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Synthesis of D-Galactosamine and D-Allosamine Derivatives via a Microwave-Assisted Preparation of 1,6-Anhydroglucosamine

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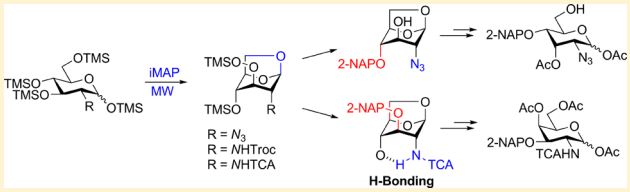
Supporting Information

ABSTRACT: We report a microwave-assisted intramolecular anomeric protection (iMAP) of glucosamine, which facilitates concise transformation of 1,6-anhydroglucosamine into 1,6-anhydrogalactosamine and 1,6-anhydroallosamine. The iMAP simultaneously obviates both the *O*1 and *O*6 protection, and the differentiation between *O*3 and *O*4 can be well-controlled by the *N*2 functionality because of the hydrogen bonding between *N*2 and *O*4. Epimerization of *O*4 afforded the galactosamine derivative and that of *O*3 yielded allosamine.



2-Acetamido-2-deoxy-D-glucose (D-Glc*N*Ac) and 2-acetamido-2-deoxy-D-galactose (D-Gal*N*Ac) are the most abundant types of 2-amino-2-deoxyhexose in nature.[1] They are found in oligosaccharides and glycoconjugates, such as glycolipids, peptidoglycan, glycoproteins, and glycosaminoglycans.[2] Their *N*-acetylated and sulfonated derivatives are widely distributed in type A blood group antigen, GPI anchors, and lipopolysaccharides. D-Glc*N*Ac is inexpensive and can be commercially purchased in large quantities.[3] However, most other 2-amino-2-deoxyhexoses, such as allosamine and galactosamine, are rare and much more expensive. Therefore, economically viable and efficient strategies must be developed for synthesizing these sugars.

Galactosamine and its derivatives are the building blocks for synthesizing numerous biologically essential carbohydrate molecules. For example, *N*-acetylated derivatives of galactosamine are present in chondroitin sulfate and Tn antigen. Bacterial cell walls contain large amounts of capsular polysaccharides (CPS) and lipopolysaccharides (LPS), which are responsible for shock absorbance and biosynthesis. These components are crucial virulence factors and promote bacterial colonization, block phagocytosis, and interfere with leukocyte migration and adhesion. Amino sugars are essential components of the bacterial glycoconjugate, responsible for host–pathogen interaction.[3] Furthermore, *N*-acetylated derivatives of allosamine are present in natural products. For example, allosamine—an insect Chitinase inhibitor isolated from the mycelium of *Streptomyces* sp—was detected in allosamidin in 1986,[4] and the allosamine core is an indispensible component in streptothricin antibiotic.[4]

Hydrolysis of chondroitin sulfate under acidic condition is the major source of D-galactosamine.[5] Several methods have been reported for the synthesis of D-galactosamine, including the extension of D-lyxose chain, epimerization of *C*4 of D-glucosamine,[6] addition of ammonia to 1,6:2,3-dianhydro-*β*-D-talopyranose.[7] and azidonitration.[8] The addition of nitrosyl chloride to tri-*O*-acetyl-D-galctal followed by the reduction of oxime also yields galactosamine.[9] However, in most of these cases, the yields were low, and a high degree of stereoselectivity cannot be achieved. Recently, Kulkarni et al. reported the rapid transformation of D-mannose into protected D-galactosamine and D-glucosamine thioglycosides.[10] Allosamine is a *C*3 epimer of glucosamine. This rare amino sugar is not commercially available; it exerts insecticidal activity through the inhibition of ecdysis.[4] Various mechanisms have been reported for the synthesis of this rare sugar, including the elongation of ribose chain,[11] hydrolysis of oxazoline,[12] inversion at *C*-3 via the Mitsunobu approach,[13] diazotransfer followed by inversion of *O*3,[14] and stereoselective formation of imine followed by reduction.[15] However, these approaches result in low stereoselectivity and poor yields.

The preparation of sugar building blocks generally entails laborious anomeric protection followed by the traditional protection and deprotection strategies. Short, efficient, and improved methods for the synthesis of these potent sugars are desired. We adopted the intramolecular anomeric protection (iMAP), an efficient strategy 1,6-cyclization of free sugar. Through our iMAP method, excellent yields of these sugars can be generated in a short time by using only catalytic amount of Lewis acid[16] with no additional or excessive reagents

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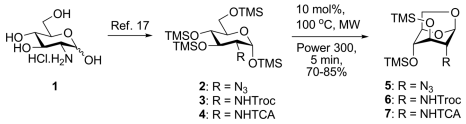
required;[16] therefore, the traditional anomeric and primary *O*6 protection can be simultaneously obviated without forming the α/β anomer mixtures; protection−deprotection sequence can therefore be greatly reduced. Besides, the configuration of the hydroxyl groups is altered from equatorial to axial after the 1,6-anhydro ring formation, thus altering the reactivity. Therefore, several factors can be used to control the regioselectivities among the remaining secondary hydroxyl groups. Here, we utilize iMAP for the synthesis of galactosamine and rare allosamine through the regioselective protection of 1,6-anhydroglucosamine.

N-functionalization of amino sugars is often tedious. To simplify the protocol, we recently reported a simple and efficient protocol for the chemoselective per-*O*-trimethylsilylation of amino sugars followed by *N*-functionalization.[17,18] Recently, we developed a microwave-assisted method for the synthesis of 1,6-anhydro sugars from free sugars using TMSOTf and TfOH as a catalyst in moderate to good yields.[16] We applied a similar protocol for the synthesis of 1,6-anhydroglucosamine. The silyl derivative of glucosamine was subjected to microwave irradiation to afford 1,6 cyclization **5**, **6**, **7** in 85%, 70%, and 70% yields, respectively (Scheme 1). The

Scheme 1. Microwave-Assisted Synthesis of 1,6-Anhydroglucosamine



structure of the bicyclo skeleton was clearly observed in a single X-ray crystal structure (Figure 1). The rigid conformation

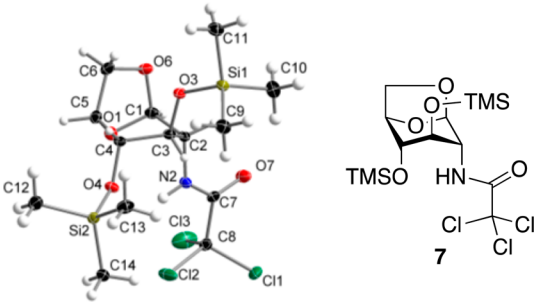


Figure 1. ORTEP diagram of 7 with the thermal ellipsoids drawn at 50% probability level.

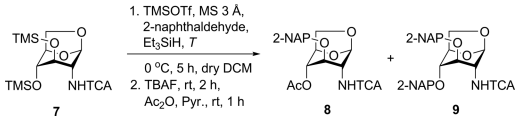
[3.2.1] bicyclo skeleton of 1,6-anhydroglucosamine derivatives **7** greatly simplifies the complexity of the glucosamine molecules by eliminating the problems of anomers and simultaneously obviating two protecting groups on the *O*1 and *O*6. In addition, the axial orientation of the equatorial bonds projects *N*HTCA and *O*4 in the same phase. We propose that the regioselective protection can be controlled by the amine functionality caused by the hydrogen bonding between *N* and *O*4 oxygen atoms.

X-ray crystallographic analysis (Figure 1) revealed that the distance between *O*4 → *C*2 amide proton is 2.325 Å and *O*4 → *C*2 nitrogen atom is 2.899 Å, indicating a strong hydrogen bonding. Thus, *O*4 can be expected to be less nucleophilic. Moreover, the rigidity of the sugar ring is expected to increase, and the steric hindrance can be used as an accurate indicator to differentiate *O*3 and *O*4. Utilizing these factors facilitates the differentiation of *O*3 and *O*4 for the efficient preparation of other amino sugars. We estimated that the amine functionalities with an *N*−*H* bond, such as TCA or Troc group, would favor the protection at *O*3, but those without the *N*−*H* bond, such as azido group, would likely favor the *O*4 because of the steric hindrance between *O*3 and *C*6−*O*6 bond.

