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Carbohydrate Research 334 (2001) 271–279

CARBOHYDRATE RESEARCH

Stereoselective synthesis of [^{13}C]methyl 2-[^{15}N]amino-2-deoxy-β-D-glucopyranoside derivatives

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Received 1 May 2001; accepted 9 July 2001

Abstract

Efficient syntheses of three [^{13}C]methyl 2-[^{15}N]amino-2-deoxy-β-D-glucopyranoside derivatives are described. Amination of the D-glucal with (saltmen)Mn(^{15}N) proceeded with 11:1 stereoselectivity favoring the gluco configuration; subsequent methylation of the [^{15}N]lactol using [^{13}C]iodomethane and silver(I) oxide afforded the doubly labeled β glucoside in high yield. This compound served as the common precursor for three [^{13}C]methyl 2-[^{15}N]aminoglucosides: (2-[^{15}N]trifluoroacetyl-), (2-[^{15}N]acetyl-), and (2-[^{15}N]azido-). Selected heteronuclear coupling constants are reported.

Keywords: Stereoselectivity; ^{13}C-Labeling; ^{15}N-Labeling; Heteronuclear coupling constants

1. Introduction

Isotopically labeled carbohydrates are valuable compounds for conformational studies by nuclear magnetic resonance (NMR) spectroscopy and for the elucidation of biosynthetic pathways of complex oligosaccharides.[1,2] Numerous synthetic and biosynthetic routes have been developed for deuterated and ^{13}C-labeled monosaccharide derivatives, many of which are commercially available.† In contrast, ^{15}N-labeled aminosaccharides are much less accessible. Although synthetic approaches to 2-[^{15}N]-D-glucosamine derivatives have been described,[3] the yields are low and would require additional steps for their use as synthetic intermediates. Stereoselective ^{15}N incorporation into protected monosaccharide derivatives at a late stage is much more efficient and is especially relevant for multistep synthetic sequences. Methods to consider for stereoselectively introducing nitrogen into carbohydrate derivatives via electrophilic addition to glycals have been developed, including nitrochlorination,[4] azidonitration,[5] phosphoramidoglycosylation,[6] [4 + 2] cycloaddition,[7] sulfonamidoglycosylation,[8] amination by Mn(V) nitrido complexes,[9] and acetamidoglycosylation.[10]

We present an efficient and stereoselective route toward doubly labeled [^{13}C]methyl 2-[^{15}N]amino - 2 - deoxy - β - D - glucopyranoside derivatives with different nitrogen-containing functional groups at C-2. We applied the saltmen(Mn)(V)nitrido methodology developed by Du Bois et al.[9] to the stereoselective [^{15}N]amination of glycals (Fig. 1) for the following reasons: (i) the amination was reported

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† Leading suppliers include Omicron Biochemicals, Inc. (http://www.omicronbio.com) and Sigma–Aldrich Chemicals (http://www.sigma-aldrich.com).

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PII: S0008-6215(01)00203-8

to proceed with good facioselectivity favoring the gluco configuration; (ii) the amination conditions were compatible with several different protecting groups, including the electron-rich and acid-sensitive *p*-methoxybenzylidene acetal; and (iii) the (saltmen)-Mn(^{15}N) reagent could be easily prepared on a gram scale from aqueous $^{15}NH_4OH$, a relatively inexpensive source of ^{15}N. An efficient synthetic route would enable us to produce sufficient quantities of ^{13}C, ^{15}N-labeled carbohydrates for solid-state NMR studies such as rotational-echo double resonance (REDOR) spectroscopy.[11]

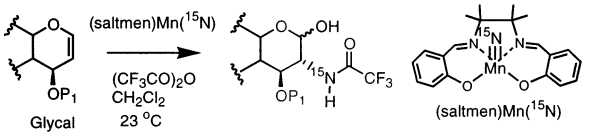
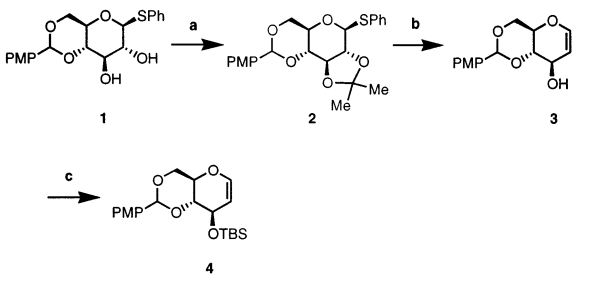
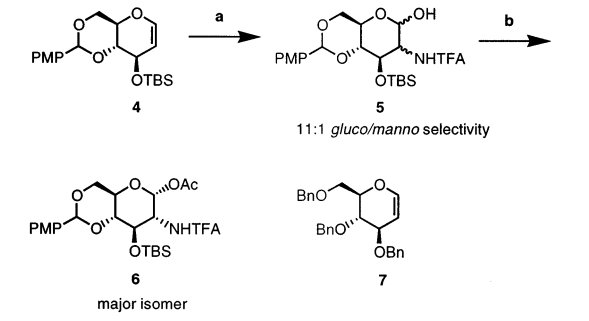


Fig. 1. ^{15}N amination of glycals using the (saltmen)Mn(N) methodology developed by Du Bois et al.[9]



Scheme 1. Reagents and conditions: (a) 2-methoxypropene, CSA, THF, 40 °C (90%); (b) lithium naphthalenide, THF, − 78 °C (75%); (c) TBSCl, imidazole, DMF, 23 °C (97%). PMP = *p*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl.



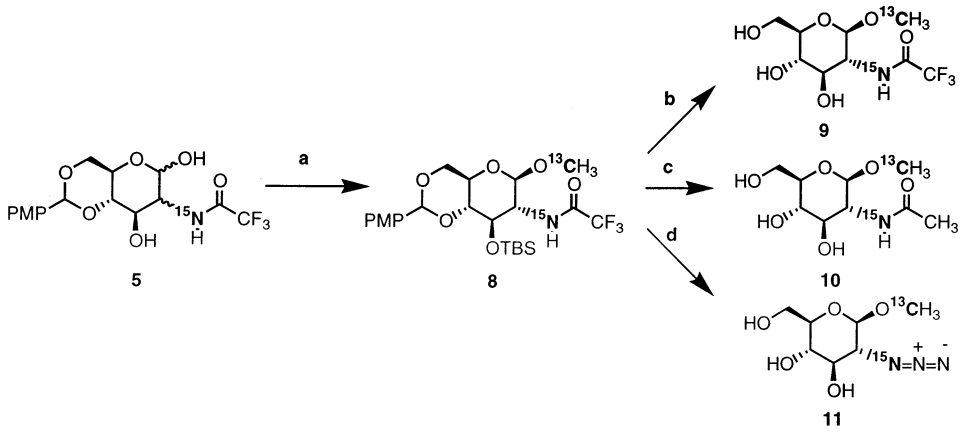
Scheme 2. Reagents and conditions: (a) (saltmen)Mn(N), $(CF_3CO)_2O$, CH_2Cl_2, 23 °C (66%); (b) Ac_2O, pyridine, 23 °C (94% overall yield, 76% isolated yield of **6**). PMP = *p*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl.

