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Stereochemical study of the CD spectral differences between anomers of alkyl glucopyranosides

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Abstract

Slightly different chair conformation geometries were demonstrated to be the origin of the CD spectral differences observed in anomers of alkyl glucopyranosides. The study, using methyl glucopyranoside derivatives as model compounds, showed excellent agreement between CD data, ^{1}H NMR data, and semiempirical calculations, and the geometries found explained satisfactorily the higher amplitudes observed for the β-anomers of tetrachromophorically substituted alkyl glucopyranosides. The pairwise interactions involving the chromophore at C2, the 2/3, 2/4 and 2/6, were the most dependent on the anomeric configuration, the 2/4 interaction even showing opposite CD signs for the anomers. In addition, the 2/3 pairwise interaction was revealed to be independent of the structural nature of the aglycon.

1. Introduction

The circular dichroic exciton chirality method,[1] which is based on the coupled oscillator theory,[2] is a powerful tool for determining absolute configurations and conformations of organic molecules.[1] The CD spectral interpretation benefits from the existence of an additivity relation in the amplitudes (*A* values)[3] of exciton-split CD spectra,[4] and by the general validity of the pairwise additivity in exciton coupled systems.[5]

The CD studies performed to prove additivities in multichromophoric systems were carried out by using methyl glycopyranoside derivatives as model compounds. In the study of the additivity of the amplitudes,[4] the observed and calculated *A* values were used independently of the anomeric configuration. However, a constant α-anomeric configuration was used in the study of the general validity of the pairwise additivity in methyl glycopyranoside derivatives,[5,6] as a consequence of the different *A* values observed for some anomers in the former study.

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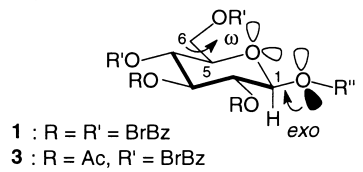
Table 1
CD data for the alkyl 2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-β-D- and α-D-glucopyranosides (compounds type **1** and **2**, respectively) (CH_3CN)[9]

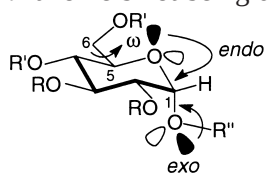
Aglycon (R")	β-Anomer *A* value	α-Anomer *A* value	$A_\beta - A_\alpha$
Methyl	31.3	23.1	10.2
Ethyl	29.1	22.2	6.9
Isopropyl	28.3	21.1	7.2
Cyclohexyl	27.1	16.4	10.7
(−)-(2R)-Bornyl	22.0	17.0	5.0
(+)-(2S)-Bornyl	20.1	15.9	4.2
(−)-(1R)-Menthyl	21.8	12.8	9.0
(+)-(1S)-Menthyl	10.0	27.9	−17.9

The choice of chromophoric glycopyranoside derivatives for the above-mentioned additivity studies was due to the fact that a CD microscale method was under development for identifying the monosaccharide units and the glycosidic linkages of oligosaccharides.[7] While the corresponding procedure to obtain the required monosaccharide derivatives yields methyl β-D-gluco-, β-D-galacto-, or α-D-mannopyranosides, most components of the available CD spectral library have the α-anomeric configuration.[7] Although the differences in the CD curves of anomers are generally small, care must be taken when CD spectra comparison of compounds of different anomeric configurations is performed.

We have recently reported, on the basis of CD and ^{1}H NMR data, that the rotational population of the hydroxymethyl group in alkyl β-D-glucopyranosides depends on the aglycon and its absolute configuration,[8] and that similar but not identical behavior occurs with their α-anomers.[9] For both types of anomers, this rotational dependence has its origin in the different values of the stereoelectronic *exo*-anomeric effect, the *endo*-anomeric effect of the α-anomers not being directly involved.



1 : R = R' = BrBz
3 : R = Ac, R' = BrBz



2 : R = R' = BrBz
4 : R = Ac, R' = BrBz

In these rotational studies it was found that β-anomers of tetrachromophorically substituted alkyl glucopyranosides (type **1** compounds) generally exhibit higher *A* values than the α-anomers (type **2** compounds) (see A_β–A_α in Table 1), these differences being justified by the different rotameric populations of the hydroxymethyl group (P_{gg}, P_{gt} and P_{tg}; Fig. 1).[10]

Unexpectedly, the almost identical *A* values obtained from the CD spectra of the 4,6-bischromophorically substituted glucopyranosides (compound types **3** and **4**, Table 2),[9] where only the pairwise interactions involving the chromophore at the 6 position are present, indicated that the 2/3, 3/4 and/or 2/4 exciton interactions, which were considered to be constant by assuming no ring distortion, are really responsible for the CD spectral differences observed in the tetrachromophorically substituted glucopyranosides, and therefore for the fact that these interactions depend on the anomeric configuration (Fig. 2).

In order to determine the origin of the CD spectral differences between glucopyranosyl anomers, as well as the degree of dependence of the pairwise interactions on the anomeric configuration, the study that follows was performed.

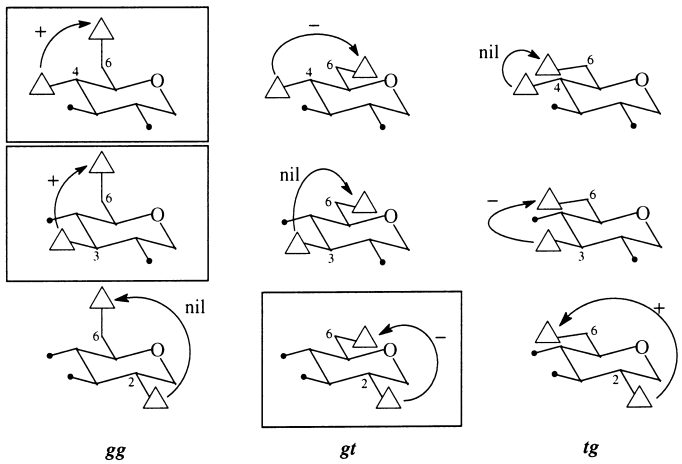


Fig. 1. Pairwise interactions involving the chromophore at C6 for the glucopyranosyl system. Interactions responsible for the CD sign for the 2/6, 3/6 and 4/6 pairwise interactions for both anomers are marked in boxes

Table 2
CD data for the alkyl 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-β-D- and α-D-glucopyranosides (compound types **3** and **4**, respectively) (CH_3CN)[9]

Aglycon	β-Anomers *A* value	α-Anomers *A* value	$A_\beta - A_\alpha$	$\Delta\varepsilon_\beta - \Delta\varepsilon_\alpha$ 251 nm
Methyl	25.0	24.1	0.9	0.1
Ethyl	25.1	24.4	0.7	0.0
Isopropyl	22.5	23.1	–0.6	–0.2
Cyclohexyl	20.4	19.8	0.6	0.3

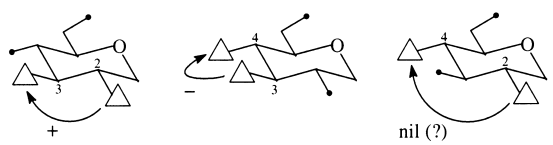
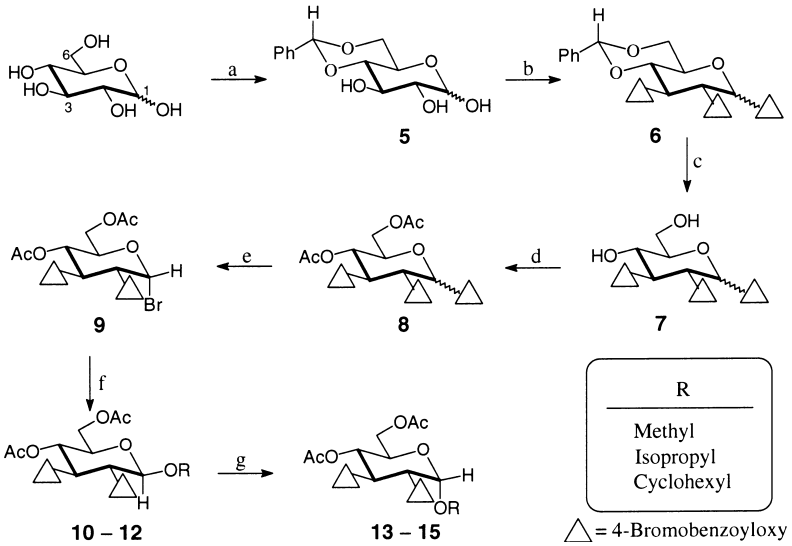


