A Straightforward Synthesis of 1-Adamantylmethyl Glycosides, and Their Binding to Cyclodextrins

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A single-step synthesis of 1-adamantylmethyl α- and β-glycosides starting from commercially available peracetylated monosaccharides is reported. The α- and β-glucopyranosides **1a** and **1b** bind to β-cyclodextrin with association constants in the order of 10^5 M^{-1}, as determined by ^1H NMR spectroscopy. The carbohydrate moiety contributes to the binding depending on the pyranose stereochemistry.

Introduction

As is the case with other biological molecules, the molecular recognition of carbohydrates is characterized by the confluence of many weak intermolecular forces, water probably playing the most important role. An important question to be answered is how polar and nonpolar groups manage to strip the water molecules from between the reactive partners to make the process energetically favourable. To answer this question both structural and energetic information is required.

Cyclodextrins (CDs)[1,2] and cyclophanes[3,4] have been shown to be useful models in the understanding of the noncovalent bonding interactions in water. We have used CDs and glycophanes[5−7] as model systems to evaluate and understand the interactions of carbohydrates in water. With a model system consisting of α-cyclodextrin (α-CD) and a series of *p*-nitrophenyl glycosides (PNPGlys) we determined by calorimetry the thermodynamic parameters of complex formation in water in an attempt to evaluate the contribution to the energetics of binding of the desolvation of the carbohydrate moieties exposed to the bulk water.[5] Although the results indicated an influence of the sugar stereochemistry on the thermodynamic parameters, the binding constants between the PNPGlys and the α-CD were too small (100−300 M^{-1}) to allow us to draw clear conclusions. Even smaller association constants were obtained in the binding of PNPGlys to β-CD. We reasoned that greater differences in the values of the enthalpic and entropic terms could be expected by increasing the binding constants. In principle, this can be achieved by increasing the favourable interactions between the aglycon and the CD cavity. To succeed in such a study, a better fitting in shape and size between the aglycon of the guest and the cyclodextrin cavity should be achieved. The globular shape of adamantane, with a diameter of about 7 Å, matches almost perfectly the size of the CD cavity.[8]

Adamantane derivatives bind to β-CD with high association constants, ranging from 10^3 M^{-1} for bromoadamantane[9] to 10^5 M^{-1} for 1-adamantanecarboxylic acid.[8] The crystal structure of the complex formed between adamantanol and methylated β-CD confirmed the inclusion of the adamantane moiety inside the cavity.[10] Thus, 1-(hydroxymethyl)adamantane was chosen as aglycon for the preparation of a series of glycosides that are expected to bind to CD with higher association constants than the PNPGlys.

We report here a straightforward preparation of the α- and β-anomers of a series of 1-adamantylmethyl glycosides (AdaGlys) and present preliminary results obtained by means of NMR spectroscopy of the interaction of the α- and β-glucopyranosides with β-CD in water. Our results confirm the formation of inclusion complexes that are presently under investigation by isothermal titration calorimetry.

Results and Discussion

Synthesis

The synthesis of adamantylmethyl glycosides has not been reported previously. However, the preparation of glycosides with a similar hydrophobic aglycon — adamantylcarbonyl — has already been reported.[11] Because we required significant amounts of α- and β-anomers, we decided to use glycosylation conditions that can afford both anomers in the same reaction step. A simple procedure for the stereoselective α-glycosidation of peracetylated sugars carrying a participating group at C-2 with aliphatic alcohols

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in the presence of $FeCl_3$ as Lewis acid has been reported recently. The α-anomer was obtained by in situ anomerization of the initially formed β-anomer.[12] Control over the anomerization step, however, should lead to α/β mixtures depending on the anomerization conditions.[13] Classical glycosidation methods demand both selective activation of the anomeric centre and differently protected monosaccharides for obtaining each anomer. In contrast, the $FeCl_3$ method, starting from the same readily available penta-*O*-acetylated monosaccharides and without the need for anomeric activation, has allowed us to prepare the α- and β-anomers in a single step.

According to this method we have prepared the α- and β-(1-adamantylmethyl) glycosides (AdaGlys) of D-glucose (**1a** and **1b**), D-galactose (**2a** and **2b**), L-fucose (**3a** and **3b**), and the α-anomer of D-mannose (**4a**) (Figure 1). The general procedure for the preparation of the 1-adamantylmethyl glycosides is shown in Scheme 1.

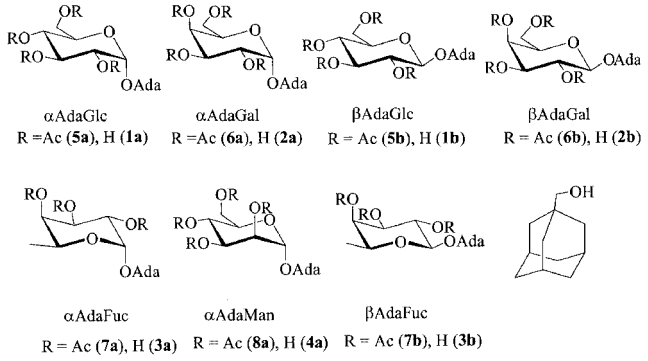


Figure 1. Molecular structure of 1-adamantylmethyl glycosides and the aglycon 1-(hydroxymethyl)adamantane

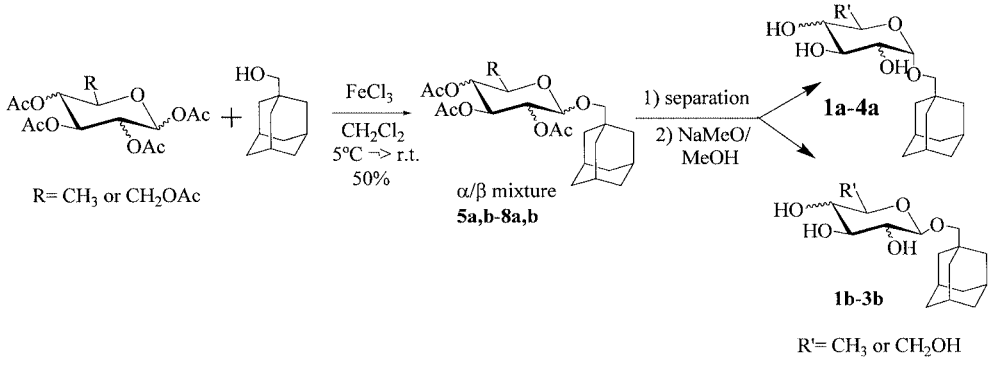
Treatment of the corresponding peracetylated monosaccharide with 1 equiv. of 1-(hydroxymethyl)adamantane in the presence of 1 equiv. of $FeCl_3$ in CH_2Cl_2 below 5 °C resulted in an α/β mixture of the expected glycosides (Scheme 1). The pure α- and β-acetylated glycosides **5a**−**8a** and **5b**−**7b** were obtained after chromatographic separation on silica gel in reasonable yields (for yields and α/β ratios see Table 1). Zemplén deprotection of the acetylated glycosides gave the 1-adamantylmethyl α-D-gluco- (αAdaGlc, **1a**), α-D-galacto- (αAdaGal, **2a**), α-L-fuco- (αAdaFuc, **3a**), and α-D-manno- (αAdaMan, **4a**) pyranosides, and their corresponding β-anomers **1b**−**3b** in quantitative yields.