2. Results and discussion

We first optimized the preparation of the D-glucal **4** as a precursor for [^{15}N]amination (Scheme 1). Treatment of the known phenyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside (**1**)[12] with 2-methoxypropene in the presence of catalytic amounts of D-camphorsulfonic acid afforded the crystalline derivative **2** in 90% yield. This compound was treated with an excess of lithium naphthalenide at − 78 °C[13] to give the crystalline glycal derivative **3** in 75% yield, which was then protected as the *tert*-butyldimethylsilyl ether derivative **4** in 97% yield.

Stereoselective amination[9] of glucal **4** was achieved by the slow addition of a stoichiometric amount of (saltmen)Mn(N) in dichloromethane to a concentrated solution of the D-glucal and trifluoroacetic anhydride (3.5 equiv) in dichloromethane at room temperature, yielding lactol **5** as a diastereomeric mixture in 66% yield (Scheme 2). The optimized reaction conditions and determination of diastereomeric ratios of the aminated product were accomplished using natural-abundance (saltmen)Mn(N). Acetylation of the lactols and careful separation by silica-gel chromatography enabled us to evaluate their D-gluco/D-manno configurations by ^{1}H NMR coupling constant analysis. Two fractions were isolated, one of them being the enantiopure 1-*O*-acetyl-α-D-glucosamine derivative **6** (76%) and the other a mixture of the remaining three diastereomers (18%), the majority being the 1-*O*-acetyl-β-D-glucosamine derivative. The D-gluco/D-manno ratio was greater than 11:1 based on the yields and the integration values of the H-1 peaks. The 4,6-*p*-methoxybenzylidene acetal was determined to be important for the high stereoselectivity at C-2: amination of tribenzyl-D-glucal **7** resulted in an approximately 1:1 gluco/manno ratio, suggesting that the *p*-methoxybenzylidene acetal stabilizes a transition state favoring the gluco configuration by restricting the conformation of glucal **4**.

The ^{15}N-labeled lactol **5** was treated with silver(I) oxide and [^{13}C]iodomethane in tetrahydrofuran at room temperature to afford the doubly ^{13}C, ^{15}N-labeled methyl glycoside **8** in



Scheme 3. Reagents and conditions: (a) Ag_2O, $^{13}CH_3I$, THF, 23 °C (76% isolated yield); (b) (i) TBAF, THF, 23 °C; (ii) AcOH–THF–water, 45 °C (94% after two steps); (c) (i) NaOH, CH_3OH–water, reflux; (ii) Ac_2O, CH_3OH, 0 °C; (iii) AcOH–THF–water, 45 °C (81% after three steps); (d) (i) NaOH, CH_3OH–water, reflux; (ii) TfN_3, K_2CO_3, $CuSO_4$ (cat), 90% CH_3OH, 0–23 °C (73% after three steps). PMP = *p*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl.

76% isolated yield (Scheme 3). Deprotection of **8** by fluoride treatment and hydrolysis under mildly acidic conditions produced [^{13}C]methyl 2-[^{15}N]trifluoroacetamido-2-deoxy-β-D-glucopyranoside (**9**) as a white solid in 94% yield over two steps. Compound **8** could also be cleanly hydrolyzed by sodium hydroxide in aqueous methanol to the free amine, then acetylated and deprotected as described above to afford [^{13}C]methyl 2-[^{15}N]acetamido-2-deoxy-β-D-glucopyranoside (**10**) as a white solid in 81% yield over three steps. Treating the free amine with freshly prepared triflyl azide (TfN_3) and catalytic quantities of copper(II) sulfate[14] produced a 2-azido-2-deoxyglucose derivative, which upon deprotection afforded [^{13}C]methyl 2-[^{15}N]azido-2-deoxy-β-D-glucopyranoside (**11**) as a white crystalline solid in 73% yield after three steps. It is worth mentioning that the rate of azide formation was significantly accelerated by increasing the concentration of water in the reaction mixture; reactions conducted in 10:9:1 CH_2Cl_2–CH_3OH–water were complete within 14 h, whereas reaction mixtures containing 1% water or less required several days to reach completion.

The ^{1}H NMR spectrum of compound **8** (300 MHz) in $CDCl_3$ confirms double isotope incorporation (Fig. 2). Interestingly, all four doubly labeled compounds **8**–**11** exhibited an identical $^3J_{C,H}$ coupling constant across the glycosidic bond (*J* 4.5 Hz in each case). In the case of compound **11**, one single peak was observed on the ^{15}N NMR spectrum (50 MHz) at 70.7 ppm, demonstrating that no isotopic scrambling occurred during the azide formation. It is also noteworthy that the $^2J_{N,H2}$ coupling constant was either undetectable or very small (<1 Hz) for compounds **9**–**11**, whereas $^3J_{N,H3}$ coupling constants (1.5–2.0 Hz) were observed in the case of compounds **9** and **10**. ^{15}N–^{13}C coupling constants were also evaluated: $^1J_{N,C2}$ for the azido compound **11** (3.2 Hz) was only a third that of the amido compounds **9** and **10** (10.2–10.6 Hz), whereas $^2J_{N,C1}$ was 3.5 Hz for compound **11** but undetectable for the other two compounds.

In summary, we have developed an expeditious and stereoselective route to [^{13}C]methyl 2-[^{15}N]amino-2-deoxy-β-D-glucopyranoside derivatives from readily available starting materials and relatively inexpensive sources of ^{15}N and ^{13}C. The 4,6-*p*-methoxybenzylidene acetal plays a key role in the high gluco:manno stereoselectivity of the ^{15}N amination step. Further solution and solid-state NMR studies of these compounds are in progress and will be reported in due course.

