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Regioselective Manipulation of GlcNAc Provides Allosamine, Lividosamine, and Related Compounds

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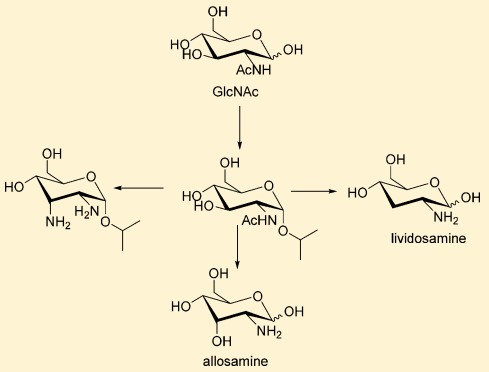
Supporting Information

ABSTRACT: Palladium-catalyzed oxidation of isopropyl *N*-acetyl-α-D-glucosamine (GlcNAc) is used to prepare the rare sugars allosamine, lividosamine, and related compounds with unprecedented selectivity. The Passerini reaction applied on 3-keto-GlcNAc provides an entry into branching of the carbon skeleton in this compound.



INTRODUCTION

The hexoses glucose, galactose, mannose, glucosamine, and rhamnose are commonly found in nature. They are part of various O- and N-glycosylated proteins, glycolipids, and glycans. Besides these hexoses, a large variety of rare sugars have been isolated from natural sources. Altrose, allose, and talose configured monosaccharides have been found in natural products of bacteria in particular. Often these rare monosaccharides are also deoxygenated on one or multiple positions, contain amino groups, and/or have a branched carbon skeleton.[1] The biological activity of the natural products containing rare sugars necessitates the development of synthesis routes that provide access to these sugars. These less frequently occurring monosaccharides are generally prepared from the readily available hexoses glucose, galactose, mannose, and rhamnose.[2] This nearly invariably comprises a strategy that protects all-but-one hydroxyl groups, followed by manipulation of the hydroxy group singled out, and finally deprotection. Over the years this approach has reached a high level of sophistication.[3−5] Inversion of stereocenters has been achieved by converting the singled out hydroxy group into the sulfonate ester and subsequent nucleophilic substitution in S_N2-type fashion or by oxidation and subsequent stereoselective reduction.[6a−d] Preparation of deoxysugars from protected carbohydrates involves either treatment of the corresponding sulfonate ester[7−9] (mesylate, tosylate, but preferably triflate) with reactive hydride donors, radical reduction of the corresponding halogen derivative or xanthate, or desulfurization of the corresponding thiosugar.

The protecting group strategy has also been used to convert glucosamine into allosamine; the C3-epimer of glucosamine, and lividosamine, that is C3-deoxy glucosamine. Both aminosugars, even though less frequently encountered in nature than glucosamine, galactosamine, and mannosamine, are certainly relevant. Allosamine forms the core component of the Chitinase inhibitor allosamidin.[10] Lividosamine is part of the aminoglycosides lividomycin-A and -B and is a precursor for the antibiotic thienamycin.[11,12] As a building block for novel antibiotics and inhibitors,[13,14] ready access is highly relevant all the more so because allosamine and lividosamine are not commercially available. A downside of the reported routes is that even for these apparently simple transformations, epimerization of the hydroxyl group at C3 and deoxygenation, the number of reaction steps, often involving purification, is already considerable.

With the current state of homogeneous catalysis, the development and application of so-called site-selective catalysis to prepare less accessible saccharides is an attractive strategy, also to avoid the use of protecting groups.[15] We and Waymouth's group have shown that site-selective palladium-catalyzed oxidation of unprotected carbohydrates,[16−21] including glucose and *N*-acetyl glucosamine (Scheme 1), is highly efficient. The formed carbonyl function at C3 should be amendable to several transformations without the requirement to protect the remaining hydroxyl groups, though not at all a trivial task considering the tendency of the carbonyl group to enolize or form the corresponding hydrate. Nevertheless, we considered this development an opportunity to gain a more efficient access to allosamine and lividosamine as well as related diaminosugars and branched aminosugars that are found in nature, mainly in bacteria.

We present here a route that is significantly more efficient, as it makes protection of the C4 and C6 hydroxy groups obsolete.

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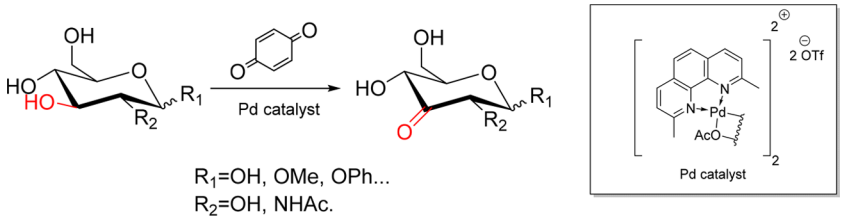
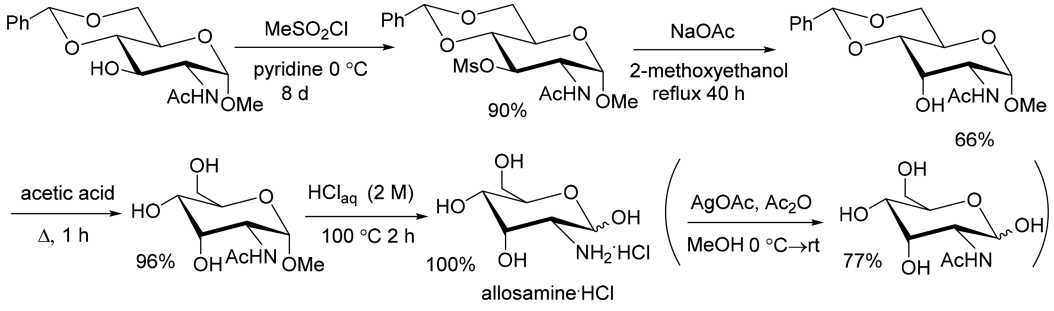
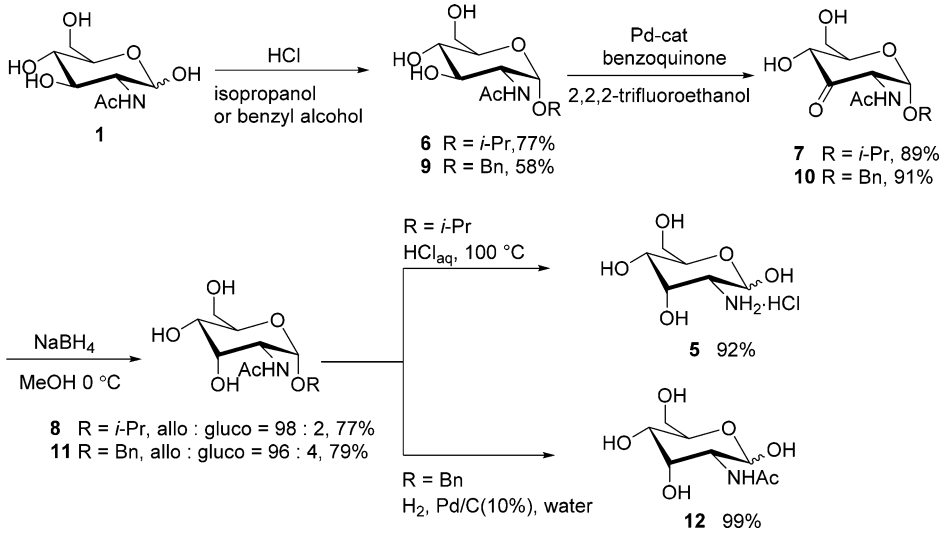
Scheme 1. Site-Selective Palladium-Catalyzed Oxidation of Unprotected Carbohydrates



Scheme 2. Jeanloz Synthesis of D-Allosamine and D-*N*-Acetyl Allosamine



Scheme 3. Synthesis of D-Allosamine and *N*-Acetyl-D-allosamine



This approach is also used in a more efficient synthesis of lividosamine and an example of the use of unprotected carbohydrates in the Passerini multicomponent reaction.

