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Deoxyhydroxyamino analogs of sugars: derivatives of methyl 2,3-dideoxy-2-hydroxyamino-α-D-*arabino*- and -*lyxo*-hexopyranosides

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ABSTRACT

N-Substituted hydroxylamines reacted both regio- and stereo-specifically with ethyl 2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**1**) to give *N*-substituted ethyl 2,3-dideoxy-2-hydroxyamino-α-D-*threo*-hexopyranosid-4-uloses (**2**–**7**), whereas *O*-methylhydroxylamine gave a mixture of *O*-methyloximes (**8**–**10**), including the product of both stereospecific conjugate addition and oximation (**10**). Sodium borohydride reduction of ethyl 2,3-dideoxy-2-(*N*-hydroxy-*N*-methylamino)- and 2,3-dideoxy-2-(*N*-hydroxy-*N*-isopropylamino)-α-D-*threo*-hexopyranosid-4-uloses proceeded stereoselectively, and the major product had the α-D-*arabino* configuration. The conformations of these compounds were established using n.m.r. spectroscopy and X-ray diffraction for **3** and **19**. The major interest of these deoxyhydroxyamino sugars was their easy oxidation into spin-labelled sugar analogs whose conformation could be studied by e.s.r. spectroscopy.

INTRODUCTION

Sugar derivatives in which one oxygen atom is replaced with a hydroxyimino group constitute potentially interesting biochemical probes. They are structurally similar to their natural counterparts and have the unique property of oxidising spontaneously in air to give a stationary concentration of the corresponding free radical sufficient to provide good e.s.r. spectra and insufficient to degrade significantly the resolution of their n.m.r. spectra. Such compounds have been prepared by nucleophilic additions to sugar nitrones[1,2], reduction of sugar oximes[3], and conjugate addition of *N*-substituted hydroxylamines to sugar enolones[4]. We now describe the application of the last method to an unblocked ethyl hex-2-enopyranosid-4-ulose.

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RESULTS AND DISCUSSION

Ethyl 2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose[5] (**1**) reacted with a series of *N*-substituted hydroxylamines to give, exclusively and in good yields, the products of conjugate addition **2**–**7**. Probably owing to stereoelectronic factors[6], the reaction proceeded stereospecifically, leading to the *threo* isomer. Compounds **6** and **7**, which were not stable, were not isolated but immediately reduced (see below). Under similar conditions, *O*-methylhydroxylamine gave mostly the *E* (**8**) and *Z* (**9**) oximes, the product of the conjugate addition being isolated as the oxime **10**. Even in the presence of an excess of reagent, **2**–**7** did not yield nitrones, thus showing a reduced reactivity of their carbonyl groups, which is explained partly by an intramolecular nucleophilic attack of the hydroxyl group on the carbonyl group. This situation was particularly clear for **3**, which existed (^{1}H-n.m.r. data) as a mixture of **3** and **11**, the *ratio* of which depended strongly on the solvent (2.5:1 in chloroform, 3.75:1 in methyl sulfoxide, > 19:1 in pyridine). From the n.m.r. data collected in Tables I and II, it is clear that C-4 of **11** is sp^3 hybridised (δ 105, $J_{3,3}$ 11.0 Hz, C-4) and that the dihedral angle H-2–C-2–C-3–H-$3_{pro\text{-}S}$ is close to 90°. Another argument in favour of this bicyclic structure is the constancy of the $J_{H,H}$ values with changes in the polarity of the solvent. This situation contrasts with the conformational instability of the 4-keto analogs **2**–**7** (Table III). An X-ray diffraction analysis (Tables IV and V) showed that **3** exists in a $^3S_5$ conformation (Fig. 1) which roughly corresponds to the n.m.r. data observed for a solution in methyl sulfoxide, whereas, in solution in chloroform, the conformation was $^3S_1$. This finding, and the fact that the related methyl 4,6-di-*O*-benzoyl-2-deoxy-2-(*N*-hydroxy-*N*-methylamino)-α-D-*arabino*-hexopyranosid-4-ulose[4] exists in a $^{3,0}B$ form, showed that this type of compound has many low-energy conformational states available. Nevertheless, Tables I–III show close conformational behaviour for **1**, **3**, and **5**.

Acetylation of **3** gave an unresolvable mixture of acetylated derivatives to which structures **12** and **13** were assigned tentatively on the basis of the n.m.r. spectrum of the mixture [major compound: Ac (2.10), H-1 (5.15), H-2 (4.05), H-3a (2.65), H-3b (2.77 p.p.m.); $J_{1,2}$ 2.5, $J_{2,3a}$ 6.0, $J_{2,3b}$ 5.5, and $J_{3a,3b}$ 15.0 Hz]. After chromatography, the only compound obtained (35%) *via* a nucleophilic displacement on nitrogen[7] was the aziridine **14** [δ 43.8 (C-2) and 45.2 (C-3); $J_{2,3}$ 7.0 Hz].

