The Conformation of Eight-membered 3,2′-*O*-Isopropylidene Acetals of some Common Disaccharides

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The conformation of the eight-membered 3,2′-*O*-isopropylidene acetals from methyl β-cellobioside, benzyl β-lactoside, and methyl β-maltoside has been investigated using ^{1}H and ^{13}C n.m.r. spectroscopy and molecular-mechanics calculations. The interglycosidic eight-membered rings strongly restrict the conformational mobility around the glycosidic bond.

The acetalation of carbohydrates with alkyl alkenyl ethers may afford new acetals that differ from those prepared under the usual thermodynamic conditions.[1] We have recently shown that the nature of the products of the reaction of benzyl β-lactoside[2] and methyl β-maltoside[3] with 2-methoxypropene depends on the catalyst, the temperature, and the time for reaction, and that compounds containing a 3,2′-eight-membered interglycosidic isopropylidene acetal ring can be obtained under carefully controlled conditions. Similar products have been previously isolated in the acetonation of maltose with 2,2-dimethoxypropane[4] and 2-methoxypropene[5] and in the reaction of methyl β-cellobioside with benzylidene bromide in pyridine.[6] The structure of the latter has been studied both in the solid state[7] and in solution.[6] These structures are particularly interesting with regard to the conformation of the interglycosidic eight-membered ring which may directly influence the conformation around the glycosidic linkage. The extent of the rigidity or lack of flexibility of oligosaccharides in solution[8] and the importance of the *exo*-anomeric effect[9] as a driving force of the conformational preferences of glycosides and related compounds is a matter of interest.[10] Thus, Bush and co-workers[11] and Kishi and co-workers[12] have recently reported that the conformational behaviour of blood-group oligosaccharides[11] and C-glycosides,[12] respectively, can be explained solely on the basis of the consideration of non-bonded interactions. Furthermore, Brisson and Carver,[13] and Bush and co-workers[11] concluded that asparagine-linked and blood-group oligosaccharides have single rigid conformations whilst Lipkind *et al.*[14] and Tvaroska and Perez[15] have interpreted experimental data assuming an equilibrium among several conformers.

We now report on a conformational study of 3,2′-eight-membered isopropylidene acetals derived from ethyl β-cellobioside (**1**), methyl β-lactoside (**2**) and methyl β-maltoside (**3**). Compound (**1**) has been synthesised from methyl 2,6,3′,6′-tetra-*O*-benzyl-3,2′-*O*-isopropylidene-β-lactoside (**5**), by inversion at C-4′ using *N*,*N*′-sulphuryldi-imidazole and its synthesis constitutes an interesting example of the use of imidazolyl sulphonate for the configurational inversion at position C-4 of galactopyranose derivatives.

The syntheses of benzyl 2,6,3′,6′-tetra-*O*-benzyl-3,2′-*O*-isopropylidene-β-lactoside (**10**) and methyl 2,6,3′-tri-*O*-acetyl-3,2′:4′,6′-di-*O*-isopropylidene-β-maltoside (**11**) have been reported elsewhere.[2,3] Methyl 2,6,3′,6′-tetra-*O*-benzyl-4′-*O*-benzoyl-3,2′-*O*-isopropylidene-β-cellobioside (**9**) was prepared from methyl β-lactoside (**4**) by *N*-methylimidazole-catalysed tributyltin alkoxide-mediated regioselective benzylation[16] to give methyl 2,6,3′,6′-tetra-*O*-benzyl-β-lactoside [(**5**) 45%], the triacetyl derivative of which showed low-field signals for 4′-H, 3-H, and 2′-H in its ^{1}H n.m.r. spectrum. The acetonation of (**5**) with 2-methoxypropene under carefully controlled conditions afforded (**6**) (65%) as previously reported for the corresponding benzyl β-lactoside derivative.[2] Treatment of (**6**) with *N*,*N*′-sulphuryldi-imidazole[17] at −45 °C for 7 h yielded methyl 2,6,3′,6′-tetra-*O*-benzyl-4′-*O*-imidazolylsulphonyl-3,2′-*O*-isopropylidene-β-lactoside [(**7**) 52%]. When the reaction was carried out at −45 °C for 3 h and then at room temperature for 1 h, an elimination product [67%, δ_H 3.1 and 5.1 (25 H)] was obtained. Reaction of (**7**) with tetrabutylammonium benzoate gave methyl 2,6,3′,6′-tetra-*O*-benzyl-4′-*O*-benzoyl-3,2′-*O*-isopropylidene-β-cellobioside [(**9**) 95%].

