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Glucofuranosylation with penta-*O*-propanoyl-β-D-glucofuranose

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Dedicated to Professor Derek Horton on the occasion of his 70th birthday

Abstract

Readily available, crystalline penta-*O*-propanoyl-β-D-glucofuranose is shown to be a suitable glycosylating agent for the acid-catalysed, direct synthesis of *O*-, *S*- and *N*-glucofuranosyl compounds. β-Linked products are formed with good selectivity. Reaction with cyanotrimethylsilane gave the 1,2-*O*-(1-cyanopropylidene)acetal rather than the *C*-glycosyl cyanide. By selective acid-catalysed hydrolysis, the title compound was converted to the 1-hydroxy analogue from which the trichloroacetimidates were made as further potential glycosylating agents.

Keywords: Glycosylation; D-Glucofuranosides; 1-Thio-D-glucofuranosides; *N*-Glucofuranosylamine

1. Introduction

A notable feature of the natural occurrence of the common monosaccharides is that while several, notably D-fructose, D-galactose, D-arabinose and most significantly D-ribose and its 2-deoxy derivative, frequently occur in the furanosyl form, the same does not apply to the most common natural sugar, D-glucose. Whether this is because the five-membered ring forms of this sugar are energetically less favoured relative to the six-membered pyranoid forms more than is the case for all other sugars is a matter for speculation.

Only a few D-glucofuranosyl compounds appear to have been isolated from natural sources (mostly plant), and some of the methods used for identifying their sugar ring sizes, for example their relative stability in acid media, may have been unreliable. Examples are cardenolide[1] and flavone[2] glucosides and the unusual *Agrobacterium tumefaciens* product Agrocin 84 that inhibits crown gall disease, a plant cancer.[3] In this last compound D-glucofuranose is linked via the anomeric centre through phosphate to the 6-amino group of an adenine nucleoside derivative. Agrocin 84 is therefore somewhat structurally related to the sugar nucleotides, for example uridine diphosphoglucose (UDPG). Otherwise, D-glucofuranose occurs in the fruit of the cuckoo-pint plant linked to N-7 of a purine derivative in an analogue of the natural nucleosides,[4] and *C*-linked in a *C*-glycosylchromone from the leaves of a species of *Aloe*[5] and in metabolites of tannins in the heartwood of Japanese Chestnut.[6] Synthetic studies of relevant aryl *C*-glucofuranosides have been reported.[7]

In consequence of the above there seems to be little incentive to synthesise glucofuranosyl compounds for the purpose of producing bioactive natural products or their analogues. However, there is reason to believe that some, like galactofuranosyl derivatives,[8] could be antigenic in nature, and, presumably, some carbohydrate-processing enzymes could bind furanosyl derivatives as substrate analogues and could perhaps be selectively inhibited by them. Otherwise, attached to appropriate bioactive compounds, furanoid units could conceivably increase bioavailability without being vulnerable to such enzymes as glucosidases. Under acidic conditions they would be particularly susceptible to hydrolysis, and that property could conceivably also be exploited.

Furanosyl glycosides can be made using classical methods[9] such as the Koenigs–Knorr reaction, or by

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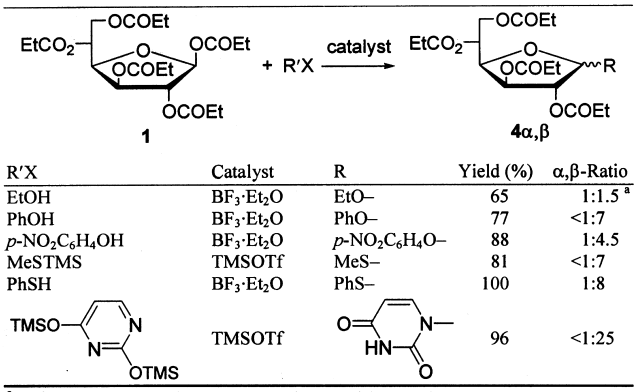
more modern procedures[10] based, for example, on *O*-substituted thio-, seleno- or *n*-pentenyl furanosides, or glycosyl trichloroacetimidates. Useful precursors for all these glycosylating agents are the corresponding glycofuranosyl peresters, crystalline and anomerically pure examples of which are rare but particularly attractive.

In the D-glucose series crystalline 1-*O*-acetyl-2,3,5,6-tetra-*O*-benzoyl-β-D-glucose can be made efficiently from ethyl tetra-*O*-benzoyl-1-thio-α-D-glucofuranoside,[11] the preparation of which requires three steps from glucose. We have recently reported the preparation of the crystalline β-penta-*O*-propanoate in 58% yield in a two-step, one-pot procedure involving the use of boric acid to lock the sugar in the furanose ring form.[12]

