Efficient Synthesis of a Stereochemically Defined Carbohydrate Scaffold: Carboxymethyl 2-Acetamido-6-Azido-4-*O*-Benzyl-2-deoxy-α-D-Glucopyranoside

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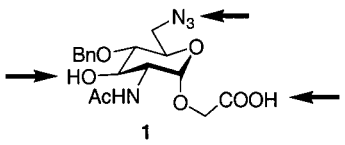
Introduction

Although natural products remain a rich source of new lead compounds for drug discovery, the ability to rapidly perform structure−function studies is limited by the synthesis. The combinatorial chemistry approach has become well-established among modern drug discovery strategies especially where generation of a large number of structurally diverse molecules is necessary in a short period of time for high throughput screening programs.[1] Such approaches can facilitate the identification of ligands that bind to biological receptors, promoting the chemical understanding of cellular processes. Recently, we have disclosed a new strategy for the construction of broad screening libraries using a carbohydrate-based universal pharmacophore mapping library strategy.[2]

Hexoses are readily available in enantiomerically pure form and offer a conformationally rigid pyran backbone with three-dimensional arrangement of substituents. For small molecule receptor ligands such a well-defined spatial arrangement of functional groups, classically defined as the "three-point motif", is necessary for the selective recognition between molecule and its protein receptors. Moreover, hexose derivatives have demonstrated high affinity to several pharmacologically important receptors (e.g., G-protein-coupled receptors),[3] which clearly suggest the potential of monosaccharides as three-dimensional chemical platforms for strategic generation of combinatorial libraries. However, success of such a strategy relies heavily on the development of carbohydrate-based novel chemical entities with appropriate spatial arrangements for diversification. Herein we describe the design and efficient synthesis of a monosaccharide scaffold **1**, containing three diversity sites that allow development of libraries with distinct chiral molecular recognition motifs.



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Results and Discussion

The design of scaffold **1** involved incorporation of a carboxymethyl group at C-1, a free hydroxyl group at C-3, and an azido functionality at C-6 on the modified hexose backbone. These three functional groups offer the desired chemoselectivity necessary for rapid combinatorial solid-phase synthesis and create the ultimate "three-point binding motif" in a relatively few number of synthetic steps.

The synthesis of compound **1** is outlined below. A modified Fisher glycosidation of 2-acetamido-2-deoxy-D-glucose with acidic allyl alcohol in the presence of $BF_3 \cdot Et_2O$ under reflux (10h) provided **2** as a 9:1 (α: *β*) mixture of anomers which after crystallization ($EtOH/Et_2O$) furnished the desired α-anomer **2** in 63% yield (Scheme 1).

Since, the target 6-azido-glucopyranoside **1** possesses a free C-3 hydroxyl group and a benzyl-protected C-4 hydroxyl group, a regioselective reductive ring-opening of the corresponding 4,6-*O*-benzylidene acetal appeared to be appropriate for incorporation of the 4-*O*-benzyl ether substituent. Thus, treatment of allyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**2**) with benzaldehyde dimethyl acetal in the presence of catalytic amount of TsOH (DMF, 60 °C) under reduced pressure afforded the 4,6-*O*-benzylidene acetal **3** in 83% yield. Acetylation of compound **3** under usual conditions (Ac_2O, pyr, DMAP) furnished the 3-*O*-acetyl-4,6-benzylidene derivative **4** (72%). The next step in the synthetic sequence was the ring-opening of the benzylidene acetal to obtain the desired 4-*O*-benzyl derivative. The most useful and widely utilized method for differentiating the C-4 and C-6 hydroxyl groups of sugars involve reductive ring-opening of a rather easily available 4,6-*O*-benzylidene acetal.[4] However, this usually produces the 6-*O*-benzyl regioisomer predominantly due to attack of the electrophile at the secondary hydroxyl oxygen (4-O, thermodynamic control).[4a,f,I,k] On the other hand, reported conditions for the production of 4-*O*-benzyl derivatives[4a,f,k−n] are often less chemoselective[4a] and offer unsatisfactory regioselectivity[4k] or yield.[4f] Reductive ring-opening of benzylidene acetal of fully protected 4,6-*O*-(4-methoxybenzylidene)-hexopyranoside with combination of $NaCNBH_3$−TMSCl in acetonitrile has been reported to give the 4-*O*-(4-methoxybenzyl)ethers in good yield and regioselectivity.[4d,e]

