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Experimental evidence on the hydroxymethyl group conformation in alkyl β-D-mannopyranosides

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Abstract—A rotational population study of the hydroxymethyl group of alkyl β-D-mannopyranosides was performed by means of CD and NMR spectroscopy. Three different benzyl, acetyl, and *p*-bromobenzoyl series of alkyl β-D-mannopyranosides with different chiral and nonchiral aglycons were synthesized and analyzed. Different rotational populations were observed for each series by changing the structure of the aglycon. The results showed a clear correlation between the rotational population of the hydroxymethyl group around the C5–C6 bond and the pK_a of the bonded alcohol (aglycon). The population of the *gt* rotamer gradually increased as the pK_a increased while that of the *gg* rotamer decreased and the population of the *tg* rotamer remained almost constant. This is explained by the *exo*-anomeric effect. For chiral alkyl derivatives, the results also showed a close dependence on the absolute configuration of the aglycon. Comparison of rotational population anomers revealed the dependence of the hydroxymethyl group on the anomeric configuration and a greater dependence on the aglycon structure in the β anomers.

1. Introduction

Apart from their well-appreciated roles as supporting matrices, energy storage, and biosynthetic starting materials, carbohydrates are cast in a variety of interesting settings such as glycoconjugate antibiotics,[1] antitumor agents[2] and cardiotonic glycosides.[3] The importance of carbohydrate domains (in the context of glycoproteins and glycolipids) as elements in cell surface recognition is clear from their role in cellular adhesion[4,5] and as blood group determinants.[6]

To understand the biological functions of saccharides from a molecular point of view, it is of primary importance[7] to know the conformational preferences of these species in solution, in addition to their three-dimensional structures. Due to the flexibility of the glycosidic linkages and the rotation of the hydroxymethyl and other pendant groups, the conformational analysis of an oligosaccharide is difficult. In fact, the factors governing the rotamer populations of the hydroxymethyl group are still not fully understood.

The conformation of the hydroxymethyl group around the C5–C6 bond can be expressed by the torsional angle ω (O5–C5–C6–O6), although it is generally defined by means of the populations of its three main rotamers, the *gauche gauche* (*gg*), the *gauche trans* (*gt*), and the *trans gauche* (*tg*) (Fig. 1).

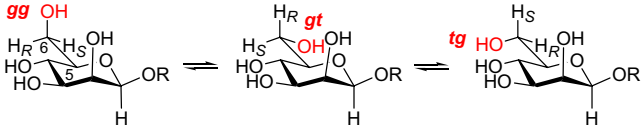

Figure 1. Molecular structure of an alkyl β-D-mannopyranoside in its three main rotamers, the *gg* ($\omega = -60°$), *gt* ($\omega = 60°$), and *tg* ($\omega = 180°$) rotamers around the C5–C6 bond.

Our previous studies on the rotational population dependence of the hydroxymethyl group in gluco-,[8] galacto-,[9] and α-D-mannopyranosides,[10] as well as in disaccharides,[11] on the aglycon and its absolute configuration, have revealed remarkable conformational properties. To complete our hydroxymethyl rotamer population studies for the three most important monosaccharides in nature, we have synthesized three different alkyl β-D-mannopyranosides series and analyzed them by means of CD and NMR spectroscopy. The

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results show a clear correlation between the hydroxymethyl rotational populations around the C5–C6 bond and the pK_a of the bonded alcohol (aglycon). The rotational populations are explained on the basis of different values of the *exo*-anomeric effect and by occasionally also taking into account nonbonded interactions. The results also establish the highest population as the *gg* or *gt* rotamer depending on the aglycon.

2. Results and discussion

The model alkyl β-D-mannopyranosides were synthesized in good yields as shown in Scheme 1. The commercially available tri-*O*-benzyl-glucal was treated with dimethyldioxirane (DMDO) to obtain the corresponding 1,2-anhydro sugar, which by adding $ZnCl_2$ and the appropriate alcohol led to the alkyl β-D-glucopyranosides **1**–**6** in good yields.[12] Oxidation with DMSO–Ac_2O and subsequent reduction with $NaBH_4$ in CH_2Cl_2/MeOH (1:1) led to the alkyl β-D-mannopyranosides **7**–**12**.[13] Deprotection of the benzyl groups and subsequent acetylation or *p*-bromobenzoylation led to the tetra-*O*-acetyl derivatives **13**–**18** or to the tetra-*O*-(*p*-bromobenzoyl) derivatives **19**–**24**, respectively. The 1-acyl derivatives **25** and **26** were obtained by per-acetylation and per-*p*-bromobenzoylation of D-mannose, respectively.

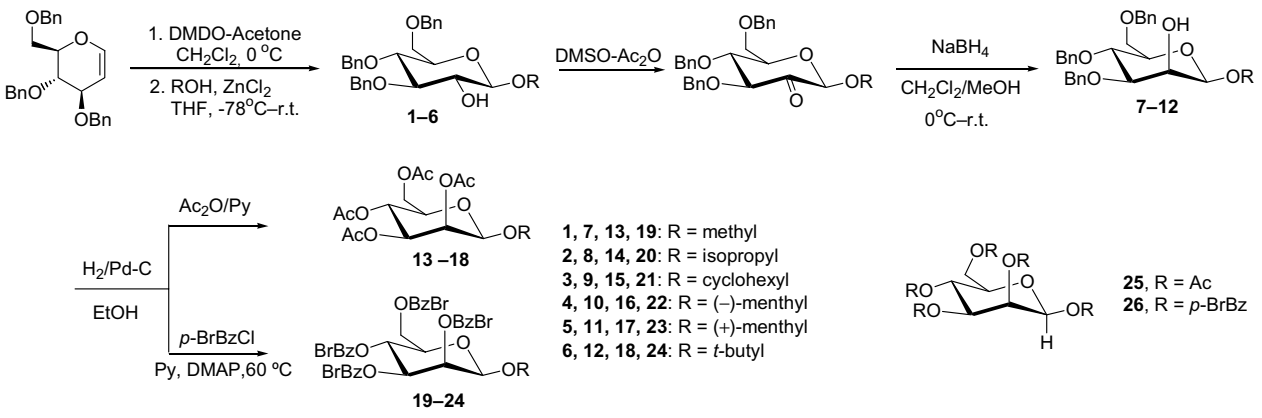
All these compounds were mainly characterized on the basis of their one- (^{1}H and ^{13}C) and two-dimensional NMR spectra. The anomeric configuration was assigned in each case on the basis of the T-ROESY NMR experiment. Furthermore, the lower chemical shift values obtained for H3 and H5 in the acetyl derivatives than in the corresponding α-anomers[10] confirmed the assignment. In addition, the T-ROESY NMR spectra also showed a strong cross-peak between the anomeric proton H1 and the aglyconic proton H*x*, confirming that for the more stable conformation, these two protons are located on the same side.

The rotamer populations of the hydroxymethyl group were calculated from the observed $J_{H5,H6R}$ and $J_{H5,H6S}$ coupling constants (accuracy ±0.1 Hz) and by using the Karplus equations recently proposed by Serianni co-workers.[14] 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,[15] on the basis of their chemical shifts and coupling constants. In general, for the D-manno-series saccharides, H6*R* proton signals appear at a higher field than H6*S* signals (δH6*S* > δH6*R*). The reverse behavior was observed for acetyl-D-manno-series saccharides (δH6*R* > δH6*S*), and $J_{H5,H6R}$ coupling constants have higher values than $J_{H5,H6S}$. Thus, compounds **7**–**12** showed chemical shifts for H6*S* between δ 3.82 and 3.74 and for H6*R* between 3.73 and 3.68, compounds **19**–**24** for H6*S* between δ 4.78 and 4.68 and for H6*R* between 4.51 and 4.43. As expected, the acetyl derivatives **13**–**18** showed the reverse behavior, chemical shifts for H6*S* were located at a higher field (δ 4.17–4.12) than those for H6*R* (δ 4.31–4.23). Independent of the substitution, all model compounds **7**–**24** showed higher $J_{H5,H6R}$ coupling constants than $J_{H5,H6S}$. Tables 1–3 show the $J_{H5,H6}$ coupling constants and calculated rotameric populations (%) around the C5–C6 bond for the β-D-mannose derivatives **7**–**26**.[16]

Analysis of the data for the three sets of model compounds (Tables 1–3) revealed a general increase in the $J_{H5,H6R}$ coupling constant values from 1-acyl, to primary, to secondary, and to tertiary alkyl β-D-mannopyranosides; the chiral (−)-menthyl mannopyranosides **10** and **22** being an exception in this behavior. On the other hand, the $J_{H5,H6S}$ coupling constant values obtained for the alkyl mannopyranosides remained almost constant in each series. To calculate rotamer populations of the hydroxymethyl group, each pair of $J_{H5,H6}$ coupling constant values were used in the Karplus equations pro-

Table 1. $J_{H5,H6}$ Coupling constants ($CDCl_3$) and calculated rotameric populations (%) for the alkyl tri-benzyl β-D-mannopyranosides **7**–**12**

Compd.	Aglycon	$J_{H5,H6S}$	$J_{H5,H6R}$	P_{gg}	P_{gt}	P_{tg}
7	Methyl	2.0	5.2	48	46	6
8	Isopropyl	1.9	5.6	44	51	5
9	Cyclohexyl	1.9	5.7	43	52	5
10	(−)-Menthyl	1.8	5.1	50	46	4
11	(+)-Menthyl	1.7	5.8	43	54	3
12	*tert*-Butyl	1.7	5.7	44	53	3



Scheme 1. Synthesis of the alkyl β-D-mannopyranosides **7**–**24**.

Table 2. $J_{H5,H6}$ Coupling constants ($CDCl_3$) and calculated rotameric populations (%) for the alkyl tetra-acetyl β-D-mannopyranosides **13**–**18** and for the penta-acetyl β-D-mannopyranoside **25**

Compd.	Aglycon	$J_{H5,H6S}$	$J_{H5,H6R}$	P_{gg}	P_{gt}	P_{tg}
25	(Acetyl)	1.5	4.9	54	45	1
13	Methyl	2.6	5.3	43	44	13
14	Isopropyl	2.3	5.8	39	51	10
15	Cyclohexyl	2.7	5.8	37	49	14
16	(−)-Menthyl	2.9	6.2	31	53	16
17	(+)-Menthyl	2.5	6.4	29	55	16
18	*tert*-Butyl	2.7	6.5	29	57	14

Table 3. $J_{H5,H6}$ Coupling constants ($CDCl_3$) and calculated rotameric populations (%) for the alkyl tetra-(*p*-bromobenzoyl)-β-D-mannopyranosides **19**–**24** and for the penta-(*p*-bromobenzoyl)-β-D-mannopyranoside **26**

Compd.	Aglycon	$J_{H5,H6S}$	$J_{H5,H6R}$	P_{gg}	P_{gt}	P_{tg}
26	(*p*-Br-benzoyl)	2.8	4.5	50	35	15
19	Methyl	3.1	4.6	47	34	18
20	Isopropyl	3.2	5.0	42	38	19
21	Cyclohexyl	3.3	5.3	38	41	21
22	(−)-Menthyl	2.9	4.5	50	34	16
23	(+)-Menthyl	3.1	5.8	34	48	18
24	*tert*-Butyl	3.2	6.1	31	51	19

posed by Serianni et al.[14] This set of equations was chosen since it provides a more accurate representation of the rotameric populations in solution and, in contrast to other Karplus equations, positive values for the *tg* rotamer population.[16]

As expected, the mentioned coupling constants behavior was reflected in the calculated rotamer populations of the hydroxymethyl group (Tables 1–3). Thus, as shown in Figures 2–4 from the 1-acyl (**25**, **26**), to the primary (**7**, **13**, **19**), to secondaries (**8**–**11**, **14**–**17**, **20**–**23**), and to the tertiary (**12**, **18**, **24**) alkyl β-D-mannopyranosides the *gt* rotamer population increased, the *gg* population decreased, and that for the least populated *tg* rotamer remained almost constant, with the (−)-menthyl derivatives **10** and **22** being an exception.