To synthesize galactosamine derivatives, our protocol involved the formation of 1,6-anhydrosugar followed by the reductive etherification at *O*3 and epimerization of *O*4. To differentiate *O*3 and *O*4, we performed the reductive etherification reaction of compound **7** using our established protocol.[18,19] For the synthesis of bacterial glycoconjugate, we preferred 2-methylnaphthyl (2-NAP), a stable and versatile protecting group for the regioselective protection that can be easily removed using DDQ and CAN under mildly acidic conditions.[20−22]

First, the reductive etherification of **7** with 2-naphthaldehyde and triethylsilane was examined at temperatures of −78 to 0 °C (Table 1). For the ease of characterization, the products were

Table 1. Optimization of the Regioselective Protection of 7



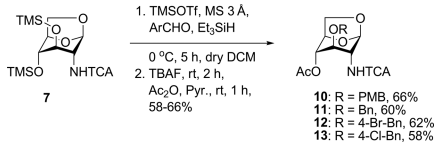
entry	T (°C)	**8**	**9**
1	−78	47	30
2	−50	50	32
3	−20	55	25
4	0	63	12
5	rt	42	23

treated with TBAF to cleave the trimethylsilyl group and then with pyridine and acetic anhydride; subsequently, the products were isolated as its acetylated derivatives. The reaction at −78 °C provided only 47% of **8** and 30% of diaryl product **9** (Table 1, entry 1). A similar result was observed at −50 °C (Table 1, entry 2), whereas a slight improvement was observed when the reaction temperature was increased to −20 °C [55% of **8** (Table 1, entry 3)]. The reaction at 0 °C provided 63% of **8** and 12% of **9** (Table 1, entry 4). This result indicates that *O*3 is more reactive than *O*4.

The regioselective reductive etherification of **7** was further screened using various aryl aldehydes and the results were consistent in all cases, namely, **10**, **11**, **12** and **13** (Scheme 2). Regioselectivity was confirmed through X-ray crystallography of **11** (see Supporting Information).

These results briefly confirmed our hypothesis that the hydrogen bonding between the *O*4 and *C*2 *N*−H lowers the nucleophilicity of *O*4 and renders *O*3 more reactive despite the steric hindrance between *O*3 and *C*6−*O*6 bond. This protocol

Scheme 2. Regioselective Reductive Etherification of 7 by Using Various Aryl Aldehydes



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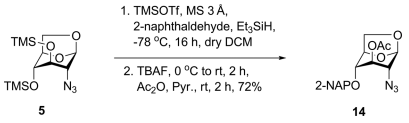
not only allows the synthesis of galactosamine but also provides the required building blocks for chain extension in oligosaccharide synthesis. The ORTEP of **11** indicates that despite the rigid [3.2.1] conformation after the 1,6-cyclization, in contrast to **11** (see Supporting Information), in the absence of the hydrogen bonding in **14**, the distance between *O*4 → *N*1 of *C*2 azide elongated to 3.439 Å because of the 1,3-diaxial repulsion.

Without the hydrogen bonding that greatly deactivates the *C*4 hydroxyl group, *O*4 is more reactive than the sterically and conformationally more hindered *O*3 toward the regioselective reductive etherification (Scheme 3). The inductive effect of the

Scheme 3. Regioselective Reductive 2-Naphthylation of 5

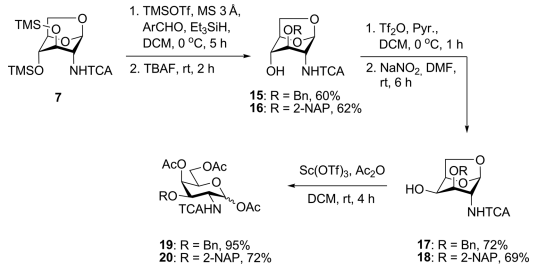


azide group must also enhance the regioselectivity by lowering the nucleophilicity of *O*3. To further verify this hypothesis, we repeated the reductive etherification by replacing the *C*2 *N*HTCA group with an azido group to 2-deoxy-2-azido-1,6-anhydroglucosamine (**5**). In the absence of the hydrogen bonding, the regioselectivity was reversed when we used **5** as the substrate (Scheme 3). For easy NMR characterization, the product was again treated first with TBAF to remove the TMS group and then with pyridine and acetic anhydride to transform the product into its acetylated derivative. The *C*4 etherified compound **14** was isolated as a single regioisomer in 72% yield. The regioselectivity was reconfirmed through X-ray crystallography of **14** (see Supporting Information).

These results showed that the regioselective protections between the *C*3 and *C*4 hydroxyl groups can be controlled on the basis of *N*-functionalization. This enabled us to efficiently differentiate *O*3 and *O*4 to synthesize partially protected galactosamine and allosamine derivatives by epimerizing *C*4 and *C*3, respectively. We initiated the synthesis of galactosamine precursors **15** and **16** following the protocols described in Scheme 2 and acetylation using pyridine and acetic anhydride, which produced 60% and 62% of the *C*4 alcohols **15** and **16**, respectively. Next, we performed the regioselective protection of **7** followed by epimerization[23] using Tf_2O and $NaNO_2$ in DMF, which afforded 72% and 69% of **17** and **18**, respectively (Scheme 4).

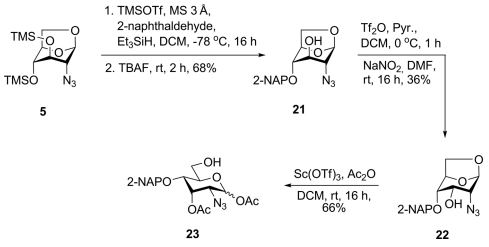
The 1,6-anhydro bridges of **17** and **18** were opened by treating with $Sc(OTf)_3/Ac_2O$,[24] which afforded **19** and **20** with excellent yield (Scheme 4). Through this method, we successfully synthesized D-galactosamine derivatives **19** and **20** from free glucosamine hydrochloride (**1**) in only 6 steps.

Scheme 4. Synthesis of Galactosamine Derivatives 19 and 20



Similarly, we developed a four-step procedure for the synthesis of allosamine derivative **23** (Scheme 5). Using the

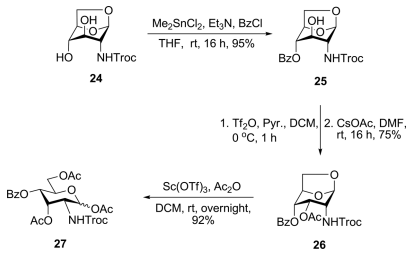
Scheme 5. Synthesis of Allosamine Derivative 23



aforementioned protocol, **5** was regioselectively protected with 2-NAP group. The sterically crowded hydroxyl group of **21** was converted to a triflate using triflic anhydride and pyridine. However, its epimerization using $NaNO_2$ in DMF provided only 36% yield of **22**, whereas 17% of the triflate derivative and 18% of **21** were recovered. This indicated the reactivity of 3-OH toward epimerization is lower probably because of the steric hindrance. Furthermore, addition of extra $NaNO_2$ and prolonged reaction time did not have any influence on **22**. The ring was opened under acidic condition to afford acetate derivative **23** in good yield, surprisingly with free 6-OH.

Alternatively, we also developed a convenient method for protecting the *C*4 hydroxyl group when the *C*2 amine contains an *N*–*H* (Scheme 6) that was applied for the synthesis of

Scheme 6. Synthesis of Allosamine Derivative 27



allosamine derivative **27**. After the microwave-assisted 1,6-cyclization of **3**, the intermediate **6** was treated with Amberlie H^+ to afford **24** in 70% over 2 steps. It was subjected to regioselective benzoylation through a tin-mediated reaction. This reaction could be completed only in the presence of 0.5 equiv of Me_2SnCl_2, and afforded **25** in an excellent 95% yield after overnight stirring at room temperature. The triflation of **25** using Tf_2O and pyridine followed by the epimerization using CsOAc in DMF[25] resulted in 75% of **26**. The 1,6-anhydro-ring opening using Ac_2O and $Sc(OTf)_3$ yielded 92% of the acetate derivative **27**.

