JOC Article

Hydroxymethyl Rotamer Populations in Disaccharides

Alfredo Roën, Juan I. Padrón, and Jesús T. Vázquez*

Instituto Universitario de Bio-Orgánica "Antonio González", Universidad de La Laguna, Avda. Astrofísico Fco. Sánchez 2, 38206 La Laguna, Tenerife, Spain

jtruvaz@ull.es

Received December 27, 2002

Sixteen methyl glucopyranosyl glucopyranoside disaccharides (methyl β-D-Glc*p*(*p*-Br-Bz)-(1→*x*)-β/α-D-Glc*p*) containing β-glycosidic linkages (1→2, 1→3, 1→4, and 1→6) were synthesized and analyzed by means of CD and NMR spectroscopy in three different solvents. For each of these four types of disaccharides, a correlation was observed between the hydroxymethyl rotational populations around the C5−C6 bond of the glucopyranosyl residue II with the substituents and the anomeric configuration of the methoxyl group in residue I, as well as with the solvent. Nonbonded interactions, the stereoelectronic *exo*-anomeric effect, and hydrogen bonding were found to be responsible for the observed rotameric differences. Whereas the rotational populations of the (1→6)-linked disaccharides are mainly dependent on the *exo*-anomeric effect, the (1→2)-bonded disaccharides are strongly dependent on the anomeric configuration at C1, and the (1→3)- and (1→4)-linked disaccharides are mainly dependent on the substituents and the solvent. The population of the *gt* rotamer decreases as nonbonded interactions increase but increases as the *exo*-anomeric effect becomes greater, as well as in the presence of intramolecular hydrogen bonding to the endocyclic oxygen O5′. Comparison of the hydroxymethyl rotational preferences between our model disaccharides revealed a dependence on the glycosidic linkage type. Thus the population of the *gg* and *gt* rotamers decreases/increases from (1→2)- (β series), to (1→6)-, to (1→2)- (α series), to (1→4)-, and to (1→3)-bonded disaccharides respectively, while the *tg* rotamer population remains almost constant (around 20%), except for the (1→3)- and (1→4)-linked disaccharides with the intramolecular hydrogen bonding to O5′, where this population decreases to 10%.

Introduction

Carbohydrates are compounds of tremendous importance in nature due to their biological functions, many of them being involved in recognition events. The involvement of these molecules in biological events, either alone or covalently linked to proteins or lipids, has led to a new research area at the chemistry−biology interface, called glycoscience or glycobiology. To understand these biological events from a molecular point of view, not only their three-dimensional structure but also their conformational preferences in solution must be known. Great difficulty may be encountered in determining the conformation of an oligosaccharide, because of the flexibility of the glycosidic linkages and the rotation of the hydroxymethyl and other pendant groups. Although many theoretical and experimental studies on the rotational preferences of the hydroxymethyl group have been carried out,[1−24] most of them were performed with monosaccharides, as the factors governing their rotamer populations are still not fully understood.

The conformation of a disaccharide in solution depends mainly on the rotations about its glycosidic linkage;

(1) Review: Bock, K.; Duus, J. *J. Carbohydr. Chem.* **1994**, *13*, 513.
(2) Tvaroška, I.; Taravel, F. R., Utille, J. P.; Carver, J. P. *Carbohydr. Res.* **2002**, *337*, 353.
(3) Kirschner, K. N.; Woods, R. J. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 10541.
(4) Molteni, C.; Parrinello, M. *J. Am. Chem. Soc.* **1998**, *120*, 2168.
(5) Brown, J. W.; Wladkowski B. D. *J. Am. Chem. Soc.* **1996**, *118*, 1190.
(6) Tvaroška, I.; Carver, J. P. *J. Phys. Chem. B* **1997**, *101*, 2992.
(7) Rockwell, G. D.; Grindley, T. B. *J. Am. Chem. Soc.* **1998**, *120*, 10953.
(8) Hoffmann, M.; Rychlewski, J. *J. Am. Chem. Soc.* **2001**, *123*, 2308.
(9) Spieser, S. A. H.; Kuik, J. A. v.; Kroon-Batenburg, L. M. J.; Kroon, J. *Carbohydr. Res.* **1999**, *322*, 264.
(10) Senderowitz, H.; Parish, C.; Still, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 2078.
(11) (a) Liu, H.-W.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5591. (b) Liu, H. W.; Nakanishi, K. *J. Am. Chem. Soc.* **1982**, *104*, 1178.
(12) Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1984**, *25*, 1575.
(13) Ohrui, H.; Nishida, Y.; Watanabe, M.; Hori, H.; Meguro, H. *Tetrahedron Lett.* **1985**, *26*, 3251.
(14) DeVries, N.; Buck, H. M. *Carbohydr. Res.* **1987**, *165*, 1.
(15) Ohrui, H.; Nishida, Y.; Higuchi, H.; Hori, H.; Meguro, H. *Can. J. Chem.* **1987**, *65*, 1145.
(16) Nishida, Y.; Hori, H.; Ohrui, H.; Meguro, H. *J. Carbohydr. Chem.* **1988**, *7*, 239.
(17) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H.; Uzawa, J. *Tetrahedron Lett.* **1988**, *29*, 4457.
(18) Nishida, Y.; Hori, H.; Ohrui, H.; Meguro, H. Uzawa, J.; Reimer, D.; Sinnwell, V.; Paulsen, H. *Tetrahedron Lett.* **1988**, *29*, 4461.
(19) Poppe, L. *J. Am. Chem. Soc.* **1993**, *115*, 8421.
(20) Barrows, S. E.; Storer, J. W.; Cramer, C. J.; French, A. D.; Truhlar, D. G. *J. Comput. Chem.* **1998**, *19*, 1111.
(21) Yamada, H.; Harada, T.; Takahashi, T. *Tetrahedron Lett.* **1995**, *36*, 3185.
(22) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Carbohydr. Chem.* **1990**, *9*, 601.
(23) De Bruyn, A.; Anteunis, M. *Carbohydr. Res.* **1976**, *47*, 311.
(24) Jansson, P.-E.; Kenne, L.; Kolare, I. *Carbohydr. Res.* **1994**, *257*, 163.

10.1021/jo026913o CCC: $25.00
Published on Web 05/13/2003

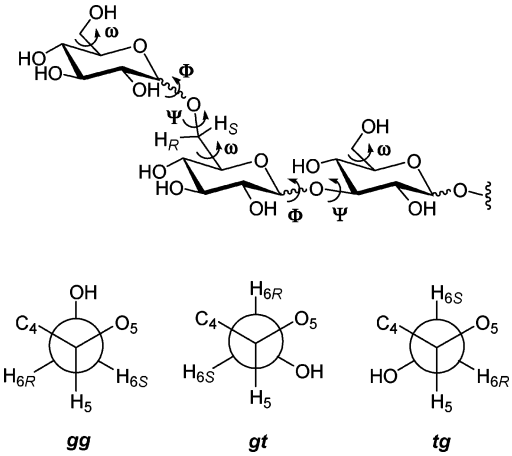
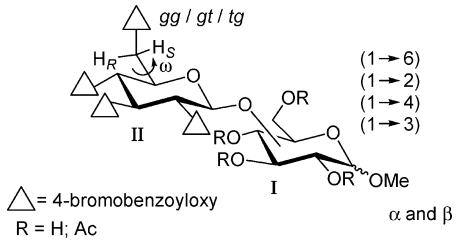


FIGURE 1. (Top) Torsion angles ϕ and ψ, around the glycosidic linkages, and torsion angles ω around the C5−C6 bonds. (Bottom) Newman projections of the *gg* ($\omega = -60°$), *gt* ($\omega = 60°$), and *tg* ($\omega = 180°$) rotamers around the C5−C6 bond.

therefore, the relative orientations of saccharide units are expressed in terms of the glycosidic linkage torsion angles ϕ (O5′−C1′−O−C*x*) and Ψ (C1′−O−C*x*−C(*x*−1)), for a 1−*x* linkage. Besides NMR[25] and X-ray diffraction, molecular modeling of carbohydrates has been devised as an important tool for structural studies of these compounds, which permits evaluation of the range of attainable conformations in terms of the potential energy at each point specified by a pair of ϕ and Ψ.[26] In addition to the torsion angles ϕ and ψ, a third torsion angle ω (O5−C5−C6−O6) needs to be considered when the hydroxymethyl group is involved in the linkage (see Figure 1). This torsion angle is also used to describe the conformation of unsubstituted hydroxymethyl groups. The conformation of the hydroxymethyl group around the C5−C6 bond is generally described by means of the populations of the *gauche*−*gauche* (*gg*), *gauche*−*trans* (*gt*), and *trans*−*gauche* (*tg*) rotamers (see Figure 1). The first descriptor indicates the torsional relationship between O6 and O5, and the second is that between O6 and C4.

Our research in this field has confirmed the existence, on the basis of CD and NMR data, of a rotational population dependence of the hydroxymethyl group in gluco-[27,28] and galactopyranosides[29] on the aglycon and its absolute configuration, revealing a clear correlation between the rotamer distributions and the stereoelectronic *exo*-anomeric effect. Furthermore, low-temperature CD measurements with the alkyl galactopyranosides confirmed that the most stable rotamer is the *gt* and not the *tg*, as previously reported from CD results.[11] Additionally, a comparative study between anomers of alkyl glucopyranosides revealed that the rotational population

CHART 1



of the hydroxymethyl group also depends on the anomeric configuration.[30,31]

Since in our previous studies NMR and CD proved to be a good experimental tandem for this type of conformational study[27−31] and a general experimental study of the rotational dependence of the hydroxymethyl group on the glycosidic linkage has not been carried out so far, our aim in this work is to study the rotational preferences of hydroxymethyl groups in disaccharide derivatives in solution and to provide experimental evidence on all the factors affecting the rotamer population around the C5−C6 bond for each of the glycosidic linkages analyzed. Because disaccharides are repeating units in oligo- and polysaccharides, knowledge of the factors governing their conformational preferences can be of great help in determining the conformation of oligosaccharides.

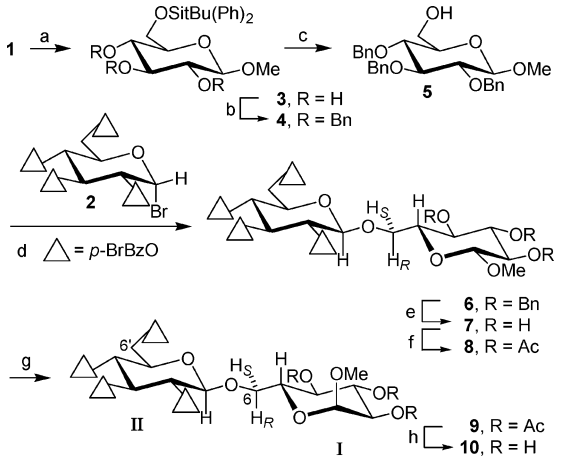
The present study performed with methyl *O*-(2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-(1→2)-, (1→3)-, (1→4)-, and (1→6)-*β*-D- and -α-D-glucopyranosides demonstrates the existence of a rotational population dependence of the hydroxymethyl group in the glucopyranosyl residue II on the glycosidic linkage type, as well as on the structural nature of the substituents in residue I. Chemical transformations of these disaccharides and CD and NMR analyses in protic and aprotic solvents show how the rotamer population depends on stereoelectronic effects (for all linkage types), on nonbonded interactions (for 1→2, 1→3, and 1→4 disaccharides), and on the intramolecular hydrogen bonding to O5′ (only for disaccharides having 1→3 and 1→4 linkages). In addition, the (1→2)-bonded disaccharides exhibit a strong dependence on the anomeric configuration of the methoxyl group at C1.

Results and Discussion

Synthesis. The model disaccharides used in the present spectroscopic work contain exciton-coupled chromophores, namely, *p*-bromobenzoate esters, to facilitate the analyses by CD and, in addition, because these groups affect the proton and carbon resonances where they are located, leading therefore to less crowded NMR spectra, allowing the coupling constants under study to be measured accurately by means of a first-order NMR analysis (ABX instead of ABC spin system). They were synthesized (Schemes 1−4) in moderate to good yields by coupling different glucosyl acceptors obtained from commercially available methyl *β*-D-glucopyranoside (**1**) with the same glucosyl donor: 2,3,4,6-tetrakis-*O*-(*p*-

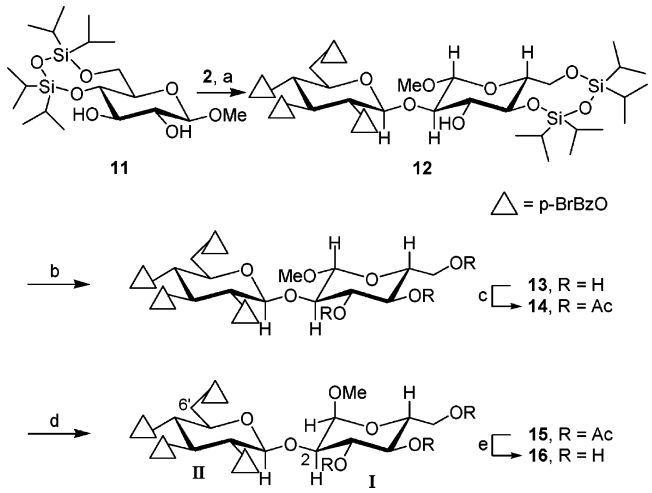
(25) Duus, J. Ø.; Gotfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589.
(26) Imberty, A.; Pérez, S. *Chem. Rev.* **2000**, *100*, 4567.
(27) Vázquez, J. T. Recent Applications of Circular Dichroic to Carbohydrate Conformational Analysis and Direct Determination of Drug Levels. In *The Biology-Chemistry Interface*; Cooper, R., Snyder, J. K., Eds.; Marcel Dekker: New York, 1999.
(28) Morales, E. Q.; Padrón, J. I.; Trujillo, M.; Vázquez, J. T. *J. Org. Chem.* **1995**, *60*, 2537.
(29) Padrón, J. I.; Morales, E. Q.; Vázquez, J. T. *J. Org. Chem.* **1998**, *63*, 8247.
(30) Padrón, J. I.; Vázquez, J. T. *Chirality* **1997**, *9*, 626.
(31) Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1998**, *9*, 613.

SCHEME 1. Synthesis of Model (1→6)-Linked Disaccharides[a]



[a] Conditions: (a) ^{t}Bu(Ph)$_2$SiCl, imidazole, dry DMF; (b) BnBr, NaH, dry DMF; (c) (nBu)$_4$NF·3H$_2$O, dry THF; (d) AgOTf, TMU, dry CH_2Cl_2, −40 °C; (e) anhydrous $FeCl_3$, dry CH_2Cl_2, 0 °C; (f) Ac_2O/Py; (g) anhydrous $FeCl_3$, dry CH_2Cl_2; (h) p-TsOH, CH_2Cl_2/MeOH (1:1).

