JOC Featured Article

pubs.acs.org/joc

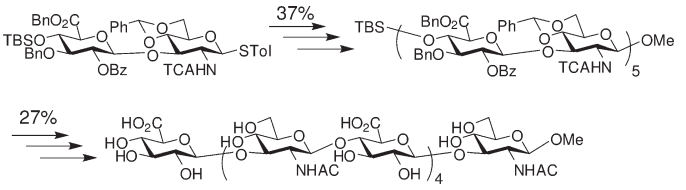
Chemical Synthesis of a Hyaluronic Acid Decasaccharide

Xiaowei Lu, Medha N. Kamat, Lijun Huang,† and Xuefei Huang*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824. †*Current address: Anatrace, Inc., 434 W. Dussel Dr., Maumee, OH 43537.*

xuefei@chemistry.msu.edu

Received August 3, 2009



The chemical synthesis of a hyaluronic acid decasaccharide using the preactivation-based chemoselective glycosylation strategy is described. Assembly of large oligosaccharides is generally challenging due to the increased difficulties in both glycosylation and deprotection. Indeed, the same building blocks previously employed for hyaluronic acid hexasaccharide syntheses failed to yield the desired decasaccharide. After extensive experimentation, the decasaccharide backbone was successfully constructed with an overall yield of 37% from disaccharide building blocks. The trichloroacetyl group was used as the nitrogen protective group for the glucosamine units, and the addition of TMSOTf was found to be crucial to suppress the formation of trichloromethyl oxazoline side product and enable high glycosylation yield. For deprotections, the combination of a mild basic condition and the monitoring methodology using ^{1}H NMR allowed the removal of all base-labile protective groups, which facilitated the generation of the fully deprotected HA decasaccharide.

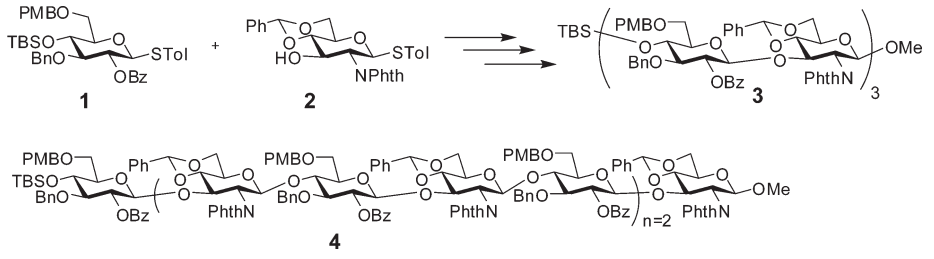
Introduction

Hyaluronic acid (HA), a component of the extracellular matrix and a member of the glycosaminoglycan family, contains linear tandem disaccharide repeats of D-glucuronic acid and 2-deoxy-2-*N*-acetyl-D-glucose [β-D-Gl*cp*A-(1→3)-β-D-Gl*cp*NAc-(1→4)-].[1] HA can interact with a wide variety of cell surface receptors, including the lymphatic vessel endothelial receptor, CD44, TNF-simulated gene-6, and HA receptor for endocytosis.[2−4] The biological activities of HA can be length dependent.[5] For example, HA polymers have been found to be antiangiogenic, while its oligomers promote angiogenesis.[6,7] HA is the major ligand of CD44, a transmembrane protein involved in cell−cell, cell−matrix interactions and signal transduction.[3] Evidence is accumulating suggesting that the size of HA fragments recognized by CD44 provides a physiologically important switch between its adhesion and signaling functions.[8] Binding of HA polymers to CD44 usually leads to cell adhesion[9,10] rather than activation. In contrast, recognition of HA fragments instead of the polymer leads to CD44 signaling, which is involved in diseases such as cancer and inflammation.[11−14] CD44 requires at least an HA hexasaccharide sequence for binding,

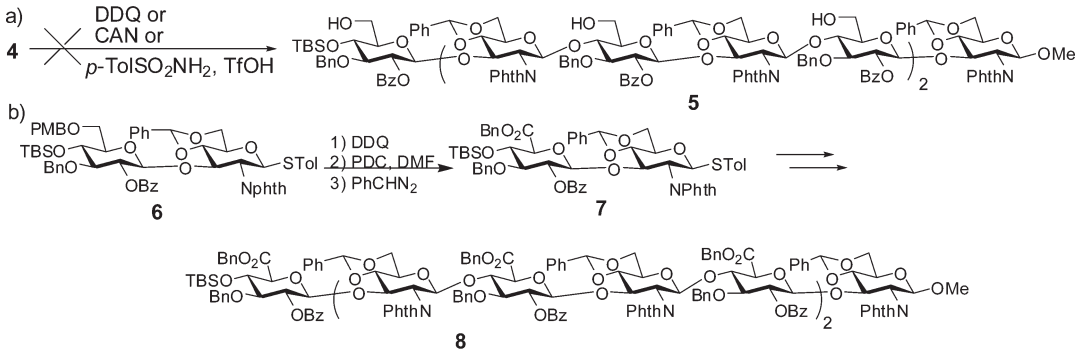
(1) Lapcik, L. Jr.; Lapcik, L.; De Smedt, S.; Demeester, J.; Chabrecek, P. *Chem. Rev*. **1998**, *98*, 2663–2684.
(2) Harris, E. N.; Weigel, P. H. *Glycobiology* **2008**, *18*, 638–648 and references cited therein.
(3) Ponta, H.; Sherman, L.; Herrlich, P. A. *Nat. Rev. Cell Biol*. **2003**, *4*, 33–45.
(4) Prevo, R.; Banerji, S.; Ferguson, D. J. P.; Clasper, S.; Jackson, D. G. *J. Biol. Chem*. **2001**, *276*, 19420–19430.
(5) Asari, A. *Glycoforum Hyaluronan Today* **2005**, http://www.glycoforum.gr.jp/science/hyaluronan/hyaluronanE.html.
(6) West, D. C.; Fan, T.-P. D. In *New Angiotherapy*; Fan, T.-P. D., Kohn, E. C., Eds.; Humana Press: Totowa, NJ, 2002; pp 177−188.
(7) West, D. C.; Hampson, I. N.; Arnold, F.; Kumar, S. *Science* **1985**, *228*, 1324–1326.
(8) Aruffo, A. *J. Clin. Invest*. **1996**, *98*, 2191–2192.
(9) DeGrendele, H. C.; Estess, P.; Picker, L. J.; Siegelman, M. H. *J. Exp. Med*. **1996**, *183*, 1119–1130.
(10) Jalkanen, S.; Bargatze, R. F.; de los Toyos, J.; Butcher, E. C. *J. Cell Biol*. **1987**, *105*, 983–990.
(11) Jiang, D.; Liang, J.; Fan, J.; Yu, S.; Chen, S.; Luo, Y.; Prestwich, G. D.; Mascarenhas, M. M.; Garg, H. G.; Quinn, D. A.; Homer, R. J.; Goldstein, D. R.; Bucala, R.; Lee, P. J.; Medzhitov, R.; Noble, P. W. *Nat. Med*. **2005**, *11*, 1173–1179.
(12) Misra, S.; Ghatak, S.; Zoltan-Jones, A.; Toole, B. P. *J. Biol. Chem*. **2003**, *278*, 25285–25288.
(13) Ghatak, S.; Misra, S.; Toole, B. P. *J. Biol. Chem*. **2002**, *277*, 38013–38020.
(14) McKee, C. M.; Penno, M. B.; Cowman, M.; Bao, C.; Noble, P. W. *J. Clin. Invest*. **1996**, *98*, 2403–2413.

Published on Web 09/21/2009 DOI: 10.1021/jo9016925

SCHEME 1. Previous Synthesis of HA Hexasaccharide 3



SCHEME 2



and only a decasaccharide or higher can effectively compete with polymeric HA.[15] Therefore, access to synthetic HA with variable length and sequence can greatly facilitate the establishment of its structure−activity relationship.[5]

HA can be synthesized via either enzymatic or chemical methods.[16] Based on the understanding of HA biosynthetic and catabolism pathways, innovative studies have been carried out utilizing HA synthases or hyaluronidases to acquire synthetic HA.[17−19] While impressive synthetic efficiency has been achieved, the inherent substrate specificities of enzymes limit the structural diversity of HA analogues that can be generated. Chemical synthesis can thus complement the enzymatic approaches to create greater varieties of HA structures.

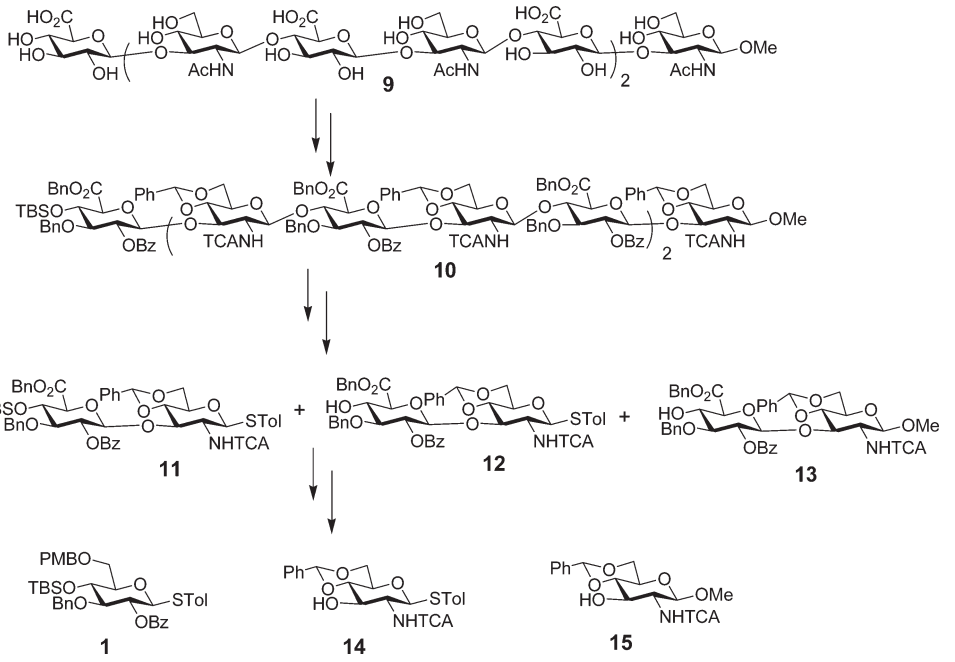
Chemical syntheses of HA oligomers have been performed with the majority of studies focusing on di- and hexasaccharides.[16,20−25] The longest HA oligosaccharides chemically assembled to date are an HA octasaccharide[26] and heptasaccharide.[27] Previously, our group has developed a synthetic strategy to acquire HA oligosaccharides ranging from di- to hexasaccharides.[21] With the fascinating biological activities of longer HA oligosaccharides, we became interested in pursuing their chemical synthesis, which is not a trivial extension of shorter oligomers because elongation of the sugar sequences can create significant new challenges in both glycosylation and deprotection. Herein, we report our results on overcoming the obstacles for chemical synthesis of an HA decasaccharide.