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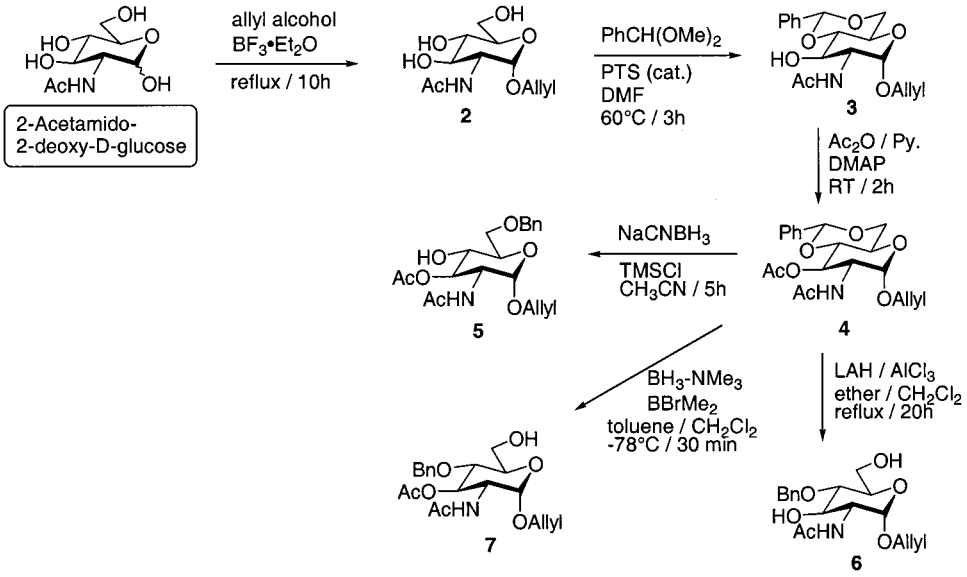
Scheme 1



Interestingly, compound **4** under identical experimental conditions ($NaCNBH_3$−TMSCl) showed the opposite regioselectivity, giving the 6-*O*-benzyl regioisomer **5** in 76% yield. This striking reversal of regioselectivity could be attributed to the enhanced transition state stabilization of the electrophile (TMS^+) by the neighboring C-3 acetoxy group.[5] The acetal-opening with LAH/$AlCl_3$ reagent system has been used to obtain 4-*O*-benzyl ether derivative in the presence of benzyl or allyl ether.[4a] However, reduction of acetal **4** with LAH/$AlCl_3$ under carefully controlled conditions gave 4-*O*-benzyl ether derivative **6** in only 25% yield due to competitive reductive and hydrolytic pathways. The "borane-amine complex/Lewis acid" combination have also been reported to be either nonselective (BH_3·Me_3N−$AlCl_3$),[4f] or low-yielding (BH_3·Me_2NH−BF_3·Et_2O).[4k] Recently, a combination of BH_3/Bu_2BOTf has been used for reductive cleavage of 4,6-*O*-benzylidene acetals of hexopyranosides to the corresponding 4-*O*-benzyl ethers in modest yields.[4l] However, to avoid potential problems associated with scale-up and for ease of handling, we needed to develop a mild, selective, and stable reagent system for this transformation. Interestingly, treatment of compound **4** with H_3B·NMe_3/Me_2BBr at −78 °C afforded the desired 4-*O*-benzyl derivative **7** in 90% yield (column chromatography) without affecting other protecting groups.[6] The high regioselectivity of the process could be rationalized considering the controlled reactivity of H_3B·NMe_3/Me_2BBr reagent system. Although $AlCl_3$ and BF_3·Et_2O have similar steric environments compared to Me_2BBr, moderate acidity of Me_2BBr proved optimal for preferential coordination to the least hindered oxygen (6-O, kinetic control) of the benzylidene acetal prior to opening of the acetal. For the subsequent reduction, on the other hand, the H_3B·NMe_3 complex was conveniently chosen as a stable and modest hydride source. This procedure turned out to be very mild to surrounding functionalities and was used to obtain multigram quantities of **7**.