SCHEME 2. Synthesis of Model (1→2)-Linked Disaccharides[a]

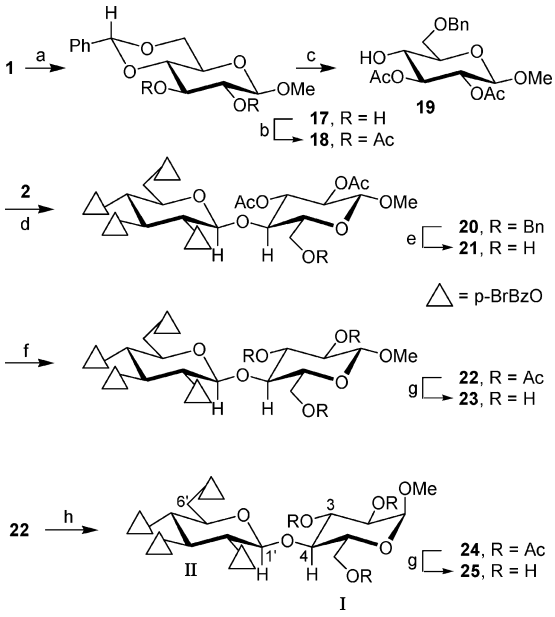


[a] Conditions: (a) AgOTf, TMU, CH_2Cl_2, −40 °C; (b) (n-Bu)$_4$NF, pyridinium chlorhydrate, dry THF; (c) Ac_2O/Py; (d) anhydrous $FeCl_3$, dry CH_2Cl_2; (e) p-TsOH, CH_2Cl_2/MeOH (1:1).

bromobenzoyl)-α-D-glucopyranosyl bromide (**2**)[28] by means of modified Koenigs−Knorr methods.[32]

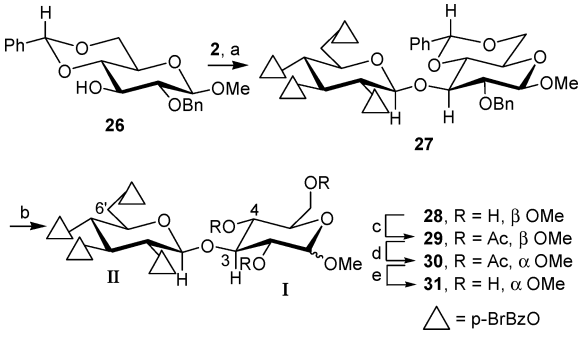
For the synthesis of the β-(1→6)-linked disaccharides, the glucosyl acceptor **5** (Scheme 1) was obtained in three steps by protection of the primary hydroxyl group with ^{t}Bu(Ph)$_2$SiCl and imidazole in DMF,[33] then perbenzylation of the secondary hydroxyl groups with benzyl bromide and sodium hydride in DMF, and finally deprotection of the silyl group with tetra-*n*-butylammonium fluoride (TBAF) in THF. By coupling the resulting glucosyl acceptor (**5**) with the glucosyl donor (**2**) and using

SCHEME 3. Synthesis of Model (1→4)-Linked Disaccharides[a]



[a] Conditions: (a) PhCH(OCH$_3$)$_2$, p-TsOH, dry DMF, 50 °C, vacuum; (b) Ac_2O/Py; (c) Na(CN)BH$_3$, CF_3CO_2H, dry THF; (d) AgOTf, *sym*-collidine, PhCH$_3$/CH$_3$NO$_2$ (1:1), −40 °C; (e) anhydrous $FeCl_3$, dry CH_2Cl_2, 0 °C; (f) Ac_2O/Py; (g) p-TsOH, CH_2Cl_2/MeOH (1:1); (h) anhydrous $FeCl_3$, dry CH_2Cl_2.

SCHEME 4. Synthesis of Model (1→3)-Linked Disaccharides[a]



[a] Conditions: (a) AgOTf, dry PhCH$_3$, −40 °C; (b) anhydrous $FeCl_3$, dry CH_2Cl_2, 0 °C; (c) Ac_2O/Py; (d) anhydrous $FeCl_3$, dry CH_2Cl_2; (e) p-TsOH, CH_2Cl_2/MeOH (1:1).

silver triflate (AgOTf) as catalyst and 1,1,3,3-tetramethylurea (TMU) as proton acceptor in CH_2Cl_2 at −40 °C,[32c] the β-(1→6)-bonded disaccharide **6** was obtained with a 92% yield. This compound was debenzylated[34] with anhydrous $FeCl_3$ in dry CH_2Cl_2 at 0 °C to give compound **7** (76%), which was acetylated to obtain the model β-(1→6)-linked disaccharide **8**. See below for the synthesis of the α-anomers **9** and **10**.

The β-(1→2)-linked disaccharide **12** (Scheme 2) was obtained in moderate yield (52%) by coupling the glucosyl donor **2** and the glucosyl acceptor **11** under the modified Koenings−Knorr method[32b] and taking advantage of the bulkiness of the protecting group present in **11**, which

(32) (a) Hanessian, S.; Banoub, *J. Carbohydr. Res.* **1977**, *53*, C13. (b) Banoub, J.; Bundle, D. R. *Can. J. Chem.* **1979**, *57*, 2091. (c) Garegg, P. J.; Norberg, T. *Acta Chem. Scand.* **1979**, *B33*, 116. (d) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.

(33) Wood, W. W.; Rashid, A. *Tetrahedron Lett.* **1987**, *28*, 1933.

(34) (a) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823. (b) Ikemoto, N.; Kim, O. K.; Lo, L. C.; Satyanarayana, V.; Chang, M.; Nakanishi, K. *Tetrahedron Lett.* **1992**, *33*, 4295. (c) Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1995**, *6*, 857.

deeply decreased the reactivity of the free hydroxyl group at C3. This acceptor was obtained in 66% yield from **1** by treatment with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$) in dry pyridine.[35] The disaccharide **12** was deprotected with TBAF and pyridinium chlorhydrate in dry THF to provide the model disaccharide **13** (92%), which was acetylated to give its corresponding triacetate **14**.

The glucopyranosyl acceptor **19**, used for the synthesis of the model β-(1→4)-linked disaccharides, was obtained with a good yield in three steps (Scheme 3). Benzylidenation of methyl β-D-glucopyranoside (**1**) with benzaldehyde dimethyl acetal and *p*-TsOH, acetylation of the resulting 4,6-*O*-benzylidene **17**, and regioselective opening of the benzylidene group in the 2,3-di-*O*-acetyl-4,6-*O*-benzylidene derivative **18** with sodium cyanoborohydride and trifluoroacetic acid[36] afforded the desired acceptor **19**. The Koenigs−Knorr coupling reaction between **19** and **2** using as solvent a mixture of toluene and nitromethane (1:1)[32a] led to the disaccharide **20** with a 73% yield. Subsequent debenzylation with anhydrous $FeCl_3$ in CH_2Cl_2 at 0 °C gave compound **21** (95% yield), which was acetylated to give the triacetyl derivative **22**. Finally, chemoselective deprotection[37] of the acetyl groups against the benzoyl groups, under catalytic acid conditions (*p*-TsOH·H_2O) in a mixture of MeOH/CH_2Cl_2 (1:1), led to a good yield (77%) of the triol **23**.

In the case of β-(1→3)-bonded disaccharides (Scheme 4), partial benzylation of the 4,6-*O*-benzylidene derivative **17**, with 1.1 equiv of benzyl bromide and sodium hydride in DMF, gave a mixture of compounds having the benzyl group at C-2 or C-3 (1.2/1 ratio). These were separated by chromatography, a low yield (23%) of compound **26** being isolated. Then, the glucopyranoside **26** was coupled with the glucosyl donor (**2**) to obtain the disaccharide **27** (45%), which by treatment with anhydrous $FeCl_3$ at room temperature led directly to the desired triol **28** (85%). Acetylation of **28** produced the model (1→3)-linked disaccharide **29**.

The synthesis of the disaccharides having an α configuration at the glycosidic linkage supporting the methoxyl group, compounds **9**, **15**, **24**, and **30** (Schemes 1−4), were obtained in high yields from the corresponding β-anomers, compounds **8**, **14**, **22**, and **29**, by treatment with anhydrous $FeCl_3$ in CH_2Cl_2 at room temperature.[34] Deprotection of the acetyl groups[37] under catalytic acid conditions (*p*-TsOH·H_2O) in a mixture of MeOH/CH_2Cl_2 (1:1) led finally to the triols **10**, **16**, **25**, and **31** with good yields.

Characterization and Spectroscopic Analysis. All of these compounds[38] were characterized on the basis of their one- (^1H and ^{13}C) and two-dimensional (COSY-G, HMQC, and T-ROESY) NMR spectra. The type of glycosidic linkage of model compounds was confirmed by means of the T-ROESY experiments, i.e., by observing

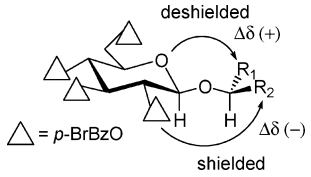


FIGURE 2. Illustration of the configurational correlation and the ^1H NMR anisotropic chemical shifts for alkyl β-D-glucopyranosides.

three clear cross-peaks between the anomeric proton H1′ and H3′, H5′, and HX. The anomeric configurations were assigned in each case by measuring the coupling constant between H1 and H2 for each glucopyranosidic ring ($CDCl_3$, doublet; β-configuration 7.4−8.1 Hz, α-configuration 3.3−3.8 Hz) and confirmed by the chemical shift in ^{13}C NMR (β-configuration 100.2−104.8 Hz; α-configuration 96.3−99.4 Hz).[39] Infrared spectra of the triol disaccharides **23** and **28** were recorded in anhydrous acetonitrile over a range of concentrations in order to confirm the existence of intramolecular hydrogen bonding. Since no spectral changes were observed over the concentration range used, the two sharp bands observed around 3630 and 3540 cm^{-1} were assigned, respectively, to free OH and to intramolecular hydrogen bonding OH-stretching vibrations.[40]

In addition,because the tetra-*O*-benzoyl-β-glucosylation of alcohols induces dramatic shifts in the aglycon ^1H NMR peaks,[28−30,41,42] some proton signals in residue I were shielded or deshielded, depending on whether the corresponding protons are located *anti* or *syn*, respectively, to the endocyclic oxygen O5, giving rise to further structural information (Figure 2). Thus, for example, protons located *syn* to the benzoyl group at C2′ in our model (1→6)-linked disaccharides (Me, H1) exhibited chemical shifts at upper field (Δδ −), while H6*S* located near O5′ exhibited them at lower field (Δδ +). On the other hand, for the (1→2)-linked disaccharides the signals of the Me group and H1 were located at lower field (Δδ +) and H3 at upper field. In addition, substantial shieldings were observed for the acetyl group located at C3, with chemical shifts at upper field, up to δ 1.45 in the case of compound **16**. Similarly, for the (1→4)-linked disaccharides shielded (Δδ −) and deshielded (Δδ +) chemical shifts were observed for protons H6*R* and H3, respectively. In the case of the (1→3)-linked disaccharides, deshielded chemical shifts were observed for H4.

The ^1H NMR signals of the prochiral protons at C6, H6*R*, and H6*S* were differentiated according to the data in the literature,[1,12,13,16] namely, on the basis of their chemical shifts and coupling constants (accuracy ±0.1 Hz). In general, for the D-*gluco*-series saccharides, H6*R* proton signals appear at a higher field than H6*S* signals ($\delta_{H6S} > \delta_{H6R}$) and $J_{H5,H6R}$ coupling constants have higher values than $J_{H5,H6S}$. Different types of Karplus equations

(35) (a) Verdegaal, C. H. M.; Jansse, P. L.; de Rooij, J. F. M.; van Boom, J. H. *Tetrahedron Lett.* **1980**, *21*, 1571. (b) van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron* **1985**, *41*, 4545.

(36) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

(37) González, A. G.; Brouard, I.; León, F.; Padrón, J. I.; Bermejo, J. *Tetrahedron Lett.* **2001**, *42*, 3187.

(38) The nomenclature is given as proposed by the IUPAC−IUBMB Joint Commission on Biochemical Nomenclature; http://www.chem-.qmul.ac.uk/iupac/2carb/.

(39) (a) Bock, K.; Lundt, I.; Pedersen, C. *Tetrahedron Lett.* **1973**, *13*, 1037. (b) Usui, T.; Yamaoka, N.; Matsuda, K.; Tuzimura, K. Sugiyama, H.; Seto, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2425.

(40) Nakanishi, K.; Solomon, P. H. *Infrared Absorption Spectroscopy*; Holden-Day, Inc.: Oakland, 1977.

(41) Trujillo, M.; Morales, E. Q.; Vázquez, J. T. *J. Org. Chem.* **1994**, *59*, 6637.

(42) Nukada, T.; Berces, A.; Whitfield, D. M. *J. Org. Chem.* **1999**, *64*, 9030.

have been proposed[16,43−45] to calculate the rotamer populations of the hydroxymethyl group from the $^3J_{H5,H6}$ coupling constants, those reported by Nishida et al.[16] and by Haasnoot et al.[43] being widely used. These approaches have also been applied to disaccharides.[13,17,46,47] In a comparative study of the various strategies used for obtaining these values, Bock and Duus[1] were unable to decide which method gives the best results, although they suggested the use of that of Haasnoot et al.[43] In addition, they showed that although the values of the coupling constants reported by Nishida et al.[16] or those by Manor et al.[44] do not give negative populations, unlike the other types of Karplus equations, these values could result in an overestimation of the population of *gg* relative to *gt* and commented that the values reported by Manor et al.[44] might not be appropriate as they are based on coupling in strained five-membered rings. Rockwell and Grindley[7] almost eliminate in monosaccharides the problem of negative populations by using the values of the limiting coupling constants from nonstaggered geometries calculated by MM3. Serianni and co-workers[45] have just proposed new limiting values for $J_{H5,H6R}$ and $J_{H5,H6S}$, based on *J*-couplings computed from density functional theory (DFT), and applied them to several mono- and oligosaccharides. The calculations yielded a more accurate representation of the rotameric populations in solution and positive values for the *tg* rotamer population in all cases. Therefore, we have chosen this last improved approach for the study of the rotamer populations of our sixteen disaccharides,[48] because the alternative of using different values of the limiting coupling constants obtained by MM calculations in the set of equations for each case would introduce another variable into the present comparative study.

CD Analysis. Since all model disaccharides contain exciton-coupled chromophores,[49] namely, *p*-bromobenzoates, UV and CD spectroscopy was also used to characterize these compounds. The intramolecular charge-transfer band was around 245 nm in the UV, and the exciton Cotton effects were around 251 and 234 nm in the CD spectra. In addition, it is well-known that the CD spectrum of a chromophorically 2,3,4,6-tetra-substituted glucopyranosyl system is composed of six pairwise interactions:[50] three having constant intensity and sign, the positive 2/3, the negative 3/4, and the nil 2/4 pairwise interactions; and three with variable intensity and sign,

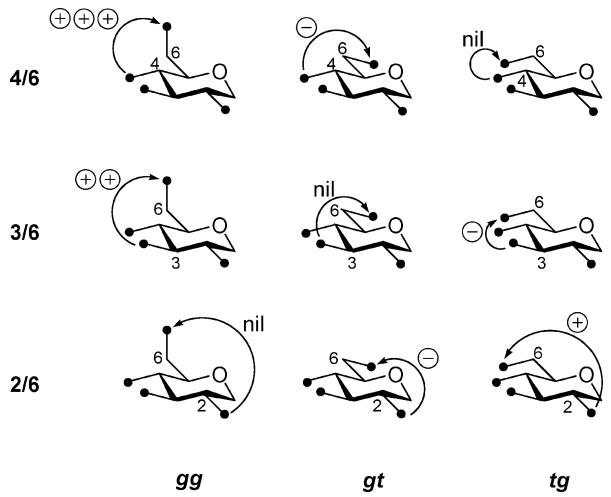


FIGURE 3. 2/6, 3/6, and 4/6 pairwise interactions involving the chromophore at the 6 position in each of the three stable rotamers (*gg*, *gt*, and *tg*) for the glucopyranosyl system.

the 2/6, the 3/6, and the 4/6 pairwise interactions that involve the chromophore at the 6 position. Because the 2/3 and 3/4 pairwise interactions possess equal magnitudes and opposite signs and no ring distortion has been observed for these model compounds, the CD contribution of these interactions to the total CD spectrum is nil. Therefore, the CD spectra of these compounds come from the pairwise interactions involving the chromophore at position 6, and because there are three main rotamers around the C5−C6 bond, the *gg*, *gt*, and *tg* rotamers, the 2/6, 3/6, and 4/6 pairwise interactions must be considered as nine in order to interpret the CD spectral differences correctly (see Figure 3).[28,30,31] Note that the net CD contribution for the *gg* rotamer for the 2/6, 3/6, and 4/6 interactions is positive, whereas those for the *gt* and *tg* rotamers are negative and nil, respectively. The amplitude (*A* value) of split CD Cotton effects is defined as $A = \Delta\epsilon_1 - \Delta\epsilon_2$ where $\Delta\epsilon_1$ and $\Delta\epsilon_2$ are the intensities of the first and second Cotton effects.[51]

In accordance with the exciton chirality method,[49] the amplitude of split Cotton effects depends on the interchromophoric distance and the dihedral angle. Because the amplitude is inversely proportional to the square of the interchromophoric distance, the 4/6 pairwise interaction contributes more significantly to the observed spectra than the 3/6 or 2/6 pairwise interactions,[17,18] and for the same reason, the *gg* rotamer CD contribution is stronger than for the *gt* rotamer. These points must be considered in order to understand the positive exciton coupling observed in our model disaccharides, including those compounds where the *gt* rotamer, having a net negative CD contribution, has the greatest population.

