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Design and Synthesis of Dimeric Heparinoid Mimetics

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Received May 30, 2004

Synthetic oligosaccharide constructs exhibiting tailored and well-defined heparan sulfate (HS) like sequences offer the potential to modulate dynamic HS-dependent biomolecular recognition processes. We report an efficient strategy for the generation of HS-like fragments [Glc*A*-β-(1,4)-Glc*N*Ac] and related dimerized (*gemini*) disaccharides (**4a** and **4b**) via *n*-pentenyl glycoside formation. When a convergent synthetic approach was utilized, construction of target molecules was achieved through a combination of chemoselective protection/deprotection protocols, imidate and *n*-pentenyl glycosylations, and functional group manipulations followed by ozonolysis and reductive amination. For example, glycosylation of a 2-azido glycoside (**25**) with a trichloroacetimidate glucuronic acid donor (**13**), using a catalytic amount of TMSOTf, furnished heparin-like disaccharides (**28a** and **28b**) that were equipped with an *n*-pentenyl tether at the anomeric end. In turn, heparinoid-like gemini disaccharides (**4a** and **4b**) were produced by selective transformation of the olefinic unit in the *n*-pentenyl glycoside to the four-carbon aldehyde followed by reductive amination with ethylenediamine. The described synthetic approach provides access to structural variants of small heparinoid oligomers as versatile building blocks for generating novel HS mimetic pharmacotherapeutics, diagnostic reagents, and biomaterials.

Introduction

Heparin/heparan sulfate like (H/HS, **1**)[1,2] glycosaminoglycans (GAGs), found in the extracellular matrix, are complex linear biopolymers; more specifically, they are structurally heterogeneous, polyanionic polysaccharides that sequester and modulate the activity of a variety of soluble, membrane-bound, and matrix proteins. As such, H/HS oligosaccharides play a key role in regulating the biological activity of a variety of critical protein modulators of coagulation and inflammatory cascades, cell growth, migration, and proliferation, and bacterial and viral recognition. Characteristically, H/HS consists of repeating disaccharide units comprised of an alternating uronic acid [D-glucuronic acid (D-Glc*A*) or the epimeric L-iduronic acid (L-Ido*A*)] linked to a D-glucosamine (Glc*N*Ac) through a (1,4) glycosidic bond.[1,2] Unique structural modifications of these disaccharide building blocks add to the structural heterogeneity and molecular complexity associated with H/HS (Figure 1).

Given the potential significance of therapies based on the control of GAG−protein interactions, the chemical preparation of simpler HS oligosaccharides and their analogues remains an area of active investigation. In this regard, a variety of synthetic methods directed at the preparation of H/HS fragments have been reported in the literature, including, for example, the total synthesis of ATIII-binding oligosaccharides.[3−5] In addition, approaches involving the modular synthesis of larger heparin oligosaccharides,[6] heparin-related fragments varying in length and composition,[7] and the synthesis of heparin disaccharide subunits have also been disclosed.[8]

Although most structural and biochemical studies have been focused on sulfated H/HS oligosaccharide variants,[4d,9−11] nonsulfated HS-derived di- and trisaccha-

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10.1021/jo049092r CCC: $27.50
Published on Web 11/17/2004

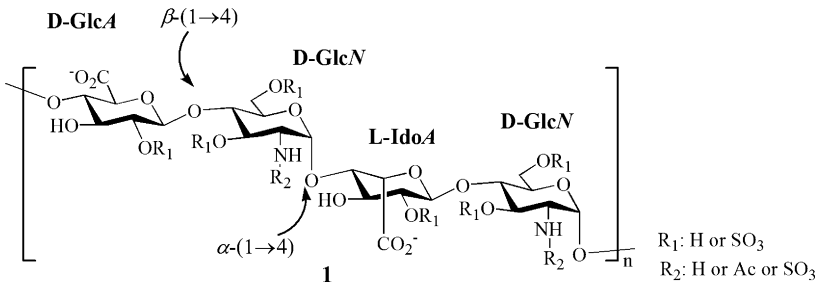

FIGURE 1. Structure of natural heparin/heparan sulfate (H/HS), **1**.

ride motifs, which are abundant in H/HS, may also exhibit significant biological activity. For example, Ornitz and co-workers have shown that nonsulfated disaccharides (**2**) and trisaccharides can stimulate or inhibit (fibroblast growth factor) FGF-1 and FGF-2.[12] Although the potency of these oligosaccharides appeared to be less pronounced than that of H/HS, both binding of FGF to FGF receptors and FGF-mediated mitogenic activity were significantly enhanced. Similarly, a diverse library of nonsulfated glucuronic acid (monosaccharide) derivatives (**3**) has been recently generated, several members of which competitively inhibited heparin binding to FGF-2.[13] Consequently, these results support the notion that tailored and precisely defined nonsulfated HS-related disaccharide modules or their homologues could serve as a significant tool for studying receptor protein binding in GAG-mediated events (Figure 2).

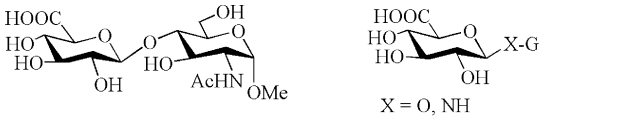

FIGURE 2. Glucuronic acid derivatives capable of inhibiting the bioactivity of FGF-2.

To this end, we have recently postulated that head-to-head tethering of Glc*A*-β-(1,4)-Glc*N*Ac by a flexible molecular spacer might provide a rational strategy for the synthesis of HS-like glycomimetic probes for studying GAG-dependent protein-binding events. In response to this goal, a synthetic route was designed for the insertion of an *n*-pentenyl group at the anomeric terminus of a glycosidic acceptor, in order to facilitate direct access to higher ordered glycoconjugates.[14,15] As an initial assessment of this approach, gemini disaccharides were produced via a reductive amination strategy with ethylenediamine, after conversion of the terminal olefinic bond to an aldehyde (Scheme 1 and Figure 3).

Results and Discussion

The success of any strategy that targets the synthesis of a HS mimetic depends on the preparation of a suitable glycosyl acceptor and donor and the use of appropriate protecting groups, as well as careful consideration of the order of glycosidic bond formation, facile removal of protecting groups, and incorporation of amino or sulfate functionalites where appropriate. On the basis of a retrosynthetic analysis of **4** (Figure 4), a strategy was devised to obtain the desired imidate donor (**B**) and the *n*-pentenyl glycosyl acceptor (**C**) on a multigram scale.

The synthesis of heparinoids is often complicated by the inherent difficulty associated with the formation of a β-(1,4) glycosidic linkage between uronic acid and hexosamine residues because of the low nucleophilicity and steric deactivation of C-4 hydroxyl groups.[16] Consequently, the synthesis of a HS mimetic requires the proper installation and protection of a 2-deoxy-2-amino functionality. In developing an efficient route to Glu*A*-β-(1,4)-Glc*N*Ac, we postulated that the ready availability

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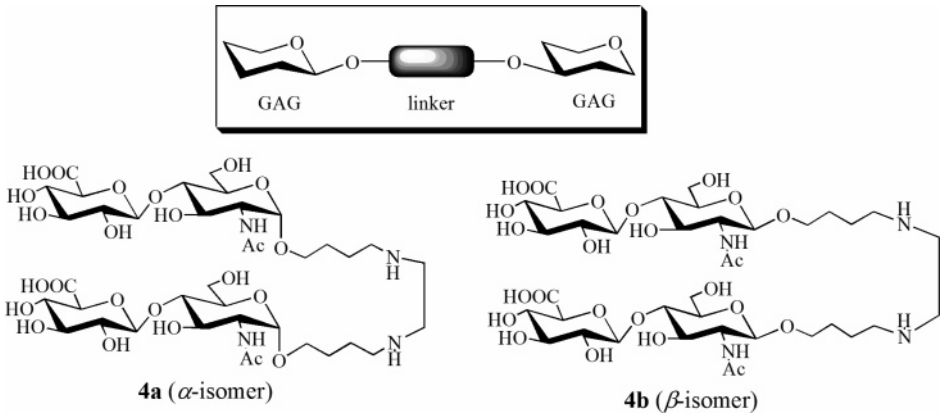
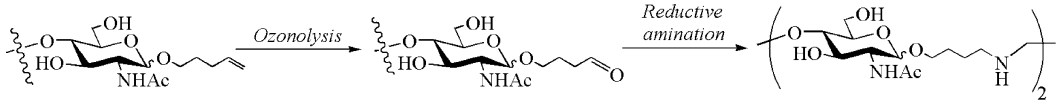


FIGURE 3. Gemini oligosaccharides of H/HS-derived disaccharides.

SCHEME 1. Strategy for Functionalization of *n*-Pentenyl Glycoside To Obtain Tethered Head-to-Head H/HS Mimetic Homodimers



and low cost of *N*-acetyl β-D-glucosamine (**5**) would provide an ideal starting point for the preparation of the nucleophilic glycosyl acceptor. Furthermore, we speculated that the presence of a 2-*N*-acyl group on the hexosamine unit would allow us to incorporate the 2-acetamido functionality into Glu*A*-β-(1,4)-Glc*N*Ac during glycosylation, thereby eliminating the need for a potentially cumbersome N deprotection and acetylation sequence at the conclusion of dimer synthesis. Thus, our initial efforts involved the substitution of the anomeric center in *N*-acetyl D-glucosamine (**5**) using *n*-pentenyl alcohol, with camphorsulfonic acid (CSA) as a catalyst, to give **6** (Scheme 2). The α/β (3:1) anomers were separated using column chromatography (9:1 $CHCl_3$/MeOH).[17]

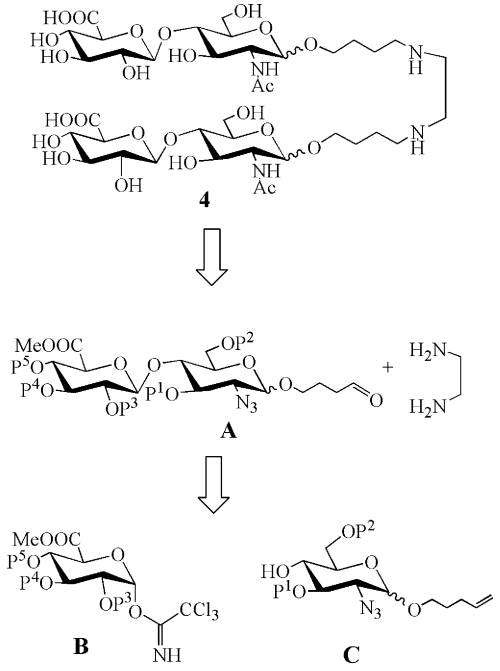


FIGURE 4. Retrosynthetic strategy for the synthesis of biscarbohydrates possessing β-(1,4)-linked H/HS disaccharides (P^1–P^5 = protecting groups).

The C-4 and C-6 hydroxyl groups of the β isomer were then capped with benzylidene acetal to yield the 4,6-benzylidene alkenyl glycoside (**7**). The 3-OH position was then protected using a standard benzylation procedure to yield the 3-*O*-benzyl derivative (**8**). Deprotection of the benzylidene group using a 2:1 TFA/H_2O mixture yielded the 4,6-diol (**9**), which was regioselectively acetylated at the C-6 hydroxyl position using acetyl chloride/pyridine, furnishing the *N*-acetyl D-glucosamine glycosyl acceptor (**10**).

The highly reactive glucuronic acid imidate donor was synthesized in 50% yield in two steps from commercially available acetobromo-α-D-glucuronic acid methyl ester (**11**; Scheme 3). The methyl ester **11** was converted to its corresponding free hemiacetal **12** using $CdCO_3$/H_2O, which was subsequently converted to the α-imidate glycosyl donor **13** using trichloroacetonitrile and 1,8-diazabicyclo[5.4.0]undec-7-ene. Unfortunately, glycosylation of the *n*-pentenyl-terminated *N*-acetyl D-glucosamine acceptor **10** with either glycosyl donor **11** or **13** was unsuccessful (Scheme 4 and Table 1).

