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Unexpected furanose / pyranose equilibration of N-glycosyl sulfonamides, sulfamides and sulfamates

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De-protected *arabino* N-glycosyl sulfamides, sulfonamides and sulfamates were found to mutarotate and convert from the furanose to the thermodynamically more stable pyranose form in aqueous solution. The presence of a strongly electron withdrawing group in the alkyl chain stopped mutarotation and furanose / pyranose equilibration, allowing the isolation of the first unprotected furanose N-glycosyl sulfonamide.

Introduction

The intermediacy of glycosyl phosphates in important biological processes, combined with their instability, has led to the synthesis of a variety of glycomimetics in the search for new bioactives for the treatment of a variety of disease states and infectious agents.[1] As part of an on-going program[2] into the synthesis of mimics of decaprenolphosphoarabinose **1** (DPA, Scheme 1) as novel anti-mycobacterial agents, suitable isosteric replacement for the labile glycosyl phosphate was sought. DPA is the donor substrate used by arabinosyl transferases[3] during the stepwise assembly of mycobacterial arabinan, a key component of the mycobacterial cell wall. Metabolically stable analogues of DPA may inhibit arabinan biosynthesis, and therefore compromise mycobacterial viability.[4] Previous studies have demonstrated biological activity of configurationally stable S-glycosyl sulfonamides,[5] and sulfenamides.[6] By extrapolation one could envisage that N-glycosyl sulfonamides,[7] sulfamides,[8] and sulfamates may also be effective, and indeed may represent new classes of mimics of glycosyl phosphates. Several synthetic approaches to N-glycosyl sulfonamides,[9] in which the sulfonamide nitrogen is attached to the anomeric centre, have been reported,[10] and some conformational studies of these materials have also been undertaken.[11] It was therefore envisaged that the synthesis of sulfamides, sulfonamides and sulfamates of arabinofuranose, and elaboration with suitable hydrophobic chains, would produce mimics of DPA that may display useful anti-mycobacterial activity.

Results and Discussion

A series of *arabino* furanose N-glycosyl sulfamides, sulfonamides, and sulfamates was synthesised starting from D-arabinose **2** (Scheme 1), by conversion to methyl arabinofuranoside, benzylation, and acid catalysed hydrolysis to give the furanose hemiacetal **3**.[12] Although **3** has been previously described in the literature, following the unexpected formation of pyranose materials (*vide infra*) the structure of **3** was unambiguously confirmed as the furanose form by X-ray crystallography (Fig. 1).

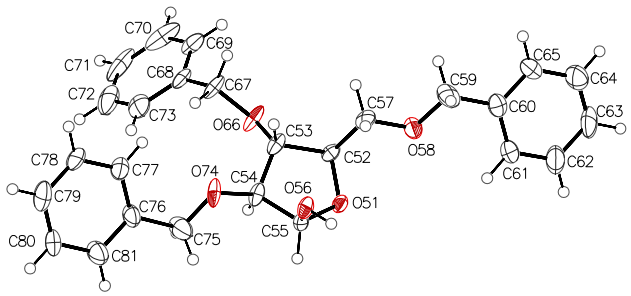

Fig. 1 X-ray structure of arabinofuranose hemiacetal **3**.†

TMS Triflate mediated glycosylation of **3** with decylsulfamide, methanesulfonamide and decyl sulfamate gave the furanose sulfamide **4a**, sulfonamide **4b** and sulfamate **4c** respectively. In each case a mixture of anomers was produced that could not be separated by chromatography. De-protection of sulfamide **4a** by catalytic hydrogenation in the presence of Pd/C yielded a mixture of compounds, which were partially separated by HPLC (see SI). NMR analysis of the individual components by HMBC and HMQC was ambiguous, and so the structure of the major component **5a** was confirmed by X-ray crystallography (Fig. 2). Surprisingly this revealed **5a** to be the α-pyranose isomer, in a $^1C_4$ conformation in which the anomeric nitrogen occupies an equatorial position, and in which the OH groups at positions 2 and 3 are also equatorial (OH-4 is axial). Fig. 2 additionally shows that the pyranose sulfamide **5a**

