Synthesis and Structure of 1-D-6-*O*-(2-Amino-2-deoxy-α- and -β-D-gluco- and -galactopyranosyl)-3-*O*-methyl-D-*chiro*-inositol

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Keywords: Natural products / Insulin mediators / NMR spectroscopy / Oligosaccharides / Pinitol

A convenient preparative synthesis of 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-3-*O*-methyl-*chiro*-inositol (**Ia**), 1-D-6-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-3-*O*-methyl-*chiro*-inositol (**Ib**), 1-D-6-*O*-(2-amino-2-deoxy-α-D-galactopyranosyl)-3-*O*-methyl-*chiro*-inositol (**IIa**), and 1-D-6-*O*-(2-amino-2-deoxy-β-D-galactopyranosyl)-3-*O*-methyl-*chiro*-inositol (**IIb**) from 3-*O*-methyl-D-*chiro*-inositol (pinitol) as starting material is reported. These compounds contain some of the basic structural motifs proposed for insulin mediators. The three-dimensional structures of these compounds have been determined by NMR spectroscopy and molecular dynamics simulations.

Introduction

Many of the actions of insulin have been suggested to be mediated by inositolphosphoglycans (IPGs), the number and structures of which have not yet been completely evaluated.[1] These insulin second messengers seem to be generated after cleavage of membrane-associated glycosylphosphatidylinositols (GPIs) by the action of a phospholipase activated after receptor ligation by insulin. The existence of a family of IPG structures, composed of functionally and chemically distinct A-type and P-type subfamilies, is generally accepted. A-type mediators, which have been suggested to include *myo*-inositol, glucosamine, and galactose, mimic the lipogenic activity of insulin in adipocites, whereas P-type mediators, which have been postulated to comprise *chiro*-inositol, galactosamine, and mannose, mimic the glycogenic activity of insulin in muscle.[1,2]

Determination of the structures of these putative second messengers is seriously hampered by the scarcity of biologically active material that can be obtained from mammalian tissues, and so a variety of synthetic molecules containing the structural motifs thought to be present in the IPG mediators have been prepared by us[3] and by others[4−8] in attempts to determine the minimum structural requirements for biological activity.

In a comparative study of the effects of infusion of a naturally occurring P-type IPG and insulin to diabetic rats, which showed that the putative mediator promoted a considerable decrease in plasma glucose, the authors indicated that the structure of this biologically active material basically consisted of a pseudodisaccharide of pinitol (3-*O*-methyl-D-*chiro*-inositol, **1**) and galactosamine chelated to manganese.[9] This surprising finding and the lack of published consistent structural data to support this observation, prompted us to synthesize some well defined pinitol-containing pseudodisaccharides for structural and biological investigation. Here we report the synthesis of 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-3-*O*-methyl-*chiro*-inositol (**Ia**), 1-D-6-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-3-*O*-methyl-*chiro*-inositol (**Ib**), 1-D-6-*O*-(2-amino-2-deoxy-α-D-galactopyranosyl)-3-*O*-methyl-*chiro*-inositol (**IIa**), and 1-D-6-*O*-(2-amino-2-deoxy-β-D-galactopyranosyl)-3-*O*-methyl-*chiro*-inositol (**IIb**). We have also investigated the three-dimensional structure of these compounds in solution, in an attempt to understand the proposed chelation of these compounds with divalent cations and their interaction with key enzymes involved in insulin signaling.[3e] The choice of position 6 of the 3-*O*-methyl-D-*chiro*-inositol moiety to establish the glycosidic linkage in this series was a consequence of our previous observations that D-*chiro*-inositol-containing IPG-like molecules that present the $GlcNH_2$ α1→6 D-*chiro*-Ins structural motif behave as P-type naturally occurring IPGs in inducing differentiation in cultures of chicken embryo.[10]

Results and Discussion

Synthesis

The synthesis of compounds **Ia**, **Ib**, **IIa**, and **IIb** involves the preparation of a 3-*O*-methyl-D-*chiro*-inositol glycosyl acceptor with position 6 differentiated for treatment with the corresponding glycosyl donor. The key protection of the 4,5-diequatorial diol system of **1** was first attempted with

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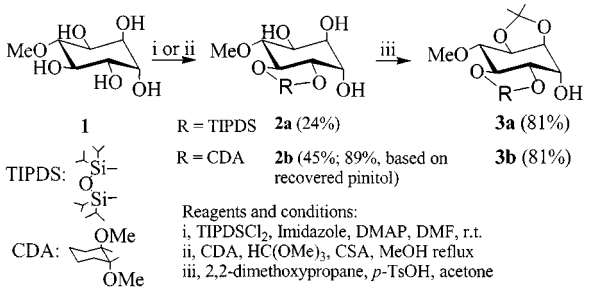
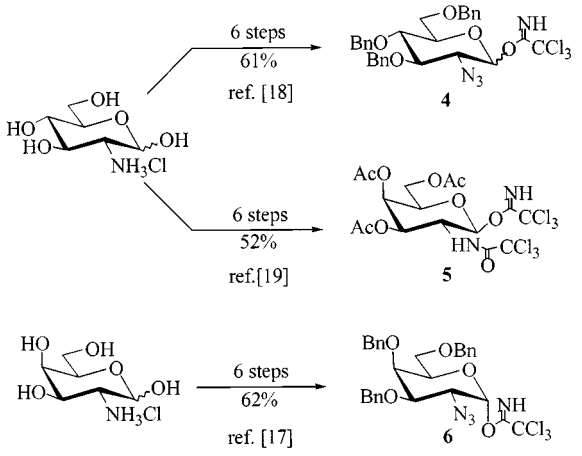
the bifunctional protecting agent 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$)[11] previously used by us for the protection of the 2,3- and 4,5-diol systems in D-*chiro*-inositol.[3c] Treatment of pinitol with $TIPDSCl_2$ under Corey's conditions[12] gave compound **2a** in only 24% yield (Scheme 1). The 1,2-*cis*-oriented free hydroxy groups in **2a** were protected by treatment with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid[13] to afford **3a** in 81% yield. Attempted glycosylation of **3a** with various glycosyl donors under different conditions failed, most probably due to the steric hindrance induced by the large TIPDS group.



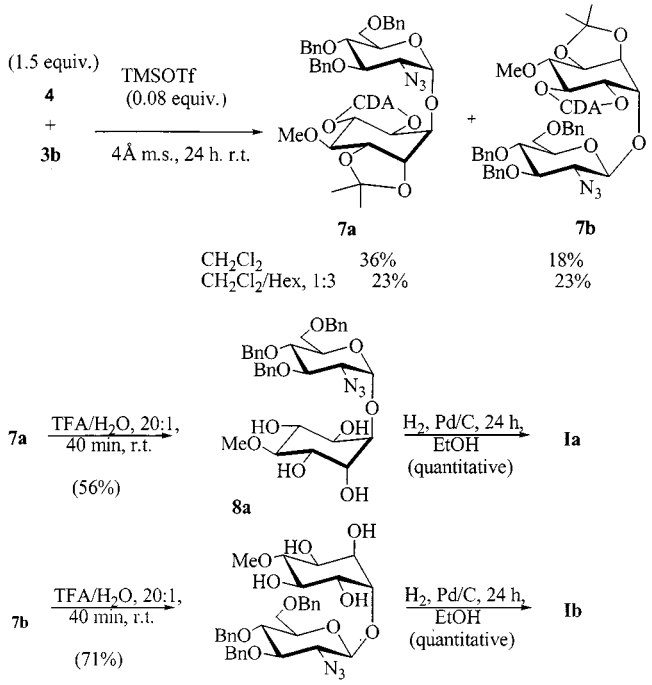
Scheme 1

It was then decided to examine different protecting groups for the diequatorial diol unit in **1**, and so protection of this unit as a cyclohexane-1,2-diacetal was attempted. The selectivity of treatment of **1** with 1,1,2,2-tetramethoxycyclohexane arises from the stabilizing influence of the four anomeric effects in the resulting acetal **2b** and the equatorial arrangement of all four sterically demanding alkyl substituents in the central 1,4-dioxane unit (Scheme 1).[14] Compound **2b** was obtained in 45% yield. Treatment of **2b** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid gave **3b** in 81% yield. Further $^3J_{H\text{-}H}$ NMR and comparative modeling studies of **3a** and **3b** showed similar chair conformations. Therefore, the different reactivity observed between **3a** and **3b** must be a consequence of steric hindrance of the TIPDS group in **3a**.[15]

The glycosylation of **3b** was carried out by the trichloroacetimidate method,[16] which in our hands has proven to be effective for cyclitol glycosylation.[3] Glycosyl donors **4**, **5**, and **6** were prepared by well-established procedures[17–19] (Scheme 2). Glycosylation of **3b** with 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl trichloroacetimidate (**4**) in dichloromethane with TMSOTf as promoter[16] gave a 2:1 mixture of the α- (**7a**) and β-linked (**7b**) pseudodisaccharides in 54% yield (Scheme 3). Both yield and selectivity decreased when a 1:3 mixture of dichloromethane/hexane was used as solvent and all attempts to improve the outcome of the glycosylation reaction were unsuccessful. However, since the reaction mixture could easily be fractionated and both the α- (**7a**) and the β-linked (**7b**) compounds were needed for biological and structural investigation, both pseudodisaccharides were isolated. The acetal groups in **7a** and **7b** were removed[14] to give **8a** (56%) and **8b** (71%), respectively, and these were subjected to hydrogenolysis to afford **Ia** and **Ib** in quantitative yields (Scheme 3).



