Stereoselective Preparation of Deuterium-Labeled Sugars: (6*R*)-(6-$^2H_1$)-*N*-Acetylglucosamine Derivatives

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The preparation of methyl (6*R*)-(6-$^2H_1$)-2-deoxy-2-*N*-acetamido-α-D-glucose (**8**α-*d*) and methyl (6*R*)-(6-$^2H_1$)-2-deoxy-2-*N*-acetamido-*β*-D-glucose (**8***β*-*d*) is described. The key step in the synthesis was the stereoselective reduction of a C6-aldehydo-GlcNAc derivative with (*R*)-(+)-Alpine-Borane-*d*. Reduction of either methyl 6-aldehydo-3,4-di-*O*-benzyl-α-GlcNAc (**6**α) or methyl 6-aldehydo-3,4-di-*O*-benzyl-*β*-GlcNAc (**6***β*) using (*R*)-(+)-Alpine-Borane-*d* in CH_2Cl_2 was significantly more stereoselective (>15:1 stereoselectivity for both anomers) than was reduction with $NaBD_4$ in MeOH. The absolute stereochemistry at C6 of the deuterated GlcNAc derivatives was determined from ^{1}H NMR analysis of the conformationally locked sugars, methyl (6*R*)-(6-$^2H_1$)-4,6-*O*-benzylidene-2-deoxy-2-*N*-acetamido-α-D-glucose (**9**α-*d*) and methyl (6*R*)-(6-$^2H_1$)-4,6-*O*-benzylidene-2-deoxy-2-*N*-acetamido-*β*-D-glucose (**9***β*-*d*). Comparison of $^3J_{H5,H6}$ values and ^{1}H−^{1}H NOEs for the nondeuterated and deuterated benzylidene derivatives showed that reduction with (*R*)-(+)-Alpine-Borane-*d* gave the (6*R*)-(6-$^2H_1$) epimer as the major product for both the GlcNAc α and *β* methyl glycosides. This stereoselective reduction enabled the ^{1}H NMR signals for the prochiral H6 and H6′ protons in a series of GlcNAc derivatives to be assigned.

Introduction

Asparagine glycosylation (N-glycosylation) of the Asn-Xaa-Ser/Thr consensus sequence is a cotranslational process important in many biological functions,[1] including protein folding.[2] NMR studies on intact glycoproteins,[3] glycopeptide fragments,[4] and smaller glycopeptides[5] have shown that N-glycosylation can influence peptide structure. What has been less well documented, however, is the influence that the peptide domain might have on carbohydrate conformation. While some NMR studies have concluded that carbohydrate structure is not affected by the attached peptide,[6] other papers suggest that the sugar conformation can be modulated by peptide−carbohydrate interactions.[3,4b,7]

We have previously used ^{1}H NMR spectroscopy to study the conformation of N-glycopeptides in both water and in organic solvents.[4b,5a] Recent ROESY experiments in an organic solvent revealed that glycopeptide Ac-Asn-(*β*1-*N*-GlcNAc)Leu-Thr-NH_2 (**1**) had peptide−sugar NOEs indicating intramolecular interactions between the peptide and carbohydrate domains (Figure 1B).[5a] These peptide−sugar interactions for **1** were sequence-specific in that the homologous Ac-Gln(*β*1-*N*-GlcNAc)Leu-Thr-NH_2, an unnatural N-glycopeptide, did not exhibit long-range NOEs. We concluded that the N-linked sugar in glycopeptide **1** stabilized a side-chain−main-chain peptide interaction known as the Asx-turn.[8] The carbohydrate's C5−C6 side chain may be important in stabilizing structure in glycopeptide **1**, particularly since an NOE was observed from the C-terminal cis amide NH to one of the two prochiral GlcNAc H6 protons (Figure 1B). While our initial NMR studies addressed the peptide conformation in glycopeptide **1**, we were unable to determine the GlcNAc C5−C6 side-chain conformation without the stereospecific assignment of the sugar's hydroxymethylene protons.

Figure 2 shows Newman projections for the three major staggered conformations about the GlcNAc C5−C6 bond. These rotamers are designated gt, gg, and tg where the first letter designates the relative orientation between O6 and O5 and the second letter designates the relative orientation between O6 and C4. Solution ^{1}H NMR spectroscopy has shown that the preference for the C5−C6 conformation in most glucopyranoses is gg > gt ≫ tg, independent of solvent.[9]

One of our goals is to determine if the peptide chain in N-linked glycopeptides influences the global conformation of the sugar's C5−C6 bond by altering the relative population of the three major rotamers. Without the assignment of the diastereotopic hydroxymethylene protons, however, ^{1}H NMR spectroscopy cannot unequivocally distinguish between the gt and tg rotamers.

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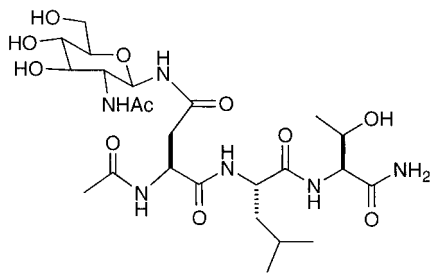
A)



1 Ac-Asn(β-1-N-GlcNAc)-Leu-Thr-NH_2

B)

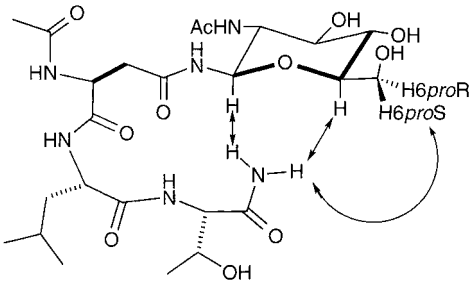


Figure 1. (A) Sequence and B) secondary structure of glycopeptide **1**. Peptide−sugar NOEs are indicated by arrows. The peptide's C-terminal NH_{cis} has an NOE to one of the diastereotopic C6 hydroxymethylene protons (ref 5a).

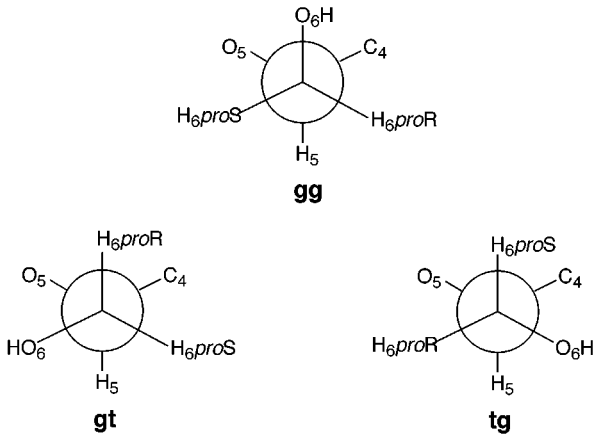


Figure 2. Newman projections of the three major rotamers about the GlcNAc C5−C6 bond.