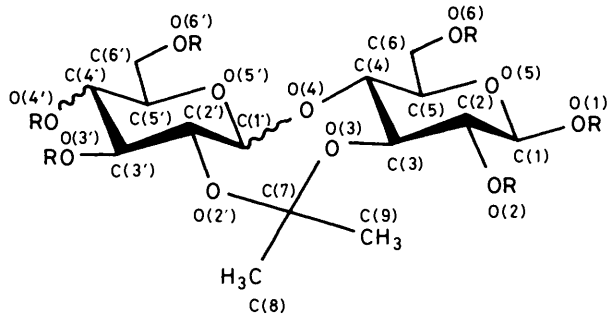


Figure 1. Schematic view of the structure of compounds (**1**), (**2**), and (**3**) showing the atomic numbering.

The above results indicate that *N*-methylimidazolyl sulphonates behave as a convenient leaving group for the configurational inversion at position C-4 in galactopyranose derivatives. However, care should be taken when preparing these compounds since elimination could occur simultaneously (due to the presence of the imidazolate anion released in the process).

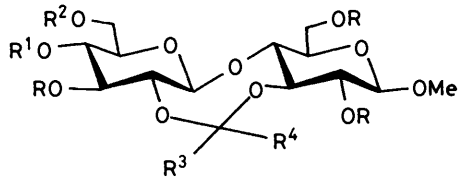
The conformation of (**1**)–(**3**) has been studied using well established methodologies, *i.e.* theoretical calculation and n.m.r. spectroscopy.[8,15]

Results and Discussion

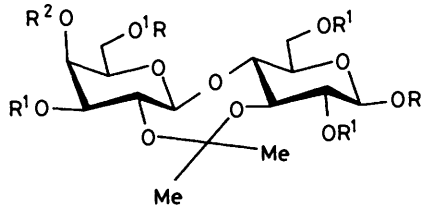
First, the conformation of (**1**)–(**3**) was calculated using the MM2 program.[18] The relative steric energy for the local minima and some geometrical features are given in Table 1 and a stereoscopic view of the global minima for compounds (**2**)–(**3**) is shown in Figure 2. The ^{1}H n.m.r. spectra of (**9**)–(**11**) have been analysed using one- and two-dimensional techniques including partially relaxed, COSY, and RELAY–COSY experiments[19] (Table 2). The ^{13}C n.m.r. spectra have been assigned through DEPT and heteronuclear correlated experiments (HETCOR and H–H–C RELAYED coherence transfer)[19] (Table 3). An

Table 1. Relative steric energy and some relevant torsion angles for the local minima of compounds (**2**), [1], and (**3**).

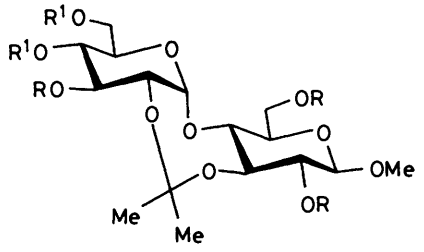
	Conformer					
Compound (**2**)	A	B	C	D	E	F
O(5′)–C(1′)–O(4)–C(4) (Φ)	−133.2	−140.5	−178.3	80.0	69.1	−126.6
C(5)–C(4)–O(4)–C(1′) (Ψ)	77.1	81.9	167.1	−123.0	−131.2	86.9
C(4)–C(3)–O(3)–C(7)	81.7	78.0	−42.5	−43.7	79.9	97.5
C(3)–O(3)–C(7)–O(2′)	17.5	34.3	61.6	85.4	−93.5	−88.0
C(1′)–O(2′)–C(2′)–O(7)	77.9	85.8	−50.1	95.9	85.9	−43.9
C(2′)–O(2′)–C(7)–O(3)	−96.8	−112.1	38.9	80.0	9.7	85.6
Relative steric energy (kcal mol^{-1})	7.53	>100	9.23	10.42	0.00	14.85
Compound (**3**)						
O(5′)–C(1′)–O(4)–C(4) (Φ)	120.1	177.9	133.4			
C(5)–C(4)–O(4)–C(1′) (Ψ)	−149.7	−137.4	−176.3			
C(4)–C(3)–O(3)–C(7)	94.1	−84.6	111.4			
C(3)–O(3)–C(7)–O(2′)	−119.4	102.4	−43.5			
C(1′)–C(2′)–O(2′)–C(7)	−46.6	−94.0	56.0			
C(2′)–O(2′)–C(7)–O(3)	70.9	29.3	−68.2			
Relative steric energy	8.50	>100	0.00			



(**1**) R = R^1 = R^2 = H, R^3 = R^4 = Me
(**9**) R = R^2 = CH_2Ph, R^1 = COPh, R^3 = R^4 = Me
(**8**) R = Ac, R^1, R^2 = PhCh, R^3 = Ph, R^4 = H