In short, our methodology using microwave-assisted heating allows the synthesis of 1,6-anhydroglucosamine derivative by using TMSOTf as a catalyst and obviates the traditional anomeric protections, which generally require 2 or 3 steps and need to be removed in the later stage of oligosaccharide synthesis. This method is straightforward and does not entail lengthy steps, and the compounds prepared from inexpensive glucosamine hydrochloride (**1**) are easy to handle and accessible within a short time. This transformation also renders the differentiation among all the hydroxyl groups of 2-deoxy-aminosugars easier, of which the differentiation of the remaining *C*3 and *C*4 secondary hydroxyl groups can be

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controlled by the presence/absence of hydrogen bonding between the *O*4 and the *C*2 amine functionality. The synthesis of a galactosamine derivative, including regioselective protection of 1,6 anhydroglucosamine, *C*4-epimerization followed by ring opening under acidic condition, could be achieved in 6 steps from free glucosamine hydrochloride (**1**). A rare allosamine derivative could be synthesized via either the *C*4 regioselective reductive etherification or the regioselective tin-mediated benzoylation of the 1,6-anhydroglucosamine in good overall yields.

EXPERIMENTAL SECTION

General Information. All the reactions were conducted in flame-dried glassware, under nitrogen atmosphere. Methanol, acetonitrile and dichloromethane were purified and dried by using a safe purification system filled with anhydrous Al_2O_3. All other reagents were obtained from commercial sources and used without further purification unless otherwise mentioned. Water was distilled. Flash column chromatography was carried out on Silica Gel 60 (230−400 mesh). TLC was performed on recoated glass plates of Silica Gel 60 F254 (0.25 mm); detection was executed by spraying a solution of $Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$, and H_2SO_4 in water and subsequent heating on a hot plate. Specific rotations were taken at ambient temperature conditions and reported in 10^{-1}·deg·cm^2·g^{-1}; the sample concentrations are in g·dL^{-1}. The microwave-assisted reactions were performed using the Discover SP system (CEM) in the sealed reaction vessels in dynamic mode with the temperature monitored using a vertically focused IR sensor. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 600 MHz instruments. Chemical shifts are in ppm from Me_4Si, calibrated at δ 7.24 or δ 0.00 for ^{1}H spectra (residual $CHCl_3$ or TMS respectively), and δ 77.23 for ^{13}C spectra. Splitting patterns were designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Proton peak were assigned based on 2D NMR spectra (^{1}H−^{1}H COSY, HSQC, and NOESY). The Infrared Spectra were recorded using thin film method in the region 4000−600 cm^{-1}. The X-ray intensity data were measured at low temperature 100 K using Mo Kα radiation diffractometer equipped with a kappa geometry goniometer and corrected for absorption effects using the Multi-Scan method (SADABS).

General Procedure for the Microwave Assisted Synthesis of 1,6-Anhydrosugars (5−7). In a dried 35 mL microwave vial, the per-*O*-trimethylsilylated glucosamine derivative (2.025 mmol, 1.0 equiv) was dissolved in MeCN (20 mL), followed by the addition of TMSOTf (37 μL, 0.203 mmol, 0.1 equiv). The mixture was subjected to microwave irradiation at 100 °C for 5 min. The consumption of the starting material was confirmed by TLC. The reaction was treated with HMDS (844 μL, 4.050 mmol, 2.0 equiv) and further stirred for 30 min at rt. The mixture was evaporated and the crude mixture was purified by short column chromatography (10% ethyl acetate/hexane) to afford the desired compound.

*1,6-Anhydro-2-azido-2-deoxy-3,4-di-O-trimethylsilyl-β-D-glucopyranose (**5**).*[16] Colorless oil (570 mg, 85%), $[\alpha]^{28}_D$ + 36.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν 2957, 2100, 1251, 1107, 1010, 839, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (s, 1H, H-1), 4.38 (d, *J* = 4.6 Hz, 1H, H-5), 4.09 (dd, *J* = 7.0, 1.0 Hz, 1H, H-6a), 3.69−3.71 (m, 1H, H-3), 3.67 (dd, *J* = 6.9, 5.9 Hz, 1H, H-6b), 3.49 (bt, 1H, *J* = 2.0 Hz, H-4), 2.93 (s, 1H, H-2), 0.16 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.1 (CH), 77.2 (CH), 73.3 (CH), 72.6 (CH), 65.3 (CH_2), 62.8 (CH), 0.2 (CH_3), 0.1 (CH_3); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{25}N_3O_4Si_2Na$ 354.1281, found 354.1273.

*1,6-Anhydro-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-3,4-di-O-trimethylsilyl-β-D-glucopyranose (**6**).*[16] Colorless oil (523 mg, 70%), $[\alpha]^{29}_D$ −31.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν 2956, 1742, 1508, 1252, 1102, 841, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (d, *J* = 11.0 Hz, 1H, NH), 5.35 (s, 1H, H-1), 4.70 (ABq, *J* = 12.0 Hz, 2H, OCH_2), 4.32 (d, *J* = 5.5 Hz, 1H, H-5), 4.27 (d, *J* = 7.0 Hz, 1H, H-6a), 3.68 (t, *J* = 6.4 Hz, 1H, H-6b), 3.63 (d, *J* = 11.0 Hz, 1H, H-2), 3.55 (s, 1H, H-3), 3.50 (s, 1H, H-4), 0.14 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (C), 101.1 (CH), 100.8 (CH), 95.8 (CH), 76.7 (CH), 74.7 (CH_2), 73.3 (CH), 72.0 (CH), 65.1 (CH_2), 53.2 (CH), 0.1 (CH_3), 0.0 (CH_3); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}Cl_3NO_6Si_2Na$ 502.0418, found 502.0414.

*1,6-Anhydro-2-deoxy-2-trichloroacetamido-3,4-di-O-trimethylsilyl-β-D-glucopyranose (**7**).*[16] White solid (514 mg, 70%), $[\alpha]^{29}_D$ −33.3 (*c* 1.0, $CHCl_3$); mp 72−73 °C; IR ($CHCl_3$) ν 2956, 1716, 1508, 1252, 1098, 1013, 889, 839, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 9.6 Hz, 1H, NH), 5.37 (s, 1H, H-1), 4.35 (bt, *J* = 2.7 Hz, 1H, H-5), 4.32 (d, *J* = 7.0 Hz, 1H, H-6b), 3.86 (dd, *J* = 9.6, 1.2 Hz, 1H, H-2), 3.72 (t, *J* = 6.1 Hz, 1H, H-6a), 3.55 (t, *J* = 1.6 Hz, 1H, H-3), 3.54 (d, *J* = 1.2 Hz, 1H, H-4), 0.15 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (C), 100.2 (CH), 72.7 (CH), 71.8 (CH), 65.1 (CH_2), 52.8 (CH), 0.1 (CH_3), 0.0 (CH_3); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{26}Cl_3NO_5Si_2Na$ 472.0313, found 472.0322.

General Procedure for the Regioselective Protection of 1,6-Anhydrosugars and Acetylation (8−13). To a solution of compound 7 (100 mg, 0.222 mmol, 1.0 equiv) in dry CH_2Cl_2 (1.5 mL) was added 3 Å molecular sieves (0.2 g), triethylsilane (42 μL, 0.266 mmol, 1.2 equiv) and aldehyde (0.266 mmol, 1.2 equiv) under N_2 atmosphere. The reaction mixture was stirred for 30 min at room temperature. The mixture was cooled to 0 °C. TMSOTf (4 μL, 0.022 mmol, 0.1 equiv) was added at 0 °C and the mixture was stirred for another 30 min. Reaction was monitored by using TLC. A second portion of aldehyde (0.089 mmol, 0.4 equiv), triethylsilane (14 μL, 0.089 mmol, 0.4 equiv) and TMSOTf (4 μL, 0.022 mmol, 0.1 equiv) was added to the reacion mixture, which was further stirred for 5 h at 0 °C. The reaction was monitored by using TLC. Upon completion, the reaction was quenched with TBAF (444 μL, 0.444 mmol, 2.0 equiv) and stirred at room temperature for another 2 h. Pyridine (89 μL, 1.110 mmol, 5.0 equiv) and acetic anhydride (27 μL, 0.289 mmol, 1.3 equiv) were added sequentially, and the mixture was stirred for additional 2 h at room temperature. The reaction was monitored by TLC. Upon completion, the mixture was filtered through a Celite pad. The filtrate was evaporated and the crude was purified by column chromatography (30% ethyl acetate/hexane) to afford desired 1,6-anhydrosugar derivatives (**8**−**13**).

