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

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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 O1 and O6 protection, and the differentiation between O3 and O4 can be well-controlled by the N2 functionality because of the hydrogen bonding between N2 and O4. Epimerization of O4 afforded the galactosamine derivative and that of O3 yielded allosamine.

2-Acetamido-2-deoxy-D-glucose (p-GlcNAc) and 2-acetamido-2-deoxy-D-galactose (p-GalNAc) are the most abundant types of 2-amino-2-deoxyhexose in nature. They are found in oligosaccharides and glycoconjugates, such as glycolipids, peptidoglycans, glycoproteins, and glycosaminoglycans. Their N-acetylated and sulfonated derivatives are widely distributed in type A blood group antigen, GPI anchors, and lipopolysaccharides. p-GlcnAc is inexpensive and can be commercially purchased in large quantities. 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. 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 allosaminid in 1986, and the allosamine core is an indispensable component in streptothricin antibiotic.

Hydrolysis of chondroitin sulfate under acidic condition is the major source of D-galactosamine. Several methods have been reported for the synthesis of D-galactosamine, including the extension of D-lyxose chain, epimerization of C4 of D-glucosamine, addition of ammonia to 1,6,2,3-dianhydro-β-D-talopyranose, and azidonitration. The addition of nitrosyl chloride to tri-O-acetyl-D-galactal followed by the reduction of oxime also yields galactosamine. 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. Allosamine is a C3 epimer of glucosamine. This rare amino sugar is not commercially available; it exerts insecticidal activity through the inhibition of ecdysis. Various mechanisms have been reported for the synthesis of this rare sugar, including the elongation of ribose chain, hydrolysis of oxazoline, inversion at C-3 via the Mitsunobu approach, diazotransfer followed by inversion of O3, and stereoselective formation of imine followed by reduction. However, these approaches result in low stereoselectivity and poor yields.

The preparation of sugar building blocks generally entails laborious anomerization, which is 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 with no additional or excessive reagents.

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required, therefore, the traditional anomeric and primary O6 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. Recently, we developed a microwave-assisted method for the synthesis of 1,6-anhydro sugars from free sugars using TMSOTf and TIOH as a catalyst in moderate to good yields. 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 in 85%, 70%, and 70% yields, respectively (Scheme 1). The 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] bicyclic skeleton of 1,6-anhydroglucosamine derivatives greatly simplifies the complexity of the glucosamine molecules by eliminating the problems of anomers and simultaneously obviating two protecting groups on the O1 and O6. In addition, the axial orientation of the equatorial bonds projects NHtca and O4 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 O4 oxygen atoms.

X-ray crystallographic analysis (Figure 1) revealed that the distance between O4 → C2 amide proton is 2.325 Å and O4 → C2 nitrogen atom is 2.899 Å, indicating a strong hydrogen bonding. Thus, O4 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 O3 and O4. Utilizing these factors facilitates the differentiation of O3 and O4 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 O3, but those without the N−H bond, such as azido group, would likely favor the O4 because of the steric hindrance between O3 and C6−O6 bond.

To synthesize galactosamine derivatives, our protocol involved the formation of 1,6-anhydro sugar followed by the reductive etherification at O3 and epimerization of O4. To differentiate O3 and O4, we performed the reductive etherification reaction of compound 7 using our established protocol. 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.

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 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 O3 is more reactive than O4.

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 O4 and C2 N−H lowers the nucleophilicity of O4 and renders O3 more reactive despite the steric hindrance between O3 and C6−O6 bond. This protocol

![Scheme 1. Microwave-Assisted Synthesis of 1,6-Anhydroglucosamine](image1)

![Table 1. Optimization of the Regioselective Protection of 7](image2)

![Scheme 2. Regioselective Reductive Etherification of 7 by Using Various Aryl Aldehydes](image3)
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 O4 → N1 of C2 azide elongated to 3.439 Å because of the 1,3-diaxial repulsion.

