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Influence of protecting groups on the anomeric equilibrium; case of the 4,6-*O*-benzylidene acetal in the mannopyranose series

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ABSTRACT

It is reported that the replacement of the 4- and 6-*O*-benzyl ethers in 2,3,4,6-tetra-*O*-benzyl-α,β-mannopyranose by a 4,6-*O*-benzylidene acetal results in an increased population of the β-anomer at equilibrium in $CDCl_3$ solution. The phenomenon is considered to arise from the lower steric bulk of the benzylidene acetal that, through diminished buttressing interactions, reduces steric interactions normally present in the β-anomer.

1. Introduction

Cyclic protecting groups have come to be recognized as having a major influence on the reactivity and stereoselectivity of numerous glycosylation reactions.[1–6] Fraser-Reid and co-workers were the first to note the retarding influence of 4,6-*O*-benzylidene acetals on the hydrolysis of a pentenyl glucopyranoside; a phenomenon they attributed to a torsional disarming effect.[7,8] Bols and co-workers subsequently attributed the disarming nature of the benzylidene acetal to the locking of the C5–C6 bond in the *trans–gauche* (*tg*)[9] conformation that maximizes the electron-withdrawing capacity of the C6–O6 bond toward incipient positive charge at the anomeric position.[10] Ley and co-workers noted the effects of cyclic bisacetal groups on the reactivity of various thio and seleno-glycosides and exploited them in one pot oligosaccharide synthesis protocols.[11] The influences of many different acetals on the reactivity of thioglycosides on activation with the NIS/TfOH pair under a standard set of conditions are quantified in Wong's extensive series of relative reactivity values (RRV's).[12] The influence of a 4,6-*O*-benzylidene acetal on glycosylation stereoselectivity was noted in our laboratory[13,14] and has been extensively studied.[15,16] A 3,5-*O*-silylene acetal and a related disiloxane acetal has been found to have a stereodirecting influence in arabinofuranosylation.[17–19] Cyclic carbonates and oxazolidinones have been found to enhance the reactivity of certain glycosyl acceptors[20–23] and to have beneficial effects on the stereoselectivity of various glycosyl donors.[24–36] With the possible exception of the 2N,3O-oxazolidinone protected 2-amino-2-deoxy-α-D-glucopyranosyl donors,[24–28,30] these effects are best rationalized as kinetic phenomena, that is, phenomena in which the cyclic protecting group exerts its influence by either accelerating or decelerating a particular reaction pathway.

Protecting groups are also known to influence reactions under equilibrium control, that is, by influencing thermodynamic factors, of which the anomeric effect is a case in point. Thus, it has long been known that protecting groups influence the position of the anomeric equilibrium.[37] For example, in the series of mannopyranose, 2-*O*-methylmannopyranose, 2,3-di-*O*-methylmannopyranose and 2,3,4,6-tetra-*O*-methylmannopyranose the percentage of the axial isomer at equilibrium increases regularly from 68 through 75 and 80% to 85% (Fig. 1a).[38] Likewise, in a series of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-D-glucopyranose derivatives the anomeric effect increases along the series as the substituent at the 6-position is changed from hydrogen to iodide to chloride, to acetoxy and to tosyloxy (Fig. 1b).[39] It also has been reported that the installation of a 4,6-*O*-ethylidene group onto mannopyranose causes a modest decrease in the proportion of the β-anomer at equilibrium in both water and DMSO, but essentially no change in the glucopyranose series (Fig. 1c).[38] Concerning the influence of cyclic protecting groups on the anomeric equilibrium, we noted that a 2N,3O-oxazolidinone in the glucosamine series both facilitates the interconversion of β- to α-anomers and strongly favors the α-anomer.[23] Similar observations were made by the Oscarson, Ye, and Ito groups,[25,26,28,29,40–43] all of which concluded that the equilibration occurs via an endocyclic cleavage mechanism.