*4-O-Acetyl-1,6-anhydro-2-deoxy-3-O-(2-naphthylmethyl)-2-trichloroacetamido-β-D-glucopyranose (**8**).* White solid (68 mg, 63%), $[\alpha]^{29}_D$ −39.7 (*c* 1.0, $CHCl_3$); mp 121−122 °C; IR ($CHCl_3$) ν 3411, 2960, 2902, 1714, 1508, 1285, 1173, 1020, 789, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.83 (m, 4H, ArH), 7.44−7.47 (m, 3H, ArH), 7.12 (d, *J* = 9.5 Hz, 1H, NH), 5.50 (s, 1H, H-1), 4.86 (ABq, *J* = 12.0 Hz, 2H, $ArCH_2$), 4.85 (s, 1H, H-4), 4.63 (d, *J* = 5.4 Hz, 1H, H-5), 4.37 (d, *J* = 7.6 Hz, 1H, H-6b), 4.21 (d, *J* = 9.4 Hz, 1H, H-3), 3.83 (t, *J* = 6.2 Hz, 1H, H-6a), 3.48 (s, 1H, H-2), 2.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (C), 161.4 (C), 134.6 (C), 133.3 (C), 133.2 (C), 128.5 (CH), 128.1 (CH), 127.8 (CH), 126.7 (CH), 126.3 (CH), 126.2 (CH), 125.6 (CH), 100.1 (CH), 92.4 (CH), 76.2 (CH), 73.8 (CH), 72.5 (CH_2), 70.4 (CH), 65.6 (CH_2), 49.6 (CH), 21.1 (CH_3); HRMS (ESI-TOF) *m*/*z* [M − H]$^-$ calcd for $C_{21}H_{19}Cl_3NO_6$ 486.0278, found 486.0270.

*4-O-Acetyl-1,6-anhydro-2-deoxy-3-O-p-methoxybenzyl-2-trichloroacetamido-β-D-glucopyranose (**10**).* Colorless oil (69 mg, 66%), $[\alpha]^{28}_D$ −16.4 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) ν 3412, 2957, 2905, 1715, 1512, 1228, 1035, 889, 789, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 11.6, 2.6 Hz, 2H, ArH), 7.10 (d, *J* = 9.4 Hz, 1H, NH), 6.86 (dd, *J* = 9.9, 3.0 Hz, 2H, ArH), 5.46 (s, 1H, H-1), 4.78 (bs, 1H, H-4), 4.62 (ABq, *J* = 11.5 Hz, 2H, $ArCH_2$), 4.6 (d, *J* = 5.6 Hz, 1H, H-5), 4.32 (d, *J* = 7.4 Hz, 1H, H-6a), 4.13 (d, *J* = 9.4 Hz, 1H, H-2), 3.80 (dd, *J* = 7.1, 6.6 Hz, 1H, H-6b), 3.78 (s, 3H, OCH_3), 3.40 (bs, 1H, H-3), 2.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (C), 161.2 (C), 159.6 (C), 129.4 (CH), 129.3 (CH), 114.0 (CH), 100.2 (CH), 76.0 (CH), 73.8 (CH), 72.1 (CH), 70.5 (CH), 65.5 (CH_2), 55.4 (CH), 49.7 (CH), 21.1 (CH_3); HRMS (ESI-TOF) *m*/*z* [M − H]$^-$ calcd for $C_{18}H_{19}Cl_3NO_7$ 466.0227, found 466.0225.

*4-O-Acetyl-1,6-anhydro-3-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranose (**11**).* White solid (58 mg, 60%), $[\alpha]^{28}_D$ −50.3 (*c* 1.0, $CHCl_3$); mp 153−154 °C; IR ($CHCl_3$) ν 1714, 1507, 1225, 1019, 818, 741, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 4.3 Hz, 4H, ArH), 7.29−7.25 (m, 1H, ArH), 7.11 (d, *J* = 9.4 Hz, NH),

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5.47 (s, 1H, H-1), 4.80 (s, 1H, H-4), 4.69 (ABq, J = 11.8 Hz, 2H, $ArCH_2$), 4.60 (s, 1H, H-5), 4.33 (d, J = 7.4 Hz, 1H, H-6a), 4.13 (d, J = 9.4 Hz, 1H, H-2), 3.80 (dd, J = 7.0, 6.0 Hz, 1H, H-6b), 3.42 (s, 1H, H-3), 2.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (C), 161.3 (C), 128.6 (CH), 128.0 (CH), 127.6 (CH), 127.1 (CH), 100.1 (CH), 76.3 (CH), 73.8 (CH), 72.4 (CH), 70.3 (CH), 65.5 (CH_2), 49.7 (CH), 21.1 (CH_3); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{17}H_{17}Cl_3NO_6$ 436.0121, found 436.0125.

*4-O-Acetyl-1,6-anhydro-2-deoxy-3-O-p-bromobenzyl-2-trichloroacetamido-β-D-glucopyranose (**12**).* Colorless oil (71 mg, 62%), $[\alpha]^{29}_D$ −44.8 (c 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3411, 2960, 2902, 1714, 1507, 1370, 1189, 1012, 924, 818, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, J = 2.4 Hz, 1H, ArH), 7.44 (t, J = 2.0 Hz, 1H, ArH), 7.22 (t, J = 2.3 Hz, 1H, ArH), 7.19 (t, J = 2.0 Hz, 1H, ArH), 7.26 (dd, J = 11.7, 2.6 Hz, 2H, ArH), 7.10 (d, J = 9.5 Hz, 1H, NH), 5.48 (bs, 1H, H-1), 4.80 (m, 1H, H-4), 4.65 (ABq, J = 12.8 Hz, 2H, $ArCH_2$), 4.62, (m, 1H, H-5), 4.30 (dd, J = 7.5, 0.85 Hz, 1H, H-6a), 4.11 (dd, J = 9.4, 1.2 Hz, 1H, H-2), 3.81 (dd, J = 7.5, 5.8 Hz, 1H, H-6b), 3.40 (ddd, J = 4.4, 3.0, 1.6 Hz, 1H, H-3), 2.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (C), 161.5 (C), 136.3 (C), 131.7 (CH), 129.3 (CH), 121.9 (CH), 100.0 (CH), 92.4 (CH), 76.4 (CH), 73.8 (CH), 71.6 (CH_2), 70.3 (CH), 65.5 (CH_2), 49.5 (CH), 21.1 (CH_3); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{17}H_{16}BrCl_3NO_6$ 513.9227, found 513.9235.

*4-O-Acetyl-1,6-anhydro-2-deoxy-3-O-p-chlorobenzyl-2-trichloroacetamido-β-D-glucopyranose (**13**).* Colorless oil (61 mg, 58%), $[\alpha]^{29}_D$ −42.3 (c 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3415, 2963, 2903, 1714, 1712, 1506, 1225, 1088, 1016, 817, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.24 (m, 4H, ArH), 7.11 (d, J = 9.3 Hz, 1H, NH), 5.48 (s, 1H, H-1), 4.80 (d, J = 1.3 Hz, 1H, H-4), 4.66 (ABq, J = 11.9 Hz, 2H, $ArCH_2$), 4.62 (m, 1H, H-5), 4.30 (dd, J = 7.5, 0.8 Hz, 1H, H-6a), 4.11 (dd, J = 9.5, 1.3 Hz, 1H, H-2), 3.82 (dd, J = 7.4, 5.8 Hz, 1H, H-6b), 3.40 (ddd, J = 4.4, 3.0, 1.5 Hz, 1H, H-3), 2.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C), 161.5 (C), 135.8 (C), 133.8 (C), 129.0 (CH), 128.8 (CH), 100.0 (CH), 92.4 (CH), 76.3 (CH), 73.8 (CH), 71.6 (CH_2), 70.3 (CH), 65.5 (CH_2), 49.5 (CH), 21.1 (CH_3); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{17}H_{16}Cl_4NO_6$ 469.9732, found 469.9724.