The β-mannoside (βAdaMan, **4b**) was obtained using the trichloroacetimidate method also starting from the per-*O*-acetylated mannose derivative (Scheme 2). Formation of the thiophenyl glycoside **9** followed by deacetylation and subsequent benzylation gave compound **10** in 60% overall yield (three steps). Selective deprotection of the anomeric centre and treatment with trichloroacetonitrile in the presence of DBU yielded the glycosyl donor **12** in 70% yield (two steps). Reaction of **12** with 1-(hydroxymethyl)adamantane in the presence of trimethylsilyl triflate gave a 1:2 α/β mixture of the benzylated glycosides **13** in 60% yield. The separation of both anomers was impossible at this stage. However, deprotection of the benzyl groups in **13** followed by acetylation allowed the separation of the acetylated isomers **14a** (α, identical to **8a**) and **14b** (β). Zemplén deprotection of **14a** and **14b** yielded **4a** and **4b**, respectively, in quantitative yield. The structure of the compounds was confirmed by ^1H and ^{13}C NMR spectroscopy, elemental analysis and MALDI-TOF mass spectrometry.

Binding Studies

The inclusion of small molecules into the cavity of CDs has served as an excellent model system for understanding noncovalent interactions in aqueous solution. NMR spectroscopy, in combination with calorimetric measurements, has provided insight into the geometry and the energetics of complex formation.[2,14,15] The thermodynamic properties of complexation of CDs with neutral guests in water (favourable $\Delta H°$ offset by unfavourable $T\Delta S°$)[2,5] make these studies good models for understanding the thermodynamics of carbohydrate−lectin associations.[16]

Our goal in synthesising the adamantylmethyl glycosides was to carry out a calorimetric study to determine the enthalpy, entropy, and heat-capacity changes in their interaction with CDs. A preliminary study, however, was necessary to confirm the inclusion of the AdaGlys into CDs. Monitoring of the induced chemical shifts of the H_β and H_γ protons of the AdaGlys by ^1H NMR titration was a simple and rapid way to gain insight into these associations. A similar induced-shift pattern was observed for all glycosides upon

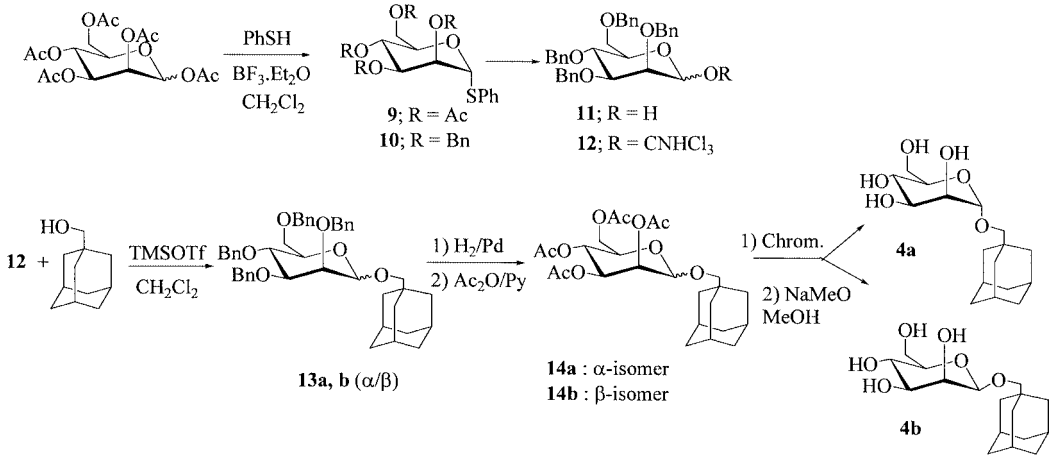


Scheme 1

Table 1. Selected data of the 1-adamantylmethyl glycosides

AdaGly	Acetylated sugar	Yield [%]	α/β ratio[a]	$[\alpha]_D$	^{1}H NMR δ [ppm]
1a/1b	D-Glucose (Glc)	30	8:1	5.98 (α)	4.71 (d, J = 3.6 Hz, 1 H H-1α)
				1.72 (β)	4.20 (d, J = 8.5 Hz, 1 H H-1β)
2a/2b	D-Galactose (Gal)	50	1:2	108.25 (α)	4.75 (br. s, 1 H, H-1α)
				2.32 (β)	4.16 (d, J = 7.5 Hz, 1 H, H-1β)
3a/3b	L-Fucose (Fuc)	65	6:1	−102.78 (α)	4.67 (d, J = 2.7 Hz, 1 H, H-1α)
				13.23 (β)	4.23 (d, J = 8 Hz, 1 H, H-1β)
4a/4b[b]	D-Mannose (Man)	65	1:0	51.15 (α)	4.63 (d, J = 1 Hz, 1 H, H-1α)
				−3.71 (β)[b]	4.43 (d, J = 0.9 Hz, 1 H, H-1β)

[a] The anomeric ratio were determined after separation of the acetylated glycosides. [b] The β-anomer was obtained by the trichloroacetimidate method.



Scheme 2

complexation with β- and γ-CDs, suggesting a similar binding geometry for all complexes.

The stability constants (K_a) of the interaction between β-CD and the α- and β-adamantylmethyl glucopyranosides **1a** and **1b** in D_2O were determined by ^{1}H NMR titration at three different temperatures. The K_a of the free aglycon, the 1-(hydroxymethyl)adamantane, was also determined to evaluate the contribution of the pyranose moiety to the binding. In our binding experiments, the guest concentration (AdaGlys) was held constant while increasing the concentration of the host (β-CD). Upon addition of the host, the signals of the H_β and H_γ protons of the adamantane moiety shifted downfield (Figure 2).