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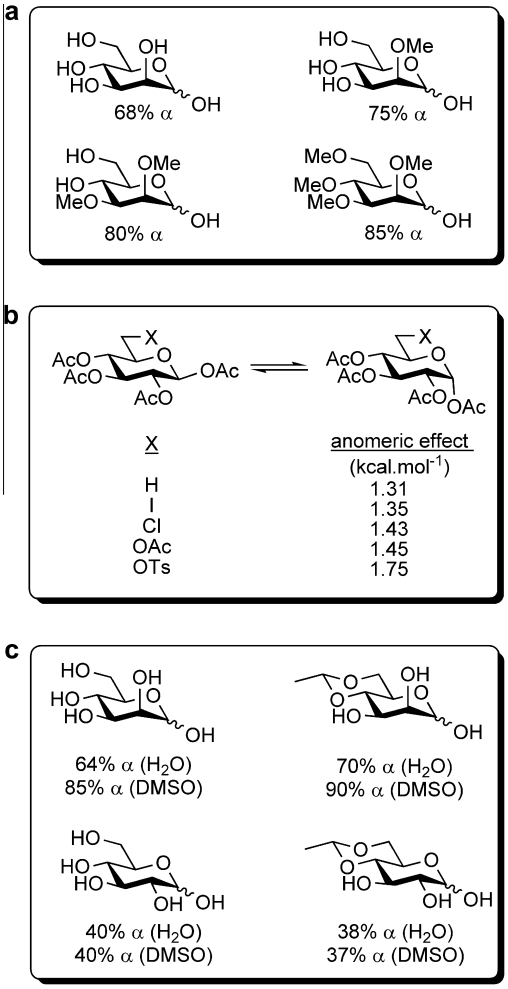


Figure 1. (a) Influence of methylation on the mannopyranose anomeric equilibrium.[38] (b) Effect of the 6-substituent on the anomeric effect in glucopyranosyl acetates.[39] (c) Influence of a 4,6-*O*-ethylidene group on the anomeric equilibrium in manno and glucopyranose.[38]

In the course of our ongoing studies we isolated benzylidene-protected mannopyranose hemicacetals and have found them to contain an unexpectedly high proportion of the β-anomer. We report here on this observation and on the influence of 3-*O*-esters on the anomeric effect both alone and in combination with a 4,6-*O*-benzylidene group.

2. Results and discussion

Our study began with the preparation of various mannopyranosyl esters carrying different protecting groups suitable for the release of hemiacetals. Anomeric mixtures of tetra-*O*-benzyl-D-mannopyranosyl acetate **1α,β** and 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl acetate **2α,β** (Fig. 2) were prepared and separated into the constituent anomers as described in the literature.[44,45] The corresponding 3-*O*-benzoyl analogs **3α,β** and **4α,β** were prepared as outlined in Scheme 1 from the thioglycosides **6**, obtained from the alcohol **5**,[46] and **7**[47] by hydrolysis of the thioglycoside function with N-bromosuccinimide and aqueous acetone, and acetylation.

The various α- and β-acetates were cleaved selectively with potassium *tert*-butoxide in methanolic solution and after work-up the resulting hemiacetals were examined by ^{1}H NMR spectroscopy in $CDCl_3$ solution until no further change was observed. The so-obtained anomeric ratios are presented in Table 1, from which it is apparent that essentially the same ratios of a given hemiacetal were observed irrespective of the configuration of the starting acetate, thereby ensuring that the values recorded present true equilibrium positions.

Comparison of the equilibrated anomeric ratio for the perbenzylated system **8αβ** (Table 1, entries 1 and 2) with that of the corresponding 4,6-*O*-benzylidene acetal **9αβ** (Table 1, entries 3 and 4) reveals the effect of the benzylidene group on the anomeric effect. This effect is maintained in systems containing a carboxylate ester at the 3-position, as is clear from comparison of the equilibrated ratios for **10αβ** (Table 1, entries 5 and 6) with those for **11αβ** (Table 1, entries 7 and 8). In both instances the introduction of a 4,6-*O*-benzylidene acetal in the place of two benzyl ethers at the 4- and 6-positions results in an increased proportion of the β-hemiacetal at equilibrium. The benzylidene acetal therefore either stabilizes the β-anomer of the hemiacetal and/or destabilizes the α-anomer with respect to the corresponding 4,6-di-*O*-benzyl ether. It is known that the population of the different conformers of the C5–C6 bond in glycopyranosides is affected by the aglycone and by the anomeric configuration both in general,[9,48–50] and in the mannopyranosides,[51,52] and that this effect is transmitted through multiple glycosidic linkages in oligosaccharides.[53] Such effects are usually interpreted (i) in terms of changes in the hydrogen bonding pattern around the pyranoside ring and (ii) as changes in the relative populations of the *gauche–gauche* (*gg*) and *gauche–trans* (*gt*) conformers (Fig. 3). The *trans–gauche* (*tg*) conformer is usually excluded from such considerations owing to its low incidence in all but the galactopyranose series. However, it is apparent that such effects, albeit small, persist in fully protected mannopyranosides in aprotic organic solvents, and moreover that the *tg* conformer is not an insignificant bystander.[51,52]

For example, in the tetra-*O*-acetylmannopyranosides (Fig. 4) the *tg* conformer was more highly populated in the β-anomer in deuteriochloroform solution for three out of the four systems available for comparison.[51,52] More data exist in the glucopyranoside series, where the same trend is seen in the same solvent (Fig. 5).[48] Similar comparisons made in perdeuterioacetonitrile, however, do not show the same differences in rotomer populations and hence highlight the effect of solvent on such distributions.