3. Experimental

General methods.—Melting points were determined with a capillary tube melting point apparatus and are uncorrected. IR spectra were acquired with a Perkin–Elmer Spectrum

2000 FTIR spectrometer. Optical rotations were measured at 20–25 °C with a Rudolph Research AUTOPOL® III polarimeter. ^{1}H and ^{13}C spectra were recorded on a Varian Unity Inova NMR spectrometer operating at 300 and 75 MHz, respectively, or a Bruker DRX 500 operating at 500 and 125 MHz, respectively. The spectra were referenced to the solvent used: (7.27 and 77.23 ppm for $CDCl_3$, 3.31 and 49.15 ppm for CD_3OD, 7.16 and 128.39 ppm for C_6D_6), unless otherwise stated. ^{15}N spectra were recorded on a Bruker DRX 500 operating at 50 MHz and referenced to an external 1 M solution of ^{15}N-labeled urea in Me_2SO at 77 ppm (liquid $^{15}NH_3$ is referenced to 0 ppm). Mass spectra were acquired using either a Hewlett–Packard 5989B or a Finnigan 4000 mass spectrometer. The purity of the products was assessed using TLC on Silica Gel 60 F_{254} (E. Merck) with either ethanolic *p*-anisaldehyde or ninhydrin staining solutions. Chromatographic separations were performed using silica gel (ICN SiliTech, 32–63 μm). Elemental analyses were performed in the Department of Chemistry, Purdue University.

*Phenyl 2,3-di-*O*-isopropylidene-4,6-*O*-p-methoxybenzylidene-1-thio-β-*D*-glucopyranoside* (**2**).—2-Methoxypropene (5.5 mL, 57 mmol) was added to a solution of **1** (4.48 g, 11.4 mmol) and D-camphorsulfonic acid (133 mg, 0.6 mmol) in dry THF (100 mL), and the mixture was stirred under Ar in the dark at 40 °C for 1 h. The mixture was cooled to 0 °C, quenched with satd aq $NaHCO_3$ (30 mL), extracted with EtOAc (150 mL), dried over Na_2SO_4, and concentrated. The residue was crystallized from 95% hot EtOH (150 mL) to give **2** as a white crystalline solid (4.46 g, 90%): mp 145–148 °C; $[\alpha]_D$ −47° (*c* 1, $CHCl_3$); IR (thin film): 2986, 2893, 1615, 1518, 1382, 1249, 1099, 1067, 1041, 963, 831, 751 cm^{-1}; ^{1}H NMR (C_6D_6): δ 7.64 (m, 2 H, Ar–H), 7.52 (m, 2 H, $J_{A,A'} = J_{X,X'}$ 2.1, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 7.03 (m, 3 H, Ar–H), 6.79 (m, 2 H, $J_{A,A'} = J_{X,X'}$ 2.1, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 5.20 (s, 1 H, C*H*–PMP), 4.57 (d, 1 H, $J_{1,2}$ 9.6 Hz, H-1), 4.14 (dd, 1 H, $J_{5,6a}$ 4.8, $J_{6a,6b}$ 10.2 Hz, H-6a), 3.65 (dd, 1 H, $J_{3,4}$ 9.6, $J_{4,5}$ 8.7 Hz, H-4), 3.49 (t, 1 H, $J_{5,6b}$ 10.2 Hz, H-6b), 3.44 (dd, 1 H, $J_{2,3}$ 8.7 Hz, H-2), 3.35 (dd, 1 H, H-3), 3.24 (s, 3 H, OCH_3), 3.07 (ddd, 1 H, H-5), 1.37 (s, 3 H, CH_3), 1.35 (s, 3

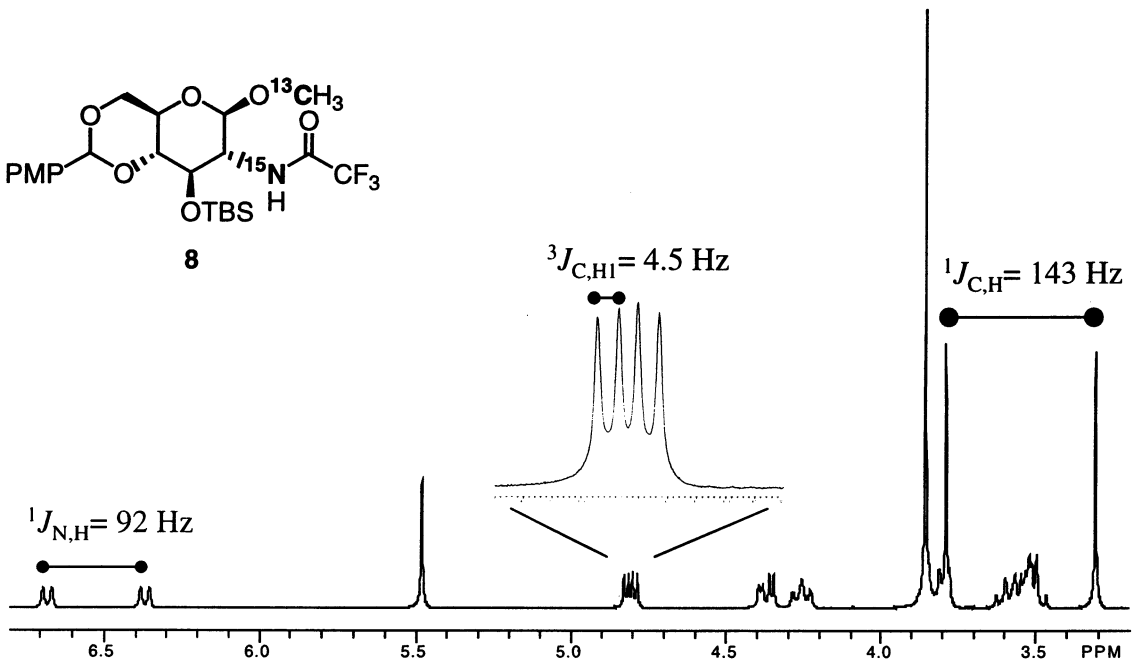


Fig. 2. Partial ^{1}H NMR (300 MHz, $CDCl_3$) of compound **8** which served as the common precursor for the synthesis of the doubly labeled compounds **9**–**11**.

H, CH_3); ^{13}C NMR (C_6D_6): δ 160.93 (1 C, *C*–OCH$_3$ Ar), 134.51, 132.51, 130.74, 129.32, 128.78, 128.38, 114.10 (11 C, C Ar), 111.52, 101.70 (2 C, C acetal), 85.78 (1 C, C-1), 80.55, 79.71, 77.09, 72.58, 68.98 (5 C, C-2,-3,-4,-5,-6), 55.09 (1 C, O*C*H$_3$), 27.15, 26.99 (2 C, C(*C*H$_3$)$_2$); CIMS: m/z 431, $[M+1]^+$. Anal. Calcd for $C_{23}H_{26}O_6S$: C, 64.17; H, 6.09; S, 7.45. Found: C, 64.03; H, 6.08; S, 7.21.