Conformational Analysis of the Disaccharides. General. The values of the ^{1}H NMR coupling constants for the prochiral protons at C6′ indicated that in general *gg* is the most stable rotamer for the hydroxymethyl group (residue II) in the model disaccharides. For com-

(43) Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
(44) Manor, P. C.; Saenger, W.; Davies, D. B.; Jankowski, K.; Rabczenko, A. *Biochim. Biophys. Acta* **1974**, *340*, 472.
(45) Stenutz, R.; Carmichael, I.; Widmalm, G.; Serianni, A. S. *J. Org. Chem*. **2002**, *67*, 949.
(46) Ohrui, H.; Nishida, Y.; Itoh, H.; Meguro, H. *J. Org. Chem*. **1991**, *56*, 1726.
(47) (a) Bock, K.; Refn, S. *Acta Chem. Scand*. **1987**, *B 41*, 469. (b) Bock, K.; Pedersen, H. *Acta Chem. Scand*. **1988**, *B 42*, 190.
(48) Software for the calculation of rotameric populations is available upon request from E. Q. Morales, Instituto de Investigaciones Químicas, Centro de Investigaciones Científicas Isla de la Cartuja, c/ Americo Vespucio s/n, 41092 Seville, Spain. E-mail: ezequiel@cica.es.
(49) For a monograph on exciton CD spectroscopy, see: (a) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy Exciton Coupling in Organic Stereochemistry*; University Science Books: California, 1983. (b) Nakanishi, K.; Berova, N. *The Exciton Chirality Method* in *Circular Dichroism, Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers: New York, 1994.
(50) (a) Wiesler, W. T.; Vázquez, J. T.; Nakanishi, K. *J. Am. Chem. Soc*. **1986**, *108*, 6811. (b) Wiesler, W. T.; Vázquez, J. T.; Nakanishi, K. *J. Am. Chem. Soc*. **1987**, *109*, 5586.
(51) Occasionally the presence of a background ellipticity alters the intensity of the Cotton effects at short wavelengths. For this reason, the intensities of the second Cotton effects and the amplitudes (*A* values) of the CD spectra of our model compounds may not be precise; the intensities of the first Cotton effects are thus more accurate for comparative analysis.

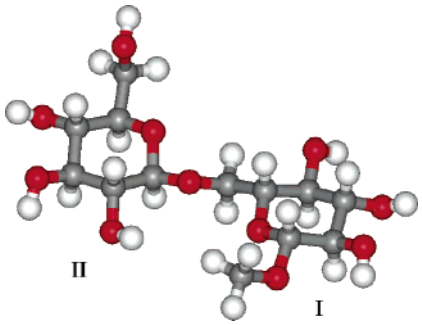


FIGURE 4. Perspective view of methyl 6-*O*-(*β*-D-glucopyranosyl)-*β*-D-glucopyranoside.

pounds **16**, **20**, and **25** (in $CDCl_3$) and **23**, **28**, and **31** (in $CDCl_3$ and CD_3CN), *gt* was the most stable rotamer. Furthermore, an excellent agreement was observed between the $J_{H5',H6'}$ coupling constants in different solvents and the magnitudes obtained by CD. Thus, as the $J_{H5',H6'R}$ and the $J_{H5',H6'S}$ coupling constants increase and decrease, respectively, the Cotton effects of the split CD spectra are reduced. Note that an increase in $J_{H5',H6'R}$ means an increase in the population of the *gt* rotamer (see Figure 1), which has a net negative CD contribution (see Figure 3), explaining therefore a decrease in the CD spectrum.

(1→6)-Linked Disaccharides. The T-ROESY experiment performed with the (1→6)-linked disaccharide **7** showed a strong cross-peak for the anomeric H1′ proton with the prochiral H6*R* proton and a weak one with H6*S*. A strong cross-peak between H5 and H6*S* was also detected, but no cross-peak at all was found between H5 and H6*R*. These experimental data, together with the chemical shifts and coupling constants of the prochiral H6 protons (H6*S*, δ 4.19, $J_{H5,H6S} = 1.9$ Hz; H6*R*, δ 3.71, $J_{H5,H6R} = 6.9$ Hz), revealed that the most stable rotamer for the hydroxymethyl group involved in the β interglycosidic bond (C6) is *gt*, with a calculated rotational population of P_{gg}:P_{gt}:P_{tg} = 30:65:5, based on the experimental coupling constants (Figure 4). Further confirmation of the fact that the *gt* rotamer at C6 is the most stable comes from the observed magnitudes and signs of the chemical shift changes on glucosylation compound **5**.[41] A chemical shift difference of $\Delta\delta_{7-5} = -0.33$ ppm, induced by the benzoyl group at C2′, was observed for the methoxyl group, a $\Delta\delta_{7-5} = +0.30$ ppm for the H6*S*, induced by the endocyclic glucopyranoside oxygen (O5′), and a $\Delta\delta_{7-5} = -0.02$ ppm for the H6R. Moreover, these results are completely in agreement with other studies where two major conformations were found, the *gt* (66%) and *gg* (34%) for *β*-gentiobiose (*β*-D-Glc*p*-(1→6)-*β*-D-Glc*p*),[19] and the *gt* (69%) and *gg* (31%) for its per-*O*-benzoyl derivative.[13]

The spectroscopic data from the rotational population study of the model *β*-(1→6)-bonded disaccharides **6**−**10**, along with the calculated population of the *gg*, *gt*, and *tg* rotamers, is summarized in Table 1. For all of these (1→6)-linked disaccharides, *gg* was the most stable rotamer for the hydroxymethyl group at C6′. The values of the ^{1}H NMR coupling constants for the prochiral protons at C6′, as well as the CD *A* values, showed only minor differences, and therefore negligible variations can be expected in their rotameric populations. Furthermore, these NMR and CD values match those of the monosaccharide methyl 2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranoside ($J_{H5,H6R} = 4.7$, $J_{H5,H6S} = 3.4$, in $CDCl_3$; $A = 29.9$, CH_3CN; $A = 27.4$, CH_3OH),[28] corroborating this conclusion. Thus, a general rotamer population of P_{gg}:P_{gt}:P_{tg} ≅ 45:35:20 can be established for these (1→6)-bonded disaccharides in chloroform.

In addition, Table 1 shows for both series of anomers a weak dependence between the solvent and the rotamer populations; that is, the polar solvents CD_3CN and CD_3OD induce slightly greater/smaller *gg*/*gt* populations (P_{gg}:P_{gt}:P_{tg} ≅ 50:30:20) than the less polar solvent $CDCl_3$ (for example, see compound **7**, entries 2 ($CDCl_3$), 6 (CD_3CN), and 10 (CD_3OD)).

Independently of the solvent, compounds with the *β*-configuration showed slightly more *gg* and less *gt* rotamers than those compounds with the α-configuration. To confirm this tendency, low-temperature CD measurements of compounds **7** and **10** were performed in methanol. Thus, striking increases were seen in the *A* values, from 26.8 to 48.2 in the case of compound **7** and from 26.0 to 42.8 for compound **10**, which can only be explained by a rise in the population of the *gg* rotamer (with a net positive CD contribution) and a drop in the population of the *gt* rotamer (with a negative CD contribution). Therefore, low-temperature CD data confirm that the most stable rotamer is the *gg* and that those (1→6)-bonded disaccharides having the *β* anomeric configuration at C1 led to tiny but appreciable increases/decreases in *gg*/*gt* rotamer populations.

(1→2)-Linked Disaccharides. As can be observed in Table 2, the rotamer populations obtained for the model (1→2)-linked disaccharides mainly depend on the anomeric configuration of the methoxyl group. In all cases but one (compound **16** in $CDCl_3$, entry 16), *gg* was the most stable rotamer. In addition, compounds having the methoxyl group in the α-configuration showed larger *gt* populations, smaller *tg* populations, and smaller or identical *gg* populations than the corresponding compounds with a *β*-configuration. Thus, for example, the populations obtained for compound **16** (entry 16) are P_{gg}:P_{gt}:P_{tg} = 42:43:15, whereas those obtained for its *β*-anomer **13** (entry 13) are 50:29:21. For those compounds having the *β*-anomeric configuration, these rotamer population differences point to the existence of a nonbonded interaction between the methoxyl group and the hydroxymethyl group in its *gt* rotamer and therefore to a decrease in its population. ROESY experiments performed with disaccharide **14** showed the typical strong cross-peak between the anomeric proton H1′ and H2, confirming the 1→2 glycosidic union, and also interresidue cross-peaks between the methoxyl group and H1′, H5′ and the prochiral proton H6′*S*. This shows the closeness of their disposition and confirms the nonbonded interaction (Figure 5).

As occurred with the (1→6)-bonded disaccharides, an increase in solvent polarity led to an increase/decrease in the population of the *gg*/*gt* rotamers, respectively (Table 2). This result can be checked by comparing the coupling constants of prochiral H6 protons or the calculated rotamer populations of compound **16** (entries 16 and 20).

Compound **13** (R = H) has a very low solubility in the solvents employed in the present study ($CHCl_3$, CH_3OH,

TABLE 1. $J_{H5',H6'}$ Coupling Constants, Calculated Rotameric Populations (%) around the C5′−C6′ Bond (Residue II), and CD Data for the Model (1→6)-Linked Disaccharides 6−10

no.	compd	R	MeO (C1)	solvent[a]	$J_{H5',H6'R}$	$J_{H5',H6'S}$	P_{gg}	P_{gt}	P_{tg}	Δε (nm) 251/234	*A* value	*A* value −80 °C
1	**6**	Bn	*β*	$CHCl_3$	4.7	3.4	45	34	21			
2	**7**	H	*β*	$CHCl_3$	4.4	3.3	48	31	21			
3	**8**	Ac	*β*	$CHCl_3$	4.7	3.1	46	36	18			
4	**9**	Ac	α	$CHCl_3$	4.7	3.3	45	35	20			
5	**10**	H	α	$CHCl_3$	4.6	3.2	47	34	19			
6	**7**	H	*β*	CH_3CN	4.1	3.2	52	29	19	21.8/−6.3	28.1	
7	**8**	Ac	*β*	CH_3CN	4.3	3.3	50	30	20	20.3/−7.4	27.7	
8	**9**	Ac	α	CH_3CN	4.0	3.4	52	26	22	21.4/−6.5	27.9	
9	**10**	H	α	CH_3CN	4.3	3.2	50	31	19	20.4/−7.0	27.4	
10	**7**	H	*β*	CH_3OH	4.0	3.3	53	27	20	20.2/−6.6	26.8	48.2
11	**10**	H	α	CH_3OH	4.3	3.4	49	30	21	17.4/−8.6	26.0	42.8

[a] Deuterated solvent for NMR analysis.

TABLE 2. $J_{H5',H6'}$ Coupling Constants, Calculated Rotameric Populations (%) around the C5′−C6′ Bond (Residue II), and CD Data for the Model (1→2)-Linked Disaccharides 12−16

no.	compd	R	MeO (C1)	solvent[a]	$J_{H5',H6'R}$	$J_{H5',H6'S}$	P_{gg}	P_{gt}	P_{tg}	Δε (nm) 251/234	*A* value
12	**12**	-	*β*	$CHCl_3$	4.4	3.0	50	33	17		
13	**13**	H	*β*	$CHCl_3$[b]	4.2	3.4	50	29	21		
14	**14**	Ac	*β*	$CHCl_3$	4.3	3.6	47	29	24		
15	**15**	Ac	α	$CHCl_3$	4.8	3.0	46	37	17		
16	**16**	H	α	$CHCl_3$	5.3	2.8	42	43	15		
17	**13**	H	*β*	CH_3CN						23.9/−6.9	30.8
18	**14**	Ac	*β*	CH_3CN	3.7	3.4	55	23	22	26.5/−7.9	34.4
19	**15**	Ac	α	CH_3CN	4.4	2.9	51	33	16	19.3/−6.2	25.5
20	**16**	H	α	CH_3CN	4.3	3.0	51	32	17	19.4/−6.7	26.1
21	**13**	H	*β*	CH_3OH						21.5/−7.5	29.0
22	**16**	H	α	CH_3OH	4.5	3.2	48	33	19	20.6/−7.1	27.7

[a] Deuterated solvent for NMR analysis. [b] $CDCl_3$ /CD_3OD 5%.

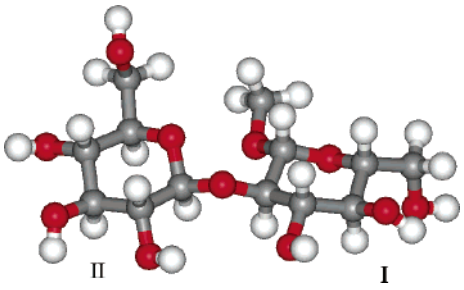


FIGURE 5. Perspective view of methyl 2-*O*-(*β*-D-glucopyranosyl)-*β*-D-glucopyranoside.

and CH_3CN), making the NMR spectra difficult to obtain. Unlike the other disaccharides synthesized in this work, this one presents completely different polarity at each end of the glucopyranosidic rings, which explains this physical property. However, it was possible to obtain the corresponding CD data in CH_3OH and CH_3CN as a result of the extreme sensitivity of this technique, which allows very dilute solutions to be analyzed. Thus, disaccharide **13** exhibited *A* values of 30.8 (CH_3CN) and 29.0 (CH_3OH), higher in magnitude than those obtained for its α-anomer **16** (*A* values 26.1 and 27.7, respectively). Therefore, these higher *A* values obtained for the *β*-anomers are in total agreement with higher *gg* (net positive CD contribution) and lower *gt* (net negative) populations for these disaccharides compared to their corresponding α-anomers.

(1→4)-Linked Disaccharides. Analysis of NMR data for the model *β*-anomers showed a dependence on the structural nature of the substituents located *syn*, but not *anti*, to the endocyclic oxygen (O5′) and the rotamer populations (Table 3). Thus, compounds **20**−**22**, having the same substituents in the *syn* disposition (acetyl) but different in the *anti* (R = Bn, H, Ac), exhibited very similar rotamer populations in $CDCl_3$ (entries 23−25), whereas the unprotected compound **23** (R = H) showed an increase in the *gt* and a decrease in the *tg* rotamer population in this solvent (entry 26). The same behavior, either in $CDCl_3$ or CD_3CN, occurs when the methoxyl group has the α-configuration; for example, the populations observed for the triacetate **24** (entry 27) P_{gg}:P_{gt}:P_{tg} = 48:34:18 changed to 41:51:8 in the triol **25** (entry 28). CD data (CH_3CN) support these rotational populations; the lower *A* value found for compound **25** (18.5, entry 32) than for **24** (23.8, entry 31) means less *gg* and more *gt*.