RESULTS AND DISCUSSION

To prepare allosamine, Jeanloz et al. inverted the stereocenter at C3 in GlcNAc (Scheme 2).[22] First GlcNAc was converted into methyl-GlcNAc, and subsequently into its 4,6-benzylidene derivative. Mesylation at C3 in a slow reaction is then followed by S_N2-substitution with acetate and hydrolysis to provide methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside. Hydrolysis of the benzylidene group results in methyl *N*-acetyl-α-D-allosamine. Finally, hydrolysis with aqueous hydrochloric acid provides allosamine. Alternatively, treatment with silver acetate in acetic anhydride leads to *N*-acetyl-D-allosamine. Even though this route reported by Jeanloz in 1957 is laborious, it still appears to be the method of choice. The alternative routes to prepare allosamine that have been reported over the years occasionally have comparable or somewhat higher yields, but the step-count is invariably higher also because the required starting materials are not available and therefore have to be prepared.[23−25]

For the synthesis of lividosamine, GlcNAc is deoxygenated at C3. Arguably the most efficient procedure to lividosamine (2,3-dideoxy-2-aminoglucose) currently is the approach reported by Zhao et al.[26] GlcNAc is converted into the corresponding isopropylidene protected furanosyl oxazoline, and the C3 hydroxy group is converted into a xanthate, followed by radical deoxygenation with Bu_3SnH, and finally hydrolysis to provide lividosamine.[27a−f]

We first focused our attention on the synthesis of allosamine by site-selective oxidation followed by stereoselective reduction. Although our palladium-catalyzed oxidation is effective on the parent GlcNAc,[19] subsequent reduction with $NaBH_4$ is not selective toward *N*-acetyl allosamine, whereas reduction of the corresponding α-methyl analogue is. L-Selectride was effective for the stereoselective reduction of 3-ketoglucose,[19] but subsequent purification was not straightforward. As we desired

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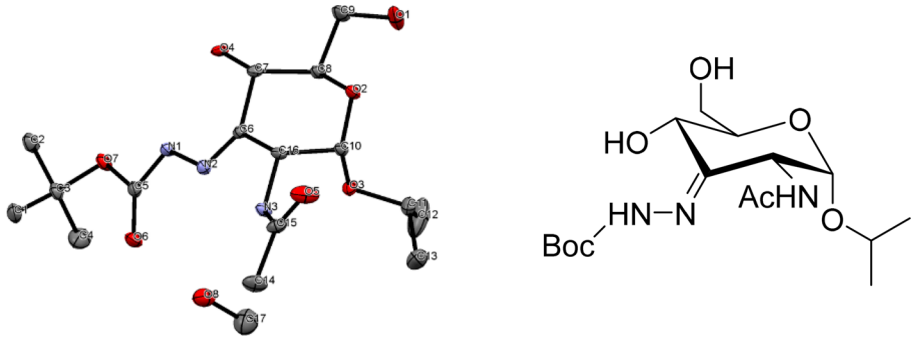
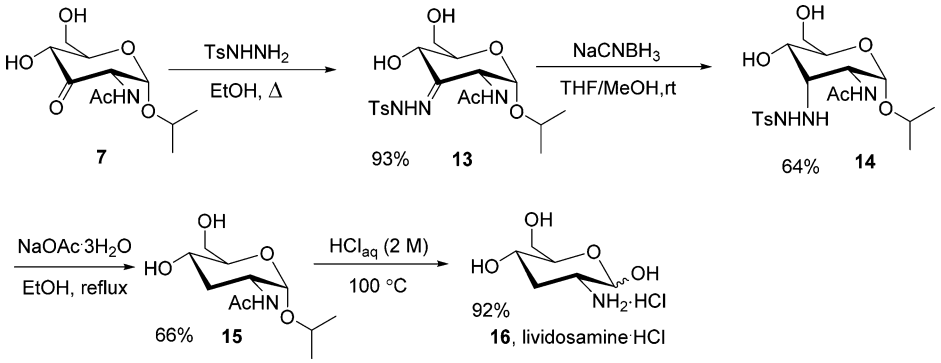
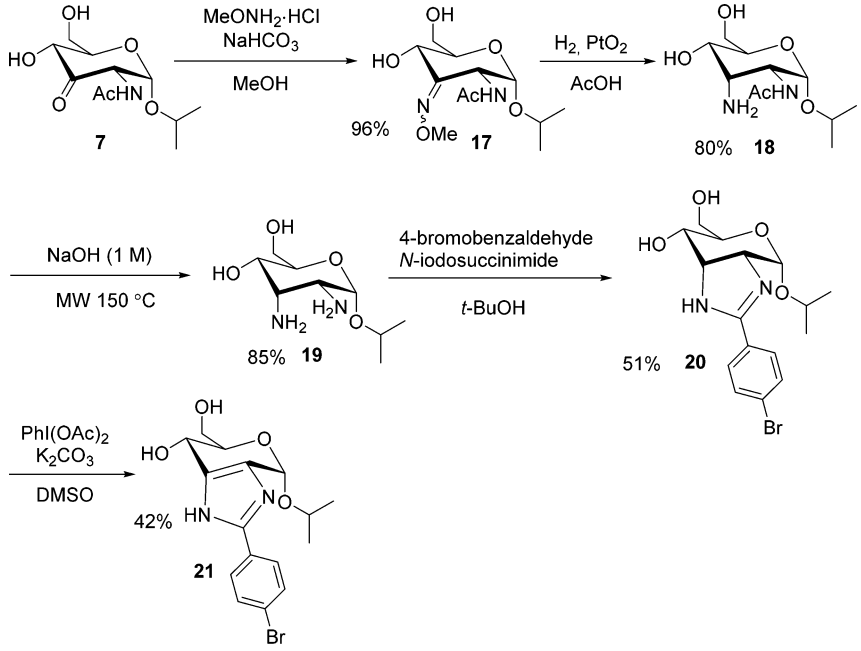


Figure 1. X-ray structure of boc-hydrazone **24**.

Scheme 4. Synthesis of D-Lividosamine



Scheme 5. Synthesis of 2,3-Di-amino Glucose and a Corresponding Fused Imidazole



preparative amounts of allosamine, the reduction of 3-keto-GlcNAc with L-selectride was discarded. Attempts to oxidize methyl α-D-glucosamine in which the amino group was protected by protonation failed; no reaction was observed.

Fischer glycosylation of GlcNAc with methanol affords an anomeric mixture with a 9.8 to 1 ratio of the α and β anomers of **2**, respectively (see SI Scheme S1 for compounds **2** and **4** and an X-ray structure of **4**), but removal of the β-anomer of **2** by column chromatography is difficult. Carrying out the reaction with isopropyl alcohol gave a comparable α to β ratio of 9 to 1, but in this case, the anomeric mixture was readily separated by column chromatography. We observed in a later stage (vide infra) that the reduction of the C3 carbonyl in the α-isopropyl analogue was slightly more stereoselective. Oxidation of the β-anomer of isopropyl *N*-acetyl-D-glucosamine and subsequent reduction was, as expected, considerably less selective and afforded a 2:1 mixture of the gluco- and allo-configured products (see SI). This observation made

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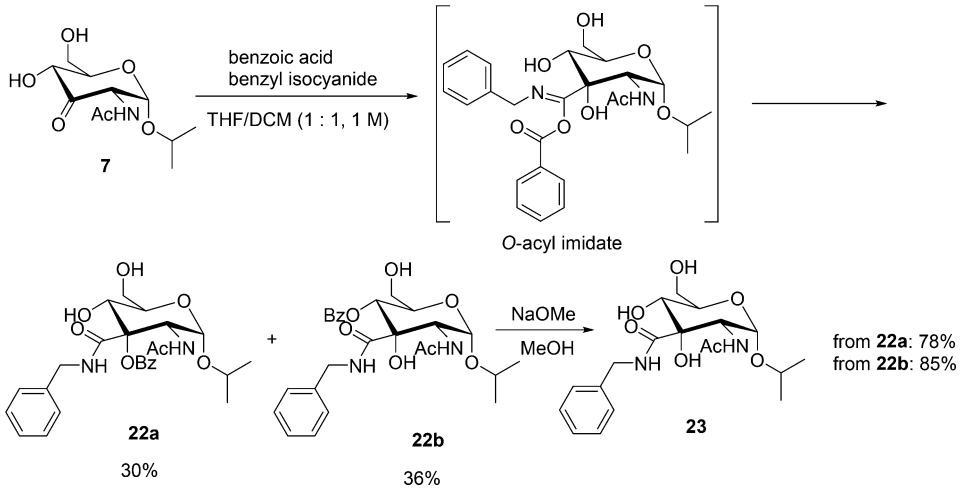
Scheme 6. Passerini Reaction with 1-Isopropyl-3-keto GlcNAc



isopropyl-α-GlcNAc **6** the starting material of choice (Scheme 3). In addition, benzyl-α-GlcNAc **9** was prepared as the benzyl substituent and can be removed with mild hydrogenolysis (Scheme 3).

