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3,4-Dipyranosyl-1,2,5-oxadiazole 2-oxides: synthesis and X-ray structure

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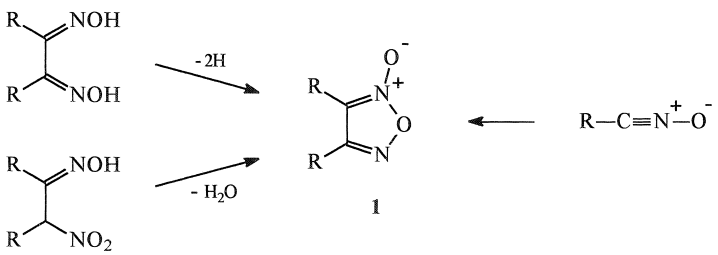
Abstract—3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (**7**) has been synthesised from D-mannose by a route involving as the key step dimerisation of mannopyranosyl nitrile oxide **2**. Three methods were used for the generation of the nitrile oxide: isocyanate-mediated dehydration of nitromethylmannose derivative **4**, treatment of aldoxime **5** with aq. hypochlorite, and base-induced dehydrochlorination of hydroximoyl chloride **6**. D-Gluco, D-galacto, D-xylo, and L-fucopyranosyl analogues **8**–**11** were prepared similarly. The structure of D-mannose-derived 1,2,5-oxadiazole 2-oxide **7** was established by X-ray crystallography.

1. Introduction

1,2,5-Oxadiazole 2-oxides (furoxans, **1**) have been known since 1850s and much attention has been paid to structure determination, development of preparative methods, and examining their reactions.[1–3] A wide variety of substituents can be accommodated at the 3- and 4-positions, including alkyl, aryl, amino, halogeno, nitro and thio groups. To date, however, there have been few examples of carbohydrate-substituted furoxans.[4] While investigating synthetic routes to *C*-glycosides and carbon-linked disaccharides (*C*-disaccharides), we have sought novel methods for forming functionalised carbon bridges between pyranose rings, and now report that furoxans bearing pyranosyl substituents at both the 3- and 4-positions can readily be prepared in two steps from the parent monosaccharide.

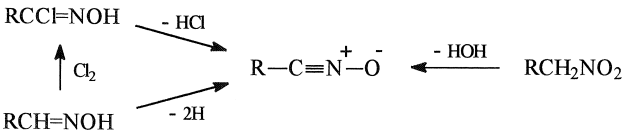
2. Results and discussion

The furoxan ring can be constructed by various methods,[1–3] the most synthetically useful of which are: the oxidative cyclisation of 1,2-dioximes, the dehydration of α-nitroketoximes and, for symmetrically substituted furoxans, the dimerisation of nitrile oxides (Scheme 1). As suitably substituted carbohydrate dioxime and nitroketoxime precursors are not readily available we selected the nitrile oxide dimerisation approach.



Scheme 1.

Nitrile oxides have been identified as intermediates in various reactions,[5] and of these three provide synthetically useful methods of generation (Scheme 2). Hydroximoyl chlorides (RCCl=NOH), which can be prepared from the parent aldoxime using chlorine, *N*-chlorosuccinimide, or nitrosyl chloride, undergo facile dehydrochlorination to the



Scheme 2.

Keywords: nitrile oxides; *C*-glycosides, pyranosylcarbaldoximes; pyranosylnitromethanes; X-ray crystallography.

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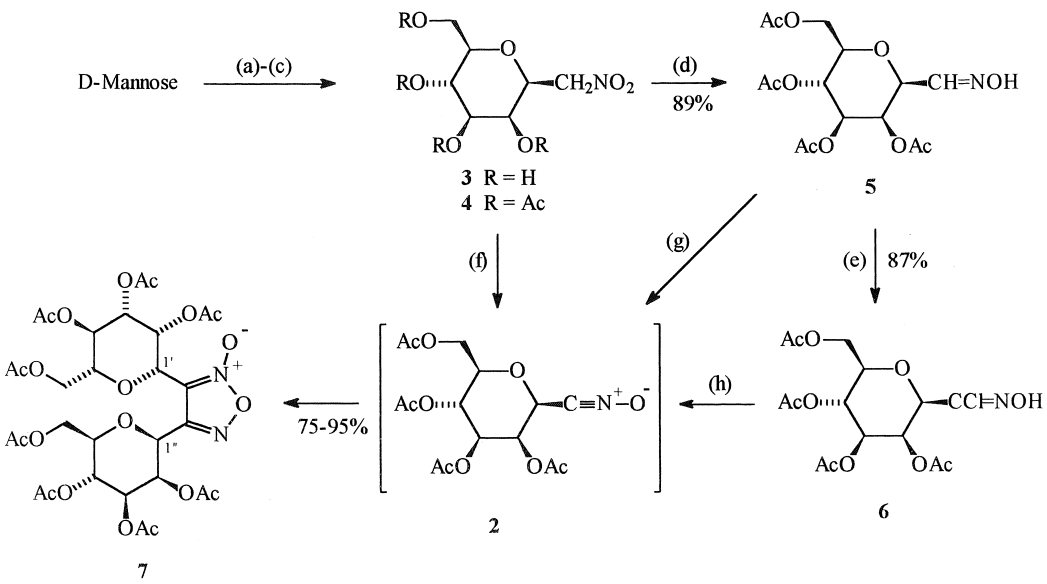


Scheme 3. *Reagents*: (a) $MeNO_2$/NaOMe, MeOH; (b) H_2O, reflux; (c) Ac_2O/CF_3SO_3H; (d) $SnCl_2$/PhSH/Et_3N, THF; (e) Cl_2, CH_2Cl_2; (f) TDI/Et_3N, PhMe, reflux, quench with $H_2NCH_2CH_2NH_2$; (g) aq NaOCl, CH_2Cl_2; (h) Et_3N, Et_2O.