This assignment can be achieved by stereoselective monodeuteration of the GlcNAc hydroxymethylene. Ohrui has made an α,*β* mixture of (6*S*)-(6-$^2H_1$)-GlcNAc[10] from a 1,6-anhydroglucose derivative.[11] We sought a more direct approach for preparation of C6-deuterated GlcNAc from GlcNAc itself. The key step is the stereoselective reduction of 6-aldehydo GlcNAc derivatives using the homochiral and deuterated reagent, (*R*)-(+)-Alpine-Borane-*d*.[12] Aldehyde reduction by (*R*)-(+)-Alpine-Borane-*d* proceeds with excellent stereoselectivity to give monodeuterated primary alcohols with the (*R*-$^2H_1$) configuration.[13] This reagent has been recently used to prepare a labeled sugar, (6*R*)-(6-$^2H_1$)-1,2:3,4-di-*O*-isopropylidene-galactose in 20:1 diasteroselectivity.[14] Below, we describe the preparation and NMR analysis of various (6*R*)-(6-$^2H_1$)-GlcNAc derivatives.

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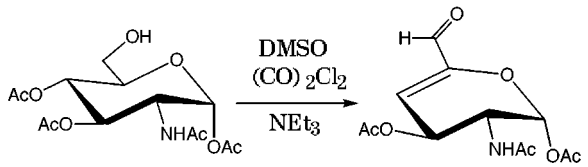
Results and Discussion

Preliminary Studies. Our approach involves the stereoselective reduction of a C6-aldehydo GlcNAc derivative. After several failed approaches, we recognized that appropriate protecting groups are important for the smooth oxidation of the GlcNAc hydroxymethylene. Initially, we used acetates to protect O1, O3, and O4. However, the basic Swern conditions[15] used to oxidize 1,3,4-tri-*O*-acetyl-α-GlcNAc **2**α[16] led to α,*β*-elimination of the C4-acetate to give the unsaturated aldehyde **3**α as the major product.[17] Attempts to suppress α,*β*-elimination with neutral variants of the Swern oxidation were unsuccessful. Thus, treatment of **2**α with the Moffat modification (DMSO, DCC, pyr-CF_3COOH)[18] resulted in primarily 4,6-*O*-acyl migration and no oxidation.



2α **3**α

Benzyl groups are not as prone as *O*-acetates toward α,*β*-elimination. As outlined in Scheme 1, the use of the 3,4-*O*-benzyl protecting groups enabled straightforward preparation of the deuterated GlcNAc derivatives. We investigated reduction of the separate anomers, methyl 3,4-di-*O*-benzyl-6 aldehydo α-GlcNAc **6**α and methyl 3,4-di-*O*-benzyl-6-aldehydo *β*-GlcNAc **6***β* (see Scheme 2), so as to minimize the complexity of the NMR analysis of the products, **7**α-*d* and **7***β*-*d*. We also wanted to determine if reduction would give similar stereoselectivities and the same absolute configuration for the two anomeric methyl glycosides. Indeed, reduction with (*R*)-(+)-Alpine-Borane-*d* provides excellent yields of the (6*R*)-(6-$^2H_1$)-GlcNAc derivative in both cases.

Synthesis of Methyl (6-*R*)-(6-$^2H_1$)-2-Deoxy-2-*N*-acetamido-α-glucose. Acid-promoted cleavage of the trityl group from methyl 3,4-di-*O*-benzyl-6-*O*-trityl α-GlcNAc **4**α[19] gave **5**α in 80% yield. Aldehyde **6**α was prepared from **5**α in 96% yield by oxidation under the standard Swern conditions.[15] While easily hydrated,[20] azeotropic drying with toluene provided **6**α in the aldehyde form, with no hydrate detectable by ^1H NMR or IR spectroscopy. The ^1H NMR of **6**α in $CDCl_3$ showed a

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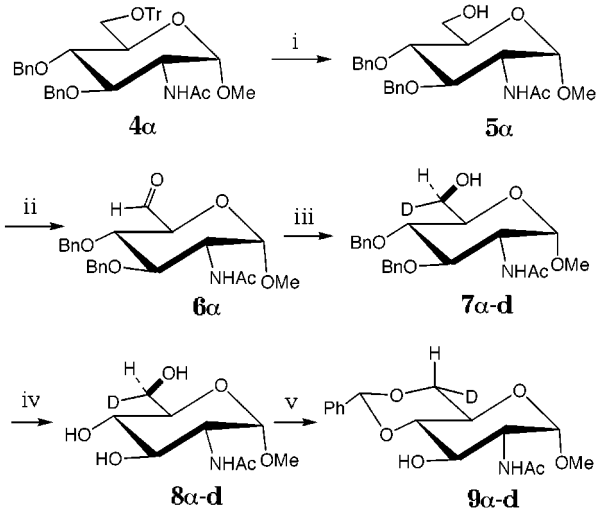
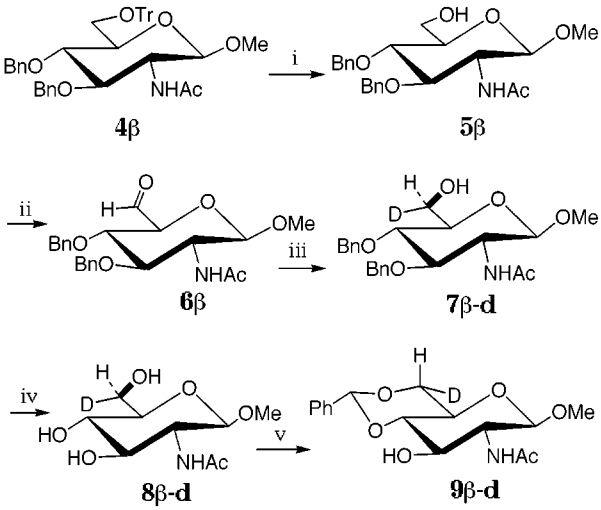
Scheme 1[a]



[a] Key: (i) HBr/HOAc, 80%; (ii) DMSO, $(CO_2)Cl_2$, 96%; (iii) (*R*)-Alpine-Borane-*d*, CH_2Cl_2, 90%; (iv) H_2, $Pd(OH)_2/C$, EtOH 85%; (v) $PhCH(OMe)_2$, *p*-TsOH, DMF.

Scheme 2[a]



[a] Key: (i) HBr/HOAc, 100%; (ii) DMSO, $(CO_2)Cl_2$, 96%; (iii) (*R*)-Alpine-Borane-*d*, CH_2Cl_2, 74%; (iv) H_2, $Pd(OH)_2/C$, EtOH, 83%; (v) PhCHO, $ZnBr_2$.

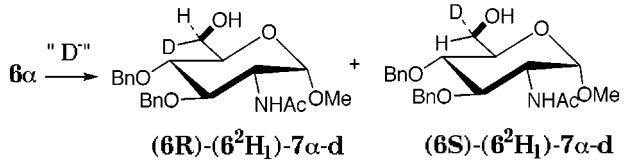
signal at δ 9.64 ppm for the aldehyde proton, while the ^{13}C NMR spectrum in CD_2Cl_2 had a carbonyl resonance at 197.7 ppm.[21] Aldehyde **6**α was typically reduced immediately after its isolation and azeotropic drying.

