Studies on bis(2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl)amine and its protected and deprotected *N*-acyl derivatives – an approach to novel non-ionic surfactants

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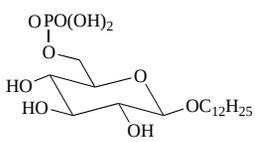
Optimum conditions for the formation of N-acyl derivatives of bis(2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl)amine with long-chain acid chlorides have been determined. The anomeric equilibrium of the parent bis(sugar)amine has been investigated and the amide rotation barrier measured for these protected sugar derivatives and the analogous compounds with the protecting groups removed.

Introduction

The surfactant properties of compounds with a long alkyl chain linked to a carbohydrate moiety (or a similar derived species) are well known. Such amphiphilic structures can form both lyotropic and thermotropic mesophases and have great potential in a variety of applications.[1,2] The link between the hydrophobic and hydrophilic parts of these compounds is usually either an ether group, an acetal (glycoside) function (a recent example[3] is dodecyl β-D-glucopyranoside 6-phosphate **1**), or an amide group as in *N*-octyl-D-gluconamide **2**[4] or the 1-(*N*-acylmethylamino)-1-deoxyglucitols **3**.[5] The exploration of further structural diversity has led to the synthesis[6] of the double-headed bis-D-gluconamide **4** (a so-called bola-amphiphile). The cyclohexane derivative **5** can be regarded as an analogous double-headed amphiphile with the two heads brought close together.[7] Similar structural variation has been explored for amphiphiles with a bis ether link as in compound **6** and similar species.[2,8]

In essentially all amphiphilic compounds with an amide link, the hydrophobic part has an extended shape and is about the same length as the hydrophilic part. Thus gluconamide **2** has an octyl chain linked to an hydroxylated chain of eight atoms (from N to O-6). This extended shape, in which the ratio between hydrophilic and lipophilic parts is about 1:1, is typical of molecules commonly found as natural membrane constituents and is reflected in the tendency to form bilayers and micellar fibres.[9] In this paper we report a different approach to obtaining interesting double-headed amphiphiles in which the hydrophilic heads are close together but the overall extended molecular shape is retained. This is achieved by coupling a diglycosylamine to a long-chain acyl group to access the class of compound with structure **7** or the analogous furanose form.



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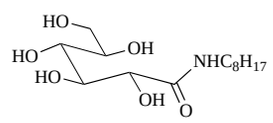

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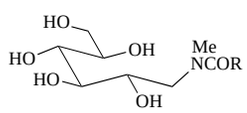

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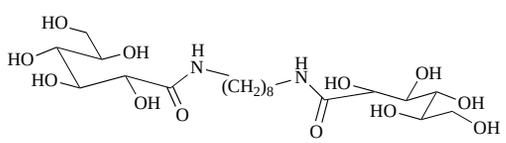

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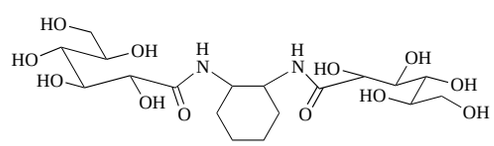

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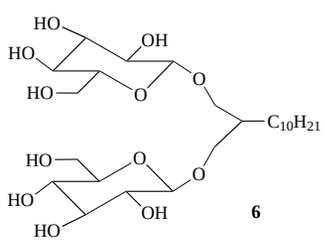

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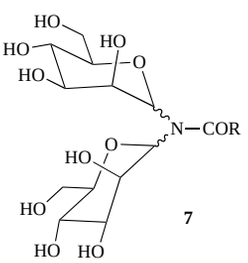