Although the above rotamer population differences could be explained by nonbonded interactions, analysis of the populations obtained in different solvents revealed a new feature. On changing to the protic solvent CD_3OD, the unprotected disaccharides **23** and **25** showed similar *gg*, decreased *gt*, and increased *tg* populations compared to those obtained when aprotic solvents were used (compare entries 26 and 33, or 28 and 34). CD also detected the different behavior of compounds **23** and **25** with the protic nature of the solvent. They exhibited *A* values of +18.9 and +18.5 in acetonitrile while showing +23.4 and +22.1 in methanol, these higher intensities being in agreement with decreased *gt*. Therefore, all of these spectroscopic data point to two different effects probably acting simultaneously on the rotamer popula-

TABLE 3. $J_{H5',H6'}$ **Coupling Constants, Calculated Rotameric Populations (%) around the C5′−C6′ Bond (Residue II), and CD Data for the Model (1→4)-Linked Disaccharides 20−25**

no.	compd	R	MeO (C1)	solvent[a]	$J_{H5',H6'R}$	$J_{H5',H6'S}$	P_{gg}	P_{gt}	P_{tg}	$\Delta\epsilon$ (nm) 251/234	*A* value
23	**20**	Bn	*β*	$CHCl_3$	5.3	2.9	41	43	16		
24	**21**	H	*β*	$CHCl_3$	5.2	3.0	42	41	17		
25	**22**	Ac	*β*	$CHCl_3$	5.0	3.2	43	38	19		
26	**23**	H	*β*	$CHCl_3$	5.7	2.5	39	49	12		
27	**24**	Ac	α	$CHCl_3$	4.6	3.1	48	34	18		
28	**25**	H	α	$CHCl_3$	5.7	2.2	41	51	8		
29	**22**	Ac	*β*	CH_3CN	4.8	3.1	45	37	18	17.3/−6.3	23.6
30	**23**	H	*β*	CH_3CN	5.4	2.6	42	45	13	14.7/−4.2	18.9
31	**24**	Ac	α	CH_3CN	4.6	3.0	48	35	17	16.2/−7.6	23.8
32	**25**	H	α	CH_3CN	5.3	1.9	48	47	5	14.3/−4.2	18.5
33	**23**	H	*β*	CH_3OH	5.1	3.2	41	40	19	18.8/−4.6	23.4
34	**25**	H	α	CH_3OH	4.8	3.1	45	37	18	16.0/−6.1	22.1

[a] Deuterated solvent for NMR analysis.

tions of (1→4)-bonded disaccharides, namely, nonbonded interactions and intramolecular hydrogen bonding. The observed differences between compounds **22** and **23** in acetonitrile could be explained by a nonbonded interaction between the acetyl group at C3 and the hydroxymethyl group in compound **22** (R = Ac), absent in compound **23** (R = H). However, the differences observed for compound **23** by changing the protic nature of the solvent point to the hydrogen bond (O3H···O5′, see below) favoring the *gt* population.

Infrared spectra of the triol disaccharide **23** carried out in anhydrous acetonitrile at different concentrations confirmed the existence of intramolecular hydrogen bonding. In addition, a simple experiment performed by NMR confirmed this along with its influence on the rotamer population. The ^{1}H NMR spectrum of compound **23** in CD_3CN showed the three corresponding peaks of the hydroxylic protons, which were characterized by 2D-NMR experiments. These peaks gradually disappeared by successively adding a few microliters of CD_3OD into the NMR tube. After the first addition, the NMR signal from the hydroxylic proton at C2 disappeared completely, that from the one at C6 diminished, and that corresponding to the hydroxyl group at C3 remained almost unaltered, having the highest downfield chemical shift. Successive additions led first to a pronounced drop in the signal from the hydroxylic proton at C6 and to a lesser decrease of that at C3 and then to the complete disappearance of these signals. In addition, the $J_{H5',H6'R}$ coupling constant decreased from 3.4 to 3.2 Hz during these additions. The results of this NMR experiment are completely in concordance with the increase in the *gt* rotamer in the presence of the intramolecular hydrogen bond (O3H···O5′).

MM calculations[52] were performed using methyl 4-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside as model to test for hydrogen bonding. The structure with lowest energy (Figure 6) found using the default dielectric constant (ϵ = 1.5) exhibited two intramolecular hydrogen bonds: (O3H···O5′) and (O6H···O2′), the total stabilization energy being ca. 9.3 kcal·mol^{-1}, approximately 8 kcal·mol^{-1} coming from the former hydrogen bond. The distance between the oxygen atoms involved in the seven-membered O3H···O5′ hydrogen bond was found to be 2.67 Å and its angle was 157°, and the distance for the nine-membered hydrogen bond was 3.09 Å with an angle of 161°. An almost identical structure, but without the O6H···O2′ hydrogen bond, was found when the calculations were performed using a high dielectric constant (ϵ = 80), proving the strength of the O3H···O5′ hydrogen bond. When this structure (*gt* rotamer at C6′) was minimized with the hydroxymethyl in the *gg* disposition, an increase of 1.6 kcal·mol^{-1} (ϵ = 80) was obtained. In general, use of force fields does not lead to a good correlation for the rotamer populations of the hydroxymethyl group in solution, but recent studies with monosaccharides[2−4] have shown that a correct prediction of the rotamer populations in solution could only be obtained when solvent contributions were included in the calculations, a rather complicated study to perform with our disaccharides. In any case, the structures obtained for these two rotamers included the O3H···O5′ hydrogen bond, which supports the CD and NMR data interpretation given in terms of the protic nature of the solvent.

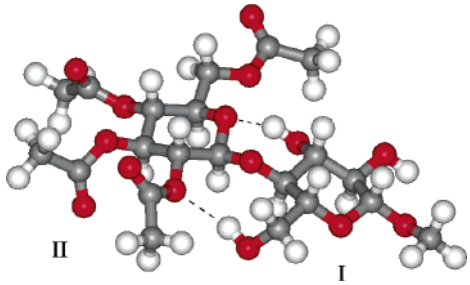


FIGURE 6. Lowest energy conformation of model methyl 4-*O*-(2,3,4,6-tetrakis-*O*-acetyl-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside.

(1→3)-Linked Disaccharides. Analysis of the coupling constants of the prochiral protons at C6′, or their calculated rotamer populations, clearly reveals (Table 4) a relationship with the structure of these (1→3)-linked disaccharides, independently of the solvent. Thus, for example, acetylation of the disaccharide **28**, having a ratio P_{gg}:P_{gt}:P_{tg} = 32:55:13 (entry 36), led to the triacetylated disaccharide **29**, which showed very different values of 44:36:20 (entry 37). Furthermore, CD data show a total agreement with the NMR data, compound **28** (entry 40)

(52) The MMX force field, including the extra term for hydrogen bonding, was used to perform the molecular mechanics calculations. PCMODEL (v. 7.0). Serena Sofware. Since the conformations of acetates are similar to those of benzoates, and calculations do not need the more complex *π*-minimization, acetates were used instead of the more complicated per-*p*-bromobenzoates.

TABLE 4. $J_{H5',H6'}$ **Coupling Constants, Calculated Rotameric Populations (%) around the C5′−C6′ Bond (Residue II), and CD Data for the Model (1→3)-Linked Disaccharides 27−31**

no.	compd	R	MeO (C1)	solvent[a]	$J_{H5',H6'R}$	$J_{H5',H6'S}$	P_{gg}	P_{gt}	P_{tg}	Δε (nm) 251/234	*A* value
35	**27**		*β*	$CHCl_3$	4.5	3.6	45	31	24		
36	**28**	H	*β*	$CHCl_3$	6.3	2.6	32	55	13		
37	**29**	Ac	*β*	$CHCl_3$	4.8	3.3	44	36	20		
38	**30**	Ac	α	$CHCl_3$	4.9	3.1	44	38	18		
39	**31**	H	α	$CHCl_3$	6.4	2.4	32	57	11		
40	**28**	H	*β*	CH_3CN	5.7	2.3	41	50	9	14.4/−4.4	18.8
41	**29**	Ac	*β*	CH_3CN	4.8	3.2	45	36	19	15.4/−7.0	22.4
42	**30**	Ac	α	CH_3CN						14.2/−6.7	20.9
43	**31**	H	α	CH_3CN	5.8	2.3	40	51	9	13.1/−4.5	17.6
44	**28**	H	*β*	CH_3OH	5.0	3.2	43	38	19	18.1/−6.4	24.5
45	**31**	H	α	CH_3OH	5.0	3.4	41	38	21	16.5/−6.3	22.8

[a] Deuterated solvent for NMR analysis.

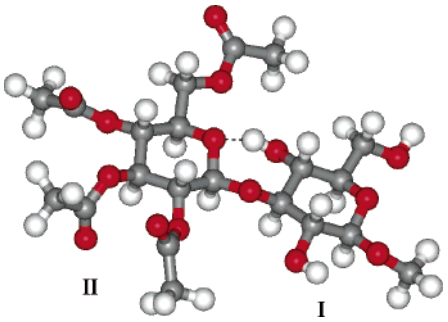


FIGURE 7. Lowest energy conformation of model methyl 3-*O*-(2,3,4,6-tetrakis-*O*-acetyl-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside.

exhibiting an *A* value (+18.8) smaller than that of **29** (+22.4) (entry 41) as consequence of its somewhat smaller *gg* and much larger *gt* populations. These results are clearly a consequence of nonbonded interactions between the acetyl group at C4 and the hydroxymethyl group in residue II in its *gt* rotamer. This reduced *gt* rotamer population was also obtained for compound **27** (entry 35), which exhibits nonbonded interactions between this rotamer and the benzylidene group, confirming the above relationship.

In addition, rotamer population comparison between the corresponding *β* and α epimers reveals no significant differences, independently of the solvent. In chloroform it was found that P_{gg}:P_{gt}:P_{tg} ≅ 32:56:12 (R = H) and P_{gg}:P_{gt}:P_{tg} ≅ 44:37:19 (R = Ac), whereas in acetonitrile P_{gg}:P_{gt}:P_{tg} ≅ 40:50:10 (R = H) with the same rotamer populations as in chloroform (45:36:19) for R = Ac.

CD and NMR data for the unprotected disaccharides **28** and **31** in methanol showed similar *gg*, decreased *gt*, and increased *tg* populations compared to those in aprotic solvents (compare entries 40 and 44, and 43 and 45). As with the (1→4)-bonded disaccharides, this result points to the fact that the intramolecular hydrogen bond between the hydroxyl group at C4 and the endocyclic oxygen O5′ led to an increase in *gt* and a decrease in the *tg* rotamer populations. The *gt* rotamer even had the highest population in $CDCl_3$ and CD_3CN.

The molecular structure of the most stable conformer obtained by MM calculations[52] with the model (1→3)-bonded disaccharide shows (Figure 7) the existence of the intramolecular hydrogen bond O4H···O5′, with a stabilization energy of 7.4 or 6.6 kcal·mol^{-1} using a dielectric constant of 1.5 or 80, respectively. The distance between the oxygen atoms involved in this hydrogen bond was found to be 2.65 Å and the angle O4H···O5′ was 153°. Therefore, this result agrees with the observed experimental dependence of this type of disaccharide on the protic (CH_3OH) or aprotic ($CHCl_3$ and CH_3CN) nature of the solvent. The existence of the above-mentioned intramolecular hydrogen bond was observed in a series of studies based on crystallographic data of laminarabiose and laminarabioside derivatives.[53] The negative Ψ [C1′−O−C3−H(C3)] dihedral angle of −47° obtained in our calculations is in excellent agreement with the fact that when such intramolecular hydrogen bonds are formed this dihedral angle assumes a negative value [for methyl *β*-D-laminarabioside (methyl *β*-D-Glc*p*-(1→6)-*β*-D-Glc*p*) Ψ [C1′-O−C3−H(C3)] = −52°].[53b] The introduction of acetyl groups prevents the formation of the intramolecular hydrogen bond, giving rise to a small positive value (for methyl hepta-*O*-acetyl-*β*-D-laminarabioside, Ψ [C1′-O−C3−H(C3)] = +5°). [53c]

Comparative Conformational Analysis of the Disaccharides. The previous rotational studies performed with chiral and nonchiral alkyl glycopyranosides[28−31] demonstrated the existence of a rotamer distribution dependence of the hydroxymethyl group on the structure of the aglycon. For alkyl *β*-D-glucopyranoside derivatives, it was concluded that the population of the *gg* rotamer decreased and *gt* increased as the pK_a of the bonded alcohol (aglycon) increased, whereas the *tg* population remained almost constant. This relationship was explained by the stereoelectronic *exo*-anomeric effect,[9,54] which grows with increasing ease for charge delocalization from the aglycon to the anomeric carbon.[55,56] Furthermore, the magnitude of this stereoelectronic effect

(53) (a) Kajiwara, K.; Miyamoto, T. *Progress in Structural Characterization of Functional Polysaccharides* in *Polysaccharides*; Dumitriu, S., Ed.; Marcel Dekker: New York, 1998. (b) Noguchi, K.; Okuyama, K.; Kitamura, S.; Takeo, K. *Carbohydr. Res.* **1992**, *237*, 33 (c) Ikegami, M.; Noguchi, K.; Okuyama, K.; Kitamura, S.; Takeo, K.; Ohno, S. *Carbohydr. Res.* **1994**, *253*, 29.

(54) (a) Thatcher, G. R. J. *Anomeric and Associated Stereoelectronic Effects. Scope and Controversy* in *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993. (b) Juaristi, E.; Cuevas, G. *The Anomeric Effect* in *New Directions in Organic and Biological Chemistry*; Rees, C. W., Ed.; CRC Press: Boca Raton, FL, 1995.

(55) Tvaroška, I.; Kozár, T. *J. Am. Chem. Soc.* **1980**, *102*, 6929.

(56) Praly, J. P.; Lemieux, R. U. *Can. J. Chem.* **1987**, *65*, 213.

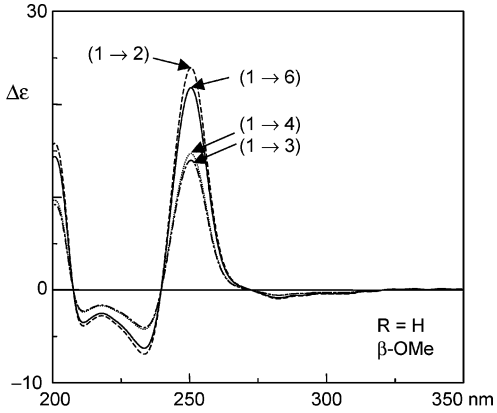


FIGURE 8. CD spectra comparison of model methyl β-D-Glc*p*-(1→*x*)-β-D-Glc*p* (R = H, in CH_3CN): 1→2 (**13**, dashed line), 1→6 (**7**, solid line), 1→4 (**23**, dotted line), and 1→3 (**28**, dashed dotted line).

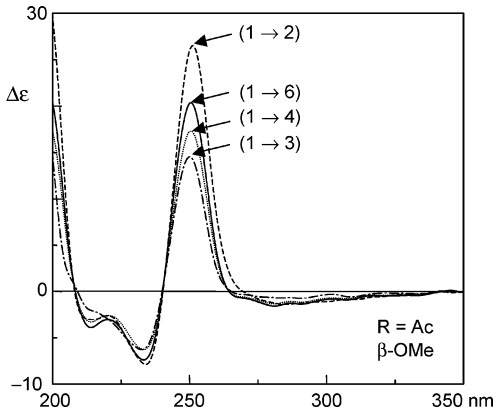


FIGURE 9. CD spectra comparison of model methyl β-D-Glc*p*-(1→*x*)-β-D-Glc*p* (R = Ac, in CH_3CN): 1→2 (**14**, dashed line), 1→6 (**8**, solid line), 1→4 (**22**, dotted line), and 1→3 (**29**, dashed dotted line).