Next, we needed to convert the 6-OH group to a better leaving group, to introduce the 6-azido functionality in an S_N2 fashion. A brief attempt to convert compound **7** to the corresponding triflate **8** using triflic anhydride in the presence of pyridine led to the formation of the trifloromethanesulfinyl ester. Such an unexpected sulfinyl ester formation under similar conditions have been reported recently with a mechanistic explanation.[7] However, treatment of 6-OH derivative **7** with TsCl in Py in the presence of catalytic amount of DMAP provided the fully protected 6-tosyl-gluco derivative **8a** in 72% yield (Scheme 2). Nucleophilic displacement of tosyl group with azide (NaN_3) was achieved in DMF or DMSO at 90 °C within 3 h (70−80%). At this point, we needed to perform the oxidation of C1-*O*-allyl substituent to the desired carboxymethyl derivative. Use of oxidants, such as $KMnO_4$, was not suitable for this purpose due to the presence of the benzyl ether functionality in **9**. Although ozonolytic cleavage of olefin in the presence of an azido functionality has been reported, to our knowledge, use of ruthenium for oxidation of such a system has no literature precedence. Thus, catalytic ruthenium trichloride-mediated modified Sharpless conditions ($RuCl_3$·H_2O/$NaIO_4$ oxidant in CCl_4:CH_3CN:H_2O) appeared to be most practical for large scale oxidation of **9**.[8] However, when compound **9** was treated with cat. amount of $RuCl_3$·H_2O in the presence of 8 equiv of co-oxidant $NaIO_4$, the 4-*O*-benzoate acid derivative **10** was obtained exclusively due

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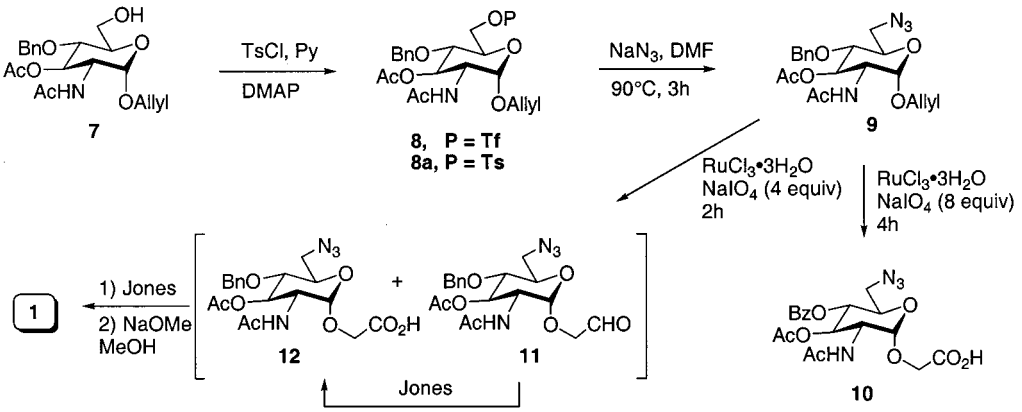
Scheme 2



to over oxidation. A carefully controlled reaction conditions using 4.0 equiv of $NaIO_4$ and with reduced reaction time (2 h), however, provided the desired acid **12** and the intermediate aldehyde **11** in 1:3 ratio. Although aldehyde **11** was easily separated and further oxidized, this mixture was routinely oxidized further under Jones conditions to obtain acid **12**, cleanly.[9] The conditions are mild, catalytic in ruthenium, and suitable for scale-up purposes with a very simple postreaction workup. Finally, deacetylation of 3-*O*-acetyl group of **12** using NaOMe/MeOH provided the desired product **1**.

In conclusion, we have described a highly efficient synthesis of scaffold **1** with appropriate orientation of the functional group triad for the generation of broad spectrum libraries. The described approach is amenable for multigram-scale preparation in the laboratory and gave access to a library of 12000 compound for broad spectrum screening. The regioselective ring-opening of the benzylidene acetal to obtain the 4-*O*-benzyl derivative using $H_3B{\cdot}NMe_3/Me_2BBr$, and efficient oxidation of the 1-*O*-allyl to the 1-*O*-carboxymethyl group in the presence of a benzyl ether as well as an azido functionality, are the two noteworthy transformations of the synthetic scheme and may find broader application for the preparation of highly functionalized carbohydrate derivatives.