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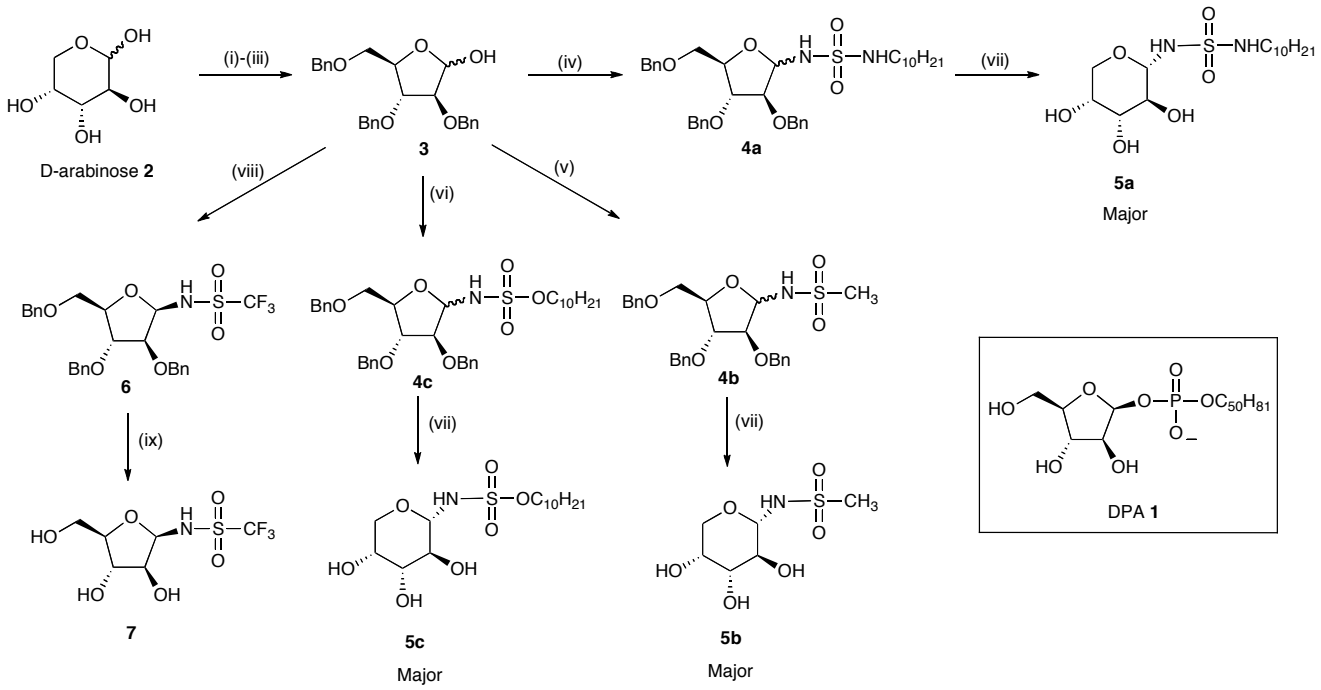

Scheme 1. Synthesis of N-glycosyl sulfamides, sulfonamides and sulfamates. *Reagents and conditions*: (i) AcCl, MeOH rt, 6 h, 80%, α:β, 4:1; (ii) NaH, BnBr, DMF, rt, 16 h, 87%; (iii) 80% aqueous AcOH, 115 °C, 48 h, 73%; (iv) $NH_2SO_2NHC_{10}H_{21}$, TMSOTf,CH_2Cl_2, 77%; (v) $NH_2SO_2CH_3$, TMSOTf, CH_2Cl_2, rt, 53%; (vi) $NH_2SO_2OC_{10}H_{21}$, TMSOTf, CH_2Cl_2, rt, 56%; (vii) H_2, Pd/C, MeOH, rt; **5a**, 46% from **4**a, plus 28% other isomers; **5b**, 33% from **4b**, plus 19% other isomers; **5c**, 45% from **4c**, plus 24% other isomers; (viii) $NH_2SO_2CF_3$, TMSOTf, Et_2O, rt, 44%; (ix) H_2, Pd/C, MeOH, rt; 65%.

is stabilised by an exo-anomeric effect (n-σ* donation of the N lone pair into the C1-O bond), a phenomenon that has been observed previously in a variety of N-glycosides.[13] The fact that a $^1C_4$ conformation is preferred, with the anomeric N equatorial, suggests that any *endo*-anomeric effect is relatively unimportant in overall energetic terms. The other components of the mixture produced during de-protection of **4a** were identified as the β-pyranose and the α- and β-furanose isomers (see SI).

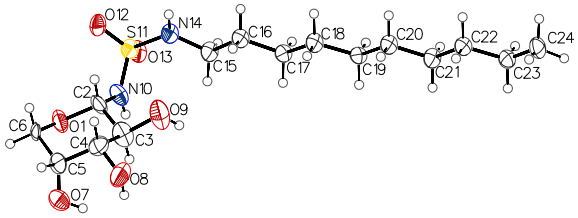

Fig. 2 X-ray structure of α-pyranose sulfamide **5a**.‡

A similar outcome was observed upon de-protection of both sulfonamide **4b** and sulfamate **4c**; in each case the major product of these reactions was the α-pyranose isomer. The structure of methyl sulfonamide **5b** was also confirmed by single X-ray crystallography (Fig. 3). Sulfonamide **5b** also adopts a $^1C_4$ conformation with two of the three OH groups equatorial, and the anomeric nitrogen also in an equatorial position; the N lone pair is orientated *anti* to the C1-O bond (C2-O1 in the X-ray structure) demonstrating operation of the *exo*-anomeric effect.