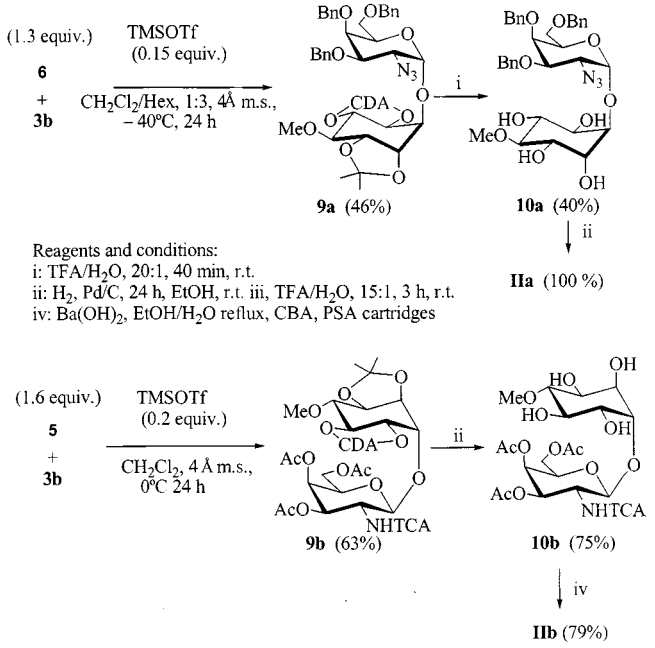
Scheme 2



Scheme 3

Glycosylation of **3b** with 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl thrichloroacetimidate (**6**)[17,18] under different conditions exclusively gave the α-linked[19] pseudodisaccharide **9a** in moderate yield (Scheme 4). Glycosylation of **5**[18] with the acceptor **3b** exclusively provided the β-linked pseudodisaccharide **9b** in 63% yield (Scheme 4).

Deprotection of pseudodisaccharide **9a** (Scheme 4) was carried out by the same sequence as used for pseudodisaccharides **7a** and **7b** (Scheme 3). Acidic hydrolysis of the acetal groups[14c] to give **10a** (40%) was followed by hydrogenolysis to give the completely deprotected disaccharide **IIa** without any need for further purification. The fully deprotected pseudodisaccharide **IIb** was obtained as follows.



Scheme 4

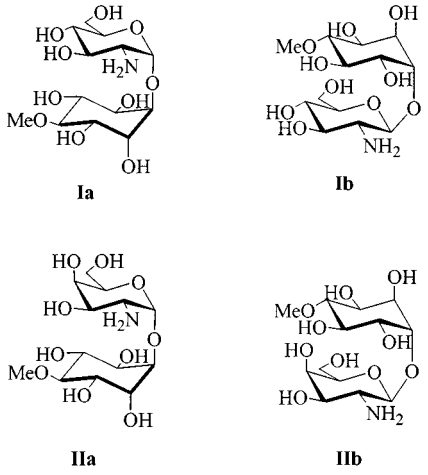
The acetal protecting groups of **9b** were removed under acidic conditions to give **10b** (75%) (Scheme 4). The removal of the protecting groups in **10b** and the final purification[20] of the desired compound **IIb** were carried out by treatment with barium hydroxide[21] in ethanol/water (1:1) and final purification with silica gel cartridges.[22]

Structure

The NMR spectra of the pseudodisaccharides **Ia**, **Ib**, **IIa**, and **IIb** in D_2O were assigned by use of dqf-COSY, TOCSY, and NOESY experiments and HMQC when possible (Table 1).

Table 1. 500 MHz NMR spectroscopic data (δ values) for compounds **Ia**, **IIa**, **Ib**, and **IIb** in D_2O at 298 K

		Ia	IIa	Ib	IIb
O-methyl-*chiro*-inositol	H^1	4.12	4.16	4.21	4.30
	H^2	3.74	3.74	3.80	3.85
	H^3	3.31	3.34	3.30	3.35
	H^4	3.65	3.68	3.65	3.71
	H^5	3.85	3.89	3.82	3.91
	H^6	4.02	4.11	4.00	4.09
Hexosamine	H^1	5.07	5.31	4.52	4.78
	H^2	2.97	3.54	2.66	3.20
	H^3	3.70	4.11	3.37	3.85
	H^4	3.43	4.02	3.33	3.91
	H^5	3.99	4.26	3.42	3.75
	H^{6a}	3.77	3.74	3.70	3.76
	H^{6b}	3.77	3.74	3.88	3.80



The spin systems corresponding to the hexosamine or to the pinitol units were detected by scalar coupling experiments. The six-membered rings adopted the expected $^4C_1$ conformation according to the coupling constant values determined by frequency domain *F*2 dimension deconvolution of antiphase dqf-COSY cross peaks (Table 2). The complete assignment of the signals of the pinitol moiety presented

Table 2. 500 MHz NMR coupling constants [Hz] for compounds **Ia**, **Ib**, **IIa**, and **IIb** in D_2O at 298 K

		Ia	IIa	Ib	IIb
O-methyl-*chiro*-inositol	J_{H1-H2}	3.5	3.4	3.2	3.3
	J_{H2-H3}	10.1	10.0	10.2	10.2
	J_{H3-H4}	9.4	9.3	9.5	9.4
	J_{H4-H5}	10.4	10.5	10.3	10.2
	J_{H5-H6}	3.7	3.5	3.5	3.2
	J_{H6-H1}	3.8	3.8	4.1	4.1
Hexosamine	J_{H1-H2}	3.5	3.85	8.39	8.53
	J_{H2-H3}	–	11.2	9.6	11.1
	J_{H3-H4}	9.4	3.3	–	3.35
	J_{H4-H5}	10.4	2	9.54	2.84
	J_{H5-H6a}	4.2	6.5	5.6	–
	J_{H5-H6b}	2.7	2.5	2.84	–
	$J_{H6a-H6b}$	–	–	12.47	–

Table 3. Hydroxymethyl conformer population along 5 ns stochastic dynamic simulations for **Ia**, **Ib**, **IIa**, and **IIb**, using Homans, Senderowitz with ε = 80, and Senderowitz GB/SA parameters, frictional forces coefficient in stochastic dynamics simulation was 0.2

				gg	*gt*	*tg*
Ia	*gg*	Senderowitz	ε = 80	8.4	14.4	77.2
	gg	Senderowitz	GB/SA	8.2	20.2	71.5
	tg	Homans	ε = 80	35.6	53.4	11.0
IIa	*gt*	Senderowitz	ε = 80	0	18.8	81.2
	gt	Senderowitz	GB/SA	0	21.0	79.0
	gt	Homans	ε = 80	12.6	76.6	10.8
Ib	*gg*	Senderowitz	ε = 80	11.0	4.6	84.4
	gg	Senderowitz	GB/SA	3.2	12.4	84.4
	gt	Homans	ε = 80	22.8	56.0	21.2
IIb	*gt*	Senderowitz	ε = 80	0	2.0	98.0
	gt	Senderowitz	GB/SA	0	2.8	97.2
	gt	Homans	ε = 80	28.6	67.8	3.6

problems, as the pairs 1-H/6-H, 2-H/4-H and 3-H/5-H are exchangeable, but this ambiguity could be solved on the basis of the strong NOE between 1′-H and 6-H and the downfield shift of the C-6 signal resulting from the anomeric linkage. 1D dpfgse-NOESY experiments with mixing times from 200 to 600 ms were recorded with selection of the hexosamine anomeric protons; this allowed key interglycosidic NOEs to be detected.[23] NOESY data were evaluated, assuming the isolated pair approximation, by fitting of growing normalized NOE intensities. The obtained NOE build-up constant rates (σ^{NOE}) were used to evaluate interglycosidic linkages, using known hexosamine distances as references (H^1/H^2 or H^1/H^5 for α and β anomers respectively).[24]

We have previously described the different behavior of the glycosidic linkages of molecules containing the $GlcNH_2$ α- or β1→6*myo*-Ins and $GlcNH_2$ α- or β1→6D-*chiro*-Ins structural motifs.[25] The glycosidic linkages of the D-*chiro*-Ins-containing pseudodisaccharides oscillate around single broad *syn*-Ψ minima, while those of *myo*-Ins containing pseudodisaccharides show higher flexibility, oscillating around major *syn*-Ψ minima and minor *anti*-Ψ minima (Figure 1). As was to be expected, the glycosidic linkage of compounds **Ia**, **Ib**, **IIa**, and **IIb** showed the general conformational behavior of the previously studied D-*chiro*-Ins pseudodisaccharides.

Molecular modeling was performed with the AMBER* force field[26] as implemented in MACROMODEL 6.0[27]