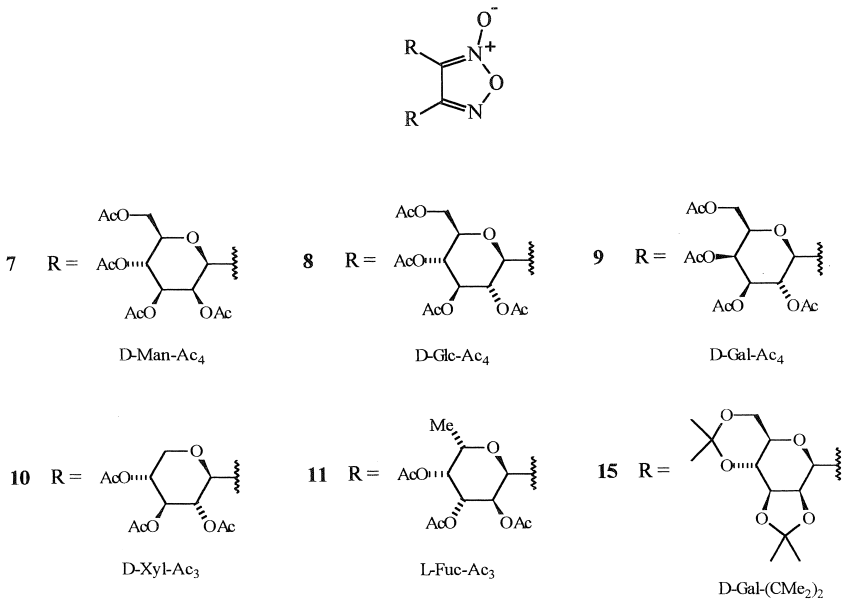
nitrile oxide in the presence of triethylamine; in the absence of base the nitrile oxide may be released by thermolysis in an inert solvent such as toluene.[6] There are also several one-pot methods[7,8] for generation of nitrile oxides from aldoximes including treatment with Chloramine-T or aq. NaOCl/CH_2Cl_2. The third approach, which was originally reported by Mukaiyama and Hoshino,[9] involves dehydration of the corresponding nitromethyl compound (RCH_2NO_2) with phenyl isocyanate; alternative dehydrating agents include $POCl_3$,[10] TsOH,[11] $ClCO_2Me$[12] and $PhSO_2Cl$.[13]

For the present work the choice of method is determined by the accessibility of the precursors. We initially considered a conventional approach to pyranose-1-carbaldoximes—and hence to the corresponding hydroximoyl chlorides—via oximation of *C*-pyranosyl aldehydes. The literature routes[14–16] to the aldehydes, however, all require several stages, some of which need expensive reagents and/or forcing conditions, and the products are prone to oxidation and hydration. We therefore selected pyranosylnitromethanes (2,6-anhydro-1-deoxy-1-nitroalditols) as the sources of the target pyranosyl nitrile oxides. These can readily be prepared[17] from the parent monosaccharide by base-catalysed addition of nitromethane (the Fischer–Sowden reaction). Subsequent reduction to the aldoximes, followed by chlorination should then afford the corresponding hydroximoyl chlorides. This sequence can thus provide access to all three potential precursors of the pyranosyl nitrile oxides. These approaches are illustrated in Scheme 3 for generation of nitrile oxide **2** derived from D-mannose.

D-Mannose was converted into β-D-mannopyranosylnitromethane (**3**) using the general procedure of Köll et al.[17] which involves reaction with nitromethane and sodium methoxide in methanol, followed by heating the resulting adduct to achieve dehydration and cyclisation. As an isocyanate was to be used as the dehydrating agent it was necessary to protect all free hydroxyl groups, and compound **3** was therefore converted into its peracetate derivative **4** using $Ac_2O/MeSO_3H$. The aldoxime **5** was prepared from the nitromethyl compound by reduction with $SnCl_2$/PhSH/Et_3N. We have found that this protocol, which is based on a report by Bartra et al.,[18] and depends on the reducing ability of the stannate species $(PhS)_3Sn^-$, is an effective and general method for reducing nitromethyl monosaccharides. Hydroximoyl chloride **6**, the third potential precursor for nitrile oxide **2**, was prepared by chlorination of oxime **5**. Although direct chlorination of aldoximes can be a capricious reaction, and alternative reagents such as NCS and NOCl are often used,[5] it proved to be very successful in this case. Bubbling chlorine through a solution of the oxime in CH_2Cl_2 at −78°C resulted in a colour change (colourless→blue→green) attributable to formation of the nitroso tautomer of the hydroximoyl chloride, and work-up of the reaction mixture afforded the desired product **6** as a white solid in 87% yield. Complete aldoxime to hydroximoyl chloride conversion is evident from the NMR spectra. In the proton spectrum the 1-H signal at 7.37 ppm for the aldoxime is absent and the 2-H signal simplifies from a doublet of doublets to a doublet (1.9 Hz); and in the carbon spectrum the aldoxime CH peak at 146.1 ppm is replaced by a new quaternary carbon signal at 134.6 ppm. Although the starting material was a mixture of *E*- and *Z*-oximes, NMR spectroscopy showed the product to be a single isomer. The same approach was used to prepare the aldoximes and hydroximoyl chlorides from D-glucose, D-galactose, D-xylose and L-fucose.

The nitrile oxide **2** was first generated by heating under reflux a toluene solution of nitromethyl compound **4** and tolylene diisocyanate (TDI) (3 equiv.) with a catalytic amount of triethylamine. On completion the reaction was quenched by addition of 1,2-diaminoethane to remove excess isocyanate, and the solvent evaporated to afford the nitrile oxide dimer 3,4-di-(tetra-*O*-acetyl-β-D-mannopyranosyl)furoxan (**7**) as a crystalline solid in 90% yield (Table 1, entry 1). TDI was used for the dehydration in place of the traditional phenyl isocyanate for ease of work-up, as the by-product is then a polymeric urea which is readily separated by filtration.[19] The second approach to the nitrile

Table 1. 3,4-Dipyranosylfuroxans



Entry	Furoxans	R	Method[a]	Yield (%)
1	**7**	D-Man-Ac_4	A	90
2	**7**	D-Man-Ac_4	B	75
3	**7**	D-Man-Ac_4	C	95
4	**8**	D-Glc-Ac_4	B	88
5	**8**	D-Glc-Ac_4	C	96
6	**9**	D-Gal-Ac_4	B	90
7	**10**	D-Xyl-Ac_3	A	81
8	**10**	D-Xyl-Ac_3	B	89
9	**11**	L-Fuc-Ac_3	A	79
10	**15**	D-Man-$(CMe_2)_2$	A	92

[a] Method A: RCH_2NO_2/TDI; Method B: RCH=NOH/NaOCl; Method C: RCCl=NOH/Et_3N.

oxide involved oxidation of the aldoxime with hypochlorite using the two-phase procedure reported by Lee et al.[8] A solution of oxime **5** in dichloromethane was added dropwise to a stirred mixture of aqueous sodium hypochlorite and dichloromethane containing a catalytic amount of triethylamine. Separation of the phases and work-up of the organic layer afforded furoxan **7** in 75% yield (Table 1, entry 2). Finally the nitrile oxide was generated by base-mediated dehydrochlorination of hydroximoyl chloride **6**. A solution of triethylamine (1.1 equiv.) in Et_2O was added to a solution of **6** (1.0 equiv.) in Et_2O at 0°C and the mixture stirred at room temperature for 16 h. After filtration and washing with water to remove triethylamine hydrochloride, the solution was concentrated to afford furoxan **7** (95%) (Table 1, entry 3).