Reduction of **2** with sodium borohydride gave a resolvable mixture of **15** (40%) and **16** (15%) which were acetylated to give **17** and **18**, respectively. From their n.m.r. data (Tables II and III), pure $^4C_1$ conformations could be assigned to **15** and **17**, whereas **18** most probably existed as a mixture of *S* forms. Similar reduction of **6** led almost exclusively to **19**, readily acetylated to give **20**. Reduction of **7** gave **21**, a deuterated analog of **19**. An X-ray diffraction study of **19** (Tables IV and V) revealed the $^4C_1$ conformation (Fig. 2). Compounds **15**, **16**, and **19** are close analogs of natural glycosides, but neither **15** nor **19** inhibited α-D-mannosidase. In contrast, the similarity in structure of **19** and α-D-mannopyranosides was reflected in its immunochemical properties. The concentration of **19** necessary to inhibit the glycogen–concanavalin A precipitation (to halve the absorbance) was twice that of methyl α-D-mannopyranoside. For

TABLE I

^{1}H-N.m.r. data

Compound	Chemical shifts (δ in p.p.m.)									Coupling constants (Hz)								
	H-1	*H-2*	*H-3a*	*H-3b*	*H-4*	*H-5*	*H-6a*	*H-6b*	*Other*	$J_{1,2}$	$J_{2,3a}$	$J_{2,3b}$	$J_{3a,3b}$	$J_{3a,4}$	$J_{3b,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$
2[a]	5.15	3.08	2.73	2.73		4.09	3.85	3.92	NMe (2.70)	1.5	5.5	5.5					3.0	3.0
3[a]	5.13	~3.8	2.60	2.73		4.08	4.10	4.10		1.8	6.0	4.0	16.5				4.0	4.0
5[a]	5.18	3.23	2.74	2.84		4.07	~3.80	~3.80	N-CH_2Ph (3.80)	2.0	5.5	5.5	16.0				3.0	3.0
[6][a]	5.10	3.10	2.72	2.72					N-CH (3.10)									
8[a]	5.13	6.16	6.48			4.62	3.90	3.90	NOMe (3.87)	3.5	10.0						5.0	5.0
9[a]	5.29	6.18	6.31			4.88	3.96	4.08	NOMe (3.89)	3.0	10.0						3.5	5.5
10[a]	4.93	3.27	2.59	2.95		4.34	3.80	3.92	NOMe (3.52, 3.86)	2.5	5.5	4.0	16.0				5.0	5.0
11[a]	4.98	~3.8	2.23	2.73						3.0	5.0	0	11.0					
14[a]	5.37	3.08	3.0			4.15	~3.9	~3.9		1.0	7.0						3.0	3.0
15[b]	5.51	3.11	2.40	2.51	4.50	4.20	4.28	4.43	NMe (2.88)	2.0	4.0	4.0	14.0	10.0	5.5	9.0	6.0	3.0
16[b]	5.65	2.88	2.22	2.22	4.04	~4.25	~4.25	~4.25	NMe (2.86)									
17[a]	4.88	3.03	1.94	2.27	5.01	3.96	4.20	4.20	NMe (2.83) Ac (2.04, 2.08, 2.11)	2.0	4.5	4.5	13.0	9.5	5.0	9.5	4.5	4.5
18[a]	4.88	2.80	1.92	2.26	4.98	~4.15	~4.15	~4.15	NMe (2.78) Ac (2.04, 2.07, 2.07)	3.5	8.0	5.0	14.0	6.0	6.0	3.5		
19[c]	4.82	2.74	1.64	1.78	———	3.3–3.8	———		N-CH (3.05)	1.0	4.0	4.0	13.0	9.0	4.0			
20[a]	4.90	3.33	1.88	2.21	5.09	3.94	4.18	4.24	N-CH (3.33) Ac (2.04, 2.07, 2.12)	2.0	5.0	5.0	14.0	9.5	5.0	9.5	3.0	5.5

[a] In $CDCl_3$. [b] In pyridine-d_5. [c] In methyl sulfoxide-d_6.