Bols has suggested and has provided evidence in favor of the rate retarding effect of a 4,6-*O*-acetal on glycoside hydrolysis being

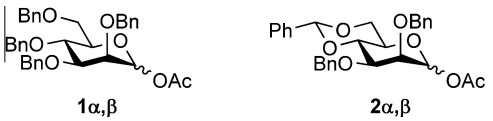
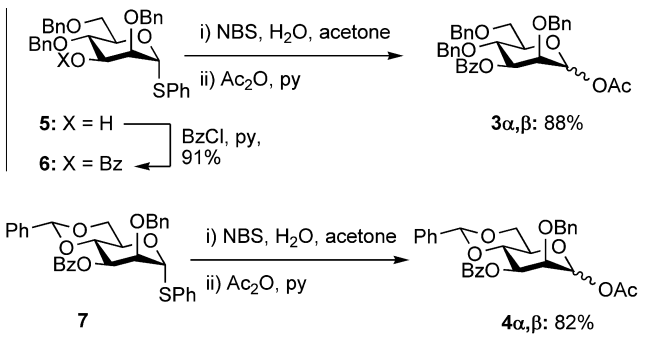
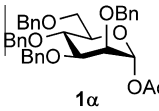
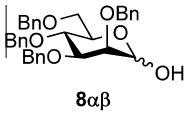
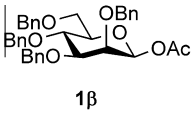
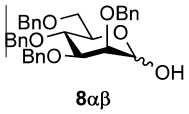
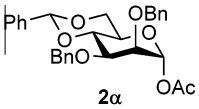
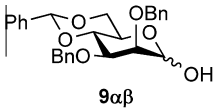
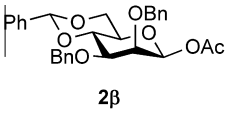
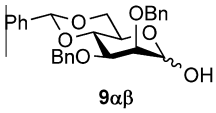
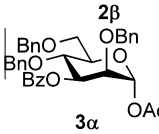
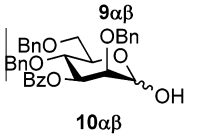
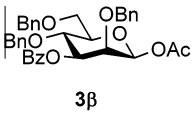
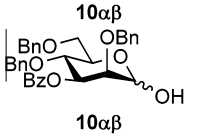
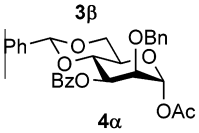
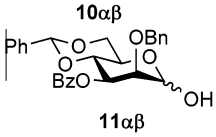
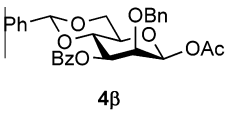
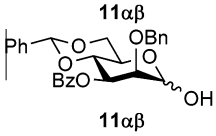


Figure 2. Anomeric D-mannopyranosyl acetates **1** and **2**.



Scheme 1. Preparation of the anomeric acetates **3** and **4**.

Table 1
The effect of protecting groups on the mannopyranoside anomeric equilibrium in $CDCl_3$ solution

Entry	Substrate	Product	α:β Ratio[a]	$\Delta,\Delta G^{a}$ (kcal mol^{-1})
1	 **1α**	 **8αβ**	80:20	−0.82
2	 **1β**	 **8αβ**	80:20	−0.82
3	 **2α**	 **9αβ**	54:46	−0.10
4	 **2β**	 **9αβ**	54:46	−0.10
5	 **3α**	 **10αβ**	73:27	−0.59
6	 **3β**	 **10αβ**	73:27	−0.59
7	 **4α**	 **11αβ**	55:45	−0.12
8	 **4β**	 **11αβ**	55:45	−0.13

[a] At 298 K.

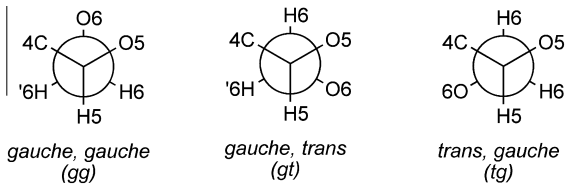
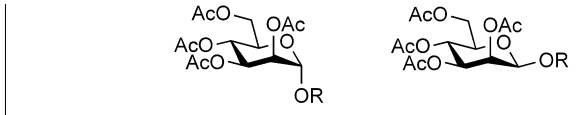


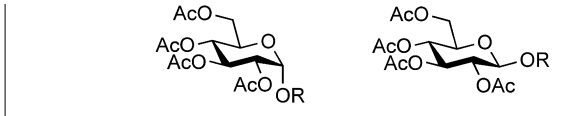
Figure 3. Staggered conformations of the C5–C6 bond in the hexopyranosides.