*3-O-Acetyl-1,6-anhydro-2-azido-2-deoxy-4-O-(2-naphthylmethyl)-β-D-glucopyranose (**14**).* To a solution of **5** (100 mg, 0.302 mmol, 1.0 equiv) in dry CH_2Cl_2 (1.5 mL) was added 3 Å molecular sieves (0.2 g), triethylsilane (58 μL, 0.362 mmol, 1.2 equiv) and 2-naphthaldehyde (56 mg, 0.362 mmol, 1.2 equiv) under N_2 atmosphere. The mixture was stirred for 30 min at room temperature. The mixture was cooled to −78 °C. TMSOTf (5 μL, 0.030 mmol, 0.1 equiv) was added at −78 °C and the mixture was stirred for another 30 min. Reaction was monitored by using TLC. A second portion of 2-naphthaldehyde (19 mg, 0.121 mmol, 0.4 equiv), triethylsilane (19 μL, 0.121 mmol, 0.4 equiv) and TMSOTf (5 μL, 0.030 mmol, 0.1 equiv) was added to the reacion mixture, which was further stirred for 16 h at −78 °C. The reaction was monitored by using TLC. Upon completion, the reaction was quenched with TBAF (604 μL, 0.604 mmol, 2.0 equiv) and stirred at room temperature for another 2 h. Pyridine (122 μL, 1.510 mmol, 5.0 equiv) and acetic anhydride (37 μL, 0.393 mmol, 1.3 equiv) were added sequentially, and the mixture was stirred for additional 2 h at room temperature. The reaction was monitored by TLC. Upon completion, the mixture was filtered through a Celite pad. The filtrate was evaporated and the crude was purified by column chromatography (30% ethyl acetate/hexane) to afford desired compound **14**. White solid (80 mg, 72%), $[\alpha]^{29}_D$ + 66.2 (c 1.0, $CHCl_3$); mp 92−93 °C; IR ($CHCl_3$) ν 2962, 2903, 2153, 2099, 1736, 1219, 1023, 817, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84−7.80 (m, 4H, ArH), 7.52 (dd, J = 8.4, 1.5 Hz, 1H, ArH), 7.49−7.44 (m, 2H, ArH), 5.50 (s, 1H, H-1), 5.09 (t, J = 1.4 Hz, 1H, H-3), 4.91 (ABq, J = 12.7 Hz, 2H, $ArCH_2$), 4.60 (d, J = 5.5 Hz, 1H, H-5), 3.89 (dd, J = 7.6, 0.9 Hz, 1H, H-6a), 3.71 (dd, J = 7.4, 5.8 Hz, 1H, H-6b), 3.29 (d, J = 0.76 Hz, 1H, H-4), 3.20 (s, 1H, H-2), 2.06 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (C), 134.8 (C), 133.3 (C), 133.2 (C), 128.6 (CH), 128.0 (CH), 127.8 (CH), 127.2 (CH), 126.4 (CH), 126.2 (CH), 126.0 (CH), 100.2 (CH), 74.7 (CH), 73.78 (CH), 73.77 (CH), 71.5 (CH_2), 69.6 (CH), 65.2 (CH_2), 59.1 (CH), 21.2 (CH_3); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{19}N_3O_5Na$ 392.1222, found 392.1223.

General Procedure for the Regioselective Protection of 1,6-Anhydrosugars (15 and 16). To a solution of compound **7** (100 mg, 0.222 mmol, 1.0 equiv) in dry CH_2Cl_2 (1.5 mL) was added 3 Å molecular sieves (200 mg), triethylsilane (42 μL, 0.266 mmol, 1.2 equiv) and aldehyde (0.266 mmol, 1.2 equiv) under N_2 atmosphere. The reaction mixture was stirred for 30 min at room temperature. The mixture was cooled to 0 °C. TMSOTf (4 μL, 0.022 mmol, 0.1 equiv) was added at 0 °C and the mixture was stirred for another 30 min. Reaction was monitored by using TLC. A second portion of aldehyde (0.36 equiv), triethylsilane (14 μL, 0.089 mmol, 0.4 equiv) and TMSOTf (4 μL, 0.022 mmol, 0.1 equiv) was added to the reacion mixture, which was further stirred for 5 h at 0 °C. The reaction was monitored by using TLC. Upon completion, the reaction was quenched with TBAF (444 μL, 0.444 mmol, 2.0 equiv) and stirred at room temperature for another 2 h. The reaction mixture was then filtered by passing through a short pad Celite bed. The filtrate was concentrated and purified by column chromatography (30% ethyl acetate/hexane) to afford the desired product.

*1,6-Anhydro-3-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranose (**15**).* Colorless oil (53 mg, 60%), ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 6H, ArH, NH), 5.45 (s, 1H, H-1), 4.65 (ABq, J = 12.0 Hz, 2H, $ArCH_2$), 4.51 (s, 1H, H-5), 4.30 (d, J = 7.2 Hz, 1H, H-6a), 4.13 (d, J = 9.4 Hz, 1H, H-2), 3.8 (s, 1H, H-4), 3.76 (d, J = 6.6 Hz, 1H, H-6b), 3.45 (s, 1H, H-3), 2.38 (bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6 (C), 137.5 (C), 128.6 (CH), 128.0 (CH), 127.8 (CH), 100.2 (CH), 92.4 (CH), 78.2 (CH), 76.2 (CH), 72.2 (CH_2), 69.6 (CH), 65.2 (CH_2), 49.4 (CH); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{16}Cl_3NO_5Na$ 417.9992 found 417.9999.

*1,6-Anhydro-2-deoxy-3-O-(2-naphthylmethyl)-2-trichloroacetamido-β-D-glucopyranose (**16**).* White solid (61 mg, 62%), $[\alpha]^{27}_D$ −96.6 (c 0.4, $CHCl_3$); mp 116−117 °C; IR ($CHCl_3$) ν 1373, 1317, 1094, 1013, 924, 819, 784, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82−7.81 (m, 3H, ArH), 7.77 (s, 1H, ArH), 7.48−7.44 (m, 3H, ArH), 7.30 (d, J = 9.0 Hz, 1H, NH), 5.48 (s, 1H, H-1), 4.82 (ABq, J = 12.0 Hz, 2H, $ArCH_2$), 4.53 (d, J = 5.4 Hz, 1H, H-5), 4.34 (d, J = 7.6 Hz, 1H, H-6a), 4.20 (d, J = 9.4 Hz, 1H, H-2), 3.80 (q, J = 5.8 Hz, 2H, H-4, H-6b), 3.49 (s, 1H, H-3), 2.01 (d, J = 4.2 Hz, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7 (C), 134.9 (C), 133.4 (C), 133.3 (C), 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.0 (CH), 126.4 (CH), 126.3 (CH), 125.9 (CH), 100.3 (CH), 92.5 (CH), 78.1 (CH), 76.3 (CH), 72.3 (CH_2), 69.8 (CH), 65.3 (CH_2), 49.4 (CH); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{19}H_{17}Cl_3NO_5$ 444.0172, found 444.0178.

*1,6-Anhydro-3-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranose (**17**).* Trifluoromethanesulfonic anhydride (0.12 mL, 0.726 mmol, 2.4 equiv) was added to a solution of compound **15** (120 mg, 0.302 mmol, 1.0 equiv) in pyridine (0.10 mL, 1.268 mmol, 4.2 equiv) and dry DCM (2 mL) at 0 °C. After stirring for 30 min, the reaction was monitored by TLC. Upon completion, DCM was evaporated and the crude material was used directly in the next reaction. To a solution of the crude triflate derivative in DMF (2 mL) was added sodium nitrite (0.21 g, 3.020 mmol, 10.0 equiv) at room temperature and the mixture was stirred overnight at same temperature. The reaction was diluted with water and extracted with ethyl acetate (15 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrate under a reduced pressure. The residue was purified by column chromatography (30% ethyl acetate/hexane) to give **17** as a colorless oil. Colorless oil (86 mg, 72%, over two steps), IR ($CHCl_3$) ν 2957, 2100, 1251, 1107, 1010, 839, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.3 Hz, 2H, ArH), 7.33 (t, J = 7.0 Hz, 2H, ArH), 7.27 (t, J = 7.3 Hz, 1H, ArH), 6.83 (d, J = 8.4 Hz, 1H, NH), 5.46 (s, 1H, H-1), 4.76 (ABq, J = 12.0 Hz, 2H, $ArCH_2$), 4.61 (d, J = 7.4 Hz, 1H, H-6a), 4.50 (t, J = 4.2 Hz, 1H, H-5), 4.27 (d, J = 8.4 Hz, 1H, H-2), 4.21 (t, J = 4.1 Hz, 1H, H-4), 3.75 (t, J = 6.4 Hz, 1H, H-6b), 3.68 (dd, J = 3.3, 0.97 Hz, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (C), 137.4 (C), 128.2 (CH), 127.6 (CH), 99.8 (CH), 91.9 (CH), 75.9 (CH), 75.6 (CH),

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73.3 (CH_2), 64.8 (CH_2), 54.8 (CH), 53.1 (CH); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{16}Cl_3NO_5Na$ 417.9992, found 417.9988.