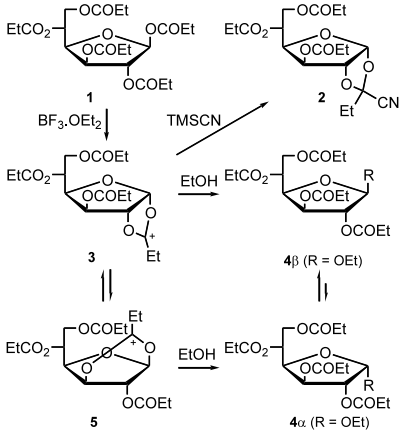
In the report of the preparation of the pentapropanoate,[12] it was shown that phenyl β-D-glucofuranoside could be made by application of the Helferich reaction to the syrupy, anomerically mixed penta-*O*-acetyl-D-glucofuranoses derived from the free sugar by the boric acid procedure. We now report the use of the crystalline penta-*O*-propanoyl-β-D-glucofuranose in the preparation of representative *O*-, *S*- and *N*-glycosylated compounds, 1,2-*O*-(1-cyanopropylidene)-3,5,6-tri-*O*-propanoyl-α-D-glucofuranose, 2,3,5,6-tetra-*O*-propanoyl-D-glucose and the derived mixed glucofuranosyl trichloroacetimidate tetraesters.

Table 1
Glycosylations with 1,2,3,5,6-penta-*O*-propanoyl-β-D-glucofuranose



R′X	Catalyst	R	Yield (%)	α,β-Ratio
EtOH	$BF_3{\cdot}Et_2O$	EtO–	65	1:1.5 [a]
PhOH	$BF_3{\cdot}Et_2O$	PhO–	77	<1:7
p-$NO_2C_6H_4OH$	$BF_3{\cdot}Et_2O$	*p*-$NO_2C_6H_4O$–	88	1:4.5
MeSTMS	TMSOTf	MeS–	81	<1:7
PhSH	$BF_3{\cdot}Et_2O$	PhS–	100	1:8
	TMSOTf		96	<1:25

[a] α,β-Ratio = 1:2.8 when excess catalyst used (see text).



Scheme 1.

2. Results and discussion

Penta-*O*-propanoyl-β-D-glucofuranose was treated separately with ethanol, phenol, 4-nitrophenol, thiophenol, (methylthio)trimethylsilane and trimethylsilylated uracil (1.5–3 mol equiv) in dichloromethane or acetonitrile (for the uracil derivative) in the presence of boron trifluoride etherate (0.5–1.2 mol equiv) or trimethylsilyl triflate (0.3–2 mol equiv for the silylated nucleophiles). The conversions were efficient and showed β-selectivities ranging from >25:1 for the uracil derivatives to 1.5:1 in the case of the ethyl glycosides (Table 1). In this latter example, however, when proportionately more ethanol (5 instead of 2 mol equiv) and more catalyst (6 instead of 1 mol equiv) were used, the β,α-ratio improved to 2.8:1. These results show that, with the ethyl glycosides, at least, the unexpected α-product is present in considerable proportions at early stages in the reaction. This could be accounted for as indicated in Scheme 1. Initial ionisation of the starting perester (**1**) at the anomeric centre with neighbouring group participation would give the acyloxonium ion **3**, the precursor of the β-glycoside **4**β. However, rearrangement of ion **3** to ion **5** could lead to kinetically favoured products **4**α. No direct evidence for the participation of ion **5**, for example the isolation of 1,3-orthoesters, was found.

Deacylations of the glycosidic tetraesters (except in the case of the methyl β-1-thioglycoside tetraester which was not deacylated) were effected efficiently by standard, base-catalysed reactions. Anomerically pure β-glycosides were isolated in the majority of cases.

In an analogous reaction of β-D-glucofuranose pentapropanoate with trimethylsilyl cyanide[13] as nucleophile, in the presence of boron trifluoride etherate, no cyano *C*-glucoside was obtained; instead the 1,2-*O*-(1-cyanopropylidene)acetal (**2**) was isolated in low yield (24%) in consequence of attack by the nucleophile at the ionic centre of the acyloxonium species **3**. That the product was a 1,2- and not a 1,3-cyanopropylidene derivative was shown by the chemical shifts of H-2 and H-3 (δ 4.71 and 5.41, respectively) which revealed that the deshielding ester group was at C-3 and that the new ring involved C-2.

Selective hydrolysis of the pentapropanoate, which could have been attempted using a wide range of catalysts,[14] occurred in acid conditions in the presence

of water, and the resulting α,β-2,3,5,6-tetraesters (**4**α,β; R = OH, α:β 1:1.5) were converted into the corresponding trichloroacetimidates (**4**α,β; R = OC(=NH)CCl_3, α:β 1:1.5)[15] by treatment with trichloroacetonitrile and DBU in acetonitrile. Although these products are rather reactive, they can serve potentially as other glucofuranosylating agents.

