmol) in acetonitrile (40 mL) at 0 °C was treated with TMSOTf (2.24 mL, 11.6 mmol). The ice bath was removed, and the reaction was stirred 48 h and then added to 150 mL cold saturated sodium bicarbonate solution. The aqueous solution was extracted with $CHCl_3$ (2 × 75 mL). The combined organic extracts were washed with brine (1 × 100 mL), dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography (hexane/ethyl acetate = 4:1) afforded **18** (1.51 g, 4.1 mmol) as a mixture of anomers ($\alpha/\beta \approx 4$) in 39% yield. $R_f = 0.35$ (hexane/ethyl acetate = 3:1); IR (film) 1745, 1370, 1227, 1050 cm^{-1}; ^1H NMR (α anomer) (300 MHz, $CDCl_3$) δ 5.70−5.83 (m, 1H), 5.08−5.34 (m, 5H), 4.33 (dd, 1H), 4.03−4.15 (m, 2H), 3.88−3.93 (m, 1H), 2.38−2.60 (m, 2H), 2.12 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H); FABMS: 373 $(M + H)^+$.

Silyl Ether 19. A solution of lithium methoxide (20 mg) in methanol (10 mL) was added to tetraacetate **18** (654 mg, 1.76 mmol). After stirring 30 min, cation exchange resin was added to neutralize the solution. The resin was removed by filtration, and the filtrate was concentrated to an oil, which was dissolved in anhydrous pyridine (10 mL), cooled to 0 °C, and treated with *tert*-butyldiphenylsilyl chloride (1.3 mL, 5.0 mmol). After 16 h, the reaction was quenched with methanol (150 μL). The reaction flask was cooled to 0 °C, and acetic anhydride (2 mL) was added. After 20 h, water (30 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with water (1 × 50 mL), $KHSO_4$ (1 × 50 mL), sodium bicarbonate (2 × 50 mL), and brine (1 × 50 mL), then dried over sodium sulfate, filtered, and concentrated to an oil. Purification by flash chromatography (hexane/ethyl acetate = 4.5:1) afforded **19** (521 mg, 0.91 mmol) as an anomeric mixture in 52% yield. $R_f = 0.5$ (hexane/ethyl acetate = 3:1); IR (film) 2932, 2857, 1748, 1371, 1248, 1224, 1112 cm^{-1}; ^1H NMR (α anomer) (300 MHz, $CDCl_3$) δ 7.64−7.76 (m, 4H), 7.35−7.45 (m, 6H), 5.76−5.89 (m, 1H), 5.07−5.32 (m, 5H), 3.97−4.02 (m, 1H), 3.69−3.81 (m, 3H), 2.47−2.58 (m, 1H), 2.35−2.43 (m, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H), 1.08 (s, 9H); FABMS: 569 $(M + H)^+$.

Alcohol 20. A solution of the silyl ether **19** (486 mg, 0.85 mmol) in THF (6 mL) at 0 °C was treated with HF/pyridine complex (1.6 mL). The ice bath was removed, and the reaction proceeded for 16 h at room temperature, at which time it was again cooled to 0 °C and sodium bicarbonate (25 mL) was slowly added. The aqueous solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (1 × 40 mL), then dried over sodium sulfate, filtered, and concentrated to an oil. Purification by flash chromatography (hexane/ethyl acetate = 1.8:1) afforded the alcohol **20** (238 mg, 0.72 mmol) as a mixture of anomers in 84% yield. R_f = 0.4 (hexane/ethyl acetate = 1.1:1); IR (film) 3487 (br), 2943, 1745, 1372, 1227, 1048 cm^{-1}; ^1H NMR (α anomer) (300 MHz, $CDCl_3$) δ 5.81−5.94 (m, 1H), 5.10−5.32 (m, 5H), 4.02−4.08 (m, 1H), 3.63−3.70 (m, 3H), 2.54−2.65 (m, 1H), 2.39−2.48 (m, 1H), 2.26 (dd, 1H, J = 6.9, 6.4), 2.14 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H); FABMS: 331 $(M + H)^+$.

Azide 21. Methanesulfonyl chloride (85 μL, 1.1 mmol) was added to a 0 °C solution of the alcohol **20** (234 mg, 0.71 mmol) and TEA (200 μL, 1.5 mmol) in CH_2Cl_2 (5 mL). The ice bath was removed, and the reaction proceeded for 18 h at room temperature before water (10 mL) was added, followed by saturated sodium bicarbonate solution (2 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 7 mL), and the combined organic extracts were washed with brine (1 × 10 mL), dried over sodium sulfate, filtered, and concentrated to an oil, which was used directly without further purification. The mesylate was dissolved in DMF (6 mL) and added to sodium azide (310 mg, 4.8 mmol). The reaction was heated to 80 °C and proceeded for 48 h before being cooled to room temperature and added to water (12 mL). The aqueous suspension was extracted with ether (3 × 10 mL), and the combined organic extracts were washed with brine (1 × 20 mL), dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography (hexane/ethyl acetate = 3.8:1) afforded the azide **21** (158 mg, 0.44 mmol) as an anomeric mixture in 63% yield. R_f =

0.4 (hexane/ethyl acetate = 3:1); IR (film) 2101, 1746, 1370, 1247, 1223, 1045 cm^{-1}; ^1H NMR (α anomer) (300 MHz, $CDCl_3$) δ 5.72−5.88 (m, 1H), 5.08−5.30 (m, 5H), 4.01−4.07 (m, 1H), 3.81−3.88 (m, 1H), 3.41 (dd, 1H, *J* = 12.7, 7.0), 3.24 (dd, 1H, *J* = 12.7, 3.0), 2.53−2.63 (m, 1H), 2.39−2.48 (m, 1H), 2.15 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H); FABMS: 356 $(M + H)^+$.