The chemical shifts induced by β-CD on the adamantane moiety were large enough (ca. 0.2 ppm) to be used for NMR titration. Attempts to monitor the chemical-shift changes of the H-3 and H-5 protons of the β-CD failed due to signal overlapping with the proton signals of the glucose moiety of the guest. The stability-constant values (K_a), the corresponding free energies of binding ($-\Delta G$) at 298, 303, and 313 K, and the observed and calculated chemical-induced shifts for the H_β and H_γ protons of the adamantane moiety are given in Table 2. To calculate the K_a values, the downfield chemical-shift changes of the H_β and H_γ protons of the adamantane moiety versus the β-CD concentration

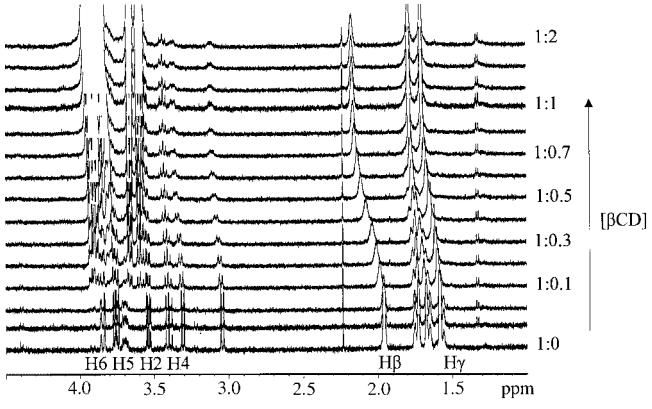


Figure 2. ^{1}H NMR titration of 1-adamantylmethyl α-D-glucopyranoside (**1a**) with increasing amounts of β-CD in D_2O at 298 K

were used. Association constants and calculated induced shifts (CIS values at 100% binding) were obtained using two different non-linear fitting programs.[17] All titration curves were carried out at least twice.

The results obtained indicate that α- and β-adamantylmethyl glucosides associate to β-CD with large association constants (10^5 M^{-1}). These values are three orders of magnitude higher than those obtained for the binding of

Table 2. Association constant (K_a [M^{-1}]), free energies ($-\Delta G°$ [kcal/mol]) and observed and calculated induced shifts [ppm] of α- and β-glycosides **1a** and **1b** with β-CD at 298, 303 and 313 K in D_2O

Glycosides	T [K]	K_a	$-\Delta G°$	H_β calcd.	obsd.	H_γ calcd.	obsd.
αAdaGlc (**1a**)	298	$(1.383 \pm 0.909) \times 10^5$	6.98 ± 0.9	0.220	0.246	0.127	0.125
	303	$(1.375 \pm 0.231) \times 10^5$	7.09 ± 0.2	0.212	0.207	0.120	0.118
	313	$(1.026 \pm 0.211) \times 10^5$	7.15 ± 0.2	0.198	0.191	0.110	0.106
βAdaGlc (**1b**)	298	$(4.376 \pm 0.361) \times 10^5$	7.66 ± 0.1	0.241	0.208	0.167	0.143
	303	$(4.514 \pm 0.343) \times 10^5$	7.81 ± 0.1	0.225	0.205	0.157	0.139
	313	$(5.190 \pm 0.587) \times 10^5$	8.15 ± 0.1	0.198	0.195	0.152	0.135
$AdaCH_2OH$	298	$(2.800 \pm 0.386) \times 10^5$	7.40 ± 0.2	0.175	0.174	–	–

PNPGlys to α-CD (10^2 M^{-1})[5] and one order of magnitude higher than those reported in the literature for the binding of adamantane-1-carboxylate to β-CD.[8,18] The K_a value for the aglycon $AdaCH_2OH$ is similar to those of the glycosides, indicating that the sugar moiety does not destabilise the binding. The differences in the free energy of binding ($\Delta\Delta G = 0.6-1.0$ kcal·mol^{-1}) between the α- and the β-glucosides clearly indicate that the presence of the pyranose moiety influences the binding depending on the sugar stereochemistry.[5] In addition, the free energy of binding of the β-glycosides slightly increases with increased temperature, while in the α-glycosides no changes are observed. Attempts to evaluate the binding of **1a** and **1b** to αC-CD failed, probably due to the non-inclusion of the aglycon into the α-CD cavity.

Ongoing isothermal titration calorimetry (ITC) measurements also support the influence of the sugar stereochemistry in the enthalpy and entropy of binding to cyclodextrins.[19] Accurate thermodynamic data for the enthalpy and entropy of binding of the different AdaGlys to α-, β-, and γ-cyclodextrins could give a picture of the influence of the sugar stereochemistry in the water rearrangement process when the carbohydrate moiety is exposed to the bulk water.[16,20,21]

Experimental Section

General Remarks: Chemicals, including 1-(hydroxymethyl)adamantane, galactose, glucose, fucose, mannose, iron trichloride, and β-cyclodextrin, were obtained from commercial sources (Sigma, Aldrich or Fluka). Dichloromethane was distilled from calcium hydride, methanol was distilled from sodium and diethyl ether from sodium/benzophenone. TLC was performed on silica gel $60F_{254}$ (Merck) with detection by charring with 10% $EtOH/H_2SO_4$, phosphomolybdic acid/EtOH or $Ce(SO_4)_2$ in phosphomolybdic acid/H_2SO_4/H_2O. For flash chromatography, silica gel (Merck 15−200 mesh) was used. Chromatography eluents are given as volume/volume ratios (v/v). NMR spectra were recorded at 25 °C with Bruker Avance DPX300 (^1H, 300 MHz) and Bruker Avance DRX500 (^1H, 500 MHz) spectrometers with the solvent as internal reference. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Signals were assigned by means of 2D spectra (COSY, HMQC). The deuterated solvents used were $CDCl_3$ (99.8% purity), CD_3OD (99.8%, purity), and D_2O (99.8% purity). Mass spectra were recorded with an HP-G2025 apparatus. Optical rotations were measured with an optical Perkin-Elmer 341 polarimeter. Elemental analyses were determined with a Leco CHNS-932 apparatus.

Binding Studies: Titration experiments were performed with the Bruker Avance DRX500 (1 H, 500 MHz) spectrometer at different temperatures (298, 303, and 313 K). Chemicals shifts in D_2O were referenced to internal D_2O ($\delta = 4.79$ ppm). Solutions of αAdaGly (**1a**) and βAdaGly (**1b**) were freshly prepared for every new experiment ([αAdaGlc] = 0.152 mM; [βAdaGlc] = 0.160 mM in D_2O solution). Solutions of β-cyclodextrin (0.9 or 2 mM) were prepared from the guest solution in order to have a constant concentration of the guest during the titration. Binding constants were determined by adding aliquots of a solution of host (0, 2, 3, 4, 5, 10, 20, 50 μL) to a solution of guest with a microsyringe. The ^1H NMR spectrum of each solution was recorded and the chemical shifts of the H_β and H_γ protons of the adamantylmethyl group, obtained at 16 different host/guest concentration ratios were used in an interactive least-squares fitting procedure, assuming formation of a 1:1 complex.[17] Each titration experiment was performed two or three times and the association constants given in Table 2 are the weighted averages of the protons H_β and H_γ. The maximum percent of estimated error was 20%.