Experimental Section

General Methods. All moisture-sensitive reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. THF was freshly distilled from sodium−benzophenone ketyl; ethyl acetate, toluene, and CH_2Cl_2 were freshly distilled from CaH_2. Products were routinely analyzed by ^1H and ^{13}C NMR spectroscopy and by liquid chromatography (LC) with light-scattering (LSD) and mass spectrometry (MS) detectors. ^1H NMR spectra were obtained at 300 MHz, and ^{13}C NMR spectra were obtained at 75.4 MHz.

Allyl 2-Acetamido-2-deoxy-α-D-glucopyranoside (2). A mixture of 2-acetamido-2-deoxy-D-glucose (50 g, 226 mol), allyl alcohol (500 mL, dried over molecular sieve), and $BF_3{\cdot}Et_2O$ (8 mL, 67.8 mmol) is refluxed for 2 h. Allyl alcohol (100 mL, containing 5% of concd HCl) is then added to the above, and the reaction is heated under reflux for 10 h. The reaction mixture is concentrated under reduced pressure, and the resulting gummy residue is crystallized from EtOH−Et_2O to afford compound **2** (37 g, 63%) as a light brown solid. ^1H NMR (300 MHz, DMSO-d_6) δ 7.79(d, J = 6.0 Hz, 1H, NH), 5.94−5.78 (m, 1H, vinylic CH), 5.28, 5.13 (2d, J = 17.4, 10.5 Hz, 2H, vinylic CH_2), 4.65 (d, J = 3.3 Hz, 1H, H-1), 4.07 (dd, J = 13.8, 3.0 Hz, 1H, allylic CH_2), 4.87 (dd, J = 14.1, 4.8 Hz, 1H, allylic CH_2), 3.72−3.54 (m, 2H, H-2, H-6,), 3.52−3.32 (m, 3H, H-6, H-3, H-5), 3.11(t, J = 9.0 Hz, 1H, H-4), 1.82 (s, 3H, $NCOCH_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.58, 134.69, 116.53, 95.99 (C-1), 72.99 (C-5), 70.92 (C-3), 70.63, 66.87 (C-4), 60.87 (C-6), 53.79 (C-2), 22.65; EIMS m/z 262 (MH^+), 260.2 ($M - 1^+$).

Allyl 2-Acetamido-4,6-*O*-benzylidine-2-deoxy-α-D-glucopyranoside (3). To a solution of compound **2** (26 g, 101.5 mmol) in anhydrous DMF (200 mL) are added benzaldehyde dimethylacetal (45 mL, 304.5 mmol) and TsOH (2 g), and the mixture is heated at 60 °C under reduced pressure (ca. 10 mm/Hg) for constant removal of MeOH formed. After 3 h, the reaction mixture is cooled, poured into saturated solution of $NaHCO_3$ (500 mL) to precipitate out the product as solid, filtered, and washed with Et_2O to furnish compound **3** (30 g, 86%) as a white crystalline solid;^1H NMR (300 MHz, DMSO-d_6) δ 8.11 (d, J = 6.0 Hz, 1H, NH), 7.5−7.3 (m, 5H, ArH), 5.98−5.83 (m, 1H, vinylic CH), 5.62 (s, 1H, PhCH), 5.35, 5.18 (2d, J = 17.4, 10.5 Hz, 2H, vinylic CH_2), 5.30 (brs, 1H, 3-OH), 4.79 (d, J = 3.0 Hz, 1H, H-1), 4.22−4.15 (m, 2H, H-2, allylic CH_2), 3.96 (dd, J = 13.5, 5.4 Hz, 1H, allylic CH_2), 3.91−3.41 (m, 5H, H-6, H-3, H-5, H-4), 1.87 (s, 3H, $NCOCH_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.74, 162.45, 137.79, 134.48, 129.56, 129.24, 128.95, 128.10, 126.47, 111.92, 100.98, 96.90 (C-1), 82.00 (C-5), 68.08, 67.64, 67.24, 62.83 (C-6), 54.43 (C-2), 22.62; EIMS m/z 350 (MH^+), 348.3 ($M - 1^+$).

