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Conformational study of the hydroxymethyl group in α-D-mannose derivatives

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Abstract—A study of the dependence of the hydroxymethyl group in α-D-mannose derivatives on the aglycon and its absolute configuration was performed by means of circular dichroism (CD) and NMR data. Depending mainly on the aglycon present, the *gg* or the *gt* rotamer was the most populated, the *tg* rotamer having a small population. In addition, the study showed a correlation between the rotational populations and the aglycon, the population of the *gt* rotamer increasing as the pK_a of the bonded alcohol (aglycon) increased. Furthermore, the results revealed a strong dependence on the absolute configuration of the aglycon and point to the stereoelectronic *exo*-anomeric effect being responsible for these rotational dependencies besides nonbonding interactions.

1. Introduction

To understand the biological functions of saccharides and protein-bound saccharides from a molecular point of view, it is necessary to know their conformational preferences in solution, in addition to their three-dimensional structure. The conformational analysis of an oligosaccharide normally presents great difficulty due to the flexibility of the glycosidic linkages and to the rotation of the hydroxymethyl and other pendant groups, the relative orientations of saccharide units being expressed in terms of the glycosidic linkage torsion angles ϕ (O5′–C1′–O–Cx) and Ψ (C1′–O–Cx–C(x–1)), for a 1–x linkage (Fig. 1). In addition to these, a third torsion angle ω (O5–C5–C6–O6) needs to be considered when the hydroxymethyl group is involved in a linkage (see Fig. 1). This torsion angle is also used to describe the conformation of unsubstituted hydroxymethyl groups. The conformation of the hydroxymethyl group around the C5–C6 bond is generally described by means of the populations of the *gauche–gauche* (*gg*), *gauche–trans* (*gt*) and *trans–gauche* (*tg*) rotamers (see Fig. 2). The first descriptor indicates the torsional relationship between O6 and O5, and the second that between O6 and C4.

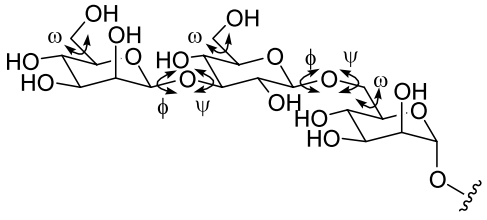

Figure 1. Torsion angles ϕ and ψ around the glycosidic linkages, and torsion angles ω around the C5–C6 bonds.

The rotamer populations of the hydroxymethyl group[1] are generally determined from $J_{H5,H6R}$ and $J_{H5,H6S}$ coupling constants by means of a set of Karplus-equations,[1–5] the unequivocal assignments of $H6_{proR}$ and $H6_{proS}$ are therefore of major importance for this type of study. The ^{1}H NMR study performed by Hori et al.[6] with D-mannose derivatives stereospecifically deuterated at C6 led to the definite assignment of $H6_{proR}$ and $H6_{proS}$, and to the preferred conformation of the hydroxymethyl group in these compounds. The greatest rotamer populations around the C5–C6 single bond were *gg* and *gt*, with a ratio *gg*/*gt* of 60/40 for the protected derivatives, the population of the *tg* rotamer usually being negligible. These results were explained in terms of both the gauche effect, which stabilizes the *gg* and *gt* rotamers, and the 1,3-*syn* interaction between O4 and O6, which destabilizes the *tg* rotamer.

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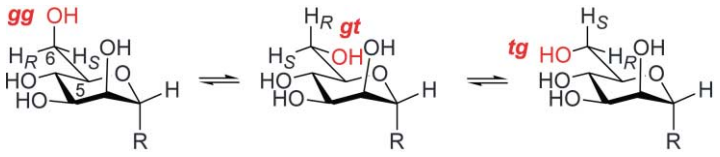


Figure 2. Molecular structure of an α-D-mannopyranoside in its three main rotamers, the *gg* ($\omega = -60°$), *gt* ($\omega = 60°$), and *tg* ($\omega = 180°$) rotamers around the C5–C6 bond.

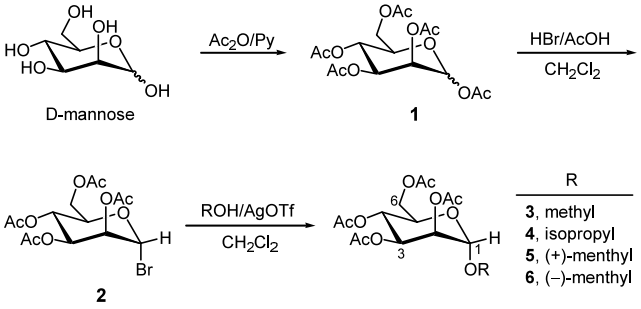
Although several conformational studies on the hydroxymethyl group of D-mannose derivatives have already been performed,[6–9] we present here a systematic study of the influence of the aglycon and its absolute configuration on the populations of the hydroxymethyl group in two series of α-D-mannose derivatives: 2,3,4,6-tetrakis-*O*-acetyl- and 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannose, having different substituents at the anomeric carbon. On the basis of CD and NMR data the results show a dependence of the hydroxymethyl group rotational population on the aglycon and its absolute configuration, and that the *gg* or the *gt* rotamer has the highest population depending mainly on the aglycon. Furthermore, the results indicate that the stereoelectronic *exo*-anomeric effect has an effect on the rotational population of the hydroxymethyl group, in addition to the steric effects, increasing the *gt* population as the pK_a of the aglycon increases.

2. Results

The ^{1}H NMR signals of the prochiral protons at C6, H6*R* and H6*S* were differentiated according to the data in the literature,[6] on the basis of their chemical shifts and coupling constants (accuracy ±0.1 Hz). In general, for the D-*manno*-series saccharides, H6*R* proton signals appear at a higher field than H6*S* signals ($\delta_{H6S} > \delta_{H6R}$), the reverse behavior being observed for *acetyl*-D-*manno*-series saccharides ($\delta_{H6R} > \delta_{H6S}$), and $J_{H5,H6R}$ coupling constants have higher values than $J_{H5,H6S}$. The rotamer populations of the hydroxymethyl group were calculated from the observed $J_{H5,H6R}$ and $J_{H5,H6S}$ coupling constants and by using the Karplus-equations recently proposed by Serianni and co-workers.[5] This approach yields a more accurate representation of the rotamer populations in solution and positive values for the *tg* rotamer population in all cases, in contrast to other Karplus-equations used before.