R	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}
Me	43	46	11	43	44	13
iPr	44	45	11	39	51	10
(+)-menthyl	48	46	6	29	55	16
(-)-menthyl	43	51	6	29	55	16

Figure 4. Rotomeric populations (%) of the C5–C6 bond in tetra-*O*-acetyl mannopyranosides in $CDCl_3$ as determined by measurement of $^{3}J_{H5,H6}$ coupling constants.[51,52]

in part a consequence of the locking of C5–C6 bond in the *tg* conformation in which the C5–O5 and C6–O6 bonds are antiperiplanar. Such a conformation maximizes the electron-withdrawing effect of O6 and destabilizes any incipient positive charge at the



R	P_{gg}	P_{gt}	P_{tg}	P_{gg}	P_{gt}	P_{tg}
Me	58	30	12	57	26	17
cyclohexyl	59	34	7	51	32	17
(+)-menthyl	70	24	6	45	40	15
(-)-menthyl	51	41	8	54	28	18
(-)-bornyl	59	39	2	51	30	19

Figure 5. Rotomeric populations (%) of the C5–C6 bond in tetra-*O*-acetyl glucopyranosides in $CDCl_3$ as determined by measurement of $^{3}J_{H5,H6}$ coupling constants.[51,52]

anomeric center.[10] By extrapolation it can be argued that the presence of a 4,6-*O*-acetal reduces the anomeric effect by lowering the availability of the electron density in the lone pairs of the ring oxygen and, thus, its availability to participate in the *endo*-anomeric effect. By the same token the imposition of the electron withdrawing *tg* conformation through the installation of a 4,6-*O*-benzylidene acetal should be expected to augment the *exo*-anomeric effect by lowering the energy of the O5–C1 σ^{*}-orbital. As the *endo*-anomeric effect only operates for the axial glycoside whereas the *exo*-anomeric effect exists for both anomers the benzylidene acetal might reasonably be expected to increase the population of the equatorial glycoside in line with the observations reported in Table 1, and consistent with the greater population of the *tg* conformer in

β-manno and glucopyranosides with respect to the corresponding α-anomers (Figs. 3 and 4). In apparent conflict with this line of reasoning is the observation (Fig. 1a)[38] that increasing the degree of methylation of mannopyranose increases the anomeric effect as methyl ethers are considered[54] to be more electron-withdrawing than alcohols. Similarly, Lemieux's observation (Fig. 1b) that in a conformationally mobile system increasing the electron withdrawing capability of the O6 protecting group leads to an increase in the anomeric effect,[39] conflicts with the suggestion that the benzylidene acetal exerts its influence on the anomeric effect by maximizing the electron-withdrawing effect of the C6–O6 bond.

Steric effects transmitted through buttressing interactions provide an alternative explanation for the observed phenomena. A 4,6-*O*-benzylidene acetal has five degrees of freedom less than the corresponding 4,6-di-*O*-benzyl ether (Fig. 6) and is therefore considerably less bulky.

The greater steric bulk of a 4,6-di-*O*-benzyl ether with respect to a benzylidene acetal will affect the anomeric equilibrium in two ways. First, there will be a direct steric interaction between the benzyloxy group at the 6-position and the aglycone, owing to the population of the *gg* and especially the *gt* conformers (Fig. 7). This direct interaction will be greater for the β-anomer than for the α-one and so will favor the α-anomer.

Second, the bulk of the benzyloxy group at the 4-position will restrict the conformational space available to the 3-*O*-benzyl ether, which in turn will impinge on the conformation of the 2-*O*-benzyl ether, ultimately destabilizing the β-anomer with respect to the α-one in the mannose series. Indeed, we have remarked previously[55] on the importance of such steric buttressing interactions in mannopyranosylation and have demonstrated how they may be affected by manipulating the steric bulk of the protecting groups at O2 and O3.[56,57] Taking all things into consideration, we believe that steric arguments of this kind appear best suited to rationalize the effect of the 4,6-*O*-benzylidene acetal on the anomeric effect reported in Table 1 as well as the literature observations on the increased population of the *tg*-conformer in β-manno- and glucopyranosides with respect to the corresponding α-anomers.