Allyl 2-Acetamido-3-O-acetyl-4,6-*O*-benzylidine-2-deoxy-α-D-glucopyranoside (4). To a solution of compound **3** (29.3 g, 84.19 mmol) in anhydrous pyridine (200 mL) are added Ac_2O (11.9 mL, 102 mmol) and DMAP (4 g). The resulting mixture is stirred at room temperature for 2.5 h under nitrogen and then poured into ice-cold water. The precipitated white solid is filtered, washed repeatedly with water to remove residual pyridine, and redissolved in CH_2Cl_2. The organic layer is dried over anhydrous Na_2SO_4 and then concentrated to obtain compound **4** (23 g, 72%) as a solid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51−7.31 (m, 5H, ArH), 6.02−5.98 (brs, 1H, NH), 5.94−5.81 (m, 1H, vinylic CH), 5.52 (s, 1H, PhCH), 5.35, 5.22 (2d, J = 10.2, 12.0 Hz, 2H, vinylic CH_2), 5.31−5.25 (m, 1H, H-3), 4.87 (d, J = 3.0 Hz, 1H, H-1), 4.36 (td, J = 9.6, 3.6 Hz, 1H, H-2), 4.28 (dd J = 9.9, 4.5 Hz, 1H, H-6), 4.19 (dd, J = 12.0, 6.0 Hz, 1H allylic CH_2,), 3.98 (dd, J = 12.9, 6.6 Hz, 1H, allylic CH_2), 3.91 (dd, J = 9.9, 4.5 Hz, 1H, H-6), 3.77 (t, J = 10.2, 1H, H-5), 3.72 (t, J = 9.3 Hz, 1H, H-4), 2.05 (s, 3H, $OCOCH_3$), 1.96 (s, 3H, $NCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.19, 169.99, 136.82, 133.07, 128.94, 128.05, 126.01, 118.15, 101.36, 96.91 (C-1), 78.85 (C-5), 70.11 (C-3), 68.65, 68.46 (C-4), 62.79 (C-6), 52.32 (C-2), 23.01, 20.76; EIMS m/z 392 (MH^+), 390.3 ($M - 1^+$).

Allyl 2-Acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (5). To a suspension of compound **4** (4.9 g, 10 mmol), $NaCNBH_3$ (60 mmol), and 3 Å molecular sieves in anhydrous acetonitrile (200 mL) at 0 °C is dropwise added TMSCl (60 mmol) and then stirred for 5 h at room temperature. The reaction mixture is filtered through a pad of Celite, poured into a saturated solution of $NaHCO_3$, and extracted three times with methylene chloride. The methylene chloride extract is dried over anhydrous Na_2SO_4 and concentrated, and the residue is purified by column chromatography (EtOAc) to obtain compound **5** (3.0 g, 60%) as an oil;^1H NMR (300 MHz, CD_3OD) δ 7.78 (d, J

(9) For an example of ozonolytic functionalization of *O*-allyl glycosides, see: Park. W. K. C.; Auer, M.; Jaksche, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 10150.

= 6.0 Hz, 1H, NH), 7.42−7.21 (m, 5H, ArH), 6.01−5.86 (m, 1H, vinylic CH), 5.43 (d, J = 6.3 Hz, 1H, C-4-OH), 5.33, 5.17 (2d, J = 17.1, 10.5 Hz, 2H, vinylic CH_2), 4.51 (s, 2H, $PhCH_2$), 5.00 (dd, J = 11.1, 9.3 Hz, 1H, H-3), 4.69 (d, J = 3.6 Hz, 1H, H-1), 4.12 (dd, J = 13.5, 4.8 Hz, 1H, H-2), 4.03−3.93 (m, 2H, allylic CH, H-6), 3.73−3.58 (m, 2H, allylic CH, H-6), 3.46−3.32 (m, 2H, H-4, H-5), 1.95 (s, 3H, $OCOCH_3$), 1.80 (s, 3H, $NCOCH_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 173.36, 173.04, 138.99, 134.73, 129.17, 128.90, 128.59, 128.54, 118.20, 97.34 (C-1), 74.74 (C-3), 74.30 (C-5), 72.31, 69.84 (C-4), 69.59, 69.35 (C-6), 52.87 (C-2), 22.56, 20.91; EIMS m/z 394 (MH^+), 392.3 ($M - 1^+$).