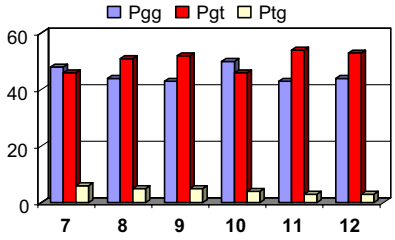


Figure 2. Calculated rotameric populations for compounds **7**–**12** (benzyl series).

As can be observed in Figure 5 there is a clear correlation between the rotamer population (Tables 1–3) and the pK_a of the alcohol[17] bonded to the mannopyranosyl system for all model compounds, except the (−)-menthyl derivatives **10** (benzyl series) and **22** (benzoyl series) (see below).[18] This correlation can be explained by the stereo-

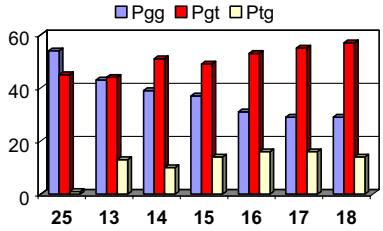


Figure 3. Calculated rotameric populations for compounds **13**–**18** and **25** (acetyl series).

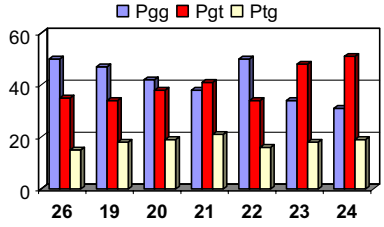


Figure 4. Calculated rotameric populations for compounds **19**–**24** and **26** (benzoyl series).

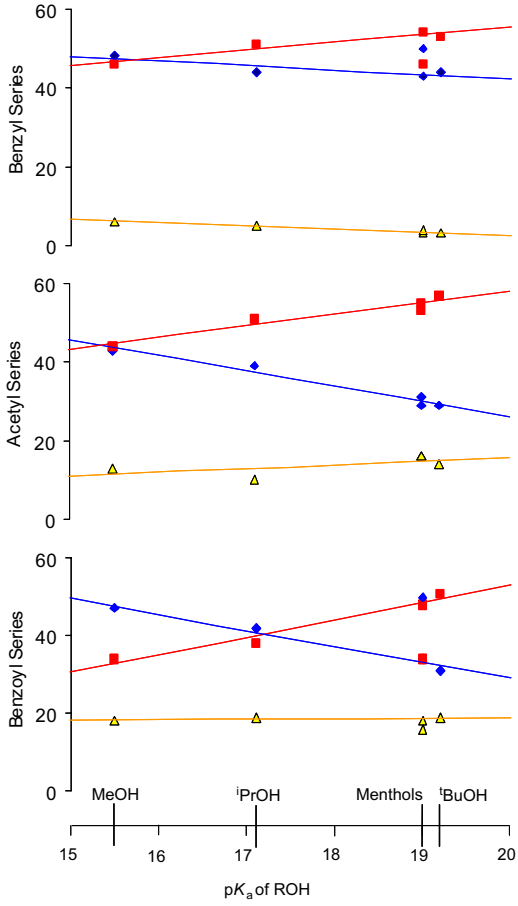


Figure 5. Plots of rotamer populations versus pK_a of bonded alcohols for the three different series. P_{gg} (blue lines), P_{gt} (red lines) and P_{tg} (yellow lines).

electronic *exo*-anomeric effect (Fig. 6)[19] but not by steric effects, since the bulkier secondary and tertiary alkyl

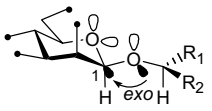


Figure 6. Illustration of the molecular orbitals involved in the *exo*-anomeric effect.

group (compared to the methyl) would lead to decreased *gt* populations through nonbonded interactions with the hydroxymethyl group. The value of the *exo*-anomeric effect must increase from primary, to secondary, and to tertiary alkyl mannopyranoside derivatives,[20] producing a gradual shortening and 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 *gg* populations, respectively. The smaller $J_{H5,H6}$ coupling constant values obtained for the 1-acyl derivatives **25** and **26** compared to the alkyl mannopyranosides **13**–**18** and **19**–**24**, respectively, support this explanation. The delocalization of the nonbonding electron pair of the exocyclic oxygen with the C=O bond in the 1-acyl derivatives lead to a low or nil participation of the stereoelectronic *exo*-anomeric effect and therefore high *gg* and low *gt* rotamer populations were obtained. This relationship between the *exo*-anomeric effect and the rotamer population of the hydroxymethyl group seems to be general, since in alkyl gluco-[8] and galactopyranosides,[9] an increase in the stereoelectronic *exo*-anomeric effect also led to an increase in the population of the *gt* rotamer. Additionally, according to the pyranoside substitution (benzyl, acetyl, or benzoyl) and the aglycon, the *gg* or *gt* rotamer has the highest population.

The (−)-menthyl mannopyranosides **10**, **16**, and **22** deserve special consideration. Depending on the series, this aglycon led to the *gg* (benzyl and benzoyl series) or *gt* (acetyl series) rotamer as the most populated. For these stereoisomers, the isopropyl group, located *syn* to the endocyclic oxygen O5 in its most stable conformation, is close to the hydroxymethyl group at C6 and therefore nonbonded interactions between these two groups are possible (Fig. 7). This explains why for these benzyl and benzoyl derivatives the *gg* rotamer is the most populated and in the acetyl series it is *gt*. The larger size of the benzyl and benzoyl groups than the acetyl group led the former derivatives to higher nonbonded interactions with the isopropyl group. For this reason, the rotamer populations of the (−)-menthyl derivatives **10** and **22** do not show the above mentioned correlation with its pK_a (Fig. 5).

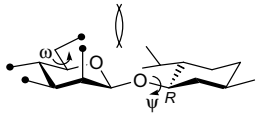


Figure 7. (−)-Menthyl β-D-mannopyranosides **10**, **16**, and **22**.

On the other hand, the (+)-menthyl derivatives have the isopropyl group in an *anti* disposition with respect to the endocyclic oxygen O5 and therefore without nonbonded interactions. In addition, these secondary alkyl mannopyranosides possess higher *gt* and lower *gg* rotamer populations than the other secondary alkyl mannopyranosides (Tables 1–3). This result can be explained in terms of a stronger *exo*-anomeric effect, as a consequence of its high pK_a value.

The alkyl β-D-mannopyranosides have been substituted with *p*-bromobenzoyl groups in order to accurately analyze the $J_{H5,H6}$ coupling constant of the prochiral H6 proton signals, since these groups affect the proton and carbon resonances where they are located, leading therefore to less crowded NMR spectra. In addition, these exciton-coupled chromophores permit their circular dichroism (CD) spectra to be measured. The high sensitivity and straightforward spectral interpretation of the circular dichroic exciton chirality method[21] provides additional conformational information. On the basis of the additivity of the amplitude (*A* value)[22,23] or the principle of pairwise additivity,[24] and taking into account the interchromophoric distance and the dihedral angle of the chromophores involved in a pairwise interaction, the CD spectra of our model alkyl mannopyranosides must show deep negative split CD curves, mainly as a consequence of the intense negative sign of the 2/3, 3/4, and 2/4 pairwise interactions (Fig. 8). However, the amplitudes of the CD curves cannot be identical, because the alkyl mannopyranosides with different rotamer populations will exhibit different contributions of the pairwise interactions involving the chromophore at the 6 position (Fig. 9).

Figure 8. Pairwise interactions with constant intensity and negative sign for mannopyranosides.

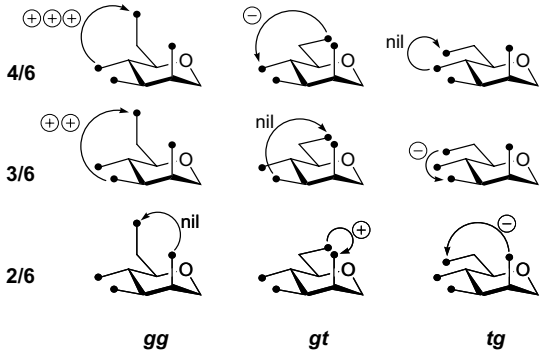


Figure 9. Pairwise interactions involving the chromophore at the 6 position in each of the three stable rotamers.

The alkyl tetra-*O*-(*p*-bromobenzoyl)-β-D-mannopyranosides exhibited negative split CD curves, more specifically, negative first Cotton effects at 250 nm and

positive second Cotton affects at 232 nm, centered on the *p*-bromobenzoate λ_{max} 245 nm (Figs. 10 and 11).

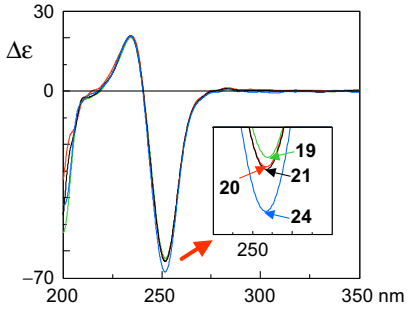


Figure 10. CD spectra comparison of the model methyl, isopropyl, cyclohexyl, and *tert*-butyl β-D-mannopyranosides **19**–**21** and **24**, respectively (in CH_3CN).

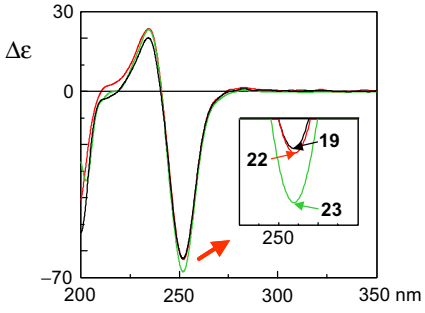


Figure 11. CD spectra comparison of the model methyl, (−)-menthyl, and (+)-menthyl β-D-mannopyranosides **19**, **22** and **23**, respectively (in CH_3CN).

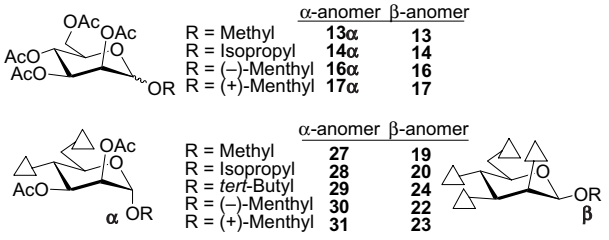
For comparative analysis, the intensities of the first Cotton effects are more accurate, because occasionally the presence of a background ellipticity alters the intensity of the Cotton effects at short wavelengths and therefore, the intensities of the second Cotton effects and the amplitudes (*A* values) of the CD spectra of our model compounds may not be precise. For this reason, Figures 10 and 11 contain an amplified view of these first Cotton effects at 250 nm and Table 4, their intensities ($\Delta\varepsilon_1$).

