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Synthesis and Conformational Analysis of 6-*C*-Methyl-Substituted 2-Acetamido-2-deoxy-β-D-glucopyranosyl Mono- and Disaccharides

Jihane Achkar, **Isabel Sanchez-Larraza**, **Carol A. Johnson**, and **Alexander Wei**
Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084
alexwei@purdue.edu

Abstract

Several 6-*C*-substituted 2-acetamido-2-deoxy-β-D-glucopyranosides (β-D-GlcNAc monosaccharides **1a**–**3a** and 1,4-linked disaccharides **1b**–**3b**) were studied by solution NMR spectroscopy. Conformational analysis of the (*6S*)- and (*6R*)–*C*-methyl-substituted β-D-GlcNAc monosaccharides indicates that the stereodefined methyl groups impose predictable conformational biases on the exocyclic C-5–C-6 bond, as determined by ^{1}H-^{1}H and ^{13}C–^{1}H coupling constants. Variable-temperature NMR experiments in methanol-d_4 were performed to determine $\Delta\Delta H$ and $\Delta\Delta S$ values derived from the two lowest energy conformers. These indicate that while the influence of 6-*C*-methyl substitution on conformational enthalpy is in accord with the classic principles of steric interactions, conformational preference in solution can also be strongly affected by other factors such as solvent-solute interactions and solvent reorganization.

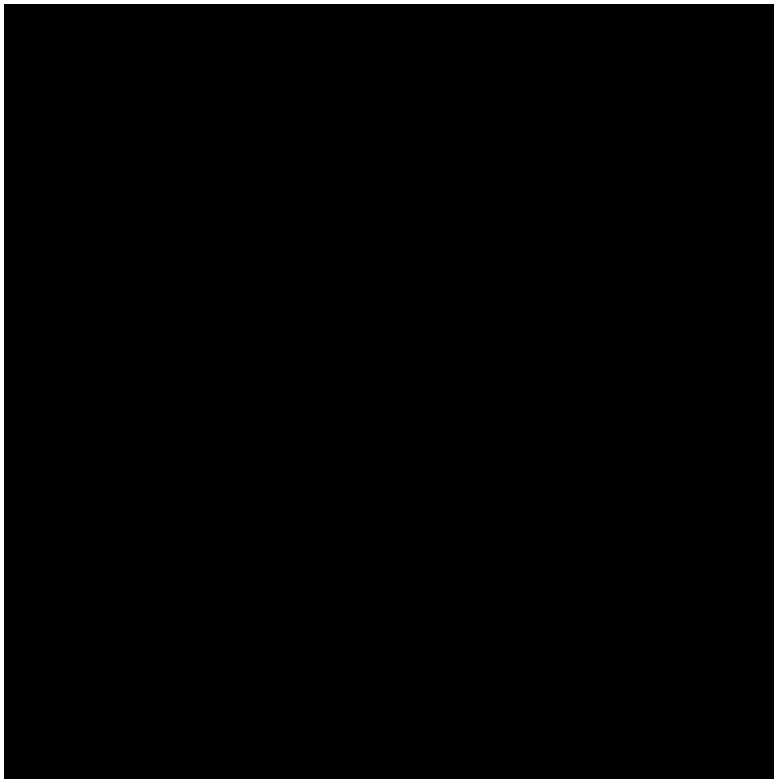
Introduction

Protein–carbohydrate and carbohydrate–carbohydrate interactions play essential roles in the recognition of cell surfaces and polysaccharides in the extracellular matrix.[1] For pyranosidic carbohydrates, the exocyclic C-5 hydroxymethyl substituent has particular significance and often provides key interactions at biological interfaces.[2,3] The exocyclic C-5–C-6 bond is known to be torsionally flexible;[3] however, a number of systems recognize or require specific orientations. For example, the polymorphic forms of the crystalline polysaccharide chitin (β-1,4-linked poly-*N*-acetyl-D-glucosamine) are likely determined by hydrogen bonding between interstrand O-6 hydroxyl groups, which are in turn directed by the C-5 hydroxymethyl conformations.[4-6] There is also strong evidence that the O-6 hydroxyl is intimately involved in stabilizing the interaction between chitin and various chitinases.[7] Understanding the factors which affect the conformation of the C-5–C-6 bond may reveal insights for designing interfaces with selective recognition properties, or for directing the supramolecular architecture of polysaccharides such as chitin.

Supporting Information Available: Spectroscopic data for title compounds **1a**–**3b** and synthetic intermediates **4**–**19**, including ^{1}H, ^{13}C, {^{1}H}-coupled-^{13}C, DQF-COSY, and HMQC NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The conformation of this exocyclic bond can be rationally biased by introducing a small but sterically demanding methyl group at the (6*S*)- or (6*R*)-position (see Figure 1). This conformational director destabilizes staggered rotamers via 1,3-diaxial-like interactions, which increases steric repulsion energies by 1–3 kcal/mol.[8] The steric director approach has been used to probe the effect of conformational bias on protein-carbohydrate binding and enzymatic hydrolysis, using 6-*C*-substituted glucoand galactopyranosides[9] and related 1,6-linked oligosaccharide derivatives.[10]

Here we describe the conformational analysis of 6-*C*-monodeuterated and 6-*C*-methyl-substituted 2-acetamido-2-deoxy-β-D-glucopyranosyl (β-D-GlcNAc) monosaccharides (**1a**–**3a**) and their corresponding 1,4-linked disaccharides (**1b**–**3b**), using vicinal coupling constants from variable-temperature nuclear magnetic resonance (VT-NMR) spectroscopy. A previous analysis of these compounds at 298 K in methanol-d_4 has established that the stereodefined 6-*C*-methyl group imposes a strong conformational bias on the C-5–C-6 bond, with predictable outcomes for the lowest energy conformations.[11] In this article, further evaluation of $^3J_{H,H}$ coupling constants over a wide temperature range (229–320 K) permits these conformational preferences to be described in thermodynamic terms with use of three-state conformer models. Parametrized Karplus analyses of this type allow us to estimate relative differences in enthalpy, which is pertinent for understanding conformational effects in crystal polymorphism and ligand-receptor binding. With respect to the latter, it is interesting to note that aminoglycoside antibiotics in the gentamicin family including Geneticin (G418) possess 6-*C*-methyl-substituted glucosamines (see Figure 2).[12,13] A recent X-ray crystal structure of G418 complexed to an RNA fragment suggests that the (6*R*)-*C*-methyl group may destabilize a specific G–C base pair.[13] Conformational analysis of these units may contribute toward structure–activity studies of gentamicin analogues, whose medicinal utility is hampered by the evolution of drug-resistant bacterial strains.[14]



SCHEME 1.

Synthesis of 6-*C*-Substituted Monosaccharides[a]

[a] Reagents and conditions: (a) (i) AcOH, THF:H_2O, 45 °C, (ii) TBS-Cl, Et_3N, imidazole, CH_2Cl_2:THF (93%, two steps); (b) (i) dihydropyran, PPTS, CH_2Cl_2, (ii) *n*-Bu_4NF, THF (76%, two steps); (c) **7**: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, Et_3N, 0 °C (62%), (ii) $NaBD_4$, CH_2Cl_2:MeOH, −10 °C (6*S*:6*R* 2:1), (iii) *p*-TsOH, MeOH (46%, two steps); (d) **8**: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, Et_3N, 0 °C, (ii) $AlMe_3$, CuCN, THF, −55 °C to rt (6*S*:6*R* 6:1), (iii) *p*-TsOH, MeOH (25%, three steps); (e) **9**: (i) and (ii) same as (d), (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, 0 °C (81%), (iv) $ZnCl_2$, *i*-Bu_2AlH, THF, −78 °C (6*S*:6*R* 1:6), (v) *p*-TsOH, MeOH (44%, two steps); (f) (i) $(CH_2NH_2)_2$, *n*-BuOH, 100 °C, (ii) Ac_2O, pyridine (**10**: 74%, **11**: 87%, **12**: 93%, two steps); (g) NaOMe, MeOH:CH_2Cl_2 (1:1, v/v) (**1a**: 71%, **1b**: 98%, **1c**: 100%). Selected acronyms: All = allyl, Phth = phthalimido, PMP = *p*-methoxyphenyl, TBS = *tert*- butyldimethylsilyl, THP = tetrahydropyranyl.

Results and Discussion

Synthesis

Multigram quantities of protected glucosamine derivative **4** were prepared from glucosamine hydrochloride according to literature procedures (see Scheme 1).[15] Reductive cleavage of the 4,6-*O*-*p*-methoxybenzylidene acetal with borane and Bu_2BOTf to the corresponding 4-*O*-*p*-methoxybenzyl (PMB) ether[16] were problematic due to the reactivity of the allyl ether at 0 °C;[17] however, the 4,6-diol could be regioselectively protected as 6-*O*-*tert*-butyldimethylsilyl (TBS) ether **5**, then converted to 4-*O*-tetrahydropyranyl (THP)-protected primary alcohol **6** in 71% overall yield from **4**.

Compound **6**, which served as the common intermediate for the 6-*C*-substituted β-D-GlcNAc derivatives, was oxidized to the corresponding aldehyde with Swern conditions.[18] This was reduced with $NaBD_4$ and deprotected at O-4 to yield 6-*C*-*d*-substituted diol **7** as a 7:3 6*S*:6*R* mixture of diastereomers, with 6*S*- or 6*R*-stereo-chemical assignments based on $^3J_{5,6}$ coupling constants of the corresponding 4,6-*O*-isopropylidene acetal derivative ($^3J_{5,6R}$ = 5.2 Hz, $^3J_{5,6S}$ = 10.2 Hz). Monodeuteration simplifies the coupling of H-5 to H-6*R* and H-6*S* to two-spin systems, making conformational analysis straightforward. Next, the aldehyde was reacted with methyl Grignard reagents, which have been shown to add to similar substrates in good yields and stereoselectivity;[9] unfortunately, the aldehyde proved to be a remarkably poor electrophile. After a broad survey of nucleophiles and reaction conditions (see Table 1 for selected conditions), we were able to achieve methylation with 6:1 6*S*: 6*R* stereoselectivity using $AlMe_3$ in the presence of a stoichiometric amount of CuCN in THF at low temperatures, in 40% yield over two steps from **6**.[19]

The 4-*O*-THP group had an important role in the reaction outcome. Replacing this group with benzyl ether caused the stereoselectivity to drop to a 3:1 6*S*:6*R* ratio, whereas the 4-*O*-methoxyethoxymethyl (MEM)-protected aldehyde was unreactive to $AlMe_3$. The chiral THP group did not drastically influence methylation stereochemistry, as both diastereomers yielded the 6*S*-epimer as the major product.

Separation of the C-6 diastereomers was achieved upon cleavage of the THP group and recrystallization of the (6*S*)-*C*-methyl β-D-GlcNAc precursor **8**. Assignments of C-6 stereochemistry were confirmed by vicinal coupling constant analysis of the corresponding 4,6-*O*-anisylidene acetals (from **8**: $^3J_{5,6}$ = 5.7 Hz; **9**: $^3J_{5,6}$ = 9.2 Hz). Larger quantities of the (6*R*)-*C*-methyl derivative **9** were obtained by oxidation of the diastereomeric 6-*C*-methyl adducts and reduction of the corresponding methyl ketone under chelate-controlled conditions with use of *i*Bu_2AlH in the presence of $ZnCl_2$ with 6:1 6*R*:6*S* stereo-selectivity,[20] followed by THP cleavage and careful separation by silica gel chromatography. It is worth mentioning that bulky reducing agents such as $NaAl(OCH_2CH_2OCH_3)_2H_2$, $LiAl(sBu)_3H$, or $LiAl(OtBu)_3H$ did not deliver the desired 6*R* epimer with high selectivities, whereas several other

conditions produced the 6*S*-epimer preferentially. Diols **7**–**9** were then transformed into β-D-GlcNAc derivatives **10**–**12** in excellent yields by ethylenediamine-mediated cleavage of the phthalimide group and peracetylation. Last, methanolysis afforded the desired 6-*C*-substituted β-D-GlcNAc monosaccharides **1a**–**3a** in quantitative yields.

SCHEME 2.

Synthesis of 6-*C*-Substituted Disaccharides[a]

[a] Reagents and conditions: (a) **13**: TBS–Cl, Et_3N, imidazole, CH_2Cl_2:THF (89%); (b) **14**, **15**: (i) *p*-$MeOC_6H_4CH(OMe)_2$, camphorsulfonic acid, 4A mol sieves, toluene, 90 °C, (ii) $NaBH_3CN$, HCl, THF:Et_2O, 4A mol sieves, −30 °C (**14**: 43%, **15**: 27%, two steps); (c) **16** (2 equiv), TMSOTf, 4A mol sieves, CH_2Cl_2, −30 °C (**17**: 51%, **18**: 98%, **19**: 78%); (d) **1b**: *n*-Bu_4NF, THF; (e) **2b**, **3b**: DDQ, *t*-BuOH, pH 7 buffer, CH_2Cl_2; (f) (i) $(CH_2NH_2)_2$, *n*-BuOH, 100 °C, (ii) Ac_2O, pyridine, (iii) NaOMe, MeOH:CH_2Cl_2 (**1b**: 99%, **2b**: 79%, **3b**: 71%, four steps). Selected acronyms: All = allyl, Phth = phthalimido, PMB = *p*-methoxybenzyl, TBS=*tert*-butyldimethylsilyl.

To determine the relative influence of a neighboring glycosidic unit at C-4 on sidechain conformations, disaccharides **1b**–**3b** were also synthesized (see Scheme 2). Monodeuterated diol **7** was protected as 6-*O*-TBS ether **13**, whereas 6-*C*-methyl-substituted diols **8** and **9** were protected as 4,6-*O*-*p*-methoxybenzylidene acetals, and converted to their respective 6-*O*-PMB ethers **14** and **15** by reductive cleavage under acidic conditions.[21] These alcohols were coupled straightforwardly with trichloroacetimidate **16**[22] to produce the protected β-1,4-linked disaccharides **17**–**19** in excellent yields. Global deprotection, peracetylation, and methanolysis afforded the desired 6-*C*-substituted β-D-GlcNAc disaccharides **1b–3b** in high overall yields.