As an alternative approach, a 2-azido-2-deoxy glycoside acceptor was synthesized (Scheme 5). Specifically, 2-azido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucopyranosyl acetate (**16**) was initially synthesized from TfN_3 and D-glucosamine hydrochloride (**15**).[18] Although the synthesis of an *n*-pentenyl glycoside from the mannose analogue, 2-azido-2-deoxy-3,4,6-tri-*O*-acetyl-D-mannosepyranosyl acetate,[19] using 4-penten-1-ol and $BF_3{\cdot}Et_2O$ was successful, similar attempts using compound **16** in the presence of $BF_3{\cdot}Et_2O$, $SnCl_4$, or TMSOTf as the promoter did not succeed. Thus, selective hydrolysis of the anomeric acetate to the hydroxyl group **17** was performed using hydrazine acetate. The hydroxyl group was subsequently converted to the trichloroacetimidate derivative **18** in 74% yield. The

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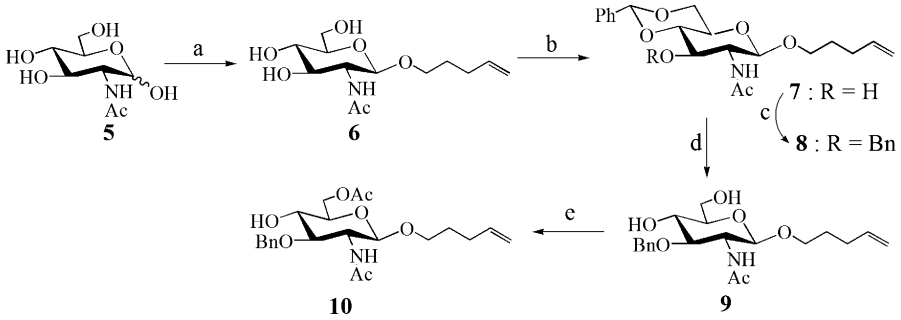
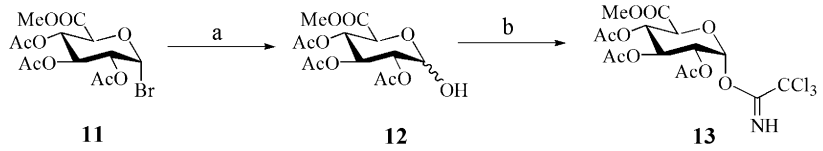
SCHEME 2. Synthesis of an *N*-Acetyl D-Glucosamine Glycosyl Acceptor 10[a]



[a] Reaction conditions: (a) CSA, 1-penten-1-ol, DMF, 75 °C, yield = 50% [α and β isomers were separated by silica gel column chromatography, α/β (3:1)]; (b) CSA, dry THF, $C_6H_5CH(OMe)_2$, reflux, 8 h, yield = 75%; (c) NaH, $C_6H_5CH_2Br$, dry THF, reflux, 8 h, 75%; (d) 2:1 TFA/H_2O, CH_2Cl_2, 0 °C, 5 h, yield: 85%; (e) AcCl, pyridine, 25 °C, 15 h, yield = 80%.

SCHEME 3. Synthesis of Imidate Donor 13[a]



[a] Reaction conditions: (a) $CdCO_3$, H_2O (2 equiv), CH_3CN, 70 °C, 4 h, yield = 75%; (b) CCl_3CN, 1,2-dichloroethane, 1,8-DBU, −10 to 0 °C, 1 h, yield = 60%.

SCHEME 4. Attempted Strategy for the Synthesis of Heparin Disaccharide 14

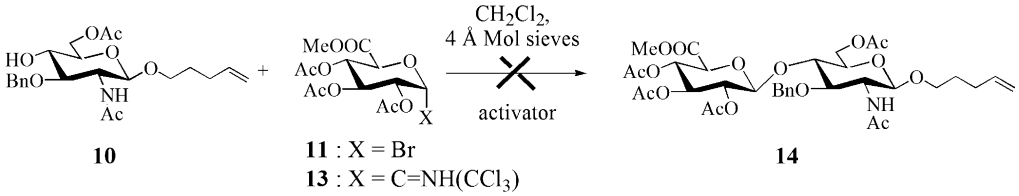


TABLE 1. Glycosylation Reaction between *n*-Pentenyl Glycoside Acceptor 10 and Glycosyl Donors

entry	reactants[a]	activator[b]	reaction conditions[c]	yield (%)[d]
1	**10** + **11**	AgOTf	−15 to +25 °C, 4.0 h	No reaction
2	**10** + **13**	$BF_3{\cdot}OEt_2$ [e]	−15 to +25 °C, 5.0 h	*g*
3	**10** + **13**	TMSOTf [e,f]	−15 to +25 °C, 3.5 h	*g*

[a] Ratio of acceptor/donor = 1:1.8−2.0 equiv. [b] Equivalents of activator: AgOTf (0.14 equiv), TMSOTf (0.1 equiv, 0.22 M solution in CH_2Cl_2), $BF_3{\cdot}OEt_2$ (1.5 equiv). [c] All reactions were carried out in anhydrous CH_2Cl_2/4 Å molecular sieves. [d] Reactions were monitored at regular intervals by TLC by removing small aliquots of the reaction mixture with a syringe. [e] No disaccharide formation was observed even after carrying out the glycosidation reaction with an excess amount of activators $BF_3{\cdot}OEt_2$ (2.0 and 3.0 equiv) and TMSOTf (0.2 and 0.3 equiv). [f] Reaction when carried out in the absence of molecular sieves did not have any appreciable effect on the disaccharide product formation. [g] A trace amount (less than 10%) of ortho ester was isolated. NMR of the intermediate ortho ester showed characteristic resonance signals at δ 1.74 (s, 3H, CH_3) and 5.92 (d, 1H, H-1′, J = 4.4 Hz) corresponding to the methyl and H−1′ anomeric protons, respectively.

n-pentenyl group was then introduced at the anomeric position using a catalytic amount of TMSOTf at 0 °C. Despite variations in temperature, promoter, and solvents, the selectivity ratio for α/β isomers (2:3) did not substantially change. Removal of the ester protecting group by Zemplen conditions[20] produced the *n*-pentenyl glycoside triol **19** in 80% yield.

Protection of C-4 and C-6 hydroxyl groups as a benzylidene acetal provided **20** in 75% yield. The α (**20a**) and β (**20b**) anomers were separated using column chromatography with 40:60 EtOAc/hexane as the eluant. To explore the influence of 3-position neighboring group participation on the rate of the glycosylation reaction, the 3-OH group in **20** was functionalized using different protecting groups. Specifically, benzylation of α/β isomers **20a/20b** and acetylation of the β derivative **20b** at the 3-OH position using NaH/benzyl bromide and acetyl chloride/pyridine afforded the 3-*O*-benzyl derivative **21a/21b** and the 3-*O*-acetyl derivative **22b**, respectively. Deprotection of the benzylidene acetal afforded the 4,6-dihydroxylated products **23a/23b** and **24b**. Regioselective acetylation of the 6-OH position using acetyl chloride/pyridine gave the orthogonally protected acceptor **25a/25b** and 3,6-diacetylated glycoside **26b**. Further reactions were carried out independently for each anomer (**25a**, **25b**, and **26b**).

Glycosylation of the *n*-pentenyl glycoside acceptors **25a/25b** and **26b** was carried out separately for both α and β isomers using the trichloroacetimidate donor **13** in the presence of acid promoters. The preparation of the disaccharide is outlined in Scheme 6, and the results of coupling reactions are summarized in Table 2. Attempts to glycosylate the sugar alcohol **25b** with imidate **13** in the presence of TBDSOTf or TMSOTf and molecular

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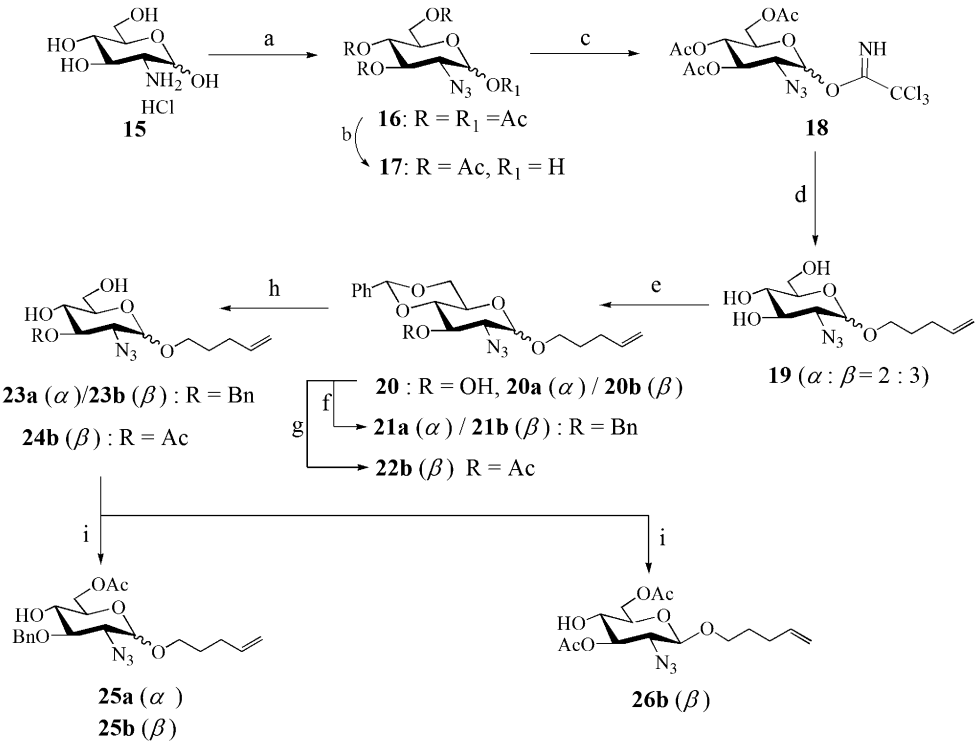
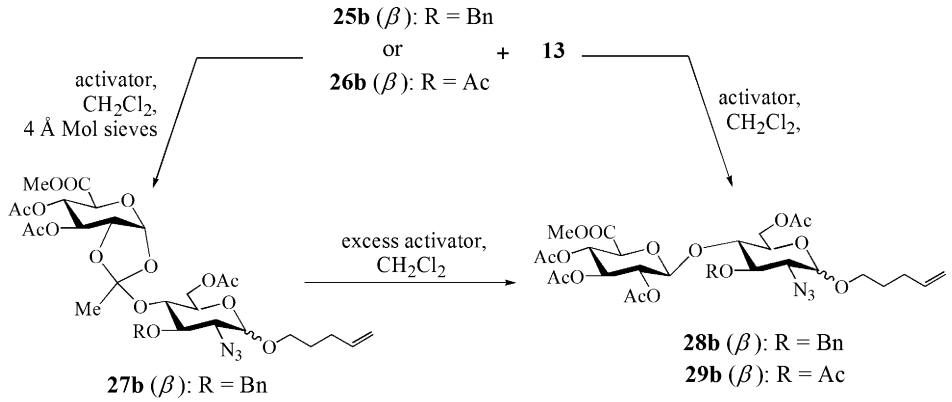
SCHEME 5. Synthesis of a D-Glucosamine Glycosyl Acceptor[a]



[a] Reagents and conditions: (a) (1) TfN_3, MeOH, DMAP, 25 °C, 18 h, (2) Ac_2O, pyridine, 0 °C, 10 h, yield = 75%; (b) H_2NNH_2·AcOH, DMF, 0 to 25 °C, 45 min, yield = 70%; (c) anhydrous K_2CO_3, CCl_3CN, CH_2Cl_2, 25 °C, 48 h, yield = 74%; (d) (1) TMSOTf, 4-penten-1-ol, dry CH_2Cl_2, 0 °C, 1 h, (2) MeONa, MeOH, 0 °C to 25 °C, 6 h, yield: 80% over two steps; (e) CSA, THF, $C_6H_5CH(OMe)_2$, reflux, 6 h, yield = 75%; (f) NaH, $C_6H_5CH_2Br$, dry THF, reflux, 10 h, yield = 82%; (g) AcCl, pyridine, 25 °C, 15 h, yield: 86%; (h) 2:1 TFA/H_2O, CH_2Cl_2, 0 °C, 5 h; (i) AcCl, pyridine, 25 °C, 12 h.