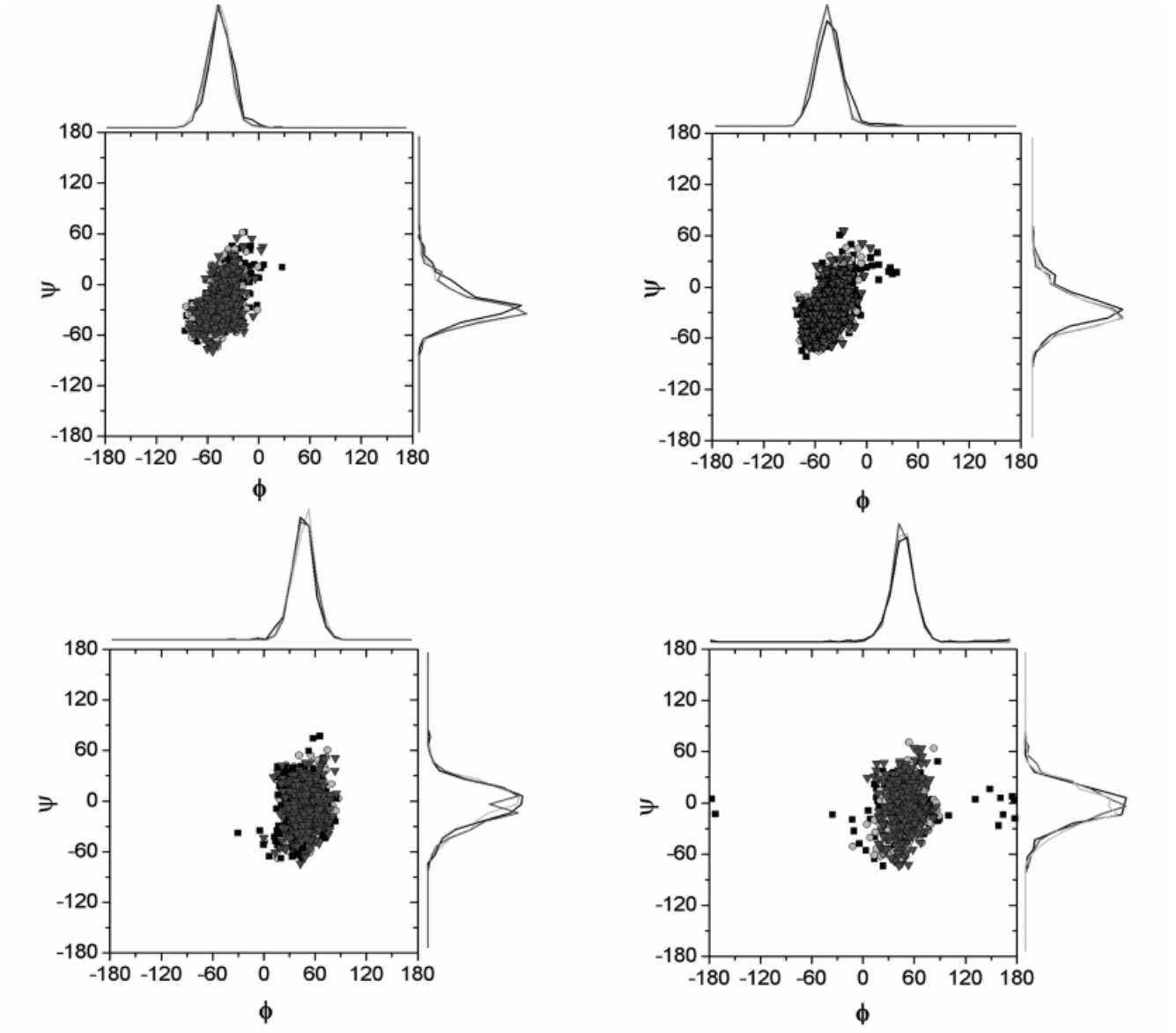


Figure 1. Glycosidic torsion angles (Ψ, Φ) trajectories and distribution along 5 ns MD for **Ia** (top left), **IIa** (top right), **Ib** (bottom left), and **IIb** (bottom right), using Homans with ε = 80 (square, dash line); all atom Senderowitz, with ε = 80 (circle, solid line) and all atom Senderowitz, with GB/SA (triangle, dots) parameters

Two sets of all-atom carbohydrate specific parameters were evaluated: the Homans[28] with ε = 80 and the more recent one by Senderowitz et al.,[29] with both ε = 80 and the GB/SA solvation model. Initial 1 ns molecular dynamics simulations at constant temperature (300 K) were run for compounds **Ia** and **IIa** using Senderowitz parameters and ε = 80 in order to optimize the conditions. Newtonian molecular dynamics at constant temperature with thermal bath coupling (0.1 ps), did not reach a stable geometry. Severe damping of fluctuations in both glycosidic torsion angles and energies was observed. This aspect was independent of the starting geometry and of the thermal bath coupling, which was relaxed down to 0.5 ps. The simulations performed better when a gradual warming period of 60 ps from 0 to 300 K was included. Structural parameters then became stable, but strong oscillations in the total energy were still observed. Finally, simulations with both stable structure and energy along the trajectory were obtained by using stochastic dynamic simulations[30] at constant (300 K) temperature (Table 3). These conditions were chosen for further simulations. Prior to the definitive MD, their ability to simulate the flexible behavior of the hydroxymethyl and methoxy group rotamers had been tested. Six structures were constructed, considering the *gg*, *gt*, and *tg* hydroxymethyl rotamers as well as the orientation of the methoxy group and according to our previous results on glycosidic linkage angles of glycosyl *myo*-inositol derivatives. Then, 1 ns stochastic MD was performed with both Homans[28] and Senderowitz[29] parameters with ε = 80 (data not shown) for each structure. Interconversion between single-bond rotamers was simulated in all cases.

The data for structural analysis were collected from 5 ns stochastic dynamics, by using as initial structures those with the more stable 3-*O*-methoxy rotamer and the *gg* conformer for **Ia** and **Ib**, or the *gt* for **IIa** and **IIb**. The Φ and Ψ angle trajectories for **Ia**, **Ib**, **IIa**, and **IIb** are shown in Figure 2 and are consistent with a single *syn*-Ψ type conformation. This result is in agreement with the observed $H^{1'}/H^{6}$ and $H^{1'}/H^{1}$ NOEs, which are exclusive for this conformer. The lack of any $H^{1'}/H^{2}$ NOE, exclusive to an *anti*-Ψ conformation, also validate the simulations. Moreover, quantitative comparison between experimental NOE distances and the r^{-6} average along the trajectory was also in good agreement for all three sets of force fields and solvent model used (Table 4). Small discrepancies between the experimental data can be explained by the lower quality of the experimental data. Thus, a deviation was observed in the case of **Ib**, and can be attributed to signal overlap in the NMR spectra, which reduced the precision of the NOE peak integration. In the case of the β anomers, on the other hand, the lower precision in the integration of long-distance weak $H^{1'}/H^{1}$ NOE peaks resulted in slightly worse agreement between experimental and theoretical data.

In conclusion, the overall structures of **Ia**, **Ib**, **IIa**, and **IIb** are consistent with the glycosidic linkage oscillating around a single *syn*-Ψ minimum (Figure 1), exhibiting the usual flexibility expected for a carbohydrate. This feature has been found for other *chiro*-inositol analogues and is inconsistent with *myo*-inositol derivatives.[25] Thus, as the introduction of a methoxy group in the cyclitol position 3 does not alter the geometry, the described new derivatives should be interesting for further SAR studies addressing the role of the 3-hydroxy group in the interaction with key metabolic enzymes.

Figure 2. Structure superimposition of **Ia**, **IIa**, and 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*chiro*-inositol (left), and **Ib**, **IIb**, and 1-D-6-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-*chiro*-inositol (right); structures have been superimposed by using the hexosamine heavy atoms' smaller rmsd as criteria

Table 4. NMR experimental and MD r^{-6} averaged distances [Å]

Proton pair		**Ia**	**IIa**	**Ib**	**IIb**
1′-H/6-H	Experimental, NMR	2.5	2.4	2.6	2.3
	Senderowitz ε = 80	2.5	2.4	2.4	2.4
	Senderowitz GB/SA	2.5	2.5	2.4	2.4
	Homans	2.4	2.4	2.4	2.4
1′-H/1-H	Experimental, NMR	2.4	2.4	3.3	3.2
	Senderowitz ε = 80	2.4	2.4	3.7	3.6
	Senderowitz GB/SA	2.4	2.4	3.6	3.7
	Homans	2.5	2.5	3.6	3.7

Experimental Section

General Remarks: Dichloromethane was distilled from calcium hydride; hexane (abbreviated Hex) from sodium/benzophenone. Molecular sieves (4 Å, powdered) were predried in the oven and activated for 5 min under vacuum at 300 °C. All aqueous (aq) solutions were saturated unless otherwise stated. All reactions were carried out under argon in predried glassware unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded at 298 K with Bruker Avance DRX 500, DRX 400 and DPX 300 spectrometers with TMS as indirect reference signal. Resonances were assigned by means of 2D spectra (COSY, HMQC, NOESY). High-resolution mass spectra were recorded with a Micromass Autospec apparatus. Microanalyses were determined with a Leco CHNS-932 apparatus. Optical rotations were measured with a Perkin−Elmer 341 polarimeter. Column chromatography was carried out with Merck 60 silica gel (15−200 mesh), under pressure. Chromatography eluents are given as volume ratios (v/v). For purification of free pseudoligosaccharide **IIb**, CBA and PSA cartridges (Varian Bond elut cartridges, 100 mg/1 mL or 500 mg/3 mL) were used. Analytical thin layer chromatography (TLC) was performed on Merck 60F_{254} silica gel with detection by heating with phosphomolybdic acid/EtOH and $Ce(SO_4)_2$ in phosphomolybdic acid/H_2SO_4/H_2O. Preparative thin layer chromatography (PLC) was performed with precoated, glass-backed plates (Merck 60F_{254} silica gel) with viewing under ultraviolet radiation (254 nm). The organic extracts were dried with anhydrous sodium sulfate and concentrated under vacuum.

Syntheses

3-*O*-Methyl-4,5-*O*-(tetraisopropyldisiloxane-1′,3′-diyl)-D-*chiro*-inositol (2a): TIPDSCl_2 (178 μL, 0.54 mmol, 1.0 equiv.) was added dropwise to a solution of 3-*O*-methyl-D-*chiro*-inositol (D-pinitol) (**1**, 100 mg, 0.52 mmol, 1 equiv.), imidazole (43 mg, 1.29 mmol, 2.5 equiv.), and dimethylaminopyridine (26 mg, 0.21 mmol, 0.4 equiv.) in dimethylformamide (1 mL). The reaction mixture was stirred for 2 h, diluted with CH_2Cl_2, and washed successively with a saturated solution of ammonium chloride, water, and brine, dried with sodium sulfate, and concentrated. The residue was purified by flash chromatography (Hex/EtOAc, 1:2) to give **2a** (54 mg, 0.12 mmol, 24%) as a white solid. R_f (Hex/EtOAc, 2:1) = 0.64. $[\alpha]_D^{20}$ = +12 (c = 0.91, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.19 (dd, J_{H1-H2} = 3.0 Hz, J_{H1-H6} = 2.7 Hz, 1 H, H^1), 4.01 (dd, J_{H6-H5} = 3.2 Hz, J_{H6-H1} = 2.7 Hz, 1 H, H^6), 3.98 (dd, J_{H5-H4} = 8.8 Hz, J_{H5-H6} = 3.2 Hz, 1 H, H^5,), 3.90 (t, J = 8.8 Hz, 1 H, H^4), 3.82 (dd, J_{H2-H3} = 8.8 Hz, J_{H2-H1} = 3.0 Hz, 1 H, H^2), 3.66 (s, 3 H, OCH_3), 3.32 (t, J = 8.8 Hz, 1 H, H^3), 2.65 (br. s, 1 H, OH), 2.63 (br. s, 1 H, OH), 2.50 (br. s, 1 H, OH), 1.10−1.04 (m, 28 H, CH, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 83.4 (C^3), 77.8 (C^4), 75.6 (C^5), 72.2 (C^6), 70.9 (C^1), 70.6 (C^2), 62.1 (OCH_3), 17.3, 17.6, 17.7 (8 CH_3), 13.1 (2 CH), 12.4 (CH), 12.3 (CH). MALDI-TOF calcd. for $C_{19}H_{40}O_7Si_2$ + Na^+: 459.7, found 459.7, calcd. for $C_{19}H_{40}O_7Si_2$+K^+: 475.8, found 476.9.