Esters 5 and 6. A 1:1 solution (1 mL) of acetonitrile/carbon tetrachloride was added to a mixture of the C-allyl glycoside **21** (153.5 mg, 0.43 mmol) and sodium periodate (540 mg, 2.50 mmol). Water (0.75 mL) was added to the suspension, followed by catalytic ruthenium chloride trihydrate (7 mg). The reaction immediately turned brown, and soon thereafter developed a green color. After 40 min, isopropyl alcohol (1 mL) was added to the flask, and the contents were filtered through Celite, rinsing with EtOAc. The filtrate was concentrated to an oil, dissolved in EtOAc, and dried over sodium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated to an oil. The oil was dissolved in DMF (2 mL) and treated with sodium bicarbonate (120 mg) and methyl iodide (90 μL). After 20 h, water (2 mL) was added to the flask, and the reaction contents were partitioned between water (additional 4 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), and the combined organic extracts were washed with sodium bicarbonate (1 × 10 mL) and brine (1 × 8 mL), dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography (hexane/ethyl acetate = 3:1) afforded the glycosazido esters (138 mg, 0.36 mmol) as an anomeric mixture in 83% yield. The anomers were resolved by a deacetylation and subsequent acetonide formation. Lithium methoxide (7 mg, 0.18 mmol) was added to a solution of the azido ester mixture (125 mg, 0.32 mmol) in methanol (4 mL). After 30 min, cation exhange resin was added. The resin was removed by filtration, and the filtrate was concentrated. The residual oil was dissolved in dimethoxypropane (3 mL) and treated with catalytic PPTSA (3 mg). The reaction was heated on an oil bath to 45 °C and proceeded for 1 h. The solution was concentrated to an oil that was purified by flash chromatography (hexane/ethyl acetate = 3:1) to give the α-glycoside **5** (62.1 mg, 0.21 mmol), the β-glycoside **6** (6.6 mg, 0.02 mmol), and a fraction containing a mixture of the two anomers (13.5 mg, 0.04 mmol) as oils in 85% yield (70% from **21**). (**5**) R_f = 0.5 (hexane/ethyl acetate = 1:1); IR (film) 3456 (br), 2989, 2936, 2101, 1783, 1276, 1082, 1053, 865 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10−4.22 (m, 3H), 3.84−3.91 (m, 1H), 3.72 (s, 3H), 3.64−3.71 (m, 1H), 3.53 (dd, 1H, *J* = 13.2, 6.0), 3.42 (dd, 1H, *J* = 13.2, 3.0), 2.71 (dd, 1H, *J* = 15.4, 4.0), 2.55 (dd, 1H, *J* = 15.4, 8.9), 2.32 (d, 1H, *J* = 3.9), 1.50 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 110.2, 78.4, 75.6, 74.2, 70.0, 69.8, 52.0, 51.6, 38.1, 27.3, 25.1; HRMS Calcd for $C_{12}H_{19}N_3O_6$ $(M + H)^+$: 302.1352; found: 302.1347. (**6**) R_f = 0.45 (hexane/ethyl acetate = 1:1); IR (film) 3444, 2934, 2100, 1738, 1376, 1220, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19−4.26 (m, 2H), 4.02 (dd, 1H, *J* = 7.0, 5.5), 3.71 (s, 3H), 3.54−3.61 (m, 1H), 3.43−3.45 (m, 2H), 3.36 (dd, 1H, *J* = 12.2, 7.0), 2.83 (dd, 1H, *J* = 16.3, 7.6), 2.71 (dd, 1H, *J* = 16.3, 5.5), 2.33 (d, 1H, *J* = 3.6), 1.52 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 110.0, 79.8, 77.5, 75.0, 72.6, 71.1, 51.9, 51.4, 36.2, 28.2, 26.3; HRMS Calcd for $C_{12}H_{19}N_3O_6$ $(M + H)^+$: 302.1352; found: 302.1356.

Benzyl Ether 22. A solution of 1,6-β-D-anhydroglucose (1.00 g, 6.17 mmol) in DMF (20 mL) was added to a 0 °C suspension of NaH (1.1 g, 27.5 mmol, 60% dispersion in mineral oil, washed with hexanes) in DMF (10 mL) and stirred for 15 min before being treated with benzyl bromide (7 mL, 58 mmol). The ice bath was removed, and the reaction was allowed to proceed at room temperature for 16 h. Methanol (20 mL) was added, and 15 min later the reaction was partitioned between EtOAc (50 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (1 × 50 mL), and the combined organic extracts were washed successively with water (2 × 50 mL), sodium bicarbonate (2 × 50 mL), $KHSO_4$ (1 × 50 mL), and brine (1 × 50 mL). The organic solution was dried over magnesium sulfate, filtered, concentrated to an oil that was purified by flash chromatography (hexane/EtOAc = 3:1), and then recrystallized from ethanol to afford **22** (1.88 g, 4.35 mmol) as white crystals in 70% yield. R_f = 0.6 (hexane/ethyl acetate = 2:1); IR (film) 2918, 1454, 1073, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21−7.35 (m, 15H), 5.46 (d, 1H, *J* < 1), 4.51−4.64 (m, 5H), 4.45 (d, 1H, *J* = 12.1), 4.40 (d, 1H, *J* = 12.1), 3.91 (dd, 1H, *J* = 7.2, 1.0), 3.68 (dd, 1H, *J* = 7.2, 5.9), 3.58−3.60 (m, 1H), 3.34−3.35 (m, 2H); FABMS: 433 $(M + H)^+$.

C-Glycoside 23. A solution of **22** (1.088 g, 2.52 mmol) and allyl TMS (1.25 mL, 7.86 mmol) in acetonitrile (11 mL) at 0 °C was treated with TMSOTf (500 μL, 2.60 mmol). The ice bath was removed, and the reaction was stirred 16 h and then added to 50 mL cold saturated sodium bicarbonate solution. The aqueous solution was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over magnesium sulfate, filtered, and concentrated. Purification by flash chromatography (hexane/ethyl acetate, 3.8:1) afforded the α-C-glycoside **23** (459 mg, 0.97 mmol) as a white solid in 38% yield. A second product, presumably the β anomer, was isolated but not purified to homogeneity. R_f = 0.3 (hexane/ethyl acetate = 3:1); IR (film) 3250, 2899, 1453, 1096, 1067, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.37 (m, 15H), 5.70−5.83 (m, 1H), 5.07−5.14 (m, 2H), 4.61−4.96 (m, 6H), 4.01−4.09 (m, 1H), 3.48−3.84 (m, 6H), 2.46−2.51 (m, 2H), 1.77 (t, 1H, *J* = 6.4); FABMS: 475 $(M + H)^+$.

Azide 24. Methanesulfonyl chloride (100 μL, 1.29 mmol) was added to a 0 °C solution of the alcohol **23** (388 mg, 0.82 mmol) and TEA (230 μL, 1.66 mmol) in CH_2Cl_2 (5 mL). The ice bath was removed, and stirring was continued for 18 h before methanol (50 μL) was added. The solution was concentrated to a solid, dissolved in EtOAc (20 mL), and washed successively with water (1 × 20 mL), sodium bicarbonate (2 × 20 mL), and brine (1 × 20 mL). The organic solution was dried over sodium sulfate, filtered, and concentrated to an oil, which was used directly without further purification. The mesylate was dissolved in DMF (8 mL) and added to sodium azide (300 mg, 4.6 mmol). The reaction was heated to 90 °C and proceeded for 20 h before being cooled to room temperature and added to water (15 mL), causing formation of a white precipitate. The aqueous suspension was extracted with ether (3 × 15 mL), and the combined organic extracts were washed with brine (1 × 25 mL), dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography (hexane/ethyl acetate = 10:1) afforded the azide **24** (340 mg, 0.68 mmol) as a white solid in 83% yield. R_f = 0.4 (hexane/ethyl acetate = 10:1); IR (film) 2919, 2099, 1454, 1285, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21−7.31 (m, 15H), 5.69−5.82 (m, 1H), 5.04−5.11 (m, 2H), 4.51−4.92 (m, 6H), 4.03−4.11 (m, 1H), 3.53−3.89 (m, 3H), 3.34−3.43 (m, 2H), 3.25 (dd, 1H, *J* = 13.7, 5.4), 2.41−2.46 (m, 2H); FABMS: 500 $(M + H)^+$.

