JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

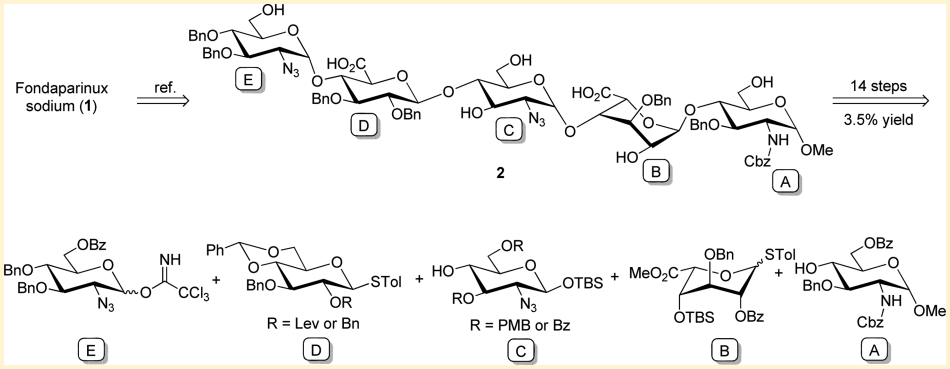
Formal Synthesis of Anticoagulant Drug Fondaparinux Sodium

Xiang Dai,[†,§] Wentao Liu,[†,§] Qilong Zhou,[†,§] Chunwei Cheng,[‡] Chao Yang,[†] Shuqing Wang,[†] Min Zhang,[†] Pei Tang,[*,†] Hao Song,[‡] Dan Zhang,[‡] and Yong Qin[*,‡]

[†]Innovative Drug Research Centre, Chongqing University, Chongqing, 401331, China

[‡]Key Laboratory of Drug Targeting and Drug Delivery Systems of the Ministry of Education, West China School of Pharmacy, Sichuan University, Chengdu, 610041, China

Supporting Information



ABSTRACT: The practical formal synthesis of the anticoagulant drug fondaparinux sodium **1** was accomplished using an optimized modular synthetic strategy. The important pentasaccharide **2**, a precursor for the synthesis of fondaparinux sodium, was synthesized on a 10 g scale in 14 collective steps with 3.5% overall yield from well-functionalized monosaccharide building blocks. The strategy involved a convergent [3 + 2] coupling approach, with excellent stereoselectivity in every step of glycosylation from the monosaccharide building blocks. Efficient routes to the syntheses of these fully functionalized building blocks were developed, minimizing oligosaccharide stage functional-group modifications. The syntheses of all building blocks avoided rigorous reaction conditions and the use of expensive reagents. In addition, common intermediates and a series of one-pot reactions were employed to enhance synthetic efficiency, improving the yield considerably. In the monosaccharide-to-oligosaccharide assembly reactions, cheaper activators (e.g., NIS/TfOH, TESOTf, and TfOH) were used to facilitate highly efficient glycosylations. Furthermore, crystallization of several monosaccharide and oligosaccharide intermediates significantly simplified purification procedures, which would be greatly beneficial to the scalable synthesis of fondaparinux sodium.

1. INTRODUCTION

Heparin and its structurally related heparan sulfate are linear polysulfated polysaccharides with alternating D-glucosamine and either D-glucuronic acid or L-iduronic acid units.[1] They are present on the surface of most animal cells as well as in the basement membranes and extracellular matrixes[2] and play significant roles in diverse biological processes such as blood coagulation, bacterial and viral infections, tumor metastasis, cell growth, cell adhesion, wound healing, inflammation, lipid metabolism, and diseases of the nervous system.[1c,3] Heparin, which is isolated from animal organs, has been widely used clinically as an anticoagulant drug for major cardiovascular and orthopedic surgeries such as knee surgery and in repairing hip fractures or hip replacement. Since the 1940s, it has also been used to prevent the occurrence of venous thrombosis, owing to its high affinity to bind with antithrombin III.[4] Despite its widespread use, current heparin therapies present challenges in product quality control and material supply safety, due to the many diverse sources and nonuniformity of the organs used to produce the drug.[5] Furthermore, serious complications such as heparin-induced thrombocytopenia, uncontrolled bleeding, and osteoporosis may occur during administration of heparin.[6] In the early 1980s, a unique pentasaccharide domain in heparin chains capable of activating antithrombin III was discovered. This domain is a serine protease inhibitor that blocks factor Xa in the coagulation cascade.[7] Two pharmaceutical companies, Sanofi and Organon, synthesized an analogue of this pentasaccharide, which was developed into a novel antithrombotic drug, fondaparinux sodium (**1**, Arixtra, Figure 1) in 2002.[8] Fondaparinux sodium displays superior antithrombotic activity to unfractionated heparin (molecular weight average 14 000) and its low-molecular-weight variants (molecular weight average 6000),[9] and brings about antithrombin-mediated activity exclusively against factor Xa but with no effect on thrombin.[10] Moreover, it is much easier to control product

Received: October 26, 2015
Published: December 9, 2015

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

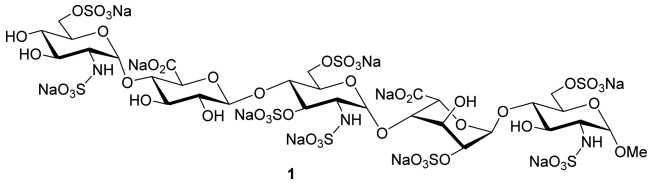
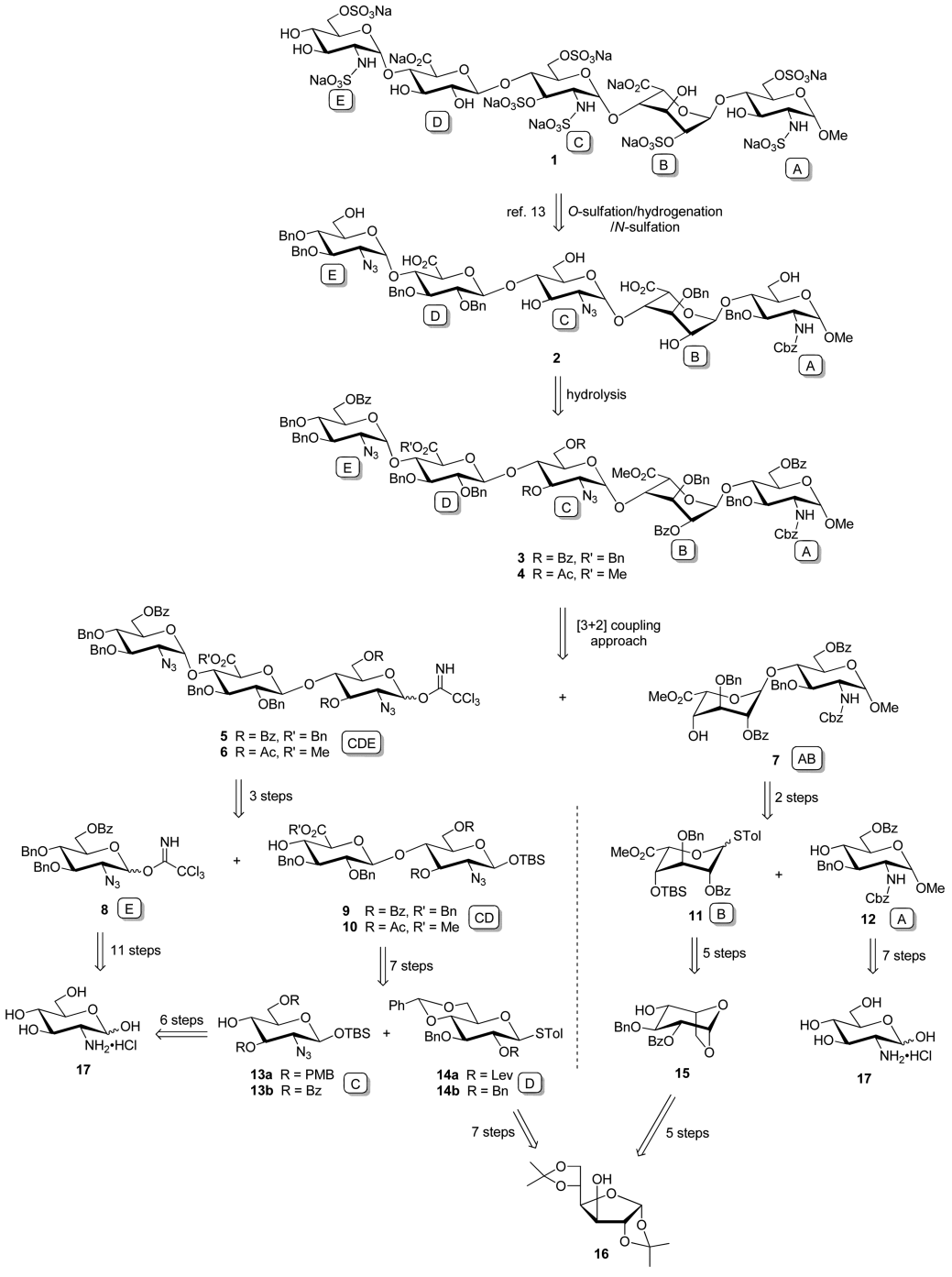


Figure 1. Structure of fondaparinux sodium (Arixtra).

quality during the production process of the artificial synthetic pentasaccharide agent, which also has several advantages over the aforementioned naturally derived heparins in terms of pharmacokinetics.[11]

Although fondaparinux sodium is an outstanding anticoagulant drug compared to traditional heparins, its high manufacturing cost restricts widespread use as the synthesis is difficult and tedious.[7,8] Indeed, fondaparinux sodium and other heparin oligosaccharides are generally perceived to be difficult to synthesize.[7,8,12d] Most of the time, lengthy chemical processes are required because of the repeated introduction and removal of protecting groups, and the separation of side products from desired intermediates is often inefficient, both of which drastically decrease the synthetic efficiency. Therefore, it is imperative to develop highly efficient strategies for producing the homogeneous pentasaccharide for clinical applications.

Scheme 1. Retrosynthetic Analysis of Fondaparinux Sodium 1



DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

Recently, some progress toward a more efficient synthesis of this pentasaccharide has been made:[12] Hung and co-workers elegantly applied a [4 + 1] approach to finish the total synthesis of fondaparinux sodium in 22 linear steps from D-glucosamine·HCl, and the use of common intermediates and a series of one-pot reactions considerably reduced the synthetic steps and improved the yield.[12a] Moreover, Lin[12b] and Wang[12c] completed the synthesis of this pentasaccharide by a convergent [3 + 2] manner separately. In contrast to the chemical methods mentioned above, Linhardt and Liu used a chemoenzymatic synthesis to obtain heparin pentasaccharide in their syntheses of two structurally homogeneous ultralow molecular weight heparins in 45% and 37% overall yield over 10 and 12 steps, respectively.[12d] Herein, we describe the formal synthesis of fondaparinux sodium using a [3 + 2] optimized modular synthetic strategy from well-functionalized building blocks, which significantly decreases the number of total synthetic steps and enhances the synthetic efficiency.

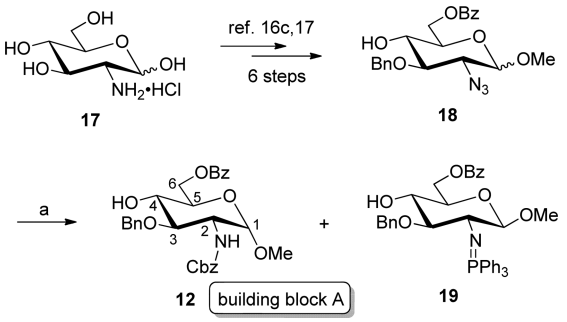
2. RESULTS AND DISCUSSION

2.1. Retrosynthetic Analysis for Fondaparinux Sodium. Our synthetic route to the pentasaccharide required a modular and convergent strategy using a set of suitably functionalized monosaccharide building blocks. These were readily accessible and convenient for regioselective placement of multiple sulfonate groups, allowing the critical stereochemical aspects of glycosylation to be controlled by the anomeric effect and neighboring group participation. Through retrosynthetic design (Scheme 1), fondaparinux sodium **1** could be generated from pentasaccharide **2** via the well-known *O*-sulfation/hydrogenation/*N*-sulfation process, with free hydroxyl groups and carboxylic groups.[13] The latter was accessible from fully protected pentasaccharides **3** or **4** under hydrolysis conditions. To provide efficient access to pentasaccharides **3** or **4**, we conceived a [3 + 2] coupling approach through the disaccharide acceptor **7** (building block AB) and trisaccharide donors **5** or **6** (building block CDE). Compounds **5** and **6** could be prepared from condensation of the known glucosazide trichloroacetimidate **8** (building block E)[14] and disaccharide acceptors **9** or **10** (building block CD). These latter disaccharides could be constructed by functionalized monosaccharide donor **14** (building block D)[12c] and acceptor **13** (building block C). In contrast, disaccharide **7** may also be assembled through 1-thio iduronic acid donor **11** (building block B) and glucosamine acceptor **12** (building block A).[15]

The aforementioned five monosaccharide building blocks (**8**, **11**, **12**, **13**, and **14**) can be prepared from two convenient starting materials with several different methods. In detail, the glucosazide units **8**, **13** and glucosamine unit **12** are all readily attainable from commercially available D-glucosamine·HCl **17**. The iduronic acid unit **11** can be prepared from the known anhydro-L-idose **15**, which was obtained from diacetone D-glucose **16** in five steps,[16] while **16** could also be converted into glucose derivative **14** in several steps.[12c] Furthermore, a protection strategy was established for *O*-sulfation and selective *N*-sulfation, as well as for glycosylation stereoselectivity. Acetyl and benzoyl protecting groups allowed the introduction of the crucial sulfate groups at the corresponding hydroxy groups. Benzoyl and levulinoyl (Lev) groups (building blocks **11** and **14a**) were selected to facilitate neighboring-group participation for the stereoselective introduction of 1,2-*trans*-glycosidic linkages, while benzyl ethers were used as permanent protecting groups for releasing the hydroxy groups in a later stage of the synthesis. Azido groups in building blocks **8**, **9**, and **10** were used as amino functionalities for subsequent *N*-sulfation, as well as for utilizing the anomeric effect (bearing a C2-non-participating group) to install 1,2-*cis*-glycosidic linkages between the E and CD fragments.[12a] Furthermore, ester groups (acetyl or benzoyl) at the *O*6 position of these intermediates potentially enhance the stereochemical aspects of the glycosylation by remote participation.

2.2. Preparation of Building Block A (Monosaccharide 12). From the retrosynthetic perspective, we began our synthesis with the preparation of disaccharide **7** (building block AB), obtained from the coupling of 1-thio iduronic acid donor **11** and glucosamine acceptor **12**. The α-methyl glycoside **12** (building block A) was prepared from known 2-azidoglucoside **18** (Scheme 2), the latter was synthesized from D-glucosamine·HCl **17** in six steps.[16c,17] However, at this stage, the anomeric mixture **18** (α/β = 6:1) proved difficult to separate by chromatography: eluting with 33% ethyl acetate/petroleum ether, the desired α-methyl glycoside anomer had an R_f value of 0.40, in contrast to the β-anomer with an R_f value of 0.35. We were fortunately able to circumvent this problem using an azide reduction−protection protocol. Staudinger reaction of the azide anomeric mixture with PPh_3 and silica gel in a THF−water mixture proceeded smoothly, and the resulting crude products were carried forward without further purification. After the protection of the amino group with CbzCl and $NaHCO_3$, the desired α-methyl glycoside **12** ($J_{1,2}$ = 3.6 Hz) could be separated easily in 56% yield via column chromatography, due to the significantly different R_f values of **12** and **19** (0.40 for **12** and 0.05 for **19**, eluting with 50% ethyl acetate/petroleum ether), while β-anomer iminophosphorane **19** ($J_{1,2}$ = 8.4 Hz) was also obtained in 11% yield. We note that, because the iminophosphorane group in **19** cannot be further hydrolyzed to the corresponding amine under these mild conditions, this efficient separation is highly suitable for scalable preparation of α-methyl glycoside **12** (building block A).

Scheme 2. Synthesis of Glucosamine 12 (Building Block A)[a]

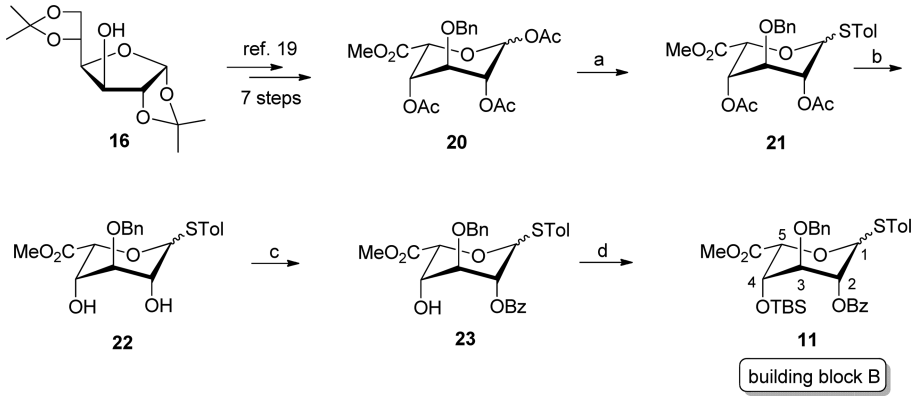


[a]Reagents and conditions: (a) (1) PPh_3, silical gel, THF−H_2O (9:1), RT, 3 h; (2) CbzCl, $NaHCO_3$, THF−H_2O (9:1), 0 °C, 3 h, 56% for **12** and 11% for **19**.

2.3. Preparation of Building Block B (Monosaccharide 11). The generation of rare L-idose was one of the most frequently encountered problems in the synthesis of heparin derivatives.[16c,18] To minimize functional-group transformations and circumvent the oxidation steps at subsequent oligosaccharide stages, we prepared donor **11** (building block B) with suitable protecting groups and a C5 methyl ester to enhance the efficiency of the entire synthesis. Wang and co-workers prepared a similar building block B from commercially available

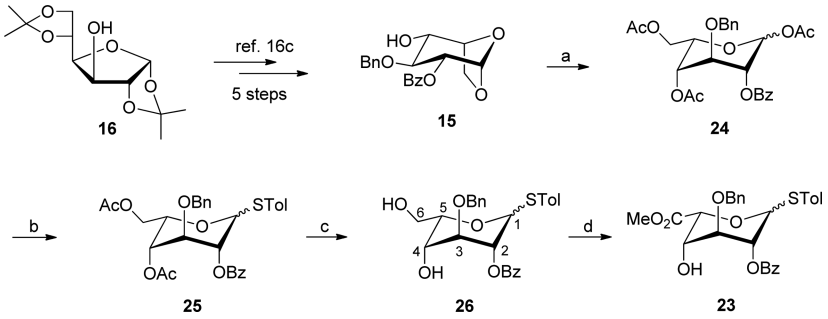
DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

Scheme 3. Initial Synthesis of Monosaccharide 11 (Building Block B)[a]



[a]Reagents and conditions: (a) TolSH, $BF_3{\cdot}Et_2O$, DCM, 0 °C to RT, 12 h, 65%, α/β = 5:2; (b) MeONa, MeOH, RT, 76%; (c) (1) Bu_2SnO, MeOH, reflux, 1 h; (2) BzCl, Et_3N, dioxane, 0 °C, 1 h, 65%; (d) TBSOTf, 2,6-lutidine, DCM, 0 °C to RT, 30 min, 86%.

Scheme 4. Optimized Synthesis of Monosaccharide 23 (Building Block B)[a]



[a]Reagents and conditions: (a) Ac_2O–TFA (6:1), 60 °C, overnight; (b) TolSH, TfOH, DCM, 0 °C; (c) AcCl, MeOH, 0 °C to RT, overnight, 60% over 3 steps, α/β = 5:1; (d) (1) $PhI(OAc)_2$, TEMPO, DCM–H_2O (2:1), RT; (2) Me_2SO_4, K_2CO_3, acetone, RT, 80%. TFA = trifluoroacetic acid, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical.

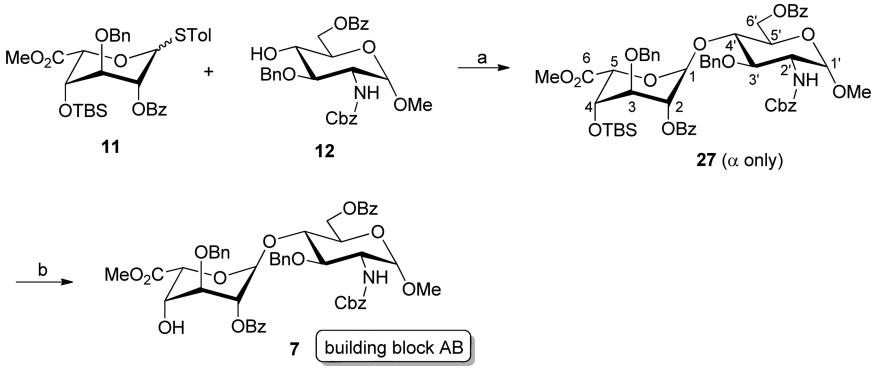
diacetone glucose **16** in 11 steps in their fondaparinux sodium synthesis;[12c] however, the repeated introduction and removal of protecting groups decreased the overall synthetic yield of the building block to 6%. In our initial synthesis of building block B, we also prepared 1-thio iduronic acid donor **11** from known compound **20** (Scheme 3), which was synthesized from **16** via seven steps as in reported methods.[19] Treatment of **20** with *p*-toluenethiol in the presence of $BF_3{\cdot}Et_2O$ gave thioglycoside **21** in 65% yield as an anomeric mixture (α/β = 5:2). Removal of the acetyl groups in **21**, followed by the Bu_2SnO-mediated regioselective protection of the C2 hydroxyl as a benzoate ester, afforded alcohol **23**. The benzoate ester in **23** served as a participating group to assist the later glycosylation reaction. Finally, blocking the remaining C4 hydroxyl group with *t*-butyldimethylsilyl ether led to the desired 1-thio iduronic acid donor **11** in 86% yield. However, this synthesis was inefficient (11 steps and 4% overall yield) and required expensive reagents and rigorous reaction conditions (low temperature, anhydrous environments, strong bases, etc.). These issues prompted us to look for a superior approach more amenable to large-scale preparation.

Anhydro-L-idopyranoside **15**, a crystallizable L-idose intermediate generated from **16** in five steps with 37% overall yield,[16c] was chosen as a building block for glycosylation in Hung's elegant synthesis of fondaparinux sodium.[12a] We were thus inspired to employ **15** as an intermediate for our optimized synthesis of building block B. Unlike Hung's strategy, we converted **15** into fully functionalized **11** to reduce oligosaccharide-stage modifications (Scheme 4). Acetolysis of the anhydro ring with an Ac_2O/TFA mixture (**24**),[20] followed by preparation of thioglycoside in the presence of *p*-toluenethiol and TfOH (**25**) with subsequent removal of the acetyl groups with acetyl chloride in methanol, was accomplished in a one-pot reaction to give known compound **26**[8e] in 60% overall yield as an anomeric mixture (α/β = 5:1). Selective oxidation of **26** with TEMPO-$PhI(OAc)_2$ and subsequent esterification with Me_2SO_4 provided intermediate **23** in 80% yield. This approach toward **11** (10 steps and 15% overall yield from **16**) was more straightforward and gave better overall yield compared to the original procedure. Moreover, our one-pot protocol (**15** → **26**) and crystallization procedure (**16** → **15**) considerably simplified the overall synthetic procedures and minimized wasteful purification steps. Furthermore, mild reaction conditions and inexpensive reagents were used throughout the process. These advantages make this approach more convenient for scalable preparation.