Comparison of Table 1 (entries 1 and 2) with Table 1 (entries 5 and 6) reveals that in 2,3,4,6-tetra-*O*-benzylmannopyranose the exchange of the 3-*O*-benzyl ether for a benzoate ester results in a small reduction in the anomeric effect. On the other hand no such effect is observed in the 4,6-*O*-benzylidene acetal protected series as is clear from the comparison of Table 1 (entries 3 and 4) with Table 1 (entries 7 and 8). With their well-defined conformations and planar topologies[58,59] carboxylate esters are typically considered to be less bulky than the corresponding ethers, which accounts for the well-known ability of peresterified β-pentopyranosyl glycosides, esters, and halides to adopt inverted chair and twist conformations when compared to their peretherified analogs.[37,60,61] Thus, the 3-*O*-benzoate ester in the hemiacetal **10** has less of a buttressing interaction with the flanking benzyl ethers than the 3-*O*-benzyl ether in **8** and thereby opens up more conformational space for the 2- and 6-*O*-benzyl ethers and relieves steric interactions of these later with the β-hemiacetal, thereby reducing the anomeric effect. In the benzylidene acetal series changing a 3-*O*-benzyl ether **9** for a 3-*O*-benzoate ester **11** has no measurable influence on the anomeric effect, which simply implies

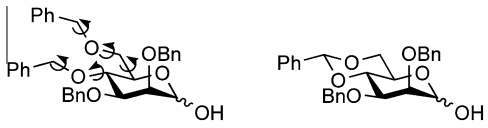


Figure 6. Degrees of freedom of a dibenzyl ether not available to a benzylidene acetal.

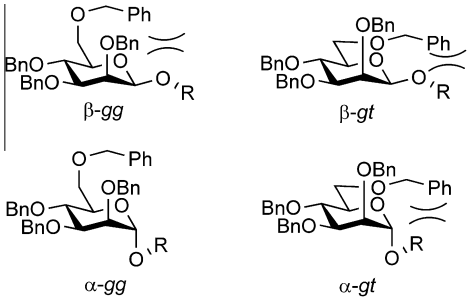


Figure 7. Direct steric interactions of a 6-*O*-benzyl ether with the aglycone in the preferred *exo*-anomeric effect conformation.

that steric interactions between the 2- and 3-O-substituents are negligible in this series.

We conclude that the reduction of steric interactions between the aglcyone on the one hand and O2 and O6 substituents are adequate to rationalize the change in the anomeric ratio on replacement of a 4,6-di-*O*-benzyl ether by a 4,6-*O*-benzylidene acetal. By the same token the greater steric interactions between the C6-substituent and the aglycone in the β- as opposed to the α-glycosides are sufficient to explain the increased population of the *tg*-conformer in the β-glycosides. Steric arguments also appear sufficient to rationalize the same change in the anomeric ratio observed on the replacement of a 3-*O*-benzyl ether by a 3-*O*-benzoate ester in the presence of benzyl ethers at the 2-, 4-, and 6-*O*-positions of mannopyranose.

3. Experimental

3.1. Phenyl 3-*O*-benzoyl-2,4,6-tri-*O*-benzyl-1-deoxy-α-D-thiomannopyranoside (6)

To a stirred solution of phenyl 2,4,6-tri-*O*-benzyl-1-deoxy-1-thio-α-D-mannopyranoside **5**[46] (300 mg, 0.55 mmol) at room temperature in dry pyridine (5 mL) was added benzoyl chloride (315 mg, 2.25 mmol) followed by DMAP (67 mg, 0.55 mmol). After 3 h, pyridine was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with 5% aqueous sodium carbonate, water and brine, dried over sodium sulfate and concentrated under reduced pressure. Chromatographic purification on silica gel (eluent 10–20% ethyl acetate/hexane) afforded the title product (325 mg, 91%); $[\alpha]_D^{23}$ +33 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.09 (d, *J* = 7.5 Hz, 2H), 7.63–7.13 (m, 23H), 5.70 (d, *J* = 1.5 Hz, 1H), 5.53 (dd, *J* = 3.5, 9.5 Hz, 1H), 4.78–4.72 (m, 3H), 4.61–4.53 (m, 3H), 4.47–4.44 (m, 1H), 4.35 (t, *J* = 9.5 Hz, 1H), 4.31–4.29 (m, 1H), 3.94 (dd, *J* = 4.5, 11.0 Hz, 1H), 3.80 (dd, *J* = 1.5, 11.0 Hz, 1H), ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 166.0, 138.5, 138.1, 134.6, 133.5, 132.0, 130.2, 130.1, 129.3, 128.7, 128.6, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 85.9, 75.2, 74.8, 73.9, 73.7, 72.8, 72.6, 69.2; ESI-HRMS Calcd for $C_{40}H_{38}O_6SNa$ $[M+Na]^+$, 669.2287; Found, 669.2292.