Ester 7. Water (1.2 mL) and acetic acid (250 μL) were added to a solution of the C-allyl glycoside **24** (116.3 mg, 0.23 mmol) in CH_2Cl_2 (1.2 mL). Aliquat 336 (15 mg) was added as a phase transfer catalyst, and the reaction vessel was cooled to 0 °C before addition of $KMnO_4$ (134 mg, 0.85 mmol) in two portions. The ice bath was removed, and the reaction proceeded 20 h at room temperature, at which point all starting material had been consumed. Sodium sulfite (150 mg) was added to quench the reaction, which was partitioned between CH_2Cl_2 (3 mL) and water (2.5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 mL), and the combined organic extracts were washed with brine (1 × 5 mL), dried over sodium sulfate, filtered, and concentrated to an oil that was dissolved in DMF (1 mL). Sodium bicarbonate (20 mg) was added to this solution, followed by methyl iodide (20 μL). After 40 h, water (1 mL) was added, and the reaction was partitioned between water (8 mL) and ether (8 mL). The aqueous layer was extracted with ether (2 × 5 mL), and the combined organic extracts were washed with brine (1 × 10 mL), dried over sodium sulfate, filtered, and concentrated to an oil. Purification by flash chromatography (hexane/EtOAc = 10:1) gave the glycosazido ester **7** (62.3 mg, 0.12 mmol) as an oil in 50% yield. R_f = 0.7 (hexane/ethyl acetate = 3:1); IR (film) 3030, 2908, 2100, 1738, 1283, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23−7.36 (m, 15H), 4.88 (d, 1H, *J* = 10.9), 4.87 (d, 1H, *J* = 11.0), 4.78 (d, 1H, *J* = 10.9), 4.62−4.69 (m, 3H), 4.57 (d, 1H, *J* = 11.0), 3.69−3.80 (m, 3H), 3.65 (s, 3H), 3.38−3.47 (m, 2H), 3.30 (dd, 1H, *J* = 13.0, 5.4), 2.78 (dd, 1H, *J* = 15.0, 5.4), 2.68 (dd, 1H, *J* = 15.0, 9.4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 138.3, 137.8, 137.7, 127.7−128.5 (m), 81.7, 79.1, 78.4, 75.3, 75.1, 73.2, 72.0, 71.4, 51.8, 51.5, 32.5; HRMS Calcd for $C_{30}H_{33}N_3O_6$ $(M + H)^+$: 532.2448; found: 532.2446.

Azide 25. Pyridine (50 mL) was added to a 0 °C mixture of 1,2-*O*-isopropylidene-α-D-xylofuranose (5.85 g, 30.8 mmol) and tosyl

chloride (6.5 g, 34.0 mmol). The reaction was allowed to warm to room temperature and stirred 16 h. Methanol (3 mL) was added to destroy excess tosyl chloride. After 15 min, the solution was concentrated to a syrup, then taken up in EtOAc (50 mL), and washed successively with water (1 × 40 mL), sodium bicarbonate (1 × 40 mL), and brine (1 × 40 mL). The organic solution was dried over sodium sulfate, filtered, and concentrated to a solid. Recrystallization from absolute ethanol provided the tosylate (5.94 g, 17.3 mmol) in 56% yield. A portion of the crystals (578 mg, 1.68 mmol) and NaN_3 (513 mg, 7.9 mmol) was combined in a flask, to which was added DMF (12 mL). The suspension was stirred 72 h in an oil bath heated to 70 °C. After cooling to room temperature, the contents of the reaction flask were added to water (25 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (1 × 30 mL) and concentrated to an oil. Purification by flash chromatography (hexane/EtOAc = 2:1) gave the azide **25** (338 mg, 1.57 mmol) as white crystals (cyclohexane was determined to be a suitable solvent for recrystallization) in 94% yield (53% from 1,2-*O*-isopropylidene-α-D-xylofuranose). $R_f = 0.3$ (hexane/ethyl acetate = 3:1); IR (film) 3404 (br), 2987, 2931, 2098, 1375, 1215, 1070, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (d, 1H, $J = 3.7$), 4.52 (dd, 1H, $J = 3.7, < 1$), 4.24−4.30 (m, 2H), 3.57−3.63 (m, 2H), 2.22 (d, 1H, $J = 5.2$), 1.51 (s, 3H), 1.32 (s, 3H); FABMS Calcd for $C_8H_{13}N_3O_4$ $(M + H)^+$: 216.0984; found: 216.0986.

Ketone 26. A solution of DMSO (185 μL, 2.6 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of oxalyl chloride (650 μL of 2.0 M solution in CH_2Cl_2, 1.3 mmol) in CH_2Cl_2 cooled to below −60 °C. The reaction flask was stirred 15 min at this temperature before a cooled solution of **25** (217 mg, 1.01 mmol) in CH_2Cl_2 (2 mL) was added. Stirring continued for 20 min with gradual warming to −40 °C, at which point DIEA (1.05 mL, 6 mmol) was added. The ice bath was removed, and the reaction proceeded for 3 h. Water (7 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (2 × 5 mL). The combined organics were washed with 1 M HCl (1 × 7 mL), saturated $NaHCO_3$ (1 × 7 mL), and brine (1 × 7 mL), then dried over sodium sulfate, filtered, and concentrated to an oil. Purification by flash chromatography (hexane/EtOAc = 4:1) afforded the ketone **26** (122.8 mg, 0.58 mmol) as a colorless oil in 57% yield. $R_f = 0.25$ (hexane/ethyl acetate = 2:1); IR (film) 3400 (small, br), 2992, 2110, 1775, 1377, 1220, 1158, 1081 cm^{-1}; ^1H NMR of **26** showed a mixture of two products, presumably the ketone and the hydrate. HRMS Calcd for $C_8H_{11}N_3O_4$ $(M + H)^+$: 214.0828; found: 214.0827.