2.4. Preparation of Building Block AB (Disaccharide 7). With suitably functionalized donor **11** and acceptor **12** in hand, we investigated the synthesis of disaccharide **7**. In Wang's synthesis, the glucosazide uronate disaccharide (building block AB) was prepared via a BSP/Tf_2O-mediated condensation, which proceeded in 56% yield with excellent α-selectivity.[12c] Lin and co-workers employed more reactive L-idosyl donors to deliver a series of disaccharides with satisfactory stereochemical outcome in higher yield,[12b] but this route required the inevitable protection and oxidation reactions at the disaccharide

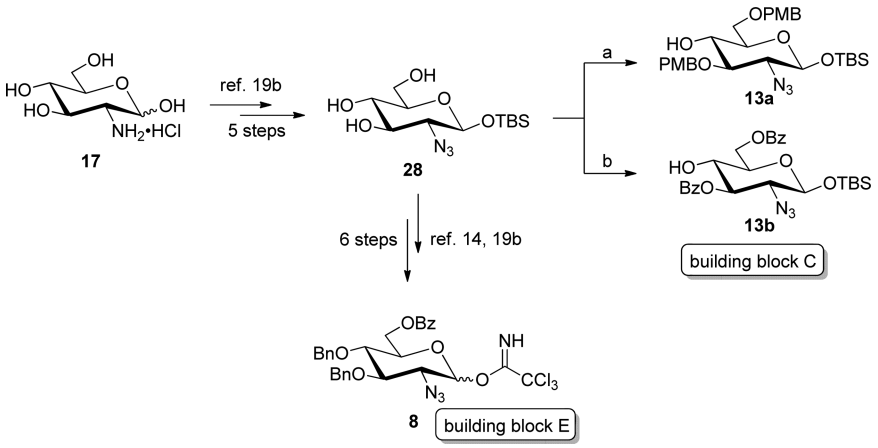
DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162–184

Scheme 5. Synthesis of Disaccharide 7 (Building Block AB)[a]



[a]Reagents and conditions: (a) NIS, TfOH, 4 Å molecular sieve, DCM, −40 °C, 1 h, 67%; (b) HF·pyridine, RT, 1 h, 90%. NIS = *N*-iodosuccinimide, TfOH = trifluoromethanesulfonic acid.

Scheme 6. Synthesis of Building Blocks C and E[a]



[a]Reagents and conditions: (a) Bu_2SnO, PMBCl (2.5 equiv), TBAI, PhMe, reflux, 11 h, 70%; (b) Bu_2SnO, BzCl (2.1 equiv), TBAI, PhMe, reflux, 4 h, then RT overnight, 50%. TBAI = tetrabutylammonium iodide.

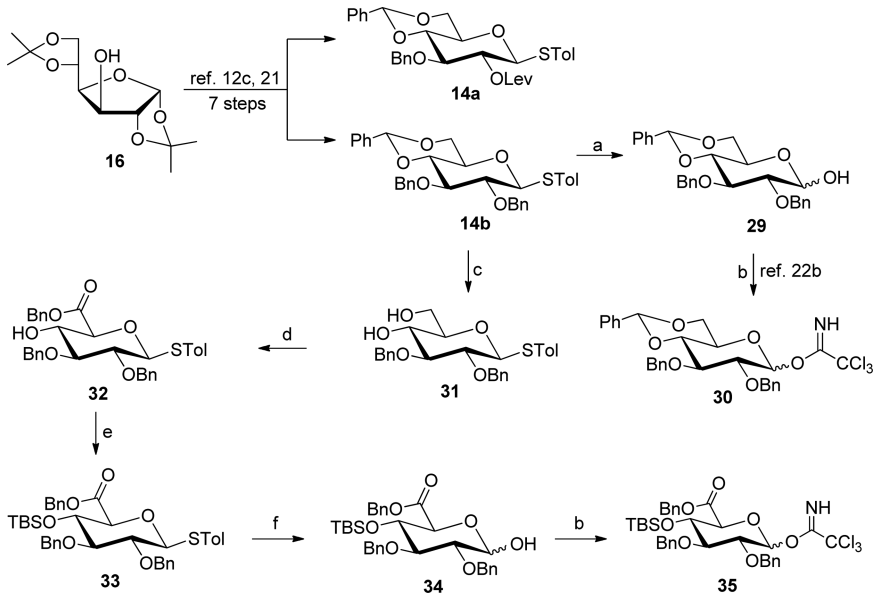
stage for the preparation of suitable uronate acceptors. In our work, we adopted a similar strategy to Wang's synthesis for preparing glucosamine uronate disaccharide acceptor **7**, without the additional transformations of functional groups for the designed glycosylation between building blocks AB and CDE. As shown in Scheme 5, activation of the anomeric thiophenyl group of idouronate **11** with the NIS/TfOH reagent proceeded efficiently for condensation with the glucosamine building block **12** to afford desired disaccharide **27** with full α-selectivity in 67% yield ($J_{1,2}$ = 5.6 Hz). Subsequently, the TBS ether group could be readily removed with HF·pyridine to give **7** as an acceptor for the next glycosylation with trisaccharides **5** and **6** (building block CDE).

2.5. Preparation of Building Blocks C and E (Monosaccharides 13 and 8). On the basis of the synthetic plan shown in Scheme 1, an intensive investigation on the synthesis of crucial trisaccharides **5** and **6** (building block CDE) was carried out. Target trisaccharides **5** and **6** can be assembled through the glucosazide trichloroacetimidate acceptor **8** (building block E)[14] and disaccharide acceptors **9** or **10** (building block CD). Disaccharides **9** and **10** (building block CD) can be prepared from the condensation of monosaccharide donor **14** (building block D) with glucosazide acceptor **13** (building block C). In our synthetic scheme, the glucosazide monosaccharides **13** (building block C) and **8** (building block E) were readily prepared using the common intermediate **28** (Scheme 6), which could be easily synthesized over a 500 g scale from **17** in five steps based on previously reported methods.[19b] First, Bu_2SnO-mediated protection of the C4 and C6 hydroxyl groups in the presence of excess PMBCl or BzCl generated the desired monosaccharide acceptors **13a** (70%) and **13b** (50%), respectively. Then, the known azidoglucose trichloroacetimidate acceptor **8** (building block E) was readily synthesized by the reported procedures[14,19b] or the alternative method (see the Experimental Section). The synthetic approaches employing a common intermediate significantly reduce the number of steps and enhance synthetic efficiency.

2.6. Preparation of Building Block D (Monosaccharides 14, 30, and 35). To provide the crucial β-selectivity in the coupling of building block C with building block D, four types of monosaccharides (**14a**, **14b**, **30**, and **35**) were prepared as donors to probe the critical glycosylations (Scheme 7). Three of the monosaccharides (**14b**, **30**, and **35**) have a Bn group at the *O*2 and *O*3 positions, which serve as permanent protecting groups for this synthesis. The C5 ester group in **35** was installed at the monosaccharide stage to avoid additional oxidation operations in the subsequent oligosaccharide stage. Moreover, the Lev group in monosaccharide **14a** was employed to facilitate neighboring-group participation in the stereo-

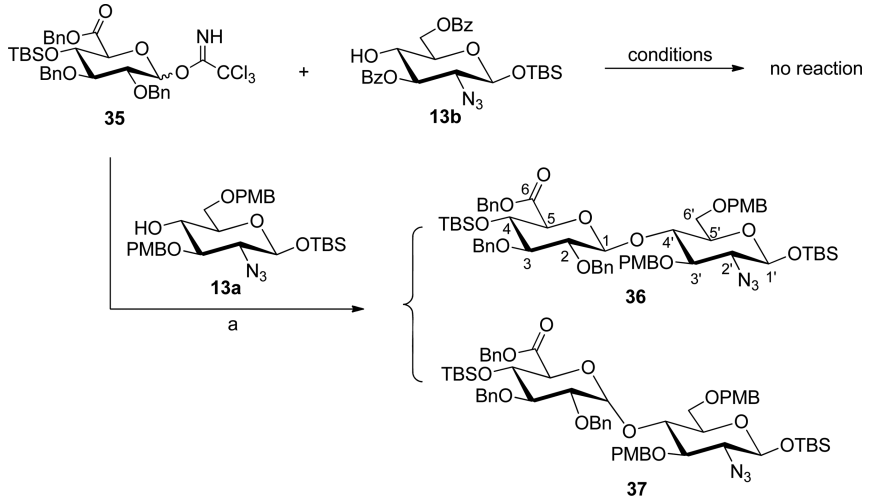
DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

Scheme 7. Synthesis of Building Block D[a]



[a]Reagents and conditions: (a) TCCA, acetone−H_2O (3:1), RT, 1 h, 81%; (b) Cl_3CCN, DBU, DCM, 0 °C to RT, 85% for **30** (α/β = 2:1), 64% for **35** (α/β = 7:1); (c) TFA, DCM−H_2O (5:1), 0 °C to RT, 1 h, 85%; (d) (1) $PhI(OAc)_2$, TEMPO, DCM−H_2O (2:1), RT, 2.5 h; (2) K_2CO_3, BnBr, Et_3N, acetone, 55 °C, 2 h, 50%; (e) TBSOTf, 2,6-lutidine, DCM, 0 °C to RT, 30 min, 82%; (f) NBS, acetone−H_2O (9:1), RT, 1 h, 85%, α/β = 5:2. TCCA = trichloroisocyanuric acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFA = trifluoroacetic acid, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical, NBS = *N*-bromosuccinimide.

Scheme 8. Glycosylations of Donor 35 with Glucosazide Acceptors 13a and 13b[a]



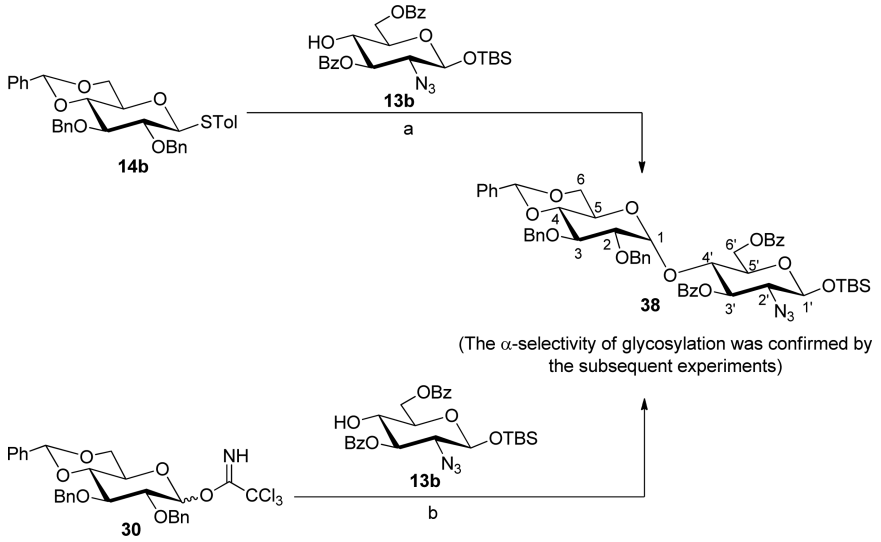
[a]Reagents and conditions: (a) TESOTf, 4 Å molecular sieve, cyclohexane, RT, overnight, 45% for **36** and 38% for **37**.

selective introduction of the β-glycosidic linkage. Two known thioglycoside donors **14a** and **14b** were readily synthesized without column chromatography purification from **16** using the reported procedures.[12c,21] (Scheme 7). The other two donors with different anomeric leaving groups, trichloroacetimidates **30** and **35**, were also prepared from the common intermediate **14b**. Monosaccharide **30** could be readily prepared from the corresponding thioglycoside **14b** by the TCCA-mediated removal of the *p*-tolylthio group and a trichloroacetimidate formation sequence.[22] In contrast, selective removal of the 4,6-*O*-benzylidene group in **14b** with TFA generated the corresponding diol **31**.[23] TEMPO-$PhI(OAc)_2$ oxidation of the primary hydroxyl group, followed by esterification, delivered **32**. After TBS protection, the resulting thioglycoside **33** was converted into trichloroacetimidate **35** by a similar sequence with *p*-tolylthio group removal and trichloroacetimidate formation.

2.7. Preparation of Building Block CD (Disaccharides 9 and 10). With compounds **14**, **30**, and **35** (building block D) in hand, the glycosylation step with azidoglucose acceptors **13a** and **13b** (building block C) was then carefully investigated. The Ag_2CO_3-mediated coupling of the glycosyl bromide donor with a 1,6-anhydro glucosazide acceptor was used by Wang and co-workers to form the desired disaccharide (building block CD) with moderate yield, in a 7:1 β/α ratio.[12c] Although this mild glycosylation proceeded slowly (4 days), the resulting disaccharide could be employed in the forthcoming glycosylation reaction without further modification other than a one-

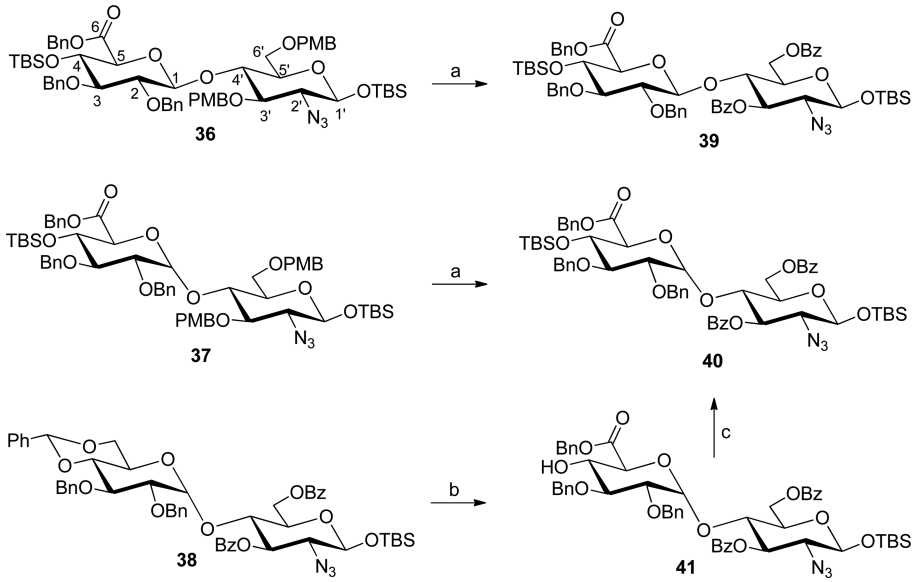
DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

Scheme 9. Glycosylations of Donors 14b and 30 with Glucosazide Acceptor 13b[a]



[a]Reagents and conditions: (a) NIS, TfOH, 4 Å molecular sieve, DCM, −40 °C, 1 h, 80%; (b) TESOTf, 4 Å molecular sieve, DCM, −40 °C, overnight, 35%. NIS = *N*-iodosuccinimide, TfOH = trifluoromethanesulfonic acid.

Scheme 10. Experimental Verification of Glycosylation[a]

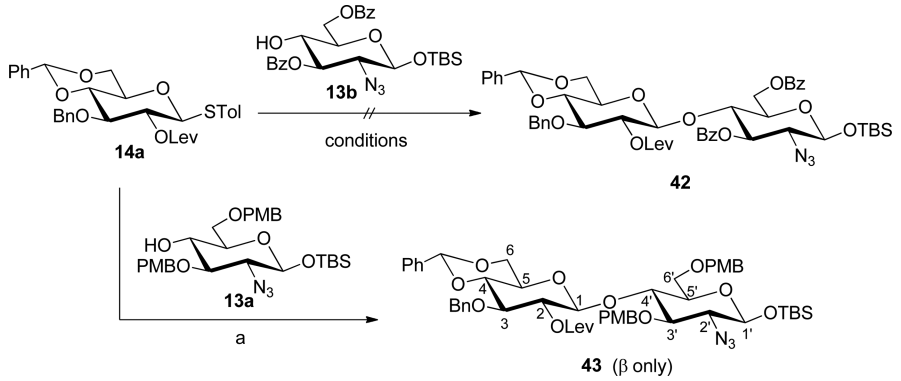


[a]Reagents and conditions: (a) (1) DDQ, DCM−H_2O (9:1), RT, 3 h; (2) Bz_2O, DMAP, PhMe, reflux, 30 h, 56% (when using **36**), 52% (when using **37**); (b) (1) TFA, DCM−H_2O (15:1), 0 °C to RT; (2). $PhI(OAc)_2$, TEMPO, DCM−H_2O (2:1), RT; (3) K_2CO_3, BnBr, Et_3N, acetone, 50 °C, 61%; (c) TBSOTf, 2,6-lutidine, DCM, 0 °C to RT, 30 min, 80%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TFA = trifluoroacetic acid, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical.

step deprotection. Unlike Wang's strategy, the Lin group straightforwardly synthesized building block CD from cellobiose,[12b] with a subsequent selective oxidation that effectively yielded the required uronate disaccharide. Ideally, we planned to choose uronate donor **35** for the construction of the β-1,4-linked disaccharide with azidoglucose acceptors, because the essential permanent protection of C2, C3 hydroxy groups and an ester group at the C5 position in this synthesis had been performed at the monosaccharide stage. With respect to acceptors (building block C), the Bz-acceptor **13b** was preferable to the PMB-acceptor **13a** because no further conversion of the PMB group to a Bz group was needed after formation of the disaccharide. Unfortunately, the glycosylation of **35** with **13b** did not work under various conditions, and we were not able to generate the desired product (Scheme 8). To our delight, by using PMB-acceptor **13a** instead of **13b**, the glycosylation with **35** in the presence of TESOTf proceeded smoothly to afford the corresponding glycoside products **36** ($J_{1,2}$ = 7.2 Hz) and **37** ($J_{1,2}$ = 3.2 Hz) in 83% combined yield. This reaction had poor stereoselectivity (β/α = 1.2:1), but the anomers could be separated by silica gel column chromatography. In contrast, using thioglycoside glycosyl donor **14b** instead of uronate donor **35**, the NIS/TfOH-assisted glycosylation of azidoglucose acceptor **13b** led to disaccharide **38** as the sole product in 80% yield (Scheme 9). However, at this stage, the product stereochemistry in **38** could

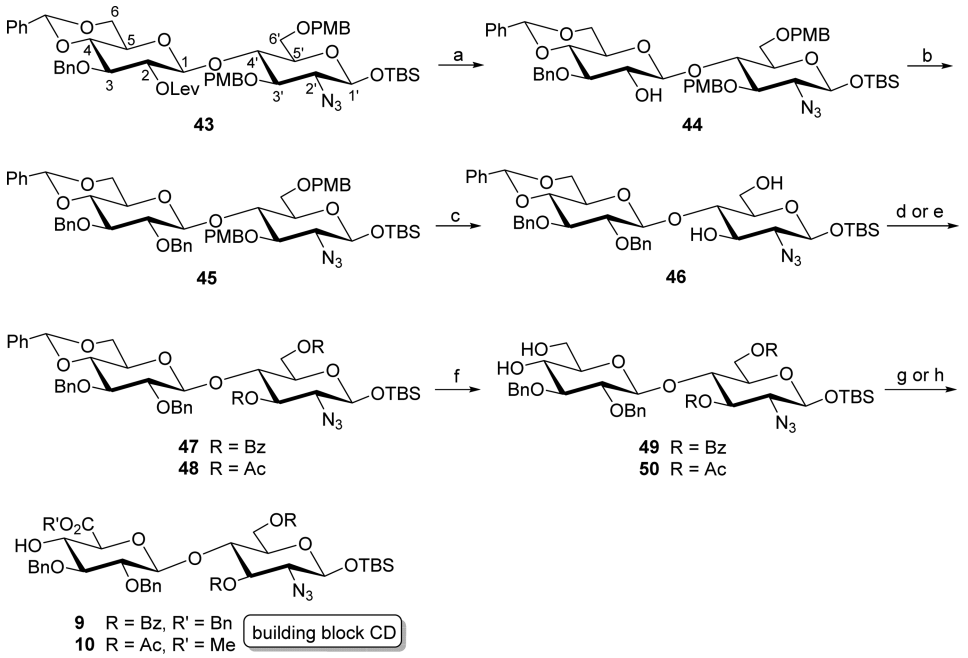
DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

Scheme 11. Glycosylations of Donor 14 with Glucosazide Acceptors 13a and 13b[a]



[a]Reagents and conditions: (a) NIS, TfOH, 4 Å molecular sieve, DCM, RT, 1 h, then −40 °C, 1 h, 80%. NIS = *N*-iodosuccinimide, TfOH = trifluoromethanesulfonic acid.

Scheme 12. Synthesis of Disaccharide Acceptors 9 and 10[a]



[a]Reagents and conditions: (a) $N_2H_4{\cdot}H_2O$, pyridine−AcOH (3:1), RT, 1 h; (b) BnBr, NaH, TBAI, DMF, RT, 50 min, 70% over 2 steps; (c) DDQ, DCM−H_2O (10:1), RT, 30 min, 81%; (d) preparation of **47**, Bz_2O, DMAP, PhMe, 60 °C, 12 h; (e) preparation of **48**, Ac_2O, DMAP, PhMe, 60 °C, 12 h; (f) TFA, DCM−H_2O (10:1), RT, 75% over 2 steps for **49**, 78% over 2 steps for **50**; (g) preparation of **9**, (1) TEMPO, $PhI(OAc)_2$, DCM−H_2O (2:1), RT; (2) BnBr, K_2CO_3, Et_3N, acetone, 60 °C, 93%; (h) preparation of **10**, (1) TEMPO, $PhI(OAc)_2$, DCM−H_2O (2:1), RT; (2) Me_2SO_4, K_2CO_3, Et_3N, acetone, RT, 65%. TBAI = tetrabutylammonium iodide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TFA = trifluoroacetic acid, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical.

not be determined on the basis of the coupling constant between the protons at C1 and C2 positions due to the complicated overlapping in the ^{1}H NMR spectrum of **38**. Meanwhile, the trichloroacetimidate **30** (anomeric mixture, α/β = 2:1) was also used for the critical glycosylation. Subjecting **30** and **13b** to the TESOTf-promoted glycosylation provided the same product **38** in 35% yield, together with a large amount of starting material, which could be recycled.

In order to confirm the glycosidic bond configuration of disaccharide **38**, we conducted the following experiments. As shown in Scheme 10, PMB cleavage of glycoside products **36** and **37** with DDQ, followed by benzoylation with Bz_2O and DMAP in one pot, provided the β-disaccharide **39** and α-disaccharide **40** in 56% and 52% yield, respectively. In contrast, the sequential 4,6-*O*-benzylidene removal of disaccharide **38** with TFA and $PhI(OAc)_2$-TEMPO-mediated oxidation, followed by esterification, gave compound **41**. Blocking the remaining 4-hydroxyl group in **41** by replacement with the TBS group delivered the corresponding α-disaccharide **40** in 80% yield, which unambiguously demonstrated that the glycosylation of donors **14b** or **30** with acceptor **13b** exhibited full α-selectivity, contrary to our expectations.

Using 2-*O*-Bn donors (**14b**, **30**, and **35**) proved challenging for the stereochemical aspect of the glycosylations, presumably due to the anomeric effect. To circumvent this problem, we turned to use a Lev group in place of Bn at the donor *O*2 position to achieve a β-selectivity resulting from neighboring participation in the glycosylation. To test this hypothesis, we

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

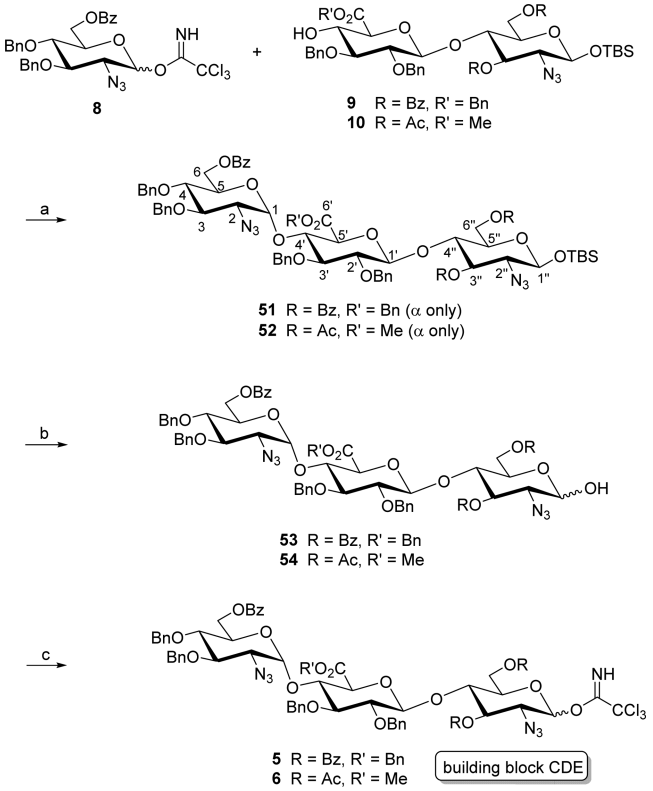
first carried out the condensation of Lev-donor **14a** with Bz-acceptor **13b**. Unfortunately, the desired product **42** was not formed under various conditions, and we observed substantial decomposition of the starting materials (Scheme 11). The inefficient glycosylation likely results from the electron-withdrawing esters in both the glycosyl donor and the azidoglucose acceptor.[12a] Pleasingly, use of the PMB-acceptor **13a** instead of **13b** allowed the NIS/TfOH-promoted glycosylation to proceed well, delivering desired disaccharide **43** with complete β-selectivity (no α-anomer detected) in 80% yield ($J_{1,2}$ = 7.6 Hz).