TABLE II

^{13}C-N.m.r. data ($CDCl_3$)

Compound	*Chemical shifts (p.p.m.)*							*Coupling constants (Hz)*		
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Other*	$J_{H\text{-}1,C\text{-}1}$	$J_{H\text{-}2,C\text{-}2}$	$J_{H\text{-}3,C\text{-}3}$
2	97.1	66.55	36.2	208.1	76.2	62	NCH_3=45.3	172	151	125
3	98.0	66.5	35.7	207.2	75.5					
5	97.5	64.3	36.4	208.3	75.7	63.2		170	138	134
11	97.2	68.05	33.1	105	74.1					
14	93.5	43.8 or 45.2	45.2 or 43.8	201.4	76.8					

TABLE III

Effect of solvent on the $J_{H,H}$ values of the methyl 2,3-dideoxy-3-hydroxyamino-α-D-hexopyranosid-4-ulose derivatives **2**, **3**, and **5**

Compound	*Solvent*	*Coupling constants (Hz)*		
		$J_{1,2}$	$J_{2,3a}$	$J_{2,3b}$
2	$CDCl_3$	~1.5	5.5	5.5
	$(CD_3)_2SO$	3.0	5.0	11.0
3	$CDCl_3$	1.8	6.0	4.0
	$(CD_3)_2SO$	4.0	5.0	11.0
5	$CDCl_3$	2.0	5.5	5.5
	$(CD_3)_2SO$	3.8	4.5	11.0

the complete inhibition of agglutination of rabbit red cells by the same lectin, the necessary molar concentration of **19** was ~8 times that of methyl α-D-mannopyranoside.

The major interest of these compounds resides in their spontaneous oxidation in air to give nitroxyl radicals whose e.s.r. data, measured in solvents more polar than chloroform, are collected in Table VI. Although the values observed correspond to time-averaged spectra, they provide useful information. The nitroxyl derived from **2** presented three equal, long-range, hyperfine coupling constants. When submitted to base-catalysed exchange with deuterium oxide, **2** gave a mixture of the two monodeuterated 3-epimers, each of which had two long-range couplings. Three hyperfine couplings with H-1 and H-3 were also observed for **5**, but only one for **3**, **4**, and **16**, and none for **15** and **19**. Some correlation seems to exist between these couplings with vicinal protons (H-1, H-3a, H-3b) and $a_{H\text{-}2}$, indicative of torsion along the N–C-2 bond. As already stated[1,4,8], hyperfine couplings as $a_{H\text{-}2}$ furnish information on structure. The small values encountered for **2**–**5** correspond to a di(pseudo-equatorial) orientation of RNO· and EtO in the $^3S_5$ conformation. This situation favours the conformer in which the plane of the nitroxyl group eclipses the H-2–C-2 bond, and leads to a small hyperfine coupling. For compounds in which the RNO· group is axial, as in the $^4C_1$ chair forms of

TABLE IV

Crystal data for **3** and **19**

Compound	**3**	**19**
Formula	$C_{14}H_{19}NO_5$	$C_{11}H_{23}NO_5$
Molecular weight	281.3	249.3
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
Crystal size (mm)	$0.30 \times 0.35 \times 0.45$	$0.10 \times 0.25 \times 0.25$
Unit-cell determination[a]		
No. of reflections	28	28
2θ range (°)	28–38	24–30
a (Å)	9.8476(6)	8.1254(5)
b (Å)	7.4861(6)	11.2219(8)
c (Å)	10.3660(7)	15.3255(7)
β (°)	110.388(5)	–
V (Å^3)	716.31(9)	1397.3(2)
Z	2	4
D_c (g.cm^{-3})	1.30	1.19
F_{000}	300	544
μ (mm^{-1})	0.093	0.087
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.62	0.60
No. of measured reflections	1587	1484
No. of observed reflections	1385	942
Criterion for observed	$\|F_o\| > 4\sigma(F_o)$	$\|F_o\| > 4\sigma(F_o)$
No. of parameters	186	163
Refinement (on F)	full-matrix	full-matrix
Weighting scheme	$\omega = 1/\sigma^2(F)$	$\omega = 1/\sigma^2(F)$
Max. and average Δ/σ	0.138, 0.058	0.338, 0.022
Max. and min. $\Delta\rho$ (eÅ^{-3})	0.21, −0.20	0.34, −0.42
S	3.12	1.85
R, ωR (%)	4.5, 4.2	6.0, 4.1

[a] Unit-cell determined by least-squares fit.

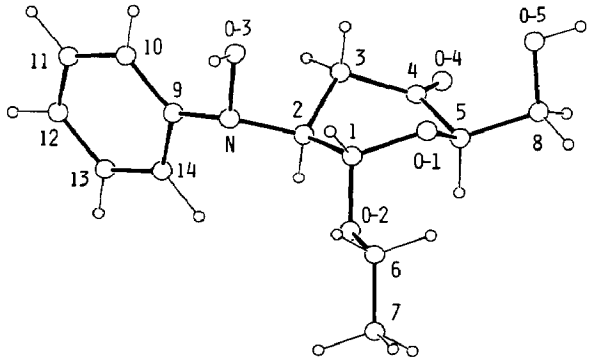


Fig. 1. Crystal structure of compound **3**

TABLE V

Selected bond lengths (Å), bond angles (°), and torsion angles (°) for **3** and **19**