Esters 27a and 27b. A solution of the ketone **26** (36.6 mg, 0.17 mmol) in DMF (1 mL) was added to a 0 °C solution of trimethyl phosphonoacetate (100 μL, 0.62 mmol) and potassium *tert*-butoxide (20.2 mg, 0.18 mmol) in DMF (0.5 mL). The reaction was warmed to room temperature and stirred 2 h. Water (3 mL) was added, and the aqueous solution was extracted with ether (2 × 3 mL). The combined organic extracts were washed with water (1 × 5 mL), $KHSO_4$ (1 × 5 mL), and brine (1 × 5 mL). After drying over sodium sulfate, the organic solution was filtered and concentrated. Purification by flash chromatography (hexane/EtOAc = 5:1) afforded **27a** (4.2 mg, 0.015 mmol) and **27b** (23.9 mg, 0.088 mmol) as a mixture of cis-trans isomers in 61% yield. (**27a**) $R_f = 0.75$ (hexane/ethyl acetate = 2.5:1); IR (film) 2994, 2953, 2112, 1717, 1371, 1227, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (dd, 1H, $J = 2.0, 2.0$), 5.98 (d, 1H, $J = 4.7$), 5.63−5.66 (m, 1H), 5.11−5.14 (m, 1H), 3.75 (s, 3H), 3.73 (dd, 1H, $J = 12.7, 3.0$), 3.64 (dd, 1H, $J = 12.7, 2.9$), 1.43 (s, 3H), 1.39 (s, 3H); HRMS Calcd for $C_{11}H_{15}N_3O_5$ $(M + H)^+$: 270.1090; found: 270.1091. Upon irradiation at δ 5.13 (H2), an NOE was observed at δ 6.20 (vinylic proton). Upon irradiation at δ 5.64 (H4), an NOE was observed at δ 1.39 (isopropylidene CH_3). (**27b**) $R_f = 0.5$ (hexane/ethyl acetate = 2.5:1); IR (film) 2991, 2954, 2107, 1727, 1436, 1374, 1216, 1069, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (d, 1H, $J = 4.1$), 5.87 (dd, 1H, $J = 2.0, 1.5$), 5.74−5.76 (m, 1H), 4.97−5.02 (m, 1H), 3.80 (s, 3H), 3.65 (dd, 1H, $J = 13.2, 3.7$), 3.40 (dd, 1H, $J = 13.2, 4.3$), 1.50 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 155.6, 117.2, 113.5, 105.5, 79.2, 78.6, 53.2, 52.4, 27.8, 27.6; HRMS Calcd for $C_{11}H_{15}N_3O_5$ $(M + H)^+$: 270.1090; found: 270.1087. Upon irradiation at δ 5.00 (H4), an NOE was observed at δ 5.87 (vinylic proton).

Thioether 8. Lithium methoxide (3.0 mg, 0.08 mmol) was added to a solution of benzyl mercaptan (20 μL, 0.017 mmol) and the α,β-unsaturated ester **27b** (3.1 mg, 0.012 mmol) in methanol (0.7 mL). After stirring 5 min, cation exchange resin was added to neutralize the solution, which was filtered and concentrated. Purification by flash chromatography (hexane, then hexane/EtOAc = 2:1) afforded **8** (4.7 mg, 0.012 mmol) as a colorless oil in quantitative yield. $R_f = 0.6$ (hexane/EtOAc = 3:1); IR (film) 2976, 2965, 2359, 2099, 1738, 1201, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.33 (m, 5H), 5.85 (d, 1H, $J = 3.3$), 4.83 (d, 1H, $J = 3.3$) 4.32 (dd, 1H, $J = 6.8, 5.0$), 3.92 (s, 2H), 3.73 (s, 3H), 3.59−3.62 (m, 2H), 2.98 (d, 1H, $J = 15.6$), 2.85 (d, 1H, $J = 15.6$), 1.52 (s, 3H), 1.32 (s, 3H); HRMS Calcd for $C_{18}H_{23}N_3O_5S$ $(M + H)^+$: 394.1437; found: 394.1428. Upon irradiation of the benzylic protons (δ 3.92), an NOE was observed at the C-2 hydrogen (δ 4.83).

Thioether 9. Cyclohexyl mercaptan (20 μL, 0.16 mmol) was added to a solution of lithium methoxide (1.5 mg, 0.04 mmol) and the α,β-unsaturated ester **27b** (5.6 mg, 0.021 mmol) in methanol (0.7 mL). After stirring 15 min, cation exchange resin was added to neutralize the solution, which was filtered and concentrated. Purification by flash chromatography (hexane/EtOAc = 6:1) afforded the Michael adduct **9** (7.3 mg, 0.019 mmol) as a colorless oil in 91% yield. Michael addition of cyclohexyl mercaptan to **27a** also gave **9** as the only product. $R_f = 0.7$ (hexane/EtOAc = 2.5:1); IR (film) 2987, 2932, 2853, 2099, 1740, 1437, 1373, 1200, 1166, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (d, 1H, $J = 3.4$), 4.82 (d, 1H, $J = 3.4$), 4.37 (dd, 1H, $J = 6.9, 4.8$), 3.72 (s, 3H), 3.54−3.57 (m, 2H), 2.79−2.93 (m, 3H), 1.89−1.99 (m, 2H), 1.71−1.76 (m, 2H), 1.19−1.59 (m, 6H), 1.51 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 112.4, 104.4, 86.1, 82.6, 58.3, 51.8, 51.0, 41.6, 37.8, 36.5, 36.1, 26.8, 26.7, 26.3, 26.3, 25.2; HRMS Calcd for $C_{17}H_{27}N_3O_5S$ $(M + H)^+$: 386.1750; found: 386.1747. Upon irradiation at δ 4.37 (H4), NOE's were observed at δ 2.87 (protons α to ester) and 1.51 (isopropylidene CH_3). Upon irradiation at δ 4.82 (H2), an NOE was observed at 2.90 (methine proton of cyclohexyl ring).

Silyl Ether 28. Under an argon atmosphere, *tert*-butyldiphenylchlorosilane (1.23 mL, 4.74 mmol) was added to a 0 °C solution of 1,2-*O*-isopropylidene-α-D-xylofuranose (601 mg, 3.16 mmol) in pyridine (7 mL). The reaction vessel was warmed to room temperature and stirring proceeded for 18 h before methanol (100 μL) was added to destroy residual TBDPSCl. Water (20 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were concentrated to a volume of 15 mL and washed with brine (1 × 15 mL), dried over sodium sulfate, and concentrated under reduced pressure to an oil. Purification by flash chromatography (hexane/EtOAc = 7:1) gave the silyl ether **28** (1.326 g, 3.09 mmol) as a colorless oil in 98% yield. $R_f = 0.75$ (hexane/ethyl acetate = 2:1); IR (film) 3460 (br), 2932, 1428, 1374, 1216, 1113, 1075, 1014 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.73 (m, 4H), 7.38−7.47 (m, 6H), 6.01 (d, 1H, $J = 3.7$), 4.55 (dd, 1H, $J = 3.7, < 1$), 4.37 (dd, 1H, $J < 1$), 4.10−4.14 (m, 3H), 4.06 (d, 1H, $J = 3.1$), 1.47 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H); HRMS Calcd for $C_{24}H_{32}SiO_5$ $(M + H)^+$: 429.2097; found: 429.2092.