Following our synthetic plan, functional-group transformations were then carried out to complete the synthesis of suitable acceptors **9** and **10** (Scheme 12). Hydrazine-mediated cleavage of the Lev group in **43**, followed by benzylation with BnBr for permanent protection, furnished disaccharide **45** in 70% overall yield for the two steps. After removal of the PMB groups in **45** with DDQ in a mixture of DCM and water, the obtained diol **46** was esterified as a benzoate ester or acetate ester to give **47** or **48**, respectively. Subsequently, the 4,6-*O*-benzylidene group in **47** and **48** was selectively removed using TFA to yield diols **49** and **50**, respectively. Selective oxidation of the primary alcohol, followed by esterification, delivered acceptors **9** and **10** for the later glycosylation in 93% and 65% yield over two steps, respectively. The preparation of building block CD required 6-step adjustment of protecting groups. However, the mild conditions, easy operation, crystallizable intermediates (e.g., **43**, **45**, and most of intermediates toward **14a**), and high synthetic yield (32% overall for **9** and 23% overall for **10** from **14a**) demonstrate that this route is scalable. Indeed, in our laboratory, disaccharides **9** and **10** were successfully prepared on a 100 g scale.

2.8. Preparation of Building Block CDE (Trisaccharides 5 and 6). With the crucial disaccharide acceptors **9** and **10** in hand, the construction of trisaccharides **5** and **6** were investigated next (Scheme 13). As anticipated, the highly stereoselective glycosylations of **9** or **10** with azidoglucose donor **8** worked well. The combined effects of the anomeric effect and potentially remote participation, as caused by the orthogonal protecting groups in **8** (N_3, *O*6-Bz, and Bn), induced exclusive α-selectivity for this TfOH-promoted glycosylation and delivered the corresponding trisaccharides **51** ($J_{1,2}$ = 3.6 Hz) and **52** ($J_{1,2}$ = 3.2 Hz) in 64% and 85% yield, respectively. Selective removal of the anomeric TBS ether group with HF·pyridine in MeCN afforded alcohols **53** (85%, α/β = 3:2) and **54** (84%, α/β = 2:1). These compounds were converted by addition of CCl_3CN to trichloroacetimidate donors **5** (85%, α/β = 4:1) and **6** (77%, α/β = 5:1) for the ultimate glycosylation step. Because of the functionalization of monosaccharide donor **8** and disaccharide acceptors **9** and **10**, the condensation proceeded quickly (within 2 h) in high yield and with excellent α-selectivity. The obtained trisaccharides **51** and **52** could be readily converted to donors **5** and **6** simply by minor modifications at the anomeric position.

2.9. Preparation of Pentasaccharide 2. To complete the synthesis, the convergent [3 + 2] couplings of trichloroacetimidate donors **5** and **6** with acceptor **7** in the presence of TfOH effectively achieved both fully protected pentasaccharide targets **3** ($J_{1'',2''}$ = 3.6 Hz) and **4** ($J_{1'',2''}$ = 3.6 Hz), with complete α-selectivity, in 65% and 57% yield, respectively (Scheme 14). The glycosylations were exclusively stereoselective, presumably as a result of the dual effects of the ester (R) and N_3 groups in building block CDE. Subsequent removal of the ester groups

Scheme 13. Synthesis of Trisaccharides 5 and 6 (Building Block CDE)[a]



[a]Reagents and conditions: (a) TfOH, 4 Å molecular sieve, PhMe, −40 °C, 2 h, 64% for **51** and 85% for **52**; (b) HF·pyridine, MeCN, RT, 1 h, 85% for **53** (α/β = 3:2) and 84% for **54** (α/β = 2:1); (c) Cl_3CCN, DBU, MeCN, 0 °C to RT, overnight, 85% for **5** (α/β = 4:1) and 77% for **6** (α/β = 5:1). TfOH = trifluoromethanesulfonic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

from pentasaccharides **3** and **4** under a careful $LiOH/H_2O_2$-NaOH-mediated hydrolysis condition resulted in reported compound **2** in acceptable yields after crystallization (60% from **3** and 65% from **4**).[12b,c] Notably, pentasaccharide **2** can then be readily converted into the anticoagulant drug fondaparinux sodium **1** by the well-known *O*-sulfation/hydrogenation/*N*-sulfation process.[13]

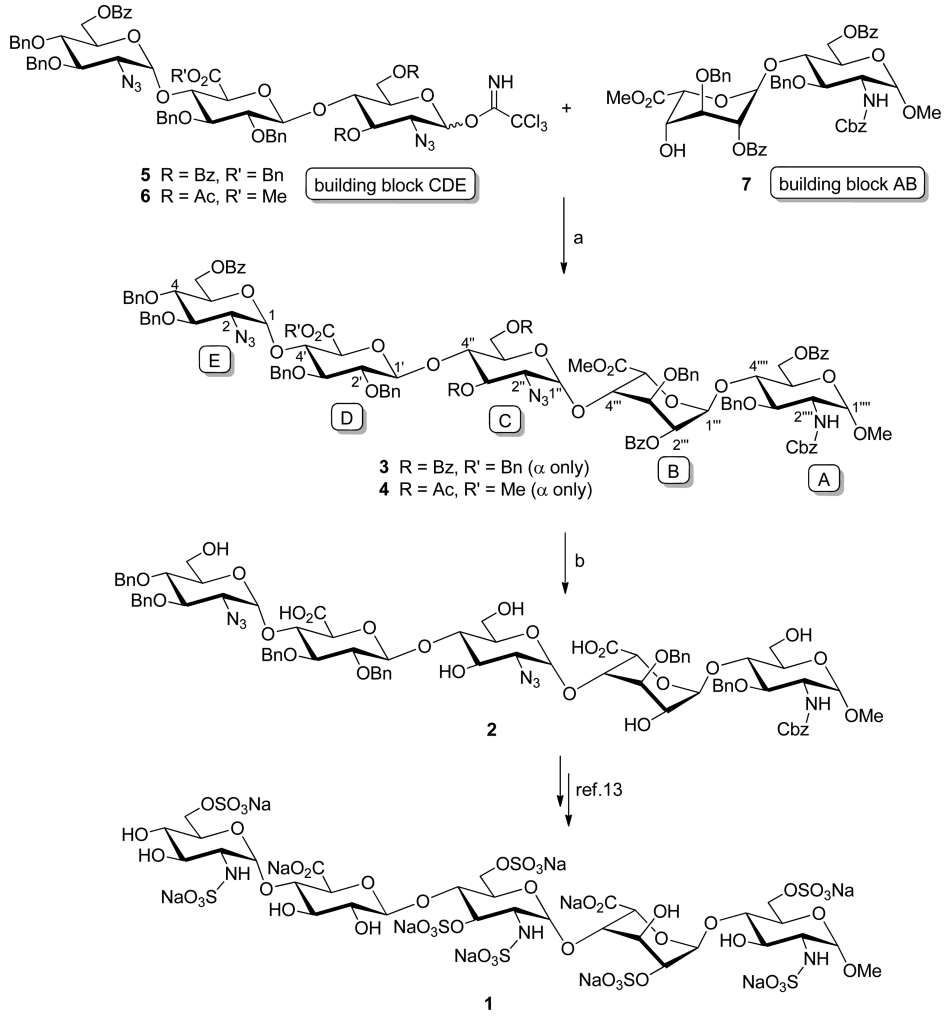
3. CONCLUSION

Pentasaccharide **2**, an important precursor for the synthesis of fondaparinux sodium, has been synthesized in 14 steps with 3.5% overall yield from well-functionalized monosaccharide building blocks and in 48 collective steps from commercially available starting materials. We have established a modular and convergent [3 + 2] strategy using a series of appropriately orthogonal protecting groups and readily accessible monosaccharide building blocks. Pentasaccharide **2** could then be easily converted into fondaparinux sodium in 41% overall yield over 3 steps based on previously reported methods.[13]

At the monosaccharide stage, several new and efficient routes to these building blocks were developed, in particular, the use of 1-thio iduronic acid donor **11** (building block B), glucosamine acceptor **12** (building block A), and azidoglucose acceptor **13** (building block C). All reactions avoided rigorous reaction conditions (avoiding low temperature, anhydrous environments, strong bases, etc.). The use of common

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

Scheme 14. Synthesis of Pentasaccharide 2[a]



[a]Reagents and conditions: (a) TfOH, 4 Å molecular sieve, PhMe, −40 °C, 2 h, 65% for **3** and 57% for **4**; (b) 1.25 M LiOH (aq.), H_2O_2 (30%), THF, −5 °C to RT, 16 h, then 4 M NaOH (aq.), MeOH, RT to 35 °C, 26 h, 60% (when using **3**), 65% (when using **4**). TfOH = trifluoromethanesulfonic acid.

intermediates and a series of one-pot operations considerably enhanced the synthetic efficiency and improved the overall yield. Moreover, many intermediates, such as those used to prepare **15**, **14**, and **30**, could be purified by crystallization, simplifying purification procedures and minimizing waste.

Using these suitably functionalized monosaccharide and oligosaccharide building blocks, all crucial glycosylations proceeded efficiently in a short time with satisfactory yield (ranging from 57% to 85%) and excellent stereoselectivity; i.e., the desired coupling product was delivered as a sole anomer in every glycosylation. Cheaper activators (e.g., NIS/TfOH, TESOTf, and TfOH) were employed, and metallic and expensive reagents were successfully avoided throughout the glycosylation procedures.

Given such improved purification and efficiency of the glycosylations, our developed synthetic strategy has great potential for use in the mass production of pentasaccharide **2**. As a common intermediate for the preparation of fondaparinux sodium, these results can significantly improve the scalability of this important drug.

4. EXPERIMENTAL SECTION

General Methods. All commercially available reagents were used without further purification. All solvents were dried and distilled before use. THF and PhMe were distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride; and MeOH was distilled from magnesium methoxide. Chromatography was conducted by using 200−300 mesh silica gel. Petroleum ether refers to the 60−90 °C boiling fraction. All new compounds gave satisfactory spectroscopic analyses (^{1}H NMR, ^{13}C NMR, HRMS). IR spectra were recorded on an FT IR spectrometer. NMR spectra were recorded on 600/400 MHz NMR spectrometers. HRMS spectra were obtained by the ESI-TOF method.

Synthetic Procedures and Characterization Data. *Methyl 2-Benzyloxy Carbonylamino-3-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranoside (**12**) and Methyl 2-(Triphenylphosphoranylidene)-amino-3-O-benzyl-6-O-benzoyl-2-deoxy-β-D-glucopyranoside (**19**).* The known intermediate methyl 2-azido-3-*O*-benzyl-6-*O*-benzoyl-2-deoxy-D-glucopyranoside (**18**) was prepared from D-glucosamine hydrochloride **17** by the reported methods.[16c,17a,e] To a solution of α/β anomers **18** (270 g, 654 mmol) in a THF−water mixture (9:1, 2.5 L) were added PPh_3 (257 g, 981 mmol) and silica gel (28 g) at room temperature. After stirring at room temperature for 3 h, the reaction was cooled to 0 °C and $NaHCO_3$ (110 g, 1310 mmol) and CbzCl (138 mL, 1012 mmol) were sequentially added. The resulting solution was kept for 3 h at 0 °C, and then water (1 L) and EtOAc (1 L) were

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

added. After separation, the aqueous phase was extracted with EtOAc (3 × 1 L). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to dichloromethane/methanol = 50:1) to yield **12** (190 g, 56%)[15] and **19** (46 g, 11%).

Compound ***12***. R_f = 0.4 (petroleum ether/ethyl acetate, 2/1, v/v); mp 152−154 °C; $[\alpha]_D^{23}$ +63.2 (*c* 0.3, CH_2Cl_2); IR (KBr) 3496, 3316, 2909, 1706, 1689, 1541, 1320, 1298, 1267, 1118, 1053, 1028, 711, 695; NMR data in $CDCl_3$: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 2H), 7. 50 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.28−7.19 (m, 10H), 5.08 (d, J = 12.0 Hz, 1H), 5.01 (d, J = 12.4 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H, NH), 4.67 (s, 2H), 4.65−4.59 (m, 2H), 4.44 (dd, J = 12.4, 2.0 Hz, 1H), 3.96−3.90 (m, 1H), 3.80−3.76 (m, 1H), 3.60 (t, J = 9.2 Hz, 1H), 3.50 (t, J = 9.2 Hz, 1H), 3.30 (s, 3H), 2.95 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 155.9, 138.2, 136.2, 133.2, 129.7, 129.5, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 99.0, 80.4, 74.7, 70.3, 70.0, 67.0, 63.5, 55.1, 54.3. The spectral data were in agreement with the reported data.[15] NMR data in Acetone-*d6*: ^{1}H NMR (600 MHz, Acetone-*d6*) δ 8.07 (d, J = 7.8 Hz, 2H), 7. 64 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.37−7.23 (m, 10H), 6.30 (d, J = 9.6 Hz, 1H), 5.13 (d, J = 12.6 Hz, 1H), 5.04 (d, J = 12.6 Hz, 1H), 4.93−4.90 (m, 2H), 4.79 (d, J = 10.8 Hz, 1H), 4.72 (d, J = 3.6 Hz, 1H), 4.66 (dd, J = 12.0, 2.4 Hz, 1H), 4.52 (dd, J = 12.0, 6.0 Hz, 1H), 3.95−3.88 (m, 2H), 3.78−3.70 (m, 2H), 3.40 (s, 3H); ^{13}C NMR (150 MHz, Acetone-*d6*) δ 166.7, 157.0, 140.3, 138.3, 133.9, 131.2, 130.2, 129.4, 129.1, 128.8, 128.6 128.5, 128.4, 127.9, 100.0, 81.4, 75.3, 71.0, 66.6, 64.8, 55.9, 55.3; HRMS $[M + Na]^+$ calcd for $C_{29}H_{31}NO_8Na$ 544.1947, found 544.1958.

Compound ***19***. R_f = 0.05 (petroleum ether/ethyl acetate, 2/1, v/v), R_f = 0.25 (dichloromethane/methanol, 50/1, v/v); $[\alpha]_D^{23}$ −7.1 (*c* 0.2, CH_2Cl_2); IR (KBr) 3476, 2924, 2107, 1720, 1453, 1276, 1116, 1056, 740, 713; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01−7.99 (d, J = 11.4 Hz, 2H), 7.81−7.76 (m, 6H), 7.69−7.65 (t, J = 7.8 Hz, 3H), 7.55−7.51 (m, 7H), 7.42−7.38 (m, 2H), 7.26−7.23 (m, 5H), 5.15 (d, J = 11.4 Hz, 1H), 4.99 (d, J = 8.4 Hz, 1H), 4.95 (d, J = 11.4 Hz, 1H), 4.59 (dd, J = 12.0, 5.4 Hz, 1H), 4.55−4.49 (m, 2H), 3.83−3.79 (m, 1H), 3.35 (t, J = 9.0 Hz, 1H), 3.10 (s, 3H), 2.63 (dd, J = 18.0, 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 138.9, 134.2, 134.1, 134.0, 133.9, 133.0, 129.8, 129.5, 129.4, 128.3, 128.2, 127.5, 127.4, 122.9, 122.2, 102.9, 82.4, 75.2, 73.7, 72.0, 64.0, 59.5, 56.3; HRMS $[M + H]^+$ calcd for $C_{39}H_{39}NO_6P$ 648.2510, found 648.2504.

*Methyl (4-Methylphenyl 2,4-di-O-acetyl-3-O-benzyl-1-thio-*L*-idopyranoside)uronate (**21**).* The known intermediate methyl 1,2,4-tri-*O*-acetyl-3-*O*-benzyl-L-idopyranoate (**20**) was prepared from diacetone glucose **16** by the reported methods.[19] Under nitrogen, to a solution of **20** (50 g, 118 mmol) in CH_2Cl_2 (1 L) were successively added $BF_3{\cdot}OEt_2$ (75 mL, 594 mmol) and *p*-toluenethiol (TolSH, 16 g, 155 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Et_3N (72 mL) was added to quench the reaction, and water (100 mL) was subsequently added into the reaction flask. After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 6:1) to afford compound **21** (37 g, 65%, α/β = 5:2). R_f = 0.4 (petroleum ether/ethyl acetate, 3/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.23 (m, 9.8H), 7.13−7.07 (m, 2.8H), 5.64 (br s, 0.4H), 5.56 (s, 1H), 5.39 (br s, 1H), 5.19 (br s, 1H), 5.16 (br s, 0.4 H), 5.13 (br s, 1H), 5.09 (s, 0.8H), 4.82 (d, J = 11.6 Hz, 1H), 4.74−4.70 (m, 1.8H), 3.91−3.89 (m, 0.4H), 3.85−3.83 (m, 1H), 3.77 (s, 4.2H), 2.32 (s, 1.2H), 2.30 (s, 3H), 2.11 (s, 1.2H), 2.04 (s, 1.2H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.5, 168.7, 137.5, 136.9, 136.8, 133.2, 132.5, 131.8, 131.3, 130.2, 129.7, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.8, 127.7, 86.4, 85.1, 74.3, 72.9, 72.7, 72.2, 71.4, 69.0, 68.6, 67.9, 66.9, 66.8, 52.5, 21.0, 21.0, 20.9, 20.7; HRMS $[M + Na]^+$ calcd for $C_{25}H_{28}O_8SNa$ 511.1403, found 511.1405.

*Methyl (4-Methylphenyl 3-O-benzyl-1-thio-*L*-idopyranoside)-uronate (**22**).* To a solution of **21** (42 g, 86 mmol) in MeOH (550 mL) was added MeONa (3.7 g, 68 mmol) at room temperature, and the reaction was stirred at the same temperature. Once the reaction was complete, the reaction mixture was neutralized with 2 M HCl (aq.) at 0 °C, and then extracted with CH_2Cl_2 (3 × 500 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 2:1) to afford compound **22** (26 g, 76%, α/β = 5:2). R_f = 0.3 (petroleum ether/ethyl acetate, 1/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.25 (m, 9.8H), 7.14−7.09 (m, 2.8H), 5.49 (s, 1H), 5.24 (br s, 1H), 5.12 (s, 0.4 H), 4.78 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1.4H), 4.49 (s, 0.4 H), 4.18−4.10 (m, 2H), 3.95−3.90 (m, 0.8H), 3.82 (s, 4.2H), 3.60 (d, J = 7.6 Hz, 1.4H), 3.45 (d, J = 6.8 Hz, 1H), 3.39 (d, J = 6.4 Hz, 0.4H), 2.34 (s, 1.2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 137.5, 137.3, 132.4, 132.3, 131.6, 129.8, 129.7, 128.6, 128.5, 128.2, 128.0, 127.7, 90.0, 87.1, 75.2, 74.5, 72.5, 72.4, 69.0, 68.6, 68.5, 67.4, 52.6, 21.1; HRMS $[M + Na]^+$ calcd for $C_{21}H_{24}O_6SNa$ 427.1191, found 427.1193.

*Methyl (4-Methylphenyl 2-O-benzoyl-3-O-benzyl-1-thio-*L*-idopyranoside)uronate (**23**).* To a solution of diol **22** (45 g, 111 mmol) in anhydrous MeOH (800 mL) was added dibutyltin oxide (Bu_2SnO, 30 g, 120 mmol). The resulting reaction mixture was refluxed under nitrogen for 1 h and then concentrated and dried under vacuum. Next, the residue was dissolved in 1,4-dioxane (1.5 L); benzoyl chloride (120 mL, 1042 mmol) and Et_3N (150 mL, 1082 mmol) were added sequentially into the reaction vessel at 0 °C. The reaction was stirred at the same temperature for 1 h and neutralized with 2 M HCl (aq.). After concentration, water (200 mL) was added and then extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to afford compound **23** (37 g, 65%, α/β = 5:2). R_f = 0.4 (petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.6 Hz, 0.8H), 7.99 (d, J = 8.0 Hz, 2H), 7.60−7.30 (m, 14H), 7.11 (d, J = 8.0 Hz, 2.8H), 5.67 (s, 1H), 5.50 (br s, 1H), 5.42 (br s, 1.4H), 5.25 (s, 0.4H), 4.92 (d, J = 12.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 0.4H), 4.72 (d, J = 11.6 Hz, 0.4H), 4.70 (d, J = 12.0 Hz, 1H), 4.60 (br s, 0.4H), 4.17−4.11 (m, 1.4H), 4.04−4.02 (m, 0.4H), 3.95−3.92 (m, 1H), 3.84 (s, 4.2H), 2.84 (d, J = 11.6 Hz, 1.4H, OH), 2.33 (s, 4.2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.6, 165.2, 164.7, 137.9, 137.7, 136.9, 133.6, 132.4, 132.0, 131.7, 131.6, 129.8, 129.7, 129.6, 128.7, 128.5, 128.4, 128.0, 127.9, 127.6, 87.0, 85.4, 76.2, 74.4, 73.5, 72.5, 72.2, 70.2, 69.5, 68.8, 68.1, 67.3, 52.4, 20.9; HRMS $[M + Na]^+$ calcd for $C_{28}H_{28}O_7SNa$ 531.1453, found 531.1458.

*Methyl (4-Methylphenyl 2-O-benzoyl-3-O-benzyl-4-O-tert-butyl-dimethylsilyl-1-thio-*L*-idopyranoside)uronate (**11**).* Under a nitrogen atmosphere, to a solution of **23** (10 g, 20 mmol) in CH_2Cl_2 (500 mL) was added 2,6-lutidine (7 mL, 60 mmol). The reaction was cooled to 0 °C, and TBSOTf (5.5 mL, 24 mmol) was added slowly. The resulting reaction mixture was allowed to warm to room temperature and stirred for 30 min; then water (100 mL) was added to quench the reaction. After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1) to afford compound **11** (10.7 g, 86%, α/β = 9:1). R_f = 0.6 (petroleum ether/ethyl acetate, 5/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 0.2H),8.07 (d, J = 7.6 Hz, 1.8H), 7.56−7.27 (m, 10H), 7.10 (d, J = 7.6 Hz, 2H), 5.76 (br s, 0.9H), 5.37 (br s, 0.9H), 5.30 (s, 0.1H), 5.26 (d, J = 2.4 Hz, 1H), 4.95 (d, J = 12.0, 0.9H), 4.85 (d, J = 11.6, 0.1H), 4.71 (d, J = 12.0 Hz, 1H), 4.12−4.10 (m, 0.9H), 4.01 (br s, 0.1H), 3.92 (br s, 0.1H), 3.84−3.82 (m, 0.9H), 3.80 (s, 1H), 2.30 (s, 3H), 0.68 (s, 9H), −0.10 (s, 3H), −0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 165.6, 137.3, 137.2, 133.2, 131.6, 131.5, 130.0, 129.6, 129.4, 128.4, 128.2, 128.1, 128.0, 86.4, 73.6, 72.3, 70.0, 69.3, 68.9, 52.0, 25.4, 21.0, 17.6, −4.4, −6.0; HRMS $[M + Na]^+$ calcd for $C_{34}H_{42}O_7SSiNa$ 645.2318, found 645.2325.