(A) Series 2,3,4,6-tetrakis-O-acetyl-α-D-mannose derivatives. These model compounds were synthesized as shown in Scheme 1. Peracetylation of D-mannose followed by treatment with HBr in acetic acid led to the mannosyl bromide **2** in high yield. This mannosyl donor was then coupled with the corresponding alcohol by means of a modified Koenigs–Knorr method to give the desired alkyl α-D-mannopyranosides **3**–**6**.[10]

All these compounds were characterized on the basis of their one- (^{1}H and ^{13}C) and two-dimensional (COSY-G, HMQC and T-ROESY) NMR spectra. The anomeric



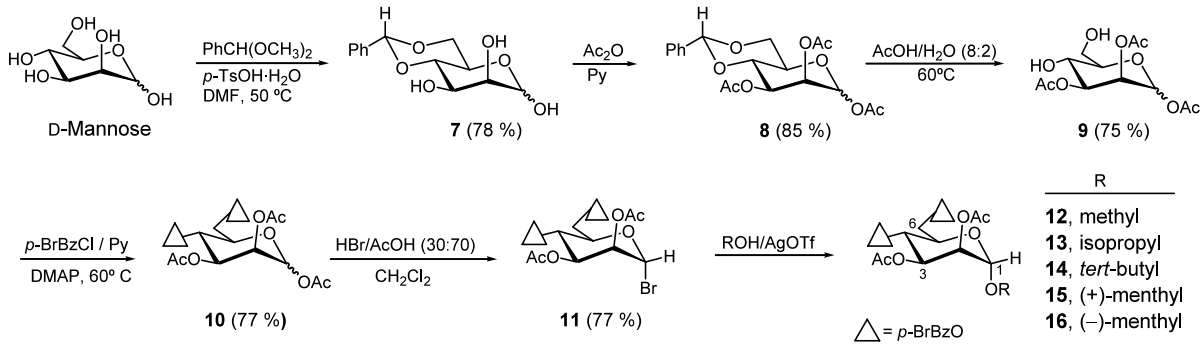
Scheme 1. Synthesis of the alkyl 2,3,4,6-tetrakis-*O*-acetyl-α-D-mannopyranosides.

configuration was assigned in each case on the basis of T-ROESY NMR experiments, and confirmed by the chemical shift in ^{13}C NMR (92.3–99.2 ppm). Table 1 shows the results obtained for these model compounds.

Table 1. $J_{H5,H6}$ coupling constants and calculated rotameric populations (%) around the C5–C6 bond for the α-D-mannose derivatives **1**–**6** ($CDCl_3$)

Compd.	Aglycon	$J_{H5,H6R}$	$J_{H5,H6S}$	P_{gg}	P_{gt}	P_{tg}
1α	(Acetyl)	4.8	2.4	50	40	10
2	(Br)	4.9	2.2	50	41	9
3	Methyl	5.4	2.4	43	46	11
4	Isopropyl	5.3	2.4	44	45	11
5	(+)-Menthyl	5.2	1.9	48	46	6
6	(−)-Menthyl	5.7	2.0	43	51	6

(B) Series 2,3-bis-O-acetyl-4,6-bis-O-(p-bromobenzoyl)-α-D-mannose derivatives. Similarly to the studies performed with alkyl gluco-[11–13] and galactopyranosides,[14] this series possesses two chromophores with a high molar extinction coefficient, namely the *p*-bromobenzoates, to be able to perform the analysis by the circular dichroic exciton chirality method (CD),[15] in addition to those by ^{1}H NMR. These model compounds were synthesized according to Scheme 2. Benzylidenation of D-mannose with benzaldehyde dimethyl acetal and *p*-TsOH, acetylation of the resulting 4,6-*O*-benzylidene **7**, and removal of this protecting group by treatment with AcOH/H_2O (8:2) led to a good yield of the mixture of anomers **9** (α:β = 2:1). Then, *p*-bromobenzoylation of **9** and treatment of **10** with HBr/AcOH led to 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannopyranosyl bromide **11** with a 77% yield.



Scheme 2. Synthesis of the alkyl 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannopyranosides.

The Koenigs–Knorr coupling reaction between the mannosyl donor **11** and the corresponding alcohols led to the desired alkyl α-D-mannopyranosides **12**–**16**, which were characterized in the same way as the previous series, on the basis of their one- and two-dimensional NMR spectra.

The observed $J_{H5,H6R}$ and $J_{H5,H6S}$ coupling constants obtained for the model 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannopyranosides, and the rotamer populations of the hydroxymethyl group calculated on the basis of the Karplus equations proposed by Serianni and co-workers,[5] are shown in Table 2.

Table 2. $J_{H5,H6}$ coupling constants and calculated rotameric populations (%) around the C5–C6 bond for the α-D-mannose derivatives **10**–**16** ($CDCl_3$)

Compd.	Aglycon	$J_{H5,H6R}$	$J_{H5,H6S}$	P_{gg}	P_{gt}	P_{tg}
10α	(Acetyl)	4.2	2.2	57	34	9
11	(Br)	4.5	2.3	54	37	9
12	Methyl	5.1	2.9	43	41	16
13	Isopropyl	5.3	2.7	42	44	14
14	*tert*-Butyl	5.4	2.4	43	46	11
15	(+)-Menthyl	4.7	2.7	49	37	14
16	(–)-Menthyl	5.7[a]	2.7[a]	38	48	14

[a] Calculated value (second order).

3. Discussion

As mentioned above, we have used the Karplus equations proposed by Serianni et al. to calculate rotamer populations of the hydroxymethyl group since this set of equations yields a more accurate representation of the rotameric populations in solution. The set of equations used in the calculations must be taken into account when comparing rotamer population data. Thus, using the values of the coupling constants $J_{H5,H6R}=5.4$ Hz and $J_{H5,H6S}=2.4$ Hz and applying the equations of Wu et al.[16] used by Hori et al.,[6] the already mentioned 60/40 ratio is obtained for the rotamers *gg*/*gt* in protected D-mannose derivatives, while using the same coupling constant and the Serianni and co-workers' equations[5] a 43/46/11 ratio is obtained for *gg*/*gt*/*tg*.

In general, similar rotamer behavior was observed for the two structural series analyzed, although slightly higher *tg* populations were obtained for the series containing benzoates than for the tetra-acetyl series (Tables 1 and 2). The increases in the rotational population of the *tg* rotamer in the former series can be explained by favourable π–π interactions between the two aromatic rings in this array.

Analysis of the data reveals higher *gg* and smaller *gt* populations for the acetyl derivatives **1α** and **10α** and for the bromides **2** and **11** than for the alkyl mannopyranosides **3**–**6** and **12**–**16**, as consequence of the smaller $J_{H5,H6R}$ coupling constant for the former compounds. As occurred with gluco-[11–13] and galactopyranosides,[14] this result points to a low participation of the stereoelectronic *exo*-anomeric effect[17,18] (Fig. 3) for the acetyl and bromide derivatives and can be explained in terms of the longer C–Br bond in the bromides, and the delocalization of the nonbonding electron pair of the exocyclic oxygen with the C=O bond in the acetyl derivatives.

Figure 3. Illustration of the molecular orbitals involved in the *exo*- and *endo*-anomeric effects.