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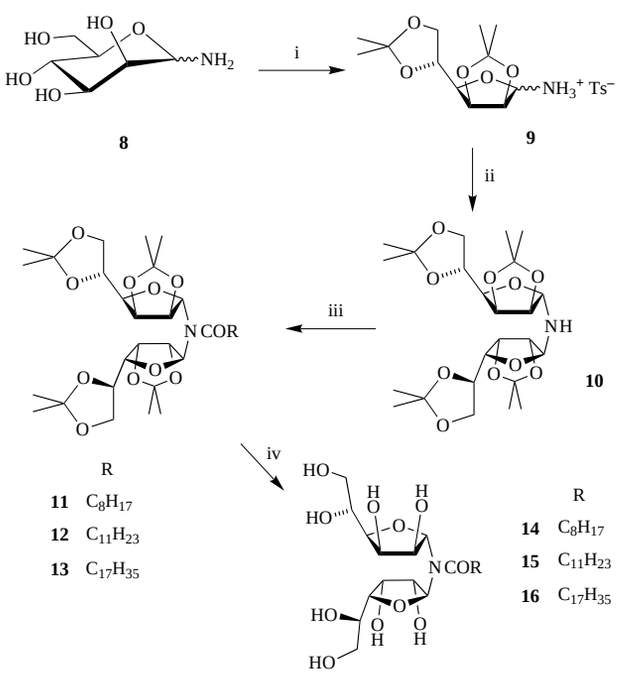
Results and discussion

Diglycosylamines are generally accessible by self-condensation of the corresponding glycosylamine but this reaction only affords the sugar in its pyranose form. We were interested in end products with a furanose structure and thus required a diglycosylamine which could be maintained in the furanose form prior to acylation (after which isomerisation was unlikely). This was achieved (Scheme 1) by conversion of α,β-D-mannopyranosylamine **8** to its diisopropylidene derivative, isolated as the toluenesulfonate salt **9** (α,β ratio 3:1, by ^{13}C NMR spectroscopy). The free amine was obtained by treatment with triethylamine and the dimerisation to bis(2,3:5,6-di-*O*-isopropylidene-α,β-D-mannofuranosyl)amine **10** promoted by heating under reflux in MeOH in a stream of nitrogen (to remove ammonia). Compound **10** was obtained as a gum (74%) which was a mixture of the α,α-, α,β- and β,β-isomer but was otherwise chemically pure (by NMR spectroscopy and elemental analysis). In repeated experiments the anomeric composition of the foam was quite

variable. However, a solid product was obtained by crystallisation from ethanol. This was the anomerically pure α,α-isomer as established from the ^{1}H and ^{13}C NMR spectra. Typically for an α-configuration the coupling between H-1 and H-2 is less than 0.8 Hz (the dihedral angle H-1–C-1–C-2–H-2 for a South conformation of the furanose ring is ~−80°). Notably, the NH proton is coupled in dimethyl sulfoxide (DMSO) ($J_{\mathrm{H\text{-}1,NH}}$ 6.9†) but not in $CDCl_3$. It is unlikely that this lack of coupling is due to exchange since the α,β-isomer in the same solvent shows coupling of the NH proton with both anomeric protons ($J_{\mathrm{H\text{-}1,NH}}$ 6.2, $J_{1',\mathrm{NH}}$ 11.5). Thus the absence of coupling ($J_{1,\mathrm{NH}} < 1$) in the α,α-isomer suggests that the dihedral angle φ(H-1–C-1–N-1–H-1) is close to 90° in $CDCl_3$ solution. Evidently the conformation of the α,α-isomer is solvent dependent.



Scheme 1 *Reagents and conditions:* i, PTSA, 2,2-dimethoxypropane in acetone; ii, Et_3N, filter; then reflux, 36 h; iii, RCOCl, DMAP in pyridine, 48 h, 20 °C; iv, H_2SO_4, EtOH, 36 h at 50 °C

In order better to understand the relative stability of these isomeric diglycosylamines the anomerisation of bis(2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl)amine was studied in detail. The anomerisation is most conveniently followed by ^{1}H NMR spectroscopy. In $CDCl_3$ the rate of anomerisation is quite fast and was evaluated at 22 °C by using the H-4 signals at δ 3.88 (α,α-isomer), δ 3.38 (α,β-isomer) and δ 3.42 (β,β-isomer), together with the NH signal at δ 2.64 (α,β-isomer). The change in composition with time is given in Table 1. The initial changes are too fast at 22 °C for reliable estimation of the rate but a similar experiment at 0 °C (data not shown) showed an initial α,β quotient of 9.2 falling to 7.6 after *ca.* 5 min. This corresponds to a rate constant of ~10^{-4} s^{-1}. The limiting α,β quotient shows that the α-anomer is the most stable, with $\Delta G^{22}_{\alpha\rightarrow\beta}$ −3.6 kJ mol^{-1}.