Results and Discussion

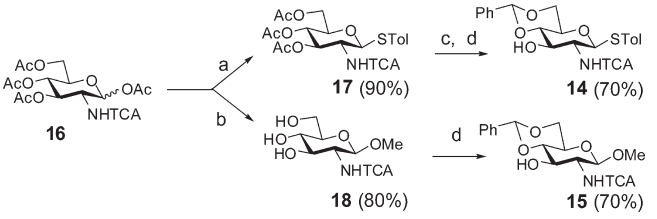
The design of a successful route to HA oligosaccharides must take into account three factors: (1) stereochemical control in glycosylation; (2) introduction of the glucuronic acid; and (3) protective groups for the glucosamine nitrogen moieties. In our previous hexasaccharide synthesis, we used two key building blocks **1** and **2**, which led to high yield of hexasaccharide **3** in one pot (Scheme 1).[21] The benzoyl (Bz) and phthalimido (Phth) groups were crucial to facilitate the formation of 1,2-*trans* glycosidic linkages. Due to its high inherent reactivities,[28] glucoside building block **1** was utilized as a glucuronic acid surrogate.[21] The *p*-methoxybenzyl (PMB) groups in **3** masking the glucoside 6-O-position were selectively removed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation, and the resulting triol was successfully oxidized and deprotected producing HA hexasaccharide. Following the success of hexasaccharide synthesis, our initial attempt toward HA decasaccharide hinged upon the usage of monosaccharides **1** and **2**, from which decasaccharide **4** was assembled. However, removal of the five PMB groups in **4** turned out to be very problematic

(15) Tammi, R.; MacCallum, D.; Hascall, V. C.; Pienimäki, J. P.; Hyttinen, M.; Tammi, M. *J. Biol. Chem.* **1998**, *273*, 28878–28888.
(16) Huang, L.; Lu, X.; Huang, X. In *Chemical Glycobiology*; Chen, X., Halcomb, R. L., Wang, P. G., Eds.; ACS Symp. Ser. 990; American Chemical Society: Washington, DC, 2008; pp 29−53 and references cited therein.
(17) DeAngelis, P. L.; Oatman, L. C.; Gay, D. F. *J. Biol. Chem.* **2003**, *278*, 35199–35203 and references cited therein.
(18) Kobayashi, S.; Morii, H.; Itoh, R.; Kimura, S.; Ohmae, M. *J. Am. Chem. Soc.* **2001**, *123*, 11825–11826.
(19) Luca, C. D.; Lansing, M.; Martini, I.; Crescenzi, F.; Shen, G.-J.; O'Regan, M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 5869–5870.
(20) Dinkelaar, J.; Codee, J. D. C.; van den Bos, L. J.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *J. Org. Chem.* **2007**, *72*, 5737–5742.
(21) Huang, L.; Huang, X. *Chem.—Eur. J.* **2007**, *13*, 529–540.
(22) Palmacci, E. R.; Seeberger, P. H. *Tetrahedron* **2004**, *60*, 7755–7766.
(23) Iyer, S. S.; Rele, S. M.; Baskarana, S.; Chaikof, E. L. *Tetrahedron* **2003**, *59*, 631–638.
(24) Yeung, B. K. S.; Chong, P. Y. C.; Petillo, P. A. In *Glycochemistry. Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Marcel Dekker, Inc.: New York, 2001; pp 425-492.
(25) Halkes, K. M.; Slaghek, T.; Hypponen, T. K.; Kruiskamp, P. H.; Ogawa, T.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1998**, *309*, 161–174.
(26) Blatter, G.; Jacquinet, J.-C. *Carbohydr. Res.* **1996**, *288*, 109–125.
(27) Dinkelaar, J.; Gold, H.; Overkleeft, H. S.; Codee, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4208–4216.
(28) Zeng, Y.; Wang, Z.; Whitfield, D.; Huang, X. *J. Org. Chem.* **2008**, *73*, 7952–7962.

SCHEME 3. Retrosynthetic Scheme toward HA Decasaccharide 9



SCHEME 4. Syntheses of Monosaccharide Building Blocks 14 and 15[a]



[a]Key: (a) *p*-TolSH, $BF_3 \cdot OEt_2$, DCM; (b) (i) HBr/AcOH, (ii) Ag_2CO_3, $CaSO_4$, MeOH; (c) NaOMe/MeOH; (d) $Ph(OMe)_2$, camphorsulfonic acid.

(Scheme 2a). The previously employed DDQ oxidation[21] decomposed the oligosaccharide. Cerium ammonium nitrate (CAN) oxidation[29] or the combination of *p*-tolyl sulfonamide and triflic acid[30] also failed to lead to the desired pentaol. To circumvent this problem, the 6-hydroxyl group liberation and oxidation state adjustment were performed on disaccharide **6** (Scheme 2b). DDQ-mediated PMB removal followed by primary hydroxyl oxidation and benzyl ester formation produced disaccharide **7** containing the glucuronic acid moiety. Condensations of the resulting disaccharides afforded decasaccharide **8** with the glucuronic acids already installed, which set the stage for deprotection. Although it has been shown previously that Phth groups could be deprotected in molecules containing carboxylic esters,[21,25,31] despite repeated trials and screening of a variety of reagents and reaction conditions, the conditions required to remove all five Phth groups in **7** turned out to be incompatible with the five carboxylic ester moieties present and vice versa. This prompted us to abandon the Phth group and utilize the trichloroacetyl (TCA) group[26,27] as an alternative protective group for nitrogen.

Based on these considerations, a new retrosynthetic route toward HA decasaccharide **9** is designed (Scheme 3). The fully protected decasaccharide **10** will be assembled from disaccharides **11**, **12**, and **13**, which in turn will be derived from monosaccharide building blocks **1**, **14**, and **15**.

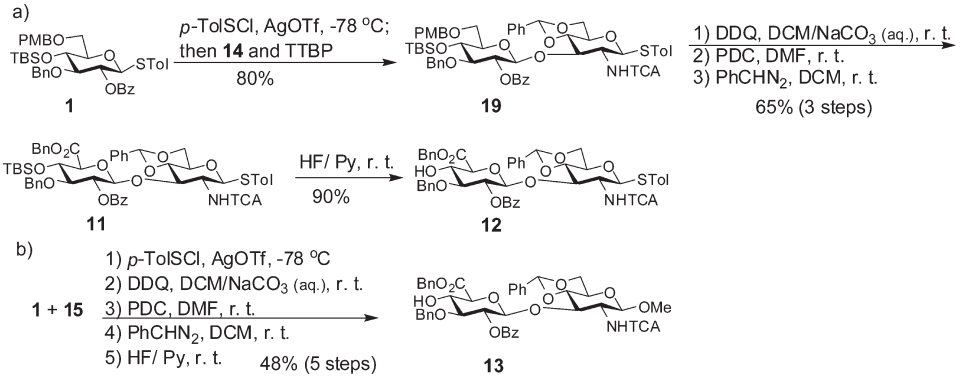
Glucoside donor **1** was prepared according to a literature procedure,[21] and the syntheses of glucosamine building blocks **14** and **15** are outlined in Scheme 4. Peracetylated *N*-trichloroacetylglucosamine **16**[26] was transformed into the corresponding 1-β-*p*-tolyl thioglycoside **17** and the 1-β-methoxy derivative **18**. Compound **17** was then deacetylated and protected with a benzylidene group to afford **14**, whereas compound **18** was protected by benzylidene to give **15**.

With the monosaccharides in hand, disaccharide synthesis was performed. Preactivation of glucoside donor **1** by the reagent combination of silver triflate (AgOTf) and *p*-toluenesulfenyl chloride (*p*-TolSCl)[21,32] at -78 °C was performed followed by the addition of acceptor **14** and a bulky base 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[33] leading to disaccharide **19** in 80% yield. The primary hydroxyl group in **19** was liberated by treatment with DDQ and oxidized by pyridinium dichromate (PDC) in dimethylformamide (DMF) to afford its carboxylic acid derivative, which was protected as a benzyl ester (disaccharide **11**) in 65% yield for the three steps. Subsequent removal of the TBS group led to the disaccharide acceptor **12** bearing a free secondary hydroxyl group (Scheme 5a). Disaccharide **13** was constructed through a similar sequence from **1** and **15** in an overall yield of 48% for the five steps (Scheme 5b).

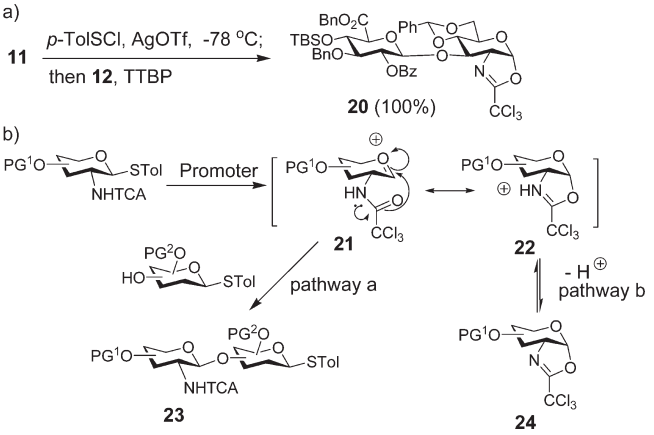
Following the same glycosylation protocol as used in the preparation of disaccharide **19**, coupling of disaccharide

(29) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2006.
(30) Hinklin, R. J.; Kiessling, L. L. *Org. Lett.* **2002**, *4*, 1131–1133.
(31) Sun, B.; Srinivasan, B.; Huang, X. *Chem.—Eur. J.* **2008**, *14*, 7072–7081.
(32) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221–5224.
(33) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323–326.

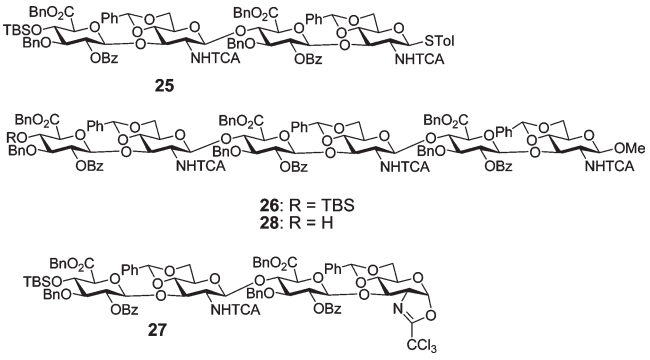
SCHEME 5. Assembly of Disaccharide Building Blocks



SCHEME 6



donor **11** with acceptor **12** was attempted (Scheme 6a). However, no desired tetrasaccharide was obtained with full recovery of acceptor **12**. Oxazoline derivative **20** ($^3J_{H1-H2}$ = 8.0 Hz[34,35]) was isolated from the reaction in quantitative yield with the possible mechanism for its formation depicted in Scheme 6b. Neighboring group participation by the TCA group through attachment of its carbonyl oxygen to the oxacarbenium ion forms the oxazolinium ion intermediate **22**, which can react with an acceptor to afford the expected 1,2-*trans*-glycoside **23** (pathway a, Scheme 6b). Alternatively, deprotonation of the oxazolinium ion produces the stable trichlorooxazoline **24** (pathway b). Following this mechanism, the failure of glycosylation could be attributed to the addition of TTBP,[27] which is used to scavenge the triflic acid accumulated upon productive glycosylation. Therefore, a second-generation glycosylation protocol was adopted by omitting TTBP from the reaction. Following this protocol, **11** (1 equiv) was condensed with **12** (1 equiv) to produce tetrasaccharide **25** in 55% yield with 40% oxazoline byproduct **20** (Table 1, entry 2). The next condensation of tetrasaccharide donor **25** (1 equiv) with disaccharide acceptor **13** gave hexasaccharide **26** in 40% yield and oxazoline **27** (50% yield). Subsequent cleavage of the TBS group in **26** gave the hexasaccharide acceptor **28** in 90% yield. Disappointingly, the final coupling of **25** (1.25 equiv) and **28** (1 equiv) only gave decasaccharide **10** in 10% yield, with the majority of **25** converted to oxazoline **27** (85% yield, Table 1, entry 2). The substantial increase of the amounts of oxazoline side products is presumably because with the increasing sizes of the glycosyl donor and acceptor, the compounds become less reactive toward glycosylation (Scheme 6b, pathway a), which in turn favors the competing reaction of oxazoline formation even in the absence of base (Scheme 6b, pathway b).