1,2-*O*-Isopropylidene-3-*O*-methyl-4,5-*O*-(tetraisopropyldisiloxane-1′,3′-diyl)-D-*chiro*-inositol (3a): A solution of 3-*O*-methyl-4,5-*O*-(tetraisopropyldisiloxane-1′,3′-diyl)-D-*chiro*-inositol (**2a**, 240 mg, 0.55 mmol, 1 equiv.) and 2,2-dimethoxypropane (752 μL, 0.61 mmol, 1.1 equiv.) in acetone (1 mL) was treated with *p*-toluenesulfonic acid monohydrate (5.3 mg, 0.03 mmol, 0.05 equiv.). The reaction mixture was stirred for 3 h at room temperature, whereupon it was quenched with solid $NaHCO_3$, the solvent was evaporated, and the residue was purified by flash chromatography (Hex/ EtOAc, 10:1) to give **3a** (213 mg, 0.45 mmol, 81%) as a crystalline, white solid. R_f (Hex/EtOAc, 3:1) = 0.78. $[\alpha]_D^{20}$ = +39 (c = 0.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.28 (dd, J_{H1-H2} = 5.5 Hz, J_{H1-H6} = 2.5 Hz, 1 H, H^1), 4.16 (br. s, 1 H, H^6), 4.13 (dd, J_{H2-H3} = 8.7 Hz, J_{H1-H2} = 6.2 Hz, 1 H, H^2), 3.91 (dd, J_{H5-H4} = 8.7 Hz, J_{H5-H6} = 3.5 Hz, 1 H, H^5), 3.86 (t, J = 8.7 Hz, 1 H, H^4), 3.62 (s, 3 H, OCH_3), 3.19 (t, J = 8.7 Hz, 1 H, H^3), 2.79 (s, 1 H, OH), 1.54 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.11, 1.10, 1.08, 1.06, 1.05, 1.04, 1.01, 1.00 (8 s, 24 H, 8 CH_3). ^{13}C NMR: δ = 108.9 (C), 85.4 (C^3), 78.5 (C^2), 75.9 (C^1), 69.9, 75.3 (C^4, C^5), 61.3 (OCH_3), 28.2 (CH_3), 25.8 (CH_3), 17.4 (4 CH_3, TIPDS), 17.3 (CH_3, TIPDS), 17.1 (2 CH_3, TIPDS), 17.0 (CH_3, TIPDS), 12.9 (CH), 12.8 (CH), 12.3 (CH), 12.0 (CH). $C_{22}H_{44}O_7Si_2$ (476.760) calcd.: calcd. C 55.42, H 9.30; found C 55.00, H 9.19. MALDI-TOF calcd. for $C_{22}H_{44}O_7Si_2$ + Na^+: 499.8, found 499.6; CI MS calcd. for $C_{22}H_{44}O_7Si_2$: 476.8, found 477.0.

4,5-*O*-(1′,2′-Dimethoxycyclohexane-1′,2′-diyl)-3-*O*-methyl-D-*chiro*-inositol (2b): D-Pinitol (**1**, 283 mg, 1.46 mmol, 1 equiv.) was dissolved in methanol (15 mL) in an ultrasound bath, and 1,2-cyclohexane diacetal (507 mg, 2.46 mmol, 1.7 equiv.), trimethyl orthoformate (200 μL, 1.75 mmol, 1.2 equiv.), and 1-(*S*)-(+)-10-camphorsulfonic acid (24 mg, 0.10 mmol, 0.07 equiv.) were then added. The reaction mixture was heated at 70 °C for 24 h, diluted with MeOH, and quenched with solid $NaHCO_3$. The residue was concentrated and purified by flash chromatography (Hex/EtOAc, 1:15) to give **2b** [222 mg, 0.66 mmol, 45%; 89% based on 134 mg of recovered D-pinitol (**1**)]. R_f (Hex/EtOAc, 1:20) = 0.22. $[\alpha]_D^{20}$ = −23 (c = 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.12 (br. s, 1 H, H^1), 4.10 (s, 2 H, H^4, H^5), 4.07 (br. s, 1H, H^6), 3.81 (ddd, J_{H2-H3} = 9.0 Hz, J_{H2-H1} = 3.6 Hz, J_{H2-OH} = 1.8 Hz, 1 H, H^2), 3.47 (t, J = 9.0 Hz, 1 H, H^3), 3.23 (s, 3 H, OCH_3), 3.21 (s, 3 H, OCH_3), 2.76 (d, 1 H, J_{OH-H2} = 1.8 Hz, OH^2), 2.60 (s, 1 H, OH^1), 2.56 (s, 1 H, OH^6), 1.86−1.78 (m, 1 H, CDA), 1.77−1.66 (m, 3 H, CDA), 1.57−1.50 (m, 2 H, CDA), 1.42−1.34 (m, 2 H, CDA). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 98.9 (C), 98.0 (C), 80.2 (C^3), 71.5(C^2), 70.8, 70.4, 70.3 (C^1, C^4, C^6), 68.7 (C^5), 61.1 (OCH_3), 47.0 (OCH_3, CDA), 46.8 (OCH_3, CDA), 27.1 (CH_2), 27.0 (CH_2), 21.5 (CH_2), 21.4 (CH_2). FAB HRMS calcd. for $C_{15}H_{26}O_8$ + Na^+: 357.1525 found 357.1528. MALDI-TOF calcd. for $C_{15}H_{26}O_8$ + Na^+: 357.4, found 357.5, calcd. for $C_{15}H_{26}O_8$+K^+: 373.5, found 374.1.

4,5-*O*-(1′,2′-Dimethoxycyclohexane-1′,2′-diyl)-1,2-*O*-isopropylidene-3-*O*-methyl-D-*chiro*-inositol (3b): 4,5-*O*-(1′,2′-Dimethoxycyclohexane-1′,2′-diyl)-3-*O*-methyl-D-*chiro*-inositol (**2b**) (326 mg, 0.98 mmol, 1 equiv.) and 2,2-dimethoxypropane (1.32 mL, 1.07 mmol, 1.1 equiv.) in acetone (4 mL) were treated with *p*-toluenesulfonic acid monohydrate (9.3 mg, 0.05 mmol, 0.05 equiv.). The reaction mixture was stirred for 1 h and then quenched with solid $NaHCO_3$. The solvent was evaporated and the residue was purified by flash chromatography (Hex/EtOAc, 1:1) to give **3b** (292 mg, 0.87 mmol, 81%) as a white solid. R_f (Hex/EtOAc, 3:1) = 0.71. $[\alpha]_D^{20}$ = −18 (c = 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.27 (dd, J_{H1-H2} = 7.3 Hz, J_{H1-H6} = 3.2 Hz, 1 H, H^1), 4.24 (t, J = 3.2 Hz, 1 H, H^6), 4.16 (t, J = 7.3 Hz, 1 H, H^2), 4.06 (t, J = 10.2 Hz, 1 H, H^4), 3.94 (dd, J_{H5-H4} = 10.2 Hz, J_{H5-H6} = 3.2 Hz, 1 H, H^5), 3.61 (s, 3 H, OCH_3), 3.39 (dd, J_{H3-H4} = 10.2 Hz, J_{H3-H2} = 7.3 Hz, 1 H, H^3), 3.23 (s, 3 H, OCH_3, CDA), 3.22 (s, 3 H, OCH_3, CDA), 1.86−1.78 (m, 1 H, CDA), 1.77−1.66 (m, 3 H, CDA), 1.52 (s, 3 H, CH_3), 1.57−1.51 (m, 2 H, CDA), 1.36 (s, 3 H, CH_3), 1.41−1.33 (m, 2 H, CDA). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 109.0 (C), 98.4 (C, CDA), 97.8 (C, CDA), 82.7 (C^3), 79.6 (C^2), 76.4 (C^1), 68.5 (C^5), 68.3 (C^6), 67.4(C^4), 60.2 (OCH_3), 47.1 (OCH_3, CDA), 46.9 (OCH_3, CDA), 27.0 (CH_3), 27.1 (CH_2), 26.9 (CH_2), 26.0 (CH_3), 21.4 (2 CH_2). $C_{18}H_{30}O_8$ (374.432) calcd.: calcd. C 57.74, H 8.08; found 57.46, H 7.86. FAB HRMS calcd. for

$C_{18}H_{30}O_8 + Na^+$: 397.1838, found 397.1854. MALDI-TOF calcd. for $C_{18}H_{30}O_8 + Na^+$: 397.4, found 397.3 calcd. for $C_{18}H_{30}O_8 + K^+$: 413.5, found 413.8.

2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl-α(1→6)-4,5-*O*-(1′,2′-dimethoxycyclohexane-1′,2′-diyl)-1,2-*O*-isopropylidene-3-*O*-methyl-D-*chiro*-inositol (7a) and 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl-β(1→6)-4,5-*O*-(1′,2′-dimethoxycyclohexane-1′,2′-diyl)-1,2-*O*-isopropylidene-3-*O*-methyl-D-*chiro*-inositol (7b): A 10-mL round-bottomed flash was charged with **4** (809 mg, 1.30 mmol, 1.5 equiv.), **3b** (295 mg, 0.79 mmol, 1 equiv.), freshly activated 4 Å molecular sieves, and CH_2Cl_2 (4 mL), and the mixture was stirred under argon for 1 h at room temperature. TMSOTf (12.6 μL, 0.10 mmol, 0.08 equiv.) was then added and the reaction mixture was stirred for 24 h. The suspension was filtered through a short pad of Celite and the solvent was evaporated under vacuum to provide a mixture of two disaccharides (α/β = 2:1), which could be separated by flash chromatography (Hex/EtOAc, 4:1) to obtain **7a** (235 mg, 0.28 mmol, 36%) and **7b** (118 mg, 0.14 mmol, 18%).