Catalytic oxidation proceeded smoothly to produce ketone **7** in 89% yield. Its structure was confirmed by X-ray crystal analysis of the corresponding Boc-hydrazone **24** (Figure 1, see also SI). Trifluoroethanol was chosen as the solvent for this reaction, according to Waymouth et al.,[21] as it is more readily removed compared to DMSO. Subsequent $NaBH_4$ reduction provided isopropyl *N*-acetyl allosamine in a 98 to 2 allo to glucose ratio, the latter being readily removed by column chromatography. Hydrolysis under acidic conditions provided allosamine in 92% yield. Overall, this route provides pure allosamine in 4 steps, 49% yield, a significant improvement in yield and stepcount compared to the existing procedures; also compared to the one of Jeanloz, as in that procedure, the starting material requires an additional two steps. When the synthesis was carried out with the benzyl analogue, hydrogenolysis afforded *N*-acetyl allosamine **12** in 41% overall yield.

We next focused our attention on the synthesis of lividosamine. We reasoned that deoxygenation of the carbonyl function in **7**, in the presence of hydroxyl groups, would lead directly to isopropyl *N*-acetyl lividosamine **15**. The number of reactions that converts ketones directly into the corresponding methylene group is limited, and the most appropriate one in the current situation seemed a Caglioti-type reaction, that is, reduction of the corresponding tosylhydrazone.[28] This reaction, however, had not been applied on unprotected carbohydrates. As expected, synthesis of the tosylhydrazone was uneventful. We were pleased to see that subsequent reduction with $NaCNBH_3$ in methanol and tetrahydrofuran under slightly acidic conditions, followed by elimination with NaOAc provided **15** (isopropyl 2,3-dideoxy-2-*N*-acetyl glucosamine). Subsequent hydrolysis provided lividosamine (Scheme 4). Our route to lividosamine is not more efficient than the one of Zhao et al.,[26] but it does avoid the use of tin reagents and applies the same building block as the synthesis of allosamine.

We had shown earlier in the glucose series that reductive amination of the C3 carbonyl provides an efficient route to 3-amino glucose.[16] Here, we used this strategy on 3-keto GlcNAc **7** as well. Synthesis of the methyl oxime **17** (formed as a 1:1 mixture of *E* and *Z* isomers) was followed by hydrogenolysis/hydrogenation with Adams' catalyst and hydrogen (Scheme 5). This provided the axially oriented 3-amino group, as expected, because of the shielding by the anomeric isopropyl substituent. After hydrolysis of the acetamide, 2,3-dideoxy-2,3-diaminoallose **19** is obtained. As an illustration that this compound, next to being valuable itself, is a suitable building block for heterocycle synthesis, **19** was condensed with benzaldehyde to provide imidazoline **20**. Subsequent oxidation with PIDA provides the corresponding imidazole **21**. Remarkably, compounds with this or related scaffolds have hardly been reported[29] and are therefore a viable addition to the "chemical space" used in medicinal chemistry.

Carbon−carbon bond formation reactions involving unprotected carbohydrates have recently received attention due to the work of Mahrwald et al.[30] Our group reported on site-selective carbon−carbon bond formation in unprotected monosaccharides at C3 using photoredox catalysis that allows the formation of branched scaffolds.[31] Furthermore, we have shown that overoxidation during the palladium-catalyzed oxidation results in branched scaffolds as well.[19] Also nucleophilic attack of carbon nucleophiles at the carbonyl function in **7** falls in this class.[32−34] Here we present the use of the multicomponent Passerini reaction in this context. Treatment of **7** with benzyl isocyanide and benzoic acid in THF/DCM (1:1, 1 M) provided the expected 3-acyloxy Passerini product **22a**. NMR analysis of this product showed that it had the indicated stereochemistry. Presumably, the shielding by the anomeric isopropyl substituent blocks attack from the bottom face and thus prevents the formation of the other epimer. In addition to **22a**, we isolated a second product **22b**, which revealed to be a regioisomer of **22a** (Scheme 6). The formation of **22b** may be explained by the mechanism of Passerini reaction. During the reaction, a reactive *O*-acyl imidate intermediate is formed. This intermediate acylates a neighboring hydroxyl group. Normally, the newly formed hydroxy group is the only that qualifies for acyl transfer, but in our case, both the C3OH and the C4OH are in proximity. Hydrolysis of the product **22a** and **22b**, respectively, provided the same product **23** (Scheme 6).

CONCLUSION

Site-selective catalytic oxidation of GlcNAc is the key step in novel entries to several rare aminosugars and related building blocks. This study shows that unprotected carbohydrates, in

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the present case GlcNAc, are more amendable to selective modification and conversion than generally assumed and that with a careful selection of reaction conditions, many transformations, in the presence of several free hydroxyl groups, are possible.

EXPERIMENTAL SECTION

General Information. All solvents used for reaction, extraction, filtration, and chromatography were of commercial grade and used without further purification. [(neocuproine)Pd(μ-OAc)]$_2$(OTf)$_2$ was prepared according to the literature procedure.[35] Flash chromatography was performed on a Reveleris X2 Flash Chromatography, using Grace Reveleris Silica flash cartridges (4 g, 12 g, 15 g, 24 g, 40 g, 80 g, and 120 g) and Scorpius Diol (OH) 48 g. ^{1}H-, ^{13}C-, APT-, HSQC-, and COSY-NMR were recorded on a Varian AMX400 spectrometer (400, 100 MHz, respectively) using DMSO-d_6, D_2O, or methanol-d_4 as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (DMSO-d_6: δ 2.50 for ^{1}H, δ 39.52 for ^{13}C, CD_3OD: δ 3.31 for ^{1}H, δ 49.15 for ^{13}C; D_2O: δ 4.80 for ^{1}H). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, appt = apparent triplet, q = quartet, m = multiplet), coupling constants J (Hz), and integration. High-resolution mass measurements were performed using a Thermo-Scientific LTQ OribitrapXL spectrometer.

Compound Synthesis and Characterization. *Methyl 2-Acetamido-2-deoxy-α-D-glucopyranoside (**2**).* A suspension of *N*-acetyl glucosamine (10 g, 0.045 mol) and dry Amberlite IR 120H$^+$ (12 g) in MeOH (300 mL) was heated at reflux for 48 h. Upon cooling, the Amberlite resin was removed by filtration, and the methanol removed in vacuo to provide the product 9.98 g as a mixture of α and β, yield: 94%, as a white solid (α:β = 9.8:1). Five g of this mixture was purified by flash chromatography on a 120 g silica cartridge with DCM/MeOH, and increasing ratio of MeOH from 0 to 20% in 50 min, the product eluted at 14% MeOH to afford pure methyl 2-acetamido-2-deoxy-D-glucopyranoside as white solid (2.37 g, yield: 47%) mp 188−189 °C (lit.[36] 186−188 °C); ^{1}H NMR (400 MHz, methanol-d_4) δ 4.65 (d, J = 3.5 Hz, 1H), 3.90 (dd, J = 10.7, 3.6 Hz, 1H), 3.83 (dd, J = 11.9, 2.4 Hz, 1H), 3.69 (dd, J = 11.9, 5.7 Hz, 1H), 3.63 (dd, J = 10.7, 8.7 Hz, 1H), 3.54 (ddd, J = 10.0, 5.7, 2.4 Hz, 1H), 3.37 (s, 3H), 3.36−3.32 (m, 1H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.8, 100.0, 73.8, 73.1, 72.5, 62.9, 55.6, 55.5, 22.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_9H_{18}NO_6$ 236.1129 and $C_9H_{17}NO_6Na$ 258.0954; found 236.1132 and 258.0953.