Azide 29. Pyridine (270 μL, 3.0 mmol) was added to a −10 °C solution of the alcohol **28** (751 mg, 1.75 mmol) in CH_2Cl_2. After stirring the solution briefly, trifluoromethanesulfonic anhydride (324 μL, 1.93 mmol) was added, and the reaction was allowed to warm gradually to room temperature. Monitoring of the reaction by TLC indicated that it had not gone to completion after 8 h, at which time additional pyridine (100 μL) and $(Tf)_2O$ (50 μL) were added. Within an hour, all starting material was consumed, and the reaction contents were added to cold water (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organics were washed with brine (1 × 40 mL), dried over sodium sulfate, and concentrated. Traces of pyridine and pyridinium salts were separated from the desired triflate product by flash chromatography (hexane/EtOAc = 3:1) through a short plug of silica gel, yielding the crude triflate, which was used directly in the next step. The triflate was dissolved in DMF (18 mL), to which NaN_3 (500 mg, 7.7 mmol) was added. After stirring 18 h at room temperature, all starting material was consumed, leaving the desired azide product and a significant side-product, presumably resulting from triflate elimination. Water (60 mL) was added to the reaction, and the aqueous solution was extracted with ether (3 × 50 mL). The combined ether extracts were washed (1 × 100 mL) with

brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude azide as an oil, which was used directly without further purification. The crude azide was dissolved in THF (3 mL) and added to a solution of TBAF (3 mL of 1.0 M solution in THF, 3 mmol) in THF (5 mL). After 18 h, the solution was concentrated to an oil. Water (50 mL) was added, and the aqueous solution was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (1 × 100 mL) and brine (1 × 100 mL) before drying over magnesium sulfate. Filtration, followed by concentration *in vacuo*, produced an oil that was purified by flash chromatography (hexane/EtOAc = 3:1) to give the alcohol **29** (260.2 mg, 1.21 mmol) in 69% yield from **28**. $R_f = 0.5$ (hexane/ethyl acetate = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, 1H, $J = 5.4$), 5.29−5.32 (m, 1H), 5.19−5.20 (m, 1H), 4.17−4.20 (m, 3H), 1.77 (t, 1H, $J = 6.5$), 1.47 (s, 3H), 1.45 (s, 3H).

Ester 10. Water (0.7 mL) and acetic acid (125 μL) were added to a solution of the primary alcohol **29** (29.8 mg, 0.138 μmol) in CH_2Cl_2 (1.2 mL). Aliquat 336 (7 mg) was added as a phase transfer catalyst, and the reaction vessel was cooled to 0 °C before addition of $KMnO_4$ (75 mg, 0.48 mmol). The ice bath was removed, and the reaction proceeded 24 h at room temperature, at which point all starting material had been consumed. Sodium sulfite (75 mg) was added to quench the reaction, which was concentrated to an oil and dissolved in DMF (1 mL). Sodium bicarbonate (10 mg) was added to this solution, followed by methyl iodide (10 μL). After 40 h, water (1 mL) was added, and the reaction was partitioned between water (5 mL) and ether (5 mL). The aqueous layer was extracted with ether (2 × 5 mL), and the combined organic extracts were washed with brine (1 × 10 mL), dried over sodium sulfate, filtered, and concentrated to an oil. Purification by flash chromatography (hexane/EtOAc = 4:1) afforded the glycosazido ester **10** (3.2 mg, 13.2 μmol) as an oil in 10% yield. R_f = 0.6 (hexane/ethyl acetate = 2:1); IR (film) 2110, 1748, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (d, 1H, $J = 3.4$), 4.75 (dd, 1H, J = 4.4, 3.4), 4.57 (d, 1H, $J = 9.6$), 3.86 (s, 3H), 3.70 (dd, 1H, $J = 9.6$, 4.4), 1.58 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 113.8, 104.7, 79.9, 75.9, 63.3, 52.9, 26.5, 26.4; HRMS Calcd for $C_9H_{13}N_3O_5$ $(M + H)^+$: 244.0933; found: 244.0934.

C-Glycosides 30a and 30b. A solution of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (2.65 g, 8.3 mmol) and allyltrimethylsilane (4.0 mL, 24.1 mmol) in acetonitrile (25 mL) at 0 °C was treated with TMSOTf (2.22 g, 10 mmol). The ice bath was removed, and the solution was stirred for 6 h and then added to cold sodium bicarbonate solution (150 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried over magnesium sulfate, filtered, and concentrated. Purification by flash chromatography (hexane/ethyl acetate = 3:1) afforded the α anomer **30a** (512 mg, 1.70 mmol) as a colorless oil and the β anomer **30b** (1.663 g, 5.54 mmol) as a white solid that was recrystallized from EtOAc. The reaction proceeded with a cumulative 87% yield and a ratio of β to α anomers of approximately 3:1. (**30b**) $R_f = 0.6$ (hexane/ethyl acetate = 2:1); IR (film) 2978, 1741, 1368, 1260, 1228, 1115 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70−5.84 (m, 1H), 5.06−5.24 (m, 5H), 4.14 (dd, 1H, $J = 13.3$, 1.9), 3.71 (dd, 1H, J =13.3, 1.6), 3.53−3.58 (m, 1H), 2.41−2.51 (m, 1H), 2.18−2.29 (m, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H); FABMS 301 $(M + H)^+$.

Tosylate 31. A solution of lithium methoxide (50 mg) in methanol (5 mL) was added to a solution of **30b** (979 mg, 3.26 mmol) in methanol (10 mL). After stirring 3 h, the reaction was neutralized by the addition of cation exchange resin. Filtration, followed by concentration, afforded the sugar triol as white crystals (556 mg, 3.19 mmol) in 98% yield. A portion of the crystals (556 mg, 3.19 mmol) were dissolved in a solution of tosyl chloride (651 mg, 3.41 mmol) in pyridine (10 mL). After stirring 48 h at room temperature, the reaction contents were added to water (20 mL), and the aqueous solution was extracted wtih CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with sodium bicarbonate (1 × 20 mL), $KHSO_4$ solution (1 × 20 mL), and brine (1 × 20 mL). The organic solution was concentrated and recrystallized (153 mg) from dichloromethane. The filtrate was concentrated and purified by flash chromatography (hexane/ethyl acetate = 2:1) to afford the tosylate **31** (415.3 mg, 1.27 mmol) as a syrup which crystallized almost immediately. The combined crystals (568.3 mg, 1.73 mmol) totaled a 53% yield. $R_f = 0.2$ (hexane/ethyl acetate = 1.5:1); IR (film) 3474, 1359, 1190, 1176, 1096, 855 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.88 (m, 2H), 7.37 (d, 2H, $J = 8.0$), 5.70−5.84 (m, 1H), 5.07−5.17 (m, 2H), 4.52 (ddd, 1H, J = 3.4, 2.5, <1), 4.08 (dd, 1H, J = 12.6, 2.5), 3.91−3.95 (m, 1H), 3.83−3.87 (m, 1H), 3.51 (dd, 1H, J = 12.6, < 1), 3.31 (ddd, 1H, J = 7.5, 6.9, < 1), 3.12 (d, 1H, $J = 6.9$), 2.95 (d, 1H, $J = 7.8$), 2.46−2.57 (m, 1H), 2.46 (s, 3H), 2.32−2.41 (m, 1H); FABMS 329 $(M + H)^+$.