Data for 7a: R_f (Hex/EtOAc, 3:1) = 0.17. $[\alpha]_D^{20}$ = +49 (*c* = 0.25, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.43−7.22 (m, 15 H, Ph), 4.94 (d, 1 H, $J_{1'\text{-}2'}$ = 3.2 Hz, $H^{1'}$), 4.88−4.79 (m, 3 H, 3 CHPh), 4.82 (AB, 2 H, 2 CHPh), 4.58 (AB, 1 H, CHPh), 4.58 (m, 1 H, $H^{5'}$), 4.57 (AB, 1 H, CHPh), 4.42 (AB, 1 H, CHPh), 4.25 (t, *J* = 6.4 Hz, 1 H, H^2), 4.18 (t, *J* = 2.5 Hz, 1 H, H^1), 4.16 (t, *J* = 2.5 Hz, 1 H, H^6), 4.11 (t, *J* = 10.5 Hz, 1 H, H^4), 3.96 (t, *J* = 10.1 Hz, 1 H, $H^{3'}$), 3.90 (dd, $J_{H5\text{-}H4}$ = 10.5 Hz, $J_{H5\text{-}H6}$ = 2.5 Hz, 1 H, H^5), 3.79 (t, *J* = 10.1 Hz, 1 H, $H^{4'}$), 3.71 (dd, 1 H, $J_{H6a'\text{-}H6b'}$ = 10.8 Hz, $J_{H6a'\text{-}H5'}$ = 2.4 Hz, $H^{6a'}$), 3.60 (s, 3 H, OCH_3), 3.59 (dd, 1 H, $J_{H6a'\text{-}H6b'}$ = 10.8 Hz, $J_{H6b'\text{-}H5'}$ = 1.6 Hz, $H^{6b'}$), 3.41 (dd, $J_{H3\text{-}H4}$ = 10.5 Hz, $J_{H3\text{-}H2}$ = 6.4 Hz, 1 H, H^3), 3.36 (dd, 1 H, $J_{H2'\text{-}H3'}$ = 10.1 Hz, $J_{H2'\text{-}H1'}$ = 3.2 Hz, $H^{2'}$), 3.19 (s, 6 H, 2 OCH_3, CDA), 1.83−1.78 (m, 1 H, CDA), 1.72−1.61 (m, 3 H, CDA), 1.52 (s, 3 H, CH_3), 1.55−1.43 (m, 2 H, CDA), 1.40−1.30 (m, 2 H, CDA), 1.36 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 139.0 (C, Bn), 138.0 (C, Bn), 137.9 (C, Bn), 128.4 (2 CH, Bn), 128.3 (2 CH, Bn), 128.2 (2 CH, Bn), 128.1 (2 CH, Bn), 127.9 (CH, Bn), 127.8 (2 CH, Bn), 127.6 (CH, Bn), 127.2 (CH, Bn), 126.7 (2 CH, Bn), 110.0 (C), 97.9 ($C^{1'}$), 97.6 (C, CDA), 97.5 (C, CDA), 83.4 (C^3), 80.2 (C^2), 79.9 ($C^{3'}$), 78.2 ($C^{4'}$), 75.4 (*C*H_2Ph), 74.9 (C^1), 74.0 (*C*H_2Ph), 73.8 (C^6), 73.5 (*C*H_2Ph), 70.7 ($C^{5'}$), 68.5 ($C^{6'}$), 67.7 (C^4), 68.9 (C^5), 63.4 ($C^{2'}$), 60.0 (OCH_3), 47.1 (OCH_3, CDA), 46.9 (OCH_3, CDA), 28.0 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 21.6 (CH_2), 21.5 (CH_3). MALDI-TOF calcd. for $C_{45}H_{57}N_3O_{12} + Na^+$: 855.0, found 854.3, calcd. for $C_{45}H_{57}N_3O_{12} + K^+$: 871.1, found 870.5; CI HRMS calcd. for $C_{45}H_{57}N_3O_{12}$: 831.3942, found 831.3920.

Data for 7b: R_f (Hex/EtOAc, 3:1) = 0.20. $[\alpha]_D^{20}$ = −8 (*c* = 1.18, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.40−7.24 (m, 13 H, Ph), 7.21−7.13 (m, 2 H, Ph), 4.97 (d, 1 H, $J_{H1'\text{-}H2'}$ = 8.1 Hz, $H^{1'}$), 4.92 (AB, 1 H, CHPh), 4.82 (AB, 1 H, CHPh), 4.78 (AB, 1 H, CHPh), 4.62 (AB, 1 H, CHPh), 4.58 (2AB, 2 H, 2CHPh), 4.49 (t, *J* = 2.5 Hz, 1 H, $H^{6'}$), 4.30 (m, 1 H, H^1), 4.20 (t, *J* = 10.8 Hz, 1 H, H^4), 4.17 (t, *J* = 5.1 Hz, 1 H, H^2), 3.98 (dd, $J_{H5\text{-}H4}$ = 10.8 Hz, $J_{H5\text{-}H6}$ = 2.5 Hz, 1 H, H^5), 3.71−3.57 (m, 3 H, $H^{5'}$, $H^{6'}$, $H^{4'}$), 3.61 (s, 3 H,OCH_3), 3.47−3.39 (m, 3 H, $H^{3'}$, H^3, $H^{6'}$), 3.30 (dd, *J* = 8.1 Hz, 1 H, $H^{2'}$), 3.23 (s, 3 H, OCH_3, CDA), 3.18 (s, 3 H, OCH_3, CDA), 1.83−1.77 (m, 1 H, CDA), 1.80−1.43 (m, 5 H, CDA), 1.52 (s, 3 H, CH_3), 1.41−1.28 (m, 2 H, CDA), 1.33 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.5, 138.4, 138.3, (3 C, 3Bn), 128.9, 128.8 (4 CH, Bn), 128.8 (CH, Bn), 128.8, 128.4 (4 CH, Bn), 128.3 (2 CH, Bn), 128.3 (CH, Bn), 128.2 (2 CH, Bn), 128.1 (CH, Bn), 109.9 (C), 101.3 ($C^{1'}$), 98.4 (C, CDA), 98.0 (C, CDA), 83.9 ($C^{3'}$), 83.6 (C^3), 78.1 ($C^{4'}$), 76.7 (C^1), 76.0 (CH_2), 75.9 (C^6), 75.5 (CH_2), 75.4 (CH_2), 73.9 ($C^{6'}$), 72.6 ($C^{5'}$), 68.8 (C^5), 68.7 (C^2), 68.1 (C^4), 67.5 ($C^{2'}$), 60.4 (OCH_3), 47.4 (OCH_3, CDA), 47.3 (OCH_3, CDA), 28.4 (CH_3), 27.5 (CH_2), 27.4 (CH_2), 26.3 (CH_3), 21.8 (2 CH_2). FAB HRMS calcd. for $C_{45}H_{57}N_3O_{12} + Na^+$: 854.3840, found 854.3872. MALDI-TOF calcd. for $C_{45}H_{57}N_3O_{12} + Na^+$: 855.0, found 854.3, calcd. for $C_{45}H_{57}N_3O_{12} + K^+$: 871.1, found 870.4.

2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl-α(1→6)-3-*O*-methyl-D-*chiro*-inositol (8a): Pseudodisaccharide **7a** (9 mg, 0.01 mmol) was dissolved in a mixture of trifluoroacetic acid/water (20:1, 3.7 mL) and stirred at room temperature for 40 min. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and immediately poured into an ice-cold, vigorously stirred solution of saturated aqueous sodium bicarbonate (90 mL). The layers were separated, and the aqueous phase was extensively extracted (CH_2Cl_2, 4 × 30 mL), dried with Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Cl_2CH_2/MeOH, 11:1) gave incompletely pure **8a**; further preparative chromatography (CH_2Cl_2/MeOH, 15:1) was therefore necessary to obtain pure **8a** (4 mg, 0.06 mmol, 56%). R_f (Cl_2CH_2/MeOH, 9:1) = 0.3. $[\alpha]_D^{20}$ = +38 (*c* = 0.19, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.34−7.16 (m, 15 H, Ph), 4.94 (d, *J* = 3.5 Hz, 1 H, $H^{1'}$), 4.84 (AB, 2 H, 2 CHPh), 4.79 (AB, 1 H, CHPh), 4.57−4.46 (m, 3 H, 3 CHPh), 4.16 (br. s, 1 H, H^1), 4.12 (m, 1 H, $H^{5'}$), 4.04 (br. s, 1 H, H^6), 3.92 (m, 1 H, H^2), 3.87−3.84 (m, 2 H, $H^{3'}$, H^5), 3.71 (br. t, 1 H, *J* = 8.0 Hz, H^4), 3.56 (m, 3 H, $H^{4'}$, 2 $H^{6'}$), 3.63 (s, 3 H, OCH_3), 3.44 (dd, 1 H, $J_{H2'\text{-}H3'}$ = 10.0 Hz, $J_{H1'\text{-}H2'}$ = 3.5 Hz, $H^{2'}$), 3.37 (br. t, 1 H, *J* = 8.0 Hz, H^3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.6 (3 C, 3OBn), 128.5 (8CH, Bn), 128.0 (3 CH, Bn), 127.9 (2 CH, Bn), 127.8 (2 CH, Bn), 98.8 ($C^{1'}$), 82.4 (C^3), 80.1 (C^6), 80.0 ($C^{3'}$), 78.4 ($C^{4'}$), 75.5, 75.1, 73.6 (3 *C*H_2Ph), 71.4 ($C^{5'}$), 71.1 (C^2), 71.0 (C^5), 69.2 (C^1), 68.5 (C^4), 63.6 ($C^{2'}$), 60.5 (OCH_3), 60.4 ($C^{6'}$). FAB HRMS calcd. for $C_{34}H_{41}N_3O_{10} + Na^+$: 674.2690, found 674.2696.