The intensity of the first Cotton effect of the CD spectra for nonchiral alkyl β-D-mannopyranosides **19**–**21** and **24** gradually increased from the methyl (−62.8), isopropyl (−63.7), cyclohexyl (−63.9), and *tert*-butyl (−67.9) β-D-mannopyranosides, while for the chiral alkyl β-D-mannopyranosides, a higher intensity of the first Cotton effect was observed for the (−)-menthyl derivative **22** (−63.2) than for its stereoisomer (+)-menthyl **23** (−67.9), as expected. These intensities are consistent only with a gradual decrease in the contribution of the positively coupled 4/6 pairwise interaction (*gg* rotamer) (Fig. 9).

For CD and NMR data comparison, ^1H NMR spectra of compounds **19**–**24** were also recorded in CD_3CN (Table 4), since rotamer populations might be solvent dependent. As listed in Table 4, the intensities of the CD first Cotton effects ($\Delta\varepsilon_1$) and the rotamer populations calculated from the $J_{H5,H6}$ coupling constants of the NMR spectra are in good agreement.

In addition, comparison of the NMR data in $CDCl_3$ (Table 3) with those in CD_3CN (Table 4) reveals a slight solvent dependence of the rotamer populations, the population of the *gg* rotamer increasing at the expense of the *gt* for the polar solvent.

Comparative analysis, β versus α: The calculated rotational populations of the α-[10] and β-anomers of alkyl mannopyranosides, obtained by applying the same set of equations, were compared (Scheme 2). The analysis shows a higher dependence on the structure of the aglycon and a clearer behavior for the β than for the α anomers (Fig. 12 for the acetyl series, Fig. 13 for benzoyl).



Scheme 2.

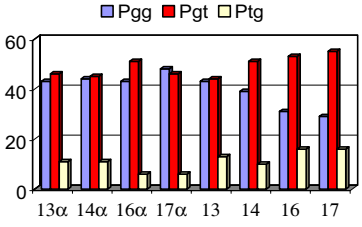


Figure 12. Comparison between rotational population of anomers for the acetyl series.

Table 4. $J_{H5,H6}$ Coupling constants (CD_3CN), calculated rotameric populations (%), and CD data (CH_3CN) for the alkyl tetra-(*p*-bromobenzoyl)-β-D-mannopyranosides **19**–**24**

Compd.	Aglycon	$J_{H5,H6S}$	$J_{H5,H6R}$	P_{gg}	P_{gt}	P_{tg}	$\Delta\varepsilon_1$
19	Methyl	3.0	3.9	56	27	17	−62.8
20	Isopropyl	3.0	4.2	52	30	17	−63.7
21	Cyclohexyl	3.1	4.6	47	34	18	−63.9
22	(−)-Menthyl	2.9	4.0	55	29	16	−63.2
23	(+)-Menthyl	3.0	5.1	43	40	17	−67.9
24	*tert*-Butyl	3.0	4.9	44	38	17	−67.9

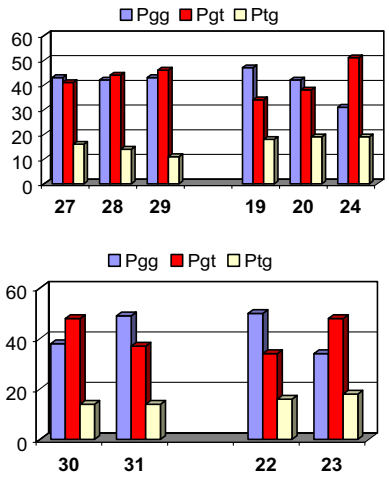


Figure 13. Comparison between rotational population of anomers for the benzoyl series: nonchiral alkyl (top) and chiral alkyl (bottom) mannopyranosides.

In addition, as the pK_a of the aglycon increases, the population of the *gt* rotamer does also, independently of the anomeric configuration, and the population of the *gg* or *tg* rotamer decreases, depending respectively on the β or α anomeric configuration.

As can be observed at the bottom of Figure 13, the rotational population of the hydroxymethyl group in the menthyl mannopyranosides depends on the nonbonded interactions between this group and the isopropyl group. Thus the *syn* location to the endocyclic oxygen O5 of the isopropyl group for the (−)-menthyl β-D- and (+)-menthyl α-D-mannopyranosides leads to higher *gg* and smaller *gt* population than the (+)-menthyl β-D- and (−)-menthyl α-D-mannopyranosides, which have the isopropyl group in the *anti* location.

This analysis reveals that the hydroxymethyl group rotational population depends on the anomeric configuration. The β-anomers show a higher dependence and unambiguous rotational behavior.

3. Conclusions

The rotational population of the hydroxymethyl group of alkyl β-D-mannopyranosides is dependent on the structure of the aglycon and its absolute configuration, as well as on the anomeric configuration. This was determined by analyzing the $^3J_{H5,H6R}$ and $^3J_{H5,H6S}$ values and CD spectral data. Furthermore, a clear relationship between this population around the C5–C6 bond and the pK_a of the bonded alcohol (aglycon) was observed. Thus, as the pK_a increased, the population of the *gt*/*gg* rotamers gradually increased/decreased respectively, while the population of the *tg* rotamer remained almost constant. These results point to a stereoelectronic *exo*-anomeric effect as responsible for this, along with steric effects. In addition, a different, higher dependence on the structure of the aglycon was observed for the β-anomers than for the α-anomers.

4. Experimental

4.1. 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 77.0 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. The concentrations of the CD samples were ascertained from the UV spectra, using the experimentally determined ε values at 245 nm: tetra-(*p*-bromobenzoate) ε 76,400.

For analytical and preparative thin-layer chromatography, silica gel ready-foils and glass-backed plates (1 mm) were used, being respectively, 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 (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 nitrogen atmosphere. The compounds prepared were characterized on the basis of their one- (^{1}H and ^{13}C) and two-dimensional (COSY, HMQC, and TROESY) NMR spectra, as well as by elemental analysis, MS, UV, and CD spectroscopy.

4.2. General procedure for the preparation of β-glucopyranosides

A solution of dimethyldioxirane in acetone (2 equiv, ca. 0.075 M) was added to a stirred solution of the tri-*O*-benzyl-D-glucal in dry CH_2Cl_2 (5 mL/mmol) at 0 °C under nitrogen atmosphere, and the reaction stirred at 0 °C for 30 min. The 1,2-anhydro sugar thus obtained was concentrated under reduced pressure and left under vacuum for 2 h. Then it was dissolved in dry THF (10 mL/mmol) under dry nitrogen, and molecular sieves and the corresponding alcohol (10 equiv) added. The reaction mixture was cooled to −78 °C and 0.5 equiv of a 1.0 M solution of $ZnCl_2$ in diethyl ether then added. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was diluted with EtOAc, filtered, and washed with water; then the combined organic layers were dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by flash column chromatography.

4.3. General procedure for the preparation of β-mannopyranosides

The sugar was treated with a 1:2 acetic anhydride/dimethyl sulfoxide (8 mL/mmol) mixture, that was previously stirred for 15 min. The reaction was left 1–2 days at room temperature under a nitrogen atmosphere. Then it was concentrated to dryness, dissolved in CH_2Cl_2, and washed with water. The combined

organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated in vacuum. Then, 2 equiv of sodium borohydride was added to a solution of the crude reaction mixture in dry 1:1 CH_2Cl_2/MeOH (10 mL/mmol) at 0 °C in a nitrogen atmosphere and then the ice bath removed. When the reaction was complete (approx. 2 h), it was diluted with CH_2Cl_2 and washed with water, 1% citric acid solution, $NaHCO_3$, and brine. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated in a vacuum. The product was purified by silica gel column chromatography.

4.4. General procedure for the debenzylation and acetylation or benzoylation

To a solution of the substrate in dry ethanol (10 mL/mmol) was added 50 mg/mmol of palladium at 5% on activated carbon with sufficient hydrogen. After the reaction was complete, the mixture was diluted in ethanol, filtered through a bed of Celite and evaporated under reduced pressure. Then the crude reaction mixture was divided between two round-bottom flasks. To the first flask, 20 mL/mmol of a 1:1 solution of dry pyridine/acetic anhydride was added at room temperature and stirred overnight. Excess solvent was removed under reduced pressure in the presence of toluene, and the residue purified with column chromatography. Dry pyridine (10 mL/mmol) was added to the second flask, and then treated with 6 equiv of *p*-bromobenzoyl chloride and DMAP as catalyst. The solution was heated at 60 °C and stirred overnight. The solvent was removed under reduced pressure in the presence of toluene and the residue chromatographed.

4.5. Methyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside 1

Following the general procedure for the preparation of β-glucosides, a solution of DMDO in acetone (10.0 mL, 0.75 mmol) was added to a solution of 222 mg (0.53 mmol) of the tri-*O*-benzyl-D-glucal in CH_2Cl_2 (2.5 mL) at 0 °C. The anhydro sugar was dissolved in 5.0 mL of dry THF and MeOH (1.0 mL, 24.7 mmol) and a 1.0 M solution of $ZnCl_2$ in Et_2O (250 μL, 0.25 mmol) were added. The crude reaction mixture was purified by chromatography on silica gel (*n*-hexane/EtOAc, 7.5:2.5) to give **1** (189 mg, 0.41 mmol, 77% yield): TLC R_f = 0.29 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D$ = +1.9 (*c* 1.4, $CHCl_3$); MS (EI) *m/z* (relative intensity) 373 ($[M^+-C_7H_7]$, 8.9), 341 (5.2), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.36–7.18 (m, 15H), 4.91 (d, J = 11.2 Hz, 1H), 4.85 (d, J = 11.2 Hz, 1H), 4.83 (d, J = 10.7 Hz, 1H), 4.63 (d, J = 12.2 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.54 (d, J = 10.7 Hz, 1H), 4.18 (d, J = 7.4 Hz, H-1), 3.75 (dd, J = 1.9 and 10.8 Hz, H-6_{proS}), 3.71 (dd, J = 4.5 and 10.8 Hz, H-6_{proR}), 3.63–3.52 (m, 3H), 3.55 (s, 3H), 3.49 (m, H-5); ^{13}C NMR ($CDCl_3$) δ 138.5 (s), 137.9 (s×2), 128.2–127.4 (aromatic Cs), 103.6 (d, C-1), 84.4 (d, C-3), 77.4 (d, C-4), 74.9 (t×2), 74.8 (d, C-5), 74.4 (d, C-2), 73.3 (t), 68.7 (t, C-6), 56.9 (q, C-1′). Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.33; H, 7.12.