SCHEME 6. Generation of a Protected Glc*A*-β-(1,4)-Glc*N* Disaccharide



sieves produced an undesired ortho ester intermediate (**27b**) as the major product. The exclusive formation of ortho ester was confirmed by ^{1}H NMR resonance signals at δ 5.96 (doublet, J = 4.2 Hz) and 1.78 (singlet), corresponding to H-1 and methyl protons along with three acetyl peaks. We believe that the molecular sieves, which are alumino silicates and are inherently basic in nature, hindered acid-catalyzed 1,2-trans glycosidic bond formation. Indeed, in the absence of molecular sieves, boron trifluoride etherate mediated glycosylation of **25b** with imidate **13** afforded the thermodynamically favored β-(1,4) disaccharide without a trace of ortho ester, albeit in 30% yield after 14 h. Significantly, TMSOTf-catalyzed conditions provided the most efficient route for coupling of the acceptor **25b** with glycosyl donor **13**, producing the fully protected β-(1,4)-linked disaccharide **28b** in moderate (60%) yield. Of note, the ortho ester **27b** could be converted to disaccharide **28b** using an excess amount of acid catalyst in the absence of molecular sieves. Similarly, we also observed that replacing the 3-*O* benzyl protecting group by a 3-*O* acetyl functionality had a retarding influence on β-(1,4) glycosidic bond formation (Table 2, compare entries 5 and 7). Likely, the electron-withdrawing nature of the 3-*O* benzyl group enhanced the nucleophilicity of the glycosyl acceptor at the 4 position.

Comparing the glycosylation reaction pattern between the imidate donor **13** and either *N*-acetyl **10** or azido **25** acceptors revealed that the 4-hydroxy of a 2-azido-2-deoxyglucose derivative was a more reactive nucleophile

TABLE 2. Influence of Activators on the Glycosylation Reaction Involving 2-Azido Acceptors and Tricholoroacetimidate Donor 13

entry	reactants[a]	activator	temperature (°C), time (h)	product (% yield)[b,c] ortho ester	product (% yield)[b,c] disaccharide
1	**25b** + **13**	TBDSOTf + 4 Å mol sieves	0, 5.0	No reaction	
2	**25b** + **13**	TMSOTf + 4 Å mol sieves	0, 1.5	**27b** (40)	
3	**25b** + **13**	TMSOTf + 4 Å mol sieves	0−25, 6.5	**27b** (65)	
4	**25b** + **13**	$BF_3{\cdot}OEt_2$	0−25, 14		**28b** (30)
5	**25b** + **13**	TMSOTf	0−25, 4.5		**28b** (60)
6	**27b**	TMSOTf[d]	0−25, 4.0		**28b** (58)
7	**26b** + **13**	TMSOTf	0−25, 24		**29b** (25)[e]
8	**25a** + **13**	TMSOTf	0−25, 4.5		**28a** (60)

[a] Ratio of acceptor/donor = 1:1.5−2.0 equiv. [b] Isolated yields. [c] Reactions were monitored at regular intervals to confirm the conversion of the intermediate 1,2-ortho ester derivative to the 1,2-trans disaccharide using ^{1}H NMR. [d] Reaction was carried out in the absence of molecular sieves. [e] Reaction is not clean; a number of byproducts are observed.

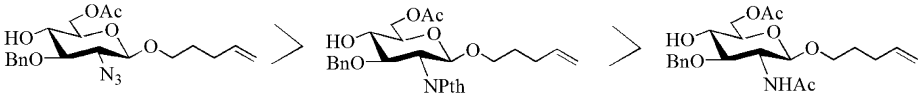


FIGURE 5. Structures of glucosamine acceptors in decreasing order of reactivity.

than that of the corresponding *N*-acetyl derivative (Figure 5). We suspect that the absence of a hydrogen-bonding moiety in the azido precursor, such as the acetamido group, enhances the nucleophilicity of the C-4 hydroxy group. Indeed, recent experimental evidence by Crich and Dudkin[16] involving β-mannosylation reactions with various glucosamine acceptors suggests that the lack of reactivity of the *N*-acetyl derivative in comparison to azido (N_3) and pthalimido (NPth) groups is primarily a result of amide *N*H-induced intramolecular hydrogen bonding with the free 4-hydroxy group.

Further synthetic manipulation of the *n*-pentenyl spacer group was necessary to obtain the desired final target molecule **4** (Scheme 7). The presence of unsaturation in **28b** precluded debenzylation by hydrogenation. As a result, deacetylation and saponification of **28b** using 3 M NaOH in a MeOH/water mixture yielded the tetraol glucuronic acid derivative in which the terminal olefinic unit was transformed to an aldehyde using reductive ozonolysis, yielding **30b**. We had anticipated that hydrogenolysis of **30b** by 10% Pd−C/H_2 would reduce the azide to a free amine and debenzylate the C-3 position while preserving the chemical integrity of the aldehyde group. Unfortunately, several attempts to carry out the hydrogenation reaction of **30b** afforded a complex mixture of products.[21−23]

In response to this limitation, we converted the azido group to an acetamido functionality. To this end, initial attempts to reduce the azido group to the acetamido functionality using standard Staudinger reaction[24] conditions ($PPh_3/CH_2Cl_2/Ac_2O$) led to very low yields. Alternatively, conversion of the azido functionality to the acetamido (−*N*HAc) group was performed using thioacetic acid,[25] which furnished **32b** in appreciable yield (55%), with ^{1}H NMR spectroscopy demonstrating the *N*H$COCH_3$ peak at δ 1.83. Subsequent saponification of **32b**, using 3 M NaOH in 9:1 MeOH/water, afforded the disaccharide **33b** in 86% yield. The crude product was purified using Sephadex LH-20 with MeOH as the eluant, and the structure was confirmed by ^{13}C NMR, which showed the presence of two carbonyl groups (C=O) at δ 176 and 175, and by FAB−MS (m/z = 562.24 for M^+ + Li).

The presence of an *n*-pentenyl group in compound **33b** provides a versatile handle for diverse conjugation reactions by transformation of the terminal olefin to either an aldehyde, carboxylic acid, ester, thioether, thioester, or hydroxyl group.[14] In the current reaction scheme, ozonolysis of **33b** afforded the terminal aldehyde glycoside intermediate **34b**. The formation of **34b** was confirmed by FAB−MS (m/z = 570.23 for M^+ + 2Li − H) and the appearance of an aldehyde signal at δ 9.72 and 203 in ^{1}H and ^{13}C NMR spectra, respectively, along with the disappearance of the olefinic double bond peaks at δ 5.85 (δ_c 132.1) and 5.1−4.9 (δ_c 118.1). Subsequent debenzylation of the four-carbon aldehyde **34b** using 10% Pd−C/H_2 afforded **35b**, which was confirmed by NMR and FAB−MS (m/z = 474.25 for M^+ + Li).

Reductive amination of **35b** (Scheme 8) with ethylenediamine produced the homodimerized β-(1,4)-linked H/HS

(21) Rele, S. M.; Iyer, S. S.; Chaikof, E. L. Unpublished results. Reactions were carried out using different stoichiometries (2, 5, and 7.5 equiv) of Pd−C reagents including Pearlmans catalyst (20%); 10% Pd−C still afforded complex mixtures. In some cases, according to the NMR spectrum, the benzyl group appeared to stay intact despite using an excess of reagent. Use of anhydrous $FeCl_3$ to selectively debenzylate the 3-*O* benzyl group in the presence of the *n*-pentenyl group, as reported by Fraser-Reid (see *Tetrahedron Lett*. **1996**, *37*, 5477−5478), again resulted in a complex mixture. Also, reaction of the saponified product obtained from **28b** with $NiCl_2{\cdot}6H_2O/NaBH_4$/MeOH converted the N_3 to NH_2 and reduced the terminal olefinic double bond without knocking off the benzyl group.

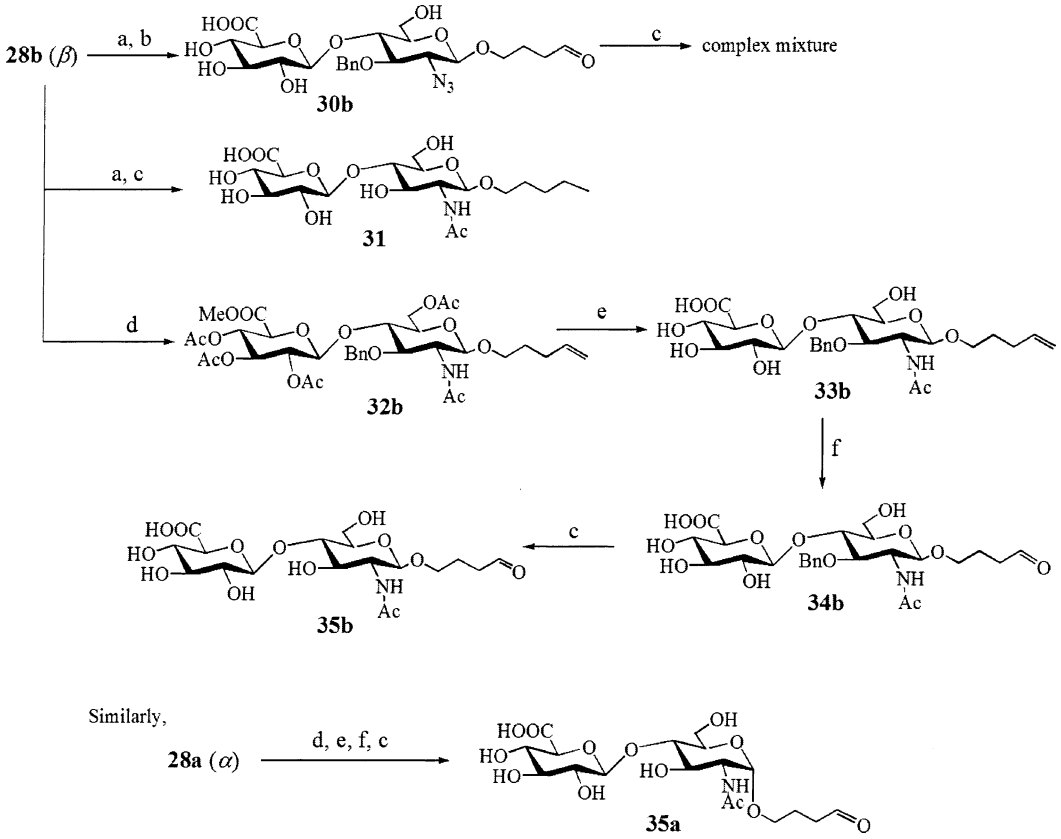
(22) Removal of benzyl groups was found to be problematic during fluorescence labeling of carbohydrates. For reference, see: France, R. R.; Cumpstey, I.; Butters, T. D.; Fairbanks, A. J.; Wormald, M. R. *Tetrahedron: Asymmetry* **2000**, *11*, 4985−4994.