In order to suppress the amount of oxazoline, exogenous triflic acid (~0.4 equiv) was introduced to the reaction mixture after the donor activation to shift the equilibrium from oxazoline **24** to the oxazolinium ion **22** (Scheme 6b). Following this third-generation procedure, although the reaction of **11** and **12** was not affected, the yields for **25** with **13** and **28** were enhanced to 60% and 40%, respectively (Table 1, entry 3). The acid-sensitive benzylidene moieties were found to be stable under these conditions. To further improve on the glycosylation, Lewis acid trimethylsilyl triflate (TMSOTf) was examined as an alternative to TfOH. Based on this protocol, significant enhancements were observed for all three reactions (Table 1, entry 4), with the yield of decasaccharide **10** reaching 77%, which enabled us to acquire over 200 mg of this decasaccharide. These results suggest that the addition of TMSOTf successfully suppressed the formation of trichlorooxazoline byproduct.

Deprotection of large complex oligosaccharides could be very challenging due to the presence of multiple protective groups, as observed in our attempts on decasaccharides **4** and **8**. To deprotect decasaccharide **10**, its TBS group was removed first by hydrogen fluoride (HF) in pyridine to give **29** in 79% yield. This was followed by a mild basic condition

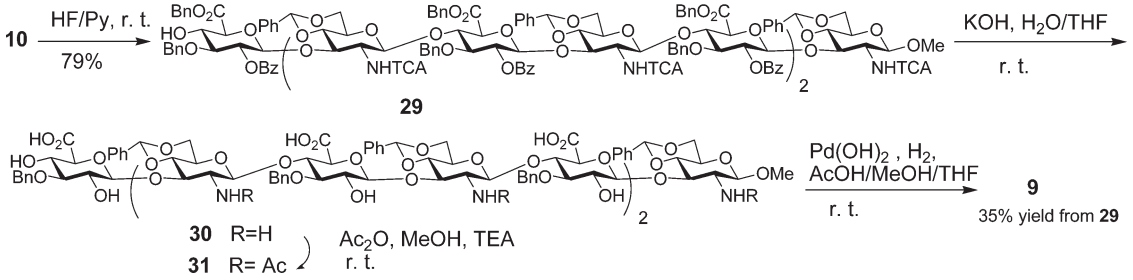
(34) Donohoe, T. J.; Logan, J. G.; Laffan, D. D. P. *Org. Lett.* **2003**, *5*, 4995–4998.

(35) Sherman, A. A.; Yudina, O. N.; Mironov, Y. V.; Sukhova, E. V.; Shashkov, A. S.; Menshov, V. M.; Nifantiev, N. E. *Carbohydr. Res.* **2001**, *336*, 13–46.

TABLE 1. Effects of Additives on Glycosylation Product Distribution

entries	reaction conditions	donor **11** + acceptor **12**	donor **25** + acceptor **13**	donor **25** + acceptor **28**
1	first generation	**20** (100%)		
	TTBP was added after donor was activated			
2	second generation	**25** (55%) + **20** (40%)	**26** (40%) + **27** (50%)	**10** (10%) + **27** (85%)
	no TTBP was added after donor was activated			
3	third generation	**25** (55%)	**26** (60%)	**10** (40%)
	TfOH was added after donor was activated			
4	fourth generation	**25** (82%)	**26** (71%)	**10** (77%)
	TMSOTf was added after donor was activated			

SCHEME 7



(20 equivalents of KOH added in 10 portions to a solution of **29** over 2 days[20]) in order to cleave all ten carboxylic esters and five trichloroacetamides (Scheme 7). Harsh basic conditions should be avoided to prevent epimerization of the glucuronic acids. The progress of the hydrolysis turned out to be difficult to monitor by TLC for two reasons. First, the liberated amino groups gave no ninhydrin test presumably due to steric hindrance. Second, the compounds with free carboxylic acid and amino groups became zwitterionic, which streaked on TLC. Mass spectrometry analysis of the crude reaction mixture did not yield much information resulting from signal suppression by the presence of salts. NMR analysis of the reaction mixture turned out to be most informative. The cluster of peaks around 8.0 ppm in ^{1}H NMR assigned to the ortho-hydrogens of benzoyl groups merged into a doublet-like pattern over time signifying the cleavage of benzoyl esters to benzoate salt. Another characteristic of the NMR is that the set of four doublets around 7.0 ppm, representing the amide protons of trichloroacetamide groups in **29**, became smaller and eventually disappeared as the reaction proceeded. The rate of trichloroacetamide cleavage was much slower compared with that of the benzoates. When the crude NMR spectra did not show much change after week 5, the reaction was stopped. The reaction mixture was *N*-acetylated followed by hydrogenation and size exclusion chromatography to produce the fully deprotected HA decasaccharide **9** in 35% yield from **29**. NMR analysis indicated all the glycosyl linkages were β, confirming no epimerizations occurred despite the prolonged reaction time.

Conclusions

We report here the first chemical synthesis of a fully deprotected HA decasaccharide. Our preactivation-based thioglycoside strategy with *p*-TolSCl/AgOTf as the promoter was successfully applied for efficient construction of the decasaccharide backbones. However, considerable difficulties were encountered in deprotection, when the selection of nitrogen protective group turned out to be crucial. While removal of all five Phth was found to be incompatible with the carboxylic esters present in the decasaccharide, TCA could be removed together with the esters under a mild basic condition. The TCA-associated oxazoline formation side reaction during glycosylation was suppressed by addition of TMSOTf to the reaction mixture. Our experience highlights the challenges associated with assembly of large oligosaccharides, as the conditions employed for synthesis of shorter counterparts may not be directly translatable and each synthesis needs individual optimization and development. We believe our strategy on the HA decasaccharide assembly can open up possibilities to chemical synthesis of longer HA oligomers and facilitate the structure−activity relationship studies of this important class of molecules.

Experimental Section

General Procedure for Deprotection of *p*-Methoxybenzyl (PMB) Group. PMB-protected compound (1 mmol) and DDQ (1.3 equiv) were dissolved in a solvent mixture of dichloromethane (CH_2Cl_2) and a saturated aqueous solution of $NaHCO_3$ (v/v 19:1), which was kept in dark. The reaction mixture was stirred for 2 h from 0 °C to room temperature. A second portion of DDQ (0.5 equiv) was added to the reaction mixture, and a third portion of DDQ (0.5 equiv) could be added 15 min after the addition of the second portion to further push the reaction to completion. When most starting material disappeared, the reaction mixture was diluted with CH_2Cl_2 and washed repeatedly with a saturated aqueous solution of $NaHCO_3$ until the organic layer become colorless. The organic layer was concentrated, and the resultant residue was purified by silica gel chromatography to give the desired compound.

General Procedure for Oxidation of Alcohols to Carboxylic Acids. After a mixture of alcohol (1 mmol) and MS-4 Å (5 g) in anhydrous DMF was stirred at room temperature for 2 h, a solution of PDC (6 mmol) in DMF was added dropwise to the reaction. The reaction mixture was stirred at room temperature until TLC indicated completion of the reaction, which typically required overnight. The reaction was diluted with ethyl acetate and filtered to remove the insoluble PDC. The filtrate was washed with brine to remove DMF. The crude product was then purified by silica gel chromatography with ethyl acetate/CH_2Cl_2/methanol solvent systems.

General Procedure for Benzyl Ester Formation. The carboxylic acid containing compound was dissolved in CH_2Cl_2 (5 mL) and treated with phenyldiazomethane solution in diethyl ether (~2 equiv)[21,36] for 2−3 h until the disappearance of all the starting material. The crude product was purified by silica gel chromatography.

General Procedure for Removal of *tert*-Butyldimethylsilyl (TBS) Groups. The TBS-protected compound (0.5 mmol) was dissolved in pyridine (4 mL) in a plastic flask followed by the addition of 65−70% HF·pyridine solution (2 mL) at 0 °C. The solution was stirred for 24 h until TLC indicated completion of the reaction. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with 10% aqueous $CuSO_4$ solution (20 mL). The aqueous phase was extracted with ethyl acetate (30 mL) twice, and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ to remove HF. The crude product was purified by silica gel chromatography.

***p*-Tolyl 4,6-*O*-Benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (14).** After D-glucosamine hydrochloride (10.78 g, 50 mmol) and sodium methoxide (50 mL 1 M NaOMe/ MeOH, 50 mmol) in methanol were stirred at room temperature under N_2 protection for 45 min, trichloroacetyl chloride (5.61 mL, 50 mmol) and triethylamine (6.95 mL, 50 mmol) were added. After overnight when ESI-MS indicated that D-glucosamine hydrochloride has completely disappeared, methanol was removed by a rotary evaporator and the flask was placed under high vacuum for 2 h. Acetic anhydride and pyridine (150 mL, v/v 1:2) were then added, and the reaction mixture was stirred for 2 days. The mixture was concentrated, and the resulting residue was diluted with ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$, 10% HCl, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. After recrystallization, 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-D-glucopyranoside (**16**) was obtained as a white solid (16.26 g, 33 mmol, 66% for two steps). Boron trifluoride dimethyl etherate (7.75 mL, 89 mmol) was added to a solution of **16** (4.93 g, 10 mmol) and *p*-toluenethiol (1.99 g, 16 mmol) in dry CH_2Cl_2 (200 mL). The reaction mixture was stirred at room temperature under N_2 protection overnight, diluted with CH_2Cl_2 (300 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. Recrystallization afforded *p*-tolyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside (**17**) as a white solid (5.01 g, 9 mmol, 90%). Compound **17** (5.01 g, 9.0 mmol) was dissolved in a mixed solvent of CH_2Cl_2 and methanol (v/v = 1/1, 200 mL). Sodium methoxide (2.7 mL 1 M NaOMe/ MeOH, 2.7 mmol) in methanol was added, and the mixture was stirred at room temperature under N_2 protection for 2 h, neutralized with Amberlite IR-120, concentrated, and dried under vacuum. Benzaldehyde dimethyl acetal (1.52 mL, 10.8 mmol) was added to a solution of the resulting residue and camphorsulfonic acid (0.94 g, 4.05 mmol) in anhydrous toluene (200 mL). The reaction mixture was stirred under N_2 protection at 80 °C for 1 h. When TLC showed around 70% conversion of starting material to product, the reaction flask was placed on a high vacuum rotary evaporator to further push the reaction to completion. When toluene was completely removed by the high vacuum rotary evaporator, the reaction mixture was neutralized with triethylamine in CH_2Cl_2. The mixture was diluted with CH_2Cl_2 (300 mL) and washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. Recrystallization afforded **14** as a white solid (3.27 g, 6.3 mmol, 70% for two steps), the structure of which was confirmed by comparison of NMR spectra.[21]

Methyl 4,6-*O*-Benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (15). Compound **16** (4.93 g, 10 mmol) was dissolved in HBr in acetic acid (30 mL, 33% w/w, 173.6 mmol). After 6 h, the mixture was diluted with CH_2Cl_2 (240 mL) and poured onto crushed ice in saturated $NaHCO_3$ (600 mL). The organic phase was separated and washed again with saturated $NaHCO_3$ until the pH reached 7, which was then dried over Na_2SO_4, filtered, and concentrated. The resulting crude residue was mixed with Ag_2CO_3 (2.76 g, 10 mmol), $CaSO_4$ (2.72 g, 20 mmol), and anhydrous methanol (100 mL). The mixture was stirred at room temperature under N_2 protection for 1 day until TLC showed one major product, on which all three acetyl groups has already been cleaved because of the basic reaction condition. The mixture was concentrated and purified by silica column with CH_2Cl_2/ MeOH system. Methyl 2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**18**) was afforded (2.70 g, 8.0 mmol, 80% for two steps). Compound **18** (2.70 g, 8.0 mmol) was mixed with camphorsulfonic acid (0.84 g, 3.6 mmol) and benzaldehyde dimethyl acetal (1.35 mL, 9.6 mmol) in anhydrous toluene (200 mL). The reaction mixture was stirred under N_2 protection at 80 °C for 1 h. When TLC showed around 70% conversion of starting material to product, the reaction flask was placed on a high vacuum rotary evaporator to further push the reaction to completion. When toluene was completely removed by the high vacuum rotary evaporator, the reaction mixture was neutralized with triethylamine in CH_2Cl_2. The mixture was diluted with CH_2Cl_2 (300 mL) and washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. Recrystallization afforded **15** as a white solid (2.39 g, 5.6 mmol 70%): $[\alpha]^{20}_D$ −29.3 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46−3.59 (m, 6 H, $-OCH_3$, H-2, H-4, H-5), 3.80−3.84 (m, 1 H, H-6), 4.38−4.42 (m, 2 H, H-3, H-6), 4.87 (d, 1 H, J = 8.0 Hz, H-1), 5.57 (s, 1 H, C*H*Ph), 6.93 (d, 1 H, J = 7.0 Hz, NH), 7.38−7.51 (m, 5 H, CH_{arom}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.8 ($-OCH_3$), 59.8 (C-2), 66,4 (C-5), 68,8 (C-6), 69.8 (C-3), 81.8 (C-4), 92.5 (CCl_3), 101,2 (C-1), 102,2 (*C*HPh), 126.5−129.6 (C_{arom}), 137.12 (C_q C_{arom}), 162.6 (C=O TCA); HRMS $[M + Na]^+$ m/z calcd for $C_{16}H_{18}Cl_3NNaO_6$ 448.0097, found 448.0088.