*1,6-Anhydro-2-deoxy-3-O-(2-naphthylmethyl)-2-trichloroacetamido-β-D-galactopyranose (**18**).* Trifluoromethan-esulfonic anhydride (0.17 mL, 0.983 mmol, 2.2 equiv) was added to a solution of compound **16** (200 mg, 0.447 mmol, 1.0 equiv) in pyridine (0.15 mL, 1.877 mmol, 4.2 equiv) and dry DCM (2 mL) at 0 °C. After stirring for 30 min, the reaction was monitored by TLC. Upon completion, the DCM was evaporated and the crude material was used without further purification for the next reaction. To a solution of the triflate derivative in DMF (2 mL) was added sodium nitrite (0.30 g, 4.47 mmol, 10.0 equiv) at room temperature, and the mixture was stirred overnight at the same temperature. The reaction was quenched with water (15 mL) and the mixture was extracted with ethyl acetate (15 mL × 3). The layers were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated under a reduced pressure. The residue was purified by column chromatography (30% ethyl acetate/hexane) to give compound **18**. White solid (138 mg, 69% over 2 steps), $[\alpha]^{27}_D$ −100.5 (c 0.5, $CHCl_3$); mp 131−132 °C; IR ($CHCl_3$) ν 1991, 1698, 1575, 1396, 1317, 1027, 937, 820, 753 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85−7.81 (m, 4H, ArH), 7.49−7.45 (m, 3H, ArH), 6.83 (d, J = 8.5 Hz, 1H, NH), 5.44 (s, 1H, H-1), 4.91 (ABq, J = 11.7 Hz, 2H, $ArCH_2$), 4.43 (t, J = 4.6 Hz, 1H, H-5), 4.34 (d, J = 8.5 Hz, 1H, H-2), 4.31 (d, J = 7.6 Hz, 1H, H-6a), 3.9 (pentet, J = 9.4, 5.0 Hz, 1H, H-4), 3.74 (d, J = 5.3 Hz, 1H, H-3), 3.71 (t, J = 6.2 Hz, 1H, H-6b), 3.07 (d, J = 9.5 Hz, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.9 (C), 134.3 (C), 133.4 (C), 133.3 (C), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 126.5 (CH), 126.4 (CH), 125.9 (CH), 99.7 (CH), 92.1 (CH), 75.5 (CH), 75.1 (CH), 72.8 (CH_2), 64.7 (CH), 64.3 (CH_2), 51.7 (CH); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{19}H_{17}Cl_3NO_5$ 444.0172, found 444.0169.

*1,4,6-Tri-O-acetyl-3-O-benzyl-2-deoxy-2-trichloroacetamido-D-galactopyranose (**19**).* To a stirred solution of compound **17** (100 mg, 0.252 mmol, 1.0 equiv) in dry CH_2Cl_2 (1.5 mL) was added Ac_2O (238 μL, 2.52 mmol, 10.0 equiv) at room temperature. $Sc(OTf)_3$ (12.4 mg, 0.0252 mmol, 0.1 equiv) was added to the above mixture, which was stirred 4 h at room temperature. The reaction was monitored by TLC. Upon completion, the mixture was evaporated and was directly loaded on column and the chromatography (50% ethyl acetate/hexane) afforded the desired product in 95% yield.

*1,4,6-Tri-O-acetyl-3-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranose (**19β**).* Colorless oil, $[\alpha]^{29}_D$ −0.13 (c 0.6, $CHCl_3$); IR ($CHCl_3$) ν 3361, 3032, 2919, 1742, 1520, 1315, 1215, 1140, 1045, 880, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (m, 5H, ArH), 6.61 (d, J = 8.7 Hz, 1H, NH), 5.85 (d, J = 8.8 Hz, 1H, H-1), 5.56 (d, J = 3.0 Hz, 1H, H-4), 4.70 (d, J = 11.5 Hz, 1H, $ArCH_2$), 4.38 (d, J = 11.5 Hz, 1H, $ArCH_2$), 4.20 (dd, J = 11.3, 6.0 Hz, 1H, H-6b), 4.12−4.03 (m, 2H, H-2, H-6a), 3.96 (t, J = 6.7 Hz, 1H, H-5), 3.89 (dd, J = 10.8, 3.3 Hz, 1H, H-3), 2.14 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C), 170.1 (C), 169.1 (C), 162.0 (C), 136.7 (C), 128.6 (CH × 2), 128.4 (CH × 2), 128.3 (CH), 91.8 (CH), 74.7 (CH), 72.2 (CH), 71.6 (CH_2), 64.9 (CH), 61.8 (CH_2), 53.4 (CH), 20.7 (CH_3); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{24}Cl_3NO_9Na$ 562.0414, found 562.0416.

*1,4,6-Tri-O-acetyl-3-O-benzyl-2-deoxy-2-trichloroacetamido-α-D-galactopyranose (**19α**).* Colorless oil, $[\alpha]^{29}_D$ + 92.6 (c 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3361, 3032, 2919, 1742, 1520, 1315, 1215, 1140, 1045, 880, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H, ArH), 6.36 (d, J = 3.6 Hz, 1H, H-1), 6.32 (d, J = 7.4 Hz, 1H, NH), 5.62 (d, J = 2.8 Hz, 1H, H-4), 4.57 (ABq, J = 11.9 Hz, 2H, $ArCH_2$), 4.37−4.42 (m, 1H, H-2), 4.05−4.19 (m, 3H, H-5, H-6a, H-6b), 3.77 (dd, J = 11.0, 3.04 Hz, 1H, H-3), 2.15 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.04 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C), 170.2 (C), 168.4 (C), 161.8 (C), 136.8 (C), 128.7 (CH), 128.2 (CH), 128.1 (CH), 92.1 (CH), 90.2 (CH), 72.4 (CH), 70.9 (CH_2), 68.8 (CH), 64.8 (CH), 61.7 (CH_2), 50.1 (CH), 20.6 (CH_3), 20.6 (CH_3); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{24}Cl_3NO_9Na$ 562.0414, found 562.0416.

*1,4,6-Tri-O-acetyl-2-deoxy-3-O-(2-naphthylmethyl)-2-trichloroacetamido-α-D-galactopyranose (**20**).* The general procedure was similar as compound **19**. White solid (95 mg, 72%), $[\alpha]^{27}_D$ −16.75 (c 0.5, $CHCl_3$); mp 88−89 °C; IR ($CHCl_3$) ν 3311, 2923, 1507, 1472, 1396, 1224, 1017, 818, 753 cm^{-1} ; ^1H NMR (600 MHz, $CDCl_3$) δ 7.79−7.82 (m, 3H, ArH), 7.74 (s, 1H, ArH), 7.46−7.51 (m, 2H, ArH), 7.41 (dd, J = 1.4, 8.4 Hz, 1H, ArH), 6.36 (d, J = 3.7 Hz, 1H, H-1), 6.33 (d, J = 7.6 Hz, 1H, NH), 5.67 (d, J = 2.8 Hz, 1H, H-4), 4.74 (ABq, J = 12.2 Hz, 2H, $ArCH_2$), 4.44 (ddd, J = 3.8, 7.6, 11.2 Hz, 1H, H-2), 4.2−4.14 (m, 2H, H-5, H-6a), 4.08 (ddd, J = 5.4, 9.5, 17.9 Hz, 1H, H-6b), 3.82 (dd, J = 3.1, 11.1 Hz, 1H, H-3), 2.18 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.01 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7 (C), 170.4 (C), 168.6 (C), 162.0 (C), 134.7 (C), 133.3 (CH), 128.9 (CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 126.6 (CH), 126.5 (CH), 125.8 (CH), 92.3 (CH), 90.4 (CH), 72.5 (CH), 71.1 (CH_2), 69.0 (CH), 65.0 (CH), 62.0 (CH_2), 50.3 (CH), 20.9 (CH_3), 20.9 (CH_3); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{25}H_{26}NO_9Cl_3Na$ 612.0571, found 612.0578.