(**2**) R = Me, R^1 = R^2 = H
(**10**) R = R^1 = Ch_2Ph, R^2 = H

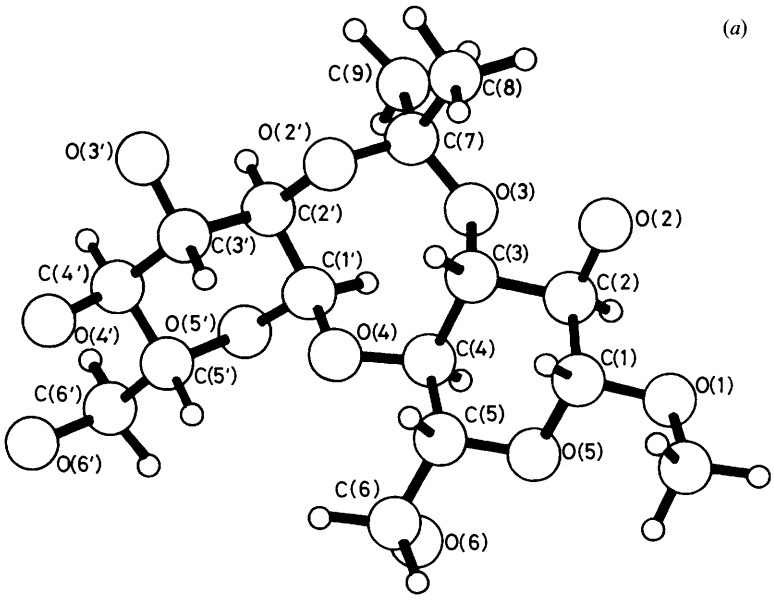


(**3**) R = R^1 = H
(**11**) R = Ac, R^1 = Me_2C

estimation of the ^{13}C relaxation times (Table 4) using the inversion–recovery method indicated that (**9**) tumbles isotropically in solution and, therefore, the n.O.e. data[20] can be used for estimating the conformational behaviour of these molecules in solution. The values of $^3J_{HH}$ coupling constants observed for (**9**)–(**11**) indicate a $^4C_1$ conformation for the pyranoid rings. The results of n.O.e. experiments are given in Table 5. The similar n.O.e.s observed for (**9**) and (**10**) seem to indicate an almost equal conformation for both molecules, as expected. Thus, on saturation of the resonance of the methyl groups on the acetalic carbon, intensity enhancements were observed for signals assigned to 3-H and 2-H, respectively, indicating spatial proximity of one methyl group to 3-H and the other to 2′-H. On the other hand, on irradiation at 2′-H, n.O.e. could be observed for the signal corresponding to one methyl group and 4-H. No n.O.e. could be detected when 1′-H was irradiated. These experimental results fit satisfactorily with the lowest energy geometry provided by the MM2 program (Table 1).

In the case of the maltoside derivative (**11**), the n.O.e. experiments also allowed us to assign the four methyl groups attached to the molecule. One of these methyl groups must be close to 3-H while a second has a spatial proximity to 2′-H. Besides, irradiation of the signal assigned to 4-H induced a 10 and 9% increase in the intensities of 1′-H and 2-H, respectively. In contrast, no n.O.e. could be observed at 4-H when 2′-H was saturated, while a 7% enhancement was measured when the signal corresponding to 1′-H was irradiated. Therefore, for the α(1 ⟶ 4) linked maltoside derivative (**11**) there is spatial proximity between 1′-H and 4-H, and not between 2′-H and 4-H which is the case for (**9**) and (**10**). This fact is also supported by MM2 calculations.

The above results seem to indicate a fairly rigid conformation for compounds (**9**)–(**11**). In the case of the β(1 ⟶ 4) linked derivatives (**9**) and (**10**), the conformation in solution (Φ_H *ca.* 180°; Ψ_H *ca.* −13°) is quite similar to that found in the solid state[7] for (**8**), an analogue of (**1**), although different from that found in the crystal for β-lactose (Φ_H = 39°; Ψ_H = −22°)[21] and from those predicted by HSEA calculations for lactose and cellobiose (Φ_H = 50–60°; Ψ_H = 0–10°).[10a,22] It is important to mention that there exists a quasi-antiperiplanar relationship between one lone pair on the glycosidic oxygen and the ring oxygen of the non-reducing moiety (torsion angle *ca.* −165°). This antiperiplanar arrangement has been stated as one of the possible causes of additional stabilization, due to an interaction between the lone pair on the glycosidic oxygen with the antibonding σ-orbital of the C–O bond.[9] Two such orientations are possible in glycosides and oligosaccharides, and one of them