*1,4,6-Tri-O-acetyl-2-O-benzoyl-3-O-benzyl-*L*-idopyranose (**24**).*[17b] 1,6-Anhydride **15** (230 g, 646 mmol), prepared from diacetone glucose **16** by the reported methods,[16c] was dissolved in the mixed

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

solvent Ac_2O−TFA (6:1, 480 mL), and the reaction was stirred at 60 °C overnight. When TLC showed that the reaction was complete, the mixture was neutralized with saturated $NaHCO_3$ (aq.) (600 mL) and then water (500 mL) was added as well. The resulting reaction mixture was extracted with CH_2Cl_2 (5 × 800 mL). The combined organic layers were sequentially washed with brine and saturated $NaHCO_3$ (aq.), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford crude compound **24**[17b] as an α/β mixture (5:4), which was directly used without further purification for the ensuing reaction. An analytic sample was obtained by column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1.6H), 8.01 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 7.4 Hz, 2H), 7.53−7.20 (m, 14.4H), 6.19 (br s, 1H), 6.16 (br s, 0.8H), 5.28 (br s, 0.8H), 5.18 (br s, 1H), 4.97 (br s, 1H), 4.91 (br s, 0.8H), 4.78−4.67 (m, 3.6H), 4.58 (t, J = 6.4 Hz, 1H), 4.42 (t, J = 6.4 Hz, 0.8H), 4.28−4.16 (m, 3.6H), 3.97 (br s, 0.8H), 3.88 (br s, 1H), 2.01 (s, 3H), 1.96 (br s, 3 × OAc, 7.8H), 1.87 (s, 3H), 1.85 (s, 2.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 170.0, 169.6, 168.4, 168.2, 164.9, 164.5, 137.1, 136.6, 133.3, 133.1, 129.6, 129.5, 129.4, 129.0, 128.8, 128.2, 128.2, 128.1, 128.0, 128.0, 127.8, 127.5, 127.4, 127.1, 90.9, 90.1, 73.2, 72.6, 71.9, 71.6, 71.4, 66.4, 66.0, 65.8, 65.6, 65.2, 61.9, 20.5, 20.4, 20.3, 20.2, 20.1. The spectral data were in agreement with the reported data.[17b]

*4-Methylphenyl 2-O-Benzoyl-3-O-benzyl-4,6-di-O-acetyl-1-thio-L-idopyranoside (**25**).* Under nitrogen, to a solution of crude **24** in CH_2Cl_2 (1.7 L) were successively added *p*-toluenethiol (TolSH, 75 g, 681 mmol) and triflic acid (TfOH, 5.9 mL, 67 mmol) at 0 °C. The reaction mixture was stirred at the same temperature. Once the reaction was complete, Et_3N (15 mL) was added to quench the reaction and evaporated in vacuo. The resulting oil **25** was directly used without further purification for the ensuing reaction. An analytic sample was obtained by column chromatography (α/β = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 0.4H), 8.06 (d, J = 7.6 Hz, 2H), 7.59−7.29 (m, 12H), 7.23 (d, J = 7.6 Hz, 0.4H), 7.11 (d, J = 7.6 Hz, 2H), 5.56 (br s, 1H), 5.46 (br s, 1H), 5.34 (br s, 0.2H), 5.29 (br s, 0.2H), 5.13−5.10 (m, 1.2H), 4.99 (br s, 1H), 4.92 (d, J = 12.0 Hz, 1.2H), 4.81 (d, J = 11.6 Hz, 0.2H), 4.76 (d, J = 11.6 Hz, 1H), 4.33−4.22 (m, 2.4H), 4.02 (br s, 0.2H), 3.91 (br s, 1H), 2.32 (s, 3.6H), 2.07 (s, 3.6H), 1.95 (s, 3.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.9, 164.9, 137.7, 137.0, 133.4, 132.3, 131.9, 131.3, 129.9, 129.7, 129.6, 129.3, 128.4, 128.3, 127.9, 127.7, 127.6, 86.4, 84.5, 72.9, 72.6, 71.6, 69.6, 68.7, 67.0, 65.8, 64.4, 62.9, 21.0, 20.7, 20.6, 20.4; HRMS $[M + Na]^+$ calcd for $C_{31}H_{32}O_8SNa$ 587.1716, found 587.1721.

*4-Methylphenyl 2-O-Benzoyl-3-O-benzyl-1-thio-L-idopyranoside (**26**).*[8e] To a solution of crude **25** in MeOH (2.3 L) was added AcCl (80 mL, 1131 mmol) at 0 °C. After stirring at room temperature overnight, the reaction was cooled to 0 °C and neutralized with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with CH_2Cl_2 (3 × 800 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to afford compound **26**[8e] (186 g, α/β = 5:1, 60% from compound **15**) as a light yellow syrup. R_f = 0.4 (petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 0.4H), 8.05 (d, J = 7.6 Hz, 2H), 7.60−7.29 (m, 12H), 7.12 (d, J = 7.6 Hz, 2.4H), 5.57 (br s, 1H), 5.53 (br s, 1H), 5.44 (br s, 0.2H), 5.33 (br s, 0.2H), 4.91 (d, J = 12.0 Hz, 1H), 4.81−4.79 (m, 1.2H), 4.67 (d, J = 12.0 Hz, 1.2H), 4.15−4.03 (m, 0.4H), 3.96−3.88 (m, 4H), 3.72 (br s, 0.2H), 2.98 (br s, OH), 2.32 (s, 3.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 164.9, 137.8, 137.2, 133.5, 132.4, 131.8, 131.2, 129.7, 129.6, 129.0, 128.5, 128.4, 127.9, 127.7, 87.0, 85.1, 74.9, 74.1, 72.5, 72.2, 70.8, 69.8, 68.2, 68.0, 66.7, 63.0, 62.6, 21.0. The spectral data were in agreement with the reported data.[8e]

*Methyl (4-Methylphenyl 2-O-benzoyl-3-O-benzyl-1-thio-L-idopyranoside)uronate (**23**).* To a solution of diol **26** (281g, 585 mmol) in the mixed solvent CH_2Cl_2−water (2:1, 5.2 L) containing TEMPO (18.3 g, 117 mmol) was added iodobenzene diacetate ($PhI(OAc)_2$, 468 g, 1453 mmol); the mixture was stirred vigorously at ambient temperature. After TLC indicated complete conversion of the starting material, the reaction was quenched by the addition of a saturated solution of Na_2SO_3 (1.0 L). After further stirring for 5 min, HCl (aq.) was added to adjust the final pH value of the mixture to pH 3. The resulting mixture was diluted with CH_2Cl_2 (1.5 L). The organic phase was separated, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, and then filtered and concentrated in vacuo to yield the corresponding crude glucuronic acid, which was used without further purification. The crude glucuronic acid was dissolved in acetone (2.6 L) and treated with dimethyl sulfate (Me_2SO_4, 77 mL, 813 mmol) and K_2CO_3 (164 g, 1187 mmol) at 0 °C under a nitrogen atmosphere. After complete disappearance of the glucuronic acid, the mixture was neutralized with 1 N HCl and extracted with CH_2Cl_2 (4 × 500 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to afford compound **23** (238 g, α/β = 5:1, 80%). R_f = 0.4 (petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.6 Hz, 0.4H), 7.99 (d, J = 8.0 Hz, 2H), 7.60−7.30 (m, 12H), 7.11 (d, J = 8.0 Hz, 2.4H), 5.67 (s, 1H), 5.50 (br s, 1H), 5.42 (br s, 1.2H), 5.24 (s, 0.2H), 4.92 (d, J = 11.6 Hz, 1H), 4.80 (d, J = 12.0 Hz, 0.2H), 4.72 (d, J = 12.0 Hz, 0.2H), 4.70 (d, J = 12.0 Hz, 1H), 4.60 (br s, 0.2H), 4.17−4.11 (m, 1.2H), 4.04−4.02 (m, 0.2H), 3.95−3.92 (m, 1H), 3.84 (s, 3.6H), 2.84 (d, J = 11.6 Hz, 1H, OH), 2.33 (s, 3.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.6, 165.2, 164.7, 137.7, 136.9, 133.6, 132.4, 132.0, 131.7, 131.6, 129.8, 129.7, 129.6, 128.7, 128.5, 128.4, 128.0, 127.9, 127.6, 87.0, 85.4, 76.2, 74.4, 73.5, 72.5, 72.2, 70.2, 69.5, 68.8, 68.1, 67.3, 52.4, 20.9; HRMS $[M + Na]^+$ calcd for $C_{28}H_{28}O_7SNa$ 531.1453, found 531.1460.

*Methyl (4-Methylphenyl 2-O-benzoyl-3-O-benzyl-4-O-tert-butyldimethylsilyl-1-thio-L-idopyranoside)uronate (**11**).* Under a nitrogen atmosphere, to a solution of **23** (238 g, 468 mmol) in CH_2Cl_2 (2.0 L) was added 2,6-lutidine (160 mL, 1373 mmol). The reaction was cooled to 0 °C, and TBSOTf (126 mL, 550 mmol) was added slowly. The resulting reaction mixture was allowed to warm to room temperature and stirred for 1 h; then water (1.0 L) was added to quench the reaction. After separation, the aqueous phase was extracted with CH_2Cl_2 (5 × 800 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1) to afford compound **11** (250 g, 86%, α/β > 9:1). The product could be recrystallized from petroleum ether in 78% yield. The dominant anomer (**11**$\boldsymbol{\alpha}$) was obtained by column chromatography for spectrographic analysis. R_f = 0.6 (petroleum ether/ethyl acetate, 5/1, v/v). **11**$\boldsymbol{\alpha}$: $[\alpha]_D^{23}$ −81.1 (*c* 0.5, CH_2Cl_2); IR (KBr) 3064, 3032, 2953, 2929, 2858, 1770, 1737, 1719, 1602, 1494, 1454, 1438, 1373, 1317, 1299, 1270, 1213, 1179, 1127, 1095, 1074, 1028, 942, 921, 904, 839, 811, 778, 739, 713, 630, 565, 500; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.6 Hz, 2H), 7.56−7.24 (m, 10H), 7.09 (d, J = 7.6 Hz, 2H), 5.76 (br s, 1H), 5.37 (br s, 1H), 5.26 (br s, 1H), 4.93 (d, J = 12.4, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.13−4.09 (m, 1H), 3.84−3.79 (m, 1H), 3.78 (s, 1H), 2.30 (s, 3H), 0.67 (s, 9H), −0.12 (s, 3H), −0.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 165.6, 137.3, 137.2, 133.2, 131.6, 131.5, 130.0, 129.6, 129.4, 128.4, 128.2, 128.1, 128.0, 86.4, 73.6, 72.3, 70.0, 69.3, 68.9, 52.0, 25.4, 21.0, 17.6, −4.4, −6.0; HRMS $[M + Na]^+$ calcd for $C_{34}H_{42}O_7SSiNa$ 645.2318, found 645.2323.

*Methyl O-(Methyl 2-O-benzoyl-3-O-benzyl-4-O-tert-butyldimethylsilyl-α-L-idopyranosyluronate)-(1→4)-2-benzyloxy Carbonylamino-3-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranoside (**27**).* A mixture of the thioglycoside **11** (39 g, 63 mmol) and acceptor **12** (36 g, 69 mmol) in dry CH_2Cl_2 (1.5 L) was added to a reaction flask containing freshly dried 4 Å molecular sieves (60 g) under a N_2 atmosphere. The mixture was stirred at room temperature for 1 h, and the solution was cooled to −40 °C. NIS (19 g, 84 mmol) and TfOH (7 mL, 79 mmol) were added to the reaction flask. The resulting solution was kept stirring for 1 h, and Et_3N (22 mL) was added to quench the reaction. The whole mixture was filtered through Celite, followed by washing with CH_2Cl_2, and the filtrate was sequentially washed with saturated Na_2SO_3 (aq.) and $NaHCO_3$ (aq.). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated

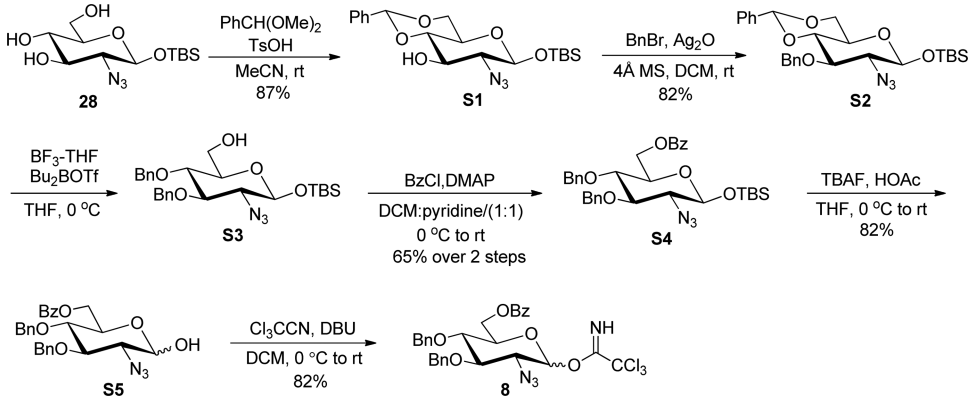
DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

under reduced pressure to get the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to get the disaccharide **27** (43 g, 67%) as a white solid. R_f = 0.4 (petroleum ether/ethyl acetate, 4/1, v/v); mp 72−73 °C; $[\alpha]_D^{23}$ +30.7 (*c* 0.3, CH_2Cl_2); IR (KBr) 3033, 2930, 2857, 2353, 1765, 1723, 1646, 1602, 1517, 1453, 1366, 1315, 1269, 1212, 1099, 1070, 1026, 911, 839, 778, 737, 712, 529, 467, 438; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, *J* = 6.8 Hz, 4H), 7.56−7.48 (m, 2H), 7.44−7.36 (m, 4H), 7.31−7.16 (m, 15H), 5.61 (d, *J* = 5.6 Hz, 1H), 5.19 (t, *J* = 5.2 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 4.94 (d, *J* = 11.2 Hz, 1H), 4.84 (d, *J* = 9.6 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.69−4.57 (m, 4H), 4.48 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.10 (t, *J* = 9.6 Hz, 1H), 4.04−3.98 (m, 2H), 3.89 (t, *J* = 6.0 Hz, 1H), 3.82 (t, *J* = 9.2 Hz, 1H), 3.64 (t, *J* = 9.6 Hz, 1H), 3.46 (s, 3H), 3.28 (s, 3H), 0.74 (s, 9H), −0.05 (s, 3H), −0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 166.0, 165.4, 155.8, 138.5, 137.7, 136.3, 133.2, 132.8, 129.8, 129.7, 129.2, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.2, 98.6, 98.1, 78.4, 76.4, 74.6, 73.6, 72.7, 71.9, 69.8, 69.1, 66.8, 62.6, 55.1, 54.3, 51.5, 25.5, 17.6, −4.7, −5.5; HRMS $[M + Na]^+$ calcd for $C_{56}H_{65}NO_{15}SiNa$ 1042.4016, found 1042.4007.

*Methyl O-(Methyl 2-O-benzoyl-3-O-benzyl-α-L-idopyanosyluronate)-(1→4)-2-benzyloxy carbonylamino-3-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranoside (**7**).* A 70% solution of HF in pyridine (200 mL) was added to an ice-cooled solution of compound **27** (43 g, 42 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. Next, the mixture was diluted with CH_2Cl_2 (150 mL) and quenched by addition of saturated $NaHCO_3$ (aq.). After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The product was recrystallized from ethyl acetate/isopropyl ether to afford the desilylated compound **7** as a white solid (32 g, 84%). The yield increased to 90% when residue was purified by column chromatography (petroleum ether/ethyl acetate = 2:1). R_f = 0.4 (petroleum ether/ethyl acetate, 3/2, v/v); mp 146−147 °C; $[\alpha]_D^{23}$ +42.0 (*c* 0.3, CH_2Cl_2); IR (KBr) 2961, 1723, 1601, 1515, 1453, 1315, 1263, 1214, 1098, 1051, 1026, 800, 739, 712; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.55−7.49 (m, 2H), 7.43−7.18 (m, 19H), 5.35 (br s, 1H), 5.20 (br s, 1H), 5.02−4.98 (m, 3H), 4.90 (d, *J* = 10.0 Hz, 1H), 4.83−4.66 (m, 4H), 4.57−4.47 (m, 2H), 4.10−4.03 (m, 3H), 3.97−3.88 (m, 2H), 3.68−3.62 (m, 1H), 3.47 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.0, 164.9, 155.7, 138.0, 137.3, 136.1, 133.5, 133.0, 129.7, 128.7, 128.4, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.4, 127.1, 98.7, 98.1, 79.1, 75.4, 75.0, 74.4, 72.5, 69.3, 68.7, 68.1, 67.9, 66.9, 62.8, 55.2, 54.6, 52.0; HRMS $[M + Na]^+$ calcd for $C_{50}H_{51}NO_{15}Na$ 928.3156, found 928.3179.

*tert-Butyldimethylsilyl 3,6-Di-O-p-methoxybenzyl-2-azido-2-deoxy-β-D-glucopyranoside (**13a**).* The known intermediate *tert*-butyldimethylsilyl 2-azido-2-deoxy-β-D-glucopyranoside (**28**) was successfully prepared over a 500 g scale with only one time column chromatography from D-glucosamine hydrochloride **17** by the reported methods.[19b] To a solution of triol **28** (60 g, 188 mmol) in toluene (1.0 L) was added dibutyltin oxide (Bu_2SnO, 94 g, 377 mmol), and the mixture was refluxed with azeotropic removal of water for 6 h using a Dean−Stark tube. The reaction was cooled to room temperature, PMBCl (64 mL, 472 mmol) and tetrabutylammonium iodide (TBAI, 35 g, 95 mmol) were added, and the reaction was kept faint boiling for 5 h. Once the reaction was complete, the reaction mixture was concentrated and the residue was dissolved in EtOAc (500 mL) again. The resulting mixture was washed with water (3 × 500 mL), and the organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give compound **13a** (73.2 g, 70%) as a light yellow oil. R_f = 0.5 (petroleum ether/ethyl acetate, 2/1, v/v); $[\alpha]_D^{23}$ −32.0 (*c* 0.5, CH_2Cl_2); IR (KBr) 3489, 3000, 2955, 2930, 2858, 2218, 1613, 1587, 1514, 1464, 1391, 1362, 1303, 1251, 1175, 1113, 1080, 1038, 956, 842, 784, 691, 597, 517; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.20 (m, 4H), 6.90−6.86 (m, 4H), 4.82 (d, *J* = 10.8 Hz, 1H), 4.69 (d, *J* = 11.2 Hz, 1H), 4.52−4.45 (m, 3H), 3.80 (s, 6H), 3.67−3.56 (m, 3H), 3.40−3.35 (m, 1H), 3.31−3.26 (m, 1H), 3.19 (t, *J* = 9.2 Hz, 1H), 2.66 (br s, 1H), 0.93 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 159.3, 130.3, 129.8, 129.7, 129.3, 114.0, 113.8, 97.2, 81.9, 74.6, 73.9, 73.2, 72.1, 70.1, 68.1, 55.3, 25.60, 18.0, −4.3, −5.2; HRMS $[M + Na]^+$ calcd for $C_{28}H_{41}N_3O_7SiNa$ 582.2611, found 582.2618.

*tert-Butyldimethylsilyl 2-Azido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**13b**).* To a solution of triol **28** (54 g, 169 mmol) in toluene (900 mL) was added Bu_2SnO (85 g, 341 mmol), and the mixture was refluxed with azeotropic removal of water for 4 h using a Dean−Stark tube. The reaction was cooled to room temperature, BzCl (42 mL, 364 mmol) and TBAI (32 g, 87 mmol) were added, and the reaction was kept at room temperature for overnight. Once the reaction was complete, the reaction mixture was concentrated and the residue was dissolved in EtOAc (500 mL) again. The resulting mixture was washed with water (3 × 500 mL), and the organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give compound **13b** (44.5 g, 50%) as a white powder. R_f = 0.6 (petroleum ether/ethyl acetate, 2/1, v/v); mp 153−155 °C; $[\alpha]_D^{23}$ +30.7 (*c* 0.4, CH_2Cl_2); IR (KBr) 3646, 2925, 2112, 1721, 1452, 1270, 1178, 1119, 841, 784, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.03 (m, 4H), 7.61−7.55 (m, 2H), 7.48−7.42 (m, 4H), 5.07 (t, *J* = 8.0 Hz, 1H), 4.75 (d, *J* = 7.6 Hz, 1H), 4.68−4.57 (m, 2H), 3.75−3.68 (m, 1H), 3.57−3.52 (m, 1H), 3.43 (dd, *J* = 6.4, 4.4 Hz, 1H), 1.73 (d, *J* = 6.4 Hz, 1H), 0.92 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.7, 133.7, 133.2, 130.00, 129.8, 129.6, 129.0, 128.5, 128.3, 97.2, 76.1, 74.4, 69.9, 66.2, 63.8, 25.5, 17.9, −4.4, −5.2; HRMS $[M + Na]^+$ calcd for $C_{26}H_{33}N_3O_7SiNa$ 550.1985, found 550.1987.



*2-Azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy-D-glucopyranosyl Trichloroacetimidate (**8**).*[14] To a solution of triol **28** (5 g, 15.7 mmol) in MeCN (100 mL) were added *p*-TsOH (74 mg, 0.43 mmol) and benzaldehyde dimethyl acetal (4.7 mL, 31.3 mmol). After stirring at room temperature for 4 h, Et_3N (1 mL) was added and the resulting mixture was concentrated in vacuo. The crude product was purified by

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give compound **S1** (5.6 g, 87%). R_f = 0.5 (petroleum ether/ethyl acetate, 5/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.36 (m, 5H), 5.53 (s, 1H), 4.64 (d, J = 7.6 Hz, 1H), 4.29 (dd, J = 10.8, 4.8 Hz, 1H), 3.78 (t, J = 10.0 Hz, 1H), 3.64−3.53 (m, 2H), 3.43−3.37 (m, 1H), 3.32 (t, J = 8.4 Hz, 1H), 0.95 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 129.3, 128.4, 126.3, 102.0, 97.5, 80.7, 71.7, 69.0, 68.5, 66.3, 25.5, 17.9, −4.4, −5.2.

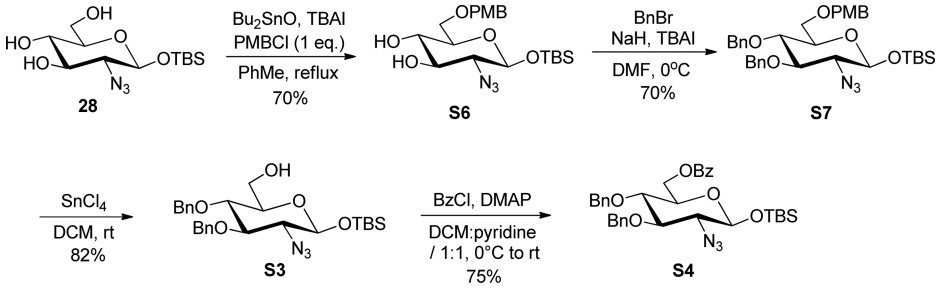
S1 (5 g, 12.2 mmol) was dissolved in CH_2Cl_2 (50 mL), and freshly activated 4 Å molecular sieves (10 g) and benzyl bromide (3 mL, 25 mmol) were added. The mixture was stirred for 30 min. Silver(I) oxide (Ag_2O, 8.3 g, 36 mmol) was added, and the reaction vessel was covered in aluminum foil to exclude light. After 10 h, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 50:1) afforded **S2** (5 g, 82%) as a white solid. R_f = 0.5 (petroleum ether/ethyl acetate, 20/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.27 (m, 10H), 5.57 (s, 1H), 4.91 (d, J = 11.6 Hz, 1H), 4.79 (d, J = 11.2 Hz, 1H), 4.59 (d, J = 7.6 Hz, 1H), 4.30 (dd, J = 10.4, 5.2 Hz, 1H), 3.79 (t, J = 10.4 Hz, 1H), 3.72 (t, J = 9.2 Hz, 1H), 3.52 (t, J = 9.2 Hz, 1H), 3.42−3.34 (m, 2H), 0.94 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.2, 129.0, 128.3, 128.2, 128.1, 127.8, 126.0, 101.3, 97.5, 81.6, 78.8, 74.8, 68.7, 68.6, 66.3, 25.5, 17.9, −4.4, −5.2. The spectral data were in agreement with the reported data.[14d]

S2 (4.2 g, 8.5 mmol) was dissolved in BH_3·THF (1.0 M, 85 mL, 85 mmol) under nitrogen and cooled to 0 °C. After 15 min, Bu_2B·OTf (1 M, 8.8 mL, 8.8 mmol) was added dropwise, and stirring was continued at 0 °C for 4 h. The reaction mixture was quenched by the addition of Et_3N (5 mL), and the excess BH_3·THF was consumed by slowly adding methanol. The solvent was removed in vacuo, coevaporated with methanol twice, affording **S3**, which was used for the next step without further purification. An analytic sample was obtained by column chromatography. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41−7.30 (m, 10H), 4.92 (d, J = 10.8 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 4.83 (d, J = 10.8 Hz, 1H), 4.67 (d, J = 10.8 Hz, 1H), 4.58 (d, J = 7.8, 1H), 3.89−3.69 (m, 3H), 3.59 (t, J = 9.6 Hz, 1H), 3.45 (t, J = 10.2 Hz, 1H), 3.38−3.33 (m, 2H), 0.98 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.9, 137.8, 128.5, 128.4, 128.0, 127.9, 127.8, 97.0, 82.8, 77.4, 75.4, 75.3, 75.0, 68.8, 61.9, 25.6, 17.9, −4.3, −5.2.