	3	**19**		**3**	**19**
O-1–C-1	1.424(4)	1.430(8)	C-2–N	1.465(5)	1.488(8)
O-1–C-5	1.435(4)	1.443(7)	C-2–C-3	1.550(5)	1.519(9)
O-2–C-1	1.414(4)	1.408(8)	C-3–C-4	1.500(6)	1.508(9)
O-2–C-6	1.447(4)	1.414(10)	C-4–C-5	1.528(5)	1.521(9)
O-3–N	1.438(5)	1.468(7)	C-5–C-8	1.518(6)	1.514(9)
O-4–C-4	1.214(4)	1.453(8)	C-6–C-7	1.479(7)	1.465(12)
O-5–C-8	1.420(6)	1.417(9)	C-9–N	1.436(4)	1.505(9)
C-1–C-2	1.538(4)	1.523(9)			
C-1–O-1–C-5	115.4(2)	114.0(5)	C-1–C-2–C-3	109.9(3)	108.3(5)
C-1–O-2–C-6	111.7(3)	115.0(6)	C-2–C-3–C-4	108.9(3)	112.2(5)
O-3–N–C-2	106.4(3)	103.7(5)	O-4–C-4–C-3	124.2(3)	106.1(5)
O-3–N–C-9	110.0(3)	105.3(4)	O-4–C-4–C-5	121.2(4)	111.9(5)
C-2–N–C-9	115.5(3)	113.9(5)	C-3–C-4–C-5	114.5(3)	109.1(5)
O-1–C-1–O-2	111.2(3)	111.8(5)	O-1–C-5–C-4	109.4(3)	108.5(5)
O-1–C-1–C-2	112.7(3)	112.4(5)	O-1–C-5–C-8	106.4(3)	105.9(5)
O-2–C-1–C-2	107.7(3)	106.2(5)	C-4–C-5–C-8	111.6(3)	114.9(5)
N–C-2–C-1	108.7(3)	106.6(5)	O-2–C-6–C-7	109.9(4)	109.7(8)
N–C-2–C-3	113.3(3)	113.5(5)	O-5–C-8–C(5)	106.4(4)	114.4(5)
C-5–O-1–C-1–C-2	−43.2(4)	−58.5(7)	O-1–C-1–O-2–C-6	73.7(4)	66.7(7)
O-1–C-1–C-2–C-3	−18.4(4)	52.2(7)	C-1–O-2–C-6–C-7	−177.8(4)	175.5(6)
C-1–C-2–C-3–C-4	58.8(4)	−53.1(7)	O-1–C-1–C-2–N	−142.9(3)	−70.3(6)
C-2–C-3–C-4–C-5	−40.6(4)	57.4(7)	C-1–C-2–N–O-3	71.1(3)	−76.7(5)
C-3–C-4–C-5–O-1	−16.3(5)	−58.4(6)	C-2–C-3–C-4–O-4	138.1(4)	178.2(5)
C-4–C-5–O-1–C-1	62.4(4)	60.4(6)	C-3–C-4–C-5–C-8	−133.7(4)	−176.6(5)
C-5–O-1–C-1–O-2	77.8(3)	60.9(7)	C-4–C-5–C-8–O-5	61.3(4)	39.3(8)

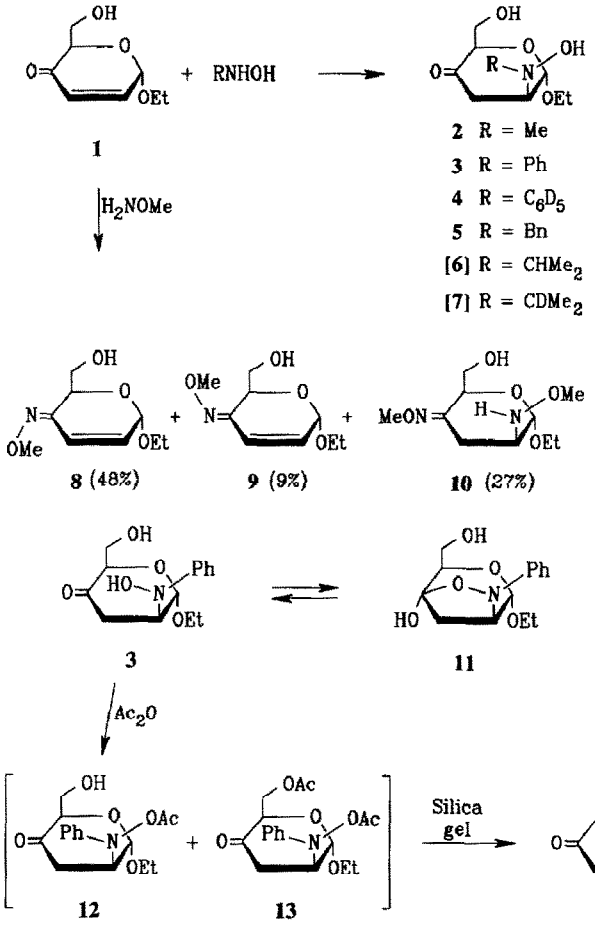
15 and **19** and in some *S* conformations of **16**, some conformers that correspond to large hyperfine couplings are energetically favourable, thus increasing the time-averaged value of $a_{H\text{-}2}$. A detailed study, involving quantum mechanics, molecular mechanics, and variable temperature e.s.r., of the conformational properties of the nitroxyl derived from **19** will be reported elsewhere[9].