Reduction of GlcNAc aldehyde **6**α in CH_2Cl_2 at room temperature with (*R*)-(+)-Alpine-Borane-*d*, prepared from (+)-pinene (97% ee),[12] gave **7**α-*d* in 90% yield and high stereoselectivity. As described below, the absolute C6 configuration was determined by transformation of **7**α-*d* into the conformationally locked 4,6-*O*-benzylidene derivatives **9**α-*d*. The incorporation of a single deuterium into the C6 position of **7**α-*d* was confirmed by ^1H, ^2H, and ^{13}C (J_{CD} = 21.8 Hz) NMR spectroscopy and by FAB mass spectrometry. Although clearly excellent, the stereoselectivity of deuterium incorporation was difficult to determine using ^1H NMR since the residual H6R resonance for the minor product (δ 3.72 ppm) overlapped with the H3 and H4 resonances. The stereoselectivity was better determined by integration of the ^2H NMR spectrum of **7**α. Separate ^2H signals for the two epimers, (6*R*)-(6-$^2H_1$)-**7**α-*d* (δ 3.72 ppm) and (6*S*)-(6-$^2H_1$)-**7**α-*d* (δ 3.80 ppm), were resolved in $CDCl_3/CD_3CN$ (1:1) at 60 °C (see Figure 2 in the Supporting Information). Integration of the ^2H NMR showed a 16:1 ratio of (6*R*)-(6-$^2H_1$)-**7**α-*d* and (6*S*)-(6-$^2H_1$)-**7**α-*d* after reduction of **6**α with (*R*)-(+)-Alpine-Borane-*d* (Table 1). Alpine-Borane-*d* was superior to $NaBD_4$ with regard to stereoselectivity. Thus, ^2H NMR analysis indicated that $NaBD_4$ reduction of **6**α gave a 1:1.6 ratio of (6*R*)-(6-$^2H_1$)-**7**α-*d* and (6*S*)-(6-$^2H_1$)-**7**α-*d*. This low stereoselectivity is similar to that observed for the monodeuteration of other glucosyl 6-aldehydes with $NaBD_4$.[17c,22]

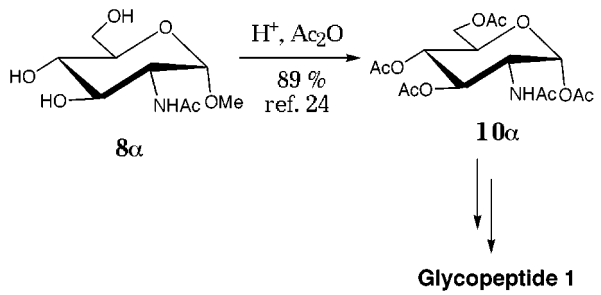
Table 1. Stereoselectivity of Reduction of Aldehyde 6α

reductant	solvent[a]	% (6*R*)-7α-*d*	% (6*S*)-7α-*d*	6*R*:6*S*[b]
(*R*)-(+)-Alpine-Borane-*d*	CH_2Cl_2	94	6	16:1
$NaBD_4$	MeOH	37	63	1:1.6

[a] Both reactions were carried out at room temperature. [b] Ratios were determined from ^2H NMR analysis in 1:1 $CDCl_3/CD_3CN$ at 60 °C.



The O3 and O4 benzyl ethers were removed from **7**α-*d* by hydrogenation over Pearlman's catalyst ($Pd(OH)_2/C$)[23] to give (6*R*)-(6$^2H_1$)-methyl α-GlcNAc **8**α-*d* in 85% yield. The nondeuterated GlcNAc α-methyl glycoside **8**α has been previously converted into GlcNAc peracetate **10**α in high yield via acetolysis.[24] Peracetate **10**α is a key intermediate in the synthesis of N-linked glycopeptides.[25] Thus, access to the labeled sugar, (6*R*)-(6$^2H_1$)-methyl α-GlcNAc **8**α-*d*, should enable the preparation of deuterated N-linked glycopeptides.



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(20) Hydrate formation from related sugar aldehydes is known; see: ref 17c and: Jenkins, D. J.; Riley, A. M.; Potter, B. V. L. *J. Org. Chem.* **1996**, *61*, 7719−7726.

(21) Aldehyde **6**α was unstable in $CDCl_3$, presumably due to the presence of acid. It was, however, stable in CD_2Cl_2, and the ^{13}C NMR spectra were taken in this solvent.

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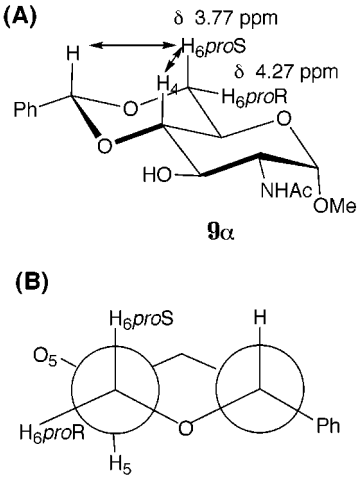

Figure 3. (A) Benzylidene **9**α with key NOEs to H6*pro*S from H4 and acetal proton indicated with arrows; (B) Newman projection of benzylidene **9**α.

Determination of Stereochemistry and Assignment of Prochiral H6 NMR Resonances. The H6*pro*S proton normally resonates downfield of H6*pro*R in glucopyranose derivatives.[17c] This "rule" is often used to assign chemical shifts for the prochiral hydroxymethylene protons in glucopyranoses. Ohrui has shown, however, that all glucopyranoses do not conform to this rule.[26] In the present work, we firmly established the assignment of the prochiral hydroxymethylene protons by converting the major reduction product, (6*R*)-(6-$^2H_1$)-**7**α-*d*, into the conformationally locked derivative (6*R*)-(6-$^2H_1$)-**9**α-*d*. Thus, the nondeuterated and deuterated 4,6-*O*-benzylidene GlcNAc derivatives, **9**α[27] and **9**α-*d*, were prepared from the corresponding methyl-α-GlcNAc, either **8**α or **8**α-*d*, and benzaldehyde dimethyl acetal. As described below, both ^3J coupling constants and NOEs were used to assign the H6, H6′ NMR resonances in **9**α and **9**α-*d*. This NMR analysis confirmed that reduction of aldehyde **6**α by (*R*)-(+)-Alpine-Borane-*d* gave (6*R*)-[6-$^2H_1$]-**7**α-*d* as the predominant product.