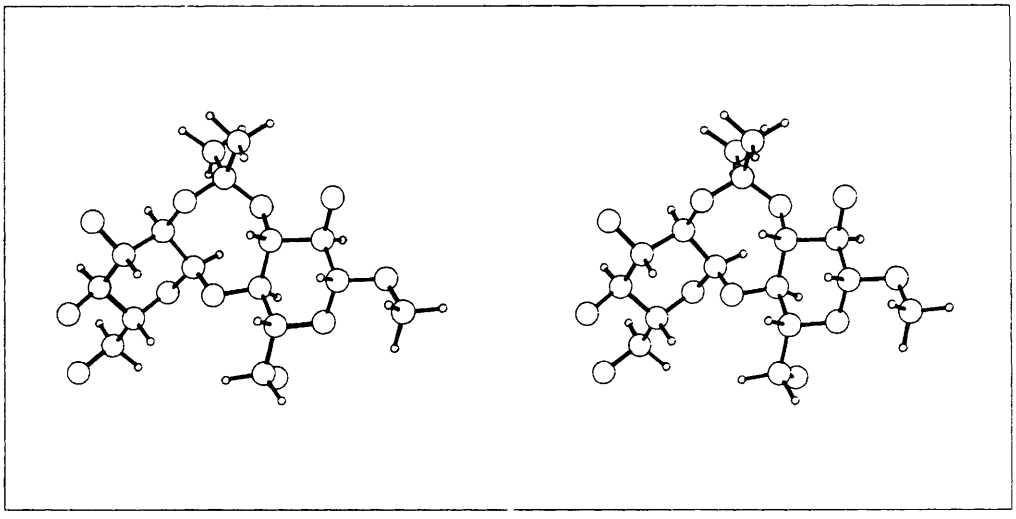


Figure 2(*a*). (For caption, see over).

(Φ_H *ca.* 60°; Ψ_H *ca.* 0°) is expected to be energetically more favourable since the aglycone is *syn*-orientated with respect to 1′-H and O-5′ while for the other, the aglycone is synclinal to C-2′ and O-5′.[9] While for the unsubstituted glycosides, the population of this second conformer seems to be insignificant,[23] it is the only possibility for (**1**) and (**2**) due to the presence of the acetal bridge which precludes the existence of conformers with Φ_H *ca.* 60°. The other local minima provided by the MM2 program show substantially larger values of the steric energy ($\Delta E > 7$ kcal mol^{-1} *) and besides cannot account for the n.O.e. data.

The conformation in solution of the β-maltoside derivative (**11**) ($\Phi_H = 24°$, $\Psi_H = -60°$) agrees reasonably with the experimental results for a number of crystalline maltose derivatives[24] in terms of Φ_H angle (Φ_H *ca.* 10°) but the value of Ψ_H is considerably larger than those found for maltose derivatives in the solid state (Ψ_H 0 − 30°). This geometry does not correspond to any of the local minima proposed by Lipkind *et al.*[25,26] and Pérez *et al.*[27] for maltose derivatives probably due to the presence of the acetal bridge that causes an increase in the Ψ_H angle to avoid unfavourable steric interactions. Besides, the presence of the acetal ring does not allow an antiperiplanar disposition between the lone pairs on the glycosidic oxygen and the ring oxygen, due to the great steric hindrance which would be present in such arrangement (Φ_H *ca.* −60 or *ca.* 180°). As for (**1**) and (**2**), the other local minima provided by the MM2 program have higher steric energy values ($\Delta E > 7$ kcal mol^{-1}) and do not account for the experimental n.O.e.

Table 6 shows the torsion angles for the eight-membered rings of compounds (**2**) and (**3**) provided by the MM2 program for the global minima of these compounds, in comparison with the angles observed in the solid state for the analogue (**8**) and those expected for a boat–chair conformation. The 1,3,6-

* 1 cal = 4.1682 J.

(*b*)