To a solution of crude **S3** in the mixed solvent CH_2Cl_2−pyridine (1:1, 90 mL) were added benzoyl chloride (1.8 mL, 15.6 mmol) and DMAP (500 mg, 4 mmol) under nitrogen at 0 °C. The reaction mixture was allowed to warm up to room temperature. Stirring was continued until TLC indicated the disappearance of the starting material. The reaction mixture was quenched by the addition of water. The mixture was poured into CH_2Cl_2 and washed with brine twice. The organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10:1) to give **S4** (3.3 g, 65% from compound **S2**). R_f = 0.4 (petroleum ether/ethyl acetate, 5/1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.43−7.24 (m, 12H), 4.92 (d, J = 10.8 Hz, 1H), 4.87 (d, J = 11.4 Hz, 1H), 4.80 (d, J = 10.8 Hz, 1H), 4.63−4.55 (m, 3H), 4.37 (dd, J = 12.0, 6.0 Hz, 1H), 3.64−3.61 (m, 1H), 3.56 (t, J = 8.4 Hz, 1H), 3.45 (t, J = 8.4 Hz, 1H), 3.39−3.35 (m, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 137.8, 137.4, 133.1, 129.8, 129.6, 128.5, 128.3, 128.1, 128.0, 128.0, 127.9, 97.1, 83.0, 77.7, 75.6, 75.1, 73.3, 68.7, 63.5, 25.5, 17.9, −4.3, −5.2. The spectral data were in agreement with the reported data.[14a]

TBAF (165 g, 631 mmol) and acetic acid (15 mL, 262 mmol) were added to an ice-cooled solution of compound **S4** (225 g, 373 mmol; **S4** could be synthesized over a 200 g scale by the undermentioned alternative method) in THF (5 L). The mixture was allowed to warm to room temperature and stirred for 3 h. Next, the mixture was diluted with CH_2Cl_2 (500 mL) and quenched by addition of saturated $NaHCO_3$ (aq.). After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to afford the desilylated compound **S5** (150 g, 82%) as an α/β mixture (α/β = 3:1). R_f = 0.5 (petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02−8.00 (m, 2.6H), 7.58−7.54 (m, 1.3H), 7.47−7.22 (m, 16H), 5.33 (br s, 1.3H), 4.96−4.83 (m, 4H), 4.67−4.59 (m, 2.6H), 4.49−4.43 (m, 1.3H), 4.25−4.23 (m, 1H), 4.09 (t, J = 9.0 Hz, 1H), 3.77−3.63 (m, 1.6H), 3.54−3.39 (m, 1.6H), 3.03 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 137.5, 137.4, 137.3, 133.2, 133.1, 129.8, 129.7, 129.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 96.2, 92.1, 83.1, 80.2, 78.2, 75.8, 75.7, 75.2, 75.2, 73.5, 69.5, 67.6, 64.1, 63.0, 62.9.

Under a nitrogen atmosphere, the lactol **S5** (150 g, 307 mmol) was dissolved in CH_2Cl_2 (3 L), and trichloroacetonitrile (93 mL, 927 mmol)) and DBU (16.5 mL, 110 mmol) were added at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred for 2 h. Then, the reaction was quenched by the addition of water (500 mL), and the separated aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to deliver trichloroacetimidate **8** (159 g, 82%) as an α/β mixture (α/β = 10:1). R_f = 0.4 (petroleum ether/ethyl acetate, 5/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1.1H), 7.98 (d, J = 7.6 Hz, 2.2H), 7.58−7.13 (m, 14.3H), 6.44 (d, J = 3.6 Hz, 1H), 5.67 (d, J = 8.4 Hz, 0.1H), 5.02−4.75 (m, 3.3H), 4.65 (d, J = 10.8 Hz, 1.1H), 4.58−4.54 (m, 1.1H), 4.50−4.46 (m, 1.1H), 4.24−4.08 (m, 2.2H), 3.82−3.70 (m, 2.2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 160.7, 137.3, 137.0, 133.2, 129.7, 129.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 128.1, 94.5, 90.8, 80.3, 77.6, 75.8, 75.5, 72.0, 63.1, 62.6. The spectral data were in agreement with the reported data.[14c]



Alternative synthesis of **S4**: To a solution of triol **28** (295 g, 925 mmol) in toluene (1.0 L) was added dibutyltin oxide (Bu_2SnO, 276 g, 1108 mmol), and the mixture was refluxed with azeotropic removal of water for 6 h using a Dean−Stark tube. The reaction was cooled to 60 °C, tetrabutylammonium iodide (TBAI, 34 g, 92 mmol) and PMBCl (126 mL, 929 mmol) were added, and the reaction was kept faint boiling overnight. Once the reaction was complete, the reaction mixture was concentrated and the residue was dissolved in EtOAc (1.0 L) again. The resulting mixture was washed with water (3 × 500 mL), and the organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to give compound **S6** (284 g, 70%) as a brown oil. $[\alpha]_D^{23}$ −8.9 (c 1.1, CH_2Cl_2); IR (KBr) 3406, 2956, 2930, 2858, 1614, 1587, 1515, 1464, 1391, 1364, 1252, 1176, 1113, 1078, 842, 784, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz,

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

2H), 4.53−4.49 (m, 2H), 3.79 (s, 3H), 3.69−3.67 (m, 2H), 3.56−3.52 (m, 2H), 3.41−3.37 (m, 1H), 3.34−3.29 (m, 1H), 3.24−3.19 (m, 1H), 0.93 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 129.6, 129.3, 113.8, 113.8, 97.1, 74.5, 73.9, 73.4, 71.9, 69.8, 68.0, 55.2, 25.5, 17.9, −4.3, −5.3; HRMS $[M + Na]^+$ calcd for $C_{20}H_{33}N_3O_6SiNa$ 462.2036, found 462.2032.

To a cooled (0 °C) solution of diol **S6** (122 g, 278 mmol) in DMF (1.2 L) was added NaH (60% dispersion in mineral oil, 28 g, 700 mmol). After the mixture had been stirred for 30 min, TBAI (5.1 g, 14 mmol) and benzyl bromide (BnBr, 132 mL, 1111 mmol) were added. After stirring for 50 min at 0 °C, to the reaction mixture was added water (800 mL), and the mixture was extracted with EtOAc (3 × 1 L). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered. To the resulting mixture was added Et_3N (170 mL), and the mixture was stirred for another 6 h. Next, the solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (5% to 10%, ethyl acetate/petroleum ether) to afford **S7** (120.5 g, 70%) as a light yellow oil. $[\alpha]_D^{23}$ −17.0 (*c* 0.6, CH_2Cl_2); IR (KBr) 3065, 3032, 2930, 2858, 2212, 1744, 1613, 1587, 1514, 1498, 1455, 1391, 1361, 1303, 1251, 1208, 1174, 1150, 1117, 1066, 1038, 1006, 841, 784, 736, 698, 574, 513; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.22 (m, 12H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.92 (d, *J* = 10.8 Hz, 1H), 4.85−4.81 (m, 2H), 4.61−4.48 (m, 4H), 3.82 (s, 3H), 3.72−3.64 (m, 3H), 3.46−3.39 (m, 3H), 1.00 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 138.1, 138.0, 130.1, 129.7, 129.3, 128.4, 128.3, 127.9, 127.8, 127.8, 127.7, 113.7, 97.2, 82.9, 77.7, 75.4, 75.0, 74.9, 73.0, 68.7, 68.3, 55.2, 25.6, 18.0, −4.2, −5.3; HRMS $[M + Na]^+$ calcd for $C_{34}H_{45}N_3O_6SiNa$ 642.2969, found 642.2955.

To a solution of **S7** (148 g, 239 mmol) in CH_2Cl_2 (1.0 L) was added $SnCl_4$ (5.6 mL, 50 mmol), and the resulting solution was stirred for 2 h at room temperature. Then, to the reaction mixture was added water (500 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo to provide pure **S3** (98 g, 82%) for the next reaction without further purification.

Alcohol **S3** (273 g, 547 mmol) was dissolved in the mixed solvent CH_2Cl_2−pyridine (1:1, 1.0 L), and DMAP (33.3 g, 272 mmol) and benzoyl chloride (95 mL, 824 mmol) were added consecutively at 0 °C. The reaction was allowed to warm to room temperature for stirring overnight, and then quenched by the addition of water (500 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 800 mL). The combined organic phases were washed with 1 N HCl (aq.) and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give compound **S4** (249 g, 75%) as a colorless oil.

*4-Methylphenyl 2-O-Levulinyl-3-O-benzyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (**14a**) and 4-Methylphenyl 2,3-Di-O-benzyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (**14b**).*[12c,21] The known thioglycoside donors **14a** and **14b** were synthesized from **16** using the reported procedures without column chromatography in the whole course.[12c,21] **Compound 14a** (**14a** could be synthesized on a 160 g scale, and could be recrystallized in petroleum ether/ethyl acetate, 4/1, v/v): R_f = 0.5 (petroleum ether/ethyl acetate, 3/1, v/v); mp 139−140 °C; $[\alpha]_D^{23}$ −46.0 (*c* 0.6, CH_2Cl_2); IR (KBr) 3064, 3032, 2922, 2882, 1957, 1906, 1739, 1711, 1606, 1493, 1472, 1453, 1419, 1398, 1372, 1315, 1273, 1189, 1155, 1102, 1068, 1028, 1003, 982, 936, 923, 876, 839, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.24 (m, 12H), 7.11 (d, *J* = 7.6 Hz, 2H), 5.56 (s, 1H), 4.98 (dd, *J* = 10.0, 8.0 Hz, 1H), 4.84 (d, *J* = 12.0, 1H), 4.68 (d, *J* = 12.0, 1H), 4.62 (d, *J* = 10.0 Hz, 1H), 4.37 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.81−3.67 (m, 3H), 3.50−3.44 (m, 1H), 2.76−2.72 (m, 2H), 2.59−2.53 (m, 2H), 2.33 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 171.2, 138.5, 138.0, 137.1, 133.5, 129.6, 129.0, 128.2, 128.1, 127.9, 127.6, 125.9, 101.1, 87.0, 81.2, 79.7, 74.3, 71.6, 70.4, 68.5, 37.8, 29.9, 28.0, 21.2; HRMS $[M + Na]^+$ calcd for $C_{32}H_{34}O_7SNa$ 585.1923, found 585.1930; **Compound 14b** (**14b** was synthesized on a 200 g scale easily in our laboratory): R_f = 0.6 (petroleum ether/ethyl acetate, 3/1, v/v); mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.31 (m, 17H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.61 (s, 1H), 4.97 (d, *J* = 11.2 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 4.85 (d, *J* = 10.0 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.73 (d, *J* = 9.6 Hz, 1H), 4.41 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.88−3.80 (m, 2H), 3.72 (t, *J* = 9.2 Hz, 1H), 3.54−3.45 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.1, 138.0, 137.2, 133.0, 129.7, 129.1, 128.9, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 125.9, 101.1, 88.5, 83.0, 81.4, 80.4, 75.8, 75.3, 70.2, 68.7, 21.1. The spectral data were in agreement with the reported data.[12c,21]

*2,3-Di-O-benzyl-4,6-O-benzylidene-β-D-glucopyranose (**29**).*[22a] To a solution of **14b** (5.1 g, 9.2 mmol) in the mixed solvent acetone−water (3:1, 200 mL) was added TCCA (3.2 g, 13.8 mmol); the mixture was stirred vigorously at ambient temperature for 1 h. The resulting mixture was diluted with CH_2Cl_2 (200 mL). The organic phase was separated, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 3:1) to afford compound **29** (3.5 g, 85%, α/β = 2:1).[22a] R_f = 0.4 (petroleum ether/ethyl acetate, 6/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.30 (m, 22.5H), 5.57 (s, 1H), 5.19 (d, *J* = 3.6 Hz, 0.5H), 4.99−4.71 (m, 7.5H), 4.37−4.30 (m, 1.5H), 4.13−4.02 (m, 1.5H), 3.81−3.60 (m, 4.5H), 3.48−3.42 (m, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 138.2, 137.6, 137.3, 137.2, 128.9, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 126.0, 125.9, 101.2, 101.1, 97.7, 92.1, 83.0, 81.9, 81.5, 80.8, 79.3, 78.3, 75.2, 75.1, 75.0, 73.7, 69.0, 68.6, 66.2, 62.5. The spectral data were in agreement with the reported data.[22a]

*2,3-Di-O-benzyl-4,6-O-benzylidene-β-D-glucopyranosyl trichloroacetimidate (**30**).*[22b] Under a nitrogen atmosphere, the lactol **29** (880 mg, 1.96 mmol) was dissolved in DCM (20 mL), and trichloroacetonitrile (1.2 mL, 12.0 mmol) and DBU (105 uL, 0.70 mmol) were added at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred for 2 h. Then, the reaction was quenched by the addition of water (10 mL), and the separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to deliver trichloroacetimidate **30**[22b] (980 mg, 85%) as an α/β mixture (α/β = 2:1). R_f = 0.4 (petroleum ether/ethyl acetate, 5/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 0.5H), 8.65 (s, 1H), 7.55−7.31 (m, 22.5H), 6.48 (br s, 1H), 5.97 (d, *J* = 7.6 Hz, 0.5H), 5.60 (s, 1.5H), 4.99−4.75 (m, 6H), 4.44 (dd, *J* = 10.8, 4.8 Hz, 0.5H), 4.36 (dd, *J* = 10.8, 4.8 Hz, 1H), 4.19−4.04 (m, 1.5H), 3.94−3.62 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 161.0, 138.5, 138.2, 137.8, 137.7, 137.1, 128.9, 128.3, 128.3, 128.2, 128.2, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 126.0, 125.9, 101.2, 98.2, 94.6, 91.0, 90.7, 81.4, 81.1, 80.8, 80.6, 78.6, 77.9, 75.2, 75.2, 75.0, 73.3, 68.7, 68.6, 66.6, 65.0. The spectral data were in agreement with the reported data.[22b]

*4-Methylphenyl 2,3-Di-O-benzyl-1-thio-β-D-glucopyranoside (**31**).*[23] To a solution of **14b** (10.1 g, 18.2 mmol) in the mixed solvent CH_2Cl_2−water (5:1, 48 mL) was added TFA (14 mL, 188.5 mmol) at 0 °C, and the resulting solution was allowed to warm up to room temperature and was stirred for 1 h. The reaction mixture was neutralized with Et_3N and evaporated in vacuo. The residue was purified by column chromatography (dichloromethane/ethyl acetate = 12:1) to give the corresponding diol **31** (7.2 g, 85%).[23] R_f = 0.4 (dichloromethane/ethyl acetate, 5/1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.29 (m, 12H), 7.12 (d, *J* = 7.8 Hz, 2H), 4.97 (d, *J* = 10.2, 1H), 4.95 (d, *J* = 12.0, 1H), 4.75 (d, *J* = 10.2, 1H), 4.72 (d, *J* = 11.4, 1H), 4.66 (d, *J* = 9.6 Hz, 1H), 3.87 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.75 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.57 (t, *J* = 9.0 Hz, 1H), 3.51 (t, *J* = 8.4 Hz, 1H), 3.46 (t, *J* = 9.0 Hz, 1H), 3.34−3.31 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 138.0, 137.8, 132.5, 129.8, 129.5, 128.7, 128.5, 128.3, 128.1, 127.9, 127.8, 88.0, 86.1, 80.8, 79.1, 75.4, 75.3, 70.4, 62.7, 21.1. The spectral data were in agreement with the reported data.[23]

*Benzyl (4-Methylphenyl 2,3-di-O-benzyl-1-thio-D-glucopyranoside)uronate (**32**).* To a solution of diol **31** (10 g, 21.5 mmol) in the mixed solvent CH_2Cl_2−water (2:1, 450 mL) containing TEMPO (672 mg, 4.30 mmol) was added $PhI(OAc)_2$ (17.3 g, 53.7

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

mmol), and the mixture was stirred vigorously at ambient temperature for 2.5 h. After TLC indicated complete conversion of the starting material, the reaction was quenched by the addition of a saturated solution of Na_2SO_3 (200 mL). After further stirring for 5 min, HCl (aq.) was added to adjust the final pH value of the mixture to pH 3. The resulting mixture was diluted with CH_2Cl_2 (200 mL). The organic phase was separated, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, and then filtered and concentrated in vacuo to yield the corresponding crude acid, which was used without further purification. The crude acid was dissolved in acetone (300 mL) and treated with BnBr (5.1 mL, 42.9 mmol), K_2CO_3 (4.5 g, 32.6 mmol), and Et_3N (3.2 mL, 23.1 mmol) at 55 °C under a nitrogen atmosphere. After complete disappearance of the acid, the mixture was neutralized with 1 N HCl and extracted with CH_2Cl_2 (4 × 300 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 3:1) to afford compound **32** (6.1 g, 50%). R_f = 0.3 (petroleum ether/ethyl acetate, 2/1, v/v); $[\alpha]_D^{23}$ −29.1 (*c* 0.3, CH_2Cl_2); IR (KBr) 3445, 2910, 2850, 2050, 1737, 1650, 1500, 1458, 1399, 1354, 1268, 1240, 1209, 1176, 1123, 1101, 1061, 1020, 920, 938, 862, 735, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 2H), 7.43−7.29 (m, 15H), 7.01 (d, *J* = 7.6 Hz, 2H), 5.25 (s, 2H), 4.91−4.84 (m, 3H), 4.75 (d, *J* = 10.4 Hz, 1H), 4.63 (d, *J* = 9.6 Hz, 1H), 3.92 (t, *J* = 9.2 Hz, 1H), 3.85 (d, *J* = 9.6 Hz, 1H), 3.59 (t, *J* = 8.8 Hz, 1H), 3.46 (t, *J* = 9.2 Hz, 1H), 2.95 (br s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 138.3, 138.2, 137.9, 135.0, 133.3, 129.6, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 88.4, 85.2, 79.7, 77.5, 75.6, 75.5, 71.9, 67.4, 21.1; HRMS $[M + Na]^+$ calcd for $C_{34}H_{34}O_6SNa$ 593.1974, found 593.1984.

*Benzyl (4-Methylphenyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl 1-thio-D-glucopyranoside)uronate (**33**).* Under a nitrogen atmosphere, to a solution of **32** (5.6 g, 9.8 mmol) in CH_2Cl_2 (200 mL) was added 2,6-lutidine (6.8 mL, 58.4 mmol), and the reaction was cooled to 0 °C. TBSOTf (6.8 mL, 29.6 mmol) was added slowly. The resulting reaction mixture was allowed to warm to room temperature and stirred for 30 min; then water (100 mL) was added to quench the reaction. After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1) to afford compound **33** (5.5 g, 82%). R_f = 0.4 (petroleum ether/ethyl acetate, 10/1, v/v); $[\alpha]_D^{23}$ +13.4 (*c* 0.5, CH_2Cl_2); IR (KBr) 3033, 2952, 2928, 2875, 1752, 1598, 1528, 1492, 1455, 1400, 1352, 1322, 1270, 1258, 1200, 1151, 1082, 1026, 930, 837, 814, 781, 734, 674; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 2H), 7.42−7.27 (m, 15 H), 7.08 (d, *J* = 7.8 Hz, 2H), 5.27 (d, *J* = 12.6 Hz, 1H), 5.18 (d, *J* = 12.6 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 10.2 Hz, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.67−4.65 (m, 1H), 4.61 (d, *J* = 10.2 Hz, 1H), 4.01−3.98 (m, 1H), 3.92 (d, *J* = 9.6, 1H), 3.55−3.51 (m, 2H), 2.36 (s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 138.5, 138.0, 137.7, 135.1, 132.9, 129.7, 129.1, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.2, 126.7, 88.1, 85.9, 80.5, 80.1, 75.1, 75.0, 71.9, 67.1, 25.7, 21.1, 17.9, −4.0, −5.1; HRMS $[M + Na]^+$ calcd for $C_{40}H_{48}O_6SSiNa$ 707.2833, found 707.2821.

*Benzyl (2,3-Di-O-benzyl-4-O-tert-butyldimethylsilyl-D-glucopyranosyl)uronate (**34**).* To a solution of **33** (9.5 g, 13.9 mmol) in the mixed solvent acetone−water (9:1, 250 mL) was added NBS (12.4 g, 71.4 mmol), and the mixture was stirred vigorously at ambient temperature for 1 h. The reaction was quenched by the addition of a saturated solution of Na_2SO_3 (200 mL). After further stirring for 5 min, the resulting mixture was diluted with CH_2Cl_2 (200 mL). The organic phase was separated, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 3:1) to afford compound **34** (6.8 g, 85%, α/β = 5:2). R_f = 0.4 (petroleum ether/ethyl acetate, 5/1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39−7.26 (m, 21H), 5.28 (d, *J* = 12.6 Hz, 0.4H), 5.26 (d, *J* = 12.6 Hz, 1H), 5.23 (t, *J* = 3.6 Hz, 1H), 5.11 (d, *J* = 12.6 Hz, 0.4H), 5.09 (d, *J* = 12.6 Hz, 1H), 5.01 (d, *J* = 11.4 Hz, 0.4H), 4.99 (d, *J* = 11.4 Hz, 1H), 4.92 (d, *J* = 10.8 Hz, 0.4H), 4.81 (t, *J* = 6.0 Hz, 0.4H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 10.8 Hz, 0.4H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 9.0 Hz, 1H), 4.03 (t, *J* = 8.4 Hz, 0.4H), 3.98−3.94 (m, 1.4H), 3.78 (t, *J* = 9.0 Hz, 1H), 3.63 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.52−3.46 (m, 0.8H), 3.40 (dd, *J* = 6.0, 1.8 Hz, 0.4H), 3.16 (d, *J* = 3.0 Hz, 1.0H), 0.85 (s, 9H), 0.84 (s, 3.6H), 0.02 (s, 3H), 0.01 (s, 4.2H), 0.00 (s, 1.2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 168.8, 138.7, 138.6, 137.9, 137.4, 135.0, 134.8, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.2, 127.1, 127.0, 126.9, 97.7, 91.3, 83.6, 82.9, 80.5, 79.7, 76.7, 74.9, 74.8, 74.5, 73.2, 72.7, 72.0, 71.9, 67.4, 67.2, 25.7, 17.9, −4.1, −5.1; HRMS $[M + Na]^+$ calcd for $C_{33}H_{42}O_7SiNa$ 601.2597, found 601.2608.

*Benzyl (2,3-Di-O-benzyl-4-O-tert-butyldimethylsilyl-D-glucopyranosyl)uronate Trichloroacetimidate (**35**).* Under a nitrogen atmosphere, the lactol **34** (6.4 g, 11.1 mmol) was dissolved in DCM (60 mL), and trichloroacetonitrile (11.1 mL, 110.7 mmol) and DBU (0.6 mL, 4.0 mmol) were added at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred until TLC analysis showed disappearance of starting material. Then, the reaction was quenched by the addition of water (60 mL), and the separated aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to deliver trichloroacetimidate **35** (5.1 g, 64%) as an α/β mixture (α/β = 7:1). R_f = 0.5 (petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 0.14H), 8.63 (s, 1H), 7.46−7.14 (m, 17.1H), 6.52 (d, *J* = 2.8 Hz, 1H), 5.96 (d, *J* = 7.2 Hz, 0.14H), 5.22 (d, *J* = 12.4 Hz, 1H), 5.17 (d, *J* = 12.8 Hz, 0.14H), 5.10 (d, *J* = 12.8 Hz, 1H), 5.02 (d, *J* = 11.2 Hz, 1H), 4.97−4.86 (m, 0.42H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.62 (overlapped, 0.14H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 9.6 Hz, 1H), 4.23−4.11 (m, 0.28H), 3.99 (t, *J* = 8.4 Hz, 1H), 3.85−3.78 (m, 2.28H), 3.60 (t, *J* = 7.2 Hz, 0.14H), 0.82 (s, 10.26H), 0.01 (s, 3.42H), −0.01 (s, 3.42); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 161.1, 138.6, 137.5, 134.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.3, 127.2, 126.9, 97.6, 93.9, 93.3, 91.0, 83.8, 80.4, 80.1, 79.3, 75.0, 74.7, 74.4, 74.3, 72.9, 71.8, 71.6, 67.4, 67.2, 25.8, 18.0, −4.0, −5.2; HRMS $[M + Na]^+$ calcd for $C_{35}H_{42}Cl_3NO_7SiNa$ 744.1694, found 744.1711.

