Alkyl Galactopyranosides: Rotational Population Dependence of the Hydroxymethyl Group on the Aglycon and Its Absolute Configuration and on the Anomeric Configuration

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The rotational populations of the hydroxymethyl group in chiral and nonchiral alkyl α- and *β*-galactopyranosides proved, on the basis of circular dichroism (CD) and ^{1}H NMR data, to be dependent on the structure of the aglycon: the population of the *gt* and *tg* rotamers increased and decreased, respectively, as the pK_a of the bonded alcohol (aglycon) increased, while the population of the *gg* rotamer remained practically constant. Furthermore, low-temperature CD measurements proved that the most stable rotamer is the *gt*, and not the *tg*. In addition, a clear correlation between the rotational populations and the absolute configuration of the chiral aglycon was observed; namely, higher and smaller *gt* and *tg* populations were observed for the (*S*)-alkyl *β*-D-galactopyranosides than for their (*R*)-alkyl *β*-D-galactopyranoside counterparts, the opposite behavior being observed for the α-anomers. The results point to the exo anomeric effect as being responsible for these rotational dependencies, as well as to nonbonding interactions between the aglycon and the chromophore at C6 for those stereoisomers having in their aglycon a bulky substituent syn to the endocyclic oxygen (O5). In addition, the chemical shift differences (Δ*δ*) of the aglyconic protons of galactosylated chiral alcohols proved to be characteristic of the absolute configuration of the bonded chiral alcohol.

Introduction

A better knowledge of the conformational properties of carbohydrates would allow a more precise and faster determination of the overall conformation of oligosaccharides and, therefore, of the interactions responsible for their biological properties. The overall conformation of oligosaccharides is determined by the torsion angles (*ϕ* and Ψ) about the glycosidic linkages. In addition, when 1−6 linkages are present in the structure the torsion angle about the C5−C6 bond (*ω*) has to be considered (Figure 1).

We have recently reported, on the basis of the CD and ^{1}H NMR spectroscopic study performed with esterified alkyl glucopyranosides, that the rotational population of the hydroxymethyl group depends on the aglycon and its absolute configuration.[1,2] Thus, it was observed that independent of the anomeric configuration the population of the *gt* rotamer increased as the pK_a of the bonded alcohol (aglycon) increased, while, depending on the anomeric configuration, either the population of the *gg* rotamer (*β*-anomers)[1] or that of the *tg* rotamer (α-anomers)[2] decreased. Moreover, the results showed the existence of a clear correlation between the stereoelectronic exo anomeric effect and the rotamer distribution, the endo anomeric effect not being directly involved. In addition, a stereochemical study was performed to prove the origin of the CD spectral differences between anomers of alkyl glucopyranosides.[3]

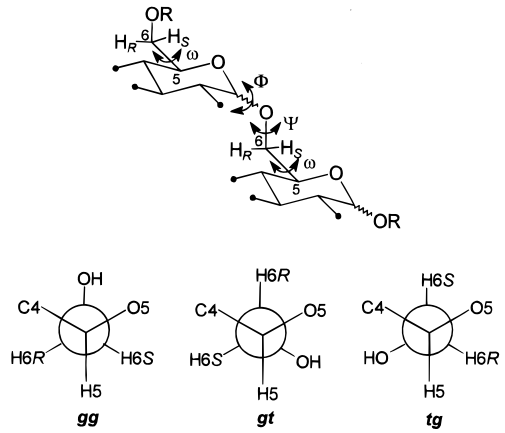

Figure 1. Torsion angles *ϕ* and *ψ*, about the glycosidic linkage, and torsion angle *ω*, around the C5−C6 bond (top). Newman projections of the rotamers around the C5−C6 bond (bottom).

The rotational population of the hydroxymethyl group in galactopyranosides is without any doubt the most controversial, thus depending on the scientists, the population of the *gt* or *tg* rotamer is assigned as the majority.[4] As a consequence of the excellent results obtained by using CD and ^{1}H NMR as a tandem in the rotational population study of alkyl glucopyranosides and of the above-mentioned controversy, a complete spectroscopic study of the rotational population of the hy-

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(2) Padrón, J. I.; Vázquez, J. T. *Chirality* **1997**, *9*, 626.

(3) Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1998**, *9*, 613.

(4) Review: Bock, K.; Duus, J. *J. Carbohydr. Chem* **1994**, *13*, 513.

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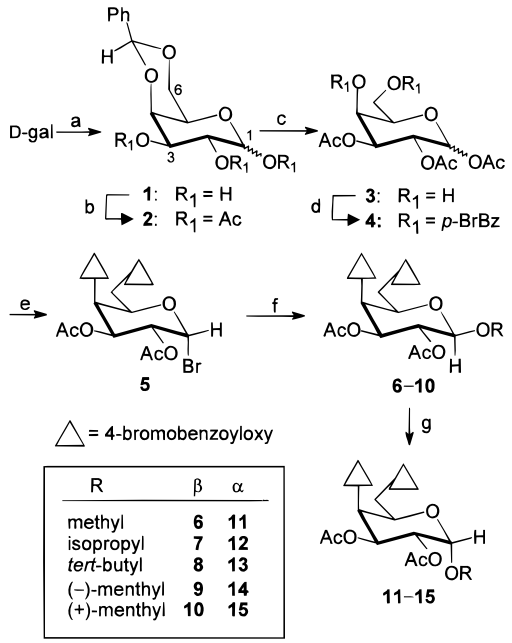
Scheme 1[a]



R	β	α
methyl	**6**	**11**
isopropyl	**7**	**12**
tert-butyl	**8**	**13**
(–)-menthyl	**9**	**14**
(+)-menthyl	**10**	**15**

[a] Key: (a) $PhCH(OCH_3)_2$, *p*-TsOH, DMF, 50 °C−vacuum; (b) Ac_2O/Py (c) AcOH/H_2O (8:2), 60 °C; (d) *p*-BrBzCl, Py, DMAP, 60 °C; (e) HBr/AcOH (3:7), dry CH_2Cl_2; (f) ROH, AgOTf, TMU, dry CH_2Cl_2, −40 °C; (g) anhydrous $FeCl_3$, dry CH_2Cl_2.

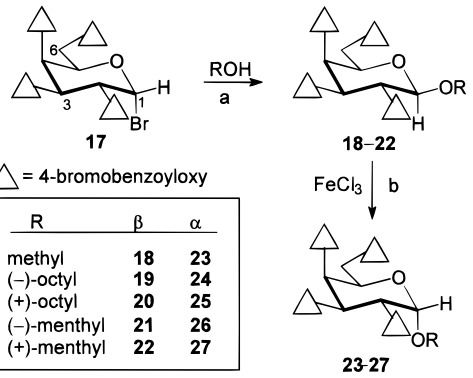
droxymethyl group in esterified chiral and nonchiral alkyl α-D- and *β*-D-galactopyranosides was performed.

Results and Discussion

Synthesis. All alkyl α-D-galactopyranosides, model compounds **11**−**15** and **23**−**27**, were obtained in high yields by epimerization of the corresponding alkyl *β*-D-galactopyranosides, **6**−**10** and **18**−**22**, with anhydrous ferric chloride in dry dichloromethane.[5] These *β*-anomers were prepared in good yields by a modified Koenigs−Knorr method:[6] by treatment of the α-D-galactopyranosyl bromide **5** or **17** with the corresponding alcohol in the presence of 1,1,3,3-tetramethylurea (TMU), as the proton acceptor, and silver trifluoromethanesulfonate, as the catalyst. All these model compounds contain two (Scheme 1) or four (Scheme 2) exciton-coupled chromophores, namely, *p*-bromobenzoate esters.

The 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranosyl bromide **5** was synthesized in good yield from D-galactose in five steps (Scheme 1). Protection of D-galactose with benzaldehyde dimethyl acetal and *p*-toluenesulfonic acid led to the 4,6-benzylidene-D-galactopyranoses (**1**, mixture of *β*- and α-anomers), which by peracetylation afforded the 1,2,3-tris-*O*-acetyl-4,6-*O*-benzylidene-D-galactopyranoses (**2**). Treatment of the anomers **2** with AcOH/H_2O, to remove the benzylidene residue, and subsequent per-*p*-bromobenzoylation gave 1,2,3-tris-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-D-galactopyranoses (**4**). Finally, treatment of **4** with HBr/AcOH led to the desired 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranosyl bromide (**5**). The 2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranosyl bromide **17** was prepared by per-*p*-bromobenzoylation of the D-galactose and subsequent treatment of the resulting pentakis-(*p*-bromobenzoyl) derivative **16**, with HBr/AcOH.

Scheme 2[a]



R	β	α
methyl	**18**	**23**
(–)-octyl	**19**	**24**
(+)-octyl	**20**	**25**
(–)-menthyl	**21**	**26**
(+)-menthyl	**22**	**27**

[a] Key: (a) AgOTf, TMU, CH_2Cl_2, −40 °C; (b) anhydrous $FeCl_3$, dry CH_2Cl_2.

Characterization. All these compounds were characterized on the basis of their spectral NMR data, one-(^{1}H and ^{13}C) and two-dimensional (COSY and HMQC), as well as UV and CD spectroscopy. The anomeric configuration was confirmed in each case by measuring the coupling constant between H1 and H2 (doublet) (*β* anomers: 7.7−7.9 Hz; α anomers: 3.5−3.8 Hz). The ^{1}H NMR signals of the prochiral protons at C6, H6*R*, and H6*S* were differentiated on the basis of their chemical shifts,[7,8] namely, H6*R* signals appear at a lower field than H6*S* signals.

^{13}C NMR data comparison of the galactosylated nonchiral alcohols showed from the methyl to the isopropyl and to the *tert*-butyl galactopyranoside **6**−**8** (*β*-anomers) and **11**−**13** (α-anomers) the following features confirming the structure of these compounds: (i) the α-effect on the aglyconic C1′ carbons; (ii) the *γ*-effect on the anomeric carbons; and (iii) a very small shift to lower field of the C6 carbon. On the other hand, the ^{13}C NMR features observed with the galactosylated chiral alcohols proved to be dependent on the anomeric configuration. Thus, the (*R*)-alkyl *β*-D-galactopyranosides showed chemical shifts at a higher field for the anomeric (2−3 ppm) and for the aglyconic carbons (2−4 ppm) than their *S*-alkyl counterparts, while the opposite behavior was observed with the α-anomers (2−5 ppm).

The model compounds exhibited the intramolecular charge-transfer band around 245 nm in the UV spectra. The wavelengths of the Cotton effects of the exciton CD spectra of bis- and tetrakis-*p*-bromobenzoates **6**−**15** and **18**−**27**, respectively, were at the correct positions, namely around 250 and 232 nm.

Calculated Rotameric Populations. Four different sets of equations were used to calculate from the $J_{H5,H6}$ coupling constants the rotamer distributions of the model compounds **6**−**15** and **18**−**27**,[9] and the results were

(5) (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.

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(8) Ohrui, H.; Nishida, Y.; Higuchi, H.; Hori, H.; Meguro, H. *Can. J. Chem.* **1987**, *65*, 1145.

(9) Software for the calculation of rotameric populations, by using any of the four sets of equations mentioned in the text, is available upon request from E.Q.M.