4,6-O-p-*Methoxybenzylidene*-D-*glucal* (**3**).—The 1 M lithium naphthalenide solution in THF was prepared according to the literature protocol.[13] To a solution of **2** (1.0 g, 2.3 mmol) in dry THF (30 mL) under Ar and at −78 °C was added the freshly prepared lithium naphthalenide solution in THF (10 mL, 9.9 mmol) dropwise for 30 min, and the mixture was stirred until complete disappearance of the starting material by TLC (2:1 hexanes–EtOAc). The reaction was quenched with 4:1 THF–AcOH (2 mL). The flask was removed from the −78 °C bath and diluted with CH_2Cl_2 (80 mL) and aq 0.5 M NaOH (10 mL). The reaction mixture was separated, dried over Na_2SO_4 and concentrated. The resulting solid residue was crystallized from 9:1 hexanes–EtOAc to afford a white crystalline solid (462 mg, 75%): mp 133–134 °C; $[\alpha]_D$ −19° (*c* 1, $CHCl_3$); IR (thin film): 3285, 2874, 1639, 1615, 1519, 1377, 1253, 1233, 1172, 1125, 1096, 1069, 1032, 1006, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.44 (m, 2 H, $J_{A,A'} = J_{X;X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.4 Hz, Ar–H), 6.91 (m, 2 H, $J_{A,A'} = J_{X;X'}$ 2.1, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.35 (dd, 1 H, $J_{1,2}$ 6.3, $J_{1,3}$ 1.8 Hz, H-1), 5.57 (s, 1 H, C*H*–PMP), 4.79 (dd, $J_{2,3}$ 2.1 Hz, H-2), 4.52 (m, 1 H, $J_{3,OH}$ 4.2, $J_{3,4}$ 6.3 Hz, H-3), 4.36 (dd, 1 H, $J_{5,6a}$ 4.5, $J_{6a,6b}$ 9.9 Hz, H-6a), 3.95 (dd, 1 H, $J_{4,5}$ 10.5 Hz, H-4), 3.85–3.77 (m, 5 H, H-5,-6b,OCH_3), 2.18 (d, 1 H, $J_{3,OH}$ 4.2 Hz, O*H*); ^{13}C NMR ($CDCl_3$): δ 160.47 (1 C, *C*–OCH$_3$ Ar), 144.30 (1 C, C-1), 129.72, 127.77, 113.93 (5 C, C Ar), 103.78 (C acetal), 101.96, 80.86, 68.54, 68.49, 66.77 (5 C, C-2,-3,-4,-5,-6), 55.51 (1 C, O*C*H$_3$); CIMS: m/z 265, $[M+1]^+$. Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.52; H, 6.15.

3-O-tert-*Butyldimethylsilyl*-*4,6*-O-p-*methoxybenzylidene*-D-*glucal* (**4**).—To a solution of **3** (432 mg, 1.6 mmol) in dry DMF (12 mL) at 23 °C was added imidazole (346 mg, 5.1 mmol) and *tert*-butylchlorodimethylsilane (731 mg, 4.8 mmol). After 18 h, satd aq $NaHCO_3$ (20 mL) was added at 0 °C along with Et_2O (50 mL) and water (10 mL). The mixture was extracted, the organic phase washed with water (3 × 10 mL), dried over Na_2SO_4, and concentrated. The crude residue was eluted from a plug of silica gel with 9:1 hexanes–EtOAc containing 0.1% of Et_3N to give **4** as a clear syrup (603 mg, 97%): $[\alpha]_D$ −59.5° (*c* 2, $CHCl_3$); IR (thin film): 2891, 2954, 2930, 2857, 1640, 1615, 1518, 1381, 1251, 1233, 1170, 1128, 1105, 1073, 1036, 1017, 1007, 867, 836, 824, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.43 (m, 2 H, $J_{A,A'} = J_{X;X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.90 (m, 2 H, $J_{A,A'} = J_{X;X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.30 (dd, 1 H, $J_{1,2}$ 6.0, $J_{1,3}$ 1.5 Hz, H-1), 5.56 (s, 1 H, C*H*–PMP), 4.67 (dd, $J_{2,3}$ 2.1 Hz, H-2), 4.50 (ddd, 1 H, $J_{3,4}$ 7.2 Hz, H-3), 4.34 (dd, 1 H, $J_{5,6a}$ 4.2, $J_{6a,6b}$ 9.6 Hz, H-6a), 3.93–3.79 (m, 6 H, H-4,-5,-6b, OCH_3), 0.94 (s, 9 H, C(CH_3)$_3$), 0.14 (s, 3 H, SiCH_3), 0.13 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$): 160.12 (1 C, *C*–OCH$_3$), 143.51 (1 C, C-1), 130.07, 127.51, 113.67 (5 C, C Ar), 105.62 (1 C, C acetal), 101.44, 80.74, 68.99, 68.50, 67.50 (5 C, C-2,-3,-4,-5,-6), 55.46 (1 C, O*C*H$_3$), 26.01 (3 C, C(*C*H$_3$)$_3$), 18.45 (1 C, *C*(CH$_3$)$_3$), −4.17 (1 C, Si*C*H$_3$), −4.60 (1 C, Si*C*H$_3$); CIMS: m/z 379, $[M+1]^+$. Anal. Calcd for $C_{20}H_{30}O_5Si$: C, 63.46; H, 7.99; Si, 7.42. Found: C, 63.13; H, 7.88; Si, 7.33.

Preparation of (saltmen)Mn(^{15}*N).*—To a stirring solution of H_2saltmen[15] (1.3 g, 4 mmol) in CH_3OH (50 mL) at 50 °C was added Mn(OAc)$_2$·4 H_2O (1.03 g, 4 mmol) portionwise. The mixture was then brought to reflux for 1 h, cooled to 23 °C, and stirred for 30 min. To the vigorously stirring dark mixture was added aq $^{15}NH_4OH$ (6 M, 5 g, 30 mmol), followed by the dropwise addition of commercial bleach (∼0.7 M NaOCl, 18 mL, 12 mmol) for 45 min. The heterogeneous mixture was cooled to 0 °C and diluted with CH_2Cl_2 (150 mL). The organic phase was abundantly washed with small portions of water (4 × 50 mL), concentrated, and passed through a Brockmann activity IV basic Al_2O_3 plug with CH_2Cl_2 (200 mL). The dark-green solution was concentrated and crystallized from 2:1 hexanes–EtOAc to afford a lustrous dark

green powder (1.25 g, 80%): ^{1}H NMR ($CDCl_3$): δ 8.05 (s, 2 H, HCN); 7.34 (dt, 2 H, *J* 7.0, *J* 2 Hz, Ar–H), 7.19 (dd, 2 H, *J* 8.0, *J* 1.5 Hz, Ar–H), 7.12 (d, 2 H, *J* 8.5 Hz, Ar–H), 6.66 (dt, 2 H, *J* 1.0, *J* 7 Hz, Ar–H), 1.44 (s, 6 H, 2 CH_3), 1.43 (s, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$): δ 168.05 (2 C, *C*=N), 162.93, 135.87, 134.14, 122.42, 120.60, 116.56 (12 C, Ar–C), 72.58 (2 C, $C(CH_3)_2$), 25.66 (2 C, 2 CH_3), 24.02 (2 C, 2 CH_3); ^{15}N NMR ($CDCl_3$) δ 1057.6 (Mn≡^{15}N).