Without the hydrogen bonding that greatly deactivates the C4 hydroxyl group, O4 is more reactive than the sterically and conformationally more hindered O3 toward the regioselective reductive etherification (Scheme 3). The inductive effect of the azide group must also enhance the regioselectivity by lowering the nucleophility of O3. To further verify this hypothesis, we repeated the reductive etherification by replacing the C2 NHHTCA 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 C4 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 C3 and C4 hydroxyl groups can be controlled on the basis of N-functionalization. This enabled us to efficiently differentiate O3 and O4 to synthesize partially protected galactosamine and allosamine derivatives by epimerizing C4 and C3, 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 product into its acetylated derivative. The 1,6-anhydro-ring of 5 was regioselectively protected with 2-NAP group. The sterically crowded hydroxyl group of 21 was converted to a triolate using triflic anhydride and pyridine. However, its epimerization using NaNO2 in DMF provided only 36% yield of 22, whereas 17% of the triolate 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 NaNO2 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 C4 hydroxyl group when the C2 amine contains an N−H (Scheme 6) that was applied for the synthesis of 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 Me3SnCl2, and afforded 25 in an excellent 95% yield after overnight stirring at room temperature. The triflation of 25 using Tf2O and pyridine followed by the epimerization using CsOAc in DMF resulted in 75% of 26. The 1,6-anhydro-ring opening using Ac2O 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 C3 and C4 secondary hydroxyl groups can be...
controlled by the presence/absence of hydrogen bonding between the O4 and the C2 amine functionality. The synthesis of a galactosamine derivative, including regioselective protection of 1,6-anhydroglucosamine, C4-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 C4 regioselective reductive etherification or the regioselective tin-mediated benzylation 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 purification system filled with anhydrous Al2O3. 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 precoated glass plates of Silica Gel 60 F254 (0.25 mm); detection was executed by spraying a solution of Ce(NO3)3(5%) in MeOH. Preparative TLC was carried out on precoated glass plates of Silica Gel 60 F254 (0.25 mm) under UV light. Specific rotations were taken at ambient temperature conditions and reported in °D as the specific rotation at 589 nm.

**General Procedure for the Microwave Assisted Synthesis of 1,6-Anhydro sugars (5–7).** In a dried 35 mL microwave vial, the per-O-trimethylsilylelated glucosamine (2.025 mmol, 1.0 equiv) was dissolved in MeCN (20 mL), followed by the addition of TMSCl (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 (0.45 mL, 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 (30% ethyl acetate/hexane) to afford the desired compound.

**4-0-Acetyl-1,6-anhydro-2-deoxy-3-O-(2-naphthylmethyl)-2-trichloroacetamido-β-D-glucopyranose (B).** White solid (68 mg, 63%), [α]259 −397 (c 1.0, CHCl3); mp 212–212 °C; IR (CHCl3) ν 3411, 2960, 2972, 1714, 1508, 1281, 1137, 1020, 789, 704 cm⁻¹; 1H NMR (400 MHz, CDCl3) 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 (J1 = 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), 2.93 (s, 1H, H-2), 0.16 (s, 9H), 0.13 (s, 9H); 13C NMR (100 MHz, CDCl3) δ 110.1 (CH1), 77.2 (CH2), 73.3 (CH3), 72.6 (CH3), 65.3 (CH2), 65.3 (CH2), 0.18 (CH1), 0.12 (CH1); HRMS (ESI-TOF) m/z [M + Na]⁺ calculated for C21H21Cl3NO5SiNa 848.0278, found 848.0270.

**4-O-Acetyl-1,6-anhydro-2-deoxy-3-O-p-methoxybenzyl-2-trichloroacetamido-β-D-glucopyranose (10).** Colorless oil (69 mg, 66%), [α]259 −16.4 (c 0.3, CHCl3); IR (CHCl3) ν 3412, 2957, 2905, 1715, 1512, 1228, 1035, 889, 789, 704 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.25 (dd, J = 11.6, 2.6 Hz, 2H, ArH), 7.10 (d, J = 9.4 Hz, 1H, H-5), 6.86 (dd, J = 9.4, 3.0 Hz, 2H, ArH), 5.46 (s, 1H, H-1), 4.78 (bs, 1H, H-4), 4.62 (ABq (J1 = 11.5 Hz, 2H, ArH), 4.62 (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, OCH3), 3.40 (bs, 3H, H-3), 2.08 (s, 3H, CH3); 13C NMR (100 MHz, CDCl3) δ 169.4 (C), 161.2 (C), 159.6 (C), 129.4 (C), 129.3 (C), 114.0 (C), 100.2 (C), 76.0 (CH2), 73.8 (CH2), 72.1 (CH2), 70.5 (CH2), 65.5 (CH2), 55.4 (CH2), 49.7 (CH2), 21.1 (CH2); HRMS (ESI-TOF) m/z [M - H]⁻ calculated for C23H21Cl3NO5SiNa 846.0278, found 846.0270.
5.47 (s, 1H, H-1), 4.80 (s, 1H, H-4), 4.69 (Abq, J = 11.8 Hz, 2H, ArCH₂), 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, CH₃); ¹³C NMR (100 MHz, CDCl₃) 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), 49.7 (CH), 21.1 (CH₃); HRMS (ESI-TOF) m/z [M – H⁻] calcd for C₂₁H₂₄Cl₂NO₅ 444.0441, found 444.0444.