For the alkyl α-D-mannopyranosides, nonbonded interactions and an active participation of the *exo*-anomeric effect must be expected, both factors acting simultaneously. In addition, there should be a higher value of the *exo*-anomeric effect for the tertiary alkyl mannopyranosides than for the secondary ones, and for these latter compared to the primary alkyl mannopyranosides, due to the increasing ease of charge delocalization from the aglycon to the anomeric carbon.[19,20] In alkyl gluco- and galactopyranosides, an increase in the stereoelectronic *exo*-anomeric effect led to an increase in the population of the *gt* rotamer.

Analysis of the data of the nonchiral alkyl α-D-mannopyranosides revealed no significant rotational population differences for the *tetra-acetyl α-D-manno*-series, compounds **3** and **4**: P_{gg} (45%); P_{gt} (45%); and P_{tg} (10%). However, differences in rotational populations were observed for the *2,3-bis-O-acetyl-4,6-bis-O-(p-bromobenzoyl)-α-D-manno*-series, compounds **12**–**14**. These compounds show a gradual increase/decrease in the rotamer population of the *gt* and *tg* rotamers respectively, from the methyl, to the isopropyl, and to the *tert*-butyl derivative, the *gg* population remaining constant. These conformational differences can only be explained on the basis of the *exo*-anomeric effect and not on steric effects, because the higher bulkiness of the secondary and tertiary alkyl group compared to the methyl one would lead to decreased *gt* populations through nonbonded interactions with the hydroxymethyl group.

The chiral alkyl mannopyranosides showed clear and similar rotamer population differences in both series. Thus, higher *gg* and smaller *gt* populations were observed for the (+)-menthyl mannopyranosides **5** and **15** than for the corresponding (−)-menthyl derivatives **6** and **16**, respectively. Nonbonded interactions can explain the higher *gg* and smaller *gt* populations observed for the (+)-menthyl mannopyranosides, because the isopropyl group of the cyclohexyl ring is *syn* (Fig. 4, left) to O5, spatial disposition confirmed by ROESY experiments, and therefore closer to the hydroxymethyl group at C6. In sharp contrast with the (+)-menthyl mannopyranosides, the calculated rotamer populations obtained for the corresponding (−)-menthyl derivatives **6** and **16** are the highest *gt* and smallest *gg* observed for all the α-D-mannose derivatives analyzed in each series. This result cannot be explained by nonbonded interaction between the aglycon and the hydroxymethyl group because it would lead to a smaller population of the *gt* rotamer. Therefore, an active participation of the stereoelectronic *exo*-anomeric effect is proposed to explain the rotamer populations obtained for these (−)-menthyl derivatives.

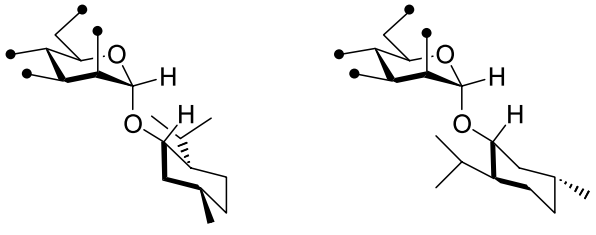


Figure 4. Structures of (1*S*,2*R*,5*S*)-(+)- and (1*R*,2*S*,5*R*)-(−)-menthyl α-D-mannopyranosides, left and right, respectively.

The circular dichroic exciton chirality method[15] has proved to be extremely sensitive to the conformational changes of chromophorically substituted hydroxymethyl groups in hexopyranosides.[21,22] Furthermore, the additivity of the amplitude (*A* value)[23] in the CD exciton curves of multichromophoric systems[21] (one type of chromophore) and the additivity of the CD curves of bichromophoric systems[22] (two types of chromophores) were studied in methyl glycopyranosides containing chromophoric esters, thus allowing an easy interpretation of the CD spectra of these types of compounds and establishing an oligosaccharide micromethod by CD spectroscopy.[24] Therefore, CD spectra of the 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannose derivatives were recorded and shown to be positive CD exciton-coupled spectra, more specifically, with positive first Cotton effects at 250 nm and negative second Cotton affects at 232 nm, centered on the *p*-bromobenzoate λ_{max} 245 nm (CH_3CN) (Fig. 5).

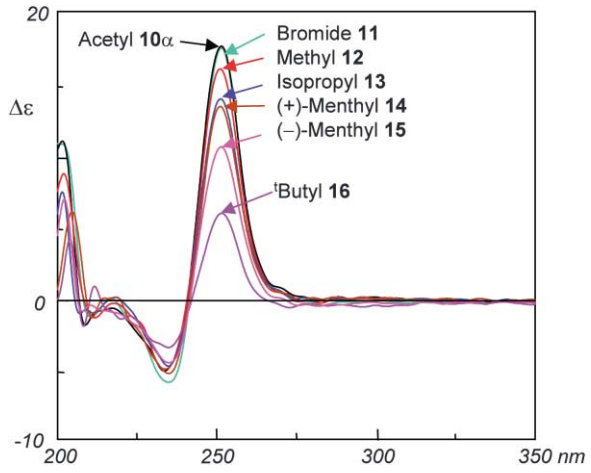


Figure 5. CD spectra comparison of the 1-acetyl **10α**, the bromide **11**, as well as the model alkyl mannopyranosides **12**–**16** (CH_3CN).

A correct CD spectral interpretation must include considerations on the interchromophoric distance and the dihedral angle of the chromophores.[15] Thus, the greater proximity and the more favourable dihedral angle for the 4/6 pairwise interaction in the *gg* disposition than in the *gt*, confers a higher CD contribution on the *gg* rotamer and explains why all CD spectra are of positive sign (Fig. 6). However, the unlike amplitudes observed for the model derivatives are a consequence of the different ratios between the populations of the *gg* (positive CD contribution), *gt* (negative CD contribution) and *tg* (nil CD contribution) rotamers.

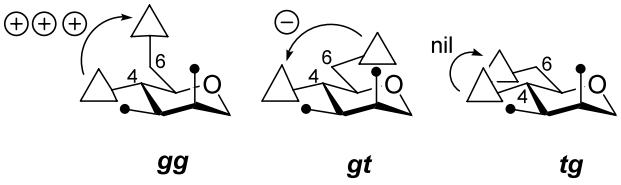


Figure 6. 4/6 Pairwise interaction for the mannopyranosyl system in each of the three stable rotamers (*gg*, *gt*, and *tg*).

The intensity of the first Cotton effect[25] of the CD spectra for 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannose derivatives **10**–**16** gradually decreased from the acetyl (17.8), to bromide (17.7), methyl (16.2), isopropyl (14.1), (+)-menthyl (13.6), (−)-

menthyl (10.8) and *tert*-butyl α-D-mannose derivatives (6.4). These intensities are consistent with a gradual decrease in the contribution of the positively coupled 4/6 pairwise interaction (*gg* rotamer) and with a gradual increase in the contribution of the negatively coupled 4/6 pairwise interaction (*gt* rotamer).