3. Experimental

General methods.—1,2,3,5,6-Penta-*O*-propanoyl-β-D-glucofuranose[12] is available from Aldrich Chemical Co. (cat. no. 53,227-4) and in bulk from New Zealand Pharmaceuticals Ltd (www.nzp.co.nz). Analytical TLC was carried out on pre-coated 0.25 mm thick E. Merck Silica Gel 60 F_{254} plates and visualisation was by thermal development after dipping in ammonium molybdate and cerium(IV) sulfate in dil H_2SO_4 or anisaldehyde in EtOH containing H_2SO_4. Flash column chromatography was conducted using Silica Gel 60 (40–60 μm). Melting points were measured on a Reichert hot-stage microscope and are uncorrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}. Microanalyses were carried out at the Campbell Microanalytical Laboratory, University of Otago. ^1H and ^{13}C NMR spectra were recorded at 300 or 400 MHz and 75 or 100 MHz, respectively. The assignments of peaks were carried out with the assistance of DEPT and COSY (^1H,^1H and ^1H,^{13}C) experiments. Mass spectra were recorded by Mr. J. M. Allen, Horticultural and Food Research Institute of New Zealand, in EI or FAB positive-ion modes at 15 keV with ionisation effected by use of a caesium ion gun in a *p*-nitrobenzyl alcohol–CH_2Cl_2 or glycerol–MeOH matrix. Petroleum spirits refers to the fraction with bp 60–80 °C.

Ethyl α- and β-D-glucofuranoside.—1,2,3,5,6-Penta-*O*-propanoyl-β-D-glucofuranose (**1**)[12] (220 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (2.5 mL), and anhyd EtOH (50 μL, 0.89 mmol) was added, followed by $BF_3{\cdot}OEt_2$ (60 μL, 0.47 mmol) dropwise. After 24 h at 20 °C, the solution was diluted with CH_2Cl_2 (100 mL), washed with $NaHCO_3$ (satd aq, 30 mL) and water and was dried ($MgSO_4$) and concentrated in vacuo. Flash silica chromatography of a portion of the residue (150 mg), elution with 1:9 EtOAc–petroleum ether, gave ethyl 2,3,5,6-tetra-*O*-propanoyl-α,β-D-glucofuranoside (**4**α,β; R = OEt) as a colourless syrup (0.92 mg, 65%). The ^1H and ^{13}C NMR spectra indicated that the unpurified product consisted of > 95% of these glycosides (α,β 1:1.5). A mixture of these compounds (830 mg, 1.9 mmol), made less efficiently (56%) under more forcing conditions (EtOH, 5.0 mol equiv; $BF_3{\cdot}OEt_2$ 6.0 mol equiv, 20 °C, 1 h), and purified by flash chromatography, was dissolved in MeOH satd with NH_3 (8 mL) and left at rt overnight. After the volatiles had been removed in vacuo, the residue was purified by flash silica chromatography, elution with MeOH (5%) in $CHCl_3$, to give ethyl α,β-D-glucofuranoside (374 mg, 94%, α:β = 1:2.8). The first fractions gave ethyl α-D-glucofuranoside as colourless needles, mp 82.5–84 °C (lit.[16] 82–83 °C), $[\alpha]_D^{21}$ +95.8° (*c* 0.8, H_2O) [lit.[16] $[\alpha]_D^{23}$ +98° (H_2O)]; NMR (D_2O): δ_H 5.18 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 4.27 (dd, 1 H, $J_{2,3}$ 3.6, $J_{3,4}$ 4.2 Hz, H-3), 4.12 (dd, 1 H, H-2), 4.08 (dd, 1 H, $J_{4,5}$ 7.9 Hz, H-4), 3.85 (ddd, 1 H, $J_{5,6a}$ 6.3, $J_{5,6b}$ 2.8 Hz, H-5), 3.79 (1 H, qd, *J* 7.2, 9.3 Hz, C*H*CH_3), 3.77 (dd, 1 H, $J_{6a,6b}$ 12.0 Hz, H-6b), 3.62 (dd, 1 H, H-6a), 3.60 (qd, 1 H, C*H*CH_3), 1.18 (t, 3 H, *J* 7.2 Hz, CH_3); δ_C (D_2O) 102.4 (C-1), 78.2 (C-4), 75.0 (C-2), 76.1 (C-3), 70.1 (C-5), 65.6 (CH_2), 63.6 (C-6), 14.7 (CH_3). The last fractions gave ethyl β-D-glucofuranoside as a colourless oil, (lit.[16] mp 59–60 °C), $[\alpha]_D^{24}$ −77.2° (*c* 1.0, H_2O) [lit.[16] $[\alpha]_D^{27}$ −86° (H_2O)]; NMR (D_2O): δ_H 4.94 (s, H-1), 4.19 (d, 1 H, $J_{3,4}$ 4.4 Hz, H-3), 4.11 (dd, 1 H, $J_{4,5}$ 8.9 Hz, H-4), 4.08 (s, 1 H, H-2), 3.93 (ddd, 1 H, $J_{5,6a}$ 6.0, $J_{5,6b}$ 2.6 Hz, H-5), 3.80 (dd, 1 H, $J_{6a,6b}$ 12.0 Hz, H-6b), 3.71 (qdd, 1 H, C*H*CH_3), 3.64 (dd, 1 H, H-6a), 3.53 (qdd, 1 H, *J* 7.1, 10.0 and 0.6 Hz, C*H*CH_3), 1.15 (td, 3 H, *J* 7.1, 0.6 Hz, CH_3); δ_C (D_2O) 108.3 (C-1), 81.4 (C-4), 80.2 (C-2), 75.3 (C-3), 70.1 (C-5), 64.8 (CH_2), 63.9 (C-6), 14.6 (CH_3).