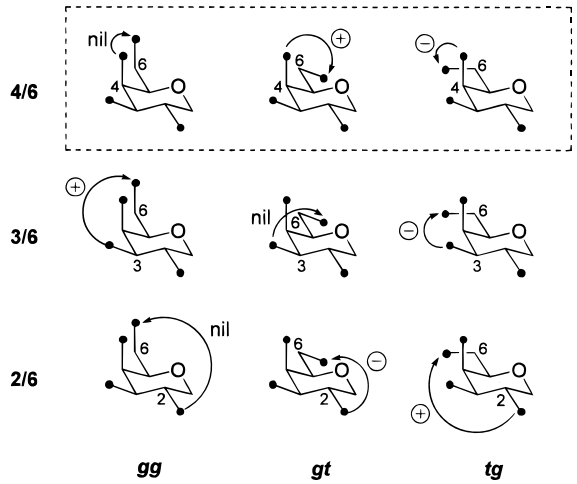

Figure 2. 2/6, 3/6, and 4/6 pairwise interactions involving the chromophore at the 6 position in each of the three stable rotamers (*gg*, *gt*, and *tg*) for the galactopyranosyl system.

compared with those from CD. The calculated rotameric populations shown in Tables 1, 2, 4, and 5 are those obtained by using the set of equations reported by Nishida et al.,[10] which showed the maximal agreement with CD data. These rotameric populations were very similar to those obtained from the set of equations reported by Haasnoot et al.[11] and from those reported by De Vries et al.,[12] although somewhat different from those obtained by using the set of equations reported by Manor et al.[13]

Rotational Population Analysis. Dichromophoric System. To study the rotational dependence of the hydroxymethyl on the structure of the aglycon by means of the CD exciton chirality method,[14] the chromophoric system 4,6-bis-*O*-(*p*-bromobenzoyl) was chosen. This system allows a straightforward interpretation of the CD data, since it contains only the 4/6 pairwise interaction (top of Figure 2), which depends on the population of the *gg*, *gt*, and *tg* rotamers of the hydroxymethyl group.

***β*-Anomers.** To have information about how the population of the hydroxymethyl group changes as the pK_a of the aglycon increases, the methyl, the isopropyl, and the *tert*-butyl *β*-D-galactopyranoside derivatives **6**−**8** were analyzed, as well as the menthyl galactopyranosides **9** and **10** (Scheme 1). As can be observed in Figure 3, negative split CD curves were obtained for the *β*-anomers **6**−**10**. Furthermore, the amplitude (*A* value)[15,16] decreased as the pK_a of the nonchiral alcohol bonded (aglycon) increased, namely, from −21.0 (methyl) to −19.5 (isopropyl) and to −13.6 (*tert*-butyl) (CH_3CN) (Table 1). The galactosylated secondary chiral alcohols **9** and **10** also exhibited lower amplitudes than the methyl derivative **6**, the stereoisomer having the *R* absolute configuration at the aglyconic carbon, compound **9**, showing a higher amplitude than the stereoisomer with the *S* configuration.

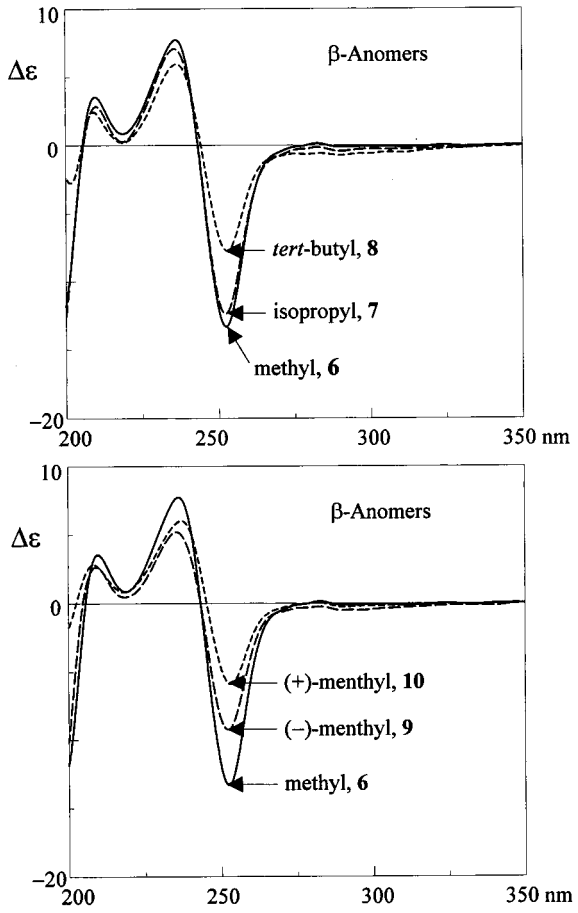

Figure 3. Comparison of the CD spectra (in CH_3CN) of methyl, isopropyl, and *tert*-butyl *β*-D-galactopyranosides **6**−**8** (top). Comparison of the CD spectra (in CH_3CN) of methyl and (−)- and (+)-menthyl *β*-D-galactopyranosides **6**, **9**, and **10**, respectively (bottom).

The same behavior was observed when the CD measurements were performed in EtOH at 25 °C (Table 1). In addition, the amplitude of the methyl and the isopropyl derivatives **6** and **7** proved to be almost independent of the temperature. However, the bulkier model compounds **8**−**10** exhibited a deep dependence on the temperature, their amplitudes decreasing significantly by lowering the temperature.

The decrease in the amplitude of the CD curves obtained either by increasing the pK_a of the nonchiral alcohol bonded to the sugar residue or by lowering the temperature can be explained by an increase in the population of the *gt* rotamer, which has a 4/6 positive contribution, and/or by a decreases in the population of the *tg* rotamer, which contributes negatively to the 4/6 pairwise interaction (top of Figure 2).[17,18] This result showed that the most stable rotamer for compounds **8**−**10**, and probably also for compounds **6** and **7**, is the *gt*, the only one having a positive contribution. To

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(12) DeVries, N.; Buck, H. M. *Carbohydr. Res.* **1987**, *165*, 1.
(13) Manor, P. C.; Saenger, W.; Davies, D. B.; Jankowski, K.; Rabczenko, A. *Biochim. Biophys. Acta* **1974**, *340*, 472.
(14) 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.
(15) 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 the second Cotton effect, respectively.
(16) Occasionally, the presence of a background ellipticity alters the intensity of the Cotton effects at short wavelengths. Thus, the intensities of the second Cotton effect and, therefore, the amplitudes (*A* value) of the CD spectra of our model compounds may not be precise, the intensities of the first Cotton effect therefore being more accurate for comparative analysis.

Table 1. CD Data, $J_{H5,H6}$ Coupling Constants, and Calculated Rotameric Populations (%) around the C5−C6 Bond for the β-Anomers 6−10 (Acetonitrile)

compd	aglycon (R)	Δε at 252/236	*A*	*A*[a] (25 °C)	*A*[a] (−110 °C)	$J_{H5,H6S}$	$J_{H5,H6R}$	P_{gg}	P_{gt}	P_{tg}
6	methyl	−13.3/7.7	−21.0	−27.2	−23.8	6.1	6.3	18	39	43
7	isopropyl	−12.4/7.1	−19.5	−25.9	−22.7	5.9	6.5	17	42	41
8	*tert*-butyl	−7.7/5.9	−13.6	−18.1	−8.8	5.2	6.6	22	45	33
9	(1*R*)-(−)-menthyl	−9.3/5.2	−14.5	−20.6	−13.6	5.4	6.4	23	42	35
10	(1*S*)-(+)-menthyl	−5.9/6.0	−11.9	−16.4	−7.4	4.9	9.0	0	72	28

[a] EtOH.

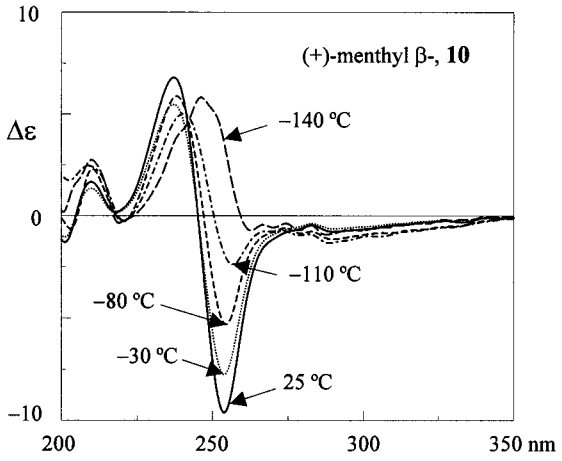

Figure 4. CD spectra of (+)-menthyl β-D-galactopyranoside **10** at room and low temperatures (25, −30, −80, and −110 °C) in EtOH and in EtOH/MeOH (4:1) (−140 °C).

confirm that this rotamer is the most stable, the (+)-menthyl galactopyranoside **10** was measured at a lower temperature (−140 °C) by using the EtOH/MeOH (4:1) solvent system. The observed negative amplitudes (Figure 4) changed to positive at −140 °C (A = +5.7), confirming that the most stable rotamer is the *gt* (the one with a positive contribution).

The rotameric populations of galactopyranosides have been shown to be dependent on the solvent.[12] Therefore, the CD and ^{1}H NMR data comparison performed in the present study was done by analyzing data in the same solvent, acetonitrile. Analysis of the $J_{H5,H6}$ coupling constants (Table 1) showed for the galactosylated nonchiral alcohols **6**−**8** an increase and a decrease in the $J_{H5,H6R}$ and $J_{H5,H6S}$, respectively, as the pK_a of the alcohol increased, in agreement with the decreases in the CD amplitudes. This result led to an increase and decrease of the *gt* and *tg* populations, respectively, from the methyl to the isopropyl and to the *tert*-butyl derivatives. For the menthyl derivatives, a higher $J_{H5,H6R}$ and a smaller $J_{H5,H6S}$ value were observed for the (1*S*)-(+)-menthyl galactopyranoside **10** than for its corresponding stereoisomer **9**, in agreement with its smaller CD amplitude and its high *gt* population.

The observed correlation between the rotamer distribution and the pK_a of the nonchiral alcohol bonded to the galactopyranosyl system can be explained by means of the stereoelectronic exo anomeric effect.[19,20] The value of this effect must increase from the methyl to the isopropyl and to the *tert*-butyl galactopyranoside derivatives,[21] producing a gradual shortening and a lengthening of the O1−C1 and O5−C1 bonds, respectively, and leading to different rotamer populations. Thus, an increase in the exo anomeric effect produces increases and decreases in the *gt* and *tg* populations, respectively.

The results described above for the alkyl galactopyranoside derivatives are opposite to those reported by Vries and Buck[12] in that by increasing the pK_a of the anomeric substituent, the *tg* population increased. These differences may be due to the fact that these authors used aromatic alcohols at the anomeric carbon and phosphate groups at the 6 position.

α-Anomers. The CD spectra of compounds **11**−**15** can be observed in Figure 5. The amplitude of the galactosylated nonchiral alcohols decreased slightly as the pK_a of the bonded alcohol increased, pointing to an increase in the *gt* population (Table 2). For the galactosylated chiral alcohols, the (1*S*)-(+)-menthyl galactopyranoside **15** exhibited higher amplitude (negative sign) than its stereoisomer **14**. However, this compound showed a higher amplitude than the methyl derivative **11**, and in addition, its amplitude increased as the temperature decreased (Table 2 and Figure 6). For this particular compound (**15**), the most stable rotamer is the *tg* instead of the *gt*.

Analysis of the $J_{H5,H6}$ coupling constants (CD_3CN and $CDCl_3$) of these compounds showed an excellent concordance with CD data. For the galactosylated nonchiral alcohols the $J_{H5,H6R}$ increased as the pK_a of the alcohol increased, while the $J_{H5,H6S}$ remained constant. For the galactosylated chiral alcohols, a higher $J_{H5,H6R}$ and a smaller $J_{H5,H6S}$ coupling constant were observed for the (1*R*)-(−)-menthyl galactopyranoside **14** than for its corresponding stereoisomer **15**, in agreement with the amplitudes observed by CD. The calculated rotameric populations are also in excellent agreement with the observed CD amplitudes at room and at low temperature.