The observed CD spectral behavior is in good agreement with the results obtained from the NMR analysis. Thus, the acetyl **10α** and bromide **11** exhibit the highest CD amplitudes reflecting the highest *gg* and smallest *gt* populations, the nonchiral alkyl α-D-mannopyranosides show gradual decreases in amplitude from methyl, to isopropyl and *tert*-butyl derivatives in agreement with the gradual increases observed by NMR for the *gt* population, and the chiral alkyl α-D-mannopyranosides exhibit different amplitudes, as a higher amplitude was expected for the (+)-menthyl derivative **15** than for the (−)-menthyl mannopyranoside **16**.

4. Conclusions

The rotational population study of the hydroxymethyl group performed on α-D-mannose derivatives, by means of CD and NMR spectroscopic techniques, shows that the two main rotamers are the *gg* and *gt*, and then in a smaller proportion the *tg*, and confirms the dependence of the rotational population of the hydroxymethyl group on the aglycon and its absolute configuration. According mainly to the aglycon, the *gg* or the *gt* rotamer has the highest population. In general, a similar rotamer behavior was observed for the two structural series analyzed, but a slightly higher *tg* populations were obtained for the series containing benzoates probably by a favourable π–π interaction between the two aromatic rings.

In addition, the results indicate that the stereoelectronic *exo*-anomeric effect is directly related to the rotational population of the hydroxymethyl group in α-D-mannose derivatives, along with the steric effects, the *gt* population increasing as the pK_a of the aglycon increases.

5. Experimental

5.1. General

^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR 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, 7.26 for proton and 7.70 ppm for the central peak for carbon NMR. 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 using 10 mm cells. Prior to measurement of CD spectra, all compounds were purified by HPLC using a μ-Porasil column, 150× 19 mm ID, 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 38200.[21]

For analytical and preparative thin-layer chromatography, silica gel ready-foils and glass-backed plates (1 mm) were used respectively, developed with 254 nm UV light and/or spraying with $AcOH/H_2O/H_2SO_4$ (80:16:4) and heating to 150°C. Flash column chromatography was performed using silica gel (60 Å). 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 compounds prepared were characterized on the basis of their one- (^{1}H and ^{13}C) and two-dimensional (COSY and HSQC) NMR spectra, as well as by UV and CD spectroscopy.

5.2. General procedure for α-mannosylation

To a stirred solution of mannosyl donor (acylmannosyl bromide) in dry CH_2Cl_2 (8 mL/mmol) at room temperature under Ar, a mannosyl acceptor (alcohol) and base were added. The reaction mixture was cooled at 0°C in an ice bath, and 1.5 equiv. of AgOTf was then added in the dark under anhydrous conditions, the reaction being monitored by TLC. After quenching the reaction with a few drops of pyridine and filtration through a bed of Celite with CH_2Cl_2, the filtrate was evaporated under reduced pressure, and column chromatography (*n*-hexane/EtOAc solvent systems) yielded the purified product.

5.3. 1,2,3,4,6-Pentakis-*O*-acetyl-D-mannopyranoside 1

To a solution of D-mannose (1 g, 5.55 mmol) in dry pyridine (4 mL) at room temperature, acetic anhydride (4 mL) was added, the reaction being monitored by TLC. Excess solvent was then removed under reduced pressure in the presence of toluene, and the residue (2.16 g, R_f=0.57 (*n*-hexane/EtOAc, 1:1)) was used directly in the next step. ^{1}H NMR showed a 3:1 ratio of the α- and β-anomers, respectively, the data of the major stereoisomer **1α** being in complete agreement with those from a commercial sample: ^{1}H NMR ($CDCl_3$) δ 6.09 (d, J=1.7 Hz, H-1), 5.35 (m, 2H), 5.26 (m, 1H), 4.28 (dd, J=4.8 and 12.4, H-6_{proR}), 4.10 (dd, J=2.4 and 12.4 Hz, H-6_{proS}), 4.05 (m, H-5), 2.18 (s, 3H), 2.17 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H).

5.4. 2,3,4,6-Tetrakis-*O*-acetyl-α-D-mannopyranosyl bromide 2

HBr/AcOH (30:70) (11.4 mL, 55.5 mmol) was added to a stirred solution of compound **1** (2.16 g, 5.53 mmol) in dry CH_2Cl_2 (16 mL) at room temperature under argon. Once the reaction was finished, CH_2Cl_2 was added and the mixture extracted with saturated solutions of $NaHCO_3$ and then NaCl. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography with *n*-hexane/EtOAc (6:4) as the eluent yielded **2** (1.84 g, 81% yield). TLC R_f=0.33 (*n*-hexane/EtOAc, 6:4); ^{1}H NMR ($CDCl_3$) δ

6.29 (brs, H-1), 5.72 (dd, $J=3.3$ and 10.2 Hz, H-3), 5.45 (brd, $J=3.3$ Hz, H-2), 5.37 (t, $J=10.1$ Hz, H-4), 4.33 (dd, $J=4.9$ and 12.4, H-6_{proR}), 4.23 (m, H-5), 4.14 (dd, $J=2.2$ and 12.4 Hz, H-6_{proS}), 2.18 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 170.32 (s), 169.52 (s), 169.39 (2×s), 83.00 (d, C-1), 72.70 (d, C-5), 71.97 (d, C-2), 67.78 (d, C-3), 65.14 (d, C-4), 61.29 (t, C-6), 20.60 (q), 20.51 (2×q), 20.41 (q).

5.5. Methyl 2,3,4,6-tetrakis-*O*-acetyl-α-D-mannopyranoside 3

Following the general procedure for α-mannosylation without base, compound **2** (163.1 mg, 0.397 mmol) was treated with dry methanol (61.8 equiv.) to produce compound **3** (35.9 mg, 0.10 mmol, 25% yield): TLC $R_f=0.27$ (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}=+53.0$ (*c* 0.2, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 331 ([M^+–MeO], 7), 243 (27), 200 (47), 157 (100); ^{1}H NMR ($CDCl_3$) δ: 5.33 (dd, $J=3.3$ and 10.0 Hz, H-3), 5.27 (t, $J=10.0$ Hz, H-4), 5.24 (dd, $J=1.4$ and 3.3 Hz, H-2), 4.71 (d, $J=1.4$ Hz, H-1), 4.28 (dd, $J=5.4$ and 12.2 Hz, H-6_{proR}), 4.12 (dd, $J=2.4$ and 12.2 Hz, H-6_{proS}), 3.96 (m, H-5), 3.40 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 170.64 (s), 170.03 (s), 169.87 (s), 169.71 (s), 98.55 (d, C-1), 69.47 (d, C-2), 69.0 (d, C-3), 68.34 (d, C-5), 66.11 (d, C-4), 62.47 (t, C-6), 55.27 (q, C-1′), 20.85(q), 20.70 (q), 20.66 (2×q). Anal. calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C 49.71; H, 6.33.