Anomerisation is much slower in [$^2H_6$]DMSO at ambient temperature but proceeds at a reasonable rate at 90 °C. At this temperature the NH protons are easily detected in the ^{1}H NMR spectrum at δ 3.65 (α,α-isomer), 3.5 (α,β-isomer) and 3.2 (β,β-isomer). The change in the composition with time is shown in Table 2. The limiting value of the α,β quotient is ~1.75 (taken as the value observed after *ca.* 2.5 days when the sample began to degrade), corresponding to $\Delta G^{90}_{\alpha\rightarrow\beta}$ 1.69 kJ mol^{-1}. It appears that the α-configuration in this sugar amine is stabilised by a polar solvent, accounting for the fact that the α,α-isomer crystallises from ethanol. From these studies we deduce that this system is likely to remain in the α-configuration under the conditions used for subsequent derivatisation. This is important since it is difficult to establish the configuration directly (see below).

† *J* Values are given in Hz.

Table 1 Anomerisation of bis(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)amine in $CDCl_3$ at 22 °C

Time (*t*/h)	Composition/mole fraction			
	[α,α]-Isomer[b]	[α,β]-Isomer[c]	[β,β]-Isomer[d]	α,β Quotient
0[a]	0.77	0.23	trace	7.6
2.0	0.20	0.79	0.01	1.3
5.0	0.19	0.73	0.10	1.2
21	0.18	0.54	0.28	0.8
74	0.07	0.35	0.58	0.3
310[a]	0.05	0.27	0.68	0.23[e]

[a] Time is measured from the first spectrum. [b] Measured as the triplet at δ 3.87 or the singlet at δ 4.88. [c] Measured as the quartet at δ 2.64. [d] Measured as the triplet at δ 3.42 with allowance for the overlapping H-4 quartet in the α,β-isomer. [e] Taken as the limiting value.

Table 2 Anomerisation of bis(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)amine in [$^2H_6$]DMSO at 90 °C

Time (*t*/h)	Composition/mole fraction			
	[α,α]-Isomer[b]	[α,β]-Isomer[c]	[β,β]-Isomer[d]	α,β Quotient
0[a]	0.88	0.12	0	15.2
4.5	0.80	0.19	0.08	8.6
18.5	0.53	0.30	0.17	2.1
66	0.50	0.28	0.22	1.8[e]

[a] Time is measured from the first spectrum. [b] Measured as the triplet at δ 3.65. [c] Measured as the pseudo-triplet at δ 3.2. [d] Measured as the triplet at δ 3.55 with allowance for the β H-4 signals. [e] Limiting value, unchanged after a further 24 h.

The normal method for the acetylation of glycosylamines with acetic anhydride in pyridine converts compound **8** into *N*-acetyl-2,3,4,6-tetra-*O*-acetyl-D-mannopyranosylamine but a similar reaction with di(D-mannopyranosyl)amine gave the octa-*O*-acetyl derivative, no reaction occurring at the nitrogen atom of this secondary amine,[10] reflecting the increased deactivation by the presence of a second β-oxygen atom and as well as the severe steric effect of the second sugar ring. N-Acetylation of diglucopyranosylamine has been reported,[11] with zinc chloride as catalyst. In order to establish the best non-aqueous conditions for the acylation of the protected dimannosylamine **10** with a long-chain acid chloride we have investigated this general reaction under a variety of conditions (Table 3). There is a large variation in yield with conditions.

Our standard reaction employed three mole equivalents of the acid chloride in dry diethyl ether with one mole equivalent of the diglycosylamine in dry pyridine. The base is required to remove the generated HCl. The use of 4-(dimethylamino)-pyridine (DMAP) as acylation catalyst gave an improved yield in reduced reaction time for the reaction at 22 °C but, owing to side-reactions, this improvement deteriorated under forcing conditions (160 °C in a sealed vessel). The required amide was not isolated when DMAP or triethylamine was used as the base, a mixture of other products being formed. Presumably this is due to the higher basicity of these compounds, which can induce formation of the corresponding ketene from the acid chloride. It is notable that diethyl ether has a crucial role as solvent and cannot be replaced in this role by the base (Et_3N or pyridine).