Conformational Analysis

The influence of C-6 substituents on side chain conformations in methanol-d_4 was evaluated primarily by $^3J_{H,H}$ coupling constant analysis, using empirically parametrized Karplus equations developed by Altona and co-workers.[23] Conformational analyses of the hydroxymethyl C-5–C-6 bond in pyranosides are typically based on Karplus curves parametrized for 1,2-dialkoxypropanes. These produce dihedral angles as a function of two coupling constants $^3J_{5,6R}$ and $^3J_{5,6S}$, which reflect the weighted average of staggered conformations.[3] In the case of 6-*C*-methyl-substituted pyranosides, the hydroxy*ethyl* C-5–C-6

bond must be considered as a 1,2-dialkoxybutane, which produces a Karplus relationship with a significantly reduced amplitude (see Figure 3). Coupling constant analysis of hydroxyethyl C-5–C-6 conformations rests on a single $^{3}J_{5,6}$ value, and requires additional data to produce a unique dihedral angle solution. To this end, geminal and vicinal $^{13}C–^{1}H$ coupling constants ($^{2}J_{C,H}$ and $^{3}J_{C,H}$) obtained from proton-coupled ^{13}C NMR spectra were employed as supporting constraints. Empirical measurements compiled by Serianni[24] and Murata[25] provide a set of limiting $^{3}J_{C,H}$ values complementary to the parametrized Karplus equations, and can be useful for defining rotamers with significant contributions to the time-averaged conformations.

Conformational analysis about the C-5–C-6 bond was performed based on the relative populations of the three staggered conformers *gt*, *tg*, and *gg* (see Figure 1).[26] Individual rotamers of 6-*C*-methyl β-D-GlcNAc derivatives (**2a**,**b** and **3a**,**b**) were correlated with $^{3}J_{H,H}$ values derived from the Karplus curves at the relative minima determined by semiempirical methods (see below), supplemented by "large" and "small" $^{2}J_{C,H}$ and $^{3}J_{C,H}$ coupling constants as defined by Serianni[24] and Murata.[25] Despite their limited precision, $J_{C,H}$ couplings allow each staggered conformer to be defined by a unique set of coupling constant parameters (see Table 2).[27] Last, we note that the ring protons of all β-D-GlcNAc derivatives in this study have $^{3}J_{H,H}$ values consistent with stable chair conformations, permitting conformational analysis to be modeled on a diamond lattice framework.[28]

Coupling constant analysis of compounds **1**–**3** at 298 K was presented in an earlier communication[11] and is briefly summarized here. In accord with previous reports,[29] the C-5C–6 bond of monodeuterated β-D-GlcNAc derivatives **1a** and **1b** preferred the *gg* and *gt* conformers over the *tg* conformer, which is destabilized by 1,3-diaxial-like interactions between O-4 and O-6 (see Figure 1). By comparison, the C-5–C-6 bond in (6*S*)-*C*-methyl β-D-GlcNAc derivatives **2a** and **2b** had a clear preference for the *gg* conformation over *gt* or *tg*, whereas that of (6*R*)-*C*-methyl β-D-GlcNAc derivatives **3a** and **3b** preferred *gt* over *tg* or *gg* (see Table 3 for $^{3}J_{5,6}$ and selected $J_{C,H}$ values). It is noteworthy that the $^{3}J_{5,6}$ values of disaccharides **2b** and **3b** at 298 K indicate a stronger preference for their lowest energy conformations (*gg* and *gt*, respectively) than their monosaccharides **2a** and **3a**. At first glance, this suggests that the neighboring C-4 glycosidic unit has a greater steric interaction with the C-6 methyl group than the C-4 hydroxyl, but a more detailed examination reveals this not to be the case (see below).

To obtain quantitative estimates of the relative conformational energies, VT-NMR studies were conducted in methanol-d_4 between 230 and 320 K and applied toward three-conformer models. The latter proved to be a challenge in the case of the (6*S*)- and (6*R*)-*C*-methyl-substituted compounds: a first-order analysis based on experimentally measured interaction energies[8] indicated a difference of less than 0.5 kcal/mol between the minor staggered conformers. This was confirmed by molecular mechanics (AMBER) calculations of conformational energies as a function of dihedral angle about the C-5–C-6 bond of methyl β-D-GlcNAc derivatives, in the gas phase (ε = 1; see Figure 4a-c) or in a dielectric continuum representing methanol (ε = 32.6; see Figure 4d-f).[30] The most stable conformations of the 6-*C*-methyl-substituted compounds were favored by more than 1 kcal/mol over the next lowest energy conformer; however, the relative energies of the minor conformers were less clearly defined. In the low-dielectric simulations, energy differences between minor conformers were 0.5 kcal/mol or less, with rotational barriers on the order of 4–6 kcal/mol. Both the energy differences and rotational barriers were reduced upon increasing the media dielectric constant; in the case of the (6*S*)-*C*-methyl derivative, the relative minima were switched. We thus elected to carry out conformational analyses using a three-conformer model under two limiting assumptions: one with the two minor isomers being isoenergetic, the other with a free-energy difference of 0.5 kcal/mol between minor isomers. These assumptions necessarily limited the precision of the

analyses, but could otherwise enable a reliable assessment of conformational stability in thermodynamic terms.

Distributions of staggered conformers about the C-5–C-6 bonds were calculated by using the Karplus relationships defined in Figure 3, with dihedral angles for *gt*, *tg*, and *gg* based on the minima calculated for methyl β-D-GlcNAc derivatives in methanol (see Table 4). For the 6-*C*-monodeuterated derivatives **1a** and **1b**, an unrestricted three-conformer model could be derived from two $^3J_{5,6}$ values, with dihedral angles for *gt*, *tg*, and *gg* defined at +60°, +170°, and −65°, respectively (see Figure 4d).[26] The negative *tg* values are artifacts of the parametrization; nevertheless, the population ratios of *gg* vs *gt* are expected to be slightly more accurate than those derived from earlier analyses, whose populations are based on dihedral angles of +60°, +180°, and −60°.[3,29] For the 6-*C*-methyl derivatives **2a**,**b** and **3a**,**b**, three-conformer models were based on a single $^3J_{5,6}$ value using the limiting assumptions above, with dihedral angles for *gt*, *tg*, and *gg* defined at +60°, +170°, and −60° for **2a**,**b** and at +60°, +175°, and −70° for **3a**,**b** (see Figure 4e,f).

In all cases, the 6-*C*-methyl-substituted derivatives favored the sterically least encumbered conformations, regardless of temperature (*gg* for **2a**,**b** and *gt* for **3a**,**b**). The population ratios of the two lowest energy conformers were used to determine relative free-energy differences ($-\Delta\Delta G$) based on each three-conformer model (see Table 4). In the case of (6*S*)-*C*-methyl monosaccharide **2a**, $-\Delta\Delta G$ values for the lower limiting case were found to be on the order of 0.5 kcal/mol, whereas those for the upper limiting case were on the order of 1.1 kcal/mol. A similar situation was observed for (6*S*)-*C*-methyl disaccharide **2b**, albeit with slightly greater free-energy differences. For (6*R*)-*C*-methyl monosaccharide **3a**, the $-\Delta\Delta G$ values were less affected by the choice of three-conformer model but more affected by temperature, with values ranging between 0.3 and 1.4 kcal/mol. Last, in the case of (6*R*)-*C*-methyl disaccharide **3b**, the preference for the lowest energy conformation was overwhelming ($-\Delta\Delta G > 1.9$ kcal/mol), to the extent that the accuracy of thermodynamic analysis was limited by the parametrized Karplus equation itself. It should be noted that the uncertainty of $\Delta\Delta G$ increases rapidly as the $J_{5,6}$ value approaches the lower limit set by the parametrized Karplus equation (2.3 Hz for **3a**,**b**). Furthermore, in some cases the $J_{5,6}$ value lay below this limit, which suggests that the preferred orientation of the C-5–C-6 bond in disaccharide **3b** is distorted away from a staggered *gt* conformation, as opposed to the model (6*R*)-*C*-methyl monosaccharide used for Figure 4f.

Linear free-energy relationships were determined for all compounds except **3b** (see Figure 5), whose $J_{5,6}$ values coincided with the lower limit imposed by the Karplus equation parametrized for 1,2-dialkoxybutanes. Least-squares analyses of the corresponding van't Hoff plots yielded approximate $\Delta\Delta H$ and $\Delta\Delta S$ values (see Table 5), which revealed additional insights into the forces influencing the conformational preference of the exocyclic C-5–C-6 bond. First, the $-\Delta\Delta H$ values for the monosaccharides (**1a**, **2a**) are comparable to or greater than those for the corresponding disaccharides (**1b**, **2b**). This indicates that the presence of the O-4 glycoside does not have a significant steric influence on the conformation of the C-5–C-6 bond; indeed, in the case of **2b** the enthalpic difference is much less than that predicted on the basis of steric interactions alone (see above). Second, the $-\Delta\Delta H$ value of (6*R*)-*C*-methyl β-D-GlcNAc **3a** is much larger than can be accounted for based on increased 1,3-diaxial-like interactions. It should be noted that the same is also true for the relative free energy difference of disaccharide **3b**.

Our observations indicate that the C-5–C-6 conformations are influenced by solvation effects.[31] These can be described in terms of solvent-solute interactions and solvent reorganization, i.e., the restructuring of solvent molecules around the cavity occupied by the solute. Solvent–solute interactions can affect conformational preferences if the quality of key polar interactions is sensitive to local environmental factors, whereas solvent reorganization can account for large changes in solvation enthalpy and entropy in rough proportion to the solvent-exposed surface

area of the solute.[32] Recent simulations on the solvation energies of hydrocarbons in water as a function of conformation (cavity size) indicate that changes in solvation free energies are dominated by entropic changes in solvent reorganization.[33]

Both solvent-solute interactions and solvent reorganization may have a significant influence on the relative changes in conformational enthalpies and entropies for 6-*C*-methyl-substituted derivatives **2a**,**b** (*gg* vs *tg*,*gt*) and **3a**,**b** (*gt* vs *tg*,*gg*). Solvation entropy should in principle favor the minor *tg* conformer, because the consolidation of polar and nonpolar groups reduces the size of the solvophobic cavity. However, the protruding 6-*C*-methyl group increases the size of the solvophobic pocket and is likely to have an adverse effect on solvation reorganization. Furthermore, solvation enthalpy disfavors the *tg* conformer, because fewer well-defined hydrogen bonds between solvent molecules around the solute cavity and the hydroxyl groups at C-4 and C-6 are possible.

The conformational preferences of the 6-*C*-methyl-substituted β-D-GlcNAc derivatives can now be evaluated in the context of both steric interactions and solvent effects. In the case of (6*S*)-*C*-methyl-substituted monosaccharide **2a**, the minor changes in entropy indicate that the preference for *gg* over the higher energy conformers is due mostly to local steric interactions, with solvation having little influence. In the case of (6*S*)-*C*-methyl-substituted disaccharide **2b**, $\Delta\Delta H$ is decreased and accompanied by a rise in $\Delta\Delta S$, indicating significant changes in solvation energy. In particular, the positive change in entropy implies that the minor conformations require greater solvent reorganization. Last, in the case of (6*R*)-*C*-methyl-substituted monosaccharide **3a**, the preference for the *gt* conformer is clearly strengthened by additional solvent-solute interactions. The addition of a bound solvent molecule to the *gt* conformer is accompanied by a large and negative change in entropy.

In summary, a thermodynamic analysis of the conformational preferences of the C-5–C-6 bond in 6-*C*-substituted β-D-GlcNAc derivatives reveals the complex balance of forces which influence their solution conformations. Overall, our results support the application of classical steric interactions to predict preferred conformations in polar solvents at ambient temperatures, and confirm the validity of the steric director concept. However, solvent–solute interactions and solvent reorganization can have a considerable impact on conformational enthalpies and entropies, and may significantly alter the conformational behavior of compounds with very similar structures.

Experimental Section

NMR Conformational Analysis

Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported (in parts per million) relative to $CDCl_3$ (δ 7.24 and 77.0 ppm, respectively) or CD_3-OD (δ 3.30 and 49.0 ppm, respectively).

Staggered conformer populations for 6-*C*-*d*-substituted compounds were calculated by using a three-conformer model (*gt* = +60°; *tg* = +170°; *gg* = −70°) based on the relative minima calculated for methyl β-D-GlcNAc in methanol (see Figure 4d) and Karplus relationships parametrized for 1,2-dialkoxypro-panes (see Figure 3). Populations were derived with eqs 1-3:

$$10.68\,\%\ gt + 1.30\,\%\ gg + 3.53\,\%\ tg = J_{5,6R} \quad (1)$$

$$3.07\,\%\ gt + 2.33\,\%\ gg + 10.36\,\%\ tg = J_{5,6S} \quad (2)$$

$$gt + gg + tg = 100 \quad (3)$$

Conformer populations for (6*S*)-*C*-CH_3-substituted compounds were calculated by using three-conformer models with limiting assumptions described in the main text, based on Karplus

relationships parametrized for 1,2-dialkoxybutanes (see Figure 3). For the case in which the two minor conformers are equal in energy (*tg* = *gt*), populations were derived with eqs 4 and 5:

$$11.8\,\%\ tg + 0.7\,\%\ gg = \mathcal{J}_{5,6} \tag{4}$$

$$2\ tg + gg = 100 \tag{5}$$

For the case in which the two minor conformers differ in energy by 0.5 kcal/mol (*tg* > *gt*), populations were derived with eqs 6-8:

$$9.2\,\%\ gt + 2.6\,\%\ tg + 0.7\,\%\ gg = \mathcal{J}_{5,6} \tag{6}$$

$$gt + tg + gg = 100 \tag{7}$$

$$gt = tg \cdot \mathrm{e}^{-0.5/RT} \tag{8}$$

Conformer populations for (6*R*)-*C*-CH_3-substituted compounds were calculated in a similar manner. For the case in which the two minor conformers are equal in energy (*tg* = *gg*), populations were derived with eqs 9 and 10:

$$2.3\,\%\ gt + 10.5\,\%\ tg = {}^{3}\mathcal{J}_{5,6} \tag{9}$$

$$gt + 2\ tg + \ = 100 \tag{10}$$

For the case in which the two minor conformers differ in energy by 0.5 kcal/mol (*tg* > *gg*), populations were derived with eqs 11-13:

$$2.3\,\%\ gt + 9.1\,\%\ tg + 1.4\,\%\ gg = {}^{3}\mathcal{J}_{5,6} \tag{11}$$

$$gt + tg + gg = 100 \tag{12}$$

$$gg = tg \cdot \mathrm{e}^{-0.5/RT} \tag{13}$$

Allyl 3-*O*-Acetyl-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-2-phthalimido-β-D-glucopyranoside (4)

A solution of allyl-2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-β-D-glucopyrano-side[11] (10.2 g, 21.5 mmol) in CH_2Cl_2 (130 mL) was treated with NaOMe (8 mL, 1 M solution in MeOH) at −5 °C. The reaction was stirred for 2 h at 0 °C, and then poured onto a column of activated Dowex 50X-W H^+ ion-exchange resin. Elution with spectral grade MeOH (500 mL) followed by solvent evaporation affords the crude triol in 93% yield (6.98 g) as a white solid.