2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl-β(1→6)-3-*O*-methyl-D-*chiro*-inositol (8b): Compound **8b** (28 mg, 0.04 mmol, 71%) was obtained by the same experimental procedure as used for compound **8a**, starting from **7b** (50 mg, 0.06 mmol, 1 equiv.). Purification was by flash chromatography (Hex/EtOAc, 1:20). R_f (EtOAc) = 0.47. $[\alpha]_D^{20}$ = −0.02 (*c* = 0.32, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.34−7.24 (m, 13 H, Ph), 7.16−7.14 (m, 2 H, Ph), 4.82 (AB, 2 H, 2 CH-Ph), 4.77 (AB, 1 H, J_{AB} = 11.0 Hz, CH-Ph), 4.53 (AB, 1 H, J_{AB} = 11.0 Hz, CH-Ph), 4.52 (AB, 2 H, 2 CH-Ph), 4.38 (d, *J* = 8.0 Hz, 1 H, $H^{1'}$), 4.20 (br. t, 1 H, *J* = 4.5 Hz, H^1), 4.10 (br. t, 1 H, *J* = 4.5 Hz, H^6), 3.92−3.90 (m, 2 H, H^2, H^5), 3.78 (t, *J* = 8.2 Hz, 1 H, H^4), 3.69 (dd, 1 H, $J_{H6a'\text{-}H6b'}$ = 10.5 Hz, $J_{H6a'\text{-}H5}$ = 2.0 Hz, $H^{6a'}$), 3.63 (m, 1 H, $H^{6b'}$), 3.61 (s, 3 H, OCH_3), 3.59 (t, *J* = 9.5 Hz, 1 H, $H^{4'}$), 3.46 (t, *J* = 9.5 Hz, 1 H, $H^{3'}$), 3.46−3.40 (m, 2 H, $H^{2'}$, $H^{5'}$), 3.38 (m, 1 H, H^3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.2, 138.1, 138.0 (3 C, 3OBn), 128.9 (4 CH, OBn), 128.8, 128.5, (2 CH, OBn), 128.4, 128.3, (CH, OBn), 128.2 (2 CH, OBn), 128.1 (2 CH, CH, OBn), 103.6 ($C^{1'}$), 83.5 ($C^{3'}$), 82.1 (C^3), 80.7 (C^6), 77.6 ($C^{4'}$), 76.0 (*C*H_2Ph), 75.5 (*C*H_2Ph), 75.4 ($C^{5'}$), 73.9 (*C*H_2Ph), 73.6 (C^4), 72.5 (C^2), 71.5 (C^5), 70.5 (C^1), 68.8 ($C^{6'}$), 66.7 ($C^{2'}$), 60.7 (OCH_3). FAB HRMS calcd. for $C_{34}H_{41}N_3O_{10} + Na^+$: 674.2690, found 674.2709.

2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranosyl-α(1→6)-4,5-*O*-(1′,2′-dimethoxycyclohexane-1′,2′-diyl)-1,2-*O*-isopropylidene-3-*O*-methyl-D-*chiro*-inositol (9a): A 10-mL round-bottomed flash was charged with donor **5** (84 mg, 0.14 mmol, 1.3 equiv.), acceptor **3b** (39 mg, 0.10 mmol, 1.0 equiv.), freshly activated 4 Å molecular sieves, and CH_2Cl_2/Hex (1:3, 2 mL) and the mixture was stirred under argon for 1 h at room temperature. TMSOTf (2.43 μL,

0.02 mmol, 0.15 equiv.) was then added at −40 °C and the reaction mixture was stirred for 24 h at 0 °C. The suspension was filtered through a short pad of Celite and the solvent was removed under vacuum to provide the crude material. Flash chromatography (Hex/EtOAc, 4:1) afforded **9a** as a solid (38 mg, 0.05 mmol, 46%). R_f (Hex/EtOAc, 1:1) = 0.67. $[\alpha]_D^{20}$ = +60 (*c* = 1.44, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.46−7.28, (m, 15 H, Ph), 4.98 (d, *J* = 3.3 Hz, 1 H, H$^{1'}$), 4.89 (AB, 1 H, CHPh), 4.78 (AB, 1 H, CHPh), 4.69 (m, 1 H, H$^{5'}$), 4.67 (AB, 1 H, CHPh), 4.59 (AB, 1 H, CHPh), 4.46, (AB, 2 H, 2 CHPh), 4.28 (br. t, 1 H, *J* = 6.3 Hz, H^2), 4.20 (m, 2 H, H^1, H^6), 4.15 (br. s, 1 H, H$^{4'}$), 4.11 (t, *J* = 10.2 Hz, 1 H, H^4), 4.04 (dd, 1 H, $J_{H3'\text{-}H2'}$ = 10.6 Hz, $J_{H3'\text{-}H4'}$ = 2.4 Hz, H$^{3'}$), 3.92 (dd, $J_{H4\text{-}H5}$ = 10.8 Hz, $J_{H5\text{-}H6}$ = 2.1 Hz, 1 H, H^5), 3.86 (dd, 1 H, $J_{H2'\text{-}H3'}$ = 10.6 Hz, $J_{H2'\text{-}H1'}$ = 3.3 Hz, H$^{2'}$), 3.66−3.60 (m, 1 H, H$^{6b'}$), 3.63 (s, 3 H, OCH_3), 3.50 (dd, 1 H, $J_{H6a'\text{-}H6b'}$ = 8.1 Hz, $J_{H6a'\text{-}H5'}$ = 5.4 Hz, $H_{6a'}$), 3.42 (dd, $J_{H3\text{-}H4}$ = 10.2 Hz, $J_{H3\text{-}H2}$ = 6.3 Hz, 1 H, H_3), 3.20 (s, 3 H, OCH_3, CDA), 3.18 (s, 3 H, OCH_3, CDA), 1.90−1.63 (m, 4 H, CDA), 1.54 (s, 3 H, CH_3), 1.60−1.33 (m, 4 H, CDA), 1.40 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.9, 138.4, 137.9 (3 C, 3OBn), 129.0 (2 CH, Bn), 128.9 (CH, Bn), 128.7, 128.6 (4 CH, Bn), 128.6, 128.5 (2 CH, Bn), 128.4, 128.3 (4 CH, Bn), 128.1, 128.0 (2 CH, Bn), 110.1 (C), 98.2 (C$^{1'}$), 98.0, 97.6 (2 C, CDA), 83.5 (C^3), 80.5 (C^2), 77.6 (C$^{3'}$), 75.2 (*C*H_2Ph), 75.0 (C^6), 74.0 (C$^{4'}$), 73.8 (*C*H_2Ph), 72.8 (C^1), 72.7 (*C*H_2Ph), 69.8 (C$^{5'}$), 68.4 (C$^{6'}$), 68.1 (C^4), 67.1 (C^5), 67.3 (C^5), 60.4 (OCH_3), 60.0 (C$^{2'}$), 47.4 (OCH_3, CDA), 47.3 (OCH_3, CDA), 28.4 (CH_3), 27.4 (CH_2), 27.1 (CH_2), 26.6 (CH_3), 21.8 (2 CH_2). MALDI-TOF calcd. for $C_{45}H_{57}N_3O_{12}$ + Na^+: 855.0 found 854.0 calcd. for $C_{45}H_{57}N_3O_{12}$ + K^+: 871.1 found 870.1. FAB HRMS calcd. for $C_{45}H_{57}N_3O_{12}$ + Na^+: 854.3840 found 854.3854.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-D-galactopyranosyl-β-(1→6)-1,2-diisopropylidene-3,4-(1′,2′-dimethoxycyclohexane-1′,2′-diyl)-3-*O*-methyl-D-*chiro*-inositol (9b): A 10-mL round-bottomed flash was charged with donor (81 mg, 0.14 mmol, 1.6 equiv.), acceptor **3b** (32 mg, 0.08 mmol, 1.0 equiv.), freshly activated 4 Å molecular sieves, and CH_2Cl_2 (2 mL), and the mixture was stirred for 1 h under argon. TfOTMS was then added (3.1 μL, 0.02 mmol, 0.2 equiv.) at 0 °C and the reaction mixture was stirred for 5 h. The suspension was filtered through a short pad of Celite and the solvent was removed to provide the crude material. Flash chromatography (Hex/EtOAc, 2:1) afforded **9b** (42 mg, 0.05 mmol, 63%). R_f (Hex/EtOAc, 1:3) = 0.52. $[\alpha]_D^{20}$ = −28 (*c* = 1.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.59 (d, 1 H, $J_{NH\text{-}H2'}$ = 9.0 Hz, NH), 5.35 (d, *J* = 2.8 Hz, 1 H, $H_{4'}$), 5.28 (d, *J* = 8.0 Hz, 1 H, $H_{1'}$), 5.16 (dd, 1 H, $J_{H3'\text{-}H2'}$ = 11.0 Hz, $J_{H3'\text{-}H4'}$ = 2.8 Hz, $H_{3'}$), 4.46 (s, 1 H, H_6), 4.26 (m, 1 H, H_1), 4.20−4.10 (m, 3 H, $H_{2'}$, $H_{6a'}$, $H_{6b'}$), 4.07 (t, *J* = 6.0 Hz, 1 H, H_2), 4.02 (t, *J* = 10.0 Hz, 1 H, H^4), 3.95 (m, 1 H, H^5), 3.85 (m, 1 H, H$^{5'}$), 3.53 (s, 3 H, OCH_3), 3.33 (t, *J* = 10.0 Hz, 1 H, H^3), 3.22 (s, 3 H, OCH_3, CDA), 3.20 (s, 3 H, OCH_3, CDA), 2.16 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 1.98 (s, 3 H, CH_3CO), 1.72−1.60 (m, 4 H, 2 CH_2), 1.52−1.48 (m, 2 H, CH_2), 1.51 (s, 1 H, CH_3), 1.36−1.31 (m, 2 H, CH_2), 1.34 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.7 (CH_3CO), 170.3 (CH_3CO), 170.2 (CH_3CO), 162.2 (CCl_3CO), 109.6 (CCl_3CO), 99.4 (C$^{1'}$), 97.9 (C, CDA), 97.8 (C, CDA), 92.2 (C), 83.5 (C^3), 79.6 (C^2), 76.0 (C^1), 72.2 (C^6), 71.2 (C$^{5'}$), 70.1 (C$^{3'}$), 68.2 (C^5), 67.7(C^4), 66.8 (C$^{4'}$), 61.4 (C$^{6'}$), 59.8 (OCH_3), 53.1 (C$^{2'}$), 47.3 (OCH_3, CDA), 46.9 (OCH_3, CDA), 28.5 (2 CH_2), 27.2 (CH_3), 27.0 (CH_3), 26.2 (2 CH_2), 21.4 (CH_3CO), 20.7 (CH_3CO), 20.6 (CH_3CO).