General Procedure for $FeCl_3$-Promoted Glycosidation: $FeCl_3$ (1 equiv.) was added slowly to a solution of penta-*O*-acetylated monosaccharide (1 equiv.) in CH_2Cl_2 (60 mL) at 5 °C and the mixture was stirred for 5 min. An equimolar amount of 1-(hydroxymethyl)adamantane in CH_2Cl_2 was then added portionwise to the reaction mixture over 15 min and stirred at room temperature. Continuous TLC monitoring showed a significant degree of formation of the α- and β-anomers. After complete disappearance of the alcohol, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution and extracted with Et_2O. Silica gel chromatography of the resultant mixture gave the expected glycosides.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-α/β-glucopyranoside (5a,b): Starting from penta-*O*-acetyl-D-glucopyranose (1 g) an α/β (8:1) mixture was obtained (30%) as a syrup. R_f (ethyl acetate/hexane, 1:2) = 0.40 (α), 0.34 (β). The mixture was chromatographed on silica gel (ethyl acetate/hexane 1:4) to give the α-anomer **5a** (325 mg) and the β-anomer **5b** (49 mg) as white solids.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (5a): ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 5.42$ (t, $J = 10$ Hz, 1 H, H-3), 5.05−5.95 (m, 2 H, H-4, H-1), 4.79 (dd $J = 4$, $J = 10.5$ Hz, H-2), 4.21 (dd, $J = 4.5$, $J = 12$ Hz, 1 H, H-6a), 4.05 (dd, $J = 2.5$, $J = 12$ Hz, 1 H, H-6b), 3.95−3.91 (m, 1 H, H-5), 3.24 (d, $J = 9.5$ Hz, 1 H, CH_2OAda), 2.87 (d, $J = 9$ Hz, 1 H, CH_2OAda), 2.03,

2.00, 1.99, 1.96 (s, 12 H, 4 × CH_3CO), 1.94 (br. s, 3 H, CH_βAda), 1.73−1.46 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.7, 170.3, 169.8, 169.4, 169.2 (CH_3CO), 90.1 (C-1), 80.8, 72.7, 72.2, 71.8, 71.6, 71.0, 68.9, 68.3, 62.2, 62.1 (C-2, C-3, C-4, C-5, C-6), 39.4, 37.0, 33.8, 28.1, 20.7, 20.6 (CH_3CO) ppm. MALDI-TOF: m/z = 520.0 [M + Na + H]$^+$, 536.0 [M + K + H]$^+$. $C_{25}H_{36}O_{10}$ (496.56): calcd. C 60.41, H 7.25; found C 60.30, H 7.15.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (5b): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.17 (t, J = 10 Hz, 1 H, H-3), 5.05 (t, J = 10 Hz, 1 H, H-4), 4.98 (dd, J = 7.5, J = 10 Hz, 1 H, H-2), 4.39 (d, J = 7.5 Hz, 1 H, H-1), 4.24 (dd, J = 7.5, J = 4.5 Hz, 1 H, H-6a), 4.10 (dd, J = 10, J = 4.5 Hz, 1 H, H-6b), 3.67−3.61 (m, 1 H, H-5), 3.47 (d, J = 10 Hz, 1 H, CH_2OAda), 2.95 (d, J = 10 Hz, 1 H, CH_2OAda), 2.06, 2.02, 1.99, 1.98 (s, 12 H, 4 × CH_3CO), 1.72−1.44 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.6, 170.1, 169.6 (CH_3CO), 96.1 (C-1), 79.2, 71.1, 70.4, 68.7, 66.9, 61.9 (C-2, C-3, C-4, C-5, C-6), 39.4, 37.0, 33.8, 28.1, 20.7, 20.6 (CH_3CO) ppm. MALDI-TOF: m/z = 519.7 [M + Na]$^+$, 535.7 [M + K]$^+$. $C_{25}H_{36}O_{10}$ (496.56): calcd. C 60.41, H 7.25; found C 60.10, H 7.15.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-α/β-D-galactopyranoside (6a,b): Starting from penta-*O*-acetyl-D-galactopyranose (500 mg) a mixture of **6a** and **6b** was obtained (50%, α/β, 1:2) as a white solid. The mixture was chromatographed on silica gel (ethyl acetate/hexane, 1:4) to give the α-anomer **6a** (105 mg) and the β-anomer **6b** (200 mg) as white solids. R_f (ethyl acetate/hexane, 1:2) = 0.50 (α), 0.45 (β).

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranoside (6a): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.46 (dd, J = 3.3, J = 1.2 Hz, 1 H, H-4), 5.28 (dd, J = 10.5, J = 3 Hz, 1 H, H-3), 5.04 (dd, J = 10.5, J = 3 Hz, 1 H, H-2), 5.01 (d, J = 3 Hz, 1 H, H-1), 4.14−4.12 (m, 1 H, H-5), 4.07 (dd, J = 11.0, J = 6 Hz, 1 H, H-6a), 4.02 (dd, J = 11.0, J = 6.0 Hz, 1 H, H-6b), 3.23 (d, J = 9 Hz, 1 H, CH_2OAda), 2.86 (d, J = 9.5 Hz, 1 H, CH_2OAda), 2.09, 2.01, 2.00, 1.95 (s, 12 H, 4 × CH_3CO), 1.93 (br. s, 3 H, CHAda), 1.70−1.59 (m, 6 H, CH_2Ada), 1.48 (br. s, 6 H, CH_2Ada) ppm. MALDI-TOF: m/z = 520.4, [M + Na + H]$^+$, 536.4 [M + K + H]$^+$. $C_{25}H_{36}O_{10}$ (496.56): calcd. C 60.41, H 7.25; found. C 60.37, H 6.95.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (6b): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.37−5.35 (m, 1 H, H-4), 5.20 (dd, J = J = 8 Hz, 1 H, H-2), 4.99 (dd, J = 10.5, J = 3.5 Hz, 1 H, H-3), 4.36 (d, J = 8 Hz, 1 H, H1), 4.16 (dd, J = 11, J = 7 Hz, 1 H, H-6a), 4.10 (dd, J = 11, J = 7 Hz, 1 H, H-6b), 3.85 (m, 1 H, H-5), 3.49 (d, J = 9.5 Hz, 1 H CH_2OAda), 2.96 (d, 1 H, CH_2OAda), 2.13, 2.04, 2.03, 1.96 (s, 12 H, 4 × CH_3CO), 1.93 (br. s, 3 H, CHAda), 1.71−1.58 (m, 6 H, CH_2Ada), 1.48 (br. s, 6 H, CH_2Ada) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 97.9 (C-1), 78.0, 70.2, 69.2, 68.9, 68.3, 60.7 (C-2, C-3, C-4, C-5, C-6a, C-6b), 38.7, 36.2, 32.8, 27.5 ppm. MALDI-TOF: m/z = 520.2 [M + Na + H]$^+$, 536.3 [M + K + H]$^+$. $C_{25}H_{36}O_{10}$ (496.56): calcd. C 60.41, H 7.25; found C 59.89, H 7.23.