*1,6-Anhydro-2-azido-2-deoxy-3-O-(2-naphthylmethyl)-β-D-allopyranose (**21**).* To a solution of compound **5** (100 mg, 0.302 mmol, 1.0 equiv) in dry DCM (1.5 mL) was added 3 Å molecular sieves (0.2 g), triethylsilane (58 μL, 0.362 mmol, 1.2 equiv) and 2-naphthaldehyde (56 mg, 0.362 mmol, 1.2 equiv) under N_2 atmosphere. The reaction mixture was stirred for 30 min at room temperature. The mixture was cooled to −78 °C. TMSOTf (5 μL, 0.030 mmol, 0.1 equiv) was added at −78 °C and the mixture was stirred for another 30 min. Reaction was monitored by using TLC. A second portion of 2-naphthaldehyde (17 mg, 0.109 mmol, 0.36 equiv), triethylsilane (17 μL, 0.109 mmol, 0.36 equiv) and TMSOTf (5 μL, 0.030 mmol, 0.1 equiv) was added to the reacion mixture, which was further stirred for 16 h at −78 °C. The reaction was monitored by using TLC. Upon completion, the reaction was quenched with TBAF (604 μL, 0.604 mmol, 2.0 equiv) and stirred at room temperature for another 2 h. The reaction mixture was then filtered by passing through a short pad Celite bed. The filtrate was concentrated and purified by column chromatography (50% ethyl acetate/hexane) to afford the desired product as a colorless oil. Colorless oil (67 mg, 68%), $[\alpha]^{27}_D$ −61.47 (c 0.5, $CHCl_3$); IR ($CHCl_3$) ν 1942, 1920, 1828, 1771, 1418, 1258, 1091, 1020, 922, 818 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85−7.80 (m, 4H, ArH), 7.51−7.46 (m, 3H, ArH), 5.47 (s, 1H, H-1), 4.88 (ABq, J = 12.4 Hz, 2H, $ArCH_2$), 4.62 (d, J = 5.2 Hz, 1H, H-5), 3.94−3.91 (m, 2H, H-3, H-6a), 3.66 (dd, J = 5.4, 7.6 Hz, 1H, H-6b), 3.42 (d, J = 2.8 Hz, 1H, H-4), 3.22 (d, J = 3.1 Hz, 1H, H-2), 2.37 (d, J = 6.3 Hz, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.8 (C), 133.2 (C), 133.1 (C), 128.5 (CH), 127.8 (CH), 127.7 (CH), 126.8 (CH), 126.3 (CH), 126.1 (CH), 125.7 (CH), 101.0 (CH), 78.4 (CH), 75.1 (CH), 72.0 (CH_2), 70.5 (CH), 66.2 (CH_2), 62.7 (CH); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{17}H_{16}N_3O_4$ 326.1141, found 326.1147.

*1,6-Anhydro-2-azido-2-deoxy-4-O-(2-naphthylmethyl)-β-D-allopyranose (**22**).* Trifluoromethanesulfonic anhydride (0.22 mL, 1.346 mmol, 2.2 equiv) was added to a solution of compound **21** (200 mg, 0.612 mmol, 1.0 equiv) in pyridine (0.21 mL, 2.570 mmol, 4.2 equiv) and dry DCM (2 mL) at 0 °C. After stirring for 30 min, the reaction was monitored by TLC. Upon completion, the DCM was evaporated and the crude material was used without further purification for the next reaction. To a solution of the triflate derivative in DMF (2 mL) was added sodium nitrite (0.42 g, 6.120 mmol, 10 equiv) at room temperature, and the mixture was stirred overnight at the same temperature. The reaction was quenched with water (15 mL) and the mixture was extracted with ethyl acetate (15 mL × 3). The layers were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated under a reduced pressure. The residue was purified by column chromatography (30% ethyl acetate/hexane) to give **22** as colorless oil. Colorless oil (72 mg, 36% over 2 steps), $[\alpha]^{27}_D$ + 12.81 (c 0.5, $CHCl_3$); IR ($CHCl_3$) ν 2922, 2101, 1844, 1810, 1662, 1143, 1121, 1100, 901, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84−7.80 (m, 4H, ArH), 7.52−7.46 (m, 3H, ArH), 5.53 (s, 1H, H-1), 5.21 (s, 1H, H-4), 4.92 (ABq, J = 12.6 Hz, 2H, $ArCH_2$), 4.61 (d, J = 5.4 Hz, 1H, H-5), 3.90 (d, J = 7.5 Hz, H-6a), 3.72 (t, J = 6.4 Hz, 1H, H-6b), 3.31 (s, 1H, H-3), 3.20 (s, 1H, H-2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.4 (C), 133.1 (C), 133.1 (C), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.1

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(CH), 126.3 (CH), 126.1 (CH), 125.7 (CH), 100.0 (CH), 74.5 (CH), 73.5 (CH), 71.5 (CH_2), 69.1 (CH), 65.1 (CH_2), 58.8 (CH); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{17}N_3O_4Na$ 350.1117, found 350.1111.

*1,3-Di-O-acetyl-2-azido-2-deoxy-4-O-(2-naphthylmeth-yl)-β-D-allopyranose (**23**).* The general procedure was similar as compound **19**. Colorless oil (87 mg, 66%), IR ($CHCl_3$) ν 2924, 2108, 1652, 1602, 1340, 1214, 1160, 1008, 857, 820, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H, ArH), 8.04 (s, 1H, ArH), 7.83−7.80 (m, 4H, ArH), 7.70 (s, 1H, ArH), 7.67 (s, 1H, ArH), 7.50−7.45 (m, 3H, ArH), 7.37−7.32 (m, 2H, ArH), 6.26 (d, J = 3.6 Hz, 1H, H-1), 5.58 (d, J = 10.0 Hz, 1H, H-3), 5.55 (d, J = 8.6 Hz, 1H, H-3), 4.74 (ABq, J = 11.2 Hz, 2H, CH_2Ar), 4.34−4.19 (m, 4H, H-6a, H-6b, H-6a, H-6b), 3.98 (dt, J = 3.0, 10.0 Hz, 1H, H-5, H-5), 3.73 (t, J = 9.4 Hz, 1H, H-4), 3.69−3.68 (m, 1H, H-4), 3.47 (dd, J = 3.6, 10.6 Hz, 1H, H-2), 2.16 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 1.91 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3 (C), 168.5 (C), 168.4 (C), 159.7 (C), 159.6 (C), 134.0 (C), 133.1 (C), 133.0 (C), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 126.4 (CH), 126.3 (CH), 125.9 (CH), 92.7 (CH), 90.2 (CH), 75.1 (CH), 74.9 (CH), 74.8 (CH), 74.7 (CH), 74.1 (CH_2), 73.8 (CH), 72.0 (CH), 70.9 (CH), 62.8 (CH), 62.0 (CH_2), 60.4 (CH), 29.6 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.5 (CH_3); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{23}N_3O_7Na$ 452.1434, found 452.1428.

*1,6-Anhydro-2-deoxy-2-(2,2,2-trichloroethoxycarbo-nylamino)-β-D-glucopyranose (**24**).* In a over dried 35 mL microwave vial per-*O*-trimethylsilylated glucosamine derivative **3** (1.0 g, 2.024 mmol, 1.0 equiv) was dissolved in MeCN (20 mL), followed by the addition of 10 mol % of TMSOTf. The resulting mixture was subjected to microwave irradiation at 100 °C for 5 min. TLC confirmed the consumption of starting material. Upon completion, Amberlite 120 H^+ resin was added and the mixture was stirred for additional 10 min at room temperature. The crude reaction mixture was purified by using a short flash column on silica gel (70% ethyl acetate/hexane) to afford desired product. White solid (366 mg, 70%), $[\alpha]^{30}_D$ −14.0 (c 1.0, MeOH); mp 138−139 °C; IR ($CHCl_3$) ν 3430, 1720, 1515, 1268, 1109, 1021, 920, 712 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 5.37 (s, 1H, H-1), 4.85 (d, J = 2.4 Hz, 2H, $TrocCH_2$), 4.55 (d, J = 5.4 Hz, 1H, H-5), 4.25 (d, J = 7.2 Hz, 1H, H-6a), 3.74 (dd, J = 7.0, 6.0 Hz, 1H, H-6b), 3.69 (m, 1H, H-4), 3.66 (s, 1H, H-2), 3.61 (s, 1H, H-3); ^{13}C NMR (100 MHz, MeOH) δ 156.0 (C), 102.4 (C), 77.8 (CH), 75.6 (CH_2), 73.6 (CH), 72.5 (CH), 66.4 (CH_2), 55.3 (CH); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_9H_{11}Cl_3NO_6$ 333.9652, found 333.9655.