Fig. 2. 2/3, 3/4 and 2/4 pairwise interactions for the glucopyranosyl system

2. Results and discussion

To study the dependence of the 2/3 pairwise interaction on the anomeric configuration and also on the structural nature of the aglycon, anomers of methyl, isopropyl, and cyclohexyl 4,6-bis-*O*-acetyl-2,3-bis-*O*-(*p*-bromobenzoyl)-D-glucopyranosides **10**–**15** were prepared according to Scheme 1. The β-anomers **10**–**12** were obtained in good yields from the glucopyranosyl bromide **9** by using a modified Koenigs–Knorr method.[11] Anomerization of β-anomers by treatment with ferric chloride[12] led to the corresponding α-anomers **13**–**15**.

CD analysis of compounds **10**–**15** revealed similar *A* values of the split CD curves for each set of anomers (Table 3), showing that the 2/3 pairwise interaction is practically independent of the structural nature of the aglycon. In addition, the *A* values obtained for the β-anomers are of a higher magnitude than those of the α-anomers, as can be observed in Fig. 3, indicating that the 2/3 pairwise interaction depends on the anomeric configuration. The proximity of the ester group at C2 to the anomeric carbon can lead for each set of anomers to slightly different geometries in this region and, therefore, those interactions involving the chromophore at C2, the 2/3, 2/4 and 2/6 pairwise interactions, exhibit different magnitudes.



Scheme 1. (a) $PhCH(OCH_3)_2$, *p*-TsOH, DMF, 50°C, vacuum; (b) *p*-BrBzCl, Py, DMAP, 60°C; (c) *p*-TsOH, CH_2Cl_2:MeOH (1:1); (d) Ac_2O/Py; (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

Table 3
CD data of β-anomers **10–12** and α-anomers **13–15** (CH_3CN). Contribution of the 2/3 pairwise interaction

Compound	Aglycon	Δε at 253/235 nm	*A* value	$A_\beta - A_\alpha$
10	Methyl	51.7/−18.9	70.6	
11	Isopropyl	52.2/−19.1	71.3	
12	Cyclohexyl	51.4/−19.7	71.1	
13	Methyl	47.5/−19.4	66.9	3.7
14	Isopropyl	49.7/−19.2	68.9	2.4
15	Cyclohexyl	46.7/−19.3	66.0	5.1

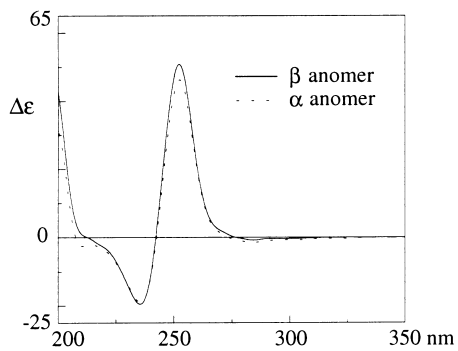
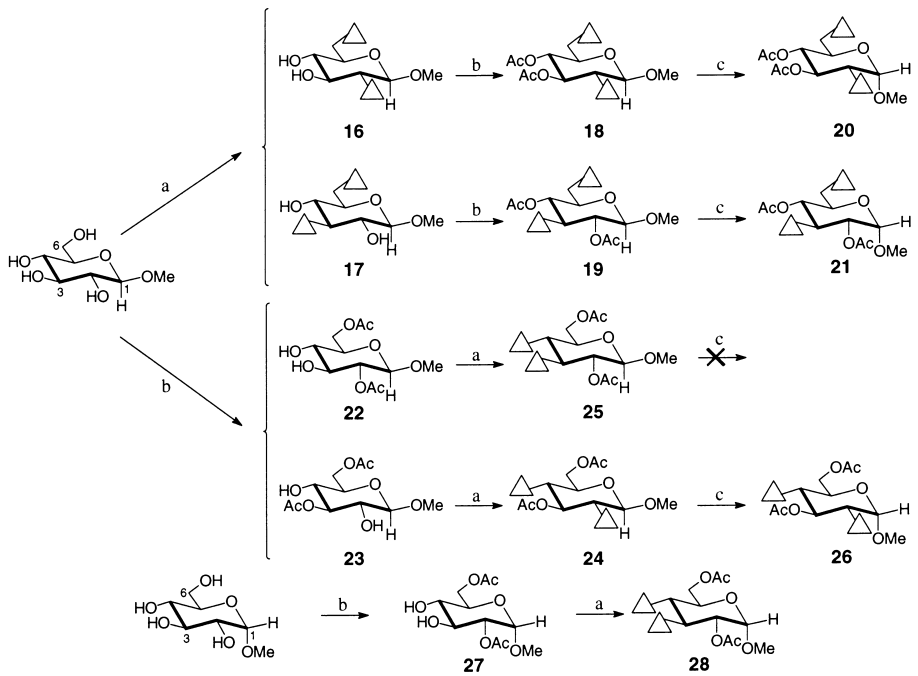


Fig. 3. CD spectra of the β- and α-anomers of cyclohexyl D-glucopyranoside derivatives **12** and **15**, respectively

As can be observed in Table 3, the A_β–A_α values of the 2/3 pairwise interaction justify only partially the *A* value differences observed in the tetrachromophoric compounds (Table 1). Therefore, the spectral differences observed for the anomers of tetrachromophoric compounds must also come from the other pairwise interactions involved in the glucopyranosyl system. Thus, all the remaining methyl bis-*O*-acetyl-

bis-*O*-(*p*-bromobenzoyl)-α- and β-D-glucopyranosides having one of the pairwise interactions present in the tetrachromophoric system were prepared (Scheme 2). The combination of partial acetylation and 4-bromobenzoylation of methyl β-D-glucopyranoside yielded the β-anomers **18**, **19**, **24** and **25**. The α-anomers **20**, **21** and **26** were obtained by anomerization of the corresponding β-anomers by means of anhydrous ferric chloride.[12] Compound **28** could not be obtained by this procedure, therefore it was prepared directly from the methyl α-D-glucopyranoside. Table 4 shows the *A* values obtained from exciton-coupled CD curves of these methyl α-D- and β-D-glucopyranoside derivatives, which represent the remainder of the pairwise interactions present in methyl 2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-β-D- and α-D-glucopyranoside (**1** and **2**, respectively). As can be observed, the higher differences in amplitude ($A_\beta - A_\alpha$) correspond to the 2/3, 2/4, 2/6 and 3/4 pairwise interactions.



Scheme 2. (a) *p*-BrBzCl, Py, DMAP, 60°C; (b) Ac_2O/Py; (c) anhydrous $FeCl_3$, dry CH_2Cl_2

The calculated *A* values for compounds **1** and **2** (R′′=methyl) were obtained by summation of their corresponding pairwise interactions and compared with the observed ones. An acceptable difference of 2.9 between calculated and observed values was obtained for the β-anomer **1**, while a large difference of 5.1 was obtained for the α-anomer **2**.