(23) Reduction of the disaccharide **28b** under similar hydrogenation conditions followed by N acetylation using AcCl/pyridine showed the disappearance of benzyl peaks (δ 7.4−7.2) and terminal olefinic double bonds (δ 5.84 and 5.02) in the ^{1}H NMR spectrum. In addition, a new set of resonance signals appeared in the reduced product **31** at δ 0.85 and 2.01, the integration of which corresponded to terminal methyl protons and acetamido protons, indicating the conversion of the azido group to an amino functionality. Thus, the outcome of the hydrogenation reaction of **30b** might be subject to the collective influence of electronic, steric, and coordination effects of the azido, benzyl, and terminal aldehyde groups.

(24) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635−646. (b) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353−1406.

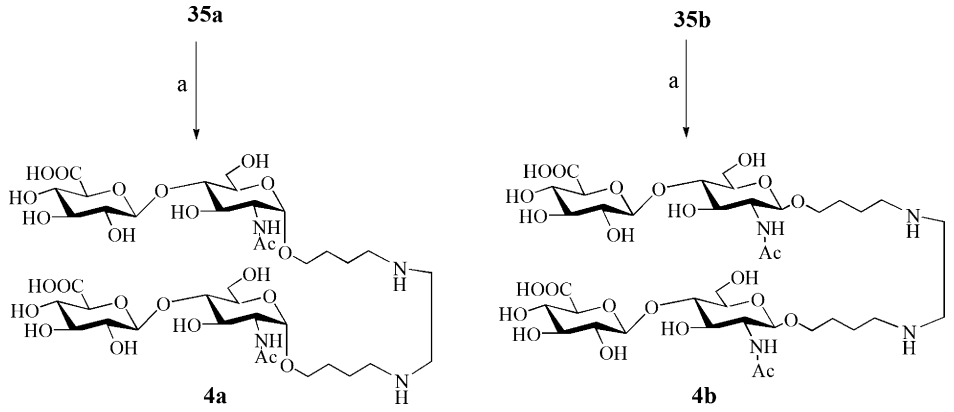
(25) Jacquinet, J. C. *Carbohydr. Res*. **1990**, *199*, 153−181.

SCHEME 7[a]



[a] Reagents and conditions: (a) 3 M NaOH, 9:1 MeOH/H_2O, 25 °C, 2 h, yield: 82%; (b) O_3 (−78 °C), Me_2S, −78 to +25 °C, 24 h, yield = 85%; (c) Pd−C/H_2, MeOH, 25 °C, 24 h; (d) thioacetic acid, 25 °C, 24 h, yield: 55%; (e) 3 M NaOH, 9:1 MeOH/H_2O, 25 °C, 2 h, yield: 86%; (f) O_3 (−78 °C), Me_2S, −78 to +25 °C, 24 h, yield: 90%.

SCHEME 8[a]



[a] Reagents and conditions: (a) $NH_2(CH_2)_2NH_2$ (0.5 equiv), 3 h, $NaCNBH_3$ (4 equiv), 25 °C, 24 h, yield = 67%.

neoglycoconjugate **4b** (yield 67%). The crude product was purified using a Sephadex G-10 gel filtration column using water as the eluant. The structure was confirmed by heteronuclear multiple-quantum coherence (HMQC) ^{13}C NMR, which showed the presence of four anomeric carbons, and by MALDI−TOF analysis (m/z = 963.45 for $M^+ + H$; Figure 6).

The biological response of receptor proteins depends, in part, on their interaction with particular structural motifs of GAGs. Computational modeling procedures[26] have suggested that the intrinsic binding affinity of oligosaccharide mimetics to target proteins depends on the distance and appropriate orientation of the sugar epitopes, as well as on the carbohydrate conformational flexibility.[27] Moreover, small and subtle differences in stereochemistry, conformation, and functionality can have a profound influence on the biological activity of glycoconjugates. To this end, while the β-linked (1,2-trans) neoglycoconjugate **4b** resembles the naturally occurring structure of Glc*A*-β-(1,4)-Glc*N*Ac within GAG

(26) (a) Kolb, H.; Ernst, B. *Chem.—Eur. J.* **1997**, *3*, 1571−1578. (b) Hanessian, S.; Reddy, G. V.; Huynh, H.; Pan, J.; Pedatella, S.; Ernst, B.; Kolb, H. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2729−2734.

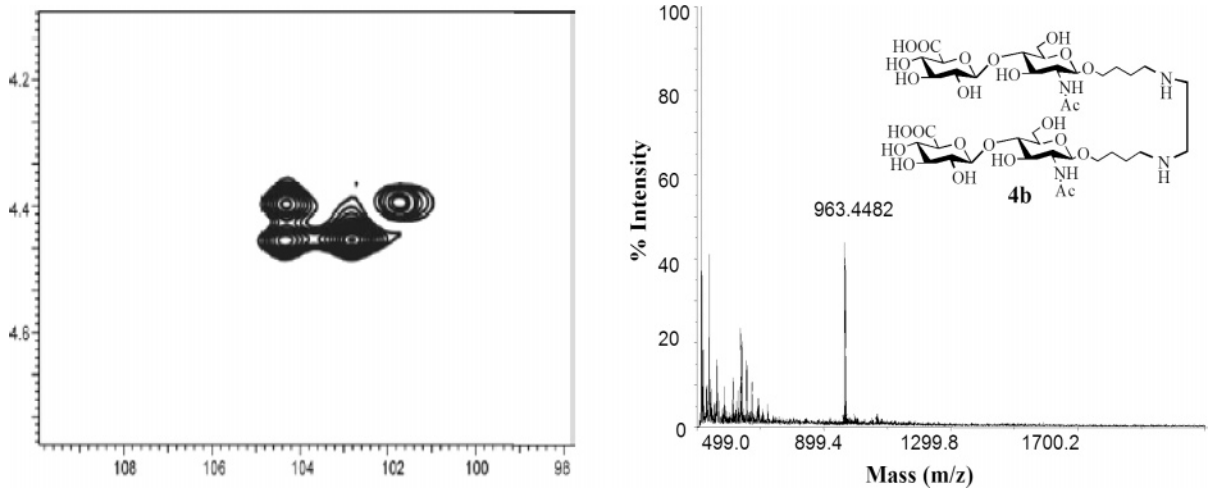


FIGURE 6. HMQC spectrum highlighting the anomeric region indicating the presence of four anomeric carbons and the MALDI-TOF spectrum of **4b**.

chains, α-linked (1,2-cis) disaccharides may well exhibit different binding affinities. Thus, the glycosidation procedure was repeated with the α acceptor (**25a**) to obtain the α-linked disaccharide module **28a**, which was further elaborated sequentially to obtain **32a**, **33a**, **34a**, and **35a**. Reductive amination of **35a** afforded the homodimeric α product **4a**. In summary, beginning with acceptors **25a/25b**, gemini homodimers **4a/4b** possessing head-to-head orientation were obtained in six steps with an overall yield of 7%.

Conclusions

In summary, the synthesis of *n*-pentenyl bearing Glc*A*-*β*-(1,4)-Glc*N*Ac disaccharides and related bis-heparinoid dimers is described. Investigations of carbohydrate−protein binding interactions are ongoing and will be reported in due course. We believe the synthetic approach described herein provides a useful foundation for the rational design and synthesis of small-molecule glycomics capable of modulating HS-dependent protein-binding events.

Experimental Section

Synthesis of Trichloroacetimidate Donor Methyl (2,3,4-Tri-*O*-acetyl-α-D-glucopyranosyl trichloacetimidate) Glucoronate (13). Acetobromo-α-D-glucuronic acid methyl ester (**11**; 0.025 mol, 10 g) was added to a flame-dried, three-necked flask containing $CdCO_3$ (0.026 mol, 4.5 g), CH_3CN (150 mL), and 0.8−1.0 mL of degassed H_2O. The reaction mixture was stirred and heated to 70 °C for a period of 4 h under argon, filtered through Celite, washed with 50 mL of CH_3CN, and concentrated in vacuo. Purification of the crude residue by flash chromatography (50:50 EtOAc/hexane) afforded the hydrolyzed product (white solid), which was subsequently dissolved in 200 mL of dichloroethane; Cl_3CCN (10 equiv, 0.142 mol, 13.6 mL) was then added to it under argon. After cooling to 0 °C, 1,8-diazabicyclo[5.4.0]undec-7-ene (1,8-DBU; 0.28 equiv, 3.96 mmol, 595 μL) was added in a dropwise manner. The reaction mixture was allowed to stir for 1 h, and the mixture was concentrated to afford a sticky, dark-brown residue. Subsequent flash column chromatography of the crude extract (40:60 EtOAc/hexane, 1% Et_3N) furnished an off-white compound **13** (60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.71 (s, 1H, NH), 6.58 (d, 1H, J = 3.6 Hz), 5.62 (t, 1H, J = 10 Hz), 5.26 (t, 1H, J = 10 Hz), 5.11 (dd, 1H, J = 3.2 Hz), 4.43 (d, 1H, J = 10.2 Hz), 3.74 (s, 3H, COOMe), 2.05 (s, 6H, OAc), 2.02 (s, 3H). HRMS−FAB: [M^+] calcd for $C_{15}H_{18}O_{10}NCl_3$, 478.9956; found, 478.9968.

Synthesis of 2-Azido-2-deoxy-3,4,6-tri-*O*-acetyl-α,*β*-D-glucopyranosyl Acetate (16). To a round-bottomed flask containing NaN_3 (0.43 mol, 28 g) and equipped with an argon balloon were added water (80 mL) and CH_2Cl_2 (75 mL). The emulsion was stirred and cooled to 0 °C followed by dropwise addition of dry Tf_2O (0.088 mol, 15 mL) via syringe. The reaction mixture was stirred at 0 °C for 2 h and at 25 °C for 15 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were neutralized with a cold saturated solution of $NaHCO_3$, washed with water, dried over $MgSO_4$, and filtered. This stock solution contains ca. 0.1 mol of TfN_3.

In a separate three-necked flask equipped with an argon inlet containing D-glucosamine hydrochloride (**15**; 0.042 mol, 9 g) dissolved in methanol (250 mL), NaOMe (80 mL of a 0.5 M solution in MeOH) was added and stirred for 30 min. DMAP (5 g) was added to it, and the reaction mixture was diluted with an additional 100 mL of MeOH. The freshly prepared solution of TfN_3 was added to this reaction mixture via a cannula under positive pressure of argon and left to stir at room temperature for 18 h. The solvent was removed in vacuo to give a sticky, yellow paste. The residue obtained was then acetylated at 0−4 °C for 10 h using anhydrous pyridine (250 mL) and dry acetic anhydride (120 mL). Upon completion of the reaction, the reaction mixture was coevaporated with toluene (3 × 50 mL) to give a light-brown, sticky residue. Flash chromatography (60:40 EtOAc/hexane) of the crude reaction mixture using silica gel gave the desired product **16**. Yield: 11.5 g (75%). ^{1}H NMR ($CDCl_3$) δ: 6.30 (d, 1H, H-1α, J = 3.6 Hz), 5.55 (d, 1H, H-1*β*, J = 8.7 Hz), 5.43 (t, 1H, J = 8.0 Hz), 5.18−5.04 (m, 3H), 4.34−4.27 (m, 2H), 4.11−4.05 (m, 4H), 3.68−3.64 (m, 2H), 2.19 (s, 6H), 2.11 (s, 3H), 2.10 (s, 3H), 2.08 (s, 6H), 2.05 (s, 3H), 2.02 (s, 3H).