The α-anomers also showed a correlation between the pK_a of the bonded alcohol and the rotamer distribution. However, the degree of dependence was smaller than that observed with the β-anomers, this fact being easily observed by CD spectra comparison of compounds **6**−**8** and **11**−**13** (tops of Figures 3 and 5). This dependence can also be explained by the exo anomeric effect, which has a smaller significance in the rotamer population than the β-anomers. The simultaneous presence of the exo

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(18) Vázquez, J. T.; Wiesler, W. T.; Nakanishi, K. *Carbohydr. Res.* **1988**, *176*, 175.
(19) The stereoelectronic exo anomeric effect is the preference for the gauche (sc) conformation about the glycosidic C−OR bond of sugar derivatives. Lemieux, R. U.; Pavia, A. A.; Martin, J. C.; Watanabe, K. A. *Can. J. Chem.* **1969**, *47*, 4427.
(20) (a) Kirby, A. J. In *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen* in *Reactivity and Structure Concepts in Organic Chemistry*; Hafner, K., Rees, C. W., Trost, B. M., Lehn, J. M., Schleyer, P. v. R., Zahradnik, R., Eds.; Springer-Verlag: Berlin, 1983; Vol. 15. (b) 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.
(21) Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswamy, P. *J. Am. Chem. Soc.* **1984**, *106*, 6200.

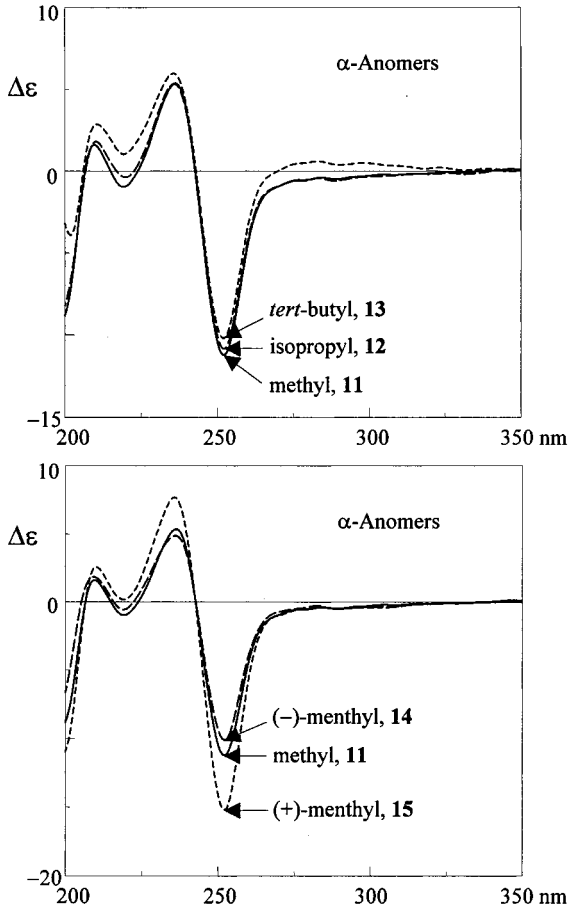

Figure 5. Comparison of the CD spectra (in CH_3CN) of methyl, isopropyl, and *tert*-butyl α-D-galactopyranosides **11**−**13** (top). Comparison of the CD spectra (in CH_3CN) of methyl and (−)- and (+)-menthyl α-D-galactopyranosides **11**, **14** and **15**, respectively (bottom).

and endo anomeric effects in the α-anomers could be the reason for the smaller effect of the exo anomeric effect.[20] This explanation is contrary to that reported by us in a previous study with alkyl α-glucopyranosides,[2] where the results pointed to the nonparticipation of the endo anomeric effect, since the same degree of correlation was observed for both anomers.

Calculation of the Rotameric Contributions to the 4/6 Pairwise Interaction. The exciton coupling between two chromophores depends on the interchromophoric distance and on the dihedral angle.[14] Therefore, the observed 4/6 pairwise interaction is the percentage sum of the interaction between the chromophore at C4 and the chromophore at C6 in the *gg*, *gt*, and *tg* rotamers.

Previous interpretation of the observed negative signs of the split CD curves of methyl 4,6-bis-*O*-(*p*-bromobenzoyl) and methyl 3,6-bis-*O*-(*p*-bromobenzoyl) galactopyranosides[17,18] led to establishing incorrectly the *tg* rotamer as the most stable one, since the contributions of this rotamer to the 3/6 and 4/6 interactions are negative (Figure 2). However, this result could not explain the negative split CD exhibited by methyl 2,6-bis-*O*-(*p*-bromobenzoyl)galactopyranoside,[17,18] which possesses a positive sign for the *tg* rotamer (Figure 2). Their confidence in this CD result also led the authors to draw the hydroxymethyl group wrongly in the *tg* disposition in their publications.[17,18,22]

The observed negative signs for the 3/6 and 4/6 pairwise interactions, the most stable rotamer being the *gt*, with a nil and a positive CD contribution, respectively (Figure 2), can be explained as follows: (i) The negative sign for the 3/6 interaction comes from the second more populated rotamer, the *tg* rotamer (with negative contribution), since the *gt* rotamer has a nil contribution for this interaction. (ii) The contribution of the *tg* rotamer to the 4/6 pairwise interaction must be much stronger than that of the *gt* rotamer, as a consequence of the shorter distance and more favorable dihedral angle. To prove this assessment, the contributions to the 4/6 pairwise interaction were estimated by correlating the calculated rotamer distributions with the observed CD amplitudes and assuming a nil contribution for the *gg* rotamer, as a consequence of its dihedral angle, which is near 0°. Thus, it was found that the contribution of the *tg* rotamer to the amplitude (*A* value) of the 4/6 pairwise interaction was 10 times higher ($A \approx -50$) than the *gt* contribution ($A \approx +5$), the amplitude following the equation: $A = 5gt - 50tg$. Therefore, this result explains satisfactorily the observed negative sign for the 4/6 pairwise interaction, although the most stable rotamer is the *gt* (positive contribution). Table 3 shows observed and calculated amplitudes for compounds **6**−**15**, as well as their differences ΔA (obsd − calcd). The very small differences obtained in general confirm the correct estimation performed of the rotameric contributions to the 4/6 pairwise interaction.

Rotational Population Analysis. Tetrachromophoric System. To complete the above rotational study of the galactosylated chiral alcohols and confirm that the galactopyranosyl system can also be used to determine the absolute configuration of chiral alcohols, the alkyl 2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-*β*- and α-D-galactopyranosides **18**−**27** were prepared (Scheme 2). These compounds contain the necessary chromophore at C2 to give rise to anisotropic shifts in the aglycon ^{1}H NMR peaks and, thus, be able to determine the absolute configuration of the bonded chiral alcohol (aglycon) (see below).[23]

***β*-Anomers.** CD analysis of the galactosylated chiral alcohols **19**−**22** showed similar amplitudes, but with slightly higher values than that of the methyl galactopyranoside derivative **18** (Table 4). Furthermore, those derivatives having an *S* absolute configuration at the aglyconic carbon exhibited higher values in the intensity of their first Cotton effects than their stereoisomer with the *R* absolute configuration.[16] Low-temperature CD measurement of compounds **18**−**22** (EtOH) revealed for each of these compounds a gradual increase in the amplitude as the temperature decreased from 25 to −110 °C.

To analyze these CD data, it is necessary to take into account all the pairwise interactions involved in the galactopyranosyl system. The CD spectrum of a chromophorically 2,3,4,6-tetra-substituted galactopyranosyl system is composed of six pairwise interactions.[17,18] These interactions can be divided into two groups: those

(22) Wiesler, W. T.; Berova, N.; Ojika, M.; Meyers, H. V.; Chang, M.; Zhou, P.; Lo, L.-C., Niwa, M.; Takeda, R.; Nakanishi, K. *Helv. Chim. Acta* **1990**, *73*, 509.

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

Table 2. CD Data, $J_{H5,H6}$ Coupling Constants, and Calculated Rotameric Populations (%) around the C5−C6 Bond for the α-Anomers 11−15 (Acetonitrile)

compd	aglycon (R)	Δε at 253/237	*A*	*A*[a] (25 °C)	*A*[a] (−110 °C)	$J_{H5,H6S}$	$J_{H5,H6R}$	P_{gg}	P_{gt}	P_{tg}
11	methyl	−11.5/5.5	−17.0	−21.5	−10.5	5.7	6.4	20	42	38
12	isopropyl	−11.2/5.5	−16.7	−20.5	−16.1	5.7	6.6	18	44	38
13	*tert*-butyl	−10.4/6.2	−16.6	−20.2	−13.7	5.7	6.8	16	46	38
14	(1*R*)-(−)-menthyl	−10.4/5.3	−15.7	−19.2	−8.7	5.3	6.9	18	48	34
15	(1*S*)-(+)-menthyl	−15.7/7.9	−23.6	−29.2	−38.3	6.0	6.4	18	40	42

[a] EtOH.

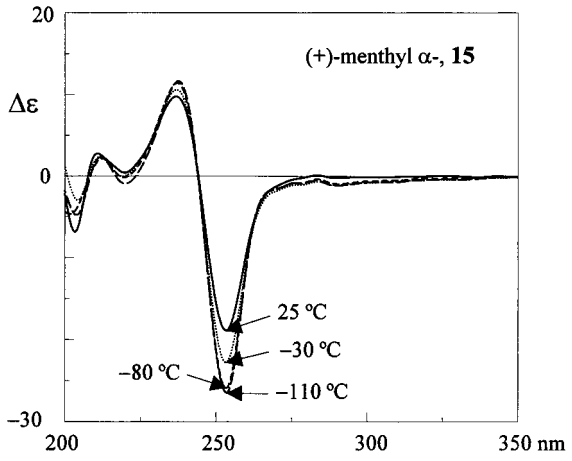

Figure 6. CD spectra of (+)-menthyl α-D-galactopyranoside **15** at room and low temperatures in EtOH.

Table 3. Observed vs Calculated Amplitudes for Compounds 6−15 (CH_3CN)

compd	*A* (obsd)	*A* (calcd)	Δ*A* (obsd − calcd)
6	−21.0	−19.5	−1.5
7	−19.5	−18.4	−1.1
8	−13.6	−14.2	0.6
9	−14.5	−15.4	0.9
10	−11.9	−10.4	−1.5
11	−17.0	−16.9	−0.1
12	−16.7	−16.8	0.1
13	−16.6	−16.7	0.1
14	−15.7	−14.6	−1.1
15	−23.6	−19.0	−4.6

having a practically constant intensity and a positive sign, the 2/3, the 3/4, and the 2/4 pairwise interactions (Figure 7), and those interactions involving the chromophore at the six position with variable intensity and sign, the 2/6, the 3/6, and the 4/6 pairwise interactions, which depend on the rotamer population of the hydroxymethyl group (Figure 2).

In accordance with the exciton chirality method,[14] the amplitude of split Cotton effects is inversely proportional to the square of interchromophoric distance; therefore, the 4/6 pairwise interaction contributes more significantly to the observed spectrum than the 3/6 or 2/6 pairwise interactions, as observed.[17,18] Therefore, the increase in the amplitude of the CD curves obtained by lowering the temperature is in agreement with an increase in the population of the *gt* rotamer, which has a 4/6 positive contribution, and with a decrease in the population of the *tg* rotamer, which contributes negatively to this 4/6 pairwise interaction (Figure 2). This result also points to the *gt* rotamer as the most stable. In addition, stereoisomers with an *S* absolute configuration should have higher and smaller *gt* and *tg* populations than their stereoisomers with the *R* configuration, as occurred in the dichromophoric system with compounds **9** and **10**. Furthermore, all galactosylated secondary alcohols showed higher *gt* and smaller *tg* populations than the methyl derivative **18**.