3.2. 1-*O*-Acetyl-3-*O*-benzoyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranose (3α) and 1-*O*-acetyl-3-*O*-benzoyl-2,4,6-tri-*O*-benzyl-β-D-mannopyranose (3β)

To a stirred solution of **6** (370 mg, 0.57 mmol) in 9:1 acetone/water (10 mL) was added at room temperature N-bromosuccinimide (306 mg, 1.72 mmol). After 45 min, the acetone was removed under reduced pressure and the residue was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate, and concentrated un-

der reduced pressure. The residue was taken up in pyridine (2 mL), treated with acetic anhydride (0.7 mL) and stirred at room temperature for 3 h. The solvents were removed under reduced pressure and the crude product was subjected to chromatographic purification on silica gel (eluent 20–30% ethyl acetate/hexane) to provide the title products (300 mg, 88%, 4:1 α/β). **3α**: $[\alpha]_D^{23}$ −37 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.06 (dd, *J* = 1.0, 7.5 Hz, 2H), 7.50–7.08 (m, 18H), 6.30 (d, *J* = 2.0 Hz, 1H), 5.51 (dd, *J* = 3.0, 10.0 Hz, 1H), 4.76–4.71 (m, 3H), 4.62–4.56 (m, 3H), 4.35 (t, *J* = 10.0 Hz, 1H), 4.02–4.00 (m, 2H), 3.87 (dd, *J* = 4.0, 11.5 Hz, 1H), 3.76 (dd, *J* = 1.5, 11.5 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 169.4, 166.0, 138.4, 137.9, 137.6, 133.5, 130.0, 128.6, 128.5, 128.2, 128.1, 127.9, 91.8, 75.3, 74.8, 74.4, 74.1, 73.9, 73.1, 73.0, 68.8, 21.4; ESI-HRMS Calcd for $C_{36}H_{36}O_8Na$ $[M+Na]^+$, 619.2308; Found, 619.2314. Compound **3β**: $[\alpha]_D^{23}$ −44 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, *J* = 7.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.41–7.04 (m, 17H), 5.82 (s, 1H), 5.24 (dd, *J* = 3.0, 9.5 Hz, 1H), 4.82 (d, *J* = 12.5 Hz, 1H), 4.73–4.67 (m, 3H), 4.54 (d, *J* = 11.5 Hz, 2H), 4.27 (t, *J* = 10.0 Hz, 1H), 4.16 (d, *J* = 2.5 Hz, 1H), 3.84–3.81 (m, 2H), 3.70 (d, *J* = 12.5 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 169.1, 165.9, 138.2, 138.1, 133.6, 130.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 92.9, 76.5, 76.2, 75.2, 75.0, 73.8, 73.0, 68.8, 21.3; ESI-HRMS Calcd for $C_{36}H_{36}O_8Na$ $[M+Na]^+$, 619.2308; Found, 619.2305.

3.3. 1-*O*-Acetyl-3-*O*-benzoyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranose (4α) and 1-*O*-acetyl-3-*O*-benzoyl-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranose (4β)