4.6. *iso*-Propyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside 2

Following the general procedure for the preparation of β-glucosides, 35.0 mL (2.63 mmol) of a solution of DMDO in acetone was added to a solution of the glucal (512 mg, 1.23 mmol) in 6.0 mL of dry CH_2Cl_2 at 0 °C. Later, the product was directly dissolved in THF (12.0 mL), and isopropanol (1 mL, 13.0 mmol) and zinc chloride (600 μL, 0.60 mmol) were added. Flash column chromatography with *n*-hexane/EtOAc (7.5:2.5) as eluent yielded **2** (451 mg, 0.92 mmol, 75% yield): TLC R_f = 0.37 (*n*-hexane/EtOAc, 7:3); $[\alpha]_D$ = −7.7 (*c* 1.4, $CHCl_3$); MS (EI) *m/z* (relative intensity) 401 ($[M^+-C_7H_7]$, 3.2), 341 (3.9), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.37–7.19 (15H), 4.95 (d, J = 11.3 Hz, 1H), 4.85 (d, J = 10.8 Hz, 1H), 4.83 (d, J = 11.3 Hz, 1H), 4.61 (d, J = 12.2 Hz, 1H), 4.58 (d, J = 12.2 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.31 (d, J = 7.6 Hz, H-1), 4.02 (sep, J = 6.1 Hz, H2′), 3.74 (dd, J = 1.7 and 10.8 Hz, H-6_{proS}), 3.68 (dd, J = 4.9 and 10.8 Hz, H-6_{proR}), 3.60–3.48 (m, 4H), 1.29 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.7 (s), 138.2 (s), 138.1(s), 128.3–127.5 (aromatic Cs), 101.1 (d, C-1), 84.6 (d, C-3), 77.6 (d, C-4), 75.1 (t), 75.0 (d, C-5), 74.9 (t), 74.7 (d, C-2), 73.3 (t), 71.8 (d, C2′), 69.0 (t, C-6), 23.4 (q), 21.9 (q); Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.15; H, 7.37. Found: C, 73.18; H, 7.49.

4.7. Cyclohexyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside 3

Following the general procedure for the preparation of β-glucosides, a solution of dimethyldioxirane (34.0 mL, 2.55 mmol) and the glucal (442 mg, 1.06 mmol) in 5.0 mL of CH_2Cl_2 were utilized. Then, a solution of the resulting substrate in 10.0 mL of THF was treated with $ZnCl_2$ (500 μL, 0.50 mmol) and cyclohexanol (1.0 mL, 9.5 mmol), to yield compound **3** (313 mg, 0.59 mmol, 55% yield) after chromatography on silica gel (*n*-hexane/EtOAc, 9:1): TLC R_f = 0.44 (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D$ = −9.9 (*c* 3.3, $CHCl_3$); MS (EI) *m/z* (relative intensity) 441 ($[M^+-C_7H_7]$, 0.8), 341 (1.9), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.39–7.22 (m, 15H), 4.98 (d, J = 11.3 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.85 (d, J = 11.3 Hz, 1H), 4.63 (d, J = 12.2 Hz, 1H), 4.57 (d, J = 12.2 Hz, 1H), 4.56 (d, J = 10.8 Hz, 1H), 4.37 (d, J = 7.5 Hz, H-1), 3.77 (dd, J = 1.8 and 10.8 Hz, H-6_{proS}), 3.70 (dd, J = 4.9 and 10.8 Hz, H-6_{proR}), 3.69 (m, H1′), 3.63–3.55 (m, 3H), 3.52 (m, H-5), 2.07 (m, 1H), 2.00 (m, 1H), 1.81 (m, 2H), 1.60 (m, 1H), 1.50 (m, 1H), 1.45–1.21 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 138.6 (s), 138.1 (s), 138.0 (s), 128.2–127.4 (aromatic Cs), 101.0 (d, C-1), 84.5 (d, C-3), 77.5 (d, C-4), 77.5 (d, C1′), 74.9 (d, C-5), 74.9 (t), 74.8 (t), 74.6 (d, C-2), 73.2 (t), 68.9 (t, C-6), 33.5 (t), 31.8 (t), 25.4 (t), 24.0 (t×2); Anal. Calcd for $C_{33}H_{40}O_6$: C, 74.41; H, 7.57. Found: C, 74.43; H, 7.81.

4.8. (1*R*,2*S*,5*R*)-Menthyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside 4

Following the general procedure for the preparation of β-glucosides, D-glucal (924 mg, 2.22 mmol), and DMDO (82.0 mL, 6.02 mmol) in dry CH_2Cl_2 (11.0 mL) were

used. Then, the residue was dissolved in 25.0 mL of THF and treated with a solution of $ZnCl_2$ in diethyl ether (1.0 mL, 1.00 mmol) and L-(−)-menthol (3.5 g, 22.2 mmol). After flash chromatography (*n*-hexane/EtOAc, 9:1), compound **4** (655 mg, 1.11 mmol, 50%) was obtained: TLC $R_f = 0.50$ (*n*-hexane/EtOAc, 8:2); $[\alpha]_D = -37.8$ (*c* 1.3, $CHCl_3$); MS (EI) *m/z* (relative intensity) 497 ($[M^+ - C_7H_7]$, 0.8), 341 (3.0), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.39–7.22 (m, 15H), 4.95 (d, $J = 11.4$ Hz, 1H), 4.85 (d, $J = 10.8$ Hz, 1H), 4.84 (d, $J = 11.4$ Hz, 1H), 4.60 (d, $J = 12.2$ Hz, 1H), 4.59 (d, $J = 10.8$ Hz, 1H), 4.54 (d, $J = 12.2$ Hz, 1H), 4.32 (d, $J = 7.7$ Hz, H-1), 3.70 (m, 2H), 3.62–3.59 (m, 2H), 3.53–3.46 (m, 3H), 2.30 (m, 1H), 2.06 (br d, $J = 12.5$ Hz, 1H), 1.66 (d, $J = 12.7$ Hz, 2H), 1.37 (m, 1H), 1.24 (m, 1H), 1.04–0.80 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 138.7 (s), 138.2 (s), 138.1 (s), 128.4–127.5 (aromatic Cs), 99.9 (d, C-1), 84.7 (d, C-3), 77.5 (d, C-4), 77.0 (d, C-1′), 75.1 (t), 75.0 (d, C-5), 75.0 (t), 74.5 (d, C-2), 73.6 (t), 69.2 (t, C-6), 47.7 (d), 40.8 (t), 34.3 (t), 31.4 (d), 25.1 (d), 23.0 (t), 22.2 (q), 21.0 (q), 15.7 (q); Anal. Calcd for $C_{37}H_{48}O_6$: C, 75.48; H, 8.22. Found: C, 75.44; H, 8.66.

4.9. (1*S*,2*R*,5*S*)-Menthyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside 5

Following the general procedure for the preparation of β-glucosides, 483 mg (1.16 mmol) of D-glucal in 5.8 mL of dry CH_2Cl_2 was treated with 44 mL (3.30 mmol) of a DMDO solution in acetone. Later, the residue was dissolved in THF (16.4 mL) and 1.3 g (8.24 mmol) of D-(+)-menthol and 0.58 mmol of $ZnCl_2$ (580 μL of a solution 1.0 M) were added. Column chromatography (*n*-hexane/EtOAc, 9:1) of the residue gave **5** (376 mg, 0.64 mmol, 55%): TLC $R_f = 0.48$ (*n*-hexane/EtOAc, 8:2); $[\alpha]_D = +17.0$ (*c* 1.5, $CHCl_3$); MS (EI) *m/z* (relative intensity) 497 ($[M^+ - C_7H_7]$, 1.4), 432 (0.4), 341 (3.4), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.42–7.25 (m, 15 H), 5.01 (d, $J = 11.2$ Hz, 1H), 4.89 (d, $J = 10.7$ Hz, 1H), 4.87 (d, $J = 10.7$ Hz, 1H), 4.64–4.59 (m, 3H), 4.36 (d, $J = 7.0$ Hz, H-1), 3.79 (br d, $J = 10.7$ Hz, H-6$_{proS}$), 3.72–3.57 (m, 5H), 3.45 (dd, $J = 3.9$ and 10.6 Hz, H-1′), 2.34–2.28 (m, 2H), 1.70–1.65 (m, 2H), 1.43–1.35 (m, 2H), 1.16 (m, 1H), 1.07–0.83 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 138.5 (s), 138.1 (s), 138.0 (s), 128.1–127.2 (aromatic Cs), 103.7 (d, C-1), 84.5 (d, C-3), 81.3 (d, C-1′), 77.4 (d, C-4), 75.1 (d, C-5), 74.9 (t), 74.8 (t), 74.6 (d, C-2), 73.0 (t), 68.9 (t, C-6), 48.2 (d), 43.1 (t), 34.0 (t), 31.4 (d), 25.1 (d), 22.7 (t), 22.1 (q), 20.9 (q), 15.7 (q); Anal. Calcd for $C_{37}H_{48}O_6$: C, 75.48; H, 8.22. Found: C, 75.47; H, 8.43.

4.10. *tert*-Butyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside 6

Following the general procedure for the preparation of β-glucosides, a solution of 526 mg (1.26 mmol) of D-glucal in CH_2Cl_2 (6.0 mL) and 33.5 mL (2.51 mmol) of DMDO were used. Treatment of the anhydro sugar with 1.0 mL of *tert*-butanol (10.5 mmol) and 650 μL (0.65 mmol) of $ZnCl_2$ in dry THF (13.0 mL), after column chromatography (*n*-hexane/EtOAc, 9:1), gave compound **6** (285 mg, 0.56 mmol, 45%, yield): TLC $R_f = 0.44$ (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D = -12.9$ (*c* 1.0, $CHCl_3$); MS (EI) *m/z* (relative intensity) 415 ($[M^+ - C_7H_7]$, 0.8), 341 (2.2), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.38–7.21 (m, 15H), 4.98 (d, $J = 11.2$ Hz, 1H), 4.86 (d, $J = 11.2$ Hz, 1H), 4.83 (d, $J = 11.7$ Hz, 1H), 4.60 (d, $J = 12.2$ Hz, 1H), 4.56 (d, $J = 11.7$ Hz, 1H), 4.54 (d, $J = 12.2$ Hz, 1H), 4.43 (d, $J = 7.7$ Hz, H-1), 3.73 (dd, $J = 1.8$ and 10.7 Hz, H-6$_{proS}$), 3.66 (dd, $J = 5.2$ and 10.7 Hz, H-6$_{proR}$), 3.63–3.48 (m, 4H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 138.7 (s), 138.2 (s), 138.1 (s), 128.2–127.4 (aromatic Cs), 97.2 (d, C-1), 84.7 (d, C-3), 77.6 (d, C-4), 76.0 (d, C-2′), 74.9 (t), 74.8 (d, C-5), 74.8 (t), 74.7 (d, C-2), 73.2 (t), 69.1 (t, C-6), 28.7 (q×3); Anal. Calcd for $C_{31}H_{38}O_6$: C, 73.49; H, 7.56. Found: C, 73.49; H, 7.78.