The best acylation conditions described above (DMAP, Et_2O, pyridine; room temp.) were completely ineffective when the acylating reagent was 4-nitrobenzoyl chloride or 4-hexyloxybenzoyl chloride. Starting materials were recovered unchanged

Table 3 Acylation reactions of the bis(2,3 : 5,6-di-*O*-isopropylidene-D-mannofuranosyl)amine **10**[a]

Reagent	Catalyst	Solvent[b]	Base[b]	Temp. (*T*/°C)	Time (*t*/h)	Yield (%)
$C_{11}H_{23}COCl$	none	Et_2O	pyridine	22	80	35
$C_{11}H_{23}COCl$	DMAP	Et_2O	pyridine	22	48	73
$C_{11}H_{23}COCl$	DMAP	Et_2O	pyridine	reflux	5	60
$C_{11}H_{23}COCl$	DMAP	Et_2O	pyridine	160[c]	3	62
$C_{11}H_{23}COCl$	DMAP	Et_2O	DMAP	160[c]	2	0
$C_{11}H_{23}COCl$	DMAP	Et_3N	pyridine	22	320	0
$C_{11}H_{23}COCl$	DMAP	Et_3N	Et_3N	reflux[d]	0.75	0
$C_{11}H_{23}COCl$	DMAP	Et_3N	Et_3N	reflux	36	0
$C_8H_{17}COCl$	DMAP	Et_2O	pyridine	160[c]	3	58
$C_8H_{17}COCl$	DMAP	Et_2O	pyridine	22	48	71

[a] Reactions were generally carried out on the anomeric mixture. [b] Both the solvent and the base were rigorously dried. [c] In a sealed vessel. [d] In a microwave oven.

Table 4 ^{13}C NMR data characterising amide exchange in diglycosylamides

Compounds **11**–**13**					Compounds **14**–**16**				
	δ[a]	$\Delta\nu$[b]/Hz	T_C/°C	$\Delta G^{\ddagger}$/kJ mol^{-1}		δ[a]	$\Delta\nu$[b]/Hz	T_C/°C	$\Delta G^{\ddagger}$/kJ mol^{-1}
C-1	93.1	0			C-1	89.4	35	19.5	61.02
C-2	84.3	284	38	59.62	C-2	73.5	206	37	60.25
C-3	81.7	117	29	60.05	C-3	70.7	70	26	60.71
C-4	85.4	113	28	59.93	C-4	80.8	57	24	60.79
C-5	73.6	46	20	60.46	C-5	69.5	0		
C-6	67.0	28	16	60.80	C-6	63.3	0		
C-α	24.2	23	14	60.83	CO	172.7	0		
C-iso	109.1	21	13	60.83					
C-iso	112.9	47	20	60.41					
CO	175.6	0							
				$\Delta H^{\ddagger}$ 75.7 ± 1[c]					$\Delta H^{\ddagger}$ 73.7 ± 0.5[c]
				$\Delta S^{\ddagger}$ 52 ± 4[d]					$\Delta S^{\ddagger}$ 43 ± 2[d]
				r = 0.98[e]					r = 0.999[e]

[a] Chemical shift of coalesced lines, determined in $CDCl_3$ at 55 °C. [b] Separation of the pair of exchanging carbons at 0 °C at 67.9 MHz. [c] In units of kJ mol^{-1}. [d] In units of J mol^{-1} K^{-1}. [e] Correlation coefficient.

even after reaction for 48 h. Both electronic and steric factors are likely to contribute to this reduced reactivity. Similarly no reaction was observed between bis(2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl)amine[12] and nonanoyl chloride under our standard conditions. In this case steric inhibition of reaction is due to the presence of protecting groups on the sugar ring.

The deprotonation of the sugar groups was achieved using acidic conditions which did not result in any significant hydrolysis of the amide function or any significant reduction in anomeric purity. Thus a series of novel *N*,*N*-di(α-D-mannofuranosyl)alkanamides **14**–**16** was obtained. The need to avoid hydrolysis of the amide meant that other products corresponding to partial removal of the protecting groups were always obtained. Generally these products were not isolated. Rather more interesting was the isolation in each of the three cases of a species with a high R_f which was identified as the corresponding *N*-acylated α-D-mannopyranosylamine, *i.e.* the product corresponding to hydrolytic cleavage of one sugar group in the bis(sugar)amide and conversion of the remaining sugar group from the α-D-furanose form into the more stable α-D-pyranose form. The structure of these products was confirmed by direct synthesis.[13]