5.6. Isopropyl 2,3,4,6-tetrakis-*O*-acetyl-α-D-mannopyranoside 4

Using 61.8 equiv. of ^{i}PrOH, 0.7 equiv. of 2,4,6-collidine as base, and 345 mg (0.839 mmol) of compound **2**, and following the general procedure for α-mannosylation, compound **4** (72.0 mg, 0.185 mmol) was obtained in 22% yield: TLC $R_f=0.35$ (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}=+57.5$ (*c* 0.2, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 331 ([M^+–C_3H_7O], 12), 157 (100); ^{1}H NMR ($CDCl_3$) δ: 5.35 (dd, $J=3.4$ and 10.0 Hz, H-3), 5.25 (t, $J=10.0$ Hz, H-4), 5.16 (dd, $J=1.8$ and 3.3 Hz, H-2), 4.90 (d, $J=1.8$ Hz, H-1), 4.25 (dd, $J=5.3$ and 12.1, H-6_{proR}), 4.09 (dd, $J=2.4$ and 12.1 Hz, H-6_{proS}), 4.04 (m, H-5), 3.90 (m, H-1′), 2.14 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 1.23 (d, $J=6.2$ Hz, 3H), 1.16 (d, $J=6.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 170.62 (s), 170.12 (s), 169.88 (s), 169.75 (s), 95.93 (d, C-1), 70.97 (d, C-1′), 70.23 (d, C-2), 69.12 (d, C-3), 68.37 (d, C-5), 66.43 (d, C-4), 62.57 (t, C-6), 23.01 (q), 21.49 (q), 20.90 (q), 20.67 (3×q). Anal. calcd for $C_{17}H_{26}O_{10}$: C, 52.30; H, 6.71. Found: C, 52.32; H, 6.82.

5.7. (1*S*,2*R*,5*S*)-(+)-Menthyl 2,3,4,6-tetrakis-*O*-acetyl-α-D-mannopyranoside 5

Following the general procedure without base, α-mannosylation of (+)-menthol (97 mg, 0.623 mmol) with compound **2** (384 mg, 0.934 mmol, 1.5 equiv.) led to **5** (56.4 mg, 0.116 mmol, 19% yield): TLC $R_f=0.46$ (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}=+85.0$ (*c* 0.2, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 331 ([M^+–$C_{10}H_{19}O$], 40), 242 (100), 157 (57); ^{1}H NMR ($CDCl_3$) δ 5.32 (dd, $J=3.1$ and 10.0 Hz, H-3), 5.27 (t, $J=10.0$ Hz, H-4), 5.12 (brd, $J=3.1$ Hz, H-2), 5.00 (brs, H-1), 4.24 (dd, $J=5.2$ and 12.2 Hz, H-6_{proR}), 4.08 (dd, $J=1.9$ and 12.2 Hz, H-6_{proS}), 4.02 (m, H-5), 3.45 (dt, $J=4.0$ and 10.6 Hz, H-1′), 2.19 (m, H-7′), 2.15 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (m, H-$6'_{ec.}$), 1.98 (s, 3H), 1.65 (m, 2H), 1.31 (m, 2H), 0.93 (d, $J=7.0$ Hz, 3H), 0.90 (d, $J=6.5$ Hz, 3H), 0.83 (m, 3H), 0.75 (d, $J=7.0$, 3H); ^{13}C NMR ($CDCl_3$) δ 170.63 (s), 170.18 (s), 169.90 (s), 169.74 (s), 94.27 (d, C-1), 77.31 (d, C-1′), 70.65 (d, C-2), 69.17 (d, C-3), 69.03 (d, C-5), 66.14 (d, C-4), 62.59 (t, C-6), 47.52 (d), 39.63 (t, C-6′), 34.21 (t), 31.37 (d), 25.40 (d, C-7′), 22.69 (t), 22.15 (q), 21.10 (q), 20.92 (q), 20.68 (3×q), 15.30 (q). Anal. calcd for $C_{24}H_{38}O_{10}$: C, 59.24; H, 7.87. Found: C, 59.23; H, 8.26.

5.8. (1*R*,2*S*,5*R*)-(−)-Menthyl 2,3,4,6-tetrakis-*O*-acetyl-α-D-mannopyranoside 6

Following the general procedure without base, α-mannosylation of (−)-menthol (100.5 mg, 0.643 mmol) with compound **2** (396 mg, 0.964 mmol, 1.5 equiv.) led to **6** (79.8 mg, 0.164 mmol, 26% yield): TLC $R_f=0.46$ (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{25}=+12.0$ (*c* 0.1, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 331 ([M^+–$C_{10}H_{19}O$], 15), 242 (69), 83 (100); ^{1}H NMR ($CDCl_3$) δ 5.37 (dd, $J=3.3$ and 10.0 Hz, H-3), 5.24 (t, $J=10.0$ Hz, H-4), 5.16 (brd, $J=3.3$ Hz, H-2), 4.89 (brs, H-1), 4.23 (dd, $J=5.7$ and 11.9 Hz, H-6_{proR}), 4.16 (m, H-5), 4.12 (dd, $J=2.0$ and 11.9 Hz, H-6_{proS}), 3.36 (dt, $J=4.3$ and 10.7 Hz, H-1′), 2.15 (s, 3H), 2.09 (s, 3H), 2.07 (m, 2H), 2.04 (s, 3H), 1.99 (s, 3H), 1.61 (m, 2H), 1.27 (m, 2H), 1.01 (m, 3H), 0.88 (d, $J=9.0$ Hz, 3H), 0.83 (d, $J=9.0$ Hz, 3H), 0.76 (d, $J=7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 170.66 (s), 170.19 (s), 169.96 (s), 169.81 (s), 99.19 (d, C-1), 82.69 (d, C-1′), 70.17 (d, C-2), 69.06 (d, C-3), 68.60 (d, C-5), 66.54 (d, C-4), 62.82 (t, C-6), 48.31 (d), 42.65 (t, C-6′), 34.16 (t), 31.62 (d), 25.80 (d, C-7′), 23.24 (t), 22.30 (q), 20.92 (q), 20.71 (4×q), 16.19 (q). Anal. calcd for $C_{24}H_{38}O_{10}$: C, 59.24; H, 7.87. Found: C, 59.25; H, 8.29.

5.9. 4,6-*O*-Benzylidene-D-mannopyranose 7

Benzaldehyde dimethyl acetal (5.5 mL, 36.63 mmol) and *p*-toluenesulfonic acid (62.7 mg, 0.33 mmol) were added to a solution of D-mannose (6 g, 33.3 mmol) in DMF (67 mL). The reaction mixture was heated to 50°C under vacuum, for 3 h. The solvent was then removed by distillation and the resulting oil chromatographed on silica gel (*n*-hexane/EtOAc, 2:8). Compound **7** (6.97 g, 26.0 mmol) was obtained with a 78% yield ($R_f=0.55$, CH_2Cl_2/MeOH, 9:1) and was then directly acetylated.