Azide 32. The tosylate **31** (415.3 mg, 1.27 mmol) was dissolved in DMF (10 mL). Sodium azide (530 mg, 8.12 mmol) was added to the solution, along with a catalytic amount of tetrabutylammonium iodide (10 mg). The reaction was heated to 110 °C and stirred for 4 days, by which time conversion of the starting material to product appeared to be approximately 50%. The suspension was cooled and added to 40 mL of water, which was extracted with ether (2 × 40 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over magnesium sulfate, filtered, and concentrated. The residual oil was directly acetylated in CH_2Cl_2 by treatment with acetic anhydride (1 mL), triethylamine (0.5 mL), and catalytic DMAP (5 mg). After stirring 24 h at room temperature, sodium bicarbonate (15 mL) was added. The organic layer was washed with brine (1 × 20 mL), dried over sodium sulfate, filtered, and concentrated to an oil. Purification by flash chromatography (hexane/ethyl acetate = 5:1) afforded **32** (105.5 mg, 0.37 mmol) as an oil in 29% yield from the tosylate (68% based on unreacted starting material). $R_f = 0.6$ (hexane/ethyl acetate = 3:1); IR (film) 2922, 2852, 2108, 1743, 1375, 1226, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70−5.84 (m, 1H), 5.09−5.15 (m, 2H), 4.70−4.74 (m, 2H), 3.98 (dd, 1H, J = 3.7, 3.3), 3.87−3.88 (m, 2H), 3.77−3.83 (m, 1H), 2.41−2.51 (m, 1H), 2.19−2.28 (m, 1H), 2.14 (s, 3H), 2.12 (s, 3H); FABMS 284 $(M + H)^+$.

Acid 11. A 1:1 solution (1 mL) of acetonitrile/carbon tetrachloride was added to a mixture of the C-allyl glycoside **32** (105.5 mg, 0.37 mmol) and sodium periodate (389 mg, 1.80 mmol). Water (0.75 mL) was added to the suspension, followed by catalytic ruthenium chloride trihydrate (6 mg). The reaction immediately turned brown, and soon thereafter the suspension developed a green color. After 15 min, isopropyl alcohol (1 mL) was added to the flask, and the contents were filtered through Celite, rinsing with EtOAc. The filtrate was concentrated to an oil and purified by flash chromatography (hexane/EtOAc = 1.1:1, then hexane/EtOAc/AcOH = 50:50:1) to afford the glycosazido acid **11** (104.6 mg, 0.35 mmol) as an oil in 93% yield. $R_f = 0.2$ (hexane/ethyl acetate/acetic acid = 50:50:1); IR (film) 3200 (br), 2940, 2112, 1747, 1732, 1714, 1378, 1242, 1092, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (dd, 1H, $J = 3.9$, 2.0), 4.71−4.74 (m, 1H), 4.25−4.30 (m, 1H), 4.00 (dd, 1H, J = 3.9, 3.4), 3.90−3.92 (m, 2H), 2.73 (dd, 1H, J = 16.1, 8.5), 2.54 (dd, 1H, J = 16.1, 4.7), 2.14 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 170.0, 169.9, 70.0, 68.6, 67.4, 65.2, 57.3, 35.4, 21.0, 20.7; HRMS Calcd for $C_{11}H_{15}O_7N_3$ $(M + H)^+$: 302.0988; found: 302.0984.

C-Glycosides 33a and 33b. A solution of 1,2,3,4-tetra-*O*-acetyl-β-D-xylofuranose (4.34 g, 13.6 mmol) and allyltrimethylsilane (6.5 mL, 4.1 mmol) in acetonitrile (50 mL) at 0 °C was treated with TMSOTf (2.90 mL, 1.50 mmol). The ice bath was removed, and the solution was stirred 24 h and then added to cold sodium bicarbonate solution (150 mL). The aqueous solution was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (1 × 125 mL) and dried over magnesium sulfate. The drying agent was removed by filtration and the solution was concentrated to an oil. Purification by flash chromatography (hexane/ethyl acetate = 5.5:1) afforded the α anomer **33a** (1.36 g, 4.5 mmol), the β anomer **33b** (253 mg, 0.8 mmol), and a fraction containing a mixture of the two anomers (1.988 g, 6.6 mmol) which were separated by additional silica gel chromatography. The C-glycosylation reaction proceeded in 88% cumulative yield with a ratio of α to β anomers of approximately 3:1. (**33a**) $R_f = 0.5$ (hexane/ethyl acetate = 3:1); IR (film) 2947, 2862, 1754, 1371, 1246, 1223, 1100, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75−5.88 (m, 1H), 4.83−5.20 (m, 5H), 4.11 (dd, 1H, J = 10.8, 5.5), 3.40−3.46 (m, 1H), 3.25 (dd, 1H, J = 10.8, 10.4), 2.18−2.27 (m, 2H), 2.03 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); HRMS Calcd for $C_{14}H_{20}O_7$ $(M + H)^+$: 301.1287; found: 301.1292.

Isopropylidene 34. A solution of **33a** (171 mg, 0.57 mmol) in methanol (2 mL) was added to a solution of LiOMe (10 mg, 0.27 mmol) in methanol (1 mL). The solution was stirred 30 min at room temperature. Cation exchange resin was added to neutralize the

solution, which was filtered and concentrated. The residual oil was dissolved in dimethoxypropane (3 mL), to which was added catalytic PPTSA (3 mg). After stirring 24 h at 50 °C, the solution was concentrated and then treated with a solution of LiOMe (10 mg) in methanol (5 mL). After stirring 5 min, the solution was filtered through cation exchange resin and concentrated to an oil. Purification by flash chromatography afforded the acetonide **34** (88.7 mg, 0.41 mmol) as an oil in 73% yield. $R_f = 0.5$ (hexane/ethyl acetate = 1.1:1); IR (film) 3448 (br), 2985, 2877, 1230, 1085, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80−5.94 (m, 1H), 5.08−5.18 (m, 2H), 3.92−4.07 (m, 2H), 3.41−3.56 (m, 2H), 3.09−3.16 (m, 2H), 2.48−2.56 (m, 1H), 2.32 (d, 1H, $J = 3.9$), 2.22−2.32 (m, 1H), 1.42 (s, 3H), 1.41 (s, 3H); HRMS Calcd for $C_{11}H_{18}O_4$ $(M + H)^+$: 215.1283; found: 215.1285.