3-O-tert-*Butyldimethylsilyl*-*4,6*-O-p-*methoxybenzylidene*-*2*-*deoxy*-*2*-*trifluoroacetamido*-D-*glucopyranose* (**5**).—To a solution of **4** (235 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) and freshly distilled trifluoroacetic anhydride (0.306 mL, 2.2 mmol) was added (saltmen)Mn(N) (10 mL, 0.06 M in CH_2Cl_2) with a syringe pump during approximately 12 h (0.8 mL/h) at 23 °C and under Ar. After the addition, silica gel (0.6 g), Celite® (0.6 g), and *n*-pentane (20 mL) were added, and the mixture was vigorously stirred at 23 °C for 10 min. The mixture was filtered, diluted in ice-cold satd aq $NaHCO_3$ (20 mL) and extracted. The organic fraction was rapidly passed through a short plug of silica gel with anhyd ether (150 mL) and concentrated to give a yellow syrup. Silica gel chromatography using a 10:90–33:67 EtOAc–hexanes gradient containing 0.1% of Et_3N yielded lactol **5** as a light-yellow foam and as a mixture of diastereomers (210 mg, 66%): $[\alpha]_D$ −30° (*c* 0.7, $CHCl_3$); IR (thin film): 3428 (OH), 2931, 1711 (C=O from $COCF_3$), 1615, 1519 (C=O from $COCF_3$), 1382, 1303, 1251, 1169, 1129, 1083, 1047, 837, 781 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.40 (m, 2 H, Ar–H), 6.89 (m, 2 H, Ar–H), 6.62 (broad d, 1 H, NH (minor)), 6.54 (d, 1 H, *J* 9.3 Hz, NH (major)), 5.55–5.43 (4 s, 1 H, C*H*–PMP), 5.41 (s, 1 H, H-1 (minor)), 5.22 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1α (gluco)), 5.00 (s, 1 H, H-1 (minor)), 4.85 (d, 1 H, $J_{1,2}$ 8.6Hz, H-1β (gluco)), 4.41–3.99 (m, 4 H, H-2,-3,-4,-6a), 3.81 (s, 3 H, OCH_3), 3.76–3.40 (m, 2 H, H-5,-6b), 2.97–2.88 (2 s, 1 H, O*H*), 0.84–0.79 (4 s, 9 H, C(CH_3)$_3$), 0.08 to −0.04 (4 s, 6 H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 160.33 (1 C, *C*–OCH_3 Ar), 129.71, 127.84, 127.60 (minor), 113.72 (5 C, C Ar), 102.27, 101.17 (minor) (1 C, C acetal), 95.84 (minor), 92.27 (1 C, C-1), 82.45, 70.13, 68.97, 66.77 (minor), 63.162, 55.45, 55.20 (6 C, C-2,-3,-4,-5,-6,OCH_3), 25.73 (3 C, C(CH_3)$_3$), 18.19 (1 C, $C(CH_3)_3$), −3.81 (1 C, SiCH_3), −4.94 (1 C, SiCH_3); CIMS: *m*/*z* 508, $[M+1]^+$. Anal. Calcd for $C_{22}H_{32}F_3NO_7Si$: C, 52.06; H, 6.35; F, 11.23; N, 2.76; Si, 5.53. Found: C, 52.27; H, 6.26; F, 11.19; N, 2.48; Si, 5.29.

The procedure described above using (saltmen)Mn(^{15}N) yielded the corresponding ^{15}N-labeled lactol in identical yield (181 mg, 66%): ^{1}H NMR ($CDCl_3$): δ 7.40 (m, 2 H, Ar–H), 6.89 (m, 2 H, Ar–H), 6.62 (broad dd, 1 H, J_{NH} 90.9 Hz, ^{15}NH (minor)), 6.46 (dd, 1 H, *J* 9.3, J_{NH} 91.8 Hz, ^{15}NH (major)), 5.55–5.47 (4 s, 1 H, C*H*–PMP), 5.28 (t, 1 H, *J* 3.3 Hz, H-1α (gluco)), 4.91 (t, 1 H, *J* 8.1Hz, H-1β (gluco)), 4.41–3.99 (m, 4 H, H-2,-3,-4,-6a), 3.82 (s, 3 H, OCH_3), 3.76–3.46 (m, 2 H, H-5,-6b), 3.02 (broad s, 1 H, O*H*), 2.93 (d, *J* 4.2 Hz, O*H*), 0.85–0.79 (4 s, 9 H, C(CH_3)$_3$), 0.08 to −0.04 (6 s, 6 H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 160.30 (1 C, *C*–OCH_3 Ar), 129.67, 127.84, 127.81 (minor), 127.60 (minor), 113.70 (5 C, C Ar), 102.24 (1 C, C acetal), 95.84 (minor), 92.14 (1 C, C-1), 82.46, 70.13, 68.95, 66.77 (minor), 63.05, 55.43 (5 C, C-3,-4,-5,-6, OCH_3), 55.30 (d, $^1J_{C,N}$ 10.5 Hz, C-2), 25.71 (3 C, C(CH_3)$_3$), 18.16 (1 C, $C(CH_3)_3$), −3.84 (1 C, SiCH_3), −4.95 (1 C, SiCH_3).