Phenyl β-D-glucofuranoside.—1,2,3,5,6-Penta-*O*-propanoyl-β-D-glucofuranose (1.0 g, 2.2 mmol) and phenol (0.41 g, 4.3 mmol) were dissolved in CH_2Cl_2 (10 mL), and $BF_3{\cdot}OEt_2$ (134 μL, 1.1 mmol) was added dropwise. The solution was left at 20 °C overnight by which time the reaction was complete (TLC). The reaction mixture was washed with $NaHCO_3$ (satd aq, 30 mL) and water, was dried ($MgSO_4$) and concentrated in vacuo. Flash silica chromatography of the residue, elution with 15:85 EtOAc–light petroleum, gave phenyl 2,3,5,6-tetra-*O*-propanoyl-α,β-D-glucofuranoside (**4**α,β; R = OPh) as a colourless syrup (0.8 g, 77%, α:β < 1:7); $[\alpha]_D^{23}$ −81.0° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$): δ_H (β anomer) 7.29 (dd, 2 H, *J* 7.4, 8.4 Hz, H-3′, 5′), 7.02 (t, 1 H, *J* 7.4 Hz, H-4′), 7.01 (d, 2 H, *J* 8.4 Hz, H-2′,6′), 5.63 (s, 1 H, H-1), 5.46 (d, 1 H, $J_{3,4}$ 5.0 Hz, H-3), 5.31 (ddd, 1 H, $J_{4,5}$ 9.4, $J_{5,6a}$ 4.6, $J_{5,6b}$, 2.4 Hz, H-5), 5.27 (s, 1 H, H-2), 4.62 (dd, 1 H, H-4), 4.54 (1 H, dd, $J_{6a,6b}$ 12.3 Hz, H-6b), 4.09 (dd, 1 H, H-6a), 2.42 (q, 2 H, *J* 7.5 Hz, CH_2), 2.39 (q, 2 H, *J* 7.5, CH_2), 2.33 (q, 2 H, *J* 7.5, CH_2), 2.25 (q, 2 H, *J* 7.5, CH_2), 1.17 (3 H, t, *J* 7.5, CH_3), 1.15 (t, 3 H, *J* 7.5, CH_3), 1.13 (t, 3 H, *J* 7.5, CH_3), 1.08 (t, 3 H, *J* 7.5, CH_3); δ_C ($CDCl_3$) 174.3, 173.3, 173.3, 173.0 (4 × C=O), 156.6 (C-1′), 130.0 (C-3′,5′), 122.9 (C-4′), 116.9 (C-2′,6′), 104.6 (C-1), 80.7 (C-2), 79.7 (C-4), 73.6 (C-3), 68.9 (C-5), 63.2 (C-6), 27.8, 27.8, 27.8, 27.7 (4 × CH_2), 9.4, 9.2, 9.2, 9.1 (4 × CH_3).

This anomeric mixture was dissolved in MeOH (10 mL), and NaOMe (1 M in MeOH) was added to pH

12. The solution was left for 2 h and then neutralised with Amberlite IRC-50 (H^+) resin, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash silica chromatography, elution with 1:9 MeOH–$CHCl_3$, to give a colourless oil (390 mg) which crystallised from 2-butanone–light petroleum to afford phenyl β-D-glucofuranoside (220 mg, 52%) identical (mp and $[\alpha]_D$) to a sample made from penta-*O*-acetyl-α,β-D-glucofuranose.[12]