EXPERIMENTAL

General methods. — See ref. 2. Optical rotations were obtained for solutions in chloroform. Column chromatography was conducted on silica gel (Merck, 70–230 mesh).

*Crystallographic data**. — The data are summarised in Table IV. Selected bond

* Lists of structure factors, hydrogen co-ordinates, and anisotropic thermal parameters have been deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/458/*Carbohydr. Res.*, 212 (1991) 65–76.



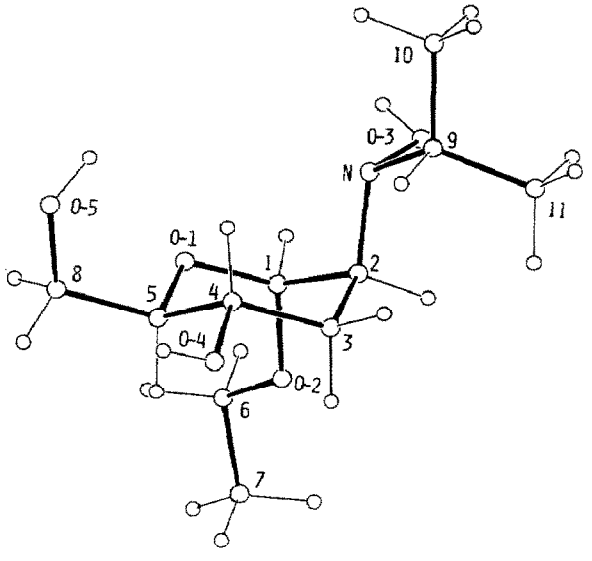
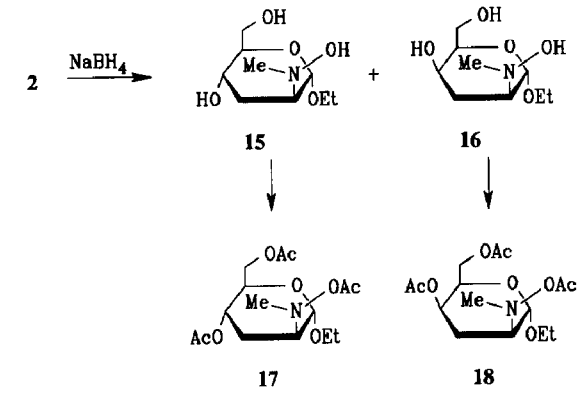
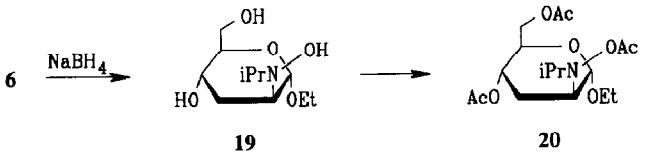


Fig. 2. Crystal structure of compound **19**

lengths, bond angles, and torsional angles are reported in Table V. Data were collected at room temperature on a Nonius CAD4 diffractometer (Mo-K_α). The structures were solved by direct methods (MULTAN 87)[10] and refined by full-matrix least squares





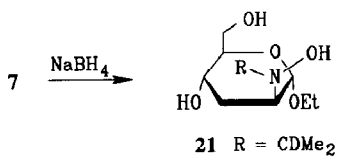


TABLE VI

E.s.r. data for the free radicals derived from deoxyhydroxyamino sugars

Compound	*Temp.* (°)	g	a_N	$a_{H\text{-}2}$	$a_{H\text{-}1'}$	$a_{H\text{-}2a}$	*or* $a_{H\text{-}2b}$	a_{CH3}	a_{CH2Ph}	a_{CHMe2}	a_{Ph}
2[a]	50	2.0058	14.7	4.8	0.7	0.7	0.7	12.3			
(3-^{2}H)-**2**[a]	50		14.7	4.8	0.7	0.7	0.7	12.3			
3[a]	25	2.0058	10.7	3.3	0.5						1, 1, 3.20, 3.20, 3.20
4[a]	60	2.0056	10.8	3.75	0.8						
5[a]	60	2.0060	14.45	3.8	0.7	0.7	0.7		9.4, 8.1		
15[b]	70	2.0057	16.3	10.5				14.0			
16[b]	60	2.0056	16.45	7.65	0.6			14.25			
19[a]	150	2.0056	14.75	6.75						5.0	

[a] In diglyme. [b] In H_2O

analysis (XTAL 2.4)[11]. All co-ordinates of the hydrogen atoms were calculated with the exception of those involved in the hydroxyl groups, which have been observed and refined.