1-O-*Acetyl*-*3*-O-tert-*butyldimethylsilyl*-*4,6*-O-p-*methoxybenzylidene*-*2*-*deoxy*-*2*-*trifluoroacetamido*-D-*glucopyranose* (**6**).—To a solution of the lactol **5** (75 mg, 0.14 mmol) in pyridine (3 mL) was added Ac_2O (2 mL) at 0 °C under Ar, and the reaction was slowly brought to 23 °C and stirred for 18 h. The mixture was quenched at 0 °C with satd aq $NaHCO_3$ (30 mL), diluted in $CHCl_3$ (60 mL), extracted, dried over Na_2SO_4, and concentrated under reduced pressure to form a yellow foam. Silica-gel chromatography using a 10:90–25:75 EtOAc–hexanes gradient containing 0.1% of Et_3N afforded the pure gluco α-acetate **6** (62 mg, 76%) and the remaining three diastereomers (15 mg, 18%) as a mixture of gluco β-acetate and manno α-/β-acetates in a 63:37 ratio, as determined by ^{1}H NMR integration. ^{1}H NMR ($CDCl_3$) for **6**: δ 7.41 (m, 2 H, $J_{A,A'} = J_{X,X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.91 (m, 2 H, $J_{A,A'} = J_{X,X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.19 (d, 1 H, $J_{1,2}$ 3.6 Hz,

H-1), 6.14 (d, 1 H, J 8.7 Hz, NH), 5.50 (s, 1 H, C*H*–PMP), 4.36 (dt, 1 H, $J_{2,3}$ 9.3 Hz, H-2), 4.28 (dd, 1 H, $J_{5,6a}$ 4.5, $J_{6a,6b}$ 9.9 Hz, H-6a), 3.99 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 3.86 (dt, 1 H, $J_{4,5} = J_{5,6b}$ 9.9 Hz, H-5), 3.83 (s, 3 H, OCH_3), 3.74 (t, 1 H, $J_{6b,6a}$ 10.2 Hz, H-6b), 3.61 (t, 1 H, H-4), 2.21 (s, 3 H, COCH_3), 0.82 (s, 9 H, C(CH_3)$_3$), 0.05 (s, 3 H, SiCH_3), 0.00 (s, 3 H, SiCH_3).

*Methyl 3-*O*-tert-butyldimethylsilyl-4,6-*O*-p-methoxybenzylidene-2-deoxy-2-trifluoroacetamido-β-*D*-glucopyranoside* (**8**).—To a solution of the lactol **5** (45 mg, 0.09 mmol) and silver(I) oxide (51 mg, 0.22 mmol) in dry THF (1 mL) at 23 °C and under an Ar atmosphere was added iodomethane (82 μL, 1.3 mmol). The mixture was allowed to stir for 5 days in a well-sealed flask then filtered over Celite®, rinsed with EtOAc (40 mL), and concentrated. Silica gel chromatography using a 10:90–33:67 EtOAc–hexanes gradient containing 0.1% of Et_3N afforded compound **8** as a white foam (35 mg, 75%): $[\alpha]_D$ −37.8° (*c* 0.7, $CHCl_3$); IR (thin film): 3305, 2931, 2858, 1704 (C=O from $COCF_3$), 1616, 1560 (C=O from $COCF_3$), 1518, 1383, 1251, 1170, 1109, 1094, 1076, 1036, 1006, 838, 781 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.39 (m, 2 H, $J_{A,A'} = J_{X;X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.89 (m, 2 H, $J_{A,A'} = J_{X;X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.37 (d, 1 H, J 8.1 Hz, NH), 5.46 (s, 1 H, C*H*–PMP), 4.79 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 4.34 (dd, 1 H, $J_{5,6a}$ 4.2, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.23 (dd, 1 H, $J_{2,3}$ 8.1 Hz, H-3), 3.82 (s, 3 H; OCH_3), 3.77 (t, 1 H, $J_{5,6b}$ 10.5 Hz, H-6b), 3.54–3.42 (m, 6 H, H-2,-4,-5 OCH_3), 0.807 (s, 9 H, C(CH_3)$_3$), −0.02 (s, 3 H, SiCH_3), −0.04 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$): δ 160.32 (1 C, *C*–OCH_3 Ar), 129.73, 127.84, 113.72 (5 C, C Ar), 102.09 (1 C, C acetal), 101.16 (1 C, C-1), 82.38, 71.29, 68.76, 66.37, 59.49, 57.46, 55.45 (7 C, C-2,-3,-4,-5,-6, 2O*C*H_3), 25.83 (3 C, C(*C*H_3)$_3$), 18.23 (1 C, *C*(CH$_3$)$_3$), −3.78 (1 C, Si*C*H_3), −5.01 (1 C, Si*C*H_3); CIMS: m/z 522, $[M+H]^+$. Anal. Calcd for $C_{23}H_{34}F_3NO_7Si$: C, 52.96; H, 6.57; N, 2.69. Found: C, 53.11; H, 6.59; N, 2.55.

The procedure described above using ^{15}N-labeled lactol yielded the corresponding doubly labeled methyl glucoside **8** (101 mg, 76%): ^1H NMR ($CDCl_3$): δ 7.39 (m, 2 H, $J_{A,A'} = J_{X;X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.89 (m, 2 H, $J_{A,A'} = J_{X;X'}$ 2.7, $J_{A,X} = J_{A',X'}$ 8.7 Hz, Ar–H), 6.48 (dd, 1 H, J 8.1, J_{NH} 92.4 Hz, ^{15}NH), 5.44 (s, 1 H, C*H*–PMP), 4.76 (dd, 1 H, $J_{1,2}$ 8.4, $^3J_{1,C}$ 4.5 Hz, H-1), 4.34 (dd, 1 H, $J_{5,6a}$ 4.2, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.21 (broad t, 1 H, J 8.4 Hz, H-3), 3.82 (s, 3 H, OCH_3), 3.77 (t, 1 H, H-6b), 3.58–3.42 (m, 3 H, H-2,-4,-5), 3.50 (d, 3 H, $^1J_{C,H}$ 143.7 Hz, O^{13}CH_3), 0.80 (s, 9 H, C(CH_3)$_3$), −0.01 (s, 3 H, SiCH_3), −0.04 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$) (coupled): δ 57.52 (dq, 1 C, $^3J_{C,H1}$ 4.5, $^1J_{C,H}$ 143.7 Hz, O^{13}CH_3).