Synthesis of 2-Azido-2-deoxy-3,4,6-tri-*O*-acetyl-α,*β*-D-glucopyranoside (17). To an ice-cooled solution of **16** (0.0241 mol, 9.0 g) dissolved in 100 mL of dry DMF was added solid hydrazine acetate (2.5 equiv, 0.06 mol, 5.5 g) under an argon atmosphere. The ice bath was then removed, and the reaction mixture was allowed to stir for 45 min. Upon completion (TLC), the reaction mixture was quenched using ethyl acetate (50 mL) and water (50 mL). The organic layer was then separated, and

(27) (a) Alibes, R.; Bundle, D. R. *J. Org. Chem.* **1998**, *63*, 6288−6301 and references therein. (b) Wacowich-Sgarbi, S.; Bundle, D. R. *J. Org. Chem.* **1998**, *64*, 9080−9089 and references therein. (c) Kretzschmar, G. *Tetrahedron* **1998**, *54*, 3765−3780.

the aqueous layer was extracted with EtOAc (3 × 25 mL). Finally, the combined organic layers were washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration of the solvent in vacuo gave a light-yellow gel, which on flash column chromatography (80:20 EtOAc/ hexane) furnished **17** as a white solid. Yield: 5.9 g (70%). ^{1}H NMR ($CDCl_3$) δ: 5.35 (t, 2H, J = 10.4 Hz, J = 9.6 Hz), 5.23 (d, 1H, H-1α, J = 3.2 Hz), 4.88 (m, 2H), 4.58 (d, 1H, H-1β, J = 8.0 Hz), 4.12 (m, 2H), 3.94 (m, 2H), 3.80 (br s, 2H, OH), 3.35−3.28 (m, 2H), 3.20 (s, 2H), 2.09 (s, 6H), 2.08 (s, 6H), 2.08 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 171.3, 171.2, 170.5, 170.4, 170.2, 170.0, 96.1, 91.9, 72.5, 71.7, 70.5, 68.7, 68.5, 67.2, 64.8, 62.2, 61.4, 20.7, 20.6.

Synthesis of 2-Azido-2-deoxy-3,4,6-tri-*O*-acetyl-α,β-D-glucopyranosyl Trichloroacetimidate (18). To the reaction flask containing compound **17** (0.024 mol, 8 g) dissolved in dry CH_2Cl_2 (35 mL) was added anhydrous K_2CO_3 (0.06 mol, 8.33 g). This was followed by the dropwise addition of Cl_3CCN (0.144 mol, 14.5 mL), after which the reaction mixture was stirred for 48 h under an argon atmosphere. Upon completion (TLC), the reaction mixture was cooled to 0 °C, diluted with 25 mL of CH_2Cl_2, and quenched with 20 mL of ice-cold water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to yield a light-yellow solid. Purification of the crude mixture by column chromatography (60:40 EtOAc/ hexane) gave compound **18** as an off-white solid. Yield: 8.5 g (74%). ^{1}H NMR ($CDCl_3$) δ: 8.81 (s, 1H, NH), 8.79 (s, 1H, NH), 6.43 (d, 1H, H-1α, J = 3.6 Hz), 5.68 (d, 1H, H-1β, J = 7.8 Hz), 5.55 (dd, 2H, J = 9.6 Hz, J = 9.6 Hz), 5.11 (t, 1H, J = 10.0 Hz), 5.09 (m, 1H), 4.23 (m, 4H), 4.05 (m, 2H), 3.76 (dd, 2H, J = 3.6 Hz), 2.05 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 2.0 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.7, 170.6, 170.0, 169.8, 169.7, 160.6, 96.5, 94.1, 90.6, 72.8, 72.7, 70.8, 70.2, 68.1, 63.4, 61.5, 60.7, 20.8, 20.7.

Synthesis of Pent-4-enyl-2-azido-2-deoxy-α,β-D-glucopyranoside (19). To an oven-dried flask containing **18** (0.016 mol, 7.5 g) dissolved in anhydrous CH_2Cl_2 (25 mL) was added 4-penten-1-ol (0.0195 mol, 2.0 mL) via syringe. The reaction mixture was initially stirred for 10 min at room temperature and then cooled to 0 °C under an argon atmosphere. A freshly prepared solution of TMSOTf (1.6 mmol, 7.4 mL of a 0.22 M solution in anhydrous CH_2Cl_2) was added dropwise through a syringe to the reaction mixture and stirred at 0 °C. Upon completion (TLC), the reaction mixture was quenched with Et_3N, filtered through a pad of Celite, and concentrated under reduced pressure to give a semicrystalline material. Flash chromatography (50:50 EtOAc/hexane) afforded a light-yellow, semicrystalline material, which was directly used for the next step. (The compound obtained was contaminated with trace amounts of 4-penten-1-ol.) The above mixture was dissolved in anhydrous MeOH followed by the addition of NaOMe (10 mL of a 0.5 M solution in MeOH, 0.05 mol) at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 6 h (monitored by TLC) and quenched with a Dowex 50W X 8-200 (H^+) ion-exchange resin at 0 °C. The resin was filtered and, upon evaporation of the solvent, gave a light-brown syrup, which on flash chromatography (50:50 EtOAc/hexane to 10:90 MeOH/$CHCl_3$) furnished **19** as a light-yellow compound. Yield over two steps: 3.56 g (80%). ^{1}H NMR ($CDCl_3$) δ: 5.81 (m, 1H, CH=CH_2), 5.02−4.92 (m, 2H, CH=CH_2), 4.87 (d, 0.3H, H-1α, J = 3.2 Hz), 4.6 (br s, 3H, OH), 4.34 (d, 0.7H, H-1β, J = 7.6 Hz), 3.98−3.74 (m, 3H), 3.68−3.31 (m, 4H), 3.28−3.20 (m, 1H), 2.11−2.05 (m, 2H, CH_2CH=CH_2), 1.80−1.65 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 138.7, 115.1, 102.2, 98.1, 75.2, 74.6, 71.4, 70.1, 70.05, 69.5, 67.7, 66.0, 62.6, 61.4, 61.1, 30.3, 30.1, 28.8, 28.6. HRMS−FAB: [M^+] calcd for $C_{11}H_{19}O_5N_3$, 273.1228; found, 273.1238.

Synthesis of Pent-4-enyl-2-azido-2-deoxy-4,6-*O*-benzylidene-α,β-D-glucopyranoside (20). To a solution of compound **19** (0.011 mol, 3.2 g) dissolved in anhydrous THF (25 mL) was added 200 mg of (+)-CSA as a catalyst, followed by the dropwise addition of benzaldehyde dimethyl acetal (0.0197 mol, 2.95 mL). The reaction mixture was refluxed under an argon atmosphere for 6 h (monitored by the complete disappearance of the starting material), cooled to room temperature, diluted with 50 mL of EtOAc, and quenched with 10 mL of a saturated solution of $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with 3 × 25 mL of EtOAc. The organic layers were combined and washed with brine, dried over Na_2SO_4, and concentrated to yield a light-yellow solid. Purification of the crude product by flash chromatography (5:95 EtOAc/hexane to 30:70 EtOAc/hexane) gave **20** as a mixture of α and β isomers (yield: 3.17 g, 75%). The anomeric isomers **20a** (α) and **20b** (β) were separated at this stage by silica gel column chromatography using a 60:40 hexane/ethyl acetate mixture as the eluant. **Pent-4-enyl-2-azido-2-deoxy-4,6-*O*-benzylidene-α,D-glucopyranoside (20a)**. $[\alpha]^{25}_D$: −37.31 (c = 0.98, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.50−7.45 (m, 2H, C_6H_5), 7.39−7.27 (m, 3H, C_6H_5), 5.81 (m, 1H, CH=CH_2), 5.59 (s, 1H, CHPh), 5.08−4.99 (m, 2H, CH=CH_2), 4.89 (d, 1H, H-1α, J = 3.6 Hz), 4.28−4.21 (m, 2H), 3.87−3.83 (m, 1H), 3.75−3.70 (m, 2H), 3.53−3.47 (m, 2H), 3.24 (dd, 1H, J = 4 Hz, J = 3.6 Hz), 2.80 (br s, 1H, OH), 2.19−2.16 (m, 2H), 1.77−1.73 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 138.1, 137.1, 129.6, 128.6, 126.5, 115.3, 102.3, 98.6, 82.1, 69.0, 68.8, 68.1, 63.2, 62.6, 30.4, 28.5. HRMS−FAB: [M^+] calcd for $C_{18}H_{23}O_5N_3$, 361.3918; found, 361.3924. **Pent-4-enyl-2-azido-2-deoxy-4,6-*O*-benzylidene-β-D-glucopyranoside (20b)**. $[\alpha]^{25}_D$: +33.6 (c = 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.48−7.45 (m, 2H, Ph), 7.38−7.26 (m, 3H, Ph), 5.83−5.79 (m, 1H, CH=CH_2), 5.56 (s, 1H, CHPh), 5.06−4.97 (m, 2H, CH=CH_2), 4.33 (d, 1H, H-1β, J = 7.8 Hz), 4.29 (m, 1H), 3.89 (m, 1H), 3.73 (t, 1H, J = 10.0 Hz), 3.56−3.48 (m, 3H), 3.45−3.38 (m, 2H), 2.65 (br s, 1H, OH), 2.17−2.15 (m, 2H), 1.76−1.73 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 138.1, 137.1, 129.6, 128.6, 126.5, 115.4, 102.7, 102.1, 80.8, 72.0, 70.1, 68.7, 66.7, 66.3, 30.22, 28.94. HRMS−FAB: [M^+] calcd for $C_{18}H_{23}O_5N_3$, 361.3918; found, 361.3926.

Synthesis of 3-*O*-Benzyl-Protected Derivative Pent-4-enyl-2-azido-2-deoxy-3-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-glucopyranoside (21a/21b). To a suspension of NaH (12 equiv, 49.8 mmol, 1.2 g) in anhydrous THF under argon was added compound **20a/20b** (4.15 mmol, 1.5 g) via a cannula, and the resulting solution was stirred for 10 min. Benzyl bromide (4 equiv, 16.62 mmol, 2.0 mL) was added to the mixture, and the reaction was refluxed under an argon atmosphere for 10 h. Upon completion (TLC), the reaction mixture was diluted with EtOAc and quenched slowly with an ice-cold solution of saturated $NaHCO_3$, and the organic layer was separated from the aqueous layer. The aqueous fraction was further extracted with small portions of EtOAc (three times); the combined organic layers were collected, subsequently washed with water and brine, and dried over Na_2SO_4. Removal of the solvent in vacuo followed by column chromatography (silica gel, 5:95 EtOAc/hexane to 25:75 EtOAc/hexane) gave the solid product **21a/21b** (α/β) (yield: 1.63 g, 82%). **21a**. ^{1}H NMR ($CDCl_3$) δ: 7.5−7.25 (m, 10H, Ph), 5.85−5.78 (m, 1H, CH=CH_2), 5.57 (s, 1H), 5.12−4.95 (m, 2H, CH=CH_2), 4.88 (d, 1H, H-1α, J = 3.6 Hz), 4.82 (d, 2H, J = 10.8 Hz), 4.35−4.25 (m, 1H), 4.15−4.07 (m, 1H), 3.97−3.86 (m, 1H), 3.82−3.88 (m, 3H), 3.52−3.48 (m, 1H), 3.37−3.34 (m, 1H), 2.13−2.08 (m, 2H), 1.80 (m, 2H). HRMS−FAB: [M^+] calcd for $C_{25}H_{29}O_5N_3$, 451.5128; found, 451.5142. **21b**. ^{1}H NMR ($CDCl_3$) δ: 7.5−7.25 (m, 10H, Ph), 5.85−5.78 (m, 1H, CH=CH_2), 5.57 (s, 1H), 5.12−4.75 (m, 4H), 4.37 (d, 1H, H-1β, J = 8.0 Hz), 4.36 (m, 1H), 4.15−4.07 (m, 1H), 3.97−3.86 (m, 1H), 3.83−3.64 (m, 2H), 3.62−3.40 (m, 2H), 3.38−3.28 (m, 1H), 2.14−2.08 (m, 2H), 1.80 (m, 2H). HRMS−FAB: [M^+] calcd for $C_{25}H_{29}O_5N_3$, 451.5130; found, 451.5142.