The configuration of the bis(sugar)amides (protected and unprotected) could not be determined from the NMR data owing to amide exchange which broadened both proton and carbon spectra. However, each compound in the series has a positive optical rotation (in the range +30 to +45°) typical of the alpha configuration of 2,3 : 5,6-di-*O*-isopropylidene-D-mannofuranose and its glycosides.[8]

Amide exchange

The NMR spectra of the N-acyl derivatives show evidence of amide exchange. Since amides of this type have not been studied previously the exchange process has been characterised fully. The length of the alkyl chain has no effect on the energetics of the exchange process since both the ^1H and ^{13}C spectra of compounds **11**, **12** and **13** are essentially identical (except for the number of methylene groups) across the compound set at all temperatures. ^1H spectra are very difficult to analyse at 20 °C since most of the protons on the mannose ring are broadened or appear as two peaks. At 55 °C exchange is rapid but H-1, H-2 and H-3 have coincident chemical shifts. At 0 °C the largest chemical shift separation, arising from amide stereoisomers, is for H-1 (292 Hz at 270 MHz) and some overlap is observed for other pairs of (broad) lines. Full details are given in the Experimental section. The ^{13}C NMR spectra are much more easily analysed and the exchange data are given in Table 4. As might be expected five of the sugar carbons can be identified as a pair of lines, coalescing at various temperatures. Even the two quaternary isopropylidene carbons show exchange behaviour. The ring quaternary carbon of the 2,3-isopropylidene group and C-5 of the sugar are both four atoms removed from the nitrogen atom and both have nearly the same chemical shift separation between stereoisomers at low temperature. Generally the frequency separation at low temperature decreases with distance from the amide group.

Curiously the anomeric carbon (C-1) appears as a single line at the lowest temperature used (0 °C) with a linewidth only slightly larger than that observed at 55 °C. This atom might have been expected to have shown a larger shift between stereoisomers and there must be a combination of shift effects of different sign leading to negligible net effect. A further unusual feature is the observation that the α-carbon in the alkyl chain also appears as a pair of lines ($\Delta\delta$ 21 Hz at 67.9 MHz) at low temperature. This suggests that a second exchange process is involved. A possible explanation is that the two sugar moi-

eties adopt different average conformations at low temperature due to steric crowding. However, there is no evidence for this second stereoisomerism in the spectrum of the sugar carbons. The existence of different conformations for the two sugar groups is supported by preliminary modelling work which will be reported in detail elsewhere. Since eight coalescence temperatures are accessible, the enthalpy and entropy of activation of amide inversion in the fully protected compounds can be estimated with excellent accuracy (Table 4). The deprotected compounds **14**–**16** show fewer carbons with a measurable shift separation at low temperature but the four measured values $\Delta G^{\ddagger}$ show excellent linearity with temperature (Table 4) and reliable values of the enthalpy and entropy of activation of amide inversion can be obtained. Again there was no detectable difference in the dynamic behaviour of the three homologues; the length of the alkyl chain has no effect on the inversion barrier. For these compounds with the isopropylidene groups removed the crowding around the amide group is reduced and the signal for the α-carbon of the alkyl chain does not show any separation at low temperature.

The energy barrier to rotation in these diglycosylamides ($\Delta G^{\ddagger}$ 60 kJ mol^{-1}) is much lower than it is for amides with unbranched N-substituents (for $MeCONMe_2$, $\Delta G^{\ddagger}$ ~75 kJ mol^{-1})[14] but is similar to the value found for amides with substituents such as $CHMe_2$ (51 kJ mol^{-1})[15] and CHMePh (60 kJ mol^{-1}).[16] Although the $\Delta G^{\ddagger}$-values are almost the same (at any particular temperature) for compounds with protected and unprotected sugar groups there is a small reduction in the value of $\Delta H^{\ddagger}$ between the protected and unprotected compounds, indicating that rotation of the amide bond is not seriously obstructed by the 2,3-isopropylidene group. The entropy of activation is positive and quite large for both systems owing to significant relief of crowding in the transition state. The slightly lower value of $\Delta S^{\ddagger}$ for the deprotected compounds reflects the reduction in steric interactions consequent upon the removal of four isopropylidene groups.