The pyranose ring adopts a twist–boat conformation in compound **3** with a pseudo C_2 axis passing through the carbonyl group and C-1 [minimum value of asymmetry parameter[12] ΔC_2(C-1) = 0.063(1)], whereas a quasi chair conformation was observed for **19**. In each compound, the molecular packing was fixed by a network of hydrogen bonds that involved all the potential donors; **3**: O-3...O-5 $1-x$, $1/2+y$, $-z = 2.852(4)$; O-5...O-2 x, $y-1$, $z = 2.884(5)$; O-3...O-1 $1-x, 1/2+y$, $-z = 3.064(3)$ Å; **17**: O-3...O-5 $1/2+x, 1/2-y$, $z = 2.755(7)$; O-5...O-4 $1/2+x$, $1/2-y$, $-z = 2.895(6)$; O-4...N $x-1/2, 1/2-y$, $-z = 3.067(7)$ Å.

*Ethyl 2,3-dideoxy-2-(*N*-hydroxy*-N*-methyl*amino*)*-α-D-threo-*hexopyranosid-4-ulose* (**2**). — A solution of **1** (0.2 g, 1.16 mmol) and *N*-hydroxy-*N*-methylammonium chloride (0.18 g, 2.15 mmol) in 10:1 ethanol–water (4 mL) was brought to pH 6 (sodium acetate). The solution was stored for 30 min at room temperature, the solvents were distilled, and toluene was evaporated from the residue. Short-column chromatography (19:1 ethyl acetate–chloroform) then gave **2** (0.17 g, 68%), m.p. 102–103° (from di-isopropyl ether), $[\alpha]_D^{24}$ +166° (*c* 1); ν_{max}^{KBr} 3250 (OH) and 1730 cm^{-1} (C=O). E.i.-mass spectrum: *m/z* 219 (3%, M^+), 189 (5), 174 (42), 156 (15), 142 (15), 127 (100), 112 (52), 97 (77), 84 (77), 73 (55), and 57 (69).

Anal. Calc. for $C_9H_{17}NO_5$ (219.34): C, 49.31; H, 7.82; N, 6.39. Found: C, 49.18; H, 7.75; N, 6.40.

*Ethyl 2,3-dideoxy-2-(*N*-hydroxy*-N*-phenylamino*)*-α-D-hexopyranosid-4-ulose* (**3**). — A solution of **1** (0.17 g, 1 mmol) and phenylhydroxylamine (0.17 g, 1.56 mmol) in tetrahydrofuran (2 mL) was kept for 30 min at room temperature, then concentrated. Column chromatography (4:1 ether–hexane) of the residue gave **3** (0.21 g, 75%), m.p. 128–129° (from CH_2Cl_2–hexane), $[\alpha]_D^{23}$ +61° (*c* 1.1), λ_{max}^{EtOH} 204 (ε 12 500) and 241 nm (7500), ν_{max}^{KBr} 3400 (OH) and 1720 cm^{-1} (C=O). E.i.-mass spectrum: *m/z* 281 (7%, M^+), 265 (11), 234 (3), 220 (7), 206 (3), 191 (8), 173 (18), 160 (12), 146 (25), 135 (32), 127 (68), 119 (100), 104 (50), 97 (27), 91 (29), 85 (73), 77 (79), 71 (11), 65 (18), 57 (48), and 51 (27).

Anal. Calc. for $C_{14}H_{19}NO_5$ (281.31); C, 59.78; H, 6.81; N, 4.98. Found: C, 59.54; H, 6.78; N, 4.95.

*Ethyl 2-(*N*-benzyl*-N*-hydroxyamino*)*-2,3-dideoxy-*α-D-threo-*hexopyranosid-4-ulose* (**5**). — A solution of **1** (0.14 g, 0.81 mmol) and *N*-benzyl-*N*-hydroxyammonium chloride (0.14 g, 0.877 mmol) in 10:1 ethanol–water (3.3 mL) was brought to pH 6 (sodium acetate), then kept for 30 min at room temperature. After distillation of the solvents, the residue was extracted with ethyl acetate (30 mL), and the extract was washed with water (20 mL), dried ($MgSO_4$), and concentrated. Column chromatography (ether) of the residue afforded **5** (0.22 g, 92%), isolated as a syrup, $[\alpha]_D^{23}$ +105° (*c* 0.8); $\nu_{max}^{CCl_4}$ 3400 (OH) and 1710 cm^{-1} (C=O). E.i.-mass spectrum: *m/z* 204 (0.8%, $[M^+ - PhCH_2]$, 167 (0.4), 149 (2), 123 (13), 127 (12), 112 (21), 91 (100), 83 (22), 65 (11), and 55 (17).