D-Glucose, D-galactose, D-xylose and L-fucose-derived furoxans **8**–**11** were prepared similarly (Table 1, entries 4–9) and in all cases the yields were very good (75–96%). The products were identified by their analytical and spectroscopic properties. ^{13}C NMR spectroscopy is of particular value in identifying these compounds. In addition to resonances attributable to the two peracetylpyranosyl substitutents, there are characteristic peaks in the ranges 110.5–111.6 (C-3) and 152.7–153.4 ppm (C-4) for the carbons of the oxadiazole ring. These values are typical for unstrained furoxans.[2] In the proton NMR spectrum of dimannosylfuroxan **7** in $CDCl_3$ the two non-equivalent pyranosyl substituents lead to overlapping and only partially resolved signals. There are, however, distinct doublets for protons H(1′) and H(1″), which are attached to the carbons adjacent to C(3) and C(4), respectively, of the furoxan ring; the observed 1 Hz couplings to H(2′)/H(2″) are in accord with the β-D-manno configuration of the pyranoid rings. The higher chemical shift doublet was assigned to H(1″) by analogy with data reported for other dialkylfuroxans.[1,2] A fuller analysis was performed for diglucosylfuroxan **8**. In $CDCl_3$ the spectra were again poorly resolved and alternative solvents were therefore examined, including C_6D_6 and CD_3COCD_3. In all solvents the expected 10 Hz doublet signals are observed for protons H(1′) and H(1″). Acetone-d_6 provided the best overall resolution and a near complete proton and carbon assignment was achieved from COSY and HETCOR spectra. Identical proton–proton ^3J couplings are observed for the two pyranoid frameworks [H(1)–H(2) 10.0, H(2)–H(3) 9.3, H(3)–H(4) 9.3, H(4)–H(5) 10.1 Hz]; these values are typical of *C*-glucosides. The separation of the H(1) signals proved to be solvent dependent ($\Delta\delta_H$ 0.01 ppm in $CDCl_3$, 0.06 ppm in CD_3COCD_3, 0.14 ppm in C_6D_6–$CDCl_3$). Smaller $\Delta\delta$ values are found for the ring protons H(2)–H(5). In the ^{13}C spectra the C(1) signals are well separated ($\Delta\delta_C$ 2.1 ppm in CD_3COCD_3), but the remaining carbon signals are near equivalent ($\Delta\delta_C \leq 0.1$ ppm). Their mass spectra are also typical of this class of heterocycle;[1,2] in addition to the molecular ion peak $(M+1)^+$ in the FAB spectrum, there is a

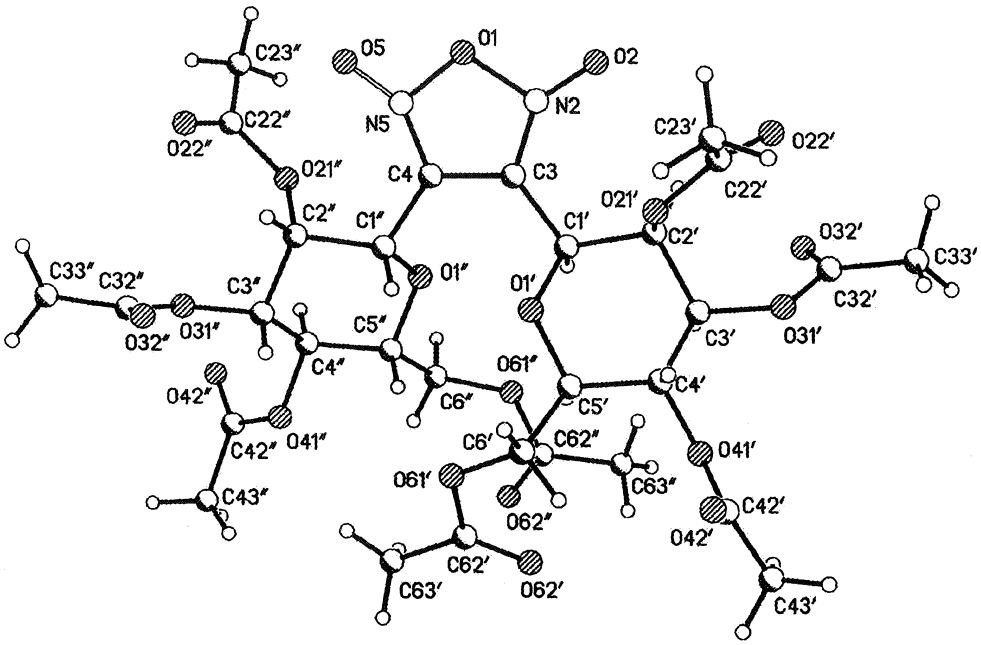


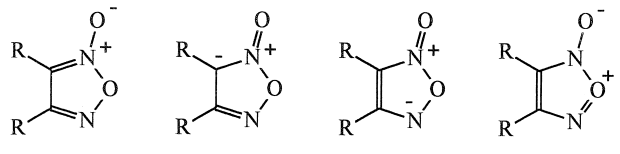
Figure 1. Structure of **7**. O2 and O5 are disordered in the ratio 0.85:0.15.

Table 2. Selected bond lengths, bond angles and torsion angles for furoxan **7**

Bond lengths (Å)	Bond angles (°)	Torsion angles (°)
O(1)–N(2) 1.465(7)	O(1)–N(2)–C(3) 105.1(5)	O(1)–N(2)–C(3)–C(4) 0.16
N(2)–C(3) 1.319(8)	N(2)–C(3)–C(4) 108.3(5)	N(2)–C(3)–C(4)–N(5) 0.29
C(3)–C(4) 1.418(9)	C(3)–C(4)–N(5) 110.6(5)	C(3)–C(4)–N(5)–O(1) −0.68
C(4)–N(5) 1.309(7)	C(4)–N(5)–O(1) 107.3(5)	C(4)–N(5)–O(1)–N(2) 0.76
N(5)–O(1) 1.355(8)	N(5)–O(1)–N(2) 108.7(4)	N(5)–O(1)–N(2)–C(3) −0.57
N(2)–O(2) 1.180(7)	O(1)–N(2)–O(2) 115.2(5)	O(1)–N(2)–C(3)–C(1′) 177.51
	C(3)–N(2)–O(2) 139.7(6)	O(2)–N(2)–C(3)–C(1′) −1.19
		O(1)–N(5)–C(4)–C(1″) −179.63

distinctive fragment peak at $(M-59)^+$ corresponding to loss of N_2O_2, whereas the peak due to loss of O, which is usually present for heterocyclic *N*-oxides, is weak.