2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranosyl-α(1→6)-3-*O*-methyl-D-*chiro*-inositol (10a): Compound **10a** (7 mg, 0.01 mmol, 41%) was obtained by the same experimental procedure as used for compound **8a**, starting from **9a** (23 mg, 0.03 mmol, 1equiv.). Purification was by flash chromatography (CH_2Cl_2/MeOH, 10:1). R_f (CH_2Cl_2/MeOH, 9:1) = 0.48. $[\alpha]_D^{20}$ = +38 (*c* = 0.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.36−7.21 (m, 15 H, Ph), 4.96 (d, 1 H, $J_{H1\text{-}H2}$ = 3.5 Hz, H$^{1'}$), 4.85 (AB, 1 H, J_{AB} = 11.5 Hz, CH-Ph), 4.71 (AB, 1 H, J_{AB} = 11.0 Hz, CH-Ph), 4.67 (AB, 1 H, J_{AB} = 11.0 Hz, CHPh), 4.49 (AB, 1 H, J_{AB} = 11.0 Hz, CH-Ph), 4.49 (AB, 1 H, J_{AB} = 11.5 Hz, CH-Ph), 4.40 (AB, 1 H, J_{AB} = 11.0 Hz, CH-Ph), 4.20 (dd, 1 H, $J_{H4'\text{-}H5'}$ = 7.5 Hz, $J_{H5'\text{-}H6'}$ = 4.5 Hz, H$^{5'}$), 4.15 (t, *J* = 4.0 Hz, 1 H, H^1), 4.01 (t, *J* = 4.0 Hz, 1 H, H^6), 3.95−3.90 (m, 2 H, H$^{2'}$, H$^{4'}$), 3.87 (m, 1 H, H^2), 3.84 (dd, $J_{H2'\text{-}H3'}$ = 10.5 Hz, $J_{H3'\text{-}H4'}$ = 2.5 Hz, H$^{3'}$), 3.82−3.77 (m, 1 H, H^5), 3.65 (t, *J* = 8.2 Hz, 1 H, H^4), 3.62 (s, 3 H, OCH_3), 3.58 (dd, 1 H, $J_{H6a'\text{-}H6b'}$ = 9.5 Hz, $J_{H5'\text{-}H6a'}$ = 7.5 Hz, H$^{6a'}$), 3.38 (dd, 1 H, $J_{H6a'H6b'}$ = 9.5 Hz, $J_{H5'\text{-}H6b'}$ = 4.5 Hz, H$^{6b'}$), 3.35 (t, *J* = 8.2 Hz, 1 H, H^3), ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 137.8, 137.6, (3 C, 3OBn), 129.0, 128.9, 128.8, 128.6 (8CH, OBn), 128.5 (2 CH, CH OBn), 128.4 (CH, OBn), 128.3 (CH, OBn), 128.1 (2 CH, OBn), 100.0 (C$^{1'}$), 82.7 (C^3), 81.1 (C^6), 77.6 (C$^{3'}$), 75.0 (*C*H_2Ph), 74.1 (*C*H_2Ph), 73.7 (C^4), 73.5 (C$^{4'}$), 72.8 (*C*H_2Ph), 71.6 (C^5), 71.5 (C^2), 71.2 (C$^{5'}$), 70.0 (C$^{6'}$), 69.9 (C^1), 60.9 (OCH_3), 60.2 (C$^{2'}$). FAB HRMS calcd. for $C_{34}H_{41}N_3O_{10}$ + Na^+: 674.2690, found 674.2684.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-D-galactopyranosyl-β-(1→6)-3-*O*-methyl-D-*chiro*-inositol (10b): Pseudodisaccharide **9b** (36 mg, 0.05 mmol, 1.0 equiv.) was dissolved in a mixture of trifluoroacetic acid/water (15:1, 3.2 mL) and stirred for 3 h at room temperature. The solvent was removed under vacuum and the crude product was purified by flash chromatography to provide **10b** (22 mg, 0.03 mmol, 75%) as a white solid. R_f (Cl_2CH_2/MeOH, 7:1) = 0.15. $[\alpha]_D^{20}$ = −2 (*c* = 0.72, MeOH). ^{1}H NMR (MeOD, 500 MHz): δ = 5.36 (d, 1 H, $J_{H4'\text{-}H5'}$ = 3.5 Hz, H$^{4'}$), 5.24 (dd, 1 H, $J_{H3'\text{-}H2'}$ = 11.1 Hz, $J_{H3'\text{-}H4'}$ = 3.5 Hz H$^{4'}$), 5.01 (d, *J* = 8.5 Hz, 1 H, H$^{1'}$), 4.16 (m, 2 H, H$^{6a'}$, H$^{6b'}$), 4.08 (dd, 1 H, $J_{H2'\text{-}H3'}$ = 11.2 Hz, $J_{H2'\text{-}H1'}$ = 8.5 Hz, H$^{2'}$), 4.05−4.02 (m, 2 H, H$^{5'}$, H^6), 3.98 (t, *J* = 3.0 Hz, 1 H, H^1), 3.79 (dd, $J_{H5\text{-}H4}$ = 9.5 Hz, $J_{H5\text{-}H6}$ = 3.0 Hz, 1 H, H^5), 3.70 (dd, $J_{H2\text{-}H3}$ = 9.7 Hz, $J_{H2\text{-}H1}$ = 3.0 Hz, 1 H, H^2), 3.58 (m, 1 H, H^4), 3.56 (s, 3 H, OCH_3), 3.22 (t, *J* = 9.7 Hz, 1 H, H^3), 2.16 (s, 3 H, *C*H_3CO), 2.05 (s, 3 H, CH_3CO), 1.93 (s, 3 H, CH_3CO). ^{13}C NMR (MeOD, 125 MHz): δ = 170.8 (CH_3CO), 170.6 (CH_3CO), 170.1 (CH_3CO), 163.2 (Cl_3CCO), 101.3 (C$^{1'}$), 92.5 (Cl_3CCO), 83.3 (C^3), 79.1 (C^6), 72.4 (C^4), 71.4 (C^1), 71.0 (C^5), 70.6 (C$^{5'}$), 70.4 (C^2), 70.3 (C$^{3'}$), 66.9 (C$^{4'}$), 61.3 (C$^{6'}$), 58.9 (OCH_3), 52.5 (C$^{2'}$), 19.2, 19.1, 19.0 (3 *C*H_3CO). FAB HRMS calcd. for $C_{21}H_{30}NO_{14}Cl_3$ + Na: 650.0600; found 650.0611.

2-Amino-2-deoxy-D-glucopyranosyl-α(1→6)-3-*O*-methyl-D-*chiro*-inositol (Ia): Compound **8a** (4 mg, 0.06 mmol, 1.0 equiv.) and 10% Pd/C (10 mg, 0.09 mmol) were stirred in methanol under hydrogen for 24 h at room temperature. The slurry was filtered and washed with water, and the filtrate was concentrated and lyophilized to give the fully deprotected pseudodisaccharide **Ia** (2.6 mg, 0.07 mmol, quantitative). R_f (EtOAc/MeOH/H_2O/AcOH, 2:2:1:1) = 0.44. $[\alpha]_D^{20}$ = +55 (*c* = 0.12, H_2O). ^{1}H NMR (D_2O, 500 MHz): δ = 5.07 (d, *J* = 3.5 Hz, 1 H, H$^{1'}$), 4.12 (br. t, 1 H, *J* = 3.5 Hz, H^1), 4.02 (br. t, 1 H, *J* = 3.5 Hz, H^6), 3.99 (ddd, 1 H, $J_{H5'\text{-}H4'}$ = 9.6 Hz, $J_{H5'\text{-}H6'}$ = 4.0 Hz, $J_{H5\text{-}H6a}$ = 2.5 Hz, H$^{5'}$), 3.84 (dd, $J_{H5\text{-}H4}$ = 9.8 Hz, $J_{H5\text{-}H6}$ = 3.3 Hz, 1 H, H^5), 3.79−3.76 (m, 2 H, H$^{6a'}$, H$^{6b'}$), 3.75 (dd, $J_{H2\text{-}H3}$ = 10.1 Hz, $J_{H2\text{-}H1}$ = 3.2 Hz, 1 H, H^2), 3.70 (t, *J* = 9.6 Hz, 1 H, H$^{3'}$), 3.64 (t, *J* = 9.5 Hz, 1 H, H^4), 3.58 (s, 3 H, OCH_3), 3.43 (t, *J* = 9.6 Hz, 1 H, H$^{4'}$), 3.30 (t, *J* = 10.1 Hz, 1 H, H^3), 2.97 (dd, 1 H, $J_{H2'\text{-}H3'}$ = 9.4 Hz, $J_{H2'\text{-}H1'}$ = 3.5 Hz, H$^{2'}$). ^{13}C NMR (D_2O, 125 MHz): δ = 95.2 (C$^{1'}$), 82.7 (C^3), 75.7 (C^6), 71.8, 71.74, 71.71 (C^4, C$^{5'}$, C$^{3'}$), 69.9 (C^2), 69.04 (C$^{4'}$), 68.98 (C^5), 67.7 (C^1), 59.9 (OCH_3), 59.8 (C$^{6'}$), 53.9 (C$^{2'}$).