Anal. Calc. for $C_{15}H_{21}NO_5$ (295.34): C, 61.00; H, 7.17; N, 4.74. Found: C, 60.85; H, 6.94; N, 4.70.

Ethyl (E)- (**8**) *and* (Z)-*2,3,4-trideoxy-4-methoxyimino*-α-D-glycero-*hex-2-enopyranosides* (**9**). — A solution of **1** (0.20 g, 1.16 mmol) and methoxyammonium chloride (0.18 g, 2.16 mmol) in 10:1 ethanol–water (4.4 mL) was kept for 30 min at pH 6 (sodium acetate) and room temperature, then concentrated. The residue was extracted with dichloromethane (30 mL), and the extract was washed with water (20 mL), dried ($MgSO_4$), and concentrated. Column chromatography (2:1 ether–hexane) of the residue afforded **8** (0.11 g, 48%), **9** (20 mg, 9%), and **10** (80 mg, 27%). Compound **8** had m.p. 93–94° (from CH_2Cl_2–hexane), $[\alpha]_D^{25}$ −76° (*c* 0.7), R_F 0.35 (Et_2O–hexane); λ_{max}^{EtOH} 204 (ε 6300) and 240 nm (8800); ν_{max}^{KBr} 3300 cm^{-1} (OH). E.i.-mass spectrum: *m/z* 201 (3%, M^+), 170 (98, $[M^+ - CH_2OH]$), 156 (35, $[M^+ - EtO]$), 142 (18), 125 (27), 114 (20), 110 (18), 99 (7), 96 (38), 82 (100), 68 (16), 55 (51), and 52 (11).

Anal. Calc. for $C_9H_{15}NO_4$ (201.22): C, 53.72; H, 7.51; N, 6.96. Found: C, 53.48; H, 7.44; N, 6.92.

Compound **9** was a syrup, R_F 0.24 (Et_2O–hexane, 2:1); ν_{max}^{film} 3400 cm^{-1} (OH). E.i.-mass spectrum: *m/z* 201 (5%, M^+), 170 (36), 156 (46), 142 (17), 125 (53), 110 (42), 96 (40), 82 (100), 68 (23), and 54 (57).

Ethyl 2,3,4-trideoxy-2-methoxyamino-4-methoxyimino-α-D-threo-*hexopyranoside* (**10**). — Prepared as described under **8** and **9**, **10** was a syrup, R_F 0.18 (2:1 ether–hexane), $[\alpha]_D^{23}$ +98° (*c* 1); ν_{max}^{film} 3440 (OH) and 3240 cm^{-1}. E.i.-mass spectrum: *m/z* 248 (2%, M^+), 217 (2, $[M^+ - CH_2OH]$), 203 (21, $[M^+ - EtO]$), 171 (45), 156 (29), 125 (40), 116 (33), 111 (93), 99 (17), 93 (60), 88 (45), 83 (100), 67 (36), 60 (36), and 56 (67).

Anal. Calc. for $C_{10}H_{20}N_2O_5$ (248.28): C, 48.38; H, 8.12; N, 11.28. Found: C, 48.58; H, 8.18; N, 11.03.

Ethyl 2,3-dideoxy-2,3-phenylepimino-α-D-lyxo-*hexopyranosid-4-ulose* (**14**). — A solution of **3** (0.12 g, 0.43 mmol) in acetic anhydride (1 mL) was kept overnight at room temperature, then concentrated. T.l.c. (ether–hexane, 4:1) of the residue revealed **12** (R_F 0.48) and **13** (R_F 0.23), the structures of which were assigned tentatively by ^{1}H-n.m.r. spectroscopy. These compounds were destroyed upon column chromatography (4:1 ether–hexane), which afforded only **14** (40 mg, 36%), m.p. 79–80° (from hexane), $[\alpha]_D^{26}$ +171° (*c* 0.4); λ_{max}^{EtOH} 204 (13 300) and 227 nm (12 000); ν_{max}^{KBr} 3380 (OH) and 1710 cm^{-1} (C=O). E.i.-mass spectrum: *m/z* (56%, M^+), 234 (6), 176 (40), 146 (58), 130 (35), 104 (98), 93 (56), 77 (100), and 57 (35).

Anal. Calc. for $C_{14}H_{17}NO_4$ (263.30): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.87; H, 6.49; N, 5.25.

Ethyl 2,3-dideoxy-2-(N-hydroxy-N-methylamino)-α-D-arabino- (**15**) *and* -α-D-lyxo-*hexopyranosides* (**16**). — To a solution of **2** (0.2 g, 0.91 mmol) in methanol (4 mL) was added a solution of sodium borohydride (0.15 g, 4 mmol) in water (0.8 mL). After 15 min at room temperature, the excess of borohydride was destroyed with acetone (5 mL), and the solvent was distilled. Column chromatography (9:1 ethyl acetate–methanol) of the residue afforded **15** (80 mg, 40%) and **16** (30 mg, 15%), both syrups. E.i.-mass spectrum: *m/z* 176 (9%, $[M^+ - EtO]$), 158 (21), 149 (7), 130 (18), 112 (11), 99 (7), 94 (7), 85 (18), 81 (16), 73 (29), and 57 (100).