*Methyl 2-Acetamido-2-deoxy-α-D-glucopyran-3-ulose (**3**).* Methyl 2-acetamido-2-deoxy-α-D-glucopyranoside **2** (474 mg, 2 mmol) and benzoquinone (324 mg, 3 mmol) were dissolved in DMSO (6.6 mL). The catalyst [(neocuproine)PdOAc]$_2$OTf$_2$ (57 mg, 2.5 mol %) was added, and the mixture was stirred at room temperature for 1 h. Upon completion of the reaction (according to TLC), water (70 mL) was added, and the mixture was lyophilized to afford the crude product. Subsequent purification by flash chromatography on a 12 g silica cartridge with DCM/MeOH, increasing ratio of MeOH from 0 to 7% in 21 min, the product eluted at 4% MeOH to afford a white solid (346 mg, 74%), mp 161−162 °C (lit.[36] 164 °C); ^{1}H NMR (400 MHz, Methanol-d_4) δ 5.09 (d, J = 4.1 Hz, 1H), 4.88 (dd, J = 4.1, 1.2 Hz, 1H), 4.29 (dd, J = 9.8, 1.3 Hz, 1H), 3.89 (dd, J = 12.1, 2.3 Hz, 1H), 3.82 (dd, J = 12.1, 4.6 Hz, 1H), 3.73−3.67 (m, 1H), 3.39 (s, 3H), 2.03 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 203.8, 173.7, 102.4, 77.0, 73.8, 62.6, 60.3, 55.8, 22.4; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_9H_{16}NO_6$ 234.0972 and $C_9H_{15}NO_6Na$ 256.0797; found 234.0973 and 256.0793.

*Methyl 2-Acetamido-2-deoxy-α-D-allopyranoside (**4**).* Methyl 2-acetamido-2-deoxy-α-D-glucopyran-3-ulose **3** (346 mg, 1.5 mmol) was dissolved in MeOH (12 mL), and the mixture was cooled to 0 °C. $NaBH_4$ (170 mg, 4.5 mmol) was added, and the mixture stirred for 1 h at 0 °C. Upon completion of the reaction, Amberlite 120 H$^+$ was added until pH ∼ 7, as indicated by pH paper to quench remaining $NaBH_4$. Subsequent filtration and removal of the solvent in vacuo afforded the crude product. This was purified by flash chromatography on a 12 g silica cartridge with DCM/MeOH, and increasing ratio of MeOH from 0 to 20% in 21 min, the product eluted at 10% MeOH to afford a brown oil (295 mg, 85%); the product elutes as the mixture of methyl 2-acetamido-2-deoxy-α-D-allopyranoside and methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (96:4), which is difficult to be separated by silica chromatography. ^{1}H NMR (400 MHz, methanol-d_4) δ 4.67 (d, J = 3.9 Hz, 1H), 4.05 (t, J = 3.6 Hz, 1H), 3.92 (t, J = 3.3 Hz, 1H), 3.86 (dd, J = 11.3, 1.7 Hz, 1H), 3.80−3.69 (m, 2H), 3.53 (dd, J = 9.8, 3.2 Hz, 1H), 3.40 (s, 3H), 2.01 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.1, 99.9, 71.5, 69.1, 68.3, 62.9, 56.1, 51.7, 22.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_9H_{18}NO_6$ 236.1129 and $C_9H_{17}NO_6Na$ 258.0954; found 236.1130 and 258.0950

*D-Allosamine (**5**).* Methyl 2-acetamido-2-deoxy-α-D-allopyranoside **4** (295 mg, 1.2 mmol) was dissolved in HCl_{aq} (2 M, 1.5 mL) and heated at 100 °C for 2 h. Subsequent evaporation of the volatiles provided allosamine·HCl (236 mg, 87%) as a brown syrup. Spectral data were identical to those obtained by hydrolysis of isopropyl *N*-acetyl-α-D-allosamine.

*Isopropyl 2-Acetamido-2-deoxy-α-D-glucopyranoside (**6**).* Acetyl chloride (1.93 mL, 27.12 mmol) was slowly added to a suspension of *N*-acetyl-D-glucosamine (4.0 g, 18.08 mmol) in isopropyl alcohol (160 mL) at room temperature. The suspension was subsequently heated to reflux. The solid dissolved gradually. After 2 h, reaction was finished (according to TLC). At room temperature, $NaHCO_3$ was added until pH ∼ 7, and the mixture was stirred for 1 h. Upon filtration and evaporation of the solvent, purification was carried out by flash chromatography on a 120 g silica cartridge with DCM/MeOH, and increasing ratio of MeOH from 0 to 15% in 38 min, the product eluted at 9% MeOH to afford a white solid (3.49 g, 77%), m.p.: 182−184 °C (lit.[37] 187−189 °C); ^{1}H NMR (400 MHz, methanol-d_4) δ 4.90 (d, J = 3.7 Hz, 1H), 3.93−3.76 (m, 3H), 3.71−3.61 (m, 3H), 3.37−3.32 (m, 1H), 1.97 (s, 3H), 1.22 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.7, 96.8, 73.9, 72.8, 72.6, 71.2, 62.9, 55.7, 23.8, 22.7, 21.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{11}H_{22}NO_6$ 264.1442 and $C_{11}H_{21}NO_6Na$ 286.1267; found 264.1445 and 286.1265.

*Isopropyl 2-Acetamido-2-deoxy-α-D-glucopyran-3-uloside (**7**).* Isopropyl 2-acetamido-2-deoxy-α-D-glucopyranoside **6** (3.33 g, 12.65 mmol) and benzoquinone (2.05 g, 18.97 mmol) were dissolved in 2,2,2-trifluoroethanol (126 mL). The catalyst [(neocuproine)Pd(μ-OAc)]$_2$(OTf)$_2$ (133 mg, 1 mol %) was added, and the mixture was stirred at 60 °C for 1 h. Next, the solvent was evaporated, and the crude product was purified by flash chromatography on a 80 g silica cartridge with pentane/EtOAc, and increasing ratio of EtOAc from 0 to 100%, the product eluted at 88% of EtOAc to afford a white solid (2.95 g, 89%), m.p.: 125−126 °C; ^{1}H NMR (400 MHz, methanol-d_4) δ 5.34 (d, J = 4.2 Hz, 1H), 4.86 (dd, J = 4.4, 1.3 Hz, 1H), 4.28 (dd, J = 9.0, 1.3 Hz, 1H), 3.93 (p, J = 6.2 Hz, 1H), 3.89−3.79 (m, 3H), 2.03 (s, 3H), 1.19 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 203.9, 173.5, 99.5, 77.2, 73.9, 71.8, 62.7, 60.4, 23.5, 22.4, 21.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{11}H_{20}NO_6$ 262.1285 and $C_{11}H_{19}NO_6Na$ 284.1110 ; found: 262.1287 and 284.1106.

*Isopropyl 2-Acetamido-2-deoxy-β-D-glucopyran-3-uloside (**25**).* This product was prepared as described for the α anomer starting from isopropyl 2-acetamido-2-deoxy-β-D-glucopyranoside. ^{1}H NMR (400 MHz, methanol-d_4) δ 4.66 (d, J = 8.3 Hz, 1H), 4.48 (d, J = 8.3 Hz, 1H), 4.22 (d, J = 10.1 Hz, 1H), 4.08−3.99 (m, 1H), 3.94 (dd, J = 12.3, 2.2 Hz, 1H), 3.80 (dd, J = 12.1, 5.0 Hz, 1H), 3.40−3.34 (m, 1H), 2.02 (s, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 204.2, 173.6, 102.4, 78.1, 74.2, 73.5, 62.9, 62.8, 23.8, 22.6, 22.3. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{11}H_{19}NO_6Na$ 284.1105; found 284.1108.