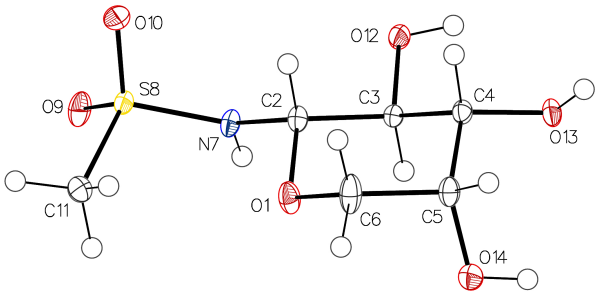

Fig. 3 X-ray structure of α-pyranose methyl sulfonamide **5b**.§

The mutarotation, configurational lability, and high reactivity of glycosyl amines are all well documented.[14] However the addition of an electron-withdrawing group on the anomeric nitrogen is usually sufficient to render these materials configurationally stable, e.g. as in the case of glycosyl amides, the key stable linkages by which carbohydrates are attached to

peptides in N-linked glycoproteins. The formation of the pyranose isomers from these reactions was therefore surprising.

Colinas has previously undertaken the synthesis of a variety of pyranose N-glycosyl sulfonamides, and reported in these cases that the β-anomers were the preferred reaction products, again indicating the relative unimportance of the *endo*-anomeric effect for these materials. However no mention of the configurational lability of either these materials or β-glycosyl sulfamides was reported.[10] Contrastingly the rapid conversion of α-N-glycosyl sulfonamides to their thermodynamically more stable β-anomers has been reported by Petillo,[9a] in a reaction that was catalysed either by acid or water; the rate of this interconversion was also dependent on protecting group regimes. It is also notable that although there are multiple reports of N-glycosyl sulfonamides in the literature, there are no previous descriptions of any de-protected furanose materials.

In order to investigate the stability and inter-conversions of these materials the isomers of sulfamide **5a** were stirred in water at pH 7 and analysed by HPLC after specific time intervals (for full details see SI). The pure α-pyranose anomer **5a** only produced minimal amounts of the other isomers after 48h. However in aqueous solution the other isomers (pure β-furanose and an α–furanose/β-pyranose mixture) all underwent interconversion to produce mixtures in which the α-pyranose isomer **5a** was predominant (~70%, see SI). Similar investigations into sulfonamide **5b** and sulfamate **5c** also indicated that in all cases mutarotation and interconversion of the furanose and pyranose forms occurred, again with the α-pyranose isomer being the thermodynamically preferred form.

The ring opening processes by which the furanose forms are converted into the pyranose forms must involve the formation of N-sulfonyl imine/iminium ion intermediates. Analogous glycosyl iminium ions have been demonstrated to be intermediates[15] in the biosynthetic interconversion of UDP-galactopyranose and UDP-galactofuranose catalysed by the FAD dependent UDP-galactopyranose mutase (UGM) enzymes that are essential for many pathogenic species of bacteria.

These facile inter-conversions provide an explanation for the absence of de-protected furanose glycosyl sulfonamides from the literature. However, DPA **1**, the donor substrate used by mycobacteria for cell wall assembly, is in the furanose form. The question therefore arose as to what structural modification could be made to an N-glycosyl sulfonamide so that pyranose / furanose equilibration would not occur at an appreciable rate under physiological conditions? Since equilibration involves opening of the furanose ring with assistance from the nitrogen lone pair, sulfonamides bearing a strongly electron withdrawing group may show a reduced tendency to isomerise. The N-glycosyl trifluoromethanesulfonamide **6** was therefore synthesised using a route analogous to that employed above (Scheme 1). De-protection of **6** by catalytic hydrogenation yielded a single compound identified as the β-furanose isomer **7**, which was demonstrated to be configurationally stable in aqueous solution (See SI). This compound therefore represents the first furanose N-glycosyl sulfonamide to be reported. Sulfonamide **7** was then assayed for biological activity against *M. smegmatis* using an Alamar Blue assay.[16] However, the measured MIC for this material was found to be greater than 1 mM, indicating the importance of an extended aliphatic chain for anti-mycobacterial activity.

Conclusions

N-Glycosyl sulfamides, sulfonamides and sulfamates of arabinose were found to be configurationally labile in aqueous solution and underwent mutatoration and furanose-pyranose equilibration; in the case of the *arabino* derivatives the α-pyranose form is thermodynamically preferred. In contrast an N-glycosyl trifluoromethylsulfonamide was shown to be configurationally stable, allowing the synthesis and characterisation of the first de-protected N-glycosyl sulfonamide of a furanose sugar.

Experimental

General methods

All reactions were carried out in oven-dried, nitrogen-purged glassware under an atmosphere of nitrogen. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 with a path length of 1 dm. Concentrations are given in g / 100 mL. Infrared spectra were recorded on a Perkin-Elmer Spectrum One. Proton and carbon nuclear magnetic resonance (δ_H, δ_C) spectra were recorded on Agilent Technologies 400 MR (400 MHz) or Varian VNMR500 (500 MHz) spectrometers. All chemical shifts are quoted on the δ-scale in ppm using residual solvent as an internal standard. High-resolution mass spectra were recorded with a Bruker maXis 3G UHR-TOF mass spectrometer. Thin Layer Chromatography (t.l.c.) was carried out on Merck silica gel $60F_{254}$ aluminium-backed plates. Visualisation of the plates was achieved using a UV lamp (λ_{max} = 254 or 365 nm), and/or 5% w/v ammonium molybdate in 2 M sulfuric acid. Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Reverse phase high performance liquid chromatography (RP-HPLC) was performed on a Dionex P680 HPLC instrument with a Phenomenex Luna C 18(2) 100 A column (5 μm, 10 x 250 mm) at 15 °C. The column was eluted with a gradient of MeCN/H_2O at a flow rate of 1 $mLmin^{-1}$. Unless preparative details are provided, all reagents were commercially available or made following literature procedures. "Petrol" refers to the fraction of light petroleum ether boiling in the range of 40-60 °C.

Methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside.[17] Acetyl chloride (3.08 mL, 43 mmol) was added drop-wise to a solution of D-arabinose **2** (5.0 g, 33 mmol) in methanol (100 mL) under nitrogen. The reaction was stirred for 3 hours at room temperature. After this time, t.l.c. (DCM: MeOH, 4:1) indicated the formation of two products, a major product (methyl α,β-D-arabinofuranoside, R_f 0.5) and the complete consumption of starting material (R_f 0.2). The reaction mixture

was neutralized by adding solid K_2CO_3 (~7 g), filtered, concentrated *in vacuo,* and the residue was co-evaporated with toluene (3 x 50 mL) to afford a crude mixture of methyl α,β-D-arabinofuranoside and methyl α,β-D-arabinopyranoside as a brown oil which was used in the next step without further purification. Sodium hydride (60 % dispersion in mineral oil, 8.2 g, 205 mmol) was added drop-wise to a solution of the mixture produced above (5.6 g, 34 mmol) in DMF (60 mL) under nitrogen. The reaction was stirred for 1 hour and then cooled to 0 °C. Benzyl bromide (24.3 mL, 205 mmol) was then added drop-wise. The reaction mixture was warmed to room temperature and then stirred for 16 hours. After this time, t.l.c. (petrol: ethyl acetate, 7:1) indicated the formation of a major product (R_f 0.2), and the complete consumption of starting material (R_f 0.0). The reaction was cooled in an ice bath, quenched by the addition of methanol (90 mL), and then concentrated *in vacuo*. The residue was dissolved in diethyl ether (50 mL), and washed with brine (3 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil, which was purified by flash chromatography (petrol: ethyl acetate, 7:1) to afford methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside (7.7 g, 54 %, α:β, 3:1) as a clear oil. δ_H (500 Hz, $CDCl_3$) α-anomer: 3.42 (3H, s, OC$\underline{H}_3$), 3.64 (2H, at, *J* 4.8 Hz, H-5, H-5'), 3.94 (1H, dd, $J_{3,4}$ 6.2 Hz, $J_{2,3}$ 2.8 Hz, H-3), 4.03 (1H, m, H-2), 4.25 (1H, td, $J_{4,5}$ 5.4 Hz, $J_{4,5'}$ 5.4 Hz, $J_{3,4}$ 4.8 Hz, H-4), 4.56-4.59(6H, m, PhC$\underline{H}_2$), 4.98 (1H, s, H-1), 7.26-7.39 (15H, m, Ar-H); β anomer: 3.35 (3H, s, OCH_3), 3.56 (1H, dd, $J_{5,5'}$ 8.9 Hz, $J_{4,5}$ 6.0 Hz, H-5), 3.61 (1H, d, $J_{4,5'}$ 5.4 Hz, H-5'), 4.08-4.12 (1H, m, H-4), 4.13-4.14 (1H, m, H-2), 4.15-4.17 (1H, m, H-3), 4.51 (5H, ABq, *J* 9.8 Hz, PhC$\underline{H}_2$) 4.62-4.66 (1H, m, PhC$\underline{H}_2$), 4.76 (1H, d, *J* 4.2 Hz, H-1), 7.26-7.39 (15H, m, Ar-H); HRMS (ESI) calculated for $C_{27}H_{30}NaO_5$ ($M+Na^+$) 457.1991. Found 457.1984.

2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranose 3.[12] Methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside (7.7 g, 18 mmol) was dissolved in a mixture of water and acetic acid (100 mL, 1:4, v/v), and then stirred at 115 ° C for 2 days. After this time, t.l.c. (petrol: ethyl acetate 3:1) indicated the formation of a single product (R_f 0.2), and the complete consumption of starting material (R_f 0.6). The reaction was quenched by the addition of ice water (100 mL), and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil, which was purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford hemiacetals **3** (4.8 g, 64 %, α:β, 1:1) as a white crystalline solid. δ_H (500 MHz, $CDCl_3$) α anomer: 3.52-3.62 (2H, m, H-5, H-5'), 3.93-3.95 (1H, m, H-3), 3.98-3.99 (1H, m, H-2), 4.46-4.48 (1H, m, H-4), 4.51-4.67 (6H, m, PhC$\underline{H}_2$), 5.40 (1H, s, H-1), 7.26-7.37 (15H, m, Ar-H); β anomer: 3.52-3.62 (2H, m, H-5, H-5'), 4.02 (1H, d, *J* 4.5 Hz, H-2), 4.09 (1H, aq, *J* 4.3 Hz, H-4), 4.17 (1H, t, *J* 4.5 Hz, H-3), 5.33 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 4.51-4.67 (6H, m, PhC$\underline{H}_2$), 7.26-7.37 (15H, m, Ar-H); HRMS (ESI) calculated for $C_{26}H_{28}NaO_5$ ($M+Na^+$) 443.1834. Found 443.1851.