As shown in Figure 3, 4,6-*O*-benzylidene sugars, such as **9**α, adopt a *trans*-decalin C1 (D) conformation, with H6*pro*S in the axial position and H6*pro*R in the equatorial position. In this fixed conformation, $^3J_{5,6R}$ does not equal $^3J_{5,6S}$, and the diastereotopic protons can be assigned on the basis of $^3J_{5,6}$ values and intramolecular ^{1}H−^{1}H NOEs. The ^{1}H NMR resonances of **9**α in $CDCl_3$ were assigned from a 2D ^{1}H−^{1}H COSY experiment (see spectra in the Supporting Information). The H6 and H6′ protons of benzylidene **9**α have chemical shifts of δ 4.27 ppm ($^3J_{5,6}$ = 2.4 Hz) and δ 3.77 ppm. The smaller ^3J coupling for the downfield-shifted resonance suggested that this signal corresponds to H6*pro*R, being located gauche to H5 (Figure 3B). The $^3J_{5,6}$ value for the upfield-shifted H6′ resonance could not be determined from the 1D NMR spectrum because of chemical shift overlap with the H5 signal. The 1D ^{1}H−^{1}H NOE experiments (see the Supporting Information) confirmed the assignments made on the basis of the $^3J_{5,6R}$ measurement. Irradiation of either the benzylidene acetal proton (δ 5.54 ppm) or GlcNAc H4 (δ 3.57 ppm) showed a positive NOE of 5−6% to the upfield-shifted H6′ resonance at δ 3.77 ppm, indicating that this was the axial H6*pro*S resonance (Figure 3A). As expected, there were no NOE enhancements to the downfield-shifted H6 resonance at δ 4.27 ppm. These NOE experiments indicated that the H6*pro*R resonance (δ 4.27 ppm) is downfield of the H6*pro*S signal (δ 3.77 ppm) in the unlabeled benzylidene **9**α.

Analysis of deuterated benzylidene, **9**α-*d*, prepared from **7**α-*d*, showed that deuterium was incorporated at the 6*R* position since the ^{1}H NMR spectrum clearly lacked the one-proton signal at δ 4.27 ppm (see Figure 3 in the Supporting Information). This stereochemical assignment for **9**α-*d* is consistent with Midland's transition-state model, which predicts that (*R*)-(+)-Alpine-Borane-*d* reduces aldehydes to give alcohols of *R* configuration.[13a] On the basis of this NMR analysis, we can assign the H6*pro*R and H6*pro*S signals for the GlcNAc derivative **5**α and the unlabeled methyl glycoside **8**α.

The β-GlcNAc Series. Synthesis and Stereochemical Analysis of Methyl (6*R*)-(6-$^2H_1$)-2-Deoxy-2-*N*-acetamido-β-glucose. The same approach that was used to prepare methyl (6*R*)-(6-$^2H_1$)-2-deoxy-2-*N*-acetamido-α-glucose **8**α-*d* was also used on the β-GlcNAc series (Scheme 2). As described below, Alpine-Borane-*d* reduction of aldehyde **6**β gave **7**β-*d* in excellent stereoselectivity, indicating that the methyl glycoside's anomeric configuration does not greatly influence the stereochemical course of C6 reductions with Alpine-Borane-*d*.

Detritylation of methyl 3,4-di-*O*-benzyl-6-*O*-trityl β-GlcNAc **4**β[19] with HBr gave **5**β in quantitative yield. In contrast to **5**α, both H6*pro*R and H6*pro*S for **5**β are resolved from other resonances. Thus, the stereoselectivity of deuterium incorporation was directly measured from the ^{1}H NMR spectra of **7**β; the use of ^{2}H NMR to determine stereoselectivity was not necessary. Swern oxidation of **5**β gave aldehyde **6**β in 96% yield. Aldehyde **6**β, without purification but after azeotropic drying with toluene, was reduced with (*R*)-(+)-Alpine-Borane-*d* in CH_2Cl_2 at room temperature to give **7**β-*d* in 74% yield after purification. The stereoselectivity of the reduction, as determined by ^{1}H NMR, was excellent; (6*R*)-(6-$^2H_1$)-**7**β-*d* was formed in a greater than 20:1 ratio (Figure 4). As for the α-series, $NaBD_4$ reduction of aldehyde **6**β gave only a modest stereoselectivity, with the (6*S*)-**7**β-*d* epimer being the major product in a 1.9:1 ratio (Figure 4).

Again, the configuration at C6 was determined by transformation of (6*R*)-(6-$^2H_1$)-**7**β-*d* into the conformationally rigid benzylidene (6*R*)-(6-$^2H_1$)-**9**β-*d*. The ^{1}H NMR spectrum of unlabeled **9**β in DMSO-d_6 was assigned from a 2D ^{1}H−^{1}H COSY experiment, and the H6*pro*R and H6*pro*S resonances in **9**β were well-separated and resolved. The H6*pro*R proton of benzylidene **9**β has a chemical shift of δ 4.20 ppm (dd, $^3J_{5,6}$ = 4.8 Hz, $^3J_{6,6'}$ = 10.0 Hz), while H6*pro*S has a signal at δ 3.72 ppm (t, $^3J_{5,6}$ = 10.0 Hz, $^3J_{6,6'}$ = 10.0 Hz). NMR analysis of the deuterated benzylidene, (6*R*)-(6-$^2H_1$)-**9**β-*d*, indicated that deuteration resulted in the loss of H6*pro*R, the equatorial proton with the smaller $^3J_{5,6}$ coupling at δ 4.20 ppm (see Figure 4 in the Supporting Information). As expected, (6*R*)-(6-$^2H_1$)-**9**β-*d* had a doublet for the 6*S* proton at δ 3.70 ($^3J_{5,6}$ = 10.0 Hz).[28] These results confirmed that (*R*)-(+)-Alpine-Borane-*d* reduced the β-linked aldehyde **6**β

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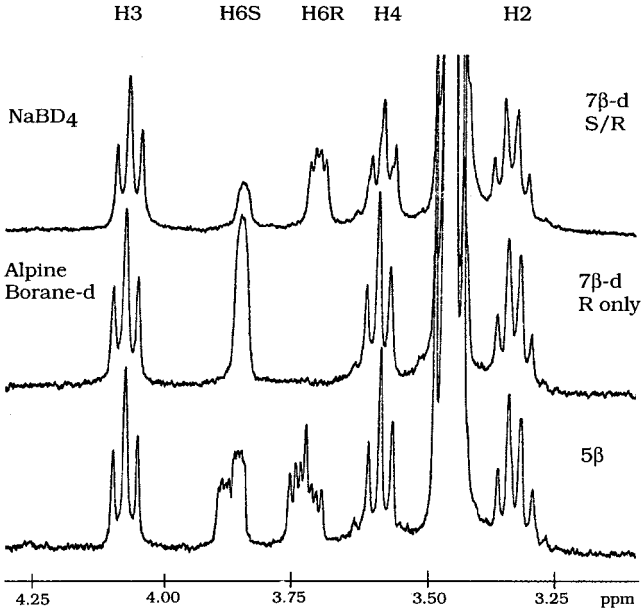

Figure 4. Selective Deuterium Incorporation into 7β-*d*. A region of the 400 MHz ^{1}H NMR spectra for alcohols **5**β and **7**β-*d* in $CDCl_3$ is shown. Selected resonances are labeled. The bottom spectrum is that for **5**β. The middle spectrum is that for (6*R*)-(6-$^2H_1$)-7β-*d*, formed by reduction of aldehyde **6**β with (*R*)-(+)-Alpine-Borane-*d*. The top spectrum shows a mixture of (6*R*)-(6-$^2H_1$)-7β-*d* and (6*S*)-(6-$^2H_1$)-7β-*d* formed from $NaBD_4$ reduction of **6**β.

with the same absolute stereochemistry as it did the α-linked aldehyde **6**α.