*Isopropyl 2-Acetamido-2-deoxy-α-D-allopyranoside (**8**).* Isopropyl 2-acetamido-2-deoxy-α-D-glucopyran-3-uloside **7** (2.0 g, 7.66 mmol) was dissolved in MeOH (50 mL), and the mixture was

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cooled to 0 °C. $NaBH_4$ (434 mg, 11.48 mmol) was added, and the mixture was stirred for 30 min at 0 °C. Upon completion of the reaction, methanolic HCl (2 M) was added slowly until pH ~ 7, as indicated by pH paper to quench remaining $NaBH_4$. The ratio of isopropyl 2-acetamido-2-deoxy-α-D-allopyranoside and isopropyl 2-acetamido-2-deoxy-α-D-glucopyranoside is approximately 98:2. Purification by flash chromatography on a 40 g silica cartridge with DCM/MeOH, increasing ratio of MeOH from 0 to 15% in 29 min, pure isopropyl 2-acetamido-2-deoxy-α-D-allopyranoside eluted at 7% MeOH to afford a white semisolid (1.56 g, 77%); ^{1}H NMR (400 MHz, methanol-d_4) δ 4.94 (d, J = 3.9 Hz, 1H), 4.02 (app t, J = 3.6 Hz, 1H), 3.98−3.91 (m, 1H), 3.89 (t, J = 3.3 Hz, 1H), 3.87−3.81 (m, 2H), 3.76−3.70 (m, 1H), 3.53 (dd, J = 10.0, 3.2 Hz, 1H), 2.02 (s, 3H), 1.26 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.2, 97.1, 72.1, 72.0, 69.4, 68.4, 62.9, 51.6, 23.8, 22.6, 21.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{11}H_{22}NO_6$ 264.1442 and $C_{11}H_{21}NO_6Na$ 286.1267; found 264.1443 and 286.1263.

*Isopropyl 2-Acetamido-2-deoxy-β-D-allopyranoside (**26**).* Isopropyl 2-acetamido-2-deoxy-β-D-glucopyran-3-uloside (**25**) was reduced as described for the α anomer. A 1 to 2 mixture of the allo and gluco configured product was obtained. ^{1}H NMR (400 MHz, methanol-d_4) δ 4.75 (d, J = 8.5 Hz, 1H), 4.02−3.91 (m, 2H), 3.84 (dd, J = 11.4, 2.0 Hz, 1H), 3.79 (dd, J = 8.5, 2.9 Hz, 1H), 3.76−3.66 (m, 1H), 3.66 (dd, J = 11.3, 5.7 Hz, 1H), 3.51 (dd, J = 9.5, 3.0 Hz, 1H), 1.98 (s, 3H), 1.19 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Methanol-d_4) δ 173.1, 99.1, 75.6, 73.0, 71.8, 68.9, 63.4, 55.0, 24.0, 22.8, 22.4. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{11}H_{21}NO_6Na$ 286.1261; found 286.1264.

*Isopropyl 2-Acetamido-2-deoxy-β-D-glucopyranoside (**27**).* ^{1}H NMR (400 MHz, methanol-d_4) δ 4.50 (d, J = 8.0 Hz, 1H), 3.96 (p, J = 6.2 Hz, 1H), 3.87 (dd, J = 11.9, 2.2 Hz, 1H), 3.68 (dd, J = 11.9, 5.6 Hz, 1H), 3.59−3.46 (m, 2H), 3.34−3.23 (m, 3H), 1.97 (s, 3H), 1.19 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.8, 101.3, 78.0, 76.1, 73.1, 72.3, 63.0, 57.9, 23.9, 23.1, 22.4.

*D-Allosamine (**5**).* Isopropyl 2-acetamido-2-deoxy-α-D-allopyranoside **8** (1.53 g, 5.81 mmol) was dissolved in HCl aq (2 M, 7.0 mL) and heated at 100 °C for 2 h. Subsequent evaporation of the volatiles provided the product (1.16 g, 92%) as a brown syrup. The product comes as a mixture of pyranose and furanose forms, the major form being the β-pyranose. The ^{1}H NMR of D-allosamine as reported in the literature[38] is in D_2O, and we found that the use of methanol-d_4 gives a much higher quality spectrum. ^{1}H NMR (400 MHz, methanol-d_4) δ 5.03 (d, J = 8.3 Hz, 1H), 4.16 (t, J = 3.0 Hz, 1H), 3.85 (dd, J = 11.7, 2.3 Hz, 1H), 3.80−3.73 (m, 1H), 3.71−3.65 (m, 1H), 3.56 (dd, J = 9.8, 2.9 Hz, 1H), 3.01 (dd, J = 8.4, 2.9 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Methanol-d_4) δ 92.6, 75.9, 69.6, 68.5, 63.0, 56.4; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_6H_{14}NO_5$ 180.0867; found 180.0868.

*Benzyl 2-Acetamido-2-deoxy-α-D-glucopyranoside (**9**).* Acetyl chloride (1.9 mL, 27.1 mmol) was slowly added to the suspension of *N*-acetyl glucosamine (4.0 g, 18.08 mmol) in benzyl alcohol (40 mL) and stirred at room temperature for 30 min. The mixture was then heated to 95 °C. After 3 h, the reaction mixture was allowed to cool down at room temperature, followed by the addition of anhydrous Na_2SO_4 (257 mg, 1.81 mmol). Subsequently the reaction was heated to 75 °C for 3 h before being cooled to room temperature. The resulting brown solution was slowly poured into Et_2O (700 mL). The precipitate was recovered by filtration and purified by flash chromatography on a 120 g silica cartridge with DCM/MeOH, and increasing the ratio of MeOH from 0 to 15% in 38 min, the product eluted at 9% MeOH to afford a white solid (3.28 g, 58%), m.p.: 175−177 °C (lit.[39] 178−180 °C); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.43−7.23 (m, 5H), 4.86 (1H, overlap with the peak of CD_3OD), 4.75 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 3.89 (dd, J = 10.7, 3.6 Hz, 1H), 3.87−3.78 (m, 1H), 3.76−3.62 (m, 3H), 3.42−3.32 (m, 1H), 1.95 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.7, 139.2, 129.5, 129.4, 129.0, 97.6, 74.2, 72.8, 72.6, 70.3, 62.9, 55.6, 22.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{15}H_{22}NO_6$ 312.1442 and $C_{15}H_{21}NO_6Na$ 334.1267; found 312.1446 and 334.1264.

*Benzyl 2-Acetamido-2-deoxy-α-D-glucopyran-3-uloside (**10**).* Benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside **9** (1.28 g, 4.11 mmol) and benzoquinone (667 mg, 6.17 mmol) were dissolved in 2,2,2-trifluoroethanol (41 mL). The catalyst [(2,9-dimethyl-1,10-phenanthroline)-Pd(μ-OAc)]$_2$(OTf)$_2$ (43 mg, 1 mol %) was added, and the mixture was stirred at 60 °C for 1 h. Subsequently the solvent was evaporated, and the crude was purified by flash chromatography on a 40 g silica cartridge with pentane/EtOAc, and increasing the ratio of EtOAc from 0 to 100% in 29 min, the product eluted at 100% EtOAc to afford a white solid (1.16 g, 91%), m.p.: 124−126 °C; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.38−7.24 (m, 5H), 5.27 (d, J = 4.2 Hz, 1H), 4.91 (dd, J = 4.2, 1.3 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.31 (dd, J = 9.4, 1.3 Hz, 1H), 3.91−3.76 (m, 3H), 2.00 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 203.7, 173.5, 138.4, 129.6, 129.5, 129.2, 100.2, 77.5, 73.9, 70.6, 62.6, 60.3, 22.4; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{15}H_{20}NO_6$ 310.1285 and $C_{15}H_{19}NO_6Na$ 332.1110; found 310.1289 and 332.1107.