4.11. Methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside 7

Following the general procedure for β-mannosides, compound **7** was obtained with a 65% yield (96 mg, 0.21 mmol) after column chromatography (*n*-hexane/EtOAc, 6:4): TLC $R_f = 0.15$ (*n*-hexane/EtOAc, 6:4); $[\alpha]_D = -18.6$ (*c* 1.6, $CHCl_3$); MS (EI) *m/z* (relative intensity) 373 ($[M^+ - C_7H_7]$, 0.2), 341 (2.8), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.21–7.37 (m, 15H), 4.89 (d, $J = 10.8$ Hz, 1H), 4.77 (d, $J = 11.9$ Hz, 1H), 4.68 (d, $J = 11.9$ Hz, 1H), 4.64 (d, $J = 12.2$ Hz, 1H), 4.57 (d, $J = 12.2$ Hz, 1H), 4.54 (d, $J = 10.8$ Hz, 1H), 4.33 (s, H-1), 4.10 (br s, H-2), 3.86 (t, $J = 9.3$ Hz, H-4), 3.79 (dd, $J = 2.0$ and 10.8 Hz, H-6$_{proS}$), 3.73 (dd, $J = 5.2$ and 10.8 Hz, H-6$_{proR}$), 3.57 (dd, $J = 3.1$ and 9.3 Hz, H-3), 3.56 (s, 3H), 3.44 (m, H-5); ^{13}C NMR ($CDCl_3$) δ 138.2 (s), 138.1 (s), 137.7 (s), 128.4–127.5 (aromatic Cs), 100.6 (d, C-1), 81.4 (d, C-3), 75.2 (d, C-5), 75.0 (t), 74.2 (d, C-4), 73.4 (t), 71.3 (t), 69.1 (t, C-6), 68.1 (d, C-2), 56.8 (q, C-1′); Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.38; H, 7.24.

4.12. *iso*-Propyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside 8

According to the general procedure for the preparation of β-mannosides, 430 mg (0.87 mmol) of glucopyranoside **2** provided, after column chromatography (*n*-hexane/EtOAc, 7.5:2.5), compound **8** (277 mg, 0.56 mmol, 64%): TLC $R_f = 0.19$ (*n*-hexane/EtOAc, 7:3); $[\alpha]_D = -27.4$ (*c* 2.2, $CHCl_3$); MS (EI) *m/z* (relative intensity) 401 ($[M^+ - C_7H_7]$, 0.7), 341 (4.4), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.38–7.22 (m, 15H), 4.90 (d, $J = 10.8$ Hz, 1H), 4.78 (d, $J = 11.9$ Hz, 1H), 4.67 (d, $J = 11.9$ Hz, 1H), 4.62 (d, $J = 12.1$ Hz, 1H), 4.58 (d, $J = 12.1$ Hz, 1H), 4.55 (d, $J = 10.8$ Hz, 1H), 4.50 (s, H-1), 4.09 (sept, $J = 6.1$ Hz, H-2′), 4.06 (br s, H-2), 3.84 (t, $J = 9.4$ Hz, H-4), 3.77 (dd, $J = 1.9$ and 10.8 Hz, H-6$_{proS}$), 3.69 (dd, $J = 5.6$ and 10.8 Hz, H-6$_{proR}$), 3.58 (dd, $J = 3.1$ and 9.4 Hz, H-3), 3.43 (m, H-5), 1.29 (d, $J = 6.1$ Hz, 3H), 1.17 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.1 (s), 138.0 (s), 137.7 (s), 128.1–127.2 (aromatic Cs), 97.4 (d, C-1), 81.4 (d, C-3), 75.0 (t), 74.8 (d, C-5), 74.0 (d, C-4), 73.1 (t), 70.9 (t), 70.7 (d, C-2′), 69.1 (t, C-6), 68.5 (d, C-2), 23.2 (q), 21.4 (q); Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.15; H, 7.37. Found: C, 73.15; H, 7.72.

4.13. Cyclohexyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside 9

Synthesis of compound **9** was carried out from **3** (437 mg, 0.82 mmol) as described in the general procedure for β-mannosides. Column chromatography (*n*-hexane/EtOAc, 7.5:2.5) of the residue gave **9** (267 mg, 0.50 mmol, 61%): TLC R_f = 0.21 (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D = -27.7$ (*c* 2.6, $CHCl_3$); MS (EI) *m/z* (relative intensity) 441 ($[M^+ - C_7H_7]$, 0.6), 341 (4.7), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.38–7.24 (m, 15H), 4.90 (d, J = 10.9 Hz, 1H), 4.79 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.9 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.58–4.53 (m, 2H), 4.54 (s, H-1), 4.07 (d, J = 2.6 Hz, H-2), 3.84 (t, J = 9.4 Hz, H-4), 3.79 (dd, J = 1.9 and 10.8 Hz, H-6$_{proS}$), 3.74 (m, H-1′), 3.69 (dd, J = 5.7 and 10.8 Hz, H-6$_{proR}$), 3.57 (dd, J = 3.1 and 9.1 Hz, H-3), 3.43 (m, H-5), 2.00 (m, 1H), 1.88 (m, 1H), 1.74 (m, 2H), 1.54 (m, 1H), 1.45 (m, 1H), 1.33–1.18 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 138.2 (s), 138.1 (s), 137.7 (s), 128.2–127.3 (aromatic Cs), 97.2 (d, C-1), 81.5 (d, C-3), 76.4 (d, C-1′), 75.0 (d, C-5), 74.9 (t), 74.1 (d, C-4), 73.2 (t), 71.0 (t), 69.2 (t, C-6), 68.6 (d, C-2), 33.3 (t), 31.5 (t), 25.4 (t), 23.9 (t), 23.8 (t); Anal. Calcd for $C_{33}H_{40}O_6$: C, 74.41; H, 7.57. Found: C, 74.42; H, 7.56.

4.14. (1*R*,2*S*,5*R*)-Menthyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside 10

Following the procedure for β-mannosides, compound **10** was obtained from glucopyranoside **4** (611 mg, 1.04 mmol) with a 65% yield (395 mg, 0.67 mmol), after column chromatography (*n*-hexane/EtOAc, 9:1): TLC R_f = 0.44 (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D = -49.6$ (*c* 1.6, $CHCl_3$); MS (EI) *m/z* (relative intensity) 497 ($[M^+ - C_7H_7]$, 0.3), 341 (2.5), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.39–7.24 (m, 15H), 4.90 (d, J = 10.9 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.63–4.56 (m, 3H), 4.53 (s, H-1), 4.02 (d, J = 2.9 Hz, H-2), 3.86 (t, J = 9.5 Hz, H-4), 3.74 (dd, J = 1.8 and 10.7 Hz, H-6$_{proS}$), 3.70 (dd, J = 5.1 and 10.7 Hz, H-6$_{proR}$), 3.60–3.54 (m, 2H), 3.40 (m, H-5), 2.28 (m, 1H), 1.98 (d, J = 12.1 Hz, 1H), 1.65 (d, J = 12.2 Hz, 2H), 1.35 (m, 1H), 1.28 (m, 1H), 1.00–0.81 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 138.4 (s), 138.3 (s), 138.0 (s), 128.4–127.5 (aromatic Cs), 96.1 (d, C-1), 81.9 (d, C-3), 76.5 (d, C-1′), 75.3 (d, C-5), 75.2 (t), 74.4 (d, C-4), 73.6 (t), 71.2 (t), 69.7 (t, C-6), 69.2 (d, C-2), 47.7 (d), 40.4 (t), 34.3 (t), 31.3 (d), 25.3 (d), 23.1 (t), 22.3 (q), 21.0 (q), 15.9 (q); Anal. Calcd for $C_{37}H_{48}O_6$: C, 75.48; H, 8.22. Found: C, 75.43; H, 8.60.

4.15. (1*S*,2*R*,5*S*)-Menthyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside 11

Following the procedure for β-mannosides, 324 mg (0.55 mmol) of glucopyranoside **5** led to compound **11** (239 mg, 0.41 mmol, 74%), after column chromatography (*n*-hexane/EtOAc, 9:1): TLC R_f = 0.42 (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D = +8.9$ (*c* 1.1, $CHCl_3$); MS (EI) *m/z* (relative intensity) 497 ($[M^+ - C_7H_7]$, 0.1), 432 (0.3), 341 (3.8), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.41–7.24 (m, 15H), 4.91 (d, J = 10.9 Hz, 1H), 4.80 (d, J = 11.8 Hz, 1H), 4.69 (d, J = 11.8 Hz, 1H), 4.63 (d, J = 12.2 Hz, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.58 (d, J = 10.9 Hz, 1H), 4.46 (s, H-1), 4.10 (d, J = 2.3 Hz, H-2), 3.86–3.78 (m, 2H), 3.70 (dd, J = 5.8 and 10.7 Hz, H-6$_{proR}$), 3.57 (dd, J = 2.4 and 9.0 Hz, H-3), 3.48–3.40 (m, 2H), 2.28 (m, 1H), 2.10 (m, 1H), 1.64 (m, 2H), 1.40–1.28 (m, 2H), 1.40 (q, J = 11.7 Hz, 1H), 1.00–0.83 (m, 8H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.2 (s), 138.1 (s), 137.7 (s), 128.1–127.2 (aromatic Cs), 100.9 (d, C-1), 81.7 (d, C-3), 81.3 (d, C-1′), 75.0 (d, C-5), 74.8 (t), 74.1 (d, C-4), 73.2 (t), 71.0 (t), 69.3 (t, C-6), 68.3 (d, C-2), 48.0 (d), 43.0 (t), 34.0 (t), 31.4 (d), 25.4 (d), 22.9 (t), 22.0 (q), 20.9 (q), 16.0 (q); Anal. Calcd for $C_{37}H_{48}O_6$: C, 75.48; H, 8.22. Found: C, 75.45; H, 8.34.

4.16. *tert*-Butyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside 12

Compound **12** was synthesized from **6** (376 mg, 0.74 mmol) as described in the general procedure for preparation of β-mannosides. Column chromatography (*n*-hexane/EtOAc, 8.5:1.5) of the residue gave compound **12** (218 mg, 0.43 mmol, 58%): TLC R_f = 0.19 (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D = -28.5$ (*c* 1.9, $CHCl_3$); MS (EI) *m/z* (relative intensity) 415 ($[M^+ - C_7H_7]$, 0.2), 341 (3.1), 91 (100); ^{1}H NMR ($CDCl_3$) δ 7.40–7.22 (m, 15H), 4.91 (d, J = 10.9 Hz, 1H), 4.79 (d, J = 11.9 Hz, 1H), 4.69 (d, J = 11.9 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.60 (s, H-1), 4.56 (d, J = 10.9 Hz, 1H), 4.55 (d, J = 12.1 Hz, 1H), 3.99 (d, J = 3.1 Hz, H-2), 3.83 (t, J = 9.4 Hz, H-4), 3.76 (dd, J = 1.7 and 10.7 Hz, H-6$_{proS}$), 3.68 (dd, J = 5.7 and 10.7 Hz, H-6$_{proR}$), 3.59 (dd, J = 3.1 and 9.1 Hz, H-3), 3.42 (m, H-5), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 138.2 (s), 138.1 (s), 137.7 (s), 128.1–127.1 (aromatic Cs), 94.1 (d, C-1), 81.7 (d, C-3), 75.9 (s, C-2′), 74.7 (t), 74.6 (d, C-5), 74.0 (d, C-4), 73.0 (t), 70.9 (t), 69.3 (d, C-2), 69.2 (t, C-6), 28.4 (q×3); Anal. Calcd for $C_{31}H_{38}O_6$: C, 73.49; H, 7.56. Found: C, 73.46; H, 7.82.