5.10. 4,6-*O*-Benzylidene-1,2,3-tris-*O*-acetyl-D-mannopyranoside 8

Acetic anhydride (8 mL) was added to a solution of compound **7** (5.02 g, 18.7 mmol) in dry pyridine (8 mL) at room temperature, the reaction being monitored by TLC. Excess solvent was then removed under reduced pressure in the presence of toluene, and the residue

chromatographed (*n*-hexane/EtOAc, 8:2), to produce compound **8**: α-anomer (4.18 g, 10.6 mmol, 57%) and β-anomer (2.09 g, 5.3 mmol, 28%). Compound **8α**: TLC $R_f = 0.38$ (*n*-hexane/EtOAc, 6:4); ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.34 (m, 3H), 6.02 (d, $J = 1.0$ Hz, H-1), 5.57 (s, H-1′), 5.41 (dd, $J = 3.5$ and 10.3 Hz, H-3), 5.34 (brd, $J = 3.5$ Hz, H-2), 4.29 (dd, $J = 4.7$ and 10.2 Hz, H-6_{proR}), 4.09, (t, $J = 10.3$ Hz, H-4), 4.01 (m, H-5), 3.82 (t, $J = 10.2$ Hz, H-6_{proS}), 2.17 (s, 3H), 2.15 (s, 3H), 2.02 (3H); ^{13}C NMR ($CDCl_3$) δ 170.6 (s), 169.9 (s), 168.6 (s), 136.9–126.2 (aromatic Cs), 101.9 (d, C-1′), 93.8 (d, C-1), 75.5 (d, C-4), 68.8 (d, C-2), 68.6 (d, C-6), 68.3 (d, C-3), 66.4 (d, C-5), 20.7 (3×q). Compound **8β**: TLC $R_f = 0.34$ (*n*-hexane/EtOAc, 6:4); ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.35 (m, 3H), 5.93 (s, H-1), 5.58 (brd, $J = 3.3$ Hz, H-2), 5.56 (s, H-1′), 5.21(dd, $J = 3.3$ and 10.3 Hz, H-3), 4.36 (dd, $J = 4.9$ and 10.4 Hz, H-6_{proR}), 4.04 (t, $J = 10.3$ Hz, H-4), 3.86 (t, $J = 10.4$ Hz, H-6_{proS}), 3.66 (m, H-5), 2.22 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.8 (s), 169.5 (s), 168.4 (s), 136.9–126.2 (aromatic Cs), 102.0 (d, C-1′), 90.7 (d, C-1), 75.3 (d, C-4), 69.9 (d, C-3), 68.9 (d, C-2), 68.4 (t, C-6), 68.2 (d, C-5), 2.07 (3×q).

5.11. 1,2,3-Tris-*O*-acetyl-D-mannopyranoside 9

Compound **8** (3.59 g, 9.10 mmol) in AcOH/H_2O (28 mL, 80:20, v/v) was heated at 60°C, monitoring the reaction by TLC. Excess solvent was then removed under reduced pressure and the residue chromatographed on silica gel (*n*-hexane/EtOAc, 2:8), to yield compound **9** (2.09 g, 6.82 mmol, 75% yield) as a 2:1 mixture of α- and β-anomers: TLC $R_f = 0.53$ (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 6.01 (s, H-1α), 5.85 (s, H-1β), 5.45 (s, H-2β), 5.22 (s, H-2α), 5.18 (dd, $J = 3.2$ and 9.9 Hz, H-3α), 4.97 (dd, $J = 2.9$ and 9.9 Hz, H-3β), 4.05 (t, $J = 9.8$ Hz, H-4α), 3.97 (t, $J = 9.8$ Hz, H-4β), 3.89 (m, 4H), 3.76 (m, H-5α), 3.54 (m, H-5β), 2.16 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.8 (s), 170.6 (s), 170.1 (s), 169.7 (s), 168.6 (s), 168.5 (s), 90.8 (d, C-1α), 90.5 (d, C-1β), 76.6 (d, C-5β), 74.4(d, C-5α), 73.3 (d, C-3β), 71.4 (d, C-3α), 62.5 (2×d, C-2α y C-2β), 65.4 (d, C-4β), 65.2 (d, C-4α), 62.0 (t, C-6β), 61.7 (t, C-6α), 20.8 (2×q), 20.7 (2×q), 20.6 (2×q).

5.12. 1,2,3-Tris-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-D-mannopyranoside 10

A solution of compound **9** (1.99 g, 6.50 mmol) in dry pyridine (18.3 mL) with DMAP as catalyst was treated with *p*-bromobenzoyl chloride (4 g, 18.25 mmol). The resulting pale yellow solution was heated at 60°C and stirred overnight. The excess solvent was then removed under reduced pressure in the presence of toluene and the residue flash chromatographed with CH_2Cl_2 as the eluent, yielding **10** (3.38 g, 5.03 mmol, 77% yield) as a 2:1 mixture of α- and β-anomers. This mixture was then chromatographed with *n*-hexane/EtOAc (7:3), giving 2.25 g (3.35 mmol, 52%) of the α-anomer and 1.13 g (1.68 mmol, 26%) of the β-anomer. Compound **10α**: TLC $R_f = 0.32$ (*n*-hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 7.83 (d, $J = 8.2$ Hz, 2H), 7.81 (d, $J = 8.2$ Hz, 2H), 7.55 (d, $J = 8.2$ Hz, 2H), 7.52 (d, $J = 8.2$ Hz, 2H), 6.14 (s, H-1), 5.72 (t, $J = 10.0$ Hz, H-4), 5.58 (dd, $J = 2.7$ and 10.0 Hz, H-3), 5.32 (brs, H-2), 4.53 (dd, $J = 2.2$ and 12.2 Hz, H-6_{proS}), 4.38 (dd, $J = 4.2$ and 12.2 Hz, H-6_{proR}), 4.30 (m, H-5), 2.20 (s, 3H), 2.18 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.9 (s), 169.6 (s), 168.0 (s), 165.2 (s), 164.6 (s), 131.9–127.6 (aromatic Cs), 90.6 (d, C-1), 70.5(d, C-5), 68.5 (d, C-2), 68.4 (d, C-3), 67.0 (d, C-4), 63.1 (t, C-6), 20.8 (q), 20.7 (q), 20.5 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 250 (17.8), 232 nm (–4.9). Compound **10β**: TLC $R_f = 0.30$ (*n*-hexane/EtOAc, 7:3); ^{1}H NMR ($CDCl_3$) δ 7.83 (d, $J = 8.5$ Hz, 2H), 7.79 (d, $J = 8.5$ Hz, 2H), 7.56 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 2H), 5.96 (brs, H-1), 5.63 (t, $J = 10.0$ Hz, H-4), 5.55 (brd, $J = 3.1$ Hz, H-2), 5.37 (dd, $J = 3.1$ and 10.0 Hz, H-3), 4.54 (d, $J = 3.2$ and 12.2 Hz, H-6_{proS}), 4.41 (dd, $J = 6.3$ and 12.2 Hz, H-6_{proR}), 4.10 (m, H-5), 2.23 (s, 3H), 2.11 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.05 (s), 169.76 (s), 168.34 (s), 165.27 (s), 164.64 (s), 131.99–127.46 (aromatic Cs), 90.47 (d, C-1), 73.02 (d, C-5), 70.36 (d, C-3), 68.34 (d, C-2), 66.94 (d, C-4), 63.22 (t, C-6), 20.73 (2×q), 20.47 (q).