4-O-Acetyl-1,6-anhydro-2-deoxy-3-O-p-chlorobenzyl-2-trichloroacetamido-β-D-glucopyranose (12). Colorless oil (71 mg, 62%), [α]°D −44.8 (c 1.0, CHCl₃); IR (CHCl₃) ν 3410, 2956, 1737, 1515, 1378, 1353, 1236, 1152, 1015, 922, 824, 753 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.69 (t, J = 4.2 Hz, 2H, ArH), 7.41 (t, J = 4.0 Hz, 1H, ArH), 7.22 (t, J = 4.0 Hz, 1H, ArH), 7.17 (t, J = 4.0 Hz, 1H, ArH), 7.20 (d, J = 11.7 Hz, 2H, ArH), 7.10 (d, J = 9.5 Hz, 1H, NH), 3.48 (bs, 1H, H-1), 4.80 (m, 1H, H-4), 4.65 (Abq, J = 12.8 Hz, 2H, ArCH₂), 4.62 (m, 1H, H-5), 3.40 (dd, J = 7.5, 0.85 Hz, 1H, H-6a), 4.11 (dd, J = 9.4, 1.2 Hz, H-2, H-3), 3.81 (dd, J = 7.5, 5.8 Hz, 1H, H-6b), 3.40 (dd, J = 4.4, 3.0, 1.6 Hz, 1H, H-3), 2.09 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.4 (C), 161.5 (C), 135.8 (C), 133.8 (C), 129.0 (CH), 128.8 (CH), 100.0 (CH₂), 92.4 (CH), 76.3 (CH), 71.6 (CH), 70.3 (CH), 65.5 (CH), 49.5 (CH), 21.1 (CH₃); HRMS (ESI-TOF) m/z [M – H⁻] calcd for C₂₁H₂₄Cl₂NO₅Na 473.9711, found 474.0047.

4-O-Acetyl-1,6-anhydro-2-deoxy-3-O-p-bromobenzyl-2-trichloroacetamido-β-D-glucopyranose (14). Colorless oil (51 mg, 58%), [α]°D −32.8 (c 1.0, CHCl₃); IR (CHCl₃) ν 3410, 2957, 1736, 1505, 1225, 1087, 717, 589 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.63–7.24 (m, 4H, ArH), 7.11 (d, J = 13.1 Hz, 1H, NH), 5.48 (s, 1H, H-1), 4.80 (d, J = 13.1 Hz, 1H, H-4), 4.66 (Abq, J = 11.9 Hz, 2H, ArCH₂), 4.62 (m, 1H, H-5), 4.30 (d, J = 7.5, 0.85 Hz, 1H, H-6a), 4.11 (dd, J = 9.5, 1.3 Hz, 1H, H-2, H-3), 3.82 (dd, J = 7.4, 5.8 Hz, 1H, H-6b), 3.40 (dd, J = 4.4, 3.0, 1.5 Hz, 1H, H-3), 2.09 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.5 (C), 161.5 (C), 135.8 (C), 133.8 (C), 129.0 (CH), 128.8 (CH), 100.0 (CH₂), 92.4 (CH), 76.3 (CH), 71.6 (CH), 70.3 (CH), 65.5 (CH), 49.5 (CH), 21.1 (CH₃); HRMS (ESI-TOF) m/z [M – H⁻] calcd for C₂₁H₂₄Cl₂NO₅Na 496.9732, found 496.9774.