*Methyl 2-deoxy-2-trifluoroacetamido-β-*D*-glucopyranoside* (**9**).—To a solution of compound **8** (32 mg, 0.06 mmol) in dry THF was added tetrabutylammonium fluoride (0.153 mL, 0.153 mmol) (1 M solution in THF). The reaction was stirred under Ar at 23 °C for 18 h, cooled to 0 °C, diluted with satd aq $NaHCO_3$ (10 mL), and extracted twice with EtOAc (2 × 15 mL). The combined organic fractions were dried over Na_2SO_4, concentrated, and eluted with a short plug of silica gel with EtOAc (100 mL) containing 0.1% of Et_3N to afford a white solid. This white solid was dissolved in 8:1:1 HOAc–THF–water (5 mL) and stirred at 45 °C for 1.5 h. The mixture was concentrated under reduced pressure, and the resulting residue dissolved in warm THF (~1 mL), transferred into a glass centrifuge tube, and triturated with distilled hexanes (5 mL) to obtain a white precipitate. This precipitate was centrifuged, washed with distilled hexanes (5 mL), and dried to afford a white powder (16 mg, 90% after two steps): mp 208–212 °C; $[\alpha]_D$ −29° (*c* 1, CH_3OH); IR (thin film): 3280, 2940, 1707 and 1562 (C=O from $COCF_3$), 1210, 1186, 1159, 1075, 1032, 882, 634 cm^{-1}; ^1H NMR (CD_3OD): δ 4.41 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 3.91 (dd, 1 H, J 1.8, J 12.0 Hz, H-6a), 3.75–3.67 (m, 2 H, H-2,-6b), 3.54 (dd, 1 H, $J_{2,3}$ 7.8 Hz, H-3), 3.49 (s, 3 H, OCH_3), 3.38–3.27 (m, 2 H, H-4,-5); ^{13}C NMR (CD_3OD): 103.06 (1 C, C-1), 78.24 (1 C, C-5), 75.42 (1 C, C-4), 72.28 (1 C, C-3), 62.84 (1 C, C-6), 57.80 (1 C, C-2), 57.26 (1 C, O*C*H_3); CIMS: m/z 290, $[M+1]^+$. Anal. Calcd for $C_9H_{14}F_3NO_6$: C, 37.38; H, 4.88; N, 4.84. Found: C, 36.99; H, 4.94; N, 4.42.

The procedure described above using ^{13}C,^{15}N-labeled methyl glucoside **8** yielded the corresponding doubly labeled *N*-trifluoroacetylglucosamine as a white powder (21 mg, 94% after two steps): ^1H NMR (CD_3OD): δ 4.40 (d, 1 H, $^3J_{1,C}$ 4.5, $J_{1,2}$ 8.4 Hz, H-1), 3.91 (dd, 1 H, *J* 1.8, *J* 12.0 Hz, H-6a), 3.75–3.67 (m, 2 H, H-2,-6b), 3.54 (ddd, 1 H, $^3J_{N,3}$ 2.0, $J_{2,3}$ 7.8 Hz, H-3), 3.47 (d, 3 H, $^1J_{C,H}$ 142.8 Hz, $O^{13}CH_3$), 3.38–3.27 (m, 2 H, H-4,-5); ^{13}C NMR (CD_3OD) (coupled): δ 55.94 (dq, 1 C, $^3J_{C,H1}$ 4.5, $^1J_{C,H}$ 142.8 Hz, $O^{13}CH_3$); ^{13}C NMR (CD_3OD): δ 159.51 (dq, 1 C, $^1J_{C,N}$ 19.2, $^2J_{C,F}$ 36.5 Hz, *C*=O), 117.76 (dq, 1 C, $^2J_{C,N}$ 11.1, $^1J_{C,F}$ 285.5 Hz, CF_3), 103.06 (d, 1 C, $^2J_{C1,C}$ 2.2 Hz, C-1), 78.24 (s, 1 C, C-5), 75.42 (s, 1 C, C-4), 72.28 (d, 1 C, $^4J_{C3,C}$ 1.6 Hz, C-3), 62.84 (s, 1 C, C-6), 57.80 (dd, 1 C, $^3J_{C2,C}$ 3.2, $^1J_{C2,N}$ 10.2 Hz, C-2), 57.26 (s, 1 C, $O^{13}CH_3$); ^{15}N NMR (CD_3OD): δ 113.7 (t, 1 N, $^1J_{N,D}$ 14 Hz, ^{15}NTFA).

*Methyl 2-acetamido-2-deoxy-β-*D*-glucopyranoside* (**10**).—To a solution of compound **8** (42 mg, 0.08 mmol) in CH_3OH (7 mL) and water (1 mL) was added NaOH (0.8 g). The reaction was brought to reflux for 7 h, cooled to 23 °C, diluted with water (4 mL), and extracted several times with $CHCl_3$ (4 × 10 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated to give the crude amine as a yellow solid. The amine was redissolved in CH_3OH (5 mL) at 0 °C and treated with Ac_2O (0.5 mL). The reaction was stirred at 0 °C under Ar for 30 min, then quenched at 0 °C with satd aq $NaHCO_3$ (4 mL), and extracted several times with $CHCl_3$ (3 × 15 mL). The combined organic fractions were dried over Na_2SO_4, and concentrated to afford a white solid. This white solid was dissolved in 8:1:1 HOAc–THF–water (5 mL) and stirred at 45 °C for 1.5 h. The solvents were removed under reduced pressure, and the residue was dissolved in hot THF ($\sim$1 mL), transferred into a glass centrifuge tube and triturated with distilled hexanes (5 mL) to obtain a white precipitate. This precipitate was centrifuged, washed with distilled hexanes (5 mL), and dried to finally afford a white powder (14 mg, 74% yield over three steps); mp 194–196 °C; $[\alpha]_D$ −42° (*c* 0.75, CH_3OH); ^1H NMR (CD_3OD); δ 4.31 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 3.88 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 12 Hz, H-6a), 3.68 (dd, 1 H, $J_{5,6b}$ 5.1 Hz, H-6b), 3.63 (dd, $J_{2,3}$ 9.9 Hz, H-2), 3.46 (s, 3 H, OCH_3), 3.43 (t, 1 H, $J_{3,4}$ 10.5 Hz, H-3), 3.34–3.22 (m, 2 H, H-4,-5), 1.97 (s, 3 H, $COCH_3$); ^{13}C NMR (D_2O, referenced to Me_4Si): δ 174.92 (C=O), 102.16 (1 C, C-1), 76.11 (1 C, C-5), 74.18 (1 C, C-3), 70.15 (1 C, C-4), 60.96 (1 C, C-6), 57.27 (1 C, C-2), 55.67 (1 C, OCH_3), 22.36 (1 C, $COCH_3$); CIMS: *m*/*z* 236, $[M+H]^+$. Anal. Calcd for $C_9H_{17}NO_6$: C, 45.95; H, 7.28; N, 5.95. Found: C, 45.69; H, 7.58; N, 5.61.