***p*-Tolyl *O*-(2-*O*-Benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-1-thio-2-trichloroacetamido-β-D-glucopyranoside (19).** The mixture of donor **1** (715 mg, 1 mmol) and freshly activated MS-4 Å (800 mg) in diethyl ether (20 mL) was stirred in a dry ice−2-propanol bath for 1 h, followed by the addition of AgOTf (771 mg, 3 mmol) in diethyl ether (10 mL). After 5 min, orange-colored *p*-TolSCl (157 μL, 1 mmol) was added via a microsyringe. Since the reaction temperature was lower than the freezing point of *p*-TolSCl, *p*-TolSCl was added directly into the reaction mixture to prevent it from freezing on the flask wall. The characteristic yellow color of *p*-TolSCl in the reaction solution dissipated rapidly within a few seconds, indicating depletion of *p*-TolSCl. The temperature at which preactivation was performed was not crucial as long as it did not exceed −50 °C. After the donor was completely consumed according to TLC analysis (about 5 min at −78 °C), a solution of acceptor **14** (467 mg, 0.9 mmol) and TTBP (248 mg, 1 mmol) in a mixture solvent of CH_2Cl_2 and acetonitrile (v/v 19:1, 3 mL) was then added dropwise within 10 min to the reaction mixture (acetonitrile was necessary as acceptors **14** were not freely soluble in CH_2Cl_2). The reaction mixture was warmed to −10 °C under stirring over 2 h. Triethylamine (0.5 mL) was then added, and the mixture was diluted with CH_2Cl_2 (100 mL) and filtered over Celite. The Celite was further washed with CH_2Cl_2 until no organic compounds were observed in the filtrate by TLC. All CH_2Cl_2 solutions were combined and washed twice with a saturated aqueous solution of $NaHCO_3$ (100 mL) and twice with water (100 mL). The organic layer was concentrated, and the crude product was purified by silica gel chromatography. Typical conditions for chromatography are silica gel/product ~2000 by weight with a flow rate of approximate 5 mL/min and a solvent gradient of R_f ~0.1−0.3 in the ethyl acetate/CH_2Cl_2/hexanes solvent systems. Compound **19**

(36) Huang, L.; Teumelsan, N.; Huang, X. *Chem.—Eur. J.* **2006**, *12*, 5246–5252.

(800 mg, 0.72 mmol, 80%) was afforded as a white solid: $[\alpha]^{20}_D$ +22.2 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.08 (s, 3 H, SiCH_3), −0.05 (s, 3 H, SiCH_3), 0.79 (s, 9 H, SiC(CH_3)$_3$), 2.35 (s, 3 H, PhCH_3), 3.35−3.43 (m, 3 H, H-5′, H-6′, H-2), 3.49 (ddd, 1 H, *J* = 4.5 Hz, 5.0 Hz, 9.0 Hz, H-5), 3.56−3.68 (m, 4 H, H-3′, H-4′, H-6, H-6′), 3.72 (t, 1 H, *J* = 9.0 Hz, H-4), 3.80 (s, 3 H, CH_3 PMB), 4.27 (dd, 1 H, *J* = 5.0 Hz, 10.5 Hz, H-6), 4.34 (d, 1 H, *J* = 12.0 Hz, CH_2PMP), 4.54 (d, 1 H, *J* = 11.0 Hz, CH_2Ph), 4.58 (d, 1 H, *J* = 11.0 Hz, CH_2Ph), 4.63 (d, 1 H, *J* = 12.0 Hz, CH_2PMP), 4.66 (t, 1 H, *J* = 9.0 Hz, H-3), 4.93 (d, 1 H, *J* = 8.0 Hz, H-1′), 5.20 (t, 1 H, *J* = 8.0 Hz, H-2′), 5.32 (s, 1 H, C*H*Ph), 5.44 (d, 1 H, *J* = 10.5 Hz, H-1), 6.89 (d, 1 H, *J* = 8.5 Hz, NH), 7.04−7.11 (m, 7 H, CH_{arom}), 7.20−7.42 (m, 14 H, CH_{arom}), 7.82−7.84 (m, 2 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5 (SiCH_3), −3.6 (SiCH_3), 18.1 (SiC(CH_3)$_3$), 21.4 (PhCH_3), 26.0 (×3, SiC(CH_3)$_3$), 55.5 (PhOCH_3), 57.6 (C-5′), 68.7 (C-6), 69.1 (C-6′), 70.9 (C-5), 71.7 (C-4′), 73.3, (CH_2PMP), 74.4 (C-2′), 75.0 (CH_2Ph), 76.0 (C-3), 77.4 (C-2), 78.8 (C-4), 83.5 (C-3′), 85.4 (C-1), 92.5 (CCl_3), 98.0 (C-1′), 101.3 (*C*HPh), 114.0 (C_{arom}-2*Ph*OCH$_3$), 126.4−130.2 (CH_{arom}), 133.3, 133.8 (×2), 137.3, 137.9, 139.0 (C_q SPhCH$_3$, C_q CHPh, C_q Bn, C_q Bz, C_{arom}-4 *Ph*OCH$_3$), 159.6 (C_{arom}-1 *Ph*OCH$_3$), 161.7, 165.3 (C═O TCA, C═O Bz); HRMS [M + Na]$^+$ *m*/*z* calcd for $C_{56}H_{64}Cl_3NNaO_{12}SSi$ 1130.2882, found 1130.2845.

***p*-Tolyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-1-thio-2-trichloroacetamido-β-D-glucopyranoside (11).** Compound **19** was converted to **11** in three steps (65% for three steps) following the general procedures for deprotection of PMB, oxidation of alcohol to carboxylic acid, and benzyl ester formation: $[\alpha]^{20}_D$ +10.2 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.16 (s, 3 H, SiCH_3), −0.13 (s, 3 H, SiCH_3), 0.74 (s, 9 H, SiC(CH_3)$_3$), 2.36 (s, 3 H, PhCH_3), 3.30 (ddd, 1 H, *J* = 7.5 Hz, 9.0 Hz, 10.5 Hz, H-2), 3.49−3.55 (m, 2 H, H-3′, H-5), 3.65−3.70 (m, 2 H, H-6, H-4), 3.83 (d, *J* = 6.5 Hz, H-5′), 4.13 (t, *J* = 6.5 Hz, H-4′), 4.32 (dd, 1 H, *J* = 5.0 Hz, 10.0 Hz, H-6), 4.54 (t, 1 H, *J* = 9.0 Hz, H-3), 4.59 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.65 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 5.03 (d, 1 H, *J* = 7.0 Hz, H-1′), 5.13 (d, 1 H, *J* = 10.5 Hz, −COOCH_2Ph), 5.17 (d, 1 H, *J* = 10.5 Hz, −COOCH_2Ph), 5.18 (dd, 1 H, *J* = 6.0 Hz, 7.0 Hz, H-2′), 5.29 (d, 1 H, *J* = 10.5 Hz, H-1), 5.32 (s, 1 H, C*H*Ph), 6.96 (d, 1 H, *J* = 7.5 Hz, NH), 7.10−7.18 (m, 7 H, CH_{arom}), 7.26−7.38 (m, 14 H, CH_{arom}), 7.51−7.54 (m, 1 H, CH_{arom}), 7.88−7.89 (m, 2 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0 (SiCH_3), −4.3 (SiCH_3), 18.0 (SiC(CH_3)$_3$), 21.4 (PhCH_3), 25.9 (×3, SiC-(CH_3)$_3$), 57.5 (C-2), 67.4 (COOCH_2Ph), 68.8 (C-6), 70.8 (C-5), 71.4 (C-4′), 73.7 (OCH_2Ph), 74.4 (C-2′), 76.5 (C-3), 77.6 (C-5′), 80.2 (C-4), 81.3 (C-3′), 84.6 (C-1), 92.2 (CCl_3), 99.0 (C-1′), 101.8 (*C*HPh), 126.5−130.2 (CH_{arom}), 133.5, 134.2, 135.3, 137.3, 137.9, 139.2 (C_q STol, C_q CHPh, C_q OBn, C_q Bz, C_q COOBn), 161.8, 165.4, 168.6 (C═O TCA, C═O COOBn, C═O Bz); HRMS [M + Na]$^+$ calcd for $C_{55}H_{60}Cl_3NNaO_{12}SSi$ 1114.2563, found 1114.2560.

***p*-Tolyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-1-thio-2-trichloroacetamido-β-D-glucopyranoside (12).** Compound **11** was converted to **12** following the general procedure for TBS removal (90%): $[\alpha]^{20}_D$ +5.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3 H, PhCH_3), 3.02 (s, 1 H, OH), 3.30 (ddd, 1 H, *J* = 7.0 Hz, 9.0 Hz, 10.5 Hz,H-2), 3.52 (ddd, 1 H, *J* = 4.0 Hz, 4.5 Hz, 9.0 Hz, H-5), 3.55−3.60 (m, 3 H, H-3′, H-5′, H-6), 3.70 (t, 1 H, *J* = 9.0 Hz, H-4), 4.03 (t, 1 H, *J* = 9.0 Hz, H-4′), 4.27 (dd, 1 H, *J* = 4.0 Hz, 10.0 Hz, H-6), 4.59 (t, 1 H, *J* = 9.0 Hz, H-3), 4.62 (d, 1H, *J* = 11.5 Hz, −CH_2Ph), 4.72 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.86 (d, 1 H, *J* = 8.0 Hz, H-1′), 5.15 (d, 1 H, *J* = 11.5 Hz, −COOCH_2Ph), 5.17 (t, 1 H, *J* = 8.0 Hz, H-2′), 5.26 (d, 1 H, *J* = 11.5 Hz, −COOCH_2Ph), 5.32 (s, 1 H, C*H*Ph), 5.37 (d, 1 H, *J* = 10.5 Hz, H-1), 7.05 (d, 1 H, *J* = 7.0 Hz, NH), 7.08−7.18 (m, 7 H, CH_{arom}), 7.30−7.45 (m, 14 H, CH_{arom}), 7.54−7.57 (m, 1 H, CH_{arom}), 7.92−7.94 (m, 2 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4 (PhCH_3), 57.4 (C-2), 68.1 (COOCH_2Ph), 68.7 (C-6), 70.7 (C-5), 72.2 (C-4′), 73.2 (C-2′), 74.0 (OCH_2Ph), 74.7 (C-3), 76.9 (C-5′), 80.1 (C-4), 81.0 (C-3′), 84.4 (C-1), 92.1 (CCl_3), 99.6 (C-1'), 101.4 (*C*HPh), 126.3−130.2 (CH_{arom}), 133.6, 134.1, 134.8, 137.3, 137.8, 139.2 (C_q STol, C_q CHPh, C_q OBn, C_q Bz, C_q COOBn), 161.8, 165.3, 169.3 (C═O TCA, C═O COOBn, C═O Bz); HRMS [M + Na]$^+$ *m*/*z* calcd for $C_{49}H_{46}Cl_3NNaO_{12}S$ 1000.1699, found 1000.1706.

Methyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (13). The mixture of donor **1** (715 mg, 1 mmol), acceptor **15** (427 mg, 1 mmol), and freshly activated MS-4 Å (800 mg) in a solvent mixture of CH_2Cl_2 and acetonitrile (v/v 40:1, 20 mL) was stirred for 1 h at −78 °C, followed by the addition of AgOTf (771 mg, 3 mmol) in diethyl ether (10 mL). After 5 min, *p*-TolSCl (157 μL, 1 mmol) was added via a syringe to activate the donor. The yellow color of the reaction disappeared quickly, and TLC analysis showed the donor was completely consumed. A solution of TTBP (248 mg, 1 mmol) in dichloromethane (1 mL) was then added dropwise to the reaction mixture. The reaction mixture was warmed to −10 °C under stirring over 2 h, followed by the same workup and purification procedures described above for the synthesis of **19**. The resulting disaccharide was subjected to deprotection of PMB, oxidation of alcohol to carboxylic acid, benzyl ester formation, and TBS removal reactions following the general procedures to afford **13** (426 mg, 0.48 mmol, 48% for five steps) as a white solid: $[\alpha]^{20}_D$ +8.2 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (d, 1 H, *J* = 2.5 Hz, OH), 3.30 (ddd, 1 H, *J* = 7.0 Hz, 8.0 Hz, 9.5 Hz, H-2), 3.48−3.50 (m, 4 H, −OCH$_3$, H-5), 3.57−3.60 (m, 3 H, H-3′, H-5′, H-6), 3.76 (t, 1 H, *J* = 9.0 Hz, H-4), 4.03 (ddd, 1 H, *J* = 2.5 Hz, 9.0 Hz, 9.0 Hz, H-4′), 4.26 (dd, 1 H, *J* = 5.0 Hz, 10.5 Hz, H-6), 4.59 (dd, 1 H, *J* = 9.0 Hz, 9.5 Hz, H-3), 4.63 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.73 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.88 (d, 1 H, *J* = 7.5 Hz, H-1′), 4.99 (d, 1 H, *J* = 8.0 Hz, H-1), 5.14 (d, 1 H, *J* = 12.0 Hz, −COOCH_2Ph), 5.20 (dd, 1 H, *J* = 7.5 Hz, 9.5 Hz, H-2′), 5.26 (d, 1 H, *J* = 12.0 Hz, −COOCH_2Ph), 5.36 (s, 1 H, C*H*Ph), 7.05 (d, 1 H, *J* = 7.0 Hz, NH), 7.08−7.09 (m, 3 H, CH_{arom}), 7.27−7.40 (m, 14 H, CH_{arom}), 7.54−7.57 (m, 1 H, CH_{arom}), 7.92−7.94 (m, 2 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 57.8 (−OCH$_3$) 59.3 (C-2), 66.3 (C-5), 68.0 (COO-CH_2Ph), 68.8 (C-6), 72.3 (C-4′), 73.2 (C-2′), 74.0 (C-5′), 74.7 (OCH_2Ph), 76.2 (C-3), 80.3 (C-4), 81.1 (C-3′), 92.1 (CCl_3), 99.7 (C-1), 100.0 (C-1′), 101.4 (*C*HPh), 126.2−130.2 (CH_{arom}), 133.5, 134.9, 137.4, 138.0 (C_q CHPh, C_q OBn, C_q Bz, C_q COOBn), 162.3, 165.3, 169.3 (C═O TCA, C═O COOBn, C═O Bz); HRMS [M + Na]$^+$ *m*/*z* calcd for $C_{43}H_{42}Cl_3NNaO_{13}$ 908.1619, found 908.1616.

2-Trichloromethyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-β-D- glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-1,2-dideoxy-α-D-glucopyrano-[2,1-*d*]-2-oxazoline (20): $[\alpha]^{20}_D$ +54.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.06 (s, 3 H, SiCH_3), −0.05 (s, 3 H, SiCH_3), 0.81 (s, 9 H, SiC(CH_3)$_3$), 3.53 (dd, 1 H, *J* = 5.0 Hz, 10.0 Hz, H-6), 3.61 (t, 1 H, *J* = 10.0 Hz, H-5), 3.68 (t, 1 H, *J* = 7.5 Hz, H-3′), 3.91 (dd, 1 H, *J* = 7.5 Hz, 10.0 Hz, H-4), 4.01 (d, 1 H, *J* = 8.0 Hz, H-5′), 4.15−4.18 (m, 2 H, H-3, H-4′), 4.22 (dd, 1 H, *J* = 5.0 Hz, 8.0 Hz, H-2), 4.34 (dd, 1 H, *J* = 5.0 Hz, 10.0 Hz, H-6), 4.66 (d, 1 H, *J* = 12.5 Hz, CH_2Ph), 4.69 (d, 1 H, *J* = 12.5 Hz, CH_2Ph), 5.02 (d, 1 H, *J* = 7.5 Hz, H-1′), 5.11 (d, 1 H, *J* = 12.0 Hz, COOCH_2Ph), 5.15 (d, 1 H, *J* = 12.0 Hz, COOCH_2Ph), 5.38 (t, 1 H, *J* = 7.5 Hz, H-2′), 5.39 (s, 1 H, C*H*Ph), 6.08 (d, 1 H, *J* = 8.0 Hz, H-1), 7.13−7.17 (m, 4 H, CH_{arom}), 7.31−7.43 (m, 13 H, CH_{arom}), 7.53−7.70 (m, 1 H, CH_{arom}), 8.00−8.10 (m, 2 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.9 (SiCH_3), −4.0 (SiCH_3), 18.1 (SiC(CH_3)$_3$), 26.1 (×3, SiC(CH_3)$_3$), 63.4 (C-5), 67.5

(COOCH_2Ph), 68.7 (C-6), 69.0 (C-2), 72.1 (C-4'), 74.1 (C-2′), 74.6 (OCH_2Ph), 77.4 (C-5′), 78.7 (C-4), 80.3 (C-3), 82.3 (C-3′), 101.1 (C-1′), 101.5 (*C*HPh), 105.3 (C-1), 110.0 (CCl_3), 125.5−128.7 (CH_{arom}), 133.5, 135.2, 137.1, 137.8 (C_q CHPh, C_q OBn, C_q Bz, C_q COOBn), 162.5, 165.5, 168.2 (C═N, C═O COOBn, C═O Bz); HRMS $[M + Na]^+$ *m*/*z* calcd for $C_{48}H_{52}Cl_3NNaO_{12}Si$ 990.2222, found 990.2231.

***p*-Tolyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-1-thio-2-trichloroacetamido-*β*-D-glucopyranoside (25).** The mixture of donor **11** (37 mg, 33.9 μmol) and freshly activated MS-4 Å (300 mg) in diethyl ether (2.0 mL) was stirred for 1 h at −78 °C, followed by the addition of AgOTf (26 mg, 101.7 μmol) in diethyl ether (1.0 mL). After 5 min, *p*-TolSCl (5.3 μL, 33.9 μmol) was added via a microsyringe to activate the donor. The characteristic yellow color of *p*-TolSCl in the reaction solution dissipated rapidly within a few seconds indicating depletion of *p*-TolSCl, and TLC analysis showed the donor was completely consumed. A solution of acceptor **12** (30 mg, 30.5 μmol) in a mixture solvent of CH_2Cl_2 and acetonitrile (v/v 19:1, 0.7 mL) was then added dropwise to the reaction mixture. After 5 min, TMSOTf (2 μL, 11.0 μmol) was added via microsyringe. The reaction mixture was warmed to −10 °C under stirring over 2 h followed by the same workup and purification procedures described above for the synthesis of **19**. Compound **25** (54 mg, 27.8 μmol, 82%) was obtained as a white solid: $[\alpha]^{20}_D$ +2.9 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.14 (s, 3 H, SiCH_3), −0.11 (s, 3 H, SiCH_3), 0.78 (s, 9 H, SiC(CH_3)$_3$), 2.31 (s, 3 H, PhCH_3), 3.09 (ddd, 1 H, *J* = 5.0 Hz, 5.0 Hz, 10.0 Hz, H-5″), 3.17−3.22 (m, 1 H, H-6″), 3.44−3.50 (m, 2 H, H-2, H-5), 3.53 (dd, 1 H, *J* = 9.5 Hz, 10.0 Hz, H-3), 3.55 (t, 1 H, *J* = 7.0 Hz, H-3‴), 3.58−3.61 (m, 2 H, H-4″, H-6), 3.64 (t, 1 H, *J* = 8.0 Hz, H-3′), 3.72 (t, 1 H, *J* = 9.0 Hz, H-2″), 3.81 (dd, 1 H, *J* = 9.0 Hz, 9.5 Hz H-4), 3.86 (d, 1 H, *J* = 7.0 Hz, H-5‴), 3.87 (d, 1 H, *J* = 8.0 Hz, H-5′), 4.02 (dd, 1 H, *J* = 5.0 Hz, 10.5 Hz, H-6″), 4.17 (t, 1 H, *J* = 7.0 Hz, H-4‴), 4.20 (t, 1 H, *J* = 8.0 Hz, H-4′), 4.29 (dd, 1 H, *J* = 5.0 Hz, 10.5 Hz, H-6), 4.41 (t, 1 H, *J* = 9.0 Hz, H-3″), 4.53 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.61 (d, 1 H, *J* = 9.0 Hz, H-1″), 4.61 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.68 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.74 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.97 (d, 1 H, *J* = 10.0 Hz, −COOCH_2Ph), 5.00 (s, 1 H, C*H*Ph), 5.00 (d, 1 H, *J* = 7.0 Hz, H-1‴), 5.06 (t, 1 H, *J* = 8.0 Hz, H-2′), 5.12 (d, 1 H, *J* = 7.5 Hz, H-1), 5.12 (d, 1 H, *J* = 10.0 Hz, −COOCH_2Ph), 5.16 (d, 1 H, *J* = 10.0 Hz, −COOCH_2Ph), 5.17 (d, 1 H, *J* = 8.0 Hz, H-1′), 5.19 (d, 1 H, *J* = 11.5 Hz, −COOCH_2Ph), 5.20 (t, 1 H, *J* = 7.0 Hz, H-2‴), 5.32 (s, 1 H, C*H*Ph), 6.49 (d, 1 H, *J* = 9.0 Hz, NH), 7.08 (d, 1 H, *J* = 7.5 Hz, NH″), 7.10−7.20 (m, 13 H, CH_{arom}), 7.26−7.42 (m, 25 H, CH_{arom}), 7.53−7.58 (m, 2 H, CH_{arom}), 7.89−7.91 (m, 2 H, CH_{arom} Bz), 7.95−7.97 (m, 2 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0 (SiCH_3), −4.2 (SiCH_3), 18.1 (Si*C*(CH$_3$)$_3$), 21.4 (PhCH_3), 26.0 (×3, SiC(*C*H$_3$)$_3$), 56.8 (C-2), 57.6 (C-2″), 66.4 (C-5″), 67.4 (COOCH_2Ph), 68.4 (COOCH_2Ph),68.0 (C-6), 68.0 (C-6″), 70.8 (C-5), 71.4 (C-4‴), 73.7 (OCH_2Ph), 74.6 (OCH_2Ph), 74.6 (C-2‴), 75.0 (C-2′), 75.0 (C-5′), 75.8 (C-4), 77.0 (C-3″), 77.3 (C-4′), 77.8 (C-5‴), 78.5 (C-3′), 79.8 (C-4″), 80.2 (C-3), 81.4 (C-3‴), 85.6 (C-1), 92.4 (CCl_3), 92.7 (CCl_3), 99.3 (*C*HPh), 100.0, 100.0 (C-1″, C-1‴), 101.0 (*C*HPh), 101.7 (C-1′), 126.2−130.1 (CH_{arom}), 133.5, 133.5, 134.1, 135.4, 135.4, 137.4, 137.4, 138.0, 138.4, 138.4 (C_q STol, C_q CHPh × 2, C_q OBn × 2, C_q Bz × 2, C_q COOBn × 2), 161.7, 165.0, 165.3, 165.7, 168.5, 169.1 (C═O TCA × 2, C═O COOBn × 2, C═O Bz × 2); HRMS $[M + H]^+$ *m*/*z* calcd for $C_{97}H_{99}Cl_6N_2O_{24}SSi$ 1949.4191, found 1949.4142.

Methyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranoside (26). After a mixture of donor **25** (33.4 mg, 17.14 μmol), acceptor **13** (15.2 mg, 17.14 μmol), and MS-AW-300 (200 mg) in a mixture solvent of CH_2Cl_2 and acetonitrile (v/v 19:1, 2 mL) was stirred at −78 °C for 1 h, AgOTf (13 mg, 51.4 μmol) in diethyl ether (0.7 mL) was added. When the temperature of the reaction mixture was reduced to −78 °C, *p*-TolSCl (17.14 μmol, 2.46 μL) was added via a microsyringe. After 5 min when the yellowish color disappeared, TMSOTf (0.75 μL, 4.13 μmol) was added via microsyringe. The reaction mixture was warmed to −10 °C under stirring over 2 h, followed by the same workup and purification procedures described above for the synthesis of **19**. Compound **26** (33 mg, 12 μmol, 71%) was afforded as a white solid: $[\alpha]^{20}_D$ −1.7 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.14 (s, 3 H, SiCH_3), −0.10 (s, 3 H, SiCH_3), 0.78 (s, 9 H, SiC(CH_3)$_3$), 3.00 (dd, 1 H, *J* = 4.5 Hz, 9.5 Hz, H-6$^{a/c/e}$), 3.13 (ddd, 1 H, *J* = 4.5 Hz, 5.0 Hz, 9.5 Hz, H-5$^{a/c/e}$), 3.15 (dd, 1 H, *J* = 4.5 Hz, 9.5 Hz, H-6$^{a/c/e}$), 3.18−3.23 (m, 1 H, H-5$^{a/c/e}$), 3.42−3.48 (m, 3 H, H-5$^{a/c/e}$, H-6$^{a/c/e}$, H-2$^{a/c/e}$), 3.50 (s, 3 H, OCH_3), 3.52−3.61 (m, 3 H, H-3$^{a/c/e}$, H-3$^{b/d/f}$ x2), 3.61−3.70 (m, 3 H, H-3$^{a/c/e}$, H-3$^{b/d/f}$, H-4$^{a/c/e}$), 3.72−3.78 (m, 2 H, H-2$^{a/c/e}$ x2), 3.81 (dd, 1 H, *J* = 9.0 Hz, 9.5 Hz, H-4$^{a/c}$), 3.81 (dd, 1 H, *J* = 9.0 Hz, 9.5 Hz, H-4$^{a/c}$), 3.85 (d, 1 H, *J* = 6.5 Hz, H-5$^{b/d/f}$), 3.86 (d, 1 H, *J* = 8.5 Hz, H-5$^{b/d/f}$), 3.90 (d, 1 H, *J* = 8.5 Hz, H-5$^{b/d/f}$), 4.02 (dd, 1 H, *J* = 4.5 Hz, 10.0 Hz, H-6$^{a/c/e}$), 4.04 (dd, 1 H, *J* = 4.5 Hz, 10.5 Hz, H-6$^{a/c/e}$), 4.17 (t, 1 H, *J* = 6.5 Hz, H-4$^{b/d/f}$), 4.19 (t, 1 H, *J* = 8.5 Hz, H-4$^{b/d/f}$), 4.25 (t, 1 H, *J* = 8.5 Hz, H-4$^{b/d/f}$), 4.29 (dd, 1 H, *J* = 5.5 Hz, 10.5 Hz, H-6$^{a/c/e}$), 4.47 (dd, 1 H, *J* = 9.0 Hz, 9.5 Hz, H-3$^{a/c/e}$), 4.52 (d, 1 H, *J* = 8.0 Hz, H-1$^{c/e}$), 4.56 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.57 (d, 1 H, *J* = 12.0 Hz, −CH_2Ph), 4.62 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.68 (d, 1 H, *J* = 12.0 Hz, −CH_2Ph), 4.72 (d, 1 H, *J* = 8.0 Hz, H-1$^{c/e}$), 4.75 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.78 (d, 1 H, *J* = 11.5 Hz, −CH_2Ph), 4.84 (d, 1 H, *J* = 8.5 Hz, H-1^{a}),4.94 (d, 1 H, *J* = 6.0 Hz, H-1$^{b/d/f}$), 4.97 (d, 1 H, *J* = 6.5 Hz, H-1$^{b/d/f}$), 4.99 (d, 1 H, *J* = 7.0 Hz, H-1$^{b/d/f}$), 5.01 (d, 1 H, *J* = 12.0 Hz, −COOCH_2Ph), 5.04 (d, 1 H, *J* = 12.0 Hz, −COOCH_2Ph), 5.07 (dd, 1 H, *J* = 6.0 Hz, 8.0 Hz, H-2$^{b/d/f}$), 5.11 (d, 1 H, *J* = 12.0 Hz, −COOCH_2Ph), 5.12 (dd, 1 H, *J* = 6.5 Hz, 8.5 Hz, H-2$^{b/d/f}$), 5.14 (s, 1 H, C*H*Ph), 5.18 (d, 1 H, *J* = 12.0 Hz, −COOCH_2Ph), 5.19 (s, 1 H, C*H*Ph), 5.20 (d, 1 H, *J* = 12.0 Hz, −COOCH_2Ph), 5.21 (d, 1 H, *J* = 12.0 Hz, −COOCH_2Ph), 5.21 (dd, 1 H, *J* = 6.0 Hz, 7.0 Hz, H-2$^{b/d/f}$), 5.32 (s, 1 H, C*H*Ph), 6.48 (d, 1 H, *J* = 8.5 Hz, NH), 6.60 (d, 1 H, *J* = 8.5 Hz, NH), 6.99 (d, 1 H, *J* = 8.0 Hz, NH), 7.13−7.60 (m, 54 H, CH_{arom}), 7.89−7.98 (m, 6 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0 (SiCH_3), −4.2 (SiCH_3), 18.1 (Si*C*(C $_3$)$_3$), 26.0 (×3, SiC(*C*H$_3$)$_3$), 57.2 (C-2$^{a/c/e}$), 57.5 (C-2$^{a/c/e}$), 57.7 (OCH_3), 58.8 (C-2$^{a/c/e}$), 66.3, 66.4, 66.4 (C-5$^{a/c/e}$, C-6$^{a/c/e}$, C-5$^{a/c/e}$), 67.4 (COOCH_2Ph), 68.0 (COOCH_2Ph), 68.1 (COOCH_2Ph), 68.3, 68.6, 68.7 (C-6$^{a/c/e}$, C-6$^{a/c/e}$, C-5$^{a/c/e}$), 71.4 (C-4^{f}), 73.7 (OCH_2Ph), 74.3 (C-2$^{b/d/f}$), 74.7 (OCH_2Ph), 74.7 (OCH_2Ph), 74.7 (×2, C-5$^{b/d/f}$ x2), 75.0 (C-2$^{b/d/f}$), 75.1 (C-2$^{b/d/f}$), 76.0 (C-3$^{a/c/e}$), 76.8 (C-4$^{a/c/e}$), 77.0 (C-4$^{a/c/e}$), 77.5 (C-4$^{b/d}$), 77.6 (C-4$^{b/d}$), 77.8 (C-5$^{b/d/f}$), 78.8 (C-3$^{b/d/f}$), 79.0 (C-3$^{b/d/f}$), 80.0 (×2, C-3$^{a/c/e}$ × 2), 82.2 (C-4$^{a/c/e}$), 81.5 (C-3$^{b/d/f}$), 92.4 (CCl_3), 92.6 (CCl_3), 92.7 (CCl_3), 99.3 (C-1$^{b/d/f}$), 99.9 (C-1$^{b/d/f}$), 100.0 (C-1$^{c/e}$), 100.1 (C-1$^{c/e}$), 100.3 (C-1$^{b/d/f}$), 100.8 (C-1^{a}), 100.9 (*C*HPh), 101.1 (*C*HPh), 101.7 (*C*HPh), 126.3−130.4 (CH_{arom}), 133.4, 133.5, 133.6, 135.0 (×2), 135.4, 137.4, 137.5, 137.5, 137.9, 138.3, 138.5 (C_q CHPh × 3, C_q OBn × 3, C_q Bz × 3, C_q COOBn × 3), 161.6, 162.0, 162.3, 165.3, 165.6, 165.6, 168.6, 169.0, 169.1 (C═O TCA × 3, C═O COOBn × 3, C═O Bz × 3); HRMS $[M + Na]^+$ *m*/*z* calcd for $C_{133}H_{132}Cl_9N_3NaO_{37}Si$ 2734.5383, found 2734.5469.

2-Trichloromethyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-

(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-1,2-dideoxy-α-D-glucopyrano-[2,1-*d*]-2-oxazoline (27): $[\alpha]^{20}_{D}$ +19.3 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.15 (s, 3 H, Si*CH₃*), −0.12 (s, 3 H, Si*CH₃*), 0.77 (s, 9 H, SiC(*CH₃*)₃), 3.02 (ddd, 1 H, *J* = 4.5 Hz, 5.0 Hz, 9.5 Hz, H-5′′), 3.26−3.31 (m, 1 H, H-6′′), 3.44−3.48 (m, 2 H, H-6, H-5), 3.55 (t, 1 H, *J* = 7.0 Hz, H-3′′′), 3.63 (t, 1 H, *J* = 9.5 Hz, H-4′′), 3.73−3.68 (m, 2 H, H-3′, H-2′′), 3.82−3.91 (m, 4 H, H-3, H-4, H-5′, H-5′′′), 4.04 (dd, 1 H, *J* = 5.0 Hz, 11.0 Hz, H-6′′), 4.13−4.23 (m, 4 H, H-2, H-3′′, H-4′, H-4′′′), 4.28−4.29 (m, 1 H, H-6), 4.55 (d, 1 H, *J* = 8.0 Hz, H-1′′), 4.57 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.60 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.67 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.77 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.89 (d, 1 H, *J* = 7.5 Hz, H-1′′′), 4.95 (d, 1 H, *J* = 12.0 Hz, −COOC*H₂*Ph), 5.02 (d, 1 H, *J* = 7.0 Hz, H-1′), 5.15 (d, 1 H, *J* = 12.0 Hz, −COOC*H₂*Ph), 5.17 (s, 1 H, C*H*Ph), 5.19 (d, 1 H, *J* = 12.0 Hz, −COOC*H₂*Ph), 5.20 (d, 1 H, *J* = 12.0 Hz, −COOC*H₂*Ph), 5.20 (t, 1 H, *J* = 7.0 Hz, H-2′), 5.24 (dd, 1 H, *J* = 7.5 Hz, 8.5 Hz, H-2′′′), 5.34 (s, 1 H, C*H*Ph), 6.09 (d, 1 H, *J* = 7.5 Hz, H-1), 6.58 (d, 1 H, *J* = 8.5 Hz, NH′′), 7.10−7.18 (m, 10 H, CH_{arom}), 7.29−7.45 (m, 22 H, CH_{arom}), 7.59−7.52 (m, 2 H, CH_{arom}), 7.95−8.00 (m, 4 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0 (Si*C*H₃), −4.2 (Si*C*H₃), 18.1 (Si*C*(CH₃)₃), 26.0 (×3, SiC(*C*H₃)₃), 57.6 (C-2′′), 63.4 (C-5), 66.4 (C-5′′), 67.4 (COO*C*H₂Ph), 67.8 (COO*C*H₂Ph), 68.6 (C-6), 68.6 (C-6′′), 68.9 (C-2), 71.4 (C-4′′′), 73.1 (C-2′′′), 73.7 (O*C*H₂Ph), 74.7 (C-2′), 74.8 (O*C*H₂Ph), 75.2 (C-5), 76.7 (C-4′′), 77.1 (C-3′′), 77.8 (C-5′′′), 78.5 (C-4), 79.9 (C-3′), 80.1 (C-4′), 80.2 (C-3), 81.4 (C-3′′′), 92.6 (CCl_3, TCA), 99.2 (C-1′), 99.4 (C-1′′), 101.0 (C-1′′′), 101.3 (*C*HPh), 101.7 (*C*HPh), 110.0 (*N*=C-CCl_3), 105.2 (C-1), 126.2−130.1 (CH_{arom}), 133.4 × 2, 135.1, 135.4, 137.1, 137.4, 138.0, 138.2 (C_q CHPh × 2, C_q OBn × 2, C_q Bz × 2, C_q COOBn × 2), 161.8, 162.5, 165.3, 165.4, 168.2, 168.5 (C=N-CCl_3, C=O TCA, C=O COOBn × 2, C=O Bz × 2); HRMS $[M + Na]^+$ *m/z* calcd for $C_{90}H_{90}Cl_6N_2NaO_{24}Si$ 1843.3682, found 1843.3724.

Methyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*- benzyl-*β*-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranoside (28). Compound **26** was converted to **28** following the general procedure for TBS removal as described previously (90%): $[\alpha]^{20}_{D}$ −3.0 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (ddd, 1 H, *J* = 5.0 Hz, 5.0 Hz, 10.0 Hz, H-5$^{a/c/e}$), 3.07 (s, 1 H, OH), 3.12−3.20 (m, 3 H, H-6$^{a/c/e}$ × 3), 3.43−3.48 (m, 3 H, H-5$^{a/c/e}$ × 2, H-2$^{a/c/e}$), 3.50 (s, 3 H, OCH_3), 3.61 (t, 2 H, *J* = 9.0 Hz, H-3$^{a/c/e}$ × 2), 3.63−3.70 (m, 3 H, H-3 $^{b/d/f}$ × 2, H-4$^{a/c/e}$), 3.72−3.79 (m, 2 H, H-2$^{a/c/e}$ × 2), 3.82 (dd, 1 H, *J* = 8.5 Hz, 9.0 Hz, H-4$^{a/c/e}$), 3.82 (dd, 1 H, *J* = 8.5 Hz, 9.5 Hz, H-4$^{a/c/e}$), 3.87 (d, 1 H, *J* = 8.5 Hz, H-5$^{b/d}$), 3.90 (d, 1 H, *J* = 8.0 Hz, H-5$^{b/d}$), 4.02 (dd, 1 H, *J* = 4.5 Hz, 9.5 Hz, H-6$^{a/c/e}$), 4.05 (dd, 1 H, *J* = 4.5 Hz, 11.0 Hz, H-6$^{a/c/e}$), 4.08−4.18 (m, 3H, H-3$^{b/d/f}$, H-4$^{b/d/f}$ × 2), 4.19 (dd, 1 H, *J* = 8.0 Hz, 8.5 Hz, H-4$^{b/d/f}$), 4.25 (d, 1 H, *J* = 8.5 Hz, H-5$^{b/d/f}$), 4.29 (dd, 1 H, *J* = 5.5 Hz, 10.5 Hz, H-6$^{a/c/e}$), 4.48 (dd, 1 H, *J* = 9.0 Hz, 9.5 Hz, H-3$^{a/c/e}$), 4.52 (d, 1 H, *J* = 8.0 Hz, H-1$^{c/e}$), 4.56 (d, 1 H, *J* = 12.0 Hz, −C*H₂*Ph), 4.57 (d, 1 H, *J* = 12.0 Hz, −C*H₂*Ph), 4.66 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.75 (d, 1 H, *J* = 7.5 Hz, H-1$^{c/e}$), 4.75 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.76 (d, 1 H, *J* = 12.0 Hz, −C*H₂*Ph), 4.79 (d, 1 H, *J* = 12.0 Hz, −C*H₂*Ph), 4.85 (d, 1 H, *J* = 8.0 Hz, H-1^{a}), 4.85 (d, 1 H, *J* = 7.5 Hz, H-1$^{b/d/f}$), 4.94−4.98 (m, 2 H, H-1$^{b/d/f}$ × 2), 5.02 (d, 1 H, *J* = 11.5 Hz, −COOC*H₂*Ph), 5.04 (d, 1 H, *J* = 12.0 Hz, −COOC*H₂*Ph), 5.06 (dd, 1 H, *J* = 8.0 Hz, 8.5 Hz, H-2$^{b/d/f}$), 5.10 (d, 1 H, *J* = 12.0 Hz, −COOC*H₂*Ph), 5.13 (s, 1 H, C*H*Ph), 5.16 (d, 1 H, *J* = 12.0 Hz, −COOC*H₂*Ph), 5.16 (d, 1 H, *J* = 12.0 Hz, −COOC*H₂*Ph), 5.17 (dd, 1 H, *J* = 7.5 Hz, 8.5 Hz, H-2$^{b/d/f}$), 5.19 (dd, 1 H, *J* = 6.5 Hz, 8.0 Hz, H-2$^{b/d/f}$), 5.21 (s, 1 H, C*H*Ph), 5.25 (d, 1 H, *J* = 11.5 Hz, −COOC*H₂*Ph), 5.32 (s, 1 H, C*H*Ph), 6.45 (d, 1H, *J* = 8.5 Hz, NH), 6.63 (d, 1 H, *J* = 9.0 Hz, NH), 7.02 (d, 1 H, *J* = 7.5 Hz, NH), 7.13−7.61 (m, 54 H, CH_{arom}), 7.90−8.04 (m, 6 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.1 (C-2$^{a/c/e}$), 57.5 (C-2$^{a/c/e}$), 57.7 (OCH_3), 58.8 (C-2$^{a/c/e}$), 66.3, 66.4 (C-5$^{a/c/e}$, C-6$^{a/c/e}$), 66.4 (COO*C*H₂Ph), 68.0 (COO*C*H₂Ph), 68.1 (COO*C*H₂Ph), 68.1, 68.3, 68.5, 68.7 (C-6$^{a/c/e}$ × 2, C-5$^{a/c/e}$ × 2), 72.0 (C-4^{f}), 73.6 (C-2$^{b/d/f}$), 74.2 (C-2$^{b/d/f}$), 74.3 (C-5$^{b/d}$), 74.6 (O*C*H₂Ph), 74.8 (O*C*H₂Ph), 74.7 (O*C*H₂Ph), 74.9 (C-5$^{b/d}$), 75.2 (C-2$^{b/d/f}$), 76.0 (C-3^{f}), 76.9 (C-4$^{a/c/e}$), 77.2 (C-4$^{b/d}$), 77.4 (C-4$^{b/d}$), 77.6 (C-5^{f}), 78.8 (C-3$^{a/c/e}$), 79.0 (C-3$^{a/c/e}$), 80.1, 80.1, 80.1 × 2 (C-3$^{b/d/f}$ × 2, C-4$^{a/c/e}$ × 2), 81.1 (C-3$^{a/c/e}$), 92.4 (CCl_3), 92.6 (CCl_3), 92.7 (CCl_3), 99.8 (C-1$^{b/d/f}$), 99.9 (C-1$^{b/d/f}$), 100.0 (C-1$^{c/e}$), 100.0 (C-1$^{c/e}$), 100.4 (C-1$^{b/d/f}$), 100.8 (C-1^{a}), 100.9 (*C*HPh), 101.1 (*C*HPh), 101.4 (*C*HPh), 126.1−130.3 (CH_{arom}), 133.5, 133.6, 133.6, 134.9, 135.0, 135.1, 137.4, 137.5 × 2, 138.0, 138.3, 138.5 (C_q CHPh × 3, C_q OBn × 3, C_q Bz × 3, C_q COOBn × 3), 161.7, 162.0, 162.4, 165.1, 165.6, 165.7, 169.0, 169.3, 169.3 (C=O TCA × 3, C=O COOBn × 3, C=O Bz × 3); HRMS $[M + Na]^+$ *m/z* calcd for $C_{127}H_{118}Cl_9N_3NaO_{37}$ 2620.4513, found 2620.4595.

Methyl *O*-(Benzyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-tert-butyldimethylsilyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-*O*-(4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranosyl)-(1→4)-*O*-(benzyl 2-*O*-benzoyl-3-*O*-benzyl-*β*-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranoside (10). After a mixture of donor **25** (33.4 mg, 17.14 μmol), acceptor **28** (25 mg, 9.62 μmol), and MS-AW-300 (200 mg) in a mixture solvent of CH_2Cl_2 and acetonitrile (v/v 19:1, 2 mL) was stirred at −78 °C for 1 h, AgOTf (51.4 mg, 20 μmol) in diethyl ether (0.7 mL) was added. When the temperature of the reaction mixture reached −78 °C, *p*-toluenesulfenyl chloride (*p*-TolSCl) (17.1 μmol, 2.5 μL) was added via a microsyringe. After 5 min when the yellowish color disappeared, TMSOTf (1.25 μL, 6.9 μmol) was added via microsyringe. The reaction mixture was warmed to −10 °C under stirring over 2 h, followed by the same workup and purification procedures described above for the synthesis of **19**. Compound **10** (32.6 mg, 7.37 μmol, 76.6%) was afforded as a white solid: $[\alpha]^{20}_{D}$ −2.7 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.14 (s, 3 H, Si*CH₃*), −0.10 (s, 3 H, Si*CH₃*), 0.79 (s, 9 H, SiC(*CH₃*)₃), 3.01 (dd, 1 H, *J* = 5.0 Hz, 9.0 Hz, H-5$^{a/c/e/g/i}$), 3.03 (dd, 1 H, *J* = 5.0 Hz, 9.0 Hz, H-5$^{a/c/e/g/i}$), 3.05 (dd, 1 H, *J* = 5.0 Hz, 9.0 Hz, H-5$^{a/c/e/g/i}$), 3.12−3.22 (m, 5 H, H-5$^{a/c/e/g/i}$, H-6$^{a/c/e/g/i}$ × 4), 3.42−3.48 (m, 3 H, H-2$^{a/c/e/g/i}$, H-5$^{a/c/e/g/i}$, H-6$^{a/c/e/g/i}$), 3.50 (s, 3 H, OCH_3), 3.53 (dd, 1 H, *J* = 7.0 Hz, 7.5 Hz), 3.55 (dd, 1 H, *J* = 6.0 Hz, 7.0 Hz), 3.56 (dd, 1 H, *J* = 5.5 Hz, 6.0 Hz), 3.60 (dd, 2 H, *J* = 8.5 Hz, 10.0 Hz), 3.66 (dd, 1 H, *J* = 6.5 Hz, 8.5 Hz), 3.67 (t, 2 H, *J* = 8.0 Hz), 3.68 (dd, 2 H, *J* = 8.5 Hz, 9.0 Hz) (H-4$^{a/c/e/g/i}$, H-3$^{a/c/e/g/i}$ × 4, H-3$^{b/d/f/h/j}$ × 5), 3.72−3.78 (m, 4 H, H-2$^{a/c/e/g/i}$ × 4), 3.80 (dd, 2 H, *J* = 9.0 Hz, 9.5 Hz, H-4$^{b/d/f/h/j}$ × 2), 3.81 (dd, 2 H, *J* = 9.0 Hz, 9.5 Hz, H-4$^{b/d/f/h/j}$ × 2), 3.85 (d, 1 H, *J* = 6.5 Hz, H-5$^{b/d/f/h/j}$), 3.86 (d, 1 H, *J* = 7.0 Hz, H-5$^{b/d/f/h/j}$), 3.88 (d, 2 H, *J* = 9.0 Hz, H-5$^{b/d/f/h/j}$ × 2), 3.90 (d, 1 H, *J* = 8.5 Hz, H-5$^{b/d/f/h/j}$), 4.01−4.06 (m, 4 H, H-6$^{a/c/e/g/i}$ × 4), 4.14 (t, 1 H, *J* = 7.0 Hz, H-4$^{b/d/f/h/j}$), 4.16 (t, 1 H, *J* = 7.0 Hz, H-4$^{b/d/f/h/j}$), 4.18 (t, 1 H, *J* = 8.5 Hz, H-4$^{b/d/f/h/j}$), 4.24 (dd, 1 H, *J* = 8.5 Hz, 9.0 Hz, H-4$^{b/d/f/h/j}$), 4.25 (dd, 1 H, *J* = 8.5 Hz, 9.0 Hz, H-4$^{b/d/f/h/j}$), 4.28 (dd, 1 H, *J* = 5.0 Hz, 10.5 Hz, H-6$^{a/c/e/g/i}$), 4.48 (dd, 1 H, *J* = 9.0 Hz, 9.5 Hz, H-3$^{a/c/e/g/i}$), 4.53 (d, 1 H, *J* = 8.0 Hz, H-1$^{a/c/e/g/i}$), 4.56 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.56 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.56 (d, 1 H, *J* = 8.5 Hz, H-1$^{a/c/e/g/i}$), 4.57 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.62 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.63 (d, 1 H, *J* = 8.0 Hz, H-1$^{a/c/e/g/i}$), 4.63 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph), 4.69 (d, 1 H, *J* = 11.5 Hz, −C*H₂*Ph),