In order to explain these spectral differences, a semiempirical calculation (MOPAC)[13] was carried out using the simpler model compounds, methyl tetrakis-*O*-acetyl-α- and β-D-glucopyranosides, in their more stable *gauche–gauche* (*gg*) rotamer. Table 5 shows the values obtained for the dihedral angles involved in each pairwise interaction of the tetrachromophoric system.[14a]

CD and dihedral angle data comparison (Tables 4 and 5) reveals a quite good agreement. The signs of all split CD curves correspond with the signs of their corresponding dihedral angles, except for those compounds representing the 2/6 pairwise interaction, compounds **18** and **20**, whose signs come mainly from the negative contribution of the second more populated rotamer (*gt*), since the contribution of the most stable rotamer (*gg*) is practically nil as a consequence of its dihedral angle being close to 180° (see Fig. 1). In addition, it is quite satisfactory to observe that the small positive and negative dihedral

Table 4
A values of all pairwise interactions present in the methyl glucopyranosyl system

	β-Anomers		α-Anomers		
Interaction	Compound	*A* value	Compound	*A* value	$A_\beta - A_\alpha$
2/3	**10**	70.6	**13**	66.9	3.7
2/4	**24**	0.9	**26**	−9.6	10.5
2/6	**18**	−9.8	**20**	−7.5	−2.3
3/4	**25**	−66.0	**28**	−60.3 (−67.9)[a]	−5.7 (+1.9)
3/6	**19**	13.5	**21**	14.6	−1.1
4/6	**3**	25.0	**4**	24.1	0.9
Calc. (2/3/4/6)		34.2		28.2 (20.6)[b]	
Obs. (2/3/4/6)	**1**	31.3	**2**	23.1	
Difference		2.9		5.1 (−2.5)[b]	

[a] Mean *A* value for the 3/4 pairwise interaction (from Table 6); [b] Using the mean *A* value of the 3/4 interaction.

Table 5
Dihedral angles obtained from semiempirical calculations, MOPAC (AM1)

Interaction	Dihedral angle	β-Anomer	α-Anomer
2/3	O2-C2-C3-O3	82.4	73.7
2/4	O2-C2-C4-O4	3.1	−4.6
2/6 (*gg*)	O2-C2-C6-O6 (*gg*)	179.5	175.9
3/4	O3-C3-C4-O4	−80.1	−76.9
3/6 (*gg*)	O3-C3-C6-O6 (*gg*)	32.5	36.3
4/6 (*gg*)	O4-C4-C6-O6 (*gg*)	113.5	113.1

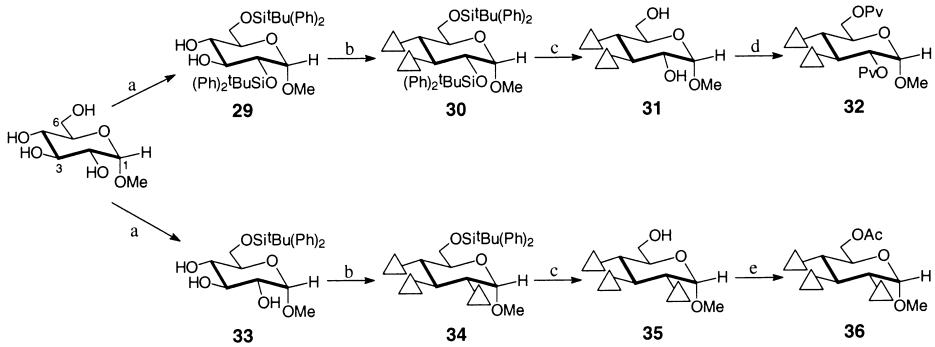
angles obtained for the 2/4 pairwise interaction are in excellent agreement with the positive and negative *A* values observed for the β- and α-anomers, respectively.[15]

An excellent correlation between the magnitude of the *A* values and the dihedral angle values cannot be expected since different compounds are being compared. Thus, the higher *A* values obtained for the β-anomers **10** and **25** compared with the α-anomers **13** and **28**, respectively, do not agree with the dihedral angle values obtained, since theoretically the closer the dihedral angle is to 70°, the higher the amplitude.[14b]

On the basis of the above comparisons, the *A* value obtained from compound **28** does not seem appropriate to represent the 3/4 pairwise interaction in the α-anomers. In order to have a more accurate *A* value for this pairwise interaction, other methyl α-D-glucopyranosides were prepared (Scheme 3).

The observed *A* values from the split CD curves of compounds **31**, **32**, **35** and **36** are shown in Table 6, as well as the corresponding *A* value from compound **28**. The contribution of the 3/4 pairwise interaction to the observed *A* values in compounds **35** and **36** was calculated by subtracting from these *A* values those from the 2/3 and 2/4 pairwise interactions. The resulting mean *A* value from these five α-anomers representing the 3/4 pairwise interaction was −67.9. This value is of a slightly higher magnitude than that of its β-anomer **25** (*A* value=−66) and is therefore now in agreement with the dihedral angle values obtained from the semiempirical calculations. By using this more accurate mean *A* value, instead of −60.3 from compound **28**, in the calculation of the *A* value of the α-anomer **2**, a value of 20.6 was obtained (Table 4), as well as an acceptable difference of −2.5 between the calculated (20.6) and the observed (23.1) *A* values for the α-anomer.

The vicinal ^{1}H NMR coupling constants of the two sets of anomers were analyzed. Data comparison

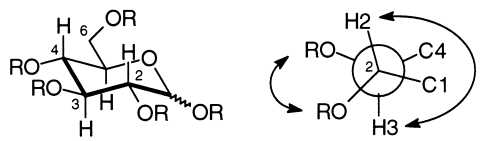


Scheme 3. (a) $^{t}Bu(Ph)_2SiCl$, imidazole, DMF; (b) *p*-BrBzCl, Py, DMAP, 60°C; (c) CH_3COCl, dry MeOH; (d) PvCl, Et_3N, DMAP, CH_2Cl_2; (e) Ac_2O/Py

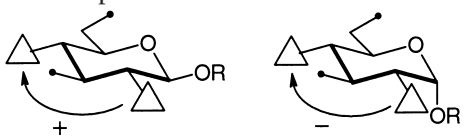
Table 6
Observed and calculated *A* values for the 3/4 pairwise interaction in methyl α-D-glucopyranosides

Compound	Obs. *A* value	Calc. *A* value
28	−60.3	−60.3
31	−68.4	−68.4
32	−70.6	−70.6
35	−12.9	−70.2
36	−12.6	−69.9
Mean		−67.9

showed slightly different coupling constants between the ring *trans* di-axial protons, the α-anomers having increased by 0.1–0.3 Hz their coupling constants with respect to the β-anomers. This result points to higher dihedral angles between the *trans* di-axial hydrogens in the α-anomers and, therefore, to smaller dihedral angles between their vicinal ester groups, in total agreement with the data from semiempirical calculations, and in acceptable concordance with CD data.



The general agreement between CD data, ^1H NMR coupling constants, and the dihedral angles from the semiempirical calculations, allows us to conclude that anomers of alkyl glucopyranosides possess slightly different geometries of the $^4C_1$ chair conformation, especially in the anomeric region, the more stable α-anomer being less distorted from the ideal chair conformation. These geometries explain satisfactorily the fact that β-anomers of tetrachromophorically substituted alkyl glucopyranosides exhibit higher amplitudes than their α-anomers, the main differences coming from the interactions involving the chromophore at C2, the 2/3, 2/4 and 2/6 pairwise interactions.