5.13. 2,3-Bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannopyranosyl bromide 11

HBr/AcOH (30:70) (10.0 mL) were added to a stirred solution of compound **10** (3.30 g, 4.91 mmol) in dry CH_2Cl_2 (15 mL) at room temperature under argon. Once the reaction was finished, CH_2Cl_2 was added and then extracted with $NaHCO_3$ and NaCl saturated solutions. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography with *n*-hexane/EtOAc (7:3) as the eluent yielded **11** (2.63 g, 3.80 mmol, 77% yield). TLC $R_f = 0.44$ (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25} = +116.5$ (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, $J = 8.6$ Hz, 2H), 7.84 (d, $J = 8.6$ Hz, 2H), 7.57 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H), 6.34 (brs, H-1), 5.96 (dd, $J = 3.2$ and 10.0 Hz, H-3), 5.74 (t, $J = 10.0$ Hz, H-4), 5.49 (brd, $J = 3.2$ Hz, H-2), 4.57 (dd, $J = 2.3$ and 12.0 Hz, H-6_{proS}), 4.47 (m, H-5), 4.42 (dd, $J = 4.5$ and 12.0 Hz, H-6_{proR}), 2.16 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.52 (s), 169.24 (s), 164.95 (s), 164.46 (s), 131.83–125.11 (aromatic Cs), 82.88 (d, C-1), 72.56 (d, C-5), 72.12 (d, C-2), 67.52 (d, C-3), 66.48 (d, C-4), 62.20 (t, C-6), 20.53 (q), 20.35 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 250 (17.7), 232 nm (–5.7).

5.14. Methyl 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannopyranoside 12

Following the general procedure for α-mannosylation and using 0.7 equiv. of 2,4,6-collidine as base, compound **11** (100 mg, 0.144 mmol) was treated with dry methanol (61.8 equiv.) to provide **12** (41.9 mg, 0.065 mmol, 45% yield): TLC $R_f = 0.33$ (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25} = +37.0$ (*c* 0.2, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 611, 613, 615 ([M^+–OMe], 0.3); 523, 525, 527 ([M^+–$C_4H_7O_4$], 8); 183, 181 ([M^+–$C_{18}H_{20}BrO_9$], 100); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, $J = 8.4$ Hz, 2H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$

Hz, 2H), 5.63 (t, $J=10.0$ Hz, H-4), 5.57 (dd, $J=3.0$ and 10.0 Hz, H-3), 5.28 (brd, $J=3.0$ Hz, H-2), 4.77 (brs, H-1), 4.54 (dd, $J=2.9$ and 12.0 Hz, H-6_{proS}), 4.41 (dd, $J=5.1$ and 12.0 Hz, H-6_{proR}), 4.22 (m, H-5), 3.44 (s, 3H), 2.15 (s, 3H), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.91 (s), 169.85 (s), 165.33 (s), 164.81 (s), 131.93–127.76 (aromatic Cs), 98.54 (d, C-1), 69.71 (d, C-2), 68.69 (d, C-3), 68.41 (d, C-5), 67.63 (d, C-4), 63.51 (t, C-6), 55.43 (q), 20.83 (q), 20.61 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 250 (16.2), 232 nm (−4.8). Anal. calcd for $C_{25}H_{24}Br_2O_{10}$: C, 46.61; H, 3.75. Found: C, 46.70; H, 4.35.

5.15. Isopropyl 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannopyranoside 13

Following the general procedure for mannosylation and using 100 mg (0.144 mmol) of compound **11**, 61.8 equiv. of ^{i}PrOH, and 0.7 equiv. of 1,1,3,3-tetramethylurea, compound **13** (48.5 mg, 0.072 mmol) was obtained with a 50% yield: TLC $R_f=0.44$ (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25}=+41.0$ (*c* 0.2, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 611, 613, 615 ([$M^+-OC_3H_7$], 2); 523, 525, 527 ([$M^+-C_6H_{11}O_4$], 11); 183, 185 ([$M^+-C_{20}H_{24}BrO_9$], 100); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, $J=8.4$ Hz, 2H), 7.83 (d, $J=8.4$ Hz, 2H), 7.55 (d, $J=8.4$ Hz, 2H), 7.52 (d, $J=8.4$ Hz, 2H), 5.62 (m, H-3 and H-4), 5.22 (brd, $J=2.8$ Hz, H-2), 4.96 (brs, H-1), 4.50 (dd, $J=2.7$ and 12.1 Hz, H-6_{proS}), 4.39 (dd, $J=5.3$ and 12.1 Hz, H-6_{proR}), 4.31 (m, H-5), 3.95 (m, H-1′), 2.15 (s, 3H), 1.89 (s, 3H), 1.26 (d, $J=6.1$ Hz, 3H), 1.19 (d, $J=6.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.03 (s), 169.88 (s), 165.36 (s), 164.88 (s), 131.91–127.80 (aromatic Cs), 96.03 (d, C-1), 71.31 (d, C-1′), 70.48 (d, C-2), 68.81 (d, C-3), 68.48 (d, C-5), 67.88 (d, C-4), 63.63 (t, C-6), 23.16 (q), 21.61 (q), 20.89 (q), 20.64 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 250 (14.1), 232 nm (−4.6). Anal. calcd for $C_{27}H_{28}Br_2O_{10}$: C, 48.23; H, 4.20. Found: C, 48.24; H, 4.66.

5.16. *tert*-Butyl 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-manopyranoside 14

Mannosylation of ^{t}BuOH (1.4 mL, 15.14 mmol, 61.8 equiv.) with compound **11** (170 mg, 0.245 mmol) was carried out as described in the general procedure using as base 2,4,6-collidine (26 μL, 0.196 mmol, 0.8 equiv.) to produce **14** (26.9 mg, 0.039 mmol) with an 16% yield: TLC $R_f=0.49$ (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25}=+42.0$ (*c* 0.1, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 611, 613, 615 ([$M^+-OC_4H_9$], 3); 522, 524, 526 ([$M^+-C_7H_{13}O_4$], 12); 183, 185 ([$M^+-C_{21}H_{26}BrO_9$], 100); ^{1}H NMR ($CDCl_3$) δ 7.84 (d, $J=8.6$ Hz, 4H), 7.56 (d, $J=8.6$ Hz, 2H), 7.51 (d, $J=8.6$ Hz, 2H), 5.63 (dd, $J=3.1$ and 10.0 Hz, H-3), 5.59 (t, $J=10.0$ Hz, H-4), 5.16 (d, $J=1.7$ Hz, H-1), 5.10 (t, $J=2.2$ Hz, H-2), 4.47 (dd, $J=2.4$ and 11.1 Hz, H-6_{proS}), 4.41 (m, H-5), 4.37 (dd, $J=5.4$ and 11.1 Hz, H-6_{proR}), 2.17 (s, 3H), 1.90 (s, 3H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.14 (s), 169.90 (s), 165.31 (s), 164.81 (s), 131.88–127.85 (aromatic Cs), 92.28 (d, C-1), 77.15 (d, C-1′), 71.46 (d, C-2), 68.77 (d, C-3), 68.13 (d, C-5), 68.06 (d, C-4), 63.79 (t, C-6), 28.36 (3×q), 20.90 (q), 20.62 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 250 (6.4), 232 nm (−3.0). Anal. calcd for $C_{28}H_{30}Br_2O_{10}$: C, 49.00; H, 4.41. Found: C, 49.03; H, 4.75.