To a stirred solution of **7** (400 mg, 0.72 mmol) in 9:1 acetone/water (10 mL) was added at room temperature pyridine (1 mL) followed by N-bromosuccinimide (386 mg, 2.16 mmol). After 45 min, the solvents were removed under reduced pressure and the residue was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was taken up in pyridine (4 mL) and treated with acetic anhydride (1 mL) and stirred at room temperature for 3 h. The solvents were removed under reduced pressure and the residue was subjected to chromatographic purification on silica gel (eluent 20–30% ethyl acetate/hexane) to give the title products (298 mg, 82%, 3:1 α/β). **4α**: $[\alpha]_D^{23}$ −30 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.08 (d, *J* = 7.5 Hz, 2H), 7.49–7.20 (m, 13H), 6.24 (d, *J* = 1.5 Hz, 1H), 5.66 (s, 1H), 5.58 (d, *J* = 7.0 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 10.0 Hz, 1H), 4.35 (dd, *J* = 5.0, 10.0, 1H), 4.10–4.05 (m, 2H), 3.91 (t, *J* = 10.0 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 169.2, 166.1, 137.4, 137.2, 133.6, 130.2, 129.3, 128.7, 128.6, 128.5, 128.3, 128.2, 126.4, 102.0, 92.1, 76.0, 73.8, 70.8, 68.8, 66.6, 21.3; ESI-HRMS Calcd for $C_{29}H_{28}O_8Na$ $[M+Na]^+$, 527.1682; Found, 527.1686. Compound **4β**: $[\alpha]_D^{23}$ −51 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz,) δ 8.07 (dd, *J* = 1.5, 8.0 Hz, 2H), 7.48–7.19 (m, 13H), 5.90 (s, 1H), 5.63 (s, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.39–4.36 (m, 2H), 4.28 (d, *J* = 3.0 Hz, 1H), 3.95 (t, *J* = 10.0 Hz, 1H), 3.71–3.67 (m, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 169.0, 166.1, 137.6, 137.2, 133.6, 130.2, 129.3, 128.7, 128.6, 128.5, 128.2, 126.4, 102.0, 93.1, 75.8, 75.7, 75.6, 73.0, 68.6, 68.4, 21.1; ESI-HRMS Calcd for $C_{29}H_{28}O_8Na$ $[M+Na]^+$, 527.1682; Found, 527.1677.

3.4. General procedure for the hydrolysis of anomeric acetates

To a stirred solution of anomeric acetate (0.1 mmol) in methanol (1 mL) was added KO^{t}Bu (11 mg, 0.1 mmol) at −30 °C. The reaction mixture was warmed up to 0 °C over 1 h and then quenched with saturated aqueous ammonium chloride (3 mL) and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure to give the crude hemiacetals which were employed as such in the equilibration experiments.

3.5. Equilibration of hemiacetals in $CDCl_3$

The α- and β-acetates were cleaved selectively as described in the general procedure and the resulting crude hemiacetals were dissolved in $CDCl_3$ (700 μL) and examined by ^1H NMR spectroscopy at 500 MHz. The spectra were monitored at intervals of 1 h for the first 6 h and then every 4 h. After 24 h in $CDCl_3$, the both anomers of a given starting material (α- and β-acetates) gave essentially the same result as reported in Table 1. Subsequent chromatographic purification on silica gel (eluent 30–40% ethyl acetate/hexane) afforded the pure products, which were again analyzed by 500 MHz ^1H NMR spectroscopy in $CDCl_3$ (700 μL).

3.6. 2,3,4,6-Tetra-*O*-benzyl-α,β-D-mannopyranose (8α,β)

Isolated following the general hydrolysis procedure and equilibration (1.0/0.24 α/β). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.29 (m, 22.40H), 7.21–7.19 (m, 2.50H), 5.28 (s, 1H), 5.10 (d, *J* = 12.0 Hz, 0.24H), 4.93–4.88 (m, 1.25H), 4.79–4.73 (m, 2.79H), 4.67 (d, *J* = 12.5 Hz, 0.50H), 4.64 (s, 2H) 4.62 (s, 0.24H), 4.59–4.54 (m, 2.24H), 4.52 (s, 0.51H), 4.08 (t, *J* = 7.5 Hz, 1H), 3.99 (dd, *J* = 3.0, 10.0 Hz, 1H), 3.96 (t, *J* = 10.0 Hz, 0.24H), 3.92 (d, *J* = 10.0 Hz, 0.24H), 3.90 (s, 3H), 3.86 (s, 1H), 3.85–3.84 (m, 0.49H), 3.82 (t, *J* = 2.5 Hz, 1H), 3.76 (d, *J* = 4.5 Hz, 1H), 3.74 (s, 1H), 3.70 (d, *J* = 7.0 Hz, 1H), 3.68 (d, *J* = 7.0 Hz, 0.24H), 3.65 (d, *J* = 3.5 Hz, 1H), 3.62 (d, *J* = 3.0 Hz, 0.24H), 3.60 (d, *J* = 3.0 Hz, 0.24H), 3.50–3.47 (m, 0.24H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 138.7, 138.6, 138.4, 138.3, 138.2, 128.8, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 94.0, 93.0, 83.3, 80.0, 77.5, 76.2, 75.5, 75.4, 75.3, 75.0, 74.9, 73.8, 73.5, 73.0, 72.9, 72.4, 71.7, 69.9, 69.3; ESI-HRMS Calcd for $C_{34}H_{36}O_6Na$ $[M+Na]^+$, 563.2410; Found, 563.2414.