4.17. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 13

Following the procedure for debenzylation and acetylation, using 72 mg (0.16 mmol) of compound **7**, compound **13** (36 mg, 0.10 mmol) was obtained with a 64% yield after chromatography on silica gel (*n*-hexane/EtOAc, 5:5): TLC R_f = 0.27 (*n*-hexane/EtOAc, 1:1); $[\alpha]_D = -43.4$ (*c* 1.1, $CHCl_3$); MS (EI) *m/z* (relative intensity) 331 ($[M^+ - CH_3O]$, 2.7), 289 (12.8), 243 (32.2), 200 (46.5), 157 (100); ^{1}H NMR ($CDCl_3$) δ 5.48 (dd, J = 0.9 and 3.3 Hz, H-2), 5.27 (t, J = 10.0 Hz, H-4), 5.06 (dd, J = 3.3 and 10.0 Hz, H-3), 4.56 (d, J = 0.9 Hz, H-1), 4.31 (dd, J = 5.3 and 12.2 Hz, H-6$_{proR}$), 4.17 (dd, J = 2.6 and 12.2 Hz, H-6$_{proS}$), 3.67 (m, H-5), 3.53 (s, 3 H), 2.19 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7 (s), 170.4 (s), 170.0 (s), 169.6 (s), 99.7 (d, C-1), 72.4 (d, C-5), 71.1 (d, C-3), 68.6 (d, C-2), 66.0 (d, C-4), 62.5 (t, C-6), 57.5 (q, C-1′), 20.8 (q), 20.7 (q), 20.6 (q), 20.5 (q); Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.72; H, 6.41.

4.18. *iso*-Propyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 14

Debenzylation and acetylation of compound **8** (120 mg, 0.25 mmol) was performed as described in the general procedure, leading to compound **14** (66 mg, 0.17 mmol, 61%) after column chromatography (*n*-hexane/EtOAc, 7.5:2.5): TLC R_f = 0.26 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D = -42.9$ (*c* 1.8, $CHCl_3$); MS (EI) *m/z* (relative intensity) 347 ($[M^+ - C_3H_7]$, 0.6), 331 ($[M^+ - C_3H_7O]$, 6.5), 289 (1.9), 243 (26.3), 200 (41.4), 157 (100); ^{1}H NMR ($CDCl_3$) δ 5.40 (d, J = 3.3 Hz, H-2), 5.21 (t, J = 10.0 Hz, H-4), 5.03 (dd, J = 3.3 and 10.0 Hz, H-3), 4.69 (s, H-1), 4.27 (dd, J = 5.8 and 12.1 Hz, H-6_{proR}), 4.12 (dd, J = 2.3 and 12.1 Hz, H-6_{proS}), 3.96 (sep, J = 6.2 Hz, H-2′), 3.65 (m, H-5), 2.17 (s, 3 H), 2.06 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6 (s), 170.4 (s), 170.0 (s), 169.5 (s), 96.7 (d, C-1), 72.2 (d, C-5), 72.1 (d, C-2′), 71.2 (d, C-3), 69.4 (d, C-2), 66.2 (d, C-4), 62.7 (t, C-6), 22.9 (q), 21.6 (q); Anal. Calcd for $C_{17}H_{26}O_{10}$: C, 52.30; H, 6.71. Found: C, 52.31; H, 6.71.

4.19. Cyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 15

Debenzylation of **9** (115 mg, 0.22 mmol) and acetylation yielded compound **15** (70 mg, 0.16 mmol, 75%), after column chromatography (*n*-hexane/EtOAc, 7.5:2.5): TLC R_f = 0.36 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D = -42.3$ (*c* 1.3, $CHCl_3$); MS (EI) *m/z* (relative intensity) 357 ($[M^+ - C_3H_5O_2]$, 2.1), 331 (5.0), 289 (2.6), 243 (15.9), 200 (56.0), 157 (100); ^{1}H NMR ($CDCl_3$) δ 5.42 (dd, J = 1.0 and 3.4 Hz, H-2), 5.23 (t, J = 10.0 Hz, H-4), 5.04 (dd, J = 3.4 and 10.0 Hz, H-3), 4.74 (d, J = 1.0 Hz, H-1), 4.30 (dd, J = 5.8 and 12.1 Hz, H-6_{proR}), 4.13 (dd, J = 2.7 and 12.1 Hz, H-6_{proS}), 3.67–3.63 (m, 2H), 2.18 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.87 (m, 1H), 1.80 (m, 1H), 1.70 (m, 2H), 1.49 (m, 1H), 1.41 (m, 1H), 1.35–1.17 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.5 (s), 170.3 (s), 169.9 (s), 169.4 (s), 96.4 (d, C-1), 77.5 (d, C-1′), 72.1 (d, C-5), 71.1 (d, C-3), 69.4 (d, C-2), 66.2 (d, C-4), 62.6 (t, C-6), 32.8 (t), 31.3 (t), 25.3 (t), 23.6 (t), 23.5 (t), 20.7 (q), 20.6 (q), 20.5 (q), 20.4 (q); Anal. Calcd for $C_{20}H_{30}O_{10}$: C, 55.81; H, 7.02. Found: C, 55.80; H, 7.21.

4.20. (1*R*,2*S*,5*R*)-Menthyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 16

After debenzylation and acetylation of 186 mg (0.31 mmol) of compound **10**, compound **16** was obtained (145 mg, 0.30 mmol, 95% yield) after chromatography on silica gel (*n*-hexane/EtOAc, 7.5:2.5): TLC R_f = 0.46 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D = -81.2$ (*c* 1.5, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 509 ($[M+Na]^+$, 7.0), 487 ($[M+H]^+$, 2.2), 331 (100), 289 (6.1); ^{1}H NMR ($CDCl_3$) δ 5.37 (d, J = 3.3 Hz, H-2), 5.21 (t, J = 10.0 Hz, H-4), 5.06 (dd, J = 3.3 and 10.0 Hz, H-3), 4.73 (s, H-1), 4.23 (dd, J = 6.2 and 12.0 Hz, H-6_{proR}), 4.16 (dd, J = 3.0 and 12.0 Hz, H-6_{proS}), 3.63 (m, H-5), 3.50 (dt, J = 4.1 and 10.6 Hz, H-1′), 2.15 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 2.15–1.94 (m, 2H), 1.64–1.59 (m, 2H), 1.32 (m, 1H), 1.22 (m, 1H), 1.00–0.75 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 170.6 (s), 170.4 (s), 170.1 (s), 169.7 (s), 95.2 (d, C-1), 77.3 (d, C-1′), 72.0 (d, C-5), 71.3 (d, C-3), 69.7 (d, C-2), 66.7 (d, C-4), 63.0 (t, C-6), 47.5 (d), 40.1 (t), 34.2 (t), 31.4 (d), 25.6 (d), 23.5 (t), 22.2 (q), 20.8 (q), 20.7 (q×2), 20.6 (q), 20.5 (q), 16.0 (q); Anal. Calcd for $C_{24}H_{38}O_{10}$: C, 59.24; H, 7.87. Found: C, 59.26; H, 7.98.

4.21. (1*S*,2*R*,5*S*)-Menthyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 17

Debenzylation and acetylation of compound **11** (52 mg, 0.09 mmol) was performed as in the general procedure, leading to compound **17** (40 mg, 0.08 mmol, 93%) after column chromatography (*n*-hexane/EtOAc, 7.5:2.5): TLC R_f = 0.42 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D = +9.0$ (*c* 0.4, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 509 ($[M+Na]^+$, 4.9), 487 ($[M+H]^+$, 1.4), 331 (100), 289 (6.9); ^{1}H NMR ($CDCl_3$) δ 5.43 (d, J = 3.3 Hz, H-2), 5.20 (t, J = 9.9 Hz, H-4), 5.05 (dd, J = 3.3 and 9.9 Hz, H-3), 4.66 (s, H-1), 4.28 (dd, J = 6.4 and 12.0 Hz, H-6_{proR}), 4.13 (dd, J = 2.5 and 12.0 Hz, H-6_{proS}), 3.68 (m, H-5), 3.35 (dt, J = 4.2 and 10.6 Hz, H-1′), 2.18 (s, 3H), 2.12–1.98 (m, 2H), 2.08 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.64–1.56 (m, 2H), 1.39–1.24 (m, 2H), 1.11 (qu, J = 11.7 Hz, 1H), 0.97–0.80 (m, 8H), 0.73 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6 (s), 170.3 (s), 170.0 (s), 169.5 (s), 99.3 (d, C-1), 82.6 (d, C-1′), 72.0 (d, C-5), 71.1 (d, C-3), 69.1 (d, C-2), 66.3 (d, C-4), 62.8 (t, C-6), 47.7 (d), 42.3 (t), 34.1 (t), 31.5 (d), 25.6 (d), 23.3 (t), 22.2 (q), 20.8 (q), 20.7 (q), 20.6 (q×2), 20.5 (q), 16.2 (q); Anal. Calcd for $C_{24}H_{38}O_{10}$: C, 59.24; H, 7.87. Found: C, 59.29; H, 7.79.

4.22. *tert*-Butyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 18

Debenzylation of compound **12** (91 mg, 0.18 mmol) and acetylation gave compound **18** (71 mg, 0.18 mmol, 97%), after column chromatography (*n*-hexane/EtOAc, 7.5:2.5): TLC R_f = 0.35 (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D = -30.4$ (*c* 2.0, $CHCl_3$); MS (EI) *m/z* (relative intensity) 347 (0.6), 331 ($[M^+ - C_4H_9O]$, 18.9), 289 (12.3), 242 (67.4), 200 (48.4), 157 (100); ^{1}H NMR ($CDCl_3$) δ 5.33 (dd, J = 1.0 and 3.4 Hz, H-2), 5.20 (t, J = 9.9 Hz, H-4), 5.08 (dd, J = 3.4 and 10.0 Hz, H-3), 4.78 (d, J = 1.0 Hz, H-1), 4.26 (dd, J = 6.5 and 12.0 Hz, H-6_{proR}), 4.12 (dd, J = 2.7 and 12.0 Hz, H-6_{proS}), 3.67 (m, H-5), 2.19 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 1.99 (s, 3 H), 1.24 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.5 (s), 170.4 (s), 169.9 (s), 169.5 (s), 93.1 (d, C-1), 76.5 (d, C-2′), 71.9 (d, C-5), 71.2 (d, C-3), 70.3 (d, C-2), 66.2 (d, C-4), 62.8 (t, C-6), 28.1 (q×3), 20.7 (q), 20.5 (q×2), 20.4 (q); Anal. Calcd for $C_{18}H_{28}O_{10}$: C, 53.46; H, 6.98. Found: C, 53.47; H, 7.10.