1-Adamantylmethyl 2,3,4-Tri-*O*-acetyl-α/β-L-fucopyranose (7a,b): Starting from tetra-*O*-acetyl-L-fucopyranose (632 mg) a mixture of **7a** and **7b** was obtained (65%, α/β 6:1). R_f (ethyl acetate/hexane, 1:2) = 0.66 (α), 0.50 (β). The mixture was chromatographed on silica gel (ethyl acetate/hexane, 1:4) to give the α-anomer **7a** (237 mg) and the β-anomer **7b** (35 mg) as white solids.

1-Adamantylmethyl 2,3,4-Tri-*O*-acetyl-α-L-fucopyranoside (7a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.33 (d, J = 3.3 Hz, 1 H, H-4), 5.31−5.29 (m, 1 H, H-2), 5.06 (dd, J = 10.2, J = 3.6 Hz, 1 H, H-3), 4.98 (d, J = 3.9 Hz, 1 H, H-1), 4.10 (br. q, J = 12.3 Hz, 1 H, H-5), 3.25 (d, J = 9.3 Hz, 1 H, CH_2OAda), 2.87 (d, J = 9.6 Hz, 1 H, CH_2OAda), 2.14, 2.04, 1.97 (s, 9 H, 3 × CH_3CO), 1.95 (br. s, 3 H, CHAda), 1.74−1.48 (m, 12 H, CH_2Ada), 1.12 (d, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.5, 170.2 (CH_3CO), 96.5 (C-1), 79.1, 71.2 (C-2), 68.6, 68.4 (C-4, C-3), 64.0 (C-5), 39.4, 39.0, 37.2, 37.1; 28.2, 28.1, 20.8, 20.6 (CH_3CO), 15.9 (CH_3) ppm. MALDI-TOF: calcd. 461.50 [$C_{23}H_{34}O_8$ + Na]; found 461.7 [M + Na]$^+$, 477.6 [M + K]$^+$.

1-Adamantylmethyl 2,3,4-Tri-*O*-acetyl-β-L-fucopyranoside (7b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.24−5.17 (m, 2 H, H-4, H-2), 5.00 (dd, J = 10.5, $J_{H3,H4}$ = 3.3 Hz, 1 H, H-3), 4.35 (d, J = 8.1 Hz, 1 H, H1), 3.77 (br. q, J = 12.3 Hz, 1 H, H-5), 3.53 (d, J = 9.6 Hz, 1 H, CH_2OAda), 2.95 (d, J = 9.6 Hz, 1 H, CH_2OAda), 2.17, 2.05, 1.98 (3s, 9 H, 3 × CH_3CO), 1.95 (br. s, 3 H, CHAda), 1.73−1.49 (m, 12 H, CH_2Ada), 1.21 (d, J = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 170.3, 169.4 (COCH$_3$), 102.4(C-1), 81.0, 71.3, 70.4, 69.2, 69.0 (C-2, C-3, C-4, C-5), 39.5, 39.3, 37.2, 37.1, 33.9, 28.2, 28.1, 20.8, 20.7, 20.6 (CH_3CO), 16.1 (CH_3) ppm. MALDI-TOF: m/z = 461.9 [M + Na]$^+$, 477.9 [M + K]$^+$.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranoside (8a): Starting from penta-*O*-acetyl-D-mannopyranose (200 mg) only the α-isomer **8a** was obtained (136m g, 65%). R_f (ethyl acetate/hexane, 1:2) = 0.52. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.37−5.22 (m, 3 H, H-2, H-3, H-4), 4.74 (br. s, 1 H, H-1), 4.27 (dd, J = 12.3, J = 5.4 Hz, 1 H, H-6a), 4.11 (dd, J = 12.3, J = 2.4 Hz, 1 H, H-6b), 4.00−3.90 (m, 1 H, H-5), 3.27 (d, J = 9 Hz, 1 H, CH_2OAda), 2.97 (d, J = 9 Hz, 1 H, CH_2OAda), 2.16, 2.11, 2.05, 2.00 (4s, 12 H, 4 × CH_3CO), 1.98 (br. s, 3 H, CHAda), 1.78−1.50 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6 (COCH$_3$), 98.3 (C-1), 86.9, 79.2, 70.0, 69.7, 68.7, 66.7, 62.9 (C-2, C-3, C-4, C-5, C-6, CAda), 39.9, 37.4, 28.4 (CH_3CO) ppm. MALDI-TOF: m/z = 518.4 [M + Na − H]$^+$, 534.3 [M + K − H]$^+$. $C_{25}H_{36}O_{10}$ (496.55): calcd. C 60.50, H 7.30; found C 60.10, H 7.55.

Zemplén Deacetylation: A solution of sodium methoxide in methanol (1 M, 0.1 equiv.) was added at room temperature to a solution of the acetylated 1-adamantylmethyl glycosides (1.0 equiv.) in methanol. After 2 h, the mixture was neutralised with Amberlite resin IRA-120, the solution was filtered and the solvents were evaporated to give the corresponding 1-adamantylmethyl glycoside.

1-Adamantylmethyl α-D-Glucopyranoside (1a): From **5a** (325 mg, 1.0 equiv.) in methanol (50 mL). **1a** was obtained as a white solid (98%). R_f (CH_2Cl_2/MeOH, 98:2) = 0.29. $[\alpha]_D^{25}$ = 5.98 (c = 1.0, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 4.71 (d, J = 3.6 Hz, 1 H, H-1), 3.80 (dd, J = 11.7, J = 2.4 Hz, 1 H, H-6a), 3.71−3.63 (m, 2 H, H-3, H-6b), 3.61−3.55 (m, 1 H, H-5), 3.40 (dd, J = 9.9, J = 3.9 Hz, 1 H, H-2), 3.36 (m, 1 H, H-4), 3.27 (d, J = 9.0 Hz, 1 H, CH_2OAda), 2.94 (d, J = 9.3 Hz, 1 H, CH_2OAda), 1.98 (br. s, 3 H, CH_βAda), 1.81−1.75 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 101.1 (C-1), 80.4, 76.0, 74.7, 74.4, 72.8, 73.6 (C-2, C-3, C-4, C-5, C-6), 41.6, 39.1, 30.6 ppm. MALDI-TOF: m/z = 351 [M + Na]$^+$, 367 [M + K]$^+$. $C_{17}H_{28}O_6$ (328): calcd. C 62.0, H 8.5; found. C 61.9, H 7.81.