4-Nitrophenyl α- and β-D-glucofuranoside.—1,2,3,5,6-Penta-*O*-propanoyl-β-D-glucofuranose (1.0 g, 2.2 mmol) and 4-nitrophenol (604 mg, 4.3 mmol) were dissolved in CH_2Cl_2 (10 mL), and $BF_3{\cdot}OEt_2$ (134 μL, 1.1 mmol) was added dropwise. The solution was left overnight and was then washed with $NaHCO_3$ (satd aq, 30 mL), water, and dried ($MgSO_4$) and concentrated in vacuo. Flash silica chromatography of the residue, elution with 1:4 EtOAc–light petroleum, gave a colourless syrup containing the 4-nitrophenyl 2,3,5,6-tetra-*O*-propanoyl-α,β-D-glucofuranosides (**4**α,β; R = $OC_6H_4NO_2(p)$) (0.99 g, 88%), which were dissolved in MeOH (20 mL), and NaOH (1 M, aq) was added to pH 10. The solution was left overnight and then neutralised with Amberlite IRC-50 (H^+) resin and filtered. The filtrate was then concentrated in vacuo. The resulting residue was purified by flash silica chromatography, elution with 1:9 MeOH–$CHCl_3$, to give 4-nitrophenyl α,β-D-glucofuranoside as a pale-yellow oil (400 mg, 61% overall, α:β = 2:9). Further chromatography allowed separation of the anomers. 4-Nitrophenyl α-D-glucofuranoside was recrystallised from 2-butanone to give colourless needles, mp 117.5–119.5 °C, $[\alpha]_D^{24}$ + 211.5° (*c* 1.0, H_2O); NMR (DMSO-d_6): δ_H 8.22 (d, 2 H, *J* 9.2 Hz, H-3′,5′), 7.17 (d, 2 H, *J* 9.2 Hz, H-2′,6′), 5.59 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 5.41 (s, 1 H, HO), 5.05 (s, 1 H, HO), 4.66 (s, 1 H, HO), 4.41 (s, 1 H, HO), 4.28 (dd, 1 H, $J_{2,3}$ 4.3 Hz, H-2), 4.14 (1 H, dd, 1 H, $J_{3,4}$ 2.7 Hz, H-3), 3.98 (1 H, dd, $J_{4,5}$ 8.4 Hz, H-4), 3.79 (ddd, 1 H, $J_{5,6a}$ 5.9, $J_{5,6b}$ 2.8 Hz, H-5), 3.55 (dd, 1 H, $J_{6a,6b}$ 11.2 Hz, H-6b), 3.34 (dd, 1 H, H-6a); δ_C (DMSO-d_6): 162.7 (C-1′), 141.9 (C-4′), 126.2 (C-3′,5′), 116.9 (C-2′,6′), 106.7 (C-1), 81.6 (C-4), 77.7 (C-2), 71.0 (C-3), 69.3 (C-5), 63.4 (C-6); FABMS: *m*/*z* 302.0874 $(MH)^+$; $C_{12}H_{16}NO_8$ requires 302.0876. Anal. Calcd for $C_{12}H_{15}NO_8$: C, 47.8; H, 5.0; N 4.7. Found: C, 47.3; H, 5.1; N, 4.7. 4-Nitrophenyl β-D-glucofuranoside was isolated as a pale-yellow gum, $[\alpha]_D^{20}$ −114.6° (*c* 3.2, H_2O); NMR (DMSO-d_6): δ_H 8.13 (d, 2 H, *J* 9.3 Hz, H-3′,5′), 7.09 (d, 2 H, *J* 9.3 Hz, H-2′,6′), 5.66 (s, 1 H, HO), 5.55 (1 H, s, H-1), 5.06 (s, 1 H, HO), 4.59 (s, 1 H, HO), 4.38 (s, 1 H, HO), 4.21 (s, 1 H, H-2), 4.13–4.09 (m, 2 H, H-3,4), 3.72 (ddd, 1 H, $J_{4,5}$ 8.1, $J_{5,6b}$ 6.0, $J_{5,6a}$ 2.8 Hz, H-5), 3.51 (dd, 1 H, $J_{6a,6b}$ 11.6 Hz, H-6a), 3.34 (dd, 1 H, H-6b); δ_C (DMSO-d_6) 161.7 (C-1′), 141.7 (C-4′), 126.0 (C-3′,5′), 116.6 (C-2′,6′), 105.9 (C-1), 83.0 (C-4), 80.5 (C-2), 74.6 (C-3), 69.3 (C-5), 63.4 (C-6); FABMS: *m*/*z* 302.0875 $(MH)^+$; $C_{12}H_{16}NO_8$ requires 302.0876.

*Methyl 2,3,5,6-tetra-O-propanoyl-1-thio-β-D-glucofuranoside (**4**β, R = SMe).*—1,2,3,5,6-Penta-*O*-propanoyl-β-D-glucofuranose (614 mg, 1.3 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. (Methylthio)trimethylsilane (567 μL, 4.0 mmol) was added dropwise, followed by trimethylsilyl trifluoromethanesulfonate (72 μL, 0.4 mmol). After 20 min at rt, the mixture was heated at 50 °C for 3 h, cooled, diluted with $CHCl_3$, washed with $NaHCO_3$ (50% aq, 30 mL) and brine, dried ($MgSO_4$) and concentrated in vacuo. Flash silica chromatography of the residue, elution with 1:9 EtOAc–petroleum ether, gave methyl 2,3,5,6-tetra-*O*-propanoyl-1-thio-β-D-glucofuranoside (**4**β, R = SMe) as a colourless solid (470 mg, 81%, α:β < 1:7). A sample was recrystallised from EtOH to give colourless needles, mp 62–63 °C, $[\alpha]_D^{22}$ −50.5° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$): δ_H 5.37 (d, 1 H, $J_{3,4}$ 4.2 Hz, H-3), 5.33 (ddd, 1 H, $J_{4,5}$ 9.3, $J_{5,6b}$ 5.1, $J_{5,6a}$ 2.5 Hz, H-5), 5.07 (d, 1 H, $J_{1,2}$ 2.2 Hz, H-2), 5.00 (d, 1 H, H-1), 4.62 (dd, 1 H, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.36 (dd, 1 H, H-4), 4.17 (dd, 1 H, H-6b), 2.39 (q, 2 H, *J* 7.6 Hz, CH_2), 2.37 (q, 2 H, *J* 7.6 Hz, CH_2), 2.35 (q, 2 H, *J* 7.6 Hz, CH_2), 2.26 (q, 2 H, *J* 7.6 Hz, CH_2), 2.23 (s, 3 H, SCH_3), 1.16 (t, 3 H, *J* 7.6 Hz, CH_3), 1.14 (t, 3 H, *J* 7.6 Hz, CH_3), 1.13 (t, 3 H, *J* 7.6 Hz, CH_3), 1.09 (t, 3 H, *J* 7.6 Hz, CH_3); δ_C 174.4, 173.3, 173.1, 173.1 (4 × C=O), 89.6 (C-1), 81.6 (C-2), 79.1 (C-4), 74.7 (C-3), 68.4 (C-5), 63.4 (C-6), 27.7 (4 × CH_2), 14.4 (SCH_3), 9.4, 9.2, 9.2, 9.1 (4 × CH_3); FABMS: *m*/*z* 435.1697 $(MH)^+$; $C_{19}H_{31}O_9S$ requires 435.1689. Anal. Calcd for $C_{19}H_{30}O_9S$: C, 52.5; H, 7.0; S 7.4. Found: C, 52.7; H, 7.2; S, 7.4.