Due to the superposition of ^{1}H NMR signals observed for the β-anomers **18**−**22** in acetonitrile and, therefore, the impossibility of measuring accurately their $J_{H5,H6}$ coupling constants, these compounds were analyzed in methanol. Analysis of the $J_{H5,H6}$ coupling constants showed higher $J_{H5,H6R}$ and smaller $J_{H5,H6S}$ values for the secondary alkyl galactopyranosides **19**−**22** than for the methyl derivative **18** (Table 4), confirming higher *gt* and smaller *tg* populations for the galactosylated secondary alcohols **19**−**22** than for the reference galactosylated primary alcohol **18**. In addition, the calculated rotameric populations for these compounds showed that $P_{gt} > P_{tg} > P_{gg}$, with the exception of the methyl derivative **18**, which showed $P_{tg} > P_{gt} > P_{gg}$. CD and calculated rotameric populations data comparison revealed an excellent agreement in all cases except for the methyl galactopyranoside **18**. This single discrepancy may be due to an overestimation in the calculation of the populations of the *tg* rotamer.

Similarly to the alkyl β-D-glucopyranosides, there are two possible ways to explain that in general stereoisomers with the *R* absolute configuration at the aglyconic carbon show smaller and higher *gt* and *tg* populations than their stereoisomers having the *S* configuration: (i) Since the stereoisomer with the *R* absolute configuration at the aglyconic carbon possesses greater bulkiness in a syn location to the endocyclic oxygen (O5) than its stereoisomer having the enantiomeric aglycon, weak nonbonded interactions between the aglycon and the chromophore at C6 in its *gt* rotamer can account for the smaller *gt* population of the (*R*)-alkyl β-D-galactopyranoside (Figure 8). (ii) The torsional angle ψ depends on the structure of the aglycon:[24] a small clockwise or counterclockwise rotation along the O1−C1′ bond occurs depending on whether the main nonbonded interactions between the aglycon and the galactopyranosyl residue are located syn or anti, respectively, to the endocyclic oxygen (O5). Thus, the nonbonding electron pair of the exocyclic oxygen involved in the exo anomeric effect could adopt a different disposition depending on the absolute configuration of the aglycon, and therefore, the stereoisomer having the *S* absolute configuration at the aglyconic carbon could adopt a better antiperiplanar disposition with respect to the C1−O5 bond than its stereoisomer with the *R* configuration (Figure 8).

α-Anomers. CD data of the alkyl α-D-galactopyranoside derivatives **23**−**27** are shown in Table 5. As occurred with the β-anomers, all galactosylated secondary alcohols **24**−**27** exhibited higher amplitudes than the methyl galactopyranoside **23**, and contrary to the β-anomers, the galactosylated chiral alcohols having an *S* absolute configuration at the aglyconic carbon exhibited

(24) Lemieux, R. U.; Koto, S. *Tetrahedron* **1974**, *30*, 1933.

Table 4. CD Data, $J_{H5,H6}$ Coupling Constants, and Calculated Rotameric Populations (%) around the C5−C6 Bond for the β-Anomers 18−22

compd	aglycon (R)	Δε at 252/234[a]	A^a	A^b (25 °C)	A^b (−110 °C)	$J_{H5,H6S}$[c]	$J_{H5,H6R}$[c]	P_{gg}	P_{gt}	P_{tg}
18	methyl	65.0/−22.6	87.6	81.4	98.7	6.1	5.9	22	35	43
19	(2*R*)-(−)-octyl	65.5/−24.3	89.8	86.7	101.9	5.5	6.5	21	43	36
20	(2*S*)-(+)-octyl	66.6/−23.2	89.8	79.5	102.1	5.7	6.5	19	43	38
21	(1*R*)-(−)-menthyl	65.7/−24.3	90.0	85.2	111.0	5.5	6.3	23	41	36
22	(1*S*)-(+)-menthyl	67.0/−22.0	89.0	87.4	111.2	4.8	7.4	17	55	28

[a] CH_3CN. [b] EtOH. [c] CD_3OD.

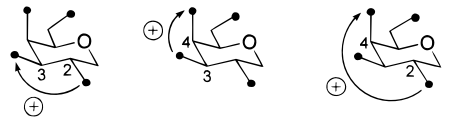

Figure 7. 2/3, 3/4, and 2/4 pairwise interactions having constant intensity and positive sign for the galactopyranosyl system.

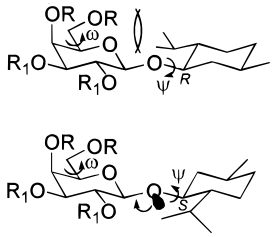

Figure 8. Top: (−)-menthyl β-D-galactopyranosides **9** (R = *p*-bromobenzoyl, R_1 = acetyl) and **21** (R = R_1 = *p*-bromobenzoyl)). Bottom: (+)-menthyl β-D-galactopyranosides **10** (R = *p*-bromobenzoyl, R_1= acetyl) and **22** (R = R_1 = *p*-bromobenzoyl).

smaller amplitudes than their stereoisomers with the *R* configuration, in agreement with the higher negative amplitude observed for compound **15** compared with **14**, analogues in the dichromophoric system.

Low-temperature CD measurements (EtOH) showed an important and gradual increase in amplitude by lowering the temperature, indicating that the most stable rotamer is the *gt*, as occurred with the β-anomers. Furthermore, while the dependence of the amplitude on the temperature was very similar for the octyl derivatives **24** and **25**, it was very different for the menthyl derivatives **26** and **27**, showing a much higher and a much lower amplitude, respectively, than the methyl galactopyranoside **23**.

Analysis of the ^{1}H NMR coupling constants between H5 and H6*R* and H6*S* showed higher $J_{H5,H6R}$ and smaller $J_{H5,H6S}$ values for the secondary alkyl galactopyranosides **24**−**27** than for the methyl derivative **23** (Table 5), with the exception of the $J_{H5,H6S}$ of the menthyl derivative **27**, which has a higher value. This general behavior means higher *gt* and smaller *tg* populations for these galactopyranosides than for the methyl galactopyranoside **23**. The calculated rotamer distributions showed the same order as for the β-anomers ($P_{gt} > P_{tg} > P_{gg}$), in total agreement with CD results. In addition, a correlation between the amplitude of the CD spectra (CH_3CN) and the percentage of the rotameric populations was observed, namely, the higher the amplitude the higher the population of the *gt* rotamer.

CD and ^{1}H NMR data of the chiral alkyl α-D-galactopyranosides, either in the di- or in the tetrachromophoric system, agree in higher and smaller populations of the *gt* and *tg* rotamers, respectively, for those stereoisomers having an *R* absolute configuration at the aglyconic carbon than for those with the opposite absolute configuration. This conduct can be explained by means of the two same arguments used for the β-anomers, but taking into account that for the α-anomers (i) the stereoisomer with the *S* absolute configuration at the aglyconic carbon possesses bulkiness in a syn location to the endocyclic oxygen (O5) greater than its stereoisomer having the enantiomeric aglycon (Figure 9) and (ii) the stereoisomer having the *R* absolute configuration at the aglyconic carbon could adopt a better antiperiplanar disposition with respect to the C1−O5 bond than its stereoisomer with the *S* configuration (Figure 9). In addition, the unusual behavior of the (1*S*)-(+)-menthyl galactopyranoside **15** points clearly to the presence of an appreciable nonbonding interaction between the chromophore at C6, in its *gt* rotamer, and the aglycon, closer to the sugar residue due to its α anomeric configuration.

Absolute Configuration of Secondary Alcohols (Aglycons) and Galactopyranosidic Conformation. The galactosylated chiral alcohols **19**−**22** (β-anomers) and **24**−**27** (α-anomers) showed important chemical shift differences (either as $\delta_D - \delta_{ROH}$ or as $\delta_D - \delta_L$) in the aglycon ^{1}H NMR peaks, as a consequence of the dramatic chemical shifts produced by the anisotropic effect and by the galactosylation-induced ^{1}H NMR shifts. As can be observed in Figure 10 and as occurred in the alkyl tetra-*O*-benzoylglucopyranosides,[1,2,23] these differences are characteristic of the absolute configuration of the secondary chiral alcohol and confirm that the galactopyranosyl system can also be used to determine the absolute configuration of chiral alcohols or the aglyconic moiety of natural glycosides. Furthermore, the chemical shift of the carbinyl protons of the β-glucosylated *R*-alcohols appears at a lower field than that of the β-glucosylated *S*-alcohol counterparts, the former giving rise to a positive sign and the latter to a negative sign of Δδ. The opposite behavior was observed for the α-anomers.

The chemical shift differences (Δδ) obtained by tetra-*O*-benzoylglycosylation of chiral alcohols of known absolute configuration, as occurs in the present study, allow the most stable conformation around the interglycosidic linkage to be determined. Thus, the negative and the positive signs obtained for those aglyconic protons located anti or syn, respectively, to the endocyclic galactopyranoside oxygen (O5) confirm that the most stable conformation for the α- and β-anomers is similar to that shown for each anomer in Figure 10. Note that the same absolute values of Δδ but with opposite signs correspond to the enantiomeric aglycons.

Conclusions

It can be concluded, on the basis of the CD and ^{1}H NMR data, that the rotational population of the hydroxymethyl group in esterified alkyl α- and β-galacto-

Table 5. CD Data, $J_{H5,H6}$ Coupling Constants, and Calculated Rotameric Populations (%) around the C5−C6 Bond for the α-Anomers 23−27 (Acetonitrile)

compd	aglycon (R)	Δε at 252/235	*A*	*A*[a] (25 °C)	*A*[a] (−110 °C)	$J_{H5,H6S}$	$J_{H5,H6R}$	P_{gg}	P_{gt}	P_{tg}
23	methyl	69.2/−28.5	97.7	105.4	133.4	5.8	6.4	19	41	40
24	(2*R*)-(−)-octyl	73.3/−31.2	104.5	107.5	137.5	5.6	6.7	18	45	37
25	(2*S*)-(+)-octyl	71.9/−27.4	99.3	107.0	137.1	5.6	6.7	18	45	37
26	(1*R*)-(−)-menthyl	74.7/−30.2	104.9	137.9	180.4	5.4	6.8	18	47	35
27	(1*S*)-(+)-menthyl	70.3/−28.2	98.5	98.8	113.8	5.9	6.5	17	42	41

[a] EtOH.

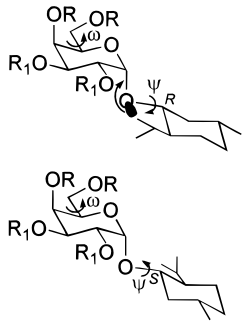

Figure 9. Top: (−)-menthyl α-D-galactopyranosides **14** (R = *p*-bromobenzoyl, R_1 = acetyl) and **26** (R = R_1 = *p*-bromobenzoyl). Bottom: (+)-menthyl α-D-galactopyranosides **15** (R = *p*-bromobenzoyl, R_1= acetyl) and **27** (R = R_1 = *p*-bromobenzoyl).