This dependence on the anomeric configuration, although to a smaller degree, resembles that of the anomers of methyl 2-(*N*-acetyl-*p*-bromobenzamido)-2-deoxy-D-galactopyranosides, where dramatic CD spectral differences were observed for the anomers, as a consequence of different conformations of the 2-NAcBz group.[16] In addition, it can be concluded for the glucopyranosyl system that:

(i) the sign of the 2/4 pairwise interaction changes depending on the anomeric configuration: a positive sign for the β-anomers and a negative sign for the α-anomers; and
(ii) that the 2/3 pairwise interaction shows higher amplitudes for the β-anomers (a mean of 3.7 units of Δε) and that this interaction is independent of the structural nature of the aglycon.

3. Experimental

3.1. General

^{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 ($CDCl_3$) 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 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 from the UV spectra, using the experimentally determined ε values at 245 nm: bis(*p*-bromobenzoate) ε 38,200; and tetrakis(*p*-bromobenzoate) ε 76,400.[4]

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 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. The prepared compounds were characterized on the basis of their one- (^{1}H and ^{13}C) and two-dimensional (COSY and HMQC) NMR spectra, as well as by UV and CD spectroscopy.

3.2. General procedures

The general procedure for *p*-bromobenzoylation, for the preparation of glucopyranosyl bromides, and for β-glucosylation are well described by Morales et al.,[8] as well as the preparation and spectroscopic data of compounds **5**–**7**. The general procedure used for anomerization is well described in the literature.[12c]

3.3. 4,6-*Bis*-O-*acetyl*-1,2,3-*tris*-O-(p-*bromobenzoyl*)-D-*glucopyranoside* ***8***

Acetylation of **7** (1.45 g, 1.99 mmol) led to compound **8** (1.37 g, 1.69 mmol, 85%) as a 3:7 mixture of α- and β-anomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98–7.27 (m, 12H), 6.75 (d, J=3.7 Hz, H-1α), 6.12 (d, J=7.7 Hz, H-1β), 6.01 (t, J=9.9 Hz), 5.72–5.69 (m), 5.55–5.39 (m), 4.45–4.30 (m), 4.25–4.06 (m), 2.13 (s), 2.12 (s), 1.97 (s), 1.96 (s).

3.4. 4,6-*Bis*-O-*acetyl*-2,3-*bis*-O-(p-*bromobenzoyl*)-α-D-*glucopyranosyl bromide* ***9***

This reaction was performed according to the general procedure for preparation of glucopyranosyl bromides, starting from **8** (980 mg, 1.205 mmol) to obtain compound **9** (707 mg, 1.02 mmol, 85%): EQ $[\alpha]_D^{25}$ +204.9 (c 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.82–7.53 (aromatic-Hs, 8H), 6.75 (t, J=4.0 Hz, H-1), 5.97 (t, J=9.9 Hz, H-3), 5.43 (t, J=9.9 Hz, H-4), 5.20 (dd, J=4.0 & 9.9 Hz, H-2), 4.41 (m, H-5 &

H-6_{proR}), 4.20 (d, J=10.6 Hz, H-6_{proS}), 2.13 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.48 (s), 169.28 (s), 164.83 (s), 164.47 (s), 131.99–127.14 (aromatic-Cs), 86.48 (d, C-1), 72.43 (d, C-5), 71.33 (d, C-2), 71.10 (d, C-3), 66.68 (d, C-4), 60.91 (t, C-6), 20.68 (q), 20.46 (q).

*3.5. Methyl 4,6-bis-*O*-acetyl-2,3-bis-*O*-(*p*-bromobenzoyl)-β-*D*-glucopyranoside **10***

Using 1 mL of dry MeOH, glucosylation of **9** (150 mg, 0.216 mmol) led to **10** (127.5 mg, 0.198 mmol, 92%): $[\alpha]_D^{25}$ +132.43 (c 3.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.78–7.50 (aromatic Hs, 8H), 5.60 (t, J=9.7 Hz, H-3), 5.36 (dd, J=7.8 & 9.7 Hz, H-2), 5.32 (t, J=9.7 Hz, H-4), 4.63 (d, J=7.8 Hz, H-1), 4.35 (dd, J=4.6 & 12.3 Hz, H-6_{proR}), 4.22 (dd, J=2.3 & 12.3 Hz, H-6_{proS}), 3.85 (ddd, J=2.3, 4.6 & 9.7 Hz, H-5), 3.52 (s, 3H), 2.12 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.68 (s), 169.33 (s), 165.09 (s), 164.38 (s), 131.88–127.53 (aromatic Cs), 101.78 (d, C-1), 73.43 (d), 71.97 (d), 71.87 (d), 68.26 (d), 61.87 (t, C-6), 57.17 (q), 20.74 (q), 20.50 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} (Δε) 253 (51.7), 242 (0.0), 236 nm (−18.9).

*3.6. Isopropyl 4,6-bis-*O*-acetyl-2,3-bis-*O*-(*p*-bromobenzoyl)-β-*D*-glucopyranoside **11***

Using 150 mg (0.216 mmol) of **9** and 1 mL of ^{i}PrOH, compound **11** was obtained in 70% yield (101 mg, 0.151 mmol): $[\alpha]_D^{25}$ +135.4 (c 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.78–7.51 (aromatic Hs, 8H), 5.58 (t, J=9.6 Hz, H-3), 5.30 (H-2 & H-4), 4.76 (d, J=8.0 Hz, H-1), 4.32 (dd, J=4.9 & 12.2 Hz, H-6_{proR}), 4.19 (dd, J=2.4 & 12.2 Hz, H-6_{proS}), 3.94 (sep, J=9.2 Hz, H-1′), 3.83 (ddd, J=2.4, 4.9 & 9.6 Hz, H-5), 2.10 (s, 3H), 1.93 (s, 3H), 1.21 (d, J=6.2 Hz, 3H), 1.04 (d, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.68 (s), 169.34 (s), 165.11 (s), 164.24 (s), 131.89–127.63 (aromatic Cs), 99.69 (d, C-1), 73.56 (d), 73.14 (d), 72.12 (d), 71.84 (d), 68.47 (d), 62.11 (t, C-6), 23.16 (q), 21.91 (q), 20.74 (q), 20.51 (q); UV (CH_3CN) λ_{max} 244 nm; CD (CH_3CN) λ_{ext} (Δε) 252 (52.2), 242 (0.0), 236 nm (−19.1).

*3.7. Cyclohexyl 4,6-bis-*O*-acetyl-2,3-bis-*O*-(p-bromobenzoyl)-β-*D*-glucopyranoside **12***

Following the general procedure for glucosylation, and using 1 mL of cyclohexanol, compound **9** (150 mg, 0.216 mmol) was transformed into compound **12** (123.1 mg, 0.173 mmol, 80%): $[\alpha]_D^{25}$ +125.7 (c 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.78–7.51 (aromatic Hs, 8H), 5.58 (t, J=9.6 Hz, H-3), 5.34 (dd, J=7.9 & 9.6 Hz, H-2), 5.30 (t, J=9.6 Hz, H-4), 4.79 (d, J=7.9 Hz, H-1), 4.33 (dd, J=4.8 & 12.2 Hz, H-6_{proR}), 4.19 (dd, J=2.3 & 12.2 Hz, H-6_{proS}), 3.83 (ddd, J=2.3, 4.8 & 9.6 Hz, H-5), 3.65 (m, H-1′), 2.11 (s, 3H), 1.93 (s, 3H), 1.84 (m, 1H), 1.68 (m, 2H), 1.57 (m, 1H), 1.43 (m, 2H), 1.21 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.69 (s), 169.34 (s), 165.12 (s), 164.24 (s), 131.86–127.65 (aromatic Cs), 99.42 (d, C-1), 78.12 (d), 73.58 (d, C-3), 72.12 (d, C-2), 71.79 (d, C-5), 68.49 (d, C-4), 62.09 (t, C-6), 33.12 (t), 31.48 (t), 25.33 (t), 23.61 (t), 23.43 (t), 20.75 (q), 20.52 (q); UV (CH_3CN) λ_{max} 244 nm; CD (CH_3CN) λ_{ext} (Δε) 252 (51.4), 242 (0.0), 236 nm (−19.7).