***N*-(Decyl)-*N*'-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide 4a.** Hemiacetals **3** (400 mg, 0.9 mmol), and *N*-(decyl)-sulfamide (0.27 g, 1 mmol) were stirred at room temperature in dry DCM (15 mL) under nitrogen. TMSOTf (0.17 mL) was added drop-wise, and the mixture stirred for 16 hours. After this time, t.l.c (petrol: ethyl acetate, 2:1) indicated the formation of a single product (R_f 0.5), and the complete consumption of starting material (R_f 0.3). The reaction mixture was then neutralized by the drop-wise addition of excess triethylamine (0.3 mL). The reaction mixture was filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo* to give a residue which was purified by flash chromatography (petrol: ethyl acetate, 2:1) afford furanose sulfamide **4a** (0.47 g, 77 %, α:β, 1:1) as a waxy yellow solid. υ_{max} (neat) 3280 (w, NH), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.89 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.24-1.29 (14H, m, 7 x C$\underline{H}_2$), 1.48-1.53 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.98-3.03 (2H, m, C$\underline{H}_2$NH), 3.46-3.50 (1H, m, H-5), 3.58 (1H, dd, $J_{5,5'}$ 8.6 Hz, $J_{4,5'}$ 6.7 Hz, H-5'), 3.95-3.97 (1H, m, H-3), 3.98-4.02 (1H, m, H-2), 4.34 (1H, at, *J* 6.6 Hz, H-4), 4.38-4.63 (6H, m, Ph-C$\underline{H}_2$), 5.42 (1H, d, $J_{NH,1}$ 10.5 Hz, H-1), 5.54 (1H, d, $J_{NH,1}$ 11.0 Hz N$\underline{H}$), 7.15-7.40 (15H, m, Ar-H); β anomer: 0.89 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.24-1.29 (14H, m, C$\underline{H}_2$), 1.48-1.53 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.98-3.03 (2H, m, C$\underline{H}_2$NH), 3.52-3.54 (1H, m, H-5, H-5'), 3.95-3.97 (1H, m, H-3), 3.98-4.02 (1H, m, H-2), 4.05-4.06 (1H, m, H-4), 4.38-4.63 (6H, m, Ph-C$\underline{H}_2$), 5.37 (1H, dd, $J_{NH,1}$ 10.2 Hz, $J_{1,2}$ 4.3 Hz, H-1), 5.52 (1H, d, $J_{NH,1}$ 10.8 Hz N$\underline{H}$), 7.15-7.40 (15H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.1 (q, CH_3), 22.6, 26.7, 29.2, 29.3, 29.4, 29.5, 29.5, 31.8, (8 x t, 8 x CH_2), 43.4 (t, $\underline{C}H_2$NH), 70.1 (t, C-5α, C-5β), 71.7, 71.8, 71.9, 72.3, 73.3, 73.4 (6 x t, Ph-$\underline{C}H_2$), 80.8 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.3 (d, C-3β), 83.3(d, C-4α), 84.2 (d, C-1β), 84.8 (d, C-3α), 88.2 (d, C-1α), 127.7, 127.8, 127.9, 128.5, 128.6 (5 x d, 5 x Ar-C), 136.7, 137.4, 137.9 (3 x s, 3 x Ar-C); HRMS (ESI) calculated for $C_{36}H_{50}N_2NaO_6S$ ($M+Na^+$) 661.3287. Found 661.3288.

***N*-(Decyl)-*N*'-(α-D-arabinopyranosyl)sulfamide 5a.** 10 % Activated Pd/C (20 mg) was added to a solution of furanose sulfamide **4a** (80 mg, 0.1 mmol) in methanol. The flask was evacuated and purged with nitrogen five times, before being placed under an atmosphere of hydrogen. The solution was then stirred for 16 hours at room temperature. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.0), and the complete consumption of starting material (R_f 0.9). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD) to afford α-pyranose sulfamide **5a** as the major product (21 mg, 45 %) as white solid; $[\alpha]_D^{20}$ -14 (*c*, 0.5 in CH_3OH); m.p. 103-105 °C (MeOH/diethyl ether); υ_{max} (neat) 3288 (br s, OH), 1340 (s, S=O), 1157 (s, S=O) cm^{-1}; δ_H (500 MHz, CD_3CN) 0.90 (3H, t,

J 6.7 Hz, C$\underline{H}_3$), 1.29-1.36 (14H, m, 7 x C$\underline{H}_2$), 1.49-1.53 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.95-2.99 (2H, t, C$\underline{H}_2$NH), 3.44 (1H, at, *J* 7.3 Hz, H-2), 3.53-3.56 (2H, m, H-3, H-5), 3.77-3.80 (1H, m, H-4), 3.84 (1H, d, $J_{4,5'}$ 4.0 Hz, H-5'), 4.27 (1H, d, $J_{1,2}$ 7.6 Hz, H-1), 5.03 (1H, t, $J_{NH,CH}$ 5.8 Hz, N$\underline{H}$CH$_2$) ; δ_C (100 MHz, CD_3OD) 13.0 (q, CH_3), 22.3, 26.5, 29.0, 29.3, 31.6 (5 x t, 8 x CH_2), 42.6 (t, $\underline{C}H_2$NH), 66.7 (t, C-5), 68.3 (d, C-4), 70.0 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{15}H_{32}N_2NaO_6S$ (M+Na$^+$) 391.1879. Found 391.1881.