2-Amino-2-deoxy-D-glucopyranosyl-β(1→6)-3-*O*-methyl-D-*chiro*-inositol (Ib): Compound **Ib** (24 mg, 0.07 mmol, 98%) was obtained by the same experimental procedure as used for compound **Ia**, starting from **8b** (46 mg, 0.07 mmol, 1 equiv.). R_f (EtOAc/MeOH/H_2O/AcOH, 2:2:1:1) = 0.42. ^{1}H NMR (D_2O, 500 MHz): δ = 4.52 (d, J = 8.5 Hz, 1 H, H$^{1'}$), 4.22 (br. t, 1 H, J = 3.5 Hz, H^1), 4.00 (br. t, 1 H, J = 3.5 Hz, H^6), 3.88 (dd, 1 H, $J_{H6a'\text{-}H6b'}$ = 12.5 Hz, $J_{H6a'\text{-}H5'}$ = 1.8 Hz, H$^{6a'}$), 3.82 (dd, $J_{H5\text{-}H4}$ = 9.8 Hz, $J_{H5\text{-}H6}$ = 3.5 Hz, 1 H, H^5), 3.80 (dd, $J_{H2\text{-}H3}$ = 9.8 Hz, $J_{H2\text{-}H1}$ = 3.5 Hz, 1 H, H^2), 3.70 (dd, 1 H, $J_{H6b'\text{-}H6a'}$ = 12.5 Hz, $J_{H6b'\text{-}H5'}$ = 5.5 Hz, H$^{6b'}$), 3.66 (t, J = 9.8 Hz, 1 H, H^4), 3.56 (s, 3 H, OCH_3), 3.42 (ddd, 1 H, $J_{H5'\text{-}H4'}$ = 9.5 Hz, $J_{H5'\text{-}H6a'}$ = 5.5 Hz, $J_{H5'\text{-}H6b'}$ = 1.8 Hz, H$^{5'}$), 3.37 (t, J = 9.2 Hz, 1 H, H$^{3'}$), 3.33 (t, J = 9.2 Hz, 1 H, H$^{4'}$), 3.30 (t, J = 9.8 Hz, 1 H, H^3), 2.66 (t, J = 8.5 Hz, 1 H, H$^{2'}$). ^{13}C NMR (D_2O, 300 MHz): δ = 85.7 (C$^{1'}$), 84.3, 79.0, 75.1, 73.5, 73.0, 72.8, 72.5, 63.4, 62.8, 59.5 (C$^{2'}$). FAB HRMS calcd. for $C_{13}H_{25}NO_{10}$ [M^+ − H] + Na^+: 378.1376, found 378.1388.

2-Amino-2-deoxy-D-galactopyranosyl-α(1→6)-3-*O*-methyl-D-*chiro*-inositol (IIa): Compound **IIa** (5.3 mg, 0.02 mmol, quantitative) was obtained by the same experimental procedure as used for compound **Ia**, starting from **9a** (7 mg., 0.01 mmol, 1 equiv.). R_f (Cl_2CH_2/MeOH, 9:1) = 0.07. $[\alpha]_D^{20}$ = +70 (c = 0.30, H_2O). ^{1}H NMR (D_2O, 500 MHz): δ = 5.31 (d, J = 3.8 Hz, 1 H, H$^{1'}$), 4.26 (m, 1 H, H^2), 4.16 (br. t, 1 H, J = 3.6 Hz, H^1), 4.14−4.09 (m, 2 H, H^{6,} H$^{3'}$), 4.02 (d, 1 H, J = 3.1 Hz, H$^{4'}$), 3.89 (dd, $J_{H5\text{-}H4}$ = 10.2 Hz, $J_{H5\text{-}H6}$ = 3.5 Hz, 1 H, H^5), 3.75−3.72 (m, 3 H, H$^{6a'}$, H$^{6b'}$, H$^{5'}$), 3.68 (t, J = 9.7 Hz, 1 H, H^4), 3.61 (s, 3 H, OCH_3), 3.54 (dd, 1 H, $J_{H2'\text{-}H3'}$ = 10.9 Hz, $J_{H2'\text{-}H1'}$ = 3.8 Hz, H$^{2'}$), 3.33 (t, J = 9.7 Hz, 1 H, H^3), ^{13}C NMR (D_2O, 125 MHz): δ = 94.0 (C$^{1'}$), 83.6 (C^3), 76.0 (C^6), 72.9 (C^4), 71.4 (C$^{5'}$), 71.0 (C^2), 69.2 (C^5), 68.4 (C^1), 68.2 (C$^{4'}$), 67.2 (C$^{3'}$), 61.0 (C$^{6'}$), 60.7 (OCH_3), 51.3 (C$^{2'}$). CI HRMS calcd. for $C_{13}H_{25}NO_{10}$ [M^+ + H]: 356.1557, found 356.1549.

2-Amino-2-deoxy-D-galactopyranosyl-β(1→6)-3-*O*-methyl-D-*chiro*-inositol (IIb): Compound **8b** (6 mg, 10 μmol) and $Ba(OH)_2$ (8 mg, 0.094 mmol, 4.8 equiv.) were stirred in water/EtOH (1:1, 4 mL) for 1 h at 90 °C, whereupon the solvent was removed under vacuum. Cold water was added to the residue, which was filtered through a paper filter to eliminate $Ba(OH)_2$. The filtrate was concentrated under vacuum and the residue was redissolved in the minimum amount of MeOH and loaded onto a Varian CBA (carboxylic acid) cartridge (3 mL/500 mg) preequilibrated with MeOH. After elution with a few column-lengths of MeOH to remove barium salts, pseudodisaccharide was neutralized by loading it directly onto a Varian PSA (ethylenediamine-*N*-propyl) cartridge preequilibrated with MeOH to give **IIb** (3 mg, 8 μmol, 79%). R_f (EtOAc/MeOH/H_2O/AcOH, 2:2:1:1) = 0.29. $[\alpha]_D^{20}$ = +8 (c = 0.28, H_2O). ^{1}H NMR (D_2O, 500 MHz): δ = 4.32 (d, J = 9.0 Hz, 1 H, H$^{1'}$), 4.15 (br. t, 1 H, J = 3.5 Hz, H^6), 3.90 (br. t, 1 H, J = 3.5 Hz, H^1), 3.75−3.71 (m, 3 H, H^5, H^2, H$^{4'}$), 3.68−3.53 (m, 4 H, H$^{6a'}$, H$^{6b'}$, H$^{5'}$, H^4), 3.47 (s, 3 H, OCH_3), 3.42 (dd, 1 H, $J_{H3'\text{-}H2'}$ = 10.0 Hz, $J_{H3'\text{-}H4'}$ = 3.5 Hz, $H_{3'}$), 3.21 (t, J = 9.5 Hz, 1 H, H^3), 2.74 (t, 1 H, J = 9.0 Hz H$^{2'}$). ^{13}C NMR (D_2O, 125 MHz): δ = 105.2 (C$^{1'}$), 82.4 (C^3), 80.7 (C^1), 74.9 (C^4), 72.5 (C$^{3'}$), 71.8 (C$^{5'}$), 70.3 (C^6), 69.9 (C^2), 69.4 (C^5), 67.4 (C$^{4'}$), 60.7 (OCH_3), 59.3 (C$^{6'}$), 52.9 (C$^{2'}$); CI HRMS calcd. for $C_{13}H_{25}NO_{10}$ [M^+ + H]: 356.1556, found 356.1548.

Structure

Nuclear Magnetic Resonance: NMR experiments were recorded with an AVANCE DRX 500 Bruker spectrometer, using ca. 3−5 mM solutions of the different compounds in D_2O. The experiments were carried out at 298 K, by using standard temperature control. DQF-COSY, TOCSY, HSQC, and HMQC experiments used for the full assignment were recorded by using the standard z-pulsed field gradient, enhanced or selected pulse sequences versions when possible. All experiments except DQF-COSY were recorded with 256−400 indirect dimension time increments and 2048 complex points in the direct dimension. Quadrature detection in $F1$ was achieved by using TPPI (Time Phase Proportional Increment). The DQF-COSY experiments were recorded with 512 $F1$ increments and not fewer than 4096 complex points in the direct dimension. Raw data were multiplied by a shifted squared sine bell function and Fourier transformed to 1024 point in $F1$ and zero filled in $F2$. ^{1}H-^{1}H coupling constants were extracted from the DQF-COSY by deconvolution of the 2D antiphase peaks with the DECO program.[31] NOESY experiments were recorded with mixing times from 150 to 600 ms. Selective inversion 1D experiments were performed by using the double pulse field gradient spin echo technique (dpfgse) proposed by Shaka and co-workers.[32] 1D-NOESY experiments were recorded with mixing times from 150 and 600 ms.[23] Experimental distance calculation from NOE data was performed by assuming the isolated spin pair approximation at short mixing times.

Molecular Modeling: Glycosidic torsion angles are defined as Φ (H1′−C1′−O1′−C6) and Ψ (C1′−O1′−C6-H6), hydroxymethyl torsion angle ω as H5−C5′−C6−O6**.** The AMBER*[26] force field was used for the molecular modeling, as modified by Homans[27] and also as modified by Senderowitz et al.,[28] and as integrated in MACROMODEL 6.0.[27] Solvent effects were including by using the GB/SA continuum model for water[33] or ε = 80. Molecular dynamics simulations were run for 1.0−5.0 ns with an integration step of 1.5 fs, at a constant temperature of 300 K and by using SHAKE for hydrogen atoms and saving structures each picosecond. When used, thermal bath coupling was 0.1 or 0.5 ps and the frictional forces coefficient in stochastic dynamics simulation was 2.5.

Acknowledgments

This work was supported by the Dirección General de Enseñanza superior e Investigación (Grant PB96 0820) and Rademacher Group Limited. We thank CSIC for fellowships to J. B. B. and J. L. M.-P.

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Received July 24, 2001
[O01363]