The intermediate triol and activated 4A molecular sieves were suspended in toluene (80 mL) and treated with *p*-anisaldehyde dimethylacetal (4.70 mL, 29.7 mmol) and camphorsulfonic acid (426 mg, 1.83 mmol). The reaction mixture was stirred at 90 °C for 20 h, diluted with EtOAc, filtered over Celite, and quenched with water. A basic aqueous workup (EtOAc) followed by recrystallization (EtOAc/hexanes, 60/140 mL) afforded the desired acetal as a white solid in 88% yield (8.13 g).

The acetal intermediate (8.00 g, 17.1 mmol) was dissolved in pyridine (40 mL) and treated with Ac_2O (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h, quenched with EtOH (100 mL), and concentrated to dryness. The crude residue was recrystallized (EtOAc/hexanes, 10/100 mL) to afford **4** as yellow needles in 68% yield (5.93 g). $[\alpha]_D$−20 (*c* 1, $CHCl_3$); IR (thin film) ν 2877, 1777, 1742, 1717, 1615, 1386, 1251, 1226, 1101, 1034, 991, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 2 H), 7.71 (m, 2 H), 7.36

(d, 2 H, *J* = 8.7 Hz), 6.86 (d, 2 H,, *J* = 8.7 Hz), 5.86 (dd, 1 H, *J* = 8.9, 10.4 Hz), 5.68 (m, 1 H), 5.48 (s, 1 H), 5.45 (d, 1 H, *J* = 8.5 Hz), 5.12 (dm, 1 H, *J* = 17.2 Hz), 5.03 (dm, 1 H, *J* = 10.4 Hz), 4.37 (dd, 1 H, *J* = 4.3 Hz, 10.2 Hz), 4.30 (dd, 1 H,, *J* = 8.5 Hz), 4.26 (ddt, 1 H, *J* = 5.0, 12.9, 1.5 Hz), 4.02 (ddt, 1 H, *J* = 6.2, 12.9, 1.3 Hz), 3.82 (t, 1 H, *J* = 9.8 Hz), 3.78 (s, 3 H), 3.75 (t, 1 H, *J* = 9.0 Hz), 3.72 (m, 1 H), 1.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 167.5, 160.1, 134.1, 133.2, 131.4, 129.4, 127.5, 123.4, 117.7, 113.5, 101.5, 97.7, 79.1, 70.2, 69.7, 68.5, 66.1, 55.3, 55.2, 20.5; HRMS (EI) calcd for $C_{27}H_{27}NO_9$ $[M + H]^+$ 510.1764, found 510.1753.

Allyl 3-*O*-Acetyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (5)

A solution of **4** (7.27 g, 14.3 mmol) in AcOH/THF/H_2O (100 mL, 8:1:1 v/v/v) was heated to 45 °C for 5 h, evaporated to dryness, and azeotroped with toluene. Upon basic aqueous workup ($CHCl_3$), the solid residue was washed with cold hexanes to afford the intermediate diol in 97% yield. The crude diol (5.40 g, 13.8 mmol) was dissolved in anhydrous THF/CH_2Cl_2 (80 mL, 1:3 v/v) and treated with Et_3N (3.26 mL, 23.4 mmol), imidazole (94 mg, 1.38 mmol), then TBSCl (3.12 g, 20.7 mmol). The reaction mixture was stirred at room temperature for 16 h, then diluted with CH_2Cl_2 (100 mL) and quenched with saturated aqueous $NaHCO_3$ solution (100 mL). Product extraction (CH_2Cl_2) was followed by 5% $CuSO_4$ aqueous solution (50 mL), water (50 mL), and brine (50 mL) washes. The crude residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:2 v/v) to afford **5** in 96% yield (6.72 g). $[\alpha]_D$ −9(*c* 1, $CHCl_3$); IR (thin film) ν 3481, 2930, 2857, 1778, 1747, 1718, 1387, 1231, 1114, 1067, 1040, 837, 779, 722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (m, 2 H), 7.66 (m, 2 H), 5.66 (m, 1 H), 5.61 (dd, 1 H, *J* = 8.8, 10.7 Hz), 5.37 (d, 1 H, *J* = 8.5 Hz), 5.06 (dm, 1 H, *J* = 17.3 Hz), 4.97 (dm, 1 H, *J* = 10.4 Hz), 4.20 (ddt, 1 H, *J* = 5.0, 12.9, 1.5 Hz), 4.15 (dd, 1 H, *J* = 8.5, 10.7 Hz), 3.99 (ddt, 1 H, *J* = 6.2, 12.9, 1.3 Hz), 3.90 (dd, 2 H, *J* = 4.9, 11.7 Hz), 3.71 (t, 1 H, *J* = 9.8 Hz), 3.57 (dt, 1 H, *J* = 4.9, 9.8 Hz), 3.44 (br s, 1 H), 1.84 (s, 3 H), 0.87, 0.86, 0.85 (3 s, 9 H), 0.07, 0.06 (2 s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 167.7, 134.1, 133.4, 131.4, 123.3, 117.3, 96.8, 74.6, 73.5, 71.7, 69.7, 64.1, 54.5, 25.7, 20.5, 18.1, −5.5, −5.6; HRMS (ESI) calcd for $C_{25}H_{35}NO_8Si$ $[M + Na]^+$ 528.2030, found 528.2021.

Allyl 3-*O*-Acetyl-2-deoxy-2-phthalimido-4-*O*-tetrahydropyranyl-β-D-glucopyranoside (6)

A solution of **5** (6.72 g, 13.3 mmol) in CH_2Cl_2 (65 mL) was treated with 3,4-dihydro-2*H*-pyran (12.1 mL, 0.133 mol) and PPTS (84.6 mg, 0.332 mmol). The reaction was stirred at room temperature for 20 h, then diluted with CH_2Cl_2 (65 mL) and quenched with saturated $NaHCO_3$ solution (60 mL). Product extraction (CH_2Cl_2) and standard aqueous workup followed. The crude residue was dissolved without further purification in anhydrous THF (70 mL) and treated with *n*-Bu_4NF (20 mL, 1 M solution in THF). The reaction mixture was stirred at room temperature for 1 h, then filtered over a silica gel plug (EtOAc). After solvent evaporation, the crude residue was coevaporated with $CHCl_3$ (thrice), then washed with cold hexanes (3 × 50 mL) to afford primary alcohol **6** as a mixture of diastereoisomers in 76% yield (4.78 g) over two steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (m, 2 H), 7.70 (m, 2 H), 5.73 (dd, 1 H, *J* = 8.6, 10.6 Hz), 5.69 (m, 1 H), 5.42 (d, 1 H, *J* = 8.5 Hz), 5.12 (dm, 1 H, *J* = 17.2 Hz), 5.04 (dm, 1 H, *J* = 10.4 Hz), 4.66 and 4.56 (dd, 1 H, *J* = 3.0, 4.0 Hz), 4.24 (ddt, 1 H, *J* = 5.3, 12.9, 1.4 Hz), 4.21 (dd, 1 H, *J* = 8.5, 10.6 Hz), 4.04 (ddt, 1 H, *J* = 6.0, 12.9, 1.3 Hz), 3.93 (ddd, 1 H, *J* = 2.6, 5.0, 11.1 Hz), 3.86 (t, 1 H, *J* = 9.2 Hz), 3.76 (m, 2 H), 3.62 (ddd, 1 H, *J* = 2.6, 3.9, 4.6 Hz), 3.42 (ddd, *J* = 3.9, 5.9, 11.1 Hz), 2.00 (dd, 1 H, *J* = 5.0, 5.9 Hz), 1.89 and 1.87 (2 s, 3H), 1.80–1.30 (6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 169.4, 167.5, 133.9, 133.2, 133.2, 130.9, 123.0, 116.9, 116.9, 102.0, 100.1, 96.8, 96.7, 75.5, 75.1, 74.6, 74.5, 72.9, 71.6, 69.6, 69.4, 65.0, 62.4, 61.2, 60.9, 54.6, 30.8, 30.8, 24.8, 24.5, 20.7, 20.3, 20.1, 19.1; HRMS (ESI) calcd for $C_{24}H_{29}NO_9$ $[M + Na]^+$ 498.1740, found 498.1746.

Allyl 3-*O*-Acetyl-2-deoxy-(6*R*/6*S*)-*C*-^{2}H-2-phthalimido-β-D-glucopyranoside (7)

Primary alcohol **6** (200 mg, 0.421 mmol) was oxidized by the usual Swern procedure to afford the corresponding aldehyde (124 mg, 0.262 mmol, 62% yield) after purification by flash chromatography on silica gel (Et_2O). A solution of aldehyde (114 mg, 0.241 mmol) in MeOH/CH_2Cl_2 (5 mL, 3:2 v/v) was treated with $NaBD_4$ (30.0 mg, 0.717 mmol) at −10 °C. The reaction mixture was stirred for 1 h. Excess reagent was destroyed with acetone (5 mL) and the reaction quenched with saturated NH_4Cl solution (12 mL). Aqueous workup (EtOAc) and purification by flash column chromatography on silica gel (30–50% EtOAc gradient in hexanes) afforded 4-*O*-THP-protected monodeuterated intermediate alcohol in 69% isolated yield.

The monodeuterated intermediate (79.1 mg, 0.166 mmol) was dissolved in spectral grade MeOH (5 mL) and treated with *p*-toluenesulfonic acid (31.6 mg, 0.166 mmol). The reaction mixture was stirred for1hat room temperature, then diluted with $CHCl_3$ (12 mL) and quenched at 0 °C with saturated $NaHCO_3$ solution (12 mL). Aqueous workup ($CHCl_3$) and solvents removal afforded compound **7** in 67% yield (45.5 mg) in pure form without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2 H), 7.72 (m, 2 H), 5.69 (m, 1 H), 5.63 (dd, 1 H, *J* = 8.8, 10.7 Hz), 5.39 (d, 1 H, *J* = 8.4 Hz), 5.11 (dm, 1 H, *J* = 17.2 Hz), 5.03 (dm, 1 H, *J* = 10.4 Hz), 4.25 (ddt, 1 H, *J* = 4.1, 12.9, 1.4 Hz), 4.24 (ddt, 1 H, *J* = 6.1, 12.9, 1.3 Hz), 4.23 (dd, 1 H, *J* = 8.4, 10.7 Hz), 3.97–3.74 (m, 2 H), 3.60 (ddd, 1H, *J* = 3.9, 4.7, 9.8 Hz), 3.20 (br s, 1 H), 2.25 (br s, 1 H), 1.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.8, 134.2, 133.4, 131.4, 123.5, 117.6, 97.2, 75.4, 73.6, 70.2, 67.0, 62.2, 61.9, 54.7, 20.6; HRMS (EI) calcd for $C_{19}H_{20}DNO_8$ $[M + H]^+$ 393.1408, found 393.1409.

Allyl 3-*O*-Acetyl-2-deoxy-(6*S*)-*C*-methyl-2-phthalimido-β-D-glucopyranoside (8)

A solution of oxalyl chloride (0.55 mL, 6.31 mmol) in CH_2Cl_2 (6.6 mL) at −78 °C was treated with a solution of DMSO (0.89 mL, 12.6 mmol) in CH_2Cl_2 (1.8 mL). The reagents were stirred for 15 min. A solution of primary alcohol **6** (1 g, 2.10 mmol) in CH_2Cl_2 (6 mL) was added over 20 min via syringe pump. After being stirred for 30 min, the reaction mixture was treated with Et_3N (2.64 mL, 18.9 mmol) at −78 °C, allowed to reach 0 °C over 20 min, then diluted in C_6H_6/Et_2O (20 mL, 4:1 v/v) and quenched with saturated NH_4Cl solution (18 mL). Upon standard aqueous workup, the residue was azeotroped with toluene (thrice) to afford the desired aldehyde in quantitative crude yield.

A suspension of crude aldehyde (996 mg, 2.10 mmol) and CuCN (188 mg, 2.10 mmol) in anhydrous THF (20 mL) was stirred at room temperature for 10 min, cooled to −55 °C, then treated with $AlMe_3$ (5.26 mL, 2 M solution in hexanes) and allowed to reach room temperature overnight. The reaction mixture was diluted with Et_2O (20 mL) and quenched with saturated Na/K-tartrate/NH_4Cl (24 mL, 1:1 v/v) solution at 0 °C. The biphasic mixture was stirred for 30 min or until the aqueous phase turned blue. Aqueous workup (EtOAc) followed by flash chromatography on silica gel (30–50% EtOAc gradient in hexanes) afforded the desired methyl adduct as a 6:1 mixture of (6*S*):(6*R*) diastereomers in 40% isolated yield (402 mg) over two steps.

A solution of methyl adduct (0.40 g, 0.821 mmol) in spectral grade MeOH (8 mL) was treated with *p*-toluenesulfonic acid (156 mg, 0.821 mmol). The reaction mixture was stirred at room temperature for 1 h, then diluted with $CHCl_3$ (12 mL) and quenched with saturated $NaHCO_3$ solution (24 mL) at 0 °C. Aqueous workup ($CHCl_3$) afforded a 6:1 mixture of (6*S*): (6*R*) diols as judged by ^{1}H NMR spectroscopy. The crude residue was dissolved in anhydrous THF (1 mL), and triturated with cold hexanes (10 mL) to afford (6*S*)-*C*-methyl epimer **8** as a white solid in 63% isolated yield (209 mg). $[\alpha]_D$+1(*c* 0.9, $CHCl_3$); IR (thin film) ν 3474, 2924, 1777, 1747, 1716, 1493, 1452, 1387, 1232, 1032, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83

(m, 2 H), 7.71 (m, 2 H), 5.71 (m, 1 H), 5.62 (dd, 1 H, *J* = 9.0, 10.5 Hz), 5.39 (d, 1 H, *J* = 8.5 Hz), 5.12 (dm, 1 H, *J* = 17.2 Hz), 5.05 (dm, 1 H, *J* = 10.4 Hz), 4.22 (ddm, 1 H, *J* = 4.1, 12.9 Hz), 4.21 (dd, 1 H, *J* = 8.5, 10.5 Hz), 4.16 (br q, 1 H, *J* = 6.6 Hz), 4.05 (ddt, 1 H, *J* = 6.3, 12.9, 1.5 Hz), 3.92 (br t, 1 H, *J* = 9.8 Hz), 3.37 (dd, 1 H, *J* = 1.7, 9.8 Hz), 3.19 (br s, 1 H), 2.22 (br s, 1 H), 1.91 (s, 3 H), 1.34 (d, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 165.0, 134.2, 133.5, 131.5, 123.5, 117.7, 97.3, 77.6, 73.9, 70.3, 69.5, 65.6, 54.7, 20.7, 19.7; HRMS (ESI) calcd for $C_{20}H_{23}NO_8$ $[M + H]^+$ 405.1424, found 405.1427.