***N*-(2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranosyl)methanesulfonamide 4b.** Hemiacetals **3** (100 mg), and methanesulfonamide (34 mg, 0.3 mmol) were stirred at room temperature in dry DCM (15 mL) under nitrogen. TMSOTf (40 µl) was added drop-wise, and the mixture stirred for 16 hours. After this time, t.l.c (petrol: ethyl acetate, 2:1) indicated the formation of a product (R_f 0.45), and the complete consumption of starting material (R_f 0.3). The reaction was then neutralized by the drop-wise addition of excess triethylamine (0.1 mL). The reaction mixture was filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo*. Purification by flash chromatography (petrol:ethyl acetate, 2:1) afforded furanose sulfonamide **4b** (63 mg, 53 %, α:β, 2:1) as a yellow waxy solid. υ_{max} (neat) 3267 (w, NH), 1328 (s, S=O), 1159 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 3.07 (3H, s, C$\underline{H}_3$), 3.47 (1H, at, *J* 9.2 Hz, H-5), 3.58 (1H, dd, $J_{5,5'}$ 9.4 Hz, $J_{4,5'}$ 5.9 Hz, H-5'), 3.94-3.97 (1H, m, H-3), 4.02-4.05 (1H, m, H-2), 4.34 (1H, at, *J* 4.0 Hz, H-4) 4.42-4.46 (1H, m, Ph-C$\underline{H}_2$), 4.49-4.57 (5H, m, PhC$\underline{H}_2$), 5.48 (1H, d, $J_{NH,1}$ 11.0 Hz, H-1), 5.63 (1H, d, *J* 11.2 Hz, NH), 7.21-7.33 (15H, m, Ar-H); β anomer: 3.07 (3H, s, C$\underline{H}_3$), 3.52 (2H, at, *J* 4.1 Hz, H-5, H-5'), 3.94-3.97 (1H, m, H-3), 4.02-4.05 (2H, m, H-2, H-4), 4.42-4.46 (1H, m, Ph-C$\underline{H}_2$), 4.49-4.57(5H, m, PhC$\underline{H}_2$), 5.42 (1H, dd, $J_{1,2}$ 4.5 Hz, $J_{NH,1}$ 10.4 Hz, H-1), 5.57 (1H, d, $J_{NH,1}$ 10.2 Hz, NH), 7.21-7.33 (15H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 42.9 (q, CH_3), 69.8, 70.1 (2 x t, C-5α, C-5β), 71.7, 71.8, 71.9, 72.3, 73.3, 73.4 (6 x t, Ph-$\underline{C}H_2$), 80.9 (d, C-4β), 81.1 (d, C-2β), 81.9 (C-3β), 82.3 (d, , C-2α), 83.3 (d, C-4α), 83.9 (d, C-1β), 84.7 (d, C-3α), 87.9 (d, C-1α), 127.7, 127.9, 128.4, 128.5, 128.7 (5 x d, 5 x Ar-C), 136.6, 136.8, 137.9 (3 x s, 3 x Ar-C); HRMS (ESI) calculated for $C_{27}H_{31}NNaO_6S$ (M+Na$^+$) 520.1770. Found 520.1767.

***N*-(α-D-Arabinopyranosyl)methanesulfonamide 5b.** 10 % Activated Pd/C (15 mg) was added to a solution of furanose sulfonamide **4b** (60 mg, 0.1 mmol) in methanol. The flask was evacuated and purged with nitrogen five times, before being placed under an atmosphere of hydrogen. The solution was then stirred for 16 hours at room temperature. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.0), and the complete consumption of starting material (R_f 0.9). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a isocratic flow of 20 % B; column oven: 15 °C; detection: CAD) to afford α-pyranose sulfonamide **5b** as the major product (9 mg, 33 %) as white solid. α-anomer: m.p. 178-180 °C (MeOH/diethyl ether); $[\alpha]_D^{20}$ -16 (*c*, 0.5 in CH_3OH); υ_{max} (neat) 3280 (br s, OH), 1328 (s, S=O), 1159 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 3.01 (3H, s, C$\underline{H}_3$), 3.48 (1H, at, $J_{1,2}$ 7.9 Hz, H-2), 3.53-3.59 (2H, m, H-3, H-5), 3.79-3.84 (1H, m, H-4, H-5'), 4.36 (1H, d, $J_{1,2}$ 7.6 Hz, H-1); δ_C (100 MHz, CD_3OD) 42.0 (q, CH_3), 66.9 (d, C-5), 68.3 (d, C-4), 69.8 (d, C-2), 73.4 (d, C-3), 85.2 (d, C-1); HRMS (ESI) calculated for $C_6H_{13}NNaO_6S$ (M+Na$^+$) 250.0361. Found 250.0365.