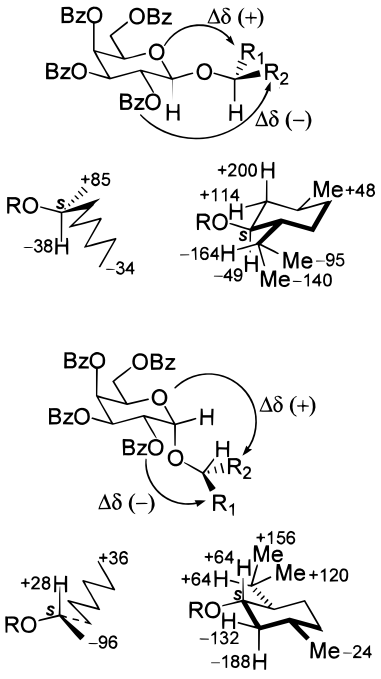

Figure 10. Chemical shift differences ($\Delta\delta = \delta_D - \delta_L$) (in hertz; 400 MHz; room temperature; solvent $CDCl_3$) of the tetra-*O*-(*p*-bromobenzoyl)galactopyranoside derivatives of (+)-2-octanol and of (+)-menthol; anomeric configuration: β (top), and α (bottom).

pyranosides depends on the structure of the aglycon and that its most stable rotamer is the *gt*, and not the *tg*. Moreover, it was observed that the population of the *gt* and *tg* rotamers increases and decreases, respectively, as the pK_a of the bonded alcohol increases, while the population of the *gg* rotamer remains practically constant. Furthermore, the results pointed to the stereoelectronic exo anomeric effect as being responsible for this rotational dependence, probably as a consequence of a better *antiperiplanar* disposition of the nonbonding electron pair of the exocyclic oxygen to the O5−C1 bond and to a higher significance of this stereoelectronic effect in the β-anomers.

Table 6. Summarized Results of the Rotational Population Study of the Hydroxymethyl Group in Alkyl Galactopyranosides

nonchiral aglycons	pK_a ↑, P_{gg} ≈ constant, P_{gt} ↑, P_{tg} ↓	
chiral aglycons	β-anomers	α-anomers
	P_{gt} (*R*) < P_{gt} (*S*) P_{tg} (*R*) > P_{tg} (*S*)	P_{gt} (*R*) > P_{gt} (*S*) P_{tg} (*R*) < P_{tg} (*S*)

The rotational populations of the hydroxymethyl group in galactosylated chiral alcohols revealed a clear correlation with the anomeric configuration as well as with the absolute configuration of the aglycon. Thus, β-anomers having an *S* absolute configuration at the aglyconic carbon showed higher and smaller *gt* and *tg* populations, respectively, than their stereoisomers of opposite absolute configuration, while for the α-anomers, the one having higher and smaller *gt* and *tg* populations, respectively, was the stereoisomer with the *R* absolute configuration at the aglyconic carbon. Similar to the chiral alkyl glucopyranosides, a more stabilizing stereoelectronic exo anomeric effect for diastereoisomers with an *S* absolute configuration (β-anomers) or an *R* configuration (α-anomers) may account for these rotational dependencies. In addition, nonbonding interactions between the aglycon and the chromophore at C6 may be involved in those stereoisomers having in their aglycon a bulky substituent syn to the endocyclic oxygen (O5), as occurred in the (+)-menthyl α-D-galactopyranoside derivative **15**. Table 6 summarizes these results.

In addition, it was confirmed that the chemical shift differences ($\delta_D - \delta_{ROH}$ or $\delta_D - \delta_L$) of the aglyconic protons of the galactosylated chiral alcohols, as either the α- or β-anomer, are characteristic of the absolute configuration of the bonded chiral alcohol. Therefore, the recently proposed ^{1}H NMR method for the determination of the absolute configuration of secondary alcohols or the aglyconic moiety of natural glycosides, based on tetra-*O*-benzoyl glucosylation, can be extended to the use of the tetra-*O*-benzoyl galactopyranosyl as a chiral auxiliary.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 400 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 and using 10 mm cells. Prior to measurement of CD spectra, all compounds were purified by HPLC 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 from the UV spectra, using the standard ε values at 245 nm: bis-(*p*-bromobenzoate) ε 38 200;

tetrakis-(*p*-bromobenzoate) 76 400.[17] Density correction was realized in all CD low-temperature measurements.

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. Flash column chromatography was performed using silica gel (0.015−0.04 mm). All reagents as well as the chiral alcohols 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 Procedures. The general procedure for *p*-bromobenzoylation is well described in ref 1, as well as the preparation of glucopyranosyl bromides and the procedure for *β*-glucosylation, which were used in the same way as for the preparation of galactopyranosyl bromides and for *β*-galactosylation.

General Procedure for Anomerization. To a stirred solution of the substrate (20−70 *μ*mol) in dry CH_2Cl_2 (20 mL/mmol) at room temperature under dry argon was added 3 equiv of anhydrous $FeCl_3$ 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 flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

4,6-*O*-Benzylidene-D-galactopyranose (1). To a solution of D-(+)-galactose (4.0 g, 22.20 mmol) in DMF (20 mL) were added benzaldehyde dimethyl acetal (3.3 mL, 22.20 mmol) and *p*-toluenesulfonic acid (42 mg, 0.222 mmol). The reaction mixture was heated to 50 °C, under vacuum, and left overnight. Then, the solvent was removed by distillation and the resulting oil chromatographed on silica gel ($CHCl_3$/MeOH 9:1). Compound **1** (8.6 mmol) was obtained in 39% yield: TLC R_f = 0.34 ($CHCl_3$/MeOH 9:1).

4,6-*O*-Benzylidene-1,2,3-tris-*O*-acetyl-D-galactopyranoside (2). To a solution of compound **1** (2.26 g, 8.43 mmol) in dry pyridine (8 mL) at room temperature was added acetic anhydride (8 mL), the reaction being monitored by TLC. Then, excess solvent was removed under reduced pressure in the presence of *n*-heptane, and the residue was chromatographed to afford compound **2** (2.99 g, 7.6 mmol, 90% yield) as a 4:6 mixture of α- and *β*-anomers: TLC R_f = 0.38 (*n*-hexane/EtOAc 7:3); ^{1}H NMR (mixture of anomers) ($CDCl_3$) *δ* 7.50 (m), 7.37 (m), 6.48 (d, *J* = 3.5 Hz, H-1α), 5.70 (d, *J* = 8.3 Hz, H-1*β*), 5.52 (m, H-2α and H-2*β*), 5.31 (dd, *J* = 3.2, 10.9 Hz, H-3α), 5.00 (dd, *J* = 3.6, 10.3 Hz, H-3*β*), 4.50 (d, *J* = 2.6 Hz, H-4α), 4.40 (d, *J* = 1.5 Hz, H-4*β*), 4.32 (brd, *J* = 1.5 Hz), 4.29 (brt, *J* = 2.6 Hz), 4.25 (d, *J* = 1.5 Hz), 4.05 (brt, *J* = 1.4 Hz), 4.02 (brt, *J* = 1.4 Hz), 3.91 (brs), 3.65 (brd, *J* = 1.0 Hz), 2.14 (s), 2.10 (s), 2.09 (s), 2.07 (s), 2.03 (s), 2.01 (s).

1,2,3-Tris-*O*-acetyl-α-D-galactopyranoside (3). A solution of compound **2** (2.11 g, 5.32 mmol) in $AcOH/H_2O$ (20 mL, 8:2, v/v) was heated at 60 °C and monitored by TLC. Then, the excess solvent was removed under reduced pressure and the residue chromatographed on silica gel (MeOH/$CHCl_3$ 5:95) to afford compound **3** (4.77 mmol, 89% yield): TLC R_f = 0.38 ($CHCl_3$/MeOH 9.5:0.5); ^{1}H NMR ($CDCl_3$) *δ* 6.24 (d, *J* = 3.7 Hz, 1H), 3.35 (dd, *J* = 3.7, 10.8 Hz, 1H), 5.09 (dd, *J* = 3.0, 10.8 Hz, 1H), 4.15 (d, *J* = 2.6 Hz, 1H), 3.89 (brt, *J* = 5.2 Hz, 1H), 3.71 (dd, *J* = 5.4, 11.7 Hz, 1H), 3.65 (dd, *J* = 5.2, 11.7 Hz, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.92 (s, 3H).

1,2,3-Tris-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-D-galactopyranoside (4). Following the general procedure for *p*-bromobenzoylation, 1.45 g (4.74 mmol) of **3** led to compound **4** (3.79 mmol, 80% yield) as a 9:1 mixture of α- and *β*-anomers: TLC R_f = 0.42 (*n*-hexane/EtOAc 7:3); ^{1}H NMR (mixture of anomers) ($CDCl_3$) *δ* 7.93−7.55 (aromatic H's), 6.50 (d, *J* = 3.4 Hz, H-1α), 5.85 (d, *J* = 2.4 Hz, H-4α), 5.79 (d, *J* = 8.3 Hz, H-1*β*), 5.48 (dd, *J* = 3.1, 11.0 Hz, H-3α), 5.43 (dd, *J* = 3.4, 10.9 Hz, H-2α), 5.23 (dd, *J* = 3.4, 11.0 Hz, H-3*β*), 4.57 (brt, *J* = 6.5 Hz, H-5α), 4.51 (dd, *J* = 6.1, 11.0 Hz, H-6α), 4.28 (dd, *J* = 6.7, 11.2 Hz, H-6α), 2.18 (s), 2.16 (s), 2.05 (s), 2.04 (s), 1.96 (s), 1.95 (s).

2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranosyl Bromide (5). Following the general procedure for the preparation of galactopyranosyl bromides, 2.07 g (3.08 mmol) of **4** led to compound **5** (2.19 mmol, 71% yield): TLC R_f = 0.61 (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D$ = +86.67 (*c* 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 7.90−7.55 (aromatic H's), 6.81 (d, *J* = 4.0 Hz, 1H), 5.86 (brd, *J* = 2.5 Hz, 1H), 5.54 (dd, *J* = 3.3, 10.6 Hz, 1H), 5.13 (dd, *J* = 4.0, 10.6 Hz, 1H), 4.73 (t, *J* = 6.4 Hz, 1H), 4.53 (dd, *J* = 6.7, 11.6 Hz, 1H), 4.35 (dd, *J* = 6.1, 11.6 Hz, 1H), 2.12 (s, 3H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 170.05, 169.77, 165.10, 164.78, 132.12−127.52 (aromatic C's), 87.91, 71.23, 68.04, 67.98, 67.94, 61.94, 20.71, 20.55. Anal. Calcd for $C_{24}H_{21}O_9Br_3$: C, 41.75; H, 3.07. Found: C, 41.78; H, 3.44.

Methyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-*β*-D-galactopyranoside (6). According to the general procedure for *β*-galactosylation, 120 mg (0.173 mmol) of **5** and 1 mL of dry MeOH led to the desired galactopyranoside **6** (0.155 mmol, 90% yield): TLC R_f = 0.5 (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D$ = −27.6 (*c* 2.33, $CHCl_3$); CI-MS (CH_4) *m*/*z* 724 (1.8, $[M + Br]^-$), 643 (2, $[M]^-$), 484 (2, $[M - 2Br]^-$), 80 (100, Br); ^{1}H NMR ($CDCl_3$) *δ* 7.94−7.55 (aromatic H's), 5.73 (brd, *J* = 3.3 Hz, 1H), 5.28 (dd, *J* = 7.9, 10.4 Hz, 1H), 5.15 (dd, *J* = 3.3, 10.4 Hz, 1H), 4.59 (dd, *J* = 6.5, 11.3 Hz, 1H), 4.49 (d, *J* = 7.9 Hz, 1H), 4.31 (dd, *J* = 6.9, 11.3 Hz, 1H), 4.14 (t, *J* = 6.7 Hz, 1H), 3.55 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 170.11, 169.40, 165.18, 165.00, 131.98−127.75 (aromatic C's), 102.21, 70.91, 68.89, 68.06, 61.91, 57.10, 20.74, 20.51. Anal. Calcd for $C_{25}H_{24}O_{10}Br_2$: C, 46.73; H, 3.77. Found: C, 46.66; H, 3.89.

Isopropyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-*β*-D-galactopyranoside (7). Following the general procedure for *β*-galactosylation, from 120 mg (0.173 mmol) of **5** and 1 mL of dry 2-propanol was obtained compound **7** (0.132 mmol, 76% yield): TLC R_f = 0.56 (*n*-hexane/EtOAc 7.5:2.5); $[\alpha]^{25}_D$ = −21.4 (*c* 2.78, $CHCl_3$); CI-MS (CH_4) *m*/*z* 753 (4, $[M+Br]^-$), 672 (2.8, $[M]^-$), 200 (100, BrBzO); ^{1}H NMR ($CDCl_3$) *δ* 7.95−7.55 (aromatic H's), 5.71 (brd, *J* = 3.4 Hz, 1H), 5.25 (dd, *J* = 7.8 , 10.4 Hz, 1H), 5.15 (dd, *J* = 3.4, 10.4 Hz, 1H), 4.59 (d, *J* = 7.8 Hz, 1H), 4.55 (dd, *J* = 6.7, 11.3 Hz, 1H), 4.30 (dd, *J* = 6.7, 11.3 Hz, 1H), 4.12 (t, *J* = 6.6 Hz, 1H), 3.94 (sep, *J* = 6.2 Hz, 1H), 2.04 (s, 3H), 1.93 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) *δ* 170.14, 169.25, 165.17, 165.09, 131.97−127.77 (aromatic C's), 100.47, 73.46, 70.96, 70.74, 69.17, 68.09, 62.05, 23.26, 22.04, 20.67, 20.52. Anal. Calcd for $C_{27}H_{28}O_{10}Br_2$: C, 48.36; H, 4.21. Found: C, 48.38; H, 4.14.

***tert*-Butyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-*β*-D-galactopyranoside (8).** This compound was prepared in 38% yield from 1 mL of dry 2-methyl-2-propanol and 120 mg (0.173 mmol) of the galactopyranosyl bromide **5**, following the general procedure for *β*-galactosylation: TLC R_f = 0.61 (*n*-hexane/EtOAc 7.5:2.5); $[\alpha]^{25}_D$ = +5.5 (*c* 1.27, $CHCl_3$); CI-MS (CH_4) *m*/*z* 685 (0.5, $[M]^-$), 116 (100, BzO); ^{1}H NMR ($CDCl_3$) *δ* 7.97−7.55 (aromatic H's), 5.70 (brd, *J* = 3.4 Hz, 1H), 5.25 (dd, *J* = 7.7, 10.4 Hz, 1H), 5.17 (dd, *J* = 3.4, 10.4 Hz, 1H), 4.69 (d, *J* = 7.7 Hz, 1H), 4.50 (dd, *J* = 7.4, 11.4 Hz, 1H), 4.33 (dd, *J* = 5.8, 11.4 Hz, 1H), 4.13 (t, *J* = 6.9 Hz, 1H), 2.04 (s, 3H), 1.93 (s, 3H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$) *δ* 170.19, 169.18, 165.20, 131.96−127.77 (aromatic C's), 96.12, 76.56, 71.16, 70.82, 69.23, 68.26, 62.45, 28.45, 20.77, 20.56. Anal. Calcd for $C_{28}H_{30}O_{10}Br_2$: C, 49.12; H, 4.42. Found: C, 49.15; H, 4.25.

(1*R*,2*S*,5*R*)-(−)-1-Menthyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-*β*-D-galactopyranoside (9). Galactosylation of (−)-menthol (120 mg, 0.769 mmol, 5 equiv) led to compound **9** (40% yield): TLC R_f = 0.47 (*n*-hexane/EtOAc 8:2); $[\alpha]^{25}_D$ = −21.3 (*c* 1.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 7.94−7.55 (aromatic H's), 5.71 (brd, *J* = 2.6 Hz, 1H), 5.22 (dd, *J* = 7.7, 10.4 Hz, 1H), 5.15 (dd, *J* = 3.4, 10.4 Hz, 1H), 4.60 (d, *J* = 7.7 Hz, 1H), 4.51 (dd, *J* = 6.6, 11.3 Hz, 1H), 4.30 (dd, *J* = 6.5, 11.3 Hz, 1H), 4.09 (t, *J* = 6.6 Hz, 1H), 3.42 (ddd, *J* = 4.2, 10.6, 14.9 Hz, 1H), 2.30 (ddd, *J* = 2.4, 6.9, 9.4 Hz, 1H), 2.07 (s, 3H), 1.97 (m, 1H), 1.94 (s, 3H), 1.64 (brdd, *J* = 2.5, 10.7 Hz, 3H), 1.33 (m, 1H), 1.25 (brt, *J* = 7.1 Hz, 2H), 0.88 (t, *J* = 7.2 Hz,

6H), 0.83 (m, 1H), 0.73 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.21, 169.30, 165.26, 165.13, 132.02−127.90 (aromatic C's), 99.65, 79.54, 71.19, 70.68, 69.29, 68.33, 62.29, 47.42, 41.00, 34.17, 31.46, 25.11, 23.05, 22.23, 20.86, 20.81, 20.58, 15.69. Anal. Calcd for $C_{34}H_{40}O_{10}Br_2$: C, 53.26; H, 5.26. Found: C, 53.42; H, 5.09.

(1*S*,2*R*,5*S*)-(+)-1-Menthyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-*β*-D-galactopyranoside (10). This compound was obtained in 31% yield from 5 equiv of (+)-menthol (120 mg, 0.769 mmol) following the general procedure for *β*-galactosylation: TLC $R_f = 0.57$ (*n*-hexane/EtOAc 8:2); $[\alpha]^{25}_D = +17.6$ (*c* 1.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.96−7.56 (aromatic H's), 5.70 (brd, $J = 2.8$ Hz, 1H), 5.31 (dd, $J = 7.9$, 10.4 Hz, 1H), 5.14 (dd, $J = 3.4$, 10.4 Hz, 1H), 4.62 (d, $J = 7.9$ Hz, 1H), 4.52 (dd, $J = 7.3$, 11.4 Hz, 1H), 4.34 (dd, $J = 5.9$, 11.4 Hz, 1H), 4.15 (t, $J = 6.5$ Hz, 1H), 3.34 (ddd, $J = 4.3$, 10.6, 14.9 Hz, 1H), 2.11 (m, 2H), 2.02 (s, 3H), 1.93 (s, 3H), 1.62 (brd, $J = 9.6$ Hz, 3H), 1.31 (m, 2H), 1.13 (q, $J = 12.2$ Hz, 1H), 0.94 (m, 1H), 0.88 (d, $J = 7.1$ Hz, 3H), 0.80 (d, $J = 6.5$ Hz, 3H), 0.75 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.18, 169.26, 165.24, 165.15, 131.97−127.76 (aromatic C's), 102.62, 83.37, 71.17, 70.76, 69.26, 68.24, 62.43, 48.01, 42.95, 34.09, 31.61, 24.94, 22.74, 22.12, 21.00, 20.59, 20.54, 15.84. Anal. Calcd for $C_{34}H_{40}O_{10}Br_2$: C, 53.26; H, 5.26. Found: C, 53.30; H, 5.61.

Methyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (11). According to the general procedure for anomerization, compound **6** (23 mg, 0.037 mmol) was treated with anhydrous $FeCl_3$ (0.111 mmol) and led to the desired compound **11** (0.022 mmol, 60% yield): TLC $R_f = 0.37$ (*n*-hexane/EtOAc 6:4); $[\alpha]^{25}_D = +54.1$ (*c* 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.93−7.56 (aromatic H's), 5.79 (brd, $J = 2.7$ Hz, 1H), 5.48 (dd, $J = 3.4$, 10.8 Hz, 1H), 5.24 (dd, $J = 3.5$, 10.8 Hz, 1H), 5.11 (d, $J = 3.5$ Hz, 1H), 4.51 (dd, $J = 6.8$, 11.0 Hz, 1H), 4.43 (t, $J = 6.2$ Hz, 1H), 4.29 (dd, $J = 5.8$, 11.0 Hz, 1H), 3.44 (s, 3H), 2.09 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.39, 169.97, 165.23, 165.05, 132.04−127.95 (aromatic C's), 97.29, 69.16, 68.29, 67.59, 66.33, 62.55, 55.62, 20.80, 20.62. Anal. Calcd for $C_{25}H_{24}O_{10}Br_2$: C, 46.73; H, 3.77. Found: C, 46.66; H, 3.89.

Isopropyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (12). Compound **12** (75% yield) was obtained from its *β*-anomer **7** (22 mg, 0.033 mmol) following the general procedure for anomerization (82% conversion): TLC $R_f = 0.31$ (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D = +67.3$ (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.93−7.55 (aromatic H's), 5.79 (brd, $J = 2.5$ Hz, 1H), 5.47 (dd, $J = 3.4$, 10.9 Hz, 1H), 5.33 (d, $J = 3.7$ Hz, 1H), 5.15 (dd, $J = 3.7$, 10.9 Hz, 1H), 4.55 (t, $J = 6.4$ Hz, 1H), 4.48 (dd, $J = 6.9$, 11.1 Hz, 1H), 4.27 (dd, $J = 5.9$, 11.1 Hz, 1H), 3.89 (sep, $J = 6.2$ Hz, 1H), 2.07 (s, 3H), 1.94 (s, 3H), 1.24 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.43, 170.07, 165.25, 165.08, 132.01−128.01 (aromatic C's), 94.84, 71.49, 69.26, 68.54, 67.74, 66.35, 62.69, 23.15, 21.66, 20.72, 20.65. Anal. Calcd for $C_{27}H_{28}O_{10}Br_2$: C, 48.36; H, 4.21. Found: C, 48.38; H, 4.14.

***tert*-Butyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (13).** According to the general procedure for anomerization, compound **8** (22 mg, 0.032 mmol) was treated with anhydrous $FeCl_3$ (15 mg, 0.096 mmol) and led to the desired compound **13** (2.3 mg, 3.3 μmol, 10% yield): TLC $R_f = 0.35$ (*n*-hexane/EtOAc 8:2); $[\alpha]^{25}_D = +70.0$ (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.93−7.55 (aromatic H's), 5.78 (brd, $J = 3.0$ Hz, 1H), 5.51 (d, $J = 3.6$ Hz, 1H), 5.48 (dd, $J = 3.2$, 10.9 Hz, 1H), 5.14 (dd, $J = 3.6$, 10.9 Hz, 1H), 4.63 (t, $J = 6.3$ Hz, 1H), 4.45 (dd, $J = 7.2$, 11.3 Hz, 1H), 4.26 (dd, $J = 6.0$, 11.3 Hz, 1H), 2.06 (s, 3H), 1.94 (s, 3H), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.47, 170.18, 165.29, 165.11, 132.01−128.06 (aromatic C's), 90.78, 75.97, 69.38, 68.65, 67.78, 66.05, 62.77, 28.37, 20.82, 20.69. Anal. Calcd for $C_{28}H_{30}O_{10}Br_2$: C, 49.12; H, 4.42. Found: C, 49.15; H, 4.15.