Azide 35. Pyridine (74 μL, 0.91 mmol) was added to a solution of the alcohol **34** (88.7 mg, 0.41 mmol) in CH_2Cl_2 (2 mL). The solution was cooled to −30 °C and then treated with $(Tf)_2O$ (97.4 μL, 0.58 mmol). The reaction was allowed to proceed at 0 °C for 1 h. Cold water (3 mL) was added, the layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (1 × 3 mL). The combined organic extracts were washed with water (1 × 4 mL), cold 3 M HCl (1 × 4 mL), and brine (1 × 4 mL), then dried over sodium sulfate, filtered, and concentrated to a yellow oil. Without further purification, the crude triflate was dissolved in DMF (3 mL) and treated with NaN_3 (160 mg, 2.5 mmol). The resulting suspension was stirred 4 h at room temperature. Water (5 mL) was added, and the aqueous solution was extracted with ether (2 × 5 mL). The ether extracts were washed with brine (1 × 10 mL), dried over sodium sulfate, filtered, and concentrated to a yellow oil. Purification by flash chromatography (hexane, then hexane/EtOAc = 8:1) afforded the azide **35** (53.6 mg, 0.22 mmol) as a pale yellow oil in 54% yield which crystallized upon standing. R_f = 0.8 (hexane/ethyl acetate = 3:1); IR (film) 2986, 2906, 2103, 1229, 1159, 1103, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81−5.96 (m, 1H), 5.09−5.19 (m, 2H), 4.14−4.16 (m, 1H), 3.98 (dd, 1H, $J = 12.9$, 1.6), 3.52−3.60 (m, 2H), 3.45−3.53 (m, 2H), 2.49−2.58 (m, 1H), 2.39−2.49 (m, 1H), 1.48 (s, 3H), 1.45 (s, 3H); FABMS Calcd for $C_{11}H_{17}N_3O_3$ $(M + H)^+$: 240.1348; found: 240.1346.

Ester 12. Water (0.5 mL) and acetic acid (100 μL) were added to a solution of the C-allyl glycoside **35** (18.0 mg, 75 μmol) in CH_2Cl_2 (0.5 mL). Aliquat 336 (2 mg) was added as a phase transfer catalyst, and the reaction vessel was cooled to 0 °C before addition of $KMnO_4$ (25 mg). The reaction proceeded 24 h at room temperature. Sodium sulfite (25 mg) was added to quench the reaction, which was then partitioned between CH_2Cl_2 (3 mL) and water (2.5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 mL), and the combined organic extracts were washed with brine (1 × 5 mL) and dried over sodium sulfate. Filtration, followed by concentration, gave an oil that could not be purified to homogeneity by flash chromatography and instead was esterified directly. The oil was dissolved in DMF (1 mL). Sodium bicarbonate (20 mg) was added to the solution, followed by methyl iodide (20 μL). The reaction was stirred 24 h at room temperature and then concentrated to an oil. Water (2 mL) was added, and the aqueous solution was extracted with ether (2 × 2.5 mL). The ether extracts were washed with brine (1 × 3 mL), dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) gave the glycosazido ester **12** (8.3 mg, 31 μmol) in 41% yield. $R_f = 0.6$ (hexane/ethyl acetate = 1:1); IR (film) 2986, 2901, 2105, 1740, 1229, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.16−4.18 (m, 1H), 3.91−3.98 (m, 2H), 3.71 (s, 3H), 3.63−3.70 (m, 2H), 3.57 (dd, 1H, $J = 12.8$, 1.8), 2.77 (dd, 1H, $J = 16.0$, 2.8), 2.58 (dd, 1H, $J = 16.0$, 9.4), 1.49 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 110.8, 79.4, 76.8, 73.5, 68.2, 58.9, 51.9, 37.7, 26.6, 26.3; HRMS Calcd for $C_{11}H_{17}N_3O_5$ $(M + H)^+$: 272.1246; found: 272.1241.

General Procedure for Hydrogenation of Azides. Ethyl acetate (approximately 0.5 mL + 1 mL per 100 mg azide) was added to a flask containing 10% palladium on activated carbon. The flask was evacuated and flushed with hydrogen several times. A solution of the azide (2−10 mg of azide per milligram of catalyst) was added to the flask, which was again flushed several times with hydrogen and stirred 4−24 h under a hydrogen atmosphere. The suspension was then filtered through Celite and rinsed with ethyl acetate, and the filtrate was concentrated *in vacuo* and used without further purification.

General Procedure for Ester Saponification. A 0.5 M solution of sodium hydroxide (250 μL per 100 mmol of ester) was added to a solution of the glycosazido ester in methanol (approximately 400 μL per 100 mmol of ester). The reaction was followed by TLC, and, upon completion, cation exchange resin was added to neutralize the solution. After filtration, the filtrate was concentrated and used without further purification.

Diglycotide 36. The glycosazido ester **3** was hydrogenated according to the general procedure to furnish the amine **3n**, while the β-glycoside **4** was saponified according to the general procedure to give **4c**. A solution of the amine **3n** (33.8 mg, 0.09 mmol) in dichloromethane (0.5 mL) was added to a mixture of **4c** (36.0 mg, 0.10 mmol), TEA (41 μL, 0.30 mmol), and EDCI (24 mg, 0.12 mmol) in dichloromethane (1.0 mL). After stirring for 24 h, the solution was concentrated, taken up in chloroform (5 mL), and extracted with water (1 × 5 mL) and brine (1 × 3 mL). After drying over sodium sulfate, the drying agent was removed by filtration, and the solution was concentrated to an oil. Purification by flash chromatography (EtOAc/hexane = 1.8:1) afforded the diglycotide **36** (19.8 mg, 0.03 mmol) as a clear oil in 28% yield. $R_f = 0.75$ (dichloromethane/acetone = 3:1); IR (film) 3389, 2937, 2109, 1735, 1674, 1538, 1354, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, 1H, $J = 6.3$, 5.9), 4.92−4.98 (m, 2H), 4.76−4.81 (m, 3H), 4.66 (dd, 1H, $J = 6.0$, 1.0), 4.49 (dd, 1H, J = 7.4, 7.1), 3.87−4.07 (m, 4H), 3.81 (dd, 1H, $J = 7.4$, 3.0), 3.71 (s, 3H), 3.62 (dd, 1H, $J = 13.8$, 5.0), 3.39−3.48 (m, 1H), 3.12 (s, 3H), 3.12 (s, 3H), 2.67 (d, 2H, $J = 6.7$), 2.52 (d, 2H, $J = 7.3$), 1.51 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); HRMS Calcd for $C_{25}H_{40}N_4O_{15}S_2$ $(M + H)^+$: 701.2010; found: 701.2004.