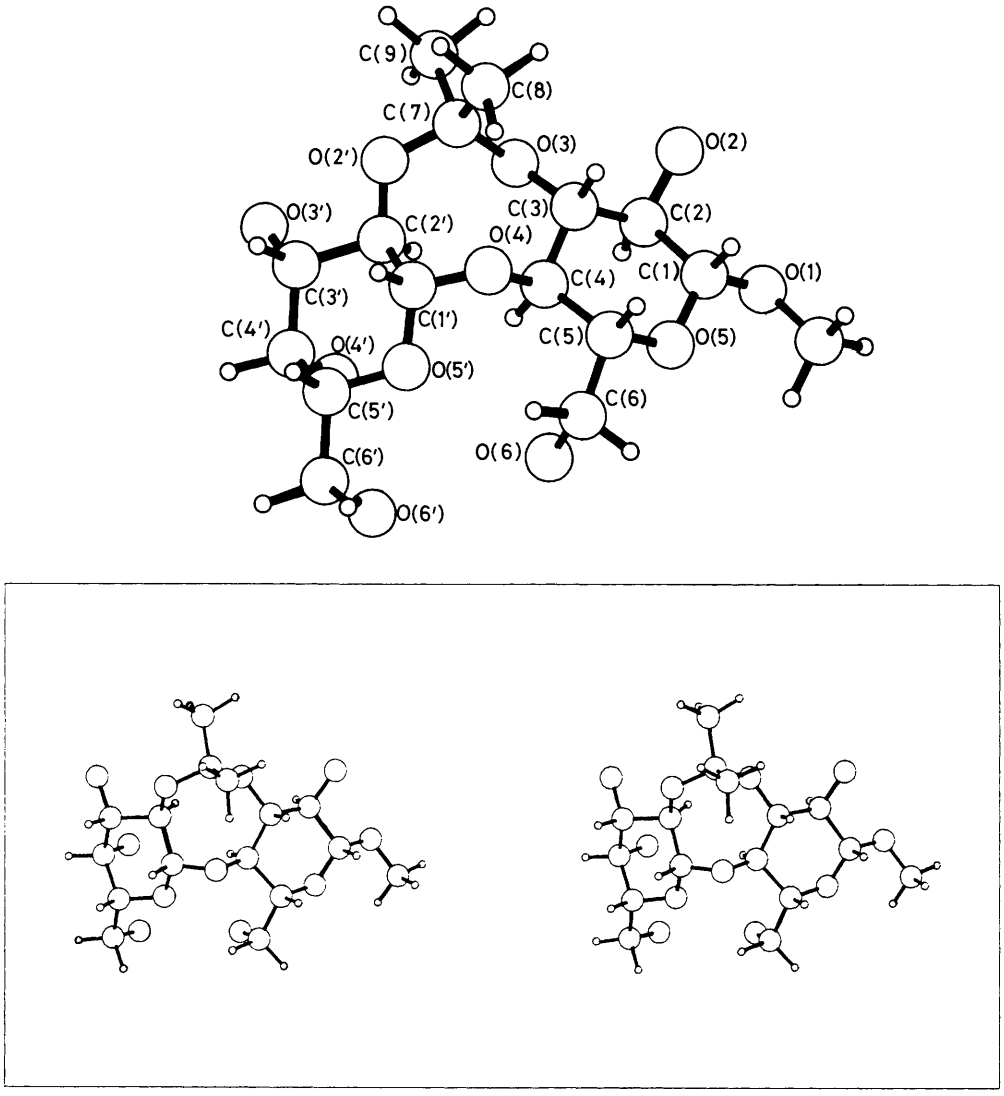


Figure 2. Stereoscopic views of the global minimum obtained by MM2CARB calculations for: (*a*) (**2**) and (*b*) (**3**).

Table 2. ^{2}H N.m.r. spectral parameters for compounds (**9**)–(**11**).

	Compound				Compound		
Parameter	(**10**)[a]	(**9**)[a]	(**11**)[b]	Parameter	(**10**)[a]	(**9**)[a]	(**11**)[b]
1-H	4.57	4.39	4.33	J_{12}	7.9	8.0	8.1
2-H	3.23	3.18	4.79	J_{23}	8.9	8.6	10.1
3-H	3.82	3.86	3.96	J_{34}	8.0	7.8	8.6
4-H	3.80	3.78	3.50	J_{45}	7.7	8.6	8.5
5-H	3.54	3.59	3.6	J_{56A}	5.7	2.0	5.4
6-H_A	4.00	4.01	4.41	J_{56B}	1.6	2.0	2.0
6-H_B	3.62	3.62	4.30	J_{6A6B}	−10.6	−12.0	−12.0
1′-H	4.47	4.68	5.46	$J_{1'2'}$	8.6	8.6	3.9
2′-H	4.30	3.98	3.77	$J_{2'3'}$	10.2	9.5	9.4
3′-H	3.47	3.80	5.23	$J_{3'4'}$	3.0	9.3	9.4
4′-H	4.16	5.26	3.62	$J_{4'5'}$	3.6	10.0	*c*
5′-H	4.06	3.91	3.6	$J_{5'6'A}$	*ca.* 0	4.3	9.3
6′-H_A	3.74	3.57	3.87	$J_{5'6'B}$	*ca.* 0	4.3	9.3
6′-H_B	3.70	3.57	3.59	$J_{6A'6B'}$	−11.0	−12.0	−9.5

[a] In $(CD_3)_2CO$ solution. [b] In $CDCl_3$ solution. [c] Not determined.

Table 3. ^{13}C N.m.r. chemical shifts for compounds (**9**)–(**11**).