The structure of D-mannose-derived furoxan **7** was confirmed by X-ray crystallography (Fig. 1). A noteworthy feature of the crystal structure is disorder in the furoxan moiety, with the *N*-oxide substituent being located at the 2- and 5-positions in the ratio 0.85:0.15. Disorder of this type has also been reported[20,21] for diphenyl- and tetramethylene-furoxans [**1**, R=Ph, $(CH_2)_4$] and some norbornane-fused furoxans.[22] Selected bond lengths, bond angles and torsion angles for the furoxan ring system are given in Table 2. The atoms of the furoxan unit O(1), N(2), C(3), C(4), N(5), O(2) are near planar (maximum deviation 0.004 Å), as are the atoms C(1′), C(3), C(4), C(1″) linking the oxadiazole to the two pyranoid substituents. The bond lengths are typical of furoxans[2] and indicate π-electron delocalisation over all six atoms with the exocyclic oxygen attached to N(2) causing significant distortion of the oxadiazole ring. Of particular note is the long O(1)–N(2) and short N(2)–O(2) bonds. C(3)–C(4) is also shortened corresponding to partial double bond character, and N(2)–C(3) is longer than C(4)–N(5), consistent with contributions from **12b**–**12d** to the resonance hybrid. The bond angles of the C=NO_2 unit are also typical of 3,4-disubstituted furoxans, with O(2)–N(2)–C(3) significantly larger than O(2)–N(2)–O(1) [139.7° cf 115.2°].



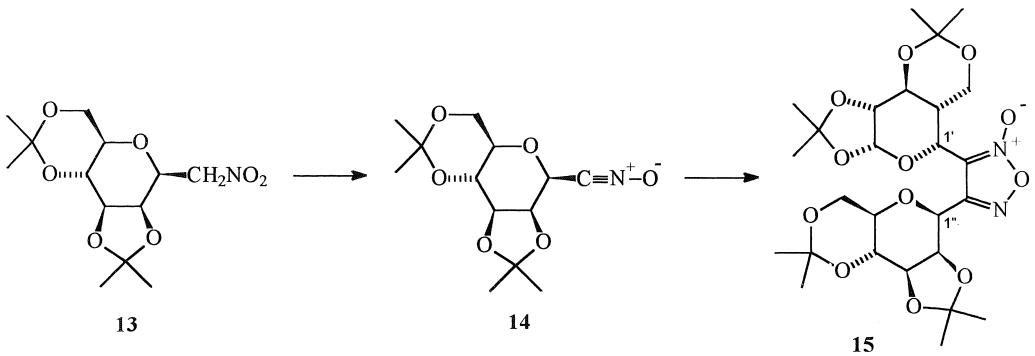
12a **12b** **12c** **12d**

The Cramer and Pople[23] puckering parameters for the two pyranoid rings are given in Table 3. Ring A attached to C-3 of the furoxan has 98% of the puckering of an ideal cyclohexane chair conformation, with Q=0.596 Å and θ=175.7° compared with Q=0.630 Å and θ=180° for the ideal chair. Similarly for ring B attached to C-4 with

Table 3. Cremer and Pople puckering parameters for pyranoid rings of furoxan **7**

Ring	Atoms	Q (Å)	θ (°)	ϕ (°)
A	O(1′)–C(5′)–C(4′)–C(3′)–C(2′)–C(1′)	0.596	175.7	105.1
B	O(1″)–C(5″)–C(4″)–C(3″)–C(2″)–C(1″)	0.593	176.7	213.7

Ref. 23.



Scheme 4.

Q=0.593 Å and θ=176.7°. Such values are typical of pyranoid rings.[24]

All the dipyranosylfuroxans described so far have been prepared as their peracetate derivatives using the acetylated nitromethylpyranose as the starting material. In order to widen the range of protecting groups, and thus ultimately increase the scope for transformations that might be accomplished on the resulting furoxans, we investigated diisopropylidene-mannose analogue **13** as a possible precursor of nitrile oxide **14** (Scheme 4). Compound **13** was prepared from β-D-mannopyranosylnitromethane (**3**) by treatment with 2-methoxypropene/TsOH/$CaSO_4$/DME as previously reported.[24] The nitrile oxide was then generated from the nitromethyl compound **13** in the usual way using TDI/Et_3N, and from the reaction mixture was isolated the nitrile oxide dimer **15** (92%), which was identified from its NMR and mass spectra. The ^{1}H NMR signals for the pyranoid ring protons were best resolved in $CDCl_3$ and a full analysis was possible from the 600 MHz COSY and 1D-TOCSY spectra. The signals for H(1′) and H(1″) are well separated ($\Delta\delta_H$ 0.16 ppm) and show the expected small couplings (2.5 Hz) to H(2′)/H(2″). As expected, the presence of the dioxolane ring fused at C(2)/C(3) results in some distortion of the regular $^4C_1$ conformation, as evidenced by the proton–proton ^3J couplings [H(1)–H(2) 2.6, H(2)–H(3) 5.2, H(3)–H(4) 7.9, H(4)–H(5) 10.1 Hz]. The chemical shifts for the isopropylidene ketal carbons provide definitive evidence for the presence of both 1,3-dioxane and 1,3-di-oxolane rings attached to both pyranosyl substituents. For the 1,3-dioxane units protecting O(4)/O(6) there are characteristic signals for the ketal carbons at 99.9 and 100.0 ppm and for the isopropylidene methyl carbons at 18.7, 18.7, 28.7 and 28.9 ppm. Corresponding signals for the dioxolane unit protecting O(2)/O(3) are observed at 110.4, 110.5 (ketal carbons) and 26.4, 27.3, 28.3, 28.4 ppm (methyl carbons). Such values are typical[25] of 2,2-dimethyl-1,3-di-oxolanes and 2,2-dimethyl-1,3-dioxanes, respectively (Scheme 4).