Conclusion

Reduction of both 6-aldehydo-α-GlcNAc and 6-aldehydo-β-GlcNAc methyl glycosides (**6**α and **6**β) with (*R*)-(+)-Alpine-Borane-*d* proceeded with excellent stereoselectivity to give (6*R*)-(6-$^2H_1$)-GlcNAc derivatives. NMR spectroscopy was used to determine the stereoselectivity of reduction and the absolute configuration at the deuterated C6 position. This methodology, in turn, allowed us to unequivocally assign ^{1}H NMR resonances for the prochiral C6 hydroxymethylene protons in a series of GlcNAc derivatives. We anticipate that these (6*R*)-(6-$^2H_1$)-GlcNAc derivatives will be useful for the synthesis and conformational analysis of specifically labeled N-linked glycopeptides.

Experimental Section

Except where noted, all reactions were carried out under dry N_2. All solvents were distilled from drying agents. Reagents were purchased from Aldrich, Sigma, or Acros Organics. ^{1}H NMR data, recorded at either 400 or 500 MHz, are reported as follows: spin multiplicity, number of protons, coupling constant (Hertz), peak assignment. Chemical shifts are reported in parts per million relative to the residual protonated solvent. The ^{1}H NMR chemical shift assignments were made using 2D COSY experiments. ^{2}H NMR was performed on a 500 MHz NMR instrument equipped with a 5 mm broad-band probe operating at 76.7 MHz. Proton broad-band decoupling was achieved through the WALTZ composite pulse scheme using 1 W of R_f power. IR spectra were recorded using either NaCl or KBr plates. Fast atom bombardment mass spectra (FAB) used glycerol as the matrix. Melting points are reported uncorrected. Elemental analyses were performed by Schwartzkopf Analytical Labs, Brooklyn, NY.

Methyl 3,4-Di-*O*-benzyl-2-deoxy-2-*N*-acetamido-α-D-glucose (5α). To a solution of **4**α[19] (0.90 g, 1.37 mmol) in $HOAc/CH_2Cl_2$ (50 mL, 1:1) at 0 °C was added a 1.38 M solution of HBr in HOAc (1.00 mL, 1.38 mmol). The reaction mixture was stirred at 0 °C for 5 min. Trityl chloride was removed by filtration of the reaction mixture into ice−water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed (saturated $NaHCO_3$ and brine), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. Flash chromatography (20% hexane/80% $CHCl_3$) gave **5**α[19] as a white solid (0.45 g, 80%). An analytical sample was recrystallized from $CHCl_3$/petroleum ether: mp = 186−188 °C; $[\alpha]^{27}_D$ = +97.7 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 10H, Ar), 5.24 (d, 1H, ^3J = 9.2, NH), 4.86 (d, 1H, ^2J = 10.9), 4.84 (d, 1H, ^2J = 11.7), 4.66 (d, 1H, ^2J = 10.9), 4.63 (d, 1H, ^3J = 3.6, H1), 4.62 (d, 1H, ^2J = 11.7), 4.17 (ddd, 1H, ^3J = 3.6, 9.6, 9.6, H2), 3.79 (m, 1H, H6*pro*S), 3.73 (m, 1H, H6*pro*R), 3.69−3.62 (m, 3H, H3, H4, H5), 3.29 (s, 3H, OMe), 1.82 (s, 3H, Ac), 1.77 (dd, ^3J = 5.6, 7.6, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 138.3, 137.9, 128.5, 128.2, 128.1, 128.0, 127.8, 98.6, 79.9, 78.2, 75.1, 74.8, 71.2, 61.8, 55.0, 52.6, 23.4; FAB MS *m*/*z* 416.3 (M^+ + 1, 2.1); HRMS (M^+ + 1) *m*/*z* calcd for $C_{23}H_{30}NO_6$ 416.2073, found 416.2067. Anal. Calcd for $C_{23}H_{29}NO_6$; C, 66.49; H, 7.04; N, 3.37. Found: C, 66.23; H, 7.10; N, 3.33.

Methyl 6-Aldehydo-3,4-di-*O*-benzyl-2-deoxy-2-*N*-acetamido-α-D-glucose (6α). To a solution of oxalyl chloride (0.25 mL, 2.88 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added DMSO (0.38 mL, 5.77 mmol). After 5 min, a solution of **5**α (0.60 g, 1.44 mmol) in CH_2Cl_2 (30 mL) was added, and the reaction mixture was stirred at −78 °C for 15 min. After this time, NEt_3 (1.20 mL, 8.65 mmol) was added, and the reaction mixture was stirred for an additional 15 min. The reaction mixture was washed (0.05% HCl, saturated $NaHCO_3$, and brine), dried (Na_2SO_4), filtered, concentrated in vacuo, and repeatedly azeotroped from toluene to give aldehyde **6**α (0.57 g, 96%) as a pale yellow solid: mp = 176−178 °C; $[\alpha]^{25}_D$ = +86.0 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H, CHO), 7.32−7.28 (m, 10H), 5.31 (d, 1H, *J* = 9.1, NH), 4.82 (d, 1H, ^2J = 11.7), 4.78 (d, 1H, ^2J = 10.7), 4.72 (d, 1H, ^3J = 3.3, H1), 4.64 (d, 1H, ^2J = 10.7), 4.63 (d, 1H, ^2J = 11.7), 4.22 (ddd, 1H, *J* = 3.3, 9.2, 9.2, H2), 4.11 (d, 1H, *J* = 9.0, H5), 3.77−3.72 (m, 2H, H3, H4), 3.35 (s, 3H, OMe), 1.81 (s, 3H, Ac); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 197.7, 169.8, 128.8, 128.5, 128.4, 128.3, 117.2, 99.2, 80.1, 78.3, 75.5, 75.3, 75.1, 55.9, 52.1, 23.5; IR (CD_2Cl_2): 3687, 3443, 3037, 1737, 1675, 1600 cm^{-1}; FAB-MS *m*/*z* 414.3 (M^+ + 1, 3.6); HRMS (M^+ + 1) *m*/*z* calcd for $C_{23}H_{28}NO_6$ 414.1916, found 414.1924. Anal. Calcd for $C_{23}H_{27}NO_6 + H_2O$; C, 64.02; H, 6.77; N, 3.25. Found: C, 63.40; H, 6.89; N, 2.97.