Synthesis of the 3-*O*-Acetyl-Protected Derivative Pent-4-enyl-2-azido-2-deoxy-3-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside (22b). The compound **20b** (4.15 mmol, 1.5

g) was dissolved in dry pyridine and stirred at 0 °C. Using a syringe, acetyl chloride (1.5 equiv, 6.23 mmol, 0.43 mL) was added dropwise to the reaction mixture and stirred overnight under an argon atmosphere. Upon completion (TLC), the crude reaction mixture was concentrated, diluted with $CHCl_3$, and extracted with water. After repeated extraction of the aqueous phase with $CHCl_3$ (two times), the organic fractions were pooled together and concentrated to afford a dark-brown residue. Flash chromatography of the crude product (30:70 EtOAc/hexane) gave the desired 3-*O*-acetylated product **22b** (*β*). Yield: 1.43 g (86%). ^{1}H NMR ($CDCl_3$) *δ*: 7.6−7.25 (m, 5H, Ph), 5.82−5.75 (m, 1H, CH═CH_2), 5.65−5.59 (m, 1H), 5.50 (s, 1H), 5.12−4.94 (m, 2H, CH═CH_2), 4.42 (d, 1H, H-1*β*, *J* = 7.6 Hz), 4.32−4.24 (m, 1H), 4.01−3.92 (m, 1H), 3.82−3.72 (m, 2H), 3.65−3.47 (m, 2H), 3.18 (dd, 1H, *J* = 3.6 Hz), 2.14 (m, 2H), 2.03 (s, 3H), 1.77 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 170.1, 137.9, 137.2, 129.3, 128.4, 126.4, 115.5, 101.9, 99.2, 79.7, 69.1, 69.0, 68.2, 62.9, 61.8, 30.4, 28.7, 21.1. HRMS−FAB: [M$^+$] calcd for $C_{20}H_{25}O_6N_3$, 403.1764; found; 403.1752.

General Procedure for Selective Acetylation of the 6-OH Position (25a/25b and 26b). To an ice-cooled solution of the 3-*O* benzyl derivative **21a/21b** (3.61 mmol, 1.63 g) or the 3-*O* acetyl derivative **22b** (3.54 mmol, 1.43 g) in anhydrous CH_2Cl_2 was added dropwise a 2.5:1 TFA/water mixture. The mixture was stirred at room temperature for 5 h, monitored by TLC, and upon disappearance of the starting compound (TLC) was cooled to 0 °C followed by quenching with a saturated $NaHCO_3$ solution. The organic layer was separated from the aqueous layer that was further extracted with CH_2Cl_2 (two times). The combined organic fractions were washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent gave a pale-yellow gel, which was then subjected to column chromatography to yield the debenzylidenated product **23a/23b** (yield: 1.02 g, 80%) or **24b** (yield: 0.93 g, 83%). **23a**. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.38−7.30 (m, 5H, Ph), 5.82−5.76 (m, 1H, CH═CH_2), 5.08−4.97 (m, 3H), 4.95 (d, 1H, H-1α, *J* = 3.6 Hz), 4.84−4.71 (m, 1H), 3.94−3.73 (m, 3H), 3.61−3.54 (m, 2H), 3.36−3.19 (m, 3H), 2.12−2.06 (m, 2H), 1.82−1.74 (m, 2H). **23b**. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.38−7.32 (m, 5H, Ph), 5.82−5.74 (m, 1H, CH═CH_2), 5.08−4.95 (m, 3H), 4.71 (d, 1H, *J* = 11.7 Hz), 4.34 (d, 1H, H-1*β*, *J* = 7.8 Hz), 3.92−3.73 (m, 3H), 3.61−3.54 (m, 2H), 3.35−3.17 (m, 3H), 2.10−2.06 (m, 2H), 1.86−1.74 (m, 2H). **24b**. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 5.82−5.79 (m, 1H, CH═CH_2), 5.33−5.27 (m, 1H), 5.07−4.97 (m, 2H, CH═CH_2), 4.38 (d, 1H, H-1*β*, *J* = 8.0 Hz), 3.86−3.84 (m, 2H), 3.75−3.70 (m, 3H), 3.51−3.46 (m, 1H), 3.23 (dd, 1H, *J* = 3.6 Hz), 2.16−2.12 (m, 2H), 2.03 (s, 3H), 1.82−1.78 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 171.2, 137.9, 115.5, 98.1, 74.1, 71.8, 70.3, 68.1, 62.2, 61.0, 30.4, 28.7, 21.1.

The deprotected product **23a/23b** (2.91 mmol, 1.02 g), or **24b** (2.95 mmol, 0.93 g), obtained above was dissolved in 25 mL of dry pyridine and cooled to 0 °C. Dropwise addition of acetyl chloride (1.1 equiv) to the above solution resulted in the immediate formation of a white precipitate. The reaction mixture was allowed to stir for 12 h at room temperature, quenched with MeOH, and concentrated to give light-brown syrup. The crude product was extracted with water and CH_2Cl_2 (two times), followed by subsequent washings with water and brine, and finally dried over Na_2SO_4. Purification of the crude mixture using column chromatography (30:60 EtOAc/hexane) gave the selective 6-*O* acetylated product **25a/25b** (yield: 1.0 g, 85%), or **26b** (yield: 0.63 g, 60%). **Pent-4-enyl-2-azido-2-deoxy-3-*O*-benzyl-6-*O*-acetyl-α-D-glucopyranoside** (**25a**). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.42−7.28 (m, 5H, ArH), 5.85−5.74 (m, 1H, ═CH), 5.06−4.97 (m, 2H, ═CH_2), 4.89−4.81 (m, 3H), 4.37 (dd, 1H, *J* = 4.8 Hz), 4.22 (d, 1H, *J* = 12 Hz), 3.85−3.73 (m, 2H), 3.71−3.64 (m, 1H), 3.47−3.44 (m, 2H), 3.23−3.20 (m, 2H), 2.14 (m, 2H), 2.14 (s, 3H, $COCH_3$), 1.78−1.68 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 400 MHz) *δ*: 171.8, 138.2, 138.1, 128.8, 128.3, 128.2, 115.3, 98.2, 79.6, 75.36, 70.9, 70.1, 67.9, 63.4, 62.9, 30.4, 28.7, 21.1. HRMS−FAB: [M$^+$ + H] calcd for $C_{20}H_{27}O_6N_3$, 406.1968; found, 406.1958. **Pent-4-enyl-2-azido-2-deoxy-3-*O*-benzyl-6-*O*-acetyl-*β*-D-glucopyranoside** (**25b**). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.42−7.32 (m, 5H, ArH), 5.86−5.74 (m, 1H, ═CH), 5.06−4.98 (m, 2H, ═CH_2), 4.90 (d, 1H, *J* = 11.6 Hz), 4.75 (d, 1H, *J* = 11.6 Hz), 4.44 (dd, 1H, *J* = 4.4 Hz), 4.27 (d, 1H, *J* = 8.0 Hz), 4.22 (d, 1H, *J* = 2.0 Hz), 3.93−3.90 (m, 1H), 3.57−3.52 (m, 1H), 3.48−3.42 (m, 1H), 3.38−3.34 (m, 2H), 3.22 (m, 1H), 2.6 (s, 1H, −OH), 2.17−2.14 (m, 2H), 2.08 (s, 3H), 1.78−1.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz) *δ*: 171.8, 138.2, 138.1, 128.8, 128.3, 128.2, 115.3, 102.4, 82.4, 75.4, 73.8, 70.2, 69.8, 66.1, 63.4, 30.2, 28.9, 21.1. HRMS−FAB: [M$^+$ + H] calcd for $C_{20}H_{27}O_6N_3$, 406.1968; found, 406.1960. **Pent-4-enyl-2-azido-2-deoxy-3,6-di-*O*-acetyl-*β*-D-glucopyranoside** (**26b**). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 5.82−5.79 (m, 1H, CH═CH_2), 5.28−5.23 (m, 1H), 5.01−4.96 (m, 2H, CH═CH_2), 4.48 (dd, 1H, *J* = 4.5 Hz), 4.40 (d, 1H, H-1*β*, *J* = 8.0 Hz), 4.28 (dd, 1H, *J* = 2.1 Hz), 3.88−3.82 (m, 1H), 3.75−3.69 (m, 1H), 3.55−3.48 (m, 2H), 3.22 (dd, 1H, *J* = 3.6 Hz), 2.99 (dd, 1H, *J* = 4.5 Hz), 2.12 (m, 2H), 2.11 (s, 3H), 2.03 (s, 3H), 1.8−1.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz) *δ*: 172.3, 170.9, 137.9, 115.5, 102.9, 73.4, 70.4, 69.7, 68.9, 63.1, 60.9, 30.3, 28.6, 21.1, 21.0. HRMS−FAB: [M$^+$ + H] calcd for $C_{15}H_{23}O_7N_3$, 358.1554; found, 358.1572.

Synthesis of *β*-(1,4)-Linked Disaccharide Units. (A) Formation of Ortho Ester 27b. The *n*-pentenylazido glycoside acceptor **25b** (2.47 mmol, 1.0 g) dissolved in dry CH_2Cl_2 was added to a flask already containing 4 Å molecular sieves and was stirred at 0 °C under an argon atmosphere. To this solution was added dropwise a freshly prepared solution of TMSOTf (0.13 mmol of a 0.22 M solution in dry CH_2Cl_2, 0.561 mL) over a period of 5 min via syringe. The imidate donor **13** (1.8 equiv, 4.5 mmol, 2.2 g), dissolved in dry CH_2Cl_2, was then added to the reaction mixture via a cannula, and the reaction mixture was stirred at 0 °C for 30 min, then allowed to warm to room temperature, and stirred for 4.0 h. Upon completion (TLC), the reaction mixture was quenched with *N*,*N*-diisopropylamine, filtered over Celite, concentrated, and subjected to column chromatography (30:70 EtOAc/hexane) to give the intermediate ortho ester derivative **27b** as an off-white solid. Yield: 1.16 g (65%). ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.42−7.28 (m, 5H, ArH), 5.96 (d, 1H, H-1′, *J* = 4.2 Hz), 5.88−5.74 (m, 1H, ═CH), 5.09−4.91 (m, 2H, ═CH_2), 4.86 (d, 1H, *J* = 10.2 Hz), 4.76 (d, 1H, *J* = 10.2 Hz), 4.39−4.33 (m, 2H), 4.23 (d, 1H, H-1, *J* = 7.2 Hz), 4.19−4.13 (m, 1H), 3.92−3.87 (m, 1H), 3.75 (s, 3H, COOMe), 3.65−3.52 (m, 2H), 3.39−3.29 (m, 3H), 2.10 (m, 2H, CH_2), 2.09 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.78 (s, 3H, ortho ester CH_3), 1.77−1.72 (m, 2H, CH_2). HRMS−FAB: [M$^+$] calcd for $C_{33}H_{43}O_{15}N_3$,721.2748; found, 721.2728.