4.75 (d, 1 H, J = 8.0 Hz, H-1[a/c/e/g/i]), 4.76 (d, 1 H, J = 11.5 Hz, $-CH_2Ph$), 4.79 (d, 1 H, J = 11.5 Hz, $-CH_2Ph$ x3), 4.83 (d, 1 H, J = 8.0 Hz, H-1[a/c/e/g/i]), 4.91 (t, 2 H, J = 6.0 Hz, H-2[b/d/f/h/j] × 2), 4.95 (d, 1 H, J = 6.0 Hz, H-1[b/d/f/h/j]), 4.96 (d, 1 H, J = 6.0 Hz, H-1[b/d/f/h/j]), 5.00 (d, 1 H, J = 7.0 Hz, H-1[b/d/f/h/j]), 4.98 (d, 1 H, J = 11.0 Hz, $-COOCH_2Ph$), 5.00 (d, 1 H, J = 12.0 Hz, $-COOCH_2Ph$), 5.02 (d, 1 H, J = 11.5 Hz, $-COOCH_2Ph$ × 2), 5.06 (d, 1 H, J = 8.0 Hz, H-1[b/d/f/h/j]), 5.06 (d, 1 H, J = 8.0 Hz, H-1[b/d/f/h/j]), 5.06 (d, 1 H, J = 12.0 Hz, $-COOCH_2Ph$), 5.09 (dd, 1 H, J = 8.0 Hz, 9.0 Hz, H-2[b/d/f/h/j]), 5.12 (d, 1 H, J = 11.5 Hz, $-COOCH_2Ph$), 5.13 (s, 3 H, CHPh × 3), 5.15 (d, 1 H, J = 11.5 Hz, $-COOCH_2Ph$), 5.15 (dd, 1 H, J = 8.0 Hz, 9.0 Hz, H-2[b/d/f/h/j]), 5.19 (d, 1 H, J = 12.0 Hz, $-COOCH_2Ph$), 5.19 (s, 1 H, CHPh), 5.20 (d, 1 H, J = 11.0 Hz, $-COOCH_2Ph$), 5.21 (d, 1 H, J = 12.0 Hz, $-COOCH_2Ph$), 5.21 (dd, 1 H, J = 7.0 Hz, 8.5 Hz, H-2[b/d/f/h/j]), 5.31 (s, 1H, CHPh), 6.50 (d, 1 H, J = 9.0 Hz, NH), 6.55 (d, 2 H, J = 8.0 Hz, NH × 2), 6.64 (d, 1 H, J = 9.0 Hz, NH), 7.02 (d, 1 H, J = 7.5 Hz, NH), 7.10−7.58 (m, 90 H, CH_{arom}), 7.90−7.95 (m, 10 H, CH_{arom} Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0 ($SiCH_3$), −4.2 ($SiCH_3$), 18.1 ($SiC(C_3)_3$), 26.0 (×3, $SiC(CH_3)_3$), 57.1, 57.1 (×2) (C-2[a/c/e/g/i] × 3), 57.8 (C-2[a/c/e/g/i]), 57.8 (OCH^3), 58.7 (C-2[a/c/e/g/i]), 66.4, 66.3 (×2), 66.3 (×2) (C-5[a/c/e/g/i] × 5), 67.4 ($COOCH_2Ph$), 68.1 (×5, $COOCH_2Ph$ × 4, C-6[a/c/e/g/i]), 68.4 (×2, C-6[a/c/e/g/i] × 2), 68.6 (C-6[a/c/e/g/i]), 68.7 (C-6[a/c/e/g/i]), 71.4 (C-4[j]), 73.7 (OCH_2Ph), 74.3 (C-2[b/d/f/h/j]), 74.6 (C-2[b/d/f/h/j]), 74.7 (OCH_2Ph), 74.8 (×7), 74.9 (OCH_2Ph × 3, C-5[b/d/f/h/j] × 5), 75.0 (C-2[b/d/f/h/j]), 75.0 (C-2[b/d/f/h/j]), 75.2 (C-2[b/d/f/h/j]), 76.0 (C-3[a/c/e/g/i]), 77.8, 77.6, 77.4 (× 2) (C-4[b/d/f/h] × 4), 77.1 (×3), 76.9 (C-4[a/c/e/g/i] × 4), 81.4, 83.3, 80.1 (×4), 79.0, 79.0 (×2), 78.8 (C-3[b/d/f/h/j] × 5, C-3[a/c/e/g/i] × 4, C-4[a/c/e/g/i]), 92.4, 92.6, 92.7, 92.8 (×2) (CCl_3 × 5), 99.3 (C-1[b/d/f/h/j]), 100.0 (C-1[a/c/e/g/i]), 100.0 (C-1[a/c/e/g/i]), 100.2 (C-1[b/d/f/h/j]), 100.3 (C-1[a/c/e/g/i] × 2), 100.3 (C-1[b/d/f/h/j] × 3), 100.8 (C-1[a/c/e/g/i]), 100.9 (CHPh), 100.9 (CHPh × 2), 101.1 (CHPh), 101.7 (CHPh), 126.2−130.2 (CH_{arom}), 133.5, 133.5 (×2), 133.5, 133.6, 135.0 (×2), 135.0 (x2), 135.4, 137.4, 137.5 (x2), 137.5, 137.5, 138.0, 138.3, 138.5 (x2), 138.5 (C_q CHPh x5, C_q OBn x5, C_q Bz × 5, C_q COOBn × 5), 161.6, 161.9 (×2), 162.0, 162.3, 165.3, 165.6, 165.6, 165.7, 165.6, 168.6, 169.1 (×2), 169.3, 169.4 (C=O TCA × 5, C=O COOBn × 5, C=O Bz × 5); MALDI $[M + Na]^+$ m/z calcd for $C_{217}H_{208}Cl_{15}N_5NaO_{61}Si$ 4442.85, found 4443.15.

Methyl *O*-(*β*-D-Glucopyranosyluronic acid)-(1→3)-*O*-(2-*N*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-(1→4)-*O*-(*β*-D-glucopyranosyluronic acid)-(1→3)-*O*-(2-*N*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-(1→4)-*O*-(*β*-D-glucopyranosyluronic acid)-(1→3)-*O*-(2-*N*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-(1→4)-*O*-(*β*-D-glucopyranosyluronic acid)-(1→3)-*O*-(2-*N*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-(1→4)-*O*-(*β*-D-glucopyranosyluronic acid)-(1→3)-2-*N*-acetyl-2-deoxy-*β*-D-glucopyranoside (9). Compound **10** was converted to **29** following the general procedure for TBS removal as described previously (79%). Compound **29** (44 mg, 10 μmol) was dissolved in 2 mL of THF. A 0.2 M KOH aqueous solution (1 mL, 200 μmol) was added in 10 portions during 2 days. The reaction mixture was stirred at room temperature during which time the ratio of water to THF was gradually increased for a better solubility of the reaction mixture. The reaction was checked by comparisons of the crude ^{1}H NMR spectra which was taken by the end of each week. The reaction was stopped by the neutralization with 0.2 M acetic acid in water by the end of the fifth week when peaks around 7.0 ppm in the ^{1}H NMR of the crude NMR indicating NHTCA groups disappeared and peaks around 8.0 peaks for ortho-hydrogens on the benzoyl groups changed from several equally height peaks into two main peaks. The solvent was completely removed by high vacuum rotary evaporator, and the crude residue was dissolved in anhydrous methanol (3 mL) and cooled to 0 °C. Triethylamine (7.0 μL, 50 μmol) and acetic anhydride (118 μL, 1.25 mmol) were added, and the reaction mixture was stirred for 2 days under N_2 protection at room temperature. The reaction was stopped when TLC (acetic acid/CH_2Cl_2/methanol solvent systems) showed formation of one main product. The reaction solvent was removed by rotary evaporation, and silica column purification (acetic acid/CH_2Cl_2/methanol solvent systems) yielded a mixture mainly composed of **31**. $Pd(OH)_2$ (50 mg) was added to a solution of the **31** in THF (0.5 mL), methanol (0.7 mL), and acetic acid (0.5 mL). The reaction flask was evacuated using a water aspirator and filled with hydrogen. This process was repeated three times, and the reaction mixture was stirred under hydrogen atmosphere for 3 days. The solution was filtered and concentrated, and the crude product was purified by Sephadex G-15 size-exclusion chromatography to give the desired product **9** (6.6 mg, 3.5 μmol, 35% from **29** for three steps): $[\alpha]^{20}_D$ −27 (c 0.05, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 1.90−1.92 (m, 15 H, $NHCOCH_3$ × 5), 3.20−3.26 (m, 5 H), 3.35−3.43 (m, 15 H), 3.45−3.48 (m, 5 H), 3.56−3.66 (m, 20 H), 3.70−3.82 (m, 10 H), 4.34 (d, 2 H, J = 8.5 Hz, anomeric H × 2), 4.36 (d, 4 H, J = 7.0 Hz, anomeric H × 4), 4.44 (d, 2 H, J = 8.5 Hz, anomeric H × 2), 4.45 (d, 2 H, J = 7.5 Hz, anomeric H × 2); HRMS $[M - 3H]^{3-}$ m/z calcd for $C_{71}H_{106}N_5O_{56}$ 641.5200, found 641.5198.

Acknowledgment. We are grateful for the National Institutes of Health (R01-GM-72667) and a CAREER award from the National Science Foundation (CHE0852308) for financial support of this work.

Supporting Information Available: General experimental procedures and selected ^{1}H, ^{13}C, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.