1-Adamantylmethyl β-D-Glucopyranoside (1b): From **5b** (49 mg) in methanol (20 mL). **1b** (99%) was obtained as a syrup. R_f (CH_2Cl_2/MeOH, 98:2) = 0.30. $[\alpha]_D^{25}$ = −21.7 (c = 0.64, MeOH). ^{1}H NMR (CD_3OD, 500 MHz): δ = 4.20 (d, J = 8.5 Hz, H-1), 3.93 (m, 1 H, H-6a), 3.73 (dd, J = 12.0, J = 5.5 Hz, 1 H, H-6b), 3.56 (d, J = 10.0 Hz, 1 H, CH_2OAda), 3.50 (t, J = 8.5 Hz, 1 H, H-3), 3.48−3.43

(m, 1 H, H-5), 3.39 (t, J = 8.5 Hz, 1 H, H-4), 3.30 (t, J = 8.5 Hz, 1 H, H-2), 3.24 (d, J = 10.0 Hz, 1 H, CH_2OAda), 1.98 (br. s, 3 H, CHAda), 1.77−1.55 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR (MeOD, 125 MHz): δ = 106.1 (C-1), 82.5, 79.1, 78.7, 76.1, 72.6, 63.6 (C-2, C-3, C-4, C-5, C-6), 41.4, 39.2, 35.9, 30.6 ppm. MALDI-TOF: calcd. 351.7 [$C_{17}H_{28}O_6$ + Na^+]; found 351.7 and 367.6 [M + K]$^+$.

1-Adamantylmethyl α-D-Galactopyranoside (2a): From **6a** (400 mg) in methanol (30 mL). **2a** (251 mg, 95%) was obtained as a white solid. R_f (CH_2Cl_2/MeOH, 95:5) = 0.33. $[\alpha]_D^{25}$ = 108.2 (c = 1.03, MeOH). ^1H NMR (300 MHz, MeOD): δ = 4.75 (br. s, 1 H, H-1), 3.91 (br. s, 1 H, H-6a), 3.83−3.75 (m, 4 H, H-2, H-3, H-5, H-6b), 3.74−3.69 (m, 1 H, H-4), 3.36 (d, J = 9.3 Hz, 1 H, CH_2OAda), 2.94 (d, J = 9 Hz, 1 H, CH_2OAda), 1.98 (br. s, 3 H, CHAda), 1.81−1.59 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 97.9 (C-1), 78.0, 70.2, 69.2, 68.9, 68.3 (C-2, C-3, C-4, C-5), 60.7 (C-6), 38.7, 36.2, 32.8, 27.5. MALDI-TOF: m/z = 351.8 [M + Na]$^+$, 367.7 [M + K]$^+$. $C_{17}H_{28}O_6{\cdot}H_2O$ (346.41): calcd. C 58.88, H 8.66; found C 58.70, H 8.80.

1-Adamantylmethyl β-D-Galactopyranoside (2b): From **6b** (900 mg) in methanol (60 mL). **2b** (98%) was obtained as a white solid. R_f (CH_2Cl_2/MeOH, 95:5) = 0.30. $[\alpha]_D^{25}$ = 2.32 (c = 0.99, MeOH). ^1H NMR (300 MHz, MeOD): δ = 4.16 (d, J = 7.5 Hz, 1 H, H-1), 3.84 (br. d, J = 3.3 Hz, 1 H, H-4), 3.74 (br. d, J = 5.7 Hz, 2 H, H-6a, H-6b) 3.58−3.41 (m, 4 H, CH2OAda, H-2, H-5, H-3), 3.06 (d, J = 9.3 Hz, 1 H, CH_2OAda), 1.96 (br. s, 3 H, CHAda), 1.80−1.60 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 106.6 (C-1), 82.5, 77.4, 75.9, 73.6, 71.2, 63.3 (C-3, C-5, C-2, C-4, C-6), 41.5, 39.2, 30.6 ppm. MALDI-TOF: m/z = 351.9 [M + Na]$^+$, 367.8 [M + K$^+$]. $C_{17}H_{28}O_6{\cdot}2H_2O$ (364.41): calcd. C 55.98, H 8.78; found C 55.50, H 8.60.

1-Adamantylmethyl α-L-Fucopyranoside (3a): From **7a** (240 mg) in methanol (8 mL). **3a** (90%) was obtained as a white solid. R_f (CH_2Cl_2/MeOH, 98:2) = 0.30. $[\alpha]_D^{25}$ = −102.78 (c = 1.04, MeOH). ^1H NMR (300 MHz, MeOD): δ = 4.67 (d, J = 2.7 Hz, 1 H, H-1), 3.93 (br. q, J = 6.6 Hz, 1 H, H-5), 3.77−3.73 (m, 2 H, H-2, H-3), 3.67 (d, J = 1.2 Hz, 1 H, H-4), 3.26 (d, J = 9 Hz, 1 H, CH_2OAda), 2.95 (d, J = 9 Hz, 1 H, CH_2OAda), 1.98 (br. s, 3 H, CHAda), 1.81−1.60 (m, 12 H, CH_2Ada), 1.22 (d, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 101.5 (C-1), 80.6 (CAda), 72.7 (C-4), 71.2 (C-2, C-3), 68.2 (C-5), 41.6, 41.1, 39.2, 39.1, 35.8, 30.6, 17.5 (CH_3) ppm. MALDI-TOF: m/z = 335.8 [M + Na]$^+$, 351.7 [M + K]$^+$. $C_{17}H_{28}O_5{\cdot}1/2H_2O$ (321.41): calcd. C 63.47, H 9.02; found C 64.10, H 9.12.

1-Adamantylmethyl β-L-Fucopyranoside (3b): From **7b** (160 mg) in methanol (5 mL). **3b** (96%) was obtained as a white solid. R_f (CH_2Cl_2/MeOH, 98:2) = 0.28. $[\alpha]_D^{25}$ = 13.23 (c = 1.02, MeOH). ^1H NMR (300 MHz, D_2O): δ = 4.23 (d, J = 8 Hz, 1 H, H-1), 3.74−3.67 (m, 1 H, H-5), 3.65 (d, J = 3 Hz, 1 H, H-4), 3.54 (dd, J = 10, J = 3.5 Hz, 1 H, H-3), 3.43 (d, J = 10.5 Hz, 1 H, CH_2OAda), 3.42−3.38 (m, 1 H, H-2), 3.12 (d, J = 10 Hz, 1 H, CH_2OAda), 1.17 (d, J = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (300 MHz, D_2O): δ = 106.1 (C-1), 82.1 (CAda), 75.7 (C-2), 73.6 (C-4), 72.9 (C-5), 72.3 (C-3), 41.1, 38.8, 35.5, 30.3, 17.2 (CH_3) ppm. MALDI-TOF: m/z = 336.0 [M + Na+H], 351.9 [M + K]$^+$. $C_{17}H_{28}O_5.1/2\ H_2O$ (321.41): calcd. C 63.47, H 9.02; found: calcd. C 63.00, H 9.45.