(1*R*,2*S*,5*R*)-(−)-1-Menthyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (14). Following the general procedure, anomerization of **9** (36 mg, 0.047 mmol) with anhydrous $FeCl_3$ (23 mg, 0.141 mmol) led to compound **14** (0.019 mmol, 89% conversion, 47% yield): TLC $R_f = 0.47$ (*n*-hexane/EtOAc 8:2); $[\alpha]^{25}_D = +41.5$ (*c* 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.92−7.54 (aromatic H's), 5.80 (brd, $J = 2.4$ Hz, 1H), 5.49 (dd, $J = 3.4$, 11.0 Hz, 1H), 5.29 (brd, $J = 3.6$ Hz, 1H), 5.20 (dd, $J = 3.6$, 11.0 Hz, 1H), 4.61 (t, $J = 6.2$ Hz, 1H), 4.44 (dd, $J = 7.1$, 11.4 Hz, 1H), 4.29 (dd, $J = 5.6$, 11.4 Hz, 1H), 3.33 (m, 1H), 2.20 (m, 1H), 2.13 (brd, $J = 11.8$ Hz, 1H), 2.04 (s, 3H), 1.97 (s, 3H), 1.62 (brd, $J = 9.8$ Hz, 2H), 1.59 (m, 2H), 1.28 (q, $J = 11.0$ Hz, 1H), 0.89 (d, $J = 7.3$ Hz, 3H), 0.84 (m, 2H), 0.74 (d, $J = 6.6$ Hz, 3H), 0.71 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.38, 170.15, 165.30, 165.09, 132.02−128.00 (aromatic C's), 98.01, 82.27, 69.48, 68.77, 67.69, 66.64, 62.97, 48.55, 42.72, 34.11, 31.58, 24.87, 23.17, 22.05, 21.05, 20.99, 20.67, 15.78. Anal. Calcd for $C_{34}H_{40}O_{10}Br_2$: C, 53.26; H, 5.26. Found: C, 53.28; H, 5.49.

(1*S*,2*R*,5*S*)-(+)-1-Menthyl 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (15). According to the general procedure for anomerization, compound **10** (10.7 mg, 0.014 mmol) was treated with anhydrous $FeCl_3$ (7 mg, 0.041 mmol) and led to the desired compound **15** (4.7 mg, 6.1 μmol, 70% conversion, 60% yield): TLC $R_f = 0.51$ (*n*-hexane/EtOAc 8:2); $[\alpha]^{25}_D = +71.0$ (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.92−7.53 (aromatic H's), 5.83 (brd, $J = 2.8$ Hz, 1H), 5.47 (dd, $J = 3.3$, 11.0 Hz, 1H), 5.41 (d, $J = 3.8$ Hz, 1H), 5.19 (dd, $J = 3.8$, 11.0 Hz, 1H), 4.52 (t, $J = 6.5$ Hz, 1H), 4.48 (dd, $J = 6.2$, 10.7 Hz, 1H), 4.25 (dd, $J = 6.2$, 10.7 Hz, 1H), 3.46 (ddd, $J = 4.0$, 10.6, 14.5 Hz, 1H), 2.22 (ddd, $J = 2.4$, 6.7, 9.5 Hz, 1H), 2.07 (s, 3H), 1.95 (s, 3H), 1.93 (m, 1H), 1.66 (brd, $J = 9.6$ Hz, 2H), 1.36 (m, 2H), 1.31 (brs, 1H), 0.92 (d, $J = 7.0$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.84 (m, 2H), 0.76 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.46, 170.09, 165.18, 165.08, 132.01−128.03 (aromatic C's), 93.12, 77.25, 69.20, 68.39, 67.59, 66.74, 62.40, 47.69, 40.07, 34.24, 31.31, 25.62, 22.66, 22. 24, 21.10, 20.79, 20.68, 15.24. Anal. Calcd for $C_{34}H_{40}O_{10}Br_2$: C, 53.26; H, 5.26. Found: C, 53.15; H, 5.46.

1,2,3,4,6-Pentakis-*O*-(*p*-bromobenzoyl)-D-galactopyranoside (16). Following the general procedure for *p*-bromobenzoylation, D-(+)-galactose (1.0 g, 5.55 mmol) led to the mixture of anomers of **16** (5.55 g, 5.05 mmol, 91%): TLC $R_f = 0.5$ (*n*-hexane/EtOAc 7:3); ^{1}H NMR (mixture of anomers) ($CDCl_3$) δ 7.95−7.42 (aromatic H's), 6.22 (brd, $J = 8.3$ Hz, 1H), 5.98 (m, 2H), 5.71 (brdd, $J = 3.4$, 10.4 Hz, 1H), 4.63 (brdd, $J = 6.4$, 11.0 Hz, 1H), 4.54 (brt, $J = 6.4$ Hz, 1H), 4.43 (brdd, $J = 6.4$, 11.0 Hz, 1H).

2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranosyl Bromide (17). This reaction was performed from the mixture of anomers of **16** (4.98 g, 4.55 mmol) and following the corresponding general procedure. Purification by flash column chromatography (*n*-hexane/EtOAc 9:1) afforded compound **17** (4.01 g, 4.11 mmol, 90%): TLC $R_f = 0.53$ (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D = +193.6$ (*c* 1.90, $CHCl_3$); FAB-MS *m*/*z* 998 (7, $[M + Na]^+$), 895 (3, $[M - Br]^+$), 711 (3, $[M - Br-BrBz]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.89−7.42 (aromatic H's), 6.92 (d, $J = 4.0$ Hz, 1H), 6.05 (brd, $J = 2.6$ Hz, 1H), 5.98 (dd, $J = 3.3$, 10.4 Hz, 1H), 5.60 (dd, $J = 4.0$, 10.4 Hz, 1H), 4.89 (t, $J = 6.3$ Hz, 1H), 4.61 (dd, $J = 6.7$, 11.6 Hz, 1H), 4.44 (dd, $J = 6.1$, 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 165.10, 164.75, 164.62, 164.55, 132.21−127.22 (aromatic C's), 87.71, 71.55, 69.08, 68.48, 68.19, 61.61. Anal. Calcd for $C_{34}H_{23}O_9Br_5$: C, 41.88; H, 2.38. Found: C, 42.26; H, 2.25.

Methyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-galactopyranoside (18). Following the general procedure for *β*-galactosylation, from 300 mg (0.31 mmol) of **17** and 1 mL of dry MeOH was obtained the desired galactopyranoside **18** (282 mg, 0.30 mmol, 98%): TLC $R_f = 0.35$ (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D = +132.63$ (*c* 3.8, $CHCl_3$); FAB-MS *m*/*z* 948 (13, $[M + Na]^+$), 895 (3, $[M - OMe]^+$), 183 (100, BrBz). ^{1}H NMR ($CDCl_3$) δ: 7.92−7.40 (aromatic H's), 5.92 (d, $J = 3.3$ Hz, 1H), 5.70 (dd, $J = 7.7$, 10.4 Hz, 1H), 5.54 (dd, $J = 3.3$, 10.4 Hz, 1H), 4.73 (d, $J = 7.7$ Hz, 1H), 4.67 (dd, $J = 6.6$, 11.2, 1H), 4.39 (dd, $J = 6.6$, 11.2 Hz, 1H), 4.30 (brt, $J = 6.6$ Hz, 1H), 3.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.28, 164.87, 164.79, 164.62, 132.13−127.45 (aromatic C's), 102.26, 71.81, 71.02, 69.86, 68.23, 61.95, 57.33. Anal. Calcd for $C_{35}H_{26}O_{10}Br_4$: C, 45.39; H, 2.83. Found: C, 45.39; H, 2.79.

(2*R*)-(−)-2-Octyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-*β*-D-galactopyranoside (19). Using the general procedure

for β-galactosylation, from 300 mg (0.31 mmol) of **17** and 417 μL (2.69 mmol) of (−)-octanol was obtained compound **19** (114.2 mg, 0.111 mmol, 36%): TLC R_f = 0.51 (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D$ = +115.9 (*c* 2.85, $CHCl_3$); FAB-MS *m/z* 1047 (9, $[M + Na]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.93−7.40 (aromatic H's), 5.91 (d, *J* = 3.3 Hz, 1H), 5.66 (dd, *J* = 7.9, 10.4 Hz, 1H), 5.53 (dd, *J* = 3.3, 10.4 Hz, 1H), 4.83 (d, *J* = 7.9, 1H), 4.63 (dd, *J* = 6.6, 11.3 Hz, 1H), 4.39 (dd, *J* = 6.6, 11.3 Hz, 1H), 4.28 (brt, *J* = 6.6 Hz, 1H), 3.81 (sep, *J* = 6.2 Hz, 1H), 1.62 (m, 1H), 1.42 (m, 1H), 1.23 (m, 8H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.86 (brt, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.22, 164.93, 164.77, 164.42, 132.05−127.54 (aromatic C's), 99.92, 76.87, 72.00, 70.90, 70.11, 68.36, 62.14, 36.83, 31.76, 29.12, 25.26, 22.55, 19.78, 14.06. Anal. Calcd for $C_{42}H_{40}O_{10}Br_4$: C, 49.25; H, 3.94. Found: C, 49.26; H, 3.97.

(2S)-(+)-2-Octyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-β-D-galactopyranoside (20). This compound was obtained by using (+)-2-octanol (425 μL, 2.69 mmol) and according to the general procedure for β-galactosylation (60% yield): TLC R_f = 0.5 (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D$ = +127.7 (*c* 2.84, $CHCl_3$); FAB-MS *m/z* 1047 (4, $[M + Na]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.93−7.39 (aromatic H's), 5.91 (brd, *J* = 3.0 Hz, 1H), 5.70 (dd, *J* = 7.9, 10.4 Hz, 1H), 5.54 (dd, *J* = 3.3, 10.4 Hz, 1H), 4.82 (d, *J* = 7.9 Hz, 1H), 4.62 (dd, *J* = 6.8, 11.3 Hz, 1H), 4.40 (dd, *J* = 6.5, 11.3 Hz, 1H), 4.29 (brt, *J* = 6.6 Hz, 1H), 3.72 (sep, *J* = 6.2 Hz, 1H), 1.46 (m, 1H), 1.26 (brd, *J* = 6.2 Hz, 5H), 1.18 (brd, *J* = 6.2 Hz, 1H), 1.09 (brt, *J* = 7.3 Hz, 1H), 1.04 (m, 3H), 0.87 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.23, 164.95, 164.78, 164.40, 132.05−127.50 (aromatic C's), 101.89, 79.32, 71.90, 70.92, 70.08, 68.31, 62.15, 36.89, 31.59, 29.25, 25.38, 22.50, 21.80, 14.02. Anal. Calcd for $C_{42}H_{40}O_{10}Br_4$: C, 49.25; H, 3.94. Found: C, 49.34; H, 3.94.

(1*R*,2*S*,5*R*)-(−)-1-Menthyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-β-D-galactopyranoside (21). This compound was prepared in 38% yield from (−)-menthol (242 mg, 1.55 mmol), following the general procedure for β-galactosylation. Chromatography was performed on Sephadex LH-20 ($CHCl_3$/MeOH/*n*-hexane 1:1:2): TLC R_f = 0.53 (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D$ = +97.6 (*c* 2.77, $CHCl_3$); FAB-MS *m/z* 1073 (13, $[M+Na]^+$), 895 (3, $[M-C_{10}H_{20}O]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.91−7.41 (aromatic H's), 5.90 (brd, *J* = 3.1 Hz, 1H), 5.64 (dd, *J* = 7.9, 10.4 Hz, 1H), 5.50 (dd, *J* = 3.3, 10.4 Hz, 1H), 4.85 (d, *J* = 7.9 Hz, 1H), 4.58 (dd, *J* = 6.6, 11.3 Hz, 1H), 4.38 (dd, *J* = 6.4, 11.3 Hz, 1H), 4.25 (t, *J* = 6.5 Hz, 1H), 3.47 (ddd, *J* = 4.2, 10.7, 14.8 Hz, 1H), 2.31 (ddd, *J* = 2.4, 6.9, 9.2 Hz, 1H), 1.92 (brd, *J* = 12.0 Hz, 1H), 1.59 (brs, 3H), 1.24 (m, 3H), 0.92 (m, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.30, 164.97, 164.82, 164.49, 132.11−127.58 (aromatic C's), 99.49, 79.74, 72.18, 70.90, 70.16, 68.50, 62.30, 47.30, 41.13, 34.02, 31.40, 25.19, 23.04, 22.03, 20.81, 15.71. Anal. Calcd for $C_{44}H_{42}O_{10}Br_4$: C, 50.31; H, 4.03. Found: C, 50.37; H, 4.01.