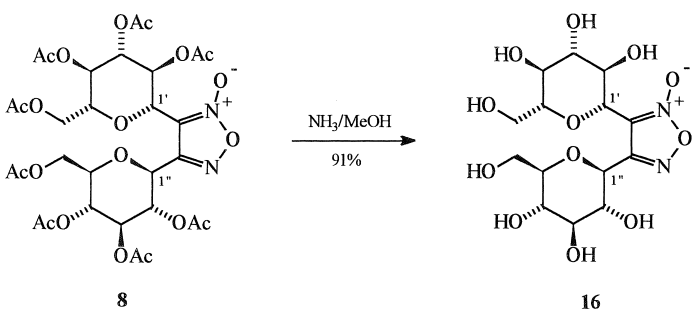
Finally, the unprotected 3,4-di-D-glucosyl-furoxan **16** was prepared by treatment of the octa-acetyl derivative **8** with NH_3/MeOH (Scheme 5). The product was identified from its spectroscopic properties. In the ^{13}C NMR spectrum in D_2O there are diagnostic peaks for the oxadiazole ring carbons C(3) and C(4) at 115.4 and 156.0 ppm, respectively, which are 3–4 ppm higher than those found for the peracetyl analogue in acetone-d_6. The glucosyl H(1′)/H(1″) doublet signals in the proton spectrum are well separated at 4.56 and 4.60 ppm, and both show the expected trans-diaxial 10 Hz coupling to H(2′)/H(2″). The product, which was isolated in high yield (91%), represents a rare example of a water-soluble furoxan.

In conclusion, dipyranosylfuroxans can be synthesised in good yield from the parent monosaccharide. Of the three procedures examined the two-step route involving conversion of the monosaccharide to a suitably protected nitromethylpyranose, followed by dehydration to the pyranosyl nitrile oxide, is in most cases the most efficient. As furoxan rings are readily reduced,[1,2] e.g. to 1,2,5-oxadiazoles (furazans) and 1,2-dioximes, there should be further scope for the preparation of novel carbon-bridged disaccharides.

3. Experimental

3.1. General

Melting points were measured on a Gallenkamp capillary apparatus and are uncorrected. Microanalyses were



Scheme 5.

obtained using a Perkin–Elmer 2400 instrument. Optical rotations were measured at 21°C on a Perkin–Elmer 141 polarimeter using 1.8 ml of filtered solution. The ^{1}H and ^{13}C NMR spectra were recorded with Brucker WP200SY, AX250, WH360 or Varian VXR600 spectrometers on solutions in $CDCl_3$ (unless otherwise stated) with Me_4Si as internal standard. Positive-ion FAB and high resolution mass spectra were obtained on a Kratos MS50TC instrument using either glycerol or thioglycerol matrices. Infrared spectra were recorded as films or nujol mulls using a Perkin–Elmer 781 spectrometer. Merck aluminium-backed plates coated with Kieselgel GF_{254} (0.2 mm) were used for analytical TLC; detection was by UV or sulfuric acid charring. Dry flash chromatography was carried out using Kieselgel GF_{254} and eluted under water pump vacuum.

3.2. Pyranosylnitromethanes

2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosylnitromethane (**4**) was prepared from D-mannose by reaction with $MeNO_2$/NaOMe/MeOH and acetylation of the resulting β-D-mannopyranosyl-nitromethane (**3**) as previously reported.[17] 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-nitromethane, 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-nitromethane, 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl-nitromethane, and 2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-nitromethane were prepared similarly from D-glucose, D-galactose, D-xylose, and L-fucose, respectively. 2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**13**) was synthesised from β-D-mannopyranosylnitro-methane by treatment with 2-methoxypropene/TsOH/$CaSO_4$/DME as described in the literature.[24]

3.3. General procedure for the synthesis of the pyranosylformaldoximes

Triethylamine (0.2 ml, 1.5 mmol) and thiophenol (0.14 ml, 1.35 mmol) were added to a solution of tin(II) chloride (100 mg, 0.45 mmol) in dry THF (6 ml) under nitrogen at 0°C. To the resulting solution was added a solution of the pyranosylnitromethane (0.3 mmol) and the mixture stirred for 16 h. After removal of the solvent in vacuo, the residue was washed with hexane to remove excess thiophenol, and the product separated by dry-flash chromatography (silica, hexane/Et_2O gradient elution) to afford compound as a mixture of *E*- and *Z*-isomers. The isomer ratio was determined by comparison of the 1-H peaks at ~7.3 and ~6.7 ppm.

3.3.1. 2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosylformaldoxime (5). 89%; white solid; mp 154–156°C (from hexane/Et_2O) (lit.[26] 152–154°C); *E*/*Z*=2.3:1.

3.3.2. Tetra-*O*-acetyl-β-D-glucopyranosylformaldoxime. 76%; mp 139–140°C (from hexane/Et_2O) (lit.[26] 155–157°C); *E*/*Z*=5:1.

3.3.3. Tetra-*O*-acetyl-β-D-galactopyranosylformaldoxime. 89%; mp 184–185°C (from hexane/Et_2O) (lit.[26] 170–172°C); *E*/*Z*=9:1.

3.3.4. Tri-*O*-acetyl-β-D-xylopyranosylformaldoxime. 83%, mp 135–137°C (from hexane/Et_2O) (lit.[26] 160–163°C).

3.3.5. Tri-*O*-acetyl-β-L-fucopyranosylformaldoxime. 90%; mp 37–39°C; *E*-isomer: $[\alpha]_D^{18}=-22$ (c=1.0, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 3311 (OH), 1744 (C=O); δ_H (250 MHz, $CDCl_3$) 1.17, (3H, d, 7-H), 1.97, 2.00, 2.17, (9H, 3s, 3×$COCH_3$), 3.83 (1H, td, 6-H), 3.98 (1H, dd, 2-H), 5.07, (1H, dd, 4-H), 5.13–5.27, (2H, m, 3-H and 5-H), 7.33, (1H, d, 1H), 8.54, (1H broad s, NOH); $J(x-y$, Hz) 1–2 6.9, 2–3 9.7, 3–4 10.2, 4–5 3.3, 5–6 1.0, 6–7 6.4; δ_C (63 MHz, $CDCl_3$) 16.2 (C-7), 20.5, 20.6 (3×$COCH_3$), 66.8, 70.4, 71.7, 72.9, 75.9, (C-2–C-6), 147.2 (C-1), 169.9, 170.1, 170.6 (3×$COCH_3$); HRMS (FAB) Found: M^++1, 318.1180. $C_{13}H_{20}NO_8$ requires 318.11889; *E*/*Z*=7:1.

3.4. General procedure for the synthesis of the hydroximoyl chlorides

Dry chlorine gas was bubbled through a solution of the pyranosylformaldoxime (ca 1 mmol) in dry dichloromethane (15 ml) at −78°C until the colour changed from blue to green. On warming to room temperature the colour faded and the solvent was removed in vacuo to afford an oil. The product was dissolved in ca 1 ml of dichloromethane and allowed to crystallise.