Allyl 3-*O*-Acetyl-2-deoxy-(6*R*)-*C*-methyl-2-phthalimido-β-D-glucopyranoside (9)

Primary alcohol **6** (1.0 g, 2.10 mmol) was oxidized by the usual Swern procedure to the corresponding aldehyde. Subsequent treatment of the crude aldehyde with $AlMe_3$ (5.3 mL,2 M in hexanes) in the presence of CuCN (188 mg, 2.10 mmol) in anhydrous THF (20 mL) afforded the corresponding secondary alcohol (521 mg, 61% yield over two steps) according to the above-described procedure. A solution of oxalyl chloride (0.74 mL, 8.5 mmol) in CH_2-Cl_2 (8.5 mL) at −78 °C was treated with a solution of DMSO (1.2 mL, 17 mmol) in CH_2Cl_2 (2.4 mL). The reagents were stirred for 25 min. A solution of secondary alcohol (0.5 g, 1.0 mmol) in CH_2Cl_2 (3 mL) was added over 20 min via syringe pump. After 20 min, the reaction solution was treated with Et_3N (2.8 mL, 20.2 mmol) at −78 °C, allowed to reach 0 °C over 20 min, then diluted with C_6H_6/Et_2O (25 mL, 4:1 v/v) and quenched with saturated NH_4Cl solution (24 mL). Aqueous workup (CH_2Cl_2) followed by flash chromatography on silica gel (10–40% EtOAc gradient in hexanes) afforded intermediate methyl ketone in 81% yield (404 mg) as a mixture of diastereomers.

A solution of methyl ketone (0.32 g, 0.66 mmol) in anhydrous THF (12 mL) was treated with $ZnCl_2$ (0.84 mL, 1 M solution in THF) and cooled to −78 °C. After 10 min, *i*-Bu_2AlH (2.65 mL, 1 M solution in hexanes) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C, then quenched with EtOAc (20 mL) and treated with $Na_2SO_4{\cdot}10H_2O$ (4 g). The suspension was stirred at room temperature for 1 h, diluted with Et_2O (50 mL), filtered over Celite, and evaporated to dryness. The crude residue was dissolved in MeOH (5 mL) and treated with *p*-toluenesulfonic acid (125 mg, 0.66 mmol) according to the procedure described above to afford a 6:1 mixture of (6*R*):(6*S*)-*C*-methyl epimers as judged by ^{1}H NMR spectroscopy. The desired (6*R*)-*C*-methyl diol **9** was separated by flash chromatography on silica gel (10–20% acetone gradient in toluene) in 44% yield over two steps (119 mg). $[\alpha]_D$ +2 (*c* 1, $CHCl_3$); IR (thin film) ν 3474, 2935, 1777, 1747, 1716, 1468, 1387, 1231, 1033, 722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2 H), 7.71 (m, 2 H), 5.71 (m, 1 H), 5.63 (dd, 1 H, *J* = 8.8, 10.7 Hz), 5.38 (d, 1 H, *J* = 8.4 Hz), 5.12 (dm, 1 H, *J* = 17.2 Hz), 5.06 (dm, 1 H, *J* = 10.4 Hz), 4.22 (dd, 1 H, *J* = 8.4, 10.7 Hz), 4.21 (ddt, 1 H, *J* = 5.3, 12.9, 1.4 Hz), 4.08 (q, 1 H, *J* = 6.2 Hz), 4.05 (ddm, 1 H, *J* = 6.1, 12.9, 1.5 Hz), 3.78 (t, 1 H, *J* = 9.5 Hz), 3.40 (dd, 1 H, *J* = 6.4, 9.5 Hz), 2.70 (br s, 2 H), 1.92 (s, 3 H), 1.34 (d, 3 H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)δ 171.4, 165.0, 134.3, 133.5, 131.5, 123.6, 117.7, 97.2, 77.2, 73.6, 73.5, 70.3, 70.2, 54.6, 20.7, 19.4; HRMS (ESI) calcd for $C_{20}H_{23}NO_8$ $[M + H]^+$ 406.1502, found 405.1427, calcd $[M + Na]^+$ 428.1321, found 428.1331.

General Procedure for Phthalimide Cleavage and Acetylation (10–12)

In a typical procedure, a solution of monosaccharide **9** (72.7 mg, 0.179 mmol) in *n*-BuOH (5 mL) was treated with ethylenediamine (0.96 mL, 14.3 mmol). The reaction mixture was stirred at 100 °C in a pressure tube for 20 h, then concentrated to dryness, coevaporated with toluene (thrice), and dried under high vacuum for 1 h. The crude amine was dissolved in pyridine (4.5 mL) and treated with Ac_2O (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 h, then quenched with EtOH (24 mL) at 0 °C and concentrated to dryness. Purification by flash column chromatography on silica gel (1.25–5% EtOH gradient in $CHCl_3$) afforded peracetylated monosaccharide **12** in 93% isolated yield over two steps (66.7 mg).

Monosaccharides **7** (21.2 mg, 53.9 μmol) and **8** (42.4 mg, 0.105 mmol) were converted to peracetates **10** (15.5 mg, 74% yield over two steps) and **11** (36.7 mg, 87% yield over two steps) by the same procedure.

Allyl 2-*N*-acetyl-2-deoxy-(6*R*/6*S*)-*C*-^{2}H-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (10):

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1 H), 5.48 (br d, 1 H, *J* = 8.5 Hz), 5.27 (dd, 1 H, *J* = 9.5, 10.3 Hz), 5.25 (dm, 1 H, *J* = 17.2 Hz), 5.17 (dm, 1 H, *J* = 10.4 Hz), 5.04 (t, 1 H, *J* = 9.9 Hz), 4.69 (d, 1 H, *J* = 8.2 Hz), 4.31 (ddm, 1 H, *J* = 5.0, 12.9 Hz), 4.21 (d, 0.7 H, *J* = 4.3 Hz), 4.13 (d, 0.3 H, *J* = 2.4 Hz), 4.06 (ddm, 1 H, *J* = 6.9, 12.9 Hz), 3.85 (dt, 1 H, *J* = 10.3, 8.2 Hz), 3.66 (dd, 1 H, *J* = 3.4, 9.9 Hz), 2.06 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.7, 170.1, 169.4, 133.5, 117.8, 99.6, 72.3, 71.7, 69.9, 68.7, 54.7, 23.3, 20.7, 20.6, 20.6; HRMS (ESI) calcd for $C_{17}H_{24}DNO_9$ $[M + Na]^+$ 411.1490, found 411.1499.

Allyl 2-*N*-acetyl-2-deoxy-(6*S*)-*C*-methyl-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (11):

$[\alpha]_D$ −21 (*c* 0.5, $CHCl_3$); IR (thin film) ν 3318, 2937, 2877, 1747, 1666, 1537, 1432, 1375, 1305, 1253, 1146, 1054 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1 H), 5.47 (br d, 1 H, *J* = 8.7 Hz), 5.27 (dd, 1 H, *J* = 9.6, 10.5 Hz), 5.23 (dm, 1 H, *J* = 17.2 Hz), 5.16 (dm, 1 H, *J* = 10.4 Hz), 5.05 (t, 1 H, *J* = 9.9 Hz), 5.02 (dq, 1 H, *J* = 2.1, 6.6 Hz), 4.70 (d,1 H, *J* = 8.4 Hz), 4.33 (ddt, 1 H, *J* = 5.2, 12.9, 1.5 Hz), 4.10 (ddt, 1 H, *J* = 6.4, 12.9, 1.2 Hz), 3.81 (q, 1 H, *J* = 9.5 Hz), 3.43 (dd, 1 H, *J* = 2.1, 9.9 Hz), 2.02 (s, 3 H), 1.98 (s, 3 H), 1.95 (s, 3 H), 1.90 (s, 3 H), 1.28 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.6, 170.2, 169.3, 133.6, 117.8, 99.9, 74.7, 72.5, 70.0, 68.3, 66.1, 55.1, 23.3, 21.0, 20.7, 20.5, 15.7; HRMS (ESI) calcd for $C_{18}H_{27}NO_9$ $[M + Na]^+$ 424.1584, found 424.1587.

Allyl 2-*N*-acetyl-2-deoxy-(6*R*)-*C*-methyl-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (12):

$[\alpha]_D$ +1(*c* 1, $CHCl_3$); IR (thin film) ν 3297, 3090, 2950, 2877, 1741, 1665, 1552, 1432, 1375, 1305, 1258, 1237, 1144, 1072, 1041 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (br d, 1 H, *J* = 8.7 Hz), 5.82 (m, 1 H), 5.21 (dm, 1 H, *J*) 17.2 Hz), 5.17 (dd, 1 H, *J* = 9.5, 10.5 Hz), 5.14 (dm, 1 H, *J*) 10.4 Hz), 4.91 (t, 1 H, *J* = 10.1 Hz), 4.88 (dq, 1 H, *J* = 2.0, 6.6 Hz), 4.59 (d, 1 H, *J* = 8.4 Hz), 4.27 (ddt, 1 H, *J* = 5.0, 12.9, 1.5 Hz), 4.05 (ddt, 1 H, *J* = 6.4, 12.9, 1.0 Hz), 3.88 (q, 1 H, *J*) 9.6 Hz), 3.58 (dd, 1 H, *J* = 2.0, 10.1 Hz), 1.99 (s, 6 H), 1.97 (s, 3 H), 1.89 (s, 3 H), 1.22 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.2, 170.1, 169.5, 133.6, 117.6, 99.5, 74.4, 72.7, 69.6, 69.3, 69.0, 54.3, 23.2, 21.1, 20.6, 20.6, 13.5; HRMS (ESI) calcd for $C_{18}H_{27}NO_9$ $[M + H]^+$ 402.1764, found 402.1781.

Typical Deacetylation Procedure (1a–3a)

A solution of monosaccharide **10** (9.0 mg, 23.2 μmol) in CH_2Cl_2/MeOH (2 mL, 1:1 v/v) was treated with NaOMe (8.5 μL, 1 M in MeOH) at 0 °C. The reaction mixture was stirred at room temperature for 20 h, diluted with MeOH (10 mL), and neutralized with activated acidic Dowex 50X-W H^+ ion-exchange resin (25 mg). The resin beads were filtered off and thoroughly rinsed with MeOH (3 × 15 mL). The filtrate was evaporated to dryness, affording monosaccharide **1a** as a white solid in 71% yield (4.3 mg). Similarly, monosaccharides **11** (57.0 mg, 0.142 mmol) and **12** (66.7 mg, 0.166 mmol) afforded polyols **2a** (38.2 mg, 98% yield) and **3a** (46.1 mg, quantitative yield), respectively, with the same procedure.

Allyl 2-*N*-acetyl-2-deoxy-(6*R*/6*S*)-*C*-^{2}H-β-D-glucopyranoside (1a):

^{1}H NMR (500 MHz, CD_3OD) δ 5.89 (m, 1 H, vinylic H-β), 5.27 (dm, 1 H, *J* = 17.3 Hz, *cis*-vinylic H-γ), 5.13 (dm, 1 H, *J* = 10.5 Hz, *trans*-vinylic H-γ′), 4.44 (d, 1 H, $J_{1,2}$) 8.4 Hz, H-1), 4.34 (ddm, 1 H, *J* = 4.8, 13.3 Hz, allylic H-α), 4.07 (ddm, 1 H, *J* = 5.7, 13.3 Hz, allylic H-α′), 3.86 (d, 0.3 H, $J_{5,6S}$ = 2.6 Hz, H-6*S*), 3.67 (m, 1.7 H, H-2 and H-6*R*), 3.45 (dd, 1 H, $J_{3,4}$ = 8.7

Hz, $J_{2,3}$ = 10.3 Hz, H-3), 3.31 (buried, 1 H, H-4), 3.25 (dd, 1 H, $J_{5,6R}$ = 6.2 Hz, $J_{4,5}$ = 9.7 Hz, H-5), 1.97 (s, 3 H, $COCH_3$); ^{13}C NMR (125 MHz, CD_3OD) δ 173.9, 135.7, 117.1, 102.0, 78.1, 76.2, 72.3, 70.8, 62.7, 57.5, 23.1; HRMS (EI) calcd for $C_{11}H_{18}DNO_6$ $[M + H]^+$ 263.1353, found 263.1354.

Allyl 2-*N*-acetyl-2-deoxy-(6*S*)-*S*-methyl-β-D-glucopyranoside (2a):

^{1}H NMR (500 MHz, CD_3OD) δ 5.90 (m, 1 H, vinylic H-β), 5.26 (dm, 1 H, *J* = 17.2 Hz, *cis*-vinylic H-γ), 5.14 (dm, 1 H, *J* = 10.5 Hz, *trans*-vinylic H-γ′), 4.43 (d, 1 H, $J_{1,2}$ = 8.4 Hz, H-1), 4.30 (ddt, 1 H, *J* = 5.0, 13.3, 1.6 Hz, allylic H-α), 4.05–4.10 (m, 2 H, allylic H-α′ and H-6), 3.68 (dd, 1 H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 10.3 Hz, H-2), 3.56 (dd, 1 H, $J_{3,4}$ = 8.9 Hz, $J_{4,5}$) 9.6 Hz, H-4), 3.45 (dd, 1 H, $J_{3,4}$ = 8.9 Hz, $J_{2,3}$ = 10.3 Hz, H-3), 3.01 (dd, 1 H, $J_{5,6}$ = 1.8 Hz, $J_{4,5}$) 9.6 Hz, H-5), 1.98 (s, 3 H, $COCH_3$), 1.28 (d, 3 H, $J_{6,7}$ = 6.6 Hz, CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 173.9, 135.8, 117.1, 102.2, 79.6, 76.4, 71.8, 70.9, 65.9, 57.5, 23.1, 20.1; HRMS (ESI) calcd for $C_{12}H_{21}NO_6$ $[M + Na]^+$ 298.1267, found 298.1265.

Allyl 2-*N*-acetyl-2-deoxy-(6*R*)-*C*-methyl-β-D-glucopyranoside (3a):

^{1}H NMR (500 MHz, CD_3OD) δ 5.89 (m, 1 H, vinylic H-β), 5.27 (dm, 1 H, *J* = 17.3 Hz, *cis*-vinylic H-γ), 5.13 (dm, 1 H, *J* = 10.5 Hz, *trans*-vinylic H-γ′), 4.42 (d, 1 H, $J_{1,2}$ = 8.4 Hz, H-1), 4.32 (ddt, 1 H, *J* = 4.9, 13.3, 1.6 Hz, allylic H-α), 4.07 (ddt, 1 H, *J* = 5.8, 13.3, 1.4 Hz, allylic H-α′), 4.05 (dq, 1 H, $J_{5,6}$ = 3.9 Hz, $J_{6,7}$ = 6.5 Hz, H-6), 3.66 (dd, 1 H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 10.3 Hz, H-2), 3.44 (dd, 1 H, $J_{3,4}$ = 8.7 Hz, $J_{2,3}$ = 10.3 Hz, H-3), 3.30 (dd, 1 H, $J_{3,4}$ = 8.7 Hz, $J_{4,5}$ = 9.7 Hz, H-4), 3.20 (dd, 1 H, $J_{5,6}$ = 3.9 Hz, $J_{4,5}$ = 9.7 Hz, H-5), 1.97 (s, 3 H, $COCH_3$), 1.24 (d, 3 H, $J_{6,7}$ = 6.5 Hz, CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 173.9, 135.8, 117.1, 102.1, 79.6, 76.3, 74.4, 70.8, 69.0, 57.4, 23.1, 17.7; HRMS (ESI) calcd for $C_{12}H_{21}NO_6$ $[M + Na]^+$ 298.1267, found 298.1262.