Allyl 2-Acetamido-4-*O*-benzyl-2-deoxy-α-D-glucopyranoside (6). To a suspension of LAH (250 mg, 6.56 mmol) in anhydrous CH_2Cl_2 (32 mL) and Et_2O (90 mL) under argon are added the acetal **4** (2.0 g, 5.11 mmol) and $AlCl_3$ (875 mg, 6.56 mmol), and the reaction is stirred under reflux for 20 h. The reaction mixture is quenched with EtOAc (15 mL), filtered through a pad of Celite, and then concentrated. The residue is purified by column chromatography on silica gel using 5% MeOH−CH_2Cl_2 as eluent to obtain compound **6** (440 mg, 25%) as a white solid; ^{1}H NMR (300 MHz,CD_3OD) δ 7.59−7.21 (m, 5H, ArH), 6.11−5.82 (m, 1H, vinylic CH), 5.28,5.15 (2d, J = 17.1, 9.6 Hz, 2H, vinylic CH_2), 4.93, 4.83(2d, J = 10.8, 11.0 Hz, 2H, $PhCH_2$), 4.64 (d, J = 10.5 Hz, 1H, H-1), 4.18−3.93 (m, 2H, allylic CH_2), 3.89−3.58 (m, 5H, H-2, H-3, H-5, H-6), 3.43 (t, J = 9.0 Hz, 1H, H-4), 1.98 (s, 3H, $OCOCH_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 173.81, 140.07, 135.54, 130.05, 129.43, 129.16, 128.78, 127.65, 117.73, 97.70, 80.18 (C-5), 76.16 (C-3), 73.39, 73.20 (C-4), 69.75, 69.24 (C-6), 62.44, 55.77 (C-2), 22.71; EIMS m/z 352 (MH^+), 350.3 ($M - 1^+$).

Allyl 2-Acetamido-3-*O*-acetyl-4-*O*-benzyl-2-deoxy-α-D-glucopyranoside (7). To a cooled (−78 °C) solution of compound **4** (10.0 g, 25.5 mmol) in CH_2Cl_2 under argon is added a solution of $H_3B{\cdot}NMe_3$ complex (7.4 g, 102 mmol) in toluene (50 mL) followed by Me_2BBr (7.44 mL, 64 mmol). After stirring for 30 min, 200 mL of 0.5 M sodium phosphate buffer (pH 7.3) is added, and the solution is allowed to warm to room temperature. The organic layer is washed with saturated $NaHCO_3$ solution and water, dried (Na_2SO_4), and evaporated. The residue is chromatographed on silica gel using EtOAc to obtain compound **7** (9 g, 90%) as a white solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.41−7.22 (m, 5H, ArH), 6.02−5.84 (m, 1H, vinylic CH_2), 5.33, 5.20 (2d, J = 17.1, 10.5 Hz, 2H, vinylic CH_2), 5.30 (m, 1H, H-3), 4.81 (d, J = 3.9 Hz, 1H, H-1), 4.67, 4.60 (2d, J = 11.7, 11.6 Hz, 2H, $PhCH_2$), 4.22−4.16 (m, allylic CH_2, H-6), 4.12−3.88 (m, 1H, allylic CH_2), 3.86−3.68 (m, 3H, H-4, H-5, H-6), 1.92 (s, 3H, OAc), 1.90 (s, 3H, $NHCOCH_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 173.35, 172.24, 139.49, 135.15, 129.36, 129.31, 128.90, 128.77, 128.66, 128.58, 118.15, 97.50 (C-1), 77.50 (C-3), 75.66 (C-5), 74.51, 73.01 (C-4), 69.29, 61.75 (C-6), 53.34 (C-2), 22.44, 20.95; EIMS m/z 394 (MH^+), 392.3 ($M - 1^+$).