Decyl-*N*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamate 4c. Hemiacetals **3** (100 mg, 0.2 mmol), and decyl sulfamate (68 mg, 0.3 mmol) were stirred at room temperature in dry DCM (15 mL) under nitrogen. TMSOTf (40 µl) was added drop-wise, and the mixture stirred for 16 hours. After this time, t.l.c. (petrol:ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.5), and the complete consumption of starting material (R_f 0.2). The reaction mixture was then neutralized by the drop-wise addition of excess triethylamine (0.3 mL). The reaction mixture was filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo* to give a residue which was purified by flash chromatography (petrol:ethyl acetate, 2:1) to afford furanose sulfamate **4c** (86 mg, 56 %, α:β, 1:1) as a waxy yellow solid. υ_{max} (neat) 3280 (w, NH), 1365 (s, S=O), 1181 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.90 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.21-1.43 (14H, m, C$\underline{H}_2$), 1.64-1.74 (2H, m, OCH$_2$C$\underline{H}_2$), 3.44-3.46 (1H, m, H-5), 3.54-3.64 (1H, m, H-5'), 4.04-4.09 (1H, m, H-3), 4.12 (2H, t, *J* 6.7 Hz, OC$\underline{H}_2$), 4.16-4.22 (1H, m, H-2), 4.38 (1H, t, *J* 4.0 Hz, H-4), 4.43-4.48 (2H, m, Ph-C$\underline{H}_2$), 4.54 (4H, ABq, *J* 12.0 Hz, Ph-C$\underline{H}_2$), 5.44 (1H, d, $J_{NH,1}$ 12.0 Hz, H-1), 5.73 (1H, d, $J_{1,NH}$ 10.6 Hz, N$\underline{H}$), 7.22-7.37 (15H, m, Ar-H); β anomer: 0.90 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.21-1.43 (14H, m, C$\underline{H}_2$), 1.64-1.74 (2H, m, OCH$_2$C$\underline{H}_2$), 3.49-3.54 (2H, m, H-5, H-5'), 4.04-4.09 (1H, m, H-3), 4.12 (2H, t, *J* 6.7 Hz, OC$\underline{H}_2$), 4.16-4.22 (2H, m, H-2, H-4), 4.54 (6H, m, Ph-C$\underline{H}_2$), 5.04 (1H, dd, $J_{1,2}$ 3.9 Hz, $J_{1,NH}$ 10.4 Hz, H-1), 5.79 (1H, d, $J_{1,NH}$ 10.2 Hz, N$\underline{H}$), 7.22-7.37 (15H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.1 (q, CH_3), 22.7, 25.5, 28.7, 29.1, 29.3, 29.4, 29.5, 31.8 (8 x t, 8 x CH_2), 69.7, 69.9 (2 x t, C-5α, C-5β), 71.2 (t, CH_2O), 71.4, 71.7, 71.9, 72.3, 73.3, 73.6 (6 x t, Ph-$\underline{C}H_2$), 80.8, 80.8 (2 x d, C-2β, C-4β), 82.0 (d, C-3β), 82.1 (d, C-2α), 83.3 (d, C-4α), 84.1 (d, C-1β), 84.7 (d, C-3α), 88.1 (d, C-1α), 127.6, 127.8, 127.9, 128.5, 128.6 (5 x d, 5 x Ar-C), 136.7, 137.4, 137.5 (3 x s, 3 x Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{36}H_{49}NNaO_7S$ (M+Na$^+$) 662.3127. Found 662.3121.

Decyl-*N*-(α-D-arabinopyranosyl)sulfamate 5c. 10 % Activated Pd/C (20 mg) was added to a solution of furanose sulfamate **4c** (80 mg, 0.1 mmol) in methanol. The flask was evacuated and purged with nitrogen five times, before being placed under an atmosphere of hydrogen. The solution was then stirred for 16 hours at room temperature. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f

0.0), and the complete consumption of starting material (R_f 0.9). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven 15 °C; detection: CAD) to afford α-pyranose sulfamate **5c** as the major product (21 mg, 45 %) as white solid. $[\alpha]_D^{20}$ -5.4 (*c*, 0.5 in CH_3OH); m.p. 138-140 °C (MeOH/diethylether); υ_{max} (neat) 3334 (br s, OH), 1344 (s, S=O), 1178 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.91 (3H, t, *J* 6.5 Hz, $C\underline{H}_3$), 1.27-1.39 (14H, m, $C\underline{H}_2$), 1.66-1.74 (2H, m, $OCH_2C\underline{H}_2$), 3.47 (1H, at, *J* 7.8 Hz, H-2), 3.52-3.58 (2H, m, H-3, H-5), 3.77-3.80 (1H, m, H-4), 3.83 (1H, d, $J_{4,5'}$ 2.7 Hz, H-5'), 4.15 (2H, t, *J* 6.5 Hz, $C\underline{H}_2O$), 4.31 (1H, d, $J_{1,2}$ 7.8 Hz, H-1); δ_C (100 MHz, CD_3OD) 13.0 (q, CH_3), 22.3, 25.2, 28.4, 29.2, 31.8 (5 x t, 8 x CH_2), 67.1 (t, C-5), 68.4 (d, C-4), 69.9 (d, C-2), 70.3 (t, CH_2O), 73.5 (d, C-3), 85.3 (d, C-1); HRMS (ESI) calculated for $C_{15}H_{31}NNaO_7S$ ($M+Na^+$) 392.1719. Found 392.1707.