Allyl 3-*O*-Acetyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy(6*R*/6*S*)-*C*-^{2}H-2-phthalimido-β-D-glucopyranoside (13)

A solution of **7** (30.5 mg, 0.078 mmol) in CH_2Cl_2/THF (750 μL, 3:1 v/v) was treated with Et_3N (18.4 μL, 0.132 mmol), imidazole (1.3 mg, 0.019 mmol), then TBSCl (41.0 mg, 0.272 mmol). The reaction mixture was stirred at room temperature for 20 h, then diluted with CH_2Cl_2 (50 mL) and quenched with saturated $NaHCO_3$ solution (12 mL). Product extraction (CH_2Cl_2) was followed by 5% $CuSO_4$ aqueous solution (50 mL), water (50 mL), and brine (50 mL) washes. The crude residue was purified by flash column chromatography on silica gel (10–40% EtOAc gradient in hexanes) to afford acceptor **13** in 89% yield (35.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (m, 2 H), 7.70 (m, 2 H), 5.69 (m, 1 H), 5.63 (dd, 1 H, *J* = 8.7, 10.7 Hz), 5.38 (d, 1 H, *J* = 8.4 Hz), 5.09 (dm, 1 H, *J* = 17.2 Hz), 5.02 (dm, 1 H, *J* = 10.4 Hz), 4.22 (ddt, 1 H, *J* = 5.0, 12.9, 1.5 Hz), 4.20 (dd, 1 H, *J* = 8.4, 10.7 Hz), 4.01 (ddt, 1 H, *J* = 6.2, 12.9, 1.4 Hz), 3.95 (d, 0.7 H, *J* = 4.9 Hz), 3.87 (d, 0.3 H, *J* = 5.9 Hz), 3.78 (br t, 1 H, *J* = 9.5 Hz), 3.58 (dd, 1 H, *J* = 5.4, 9.5 Hz), 3.35 (br s, 1 H), 1.89 (s, 3 H), 0.90 (s, 9 H), 0.10, 0.09 (2 s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 167.8, 134.1, 133.5, 131.5, 123.4, 117.5, 97.0, 74.1, 73.5, 72.4, 69.9, 64.6, 54.6, 25.8, 20.6, 18.2, −5.4, −5.5; HRMS (EI) calcd for $C_{25}H_{34}DNO_8Si$ $[M + H]^+$ 507.2273, found 507.2276.

Allyl 3-*O*-Acetyl-2-deoxy-6-*O*-(*p*-methoxybenzyl)-(6*S*)-*C*-methyl-2-phthalimido-β-D-glucopyranoside (14)

Diol **8** (179 mg, 0.441 mmol) and 4A molecular sieves were suspended in toluene (5 mL) and treated with *p*-anisaldehyde dimethylacetal (1.4 mL, 8.83 mmol) and camphorsulfonic acid (25.6 mg, 0.110 mmol). The reaction mixture was stirred at 90 °C for 3 h, then diluted with EtOAc (50 mL) and filtered over Celite. Basic aqueous workup (EtOAc) followed by flash

chromatography on silica gel (10–40% EtOAc gradient in hexanes, 0.2% Et_3N) afforded (6*S*)-*C*-Me-substituted acetal as a white solid in 71% yield (165 mg).

A suspension of the acetal (99 mg, 0.19 mmol) and 4A molecular sieves in anhydrous THF (7 mL) was cooled to −30 °C and treated with $NaBH_3CN$ (83.2 mg, 1.32 mmol). HCl (2 mL, ca. 1 M solution in Et_2O) was added dropwise to the reaction mixture, and repeated every 30 min over 1.5 h reaction time. The reaction mixture was diluted with Et_2O, filtered over Celite, then quenched with a 0.5 M HCl aqueous solution. Basic aqueous workup (EtOAc) followed by flash chromatography on silica gel (10–50% EtOAc gradient in hexanes) afforded acceptor **14** as a white solid in 61% yield (60.8 mg). $[\alpha]_D$ −13 (*c* 0.5, $CHCl_3$); IR (thin film) ν 3475, 2917, 1777, 174, 1718, 1613, 1514, 1387, 1246, 1044, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (m, 2 H), 7.69 (m, 2 H), 7.27 (d, 2 H, *J* = 8.7 Hz), 6.87 (d, 2 H, *J* = 8.7 Hz), 5.69 (m, 1 H), 5.66 (dd, 1 H, *J* = 9.0, 10.7 Hz), 5.34 (d, 1 H, *J* = 8.4 Hz), 5.09 (dm, 1 H, *J* = 17.2 Hz), 5.02 (dm, 1 H, *J* = 10.4 Hz), 4.63 (d, 1 H, *J* = 11.5 Hz), 4.43 (d, 1 H, *J* = 11.5 Hz), 4.22 (m, 1 H), 4.22 (dd, 1 H, *J* = 8.4, 10.7 Hz), 4.01 (m, 1 H), 3.97–3.89 (m, 2 H), 3.79 (s, 3 H), 3.50 (dd, 1 H, *J* = 3.2, 9.7 Hz), 2.84 (d, 1 H, *J* = 2.7 Hz), 1.90 (s, 3 H), 1.32 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 159.4, 134.1, 133.6, 131.5, 129.9, 129.6, 123.5, 117.5, 113.9, 97.3, 75.4, 73.6, 72.5, 70.9, 69.9, 69.4, 55.3, 54.6, 20.7, 14.6; HRMS (EI) calcd for $C_{28}H_{31}NO_9$ $[M + H]^+$ 526.2077, found 526.2066.

Allyl 3-*O*-Acetyl-2-deoxy-6-*O*-(*p*-methoxybenzyl)-(6*R*)-*C*-methyl-2-phthalimido-β-D-glucopyranoside (15)

(6*R*)-*C*-Me-substituted acetal (220 mg) was obtained in 76% isolated yield from diol **9** (225 mg, 0.555 mmol) by the above-described procedure. The acetal intermediate (45.0 mg, 85.9 μmol) was treated with $NaBH_3CN$ (3 × 32.7 mg, 1.56 mmol) and HCl (5 mL, ca. 1 M solution in Et_2O) over a 6-h period according to the above-described procedure. Alcohol **15** was isolated in 35% yield (15.9 mg), along with unreacted starting material (14.4 mg, 32%). $[\alpha]_D$ +53 (*c* 0.45, $CHCl_3$); IR (thin film) ν 3852, 3752, 2936, 1777, 1746, 1718, 1616, 1513, 1387, 1228, 1043, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2 H), 7.73 (m, 2 H), 7.27 (d, 2 H, *J* = 8.5 Hz), 6.90 (d, 2 H, *J* = 8.5 Hz), 5.75 (m, 1 H), 5.65 (dd, 1 H, *J* = 8.7, 10.6 Hz), 5.42 (d, 1 H, *J* = 8.4 Hz), 5.15 (dm, 1 H, *J* = 17.2 Hz), 5.09 (dm, 1 H, *J* = 10.4 Hz), 4.68 (d, 1 H, *J* = 11.1 Hz), 4.44 (d, 1 H, *J* = 11.1 Hz), 4.25 (ddt, 1 H, *J* = 5.3, 12.9, 1.0 Hz), 4.22 (dd, 1 H, *J* = 8.4, 10.6 Hz), 4.07 (ddt, 1 H, *J* = 6.2, 12.9, 1.0 Hz), 3.87 (dq, 1 H, *J* = 6.0, 7.3 Hz), 3.82 (s, 3 H), 3.78 (dd, 1 H, *J* = 8.7, 9.3 Hz), 3.43 (dd, 1 H, *J* = 7.3, 9.3 Hz), 1.92 (s, 3 H), 1.41 (d, 3 H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 167.8, 159.5, 134.1, 133.5, 131.5, 129.6, 129.1, 123.4, 117.6, 114.0, 97.0, 77.6, 76.2, 73.3, 73.2, 70.4, 70.1, 55.2, 54.5, 20.6, 16.5; HRMS (EI) calcd for $C_{28}H_{31}NO_9$ $[M + H]^+$ 526.2077, found 526.2057.

2-Deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-α/β-D-glucopyranosyl Trichloroacetimidate (16)[17]

A solution of tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (1.5 g, 3.14 mmol) in anhydrous DMF (10 mL) was treated with hydrazine acetate (0.68 g, 7.41 mmol). The reaction mixture was stirred at room temperature for 3 h, then cooled to 0 °C and quenched with saturated $NaHCO_3$ solution (36 mL). Standard aqueous workup ($CHCl_3$) and purification over a silica gel plug (30–50% EtOAc gradient in hexanes, 0.2% Et_3N) afforded the corresponding lactol in 35% yield. The lactol (471 mg, 1.09 mmol) was azeotroped with toluene (thrice), dried under high vacuum overnight, and dissolved in CH_2Cl_2 (10 mL). The solution was treated with 4A molecular sieves, CCl_3.CN (3.25 mL. 32.4 mmol), then Cs_2CO_3 (106 mg, 0.324 mmol). The reaction mixture was stirred at room temperature for 3 h, diluted with CH_2Cl_2 (50 mL), filtered over Celite, then quenched with saturated $NaHCO_3$ solution (50 mL). Standard aqueous workup (CH_2Cl_2) followed by flash chromatography over silica gel (25–50% EtOAc gradient in hexanes, 0.2% Et_3N) afforded imidate donor **16** in 74% isolated yield (461.5 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 7.84 (m, 2 H), 7.72 (m, 2 H), 6.61

(d, 1 H, *J* = 9.0 Hz), 5.90 (dd, 1 H, *J* = 9.2, 10.7 Hz), 5.26 (dd, 1 H, *J* = 9.2, 10.1 Hz), 4.61 (dd, 1 H, *J* = 9.0, 10.7 Hz), 4.37 (dd, 1 H, *J* = 4.3, 12.4 Hz), 4.18 (dd, 1 H, *J* = 2.2, 12.4 Hz), 4.05 (ddd, 1 H, *J* = 2.2, 4.3, 10.1 Hz), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.88 (s, 3 H).

Glycosidic Coupling (17–19)

In a typical procedure, both imidate donor **16** (134.1 mg, 0.23 mmol) and acceptor **14** (60.8 mg, 0.11 mmol) were azeotroped with toluene (thrice), dried under high vacuum for 45 min, then dissolved in CH_2Cl_2 (2 mL) and treated with 4A activated molecular sieves. The suspension was stirred at room temperature for 15 min then cooled to −30 °C and treated with TMSOTf (64 μL, 0.5 M solution in CH_2Cl_2). The reaction mixture was stirred at −30 °C for 2 h, then quenched with Et_3N (24 μL, 0.17 mmol), filtered over Celite, and concentrated to dryness. The crude residue was purified by flash column chromatography on silica gel (25–60% EtOAc gradient in hexanes) to afford disaccharide **18** in 98% isolated yield (107 mg). Similarly, acceptors **13** (40.0 mg, 0.079 mmol) and **15** (84.0 mg, 0.16 mmol) were respectively converted into disaccharides **17** (37.1 mg, 51% isolated yield) and **19** (118.3 mg, 78% isolated yield) with the same procedure.

Allyl 3-*O*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4-*O*-(2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(6*R*/6*S*)-*C*-^{2}H-2-phthalimido-β-D-glucopyrano-side (17):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.64 (m, 8 H), 5.74 (dd, 1 H, *J* = 9.0, 10.5 Hz), 5.63 (dd, 1 H, *J* = 9.0, 10.6 Hz), 5.63 (m, 1 H), 5.48 (d, 1 H, *J* = 8.4 Hz), 5.24 (d, 1 H, *J* = 8.4 Hz), 5.08 (dd, 1 H, *J* = 9.0, 10.1 Hz), 5.02 (dm, 1 H, *J* = 17.2 Hz), 4.97 (dm, 1 H, *J* = 10.4 Hz), 4.42 (dd, 1 H, *J* = 4.6, 12.3 Hz), 4.19 (dd, 1 H, *J* = 8.4, 10.5 Hz), 4.11 (ddt, 1 H, *J* = 5.0, 12.9, 1.4 Hz), 4.10 (dd, 1 H, *J* = 8.4, 10.6 Hz), 4.04 (dd, 1 H, *J* = 2.7, 12.3 Hz), 4.00 (t, 1 H, *J* = 9.9 Hz), 3.92 (ddt, 1 H, *J* = 6.3, 12.9, 1.3 Hz), 3.78 (ddd, 1 H, *J* = 2.7, 4.6, 10.1 Hz), 3.62 (d, 0.3 H, *J* = 1.5 Hz), 3.40 (d, 0.7 H, *J* = 3.5 Hz), 3.31 (dd, 1 H, *J* = 2.5, 9.9 Hz), 2.06 (s, 3 H), 1.98 (s, 3 H), 1.89 (s, 3 H), 1.79 (s, 3 H), 0.90 (s, 9 H), 0.05 and 0.04 (2 s, 6 H).

Allyl 3-*O*-acetyl-2-deoxy-4-*O*-(2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-6-*O*-(*p*-methoxybenzyl)-(6*S*)-*C*-methyl-2-phthalimido-β-D-glucopyrano-side (18):

$[\alpha]_D$ −12 (*c* 1, $CHCl_3$); IR (thin film) ν 2950, 1734, 1717, 1684, 1653, 1559, 1540, 1507, 1457, 1046, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.68 (m, 8 H), 7.41 (d, 2 H, *J* = 8.7 Hz), 6.91 (d, 2 H, *J* = 8.7 Hz), 5.68 (m, 1 H), 5.61 (dd, 1 H, *J* = 9.2, 10.7 Hz), 5.59 (dd, 1 H, *J* = 9.0, 10.7 Hz), 5.22 (d, 1H, *J* = 8.5 Hz), 5.16 (d, 1 H, *J* = 8.4 Hz), 5.05 (dm, 1 H, *J* = 17.2 Hz), 4.99 (dd, 1 H, *J* = 9.2, 10.4 Hz), 4.98 (dm, 1 H, *J* = 10.1 Hz), 4.67 (d, 1 H, *J* = 11.3 Hz), 4.41 (d, 1 H, *J* = 11.3 Hz), 4.22 (dd, 1 H, *J* = 6.5, 12.3 Hz), 4.20 (t, 1 H, *J* = 9.0 Hz), 4.18 (dd, 1 H, *J* = 8.4, 10.7 Hz), 4.17 (m, 1 H), 4.11 (dd, 1 H, *J* = 8.5, 10.7 Hz), 3.98 (ddt, 1 H, *J* = 6.4, 12.9, 1.6 Hz), 3.86 (dd, 1H, *J* = 2.0, 12.3 Hz), 3.82 (s, 3 H), 3.65 (dq, 1 H, *J* = 2.1, 6.4 Hz), 3.24 (dd, 1 H, *J* = 2.1, 9.8 Hz), 2.90 (ddd, 1 H, *J* = 2.0, 6.5, 10.4 Hz), 2.03 (s, 3 H), 1.97 (s, 3 H), 1.88 (s, 3 H), 1.79 (s, 3 H), 1.19 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.2, 169.4, 167.5, 159.0, 134.4, 134.1, 133.6, 131.4, 129.0, 123.6, 123.4, 117.6, 113.7, 97.1, 95.9, 73.4, 71.4, 71.2, 70.6, 69.9, 69.6, 68.4, 61.3, 55.2, 55.0, 54.9, 20.6, 20.5, 20.5, 20.4, 15.2; HRMS (ESI) calcd for $C_{48}H_{50}N_2O_{18}$ $[M + Na]^+$ 965.2956, found 965.2959.