1-Adamantylmethyl α-D-Mannopyranoside (4a): From **8a** (1800 mg) in methanol (70 mL). **4a** (99%) was obtained as a white solid. R_f (CH_2Cl_2/MeOH, 95:5) = 0.30. $[\alpha]_D^{25}$ = 51.15 (c = 1.04, MeOH). ^1H NMR (500 MHz, MeOD): δ = 4.63 (d, J = 1 Hz, 1 H, H-1), 3.81−3.75 (m, 2 H, H-2, H-6a), 3.70−3.64 (m, 2 H, H-3, H-6b), 3.57 (t, J = 10 Hz, 1 H, H-4), 3.52−3.46 (m, 1 H, H-5), 3.33 (d, J = 9 Hz, 1 H, CH_2OAda), 2.89 (d, J = 9 Hz, 1 H, CH_2OAda), 1.94 (br. s, 3 H, CHAda), 1.78−1.55 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 100.4 (C-1), 77.7 (CAda), 73.1 (C-5), 71.4 (C-3), 70.8 (C-2, C-6), 67.2 (C-4), 39.4, 36.8, 33.3, 28.4, 28.3 ppm. MALDI-TOF: m/z = 352.4 [M + Na + H]$^+$, 368.4 [M + K + H]$^+$. $C_{17}H_{28}O_6$ (328.40): calcd. C 62.00, H 8.60; found C 61.60, H 8.65.

Phenyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (9): Penta-*O*-acetyl-α-D-mannopyranose (300 mg, 1 equiv.) was dissolved in chloroform (50 mL) and benzenethiol (1.5 equiv., 4.18 mL) and boron trifluoride−diethyl ether (3 equiv., 4.81 mL) were added to this solution. The reaction was monitored by TLC (ethyl acetate/hexane, 1:2). After 6 h, the solution was washed with saturated aqueous sodium hydrogen carbonate and the organic phase dried. Removal of the solvent gave a yellow syrup which crystallized on treatment with ethanol to afford **9** (83%) as colourless needles. R_f (ethyl acetate/hexane, 1:2) = 0.4. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55−7.20 (m, 5 H, Ph), 5.47 (m, 2 H, H-1α, H-3), 5.35−5.25 (m, 2 H, H-2, H-4), 4.60−4.48 (m, 1 H, H-6a), 4.34−4.24 (dd, $J_{H5,H6}$ = 12.5, $J_{H5,H4}$ = 6 Hz, 1 H, H-5), 4.08 (br. d, $J_{H6,H5}$ = 12 Hz, H-6b), 2.15, 2.08, 2.05, 2.00 (4 × s, 12 H, 4 × CH_3CO) ppm.

Phenyl 2,3,4,6-Tetra-*O*-benzyl-1-thio-α-D-mannopyranoside (10): A solution of sodium methoxide in methanol (1 M, 591 μL, 0.1 equiv.) was added to a solution of **9** (2.6 g) in methanol (70 mL). The mixture was stirred for 1 h and then neutralised with Amberlite resin IRA-120 (H^+). After filtration and evaporation of the solvent, the residue was dissolved in DMF (50 mL) and treated with NaH powder (7 equiv., 624 mg) and the suspension was stirred at 20 °C for 30 min. The mixture was then cooled to 0 °C and benzyl bromide (14 equiv., 6.06 mL, 8.72 g) was added. The reaction mixture was stirred at 25 °C until a clear solution had formed (24−48 h), and was then quenched with methanol (10 mL) at 0 °C. The resulting clear solution was concentrated to dryness. Ethyl acetate (50 mL) and water (50 mL) were added to the residue. The ethyl acetate layer was removed and washed with water (3 × 40 mL), dried and concentrated to yield a crystalline residue which was chromatographed (ethyl acetate/hexane, 3:1) to give **10** in 81% yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60−7.10 (m, 25 H, Ph), 5.62 (d, $J_{H1,H2}$ = 1.5 Hz, 1 H, H-1α), 4.98−4.45 (m, 8 H, 4 × CH_2), 4.34−4.25 (m, 1 H, H-5), 4.20−3.70 (m, 5 H, H-2, H-3, H-4, H-6a, H-6b).

2,3,4,6-Tetra-*O*-benzyl-D-mannopyranose (11): *N*-Bromosuccinimide (1.2 equiv., 540 mg) was added in the dark to a solution of **10** (1.6 g) in acetone (27.2 mL) at −25 °C. Then water (3.3 equiv., 150 μL) was added. The solution was stirred for 3 h and the temperature was increased slowly to room temperature. Saturated aqueous sodium hydrogen carbonate was added and the acetone was evaporated in vacuo. The reaction mixture was extracted with ethyl acetate. The organic phase was dried and the solvents were evaporated to give the α- and β-anomers of **11** as a syrup (75%). R_f = 0.14. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.26 (br. s, 1 H, H-1α), 4.97−4.47 (m, 8 H, 4 × CH_2), 4.12−4.03 (m, 1 H, H-5), 3.99 (dd, $J_{H3,H2}$ = 3, $J_{H3,H4}$ = 9.3 Hz, 1 H, H-3), 3.87 (pseudo t, $J_{H4,H3}$ = $J_{H4,H5}$ = 9.6 Hz, 1 H, H-4), 3.83−3.57 (m, 3 H, H-2, H-6a, H-6b) ppm.

***O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-mannopyranosyl) Trichloroacetimidate (12):** 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 1.2 equiv., 33.4 μL) and trichloroacetonitrile (185 μL) were added to a solution of **11** (1 equiv., 100 mg) in CH_2Cl_2 (5 mL). TLC monitoring

(ethyl acetate/hexane, 1:1) showed significant formation of the α- and β-anomer. The mixture was concentrated under reduced pressure and used directly due to the very strong reactivity of these compounds.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-benzyl-α/β-mannopyranoside (13a,b): A solution of **12** (1 equiv., 130 mg) and 1-(hydroxymethyl)adamantane (1.2 equiv., 38 mg) in dry dichloromethane (5 mL) was stirred in the presence of molecular sieves (4 Å) under argon at room temperature for 10 min. Trimethylsilyl triflate (0.1 equiv., 3.4 μL) was then slowly added. The reaction mixture was stirred at room temperature for 3 h, then concentrated to give **13** (55%; α/β = 1:4) as a yellow oil. The separation of both anomers was not possible at this stage. Debenzylation and subsequent acetylation allowed the purification of both anomers.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-α/β-D-mannopyranoside (14): 10% Pd/C was added to a solution of **13** (1 equiv., 208 mg) in CH_2Cl_2/MeOH (10−15 mL) and the mixture was stirred under hydrogen at room temperature for 2 d. The mixture was filtered and the solvents were evaporated under low pressure to give the deprotected α- and β-anomers as a mixture. The residue (103 mg) was acetylated with pyridine/acetic anhydric (2:1) and the mixture was poured into ice/water and extracted with ethyl acetate. The combined organic phases were washed with a H_2SO_4 solution (2 N) and with saturated aqueous sodium hydrogen carbonate, and then dried with magnesium sulfate. Filtration and concentration of the solution gave the α- and β-glycosides as a mixture (1:4) in 64% yield. Chromatography of this mixture on silica gel (ethyl acetate/hexane, 1:6) gave the α-isomer **14a** (24 mg, 15%) and the β-isomer **14b** (75 mg). R_f (ethyl acetate/hexane, 1:2) = 0.4 (α), 0.34 (β). Isomer **14a** is identical to **8a** already described.