3.4.1. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*galacto*-heptitol (6). 87%; white powder; mp 102–103°C; $[\alpha]_D^{18}=111.8$ (c=0.7, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 3503 (OH), 1744 (C=O); δ_H (250 MHz, $CDCl_3$) 1.98, 2.04, 2.09, 2.12 (12H, 4s, 4×$COCH_3$), 3.73, (1H, ddd, 6-H), 4.23 (1H, dd, 7a-H), 4.29 (1H, dd, 7b-H), 5.06–5.33 (3H, m, 2-H, 4-H, 5-H) 5.73 (1H, t, 3-H), 8.80 (1H, broad s, NOH); $J(x-y$, Hz) 2–3 1.9, 3–4 3.3, 4–5 nd, 5–6 9.8, 6–7a 2.5, 6–7b 5.6, 7a–7b 12.3; δ_C (90 MHz, $CDCl_3$) 20.38, 20.44, 20.55 (4×$COCH_3$), 62.4 (C-7), 65.5, 67.7, 71.6, 76.5, 77.1 (C-2–C-6), 134.6 (C-1) 169.4, 169.5, 169.9, 170.2 (4×$COCH_3$); HRMS (FAB) Found: M^++1, 410.08545. $C_{15}H_{21}NO_{10}^{35}Cl$ requires 410.08540. Found: M^++1, 412.06859. $C_{15}H_{21}NO_{10}^{37}Cl$ requires 412.08245.

3.4.2. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*gulo*-heptitol. 90%; white needles; mp 157–159°C (from CH_2Cl_2); ν_{max} (cm^{-1}, Nujol) 3311 (OH), 1747 (C=O); $[\alpha]_D^{18}=-5.0$ (c=1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.97, 2.00, 2.03, 2.07 (12H, 4s, 4×$COCH_3$), 3.80 (1H, dd, 6-H), 4.14 (1H, dd, 7a-H), 4.23 (1H, dd, 7b-H), 4.31 (1H, d, 2-H), 5.14, 5.26, 5.36 (3H, 3dd, 3-H, 4-H, 5-H), 8.93 (1H, br s, NOH); $J(x-y$, Hz) 2–3 9.6, 3–4 nd, 4–5 nd, 5–6 9.8, 6–7a 2.4, 6–7b 4.6, 7a–7b 12.5; δ_C (63 MHz, $CDCl_3$) 20.4, 20.5, 20.5, 20.6 (4×$COCH_3$), 61.8 (C-7), 67.8, 68.8, 73.7, 75.7, 78.3 (C-2–C-6), 136.2 (C-1), 169.2, 169.5, 170.5, 170.8 (4×$COCH_3$); HRMS (FAB) Found: M^++1, 410.08565. $C_{15}H_{21}NO_{10}^{35}Cl$ requires 410.08540. Found: M^++1, 412.08226. $C_{15}H_{21}NO_{10}^{37}Cl$ requires 412.08245.

3.5. Synthesis of the dipyranosylfuroxans (3,4-dipyranosyl-1,2,5-oxadiazole 2-oxides)

The furoxans were prepared by dimerisation of the corresponding nitrile oxides, which were generated either by dehydration of the pyranosylnitromethane (Method A), or dehydrogenation of the pyranosylformaldoxime (Method

B), or dehydrochlorination of the pyranosyl hydroximoyl chloride (Method C). The yields are shown in Table 1.

Method A. To a solution of the pyranosylnitromethane (0.5 mmol, 1 equiv.) in dry toluene (20 ml) under nitrogen was added triethylamine (0.1–0.2 ml) and tolylene diisocyanate (3 equiv.), and the mixture heated under reflux for 7 days. After cooling to 0°C 1,2-diaminoethane (3 equiv.) was added dropwise with stirring. After 1 h the mixture was filtered through a celite pad to remove the precipitated polymeric urea. The pad was washed with toluene and chloroform and the combined organic layers evaporated to afford the product which was purified by chromatography and/or recrystallisation.

Method B. Aqueous sodium hypochlorite (5%, 16.2 mmol, 60 equiv.) was added dropwise to a stirred solution of the pyranosylformaldoxime (0.26 mmol, 1 equiv.) in H_2O/CH_2Cl_2 (1:1, 20 ml). After stirring overnight the organic layer was separated and the aqueous layer extracted with chloroform (3×50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to yield the product, which was recrystallised from the appropriate solvent.

Method C. To a solution of the pyransoyl hydroximoyl chloride (0.22 mmol, 1 equiv.) in dry Et_2O (10 ml) triethylamine (0.25 mmol, 1.1 equiv.) was added dropwise via a syringe and the solution left to stir overnight. The mixture was then poured into water, the organic layer separated and the aqueous layer extracted with chloroform (3×50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to yield the product, which was purified by recrystallisation.

3.5.1. 3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (7). White needles, mp 213–215°C (from EtOH) (Found: C, 47.9; H, 5.0, N, 3.8. $C_{30}H_{38}N_2O_{20}$ requires C, 48.2; H, 5.1, N, 3.7); $[\alpha]_D^{18}=-14.0$ (c=1.0, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 1743 (C=O), 1606 (C=N); δ_H (250 MHz, $CDCl_3$) 1.93, 1.93, 1.96, 2.02, 2.03, 2.05, 2.05, 2.06, 2.07, 2.11 (24H, 8s, 8×$COCH_3$), 3.80–3.94 (2H, m, 5′-H, 5″-H), 4.17–4.36 (4H, m, 6′a-H, 6′b-H, 6″a-H, 6″b-H), 4.93 (1H, d, $J_{1'-2'}$ 0.9, 1′-H), 5.17 (1H, d, $J_{1''-2''}$ 1.0, 1″-H), 5.10–5.36 (4H, m, 2′-H, 2″-H, 4′-H, 4″-H), 5.68–5.74 (2H, m, 3′-H, 3″-H); δ_C (63 MHz, $CDCl_3$) 20.3, 20.3, 20.4, 20.4, 20.6, 20.6 (8×$COCH_3$), 62.1, 62.7 (C-6′, C-6″), 64.9, 65.4, 66.0, 67.3, 70.5, 71.0, 71.6, 76.8, 77.1 (C-1′, C-2′, C-3′, C-4′, C-5′, C-1″, C-2″, C-3″, C-4″, C-5″), 110.5 (C-3), 152.7 (C-4), 169.2, 169.3, 169.6, 169.7, 169.9, 170.2, 170.3 (8×*C*OCH_3); m/z (FAB) 747 (M^++1), 687 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: M^++1, 747.20920. $C_{30}H_{39}N_2O_{20}$ requires 747.20962. The structure of compound **7** was confirmed by X-ray crystallography.