4.23. Methyl 2,3,4,6-tetra-*O*-(*p*-bromobenzoyl)-β-D-mannopyranoside 19

Debenzylation of compound **7** (45 mg, 0.10 mmol) and then *p*-bromobenzoylation, led to compound **19** (75 mg, 0.081 mmol) in an 83% yield, after chromatogra-

phy on silica gel (*n*-hexane/EtOAc, 7.5:2.5): TLC R_f=0.40 (*n*-hexane/EtOAc, 6:4); $[\alpha]_D$=−177.8 (*c* 0.2, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 926 (M^+, 52.0), 895 (100); ^{1}H NMR ($CDCl_3$) δ 7.92–7.41 (m, 16H), 5.90 (t, *J*=10.0 Hz, H-4), 5.88 (d, *J*=3.1 Hz, H-2), 5.57 (dd, *J*=3.1 and 10.0 Hz, H-3), 4.84 (s, H-1), 4.75 (dd, *J*=3.1 and 12.1 Hz, H-6$_{proS}$), 4.51 (dd, *J*=4.6 and 12.1 Hz, H-6$_{proR}$), 4.11 (m, H-5), 3.56 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.3 (s), 164.9 (s), 164.8 (s), 164.7 (s), 132.0–127.5 (aromatic Cs), 100.0 (d, C-1), 72.2 (d, C-5), 71.9 (d, C-3), 69.7 (d, C-2), 67.3 (d, C-4), 63.1 (t, C-6), 57.6 (q, C-1′); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 252 nm (−62.8), 234 nm (20.0); Anal. Calcd for $C_{35}H_{26}Br_4O_{10}$: C, 45.39; H, 2.83. Found: C, 45.35; H, 3.23.

4.24. *iso*-Propyl 2,3,4,6-tetra-*O*-(*p*-bromobenzoyl)-β-D-mannopyranoside 20

Debenzylation of compound **8** (120 mg, 0.25 mmol) and then *p*-bromobenzoylation was performed as in the general procedure, to give compound **20** (167 mg, 0.18 mmol, 72%) after column chromatography (*n*-hexane/EtOAc, 8.5:1.5): TLC R_f=0.50 (*n*-hexane/EtOAc, 7:3); $[\alpha]_D$=−163.4 (*c* 1.6, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 977 ($[M+Na]^+$, 10.5), 955 ($[M+H]^+$, 41.1), 895 (100); ^{1}H NMR ($CDCl_3$) δ 7.90–7.42 (m, 16H), 5.85 (t, *J*=9.9 Hz, H-4), 5.80 (d, *J*=3.1 Hz, H-2), 5.57 (dd, *J*=3.1 and 9.9 Hz, H-3), 5.00 (br s, H-1), 4.73 (dd, *J*=3.2 and 12.0 Hz, H-6$_{proS}$), 4.49 (dd, *J*=5.0 and 12.0 Hz, H-6$_{proR}$), 4.10 (m, H-5), 4.03 (sep, *J*=6.2 Hz, H-2′), 1.19–1.16 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.3 (s), 165.0 (s), 164.8 (s), 164.7 (s), 132.3–127.5 (aromatic Cs), 96.9 (d, C-1), 72.0 (d, C-3), 72.0 (d, C-5), 72.0 (d, C-2′), 70.5 (d, C-2), 67.5 (d, C-4), 63.4 (t, C-6), 23.0 (q), 21.6 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} (Dε) 252 nm (−63.7), 234 nm (20.7); Anal. Calcd for $C_{37}H_{30}Br_4O_{10}$: C, 46.57; H, 3.17. Found: C, 46.56; H, 3.20.

4.25. Cyclohexyl 2,3,4,6-tetra-*O*-(*p*-bromobenzoyl)-β-D-mannopyranoside 21

Following the procedure, debenzylation of compound **9** (115 mg, 0.22 mmol) and then *p*-bromobenzoylation led to compound **21** (196 mg, 0.20 mmol, 91%) after column chromatography (*n*-hexane/EtOAc, 8.5:1.5): TLC R_f=0.58 (*n*-hexane/EtOAc, 7:3); $[\alpha]_D$=−159.9 (*c* 1.2, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 1019 ($[M+Na]^+$, 10.5), 995 (M^+, 39.6), 895 (100); ^{1}H NMR ($CDCl_3$) δ 7.89–7.42 (m, 16H), 5.84 (t, *J*=9.9 Hz, H-4), 5.81 (d, *J*=3.2 Hz, H-2), 5.57 (dd, *J*=3.2 and 9.9 Hz, H-3), 5.04 (s, H-1), 4.71 (dd, *J*=3.3 and 11.9 Hz, H-6$_{proS}$), 4.50 (dd, *J*=5.3 and 11.9 Hz, H-6$_{proR}$), 4.09 (m, H-5), 3.72 (m, H-1′), 1.82 (m, 2H), 1.64 (m, 2H), 1.47 (m, 1H), 1.41–1.14 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 165.2 (s), 165.0 (s), 164.8 (s), 164.6 (s), 132.3–127.5 (aromatic Cs), 96.7 (d, C-1), 77.4 (d, C-1′), 72.0 (d, C-3), 71.9 (d, C-5), 70.5 (d, C-2), 67.6 (d, C-4), 63.4 (t, C-6), 33.0 (t), 31.4 (t), 25.4 (t), 23.7 (t×2); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 252 nm (−63.9), 234 nm (20.7); Anal. Calcd for $C_{40}H_{34}Br_4O_{10}$: C, 48.32; H, 3.45. Found: C, 48.54; H, 3.53.

4.26. (1*R*,2*S*,5*R*)-Menthyl 2,3,4,6-tetra-*O*-(*p*-bromobenzoyl)-β-D-mannopyranoside 22

Debenzylation of compound **10** (186 mg, 0.31 mmol) and then *p*-bromobenzoylation, gave compound **22** in an 83% yield (275 mg, 0.26 mmol) after chromatography on silica gel (*n*-hexane/EtOAc, 9:1): TLC R_f=0.59 (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D$=−155.3 (*c* 1.4, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 1050 (M^+, 10.1), 895 (100); ^{1}H NMR ($CDCl_3$) δ 7.92–7.43 (m, 16H), 5.86 (t, *J*=10.0 Hz, H-4), 5.77 (d, *J*=3.0 Hz, H-2), 5.58 (dd, *J*=3.0 and 10.0 Hz, H-3), 5.07 (s, H-1), 4.78 (dd, *J*=2.9 and 11.9 Hz, H-6$_{proS}$), 4.43 (dd, *J*=4.5 and 11.9 Hz, H-6$_{proR}$), 4.06 (m, H-5), 3.60 (m, H-1′), 2.02 (m, 1H), 1.94 (m, 1H), 1.62 (m, 2H), 1.27 (m, 1H), 1.12 (m, 1H), 0.93–0.70 (m, 6H), 0.63 (d, *J*=8.1 Hz, 3H), 0.61 (d, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.1 (s), 164.9 (s), 164.8 (s), 164.6 (s), 131.8–127.5 (aromatic Cs), 94.6 (d, C-1), 76.0 (d, C-1′), 72.1 (d, C-3), 71.9 (d, C-5), 70.7 (d, C-2), 67.4 (d, C-4), 62.8 (t, C-6), 47.4 (d), 39.5 (t), 34.2 (t), 31.3 (d), 25.5 (d), 23.4 (t), 22.2 (q), 20.4 (q), 16.0 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 252 nm (−63.2), 234 nm (23.5); Anal. Calcd for $C_{44}H_{42}Br_4O_{10}$: C, 50.31; H, 4.03. Found: C, 50.30; H, 4.22.

4.27. (1*S*,2*R*,5*S*)-Menthyl 2,3,4,6-tetra-*O*-(*p*-bromobenzoyl)-β-D-mannopyranoside 23

Debenzylation of compound **11** (52 mg, 0.09 mmol) and then *p*-bromobenzoylation led to compound **23** (81 mg, 0.08 mmol, 88%) after column chromatography (*n*-hexane/EtOAc, 9:1): TLC R_f=0.62 (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D$=−104.7 (*c* 0.8, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 1049 (M^+, 45.9), 895 (100); ^{1}H NMR ($CDCl_3$) δ 7.90–7.42 (m, 16H), 5.83 (d, *J*=3.2 Hz, H-2), 5.79 (t, *J*=9.9 Hz, H-4), 5.57 (dd, *J*=3.2 and 9.9 Hz, H-3), 4.96 (s, H-1), 4.72 (dd, *J*=3.0 and 11.9 Hz, H-6$_{proS}$), 4.48 (dd, *J*=5.8 and 11.9 Hz, H-6$_{proR}$), 4.11 (m, H-5), 3.41 (dt, *J*=4.2 and 10.6 Hz, H-1′), 2.12 (d, *J*=12.8 Hz, 1H), 2.01 (dt, *J*=2.4 and 6.9 Hz, 1H), 1.60-1.56 (m, 2H), 1.33-1.18 (m, 2H), 1.03 (q, *J*=12.0 Hz, 1H), 0.98–0.79 (m, 8H), 0.72 (d, *J*=6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.2 (s), 164.9 (s), 164.8 (s), 164.7 (s), 132.3–127.5 (aromatic Cs), 99.3 (d, C-1), 82.1 (d, C-1′), 72.0 (d, C-3), 72.0 (d, C-5), 70.1 (d, C-2), 67.6 (d, C-4), 63.5 (t, C-6), 47.9 (d), 42.4 (t), 34.1 (t), 31.6 (d), 25.5 (d), 23.2 (t), 22.1 (q), 20.8 (q), 16.2 (q); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 252 nm (−67.9), 234 nm (23.2); Anal. Calcd for $C_{44}H_{42}Br_4O_{10}$: C, 50.31; H, 4.03. Found: C, 50.34; H, 4.50.

4.28. *tert*-Butyl 2,3,4,6-tetra-*O*-(*p*-bromobenzoyl)-β-D-mannopyranoside 24

Compound **24** (131 mg, 0.14 mmol, 75%) was obtained from compound **12** (91 mg, 0.18 mmol), following the procedure for debenzylation and *p*-bromobenzoylation, after column chromatography (*n*-hexane/EtOAc, 9:1): TLC R_f=0.59 (*n*-hexane/EtOAc, 7:3); $[\alpha]_D$=−127.9 (*c* 0.4, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 992 ($[M+Na]^+$, 38.9), 895 (100); ^{1}H NMR ($CDCl_3$) δ

7.91–7.42 (m, 16H), 5.78 (t, $J=9.8$ Hz, H-4), 5.72 (d, $J=3.2$ Hz, H-2), 5.61 (dd, $J=3.2$ and 9.8 Hz, H-3), 5.08 (s, H-1), 4.68 (dd, $J=3.2$ and 11.9 Hz, H-6_{proS}), 4.49 (dd, $J=6.1$ and 11.9 Hz, H-6_{proR}), 4.12 (m, H-5), 1.25 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 165.1 (s), 165.0 (s), 164.7 (s), 164.6 (s), 132.2–127.5 (aromatic Cs), 93.4 (d, C-1), 76.7 (s, C-2′), 72.0 (d, C-3), 71.8 (d, C-5), 71.3 (d, C-2), 67.6 (d, C-4), 63.6 (t, C-6), 28.2 (q×3); UV (CH_3CN) λ_{max} 245 nm; CD (CH_3CN) λ_{ext} ($\Delta\varepsilon$) 252 nm (−67.9), 234 nm (20.7); Anal. Calcd for $C_{38}H_{32}Br_4O_{10}$: C, 47.14; H, 3.33. Found: C, 47.17; H, 3.33.