Phenyl 1-thio-β-D-glucofuranoside.—1,2,3,5,6-Penta-*O*-propanoyl-β-D-glucofuranose (2.0 g, 4.3 mmol) in CH_2Cl_2 (10 mL) was cooled in an ice–salt bath, and thiophenol (670 μL, 6.5 mmol) was added, followed by the dropwise addition of $BF_3{\cdot}OEt_2$ (640 μL, 5.2 mmol). The solution was allowed to warm to rt, and the reaction was complete after 1 h. The reaction mixture was washed with $NaHCO_3$ (satd aq, 10 mL) and water, dried ($MgSO_4$) and concentrated in vacuo. Flash silica chromatography of the residue, elution with 1:9 EtOAc–petroleum ether, gave phenyl 2,3,5,6-tetra-*O*-propanoyl-1-thio-D-glucofuranoside (**4**α,β; R = SPh) as a colourless oil [2.17 g (100%), α:β = 1:8]. This anomeric mixture was dissolved in MeOH (10 mL) and K_2CO_3 (520 mg) was added. After being stirred for 1 h, the mixture was neutralised with Amberlite IRC-50 (H^+) resin, filtered and concentrated in vacuo. The resulting residue (750 mg) was crystallised from EtOAc to give phenyl 1-thio-β-D-glucofuranoside as colourless needles (567 mg, 48% overall), mp 105–107 °C (lit.[17] 100 °C), $[\alpha]_D^{23}$ −219.6° (*c* 1.0, EtOH), (lit.[17] $[\alpha]_D^{21}$ −233° (*c* 3.0, EtOH); NMR (DMSO-d_6): δ_H 7.41 (dd, 2 H, *J* 7.2, 1.3 Hz, H-2′,6′), 7.33 (dd, 2 H, *J* 7.7, H-3′,5′), 7.22 (tt, 1 H, *J* 7.7, 1.3 Hz, H-4′), 5.63 (s, 1 H,

HO), 5.13 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 5.09 (s, 1 H, HO), 4.59 (d, 1 H, *J* 4.8, HO), 4.40 (t, 1 H, *J* 5.6, HO), 4.05 (br s, 1 H, H-2), 3.99 (br s, 1 H, H-3), 3.91 (dd, 1 H, $J_{4,5}$ 8.2, $J_{3,4}$ 3.5 Hz, H-4), 3.81 (m, 1 H, H-5), 3.60 (ddd, 1 H, $J_{6a,6b}$ 11.3, $J_{5,6a}$ 3.1 Hz, H-6a), 3.40 (ddd, 1 H, $J_{5,6b}$ 3.1 Hz, H-6b); δ_C (DMSO-d_6) 137.4 (C-1′), 129.4, 129.3 (C-2′,3′,5′,6′), 126.5 (C-4′), 92.6 (C-1), 82.9 (C-2,4), 75.5 (C-3), 69.7 (C-5), 64.0 (C-6); FABMS: *m*/*z* 272.0709 $(M)^+$, $C_{12}H_{16}O_5S$ requires 272.0718.