*tert-Butyldimethylsilyl O-(Benzyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-di-O-p-methoxybenzyl-2-deoxy-β-D-glucopyranoside (**36**) and tert-Butyldimethylsilyl O-(Benzyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl-α-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-di-O-p-methoxybenzyl-2-deoxy-β-D-glucopyranoside (**37**).* A mixture of glycosyl imidate **35** (630 mg, 0.87 mmol 53 mg, 0.07 mmol), sugar alcohol **13a** (600 mg, 1.07 mmol 50 mg, 0.09 mmol), and freshly activated 4 Å molecular sieves (1.2 g) in dry cyclohexane (25 mL) was stirred at room temperature under a nitrogen atmosphere for 30 min. Then, TESOTf (24 uL, 0.1 mmol) was added dropwise. After stirring overnight at room temperature, the reaction was quenched by the addition of Et_3N (0.1 mL). The mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was subjected to silica gel column chromatography (petroleum ether/ethyl acetate = 12:1) to provide β-disaccharide **36** (442 mg, 45%) and α-disaccharide **37** (370 mg, 38%), respectively. **Compound 36**: R_f = 0.7 (petroleum ether/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ −7.0 (*c* 0.4, CH_2Cl_2); IR (KBr) 3033, 2954, 2929, 2857, 1753, 1613, 1587, 1514, 1462, 1391, 1360, 1303, 1250, 1212, 1175, 1144, 1087, 1038, 839, 782, 750, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.21 (m, 17H), 7.14−7.12 (m, 2H), 6.86 (dd, *J* = 10.4, 8.0 Hz, 4H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.74−4.65 (m, 2H), 4.60−4.50 (m, 5H), 4.41 (d, *J* = 7.2 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.03−3.94 (m, 2H), 3.79 (s, 3H), 3.77 (overlapped, 1H), 3.75 (s, 3H), 3.46 (d, *J* = 10.8 Hz, 1H), 3.38 (t, *J* = 8.8 Hz, 1H), 3.31−3.20 (m, 3H), 3.13 (d, *J* = 9.6 Hz, 1H), 0.93 (s, 9H), 0.83 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

NMR (100 MHz, $CDCl_3$) δ 168.2, 159.2, 159.1, 138.7, 138.1, 134.9, 130.6, 130.4, 129.9, 129.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 127.1, 126.8, 113.8, 113.6, 102.4, 97.1, 83.9, 82.8, 80.1, 76.4, 76.3, 75.0, 74.8, 74.7, 74.5, 73.0, 72.1, 68.2, 67.2, 67.1, 55.2, 55.1, 25.8, 25.6, 25.62, 18.0, 17.9, −4.0, −4.2, −5.1, −5.2; HRMS $[M + Na]^+$ calcd for $C_{61}H_{81}N_3O_{13}Si_2Na$ 1142.5200, found 1142.5179; **Compound 37**: R_f = 0.6 (petroleum ether/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ −30.3 (*c* 0.4, CH_2Cl_2); IR (KBr) 2929, 2857, 1752, 1614, 1514, 1464, 1362, 1250, 1177, 1072, 1040, 840, 783, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.09 (m, 19H), 6.81 (dd, *J* = 11.2, 8.0 Hz, 4H), 5.52 (d, *J* = 3.2 Hz, 1H), 5.20 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.98 (d, *J* = 11.6 Hz, 1H), 4.76−4.66 (m, 3H), 4.53 (d, *J* = 8.0 Hz, 1H), 4.48−4.30 (m, 3H), 4.32−4.29 (m, 2H), 4.02 (t, *J* = 9.2 Hz, 1H), 3.94 (t, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75−3.64 (m, 3H), 3.55−3.47 (m, 3H), 3.39 (t, *J* = 8.8 Hz, 1H), 0.94 (s, 9H), 0.83 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 159.0, 158.9, 138.7, 137.5, 135.0, 130.4, 130.3, 129.0, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.0, 126.8, 113.7, 113.6, 97.1, 97.0, 82.5, 80.6, 79.3, 74.7, 74.6, 73.9, 73.4, 72.9, 72.9, 72.7, 72.1, 68.6, 68.0, 67.2, 55.2, 25.8, 25.6, 18.0, −4.0, −4.3, −5.1, −5.2; HRMS $[M + Na]^+$ calcd for $C_{61}H_{81}N_3O_{13}Si_2Na$: 1142.5200, found: 1142.5205.

*tert-Butyldimethylsilyl O-(2,3-Di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**38**).* A mixture of the thioglycoside **14b** (2.2 g, 4.0 mmol) and acceptor **13b** (2.3 g, 4.4 mmol) in dry CH_2Cl_2 (80 mL) was added to a reaction flask containing freshly dried 4 Å molecular sieves (8 g) under a N_2 atmosphere. The mixture was stirred at room temperature for 1 h, and the solution was cooled to −40 °C. NIS (1.2 g, 5.3 mmol) and TfOH (40 uL, 0.45 mmol) were added to the reaction flask. The resulting solution was kept stirring for 1 h, and Et_3N (0.8 mL) was added to quench the reaction. The whole mixture was filtered through Celite, followed by washing with CH_2Cl_2, and the filtrate was sequentially washed with saturated Na_2SO_3 (aq.) and $NaHCO_3$ (aq.). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate = 8:1) to get the disaccharide **38** (3.1 g, 80%) as a light yellow oil. R_f = 0.4 (petroleum ether/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ −9.6 (*c* 0.3, CH_2Cl_2); IR (KBr) 3033, 2930, 2859, 2112, 1728, 1602, 1495, 1453, 1367, 1315, 1266, 1176, 1089, 1070, 1028, 993, 840, 784, 748, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.60−7.08 (m, 21H), 5.48−5.43 (m, 2H), 4.86 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.79−4.74 (m, 3H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.48 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.26 (d, *J* = 12.4 Hz, 1H), 4.18 (dd, *J* = 10.4, 4.8 Hz, 1H), 4.02−3.81 (m, 5H), 3.63−3.55 (m, 2H), 3.46 (t, *J* = 9.2 Hz, 1H), 3.26 (dd, *J* = 9.2, 3.2 Hz, 1H), 0.91 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.2, 138.5, 138.0, 137.3, 133.1, 130.0, 129.8, 129.7, 129.6, 128.8, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 126.1, 101.3, 100.1, 97.1, 81.8, 78.4, 78.2, 75.3, 73.5, 73.4, 73.2, 68.7, 66.7, 64.0, 63.3, 25.5, 17.9, −4.4, −5.3; HRMS $[M + Na]^+$ calcd for $C_{53}H_{59}N_3O_{12}SiNa$ 980.3760, found 980.3735.

*tert-Butyldimethylsilyl O-(Benzyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**39**) and tert-Butyldimethylsilyl O-(Benzyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl-α-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**40**).* To a solution of disaccharide **36** (75 mg, 0.07 mmol) in the mixed solvent CH_2Cl_2−water (9:1, 3.0 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 38 mg, 0.17 mmol) at ambient temperature. The mixture was stirred for 3 h, and the whole mixture was filtered through Celite, followed by washing with CH_2Cl_2. The filtrate was sequentially washed with saturated aqueous $Na_2S_2O_3$ solution and brine. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product, which was purified by flash column chromatography (petroleum ether/ethyl acetate = 8:1) to get the corresponding alcohol (47 mg). To the solution of obtained alcohol (47 mg, 0.53 mmol) in toluene (5 mL) was added DMAP (3 mg, 0.03 mmol) and Bz_2O (45 mg, 0.20 mmol). The resulting reaction was heated to reflux for 30 h and then cooled to room temperature. The solution was concentrated in vacuo to get the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to provide compound **39** (41 mg, 56% from compound **36**). R_f = 0.3 (petroleum ether/ethyl acetate, 8/1, v/v); $[\alpha]_D^{23}$ −18.4 (*c* 0.3, CH_2Cl_2); IR (KBr) 3034, 2929, 2857, 1727, 1603, 1498, 1454, 1361, 1315, 1211, 1177, 1092, 1070, 1028, 839, 783, 736, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.55−7.06 (m, 21H), 5.21 (t, *J* = 9.6 Hz, 1H), 4.93 (d, *J* = 12.4 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 12.4 Hz, 1H), 4.72−4.66 (m, 3H), 4.58 (dd, *J* = 11.2, 8.8 Hz, 2H), 4.52−4.49 (m, 1H), 4.40 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.00 (t, *J* = 9.6 Hz, 1H), 3.84−3.76 (m, 1H), 3.70 (d, *J* = 9.2 Hz, 1H), 3.58−3.53 (m, 1H), 3.46 (dd, *J* = 10.4, 7.2 Hz, 1H), 3.39−3.33 (m, 2H), 0.86 (s, 9H), 0.72 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), −0.14 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 165.8, 165.7, 138.5, 137.9, 135.0, 133.1, 133.0, 130.0, 129.8, 129.7, 129.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.6, 127.4, 127.1, 126.7, 102.8, 97.2, 83.6, 82.5, 75.1, 75.0, 74.6, 73.5, 72.2, 71.7, 70.0, 66.7, 62.6, 25.7, 25.5, 17.9, −4.1, −4.4, −5.2, −5.3; HRMS $[M + Na]^+$ calcd for $C_{59}H_{73}N_3O_{13}Si_2Na$ 1110.4574, found 1110.4560.

The same procedure was employed for the preparation of **40** from **37** (75 mg, 0.07 mmol). Purification by silica gel column chromatography (petroleum ether/ethyl acetate = 8:1) afforded **40** (38 mg, 52%). R_f = 0.5 (petroleum ether/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ −15.4 (*c* 0.6, CH_2Cl_2); IR (KBr) 2929, 2857, 1603, 1497, 1454, 1363, 1315, 1266, 1178, 1070, 840, 783, 736, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.58−7.05 (m, 21H), 5.42 (t, *J* = 9.6 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.74−4.72 (m, 2H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.51−4.46 (m, 2H), 4.26 (d, *J* = 8.4 Hz, 1H), 4.10 (d, *J* = 12.4 Hz, 1H), 3.91 (t, *J* = 9.6 Hz, 1H), 3.83−3.74 (m, 3H), 3.61−3.54 (m, 2H), 3.22 (dd, *J* = 9.2, 3.2 Hz, 1H), 0.89 (s, 9H), 0.76 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), −0.08 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 165.7, 165.3, 138.6, 137.9, 135.0, 133.1, 132.9, 130.0, 129.9, 129.8, 129.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.0, 126.9, 100.0, 97.1, 79.7, 78.3, 78.2, 74.1, 74.0, 73.5, 73.4, 73.1, 71.4, 67.2, 66.5, 63.2, 25.7, 25.5, 17.9, 17.8, −4.1, −4.4, −5.3, −5.4; HRMS $[M + Na]^+$ calcd for $C_{59}H_{73}N_3O_{13}Si_2Na$ 1110.4574, found 1110.4550.

*tert-Butyldimethylsilyl O-(Benzyl 2,3-di-O-benzyl-α-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**41**).* To a solution of **38** (5.5 g, 5.8 mmol) in the mixed solvent CH_2Cl_2−water (15:1, 80 mL) was added TFA (12.0 mL, 161.6 mmol) at 0 °C, and the resulting solution was allowed to warm up to room temperature. Once the reaction was complete, the reaction mixture was neutralized with a saturated solution of $NaHCO_3$ (50 mL), and the resulting mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product as a colorless oil. To a solution of the obtained diol in the mixed solvent CH_2Cl_2−water (2:1, 120 mL) containing TEMPO (156 mg, 1.00 mmol) was added $PhI(OAc)_2$ (4.6 g, 14.3 mmol), and the mixture was stirred vigorously at ambient temperature. After TLC indicated complete conversion of the starting material, the reaction was quenched by the addition of a saturated solution of Na_2SO_3 (20 mL). After further stirring for 5 min, HCl (aq.) was added to adjust the final pH value of the mixture to pH 3. The resulting mixture was diluted with CH_2Cl_2 (30 mL). The organic phase was separated, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, and then filtered and concentrated in vacuo to yield the corresponding crude acid, which was used without further purification. The crude acid was dissolved in acetone (50 mL) and treated with BnBr (1.4 mL, 11.8 mmol), K_2CO_3 (1.2 g, 8.6 mmol), and Et_3N (0.8 mL, 5.8 mmol) at 50 °C under a nitrogen atmosphere. After complete disappearance of the acid, the mixture was neutralized with 1 N HCl and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to afford compound **41** (3.4 g, 61% from compound **38**). R_f = 0.4 (petroleum ether/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ −32.1 (*c* 0.3, CH_2Cl_2); IR (KBr) 3340, 2930, 2858, 2111, 1727, 1602, 1496, 1453, 1315, 1265, 1176, 1129, 1094, 1068, 1043, 840, 784, 743, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.6 Hz, 4H), 7.57−7.15 (m, 19H), 6.75 (d, *J* = 7.2 Hz, 2H), 5.36 (t, *J* = 10.0 Hz, 1H), 5.31 (s, 1H), 4.99 (d, *J* = 12.4 Hz, 1H), 4.94 (d, *J* = 12.0 Hz, 1H), 4.86 (d, *J* = 12.4 Hz, 1H), 4.77 (d, *J* = 8.0 Hz, 1H), 4.73−4.64 (m, 2H), 4.49 (br s, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.12 (t, *J* = 9.6 Hz, 1H), 3.99−3.94 (m, 1H), 3.90 (br s, 2H), 3.85−3.80 (m, 2H), 3.51−3.45 (m, 2H), 3.30 (d, *J* = 4.8 Hz, 1H), 0.93 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 166.0, 165.3, 137.4, 136.9, 135.1, 133.3, 132.7, 130.1, 129.8, 129.6, 129.2, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.1, 97.4, 97.1, 76.5, 76.4, 74.8, 74.7, 74.4, 74.0, 73.1, 71.4, 67.6, 66.8, 66.2, 63.6, 25.4, 18.0, −4.5, −5.4; HRMS [M + Na]$^+$ calcd for $C_{53}H_{59}N_3O_{13}SiNa$ 996.3709, found 996.3685.

*tert-Butyldimethylsilyl O-(Benzyl 2,3-di-O-benzyl-4-O-tert-butyldimethylsilyl-α-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**40**).* Under a nitrogen atmosphere, to a solution of **41** (1.0 g, 1.0 mmol) in CH_2Cl_2 (50 mL) was added 2,6-lutidine (460 uL, 4.0 mmol). The reaction was cooled to 0 °C, and TBSOTf (460 uL, 2.0 mmol) was added slowly. The resulting reaction mixture was allowed to warm to room temperature and stirred for 30 min; then water (100 mL) was added to quench the reaction. After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to afford compound **40** (894 mg, 80%). R_f = 0.5 (petroleum ether/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ −15.4 (*c* 0.6, CH_2Cl_2); IR (KBr) 2929, 2857, 1603, 1497, 1454, 1363, 1315, 1266, 1178, 1070, 840, 783, 736, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.58−7.05 (m, 21H), 5.42 (t, *J* = 9.6 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.74−4.72 (m, 2H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.51−4.46 (m, 2H), 4.26 (d, *J* = 8.4 Hz, 1H), 4.10 (d, *J* = 12.4 Hz, 1H), 3.91 (t, *J* = 9.6 Hz, 1H), 3.83−3.74 (m, 3H), 3.61−3.54 (m, 2H), 3.22 (dd, *J* = 9.2, 3.2 Hz, 1H), 0.89 (s, 9H), 0.76 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), −0.08 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 165.7, 165.3, 138.6, 137.9, 135.0, 133.1, 132.9, 130.0, 129.9, 129.8, 129.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.0, 126.9, 100.0, 97.1, 79.7, 78.3, 78.2, 74.1, 74.0, 73.5, 73.4, 73.1, 71.4, 67.2, 66.5, 63.2, 25.7, 25.5, 17.9, 17.8, −4.1, −4.4, −5.3, −5.4; HRMS [M + Na]$^+$ calcd for $C_{59}H_{73}N_3O_{13}Si_2Na$ 1110.4574, found 1110.4550.

*tert-Butyldimethylsilyl O-(2-O-Levulinyl-3-O-benzyl-4,6-O-benzylidene-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-O-p-methoxybenzyl-2-deoxy-β-D-glucopyranoside (**43**).* A mixture of the thioglycoside **14a** (87 g, 155 mmol) and acceptor **13a** (72 g, 129 mmol) in dry CH_2Cl_2 (800 mL) was added to a reaction flask containing freshly dried 4 Å molecular sieves (50 g) under a N_2 atmosphere. The mixture was stirred at room temperature for 1 h, and the solution was cooled to −40 °C. NIS (58 g, 258 mmol) and TfOH (0.3 mL, 3.4 mmol) were added to the reaction flask. The resulting solution was kept stirring for 1 h, and Et_3N (0.3 mL) was added to quench the reaction. The whole mixture was filtered through Celite, followed by washing with CH_2Cl_2, and the filtrate was sequentially washed with saturated Na_2SO_3 (aq.) and $NaHCO_3$ (aq.). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (petroleum ether/acetone = 8:1) to get the disaccharide **43** (103 g, 80%) as a white solid. This product could be crystallized in methanol with 70% yield. R_f = 0.3 (petroleum ether/acetone, 6/1, v/v); mp 102−103 °C; $[\alpha]_D^{23}$ −38.4 (*c* 0.3, CH_2Cl_2); IR (KBr) 2956, 2931, 2859, 2110, 1751, 1720, 1612, 1513, 1463, 1362, 1250, 1174, 1096, 1070, 840, 783, 750, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.23 (m, 14H), 6.88−6.85 (m, 4H), 5.50 (s, 1H), 4.91 (t, *J* = 8.8 Hz, 1H), 4.85 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 10.0 Hz, 1H), 4.68−4.59 (m, 3H), 4.48 (d, *J* = 7.6 Hz, 1H), 4.45−4.43 (m, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 4.24−4.20 (m, 1H), 3.95−3.90 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.67−3.13 (m, 8H), 2.78−2.30 (m, 5H), 2.14 (s, 3H), 0.92 (s, 9H), 0.14 (br s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 171.1, 159.3, 159.2, 138.4, 137.2, 130.6, 130.1, 129.7, 129.6, 129.0, 128.2, 128.2, 127.6, 127.5, 126.0, 113.9, 113.6, 101.2, 100.5, 97.0, 81.6, 80.5, 78.9, 76.2, 74.9, 74.8, 74.3, 73.6, 73.2, 68.7, 68.2, 67.4, 66.0, 55.3, 55.2, 37.6, 29.8, 27.7, 25.6, 18.0, −4.3, −5.1; HRMS [M + Na]$^+$ calcd for $C_{53}H_{67}N_3O_{14}SiNa$ 1020.4290, found 1020.4292.

*tert-Butyldimethylsilyl O-(3-O-Benzyl-4,6-O-benzylidene-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-O-p-methoxybenzyl-2-deoxy-β-D-glucopyranoside (**44**).* To a solution of **43** (160 g, 160 mmol) in the mixed solvent pyridine−AcOH (3:1, 800 mL) was added hydrazine hydrate (16 mL, 330 mmol) at room temperature. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2 (1.0 L) and was sequentially washed with 2 M HCl (aq.), saturated $NaHCO_3$ (aq.), and brine. The resulting organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the pure disaccharide **44** (138 g), which was used for the next step without further purification. R_f = 0.6 (petroleum ether/ethyl acetate, 3/1, v/v); mp 59−61 °C; $[\alpha]_D^{23}$ −116.5 (*c* 0.3, CH_2Cl_2); IR (KBr) 3034, 2931, 2859, 2111, 1613, 1586, 1514, 1464, 1364, 1303, 1251, 1174, 1068, 1033, 841, 785, 751, 699; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49−7.25 (m, 14H), 6.91−6.87 (m, 4H), 5.52 (s, 1H), 4.94 (d, *J* = 12.0 Hz, 1H), 4.81−4.73 (m, 3H), 4.64−4.61 (m, 2H), 4.49−4.46 (m, 2H), 4.13 (dd, *J* = 10.2, 4.8 Hz, 1H), 4.00 (t, *J* = 8.4 Hz, 1H), 3.94 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.67 (d, *J* = 12.0 Hz, 1H), 3.64−3.60 (m, 2H), 3.52−3.46 (m, 2H), 3.38 (d, *J* = 9.6 Hz, 1H), 3.35−3.29 (m, 2H), 3.25 (br s, 1H, OH), 3.20−3.16 (m, 1H), 0.95 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 159.2, 138.5, 137.3, 130.5, 129.7, 129.6, 129.0, 128.9, 128.4, 128.2, 127.9, 127.7, 126.0, 113.8, 113.7, 103.4, 101.1, 97.3, 81.4, 81.3, 80.4, 75.2, 74.7, 74.6, 74.6, 73.3, 68.7, 68.5, 68.0, 66.4, 55.3, 55.2, 25.6, 18.0, −4.3, −5.2; HRMS [M + Na]$^+$ calcd for $C_{48}H_{61}N_3O_{12}SiNa$ 922.3922, found 922.3914.

*tert-Butyldimethylsilyl O-(2,3-Di-O-benzyl-4,6-O-benzylidene-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-O-p-methoxybenzyl-2-deoxy-β-D-glucopyranoside (**45**).* To a cooled (0 °C) solution of crude **44** (138 g, 154 mmol) in DMF (1.5 L) was added NaH (60% dispersion in mineral oil, 20 g, 500 mmol). After the mixture had been stirred for 30 min, TBAI (12 g, 32 mmol) and BnBr (55 mL, 463 mmol) were added. After stirring for 50 min at room temperature, to the reaction mixture was added water (4.0 L), and the mixture was extracted with EtOAc (3 × 5.0 L). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered. To the resulting mixture was added Et_3N (60 mL), and the mixture was stirred for another 6 h. Next, the solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (petroleum ether/acetone = 8:1) to afford **45** (111 g, 70% from compound **43**). Compound **45** could be crystallized from anhydrous methanol as a white solid. R_f = 0.4 (petroleum ether/acetone, 5/1, v/v); mp 136−137 °C; $[\alpha]_D^{23}$ −29.3 (*c* 0.3, CH_2Cl_2); IR (KBr) 3732, 3608, 3307, 3033, 2929, 2857, 2110, 1513, 1548, 1362, 1265, 1249, 1173, 1088, 1071, 840, 743, 699; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.8 Hz, 2H), 7.41−7.26 (m, 15H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.54 (s, 1H), 4.92 (d, *J* = 11.4 Hz, 1H), 4.83 (d, *J* = 10.2 Hz, 1H), 4.81−4.73 (m, 3H), 4.64 (d, *J* = 10.2 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 4.45 (d, *J* = 7.2 Hz, 1H), 4.31 (d, *J* = 11.4 Hz, 1H), 4.25 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.98 (t, *J* = 9.0 Hz, 1H), 3.83−3.80 (m, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.64−3.56 (m, 3H), 3.53 (d, *J* = 11.4 Hz, 1H), 3.36 (t, *J* = 7.8 Hz, 1H), 3.32−3.18 (m, 4H), 0.94 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 159.1, 138.5, 138.4, 137.4, 130.6, 130.1, 129.7, 129.5, 128.9, 128.4, 128.3, 128.2, 128.2, 127.9, 127.8, 127.6, 127.6, 126.0, 113.8, 113.6, 102.7, 101.1, 97.1, 82.6, 81.8, 81.3, 80.6, 76.2, 75.5, 75.2, 75.1, 74.7, 72.9, 68.8, 68.1, 67.4, 65.8, 55.3, 55.2, 25.6, 18.0, −4.2, −5.1; HRMS [M + Na]$^+$ calcd for $C_{55}H_{67}N_3O_{12}SiNa$ 1012.4392, found 1012.4383.

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

*tert-Butyldimethylsilyl O-(2,3-Di-O-benzyl-4,6-O-benzylidene-β-D-glucopyranosyl)-(1→4)-2-azido-2-deoxy-β-D-glucopyranoside (**46**).* To a solution of disaccharide **45** (196 g, 198 mmol) in the mixed solvent CH_2Cl_2−water (10:1, 2.0 L) was added DDQ (112 g, 492 mmol) at ambient temperature. The mixture was stirred for 30 min, and the whole mixture was filtered through Celite, followed by washing with CH_2Cl_2. The filtrate was sequentially washed with saturated aqueous $Na_2S_2O_3$ solution and brine. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product, which was purified by flash column chromatography (petroleum ether/ethyl acetate = 6:1) to get the corresponding diol **46** as a light yellow oil (120 g, 81%). R_f = 0.4 (petroleum ether/ethyl acetate, 3/1, v/v); $[\alpha]_D^{23}$ −26.8 (*c* 0.3, CH_2Cl_2); IR (KBr) 3034, 2930, 2859, 1497, 1455, 1384, 1369, 1257, 1170, 1088, 1074, 784, 749; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.40−7.36 (m, 3H), 7.35−7.25 (m, 10H), 5.57 (s, 1H), 4.93 (d, *J* = 11.4 Hz, 1H), 4.87 (d, *J* = 11.4 Hz, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 7.8 Hz, 1H), 4.55 (d, *J* = 7.8 Hz, 1H), 4.38 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.91 (s, 1H), 3.81 (t, *J* = 9.6 Hz, 1H), 3.77 (t, *J* = 10.2 Hz, 1H), 3.73−3.69 (m, 3H), 3.61 (t, *J* = 9.0 Hz, 1H), 3.54−3.50 (m, 1H), 3.48−3.43 (m, 2H), 3.32 (dt, *J* = 9.6, 3.0 Hz, 1H), 3.23 (dd, *J* = 10.2, 7.8 Hz, 1H), 1.80 (t, *J* = 7.2 Hz, 1H), 0.94 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.1, 137.7, 136.9, 129.1, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 126.0, 103.8, 101.3, 96.8, 81.5, 81.3, 81.0, 80.2, 75.8, 75.1, 74.6, 72.7, 68.2, 67.8, 66.3, 60.9, 25.6, 17.9, −4.3, −5.1; HRMS $[M + Na]^+$ calcd for $C_{39}H_{51}N_3O_{10}SiNa$ 772.3241, found 772.3254.