3-O-Acetyl-1,6-anhydro-2-deoxy-4-O-(2-naphthylmethy lamino)-β-D-glucopyranose (16). To a solution of 5 (100 mg, 0.302 mmol, 1.0 equiv) in dry CH₂Cl₂ (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 N₂ 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. The reaction was monitored by 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 reaction 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.
column chromatography (30% ethyl acetate/hexane) to give
(CH), 75.5 (CH), 75.1 (CH), 72.8 (CH2), 64.7 (CH), 64.3 (CH2),
\[\nu\] (CHCl3) (238 \, \text{cm}^{-1}; \, \text{J} = 6.1, 5.4, 9.6, 12.3, 15.7, 18.9 \text{ Hz}, \, \text{H} - \text{H}, \, \text{H}, \, \text{H}, \, \text{H}, \, \text{H}, \, \text{H}) \), 3.71 (t, \, \text{J} = 5.3 \text{ Hz}, 1H, H-3), 3.74 (d, \, \text{J} = 5.3 \text{ Hz}, 1H, H-3), 3.71 (t, \, \text{J} = 6.2 \text{ Hz}, 1H, H-2), 3.70 (d, \, \text{J} = 9.5 \text{ Hz}, 1H, H-1); 13C NMR (150 MHz, CDCl3) δ 161.9 (C), 134.3 (C), 133.4 (C). 128.9 (C), 128.3 (C), 127.9 (C), 126.5 (C), 126.4 (C), 125.9 (C), 97.8 (7C), 92.1 (7C), 75.5 (CH), 75.1 (CH), 72.8 (CH), 64.7 (CH), 64.3 (CH), 51.7 (C). HRMS (ESI-TOF) m/z [M - Na]+ calculated for C33H30ClNO3Na, 542.1509, found 542.1508.

1,4,6-Tri-O-acetyl-3-O-benzyl-2-deoxy-2-trichloroaacetamido-\beta-D-galactopyranose (19j). Colorless oil, \([\alpha]_D^{27} = -0.13 (c, 0.6, \text{CHCl3})
\]
IR (CHCl3) \(\nu\) 3361, 3032, 2919, 1742, 1520, 1315, 1215, 1140, 1045, 880, 728 \text{ cm}^{-1}; 1H NMR (400 MHz, CDCl3) δ 7.85–7.81 \text{ (m}, 4H, ArH), 7.49–7.45 \text{ (m}, 3H, ArH), 6.83 (d, \, \text{J} = 8.5 \text{ Hz}, 1H, ArH), 6.54 (s, 1H, H-6a), 6.50 (d, \, \text{J} = 7.7 \text{ Hz}, 1H, ArH), 6.28 (d, \, \text{J} = 8.6 \text{ Hz}, 1H, ArH), 6.14 (d, \, \text{J} = 11.5 \text{ Hz}, 1H, ArH), 4.30 (dd, \, \text{J} = 11.3, 6.0 \text{ Hz}, 1H, H-6b), 4.12–4.03 (m, 2H, H-2, H-3a), 3.69 (s, 2H, CH2), 2.14 (s, 3H, CH3), 2.07 (s, 3H, CH3), 2.05 (s, 3H, CH3); 13C NMR (100 MHz, CDCl3) δ 170.4 (C), 170.1 (C), 169.1 (C), 162.0 (C), 136.7 (C), 128.6 (CH2 x 2), 128.4 (CH2 x 2), 128.3, 91.8 (CH3), 74.7 (CH2), 72.2 (CH2), 71.6 (CH2), 64.9 (CH2), 61.8 (CH2), 53.4 (CH), 20.7 (CH); HRMS (ESI-TOF) m/z [M + Na]+ calculated for C31H28Cl3NO3Na, 516.1414, found 516.1412.