3.5.2. 3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (8). White solid, mp 118–120°C (from Et_2O–hexane) (Found: C, 47.9; H, 5.0, N, 3.4. $C_{30}H_{38}N_2O_{20}$ requires C, 48.2; H, 5.1, N, 3.7); $[\alpha]_D^{18}=-40.4$ (c=0.74, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 1747 (C=O), 1599 (C=N); δ_H (360 MHz, CD_3COCD_3) 1.94, 1.95, 2.00, 2.05, 2.06, 2.08, 2.14, 2.15 (24H, 8s, 8×$COCH_3$), 4.18–4.22 (2H, m, 6′b-H, 6″b-H), 4.27 (2H, m, 5′-H, 5″-H), 4.46–4.54 (2H, m, 6′a-H, 6″a-H), 5.16 (1H, d, 1′-H), 5.22 (1H, d, 1″-H), 5.33 (1H, dd, 4′-H), 5.36 (1H, dd, 4″-H), 5.53 (2H, dd, 3′-H, 3″-H), 5.64 (1H, dd, 2″-H), 5.65 (1H, dd, 2′-H); $J(x-y$, Hz) 1′2′ 10.0, 2′–3′ 9.3, 3′–4′ 9.3, 4′–5′ 9.3, 5′–6a′ nd, 5′–6a′ nd, 6a′–6b′ nd, 1″2″ 10.0, 2″–3″ 9.3, 3″–4″ 9.3, 4″–5″ 9.3, 5″–6a″ nd, 5″–6a″ nd, 6a″–6b″ nd; δ_C (63 MHz, CD_3COCD_3) 18.6, 18.7, 18.8, 18.8, 19.1, 19.1 (8×$COCH_3$), 60.9 (C-6′, C-6″), 66.9, 67.0 (C-4′, C-4″), 68.9, 69.0 (C-2′, C-2″), 69.6 (C-1′), 71.7 (C-1″), 72.6, 72.7 (C-3′, C-3″), 75.4, 75.5 (C-5′, C-5″), 111.6 (C-3), 153.4 (C-4), 168.0, 168.1, 168.6, 168.6, 169.2 (8×*C*OCH_3); m/z (FAB) 747 (M^++1), 687 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: M^++1, 747.20936. $C_{30}H_{39}N_2O_{20}$ requires 747.20962.

3.5.3. 3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,2,5-oxadiazole 2-oxide (9). White solid, mp 167–168°C (from Et_2O–hexane); $[\alpha]_D^{18}=-6.4$ (c=0.14, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.96, 1.97, 1.98, 1.99, 2.03, 2.04, 2.21, 2.22 (24H, 8s, 8×$COCH_3$), 4.03–4.24 (6H, m), 4.79 (1H, d, $J_{1'-2'}$=10.0 Hz, 1′-H), 4.82 (1H, d, $J_{1''-2''}$=10.0 Hz, 1″-H), 5.12–5.19 (2H, m), 5.47–5.66 (4H, m); δ_C (63 MHz, $CDCl_3$) 20.3, 20.4, 20.5 (8×$COCH_3$), 61.1 (C-6′, C-6″), 65.7, 66.7, 67.0, 67.1, 70.6, 71.5, 72.7, 75.0, 75.1 (C-1′-C-5′, C-1″-C-5″), 111.5 (C-3), 153.0 (C-4), 169.0, 169.3, 169.8, 169.9, 170.2 (8×*C*OCH_3); m/z (FAB) 748 (M^++2), 687 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: (M−N_2O_2)$^+$+1, 687.21371. $C_{30}H_{39}O_{18}$ requires 687.21364.

3.5.4. 3,4-Di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazole 2-oxide (10). White solid; mp 190°C; $[\alpha]_D^{18}=-33$ (c=1.0, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 1759 (C=O), 1600 (C=N); δ_H (250 MHz, $CDCl_3$) 1.94, 2.03, 2.06, 2.07, 2.07 (18H, 6s, 6×$COCH_3$), 3.40–3.52 (2H, m), 4.10–4.22 (1H, m), 4.29–4.38 (1H, m), 4.62 (2H, 2d, $J_{1'-2'}$=9.5 Hz, $J_{1''-2''}$=9.6 Hz, 1′-H, 1″-H), 5.00–5.10 (2H, m), 5.28–5.43 (4H, m); δ_C (63 MHz, $CDCl_3$) 20.0, 20.3, 20.5 (6×$COCH_3$), 66.9, 66.9 (C-6′, C-6″), 68.3, 69.7, 70.2, 71.6, 72.3, 72.4, 73.9, 76.3 (C-1′-C-5′, C-1″-C-5″), 112.7 (C-3), 153.7 (C-4), 169.3, 169.5, 169.6, 169.8, 169.9 (6×*C*OCH_3); m/z (FAB) 603 (M^++1), 543 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: M^++1, 603.17504. $C_{24}H_{33}N_2O_{16}$ requires 603.17518.

3.5.5. 3,4-Di(2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl)-1,2,5-oxadiazole 2-oxide (11). White solid; mp 213°C (from hexane–EtOAc); $[\alpha]_D^{18}=27.8$ (c=0.29, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.23–1.28 (6H, 2t, 2×CH_3), 2.01, 2.02, 2.03, 2.04, 2.26, 2.28 (18H, 6s, 6×$COCH_3$), 3.87–4.00 (2H, 2dd, 5′-H, 5″-H), 4.85 (2H, 2dd, 1′-H, 1″-H), 5.19 (2H, 2dd, 4′-H, 4″-H), 5.39 (2H, dd, 3′-H, 3″-H), 5.63 (2H, 2dd, 2′-H, 2″-H); $J(x-y$, Hz) 1′–2′ 10.1, 2′–3′ nd, 3′–4′ nd, 4′–5′ 1.0, 5′–6′ 6.4, 1″2″ 10.1, 2″–3″ nd, 3″–4″ nd, 4″–5″ 1.0, 5″–6″ 6.4; δ_C (63 MHz, $CDCl_3$) 16.7, 16.8 (2×CH_3), 20.8, 21.0, 21.1, 21.2 (6×$COCH_3$), 66.4, 67.0, 70.7, 70.7, 71.1, 72.4, 72.7, 72.9, 74.2, 74.3 (C-1′-C-5′, C-1″-C-5″), 112.5 (C-3), 153.8 (C-4), 169.7, 170.0, 170.5, 170.6, 170.9, 170.9 (6×*C*OCH_3); m/z (FAB) 681 (M^++1), 571 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: M^++1, 631.19732. $C_{26}H_{35}N_2O_{16}$ requires 631.19866.