Experimental

General procedures

NMR spectra were recorded with JEOL GX270 or JEOL Lambda 400 spectrometers using standard conditions with a data-point resolution of ~0.1 Hz. ^{1}H Chemical shifts were measured relative to Me_4Si and ^{13}C chemical shifts relative to $CDCl_3$ (δ_C 77.05) or $(CD_3)_2SO$ (δ_C 39.5). Coupling constants are given in Hz. Assignments of the ^{1}H spectra were made by detailed analysis using decoupling or correlation techniques where appropriate. For anomeric mixtures the α,β quotient was determined from the integration of suitable peaks. Column chromatography was performed on silica gel (230–400 mesh; Aldrich) and TLC on silica gel 60, F_{254} (Merck) with detection by UV absorbance or ethanolic sulfuric acid. Rotations were obtained using an ETL-NPL automatic polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

Bis(2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl)amine 10

D-Mannose (100 g, 0.55 mol) was added portionwise to a cooled solution of ammonium chloride (0.5 g, 9.3 mmol) in MeOH (100 ml) presaturated with ammonia. The ammonia stream was maintained during the dissolution and for a further 15 min. The solution was transferred to a plastic container, stored at 4 °C and resaturated with ammonia every few days until crystallisation occurred (1–2 weeks). The solid mass was broken up, filtered, washed with cold MeOH and dried under vacuum to give D-mannopyranosylamine **8** (91% as monohydrate); R_f 0.19 (BuOH–AcOH–water, 6:2:2); mp 92–93 °C (lit.,[10] 93–94 °C); $[\alpha]_D^{23}$ −14.6 (*c* 2.7, MeOH) {lit.,[10] $[\alpha]_D^{23}$ −11.6 (water)}.

Compound **8** (33.0 g, 0.17 mol) was added to a vigorously stirred solution of dry toluene-*p*-sulfonic acid (PTSA) (63.0 g, 0.33 mol) and 2,2-dimethoxypropane (135 ml, 1.05 mol) in dry acetone (600 ml). After complete dissolution the clear brown solution was reduced to ~500 ml and then dry diethyl ether (500 ml) was added and the solution was stored at 4 °C. The crystalline precipitate was collected, washed with diethyl ether and dried *in vacuo* to afford, 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosylamine toluene-*p*-sulfonate **9** (64%); mp 132–133 °C (lit.,[17] 132–134 °C); $[\alpha]_D^{23}$ +4.2 (*c* 1.13, MeOH).

A mixture of the amine toluene-*p*-sulfonate **9** (20.0 g, 46 mmol) and triethylamine (8 ml, 46 mmol) in diethyl ether (100 ml) was refluxed for 20 min. The precipitate was removed and washed several times with diethyl ether. The filtrate was combined with the washings and then taken to dryness. The residue was taken up in MeOH (100 ml) and the solution was refluxed for 36 h in a stream of N_2, then the solvent was evaporated off and the residue taken up in dichloromethane (100 ml). This solution was washed with water (2 × 30 ml), dried ($MgSO_4$) and taken to dryness. The residue was chromatographed on silica gel ($CHCl_3$–MeOH, 95:5) to afford compound **10**, R_f 0.7 ($CHCl_3$–MeOH, 9:1) as a foam (74%). Crystallisation from EtOH gave the α,α-isomer: mp 154–155 °C; $[\alpha]_D^{23}$ +79.9 (*c* 2.2, MeOH) (Found: C, 57.8; H, 8.1; N, 2.8. Calc. for $C_{24}H_{39}NO_{10}$: C, 57.5; H, 7.8; N, 2.8%); $\delta_H(CDCl_3)$ 4.88 (s, $J_{1,2}$ <1.0, 2 H, H-1), 4.44 (d, $J_{2,3}$ 6.0, 2 H, H-2), 4.77 (m, $J_{3,4}$ 3.6, 2 H, H-3), 3.88 (dd, $J_{4,5}$ 8.0, 2 H, H-4), 4.40 (dd, 2 H, H-5), 4.02 (m, $J_{5,6a}$ 5.4, $J_{6a,6b}$ 8.8, 2 H, H^a-6), 4.10 (m, $J_{5,6b}$ 6.3, 2 H, H^b-6), 1.75 (s, 1 H, NH) and 1.33, 1.37, 1.45 and 1.49 (s × 4, 24 H, 8 × Me); δ_H(DMSO) 4.60 (d, $J_{1,2}$ <1.0, $J_{1,NH}$ 6.9, 2 H, H-1), 4.41 (d, $J_{2,3}$ 6.0, 2 H, H-2), 4.65 (dd, $J_{3,4}$ 3.5, 2 H, H-3), 3.86 (dd, $J_{4,5}$ 7.2, 2 H, H-4), 4.22 (m, 2 H, H-5), 3.81 (m, $J_{5,6a}$ 6.5, $J_{6a,6b}$ 8.3, 2 H, H^a-6), 3.99 (m, $J_{5,6b}$ 5.5, 2 H, H^b-6), 3.8 (3.65 at 90 °C) (t, 1 H, NH) and 1.23, 1.26, 1.33 and 1.36 (s × 4, 24 H, 8 × Me); $\delta_C(CDCl_3)$ 90.5 (C-1), 85.9 (C-2), 80.3 (C-3), 79.8 (C-4), 73.2 (C-5), 67.1 (C-6) and 24.4, 25.2, 25.8, 26.6 109.3 and 112.9 (2 × isopropylidene); δ_C(DMSO) 89.7 (C-1), 84.8 (C-2), 79.8 (C-3), 78.7 (C-4), 72.7 (C-5), 66.3 (C-6) and 24.4, 25.2, 25.8, 26.6, 108.0 and 111.3 (2 × isopropylidene).