Methyl (6*R*)-(6-$^2H_1$)-3,4-Di-*O*-benzyl-2-deoxy-2-*N*-acetamido-α-D-glucose ((6*R*)-(6-$^2H_1$)-7α-*d*). Method A. To a solution of aldehyde **6**α (3.75 g, 9.06 mmol) in CH_2Cl_2 (300 mL) at room temperature was added a 1.0 M solution of (*R*)-(+)-Alpine-Borane-*d*[9a] in 1:1 THF/hexane (27.2 mL, 27.2 mmol). The reaction mixture was stirred at room temperature for 16 h, after which time acetaldehyde (15.2 mL, 27.2 mmol) was added to quench the excess Alpine-Borane-*d*. After the solution was stirred for 1 h, the CH_2Cl_2 was removed in vacuo and replaced with THF. To the solution were added 3 M NaOH (75 mL) and 30% H_2O_2 (75 mL). The solution was stirred for 60 min, and the THF was removed in vacuo. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was washed (H_2O, 0.05% HCl, and brine), dried (Na_2SO_4), and concentrated in vacuo to give an oily solid. Excess pinene was removed by trituration with hexane. To remove the last traces of pinene, the product was dissolved in 70 mL of $CHCl_3$ and precipitated with petroleum ether. The solid was filtered and dried to give **7**α-*d* (3.41 g, 90%). Recrystallization from $CHCl_3$/petroleum ether gave analyti-

(28) The difference in the ^{1}H chemical shift for the 6S proton in the unlabeled benzylidene **9**β (δ 3.72 ppm) and in the deuterated benzylidene (6*R*)-(6-$^2H_1$)-**9**β-*d* (δ 3.70 ppm) is due to a deuterium isotope effect. See also: Ohrui, H.; Nishida, Y.; Higuchi, H.; Hori, H.; Marguro, H. *Can. J. Chem.* **1987**, *65*, 1145−53.

cally pure material: mp = 176−178 °C; [α] = +97.1 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 10H, Ar), 5.24 (d, 1H, ^3J = 9.2, NH), 4.86 (d, 1H, ^2J = 10.9), 4.84 (d, 1H, ^2J = 11.7), 4.66 (d, 1H, ^2J = 10.9), 4.63 (d, 1H, ^3J = 3.6, H1), 4.62 (d, 1H, ^2J = 11.7), 4.17 (ddd, 1H, ^3J = 3.6, 9.6, 9.6), 3.78 (d, 1H, ^3J = 2.7, H6S), 3.68−3.62 (m, 3H, H3, H4, H5), 3.29 (s, 3H, OMe), 1.82 (s, 3H, Ac), 1.77 (s, 1H, OH); ^{2}H NMR (76.7 MHz, $CD_3CN/CDCl_3$) δ 3.72; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 138.3, 137.9, 128.5, 128.2, 128.1, 127.9, 127.8, 98.6, 79.9, 78.2, 75.0, 74.8, 71.2, 61.4 (t, J_{CD} = 21.8), 55.0, 52.6, 23.4; FAB MS *m*/*z* 417.2 (6.6); HRMS (M^+ + 1) *m*/*z* calcd for $C_{23}H_{29}DNO_6$ 417.2136, found 417.2132. Anal. Calcd for $C_{23}H_{28}DNO_6 \cdot H_2O$: C, 63.58; H, 6.96; N, 3.22. Found: C, 64.02; H, 6.81; N, 3.18.

Mixture of (6*R*)-(6-^{2}H$_1$)-7α-*d* and (6*S*)-(6-^{2}H$_1$)-7α-*d*. To a solution of aldehyde **6**α (0.050 g, 0.120 mmol) in MeOH (10 mL) was added $NaBD_4$ (0.007 g, 0.180 mmol). After the solution was stirred at room temperature for 10 min, water (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed (0.1% HCl, saturated $NaHCO_3$, and brine), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a white solid. The crude product was dissolved in $CHCl_3$ and triturated with petroleum ether to yield a mixture of (6*R*)-(6-^{2}H$_1$)-**7**α-*d* and (6*S*)-(6-^{2}H$_1$)-**7**α-*d* (47.7 mg, 95%). ^{1}H NMR was consistent with the structure of **7**α-*d*, and ^{2}H NMR indicated that the material was a 37:63 mixture of (6*R*)-(6-^{2}H$_1$)-**7**α-*d* (^{2}H δ 3.72) and (6*S*)-(6-^{2}H$_1$)-**7**α-*d* (^{2}H δ 3.80).

Methyl (6*R*)-(6-^{2}H$_1$)-2-Deoxy-2-*N*-acetamido-α-D-glucose (8α-*d*). To a solution of (6*R*)-(6-^{2}H$_1$)-**7**α-*d* (0.83 g, 1.99 mmol) in HOAc/EtOH (15 mL/85 mL) was added Pearlman's catalyst (0.20 g, 20% $Pd(OH)_2$/C). The reaction mixture was shaken under a H_2 atmosphere (50 psi) on a Parr hydrogenator for 24 h. The catalyst was removed by filtration through Celite, and the mixture was concentrated in vacuo. The crude product was dissolved in EtOH and precipitated with Et_2O to yield **8**α-*d* (0.47 g, 85%) as a colorless solid. Recrystallization from EtOH afforded fine needles: mp = 159−161 °C; $[\alpha]^{20}_D$ = −77.1 (*c* = 0.45, H_2O); ^{1}H NMR (400 MHz, CD_3OD) δ 4.65 (d, 1H, ^3J = 3.4, H1), 3.80 (dd, 1H, ^3J = 3.4, 10.3, H2), 3.74 (s, 1H, H6S), 3.62−3.53 (m, 2H, H4, H5), 3.35 (t, 1H, ^3J = 9.4, H3), 3.27 (s, 3H, OMe), 1.92 (s, 3H, Ac); ^{13}C NMR (100 MHz, D_2O) δ 174.4, 98.1, 71.6, 71.1, 69.9, 60.2 (t, J_{CD} = 21.4), 55.1, 53.6, 21.8; FAB-MS *m*/*z* 237.1 (M^+ + 1, 100.0); HRMS (M^+ + 1) *m*/*z* calcd for $C_9H_{17}DNO_6$ 237.1197, found 237.1201.

Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*N*-acetamido-α-D-glucose (9α). To a solution of methyl-α,β-GlcNAc **8**α (1.00 g, 4.25 mmol) in DMF (15 mL) was added α,α-benzaldehyde dimethyl acetal (0.65 g, 4.25 mmol) and *p*-TsOH hydrate (2.5 mg, 0.013 mmol). The reaction mixture was heated at reflux for 2 h and cooled to room temperature, and saturated $NaHCO_3$ was added. The product was extracted with CH_2Cl_2, washed (brine), dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product (0.452 g, 33%) as a yellow solid. The α and β anomers were separated by flash chromatography (2% MeOH in $CHCl_3$). A pure fraction of **9**α (80 mg) was obtained as a white solid and recrystallized from MeOH: mp = 250−252 °C; $[\alpha]^{25}_D$ = +29.2 (*c* = 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H, Ar), 7.38−7.36 (m, 3H, Ar), 5.85 (d, 1H, *J* = 8.2, NH), 5.54 (s, 1H), 4.70 (d, 1H, *J* = 3.7, H1), 4.27 (dd, 1H, *J* = 3.2, 8.2, H6*pro*R), 4.21 (ddd, 1H, *J* = 3.7, 9.0, 9.2, H2), 3.89 (ddd, 1H, *J* = 3.0, 9.0, 9.2, H3), 3.77 (m, 2H, H5, H6*pro*S), 3.57 (dd, 1H, *J* = 9.0, 9.2, H4), 3.39 (s, 3H, OMe), 3.01 (d, 1H, *J* = 3.0, OH), 2.05 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 137.1, 129.2, 128.3, 126.3, 102.0, 98.8, 82.1, 70.8, 68.8, 62.3, 55.3, 54.1, 23.3; FAB MS *m*/*z* 324.2 (M^+ + 1, 44.8); HRMS (M^+ + 1) *m*/*z* calcd $C_{16}H_{22}NO_6$ 324.1447, found 324.1460.