*1,6-Anhydro-4-O-benzoyl-2-deoxy-2-(2,2,2-trichloro-ethoxycarbonylamido)-β-D-glucopyranose (**25**).* To a stirred solution of diol **24** (100 mg, 0.297 mmol, 1.0 equiv) in dry THF (1.5 mL) was added triethylamine (207 μL, 1.485 mmol, 5.0 equiv) at room temperature. A clear solution observed after 10 min. Me_2SnCl_2 (32 mg, 0.148 mmol, 0.5 equiv) was added to the above mixture, and white suspension was observed in the reaction. To the above suspension, benzoyl chloride (44.85 μL, 0.386 mmol, 1.3 equiv) was added dropwise. The reaction mixture turned slightly pink color solution and was stirred overnight at room temperature. The reaction was monitored by TLC. The reaction was quenched with 1 N HCl and was extracted with CH_2Cl_2. The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, concentrated and chromatographed (30% ethyl acetate/hexane) to afford the desired product **25** in 95% yield. White solid (124 mg, 95%), $[\alpha]^{29}_D$ −95.4 (c 1.0, $CHCl_3$); mp 149−150 °C; IR ($CHCl_3$) ν 3430, 1720, 1515, 1268, 1109, 1021, 920, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 2H, ArH), 7.58 (t, J = 7.0 Hz, 1H, ArH), 7.44 (t, J = 7.3 Hz, 2H, ArH), 5.63 (d, J = 9.7 Hz, 1H, NH), 5.54 (s, 1H, H-1), 5.00 (s, 1H, H-4), 4.77 (d, J = 5.6 Hz, 1H, H-3), 4.70 (ABq, J = 11.5 Hz, 2H, Troc CH_2), 4.40 (d, J = 7.5 Hz, 1H, H-6a), 3.90 (d, J = 5.1 Hz, 1H, H-5), 3.87−3.83 (m, 2H, H-2, H-6b), 3.29 (bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C), 154.0 (C), 133.8 (C), 129.8 (CH), 129.7 (CH), 128.8 (CH), 101.0 (CH), 95.4 (CH), 74.9 (CH_2), 74.1 (CH), 72.5 (CH), 70.6 (CH), 66.0 (CH_2), 53.0 (CH); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{16}H_{15}NO_7Cl_3$ 437.9914, found 437.9919.

*3-O-Acetyl-1,6-anhydro-4-O-benzoyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-allopyranose (**26**).* Trifluoromethanesulfonic anhydride (85 mL, 0.5 mmol, 2.2 equiv) was added to a solution of compound **25** (100 mg, 0.227 mmol, 1.0 equiv) in pyridine (78 mL, 0.953 mmol, 4.2 equiv) and dry CH_2Cl_2 (1.5 mL) at 0 °C. After 30 min, the reaction was monitored by TLC. Upon completion, the DCM was ecaporated and the crude material used directly for the next reaction. To a solution of the triflate derivative in DMF (1 mL) was added CsOAc (871 mg, 4.54 mmol, 20.0 equiv) at room temperature and the mixture was stirred overnight at same temperature. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated under a reduced pressure. The residue was purified by column chromatography (30% ethyl acetate/hexane) to afford **26** in 75% yield.

Note: In the case of using $NaNO_2$ for the epimerization, the spots of the desired compound and starting material were very close and difficult to isolate; however the reaction with CsOAc provided good yield and purification becomes easier.

Colorless oil (82 mg, 75%), $[\alpha]^{28}_D$ + 3.0 (c 0.15, $CHCl_3$); IR ($CHCl_3$) ν 2957, 2100, 1251, 1107, 1010, 839, 748 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 2H, ArH), 7.60 (t, J = 7.4 Hz, 1H, ArH), 7.48 (t, J = 7.7 Hz, 2H, ArH), 5.61 (d, J = 10.4 Hz, 1H, NH), 5.53 (d, J = 2.5 Hz, 1H, H-1), 5.35−5.32 (m, 2H, H-3, H-4), 4.92 (d, J = 12.2 Hz, 1H, $TrocCH_2$), 4.81 (dd, J = 5.0, 1.7 Hz, 1H, H-5), 4.55 (d, J = 11.8 Hz, 1H, $TrocCH_2$), 4.28−4.24 (m, 1H, H-2), 4.03 (d, J = 8.4 Hz, 1H, H-6b), 3.86 (dd, J = 8.3, 5.4 Hz, 1H, H-6a), 1.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 165.7 (C), 154.5 (C), 133.8 (C), 129.8 (CH), 129.3 (CH), 129.0 (CH), 101.1 (CH), 74.8 (CH_2), 74.3 (CH), 70.4 (CH), 65.8 (CH_2), 63.5 (CH), 52.4 (CH), 20.7 (CH_3); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{18}Cl_3NO_8Na$ 503.9996, found 503.9985.

*1,3,6-Tri-O-acetyl-4-O-benzoyl-2-deoxy-2-(2,2,2-trichlo-roethoxycarbonylamido)-β-D-allopyranose (**27**).* To a stirred solution of compound **26** (100 mg, 0.226 mmol, 1.0 equiv) in dry CH_2Cl_2 (1.5 mL) was added Ac_2O (21 μL, 2.26 mmol, 10.0 equiv) at room temperature. $Sc(OTf)_3$ (11 mg, 0.0226 mmol, 0.1 equiv) was added to the above mixture, which was stirred overnight at room temperature. The reaction was monitored by TLC. Upon completion, the mixture was evaporated and was directly loaded on column and the chromatography (30% ethyl acetate/hexane) afforded the desired product in 92% yield. Colorless oil (112 mg, 92%), IR ($CHCl_3$) ν 3319, 2959, 1728, 1214, 1177, 1042, 1026, 821, 759, 709 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.6 Hz, 3H, ArH), (t, J = 7.5 Hz, 1H, ArH), 7.41 (t, J = 7.8 Hz, 3H, ArH), 6.20 (d, J = 4.1 Hz, 1H, H-1α), 5.96 (d, J = 8.1 Hz, 1H, H-1β), 5.80−5.78 (m, 2H, H-3α, H-3β), 5.27−5.19 (m, 3H, H-4a, H-4b, H6aα), 4.83 (d, J = 12.0 Hz, 1H, Troc CH_2), 4.71 (d, J = 9.8 Hz, 1H, Troc CH_2), 4.60 (d, J = 12.0 Hz, 1H, Troc CH_2), 4.43−4.38 (m, 1H, H-2α), 4.33−4.18 (m, 6H, H-2β, H-5β, H-6aβ, H-6bβ, H-5α, H-6α), 2.18 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.12 (s, 3H, CH_3 × 2), 2.03 (s, 3H, CH_3), 2.01 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C), 169.7 (C), 169.5 (C), 169.3 (C), 168.9 (C), 164.7 (C), 164.5 (C), 153.8 (C), 153.6 (C). 133.6 (C), 129.8 (CH), 129.5 (CH), 128.9 (CH), 128.6 (CH), 95.3 (CH), 91.5 (CH), 89.4 (CH), 75.0 (CH2), 74.8 (CH2), 71.6 (CH), 69.0 (CH), 68.0 (CH), 67.1 (CH), 66.5 (CH), 62.4 (CH_2), 62.1 (CH_2), 51.9 (CH), 49.2 (CH), 21.0 (CH_3), 20.9 (CH_3 × 2), 20.7 (CH_3), 20.6 (CH_3); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{24}NO_{11}NaCl_3$ 606.0313, found 606.0305.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02038.

^1H and ^{13}C NMR and HRMS spectra of all new compounds (PDF)

Crystallographic data for **7** (CCDC 1498510) (CIF)

Crystallographic data for **11** (CCDC 1498511) (CIF)

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Crystallographic data for **14** (CCDC 1498512) (CIF)

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Notes

The authors declare no competing financial interest.

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