*3.8. Methyl 4,6-bis-*O*-acetyl-2,3-bis-*O*-(p-bromobenzoyl)-α-*D*-glucopyranoside **13***

Using the general procedure for anomerization, compound **10** (50 mg, 0.077 mmol) was converted in 89% into compound **13** (30.6 mg, 0.047 mmol, 69% yield): $[\alpha]_D^{25}$ +181.25 (c 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.80–7.51 (aromatic Hs, 8H), 5.89 (t, J=9.7 Hz, H-3), 5.32 (t, J=9.7 Hz, H-4), 5.17 (dd, J=3.6 & 9.7 Hz, H-2), 5.15 (d, J=3.6 Hz, H-1), 4.33 (dd, J=4.6 & 12.3 Hz, H-6_{proR}), 4.17 (dd, J=2.2 & 12.3 Hz, H-6_{proS}), 4.11 (ddd, J=2.2, 4.6 & 9.7 Hz, H-5), 3.44 (s, 3H), 2.13 (s, 3H), 1.95 (s, 3H); ^{13}C NMR

($CDCl_3$) δ 170.65 (s), 169.46 (s), 165.04 (s), 164.99 (s), 131.86–127.78 (aromatic Cs), 96.92 (d, C-1), 71.92 (d, C-2), 70.90 (d, C-3), 68.13 (d, C-4), 67.36 (d, C-5), 61.87 (t, C-6), 55.62 (q), 20.73 (q), 20.52 (q); UV (CH_3CN) λ_{max} 244 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 253 (47.5), 243 (0.0), 236 nm (−19.4).

*3.9. Isopropyl 4,6-bis-*O*-acetyl-2,3-bis-*O*-(*p*-bromobenzoyl)-α-*D*-glucopyranoside **14***

Compound **11** (36 mg, 0.054 mmol) was anomerized to compound **14** (30.5 mg, 0.046 mmol, 85%): $[\alpha]_D^{25}$ +196.55 (c 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.81–7.51 (aromatic Hs, 8H), 5.88 (t, J=9.8 Hz, H-3), 5.35 (d, J=3.8 Hz, H-1), 5.30 (t, J=9.8 Hz, H-4), 5.13 (dd, J=3.8 & 9.8 Hz, H-2), 4.32 (dd, J=4.6 & 12.1 Hz, H-6_{proR}), 4.23 (ddd, J=2.2, 4.6 & 9.8 Hz, H-5), 4.15 (dd, J=2.2 & 12.1 Hz, H-6_{proS}), 3.88 (sep, J=6.2 Hz, H-1′), 2.12 (s, 3H), 1.95 (s, 3H), 1.26 (d, J=6.2 Hz, 3H), 1.06 (d, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.68 (s), 169.51 (s), 165.09 (s), 164.99 (s), 131.88–127.90 (aromatic Cs), 94.66 (d, C-1), 72.06 (d), 71.97 (d), 71.11 (d), 68.32 (d), 67.45 (d), 62.00 (t, C-6), 23.14 (q), 21.80 (q), 20.72 (q), 20.55 (q); UV (CH_3CN) λ_{max} 244 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 253 (49.7), 243 (0.0), 235 nm (−19.7).

*3.10. Cyclohexyl 4,6-bis-*O*-acetyl-2,3-bis-*O*-(*p*-bromobenzoyl)-α-*D*-glucopyranoside **15***

Compound **12** (25 mg, 0.035 mmol) was anomerized to compound **15** (16 mg, 0.022 mmol, 64%): $[\alpha]_D^{25}$ +188.68 (c 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.81–7.52 (aromatic Hs, 8H), 5.90 (t, J=9.8 Hz, H-3), 5.39 (d, J=3.8 Hz, H-1), 5.30 (t, J=9.8 Hz, H-4), 5.13 (dd, J=3.8 & 9.8 Hz, H-2), 4.31 (dd, J=4.6 & 12.0 Hz, H-6_{proR}), 4.25 (ddd, J=1.9, 4.6 & 9.8 Hz, H-5), 4.16 (dd, J=1.9 & 12.0 Hz, H-6_{proS}), 3.58 (m, H-1′), 2.12 (s, 3H), 1.95 (s, 3H), 1.88 (m, 1H), 1.75 (m, 1H), 1.63 (m, 2H), 1.48 (m, 2H), 1.25 (brt, J=7.1 Hz, 2H), 1.16 (brt, J=9.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 170.68 (s), 169.53 (s), 165.10 (s), 164.99 (s), 131.85–127.92 (aromatic Cs), 94.51 (d, C-1), 76.84 (d), 72.03 (d), 71.17 (d), 68.34 (d), 67.47 (d), 62.00 (t, C-6), 33.25 (t), 31.48 (t), 25.38 (t), 23.88 (t), 23.51 (t), 20.73 (q), 20.56 (q). UV (CH_3CN) λ_{max} 244 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 253 (46.7), 243 (0.0), 236 nm (−19.3).

*3.11. Methyl 2,6-bis-*O*-(*p*-bromobenzoyl)-β-*D*-glucopyranoside **16** and methyl 3,6-bis-*O*-(*p*-bromobenzoyl)-β-*D*-glucopyranoside **17***

Methyl β-D-glucopyranoside (200 mg, 1.03 mmol) was partially *p*-bromobenzoylated by using 452 mg (2.06 mmol) of *p*-BrBzCl. After chromatography, compounds **16** (91 mg, 0.16 mmol) and **17** (90 mg, 0.16 mmol) were obtained in 31% yield.

Compound **16**: $[\alpha]_D^{25}$ −7.0 (c 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.94–7.59 (aromatic Hs, 8H), 5.01 (dd, J=7.8 & 9.6 Hz, H-2), 4.77 (dd, J=4.0 & 12.1 Hz, H-6_{proR}), 4.59 (dd, J=1.6 & 12.1 Hz, H-6_{proS}), 4.54 (d, J=7.8 Hz, H-1), 3.81 (t, J=9.6 Hz, H-3), 3.65 (m, H-5), 3.60 (t, J=9.6 Hz, H-4), 3.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.53 (s), 165.70 (s), 131.85–128.39 (aromatic Cs), 101.79 (d, C-1), 75.19 (d, C-3), 74.57 (d, C-2), 73.91 (d, C-5*), 70.66 (d, C-4*), 63.66 (t, C-6), 57.00 (q).

Compound **17**: $[\alpha]_D^{25}$ +25.71 (c 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.93–7.57 (aromatic Hs, 8H), 5.20 (brt, J=9.0 Hz, H-3), 4.70 (brd, J=11.9 Hz, H-6), 4.62 (d, J=12.0 Hz, H-6′), 4.36 (d, J=7.7 Hz, H-1), 3.71 (brs, H-4 & H-5), 3.64 (brt, J=9.0 Hz, H-2), 3.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.97 (s), 166.26 (s), 131.81–128.20 (aromatic Cs), 103.86 (d, C-1), 78.42 (d), 74.39 (d), 72.20 (d), 69.34 (d), 63.80 (t, C-6), 57.42 (q).