Methyl (6*R*)-(6-^{2}H$_1$)-4,6-*O*-Benzylidene-2-deoxy-2-*N*-acetamido-α-D-glucose (9α-*d*). To a solution of **8**α-*d* (0.060 g, 0.25 mmol) in DMF (6 mL) were added α,α-benzaldehyde dimethyl acetal (0.038 g, 0.25 mmol) and *p*-TsOH (1.5 mg, 0.030 mmol). The reaction mixture was heated at reflux for 18 h and cooled to room temperature, and saturated $NaHCO_3$ was added. The resulting white precipitate was extracted with CH_2Cl_2, washed (brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (2% MeOH in $CHCl_3$) to yield **9**α-*d* (17.7 mg, 21.5%) as a white solid: mp = 250−252 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H, Ar), 7.38−7.36 (m, 3H, Ar), 5.85 (d, 1H, ^3J = 8.2, NH), 5.54 (s, 1H, H7), 4.70 (d, 1H, ^3J = 3.7, H1), 4.21 (ddd, 1H, ^3J = 3.7, 9.0, 9.2, H2), 3.89 (ddd, 1H, ^3J = 1.5, 9.0, 9.0, H3), 3.77 (m, 2H, H5, H6R), 3.57 (dd, 1H, ^3J = 9.0, 9.2, H4), 3.39 (s, 3H, OMe), 3.06 (d, 1H, ^3J = 1.5, OH), 2.05 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 137.1, 129.2, 128.3, 126.3, 101.9, 98.8, 82.1, 70.8, 68.5 (t, J_{CD} = 23.6), 62.2, 55.3, 54.1, 23.3; FAB MS *m*/*z* 325.3 (M^+ + 1, 100.0); HRMS (M^+ + 1) *m*/*z* calcd for $C_{16}H_{21}DNO_6$ 325.1510, found 325.1514.

β-GlcNac Series. Methyl 3,4-Di-*O*-benzyl-2-deoxy-2-*N*-acetamido-β-D-glucose (5β). To a solution of **4**β[19] (1.53 g, 2.32 mmol) in 1:1 HOAc/CH_2Cl_2 (40 mL) was added a 1.38 M solution of HBr in HOAc (1.10 mL, 4.56 mmol). The reaction mixture was stirred for 3 min at 5 °C, followed by the addition of water and CH_2Cl_2. The organic layer was separated, washed (saturated $NaHCO_3$, brine), dried (Na_2SO_4), filtered, concentrated in vacuo, and triturated with hexane to yield a white solid (0.96 g, 100%). The solid was crystallized from $CHCl_3$/petroleum ether: mp = 202−205 °C; $[\alpha]^{27}_D$ = +16.4 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.24 (m, 10H, Ar), 5.39 (d, 1H, ^3J = 7.8, NH), 4.84 (d, 1H, ^2J = 11.5), 4.83 (d, 1H, ^2J = 11.0), 4.73 (d, 1H, ^3J = 8.1, H1), 4.65 (d, 1H, ^2J = 11.0), 4.65 (d, 1H, ^2J = 11.5), 4.07 (t, 1H, ^3J = 9.0, H3), 3.88 (m, 1H, H6*pro*S), 3.73 (m, 1H, H6*pro*R), 3.59 (t, 1H, ^3J = 9.0, H4), 3.46 (s, 3H), 3.43 (m, 1H, H5), 3.33 (m, 1H, H2), 1.89 (m, 1H, OH), 1.85 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 146.9, 138.3, 137.9, 128.5, 128.0, 127.9, 127.3, 101.0, 80.3, 78.5, 75.1, 74.8, 61.9, 57.2, 56.9, 23.6; FAB-MS *m*/*z* 438.5 (M^+ + Na, 10.2), 416.5 (M^+ + 1, 4.6); HRMS (M^+ + 1) *m*/*z* calcd for $C_{23}H_{30}NO_6$ 416.2073, found 416.2073.

Methyl 6-Aldehydo-3,4-di-*O*-benzyl-2-deoxy-2-*N*-acetamido-β-D-glucose(6β). To a solution of oxalyl chloride (0.77 mL, 8.84 mmol) in CH_2Cl_2 (50 mL) was added DMSO (1.16 mL, 17.7 mmol) at −78 °C. After the solution was stirred at −78 °C for 5 min, a solution of **5**β (1.84 g, 4.42 mmol) in CH_2Cl_2 (100 mL) was added. The reaction mixture was stirred at −78 °C for an additional 15 min before NEt_3 (3.68 mL, 26.5 mmol) was added. The reaction mixture was allowed to warm to room temperature over 30 min. The reaction mixture was washed (0.05% HCl, saturated $NaHCO_3$, brine), dried (Na_2SO_4), filtered, concentrated in vacuo, and azeotroped from toluene to give aldehyde **6**β (1.74 g, 96%) as a pale yellow solid. This material was used directly in the next reaction without further purification: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.76 (s, 1H), 7.37−7.25 (m, 10H), 6.32 (d, 1H, ^3J = 8.0), 4.69 (d, 1H, ^2J = 11.1), 4.63 (m, 3H), 4.59 (d, 1H, ^2J = 12.7), 4.22 (d, 1H, ^3J = 4.0), 4.11 (m, 1H), 3.96 (t, 1H, ^3J = 9.0), 3.75 (t, 1H, ^3J = 9.0), 3.51 (s, 3H), 1.81 (s, 3H, Ac);^{13}C NMR (100 MHz, CD_2Cl_2): δ 200.5, 169.6, 138.2, 137.7, 129.0, 128.7, 128.6, 128.3, 128.1, 101.9, 79.2, 75.8, 75.1, 73.3, 72.5, 57.1, 50.1, 23.5; IR (CD_2Cl_2) 3693, 3056, 2981, 2831, 2687, 1725, 1681; FAB-MS *m*/*z* 446.2 (M^+ + Na, 3.4), 414.2 (M^+ + 1, 5.3); HRMS (M^+ + 1) *m*/*z* calcd for $C_{23}H_{28}NO_6$ 414.1917, found 414.1913.