(B) Synthesis of 3-*O*-Benzyl-Protected *β*-(1,4)-Linked *n*-Pentenyl Disaccharide (28a/28b). The acceptor **25a/25b** (2.47 mmol, 1.0 g) was dissolved in dry CH_2Cl_2 and stirred at 0 °C under an argon atmosphere. To this solution was added dropwise a freshly prepared solution of TMSOTf (0.05 equiv, of 0.22 M TMSOTf solution in dry CH_2Cl_2, 0.13 mmol, 0.51 mL) over a period of 5 min via syringe. The imidate donor **13** (1.5 equiv, 3.71 mmol, 1.78 g), dissolved in dry CH_2Cl_2, was then added to the reaction mixture via a cannula, and the reaction mixture was warmed to room temperature over a period of 30 min and stirred for an additional 4 h. Upon completion (TLC), the reaction mixture was quenched with *N*,*N*-diisopropylamine, concentrated, and subjected to column chromatography (30:70 EtOAc/hexane) to give the desired disaccharide **28a/28b** as an off-white solid (yield: 1.07 g, 60%). **28a**. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.35−7.24 (m, 5H, ArH), 5.84−5.78 (m, 1H, ═CH), 5.17−5.15 (m, 2H, ═CH_2), 5.03−4.90 (m, 3H), 4.82 (d, 1H, H-1, *J* = 3.6 Hz), 4.75 (d, 1H, *J* = 11.6 Hz), 4.73 (d, 1H, H-1′, *J* = 8.0 Hz), 4.42 (dd, 1H, *J* = 2.4 Hz), 4.11 (dd, 1H, *J* = 4.4 Hz, *J* = 4.8 Hz), 3.92 (dd, 1H, *J* = 8.4 Hz, *J* = 8.8 Hz), 3.85−3.81 (m, 2H), 3.77−3.66 (m, 3H), 3.48 (s, 3H, COOMe), 3.47−3.45 (m, 1H), 3.25 (dd, 1H, *J* = 3.6 Hz, *J* = 3.6 Hz), 2.15−2.08 (m, 2H, CH_2), 2.09 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$),

1.78−1.71 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 170.6, 170.3, 169.5, 168.8, 166.8, 138.6, 137.9, 128.5, 127.6, 127.4, 115.4, 101.1, 97.8, 79.1, 78.1, 74.9, 72.8, 72.3, 71.9, 69.4, 68.6, 68.1, 63.1, 62.3, 52.9, 30.3, 28.6, 21.0, 20.7, 20.6. HRMS−FAB: [M^+ + Li] calcd for $C_{33}H_{43}O_{15}N_3$, 728.2854; found, 728.2858. **28b**. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.38−7.28 (m, 5H, ArH), 5.84−5.75 (m, 1H, =CH), 5.16−5.12 (m, 2H, $=CH_2$), 5.03−4.91 (m, 4H), 4.83 (d, 1H, J = 11.2 Hz), 4.73 (d, 1H, H-1′, J = 8.0 Hz), 4.42 (dd, 1H, J = 2.4 Hz), 4.23 (d, 1H, H-1, J = 7.8 Hz), 4.07 (dd, 1H, J = 5.2 Hz), 3.88−3.84 (s, 1H), 3.78 (d, 1H, J = 9.2 Hz), 3.73−3.65 (m, 1H), 3.52 (m, 1H), 3.50 (s, 3H, COOMe), 3.48−3.35 (m, 3H), 2.12−2.06 (m, 2H, CH_2), 2.03 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.96 (s, 3H, $COCH_3$), 1.72−1.60 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 170.7, 170.3, 170.1, 168.8, 166.4, 138.5, 137.2, 128.5, 127.8, 127.3, 115.1, 102.2, 101.6, 81.6, 79.8, 75.1, 72.8, 72.6, 72.1, 70.0, 69.7, 66.2, 62.1, 52.4, 30.2, 29.6, 20.8, 20.4. HRMS−FAB: [M^+ + Li] calcd for $C_{33}H_{43}O_{15}N_3$, 728.2854; found, 728.2824.

(C) Synthesis of 3-*O*-Acetyl-Protected *β*-(1,4)-Linked *n*-Pentenyl Disaccharide (29b). This procedure is the same as that above. Stoichiometric ratio: **26b** (1.76 mmol, 0.63 g), **13** (2 equiv, 3.52 mmol, 1.68 g), TMSOTf (0.05 equiv of a 0.22 M solution, 0.088 mmol, 400 μL); yield: 260 mg (25%). **29b**. ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.76−5.72 (m, 2H, =CH + ring proton), 5.63 (m, 1H), 5.48−5.42 (m, 2H), 5.02−4.91 (m, 3H), 4.58 (d, 1H, J = 8.0 Hz), 4.42 (d, 1H, J = 7.6 Hz), 4.3−4.14 (m, 1H), 3.96−3.89 (m, 2H), 3.73−3.66 (m, 4H, COOMe + ring proton), 3.50−3.48 (m, 2H), 2.95 (dd, 1H, J = 3.2 Hz), 2.15−1.95 (m, 17H, 5 × $COCH_3$ + CH_2), 1.75−1.71 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 170.9, 170.1, 169.5, 168.6, 168.5, 144.8, 137.8, 116.0, 115.4, 102.1, 96.2, 73.2, 72.6, 69.1, 68.3, 68.0, 65.7, 62.6, 61.2, 53.0, 30.3, 28.6, 21.2, 21.1, 21.0, 20.9. HRMS−FAB: [M^+ + H] calcd for $C_{28}H_{39}O_{16}N_3$, 674.2364; found, 674.2330.

Synthesis of Deprotected *β*-(1,4)-Linked 2-Azido Disaccharide 30b. Compound **28b** (1.48 mmol, 1.07 g) was dissolved in a 9:1 MeOH/H_2O mixture (5 mL) and stirred at 0 °C. A 3 M NaOH solution was added, and the reaction mixture was allowed to stir at room temperature for 2 h (monitored by TLC). The reaction was then quenched using a strongly acidic Dowex H^+ ion-exchange resin and filtered, and the filtrate was concentrated in vacuo. The crude product was then purified by gel filtration using a Sephadex LH-20 column with methanol as the eluant. Removal of the solvent followed by subsequent lyophilization gave the saponified product as a white solid. Yield: 650 mg (82%). ^1H NMR (CD_3OD, 400 MHz) δ: 7.43 (d, 2H, ArH, J = 6.8 Hz), 7.41 (m, 3H), 5.84−5.79 (m, 1H, =CH), 5.06 (d, 1H, J = 10.4 Hz), 5.05−4.98 (m, 2H, $=CH_2$), 4.66 (d, 1H, J = 10.8 Hz), 4.60 (d, 1H, H-1′, J = 8.0 Hz), 4.34 (d, 1H, H-1, J = 7.8 Hz), 3.98−3.85 (m, 4H), 3.74 (d, 1H, J = 9.6 Hz), 3.59−3.54 (m, 2H), 3.33−3.24 (m, 3H), 2.16−2.12 (m, 2H, CH_2), 1.69−1.66 (m, 2H, CH_2). ^{13}C NMR (CD_3OD, 400 MHz) δ: 171.1, 138.1, 128.4, 128.0, 127.3, 114.2, 103.4, 102.0, 81.6, 76.9, 76.1, 75.7, 75.5, 75.1, 74.2, 71.9, 69.0, 66.6, 60.0, 30.1, 28.8. HRMS−FAB: [M^+ + Li] calcd for $C_{24}H_{32}O_{11}N_3$, 546.2275; found, 546.2269.

The above deprotected compound (1.21 mmol, 650 mg) was dissolved in 3 mL of dry methanol and cooled to −78 °C. Ozone was bubbled through the light-yellow solution for 1.5 h. The pale-yellow solution appeared to turn pale blue. To this solution was added 3 mL of dimethyl sulfide at −78 °C, and the reaction was stirred and allowed to warm to room temperature overnight. The reaction mixture was concentrated, and the crude product was purified using Sephadex LH-20 with methanol as the eluant. The pure compound **30b** obtained was then lyophilized to give an off-white solid. Yield: 554 mg (85%). **30b**. ^1H NMR (CD_3OD, 400 MHz) δ: 9.72 (s, 1H, CHO), 7.43 (d, 2H, ArH, J = 7.6 Hz), 7.32−7.26 (m, 3H, ArH), 5.06 (d, 1H, J = 10.8 Hz), 4.65 (d, 1H, J = 10.8 Hz), 4.60 (d, 1H, J = 8.0 Hz), 4.56−4.54 (m, 0.5H), 4.4−4.38 (m, 0.5H), 4.35 (d, 1H, J = 8.0 Hz), 3.94−3.85 (m, 4H), 3.75 (d, 1H, J = 10 Hz), 3.58 (t, 2H, J = 9.2 Hz, J = 9.6 Hz), 3.43−3.35 (m, 3H), 3.25−3.23 (m, 1H), 1.68−1.58 (m, 4H). HRMS−FAB: [M^+ + Li] calcd for $C_{23}H_{31}O_{12}N_3$, 548.2068; found, 548.2053.

Synthesis of 32a/32b. In a flame-dried flask, compound **28a/28b** (1.48 mmol, 1.07 g) was dissolved in 5 mL of thioacetic acid (CH_3COSH). The reaction mixture was then allowed to stir for 24 h under an argon atmosphere. Upon completion of the reaction, the excess thioacetic acid was removed in vacuo, and the reaction mixture was subjected to column chromatography (100:0 $CHCl_3/CH_3OH$ to 2.5:95 $CHCl_3/CH_3OH$) to give the N-acetylated product **32a/32b** as a pale-yellow crystalline material (yield: 605 mg, 55%). **32a**. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.28−7.21 (m, 5H, ArH), 5.62−5.42 (m, 1H, =CH), 5.18−5.11 (m, 3H), 5.02−4.94 (m, 4H), 4.67−4.65 (m, 2H), 4.54 (d, 1H, J = 12.4 Hz), 4.42 (d, 1H, J = 11.6 Hz), 4.12−4.05 (m, 2H), 3.88 (d, 1H, J = 9.2 Hz), 3.75−3.72 (m, 2H), 3.59−3.56 (m, 2H), 3.50 (s, 3H, COOMe), 3.32−3.17 (m, 1H), 2.07 (s, 3H, $COCH_3$), 2.04 (m, 2H, CH_2), 2.03 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.96 (s, 3H, $COCH_3$), 1.72 (s, 3H, $NHCOCH_3$), 1.78−1.62 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 170.7, 170.2, 170.0, 169.6, 169.3, 167.0, 139.1, 138.0, 128.6, 127.9, 127.7, 115.3, 101.2, 97.4, 79.6, 78.1, 74.8, 72.6, 72.4, 71.9, 69.4, 68.8, 67.7, 62.2, 52.9, 52.5, 30.4, 28.6, 23.5, 21.1, 20.7, 20.6. HRMS−FAB: [M^+ + Li] calcd for $C_{35}H_{47}O_{16}N$, 744.3055; found, 744.3048. **32b**. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.30−7.21 (m, 5H, ArH), 5.9 (br m, 1H, NH), 5.81−5.68 (m, 1H, =CH), 5.23−5.15 (m, 2H, $=CH_2$), 5.02−4.89 (m, 3H), 4.78 (d, 1H, J = 12.4 Hz), 4.70 (d, 1H, J = 5.4 Hz), 4.65 (d, 1H, J = 12.4 Hz), 4.58 (d, 1H, H-1, J = 8.4 Hz), 4.45 (dd, 1H, J = 4 Hz, J = 3.2 Hz), 4.23 (dd, 1H, J = 6 Hz), 3.95−3.90 (m, 2H), 3.81−3.64 (m, 4H), 3.60 (s, 3H, COOMe), 3.42−3.38 (m, 1H), 2.06 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.03−1.99 (m, 2H, CH_2), 1.98 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.83 (s, 3H, $NHCOCH_3$), 1.66−1.58 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 170.7, 170.5, 170.1, 169.9, 169.6, 166.9, 138.7, 138.2, 128.5, 127.7, 115.1, 100.4, 100.0, 76.9, 73.6, 72.8, 72.5, 71.8, 71.5, 69.5, 69.1, 63.6, 53.2, 53.1, 30.2, 28.8, 23.4, 21.1, 20.7, 20.6. HRMS−FAB: [M^+ + H] calcd for $C_{35}H_{47}O_{16}N$, 738.2973; found, 738.2964.