3.12. *Methyl 3,4-bis-*O*-acetyl-2,6-bis-*O*-(*p*-bromobenzoyl)-β-*D*-glucopyranoside* **18**

Acetylation of **16** (55.8 mg, 0.099 mmol) led to compound **18** (49 mg, 0.076 mmol, 77%): $[\alpha]_D^{25}$ +46.1 (c 1.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.92–7.59 (aromatic Hs, 8H), 5.42 (t, J=9.5 Hz, H-3), 5.27 (t, J=9.5 Hz, H-4), 5.24 (dd, J=7.8 & 9.5 Hz, H-2), 4.58 (d, J=7.8 Hz, H-1), 4.55 (dd, J=2.5 & 12.3 Hz, H-6$_{proS}$), 4.42 (dd, J=4.7 & 12.3 Hz, H-6$_{proR}$), 3.90 (ddd, J=2.5, 4.7 & 9.5 Hz, H-5), 3.48 (s, 3H), 2.03 (s, 3H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.15 (s), 169.36 (s), 165.44 (s), 164.36 (s), 131.85–128.07 (aromatic Cs), 101.77 (d, C-1), 72.53 (d), 71.92 (2×d), 68.63 (d), 62.70 (t, C-6), 57.07 (q), 20.58 (q), 20.49 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} (Δε) 253 (−3.5), 246 (0.0), 237 nm (6.3).

3.13. *Methyl 2,4-bis-*O*-acetyl-3,6-bis-*O*-(*p*-bromobenzoyl)-β-*D*-glucopyranoside* **19**

Compound **17** (89.6 mg, 0.16 mmol) was acetylated to give compound **19** (95.5 mg, 0.148 mmol, 92%): $[\alpha]_D^{25}$ +33.7 (c 2.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.91–7.55 (aromatic Hs, 2H), 5.46 (t, J=9.6 Hz, H-3), 5.32 (t, J=9.6 Hz, H-4), 5.15 (dd, J=7.9 & 9.6 Hz, H-2), 4.54 (d, J=7.9 Hz, H-1), 4.53 (dd, J=2.4 & 12.3 Hz, H-6$_{proS}$), 4.42 (dd, J=4.7 & 12.3 Hz, H-6$_{proR}$), 3.91 (ddd, J=2.4, 4.7 & 9.6 Hz, H-5), 3.51 (s, 3H), 1.95 (s, 3H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.34 (s), 169.24 (s), 165.37 (s), 165.08 (s), 131.92–127.59 (aromatic Cs), 101.60 (d, C-1), 73.62 (d), 71.74 (d), 71.11 (d), 68.45 (d), 62.62 (t, C-6), 57.00 (q), 20.56 (q), 20.45 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} (Δε) 250 (11.0), 239 (0.0), 232 nm (−2.5).

3.14. *Methyl 3,4-bis-*O*-acetyl-2,6-bis-*O*-(*p*-bromobenzoyl)-α-*D*-glucopyranoside* **20**

Anomerization of 18 (26 mg, 0.040 mmol) led to compound **20** (19 mg, 0.029 mmol, 73%): $[\alpha]_D^{25}$ +89.8 (c 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.93–7.60 (aromatic Hs, 8H), 5.70 (t, J=9.8 Hz, H-3), 5.22 (t, J=9.8 Hz, H-4), 5.11 (d, J=3.4 Hz, H-1), 5.05 (dd, J=3.4 & 9.8 Hz, H-2), 4.50 (brd, J=11.9 Hz, H-6$_{proS}$), 4.40 (dd, J=4.7 & 12.2 Hz, H-6$_{proR}$), 4.16 (brd, J=9.8 Hz, H-5), 3.41 (s, 3H), 2.05 (s, 3H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.12 (s), 169.53 (s), 165.46 (s), 164.98 (s), 131.95–127.88 (aromatic Cs), 96.74 (d, C-1), 71.86 (d), 69.95 (d), 68.58 (d), 67.29 (d), 62.72 (t, C-6), 55.56 (q), 20.64 (2×q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} (Δε) 254 (−3.4), 246 (0.0), 237 nm (4.1).

3.15. *Methyl 2,4-bis-*O*-acetyl-3,6-bis-*O*-(*p*-bromobenzoyl)-α-*D*-glucopyranoside* **21**

Compound **19** (35 mg, 0.054 mmol) was anomerized to compound **21** (18 mg, 0.028 mmol, 52%): $[\alpha]_D^{25}$ +109.1 (c 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.93–7.57 (aromatic Hs, 8H), 5.74 (t, J=9.8 Hz, H-3), 5.30 (t, J=9.8 Hz, H-4), 5.08 (dd, J=3.6 & 9.8 Hz, H-2), 4.99 (d, J=3.6 Hz, H-1), 4.51 (dd, J=2.3 & 12.3 Hz, H-6$_{proS}$), 4.41 (dd, J=4.7 & 12.3 Hz, H-6$_{proR}$), 4.19 (ddd, J=2.3, 4.7 & 9.8 Hz, H-5), 3.46 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.16 (s), 169.45 (s), 165.46 (s), 164.96 (s), 131.93–127.94 (aromatic Cs), 96.99 (d, C-1), 71.02 (d), 70.72 (d), 68.57 (d), 67.37 (d), 62.67 (t, C-6), 55.56 (q), 20.65 (q), 20.53 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} (Δε) 250 (11.8), 240 (0.0), 232 nm (−2.8).

3.16. Methyl 2,6-bis-O-acetyl-β-D-glucopyranoside **22** and methyl 3,6-bis-O-acetyl-β-D-glucopyranoside **23**

Methyl β-D-glucopyranoside (300 mg, 1.54 mmol) was partially acetylated using 2 equiv. of acetic anhydride (290 μL, 3.08 mmol) to give compounds **22** (30 mg) and **23** (60 mg), the former being directly *p*-bromobenzoylated. Compound **23**: $[\alpha]_D^{25}$ −17.9 (c 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.92 (brt, J=9.4 Hz, H-3), 4.42 (dd, J=3.6 & 11.9 Hz, H-6$_{proR}$), 4.33 (brd, J=11.9 Hz, H-6$_{proS}$), 4.26 (d, J=7.8 Hz, H-1), 3.55 (s, 3H), 3.51 (brd, J=5.5 Hz, H-4 & H-5), 3.46 (dd, J=7.8 & 9.4 Hz, H-2), 2.15 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.35 (s), 171.62 (s), 103.74 (d, C-1), 77.46 (d, C-3), 74.10 (d, C-4*), 72.04 (d, C-2), 68.95 (d, C-5*), 63.07 (t, C-6), 57.32 (q), 21.01 (q), 20.83 (q).

3.17. Methyl 3,6-bis-O-acetyl-2,4-bis-O-(p-bromobenzoyl)-β-D-glucopyranoside **24**

Compound **23** (42 mg, 0.151 mmol) was *p*-bromobenzoylated to compound **24** (75.3 mg, 0.12 mmol, 78%): $[\alpha]_D^{25}$ +1.25 (c 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86–7.58 (aromatic Hs, 8H), 5.57 (t, J=9.6 Hz, H-3), 5.39 (t, J=9.6 Hz, H-4), 5.29 (brt, J=9.2, H-2), 4.62 (d, J=7.9 Hz, H-1), 4.29 (dd, J=4.8 & 12.2 Hz, H-6$_{proR}$), 4.23 (brd, J=9.7 Hz, H-6$_{proS}$), 3.91 (m, H-5), 3.52 (s, 3H), 2.04 (s, 3H) 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.57 (s), 170.10 (s), 164.44 (s), 164.35 (s), 132.01–127.63 (aromatic Cs), 101.83 (d, C-1), 72.27 (d, C-5*), 71.96 (d, C-3*), 71.91 (d, C-2*), 69.57 (d, C-4), 62.31 (t, C-6), 57.13 (q), 20.66 (q), 20.42 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} (Δε) 252 nm (+0.7).