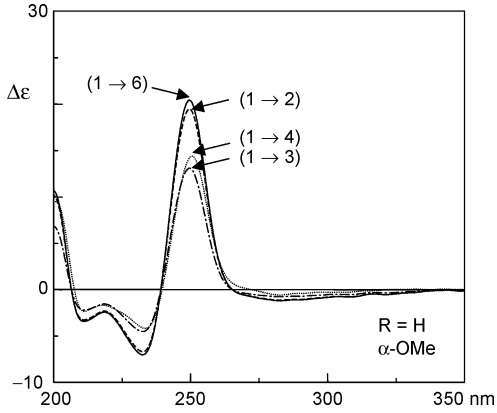


FIGURE 10. CD spectra comparison of model methyl β-D-Glc*p*-(1→*x*)-α-D-Glc*p* (R = H, in CH_3CN): 1→6 (**10**, solid line), 1→2 (**16**, dashed line), 1→4 (**25**, dotted line), and 1→3 (**31**, dashed dotted line).

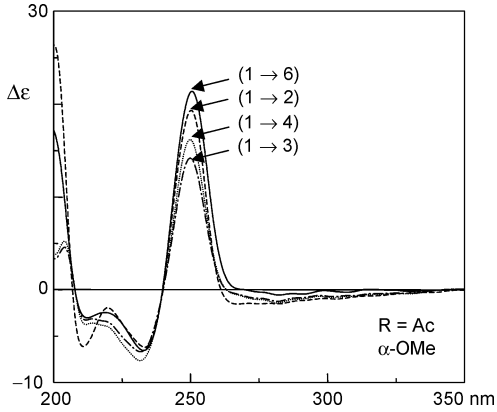


FIGURE 11. CD spectra comparison of model methyl β-D-Glc*p*-(1→*x*)-α-D-Glc*p* (R = Ac, in CH_3CN): 1→6 (**9**, solid line), 1→2 (**15**, dashed line), 1→4 (**24**, dotted line), and 1→3 (**30**, dashed dotted line).

depends on the acetal group bond lengths,[57] since linear correlations between the two C−O bond lengths at the acetal center and the pK_a of ROH have been determined in glucopyranosides.

On the basis of the above relationship between the stereoelectronic *exo*-anomeric effect and the rotamer distribution, higher *gg* and lower *gt* populations must be expected for the model (1→6)-bonded disaccharides than for the other disaccharides, as a consequence of their type of linkage (through a primary hydroxyl group). However, comparison of the $J_{H5',H6'R}$ and $J_{H5',H6'S}$ coupling constants and CD data for the (1→2)- and (1→6)-linked disaccharides (R = H, Ac) with the methoxyl group in the β anomeric configuration reveal higher *gg* and *tg* and lower *gt* populations for the former compounds, whereas the opposite behavior was found when the methoxyl group is in the α configuration. As can be observed in Figures 8 and 9 (β series) the amplitude of the first Cotton effect is higher for the (1→2)-linked disaccharides (dashed lines) than for the (1→6)-linked disaccharides (solid lines), in total agreement with higher *gg* (net positive CD contribution) and lower *gt* (net negative) populations for the former disaccharides. On the other hand, Figures 10 and 11 (α series) show higher first Cotton effect amplitudes for the (1→6)-bonded disaccharides than those obtained from the (1→2)-bonded disaccharides.

While the rotamer populations and CD data were almost independent of the substitution (R = H, Ac) and of the anomeric configuration for the (1→6)-linked disaccharides, those obtained for the (1→2)-linked disaccharides showed a strong dependence on the anomeric configuration of the methoxyl group. This behavior can be explained by the fact that for the former disaccharides the two glucopyranosidic rings are far apart, and therefore nonbonded interactions between them play almost no role. However, this is not the case for the (1→2)-bonded disaccharides. As we have already mentioned, the (1→2)-bonded disaccharides with the methoxyl group in the β anomeric configuration show a strong nonbonded interaction between the methoxyl group and the hydroxymethyl group in its *gt* rotamer, leading to larger *gg* and smaller *gt* rotamer populations. For those cases where the methoxyl group is in the α anomeric configuration, such nonbonded interaction is reduced and therefore larger *gt* populations are obtained for these compounds than for the (1→6)-linked disaccharides.

(57) (a) Jones, P. G.; Kirby A. J. *J. Chem. Soc., Chem. Commun.* **1979**, 288. (b) Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswamy, P. *J. Am. Chem. Soc.* **1984**, *106*, 6200.

Larger *gg* and smaller *gt* populations should be expected for the (1→2)-linked disaccharides than for the (1→6)-bonded disaccharides, due to the close proximity between the two glucopyranosidic rings. Although that behavior was found in the case of the disaccharides having the methoxyl group in the β anomeric configuration, it was not the case for the α anomers. This last result can be explained by a greater delocalization of the nonbonding electron pair of the interglycosidic oxygen (O1′) toward the anomeric carbon (C1′) in the (1→2)-bonded disaccharides, than in the (1→6)-linked disaccharides, as a consequence of their type of linkage (through a secondary hydroxyl group); in other words, by a greater *exo*-anomeric effect for the (1→2)-linked disaccharides.

CD and NMR data of the (1→3)- and (1→4)-bonded disaccharides showed a similar conformational behavior in general but quite different from that of the (1→6)- and (1→2)-bonded disaccharides. Their higher $J_{H5',H6'R}$ and lower $J_{H5',H6'S}$ coupling constants lead to greater populations of the *gt* rotamer and to smaller populations of *gg* and *tg* than those obtained for the (1→6)- or (1→2)-linked disaccharides. Furthermore, the smaller magnitudes of the Cotton effects for the model (1→4)- and (1→3)-bonded disaccharides (see Figures 8−11) than for the (1→6)- and (1→2)-bonded disaccharides are in total agreement with the above conclusion obtained by NMR. This general behavior can be explained by a greater *exo*-anomeric effect for these disaccharides, since steric interaction considerations should normally lead to the opposite behavior.

In addition, although this behavior was independent of the substitution (Ac, H) and anomeric configuration of the methoxyl group, different rotamer populations were obtained for the (1→4)- and (1→3)-linked disaccharides, depending apparently on the substitution (Ac, H). Thus in Figures 8-11 (CH_3CN) the unprotected (1→4)- and (1→3)-linked disaccharides (R = H) show Cotton effects of smaller magnitudes than their corresponding triacetylated disaccharides. Higher nonbonded interactions between the acetyl groups and the hydroxymethyl group for the acetylated derivatives could explain these results; however, they cannot give a satisfactory explanation for the observed change in rotamer distribution when the unprotected disaccharides (R = H) are measured in a protic solvent (MeOH), giving rotamer populations similar to those of the corresponding triacetylated derivatives (see Tables 3 and 4). Therefore, all of these data point to the intramolecular hydrogen bond in the unprotected (1→3)- and (1→4)-bonded disaccharides (R = H) favoring the population of the *gt* rotamer at the expense of the *tg*. Finally, the slightly smaller *gg* and greater *gt* rotamer populations obtained for the (1→3)-linked disaccharides than for the (1→4)-bonded disaccharides (R = H) could be due to a higher value of the *exo*-anomeric effect and/or a hydrogen bond more favorable to the former disaccharides.

Conclusions

The glycosidic linkage dependence of the rotational populations of the hydroxymethyl group of methyl glucopyranosyl-glucopyranoside derivatives having 1→2, 1→3, 1→4, and 1→6 β glycosidic linkages has been determined by analyzing the $^3J_{H5',H6'R}$ and $^3J_{H5',H6'S}$ values and CD spectral data in different solvents. Additionally, for each type of disaccharide the dependence of the hydroxymethyl rotamer population on (i) the substituents, (ii) the anomeric configuration of the methoxyl group, and (iii) the protic or aprotic nature of the solvent has been analyzed.

TABLE 5. General Average Rotameric Populations (%) around the C5′−C6′ Bond (Residue II) for the Model Disaccharides (Methyl *β*-D-Glc*p*(*p*-Br-Bz)-(1→*x*)-*β*/α-D-Glc*p*)

solvent	linkage	MeO (C1)	R	P_{gg}	P_{gt}	P_{tg}
$CDCl_3$	1→2	β	H, Ac	50	30	20
	1→6	α and β	H, Ac	45	35	20
	1→4	α	Ac	45	35	20
	1→2	α	H, Ac	45	40	15
	1→4	β	Ac	40	40	20
	1→3	α and β	Ac	40	40	20
	1→4	α and β	H	40	50	10
	1→3	α and β	H	35	55	10
CD_3CN	1→2	β	H, Ac	55	25	20
	1→6	α and β	H, Ac	50	30	20
	1→2	α	H, Ac	50	35	15
	1→4	α and β	Ac	45	35	20
	1→3	α and β	Ac	45	35	20
	1→4	α and β	H	45	45	10
	1→3	α and β	H	40	50	10
CD_3OD	1→2	β	H	55[a]	25[a]	20[a]
	1→6	α and β	H	50	30	20
	1→2	α	H	45	35	20
	1→4	α	H	45	35	20
	1→4	β	H	40	40	20
	1→3	α and β	H	40	40	20

[a] Estimated values.

The general hydroxymethyl rotational preferences around the C5′−C6′ bond (residue II) in chloroform, acetonitrile, and methanol for the model disaccharides methyl *β*-D-Glc*p*-(1→*x*)-*β*/α-D-Glc*p* are shown in Table 5. According to each specific case, nonbonded interactions, stereoelectronic effects and/or hydrogen bonds are responsible for the observed rotamer differences.

The observed rotamer populations for the (1→6)-linked disaccharides are similar to those obtained for the corresponding monosaccharide methyl 2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranoside and therefore depend mainly on the *exo*-anomeric effect. Whereas their rotamer populations are almost independent of the substituents, of the anomeric configuration of the methoxyl group, and of the nature of the solvent, this is not the case with the (1→2)-bonded disaccharides. The hydroxymethyl rotamer population for these latter disaccharides exhibits a clear relationship with the anomeric configuration of the methoxyl group, as consequence of nonbonded interactions between this group and the hydroxymethyl group in the β-anomers, which obviously have smaller *gt* populations, independently of the solvent used. In addition, the *exo*-anomeric effect dependence of the populations of the hydroxymethyl group in these (1→2)-linked disaccharides is evident by comparing the $J_{H5',H6'}$ coupling constants and CD values of (1→6)- and (1→2)-bonded disaccharides (α-anomers).

In sharp contrast to the (1→6)- and (1→2)-linked disaccharides, the (1→3)- and (1→4)-linked disaccharides show a dependence on both the substituents and the protic nature of the solvent for those derivatives having

free hydroxyl groups. Therefore, the rotational behavior of (1→3)- and (1→4)-bonded disaccharides is a consequence of a combination of effects: nonbonded interactions, the stereoelectronic *exo*-anomeric effect, and the existence, respectively, of O4H···O5′ or O3H···O5′ intramolecular hydrogen bonding. Thus, the population of the *gt* rotamer decreases as the nonbonded interactions increase, whereas it increases as the *exo*-anomeric effect increases and also when intramolecular hydrogen bonding is present.

Correlations of the NMR and CD data to the types of glycosidic linkage led to the following general information with regard to the rotational population of the hydroxymethyl group: P_{gg} (1→2)- (*β* series) > (1→6)→ (1→2)- (α series) > (1→4)→ (1→3)-linked disaccharides; P_{gt} (1→2)- (*β* series) < (1→6)- < (1→2)- (α series) < (1→4)- < (1→3)-linked disaccharides; while the P_{tg} (around 20%) is almost independent of glycosidic linkage type, solvent, and substitution, except with those disaccharides having the intramolecular hydrogen bonding to O5′, the (1→3)- and (1→4)-bonded disaccharides in aprotic solvents, when P_{tg} drops to 10%.

Experimental Section

General. ^{1}H NMR spectra were recorded at 400 and 500 MHz, and ^{13}C NMR were recorded at 100 MHz, VTU 300.0 °K. Chemical shifts are reported in parts per million. The residual solvent peak was used as an internal reference. Optical rotations were measured on a digital polarimeter in a 1-dm cell. UV and CD spectra were recorded in the range 400−200 nm by using 10-mm cells. Prior to measurement of CD spectra all compounds were purified by HPLC by using a *μ*-Porasil column, 300 × 7.8 mm i.d., 254 nm, and HPLC grade *n*-hexane/EtOAc solvent systems. The concentrations of the CD samples were ascertained for the UV spectra, using the standard ϵ values at 245 nm: tetrakis-(*p*-bromobenzoate) 76400.[11]

For analytical and preparative thin-layer chromatography, silica gel ready-foils and glass-backed plates (1 mm) were used, respectively, being developed with 254 nm UV light and/or spraying with $AcOH/H_2O/H_2SO_4$ (80:16:4) and heating at 150 °C. Column chromatography was performed using silica gel (0.015−0.04 mm) and *n*-hexane/EtOAc solvent systems or Sephadex LH-20 ($CHCl_3$/MeOH/*n*-hexane, 1:1:2). All reagents were obtained from commercial sources and used without further purification. Solvents were dried and distilled before use. All reactions were performed under a dry argon atmosphere.

General Procedure for Anomerization and/or Debenzylation.[34] To a stirred solution of the substrate (20−70 *μ*mol) in dry CH_2Cl_2 (20 mL/mmol) at the selected temperature under dry argon was added 3 equiv of anhydrous $FeCl_3$ (or 3 equiv per benzyl ether group in case of debenzylation), and the reaction left until the color of the reaction mixture changed to brown. The reaction was quenched by addition of water (1 mL). This mixture was stirred for 1 min and then extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by silica gel column chromatography. In the case of *β*-glycopyranosides, debenzylation occurred with simultaneous anomerization or retention of the anomeric configuration, depending on the reaction conditions. While anomerization was favored by increasing the equiv of $FeCl_3$, retention of the anomeric configuration was obtained by lowering the temperature to 0 or −20 °C.

General Procedure for Deacetylation.[37] The substrate was dissolved in CH_2Cl_2/MeOH (9:1), and then *p*-TsOH·H_2O (1.0 equiv per acetate) was added. The resulting mixture was stirred at room temperature or at 40 °C, and the reaction monitored by TLC. After the reaction was complete, the mixture was extracted with CH_2Cl_2, and the organic phase washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and evaporated in a vacuum. The product was purified by flash column chromatography.

2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-α-D-glucopyranosyl Bromide (2). This compound was prepared from D-(+)-glucopyranose in two steps as described in ref 28.