1,4,6-Tri-O-acetyl-3-O-benzyl-2-deoxy-2-trichloroaacetamido-\alpha-D-galactopyranose (19f). Colorless oil, \([\alpha]_D^{27} = 92.6 (c, 1.0, \text{CHCl3})
\]
IR (CHCl3) ν 3361, 3032, 2919, 1742, 1520, 1315, 1215, 1140, 1045, 880, 728 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.35–7.24 (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-1), 4.70 (d, J = 11.5 Hz, 1H, ArCH₂), 4.15 (d, J = 11.5 Hz, 1H, ArCH₂), 4.20 (dd, J = 11.3, 6.0 Hz, 1H, H-6b), 4.12–4.03 (m, 2H, H-2, H-3a), 3.69 (s, 2H, CH₂), 2.14 (s, 3H, CH₃), 2.07 (s, 3H, CH₃), 2.05 (s, 3H, CH₃); 13C NMR (100 MHz, CDCl₃) δ 170.4 (C), 170.1 (C), 169.1 (C), 162.0 (C), 136.7 (C), 128.6 (CH₂ x 2), 128.4 (CH₂ x 2), 128.3, 91.8 (CH₃), 74.7 (CH₂), 72.2 (CH₂), 71.6 (CH₂), 64.9 (CH₂), 61.8 (CH₂), 53.4 (CH), 20.7 (CH); HRMS (ESI-TOF) m/z [M + Na]⁺ calculated for C₃₁H₂₈Cl₃NO₃Na, 516.1414, found 516.1412.

1,4,6-Tri-O-acetyl-2-deoxy-3-O-(2-naphthylmethyl)-2-trichloroaacetamido-\alpha-D-galactopyranose (20). The general procedure was similar as compound 19. White solid (95 mg, 72%), \([\alpha]_D^{27} = -16.75 (c 0.5, \text{CHCl₃})
\] mp 88–89 °C; IR (CHCl₃) ν 3311, 2922, 2101, 1844, 1810, 1662, 1143, 1121, 1100, 753 cm⁻¹; 1H NMR (600 MHz, CDCl₃) δ 7.79–7.72 (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 = 6.7 Hz, 1H, NH), 5.67 (d, J = 2.8 Hz, 1H, H-4), 4.74 (Abq, J = 12.2 Hz, 2H, ArCH₂), 4.45 (t, J = 9.3 Hz, 1H, H-1), 4.14 (d, J = 2.0 Hz, H-6a, H-6b), 4.08 (ddd, J = 5.4, 9.5, 17.9 Hz, 1H, NH-H), 3.82 (dd, J = 3.1, 11.1 Hz, H-3H), 2.18 (s, 3H, CH₃), 2.06 (s, 3H, CH₃), 2.01 (s, 3H, CH₃); 13C NMR (150 MHz, CDCl₃) δ 170.7 (C), 170.4 (C), 168.6 (C), 162.0 (C), 134.7 (C), 133.7 (C), 128.9 (C), 128.0 (C), 127.9 (C), 126.7 (C), 126.5 (C), 125.8 (C), 92.3 (C), 90.4 (C), 72.5 (C), 71.1 (C), 69.0 (C), 62.0 (C), 50.3 (C), 20.9 (C), 20.9 (C); HRMS (ESI-TOF) m/z [M + Na]⁺ calculated for C₃₂H₂₁NO₃NaCl₂, 612.0571, found 612.0576.
3-O-Acetyl-1,6-anhydro-4-O-benzoyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-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 (76 mL, 0.935 mmol, 4.2 equiv) and dry CH$_2$Cl$_2$ (1.5 mL) at 0 °C. After 30 min, the reaction was monitored by TLC. Upon completion, the DCM was evaporated and the crude material used directly for the next reaction. To a solution of the trflate derivative in DMF (1 mL) was added CsOAc (871 mg, 4.54 mmol, 20 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 x 3). The organic layers were combined, dried over anhydrous MgSO$_4$, 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.

7.37

333.9655.

m

13C NMR (150 MHz, CDCl$_3$) δ 169.6 (C), 165.7 (C), 154.5 (C), 133.8 (C), 129.8 (C), 129.3 (CH), 129.0 (CH), 101.1 (CH), 74.8 (CH), 74.3 (CH), 70.4 (CH), 65.8 (CH), 63.5 (CH), 52.4 (CH), 207 (CH); HRMS (ESI-TOF) m/z [M + Na$^+$] calc for C$_{17}$H$_{17}$N$_3$O$_4$Na 350.1196, found 350.1191.
Crystallographic data for 14 (CCDC 1498512) (CIF)

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**Notes**

The authors declare no competing financial interest.

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