Synthesis of 34a/34b. To a solution of acetamido derivative **32a/32b** (0.82 mmol, 605 mg) dissolved in a 9:1 MeOH/H_2O mixture (3 mL) was added a 3 M NaOH solution at 0 °C, and the reaction mixture was allowed to stir at room temperature for 2 h (monitored by TLC). The addition of a strongly acidic Dowex H^+ ion-exchange resin to the reaction mixture not only neutralized the excess base but also changed the pH of the solution from basic to acidic. Subsequently, the reaction mixture was filtered, concentrated, and subjected to gel filtration using a Sephadex LH-20 column with methanol as the eluant. Removal of the solvent followed by subsequent lyophilization gave the deacteylated and deesterified product as a white solid **33a/33b** (yield: 391 mg, 86%). **33a**. ^1H NMR (CD_3OD, 400 MHz) δ: 7.9 (d, 1H, NH, J = 9.2 Hz), 7.35−7.24 (m, 5H, ArH), 5.85−5.76 (m, 1H, =CH), 5.03−4.99 (m, 4H), 4.71 (d, 1H, H-1, J = 3.6 Hz), 4.61 (t, 3H, J = 7.2 Hz′, J = 10.8 Hz), 4.12−4.02 (m, 1H), 4.02−3.88 (m, 2H), 3.87−3.76 (m, 2H), 3.70−3.67 (m, 2H), 3.52 (t, 1H, J = 8.8 Hz, J = 8.8 Hz), 3.42−3.35 (m, 2H), 3.29−3.26 (m, 1H), 2.18−2.10 (m, 2H, CH_2), 1.87 (s, 3H, $NHCOCH_3$), 1.71−1.65 (m, 2H, CH_2). ^{13}C NMR (CD_3OD, 400 MHz) δ: 176.1, 176.0, 143.1, 142.1, 131.9, 131.2, 118.7, 107.4, 101.4, 83.1, 81.2, 80.1, 79.4, 78.2, 75.9, 75.5, 71.1, 64.2, 57.0, 34.1, 32.5, 25.5. HRMS−FAB: [M^+ + Li] calcd for $C_{26}H_{37}O_{12}N$, 562.2476; found, 562.2465. **33b**. ^1H NMR (CD_3OD, 400 MHz) δ: 7.32−7.22 (m, 5H, ArH), 5.85−5.76 (m, 1H, =CH), 5.01−4.97 (m, 4H), 4.61 (d, 1H, H-1, J = 7.6 Hz), 4.55 (d, 1H, J = 11.2 Hz), 4.45 (d, 1H, J = 7.6 Hz), 3.98−3.83 (m, 4H), 3.76−3.67 (m, 3H), 3.56−3.54 (m, 1H), 3.48−3.36 (m, 2H), 3.29−3.26 (m, 1H), 2.08−2.06 (m, 2H, CH_2), 1.80 (s, 3H, $NHCOCH_3$), 1.62−1.58 (m, 2H, CH_2). ^{13}C NMR (CD_3OD, 400 MHz) δ: 176.0, 175.1, 143.1, 142.1, 132.2, 132.1, 131.8, 118.1, 107.5, 105.3, 85.2, 81.5, 80.1, 79.5, 78.3, 78.2, 75.9, 72.6, 64.3, 59.3, 33.9, 32.7, 25.8. HRMS−FAB: [M^+ + Li] calcd for $C_{26}H_{37}O_{12}N$, 562.2476; found, 562.2465.

The saponified product obtained, **33a/33b** (0.704 mmol, 391 mg), was dissolved in 3 mL of dry methanol and cooled to −78 °C. Ozone was bubbled through the light-yellow solution for 1.5 h. The pale-yellow solution appeared to turn pale blue. To this solution was added 3 mL of dimethyl sulfide at −78 °C, and the reaction was stirred and allowed to warm to room temperature overnight. The reaction mixture was concentrated, and the crude product was purified using Sephadex LH-20 with methanol as the eluant. The pure compound obtained was then lyophilized to give an off-white solid (yield: 353 mg, 90%). **34a**. ^{1}H NMR (CD_3OD, 400 MHz) δ: 9.70 (s, 1H, CHO), 7.96 (d, 1H, NH, J = 9.2 Hz), 7.40−7.19 (m, 5H, ArH), 5.05 (d, 2H, J = 11.2 Hz), 4.72 (d, 1H, H-1, J = 3.2 Hz), 4.62 (t, 2H, H-1′ merged), 4.52 (m, 1H), 4.12 (m, 1H), 3.94−3.91 (m, 2H), 3.83−3.66 (m, 4H), 3.56−3.49 (m, 1H), 3.47−3.37 (m, 2H), 3.29−3.26 (m, 1H), 1.88 (s, 3H, $NHCOCH_3$), 1.68−1.66 (m, 4H, CH_2). ^{13}C NMR (CD_3OD, 400 MHz) δ: 203.6, 172.7, 172.1, 139.1, 128.1, 128.0, 127.3, 103.4, 98.4, 97.5, 79.2, 77.2, 76.3, 75.4, 74.4, 72.1, 71.6, 67.5, 60.4, 53.1, 33.4, 33.3, 24.6, 21.5. HRMS−FAB: [M^+ + 2Li − H] calcd for $C_{25}H_{35}O_{13}N$, 570.2358; found, 570.2352. **34b**. ^{1}H NMR (CD_3OD, 400 MHz) δ: 9.72 (s, 1H, CHO), 7.98 (d, 1H, NH, J = 7.6 Hz), 7.33−7.23 (m, 5H, ArH), 4.64 (s, 1H), 4.62 (d, 1H, H-1, J = 8.0 Hz), 4.56 (d, 1H, J = 11.6 Hz), 4.48 (br s, 1H), 4.46 (d, 1H, H-1′, J = 7.8 Hz), 3.94−3.84 (m, 4H), 3.77−3.63 (m, 2H), 3.58−3.55 (m, 2H), 3.45−3.39 (m, 2H), 3.29−3.26 (m, 1H, H-2), 1.83 (s, 3H, $NHCOCH_3$), 1.64−1.58 (br m, 4H, CH_2). ^{13}C NMR (CD_3OD, 400 MHz) δ: 204.2, 172.2, 171.2, 139.2, 128.2, 128.1, 127.3, 103.5, 101.3, 98.4, 89.5, 81.4, 77.6, 76.2, 75.6, 74.4, 74.3, 72.0, 69.2, 60.4, 55.3, 33.2, 33.1, 28.9, 22.0. HRMS−FAB: [M^+ + 2Li − H] calcd for $C_{25}H_{35}O_{13}N$, 570.2360; found, 570.2352.

Synthesis of 35a/35b. A solution of **34a/34b** (0.64 mmol, 353 mg) in 8:2 MeOH/H_2O was hydrogenated in the presence of 10% Pd−C (4 equiv). After 24 h and upon completion of the reaction (TLC), the suspension was filtered through a pad of Celite and concentrated to give the debenzylated product. Final purification of the compound was carried out on Sephadex LH-20 using MeOH as the eluant. The absence of aromatic peaks in the ^{1}H NMR spectrum indicated complete debenzylation (yield: 207 mg, 70%). **35a**. ^{1}H NMR (DMSO, 400 MHz) δ: 9.64 (s, 1H, CHO), 7.81 (d, 1H, NH, J = 9.2 Hz), 5.2−4.98 (br peak, OH), 4.60 (d, 1H, H-1, J = 2.8 Hz), 4.34 (d, 1H, H-1′, J = 8.0 Hz), 4.32−3.94 (m, 1H), 3.68−3.52 (m, 6H), 3.48−3.35 (m, 2H), 3.28−3.24 (t, 1H, J = 8.8 Hz, J = 9.2 Hz), 3.2−3.12 (m, 2 H), 3.01−2.98 (m, 1H), 1.78 (s, 3H, $NHCOCH_3$), 1.52−1.48 (m, 4H, CH_2). ^{13}C NMR (DMSO, 400 MHz) δ: 204.1, 170.8, 170.1, 103.6, 96.9, 80.9, 76.5, 75.6, 73.7, 72.0, 71.3, 69.3, 67.4, 60.3, 54.1, 52.7, 29.4, 24.7, 23.1. HRMS−FAB: calcd for $C_{18}H_{29}O_3N$, 474.2556; found, 474.2552. **35b**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.72 (br s, 1H, −CHO), 7.82 (br s, 1H, −NH, J = 9.2 Hz), 5.4−5.2 (br peak, OH), 4.40 (d, 1H, H-1, J = 7.6 Hz), 4.34 (d, 1H, H-1′, J = 8.0 Hz), 4.30−4.25 (m, 1H), 3.81−3.54 (m, 4H), 3.42−3.38 (m, 4H), 3.33−3.30 (m, 1H), 3.22−3.11 (m, 2H), 3.02−2.96 (m, 1H), 1.75 (s, 3H, $NHCOCH_3$), 1.68−1.48 (m, 4H, CH_2). ^{13}C NMR (CD_3OD, 400 MHz) δ: 197.8, 171.2, 169.5, 104.3, 103.5, 101.5, 80.7, 76.5, 75.6, 75.4, 73.6, 72.7, 72.1, 68.8, 60.7, 55.4, 52.9, 29.1, 24.8, 23.5. HRMS−FAB: [M^+ + Li] calcd. for $C_{18}H_{29}O_3N$, 474.2556; found, 474.2550.

Synthesis of Gemini Heparinoid-Mimetic Disaccharides 4a/4b. Compound **35a/35b** (0.14 mmol, 65 mg) was dissolved in 0.5 mL of dry methanol, and ethylenediamine (0.5 equiv, 0.07 mmol, 4.67 μL) was added in a dropwise manner. There was an immediate precipitation of a white solid. The reaction mixture was stirred for 3 h at room temperature, $NaBH_3CN$ (4 equiv, 56 mmol, 36 mg) was then added , and the reaction mixture was allowed to stir overnight. Removal of the solvent gave a residue, which was purified using Sephadex G-25 with water as the eluant and subsequently lyophilized to give a pale-yellow powder (**4a/4b**) (yield: 45 mg, 67%). **4a**. ^{1}H NMR (D_2O, 400 MHz) δ: 7.86 (d, J = 7.2 Hz), [in DMSO-d_6, the α-anomeric peak appears at 4.6 (d, 2H, H-1, J = 3.2 Hz)], 4.39 (d, 1H, H-1′, J = 8.0 Hz), 4.37 (d, 1H, H-1′, J = 7.6 Hz), 3.82−3.50 (m, 20H), 3.36−3.10 (m, 12H), 2.98 (t, 2H), 2.67 (t, 2H), 1.86 (s, 6H, $NHCOCH_3$), 1.62−1.48 (m, 8H, CH_2). ^{13}C NMR (D_2O, 400 MHz) δ: 173.1, 170.2, 104.4, 103.4, 96.9, 96.8, 80.8, 76.7, 74.2, 73.7, 72.4, 71.4, 69.4, 60.5, 54.1, 53.2, 30.1, 23.9, 22.1. HRMS−FAB: [M^+ + H] calcd for $C_{38}H_{67}O_{24}N_4$, 963.4239; found, 963.4214. **4b**. ^{1}H NMR (D_2O, 400 MHz) δ: 4.46 (d, 1H, J = 8 Hz), 4.40−4.36 (merged d, 3H, J = 8.0 Hz), 3.81−3.74 (m, 3H), 3.66 (dd, 2H, J = 4.8 Hz, J = 4.8 Hz), 3.58−3.22 (m, 12H), 3.19−3.15 (m, 12H), 2.96 (t, 2H), 2.85 (m, 2H), 2.72 (t, 2H), 1.85 (s, 6H, $NHCOCH_3$), 1.52−1.41 (m, 8H, CH_2). ^{13}C NMR (D_2O, 400 MHz) δ: 175.6, 174.4, 104.7, 104.6, 102.3, 101.1, 79.1, 75.9, 75.4, 74.8, 73.1, 72.4, 71.8, 69.9, 60.2, 55.2, 53.3, 53.0, 28.5, 23.7, 22.2. HRMS−FAB: [M^+ + H] calcd for $C_{38}H_{67}O_{24}N_4$, 963.4430; found, 963.4482.

Supporting Information Available: General experimental details and ^{1}H and ^{13}C NMR spectra of compounds **4a**, **4b**, and **13**−**35b** are available free of charge via the Internet at http://pubs.acs.org.

JO049092R