The crystallisation liquors contained a mixture of the α,α-isomer, the α,β-isomer and the β,β-isomer. The following NMR data were obtained but the mixture was not characterised further.

α,β-Isomer. $\delta_H(CDCl_3)$ 4.93 (d, $J_{1,2}$ <1.0, $J_{1,NH}$ 6.2, 1 H, H-1), 4.02 (m, H-1′), 4.56 (d, $J_{2,3}$ 5.9, 1 H, H-2), 4.55 (dd, $J_{1,2}$ 3.5, $J_{2,3}$ 6.3, 1 H, H-2′), 4.79 (dd, $J_{3,4}$ 3.5, 1 H, H-3), 3.70 (dd, $J_{4,5}$ 3.5, 1 H, H-3′), 3.98 (dd, 1 H, H-4), 3.38 (dd, $J_{4,5}$ 8.2, 1 H, H-4′), 4.38 (m, 2 H, H-5, -5′), 4.07 (m, 4 H, H_2-6, -6′), 2.64 (dd, $J_{1',NH}$ 11.5, 1 H, NH) and 1.33, 1.35, 1.37, 1.43, 1.44, 1.49 and 1.50 (s × 7, 24 H, 8 × Me); $\delta_C(CDCl_3)$ 92.5 (C-1), 88.7 (C-1′), 85.4 (C-2), 78.1, 79.3, 79.9, 80.0 and 80.3 (C-2′, -3, -3′, -4, -4′), 73.0 and 73.2 (C-5, -5′), 67.1 and 67.2 (C-6, -6′) and 109.2, 109.3, 112.5 and 112.9 (4 × isopropylidene).

β,β-Isomer. $\delta_H(CDCl_3)$ 4.55 (m, 4 H, H-1, -2), 4.70 (m, $J_{3,4}$ 3.6, 2 H, H-3), 3.42 (dd, $J_{4,5}$ 7.6, 2 H, H-4), 4.38 (dd, 2 H, H-5), 4.05 (m, 4 H, H_2-6), 3.9 (br t, $J_{1,NH}$ 11, 1 H, NH) and 1.34, 1.37, 1.43 and 1.49 (s × 4, 24 H, 8 × Me); $\delta_C(CDCl_3)$ 89.6 (C-1), 79.9 and 79.85 (C-2, -3), 77.3 (C-4), 73.2 (C-5), 67.0 (C-6) and 25.0, 25.3, 25.8, 26.9, 109.0 and 112.6 (2 × isopropylidene).

N,*N*-Bis(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-alkanamides 11–13

General procedure. The dimannosylamine **10** (0.6 g, 1.2 mmol) and DMAP (75 mg) were dissolved in dry pyridine (2.5 ml). A solution of the acyl chloride (3.6 mmol) in diethyl ether (10 ml) was added dropwise. This mixture was treated in various ways (Table 3) but the best results were obtained by stirring at room temp. for 48 h. The mixture was washed with water (15 ml) and the aqueous layer was extracted with diethyl ether (15 ml). The organic phases were combined and the solvent was removed. The resulting gum was chromatographed (hexanes–ethyl acetate, 85:15) to give the amide.