*Benzyl 2-Acetamido-2-deoxy-α-D-allopyranoside (**11**).* Benzyl 2-acetamide-2-deoxy-α-D-glucopyran-3-uloside **10** (935 mg, 3.02 mmol) was dissolved in MeOH (50 mL), and the mixture was cooled to 0 °C. $NaBH_4$ (172 mg, 4.53 mmol) was added to the mixture, and the mixture was stirred for 30 min at 0 °C. Upon completion of the reaction, methanolic HCl (2 M) was added slowly until the pH reached around 7 (as indicated by pH paper) to quench remaining $NaBH_4$. The ratio of benzyl 2-acetamido-2-deoxy-α-D-allopyranoside and benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside is approximately 96:4. Subsequently, solvents were evaporated, and the crude purified by flash chromatography on a 24 g silica cartridge with EtOAc/MeOH, and increasing ratio of MeOH from 0 to 15% in 21 min, the product eluted at 7% MeOH to afford a white solid (742 mg, 79%), m.p.: 144−145 °C; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.43−7.38 (m, 2H), 7.38−7.26 (m, 3H), 4.86 (overlap with H_2O in CD_3OD, 1H), 4.78 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.06 (t, J = 3.7 Hz, 1H), 3.92 (t, J = 3.3 Hz, 1H), 3.89−3.82 (m, 2H), 3.73 (dd, J = 12.0, 5.7 Hz, 1H), 3.55 (dd, J = 10.2, 3.2 Hz, 1H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.0, 139.0, 129.6, 129.5, 129.1, 97.5, 71.6, 70.7, 69.5, 68.4, 62.9, 51.6, 22.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{15}H_{22}NO_6$ 312.1442 and $C_{15}H_{21}NO_6Na$ 334.1267; found 312.1446 and 334.1265.

*N-Acetyl-D-allosamine (**12**).* To a solution of benzyl 2-acetamido-2-deoxy-α-D-allopyranoside **11** (673 mg, 2.16 mmol) in H_2O (50 mL) was added 415 mg of 10% Pd/C (supplied by Alfa Aesar, Type 487). The atmosphere was changed to hydrogen (balloon), and the mixture was stirred overnight. The catalyst was removed by filtration, and the filtrate was concentrated to afford the product (472 mg, 99%) as a white fluffy solid. The product comes as a mixture of pyranose and furanose forms, the major form being the β-pyranose. The ^{1}H NMR is consistent with the literature;[40] ^{1}H NMR (400 MHz, D_2O) δ 4.97 (d, J = 8.7 Hz, 1H), 4.11 (t, J = 2.9 Hz, 1H), 3.91 (dd, J = 12.1, 2.2 Hz, 1H), 3.86−3.82 (m, 1H), 3.82−3.78 (m, 1H), 3.75 (dd, J = 12.6, 6.8 Hz, 1H), 3.70 (dd, J = 10.1, 3.0 Hz, 1H), 2.07 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 174.0, 92.3, 73.7, 69.6, 66.4, 61.1, 54.2, 21.8; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_8H_{15}NO_6Na$ 244.0792; found: 244.0795.

*N-((2S,3R,5S,6R,Z)-5-Hydroxy-6-(hydroxymethyl)-2-isopropoxy-4-(2-tosylhydrazono)tetrahydro-2H-pyran-3-yl)acetamide (**13**).* A mixture of isopropyl 2-acetamide-2-deoxy-α-D-ribo-hexapyranoside-3-ulose **7** (695 mg, 2.66 mmol) and *p*-toluenesulfonyl hydrazide (743 mg, 3.99 mmol) in absolute ethanol (2.6 mL) was heated at 70 °C for 3 h and stirred for 24 h at room temperature. Then acetic acid (152 μL, 2.66 mmol) was added to the reaction mixture. After 5 h, a second portion of acetic acid (152 μL, 2.66 mmol) was added, and the reaction mixture was stirred for another 24 h until the reaction completed (monitored by TLC). The solvent was evaporated, and the product was purified by flash chromatography on a 24 g silica cartridge with DCM/MeOH, and increasing the ratio of MeOH from

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0 to 4% in 22 min, the product eluted at 3% MeOH to provide a yellow oil (1.06 g, 93%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.74 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.1 Hz, 1H, −SO_2NH−), 7.38 (d, J = 8.0 Hz, 2H), 5.04 (d, J = 3.6 Hz, 1H), 4.50−4.43 (m, 2H), 3.84 (p, J = 6.2 Hz, 1H), 3.80−3.74 (m, 1H), 3.73−3.66 (m, 2H), 2.42 (s, 3H), 2.04 (s, 3H), 1.12 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.2, 173.1, 148.8, 148.7, 145.6, 137.3, 130.9, 128.7, 97.7, 75.7, 73.4, 71.7, 61.9, 55.4, 23.6, 22.6, 21.8, 21.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{18}H_{28}N_3O_7S$ 430.1643 and $C_{18}H_{27}N_3O_7SNa$ 452.1462; found 430.1640 and 452.1454.

*N-((2S,3R,4S,5S,6R)-5-Hydroxy-6-(hydroxymethyl)-2-isopropoxy-4-(2-tosylhydrazinyl)tetrahydro-2H-pyran-3-yl)acetamide (**14**).* To a stirred solution of the tosylhydrazone **13** (822 mg, 1.9 mmol) in a mixture of 1:1 THF-MeOH (15.2 mL) was added a trace of methyl orange (indicator) and sodium cyanoborohydride (120 mg, 1.9 mmol). Subsequently, methanolic HCl (2 M) was added dropwise keeping the color of the solution at the red-yellow transition point (orange, pH ∼ 3.8). The mixture was stirred at room temperature for 1 h. A second portion of sodium cyanoborohydride (60 mg, 0.95 mmol) was added, followed by the dropwise addition of methanolic HCl (2 M) to maintain the pH at ∼3.8. The mixture was then stirred at room temperature at pH ∼ 3.8 for 1 h. $NaHCO_3$ was added to the mixture until pH ∼ 7, filtered, and concentrated in vacuo at 40 °C. The residue was purified by flash chromatography on a 24 g silica cartridge with DCM/MeOH, and increasing the ratio of MeOH from 0% to 4% in 22 min, the product eluted at 3% of MeOH to afford a yellow oil (519 mg, 64%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.81 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.5 Hz, 1H, −SO_2NH−), 7.42 (d, J = 8.0 Hz, 2H), 4.78 (d, J = 3.6 Hz, 1H), 3.93 (dt, J = 8.5, 4.3 Hz, 1H), 3.87−3.77 (m, 2H), 3.67 (dd, J = 11.7, 4.5 Hz, 1H), 3.63−3.56 (m, 2H), 3.18 (t, J = 3.8 Hz, 1H), 2.44 (s, 3H), 2.03 (s, 3H), 1.06 (d, J = 6.2 Hz, 3H), 1.04 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 172.8, 145.6, 137.2, 130.9, 129.2, 96.1, 71.2, 69.9, 69.0, 63.7, 62.9, 50.4, 23.8, 22.9, 21.64, 21.59. HRMS (ESI-TOF) m/z: ([M − H]$^-$ Calcd for $C_{18}H_{28}N_3O_7S$ 430.1643; found: 430.1655.

*Isopropyl 2-Acetamido-2,3-dideoxy-α-D-ribo-hexopyranoside (**15**).* A mixture of the tosylhydrazine **14** (405 mg, 0.94 mmol) and sodium acetate trihydrate (511 mg, 3.75 mmol) in 11 mL of ethanol was refluxed for 3 h. Ethanol was removed in vacuo, and the residue was purified by flash chromatography on a 15 g silica cartridge with DCM/MeOH, increasing ratio of MeOH from 0 to 10% in 20 min, the product eluted at 5% MeOH to provide a white solid (154 mg, 66%), m.p.: 164−166 °C; ^{1}H NMR (400 MHz, methanol-d_4) δ 4.83 (d, J = 3.6 Hz, 1H), 4.02−3.88 (m, 2H), 3.79 (dd, J = 11.7, 2.0 Hz, 1H), 3.65 (dd, J = 11.7, 5.0 Hz, 1H), 3.60−3.49 (m, 2H), 1.94 (s, 3H), 1.93−1.88 (m, 1H), 1.78 (dt, J = 12.7, 10.8 Hz, 1H), 1.25 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 172.9, 95.3, 74.7, 70.7, 66.4, 63.0, 49.3, 34.0, 23.8, 22.6, 21.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{11}H_{22}NO_5$ 248.1493 and $C_{11}H_{21}NO_5Na$ 270.1317; found 248.1494 and 270.1314.