5.17. (1*S*,2*R*,5*S*)-(+)-Menthyl 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannopyranoside 15

Following the general procedure without base, α-mannosylation of (−)-menthol (34 mg, 0.216 mmol, 1 equiv.) with compound **11** (300 mg, 0.433 mmol) in dry CH_3NO_2 led to **15** (53.1 mg, 0.069 mmol, 32% yield): TLC $R_f=0.54$ (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25}=+72.0$ (*c* 0.2, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 611, 613, 615 ([$M^+-C_{10}H_{19}O_2$], 3); 522, 524, 526 ([$M^+-C_{14}H_{28}O_4$], 15); 183, 185 ([$M^+-C_{28}H_{40}BrO_9$], 100); ^{1}H NMR ($CDCl_3$) δ 7.87 (d, $J=8.5$ Hz, 2H), 7.82 (d, $J=8.5$ Hz, 2H), 7.56 (d, $J=8.5$ Hz, 2H), 7.53 (d, $J=8.5$ Hz, 2H), 5.66 (t, $J=10.0$ Hz, H-4), 5.74 (dd, $J=3.1$ and 10.0 Hz, H-3), 5.19 (brd, $J=3.1$ Hz, H-2), 5.06 (brs, H-1), 4.53 (dd, $J=2.7$ and 12.1 Hz, H-6_{proS}), 4.36 (dd, $J=4.7$ and 12.1 Hz, H-6_{proR}), 4.26 (m, H-5), 3.49 (dt, $J=4.1$ and 10.6 Hz, H-1′), 2.24 (m, H-7′), 2.15 (s, 3H), 2.05 (m, H-$6'_{ec.}$), 1.90 (s, 3H), 1.66 (m, 2H), 1.35 (m, 2H), 0.95 (d, $J=7.0$ Hz, 3H), 0.91 (d, $J=6.4$ Hz, 3H), 0.84 (m, 3H), 0.76 (d, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.06 (s), 169.90 (s), 165.33 (s), 164.85 (s), 131.92–127.79 (aromatic Cs), 94.26 (d, C-1), 77.32 (d, C-1′), 70.86 (d, C-2), 69.12 (d, C-5), 68.83 (d, C-3), 67.56 (d, C-4), 63.48 (d, C-6), 47.53 (d), 39.68 (t, C-6′), 34.21 (t), 31.41 (d), 25.57 (d, C-7′), 22.76 (t), 22.15 (q), 21.13 (q), 20.88 (q), 20.64 (q), 15.48 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 250 (13.6), 232 nm (−5.1). Anal. calcd for $C_{34}H_{40}Br_2O_{10}$: C, 53.14; H, 5.25. Found: C, 53.47; H, 5.74.

5.18. (1*R*,2*S*,5*R*)-(−)-Menthyl 2,3-bis-*O*-acetyl-4,6-bis-*O*-(*p*-bromobenzoyl)-α-D-mannopyranoside 16

The reaction of (−)-menthol (60.63 mg, 0.388 mmol) with the mannosyl bromide **11** (307 mg, 0.443 mmol) and 2,4,6-collidine (41 μL, 0.310 mmol, 0.8 equiv.) as base was performed as described in the general procedure for mannosylation, to give compound **16** (46.2 mg, 0.060 mmol) with a 15% yield: TLC $R_f=0.54$ (*n*-hexane/EtOAc, 7:3); $[\alpha]_D^{25}=+15.0$ (*c* 0.1, $CHCl_3$); MS (EI) *m*/*z* (relative intensity) 611, 613, 615 ([$M^+-C_{10}H_{19}O_2$], 4); 522, 524, 526 ([$M^+-C_{14}H_{28}O_4$], 20); 183, 185 ([$M^+-C_{28}H_{40}BrO_9$], 100); ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 8.6 Hz, 2H), 7.85 (d, $J=8.6$ Hz, 2H), 7.57 (d, $J=8.6$ Hz, 2H), 7.52 (d, $J=8.6$ Hz, 2H), 5.59 (m, H-3 and H-4), 5.21 (dd, $J=1.8$ and 2.7 Hz, H-2), 4.95 (d, $J=1.8$ Hz, H-1), 4.50 (dd, $J=2.7$ and 10.2 Hz, H-6_{proS}), 4.40 (m, H-5), 4.37 (dd, $J=5.7$ and 10.2 Hz, H-6_{proR}), 3.39 (dt, $J=4.4$ and 10.6 Hz, H-1′), 2.16 (s, 3H), 2.10 (m, H-$6'_{ec.}$ and H-7′), 1.90 (s, 3H), 1.62 (m, 2H), 1.31 (m, 2H), 0.93 (d, $J=7.0$, 3H), 0.85 (m, 3H), 0.78 (d, $J=6.0$ Hz, 3H), 0.76 (d, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.07 (s), 169.92 (s), 165.39 (s), 164.91 (s), 131.93–127.80 (aromatic Cs), 99.16 (d, C-1), 82.72 (d, C-1′), 70.37 (d, C-2), 68.78 (d, C-3), 68.70 (d, C-5), 67.85 (d, C-4), 63.79 (t, C-6), 48.41 (d), 42.74 (t, C-6′), 34.17 (t), 31.64 (d), 25.78 (d, C-7′), 23.17 (t), 22.07 (q), 20.98 (q), 20.91 (q), 20.65 (q), 16.15 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN)

λ_{ext} ($\Delta\varepsilon$) 250 (10.8), 232 nm (–4.4). Anal. calcd for $C_{34}H_{40}Br_2O_{10}$: C, 53.14; H, 5.25. Found: C, 53.36; H, 5.73.

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25. Occasionally the presence of a background ellipticity alters the intensity of the Cotton effects at short wavelengths. For this reason, the intensities of the second Cotton effects and the amplitudes (*A* values) of the CD spectra of our model compounds may not be precise; the intensities of the first Cotton effects are thus more accurate for comparative analysis.