Triglycotide 16. The diglycotide **36** was hydrogenated according to the general procedure to afford amine **36n**. A solution of **36n** (8.0 mg, 12 μmol) in dichloromethane (0.5 mL) was added to a mixture of the glycosazido acid **11** (9.0 mg, 30 μmol), TEA (10 mg, 100 μmol), and EDCI (4.5 mg, 23 μmol) in dichloromethane (1 mL). After stirring for 24 h, the solution was concentrated, taken up in chloroform (3 mL), and extracted with water (1 × 3 mL) and brine (1 × 3 mL). The organic extracts were dried over sodium sulfate, then filtered, and concentrated to an oil. Purification by flash chromatography (dichloromethane/acetone = 3.8:1) afforded the triglycotide **16** (5.0 mg, 5.2 μmol) as a clear oil in 44% yield. $R_f = 0.2$ (dichloromethane/acetone = 3:1); IR (film) 3378, 2934, 2109, 1738, 1682, 1651, 1538, 1353, 1227, 1175, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (dd, 1H, $J = 6.4$, 5.6), 6.45 (dd, 1H, $J = 6.1$, 5.7), 4.93−5.04 (m, 3H), 4.67−4.79 (m, 6H), 4.49 (dd, 1H, $J = 7.5$, 6.6), 4.27−4.32 (m, 1H), 3.86−4.12 (m, 6H), 3.71 (s, 3H), 3.60−3.70 (m, 2H), 3.33−3.42 (m, 1H), 3.12 (s, 3H), 3.11 (s, 3H), 2.47−2.77 (m, 5H), 2.36 (dd, 1H, $J = 15.4$, 4.0), 2.14 (s, 3H), 2.12 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); HRMS Calcd for $C_{36}H_{55}N_5O_{21}S_2$ $(M + H)^+$: 958.2909; found: 958.2914.

Diglycotide 17. The glycosazido ester **12** (3.0 mg, 11 μmol) was hydrogenated according to the general procedure to furnish the secondary amine **12n**. Without further purification, a solution of **12n** in dichloromethane (0.5 mL) was added to a mixture of excess **4c** (6.0 mg, 16 μmol), TEA (10 μL, 70 μmol), and EDCI (3.9 mg, 21 μmol) in dichloromethane (0.5 mL). After stirring for 48 h, the solution was concentrated, taken up in chloroform (3 mL), and extracted with water (1 × 3 mL) and brine (1 × 3 mL). The organic extracts were dried over sodium sulfate, then filtered, and concentrated to an oil. Purification by flash chromatography (EtOAc/hexane = 2.2:1) afforded the diglycotide **17** (4.4 mg, 7.4 μmol) as a clear oil in 67% yield from the glycosazido ester. $R_f = 0.75$ (dichloromethane/acetone = 3:1); IR (film) 3388 (br), 2990, 2931, 2109, 1738, 1682, 1651, 1538, 1360, 1231, 1176, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, 1H, $J = 7.8$), 4.93−4.98 (m, 1H), 4.75−4.79 (m, 2H), 4.55−4.60 (m, 1H), 3.87−4.04 (m, 4H), 3.84 (dd, 1H, $J = 7.6$, 3.0), 3.72 (s, 3H), 3.54−3.68 (m, 3H), 3.29 (dd, 1H, $J = 9.4$, 9.4), 3.13 (s, 3H), 2.78 (dd, 1H, $J = 15.6$, 2.8), 2.65 (d, 2H, $J = 6.8$), 2.54 (d, 2H, $J = 15.6$, 9.4), 1.51 (s, 3H), 1.43 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.8, 113.0, 110.4, 81.0, 80.0, 78.9, 78.7, 77.9, 77.2, 76.9, 74.1, 69.6, 52.2, 52.0, 48.6, 38.5, 37.9, 36.1, 26.6, 26.5, 25.9, 24.9; HRMS Calcd for $C_{23}H_{36}N_4O_{12}S$ $(M + H)^+$: 593.2129; found: 593.2113.

Template-Anchored Triglycotide 37. Glycosazido ester **2** (28.1 mg, 0.093 mmol) was hydrogenated by the general procedure, and the

resultant amine was dissolved in dichloromethane (1 mL) and triethylamine (30 μL) and added to 1,3,5-benzenetricarbonyl trichloride. After 10 min at 25 °C, the solution was concentrated to an oil and dissolved in chloroform. The organic phase was washed with aqueous $KHSO_4$ and brine, dried over sodium sulfate, and concentrated to a crude oil. Further purification was not pursued since this was a model for library synthesis. IR (film): 3384 (br), 2940, 1739, 1662, 1540, 1438, 1207, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 3H), 7.68 (br t, 3H, $J = 5.9$), 4.88 (dd, 3H, $J = 5.6, 3.2$), 4.76 (dd, 3H, $J = 5.6, 4.2$), 4.2 (m, 6H), 4.0 (m, 3H), 3.85 (m, 3H), 3.70 (s, 9H), 3.56 (m, 6H), 2.8 (m, 6H), 1.49 (s, 9H), 1.32 (s, 9H); HRMS Calcd for $C_{45}H_{63}N_3O_{21}$ $(M + H)^+$: 982.4032, found: 982.4035.

Synthesis of a Template-Directed Library. A mixture of glycosazido esters **5** (2.7 mg, 9.0 μmol), **4** (4.2 mg, 11.1 μmol), and **8** (2.0 mg, 5.1 μmol) was hydrogenated in accordance with the general procedure for 30 min. The products of hydrogenation were dissolved in dichloromethane (1.5 mL) and added to a mixture of triethylamine (10 μL, 72 μmol) and 1,3,5-benzenetricarbonyl trichloride (0.5 mg, 2.6 μmol). After 10 min, the solution was concentrated to an oil and taken up in chloroform (1 mL). The chloroform solution was washed with $KHSO_4$ (2 × 1 mL) and brine (1 × 1 mL), dried over sodium sulfate, filtered, and concentrated to an oil. The crude mixture was analyzed by FABMS (all $(M + H)^+$): 983 (**T**emplate(**5**)$_3$), 1061 (T(**4**)(**5**)$_2$), 1075 (T(**8**)(**5**)$_2$), 1139 (T(**4**)$_2$(**5**)), 1154 (T(**4**)(**5**)(**8**)), 1167 (T(**8**)$_2$(**5**)), 1217 (T(**4**)$_3$), 1231 (T(**4**)$_2$(**8**)), 1246 (T(**4**)(**8**)$_2$). A peak at 1260 (T(**8**)$_3$) was not detected.

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Supporting Information Available: ^1H NMR spectra for the compounds in Figures 1 and 2 and Scheme 1 (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering and Internet access instructions.

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