3.7. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α,β-D-mannopyranose (9α,β)

Isolated following the general hydrolysis procedure and equilibration (1.0/0.85 α/β). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.55–7.52 (m, 3.70H), 7.44–7.29 (m, 24H), 5.67 (s, 1H), 5.65 (s, 0.85H), 5.20–5.18 (m, 1.85H), 4.98 (d, *J* = 12.5 Hz, 0.82H), 4.85 (dd, *J* = 7.0, 12.5 Hz, 2H), 4.80–4.68 (m, 4.85H), 4.36–4.33 (m, 0.85H), 4.30–4.24 (m, 2H), 4.18 (t, *J* = 10.0 Hz, 0.86H), 4.07–4.02 (m, 2H), 3.92–3.91 (m, 1H), 3.88–3.86 (m, 3H), 3.83 (s, 0.84H), 3.78 (dd, *J* = 3.0, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 138.9, 138.5, 138.3, 137.9, 137.7, 129.2, 129.1, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 126.3, 101.7, 101.6, 94.5, 94.3, 79.5, 79.2, 79.0, 78.1, 76.6, 76.2, 75.9, 73.9, 73.8, 73.4, 69.1, 68.8, 67.1, 64.5; ESI-HRMS Calcd for $C_{27}H_{28}O_6Na$ $[M+Na]^+$, 471.1784; Found, 471.1781.

3.8. 3-*O*-Benzoyl-2,4,6-tri-*O*-benzyl-α,β-D-mannopyranose (10α,β)

Isolated following the general hydrolysis procedure and equilibration (1.0/0.35 α/β). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.09–8.05 (m, 2.74H), 7.62–7.59 (m, 1.35H), 7.49–7.46 (m, 2.89H), 7.40–7.27 (m, 11.5H), 7.20–7.18 (m, 7.2H), 7.09–7.07 (m, 2H), 7.09–7.07 (m, 2H), 7.06–7.04 (m, 0.7H), 5.63 (dd, *J* = 3.0, 7.0 Hz, 1H), 5.34 (s, 1H), 5.30 (dd, *J* = 3.0, 10.0 Hz, 0.35H), 4.89–4.85 (m, 0.66H), 4.74–4.51 (m, 8.16H), 4.23–4.18 (m, 1.35H), 4.14 (t, *J* = 9.5 Hz, 1H), 4.07 (t, *J* = 3.0 Hz, 0.35H), 4.02 (dd, *J* = 2.5, 3.0 Hz, 1H), 3.84–3.72 (m, 3.20H), 3.60–3.57 (m, 0.24H), 3.55 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 166.0, 165.9, 138.3, 138.2, 138.1,

138.0, 137.8, 133.7, 133.4, 130.3, 130.0, 129.7, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 93.9, 92.9, 77.5, 77.3, 76.5, 75.7, 75.4, 75.2, 74.4, 74.0, 73.8, 73.3, 73.1, 71.5, 69.5, 69.0; ESI-HRMS Calcd for $C_{34}H_{34}O_7Na$ $[M+Na]^+$, 577.2202; Found, 577.2208.

3.9. 3-*O*-Benzoyl-2-*O*-benzyl-4,6-*O*-benzylidene-α,β-D-mannopyranose (11α,β)

Isolated following the general hydrolysis procedure and equilibration (1.0/0.81 α/β). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13–8.08 (m, 3.61H), 7.61–7.58 (m, 1.84H), 7.49–7.22 (m, 22H), 5.67–5.63 (m, 2.83H), 5.43 (dd, J = 3.0, 10.0 Hz, 0.81H), 5.30–5.29 (m, 1H), 4.97–4.93 (m, 1.61H), 4.69–4.63 (m, 2.05H), 4.57 (d, J = 12.0 Hz, 0.79H), 4.38–4.36 (m, 1.85H), 4.31–4.21 (m, 3.72H), 4.16–4.15 (m, 1H), 3.94–3.88 (m, 1.86H), 3.71 (dd, J = 4.5, 12.5 Hz, 0.82H), 3.59–3.55 (m, 0.76H), 2.90–2.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 166.2, 166.1, 137.7, 137.5, 137.3, 133.8, 130.2, 130.1, 129.6, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.2, 126.4, 126.3, 102.0, 101.9, 94.2, 94.1, 77.8, 77.5, 76.7, 76.4, 75.9, 74.1, 73.8, 71.1, 69.1, 68.8, 67.3, 64.4; ESI-HRMS Calcd for $C_{27}H_{26}O_7Na$ $[M+Na]^+$, 485.1576; Found, 485.1573.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for compounds **3α,β**; **4α,β**; **6**; **8α,β**; **9α,β**; **10α,β**; **11α,β**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.05.025.

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