*tert-Butyldimethylsilyl O-(2,3-Di-O-benzyl-4,6-O-benzylidene-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**47**).* To a solution of disaccharide **46** (119 g, 159 mmol) in toluene (900 mL) were added benzoic anhydride (Bz_2O, 215 g, 950 mmol) and DMAP (9 g, 74 mmol). After stirring for 12 h at 60 °C, the reaction mixture was cooled to room temperature and water was added (900 mL), and the mixture was extracted with EtOAc (3 × 1.0 L). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get **47**, which was used for the next step without further purification. An analytic sample was obtained by column chromatography. R_f = 0.4 (petroleum ether/ethyl acetate, 5/1, v/v); mp 175−177 °C; $[\alpha]_D^{23}$ −7.6 (*c* 0.2, CH_2Cl_2); IR (KBr) 3064, 2963, 2928, 2858, 2112, 1727, 1603, 1495, 1453, 1365, 1315, 1263, 1176, 1094, 1027, 839, 801, 747, 710, 466; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 2H), 8.0 (d, *J* = 8.0 Hz, 2H), 7.66−7.58 (m, 2H), 7.54−7.46 (m, 4H), 7.40−7.33 (m, 5H), 7.30−7.10 (m, 10H), 5.30−5.24 (m, 2H), 4.85−4.66 (m, 6H), 4.49 (dd, *J* = 12.0, 6.8 Hz, 1H), 4.43 (d, *J* = 7.6 Hz, 1H), 3.85 (t, *J* = 9.6 Hz, 1H), 3.75−3.64 (m, 3H), 3.56 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.40−3.33 (m, 2H), 3.17−3.11 (m, 1H), 2.69 (t, *J* = 10.4 Hz, 1H), 0.89 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.1, 138.3, 137.9, 137.0, 133.3, 133.1, 130.1, 129.8, 129.8, 129.6, 129.0, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 125.9, 103.7, 100.8, 97.0, 82.1, 81.1, 80.9, 75.8, 74.9, 73.5, 72.7, 67.9, 66.3, 65.8, 62.7, 25.4, 17.8, −4.5, −5.3; HRMS $[M + Na]^+$ calcd for $C_{53}H_{59}N_3O_{12}SiNa$ 980.3766, found 980.3763.

*tert-Butyldimethylsilyl O-(2,3-Di-O-benzyl-4,6-O-benzylidene-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-O-acetyl-2-deoxy-β-D-glucopyranoside (**48**).* Disaccharide **46** (195 g, 260 mmol) was dissolved in the mixed solvent toluene−Ac_2O (8:1, 1.3 L), and DMAP was added (16 g, 131 mmol). After stirring for 12 h at 60 °C, the reaction mixture was cooled to room temperature and water was added (1.2 L), and the mixture was extracted with EtOAc (3 × 1.5 L). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide **48**, which was used for the next step without further purification. An analytic sample was obtained by column chromatography. R_f = 0.4 (petroleum ether/ethyl acetate, 4/1, v/v); $[\alpha]_D^{23}$ −3.9 (*c* 0.4, CH_2Cl_2); IR (KBr) 3643, 2926, 2858, 2111, 1748, 1455, 1367, 1227, 1089, 1034, 842, 786, 746, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.24 (m, 15H), 5.55 (s, 1H), 4.94−4.87 (m, 2H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.75−4.69 (m, 2H), 4.57 (d, *J* = 7.6 Hz, 1H), 4.40−4.34 (m, 3H), 4.16 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.75−3.69 (m, 2H), 3.64 (d, *J* = 9.2 Hz, 1H), 3.59 (d, *J* = 9.6 Hz, 1H), 3.47−3.42 (m, 1H), 3.39−3.30 (m, 3H), 2.08 (s, 3H), 1.97 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.6, 138.2, 138.0, 137.1, 129.0, 128.3, 127.9, 127.7, 127.6, 127.5, 126.0, 103.7, 101.2, 96.9, 82.0, 81.5, 80.9, 76.9, 75.6, 74.9, 73.2, 72.1, 68.7, 66.1, 66.0, 62.1, 25.5, 21.1, 20.7, 17.9, −4.5, −5.3; HRMS $[M + Na]^+$ calcd for $C_{43}H_{55}N_3O_{12}SiNa$ 856.3453, found 856.3443.

*tert-Butyldimethylsilyl O-(2,3-Di-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-O-benzoyl-2-deoxy-β-D-glucopyranoside (**49**).* To a solution of the obtained crude **47** (136 g) in the mixed solvent CH_2Cl_2−water (10:1, 5.0 L) was added TFA (226 mL, 3042 mmol) at 0 °C, and the resulting solution was allowed to warm up to room temperature. Once the reaction was complete, the mixture was washed with water (4 × 1 L) and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 L). The combined organic layer was washed with saturated $NaHCO_3$ aqueous (3 × 800 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product as a colorless oil. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to give the corresponding diol **49** as a light yellow oil (104 g, 75% from compound **46**). R_f = 0.3 (petroleum ether/ethyl acetate, 2/1, v/v); $[\alpha]_D^{23}$ −17.2 (*c* 0.2, CH_2Cl_2); IR (KBr) 3334, 3064, 3033, 2961, 2927, 2857, 2113, 1724, 1603, 1495, 1453, 1411, 1362, 1316, 1264, 1177, 1097, 1070, 1027, 840, 801, 735, 710, 458; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 2H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.64−7.57 (m, 2H), 7.51−7.44 (m, 4H), 7.32−7.12 (m, 10H), 5.22 (t, *J* = 10.0 Hz, 1H), 4.85 (d, *J* = 8.8 Hz, 1H), 4.81 (d, *J* = 8.4 Hz, 1H), 4.75−4.69 (m, 3H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.45 (dd, *J* = 12.0, 6.8 Hz, 1H), 4.38 (d, *J* = 7.2 Hz, 1H), 3.93 (t, *J* = 9.6 Hz, 1H), 3.71−3.67 (m, 1H), 3.60 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.33−3.24 (m, 4H), 3.11−3.03 (m, 2H), 2.25 (br s, 1H, OH), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.2, 138.3, 138.0, 133.5, 133.2, 129.9, 129.6, 129.5, 128.7, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 103.0, 97.1, 83.8, 82.1, 75.9, 75.2, 75.1, 73.5, 72.9, 69.9, 66.2, 62.7, 61.9, 25.5, 17.8, −4.4, −5.3; HRMS $[M + Na]^+$ calcd for $C_{46}H_{55}N_3O_{12}SiNa$ 892.3453, found 892.3473.

*tert-Butyldimethylsilyl O-(2,3-Di-O-benzyl-β-D-glucopyranosyl)-(1→4)-2-azido-3,6-di-O-acetyl-2-deoxy-β-D-glucopyranoside (**50**).* The same procedure described for the preparation of diol **49** (from **47**) was employed for the preparation of **50** from **48**. Purification by silica gel column chromatography (petroleum ether/ethyl acetate = 2:1) afforded **50** (151 g, 78% from compound **46**). R_f = 0.4 (petroleum ether/ethyl acetate, 1/1, v/v); $[\alpha]_D^{23}$ −9.2 (*c* 0.5, CH_2Cl_2); IR (KBr) 3033, 2930, 2859, 2112, 1746, 1497, 1365, 1232, 1109, 1065, 840, 785, 739, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 10H), 4.95−4.87 (m, 2H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 7.6 Hz, 1H), 4.42 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.31 (d, *J* = 7.6 Hz, 1H), 4.16 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.86 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.72−3.63 (m, 2H), 3.52−3.27 (m, 6H), 2.10 (s, 3H), 2.00 (s, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.0, 138.3, 137.9, 128.6, 128.3, 128.0, 127.8, 127.7, 127.6, 103.0, 97.0, 83.9, 82.0, 76.1, 75.2, 75.1, 75.0, 73.2, 72.0, 70.7, 66.2, 62.9, 62.3, 25.5, 20.9, 20.7, 17.9, −4.5, −5.3; HRMS $[M + Na]^+$ calcd for $C_{36}H_{51}N_3O_{12}SiNa$ 768.3140, found 768.3137.

*tert-Butyldimethylsilyl O-(Benzyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-dibenzoyl-2-deoxy-β-D-glucopyranoside (**9**).* To a solution of diol **49** (104 g, 119 mmol) in the mixed solvent CH_2Cl_2−water (2:1, 1.0 L) containing TEMPO (3.7 g, 24 mmol) was added $PhI(OAc)_2$ (96 g, 297 mmol), and the mixture was stirred vigorously at ambient temperature. After TLC indicated complete conversion of the starting material, the reaction was quenched by the addition of a saturated solution of Na_2SO_3 (900 mL). After further stirring for 5 min, HCl (aq.) was added to adjust the final pH value of the mixture to pH 3. The resulting mixture was diluted with CH_2Cl_2 (1.2 L). The organic phase was separated, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 1.0 L). The combined organic phase was washed with brine, dried with Na_2SO_4, and then filtered and concentrated in vacuo to yield the corresponding crude acid, which was used without further purification. The crude acid

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

was dissolved in acetone (2.0 L) and treated with BnBr (58 mL, 490 mmol), K_2CO_3 (27 g, 193 mmol), and Et_3N (18 mL, 130 mmol) at 60 °C under a nitrogen atmosphere. After complete disappearance of the acid, the mixture was neutralized with 1 N HCl and extracted with CH_2Cl_2 (4 × 1.0 L). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 6:1) to afford compound **9** (108 g, 93%) as a white solid. R_f = 0.4 (petroleum ether/ethyl acetate, 3/1, v/v); mp 63−64 °C; $[\alpha]_D^{23}$ −14.0 (*c* 0.5, CH_2Cl_2); IR (KBr) 3856, 3727, 3518, 3064, 3033, 2928, 2858, 2112, 1726, 1602, 1496, 1453, 1361, 1315, 1267, 1212, 1177, 1094, 1068, 1028, 840, 785, 738, 710, 586, 500, 460; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, *J* = 8.0 Hz, 4H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.44−7.17 (m, 19H), 5.31−5.26 (m, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.95 (d, *J* = 12.4 Hz, 1H), 4.81−4.71 (m, 6H), 4.51 (d, *J* = 7.6 Hz, 1H), 4.46 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.12 (t, *J* = 9.6 Hz, 1H), 3.71−3.61 (m, 3H), 3.52 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.41 (t, *J* = 8.8 Hz, 1H), 3.30 (t, *J* = 8.8 Hz, 1H), 2.66 (br s, 1H, OH), 0.93 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 165.6, 165.5, 138.2, 138.0, 134.9, 133.1, 132.9, 129.8, 129.7, 129.6, 129.5, 128.6, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 102.4, 97.1, 83.0, 81.5, 75.3, 75.2, 74.5, 74.3, 73.3, 72.1, 71.2, 66.9, 66.5, 62.6, 25.4, 17.8, −4.5, −5.4; HRMS [M + Na]$^+$ calcd for $C_{53}H_{59}N_3O_{13}SiNa$ 996.3709, found 996.3690.

*tert-Butyldimethylsilyl O-(Methyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-diacetyl-2-deoxy-β-D-glucopyranoside (**10**).* The same procedure described for the preparation of the acid (from diol **49**) was employed for the preparation of the corresponding acid from **50** (151 g, 203 mmol). The crude acid was dissolved in acetone (3.5 L) and treated with dimethyl sulfate (Me_2SO_4, 43 mL, 452 mmol) and K_2CO_3 (33 g, 238 mmol) at room temperature under a nitrogen atmosphere. After complete disappearance of the acid, the mixture was neutralized with 1 N HCl and extracted with CH_2Cl_2 (4 × 2.0 L). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 2:1) to afford compound **10** (102 g, 65%). R_f = 0.4 (petroleum ether/ethyl acetate, 1/1, v/v); $[\alpha]_D^{23}$ −12.2 (*c* 0.6, CH_2Cl_2); IR (KBr) 3031, 2955, 2931, 2859, 2360, 2341, 2112, 1748, 1365, 1230, 1133, 1067, 1039, 841, 785, 741, 699, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10H), 4.93 (t, *J* = 10.0 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.73 (br s, 2H), 4.57 (d, *J* = 7.6 Hz, 1H), 4.39−4.32 (m, 1H), 4.29 (d, *J* = 7.6 Hz, 1H), 4.16 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.80 (s, 3H), 3.78−3.73 (m, 2H), 3.63 (t, *J* = 9.6 Hz, 1H), 3.48−3.42 (m, 2H), 3.37−3.31 (m, 2H), 2.74 (br s, 1H, OH), 2.07 (s, 3H), 2.00 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 168.9, 138.3, 137.9, 128.5, 128.3, 127.8, 127.7, 127.6, 103.3, 96.9, 83.2, 81.4, 76.4, 75.3, 75.2, 74.5, 73.1, 71.6, 71.5, 66.1, 62.1, 52.5, 25.5, 20.7, 20.6, 17.9, −4.5, −5.3; HRMS [M + Na]$^+$ calcd for $C_{37}H_{51}N_3O_{13}SiNa$ 796.3089, found 796.3103.

*tert-Butyldimethylsilyl O-(2-Azide-3,4-di-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(benzyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-dibenzoyl-2-deoxy-β-D-glucopyranoside (**51**).* A mixture of trichloroacetimidate **8** (8.3 g, 13.1 mmol) and acceptor **9** (9.9 g, 10.2 mmol) in dry toluene (90 mL) was added to a reaction flask containing freshly dried 4 Å molecular sieves (20 g) under a N_2 atmosphere. The mixture was stirred at room temperature for 1 h, and the solution was cooled to −40 °C. Then, TfOH (0.35 mL, 4.0 mmol) was added dropwise. The resulting solution was kept stirring for 2 h, and Et_3N (0.5 mL) was added to quench the reaction. The whole mixture was filtered through Celite, followed by washing with CH_2Cl_2, and the solution was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate = 12:1) to get the trisaccharide **51** (9.4 g, 64%) as a light yellow oil. R_f = 0.6 (petroleum ether/ethyl acetate, 5/1, v/v); $[\alpha]_D^{23}$ +13.0 (*c* 0.3, CH_2Cl_2); IR (KBr) 2956, 2923, 2852, 2110, 1724, 1496, 1454, 1363, 1315, 1265, 1210, 1177, 1069, 1027, 840, 803, 739, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.97 (m, 6H), 7.57−7.11 (m, 34H), 5.35 (d, *J* = 3.6 Hz, 1H), 5.22 (t, *J* = 10.0 Hz, 1H), 4.95 (d, *J* = 12.4 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.81−4.64 (m, 9H), 4.55−4.37 (m, 5H), 4.02 (t, *J* = 9.6 Hz, 1H), 3.95 (t, *J* = 9.2 Hz, 1H), 3.79 (d, *J* = 9.6 Hz, 1H), 3.77−3.73 (m, 1H), 3.66−3.56 (m, 4H), 3.47 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.35 (t, *J* = 8.4 Hz, 1H), 3.24 (dd, *J* = 10.4, 3.6 Hz, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.1, 165.8, 165.7, 138.0, 137.8, 137.5, 137.4, 134.7, 133.2, 133.1, 133.1, 130.0, 129.8, 129.7, 129.7, 129.6, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.7, 127.6, 127.4, 127.3, 102.7, 97.3, 97.2, 83.6, 82.0, 80.2, 77.7, 75.6, 75.3, 75.2, 75.1, 75.0, 74.5, 73.4, 72.1, 69.7, 67.4, 66.6, 63.4, 62.5, 25.5, 17.9, −4.4, −5.3; HRMS [M + Na]$^+$ calcd for $C_{80}H_{84}N_6O_{18}SiNa$ 1467.5503, found 1467.5478.

*tert-Butyldimethylsilyl O-(2-Azide-3,4-di-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(methyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-diacetyl-2-deoxy-β-D-glucopyranoside (**52**).* The same procedure described for the preparation of trisaccharide **51** (from **8** and **9**) was employed for the preparation of **52** from **8** (9.1 g, 14.4 mmol 2.6 g, 4.1 mmol) and **10** (8.8 g, 11.4 mmol). Purification by silica gel column chromatography (petroleum ether/ethyl acetate = 10:1) afforded trisaccharide **52** (12.1 g, 85%) as a white solid. R_f = 0.6 (petroleum ether/ethyl acetate, 3/1, v/v); mp 74−66 °C; $[\alpha]_D^{23}$ +26.0 (*c* 0.3, CH_2Cl_2). IR (KBr) 3032, 2928, 2858, 2110, 1750, 1724, 1454, 1364, 1274, 1224, 1066, 1038, 841, 786, 746, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.38−7.20 (m, 20H), 5.48 (d, *J* = 3.6 Hz, 1H), 4.96−4.82 (m, 6H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.61−4.30 (m, 6H), 4.17−4.11 (m, 1H), 4.07 (t, *J* = 9.6 Hz, 1H), 3.93−3.86 (m, 2H), 3.78 (s, 3H), 3.71 (t, *J* = 9.2 Hz, 1H), 3.67−3.59 (m, 3H), 3.43−3.30 (m, 4H), 2.03 (s, 3H), 2.02 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.1, 168.3, 166.1, 138.0, 137.6, 137.4, 133.1, 129.8, 129.7, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.2, 103.2, 97.6, 97.0, 83.7, 81.9, 80.1, 77.8, 76.3, 75.6, 75.2, 75.1, 75.0, 74.5, 73.1, 71.5, 69.8, 66.1, 63.4, 62.7, 61.9, 52.7, 25.5, 20.7, 20.6, 17.9, −4.5, −5.3; HRMS [M + Na]$^+$ calcd for $C_{64}H_{76}N_6O_{18}SiNa$ 1267.4883, found 1267.4896.

*O-(2-Azide-3,4-di-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(benzyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-dibenzoyl-2-deoxy-D-glucopyranose (**53**).* A 70% solution of HF in pyridine (8 mL) was added to an ice-cooled solution of compound **51** (10 g, 6.9 mmol) in MeCN (20 mL). The mixture was allowed to warm to room temperature and stirred for 1 h. Next, the mixture was diluted with CH_2Cl_2 (40 mL) and quenched by addition of saturated $NaHCO_3$ (aq.). After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 6:1) to afford the desilylated compound **53** (7.8 g, 85%) as an α/β mixture (α/β = 3:2). R_f = 0.3 (petroleum ether/ethyl acetate, 3/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−7.98 (m, 15H), 7.59−7.18 (m, 85H), 5.79 (t, *J* = 9.6 Hz, 1.5H), 5.40−5.35 (m, 4H), 5.29 (t, *J* = 9.6 Hz, 1H), 5.04−4.98 (m, 2.5H), 4.91−4.84 (m, 5H), 4.82−4.65 (m, 16H), 4.60−4.52 (m, 4.5H), 4.48−4.37 (m, 8H), 4.24−4.10 (m, 4.5H), 4.01−3.92 (m, 2.5H), 3.82−3.74 (m, 6H), 3.68−3.56 (m, 8H), 3.51 (dd, *J* = 10.4, 8.0 Hz, 1H), 3.41−3.24 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 167.0, 166.1, 166.0, 165.9, 138.0, 138.0, 137.8, 137.7, 137.5, 137.4, 134.7, 133.3, 133.2, 133.1, 130.0, 129.8, 129.6, 129.6, 129.5, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 127.8, 127.7, 127.5, 127.3, 102.5, 102.3, 97.3, 96.3, 92.3, 83.6, 83.5, 82.0, 82.0, 80.2, 77.7, 75.6, 75.3, 75.2, 75.1, 75.0, 74.9, 74.5, 74.4, 74.0, 73.5, 72.2, 70.2, 69.7, 69.2, 67.4, 65.5, 63.4, 62.5, 62.1, 62.0; HRMS [M + Na]$^+$ calcd for $C_{74}H_{70}N_6O_{18}Na$ 1353.4639, found 1353.4616.

*O-(2-Azide-3,4-di-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(methyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-diacetyl-2-deoxy-D-glucopyranose (**54**).* The same procedure described for the preparation of trisaccharide **53** (from **11**) was employed for the preparation of **54** from **52** (10 g,

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

8.0 mmol). Purification by silica gel column chromatography (petroleum ether/ethyl acetate = 4:1) afforded trisaccharide **54** (7.6 g, 84%) as an α/β mixture (α/β = 2:1). R_f = 0.2 (petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.6 Hz, 3H), 7.57 (t, J = 7.6 Hz, 1.5H), 7.44 (t, J = 7.6 Hz, 4.5H), 7.37−7.19 (m, 28.5H), 5.54−5.47 (m, 2.5H), 5.30 (d, J = 3.2 Hz, 1H), 5.02−4.83 (m, 9H), 4.79−4.58 (m, 5H), 4.52−4.31 (m, 5H), 4.17−4.02 (m, 4H), 3.92−3.87 (m, 3H), 3.78 (s, 4.5H), 3.75−3.60 (m, 5.5H), 3.45−3.28 (m, 5.5H), 2.06, 2.05, 2.04 (each s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 168.4, 168.3, 166.1, 138.0, 138.0, 137.6, 137.5, 137.4, 133.2, 129.7, 129.6, 129.5, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.1, 128.0, 127.8, 127.7, 127.6, 127.6, 127.5, 127.2, 103.2, 103.1, 97.5, 96.0, 92.0, 83.7, 83.6, 81.9, 81.8, 80.1, 80.0, 77.7, 76.1, 75.7, 75.6, 75.3, 75.1, 75.0, 74.5, 74.4, 73.1, 71.8, 69.8, 69.5, 68.8, 64.8, 63.4, 62.7, 61.7, 61.6, 61.5, 52.7, 52.6, 20.9, 20.8, 20.7, 20.6; HRMS [M + Na]$^+$ calcd for $C_{58}H_{62}N_6O_{18}Na$ 1153.4018, found 1153.4023.

*O-(2-Azide-3,4-di-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(benzyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-dibenzoyl-2-deoxy-D-glucopyranosyl Trichloroacetimidate (**5**).* Under a nitrogen atmosphere, the lactol **53** (5.5 g, 4.1 mmol) was dissolved in dry MeCN (30 mL), and trichloroacetonitrile (4.9 mL, 49 mmol) and a catalytic amount of DBU (0.3 mL, 2.0 mmol) were added at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred for overnight until TLC analysis showed the disappearance of starting material. Then, the reaction was quenched by the addition of water (40 mL), and the separated aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 6:1) to deliver trichloroacetimidate **5** (5.1 g, 85%) as an α/β mixture (α/β = 4:1). R_f = 0.5 (petroleum ether/ethyl acetate, 3/1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 0.8H), 8.76 (s, 0.2H), 8.06−7.96 (m, 6H), 7.58−7.11 (m, 34H), 6.50 (d, J = 3.6 Hz, 0.8H), 5.83 (t, J = 9.6 Hz, 1H), 5.41−5.32 (m, 1.2H), 4.97 (d, J = 12.4 Hz, 0.2H), 4.96 (d, J = 12.4 Hz, 0.8H), 4.90 (d, J = 10.8 Hz, 0.8H), 4.85 (d, J = 5.6 Hz, 0.2H), 4.82−4.64 (m, 8H), 4.59−4.53 (m, 2H), 4.47−4.38 (m, 3H), 4.30−4.20 (m, 2H), 4.00−3.87 (m, 1H), 3.82−3.74 (m, 3H), 3.69−3.62 (m, 3H), 3.42−3.34 (m, 1H), 3.27 (dd, J = 10.4, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.1, 165.7, 165.7, 165.6, 163.5, 160.5, 137.9, 137.6, 137.4, 137.4, 134.6, 133.3, 133.1, 130.0, 129.8, 129.6, 129.6, 129.5, 129.4, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 127.7, 127.7, 127.5, 127.3, 102.6, 102.4, 97.3, 96.5, 94.4, 91.8, 90.6, 83.4, 81.9, 81.7, 80.2, 77.7, 75.5, 75.2, 75.2, 75.1, 74.9, 74.9, 74.6, 74.4, 74.3, 73.9, 73.8, 72.5, 71.8, 70.3, 69.7, 67.4, 63.7, 63.3, 62.5, 62.0, 61.9, 61.2. HRMS [M + Na]$^+$ calcd for $C_{76}H_{70}Cl_3N_7O_{18}Na$ 1496.3741, found 1496.3754.