*1-(2,3,5,6-Tetra-*O*-propanoyl-β-*D*-glucofuranosyl)-uracil (***4***β, R = uracyl-1-yl).*—To a suspension of 1,2,3,5,6-penta-*O*-propanoyl-β-D-glucofuranose (2.0 g, 4.3 mmol) and uracil (730 mg, 6.5 mmol) in CH_3CN (30 mL), *N*,*O*-bis(trimethylsilyl)acetamide (6.4 mL, 26.1 mmol) was added dropwise. The mixture was heated at 60 °C for 1 h, by which time the suspended material had dissolved. The mixture was cooled to 0 °C, and trimethylsilyl trifluoromethanesulfonate (1.6 mL, 8.7 mmol) was added dropwise. After being heated under reflux for 5 h, the solution was concentrated in vacuo to half the volume and cooled in an ice-bath. $NaHCO_3$ (satd aq, 60 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Flash silica chromatography of the residue, elution with 1:99 MeOH–$CHCl_3$, gave the title compound as a colourless syrup (2.1 g, 96%, α:β < 1:25), $[\alpha]_D^{22}$ + 14.6° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$): δ_H 9.34 (s, 1 H, NH), 7.47 (d, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 6.06 (d, 1 H, $J_{1',2'}$ 2.0 Hz, H-1′), 5.82 (d, 1 H, H-5), 5.45 (d, 1 H, $J_{3',4'}$ 3.3 Hz, H-3′), 5.36 (ddd, 1 H, $J_{4',5'}$ 9.6, $J_{5',6'b}$ 5.4, $J_{5',6'a}$ 2.4 Hz, H-5′), 5.07 (d, 1 H, H-2′), 4.61 (dd, 1 H, $J_{6'a,6'b}$ 12.3 Hz, H-6′a), 4.38 (dd, 1 H, H-4′), 4.11 (dd, 1 H, H-6′b), 2.45 (qd, 2 H, *J* 7.5, 1.5 Hz, CH_2), 2.36 (q, 2 H, *J* 7.5 Hz, CH_2), 2.35 (q, 2 H, *J* 7.5 Hz, CH_2), 2.29 (q, 2 H, *J* 7.5 Hz, CH_2), 1.18 (t, 3 H, *J* 7.5 Hz, CH_3), 1.15 (t, 3 H, *J* 7.5 Hz, CH_3), 1.12 (t, 3 H, *J* 7.5 Hz, CH_3), 1.10 (t, 3 H, *J* 7.5 Hz, CH_3); δ_C 174.3, 173.4, 172.8, 172.3 (4 × C=O), 163.2 (C-4), 150.4 (C-2), 139.4 (C-6), 103.5 (C-5), 89.7 (C-1′), 80.6 (C-2′), 79.3 (C-4′), 73.5 (C-3′), 67.1 (C-5′), 63.2 (C-6′), 27.7, 27.6, 27.6, 27.5 (4 × CH_2), 9.4, 9.1, 9.1, 9.0 (4 × CH_3); EIMS: *m*/*z* 499.1914 $(MH)^+$; $C_{22}H_{31}N_2O_{11}$ requires 499.1928). Anal. Calcd for $C_{22}H_{30}N_2O_{11}$: C, 53.0; H, 6.1; N 5.6. Found: C, 52.7; H, 6.1; N, 5.7.

*1-(β-*D*-Glucofuranosyl)uracil.*—The above product was dissolved in MeOH satd with NH_3 (15 mL) and left at rt overnight. After concentration in vacuo the resulting residue was purified by flash silica chromatography, eluting with 84:15:1 $CHCl_3$–CH_3OH–NH_3 aq, to give the title compound as a colourless solid (680 mg, 75%). A sample was recrystallised from EtOH to give the product as colourless needles, mp 175–176.5 °C, $[\alpha]_D^{21}$ + 9.91° (*c* 1.1, H_2O); NMR (D_2O): δ_H 7.82 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-6), 5.79 (d, 1 H, H-5), 5.75 (s, 1 H, H-1′), 4.27–4.25 (m, 2 H, H-2′,3′), 4.23 (dd, 1 H, $J_{4',5'}$ 8.6, $J_{3',4'}$ 2.7 Hz, H-4′), 4.12 (ddd, 1 H, $J_{5',6'a}$ 5.4, $J_{5',6'b}$ 2.7 Hz, H-5′), 3.86 (dd, 1 H, $J_{6'a,6'b}$ 12.1 Hz, H-6′a), 3.37 (dd, 1 H, H-6′b); δ_C (D_2O) 166.8 (C-4), 151.9 (C-2), 142.6 (C-6), 101.5 (C-5), 92.4 (C-1′), 82.8 (C-4′), 80.7, 74.7 (C-2′,3′), 68.9 (C-5′), 63.8 (C-6′); FABMS: *m*/*z* 275.0884 $(MH)^+$; $C_{10}H_{15}N_2O_7$ requires 275.0880. Anal. Calcd for $C_{10}H_{14}N_2O_7$ C, 43.8; H, 5.15; N, 10.2. Found: C, 44.0; H, 5.0; N, 10.35.