Allyl 3-*O*-acetyl-2-deoxy-4-*O*-(2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-6-*O*-(*p*-methoxybenzyl)-(6*R*)-*C*-methyl-2-phthalimido-β-D-glucopyrano-side (19):

$[\alpha]_D$ +7 (*c* 1, $CHCl_3$); IR (thin film) ν 2943, 1778, 1749, 1718, 1612, 1514, 1498, 1387, 1228, 1144, 1046, 722 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (m, 4 H), 7.69 (m, 4 H), 7.03 (d, 2 H, *J* = 8.7 Hz), 6.80 (d, 2 H, *J* = 8.7 Hz), 5.75 (dd, 1 H, *J* = 7.9, 10.7 Hz), 5.67 (dd, 1 H, *J* =

9.2, 10.4 Hz), 5.64 (m, 1 H), 5.45 (d, 1 H, *J* = 8.4 Hz), 5.24 (d, 1 H, *J* = 8.5 Hz), 5.12 (t, 1 H, *J* = 9.3 Hz), 5.02 (dm, 1 H, *J* = 17.2 Hz), 4.96 (dm, 1 H, *J* = 10.4 Hz), 4.38 (dd, 1 H, *J* = 4.0, 12.3 Hz), 4.21 (dd, 1 H, *J* = 8.4, 10.7 Hz), 4.15 (ddt, 1 H, *J* = 5.0, 13.0, 1.4 Hz), 4.12 (dd, 1 H, *J* = 8.5, 10.4 Hz), 4.09 (d, 2 H, *J* = 11.6 Hz), 4.01 (dd, 1 H, *J* = 2.1, 12.3 Hz), 3.94 (ddt, 1 H, *J* = 6.4, 13.0, 1.6 Hz), 3.78 (s, 3 H), 3.76–3.70 (m, 3 H), 3.52 (dq, 1 H, *J* = 1.0, 6.6 Hz), 2.04 (s, 3 H), 1.96 (s, 3 H), 1.91 (s, 3 H), 1.80 (s, 3 H), 0.96 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.1, 169.8, 169.3, 167.7, 159.0, 134.4, 134.1, 133.5, 131.3, 130.5, 128.8, 123.6, 123.4, 117.6, 113.6, 96.9, 96.7, 76.5, 75.2, 73.4, 71.9, 71.3, 70.6, 70.4, 69.8, 68.3, 61.4, 55.2, 54.8, 20.6, 20.6, 20.5, 20.3, 14.2; HRMS (ESI) calcd for $C_{48}H_{50}N_2O_{18}$ $[M + Na]^+$ 965.2956, found 965.2944.

Allyl *N*-Acetyl-4-*O*-(*N*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-deoxy-(6*R*/6*S*)-*C*-^{2}H-β-D-glucopyranoside (1b)

A solution of disaccharide **17** (37.5 mg, 40.6 μmol) in anhydrous THF was treated with TBAF (183 μL, 1 M solution in THF). The reaction mixture was stirred at room temperature for 20 h, then evaporated to dryness. The crude residue was coevaporated with $CHCl_3$ (thrice), dissolved in *n*-BuOH (5 mL), and treated with ethylenediamine (0.44 mL, 6.6 mmol) according to the above-described procedure. The resulting free amine intermediate was dissolved in pyridine (3 mL) and treated with Ac_2O (2 mL) also according to the above-described procedure. Column chromatography on silica gel (1.25–5% EtOH gradient in $CHCl_3$) afforded the desired peracetylated C-6 monodeuterated disaccharide intermediate (27.2 mg, 99% over three steps): $[\alpha]_D$ +4(*c* 1, $CHCl_3$); IR (thin film) ν 3289, 2920, 1745, 1661, 1541, 1372, 1233, 1047 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (d, 1 H, *J* = 9.1 Hz), 5.97 (d, 1 H, *J* = 9.5 Hz), 5.81 (m, 1 H), 5.22 (dm, 1 H, *J* = 17.2 Hz), 5.18 (dd, 1 H, *J* = 9.4, 10.3 Hz), 5.15 (dm, 1 H, *J* = 10.4 Hz), 5.11 (dd, 1 H, *J* = 8.2, 9.7 Hz), 5.01 (t, 1 H, *J* = 9.6 Hz), 4.59 (d, 1 H, *J* = 8.2 Hz), 4.50 (d,1H, *J* = 7.8 Hz), 4.34 (dd, 1 H, *J* = 4.3, 12.3 Hz), 4.27 (ddt, 1H, *J* = 5.0, 13.1, 1.5 Hz), 4.23 (d, 1 H, *J* = 5.6 Hz), 4.01 (ddt, 1 H, *J* = 6.1, 13.1, 1.4 Hz), 4.00 (dd, 1 H, *J* = 2.4, 12.3 Hz), 3.88–3.79 (m, 2 H), 3.72 (t, 1 H, *J* = 8.9 Hz), 3.65 (ddd, 1 H, *J* = 2.4, 4.3, 9.6 Hz), 3.61 (dd, 1 H, *J* = 5.6, 8.9 Hz), 2.10 (s, 3 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.94 (s, 3 H), 1.91 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 170.8, 170.7, 170.6, 170.3, 169.3, 133.5, 117.6, 101.1, 99.9, 99.7, 76.1, 72.7, 72.4, 72.3, 71.7, 69.7, 68.1, 62.3, 61.7, 54.7, 53.4, 23.2, 20.9, 20.7, 20.6.

A solution of C-6 monodeuterated disaccharide peracetate (25.4 mg, 37.6 μmol) in CH_2Cl_2/MeOH (3 mL, 1:1 v/v) was treated with NaOMe (25 μL, 1 M in MeOH) according to the above-described procedure to afford monodeuterated disaccharide **1b** as a white solid in quantitative yield (17.5 mg). ^{1}H NMR (600 MHz, CD_3OD:D_2O, v/v 3:1) δ 5.88 (m, 1 H, vinylic H-β), 5.27 (dm, 1 H, *J* = 17.3 Hz, vinylic H-γ), 5.17 (dm, 1 H, *J* = 10.6 Hz, vinylic H-γ′), 4.52 (d, 1 H, $J_{1',2'}$ = 8.5 Hz, H-1′), 4.46 (d, 1 H, $J_{1,2}$ = 8.3 Hz, H-1), 4.31 (ddt, 1 H, *J* = 4.9, 13.3, 1.6 Hz, allylic H-α), 4.08 (ddt, 1 H, *J* = 5.9, 13.3, 1.4 Hz, allylic H-α′), 3.91 (dd, 1 H, $J_{5',6'a}$ = 2.2 Hz, $J_{6'a,6'b}$ = 12.1 Hz, H-6′a), 3.80 (d, 0.3 H, $J_{5,6S}$ = 2.0 Hz, H-6*S*), 3.74 (dd, 1 H, $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 10.4 Hz, H-2), 3.73 (dd, 1 H, $J_{1',2'}$ = 8.5 Hz, $J_{2',3'}$ = 10.4 Hz, H-2′), 3.67 (dd, 1 H, $J_{5',6'b}$ = 6.3 Hz, $J_{6'a,6'b}$ = 12.1 Hz, H-6′b), 3.64 (dd, 1 H, $J_{3,4}$ = 8.3 Hz, $J_{2,3}$ = 10.4 Hz, H-3), 3.63 (d, 0.7 H, $J_{5,6R}$ = 4.9 Hz, H-6*R*), 3.55 (dd, 1 H, $J_{3,4}$ = 8.3 Hz, $J_{4,5}$ = 9.7 Hz, H-4), 3.48 (dd, 1 H, $J_{3',4'}$ = 8.5 Hz, $J_{2',3'}$ = 10.4 Hz, H-3′), 3.41 (ddd, 1 H, $J_{5',6'a}$ = 2.2 Hz, $J_{5',6'b}$ = 6.3 Hz, $J_{4',5'}$) 9.9 Hz, H-5′), 3.36 (m, 2 H, H-4′ and H-5), 2.04 (s, 3 H, $COCH_3$), 1.99 (s, 3 H, $COCH_3$); ^{13}C NMR (75 MHz, CD_3OD/D_2O, 4:1 v/v) δ 174.4, 174.2, 135.3, 117.7, 103.2, 101.8, 81.4, 78.0, 76.3, 75.6, 74.2, 71.8, 71.1, 62.4, 61.3, 57.2, 56.5, 23.2, 23.1; HRMS (ESI) calcd $C_{19}H_{31}DN_2O_{11}$ $[M + Na]^+$ 488.1967, found 488.1975.

6-*C*-Methyl-Substituted Disaccharides (2b, 3b)

A solution of disaccharide **18** (91.8 mg, 97.4 μmol) in CH_2Cl_2 (5.5 mL) was treated with pH 7 buffer (0.41 mL), *t*-BuOH (0.19 mL, 1.95 mmol), and DDQ (71 mg, 0.31 mmol) at 0 °C. The heterogeneous solution was stirred at room temperature for 20 h, then diluted with CH_2Cl_2 (15 mL) and quenched with saturated $NaHCO_3$ solution (12 mL) at 0 °C. Standard aqueous workup (CH_2Cl_2) followed by flash column chromatography on silica gel (25–70% EtOAc gradient in hexanes) afforded the free 6-OH disaccharide intermediate in 80% isolated yield (63.8 mg).

According to the previously described procedure, a solution of the disaccharide intermediate (50.4 mg, 61.2 μmol) in *n*-BuOH (5.5 mL) was treated with ethylenediamine (0.65 mL, 9.80 mmol) affording the free amine intermediate, which was then dissolved in pyridine (3 mL) and treated with Ac_2O (2 mL). Column chromatography on silica gel (1.25–5% EtOH gradient in $CHCl_3$) afforded the desired (6*S*)-*C*-CH_3-substituted peracetylated disaccharide intermediate (42.8 mg, quantitative yield over two steps): $[\alpha]_D$ –53 (*c* 1, $CHCl_3$); IR (thin film) ν 3347, 2940, 1745, 1664, 1532, 1431, 1375, 1231, 1150, 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, 1 H, *J* = 9.6 Hz), 5.83 (m, 1 H), 5.46 (d, 1 H, *J* = 9.5 Hz), 5.31 (dq, 1 H, *J* = 1.1, 6.6 Hz), 5.23 (dq, 1 H, *J* = 17.4, 1.6 Hz), 5.18 (dm, 1 H, *J* = 10.4, 1.6 Hz), 5.03 (t, 1 H, *J* = 9.6 Hz), 5.01 (dd, 1 H, *J* = 10.7, 8.8 Hz), 4.91 (t, 1 H, *J* = 10.2 Hz), 4.39 (d, 1 H, *J* = 8.4 Hz), 4.34 (dd, 1 H, *J* = 4.1, 12.4 Hz), 4.30 (ddt, 1 H, *J* = 11.7, 5.2, 1.6 Hz), 4.16 (q, 1 H, *J* = 8.4 Hz), 4.09 (ddt, 1 H, *J* = 6.4, 11.7, 1.6 Hz), 4.09 (q, 1 H, *J* = 8.4 Hz), 4.04 (d, 1 H, *J* = 8.4 Hz), 3.98 (dd, 1 H, *J* = 2.3, 12.4 Hz), 3.54 (t, 1 H, *J* = 9.6 Hz), 3.51 (m, 1 H), 3.27 (dd, 1 H, *J* = 8.6, 9.6 Hz), 2.16 (s, 3 H), 2.05 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 192 (s, 3 H), 1.30 (d, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 171.0, 170.8, 170.6, 170.1, 169.9, 169.2, 133.6, 117.9, 102.6, 100.4, 77.4, 76.1, 73.2, 72.8, 72.0, 70.0, 67.8, 66.7, 61.6, 54.0, 53.5, 23.3, 23.0, 21.6, 20.7, 20.6, 20.6, 20.5, 16.6; HRMS (ESI) calcd for $C_{30}H_{44}N_2O_{16}$ $[M + H]^+$ 689.2769, found 689.2742.

Disaccharide **19** (117.6 mg, 0.125 mmol) was converted to the corresponding (6*R*)-*C*-CH_3-substituted peracetate intermediate in a similar fashion (63.0 mg, 74% yield over three steps): $[\alpha]_D$ –36 (*c* 1, $CHCl_3$); IR (thin film) ν 3341, 2940, 1744, 1687, 1666, 1537, 1431, 1372, 1233, 1151, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (d, 1 H, *J* = 8.2 Hz), 6.09 (d, 1 H, *J* = 9.4 Hz), 5.82 (m, 1 H), 5.35 (t, 1 H, *J* = 10.0 Hz), 5.22 (dq, 1H, *J* = 17.2, 1.5 Hz), 5.14 (m, 2 H), 5.05 (t, 1 H, *J* = 9.5 Hz), 5.01 (t, 1 H, *J* = 8.1 Hz), 4.79 (d, 1 H, *J* = 8.2 Hz), 4.42 (d, 1 H, *J* = 7.7 Hz), 4.34 (dd, 1 H, *J* = 4.8, 12.4 Hz), 4.26 (ddt, 1 H, *J* = 4.8, 13.2, 1.5 Hz), 4.05 (ddt, 1 H, *J* = 6.1, 13.2, 1.5 Hz), 4.01 (t, 1 H, *J* = 8.6 Hz), 4.00 (dd, 1 H, *J* = 2.1, 12.4 Hz), 3.70 (m, 1 H), 3.67 (q, 1 H, *J* = 8.2 Hz), 3.60 (q, 1 H, *J* = 7.7 Hz), 3.53 (dd, 1 H, *J* = 2.9, 12 Hz), 2.03 (s, 3 H), 2.01 (s, 6 H), 1.97–1.96 (2 s, 6 H), 1.93 (s, 3 H), 1.89 (s, 3 H), 1.26 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.6, 170.6, 170.4, 170.3, 169.5, 133.7, 117.3, 100.1, 99.8, 76.2, 75.4, 72.6, 71.9, 71.7, 69.4, 68.9, 68.4, 61.9, 55.4, 53.1, 23.2, 23.1, 21.2, 20.7, 20.6, 20.6, 13.8; HRMS (ESI) calcd for $C_{30}H_{44}N_2O_{16}$ $[M + H]^+$ 689.2769, found 689.2739.