3.18. Methyl 2,6-bis-O-acetyl-3,4-bis-O-(p-bromobenzoyl)-β-D-glucopyranoside **25**

p-Bromobenzoylation of **22** (28 mg, 0.100 mmol) led to compound **25** (37.2 mg, 0.058 mmol, 58%): $[\alpha]_D^{25}$ −108.7 (c 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.75–7.51 (aromatic Hs, 8H), 5.60 (t, J=9.6 Hz, H-3), 5.46 (t, J=9.6 Hz, H-4), 5.20 (dd, J=7.9 & 9.6, H-2), 4.58 (d, J=7.9 Hz, H-1), 4.29 (dd, J=4.8 & 12.3 Hz, H-6$_{proR}$), 4.23 (dd, J=3.0 & 12.3 Hz, H-6$_{proS}$), 3.92 (ddd, J=3.0, 4.8 & 9.6 Hz, H-5), 3.56 (s, 3H), 2.04 (s, 3H) 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.59 (s), 169.40 (s), 165.09 (s), 164.44 (s), 131.88–127.55 (aromatic Cs), 101.68 (d, C-1), 73.39 (d, C-3), 71.84 (d, C-5), 71.12 (d, C-2), 69.49 (d, C-4), 62.27 (t, C-6), 57.11 (q), 20.67 (q), 20.63 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} (Δε) 253 (−49.3), 243 (0.0), 235 nm (16.7).

3.19. Methyl 3,6-bis-O-acetyl-2,4-bis-O-(p-bromobenzoyl)-α-D-glucopyranoside **26**

Anomerization of compound **24** (38.5 mg, 0.059 mmol) led to compound **26** (25 mg, 0.039 mmol, 77%) with a conversion of 84%: $[\alpha]_D^{25}$ +49.1 (c 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.87–7.59 (aromatic Hs, 8H), 5.85 (t, J=9.8 Hz, H-3), 5.36 (t, J=9.8 Hz, H-4), 5.15 (d, J=3.6 Hz, H-1), 5.10 (dd, J=3.6 & 9.8, H-2), 4.27 (dd, J=5.1 & 12.3 Hz, H-6$_{proR}$), 4.17 (m, H-5 & H-6$_{proS}$), 3.43 (s, 3H), 2.06 (s, 3H) 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.56 (s), 170.03 (s), 164.97 (s), 164.56 (s), 131.98–127.70 (aromatic Cs), 96.79 (d, C-1), 71.84 (d, C-2), 69.67 (d, C-3), 69.48 (d, C-4), 67.28 (d, C-5), 62.26 (t, C-6), 55.61 (q), 20.67 (q), 20.55 (q); UV (CH_3CN) λ_{max} 246 nm; CD (CH_3CN) λ_{ext} (Δε) 253 (−6.5), 243 (0.0), 235 nm (3.1).

3.20. *Methyl 2,6-bis-*O-*acetyl-α-*D-*glucopyranoside* **27**

Methyl α-D-glucopyranoside (400 mg, 2.06 mmol) was partially acetylated by using 389 μL (4.12 mmol) of Ac_2O, to obtain after chromatography 47 mg (0.17 mmol) of **27**, which was directly *p*-bromobenzoylated.

3.21. *Methyl 2,6-bis-*O-*acetyl-3,4-bis-*O-*(*p-*bromobenzoyl)-α-*D-*glucopyranoside* **28**

p-Bromobenzoylation of compound **27** (20 mg, 0.072 mmol) led to compound **28** in high yield: $[\alpha]_D^{25}$ −56.25 (c 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.76–7.50 (aromatic Hs, 8H), 5.89 (t, J=9.7 Hz, H-3), 5.45 (t, J=9.7 Hz, H-4), 5.14 (dd, J=3.6 & 9.7, H-2), 5.03 (d, J=3.6 Hz, H-1), 4.27 (dd, J=5.4 & 12.8 Hz, H-6_{proR}), 4.20 (m, H-5 & H-6_{proS}), 3.49 (s, 3H), 2.07 (s, 3H) 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.55 (s), 170.15 (s), 164.87 (s), 164.55 (s), 131.85–127.62 (aromatic Cs), 97.04 (d, C-1), 70.72 (d, C-2*), 70.69 (d, C-3*), 69.51 (d, C-4), 67.36 (d, C-5), 62.20 (t, C-6), 55.61 (q), 20.68 (q), 20.66 (q); UV (CH_3CN) λ_{max} 246 nm; CD (CH_3CN) λ_{ext} (Δε) 252 (−43.2), 243 (0.0), 235 nm (17.1).

3.22. *Methyl 2,6-bis-*O-*(*tert-*butyldiphenylsilyl)-α-*D-*glucopyranoside* **29**

To a stirred solution of methyl α-D-glucopyranoside (2.0 g, 10.29 mmol) in dry DMF (20 mL) and under Ar, imidazole (1.5 g, 22.65 mmol) and *tert*-butyldiphenylsilyl chloride (4.3 mL, 16.46 mmol) were added, and the reaction was monitored by TLC. Then, the solvent was removed under reduced pressure and the resulting oil chromatographed to afford compound **29** (2.33 g, 3.48 mmol): mp 46–48°C; $[\alpha]_D^{25}$ +35.5 (c 1.69, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.74–7.39 (aromatic Hs), 4.22 (d, J=3.6 Hz, H-1), 3.96 (t, J=9.2 Hz, H-3), 3.83 (dd, J=4.4 & 10.8 Hz, H-6), 3.78 (dd, J=5.0 & 10.8 Hz, H-6′), 3.62 (m, H-2 & H-5), 3.44 (t, J=9.2 Hz, H-4), 3.21 (s, 3H), 1.10 (s, 9H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.93–127.53 (aromatic Cs), 99.17 (d, C-1), 74.26 (d, C-3*), 73.96 (d, C-5*), 71.71 (d, C-4), 70.53 (d, C-2), 64.53 (t, C-6), 54.73 (q), 27.12 (3×q), 26.89 (3×q), 19.38 (s), 19.38 (s).

3.23. *Methyl 2,6-bis-*O-*(*tert-*butyldiphenylsilyl)-3,4-bis-*O-*(*p-*bromobenzoyl)-α-*D-*glucopyranoside* **30**

p-Bromobenzoylation of **29** (454 mg, 0.67 mmol) led to compound **30** (622 mg, 0.589 mmol, 88%): $[\alpha]_D^{25}$ −73.3 (c 1.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.71–7.29 (aromatic Hs), 5.92 (t, J=9.7 Hz, H-3), 5.18 (t, J=9.7 Hz, H-4), 4.34 (d, J=3.6 Hz, H-1), 3.98 (m, H-2 & H-5), 3.68 (dd, J=6.0 & 11.4 Hz, H-6′), 3.65 (dd, J=2.7 & 11.4 Hz, H-6), 3.33 (s, 3H), 0.96 (s, 9H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.11 (s), 164.61 (s), 135.86–127.52 (aromatic Cs), 98.84 (d, C-1), 73.74 (d, C-3), 71.97 (d, C-5*), 70.12 (d, C-4*), 70.08 (d, C-2*), 63.22 (t, C-6), 54.80 (q), 26.64 (3×q), 26.59 (3×q), 19.07 (s), 19.05 (s).

3.24. *Methyl 3,4-bis-*O-*(*p-*bromobenzoyl)-α-*D-*glucopyranoside* **31**

To 8 mL of dry MeOH under Ar, 768 μL (10.80 mmol) of acetyl chloride was added. After 5 min., this solution was treated with 280 mg (0.27 mmol) of **30** in dry ethyl ether (7 mL) and was monitored by TLC (5 days). Compound **31** (128 mg, 0.23 mmol) was obtained in 85% yield: $[\alpha]_D^{25}$ −63.4 (c 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.80–7.50 (aromatic Hs, 8H), 5.70 (t, J=9.8 Hz, H-3), 5.34 (t, J=9.8 Hz, H-4), 4.93 (d, J=3.8 Hz, H-1), 3.93 (m, H-5 & H-2), 3.78 (dd, J=1.8 & 12.8 Hz, H-6), 3.66 (dd, J=3.7 & 12.8 Hz, H-6), 3.52 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.93 (s), 165.59 (s), 131.93–127.41 (aromatic Cs),

99.44 (d, C-1), 73.88 (d, C-3), 71.18 (d, C-2), 69.68 (d, C-5), 69.18 (d, C-4), 60.98 (t, C-6), 55.77 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 251 (−49.6), 241 (0.0), 235 nm (18.8).