*1,2-*O*-[1-Cyanopropylidene]-3,5,6-tri-*O*-propanoyl-α-*D*-glucofuranose* (**2**).—Cyanotrimethylsilane (120 μL, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (28 μL, 0.23 mmol) were added to a solution of 1,2,3,5,6-penta-*O*-propanoyl-β-D-glucofuranose (104.0 mg, 0.23 mmol) in CH_3NO_2 (1 mL). The mixture was stirred at rt under nitrogen for 70 min, then diluted with EtOAc (50 mL), washed with water (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography, elution with a gradient of 15 → 25% EtOAc–hexanes, gave the title compound as an oil (22.2 mg, 24%); $[\alpha]_D^{23}$ + 10.2° (*c* 0.47, $CHCl_3$); NMR ($CDCl_3$): δ_H 6.09 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1) 5.41 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 5.21 (ddd, 1 H, $J_{4,5}$ 9.5, $J_{5,6b}$ 5.2, $J_{5,6a}$ 2.4 Hz, H-5), 4.71 (d, 1 H, H-2), 4.57 (dd, 1 H, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.36 (dd, 1 H, H-4), 4.12 (dd, 1 H, H-6b), 2.21–2.36 (m, 6 H, 3 × CH_2O) 2.08 (q, 2 H, *J* 7.5 Hz, 2 H, CH_2CCN), 1.08–1.18 (m, 12 H, 4 × CH_3); δ_C 174.3, 173.4, 173.2 (3 × C=O), 116.5 (CN), 105.9 (C-1), 104.0 (*C*CN), 84.6 (C-2), 78.1 (C-4), 73.7 (C-3), 67.2 (C-5), 63.3 (C-6), 31.1 (*C*H_2CCN), 27.8, 27.7, 27.6 (3 × CH_2), 9.4, 9.2, 9.1, 7.4 (4 × CH_3); FABMS: *m*/*z* 414.1772 $(MH)^+$; $C_{19}H_{28}NO_9$ requires 414.1772. This was followed by 2,3,5,6-tetra-*O*-propanoyl-α,β-D-glucofuranose (**4**α,β; R = OH) (11.4 mg, 12%) (see below) and starting material that had partly anomerised (53.4 mg, 51%).

*2,3,5,6-Tetra-*O*-propanoyl-α,β-*D*-glucofuranosyl trichloroacetimidate (***4***α,β; R = OC(=NH)CCl₃).*—1,2,3,5,6-Penta-*O*-propanoyl-β-D-glucofuranose (103 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (1 mL). Water (20 μL, 1.11 mmol) and $BF_3{\cdot}OEt_2$ (28 μL, 0.22 mmol) were added, and the mixture was kept at 40 °C for 3 h. The volatiles were evaporated, and the residue was dissolved in $CHCl_3$ (20 mL), washed with water (2 × 20 mL), brine (20 mL), and dried ($MgSO_4$), and the solvent was removed. Flash chromatography of the residue, elution with a gradient of 15 → 25% EtOAc–hexanes, gave 2,3,5,6-tetra-*O*-propanoyl-α,β-D-glucofuranose (**4**α,β; R = OH) (46 mg, 51%) with ^1H and ^{13}C NMR spectra consistent with expectations. A sample (88 mg, 0.22 mmol) was dissolved in CH_3CN (1 mL) and DBU (24 μL, 0.16 mmol) and CCl_3CN (132 μL, 1.32 mmol) were added under nitrogen. After being stirred for 1.5 h at 20 °C, the solution was transferred to a flash chromatography column and eluted with 15:85 EtOAc–hexanes containing triethylamine (1%) to give the title compounds as a syrup (88 mg, 73%; α:β 1:1.5); NMR ($CDCl_3$): δ_H 8.64 (s, 0.4 H, NHα), 8.61 (s, 0.6 H, NHβ),

6.66 (d, 0.4 H, $J_{1,2}$ 4.8 Hz, H-1α), 6.30 (s, 0.6 H, H-1β), 5.63 (dd, 0.4 H, $J_{3,4}$ 4.8, $J_{2,3}$ 2.4 Hz, H-3α), 5.48 (d, 0.6 H, $J_{3,4}$ 5.0 Hz, H-3β), 5.35 (ddd, 0.6 H, $J_{4,5}$ 9.5, $J_{5,6\alpha}$ 5.0, $J_{5,6\beta}$ 2.4 Hz, H-5β), 5.30 (m, 0.4 H, H-5α), 5.28 (s, 0.6 H, H-2β), 5.24 (dd, 0.4 H, H-2α), 4.69 (dd, 0.6 H, H-4β), 4.63 (dd, 0.6 H, $J_{6a,6b}$ 12.4, $J_{5,6b}$ 2.4 Hz, H-6bβ), 4.59 (m, 0.4 H, H-6bα), 4.55 (dd, 0.4 H, $J_{4,5}$ 2.4 Hz, H-4α), 4.15 (dd, 0.6 H, H-6aβ), 4.07 (m, 0.4 H, H-6aα), 2.30 (m, 8 H, $4 \times CH_2$), 1.15 (m, 12 H, $4 \times CH_3$); δ_C 173.7, 172.7, 172.6, 172.3 ($4 \times C{=}O$), 160.2, (C=NH), 102.1 (C-1β), 97.2 (C-1α), 80.1, 76.7, 74.0, 72.4, 68.2 (C-5β), 67.4 (C-5α), 62.8 (C-6β), 62.6 (C-6α), 27.4, 27.3, 27.2, 27.0, ($4 \times CH_2$), 9.1, 8.9, 8.7, ($4 \times CH_3$); FABMS: m/z 548.0848 $(MH)^+$; $C_{20}H_{29}Cl_3NO_{10}$ requires 548.0857.

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