4.29. 1,2,3,4,6-Penta-*O*-acetyl-β-D-mannopyranoside 25

Commercial D-(+)-mannose (2 g, 11.0 mmol) was dissolved in 20 mL/mmol of a 1:1 solution of dry pyridine–acetic anhydride and the reaction stirred overnight. The solvent was removed under reduced pressure in the presence of toluene, and the residue purified by column chromatography (*n*-hexane/EtOAc, 6:4) to yield compound **25** in a quantitative amount, as a 2:1 mixture of α- and β-anomers. The pure β-anomer was obtained by recrystallization in *n*-hexane/EtOAc. Spectroscopic data of compound **25 α** were identical to those described.[10] Compound **25 β**: TLC $R_f=0.35$ (*n*-hexane/EtOAc, 1:1); $[\alpha]_D=-22.8$ (*c* 1.6, $CHCl_3$); MS (EI) *m/z* (relative intensity) 347 ($[M-CH_3CO]^+$, 0.6), 331 (6.2), 242 (72.7), 200 (52.1), 157 (100); ^{1}H NMR ($CDCl_3$) δ 5.86 (s, H-1), 5.48 (d, $J=3.2$ Hz, H-2), 5.29 (t, $J=9.9$ Hz, H-4), 5.13 (dd, $J=3.2$ and 9.9 Hz, H-3), 4.30 (dd, $J=4.9$ and 12.4 Hz, H-6_{proR}), 4.14 (dd, $J=1.5$ and 12.4 Hz, H-6_{proS}), 3.80 (m, H-5), 2.21 (s, 3 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.2 (s), 169.7 (s), 169.4 (s), 169.2 (s), 168.0 (s), 90.1 (d, C-1), 72.7 (d, C-5), 70.3 (d, C-4), 67.9 (d, C-2), 65.1 (d, C-3), 61.7 (t, C-6), 20.3 (q×2), 20.2 (q×2), 20.1 (q); Anal. Calcd for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.24; H, 5.74.

4.30. 1,2,3,4,6-Penta-*O*-(*p*-bromobenzoyl)-D-mannopyranoside 26

DMAP as catalyst and *p*-bromobenzoyl chloride (900 mg, 4.10 mmol) were added to a solution of D-(+)-mannose (100 mg, 0.55 mmol) in dry pyridine (10 mL/mmol). The 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 chromatographed with CH_2Cl_2 as eluent, yielding **26** as a 3:1 mixture of α- and β-anomers in a quantitative amount. Compound **26 α**: TLC $R_f=0.58$ (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D=-64.7$ (*c* 1.2, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 895 ($[M^+-C_7H_4BrO_2]^+$, 27.3), 307 (100); ^{1}H NMR ($CDCl_3$) δ 8.03–7.44 (m, 20H), 6.56 (s, H-1), 6.12 (t, $J=10.1$ Hz, H-4), 5.95 (dd, $J=3.1$ and 10.1 Hz, H-3), 5.84 (br s, H-2), 4.71 (br d, $J=12.1$ Hz, H-6_{proS}), 4.51 (m, H-5), 4.51 (dd, $J=3.7$ and 12.1 Hz, H-6_{proR}); ^{13}C NMR ($CDCl_3$) δ 165.1 (s), 164.9 (s), 164.6 (s), 164.3 (s), 163.1 (s), 132.3–127.3 (aromatic Cs), 91.4 (d, C-1), 71.0 (d, C-5), 70.0 (d, C-3), 69.4 (d, C-2), 66.2 (d, C-4), 62.3 (t, C-6); Anal. Calcd for $C_{41}H_{24}Br_5O_{11}$: C, 44.96; H, 2.48. Found: C, 44.80; H, 2.63. Compound **25 β**: TLC $R_f=0.43$ (*n*-hexane/EtOAc, 7.5:2.5); $[\alpha]_D=-85.5$ (*c* 1.5, $CHCl_3$); MS (FAB) *m/z* (relative intensity) 895 ($[M^+-C_7H_4BrO_2]^+$, 3.3), 307 (100); ^{1}H NMR ($CDCl_3$) δ 7.94–7.43 (m, 20H), 6.36 (s, H-1), 6.03 (d, $J=3.2$ Hz, H-2), 6.02 (t, $J=10.0$ Hz, H-4), 5.73 (dd, $J=3.1$ and 10.0 Hz, H-3), 4.74 (dd, $J=2.8$ and 12.3 Hz, H-6_{proS}), 4.51 (dd, $J=4.5$ and 12.3 Hz, H-6_{proR}), 4.34 (m, H-5); ^{13}C NMR ($CDCl_3$) δ 165.2 (s), 164.8 (s), 164.6 (s×2), 163.3 (s), 132.2–127.2 (aromatic Cs), 91.2 (d, C-1), 73.1 (d, C-5), 71.5 (d, C-3), 69.5 (d, C-2), 66.6 (d, C-4), 62.7 (t, C-6); Anal. Calcd for $C_{41}H_{24}Br_5O_{11}$: C, 44.96; H, 2.48. Found: C, 44.89; H, 2.70.

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References and notes

1. Mallams, A. K. The Carbohydrate-Containing Antibiotics. In *Carbohydrate Chemistry*; Kennedy, J. F., Ed.; Oxford Science: Oxford, UK, 1988;, Chapter 3, pp 73–170.
2. (a) *The Chemistry of Antitumor Antibiotics*; Remers, W. A., Ed.; John Wiley & Sons: New York, 1978; (b) Lindhorst, T. K. Antitumor and Antimicrobial Glycoconjugates. In *Glycoscience—Chemistry and Chemical Biology*; Fraser-Reid, B. O., Tatsuta, K., Thiem, J., Eds.; Vol. III, 2001; Springer, pp 2393–2439; (c) Macmillan, D.; Daines, A. M. *Current Medicinal Chemistry* **2003**, *10*(24), 2733–2773.
3. Smith, T. W. N. *Engl. J. Med.* **1988**, *318*, 358–365.
4. Varki, A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 7390–7397.
5. Levy, D. E.; Tang, P. C.; Musser, J. H. In *Annual Reports in Medicinal Chemistry*; Levy Hagmann, W. K., Ed.; Academic: San Diego, 1994.
6. Lowe, J. B. The Molecular Basis of Blood Diseases. Stamatoyannopoulos, G., Nienhuis, A. W., Majerus, P. W., Varmus, H., Eds.; Saunders: Philadelphia, 1987.
7. (a) Van Halbeek, H. *Curr. Opin. Struct. Biol.* **1994**, *4*, 697–709, and references cited therein; (b) Bock, K. *Pure Appl. Chem.* **1983**, *5*, 605–622; (c) Bush, C. A. *Curr. Opin. Struct. Biol.* **1992**, *2*, 655–663; (d) Bush, C. A.; Cagas, P. *Adv. Biophys. Chem.* **1992**, *2*, 149–180; (e) Rice, K. G.; Wu, P.; Brand, L.; Lee, Y.-C. *Curr. Opin. Struct. Biol.* **1993**, *3*, 669–674; (f) Woods, R. J. *Curr. Opin. Struct. Biol.* **1995**, *5*, 591–598.
8. (a) Morales, E. Q.; Padrón, J. I.; Trujillo, M.; Vázquez, J. T. *J. Org. Chem.* **1995**, *60*, 2537–2548; (b) Padrón, J. I.; Vázquez, J. T. *Chirality* **1997**, *9*, 626–637; (c) Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1998**, *9*, 613–627.
9. Padrón, J. I.; Morales, E. Q.; Vázquez, J. T. *J. Org. Chem.* **1998**, *63*, 8247–8258.
10. Nóbrega, C.; Vázquez, J. T. *Tetrahedron: Asymmetry* **2003**, *14*, 2793–2801.
11. Roën, A.; Padrón, J. I.; Vázquez, J. T. *J. Org. Chem.* **2003**, *68*, 4615–4630.

12. Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.
13. Liu, K. K.-C.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 1892–1894.
14. Stenutz, R.; Carmichael, I.; Widmalm, G.; Serianni, A. S. *J. Org. Chem.* **2002**, *67*, 949–958. Set of equations: (i) $1.3gg+1.5gt+10.8tg=J_S$; (ii) $0.8gg+9.9gt+4.5tg=J_R$; (iii) $gg+gt+tg=1$.
15. Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Carbohydr. Chem.* **1990**, *9*, 601–618.
16. Different rotamer populations are obtained depending on the set of equations used in their calculations, therefore this must be taken into account when comparing rotamer population data obtained from different equations.
17. (a) pK_a Values for MeOH, ^{i}PrOH, and ^{t}BuOH Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205–1209, and references cited therein; (b) pK_a Value for Menthol McEwen, W. K. *J. Am. Chem. Soc.* **1936**, *58*, 1124–1129.
18. The equations of the lines drawn in Figure 5 for the three series are: (a) Benzyl series: $P_{gg}=-1.1033\ \mathrm{p}K_a+64.275$ ($r=0.8706$); $P_{gt}=1.9545\ \mathrm{p}K_a+16.411$ ($r=0.9608$); $P_{tg}=-0.8512\ \mathrm{p}K_a+19.314$ ($r=0.9929$). (b) Acetyl series: $P_{gg}=-3.8940\ \mathrm{p}K_a+104.13$ ($r=0.9848$); $P_{gt}=2.9389\ \mathrm{p}K_a-0.7772$ ($r=0.9542$); $P_{tg}=0.9551\ \mathrm{p}K_a-3.3517$ ($r=0.6227$). (c) Benzoyl series: $P_{gg}=-4.1960\ \mathrm{p}K_a+111.70$ ($r=0.9878$); $P_{gt}=4.5064\ \mathrm{p}K_a-37.003$ ($r=0.9786$); $P_{tg}=0.0985\ \mathrm{p}K_a+16.756$ ($r=0.2987$).
19. (a) Thatcher, G. R. J. Anomeric and Associated Stereoelectronic Effects. Scope and Controversy. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; Washington, D.C., 1993; (b) Juaristi, E.; Cuevas, G. In *The Anomeric Effect in New Directions in Organic and Biological Chemistry*; Juaristi Rees, C. W., Ed.; CRC: Boca Ratón, FL, 1995.
20. Praly, J. P.; Lemieux, R. U. *Can. J. Chem.* **1987**, *65*, 213–223.
21. 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. In *The Exciton Chirality Method in Circular Dichroism, Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers: New York, 1994.
22. The amplitude (A value) of split CD Cotton effects is defined as $A=\Delta\varepsilon_1-\Delta\varepsilon_2$ where $\Delta\varepsilon_1$ and $\Delta\varepsilon_2$ are intensities of the first and second Cotton effects, respectively.
23. (a) Liu, H.-W.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5591–5593; (b) Liu, H.-W.; Nakanishi, K. *J. Am. Chem. Soc.* **1982**, *104*, 1178–1185.
24. (a) Wiesler, W. T.; Vázquez, J. T.; Nakanishi, K. *J. Am. Chem. Soc.* **1986**, *108*, 6811–6813; (b) Wiesler, W. T.; Vázquez, J. T.; Nakanishi, K. *J. Am. Chem. Soc.* **1987**, *109*, 5586–5592; (c) Meyers, H. V.; Ojika, M.; Wiesler, W. T.; Nakanishi, K. *Carbohydr. Res.* **1990**, *197*, 15–32.