*O-(2-Azide-3,4-di-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(methyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-2-azido-3,6-diacetyl-2-deoxy-D-glucopyranosyl Trichloroacetimidate (**6**).* The same procedure described for the preparation of trichloroacetimidate **5** (from **53**) was employed for the preparation of **6** from **54** (7.2 g, 6.4 mmol). Purification by silica gel column chromatography (petroleum ether/ethyl acetate = 6:1) afforded trisaccharide **6** (6.2 g, 77%) as an α/β mixture (α/β = 5:1). R_f = 0.6 (petroleum ether/ethyl acetate, 3/2, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.81 (s, 0.2H), 8.01 (d, J = 7.6 Hz, 2.4H), 7.58 (t, J = 7.6 Hz, 1.2H), 7.45 (t, J = 7.6 Hz, 2.4H), 7.38−7.17 (m, 24H), 6.41 (d, J = 3.6 Hz, 1H), 5.66 (d, J = 8.4 Hz, 0.2H), 5.56−5.49 (m, 2.4H), 4.96 (d, J = 10.8 Hz, 1.2H), 4.92−4.83 (m, 4.8H), 4.76 (d, J = 11.2 Hz, 1.2H), 4.71 (d, J = 11.2 Hz, 1.2H), 4.60 (d, J = 10.8 Hz, 1.2H), 4.52 (d, J = 12.0 Hz, 1.2H), 4.43 (dd, J = 12.4, 2.8 Hz, 1.2H), 4.38−4.32 (m, 2.4H), 4.19−4.04 (m, 3.6H), 3.93−3.88 (m, 2.4H), 3.83 (t, J = 9.6 Hz, 1.2H), 3.79 (s, 3.6H), 3.73 (t, J = 9.2 Hz, 1.2H), 3.67−3.61 (m, 3.6H), 3.44 (t, J = 8.4 Hz, 1.2H), 3.34 (dd, J = 10.4, 3.6 Hz, 1.2H), 2.07 (s, 3.6H), 2.04 (s, 3.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.9, 168.3, 166.1, 160.5, 138.0, 137.5, 137.4, 133.2, 129.8, 129.7, 129.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.8, 127.5, 127.4, 127.2, 103.1, 97.5, 94.1, 90.6, 83.7, 81.7, 80.1, 77.7, 75.6, 75.4, 75.2, 75.1, 75.0, 74.6, 71.3, 69.8, 69.7, 63.4, 62.6, 61.2, 60.6, 60.4, 52.7, 21.0, 20.8, 20.6; HRMS [M + Na]$^+$ calcd for $C_{60}H_{62}Cl_3N_7O_{18}Na$ 1296.3115, found 1296.3121.

*Methyl O-(2-Azido-3,4-di-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(benzyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-O-(2-azido-3,6-di-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(methyl 2-O-benzoyl-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-2-benzyloxy Carbonylamino-3-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranoside (**3**).* A mixture of trichloroacetimidate **5** (13.7 g, 9.2 mmol) and acceptor **7** (6.7 g, 7.4 mmol) in dry toluene (300 mL) was added to a reaction flask containing freshly dried 4 Å molecular sieves (20 g) under a N_2 atmosphere. The mixture was stirred at room temperature for 1 h, and the solution was cooled to −40 °C. Then, TfOH (0.3 mL, 3.4 mmol) was added dropwise. The resulting solution was kept stirring for 2 h, and Et_3N (0.3 mL) was added to quench the reaction. The whole mixture was filtered through Celite, followed by washing with CH_2Cl_2, and the solution was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to get the pentasaccharide **3** (10.7 g, 65%) as a white solid. R_f = 0.5 (petroleum ether/ethyl acetate, 2/1, v/v); mp 81−83 °C; $[\alpha]_D^{23}$ +59.4 (c 0.2, CH_2Cl_2); IR (KBr) 3064, 3033, 2926, 2109, 1602, 1585, 1511, 1498, 1454, 1363, 1315, 1272, 1213, 1177, 1109, 1069, 1027, 913, 803, 739, 712, 619, 480; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−7.96 (m, 10H), 7.57−7.35 (m, 14H), 7.31−7.13 (m, 41H), 5.72 (d, J = 5.6 Hz, 1H), 5.59 (t, J = 10.0 Hz, 1H), 5.34 (d, J = 3.6 Hz, 1H), 5.25 (t, J = 6.0 Hz, 1H), 5.18 (d, J = 3.6 Hz, 1H), 5.03 (d, J = 4.8 Hz, 1H), 4.97 (d, J = 12.4 Hz, 1H), 4.89−4.66 (m, 13H), 4.64−4.50 (m, 6H), 4.46−4.35 (m, 4H), 4.23−4.16 (m, 3H), 4.10 (t, J = 9.2 Hz, 1H), 4.06−3.89 (m, 2H), 3.78−3.71 (m, 3H), 3.64−3.58 (m, 4H), 3.58 (s, 3H), 3.32 (t, J = 8.4 Hz, 1H), 3.27 (s, 3H), 3.27−3.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 167.0, 166.1, 166.0, 165.8, 165.6, 165.4, 155.8, 138.4, 138.0, 137.4, 137.4, 137.3, 136.3, 134.7, 133.4, 133.3, 133.2, 133.1, 132.9, 129.9, 129.8, 129.8, 129.6, 129.5, 129.5, 129.4, 129.0, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.5, 127.4, 127.2, 102.6, 98.7, 98.3, 97.9, 97.3, 83.4, 81.7, 80.2, 78.5, 77.7, 75.6, 75.2, 75.1, 74.9, 74.8, 74.4, 74.3, 74.1, 73.1, 72.1, 71.4, 70.0, 70.0, 69.7, 69.2, 67.4, 66.9, 63.4, 62.5, 61.9, 61.2, 55.2, 54.5, 52.3; HRMS [M + Na]$^+$ calcd for $C_{124}H_{119}N_7O_{32}Na$ 2240.7797, found 2240.7803.

*Methyl O-(2-Azido-3,4-di-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(methyl 2,3-di-O-benzyl-β-D-glucopyranosyluronate)-(1→4)-O-(2-azido-3,6-di-O-acetyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(methyl 2-O-benzoyl-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-2-benzyloxy Carbonylamino-3-O-benzyl-6-O-benzoyl-2-deoxy-α-D-glucopyranoside (**4**).* The same procedure described for the preparation of pentasaccharide **3** (from **5**) was employed for the preparation of **4** from **6** (17.6 g, 13.8 mmol) and **7** (10.4 g, 11.5 mmol). Purification by silica gel column chromatography (petroleum ether/ethyl acetate = 4:1) afforded pentasaccharide **4** (13.2 g, 57%). R_f = 0.4 (petroleum ether/ethyl acetate, 2/1, v/v); $[\alpha]_D^{23}$ +69.5 (c 0.7, CH_2Cl_2). IR (KBr) 3064, 3032, 2952, 2108, 1724, 1453, 1366, 1315, 1271, 1220, 1141, 1107, 1066, 1027, 740, 712, 699; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz, 2H), 8.03−8.00 (m, 4H), 7.57 (t, J = 7.2 Hz, 1H), 7.53−7.49 (m, 2H), 7.46−7.16 (m, 41H), 5.72 (d, J = 6.0 Hz, 1H), 5.49 (d, J = 3.6 Hz, 1H), 5.32 (t, J = 9.6 Hz, 1H), 5.26 (t, J = 6.0 Hz, 1H), 5.08 (d, J = 3.6 Hz, 1H), 5.05−5.00 (m, 2H), 4.97 (d, J = 10.8 Hz, 1H), 4.91−4.83 (m, 6H), 4.78−4.74 (m, 2H), 4.73−4.69 (m, 2H), 4.68−4.59 (m, 4H), 4.57−4.50 (m, 2H), 4.48−4.43 (m, 2H), 4.37 (d, J = 12.6 Hz, 1H), 4.33 (d, J = 7.8 Hz, 1H), 4.19−4.15 (m, 2H), 4.12−4.02 (m, 3H), 3.97 (td, J = 10.8, 3.6 Hz, 1H), 3.91−3.88 (m, 1H), 3.87 (d, J = 9.6 Hz, 1H), 3.78−3.75 (m, 1H), 3.76 (s, 3H), 3.71 (t, J = 9.0 Hz, 1H), 3.68−3.62 (m, 3H), 3.60−3.57 (m, 1H), 3.53 (s, 3H), 3.41 (t, J = 8.4 Hz, 1H), 3.32 (dd, J = 10.8, 4.2 Hz, 1H), 3.27 (s, 3H), 3.20 (dd, J = 10.8, 3.6 Hz, 1H), 2.00 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.9, 169.6, 168.3, 166.1, 166.0, 165.4, 155.8, 138.4, 138.0, 137.4, 137.3, 137.3, 136.3, 133.4, 133.1, 132.9, 129.9, 129.8, 129.7, 129.6, 129.0, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.3, 127.1,

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

103.3, 98.7, 98.3, 97.6, 97.5, 83.6, 81.6, 80.1, 78.6, 77.7, 76.9, 76.6, 75.9, 75.6, 75.1, 75.1, 74.8, 74.5, 74.4, 73.2, 72.1, 71.3, 69.8, 69.6, 69.3, 69.1, 66.9, 63.4, 62.6, 62.5, 61.4, 60.7, 55.2, 54.4, 52.7, 52.2, 20.8, 20.6; HRMS $[M + Na]^+$ calcd for $C_{108}H_{111}N_7O_{32}Na$ 2040.7171, found 2040.7148.

Methyl O-(2-Azido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(2,3-di-O-benzyl-β-D-glucopyranosyluronic acid)-(1→4)-O-(2-azido-2-deoxy-α-D-glucopyranosyl)-(1→4)-O-(3-O-benzyl-α-L-idopyranosyluronic acid)-(1→4)-2-benzyloxy Carbonylamino-3-benzyl-2-deoxy-α-D-glucopyranoside (2).[13] To the solution of **3** (24.4 g, 11.0 mmol) in THF (100 mL) were added 30% H_2O_2 (50 mL) and 1.25 M LiOH (aq.) (260 mL) at −5 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. Then, MeOH (500 mL) and 4 M NaOH (aq.) (330 mL) were added, and the resulting mixture was stirred for another 10 h. After that, the reaction was heated to 35 °C for an additional 16 h; then the reaction mixture was acidified (6 M HCl) and diluted with water (500 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 1.5 L) and washed with 10% Na_2SO_3 (aq.) and water. The aqueous layer was extracted with CH_2Cl_2 (6 × 2.0 L). The organic layers were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo, and the resulting crude was purified by reverse phase C18 column chromatography (CH_3CN/H_2O 1:9 to 7:3) to obtain pentasaccharide as a white powder. Subsequent recrystallization (*i*-PrOH/*n*-hexane/EtOAc = 5:10:1) afforded pure **2** (10.5 g, 60%).[13] Moreover, using pentasaccharide **4** as starting material, pentasaccharide **2** could be obtained in 65% yield through the same procedure described above. R_f = 0.6 (EtOAc/pyridine/HOAc/H_2O, 12/2/0.6/1, v/v); mp 124−126 °C; $[\alpha]_D^{23}$ −54.5 (*c* 0.3, MeOH); IR (KBr) 3405, 2923, 2107, 1721, 1512, 1496, 1454, 1358, 1310, 1142, 1025, 736, 697; ^{1}H NMR (600 MHz, CD_3OD) δ 7.43 (d, J = 7.8 Hz, 2H), 7.35−7.09 (m, 33H), 5.54 (d, J = 3.6 Hz, 1H), 5.27 (d, J = 4.2 Hz, 1H), 5.10 (d, J = 3.6 Hz, 1H), 5.01−4.95 (m, 3H), 4.92−4.82 (overlapped), 4.81−4.74 (m, 6H), 4.71−4.66 (m, 4H), 4.64 (d, J = 3.6 Hz, 1H), 4.51 (d, J = 10.8 Hz, 1H), 4.05−3.61 (m, 21H), 3.50 (t, J = 8.4 Hz, 1H), 3.38 (s, 3H), 3.34−3.27 (overlapped); ^{13}C NMR (150 MHz, CD_3OD) δ 172.6, 158.6, 140.0, 139.8, 139.7, 139.6, 139.5, 139.4, 138.2, 129.5, 129.4, 129.4, 129.3, 129.1, 129.0, 129.0, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 128.2, 103.9, 102.3, 100.4, 99.2, 98.5, 85.4, 83.1, 81.0, 80.3, 79.5, 79.2, 77.8, 77.4, 76.4, 76.3, 76.2, 76.1, 76.0, 75.9, 75.7, 75.1, 74.6, 73.5, 73.2, 72.8, 71.7, 71.4, 71.3, 67.6, 64.8, 64.7, 61.9, 61.2, 60.6, 56.6, 55.6; The NMR data match those reported in the literature;[13] HRMS $[M + Na]^+$ calcd for $C_{81}H_{91}N_7O_{27}Na$ 1616.5861, found 1616.5856.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02468.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and several known compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tangpei@cqu.edu.cn (P.T.).
*E-mail: yongqin@scu.edu.cn (Y.Q.).

Author Contributions

§(X.D., W.L., Q.Z.) These authors contributed equally to this work.

Notes

The authors declare no competing financial interest

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21132006, 21321061), the Fundamental Research Funds for the Central Universities (0236015202004), and the Chongqing Science & Technology Commission Project (cstc2013kjrc-qnrc10005). We also thank Chongqing Zein Pharmaceutical Co., Ltd. (Xianglin Deng, Daming Li, Wei Zhang) and Chongqing Liangjiang Medicine Co., Ltd. (Chunguang Zhu, Yu Wang) for the scale-up preparations of monosaccharide building blocks.

■ REFERENCES

(1) (a) Gandhi, N. S.; Mancera, R. L. *Chem. Biol. Drug Des.* **2008**, *72*, 455. (b) Desai, U. R.; Wang, H. M.; Linhardt, R. J. *Biochemistry* **1993**, *32*, 8140. (c) Capila, I.; Linhardt, R. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 390.

(2) Loeb, J. A.; Fischbach, G. D. *J. Cell Biol.* **1995**, *130*, 127.

(3) (a) Lever, R.; Page, C. P. *Nat. Rev. Drug Discovery* **2002**, *1*, 140. (b) Bernfield, M.; Gotte, M.; Park, P. W.; Reizes, O.; Fitzgerald, M. L.; Lincecum, J.; Zako, M. *Annu. Rev. Biochem.* **1999**, *68*, 729. (c) Tumova, S.; Woods, A.; Couchman, J. R. *Int. J. Biochem. Cell Biol.* **2000**, *32*, 269. (d) Esko, J. D.; Selleck, S. B. *Annu. Rev. Biochem.* **2002**, *71*, 435. (e) Lindahl, U.; Kusche-Gullberg, M.; Kjellen, L. *J. Biol. Chem.* **1998**, *273*, 24979.

(4) (a) Balasa, V. V. *Pediatr. Blood Cancer* **2005**, *45*, 741. (b) Mackman, N. *Nature* **2008**, *451*, 914. (c) Weitz, D. S.; Weitz, J. I. *J. Thromb. Thrombolysis* **2010**, *29*, 199.

(5) Blossom, D. B.; Kallen, A. J.; Patel, P. R.; Elward, A.; Robinson, L.; Gao, G.; Langer, R.; Perkins, K. M.; Jaeger, J. L.; Kurkjian, K. M.; Jones, M.; Schillie, S. F.; Shehab, N.; Ketterer, D.; Venkataraman, G.; Kishimoto, T. K.; Shriver, Z.; McMahon, A. W.; Austen, K. F.; Kozlowski, S.; Srinivasan, A.; Turabelidze, G.; Gould, C. V.; Arduino, M. J.; Sasisekharan, R. *N. Engl. J. Med.* **2008**, *359*, 2674.

(6) Weitz, J. I.; Linkins, L. A. *Expert Opin. Invest. Drugs* **2007**, *16*, 271.

(7) Petitou, M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3118.

(8) (a) Sinaÿ, P.; Jacquinet, J. C.; Petitou, M.; Duchaussoy, P.; Lederman, I.; Choay, J.; Torri, G. *Carbohydr. Res.* **1984**, *132*, C5. (b) Chiba, T.; Jacquinet, J.-C.; Sinaÿ, P.; Petitou, M.; Choay, J. *Carbohydr. Res.* **1988**, *174*, 253 and references cited therein. (c) van Boeckel, C. A. A.; Beetz, T.; Vos, J. N.; de Jong, A. J. M.; van Aelst, S. F.; van den Bosch, R. H.; Mertens, J. M. R.; van der Vlugt, F. A. *J. Carbohydr. Chem.* **1985**, *4*, 293. (d) van Boeckel, C. A. A.; Petitou, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1671 and references cited therein. (e) Polat, T.; Wong, C. H. *J. Am. Chem. Soc.* **2007**, *129*, 12795 and references cited therein.

(9) (a) Walenga, J. M.; Jeske, W. P.; Frapaise, F. X.; Bick, R. L.; Fareed, J.; Samama, M. M. *Expert Opin. Invest. Drugs* **2002**, *11*, 397. (b) Middeldorp, S. *Thromb. Res.* **2008**, *122*, 753. (c) Nagler, M.; Haslauer, M.; Wuillemin, W. A. *Thromb. Res.* **2012**, *129*, 407.

(10) Petitou, M.; Hérault, J.-P.; Bernat, A.; Driguez, P.-A.; Duchaussoy, P.; Lormeau, J.-C.; Herbert, J.-M. *Nature* **1999**, *398*, 417.

(11) (a) Petitou, M.; Duchaussoy, P.; Herbert, J. M.; Duc, G.; El Hajji, M.; Branellec, J. F.; Donat, F.; Necciari, J.; Cariou, R.; Bouthier, J.; Garrigou, E. *Semin. Thromb. Hemostasis* **2002**, *28*, 393. (b) Weitz, J. I.; Linkins, L. A. *Expert Opin. Invest. Drugs* **2007**, *16*, 271.

(12) Recent syntheses of fondaparinux sodium, see: (a) Chang, C. H.; Lico, L. S.; Huang, T. Y.; Lin, S. Y.; Chang, C. L.; Arco, S. D.; Hung, S. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 9876. (b) Lin, F.; Lian, G.; Zhou, Y. *Carbohydr. Res.* **2013**, *371*, 32. (c) Li, T. H.; Ye, H.; Cao, X. F.; Wang, J. J.; Liu, Y. H.; Zhou, L. F.; Liu, Q.; Wang, W. J.; Shen, J.; Zhao, W.; Wang, P. *ChemMedChem* **2014**, *9*, 1071. (d) Xu, Y.; Masuko, S.; Takieddin, M.; Xu, H.; Liu, R.; Jing, J.; Mousa, S. A.; Linhardt, R. J.; Liu, J. *Science* **2011**, *334*, 498.

(13) (a) Kozioł, A.; Lendzion-Paluch, A.; Manikowski, A. *Org. Process Res. Dev.* **2013**, *17*, 869. (b) Manikowski, A.; Kozioł, A.; Czajkowska-Wojciechowska, E. *Carbohydr. Res.* **2012**, *361*, 155.

(14) (a) Xu, P.; Xu, W. C.; Dai, Y. W.; Yang, Y.; Yu, B. *Org. Chem. Front.* **2014**, *1*, 405. (b) Hung, S. C.; Thopate, S. R.; Chi, F. C.; Chang, S. W.; Lee, J. C.; Wang, C. C.; Wen, Y. S. *J. Am. Chem. Soc.* **2001**, *123*, 3153. (c) Ojeda, R.; Angulo, J.; Nieto, P. M.; Martín-Lomas, M. *Can. J. Chem.* **2002**, *80*, 917. (d) Orgueira, H. A.; Bartolozzi, A. B.; Schell, P.;

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184

Litjens, R. E. J. N.; Palmacci, E. R.; Seeberger, P. H. *Chem. - Eur. J.* **2003**, *9*, 140.
(15) Jacquinet, J. C.; Petitou, M.; Duchaussoy, P.; Lederman, I.; Choay, J.; Torri, G.; Sinaÿ, P. *Carbohydr. Res.* **1984**, *130*, 221.
(16) (a) Hung, S. C.; Lu, X. A.; Lee, J. C.; Chang, M. D. T.; Fang, S. L.; Fan, T. C.; Zulueta, M. M. L.; Zhong, Y. Q. *Org. Biomol. Chem.* **2012**, *10*, 760. (b) Lu, L. D.; Shie, C. R.; Kulkarni, S. S.; Pan, G. R.; Lu, X. A.; Hung, S. C. *Org. Lett.* **2006**, *8*, 5995. (c) Lee, J. C.; Lu, X. A.; Kulkarni, S. S.; Wen, Y. S.; Hung, S. C. *J. Am. Chem. Soc.* **2004**, *126*, 476.
(17) (a) Yan, R. B.; Yang, F.; Wu, Y. F.; Zhang, L. H.; Ye, X. S. *Tetrahedron Lett.* **2005**, *46*, 8993. (b) Zhou, Y.; Lin, F.; Chen, J. F.; Yu, B. *Carbohydr. Res.* **2006**, *341*, 1619. (c) Vasella, A.; Witzig, C.; Chiara, J. L.; Martín-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073. (d) de Paz, J.-L.; Ojeda, R.; Reichardt, N.; Martín-Lomas, M. *Eur. J. Org. Chem.* **2003**, *2003*, 3308. (e) Silva, D. J.; Bowe, C. L.; Branstrom, A. A.; Baizman, E. R.; Sofia, M. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2811. (f) Pozsgay, V.; Coxon, B. *Carbohydr. Res.* **1994**, *257*, 189.
(18) Pellissier, H. *Org. Prep. Proced. Int.* **2002**, *34*, 441.
(19) (a) Whistler, R. L.; Lake, W. C. *Methods Carbohydr. Chem.* **1972**, *6*, 286. (b) Orgueira, H. A.; Bartolozzi, A. B.; Schell, P.; Litjens, R. E. J. N.; Palmacci, E. R.; Seeberger, P. H. *Chem. - Eur. J.* **2003**, *9*, 140. (c) Lohman, G. J. S.; Hunt, D. K.; Högermeier, J. A.; Seeberger, P. H. *J. Org. Chem.* **2003**, *68*, 7559. (d) Stępowska, H.; Zamojski, A. *Tetrahedron* **1999**, *55*, 5519. (e) Krajewski, J. W.; Gluzinski, P.; Pakulski, Z.; Zamojski, A.; Mishnev, M.; Kemme, A. *Carbohydr. Res.* **1994**, *252*, 97. (f) Lubineau, A.; Gavard, O.; Alais, J.; Bonnaffé, D. *Tetrahedron Lett.* **2000**, *41*, 307. (g) Dilhas, A.; Bonnaffé, D. *Carbohydr. Res.* **2003**, *338*, 681. (h) Sawant, R. C.; Liao, Y. J.; Lin, Y. J.; Badsara, S. S.; Luo, S. Y. *RSC Adv.* **2015**, *5*, 19027. (i) Gavard, O.; Hersant, Y.; Alais, J.; Duverger, V.; Dilhas, A.; Bascou, A.; Bonnaffé, D. *Eur. J. Org. Chem.* **2003**, *2003*, 3603.
(20) Lee, J. C.; Tai, C. A.; Hung, S. C. *Tetrahedron Lett.* **2002**, *43*, 851.
(21) Wang, Y. H.; Yeh, H. W.; Wang, H. W.; Yu, C. C.; Guh, J. H.; Liu, D. Z.; Liang, P. H. *Carbohydr. Res.* **2013**, *375*, 118.
(22) (a) Jalsa, N. K. *Tetrahedron Lett.* **2011**, *52*, 6587. (b) Liotta, L. J.; Capotosto, R. D.; Garbitt, R. A.; Horan, B. M.; Kelly, P. J.; Koleros, A. P.; Brouillette, L. M.; Kuhn, A. M.; Targontsidis, S. *Carbohydr. Res.* **2001**, *331*, 247.
(23) Yan, M. C.; Chen, Y. N.; Wu, H. T.; Lin, C. C.; Chen, C. T.; Lin, C. C. *J. Org. Chem.* **2007**, *72*, 299.

DOI: 10.1021/acs.joc.5b02468
J. Org. Chem. 2016, 81, 162−184