Methyl 6-*O*-(*tert*-Butyldiphenylsilyl)-*β*-D-glucopyranoside (3). To a solution of methyl *β*-D-glucopyranoside (1.0 g, 5.15 mmol) in dry DMF (5 mL) were added sequentially imidazole (771 mg, 11.33 mmol) and ^{t}Bu(Ph)$_2$SiCl (1.47 mL, 5.66 mmol). After 24 h, the solution was diluted with ether, washed with H_2O and saturated aqueous NH_4Cl, and dried over $MgSO_4$. It was then concentrated and chromatographed (flash column, *n*-hexane/EtOAc, 3:7) to provide compound **3** (2.21 g, 99% yield): TLC R_f = 0.69 (EtOAc/MeOH, 7:3); $[\alpha]_D^{25} = -33.1$ (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 7.69 (d, *J* = 7.9 Hz, 4H), 7.39 (m, 6H), 4.19 (d, *J* = 7.7 Hz, 1H), 3.92 (d, *J* = 4.9 Hz, 2H), 3.61 (t, *J* = 8.8, 1H), 3.57 (t, *J* = 8.8, 1H), 3.50 (s, 3H), 3.41 (m, 1H), 3.37 (t, *J* = 8.1 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) *δ* 135.6−127.6, 103.3, 76.4, 75.0, 73.5, 71.6, 64.5, 56.8, 26.7, 19.2. Anal. Calcd for $C_{23}H_{32}O_6Si$: C, 63.86; H, 7.46. Found: C, 63.87; H, 7.44.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-*β*-D-glucopyranoside (4). To a solution of the glucopyranoside **3** (2.19 g, 5.06 mmol) in dry DMF (10 mL) were added sodium hydride 80% dispersion in mineral oil (557 mg, 18.21 mmol) and benzyl bromide (2.71 mL, 22.77 mmol), and the reaction was stirred overnight. Then, the solution was diluted with ether, washed (H_2O and NH_4Cl), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc, 9:1) to give **4** (1.42 g, 40% yield): TLC R_f = 0.74 (*n*-hexane/EtOAc, 8:2); $[\alpha]_D^{25} = -0.8$ (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 7.82 (d, *J* = 7.8 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.48−7.31 (m, 19H), 7.25 (m, 2H), 5.01 (d, *J* = 11.4 Hz, 1H), 4.99 (d, *J* = 11.2 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 10.9 Hz, 1H), 4.79 (d, *J* = 11.1 Hz, 1H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 7.7 Hz, 1H), 3.99 (brd, *J* = 2.7 Hz, 2H), 3.82 (t, *J* = 9.1 Hz, 1H), 3.72 (t, *J* = 9.1 Hz, 1H), 3.64 (s, 3H), 3.52 (dd, *J* = 7.9 and 9.1 Hz, 1H), 3.40 (dt, *J* = 9.1 and 2.7 Hz, 1H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$) *δ* 138.7−127.5, 104.5, 84.7, 82.6, 77.7, 75.8, 75.6, 75.1, 74.8, 62.6, 56.6, 26.8, 19.3. Anal. Calcd for $C_{44}H_{50}O_6Si$: C, 75.18; H, 7.17. Found: C, 75.15; H, 7.26.

Methyl 2,3,4-Tri-*O*-benzyl-*β*-D-glucopyranoside (5). Tetrabutylammonium fluoride trihydrate (1.0 g, 3.42 mmol) was added to a solution of **4** (1.2 g, 1.71 mmol) in dry THF at room temperature. After 12 h, the reaction mixture was quenched with H_2O, diluted with CH_2Cl_2, and washed with saturated aqueous NaCl. The organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica gel (*n*-hexane/EtOAc, 6:4) to give 642 mg of **5** (81% yield): TLC R_f = 0.49 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25} = +9.8$ (*c* 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 7.36−7.28 (m, 15H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.91 (d, *J* = 10.7 Hz, 1H), 4.87 (d, *J* = 10.9 Hz, 1H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 10.9 Hz, 1H), 4.37 (d, *J* = 7.8 Hz, 1H), 3.89 (brdd, *J* = 2.2 and 11.8 Hz, 1H), 3.73 (brdd, *J* = 3.9 and 11.8 Hz, 1H), 3.68 (t, *J* = 9.0 Hz, 1H), 3.58 (t, *J* = 9.0 Hz, 1H), 3.58 (s, 3H), 3.41 (dd, *J* = 7.8 and 9.0 Hz, 1H), 3.38 (m, 1H); ^{13}C NMR ($CDCl_3$) *δ* 138.5−127.6, 104.8, 84.4, 82.4, 77.5, 75.7, 75.1, 75.0, 74.8, 62.0, 57.3. Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C 72.34; H, 6.93.

Methyl 6-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-*β*-D-glucopyranoside (6). To a solution of **5** (198 mg, 0.426 mmol) in dry CH_2Cl_2 (4 mL) at −40 °C were added TMU (51*μ*L, 0.426 mmol), silver triflate (219 mg, 0.852 mmol) and the glucosyl donor **2** (830 mg, 0.852 mmol). The reaction was quenched after 30 min by

adding a few drops of pyridine, filtered through Celite, and concentrated. Then, the residue was purified by Sephadex LH-20 ($CHCl_3$/MeOH/*n*-hexane, 1:1:2) to give the disaccharide **6** (536 mg, 92% yield): TLC R_f = 0.54 (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25}$ = +10.6 (*c* 0.94, $CHCl_3$); FAB-MS *m*/*z* 1381 (16, $[M + Na]^+$), 893 (4, $[M + Na - C_{28}H_{31}O_5]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.72 (m, 4H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.52−7.43 (m, 8H), 7.26 (m, 13H), 7.12 (dd, *J* = 1.9 and 7.6 Hz, 2H), 5.78 (t, *J* = 9.6 Hz, 1H), 5.61 (t, *J* = 9.6 Hz, 1H), 5.51 (dd, *J* = 7.9 and 9.6 Hz, 1H), 4.88 (d, *J* = 7.7 Hz, 1H), 4.86 (d, *J* = 10.6 Hz, 1H), 4.85 (d, *J* = 11.1 Hz, 1H), 4.66 (t, *J* = 12.0 Hz, 3H), 4.58 (dd, *J* = 3.4 and 12.2 Hz, 1H), 4.48 (dd, *J* = 4.7 and 12.2 Hz, 1H), 4.39 (d, *J* = 11.1 Hz, 1H), 4.18 (d, *J* = 7.7 Hz, 1H), 4.15 (dd, *J* = 1.1 and 11.0 Hz, 1H), 4.05 (m, 1H), 3.72 (dd, *J* = 5.9 and 11.0 Hz, 1H), 3.55 (t, *J* = 8.9 Hz, 1H), 3.44 (m, 1H), 3.36 (brs, 4H), 3.30 (dd, *J* = 8.0 and 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 165.3, 165.1, 164.4, 164.2, 138.4, 137.9, 131.9−127.3, 104.5, 101.1, 84.4, 82.1, 77.7, 75.6 74.8, 74.7, 74.3, 73.1, 71.9, 71.8, 69.7, 68.7, 63.1, 56.8. Anal. Calcd for $C_{62}H_{54}O_{15}Br_4$: C, 54.81; H, 4.01. Found: C 54.76; H, 4.33.

Methyl 6-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (7). Following the general procedure for debenzylation, anhydrous $FeCl_3$ (41 mg, 0.253 mmol) was added to a solution of disaccharide **6** (38 mg, 0.028 mmol) in dry CH_2Cl_2 (1.5 mL) at 0°C. The crude reaction mixture was purified by chromatography on silica gel ($CHCl_3$/MeOH, 98:2) to give **7** (23.1 mg, 76% yield): TLC R_f = 0.5 ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25}$ = +43.5 (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$/CD_3OD, 95:5) δ 7.81 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 5.77 (t, *J* = 9.6 Hz, 1H), 5.59 (t, *J* = 9.6 Hz, 1H), 5.43 (dd, *J* = 7.8 and 9.6 Hz, 1H), 4.92 (d, *J* = 7.8 Hz, 1H), 4.60 (dd, *J* = 3.3 and 12.2 Hz, 1H), 4.43 (dd, *J* = 4.4 and 12.2 Hz, 1H), 4.19 (dd, *J* = 1.9 and 11.2 Hz, 1H), 4.10 (m, 1H), 4.01 (d, *J* = 7.8 Hz, 1H), 3.71 (dd, *J* = 6.9 and 11.2 Hz, 1H), 3.39 (ddd, *J* = 1.9, 6.9 and 9.4 Hz, 1H), 3.33 (t, *J* = 9.4 Hz, 1H), 3.25 (s, 3H), 3.23 (t, *J* = 9.4 Hz, 1H), 3.14 (dd, *J* = 7.8 and 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD, 95:5) δ 165.5, 165.1, 164.4 (2C), 131.8−127.2, 103.4, 101.3, 76.3, 75.0, 73.3, 73.0, 72.0, 71.8, 70.4, 69.6, 69.5, 62.9, 56.7. Anal. Calcd for $C_{41}H_{36}O_{15}Br_4$: C, 45.25; H, 3.33. Found: C 45.28; H, 3.44.

Methyl 6-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,3,4-tri-*O*-acetyl-*β*-D-glucopyranoside (8). Acetylation of the disaccharide **7** (15 mg, 0.014 mmol) with 2 mL of acetic anhydride/pyridine (1:1) led, after chromatography on silica gel (*n*-hexane/EtOAc, 6:4), to compound **8** (15.8 mg, 95% yield): TLC R_f = 0.45 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}$ = +16.6 (*c* 1.00 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 5.80 (t, *J* = 9.6 Hz, 1H), 5.60 (t, *J* = 9.6 Hz, 1H), 5.46 (dd, *J* = 7.8 and 9.6 Hz, 1H), 5.12 (t, *J* = 9.5 Hz, 1H), 4.90 (d, *J* = 7.8 Hz, 1H), 4.81 (m, 2H), 4.60 (d, *J* = 2.9 and 12.2 Hz, 1H), 4.46 (dd, *J* = 4.8 and 12.2 Hz, 1H), 4.22 (d, *J* = 7.9 Hz, 1H), 4.11 (m, 1H), 3.96 (brd, *J* = 8.3 Hz, 1H), 3.63 (brd, *J* = 8.3 Hz, 2H), 3.16 (s, 3H), 2.00 (s, 3H), 1.96 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.1, 169.6, 169.3, 165.3, 165.0, 164.4, 164.3, 131.9−127.3, 101.2, 101.2, 73.2, 73.0, 72.6, 72.0, 71.8, 71.2, 69.6, 69.1, 68.6, 63.0, 56.5, 20.6, 20.5 (2C). Anal. Calcd for $C_{47}H_{42}O_{18}Br_4$: C, 46.48; H, 3.49. Found: C 46.50; H, 3.46.

Methyl 6-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (9). Compound **9** (14.0 mg, 11.2 μmol, 46% yield) was obtained from its *β*-anomer **8** (30 mg, 0.025 mmol) following the general procedure for anomerization: TLC R_f = 0.45 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}$ = +37.6 (*c* 0.37 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.56 (t, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 5.82 (t, *J* = 9.6 Hz, 1H), 5.61 (t, *J* = 9.6 Hz, 1H), 5.48 (dd, *J* = 7.8 and 9.6 Hz, 1H), 5.39 (t, *J* = 10.1 Hz, 1H), 4.86 (d, *J* = 7.8 Hz, 1H), 4.79 (t, *J* = 10.1 Hz, 1H), 4.70 (d, *J* = 3.6 Hz, 1H), 4.65 (dd, *J* = 3.6 and 10.1 Hz, 1H), 4.60 (d, *J* = 3.3 and 12.2 Hz, 1H), 4.46 (dd, *J* = 4.7 and 12.2 Hz, 1H), 4.11 (ddd, *J* = 3.3, 4.7 and 9.6 Hz, 1H), 3.96 (dd, *J* = 1.9 and 11.1 Hz, 1H), 3.89 (ddd, *J* = 1.9, 6.8 and 10.1 Hz, 1H), 3.57 (dd, *J* = 6.8 and 11.1 Hz, 1H), 3.10 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.0, 169.9, 169.7, 165.3, 165.0, 164.4, 164.4, 131.9−127.3, 101.4, 96.3, 72.9, 71.9, 71.8, 70.7, 69.8, 69.7, 69.0, 68.5, 68.1, 63.0, 54.9, 20.7 (2x), 20.6. Anal. Calcd for $C_{47}H_{42}O_{18}Br_4$: C, 46.48; H, 3.49. Found: C 46.51; H, 3.52.

Methyl 6-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-α-D-glucopyranoside (10). Following the general procedure, deacetylation of **9** (5.0 mg, 4.3 μmol) led to compound **10** (4.1 mg, 3.8 μmol) in 75% yield: TLC R_f = 0.6 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{25}$ = +58.1 (*c* 0.86, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 5.83 (t, *J* = 9.6 Hz, 1H), 5.63 (t, *J* = 9.6 Hz, 1H), 5.50 (dd, *J* = 7.8 and 9.6 Hz, 1H), 4.93 (d, *J* = 7.8 Hz, 1H), 4.63 (dd, *J* = 3.2 and 12.2 Hz, 1H), 4.59 (d, *J* = 3.8 Hz, 1H), 4.48 (dd, *J* = 4.6 and 12.2 Hz, 1H), 4.15 (m, 2H), 3.80 (dd, *J* = 5.6 and 11.0 Hz, 1H), 3.65 (m, 1H), 3.59 (t, *J* = 9.2 Hz, 1H), 3.35 (m, 2H), 3.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.5 (2x), 165.1, 164.4, 131.9−127.3, 101.5, 99.0, 74.7, 73.0, 72.1, 72.0, 71.9, 70.3, 69.7 (2x), 69.2, 63.0, 55.2. Anal. Calcd for $C_{41}H_{36}O_{15}Br_4$: C, 45.25; H, 3.33. Found: C 45.29; H, 3.40.

Methyl4,6-Di-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-*β*-D-glucopyranoside (11). To a solution of methyl *β*-D-glucopyranoside (2.0 g, 10.29 mmol) in dry pyridine (15 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDSCl$_2$) (4.8 mL, 15.43 mmol). After 2 h, the pyridine was distilled and the resulting oil was purified by flash chromatography (EtOAc) to give **11** (2.95 g, 66% yield): TLC R_f = 0.70 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{25}$ = −27.2 (*c* 2.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.17 (d, *J* = 7.7 Hz, 1H), 4.09 (brd, *J* = 12.4 Hz, 1H), 3.96 (brd, *J* = 12.4 Hz, 1H), 3.81 (t, *J* = 9.1 Hz, 1H), 3.58 (t, *J* = 9.1 Hz, 1H), 3.54 (s, 3H), 3.35 (t, *J* = 8.5 Hz, 1H), 3.18 (brd, *J* = 9.3 Hz, 1H), 3.04 (br s, 1H), 2.80 (br s, 1H), 1.10−1.02 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 104.0, 76.6, 76.2, 73.9, 69.2, 60.8, 57.3, 17.4, 17.3, 17.3, 17.2, 17.2, 17.0, 13.6, 13.2, 13.1, 12.5. Anal. Calcd for $C_{19}H_{40}O_7Si_2$ C, 52.26; H, 9.23. Found: C 52.11; H, 9.42.

Methyl 2-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-4,6-di-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-*β*-D-glucopyranoside (12). To a stirred solution of compound **11** (336 mg, 0.77 mmol) and TMU (92 μL, 0.77 mmol) in dry CH_2Cl_2 (7.7 mL) at −40 °C were added silver triflate (395 mg, 1.54 mmol) and the glucosyl donor **2** (1.5 g, 1.54 mmol). After being stirred 40 min, the reaction mixture was quenched with a few drops of water and filtered through a bed of Celite with CH_2Cl_2. The filtrate was evaporated under diminished pressure, and the residue was chromatographed (*n*-hexane/EtOAc 9:1) to give the disaccharide **12** (503 mg, 52% yield): TLC R_f = 0.41 (*n*-hexane/EtOAc, 7.5/2.5); $[\alpha]_D^{25}$ = +22.1 (*c* 1.07, $CHCl_3$); FAB-MS *m*/*z* MS 1352 (0.1, $[M + Na]^+$), 894 (0.05, $[M - C_{19}H_{39}O_7Si_2]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.85−7.43 (16H), 5.81 (t, *J* = 9.6 Hz, 1H), 5.65 (t, *J* = 9.6 Hz, 1H), 5.50 (dd, *J* = 7.9 and 9.6 Hz, 1H), 5.17 (d, *J* = 7.9 Hz, 1H), 4.63 (dd, *J* = 3.0 and 12.2 Hz, 1H), 4.48 (dd, *J* = 4.4 and 12.2 Hz, 1H), 4.27 (d, *J* = 7.6 Hz, 1H), 4.16 (m, 1H), 4.00 (brd, *J* = 12.4 Hz, 1H), 3.91 (brd, *J* = 12.3 Hz, 1H), 3.58 (t, *J* = 9.1 Hz, 1H), 3.48 (s, 4H), 3.33 (t, *J* = 8.3 Hz, 1H), 3.07 (brd, *J* = 9.1 Hz, 1H), 2.22 (br s, 1H), 1.06−0.78 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 165.4, 165.1, 165.0, 164.5, 131.8−127.5, 103.2, 101.8, 82.7, 76.2, 75.3, 73.1, 72.8, 72.1, 69.8, 68.8, 63.3, 60.6, 57.4, 17.3, 17.2, 17.0, 16.9, 13.4, 13.2, 12.5, 12.4. Anal. Calcd for $C_{53}H_{62}O_{16}Si_2Br_4$: C, 47.83; H, 4.70. Found: C 47.87; H, 4.70.