	(**9**)[a]	(**10**)[b]	(**11**)[c]
C-1	104.6	101.1	102.0
C-2	81.0	81.4	71.1
C-3	77.9	78.3	74.1
C-4	71.9	75.9	79.3
C-5	75.3	75.7	71.9
C-6	70.5	70.8	62.9
C-1′	100.1	102.9	98.5
C-2′	71.2	68.3	72.2
C-3′	81.7	81.5	70.8
C-4′	72.7	67.8	71.3
C-5′	75.1	72.3	62.1
C-6′	70.4	70.5	64.1
C-7	107.7	102.8	101.3
C-8	28.3	28.9	26.5
C-9	24.6	25.1	24.1

[a] Other chemical shifts: 75.9, 75.2, 73.7, 73.5 (benzyl groups), 57.4 (methyl). [b] Other chemical shifts: 75.6, 73.8, 73.8, 72.3, 71.3 (benzyl groups). [c] Other chemical shifts: 99.5, 56.7, 29.0, 21.0, 20.9, 20.7, 18.9.

Table 4. ^{13}C Relaxation times for (**9**) and ^{1}H relaxation times for (**9**)–(**11**).

Signal	T_1	Signal	T_1	Signal	T_1
Compound (**9**)					
C-2	0.49	C-2′	0.50	1-H	0.56
C-3	0.50	C-3′	0.46	2-H	0.96
C-4	0.51	C-4′	0.50	6-H_A	0.29
C-5	0.49	C-5′	0.53	1′-H	0.50
C-6	0.35	C-6′	0.32	4′-H	0.92
Compound (**10**)					
1-H	0.58	2′-H	0.53		
2-H	0.81	3′-H	0.46		
6-H_A	0.28	4′-H	0.43		
1′-H	0.64	5′-H	0.85		
Compound (11)					
1-H	0.72	1′-H	0.58		
2-H	1.44	2′-H	0.60		
3-H	0.65	3′-H	0.94		
4-H	0.77				
6-H_A	0.34	6′-H_A	0.32		
6-H_B	0.37	6′-H_B	0.45		

Table 5. Observed nuclear Overhauser enhancements for (**9**)–(**11**).

Irradiated signal	Compound	n.O.e. (%)	r/Å [a]
Me_8	(**9**)	3-H (15%)	2.35, 2.28 [b]
Me_9	(**9**)	2′-H (5%)	2.60
Me_8 + Me_9 [c]	(**10**)	3-H, 2′-H [d]	
Me_8	(11)	3-H (6%)	2.30
Me_9	(**11**)	2′-H (13%)	2.31
1-H	(**11**)	4-H (7%)	2.24
2′-H	(**9**)	4-H (5%), Me_9	2.23
2′-H	(**10**)	4-H, Me_9	
4-H	(**9**)	2′-H (4%), 2-H (2%)	
4-H	(**11**)	1′-H (10%), 2-H (9%)	

[a] Distance provided by the MM2 calculations. [b] There are two methyl protons close to 3-H. [c] Both methyl groups appear as a singlet in the ^{1}H n.m.r. spectrum. [d] Strong overlap in the 3-H, 4-H region precludes the measurement of the actual n.O.e. percentage.

Table 6. Torsion angles of the eight-membered ring for the global minimum of compounds (**2**) and (**3**).

	Compound			
Torsion angle	(**2**)	(**8**)	(**3**)	BC [a]
C(3)–C(5)–O(4)–C(1′)	109.1	107.5	62.4	65.0
C(4)–O(4)–C(1′)–O(2′)	−57.6	−54.4	−104.0	−102.2
O(4)–C(1′)–C(2′)–O(2′)	−61.3	−64.3	58.5	44.7
C(1′)–C(2′)–O(2′)–C(7)	85.9	75.7	56.0	65.0
C(2′)–O(2′)–C(7)–O(3)	9.7	28.1	−68.2	−65.0
O(2′)–C(7)–O(3)–C(3)	−93.5	−108.4	−43.5	−44.0
C(7)–O(3)–C(3)–C(4)	79.9	85.4	111.4	102.2
O(3)–C(3)–C(4)–O(4)	−70.9	−68.5	−68.1	−65.0

[a] Torsion angles for the ideal boat–chair conformation according to reference 28.

trioxacyclo-octane moiety in (**1**) and (**2**) can be described as a 'tub–chair' conformation,[6] similar to that found in the crystal for (**8**).[7] On the other hand, the conformation of the eight-membered ring of the β-maltoside derivative (**3**) closely resembles a boat–chair conformation. It is noteworthy that for this conformation of (**3**) there is a lone pair antiperiplanar to an oxygen,[9] for both O-3 and O-2′.