Allyl 2-Acetamido-3-*O*-acetyl 4-*O*-benzyl-2-deoxy-6-*O*-tosyl-α-D-glucopyranoside (8a). To a solution of compound **7** (9.0 g, 23 mmol) in pyridine (100 mL) are added TsCl (13.0 g, 63 mmol) and DMAP (3 g). The reaction mixture is stirred at room temperature for 6 h, poured into ice−water, and then extracted with methylene chloride. The organic layer is washed with brine, dried (Na_2SO_4), and evaporated. The residue is chromatographed on silica gel using EtOAc as elutent to obtain compound **8a** (8.0 g, 72%) as a gummy liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.28 (m, 7H, ArH), 7.21−7.18 (m, 2H, ArH), 5.88−5.72 (m, 2H, vinylic CH, NH), 5.27, 5.18 (2d, J = 5.4, 12.0 Hz, 2H, vinylic CH_2), 5.26−5.24 (m, 1H, H-3), 4.73 (d, J = 3.6 Hz, 1H, H-1), 4.60, 4.52 (2d, J = 10.8, 11.1 Hz, 2H, $PhCH_2$), 4.28 (dd, J = 4.2,10.8 Hz, H-6), 4.22−4.04 (m, 4H, H-2, H-6, allylic CH_2), 3.93−3.81 (m, 2H, allylic CH_2, H-5), 3.63 (t, J = 9.3 Hz, 1H, H-4), 2.44 (s, 3H, ArMe), 1.98 (s, 3H, OAc), 1.93 (s, 3H, $NCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.10, 169.90, 144.91,-137.16, 132.96, 132.59, 129.73, 128.39, 127.91, 127.87, 127.70, 118.10, 96.13 (C-1), 75.11 (C-3), 74.80 (C-5), 73.44, 68.79 (C-4), 68.97, 68.03 (C-6), 51.88 (C-2), 23.04, 21.54, 20.79; EIMS m/z 548.3 (MH^+), 546.5 ($M - 1^+$).

Allyl 2-Acetamido-3-*O*-acetyl-6-azido-4-*O*-benzyl-2-deoxy-α-D-glucopyranoside (9). To a solution of compound **8a** (7.0 g, 12.9 mmol) in DMF (50 mL) is added NaN_3 (8.0 g, 129 mmol), and the suspension is stirred at 90 °C for 3 h. The reaction mixture is poured into ice−water and extracted with methylene chloride. The combined organic layer is washed with water and brine, dried (Na_2SO_4), and evaporated. The residue is purified by column chromatography on silica gel, eluting with 50% EtOAc in hexane to obtain compound **9** (4.0 g, 75%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.21 (m, 5H, ArH), 5.97−5.79 (m, 2H, NH, vinylic CH), 5.31, 5.21 (2d, J = 9.9, 10.5 Hz, 2H, vinylic CH_2), 5.26−5.25 (m, 1H, H-3), 5.85 (d, J = 3.9 Hz, 1H, H-1), 4.65, 4.57 (2d, J = 11.1, 11.1 Hz, 2H, $PhCH_2$), 4.28 (td, J = 9.6, 3.6 Hz, 1H, H-2), 4.18, 3.99 (2dd, J = 12.6, 5.1, 12.9, 6.0 Hz, 2H, allylic CH_2), 3.87 (ddd, J = 9.6, 5.4, 2.4 Hz, 1H, H-5), 3.64 (t, J = 9.0 Hz, 1H, H-4), 3.48 (dd, J = 12.9, 2.1 Hz, 1H, H-5), 3.64 (t, J = 9.0 Hz, 1H, H-4), 3.48 (dd, J = 12.9, 2.1 Hz, H-6), 3.36 (dd, J = 13.2, 5.4 Hz, 1H, H-6), 1.98 (s, 3H, OAc), 1.94 (S, 3H, $NCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.88, 169.77, 137.21, 132.93, 128.26, 127.78, 127.64, 127.57, 117.93, 96.02, 76.28, 74.70, 73.33, 70.23, 68.25, 51.86, 50.79, 22.83, 20.63; EIMS m/z 419.3 (MH^+), 417.3 ($M - 1^+$).