Methyl (6*R*)-(6-^{2}H$_1$)-3,4-Di-*O*-benzyl-2-deoxy-2-*N*-acetamido-β-D-glucose ((6*R*)-(6-^{2}H$_1$)-7β-*d*). Reduction with Alpine-Borane-*d* was followed as described for the synthesis of (6*R*)-(6-^{2}H$_1$)-**7**α-*d*. Reduction of aldehyde **6**β (1.63 g, 3.94 mmol) with (*R*)-(+)-Alpine-Borane-*d* provided (6*R*)-(6-^{2}H$_1$)-**7**α-*d* (0.64 g, 74%) as a white solid after trituration from hexane: mp = 218−220 °C; $[\alpha]^{25}_D$ = +14.3 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.24 (m, 10H, Ar), 5.39 (d, 1H, ^3J = 7.8, NH), 4.84 (d, 1H, ^2J = 11.5), 4.83 (d, 1H, ^2J = 11.0), 4.73 (d, 1H, ^3J = 8.1, H1), 4.65 (d, 1H, ^2J = 11.0), 4.65 (d, 1H, ^2J = 11.5), 4.07 (t, 1H, ^3J = 9.0, H3), 3.86 (m, 1H, H6S), 3.59 (t, 1H, ^3J = 9.0, H4), 3.46 (s, 3H), 3.43 (m, 1H, H5), 3.33 (m, 1H, H2), 1.89 (m, 1H, OH), 1.85 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 137.9, 128.5, 128.0, 127.9, 127.8, 101.0, 80.3, 78.5, 75.0, 74.8, 61.6 (t, J_{CD} = 21.0), 57.2, 56.9, 23.6; FAB-MS *m*/*z* 439.3 (M^+ + Na, 4.4), 417.3 (M^+ + 1, 3.8); HRMS (M^+ + 1) calcd for $C_{23}H_{29}DNO_6$ 417.2136, found 417.2126. Anal.

Calcd for $C_{23}H_{28}DNO_6 + H_2O$: C, 60.38; H, 6.61; N, 3.06. Found: C, 60.05; H, 6.66; N, 3.14.

Methyl (6*R*)-(6-$^2H_1$)-2-deoxy-2-*N*-acetamido-*β*-D-glucose (8*β*-*d*). To a solution of **7***β*-*d* (1.16 g, 2.78 mmol) in HOAc/EtOAc/EtOH (20/10/85 mL) was added Pearlman's catalyst (0.40 g, 20% $Pd(OH)_2$/C). The reaction mixture was charged and shaken in a H_2 atmosphere (50 psi) on a Parr hydrogenator for 24 h. The catalyst was removed by filtration through Celite, and the solvent was concentrated in vacuo to give a white solid. This material was dissolved in EtOH and precipitated by addition of Et_2O to give **8***β*-*d* (0.55 g, 83%) as a colorless solid: mp = 187−190 °C; $[\alpha]^{25}_D = +21.3$ (*c* = 0.47, H_2O); ^{1}H NMR (400 MHz, D_2O) *δ* 4.30 (d, 1H, ^3J = 8.5, H1), 3.77 (s, 1H, H6S), 3.54 (t, 1H, ^3J = 9.0), 3.38 (m, 1H), 3.36 (s, 3H), 3.30 (m, 2H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, D_2O) *δ* 174.7, 101.9, 75.8, 73.9, 69.9, 60.4 (t, J_{CD} = 21.4), 57.0, 55.4, 22.1; FAB-MS *m*/*z* (M^+ + 1) 237.0 (100.0); HRMS (M^+ + 1) *m*/*z* calcd for $C_9H_{17}DNO_6$ 237.1197, found 237.1201.

Methyl-4,6-*O*-Benzylidene-2-deoxy-2-*N*-acetamido-*β*-D-glucose (9*β*). This compound was synthesized as described for **9**α, and a fraction was isolated after flash chromatography to give a pure sample of **9***β* (94 mg, 7.0%). Colorless needles were obtained by recrystallization from $CHCl_3$: mp = 279−281 °C; $[\alpha]^{25}_D = -59.3$ (*c* = 0.56, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.81 (d, 1H, *J* = 8.5, NH), 7.44−7.35 (m, 5H, Ar), 5.59 (s, 1H, CHPh), 5.27 (d, 1H, *J* = 5.0, OH), 4.37 (d, 1H, *J* = 8.0, H1), 4.20 (dd, 1H, *J* = 4.8, 10.0, H6*pro*R), 3.72 (t, 1H, *J* = 10.0, H6*pro*S), 3.58−3.51 (m, 2H, H2, H3), 3.39 (t, 1H, ^3J = 10.0, H4), 3.33 (m, 1H, H5), 3.32 (s, 3H, OMe), 1.81 (s, 3H, Ac); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 169.1, 137.7, 128.8, 128.0, 126.3, 102.4, 100.6, 81.2, 70.5, 67.5, 65.9, 56.0, 55.9, 23.1; FAB-MS *m*/*z* 324.2 (M^++ 1, 100.0); HRMS (M^+ + H) *m*/*z* calcd for $C_{16}H_{22}NO_6$ 324.1447, found 324.1432.

Methyl (6*R*)-(6-$^2H_1$)-4,6-*O*-Benzylidene-2-deoxy-2-*N*-acetamido-*β*-D-glucose (9*β*-*d*). To a solution of methyl (6*R*)-(6-$^2H_1$)-2-deoxy-2-*N*-acetamido-*β*-D-glucose **8***β*-*d* (0.020 g, 0.085 mmol) in benzaldehyde (0.15 mL) was added dry $ZnCl_2$ (0.020 g). The resulting suspension was stirred at room temperature for 18 h, after which time distilled water and CH_2Cl_2 were added. The CH_2Cl_2 layer was separated and evaporated to give a gum, which was triturated with Et_2O to give a white solid (20 mg). This solid was recrystallized from MeOH to give **9***β*-*d* (12.7 mg, 30%) as colorless needles: mp = 278−280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.81 (d, 1H, *J* = 8.5, NH), 7.44−7.35 (m, 5H, Ar), 5.59 (s,1H, CHPh), 5.27 (d, 1H, *J* = 5.0, OH), 4.37 (d, 1H, *J* = 8.0, H1), 3.70 (d, 1H, *J* = 10.0, H6S), 3.58−3.51 (m, 2H, H2, H3), 3.39 (t, 1H, ^3J = 10.0, H4), 3.33 (m, 1H, H5), 3.32 (s, 3H, OMe), 1.81 (s, 3H, Ac); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 169.1, 137.7, 128.8, 128.0, 126.3, 102.4, 100.6, 81.2, 70.5, 67.5 (t, J_{CD} = 22.5), 65.9, 56.0, 55.9, 23.1; FAB MS *m*/*z* 325.1 (M^+ + 1, 100.0); HRMS (M^+ + 1) *m*/*z* calcd for $C_{16}H_{21}DNO_6$ 325.1510, found 325.1504.

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Supporting Information Available: 2D ^{1}H−^{1}H DQF-COSY spectra for **9**α and **9***β*, 1D NOE ^{1}H difference spectrum for **9**α, ^{2}H NMR spectrum for **7**α-*d*, and ^{1}H NMR spectra for **5**α, **5***β*, **7**α-*d*, **7***β*-*d*, **8**α-*d*, **8***β*-*d*, **9**α, **9**α-*d*, **9***β*, and **9***β*-*d* (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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