*D-Lividosamine (**16**).* Isopropyl 2-acetamido-2,3-dideoxy-α-D-ribo-hexopyranoside **15** (143 mg, 0.58 mmol) was dissolved in HCl (aq) (2 M, 0.7 mL) and heated at 100 °C for 2 h. Subsequent evaporation of the volatiles provided the product (107 mg, 92%) as a brown syrup. In order to obtain NMR spectra with sharp signals, an analytical sample was dissolved in water, followed by the addition of activated carbon. After filtration and evaporation, the NMR spectra were obtained in DMSO-d_6. The ^{1}H NMR spectrum shows a major anomeric signal at δ 5.12 ppm, being the α-pyranose of D-lividosamine. C_4-OH and C_6-OH are too broad and are difficult to observe in the ^{1}H NMR spectrum. Characterization matches the literature.[26] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18−8.00 (m, 3H, C_2-NH_2HCl), 7.12 (d, J = 4.2 Hz, 1H, C_1-OH), 5.12 (d, J = 2.9 Hz, 1H, H-1 for α-isomer), 3.62−3.56 (m, 1H, H-6b), 3.53−3.44 (m, 2H, H-5, H-6a), 3.39−3.31 (m, 1H, H-4), 3.15−3.04 (m, 1H, H-2), 2.03−1.96 (m, 1H, H-3b), 1.65 (q, J = 11.8 Hz, 1H, H-3a); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 87.5, 73.2, 63.6, 60.7, 48.3, 31.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_6H_{14}NO_4$ 164.0917; found 164.0916.

*E/Z-Isopropyl 2-Acetamido-2-deoxy-3-O-methyloxime-α-D-ribo-hexapyranoside (**17**).* Isopropyl 2-acetamido-2-deoxy-α-D-ribo-hexapyranoside-3-uloside **7** (1.57 g, 6.01 mmol), methoxyamine hydrochloride (753 mg, 9.01 mmol), $NaHCO_3$ (757 mg, 9.01 mmol), and anhydrous Na_2SO_4 (128 mg, 0.9 mmol) were heated in anhydrous methanol (35 mL) at reflux for 2 h, and subsequently the reaction mixture was stirred at room temperature for 2 days. Evaporation of the solvent provided an oily residue, which was purified by flash chromatography on a 24 g silica cartridge with DCM/MeOH, and increasing ratio of MeOH from 0 to 4% in 22 min, the product eluted at 3% to provide an oil (1.58 g, 96% as a mixture of E/Z isomers). The ratio of E and Z is approximately 1:1; ^{1}H NMR (400 MHz, methanol-d_4) Mixture of E and Z isomers: δ 5.03 (d, J = 3.8 Hz, 1H), 4.95 (d, J = 3.8 Hz, 1H), 4.83 (m, 1H, overlap with H_2O in CD_3OD), 4.65 (d, J = 3.9 Hz, 1H), 4.45 (d, J = 9.0 Hz, 1H), 4.10 (dt, J = 8.5, 3.1 Hz, 1H), 4.00−3.92 (m, 2H), 3.91−3.86 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.80−3.70 (m, 5H), 2.01 (s, 3H), 1.98 (s, 3H), 1.24 (d, J = 6.2 Hz, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) Mixture of E and Z isomers: δ 173.2, 173.0, 153.2, 151.9, 97.5, 96.8, 77.5, 75.4, 71.7, 71.4, 69.6, 69.2, 63.2, 63.1, 62.7, 62.4, 54.3, 53.3, 23.63, 23.58, 22.7, 22.5, 21.8, 21.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{12}H_{23}N_2O_6$ 291.1551 and $C_{12}H_{22}N_2O_6Na$ 313.1370; found 291.1562 and 313.1380.

*Isopropyl 2-Acetamido-3-amino-2,3-dideoxy-α-D-allopyranoside (**18**).* E/Z-Isopropyl 2-acetamido-2-deoxy-3-O-methyloxime-α-D-ribo-hexapyranoside **17** (1.5 g, 5.45 mmol) in acetic acid (26 mL) was hydrogenated over platinum(IV) oxide (124 mg, 0.55 mmol, 10 mol %) under hydrogen pressure (5 bar) for 24 h. The reaction mixture was filtered over a short path of Celite, and the filtrate was concentrated in vacuo. Purification by Grace flash on a 15 g silica cartridge with DCM/MeOH, and increasing ratio of MeOH from 0 to 20% in 20 min, the product eluted at 8% MeOH to afford a colorless oil (1.14 g, 80%); ^{1}H NMR (400 MHz, methanol-d_4) δ 4.95 (d, J = 3.6 Hz, 1H), 4.15 (t, J = 3.8 Hz, 1H), 3.96 (p, J = 6.2 Hz, 1H), 3.87−3.81 (m, 1H), 3.80−3.69 (m, 3H), 3.44 (t, J = 4.0 Hz, 1H), 2.03 (s, 3H), 1.29 (d, J = 6.2 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.4, 96.8, 72.5, 69.3, 65.8, 62.7, 54.3, 50.2, 23.7, 22.8, 21.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{11}H_{23}N_2O_5$ 263.1602 and $C_{11}H_{22}N_2O_5Na$ 285.1426; found 263.1605 and 285.1423;

*Isopropyl 2,3-Diamino-2,3-dideoxy-α-D-allopyranoside (**19**).* Isopropyl 2-acetamido-3-amino-2,3-dideoxy-α-D-allopyranoside **18** (1.07 g, 4.08 mmol) was dissolved in aqueous NaOH (1 M, 8.6 mL). The solution was heated in the microwave for 90 min at 150 °C and then cooled down, and the water evaporated. The crude product was purified on a Scorpius Diol (OH) 48 g column using DCM/MeOH, and increasing ratio of MeOH from 0 to 30% in 30 min, the product eluted at 5% MeOH to afford a yellow oil (764 mg, 85%); ^{1}H NMR (400 MHz, methanol-d_4) δ 4.82 (d, J = 3.7 Hz, 1H), 3.92 (p, J = 6.2 Hz, 1H), 3.83 (dd, J = 11.6, 2.4 Hz, 1H), 3.69 (dd, J = 11.6, 5.5 Hz, 1H), 3.65−3.60 (m, 1H), 3.52−3.46 (m, 1H), 3.04 (t, J = 4.1 Hz, 1H), 2.85−2.80 (m, 1H), 1.25 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 99.8, 71.8, 68.9, 68.4, 63.2, 56.4, 52.7, 24.1, 21.9; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_9H_{21}N_2O_4$ 221.1496 and $C_9H_{20}N_2NaO_4$ 243.1321; found 221.1495 and 243.1314.

*(3aR,4S,6R,7S,7aS)-2-(4-Bromophenyl)-6-(hydroxymethyl)-4-isopropoxy-3,3a,4,6,7,7a-hexahydropyrano[3,4-d]imidazol-7-ol (**20**).* A solution of 4-bromobenzaldehyde (184 mg, 0.996 mmol) in *tert*-butyl alcohol (10.9 mL) and isopropyl 2,3-diamino-2,3-dideoxy-α-D-allopyranoside **19** (241 mg, 1.094 mmol) were mixed and stirred at room temperature for overnight. Subsequently, *N*-iodosuccinimide (246 mg, 1.09 mmol) was added to the mixture at room temperature and stirred for 2 h. Sat. aq $NaHCO_3$ was added to the reaction mixture. The mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography on a 15 g silica cartridge with DCM (DCM contains 0.25% Et_3N)/MeOH, and increasing the ratio of

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MeOH from 0 to 5% in 22 min, the product eluted at 4% MeOH to provide a yellow crystalline solid (216 mg, 51%), mp 178−182 °C; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 (s, 4H), 5.08 (d, J = 4.2 Hz, 1H), 4.64 (dd, J = 9.8, 4.8 Hz, 1H), 4.44 (dd, J = 9.8, 4.2 Hz, 1H), 4.12 (dd, J = 9.5, 4.9 Hz, 1H), 4.00 (p, J = 6.2 Hz, 1H), 3.88−3.75 (m, 3H), 1.16 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 168.9, 133.8, 131.2, 129.9, 124.9, 94.0, 72.3, 71.8, 63.6, 63.4, 62.9, 60.9, 23.8, 21.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{22}BrN_2O_4$ 385.0758 and 387.0737; found 385.0760 and 387.0734.