Carboxymethyl 2-Acetamido-3-*O*-acetyl-6-azido-4-*O*-benzyl-2-deoxy-α-D-glucopyranoside (12). To a solution of compound **9** (4 g, 9.6 mmol) in a mixture of CCl_4 (20 mL), CH_3CN (20 mL), and H_2O (30 mL) is added $NaIO_4$ (8.4 g,39.36 mmol). To this biphasic solution is added $RuCl_3{\cdot}3H_2O$ (43 mg, 2.2 mol %), and the resulting mixture is stirred vigorously for 2 h at room temperature. After dilution with 50 mL of CH_2Cl_2, the reaction mixture is filtered through a pad of Celite, and the phases are separated. The aqueous layer is extracted twice with CH_2Cl_2. The combined organic layer is washed with water and brine, dried (Na_2SO_4), and concentrated to obtain the mixture of aldehyde **11** and acid **12**. This crude mixture is chromatographed on silica gel eluting with a gradient of MeOH in CH_2Cl_2 to obtain aldehyde **11** (2.7 g, 67%) and acid **12** (1 g, 25%).

Jones reagent (1.17 M, 10 mL, 8.54 mmol) is added to a solution of compound **11** (2.7 g, 5.97 mmol) in acetone (30 mL), and the mixture is subjected to sonication for 30 min. After TLC analysis, excess reagent is quenched with 2-propanol (100 mL), and the chromate salt is filtered off through a pad of Celite. The green solid residue obtained after concentration is purified by flash chromatography, eluting with 20% methanol/methylene chloride to afford compound **12** as a white foamy solid (2.4 g, 86%). The overall yield for the two-step oxidation is 82%; ^{1}H NMR (300 MHz, CD_3OD) δ 7.49−7.19 (m, 5H, ArH), 5.32 (t, J = 9.9 Hz, 1H, H-3), 4.96 (brs, 1H, NH), 4.82 (brs, 1H, H-1), 4.60 (s, 2H, $PhCH_2$), 4.23−4.11 (m, 2H, H-2, CH_2CO_2), 4.01−3.81 (m, 2H, CH_2CO_2, H-5), 3.62 (t, J = 9.3 Hz, 1H, H-4), 3.53−2.28 (m, 2H, H-6), 1.94 (s, 3H, OAc), 1.91 (s, 3H, $NCOCH_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 173.45, 172.03, 139.25, 129.44, 128.95, 128.89, 98.81 (C-1), 78.17 (C-3), 75.77 (C-5), 74.73, 71.94 (C-4), 53.24 (C-6), 52.26 (C-2), 22.59, 20.94. Fab-MS m/z 437.3 (MH^+), 434.8($M - 1^+$).

Carboxymethyl 2-Acetamido-6-azido-4-*O*-benzyl-2-deoxy-α-D-glucopyranoside (1). To a stirred solution of **12** (3.4 g,6.8 mmol) in anhydrous methanol (40 mL) is added sodium methoxide (365 mg, 6.8 mmol). The reaction mixture is stirred for 45 min at room temperature by which time all the starting material has been consumed (TLC analysis). Excess base is neutralized with Amberlite-H resin, filtered, concentrated, and purified by silica gel chromatography, eluting with 25% MeOH in CH_2Cl_2 to afford compound **1** as a brownish foamy solid (2.5 g, 83%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.39−7.19 (m, 5H, ArH), 4.79 (d, J = 11.1 Hz, 1H, H-1), 4.14 (d, J = 15.9 Hz, 1H, CH_2CO_2), 4.07 (d, J = 10.8 Hz, 1H, H-2), 3.93 (d, J = 14.1 Hz, 1H, CH_2CO_2), 3.90 (t, j = 8.7 Hz, 1H, H-3), 3.82−3.72(m, 1H, H-5), 3.48−3.24 (m, 3H, H-6, H-4), 2.05 (s,3H, $NCOCH_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 178.07, 174.02, 139.67, 129.31, 129.08, 128.74, 98.87 (C-1), 80.28 (C-5), 75.98 (C-3), 73.89, 71.99 (C-4), 67.53, 55.19 (C-6), 52.55 (C-2), 22.90; FAB-MS m/z 395 (MH^+), 392.8 ($M - 1^+$). Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62; N, 14.21. Found: C, 51.52; H, 5.44; N, 14.42.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **2**−**7**, **8a**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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