(1*S*,2*R*,5*S*)-(+)-1-Menthyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-β-D-galactopyranoside (22). Following the general procedure for β-galactosylation, 2 equiv of (+)-menthol (242 mg, 1.55 mmol) led to the desired galactopyranoside **22** in 34% yield: TLC R_f = 0.49 (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D$ = +144.3 (*c* 2.8, $CHCl_3$); FAB-MS *m/z* 1072 (4, $[M + Na]^+$), 894 (3, $[M-C_{10}H_{20}O]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.94−7.39 (aromatic H's), 5.90 (brd, *J* = 3.0 Hz, 1H), 5.74 (dd, *J* = 7.9, 10.4 Hz, 1H), 5.54 (dd, *J* = 3.3, 10.4 Hz, 1H), 4.84 (d, *J* = 7.9, 1H), 4.61 (dd, *J* = 7.3, 11.3 Hz, 1H), 4.42 (dd, *J* = 5.9, 11.3 Hz, 1H), 4.31 (brt, *J* = 6.4 Hz, 1H), 3.35 (ddd, *J* = 4.2, 10.5, 14.7 Hz, 1H), 2.20 (brd, *J* = 12.4 Hz, 1H), 1.89 (ddd, *J* = 1.9, 6.8, 11.8 Hz, 1H), 1.58 (m, 2H), 1.26 (brs, 2H), 1.19 (q, *J* = 11.4 Hz, 1H), 0.95 (brt, *J* = 6.8 Hz, 1H), 0.87 (m, 1H), 0.81 (d, *J* = 6.3 Hz, 3H), 0.53 (d, *J* = 7.0 Hz, 3H), 0.40 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.26, 164.96, 164.79, 164.45, 132.06−127.46 (aromatic C's), 102.76, 83.61, 71.91, 70.93, 70.01, 68.39, 62.40, 47.95, 43.03, 34.04, 31.62, 24.75, 22.70, 22.12, 20.66, 15.56. Anal. Calcd for $C_{44}H_{42}O_{10}Br_4$: C, 50.31; H, 4.03. Found: C, 50.32; H, 4.05.

Methyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (23). Following the general procedure, anomerization of **18** (50 mg, 0.054 mmol) with anhydrous $FeCl_3$ (26 mg, 0.162 mmol) led to compound **23** (32 mg, 0.034 mmol, 64% yield): TLC R_f = 0.39 (*n*-hexane/EtOAc 7:3); $[\alpha]^{25}_D$ = +178.1 (*c* 1.16, $CHCl_3$); FAB-MS *m/z* 949 (6, $[M + Na]^+$), 895 (5, $[M - OMe]^+$), 183 (100, BrBz); ^{1}H NMR($CDCl_3$) δ 7.91−7.40 (aromatic H's), 5.97 (d, *J* = 3.3 Hz, 1H), 5.92 (dd, *J* = 3.3, 10.5 Hz, 1H), 5.62 (dd, *J* = 3.5, 10.5 Hz, 1H), 5.28 (d, *J* = 3.5 Hz, 1H), 4.58 (m, 2H), 4.39 (dd, *J* = 9.0, 11.9 Hz, 1H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.28, 165.25, 164.89, 164.71, 132.12−127.82 (aromatic C's), 97.52, 69.35, 69.26, 68.50, 66.55, 62.50, 55.79. Anal. Calcd for $C_{35}H_{26}O_{10}Br_4$: C, 45.39; H, 2.83. Found: C, 45.38; H, 2.96.

(2*R*)-(−)-2-Octyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (24). According to the general procedure for anomerization, compound **19** (48 mg, 0.046 mmol) was treated with anhydrous $FeCl_3$ (23 mg, 0.14 mmol) and led to the desired compound **24** (0.039 mmol, 95% conversion and 88% yield): TLC R_f = 0.53 (*n*-hexane/EtOAc 8:2); $[\alpha]^{25}_D$ = +165.8 (*c* 1.65, $CHCl_3$); FAB-MS *m/z* 1047 (4, $[M + Na]^+$), 894 (4, $[M - C_8H_{17}O]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.91−7.40 (aromatic H's), 5.96 (brs, 1H), 5.93 (dd, *J* = 3.4, 10.3 Hz, 1H), 5.55 (dd, *J* = 3.7, 10.3 Hz, 1H), 5.48 (d, *J* = 3.7 Hz, 1H), 4.71 (t, *J* = 6.4 Hz, 1H), 4.55 (dd, *J* = 7.0, 11.4 Hz, 1H), 4.36 (dd, *J* = 5.9, 11.4 Hz, 1H), 3.70 (sep, *J* = 6.5 Hz, 1H), 1.47 (m, 1H), 1.32 (m, 1H), 1.26 (d, *J* = 6.2 Hz, 4H), 1.07 (m, 5H), 0.90 (m, 2H), 0.77 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.29, 165.26, 164.92, 164.81, 132.11−127.87 (aromatic C's), 96.90, 77.62, 69.64, 69.52, 68.64, 66.67, 62.71, 36.83, 31.66, 29.32, 25.20, 22.57, 21.58, 14.02. Anal. Calcd for $C_{42}H_{40}O_{10}Br_4$: C, 49.25; H, 3.94. Found: C, 49.13; H, 4.04.

(2*S*)-(+)-2-Octyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (25). Compound **25** (0.028 mmol, 77 yield, 95% conversion) was obtained from its β-anomer **20** (39 mg, 0.038 mmol) following the general procedure for anomerization: TLC R_f = 0.67 (*n*-hexane/EtOAc 8:2); $[\alpha]^{25}_D$ = +190.2 (*c* 1.22, $CHCl_3$); FAB-MS *m/z* 1047 (3, $[M + Na]^+$), 894 (4, $[M - C_8H_{17}O]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.91−7.41 (aromatic H's), 5.97 (brd, *J* = 3.0 Hz, 1H), 5.91 (dd, *J* = 3.4, 10.4 Hz, 1H), 5.58 (dd, *J* = 3.7, 10.4 Hz, 1H), 5.48 (d, *J* = 3.7 Hz, 1H), 4.69 (t, *J* = 6.4 Hz, 1H), 4.52 (dd, *J* = 6.9, 11.4 Hz, 1H), 4.38 (dd, *J* = 5.8, 11.4 Hz, 1H), 3.77 (sep, *J* = 6.2 Hz, 1H), 1.60 (m, 1H), 1.45 (m, 1H), 1.28 (m, 8H), 1.02 (d, *J* = 6.1 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.30, 165.22, 164.94, 164.81, 132.11−127.88 (aromatic C's), 94.52, 75.13, 69.51, 69.34, 68.72, 66.94, 62.77, 37.07, 31.79, 29.29, 25.90, 22.63, 19.36, 14.08. Anal. Calcd for $C_{42}H_{40}O_{10}Br_4$: C, 49.25; H, 3.94. Found: C, 49.32; H, 3.93.

(1*R*,2*S*,5*R*)-(−)-1-Menthyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (26). Following the general procedure, anomerization of **21** (30 mg, 0.028 mmol) with anhydrous $FeCl_3$ (14 mg, 0.086 mmol) led to compound **26** (0.015 mmol, 83% conversion, 64% yield): TLC R_f = 0.52 (*n*-hexane/EtOAc 7.5:2.5); $[\alpha]^{25}_D$ = +154.6 (*c* 1.79, $CHCl_3$); FAB-MS *m/z* 1073 (8, $[M + Na]^+$), 895 (3, $[M - C_{10}H_{20}O]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.90−7.40 (aromatic H's), 5.95 (m, 2H), 5.59 (dd, *J* = 3.6, 10.4 Hz, 1H), 5.48 (d, *J* = 3.6 Hz, 1H), 4.74 (t, *J* = 6.3 Hz, 1H), 4.52 (dd, *J* = 7.1, 11.5 Hz, 1H), 4.37 (dd, *J* = 5.6, 11.5 Hz, 1H), 3.34 (ddd, *J* = 6.3, 10.5, 16.8 Hz, 1H), 2.18 (brd, *J* = 12.2 Hz, 1H), 2.10 (ddd, *J* = 2.2, 4.8, 7.0 Hz, 1H), 1.56 (m, 2H), 1.29 (brt, *J* = 11.7 Hz, 2H), 1.11 (q, *J* = 12.2 Hz, 1H), 0.87 (m, 2H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.62 (d, *J* = 7.0 Hz, 3H), 0.37 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.33, 165.26, 164.93, 164.84, 132.12−127.87 (aromatic C's), 98.33, 82.71, 69.82, 69.68, 68.48, 66.84, 62.92, 48.56, 42.81, 34.08, 31.60, 24.72, 22.67, 22.05, 20.84, 13.41. Anal. Calcd for $C_{44}H_{42}O_{10}Br_4$: C, 50.31; H, 4.03. Found: C, 50.31; H, 4.26.

(1*S*,2*R*,5*S*)-(+)-1-Menthyl 2,3,4,6-Tetrakis-*O*-(*p*-bromobenzoyl)-α-D-galactopyranoside (27). This compound (18.3 mg, 0.015 mmol) was obtained from its β-anomer **22** (30 mg, 0.028 mmol) following the general procedure for anomerization (90% conversion and 68% yield): TLC R_f = 0.6 (*n*-hexane/EtOAc 8:2); $[\alpha]^{25}_D$ = +166.5 (*c* 0.52, $CHCl_3$); FAB-MS *m/z* 1073 (5, $[M + Na]^+$), 895 (5, $[M - C_{10}H_{20}O]^+$), 183 (100, BrBz); ^{1}H NMR ($CDCl_3$) δ 7.90−7.41 (aromatic H's), 6.00 (brd, *J* = 2.6 Hz, 1H), 5.92 (dd, *J* = 3.3, 10.6 Hz, 1H), 5.60 (dd, *J* = 3.8,

10.6 Hz, 1H), 5.56 (d, J = 3.8 Hz, 1H), 4.66 (t, J = 6.5 Hz, 1H), 4.55 (dd, J = 6.3, 11.3 Hz, 1H), 4.34 (dd, J = 6.8, 11.3 Hz, 1H), 3.50 (ddd, J = 4.0, 10.6, 14.5 Hz, 1H), 2.26 (ddd, J = 2.4, 6.9, 9.4 Hz, 1H), 1.85 (brd, J = 12.0 Hz, 1H), 1.63 (brt, J = 12.3 Hz, 2H), 1.30 (m, 2H), 0.94 (d, J = 7.0 Hz, 3H), 0.87 (m, 1H), 0.78 (d, J = 7.0 Hz, 3H), 0.71 (d, J = 6.5 Hz, 3H), 0.66 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 165.40, 165.21, 164.93, 164.84, 132.11−127.91 (aromatic C's), 93.56, 77.91, 69.42, 69.30, 68.59, 67.02, 62.41, 47.42, 40.34, 34.09, 31.25, 25.73, 22.67, 21.99, 21.09, 15.32. Anal. Calcd for $C_{44}H_{42}O_{10}Br_4$: C, 50.31; H, 4.03. Found: C, 50.29; H, 4.34.

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Supporting Information Available: Eleven tables containing low-temperature CD data (EtOH), calculated rotameric populations by using the four mentioned sets of equations in CD_3CN and $CDCl_3$, and ^{1}H and ^{13}C NMR data ($CDCl_3$) of compounds **6**−**15** and **18**−**27** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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