*3.25. Methyl 3,4-bis-*O*-(*p*-bromobenzoyl)-2,6-bis-*O*-pivaloyl-α-*D*-glucopyranoside **32***

To a stirred solution of **31** (32 mg, 0.056 mmol) in CH_2Cl_2 (2 mL), pivaloyl chloride (17 μL, 0.140 mmol), Et_3N (8 μL), and DMAP in catalytic amounts were added. The reaction mixture was monitored by TLC and quenched by adding a few drops of H_2O. The solvent was eliminated and the resulting oil chromatographed to afford compound **32** (40 mg, 0.055 mmol, 98%): $[\alpha]_D^{25}$ −65.1 (c 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.76–7.50 (aromatic Hs, 8H), 5.92 (t, J=9.6 Hz, H-3), 5.42 (t, J=9.6 Hz, H-4), 5.01 (m, H-1 & H-2), 4.21 (m, H-5 & 2H-6), 3.46 (s, 3H), 1.22 (s, 9H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.02 (s), 177.70 (s), 164.85 (s), 164.45 (s), 131.83–127.68 (aromatic Cs), 96.94 (d, C-1), 70.74 (d, C-2*), 70.71 (d, C-3*), 69.43 (d, C-4), 67.62 (d, C-5), 62.26 (t, C-6), 55.64 (q), 38.83 (s), 38.66 (s), 27.11 (3×q), 26.73 (3×q); UV (CH_3CN) λ_{max} 246 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 253 (−52.7), 243 (0.0), 235 nm (18.0).

*3.26. Methyl 6-*O*-(*tert*-butyldiphenylsilyl)-α-*D*-glucopyranoside **33***

To a stirred solution of methyl α-D-glucopyranoside (2.0 g, 10.29 mmol) in dry DMF (7 mL) and under Ar, imidazole (1.5 g, 22.65 mmol) and *tert*-butyldiphenylsilyl chloride (2.9 mL, 11.32 mmol) were added, and the reaction was monitored by TLC (5 h). Then, the reaction was diluted with ethyl ether and washed with NH_4Cl and $NaHCO_3$. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Flash column chromatography led to compound **33** (4.29 g, 9.91 mmol) in 96% yield: mp 116–118°C; $[\alpha]_D^{25}$ +55.0 (c 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.69–7.38 (aromatic Hs, 10H), 4.70 (d, J=3.6 Hz, H-1), 3.92 (dd, J=3.4 & 10.9 Hz, H-6), 3.84 (brdd, J=5.4 & 10.9, H-6), 3.75 (t, J=9.2 Hz, H-3), 3.63 (m, H-5), 3.48 (m, H-2 & H-4), 3. 35 (s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.62–127.67 (aromatic Cs), 99.19 (d, C-1), 74.49 (d, C-3), 72.12 (d, C-2), 71.33 (2×d, C-5 & C-4), 64.21 (t, C-6), 54.99 (q), 26.80 (3×q), 19.23 (s).

*3.27. Methyl 2,3,4-tris-*O*-(*p*-bromobenzoyl)-6-*O*-(*tert*-butyldiphenylsilyl)-α-*D*-glucopyranoside **34***

p-Bromobenzoylation of **33** (200 mg, 0.46 mmol) led to compound **34** (325 mg, 0.33 mmol, 72%): $[\alpha]_D^{25}$ +26.3 (c 2.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.83–7.26 (aromatic Hs), 6.04 (t, J=9.8 Hz, H-3), 5.58 (t, J=9.8 Hz, H-4), 5.24 (dd, J=3.6 & 9.8 Hz, H-2), 5.21 (d, J=3.6 Hz, H-1), 4.11 (m, H-5), 3.81 (m, 2H-6), 3.46 (s, 3H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.15 (s), 165.07 (s), 164.36 (s), 135.58–127.59 (aromatic Cs), 96.74 (d, C-1), 72.21 (d, C-2), 71.17 (d, C-3), 70.23 (d, C-5), 69.43 (d, C-4), 62.73 (t, C-6), 55.38 (q), 26.66 (3×q), 19.14 (s).

*3.28. Methyl 2,3,4-tris-*O*-(*p*-bromobenzoyl)-α-*D*-glucopyranoside **35***

To 5 mL of dry MeOH under Ar, 241 μL (3.39 mmol) of acetyl chloride was added. After 5 min., this solution was treated with 115 mg (0.117 mmol) of **34** in dry ethyl ether (5 mL) and was monitored by TLC (1 day). Then, the solvent was evaporated, and the residue chromatographed to afford compound **35** (85.6 mg, 0.115 mmol, 98%): $[\alpha]_D^{25}$ +20.2 (c 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.81–7.44 (aromatic Hs), 6.13 (t, J=9.8 Hz, H-3), 5.48 (t, J=9.8 Hz, H-4), 5.25 (dd, J=3.6 & 9.8 Hz, H-2), 5.22 (d, J=3.6 Hz, H-1), 4.03 (brd, J=10.0 Hz, H-5), 3.82 (m, H-6), 3.71 (brd, J=12.8 Hz, H-6′), 3.47 (s, 3H); ^{13}C NMR

($CDCl_3$) δ 165.45 (s), 165.08 (s), 165.00 (s), 131.95–127.36 (aromatic Cs), 97.01 (d, C-1), 71.96 (d, C-2), 70.49 (d, C-3), 69.62 (d, C-4*), 69.53 (d, C-5*), 61.00 (t, C-6), 55.67 (q); UV (CH_3CN) λ_{max} 246 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 252 (−10.3), 241 (0.0), 236 nm (2.6).

*3.29. Methyl 6-*O*-acetyl-2,3,4-tris-*O*-(*p*-bromobenzoyl)-α-*D*-glucopyranoside **36***

Compound **35** (46 mg, 0.062 mmol) was acetylated to give compound **36** (43 mg, 0.055 mmol) in 88% yield: $[\alpha]_D^{25}$ +22.7 (c 2.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.81–7.44 (aromatic Hs), 6.06 (t, J=9.8 Hz, H-3), 5.54 (t, J=9.8 Hz, H-4), 5.26 (dd, J=3.6 & 9.8 Hz, H-2), 5.20 (d, J=3.6 Hz, H-1), 4.31 (dd, J=4.8 & 12.3 Hz, H-6_{proR}), 4.26 (m, H-5 & H-6_{proS}), 3.48 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.53 (s), 165.00 (2×s), 164.52 (s), 131.87–127.57 (aromatic Cs), 96.94 (d, C-1), 71.86 (d, C-2), 70.68 (d, C-3), 69.28 (d, C-4), 67.37 (d, C-5), 62.19 (t, C-6), 55.68 (q), 20.68 (q); UV (CH_3CN) λ_{max} 246 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 253 ((10.3), 241 (0.0), 236 nm (2.3).

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15. Negative A values have also been found in methyl α-D-glucopyranosides having a 2/4 *homo p*-methoxycinnamate interaction, as well as possessing 2/4 *hetero p*-bromobenzoate/*p*-methoxycinnamate interactions. See Ref. 5: entry 7 (CACA) in Table I, and entries 3 (BACA) and 4 (CABA) in Table II.
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