1,1,1-Trifluoro-*N*-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)methanesulfonamide 6. Hemiacetals **3** (100 mg, 0.2 mmol), and trifluoromethanesulfonamide (71 mg, 0.3 mmol.) were stirred at room temperature in dry diethyl ether (15 mL) under nitrogen. TMSOTf (40 µl) was added drop-wise, and the mixture stirred for 16 hours. After this time, t.l.c. (petrol:ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.4), and complete consumption of starting material (R_f 0.2). The reaction mixture was then neutralized by the drop-wise addition of excess triethylamine (0.1 mL), filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo* to give a residue which was purified by flash chromatography (petrol: ethyl acetate, 3:1) afford β-furanose sulfonamide **6** (58 mg, 44 %) as a white solid. m.p. 110-113 °C (DCM/petrol); $[\alpha]_D^{20}$ +9.0 (*c*, 0.35 in CH_3OH); υ_{max} (neat) 3386 (w, NH), 1382 (s, S=O), 1188 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 3.59-3.62 (2H, m, H-5, H-5'), 3.90 (1H, dd, $J_{3,4}$ 6.3 Hz, $J_{2,3}$ 2.3 Hz, H-3), 4.04-4.05 (1H, m, H-2), 4.14 (1H, aq, *J* 5.5 Hz, H-4), 4.43-4.58 (6H, m, Ph-CH_2), 5.38 (1H, s, H-1), 7.24-7.33 (15H, m, Ar-H); δ_C (100 MHz, CD_3OD) 69.6 (t, C-5), 71.5, 71.7, 72.9 (3 x t, Ph-$\underline{C}H_2$), 81.5 (d, C-4), 83.6 (d, C-3), 87.4 (d, C-2), 101.9 (d, C-1), 119.8 (q, $J_{C,F}$ 334.1 HZ, CF_3), 127.3, 127.5, 127.6, 127.9, 128.0 (5 x d, 5 x Ar-C), 137.4, 137.8, 137.9 (3 x s, 3 x Ar-C); δ_F (376.6 MHz, CD_3OD) -81.59; HRMS (ESI) calculated for $C_{27}H_{28}F_3NNaO_6S$ ($M+Na^+$) 574.1487. Found 574.1478.

1,1,1-Trifluoro-*N*-(β-D-arabinofuranosyl)methanesulfonamide 7. 10 % Activated Pd/C (10 mg) was added to a solution of protected furanose sulfonamide **6** (40 mg, 0.1 mmol) in methanol. The flask was evacuated and purged with nitrogen five times, before being placed under an atmosphere of hydrogen. The solution was stirred for 16 hours at room temperature. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.0), and the complete consumption of starting material (R_f 0.9). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50 -80 % B; column oven 15 °C; detection: CAD) to afford β-furanose sulfonamide **7** (13 mg, 65 %) as waxy yellow solid. $[\alpha]_D^{20}$ +36.4 (*c*, 0.5 in CH_3OH); υ_{max} (neat) 3288 (br s, OH), 1316 (s, S=O), 1150 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 3.64 (1H, dd, $J_{4,5}$ 5.8 Hz, $J_{5,5'}$ 11.7 Hz, H-5), 3.74 (1H, dd, $J_{4,5'}$ 4.3 Hz, $J_{5,5'}$ 12.5 Hz, H-5'), 3.84-3.86 (1H, dd, $J_{3,4}$ 5.7 Hz, $J_{2,3}$ 3.3 Hz, H-3), 3.97-4.00 (1H, aq, *J* 5.1 Hz, H-4), 4.02 (1H, m, H-2), 5.17 (1H, s, H-1); δ_C (100 MHz, CD_3OD) 61.7 (t, C-5), 77.4 (d, C-3), 81.9 (d, C-2), 84.8 (d, C-4), 103.9 (d, C-1), 118.3 (q, $J_{C,F}$ 324.2 HZ, CF_3); δ_F (376.6 MHz, CD_3OD) -81.59; HRMS (ESI) calculated for $C_6H_{10}F_3NNaO_6S$ ($M+Na^+$) 304.0079. Found 304.0090.

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Notes and references

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§ CCDC 1029227 (**5b**)

Electronic Supplementary Information (ESI) available: full experimental details for the synthesis and characterisation of all compounds, including associated spectra and X-ray crystal data of complexes (CIF), together with HPLC investigations into furanose/pyranose equilibration. See DOI: 10.1039/c000000x/

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