Methyl 2-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (13). To a solution of the disaccharide **12** (100 mg, 0.075 mmol) in dry THF (2 mL) were added pyridinium chlorhydrate (22 mg, 0.187 mmol) and TBAF (375 μL, 1 M in THF), and the reaction was stirred for 40 min. The solution was diluted with EtOAc, washed with H_2O and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. The resulting oil was chromatographed (*n*-hexane/EtOAc, 3:7) to provide compound **13** (75 mg, 92% yield): TLC R_f = 0.3 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{25}$ = +33.1 (*c* 0.62, DMF); FAB-MS *m*/*z* MS 1110 ($[M + Na - H]^+$), 894 ($[M - C_7H_{12}O_6]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$/CD_3OD, 95:5) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.50−7.40 (8H), 5.78 (t, *J* = 9.6 Hz, 1H), 5.62 (t, *J* = 9.6 Hz, 1H), 5.41 (dd, *J* = 7.9 and 9.6 Hz, 1H), 5.19 (d, *J* = 7.9 Hz, 1H), 4.61 (dd, *J* = 3.4 and 12.2 Hz, 1H), 4.43 (dd, *J* = 4.2 and 12.2 Hz, 1H), 4.28 (d, *J* = 7.6 Hz, 1H), 4.12 (m, 1H), 3.78 (dd, *J* = 3.1 and 12.1 Hz, 1H), 3.69 (dd, *J* = 4.3 and 12.1 Hz, 1H), 3.44 (s, 3H), 3.37−3.31 (3H), 3.19 (m, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD, 95:5) δ 165.5, 165.2, 165.1, 164.5, 131.8−127.3, 102.6, 101.0, 81.6, 75.6, 75.2, 73.2, 72.7, 71.8, 69.8, 69.7, 63.2, 61.7, 57.2. Anal. Calcd for $C_{41}H_{36}O_{15}Br_4$: C, 45.25; H, 3.33. Found: C 45.24; H, 3.43.

Methyl 2-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-3,4,6-tri-*O*-acetyl-*β*-D-glucopyranoside (14). Acetylation of **13** (47.1 mg, 0.043 mmol) with acetic anhydride/pyridine (2 mL) at room temperature led to compound **14** (53.1 mg, quantitative): TLC R_f = 0.47 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}$ = +42.2 (*c* 2.46, $CHCl_3$); FAB-MS *m*/*z* MS 1237 (7, $[M + Na]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 4H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 5.75 (t, *J* = 9.6 Hz, 1H), 5.64 (t, *J* = 9.6 Hz, 1H), 5.40 (dd, *J* = 7.8 and 9.6 Hz, 1H), 5.13 (t, *J* = 9.6 Hz, 1H), 5.11 (d, *J* = 7.8 Hz, 1H), 4.93 (t, *J* = 9.6 Hz, 1H), 4.64 (dd, *J* = 3.6 and 12.2 Hz, 1H), 4.46 (dd, *J* = 4.3 and 12.2 Hz, 1H), 4.45 (d, *J* = 7.4 Hz, 1H), 4.23 (dd, *J* = 4.7 and 12.3 Hz, 1H), 4.11 (m, 1H), 4.07 (dd, *J* = 2.2 and 12.3 Hz, 1H), 3.70 (dd, *J* = 7.4 and 9.6 Hz, 1H), 3.63 (ddd, *J* = 2.2, 4.7 and 9.9 Hz, 1H), 3.53 (s, 3H), 2.05 (s, 3H), 1.93 (s, 3H), 1.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 169.6, 169.6, 165.3, 165.0, 164.3, 164.2, 131.9−127.3, 102.5, 100.3, 78.7, 73.5, 73.3, 72.5, 71.7, 71.3, 69.6, 68.4, 63.0, 61.9, 57.1, 20.7, 20.5, 20.3. Anal. Calcd for $C_{47}H_{42}O_{18}Br_4$: C, 46.48; H, 3.49. Found: C 46.46; H, 3.43.

Methyl 2-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (15). Following the general procedure, anomerization of **14** with anhydrous $FeCl_3$ led to compound **15** (19.9 mg, 55% yield): TLC R_f = 0.48 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}$ = +12.6 (*c* 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 5.81 (t, *J* = 9.7 Hz, 1H), 5.62 (t, *J* = 9.7 Hz, 1H), 5.47 (dd, *J* = 8.0 and 9.7 Hz, 1H), 5.34 (t, *J* = 9.7 Hz, 1H), 4.98 (d, *J* = 3.4 Hz, 1H), 4.93 (t, *J* = 9.7 Hz, 1H), 4.92 (d, *J* = 8.0 Hz, 1H), 4.70 (dd, *J* = 3.0 and 12.2 Hz, 1H), 4.39 (dd, *J* = 4.8 and 12.2 Hz, 1H), 4.26 (dd, *J* = 4.6 and 12.3 Hz, 1H), 4.09 (m, 1H), 4.03 (dd, *J* = 1.9 and 12.3 Hz, 1H), 3.94 (m, 1H), 3.74 (dd, *J* = 3.5 and 10.0 Hz, 1H), 3.37 (s, 3H), 2.08 (s, 3H), 1.94 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 169.8, 169.3, 165.2, 165.1, 164.4, 163.9, 131.9−127.2, 102.0, 99.1, 78.4, 73.0, 72.0, 71.9, 71.0, 69.4, 68.7, 66.8, 62.6, 62.0, 55.6, 20.7, 20.5, 20.1. Anal. Calcd for $C_{47}H_{42}O_{18}Br_4$: C, 46.48; H, 3.49. Found: C 46.45; H, 3.82.

Methyl 2-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-α-D-glucopyranoside (16). According to the general procedure for deacetylation, 26 mg (0.021 mmol) of **15** led to the desired disaccharide **16** (10.4 mg, 41% yield): TLC R_f = 0.42 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{25}$ = +3.83 (*c* 0.43, THF); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 5.84 (t, *J* = 9.7 Hz, 1H), 5.60 (t, *J* = 9.7 Hz, 1H), 5.50 (dd, *J* = 8.0 and 9.7 Hz, 1H), 5.20 (d, *J* = 8.0 Hz, 1H), 4.74 (d, *J* = 3.3 Hz, 1H), 4.73 (dd, *J* = 2.8 and 12.3 Hz, 1H), 4.39 (dd, *J* = 5.3 and 12.3 Hz, 1H), 4.16 (m, 1H), 3.90 (t, *J* = 9.7 Hz, 1H), 3.80 (m, 2H), 3.62 (m, 1H), 3.54 (dd, *J* = 3.3 and 9.7 Hz, 1H), 3.52 (t, *J* = 9.7 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.4, 165.1, 164.5, 164.5, 132.0−127.3, 101.0, 99.4, 81.0, 73.0, 72.2 (x 2), 71.7, 70.8, 70.5, 69.4, 62.8, 62.4, 55.3. Anal. Calcd for $C_{41}H_{36}O_{15}Br_4$: C, 45.25; H, 3.33. Found: C 45.20; H, 3.51.

Methyl 4,6-*O*-Benzylidene-*β*-D-glucopyranoside (17). A solution of methyl *β*-D-glucopyranoside (998 mg, 5.13 mmol), *p*-TsOH·H_2O (9.7 mg, 0.05 mmol), and benzaldehyde dimethylacetal (1.16 mL, 7.73 mmol) in dry DMF (10 mL) was heated in a rotavapor at 50 °C. After 2 h, the DMF was distilled off, and then saturated aqueous $NaHCO_3$ (10 mL), ether (10 mL) and ice were added. After being stirred for 30 min, the mixture was filtered, and the solid was washed with ether and cold water, to give the benzylidene **17** (1.27 g, 87%): TLC R_f = 0.62 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{25}$ = −33.9 (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 2H), 7.38 (m, 3H), 5.54 (s, 1H), 4.36 (dd, *J* = 5.0 and 10.5 Hz, 1H), 4.33 (d, *J* = 7.8 Hz, 1H), 3.83 (t, *J* = 9.1 Hz, 1H), 3.79 (t, *J* = 10.2 Hz, 1H), 3.58 (s, 3H), 3.55 (t, *J* = 9.2 Hz, 1H), 3.50 (t, *J* = 9.2 Hz, 1H), 3.46 (m, 1H), 2.83 (br s, 1H), 2.68 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 136.9, 129.3, 128.4, 126.3, 104.1, 101.9, 80.6, 74.6, 73.2, 68.7, 66.4, 57.5. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C 59.66; H, 6.39.

Methyl 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside (18). Acetylation of **17** (923.5 mg, 3.25 mmol) with acetic anhydride/pyridine (1:1) led to compound **18** (3.05 mmol, 94% yield) after chromatography on silica gel (*n*-hexane/EtOAc, 9:1): TLC R_f = 0.51 (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25}$ = −97.9 (*c* 3.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.43 (m, 2H), 7.35 (m, 3H), 5.50 (s, 1H), 5.32 (t, *J* = 9.3 Hz, 1H), 4.99 (dd, *J* = 7.8 and 9.3 Hz, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 4.37 (dd, *J* = 5.0 and 10.5 Hz, 1H), 3.80 (t, *J* = 10.3 Hz, 1H), 3.69 (t, *J* = 9.3 Hz, 1H), 3.53 (m, 1H), 3.51 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.0, 169.6, 136.8, 129.0, 128.2, 126.1, 126.1, 102.2, 101.4, 78.3, 72.2, 71.8, 68.5, 66.2, 57.2, 20.7, 20.6. Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C 59.00; H, 5.98.

Methyl 2,3-Di-*O*-acetyl-6-*O*-benzyl-*β*-D-glucopyranoside (19). To a solution of **18** (429.6 mg, 1.34 mmol) in dry THF (10 mL) at 0 °C were added sodium cyanoborohydride (420 mg, 6.68 mmol) and a solution of trifluoroacetic acid (1.03 mL, 13.37 mmol) in dry THF (8 mL). After being stirred 1 h at 0 °C and 2 weeks at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with CH_2Cl_2 (300 mL), and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/EtOAc, 6:4) to provide the benzyl alcohol **19** (360 mg, 73%): TLC R_f = 0.44 (*n*-hexane); $[\alpha]_D^{25}$ = −29.3 (*c* 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 5.03 (t, *J* = 9.4 Hz, 1H), 4.87 (dd, *J* = 7.9 and 9.4 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 7.9 Hz, 1H), 3.76 (brd, *J* = 4.8 Hz, 2H), 3.70 (brt, *J* = 9.4 Hz, 1H), 3.51 (m, 1H), 3.46 (s, 3H), 3.30 (br s, 1H), 2.04 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 169.7, 137.5, 129.0−127.8, 101.5, 75.6, 74.2, 73.7, 71.4, 70.5, 69.9, 56.8, 20.8, 20.7. Anal. Calcd for $C_{28}H_{24}O_8$: C, 58.69; H, 6.57. Found: C 58.68; H, 6.52.

Methyl 4-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,3-di-*O*-acetyl-6-*O*-benzyl-*β*-D-glucopyranoside (20). To a solution of acceptor **19** (163.4 mg, 0.44 mmol), silver triflate (226 mg, 0.88 mmol), and *sym*-collidine (52 μL, 0.40 mmol) in dry toluene/nitromethane (1:1) was added the glucosyl bromide **2** (859 mg, 0.88 mmol). After being stirred for 75 min, a few drops of pyridine were added to the reaction, which was then filtered through a bed of Celite and concentrated under reduced pressure. The residue was purified

by chromatography on Sephadex LH-20 ($CHCl_3$/MeOH/*n*-hexane, 1:1:2) to give the disaccharide **20** (408 mg, 73% yield): TLC $R_f = 0.53$ (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25} = +10.0$ (*c* 2.5, $CHCl_3$); FAB-MS *m*/*z* 1284 (24, $[M + Na]^+$), 894 (3, $[M - C_{18}H_{21}O_8]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.6 Hz, 2H), 7.72−7.41 (19 H), 5.61 (t, J = 9.6 Hz, 1H), 5.49 (t, J = 9.6 Hz, 1H), 5.37 (dd, J = 8.0 and 9.6 Hz, 1H), 5.16 (t, J = 9.6 Hz, 1H), 4.90 (dd, J = 8.0 and 9.6 Hz, 1H), 4.78 (d, J = 12.2 Hz, 1H), 4.77 (d, J = 8.0 Hz, 1H), 4.57 (dd, J = 2.9 and 12.2 Hz, 1H), 4.41 (d, J = 12.2 Hz, 1H), 4.36 (dd, J = 5.3 and 12.2 Hz, 1H), 4.28 (d, J = 8.0 Hz, 1H), 4.03 (t, J = 9.6 Hz, 1H), 3.80 (ddd, J = 2.9, 5.3 and 9.6 Hz, 1H), 3.64 (dd, J = 2.8 and 11.3 Hz, 1H), 3.56 (brd, J = 10.2 Hz, 1H), 3.44 (s, 3H), 3.31 (brd, J = 9.8 Hz, 1H), 2.02 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.9, 169.5, 165.3, 164.9, 164.3, 163.8, 137.9, 132.0−127.3, 101.6, 100.2, 75.1, 74.3, 73.7, 73.2, 72.6, 71.8, 71.7, 71.5, 69.6, 67.0, 62.9, 56.9, 20.7, 20.6. Anal. Calcd for $C_{52}H_{46}O_{17}Br_4$: C, 49.47; H, 3.67. Found: C 49.49; H, 3.54.

Methyl 4-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,3-di-*O*-acetyl-*β*-D-glucopyranoside (21). Debenzylation of the disaccharide **20** (20 mg, 0.016 mmol), in dry CH_2Cl_2 (1.5 mL) and at 0 °C, with anhydrous $FeCl_3$ (16 mg, 0.099 mmol) led to compound **21** (17.7 mg, 95% yield) after chromatography on silica gel (*n*-hexane/EtOAc, 7:3): TLC R_f = 0.26 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25} = +4.7$ (*c* 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 5.78 (t, J = 9.7 Hz, 1H), 5.58 (t, J = 9.7 Hz, 1H), 5.46 (dd, J = 8.0 and 9.7 Hz, 1H), 5.20 (t, J = 9.6 Hz, 1H), 4.97 (d, J = 8.0 Hz, 1H), 4.86 (dd, J = 8.0 and 9.6 Hz, 1H), 4.62 (dd, J = 3.0 and 12.2 Hz, 1H), 4.41 (dd, J = 5.2 and 12.2 Hz, 1H), 4.34 (d, J = 8.0 Hz, 1H), 4.12 (ddd, J = 3.0, 5.2 and 9.7 Hz, 1H), 3.99 (t, J = 9.6 Hz, 1H), 3.76 (brd, J = 12.4 Hz, 1H), 3.68 (m, 1H), 3.44 (s, 3H), 3.26 (br d, J = 9.7 Hz, 1H), 2.03 (s, 3H), 1.96 (s, 3H). Anal. Calcd for $C_{45}H_{40}O_{17}Br_4$: C, 46.10; H, 3.44. Found: C 46.31; H, 3.47.