1-Adamantylmethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranoside (14b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.48 (d, $J_{H2,H3}$ = 3.3 Hz, 1 H, H-2), 5.25 (pseudo t, $J_{H4,H3}$ = $J_{H4,H5}$ = 9.9 Hz, 1 H), 5.05 (dd, $J_{H3,H2}$ = 3.3, $J_{H3,H4}$ = 9.9 Hz, 1 H, H-3), 4.56 (d, $J_{H1,H2}$ = 0.9 Hz, 1 H, H-1β), 4.30 (dd, $J_{H6a,H6b}$ = 5.4, $J_{H6b,H5}$ = 12.3 Hz, 1 H, H-6a), 4.13 (dd, $J_{H6b,H6a}$ = 5.4, $J_{H6b,H5}$ = 12.3 Hz, 1 H, H-6b), 3.68−3.59 (m, 1 H, H-5), 3.49 (d, J = 9.3 Hz, 1 H, CH_2OAda), 2.99 (d, J = 9.3 Hz, 1 H, CH_2OAda), 2.17, 2.08, 2.03, 2.00 (4s, 12 H, 4 × CH_3CO), 1.94 (br. s, 3 H, CHAda), 1.78−1.50 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6 (*CO*CH_3), 98.3 (C-1), 86.9, 79.2, 70.0, 69.7, 68.7, 66.7, 62.9 (C-2, C-3, C-4, C-5, C-6, CH_2Ada), 28.4 (CHAda, *CH_3*CO) ppm. MALDI-TOF: calcd. 519.54 [$C_{25}H_{36}O_{10}$ + Na]; found 520.6.

1-Adamantylmethyl β-D-Mannopyranoside (4b): A solution of sodium methoxide in methanol (1 M, 0.1 equiv., 8.75 μL) was added at room temperature to a solution of **14b** (1 equiv., 43 mg) in methanol (5 mL). After neutralisation with Amberlite resin IRA-77, the solution was filtered and the solvents were evaporated to give **4b** (99%). R_f (CH_2Cl_2/MeOH, 95:5) = 0.32. $[\alpha]_D^{25}$ = −3.71 (*c* = 0.07, MeOH). ^{1}H NMR (500 MHz, MeOD): δ = 4.43 (d, $J_{H1,H2}$ = 0.9 Hz, 1 H, H-1β), 3.91−3.85 (m, 2 H, H-2, H-6a), 3.76−3.70 (dd, $J_{H6a,H6b}$ = 5.7, $J_{H6b,H5}$ = 12 Hz, 1 H, H-6a), 3.58 (t, $J_{H4,H3}$ = 9.3 Hz, 1 H, H-4), 3.56 (d, J = 9.3 Hz, 1 H, CH_2OAda), 3.44 (dd, $J_{H3,H2}$ = 3.3, $J_{H3,H4}$ = 9.3 Hz, 1 H, H-3), 3.23−3.16 (m, 1 H, H-5), 3.06 (d, J = 9.3 Hz, 1 H, CH_2OAda), 1.97 (br. s, 3 H, CHAda), 1.83−1.59 (m, 12 H, CH_2Ada) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 100.9 (C-1), 79.7, 76.4, 73.6, 70.6, 66.8, 38.8, 38.7, 38.6, 36.5, 33.1, 27.9 ppm. MALDI-TOF: calcd. 351.39 [$C_{17}H_{28}O_6$ + Na]; found 352.5 [M + Na + H]$^+$, 368.4 [M + K + H]$^+$.

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[1] K. A. Connors, *Chem. Rev.* **1997**, *97*, 1325−1357.
[2] M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875−1917.
[3] D. B. Smithrud, T. B. Wyman, F. Diederich, *J. Am. Chem. Soc.* **1991**, *113*, 5420−5426.
[4] D. A. Stauffer, R. E. Barrans Jr., D. A. Dougherty, *J. Org. Chem.* **1990**, *55*, 2762−2767.
[5] E. Junquera, J. Laynez, M. Menéndez, S. Sharma, S. Penadés, *J. Org. Chem.* **1996**, *61*, 6790−6798.
[6] J. M. Coterón, C. Vicent, C. Bosso, S. Penadés, *J. Am. Chem. Soc.* **1993**, *115*, 10066−10076.
[7] J. C. Morales, S. Penadés, *Angew. Chem. Int. Ed.* **1998**, *37*, 654−657.
[8] M. R. Eftink, M. L. Andy, K. Bystrom, H. D. Perlmutter, D. S. Kristol, *J. Am. Chem. Soc.* **1989**, *111*, 6765−6772.
[9] P. M. Ivanov, D. Salvatierra, C. Jaime, *J. Org. Chem.* **1996**, *61*, 7012−7017.
[10] M. Czugler, E. Eckle, J. J. Stezowski, *J. Chem. Soc., Chem. Commun.* **1981**, 1291−1292.
[11] P. Brajeswar, W. Korytnyk, *Carbohydr. Res.* **1984**, *126*, 27−43.
[12] S. K. Chatterjee, P. Nuhn, *Chem. Commun.* **1998**, *98*, 1729−1730.
[13] N. Ikemoto, O. K. Kim, L.-C. Lo, V. Satyanarayana, M. Chang, K. Nakanishi, *Tetrahedron Lett.* **1992**, *33*, 4295−4298.
[14] H.-J. Schneider, F. Hacket, V. Rüdiger, *Chem. Rev.* **1998**, *98*, 1755−1785.
[15] M. V. Rekharsky, Y. Inoue, *J. Am. Chem. Soc.* **2000**, *122*, 4418−4435.
[16] N. F. Burkhalter, S. M. Dimick, E. J. Toone, in *Carbohydrates in Chemistry and Biology* (Eds. B. Ernst, G. W. Hart, P. Sinaÿ), Wiley-VCH, Weinheim **2000**, part I, vol. 2, p. 863−914.
[17] Both Sigma Plot and Hunter's curve fitting were used. We thank Prof. C. A. Hunter (Sheffield University) for kindly providing the fitting program.
[18] B. Zhang, R. Breslow, *J. Am. Chem. Soc.* **1993**, *115*, 9353−9354.
[19] F. Charbonnier, C. H. Hunter, S. Penadés, unpublished results. Preliminary results indicate that the enthalpy and entropy of binding change with the sugar stereochemistry.
[20] R. U. Lemieux, *Acc. Chem. Res.* **1996**, *29*, 373−380.
[21] C. Clarke, R. J. Woods, J. Gluska, A. Cooper, M. A. Nutley, G.-J. Boons, *J. Am. Chem. Soc.* **2001**, *123*, 12238−12247.

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