The distribution of rotamers around the C(5)–C(6) bond of the monosaccharide moieties may be estimated from the J_{H5H6a} and J_{H5H6b} values.[29] According to reported values for several glucose and galactose derivatives,[30] the observed coupling constants for (**9**) may be explained by a *gg* conformation for the reducing end and by an equilibrium between the *gg* and *gt* rotamers for the non-reducing moiety.* In the same way, for the lactoside derivative (**10**), there is an equilibrium between *gg* and *gt* rotamers around C(5)–C(6) of the glucoside part and a major *gg* conformation for the galactosyl moiety. In the case of (**11**), the equilibrium between *gg* and *gt* rotamers is repeated for the reducing end while the non-reducing one is fixed in *tg* conformation by the 4′,6′-*O*-isopropylidene moiety. It is of interest that for (**10**) the observed J_{H5H6a} and J_{H5H6b} values, smaller than 1 Hz, can only be accounted for by a major *gg* conformation, in contrast with the usual tendency for galactopyranose derivatives with a minor population of this rotamer.

Experimental

N.M.R. Data.—^{1}H N.m.r. spectra were recorded at 300 or 200 MHz using Varian XL-300 or Bruker AM-200 spectrometers. The ^{1}H shift-correlated (COSY) 2D n.m.r. spectra were acquired using the pulse sequence 90°-t_1-45°-t_2. Relayed coherence transfer 2D n.m.r. experiments used the pulse sequence 90°-t_1-90°-t_m-180°-t_m-90°-t_2. COSY and RELAY-COSY Spectra were measured with 128 × 512 data matrices, and 16 scans for each t_1 value. By zero filling in the F1 dimension a 256 × 512 data matrix was obtained. The mixing time for the RELAY-COSY experiment was 30 ms (1/4 J with J *ca.* 8 Hz). n.O.e. spectra were measured using the differential technique. A pre-irradiation time of 5 s was used with a decoupler intensity of *ca.* 30 Hz. Spin–lattice relaxation times of (**9**), (**10**), and (**11**) in degassed acetone solutions were determined by the inversion–recovery technique using a non-linear least-squares fit procedure. At least 7 delays were used in each T_1 determination. ^{13}C n.m.r. spectra were recorded at 75 or 50 MHz on the same spectrometers. The spectra were assigned combining DEPT and heteronuclear correlated experiments. The 2D-HETCOR spectra were recorded by using a 64 × 1024 data matrix size and 128 scans for each t_1 value. The XHCORRD and RELAY pulse sequences provided by Bruker were used for these heteronuclear correlated experiments, assuming an average $^{3}J_{HH}$ 7 and $^{1}J_{CH}$ 145 Hz.

Molecular-mechanics Calculations.—The MM2 program[18] was modified for carbohydrates by using the acetal segment parameters proposed by Jeffrey and Taylor.[31] The default value for the bulk dielectric constant (1.5 D) corresponding to the gas phase was substituted for a value[32] of 10 D. The co-ordinates for molecular modelling of (**1**) and (**2**) were taken from the crystallographic values[7] reported for an analogue of (**1**), and modified as necessary. The co-ordinates of other possible conformers of (**1**) and those of (**3**) were taken from Dreiding models and refined by using the MM2 program. Benzyl, benzoyl, and acetyl groups were excluded from the minimisation process. The β-methyl group of the reducing moiety was disposed such that it had a Φ angle of *ca.* −70°, according to experimental findings for methyl β-pyranosides.[9] Those conformers which led to pyranoid conformations other than $^{4}C_1$ were discarded. Calculations for (**1**) and (**2**) gave the same local minima and only the results for the lactoside derivative are given in the Tables. Torsion angles are defined as follows: Φ[O(5′)–C(1′)

* *gg* and *gt* stand for *gauche–gauche* and *gauche–trans*, respectively. The first letter refers to the O(5)–C(5) and C(6)–O(6) torsion angle and the second to the C(4)–C(5) and C(6)–O(6) torsion angle.

and O(1′)–C(4)], Φ_H[H(1′)–C(1′) and O(1′)–C(4)], Ψ[C(5)–C(4) and C(1′)–C(1′)], and Ψ_H[H(4)–C(4) and O(1′)–C(1′)]. Several starting geometries led to the same local minima in each case, and only the minimised structures are given. Driver option was used for each local minimum in order to look for other possible conformations of the eight-membered ring. Only the deepest minima are given.

Materials.—General. M.p.s were measured in capillary tubes and are uncorrected. T.l.c. was performed on silicagel GF_{254} (Merck) with detection by charring with sulphuric acid. Column chromatography was performed on Merck (70–230 mesh) silica gel.