Methyl 4-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-*β*-D-glucopyranoside (22). Compound **21** (12 mg, 0.010 mmol) was acetylated by treatment with 2 mL of acetic anhydride/pyridine (1:1) at room temperature to afford compound **22** (12.1 mg, 97% yield): TLC R_f = 0.64 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25} = +10.2$ (*c* 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 7.62 (t, J = 8.6 Hz, 4H), 7.55 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 5.76 (t, J = 9.6 Hz, 1H), 5.58 (t, J = 9.6 Hz, 1H), 5.45 (dd, J = 8.0 and 9.6 Hz, 1H), 5.21 (t, J = 9.5 Hz, 1H), 4.87 (dd, J = 7.9 and 9.5 Hz, 1H), 4.79 (d, J = 8.0 Hz, 1H), 4.59 (dd, J = 3.2 and 12.3 Hz, 1H), 4.45 (dd, J = 5.0 and 12.3 Hz, 1H), 4.31 (d, J = 7.9 Hz, 1H), 4.27 (dd, J = 1.6 and 12.2 Hz, 1H), 4.11 (dd, J = 4.6 and 12.2 Hz, 1H), 4.07 (m, 1H), 3.81 (t, J = 9.5 Hz, 1H), 3.49 (m, 1H), 3.42 (s, 3H), 2.02 (s, 6H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.8, 169.6, 165.3, 164.9, 164.4, 163.9, 132.0−127.3, 101.4, 100.9, 76.5, 73.1, 72.5, 72.4, 72.0, 72.0, 71.5, 69.4, 62.9, 61.8, 57.0, 20.7, 20.7, 20.6. Anal. Calcd for $C_{47}H_{42}O_{18}Br_4$: C, 46.48; H, 3.49. Found: C 46.47; H, 3.64.

Methyl 4-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (23). Following the general procedure for deacetylation, *p*-TsOH·H_2O was added to a solution of disaccharide **22** (6.5 mg, 5.3 μmol) to give compound **23** (4.5 mg, 77% yield): TLC R_f = 0.65 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{25} = +32.0$ (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 5.82 (t, J = 9.8 Hz, 1H), 5.59 (t, J = 9.8 Hz, 1H), 5.50 (dd, J = 8.0 and 9.8 Hz, 1H), 4.99 (d, J = 8.0 Hz, 1H), 4.78 (dd, J = 2.5 and 12.3 Hz, 1H), 4.35 (dd, J = 5.7 and 12.3 Hz, 1H), 4.24 (d, J = 7.8 Hz, 1H), 4.22 (m, 1H), 3.96 (br s, 1H), 3.74 (t, J = 9.1 Hz, 1H), 3.67 (t, J = 9.1 Hz, 1H), 3.60 (m, 1H), 3.52 (s, 3H), 3.45 (m, 1H), 3.38 (dd, J = 7.8 and 9.1 Hz, 1H), 3.28 (brd, J = 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 165.4, 164.9, 164.4, 164.2, 132.0−127.2, 103.4, 101.5, 80.2, 74.4, 74.0, 73.7, 72.9, 72.6, 71.7, 69.1, 62.5, 60.3, 57.4. Anal. Calcd for $C_{41}H_{36}O_{15}Br_4$: C, 45.25; H, 3.33. Found: C 45.35; H, 3.62.

Methyl 4-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,3,6-tri-*O*-acetyl-α-D-glucopyranoside (24). According to the general procedure for anomerization, compound **22** (24.5 mg, 0.02 mmol) was treated with anhydrous $FeCl_3$ leading to the desired compound **24** (0.01 mmol, 50% yield): TLC R_f = 0.40 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25} = +38.4$ (*c* 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 5.76 (t, J = 9.6 Hz, 1H), 5.60 (t, J = 9.7 Hz, 1H), 5.47 (m, 2H), 4.81 (m, 2H), 4.80 (d, J = 8.0 Hz, 1H), 4.57 (dd, J = 3.1 and 12.3 Hz, 1H), 4.47 (dd, J = 4.6 and 12.3 Hz, 1H), 4.21 (brd, J = 12.2 Hz, 1H), 4.16 (dd, J = 3.6 and 12.2 Hz, 1H), 4.07 (m, 1H), 3.78 (m, 1H), 3.76 (t, J = 10.1 Hz, 1H), 3.31 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.3, 169.5, 165.3, 164.9, 164.3, 163.9, 132.0−127.2, 100.9, 96.6, 76.7, 73.1, 71.9, 71.8, 70.7, 69.4, 69.3, 67.8, 62.8, 61.8, 55.3, 21.2, 20.8 (x2). Anal. Calcd for $C_{47}H_{42}O_{18}Br_4$: C, 46.48; H, 3.49. Found: C 46.44; H, 3.64.

Methyl 4-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-α-D-glucopyranoside (25). Following the general procedure, deacetylation of **24** (11.0 mg, 9.0 μmol) with *p*-TsOH·H_2O (8 mg, 0.041 mmol) led to compound **25** (7.8 μmol, 87% yield): TLC R_f = 0.56 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{25} = +33.9$ (*c* 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 5.82 (t, J = 9.7 Hz, 1H), 5.59 (t, J = 9.7 Hz, 1H), 5.51 (dd, J = 8.0 and 9.7 Hz, 1H), 4.98 (d, J = 8.0 Hz, 1H), 4.76 (dd, J = 2.2 and 12.3 Hz, 1H), 4.74 (d, J = 3.7 Hz, 1H), 4.36 (dd, J = 5.7 and 12.3 Hz, 1H), 4.22 (m, 1H), 3.88 (br s, 1H), 3.84 (t, J = 9.1 Hz, 1H), 3.67 (t, J = 9.1 Hz, 1H), 3.51 (m, 4H), 3.35 (s, 3H), 2.30 (br s, 1H), 1.63 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 165.4, 164.9, 164.4, 164.2, 132.0−127.2, 101.5, 99.1, 80.6, 72.9, 72.5, 72.3, 72.2, 71.8, 69.5, 69.2, 62.6, 60.4, 55.5. Anal. Calcd for $C_{41}H_{36}O_{15}Br_4$: C, 45.25; H, 3.33. Found: C 45.34; H, 3.60.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside (26). To a solution of **17** (677 mg, 2.38 mmol) in dry DMF (2 mL), sodium hydride 80% dispersion oil (85.7 mg, 2.86 mmol) and benzyl bromide (310 μL, 2.61 mmol) were added. After being stirred overnight, the reaction mixture was diluted with CH_2Cl_2, washed with H_2O and saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc, 9:1) to provide compound **26** (205 mg, 23% yield): TLC R_f = 0.30 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25} = -26.2$ (*c* 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 2H), 7.37−7.27 (m, 8H), 5.48 (s, 1H), 4.88 (d, J = 11.4 Hz, 1H), 4.72 (d, J = 11.4 Hz, 1H), 4.38 (d, J = 7.7 Hz, 1H), 4.31 (dd, J = 5.0 and 10.4 Hz, 1H), 3.80 (t, J = 9.3 Hz, 1H), 3.73 (t, J = 10.2 Hz, 1H), 3.54 (s, 3H), 3.50 (t, J = 9.3 Hz, 1H), 3.37 (m, 1H), 3.31 (dd, J = 7.7 and 9.3 Hz, 1H), 3.15 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 138.3, 137.0, 128.9, 128.2, 128.1, 127.8, 127.6, 126.2, 104.7, 101.5, 81.9, 80.4, 74.6, 72.9, 68.5, 65.9, 57.2. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C 70.78; H, 6.82.

Methyl 3-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside (27). To a solution of **26** (122 mg, 0.32 mmol) and silver triflate (164 mg, 0.64 mmol) in dry toluene (4.0 mL), the glucopyranosyl bromide **2** (635 mg, 0.64 mmol) was added. After 30 min the reaction mixture was quenched by adding a few drops of water and filtering through a Celite bed. Purification by flash chromatography (*n*-hexane/EtOAc, 9:1) led to the disaccharide **27** (182 mg, 45% yield): TLC R_f = 0.37 (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25} = +23.3$ (*c* 1.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ

7.75 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.51−7.54 (m, 6H), 7.40 (d, J = 8.5 Hz, 2H), 7.34−7.25 (m, 8H), 7.17 (m, 2H), 5.74 (t, J = 9.6 Hz, 1H), 5.59 (t, J = 9.6 Hz, 1H), 5.57 (s, 1H), 5.54 (dd, J = 7.9 and 9.6 Hz, 1H), 5.21 (d, J = 7.9 Hz, 1H), 4.65 (d, J = 11.2 Hz, 1H), 4.45 (dd, J = 3.6 and 11.9 Hz, 1H), 4.43 (d, J = 11.2 Hz, 1H), 4.34 (m, 1H), 4.33 (d, J = 7.5 Hz, 1H), 4.26 (dd, J = 4.5 and 11.9 Hz, 1H), 3.99 (t, J = 9.3 Hz, 1H), 3.86 (m, 1H), 3.78 (t, J = 10.3 Hz, 1H), 3.70 (t, J = 9.3 Hz, 1H), 3.47 (s, 3H), 3.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 165.2, 165.0, 164.4, 164.3, 138.2, 137.1, 131.8−126.0, 104.9, 101.3, 100.8, 81.8, 80.4, 79.2, 74.7, 73.3, 72.3, 71.6, 69.8, 68.7, 66.0, 63.1, 57.3. Anal. Calcd for $C_{55}H_{46}O_{14}Br_4$: C, 52.82; H, 3.71. Found: C 52.88; H, 3.65.

Methyl 3-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (28). To a solution of the disaccharide **27** (14 mg, 0.011 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C, anhydrous $FeCl_3$ (16 mg, 0.099 mmol) was added to afford the triol **28** (10.2 mg, 85% yield): TLC R_f = 0.4 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{25}$ = −4.2 (*c* 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 5.85 (t, J = 9.7 Hz, 1H), 5.57 (t, J = 9.7 Hz, 1H), 5.50 (dd, J = 8.0 and 9.7 Hz, 1H), 5.00 (d, J = 8.0 Hz, 1H), 4.75 (dd, J = 2.6 and 12.3 Hz, 1H), 4.34 (dd, J = 6.3 and 12.3 Hz, 1H), 4.20 (m, 1H), 4.14 (d, J = 7.8 Hz, 1H), 3.91 (dd, J = 3.4 and 11.8 Hz, 1H), 3.76 (dd, J = 5.1 and 11.8 Hz, 1H), 3.72 (brs, 1H), 3.56 (t, J = 8.9 Hz, 1H), 3.49 (m, 1H), 3.49 (s, 3H), 3.32 (m, 2H), 2.05 (brs, 1H), 1.65 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 165.4, 165.0, 164.5 (x2), 132.0−127.2, 103.6, 102.5, 88.4, 75.2, 72.7 (x2), 72.6, 72.5, 71.8, 69.4 (x 2), 62.8, 62.7, 57.3. Anal. Calcd for $C_{41}H_{36}O_{15}Br_4$: C, 45.25; H, 3.33. Found: C 45.24; H, 3.40.

Methyl 3-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,4,6-tri-*O*-acetyl-*β*-D-glucopyranoside (29). Acetylation of **28** (11.3 mg, 9.6 μmol) with acetic anhydride/pyridine (1:1) led to compound **29** (11.5 mg) in 98% yield: TLC R_f = 0.26 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}$ = −2.0 (*c* 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 7.3 Hz, 4H), 7.64 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 5.80 (t, J = 9.7 Hz, 1H), 5.60 (t, J = 9.7 Hz, 1H), 5.33 (dd, J = 7.9 and 9.7 Hz, 1H), 5.01 (t, J = 9.3 Hz, 1H), 4.94 (d, J = 7.9 Hz, 1H), 4.89 (dd, J = 7.8 and 9.3 Hz, 1H), 4.57 (dd, J = 3.3 and 12.2 Hz, 1H), 4.49 (dd, J = 4.8 and 12.2 Hz, 1H), 4.25 (d, J = 7.8 Hz, 1H), 4.17 (m, 2H), 4.11 (m, 1H), 3.95 (t, J = 9.3 Hz, 1H), 3.58 (m, 1H), 3.38 (s, 3H), 2.07 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7, 169.1, 168.4, 165.3, 165.2, 164.4, 164.3, 131.9−127.2, 101.4, 100.8, 78.7, 73.1, 72.5, 72.2, 71.9, 71.1, 69.7, 68.3, 63.1, 62.2, 56.5, 20.9, 20.8, 20.7. Anal. Calcd for $C_{47}H_{42}O_{18}Br_4$: C, 46.48; H, 3.49. Found: C 46.47; H, 3.80.

Methyl 3-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-2,4,6-tri-*O*-acetyl-α-D-glucopyranoside (30). Compound **30** (13.4 mg, 0.011 mmol, 65% yield) was obtained from its β-anomer **29** (21 mg, 0.017 mmol) following the general procedure for anomerization: TLC R_f = 0.36 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}$ = +27.6 (*c* 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H), 7.71−7.63 (m, 6H), 7.57 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 5.80 (t, J = 9.7 Hz, 1H), 5.60 (t, J = 9.7 Hz, 1H), 5.33 (dd, J = 8.1 and 9.7 Hz, 1H), 5.00 (t, J = 9.7 Hz, 1H), 4.99 (d, J = 8.1 Hz, 1H), 4.85 (d, J = 3.6 Hz, 1H), 4.71 (dd, J = 3.6 and 10.0 Hz, 1H), 4.56 (dd, J = 3.1 and 12.3 Hz, 1H), 4.49 (dd, J = 4.9 and 12.3 Hz, 1H), 4.17 (t, J = 9.4 Hz, 1H), 4.11 (m, 3H), 3.79 (m, 1H), 3.36 (s, 3H), 2.08 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7, 169.2, 169.2, 165.3, 165.2, 164.3, 164.2, 131.8−127.2, 100.9, 96.4, 76.0, 73.2, 73.0, 72.4, 71.6, 69.6, 67.9, 67.4, 63.1, 62.1, 55.4, 20.8, 20.7, 20.6. Anal. Calcd for $C_{47}H_{42}O_{18}Br_4$: C, 46.48; H, 3.49. Found: C 46.48; H, 3.74.

Methyl 3-*O*-(2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-glucopyranosyl)-α-D-glucopyranoside (31). This compound (5.0 mg, 4.6 μmol) was obtained from **30** (8 mg, 6.6 μmol) following the general procedure for deacetylation (70% yield): TLC R_f = 0.66 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{25}$ = +44.2 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 4H), 7.45 (d, J = 8.5 Hz, 2H), 5.83 (t, J = 9.7 Hz, 1H), 5.57 (t, J = 9.7 Hz, 1H), 5.49 (dd, J = 8.0 and 9.7 Hz, 1H), 5.00 (d, J = 8.0 Hz, 1H), 4.73 (dd, J = 2.4 and 12.3 Hz, 1H), 4.68 (d, J = 3.8 Hz, 1H), 4.35 (dd, J = 6.4 and 12.3 Hz, 1H), 4.19 (m, 1H), 3.85 (dd, J = 3.3 and 11.6 Hz, 1H), 3.76 (dd, J = 4.5 and 11.6 Hz, 1H), 3.67 (t, J = 8.9 Hz, 1H), 3.59 (m, 1H), 3.52 (m, 2H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.4, 165.0, 164.6, 164.5, 132.0−127.2, 102.4, 99.0, 87.4, 72.8, 72.5, 72.0, 70.9, 70.8, 69.4, 69.3, 62.9, 62.6, 55.3. Anal. Calcd for $C_{41}H_{36}O_{15}Br_4$: C, 45.25; H, 3.33. Found: C 45.28; H, 3.46.

Acknowledgment. This research was supported by the Ministerio de Ciencia y Tecnología (Spain), through grants BQU2000-0250 and 1FD97-0747-C04-01. The authors are grateful to Dr. Ezequiel Q. Morales for his help in the rotameric calculations.[48] ARM thanks the Banco Santander for a fellowship.

JO026913O