A solution of (6*S*)-*C*-CH_3-substituted disaccharide peracetate (65.0 mg, 94.4 μmol) in CH_2Cl_2/MeOH (6 mL, 1:1 v/v) was treated with NaOMe (60 μL, 1 M in MeOH) according to the above-described procedure, affording disaccharide **2b** as a white solid in 99% yield (45.0 mg). Similarly, (6*R*)-*C*-CH_3-substituted disaccharide peracetate (63.0 mg, 91.5 μmol) afforded disaccharide **3b** (43.0 mg, 96% yield).

Allyl *N*-acetyl-4-*O*-(*N*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-deoxy-(6*S*)-*C*-methyl-β-D-glucopyranoside (2b):

^1H NMR (600 MHz, CD_3OD) δ 5.89 (m, 1 H, vinylic H-β), 5.26 (dq, 1 H, *J* = 1.6, 17.3 Hz, *cis*-vinylic H-γ), 5.14 (dq, 1 H, *J* = 10.5, 1.6 Hz, *trans*-vinylic H-γ′), 4.50 (d, 1 H, $J_{1',2'}$ = 8.4

Hz, H-1′), 4.40 (d, 1 H, $J_{1,2}$ = 8.5 Hz, H-1), 4.29 (ddt, 1 H, *J* = 5.0, 13.3, 1.5 Hz, allylic H-α), 4.07 (ddt, 1 H, *J* = 5.8, 13.3, 1.5 Hz, allylic H-α′), 3.91 (dq, 1 H, $J_{5,6}$ = 1.5 Hz, $J_{6,7}$ = 6.6 Hz, H-6), 3.90 (dd, 1 H, $J_{5',6'a}$ = 2.3 Hz, $J_{6'a,6'b}$ = 11.8 Hz, H-6′a), 3.74 (dd, 2 H, $J_{1,2}$ = $J_{1',2'}$ = 8.5 Hz, $J_{2,3}$ = $J_{2',3'}$ = 10.2 Hz, H-2 and H-2′), 3.65 (dd, 1 H, $J_{5',6'b}$ = 6.1 Hz, $J_{6'a,6'b}$ = 11.8 Hz, H-6′ b), 3.64 (dd, 1 H, $J_{3,4}$ = 8.6 Hz, $J_{4,5}$ = 9.4 Hz, H-4), 3.59 (dd, 1 H, $J_{3,4}$ = 8.6 Hz, $J_{2,3}$ = 10.2 Hz, H-3), 3.42 (dd, 1 H, $J_{3',4'}$ = 8.4 Hz, $J_{2',3'}$ = 10.2 Hz, H-3′), 3.35 (dm, 1 H, $J_{4',5'}$ = 9.3 Hz, H-5′), 3.34 (t, 1 H, $J_{3',4'}$ = $J_{4',5'}$ = 8.8 Hz, H-4′), 3.08 (dd, 1 H, $J_{5,6}$ = 1.5 Hz, $J_{4,5}$ = 9.4 Hz, H-5), 1.99 (s, 3 H, $COCH_3$), 1.96 (s, 3 H, $COCH_3$), 1.29 (d, 3 H, $J_{6,7}$ = 6.6 Hz, CH_3); ^{13}C NMR (125 MHz, CD_3OD/D_2O, v/v 5:3) δ 174.7 (CO), 174.7 (CO), 134.9 (C-β), 118.4 (C-γ), 103.1 (C-1′), 101.6 (C-1), 81.4 (C-4), 77.8 (C-5), 77.5 (C-5′), 75.1 (C-3′), 74.0 (C-3), 71.4 (C-4′), 71.3 (C-α), 64.9 (C-6), 62.1 (C-6′), 56.9, 56.3 (C-2/2′), 23.2, 22.9 (NHAc), 19.9 (CH_3); HRMS (ESI) calcd for $C_{20}H_{34}N_2O_{11}$ $[M + Na]^+$ 501.2060, found 501.2063.

Allyl *N*-acetyl-4-*O*-(*N*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-deoxy-(6*R*)-*C*-methyl-*β*-D-glucopyranoside (3b):

^{1}H NMR (600 MHz, CD_3OD) δ 5.88 (m, 1 H, vinylic H-β), 5.27 (dq, 1 H, *J* = 17.3, 1.8 Hz, *cis*-vinylic H-γ), 5.13 (dq, 1 H, *J* = 10.5, 1.8 Hz, *trans*-vinylic H-γ′), 4.50 (d, 1 H, $J_{1',2'}$ = 8.4 Hz, H-1′), 4.40 (d, 1 H, $J_{1,2}$ = 8.4 Hz, H-1), 4.34 (ddt, 1 H, *J* = 4.8, 13.4, 1.8 Hz, allylic H-α), 4.08 (ddt, 1 H, *J* = 5.8, 13.4, 1.8 Hz, allylic H-α′), 4.02 (dq, 1 H, $J_{5,6}$ = 2.4 Hz, $J_{6,7}$ = 6.5 Hz, H-6), 3.91 (dd, 1 H, $J_{5',6'a}$ = 2.3 Hz, $J_{6'a,6'b}$ = 11.8 Hz, H-6′a), 3.72 (dd, 1 H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 3.65 (dd, 1 H, $J_{1',2'}$ = 8.4 Hz, $J_{2',3'}$ = 10.4 Hz, H-2′), 3.62 (dd, 1 H, $J_{5',6'b}$ = 6.7 Hz, $J_{6'a,6'b}$ = 11.8 Hz, H-6′b), 3.60 (dd, 1 H, $J_{3,4}$ = 7.9 Hz, $J_{2,3}$ = 10.2 Hz, H-3), 3.48 (dd, 1 H, $J_{3',4'}$ = 8.6 Hz, $J_{2',3'}$ = 10.4 Hz, H-3′), 3.39 (dd, 1 H, $J_{5,6}$ = 2.4 Hz, $J_{4,5}$ = 9.7 Hz, H-5), 3.35 (dm, 1 H, $J_{4',5'}$ = 9.8 Hz, H-5′), 3.33 (dd, 1 H, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 9.7 Hz, H-4), 3.28 (dd, 1 H, $J_{3',4'}$ = 8.6 Hz, $J_{4',5'}$ = 9.8 Hz, H-4′), 2.01 (s, 3 H, $COCH_3$), 1.96 (s, 3 H, $COCH_3$), 1.22 (d, 3 H, $J_{6,7}$ = 6.5 Hz, CH_3); ^{13}C NMR (125 MHz, CD_3OD/D_2O, v/v 5:1) δ 174.5 (CO), 174.3 (CO), 135.3 (C-β), 117.8 (C-γ), 103.0 (C-1′), 101.9 (C-1), 83.3 (C-4), 78.4 (C-5), 77.9 (C-5′), 75.3 (C-3′), 74.6 (C-3), 71.8 (C-4′), 71.0 (C-α), 66.8 (C-6), 62.4 (C-6′), 57.3 (C-2′), 56.4 (C-2), 23.3, 23.2 (NHAc), 16.3 (CH_3); HRMS (ESI) calcd for $C_{20}H_{34}N_2O_{11}$ $[M + Na]^+$ 501.2060, found 501.2060.

Supplementary Material

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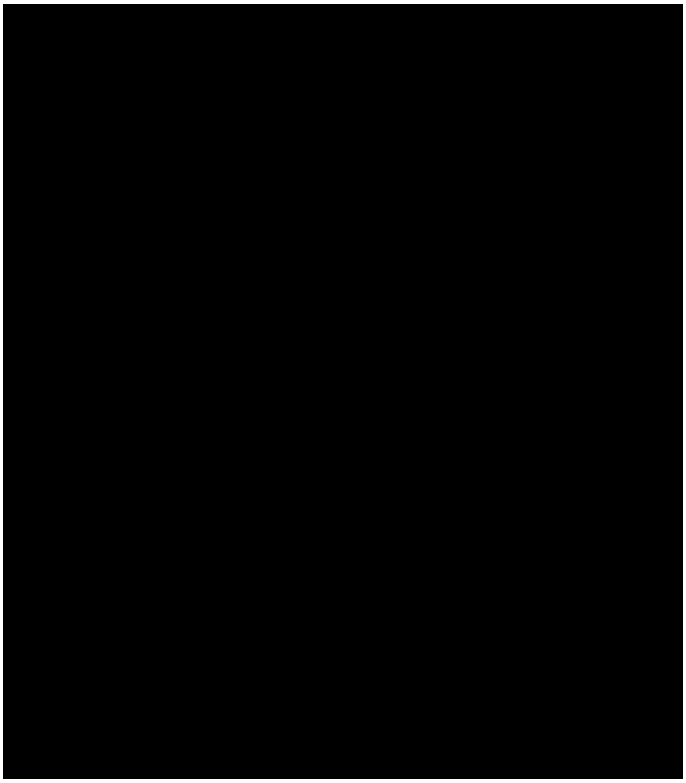


FIGURE 1.
Staggered *gt*, *tg*, and *gg* conformations of 6-*C*-substituted β-D-GlcNAc derivatives **1**–**3**.

FIGURE 2.
(6*R*)-*C*-Methyl-substituted glucosamine in Geneticin (G418).

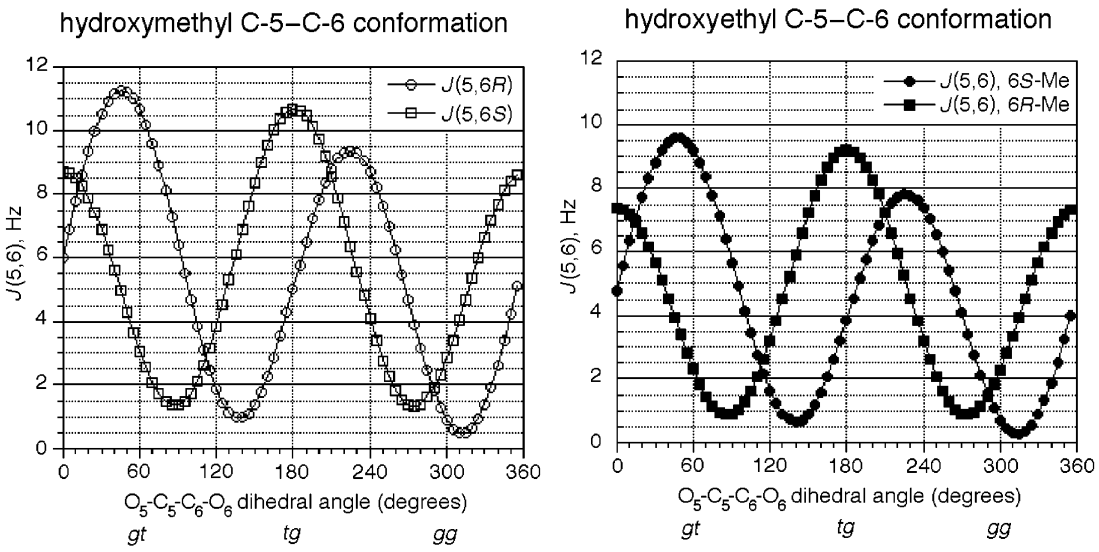


FIGURE 3.

Parametrized Karplus relationships describing C-5-C-6 conformations as a function of $^{3}J_{5,6}$, based on the empirical formulations of Haasnoot et al.[23] C-5 hydroxymethyl and C-5 hydroxyethyl conformations were evaluated by using Karplus curves parametrized for 1,2-dialkoxypropanes[3] (left) and 1,2-dialkoxybutanes (right), respectively.

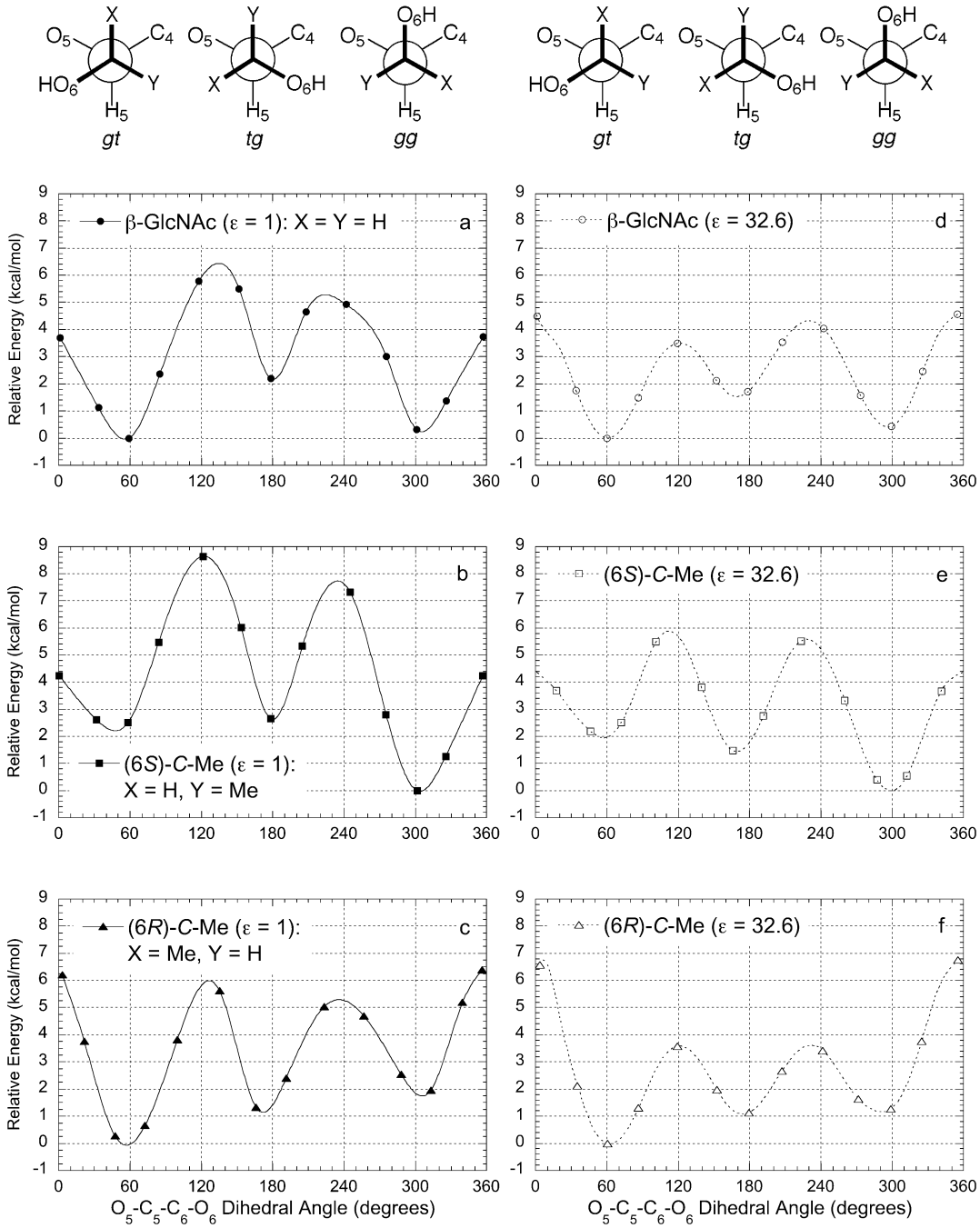


FIGURE4.