***N*,*N*-Bis(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-nonanamide 11.** Yield 0.44 g (71%) [Found: $(M + H)^+$, 642.380. $C_{33}H_{55}NO_{11}$ requires (M + H), 642.385]; R_f 0.41 (hexanes–ethyl acetate, 65:35); $[\alpha]_D^{24}$ +37.3 (*c* 0.93, $CHCl_3$); δ_H($CDCl_3$; 55 °C) 4.95 (br s, 6 H, H-1, -2, -3), 4.35 (br m, 2 H, H-4), 4.25 (m, $J_{4,5}$ 6.0, 2 H, H-5), 3.91 (m, $J_{5,6a}$ 5.2, $J_{6a,6b}$ 8.4, 2 H, H^a-6), 4.00 (m, 2 H, H^b-6) and 2.40 (t, 4 H, CH_2-α); δ_H($CDCl_3$; 0 °C) 4.45 and 5.53 (br s, H-1), 4.80 and 5.07 (br s, H-2), 4.89 and 5.07 (br s, H-3), 4.25 and 4.38 (br s, H-4); δ_C see Table 4.

***N*,*N*-Bis(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-dodecanamide 12.** Yield 0.5 g (73%) [Found: $(M + H)^+$, 684.427. $C_{36}H_{61}NO_{11}$ requires (M + H), 684.432]; R_f 0.45 (hexanes–ethyl acetate, 65:35); $[\alpha]_D^{24}$ +31.3 (*c* 0.38, $CHCl_3$); NMR data identical with those for analogue **11** except for extra methylenes.

***N*,*N*-Bis(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-octadecanamide 13.** Yield 0.5 g (70%) [Found: $(M + H)^+$, 768.518. $C_{42}H_{73}NO_{11}$ requires (M + H), 768.526]; R_f 0.45 (hexanes–ethyl acetate, 65:35); $[\alpha]_D^{23}$ +44.0 (*c* 0.21, MeOH); NMR data identical with those for analogue **11** except for extra methylenes.

General procedure for the removal of the isopropylidene groups

The protected diglycosylamide (**11**, **12** or **13**) (2.0 g) was dissolved in 90% ethanol (20 ml) containing H_2SO_4 (0.1 ml; 0.1 M) and the solution was stirred at 50 °C for 36 h. The reaction mixture was taken to pH ~5 with saturated aq. $NaHCO_3$ and concentrated to ~10% volume. Water (25 ml) was added and the solution was extracted with butan-1-ol. The organic layer was washed with water (10 ml) and then taken to dryness. The residue was chromatographed (EtOAc–MeOH, 9:1) until the product with R_f 0.70 (BuOH–AcOH–water, 6:2:2) was eluted. This species was *N*-nonanoyl-α-D-mannopyranosylamine (or the corresponding *N*-dodecanoyl or *N*-octadecanoyl derivative) identical in each case (mp and NMR data) with the same compounds obtained by direct acylation of mannosylamine.[13] Continued elution with EtOAc–MeOH (6:4) gave the deprotected bis(sugar)amide R_f 0.41 (BuOH–AcOH–water, 6:2:2) as a foam.

***N*,*N*-Di(α-D-mannofuranosyl)nonanamide 14.** Yield 38%; $[\alpha]_D^{23}$ +62.8 (*c* 0.45, MeOH) [Found: $(M + Na)^+$, 504.242. $C_{21}H_{39}NNaO_{11}$ requires *m*/*z*, 504.242]. See Table 4 for NMR data.

***N*,*N*-Di(α-D-mannofuranosyl)dodecanamide 15.** Yield 38%; $[\alpha]_D^{23}$ +60.3 (*c* 0.4, MeOH) [Found: $(M + Na)^+$, 546.296. $C_{24}H_{45}NNaO_{11}$ requires *m*/*z*, 546.289.] See Table 4 for NMR data.

***N*,*N*-Di(α-D-mannofuranosyl)octadecanamide 16.** Yield 40%; $[\alpha]_D^{27}$ +45.4 (*c* 0.11, MeOH) [Found: $(M + Na)^+$, 630.381. $C_{30}H_{57}NNaO_{11}$ requires *m*/*z*, 630.383]. See Table 4 for NMR data.

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