*(4S,6R,7S)-2-(4-Bromophenyl)-6-(hydroxymethyl)-4-isopropoxy-3,4,6,7-tetrahydropyrano [3, 4-d] imidazol-7-ol (**21**).* To a mixture of **20** (193 mg, 0.5 mmol) and K_2CO_3 (76 mg, 0.55 mmol) in DMSO (5 mL) was added PhI(OAc)$_2$ (177 mg, 0.55 mmol). Then the mixture was stirred for 24 h at room temperature under an N_2 atomosphere. After the reaction completed, water (50 mL) was added, and the mixture was lyophilized to afford the crude product. Subsequent purification by flash chromatography on a 4 g silica cartridge with pentane/EtOAc, and increasing ratio of EtOAc from 0 to 90% in 15 min, the product eluted at 88% EtOAc to provide a white amorphous solid (81 mg, 42%); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.80 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 5.71 (s, 1H), 4.69 (d, J = 9.0 Hz, 1H), 4.20 (p, J = 6.2 Hz, 1H), 4.01−3.91 (m, 2H), 3.82 (dd, J = 11.9, 5.6 Hz, 1H), 1.30 (d, J = 6.0 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 147.6, 133.2, 130.7, 128.5, 124.0, 94.3, 75.7, 71.6, 63.8, 62.5, 24.2, 22.4; HRMS (ESI-TOF) m/z: [M-H]$^-$ Calcd for $C_{16}H_{18}BrN_2O_4$ 381.0445 and 383.0424; found 381.0452 and 383.0431.

*(2S,3R,4S,5R,6R)-3-Acetamido-4-(benzylcarbamoyl)-5-hydroxy-6-(hydroxymethyl)-2-isopropoxytetrahydro-2H-pyran-4-yl benzoate and (2R,3R,4S,5R,6S)-5-Acetamido-4-(benzylcarbamoyl)-4-hydroxy-2-(hydroxymethyl)-6-isopropoxytetrahydro-2H-pyran-3-yl benzoate (**22a** and **22b**).* To a stirred suspension of isopropyl 2-acetamido-2-deoxy-α-D-ribo- hexapyranoside-3-uloside **7** (130 mg, 0.5 mmol) in DCM/THF (1:1, 0.5 mL, 1 M) were added benzoic acid (61 mg, 0.5 mmol) and benzyl isocyanide (61 μL, 0.5 mmol). The reaction was allowed to stir at room temperature for 5 days, then concentrated in vacuo, and separated by flash chromatography on a 12 g silica cartridge with pentane/EtOAc, and increasing ratio of EtOAc from 0 to 100%, **22a** eluted at 77% EtOAc as colorless oil (74 mg, 30%) and **22b** eluted at 90% EtOAc as white amorphous solid (89 mg, 36%).

22a. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.01−7.97 (m, 2H), 7.64−7.58 (m, 1H), 7.50−7.41 (m, 4H), 7.38−7.33 (m, 2H), 7.31−7.24 (m, 1H), 4.99 (d, J = 3.6 Hz, 1H), 4.82 (d, J = 3.6 Hz, 1H), 4.65 (d, J = 14.9 Hz, 1H), 4.35 (d, J = 14.9 Hz, 1H), 4.32 (d, J = 10.1 Hz, 1H), 4.14 (ddd, J = 10.1, 4.7, 2.5 Hz, 1H), 3.92 (p, J = 6.2 Hz, 1H), 3.85 (dd, J = 12.0, 2.6 Hz, 1H), 3.79 (dd, J = 11.9, 4.7 Hz, 1H), 1.97 (s, 3H), 1.13 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.2, 169.9, 167.2, 139.4, 134.7, 131.6, 131.1, 129.8, 129.7, 129.1, 128.6, 96.9, 84.5, 73.4, 71.9, 71.9, 62.7, 55.6, 44.9, 23.6, 23.1, 21.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{26}H_{33}N_2O_8$ 501.2231 and $C_{26}H_{32}N_2O_8Na$ 523.2056; found 501.2235 and 523.2054;

22b. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.03 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.07−7.02 (m, 3H), 7.00−6.94 (m, 2H), 5.57 (d, J = 10.5 Hz, 1H), 5.08 (d, J = 3.9 Hz, 1H), 4.58 (d, J = 3.9 Hz, 1H), 4.28 (d, J = 15.0 Hz, 1H), 4.23 (d, J = 14.7 Hz, 1H), 4.19 (ddd, J = 10.5, 5.1, 3.5 Hz, 1H), 4.03 (p, J = 6.2 Hz, 1H), 3.68−3.59 (m, 2H), 1.91 (s, 3H), 1.33 (d, J = 6.2 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.0, 171.9, 166.6, 139.8, 134.8, 131.2, 130.9, 129.8, 129.4, 128.4, 128.1, 97.1, 79.6, 72.9, 71.4, 68.9, 62.9, 53.0, 44.1, 23.7, 22.5, 21.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{26}H_{33}N_2O_8$ 501.2231 and $C_{26}H_{32}N_2O_8Na$ 523.2056; found 501.2226 and 523.2042.

*(2S,3R,4S,5R,6R)-3-Acetamido-N-benzyl-4,5-dihydroxy-6-(hydroxymethyl)-2-isopropoxytetrahydro-2H-pyran-4-carboxamide (**23**).* To a solution of **22** in methanol (0.05 M) was added sodium methoxide (1.2 equiv) at room temperature. The reaction was stirred at room temperature for 3 h, then concentrated in vacuo, and purified by flash chromatography on a 4 g silica cartridge with DCM/MeOH, and increasing ratio of MeOH from 0 to 15%, the product eluted at 10% MeOH to afford a colorless oil.

Obtained **23** from **22a** on a 0.116 mmol scale; yield: 36 mg (78%). Obtained **23** from **22b** on a 0.136 mmol scale; yield: 46 mg (85%). HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for $C_{19}H_{27}N_2O_7$ 395.1813; found 395.1825. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.41−7.24 (m, 5H), 4.94 (d, J = 4.4 Hz, 1H), 4.61 (d, J = 14.7 Hz, 1H), 4.33 (d, J = 14.7 Hz, 1H), 4.26 (d, J = 4.4 Hz, 1H), 4.02 (ddd, J = 10.4, 5.3, 2.5 Hz, 1H), 3.90 (p, J = 6.2 Hz, 1H), 3.82 (dd, J = 11.9, 2.5 Hz, 1H), 3.72 (dd, J = 11.9, 5.3 Hz, 1H), 3.66 (d, J = 10.4 Hz, 1H), 1.96 (s, 3H), 1.04 (d, J = 6.1 Hz, 3H), 1.02 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.8, 172.3, 139.7, 129.8, 129.2, 128.6, 96.4, 78.9, 74.5, 72.5, 72.1, 63.0, 56.8, 44.7, 23.3, 22.8, 21.6.

*tert-Butyl (Z)-2-((2S,3R,5S,6R)-3-Acetamido-5-hydroxy-6-(hydroxymethyl)-2-isopropoxytetrahydro-4H-pyran-4-ylidene)-hydrazine-1-carboxylate (**24**).* ^{1}H NMR (400 MHz, methanol-d_4) δ 8.36 (d, J = 7.0 Hz, 1H), 5.20 (d, J = 3.5 Hz, 1H), 4.56 (d, J = 9.8 Hz, 1H), 4.48 (dd, J = 7.0, 3.5 Hz, 1H), 3.91−3.85 (m, 2H), 3.80−3.72 (m, 2H), 2.04 (s, 3H), 1.51 (s, 9H), 1.19 (d, J = 6.3 Hz, 3H), 1.10 (d, J = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 173.2, 155.8, 145.2, 97.7, 82.5, 75.9, 73.5, 72.1, 62.0, 56.0, 28.7, 23.7, 22.4, 22.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ and [M + Na]$^+$ Calcd for $C_{16}H_{30}N_3O_7$ 376.2078 and $C_{16}H_{29}N_3O_7Na$ 398.1898; found 376.2075 and 398.1898.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01949.

Associated analytical data (^{1}H NMR, ^{13}C{^{1}H} NMR for all compounds (PDF)

Crystallographic data for **4** (CIF)

Crystallographic data for **24** (CIF)

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Notes

The authors declare no competing financial interest.

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