3.5.6. 3,4-Di(2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (15). White solid; mp 131–133°C (from hexane) (Found: C, 54.7; H, 6.8, N, 4.8. $C_{20}H_{38}N_2O_{12}$ requires C, 54.7; H, 6.7, N, 4.9);

$[\alpha]_D^{18}$=29.1 (c=0.23, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 1606 (C=N); δ_H (600 MHz, $CDCl_3$) 1.35, 1.37, 1.48, 1.48, 1.57, 1.58, 1.58, 1.64 (24H, 8s, 8×CCH_3), 3.28 (1H, dt, 5″-H), 3.33 (1H, dt, 5′-H), 3.73 (1H, t, 6ax′-H), 3.80 (1H, dd, 4′-H), 3.90 (1H, t, 6ax″-H), 3.97 (dd, 4″-H), 3.99 (1H, dd, 6eq″-H), 4.01 (1H, dd, 6eq′-H), 4.18 (1H, dd, 3″-H), 4.21 (1H, dd, 3′-H), 4.53 (1H, t, 2′-H), 4.54 (1H, t, 2″-H), 5.05 (H, d, 1′-H), 5.21 (1H, d, 1″-H); J(x–y, Hz) 1′–2′ 2.6, 2′–3′ 5.2, 3′–4′ 7.9, 4′–5′ 10.1, 5′–6ax′ 10.7, 5′–6eq′ 5.5, 6ax′–6eq′ 10.2, 1″–2″ 2.4, 2″–3″ 5.1, 3″–4″ 7.9, 4″–5″ 10.1, 5″–6ax″ 10.7, 5″–6eq″ 5.5, 6ax″–6eq″ 10.1; δ_H (600 MHz, CD_3COCD_3) 1.31, 1.32, 1.35, 1.36, 1.52, 1.53, 1.54, 1.56 (24H, 8s, 8×CCH_3), 3.39 (1H, dt, 5″-H), 3.48 (1H, dt, 5′-H), 3.82 (1H, t, 6ax″-H), 3.85–3.96 (5H, m, 4′-H, 4″-H, 6ax′-H, 6eq′-H, 6eq″-H), 4.19 (1H, dd, 3″-H), 4.28 (1H, dd, 3′-H), 4.64 (1H, dd, 2″-H), 4.68 (1H, dd, 2′-H), 5.31 (H, d, 1′-H), 5.46 (1H, d, 1″-H); J(x–y, Hz) 1′–2′ 2.7, 2′–3′ 5.3, 3′–4′ 7.9, 4′–5′ 10.0, 5′–6ax′ 10.0, 5′–eq′ 5.7, 6ax″–6eq″ nd, 1″–2″ 2.5, 2″–3″ 5.2, 3″–4″ 7.9, 4″–5″ 10.0, 5″–6ax″ 10.1, 5″–6eq″ 5.7, 6ax″–eq″ 10.7; δ_C (63 MHz, $CDCl_3$) 18.7, 18.7, 26.4, 27.3, 28.3, 28.4, 28.7, 28.9 (8×CCH_3), 61.5, 61.6, 71.1, 71.4, 72.3, 72.5, 72.6, 73.8, 75.4, 75.8 (C-1′–C-5′, C-1″–C-5″), 61.5, 61.6 (C-6′, C-6″), 99.9, 100.0, 110.4, 110.5 (4×CCH_3), 112.× (C-3), 153.1 (C-4); HRMS (FAB) Found: M^++1, 571.24946. $C_{20}H_{39}N_2O_{12}$ requires 571.25030.

3.6. Preparation of 3,4-di(β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (16)

A solution of 3,4-di(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (**8**) (30 mg, 0.04 mmol) in methanol (10 ml) was treated with a saturated ammonia solution in methanol (10 ml). After stirring overnight TLC indicated the absence of starting material and formation a more polar product. The reaction mixture was concentrated in vacuo and co-evaporated with methanol (3×10 ml) to afford 3,4-di-(β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (**16**) as an oil (15 mg, 91%); $[\alpha]_D^{18}$=+35.7 (c=0.14, H_2O); δ_H (250 MHz, D_2O) 3.36–3.70, 3.83–4.01 (12H, 2m, 2′-H, 3′-H, 4′-H, 5′-H, 6′a-H, 6′b-H, 2″H, 3″-H, 4″-H, 5″-H, 6″a-H, 6″b-H), 4.56, 4.60 (2H, 2d, $J_{1'-2'}$=10.0 Hz, $J_{1''-2''}$=10.0 Hz, 1′-H, 1″-H); δ_C (90 MHz, D_2O) 61.4, 61.4 (C-6′, C-6″), 69.9, 70.0, 70.7, 71.8, 72.5, 74.5, 77.2, 77.2, 80.9, 81.1 (C-1′–C5′, C-1″–C-5″), 115.4 (C-3), 156.0 (C-4); m/z (FAB) Found: M^++1, 411.12501. $C_{14}H_{23}N_2O_{12}$ requires M^++1 411.12510.

3.7. Crystal structure of furoxan 7

Diffraction data were collected with graphite-monochromated Cu Kα radiation (λ=1.54184 Å) on a Stoe Stadi-4 diffractometer equipped with an Oxford Cryosystems low-temperature device operating at 150 K. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 (Shelxtl).[27] The 2-oxide substituent of the 1,2,5-oxadiazole ring is disordered over the 2- and 5-positions in the ratio 0.85:0.15(2). All non-H atoms except for the minor component O-atom were refined with anisotropic displacement parameters; H-atoms were placed in idealised positions. Crystal data: $C_{30}H_{38}N_2O_{20}$, M=746.62, triclinic, a=7.839(3), b=8.6191(18), c=13.229(3) Å, α=97.803(11)°, β=97.599(16)°, γ=91.07(2)°, V=877.2(4) $Å^3$, space group $P1$ (the compound was known to be chiral); T=150 K, Z=1, D_c=1.413 Mgm^{-3}, colourless block, 0.38×0.20×0.20 mm^3. The final conventional R-factor (based on F and 2694 data with $F>4\sigma(F)$ was 6.71%; wR2 (based on F^2 and all 3093 data used in refinement) was 18.37%. The final difference map extremes were 0.44 and −0.37e $Å^{-3}$. The Flack parameter[28] was 0.1(3); this means that the diffraction data do not establish the 'hand' of the structure, although this is unambiguous from the synthetic route used.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number 186410. Copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033 or email: deposit@ccdc.cam.ac.uk).

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