Methyl 2,6,3′,6′-Tetra-O-benzyl-β-lactoside (**5**).—A mixture of methyl β-lactoside[33] (**4**) (3 g, 8.4 mmol), tributyltin oxide (17.1 cm^3, 33.6 mmol), molecular sieves type 3 Å (17 g), and toluene (170 cm^3) was stirred at 120 °C for 20 h. After the reaction had been cooled to 100 °C, benzyl bromide (20 cm^3) and *N*-methylimidazole (0.69 cm^3, 8.4 mmol) were added. After 7 h more *N*-methylimidazole (1.38 cm^3, 16.8 mmol) was added, and the reaction was continued with stirring for 48 h. The molecular sieves were filtered off and washed with dichloromethane and the combined filtrate and washings were concentrated. The residue was stirred with hexane (360 cm^3) and kept at −10 °C overnight, the hexane was decanted off. Column chromatography (dichloromethane–ethyl acetate 4:1) of the syrupy residue gave (**5**) (2.7 g, 45%) as a syrup, $[\alpha]_D^{20}$ +9.2° (*c* 0.65, dichloromethane) (Found: C, 68.7; H, 6.9. Calc. for $C_{41}H_{48}O_{11}$: C, 68.70; H, 6.75%).

Acetylation of (**5**) gave a triacetate δ_H 5.54 (1 H, d, $J_{3',4'}$ 3.5 Hz, 4′-H), 5.13 (1 H, t, J_{23}, J_{34} 9.5 Hz, 3-H), 4.94 (1 H, dd, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.0 Hz, 2′-H), 2.06, 1.92, and 1.86 (3 s, each 3 H, 3 Ac).

Methyl 2,6,3′,6′-Tetra-O-benzyl-3,2′-O-isopropylidene-β-lactoside (**6**).—To a solution of (**5**) (2.2 g, 3.1 mmol) and 2-methoxypropene (0.91 cm^3, 9.4 mmol) in dry *N*,*N*-dimethylformamide (25 cm^3) at 0 °C, pyridinium toluene-*p*-sulphonate (0.03 g) was added, and the mixture was stirred at 0–4 °C for 40 h. The reaction mixture was neutralized with sodium carbonate, evaporated and repeatedly concentrated with toluene in order to remove the residual DMF. Column chromatography (hexane–ethyl acetate 2:1) of the residue gave (**6**) (1.5 g, 65%) and unchanged (**5**) (0.38 g). Compound (**6**) had $[\alpha]_D^{20}$ −17.6° (*c* 1.7, chloroform), δ_C 138–139 (C-*ipso*), 127.7–128.8 (aromatic), 104.4, 102.5, and 100.4 (C-1, C-1′, and CMe_2), 57.4 (OMe), and 28.5 and 24.8 (2 Me) (Found: C, 69.95; H, 6.8. Calc. for $C_{44}H_{52}O_{11}$: C, 69.82; H, 6.92%).

Methyl 4′-O-Benzoyl-2,6,3′,6′-tetra-O-benzyl-3,2′-O-isopropylidene-β-cellobioside (**9**).—A mixture of (**6**) (0.25 g, 0.33 mmol), anhydrous DMF (1.5 cm^3), and sodium hydride (0.012 g, 0.54 mmol) was stirred at room temperature for 15 min, and at 60–70 °C for 1 h. The mixture was then cooled to −45 °C and *N*,*N*′-sulphuryldi-imidazole (0.1 g, 0.5 mmol) in DMF (1 cm^3) was added, with stirring at −30 °C for 7 h. Methanol and then water were added, and extracted with diethyl ether. The ether solution was washed with water, dried (Na_2SO_4) and evaporated to give a residue which after column chromatography (hexane–ethyl acetate 5:2) yielded (**7**) (0.15 g, 52%). δ_H 7.95 (1 H, s, imidazole), 7.05 (2 H, s, imidazole), and 5.40 (1 H, d, $J_{3',4'}$ 3.5 Hz, 4′-H). To compound (**7**) (0.13 g, 0.15 mmol) in toluene (3 cm^3), tetrabutylammonium benzoate (0.21 g, 0.58 mmol) was added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene, washed with water (twice), dried (Na_2SO_4), and evaporated to give (**9**) as a chromatographically pure, white solid (0.12 g, 95%), m.p. 168–170 °C (from ethanol–acetone), $[\alpha]_D^{20}$ −43° (*c* 1.0, dichloromethane), δ_H 7.92 (2 H, dd, *J* 8.5 and 1.5 Hz, benzoate), 7.58 (1 H, tt, *J* 7.5 and 1.5 Hz, benzoate), 5.24 (1 H, t, $J_{3',4'}$, $J_{4',5'}$ 9.8 Hz, 4′-H), 3.60 (3 H, s, OMe), 1.46 and 1.38 (2 s, each 3 H, 2 Me) (Found: C, 71.2; H, 6.6. Calc. for $C_{51}H_{56}O_{12}$: C, 71.14; H, 6.56%).

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