Potential energy curves for 6-*C*-substituted β-D-GlcNAc derivatives as a function of dihedral angle. Gas-phase conformational energies were calculated by using molecular mechanics (Amber) with ε = 1 (a–c); conformations in methanol were simulated by using ε = 32.6 (d–f).

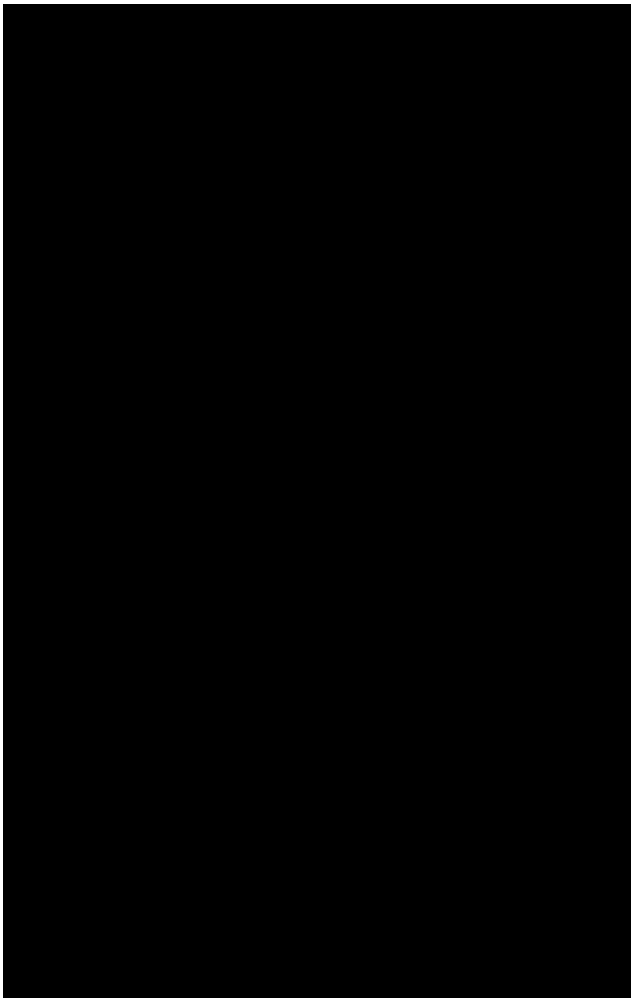
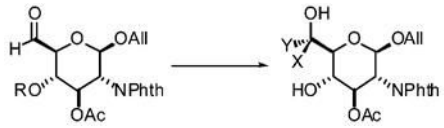


FIGURE 5.

Van't Hoff plots describing conformational preferences of the C-5–C-6 bond for 6-*C*-substituted β-D-GlcNAc derivatives. (a) *gg* vs *gt* for 6-*C*-*d*-substituted β-D-GlcNAc monosaccharide **1a** (filled circles) and disaccharide **1b** (open squares). (b) *gg* vs *tg* for (6*S*)-*C*-methyl-substituted β-D-GlcNAc monosaccharide **2a**, with *tg* = *gt* (filled circles) or *tg* > *gt* (open squares). (c) *gg* vs *tg* for (6*S*)-*C*-methyl-substituted β-D-GlcNAc disaccharide **2b**, with *tg* = *gt* (filled circles) or *tg* > *gt* (open squares). (d) *gt* vs *tg* for (6*R*)-*C*-methyl-substituted β-D-GlcNAc **3a**, with *tg* = *gg* (filled circles) or *tg* > *gg* (open squares).

TABLE 1

Stereoselectivity of Methyl Addition to Glucosamine-Derived Aldehyde[a]



8 (6*S*): X = H, Y=Me
9 (6*R*): X = Me, Y = H

entry	reagent (equiv)	R	additive (equiv)[b]	solvent	yield, %[c]	8:9 (6*S*:6*R*)[d]
1	MeMgI (2)	THP		THF	25	4:1
2	$AlMe_3$ (6)	THP		CH_2Cl_2	60	4:1
3	$AlMe_3$ (4)	Bn		CH_2Cl_2	60	3:1
4	$AlMe_3$ (4)	MEM		CH_2Cl_2	0	
5	$AlMe_3$ (5)	THP	CuCN (0.2)	THF	54	5:1
6	$AlMe_3$ (5)	THP	CuCN (1)	THF	40	6:1

[a] See Experimental Section for standard reaction conditions.

[b] Equivalents in parentheses relative to aldehyde.

[c] Combined yield after methylation and THP deprotection.

[d] In the case of R = THP, both diastereomers yielded mixtures of 6*S* and 6*R* epimers.

TABLE 2

Assignment of Selected $J_{H,H}$ and $J_{C,H}$ Values to Staggered Conformers about the Exocyclic C-5–C-6 Bond

	$^3J_{H-5,H-6}$ [a]	$^2J_{C-6,H-5}$ [b]	$^3J_{C-7,H-5}$ [c]
	(6*S*)-*C*-CH_3 substitution (**2a,b**)		
gt [d]	9.2	L	S
tg [d]	2.6	L	L
gg [d]	0.7	S	S
	(6*R*)-*C*-CH_3 substitution (**3a,b**)		
gt [e]	2.3	L	L
tg [e]	9.1	L	S
gg [e]	1.4	S	S

[a] $^3J_{H,H}$ values (in Hz) are derived from Karplus relationships parametrized for 1,2-dialkoxybutanes (Figure 3), with a standard deviation of 0.5 Hz.[23]

[b] Correlation of $^2J_{C,H}$ values with the dihedral angle defined by H-6 and O-5 suggests "L" (−4 to −6 Hz) and "S" (0 to +2 Hz) values.[24,25]

[c] Correlation of $^3J_{C,H}$ values with the dihedral angle defined by H-7 and C-5 suggests "L" (+5 to +7 Hz) and "S" (+1 to +3 Hz) values.[24,25]

[d] *gt*, *tg*, and *gg* defined by O5–C5–C6–O6 dihedral angles of +60°, +170°, and −60°, respectively.

[e] *gt*, *tg*, and *gg* defined by O5–C5–C6–O6 dihedral angles of +60°, +175°, and −70°, respectively.

TABLE 3

Selected $J_{H,H}$ and $J_{C,H}$ Coupling Constants for 6-*C*-Substituted β-D-GlcNAc Mono- and Disaccharides at 298 K[a]

compd	$^3J_{H-5,H-6}$ [b]	$^2J_{C-6,H-5}$ [c]	$^3J_{C-7,H-5}$ [c]
1a	6.2, 2.6		
1b[d]	4.9, 2.0		
2a	1.8	2.9	1.6
2b[e]	1.5	2.3	1.2
3a	3.9	4.2	3.4
3b[f]	2.4	4.5	3.8

[a] ^{1}H NMR spectra were acquired at 600 MHz in CD_3OD unless otherwise noted. Proton-coupled ^{13}C NMR spectra were acquired at 500 MHz in CD_3OD unless otherwise noted.

[b] In Hz (±0.25 Hz).

[c] In Hz (±0.3 Hz).

[d] ^{1}H NMR in CD_3OD:D_2O (3:1, v/v).

[e] ^{13}C NMR in CD_3OD:D_2O (5:3, v/v).

[f] ^{13}C NMR in CD_3OD:D_2O (5:1, v/v).

TABLE 4

$^3J_{5,6}$ Coupling Constants, Conformer Distributions, and Relative Free Energy Differences As Determined by VT-NMR Spectroscopy

compd	T^a	$J_{5,6S}{}^b$	$J_{5,6R}{}^b$	gt	tg	gg	$-\Delta\Delta G^c$
1a	239	1.76	6.15	55	−12	57	0.02 (*0.06*)
	258	2.20	6.15	53	−6	53	0.00 (*0.07*)
	278	2.20	5.72	49	−6	57	0.09 (*0.08*)
	302	2.64	6.16	52	−1	49	−0.04 (*0.09*)
	320	2.63	6.16	52	−1	49	−0.04 (*0.09*)
1b[d]	239	1.66	4.61	38	−12	74	0.31 (0.06)
	248	1.72	4.77	40	−11	71	0.29 (*0.07*)
	258	2.05	4.65	38	−7	69	0.32 (*0.07*)
	278	1.97	4.65	38	−8	70	0.34 (*0.08*)
	302	2.04	4.93	41	−8	67	0.30 (*0.08*)
	320	2.04	4.93	41	−8	67	0.32 (*0.09*)
2a[e] (*tg = gt*)	230		1.48	7.5	7.5	85	1.11 (*0.20*)
	250		1.63	9	9	82	1.10 (*0.18*)
	277		1.78	10	10	80	1.12 (*0.18*)
	298		1.83	11	11	78	1.17 (*0.18*)
	319		2.08	13	13	74	1.08 (*0.17*)
2a[f] (*tg > gt*)	230		1.48	7	21	72	0.57 (*0.23*)
	250		1.63	8.5	23	68.5	0.54 (*0.21*)
	277		1.78	10	25	65	0.53 (*0.21*)
	298		1.83	10.5	25	64.5	0.57 (*0.22*)
	319		2.08	13	29	58	0.44 (*0.21*)
2b[e] (*tg = gt*)	230		1.41	7	7	86	1.16 (*0.22*)
	247		1.41	7	7	86	1.25 (*0.24*)
	258		1.40	6.5	6.5	87	1.31 (*0.25*)
	278		1.54	8	8	84	1.29 (*0.23*)
	302		1.53	8	8	84	1.41 (*0.25*)
	320		1.60	8.5	8.5	83	1.44 (*0.24*)
2b[f] (*tg > gt*)	230		1.41	6.5	19	74.5	0.63 (*0.25*)
	247		1.41	6.5	18	75.5	0.71 (*0.27*)
	258		1.40	6.5	17	76.5	0.77 (*0.28*)
	278		1.54	8	19.5	72.5	0.73 (*0.25*)
	302		1.53	8	18	74	0.85 (*0.28*)
	320		1.60	8.5	19	72.5	0.86 (*0.27*)
3a[e] (*tg = gg*)	229	2.60		90	5	5	1.31 (*0.85*)
	233	2.59		90	5	5	1.35 (*0.95*)
	269	3.19		70	15	15	0.82 (*0.24*)
	278	3.49		60	20	20	0.60 (*0.20*)
	302	3.93		45	27.5	27.5	0.29 (*0.20*)
	320	4.18		36	32	32	0.08 (*0.22*)
3a[f] (*tg > gg*)	229	2.60		94	4.5	1.5	1.37 (*0.84*)
	233	2.59		94	4.5	1.5	1.41 (*0.94*)
	269	3.19		81	14	5	0.94 (*0.21*)
	278	3.49		74	18.5	7.5	0.77 (*0.17*)
	302	3.93		63.5	25.5	11	0.55 (*0.15*)
	320	4.18		57	29.5	13.5	0.42 (*0.15*)
3b[e] (*tg = gg*)	230	2.05					
	248	2.14					
	258	2.18					
	278	2.33		99	0.5	0.5	2.9[g]
	302	2.43		96	2	2	2.3[g]
	320	2.56		91	4.5	4.5	1.9[g]

compd	T^a	$J_{5,6S}{}^b$	$J_{5,6R}{}^b$	gt	tg	gg	$-\Delta\Delta G^c$

[a] Calibrated temperatures in K.

[b] Coupling constants in Hz (±0.25 Hz).

[c] Free-energy difference between the two lowest energy conformations, in kcal/mol (uncertainties in parentheses).

[d] Conformational analysis performed in 3:1 $CD_3OD:D_2O$.

[e] Conformer populations calculated assuming minor conformers are equal in energy.

[f] Conformer populations calculated assuming minor conformers have a free-energy difference of 0.5 kcal/mol.

[g] The accuracy of these values is affected by the lower limit set by the parametrized Karplus equation. See Experimental Section for further details.

TABLE 5

Thermodynamic Values Describing Conformational Preferences about the C-5–C-6 Bond[a]

	$\Delta\Delta G_{rt}$[b]	$\Delta\Delta H$[b]	$\Delta\Delta S$[c]
1a: *gg* vs *gt*	+0.04 (0.09)	−0.21 (*0.23*)	−0.72 (*0.84*)
1b: *gg* vs *gt*[d]	−0.30 (*0.08*)	−0.27 (*0.08*)	0.14 (*0.30*)
2a: *gg* vs *tg* (*tg* = *gt*)	−1.17 (*0.18*)	−1.07 (*0.12*)	0.16 (*0.46*)
2a: *gg* vs *tg* (*tg* > *gt*)	−0.57 (*0.22*)	−0.78 (*0.15*)	−0.92 (*0.56*)
2b: *gg* vs *tg* (*tg* = *gt*)	−1.41 (*0.25*)	−0.50 (*0.12*)	2.97 (*0.44*)
2b: *gg* vs *tg* (*tg* > *gt*)	−0.85 (*0.28*)	−0.09 (*0.13*)	2.45 (*0.50*)
3a: *gt* vs *tg* (*tg* = *gg*)	−0.29 (*0.20*)	−4.62 (*0.18*)	−14.26 (*0.66*)
3a: *gt* vs *tg* (*tg* > *gg*)	−0.55 (*0.15*)	−4.01 (*0.19*)	−11.41 (*0.72*)

[a] Thermodynamic values were derived from ^{1}H NMR coupling constants obtained at 600 MHz in CD_3OD from 229 to 320 K. Values for $\Delta\Delta H$ and $\Delta\Delta S$ were obtained from a linear leastsquares fit of the data plotted in Figure 5. Uncertainties (in parentheses) for $\Delta\Delta G$ (rt = 298 or 302 K) were derived by using indeterminate errors from $^3J_{H,H}$ measurements (±0.25 Hz); uncertainties for $\Delta\Delta H$ and $\Delta\Delta S$ were obtained from linear regression analysis and do not include propagation of indeterminate error.

[b] In kcal/mol.

[c] In cal·mol/K.

[d] Compound was dissolved in 3:1 CD_3OD:D_2O.