The procedure described above using ^{13}C,^{15}N-labeled methyl glucoside **8** yielded the corresponding doubly labeled *N*-acetylglucosamine as a white powder (11 mg, 81% after three steps): ^1H NMR (CD_3OD): δ 4.31 (dd, 1 H, $J_{1,2}$ 8.4, $^3J_{1,C}$ 4.5 Hz, H-1), 3.88 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 12 Hz, H-6a), 3.68 (dd, 1 H, $J_{5,6b}$ 5.1 Hz, H-6b), 3.63 (dt, $^2J_{N,2}$ 1.0, $J_{2,3}$ 9.9 Hz, H-2), 3.46 (d, 3 H, $^1J_{C,H}$ 142.8 Hz, $O^{13}CH_3$), 3.43 (dt, 1 H, $^3J_{N,3}$ 1.5, *J* 10.5 Hz, H-3), 3.34–3.22 (m, 2 H, H-4,-5), 1.97 (d, 3 H, $^3J_{H,N}$ 1.5 Hz, $COCH_3$); ^{13}C NMR (CD_3OD) (coupled): δ 57.06 (dq, 3 C, $^3J_{C,H1}$ 4.5, $^1J_{C,H}$ 142.8 Hz, $O^{13}CH_3$); ^{13}C NMR (CD_3OD): δ 173.94 (d, 1 C, $^1J_{C,N}$ 15.1 Hz, *C*=O), 103.72 (d, 1 C, $^2J_{C1,C}$ 2.3 Hz, C-1), 78.16 (s, 1 C, C-5), 76.40 (s, 1 C, C-4), 72.29 (d, 1 C, $^4J_{C3,C}$ 1.5 Hz, C-3), 62.94 (s, 1 C, C-6), 57.38 (dd, 1 C, $^3J_{C2,C}$ 3.2, $^1J_{C2,N}$ 10.6 Hz, C-2), 57.11 (s, 1 C, $O^{13}CH_3$), 23.06 (d, 1 C, $^2J_{C,N}$ 8.3 Hz, $COCH_3$); ^{15}N NMR (CD_3OD): δ 120.2 (t, 1 N, $^1J_{N,D}$ 14 Hz, ^{15}NAc).

*Methyl 2-azido-2-deoxy-β-*D*-glucopyranoside* (**11**).—To a solution of compound **8** (27 mg, 0.05 mmol) in CH_3OH (7 mL), water (1 mL), was added NaOH (0.8 g). The mixture was brought to reflux for 7 h, cooled to 23 °C, diluted with water (5 mL), and extracted several times with $CHCl_3$ (4 × 10 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated to afford the crude amine as a yellow solid. The solid was redissolved at 0 °C with 90% CH_3OH (7 mL), and treated with the freshly made triflyl azide[14] solution in CH_2Cl_2 (7 mL) (Note: TfN_3 is potentially explosive), $CuSO_4$ (1 mg), and K_2CO_3 (3 mg). The mixture was slowly warmed up to 23 °C and stirred for 14 h under Ar, *carefully* concentrated, and eluted with a

silica gel column using a 20:80–33:67 EtOAc–hexanes gradient containing 0.1% of Et_3N to afford a white solid. This white solid was dissolved in 8:1:1 HOAc–THF–water (5 mL) and stirred at 45 °C for 1.5 h. The reaction mixture was concentrated under reduced pressure to afford a clear oil, which was eluted with a short silica gel column with 9:1 CH_2Cl_2–CH_3OH to afford the desired compound as a solid (8.7 mg, 76% yield). This solid can be crystallized from hexanes–THF (see protocol for compounds **9** and **10**): mp 111–113 °C; $[\alpha]_D$ −22.8° (*c* 0.5, CH_3OH); IR (thin film): 3368, 2929, 2223, 2111 (N_3), 1729, 1451, 1385, 1266, 1155, 1118, 1074, 1025, 955, 892, 692 cm^{-1}; ^1H NMR (CD_3OD): δ 4.23 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 3.86 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6b,6a}$ 12.0 Hz, H-6a), 3.68 (dd, 1 H, $J_{5,6b}$ 5.1, H-6b), 3.55 (s, 3 H, OCH_3), 3.32–3.24 (m, 3 H, H-3,-4,-5), 3.11 (t, 1 H, $J_{2,3} = J_{3,4}$ 8.0 Hz, H-2); ^{13}C NMR (CD_3OD): δ 104.28 (1 C, C-1), 78.09 (1 C, C-5), 76.57 (1 C, C-4), 71.70 (1 C, C-3), 68.38 (1 C, C-2), 62.67 (1 C, C-6), 57.41 (1 C, OCH_3); CIMS: m/z 220, $[M+1]^+$. Anal. Calcd for $C_7H_{13}N_3O_5$: C, 38.36; H, 5.98; N, 19.17. Found: C, 38.27; H, 5.74; N, 18.95.

The procedure described above using ^{13}C,^{15}N-labeled methyl glucoside **8** yielded the corresponding doubly labeled 2-azido-2-deoxyglucose as a white crystalline solid (8.6 mg, 73% after three steps): ^1H NMR (CD_3OD): δ 4.23 (dd, 1 H, $^3J_{1,C}$ 4.5, $J_{1,2}$ 8.1 Hz, H-1), 3.86 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6b,6a}$ 12.0 Hz, H-6a), 3.68 (dd, 1 H, $J_{5,6b}$ 5.1 Hz, H-6b), 3.55 (d, 3 H, $^1J_{C,H}$ 142.2 Hz, $O^{13}CH_3$), 3.32–3.24 (m, 3 H, H-3,-4,-5), 3.11 (t, 1 H, $J_{2,3} = J_{3,4}$ 8.0 Hz, H-2); ^{13}C NMR (CD_3OD) (decoupled): δ 57.25 (dq, 1 C, $^3J_{C,H1}$ 4.5, $^1J_{C,H}$ 142.2 Hz, $O^{13}CH_3$); ^{13}C NMR (CD_3OD): δ 104.28 (t, 1 C, $^2J_{C1,C} = {}^2J_{C1,N}$ 2.5 Hz, C-1), 78.09 (s, 1 C, C-5), 76.57 (d, 1 C, $^3J_{C4,N}$ 3.1 Hz, C-4), 71.70 (d, 1 C, $^2J_{C3,N}$ 2.2 Hz, C-3), 68.38 (t, 1 C, $^3J_{C2,C} = {}^1J_{C2,N}$ 3.2 Hz, C-2), 62.67 (s, 1 C, C-6), 57.41 (s, 1 C, $O^{13}CH_3$); ^{15}N NMR (CD_3OD): δ 70.7 (s, 1 N, $^{15}NN_2$).

Acknowledgements

The authors gratefully acknowledge financial assistance from the American Chemical Society Petroleum Research Fund (36069-AC1), the American Heart Association Midwest Affiliates (30399Z), and the Purdue Research Foundation in the form of a fellowship to F.P.B. The authors also wish to acknowledge Dr H. Daniel Lee for providing elemental analyses, Dr Karl V. Wood and Arlene Rothwell for mass spectrometry services, and Dr Klaas Hallenga and Dr Edwin Rivera for NMR assistance.

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