Anal. Calc. for $C_9H_{19}NO_5 \cdot 0.25\,H_2O$ (221.26): C, 47.88; H, 8.71; N, 6.20. Found: C, 47.94; H, 8.65; N, 6.01.

*Ethyl 2-(*N*-acetoxy-*N*-methylamino)-4,6-di-*O*-acetyl-2,3-dideoxy-α-*D*-arabino-hexopyranoside* (**17**). — A mixture of **15** (17 mg, 0.077 mmol), acetic anhydride (1 mL), and pyridine (1 mL) was kept overnight at room temperature, and the solvents were removed by codistillation with toluene. Column chromatography (2:1 ethyl acetate–hexane) of the residue afforded **17** (21 mg, 76%), syrup, $[\alpha]_D^{21}$ +30° (*c* 0.2); ν_{max}^{film} 1740 and 1720 cm^{-1} (C=O). E.i.-mass spectrum: *m/z* 347 (0.4%, M^+), 259 (1), 242 (5), 230 (8), 214 (6), 170 (5), 140 (14), 112 (23), 94 (100), 81 (14), 73 (20), and 57 (29).

Anal. Calc. for $C_{15}H_{25}NO_8$ (347.37): C, 51.87; H, 7.25; N, 4.03. Found: C, 51.85; H, 7.27; N, 4.02.

*Ethyl 2-(*N*-acetoxy-*N*-methylamino)-4,6-di-*O*-acetyl-2,3-dideoxy-α-*D*-lyxo-hexopyranoside* (**18**). — Acetylation of **16** (14.8 mg, 0.067 mmol), as described for **17**, afforded **18** (17.7 mg, 76%), syrup, $[\alpha]_D^{22}$ +12.5° (*c* 0.2); ν_{max}^{film} 1750 and 1720 cm^{-1} (C=O). E.i.-mass spectrum: *m/z* 348 (1%, $[M^+ + 1]$), 316 (0.6, $[M^+ - CH_2OH]$), 302 (0.9, $[M^+ - EtO]$), 288 (3, $[M^+ - COOCH_3]$), 274 (2), 259 (9), 242 (9), 230 (45), 214 (1), 200 (0.5), 182 (0.5), 170 (0.8), 154 (0.5), 140 (11), 112 (23), 94 (100), 81 (11), 73 (18), and 57 (14).

Anal. Calc. for $C_{15}H_{25}NO_8$ (347.37); C, 51.87; H, 7.25; N, 4.03, Found; C, 51.91; H, 7.32; N, 3.98.

*Ethyl 2,3-dideoxy-2-(*N*-hydroxy-*N*-isopropylamino)-α-*D*-arabino-hexopyranoside* (**19**). — A solution of **1** (100 mg, 0.58 mmol) and *N*-hydroxy-*N*-isopropylammonium oxalate (150 mg, 0.625 mmol) in 10:1 ethanol–water (2.2 mL) was treated as described for the preparation of **2**, except that the intermediate **6** was not isolated but immediately reduced (excess of sodium borohydride) as described for **15**. Crystallisation (chloroform–hexane) to remove traces of the *lyxo* isomer afforded **19** (128 mg, 88%), m.p. 116–117° (from $CHCl_3$–hexane), $[\alpha]_D^{23}$ +53° (*c* 1.1); ν_{max}^{KBr} 3300 cm^{-1} (OH). E.i.-mass spectrum: *m/z* 218 (0.5%), 203 (14), 186 (25), 172 (2), 158 (7), 145 (2), 140 (6), 130 (47), 122 (3), 114 (13), 109 (2), 101 (66), 86 (78), 81 (61), 74 (31), 70 (49), 61 (16), 57 (100), and 53 (11).

Anal. Calc. for $C_{11}H_{23}NO_5 \cdot 0.25\,H_2O$ (249.31); C, 52.06; H, 9.33; N, 5.52; O, 33.09. Found C, 52.03; H, 9.12; N, 5.52; O, 33.00.

The *N*-(2-^{2}H)isopropylamino analogue (**21**) of **19** was prepared from *N*-hydroxy-*N*-(2-^{2}H)isopropylammonium oxalate, as described above, *via* the intermediate **7**.

Anal. Calc. for $C_{11}H_{22}DNO_5$ (250.30): C, 52.79; N, 5.60. Found: C, 52.76; N, 5.76.

*Ethyl 2-(*N*-acetoxy-*N*-isopropylamino)-4,6-di-*O*-acetyl-2,3-dideoxy-α-*D*-arabino-hexopyranoside* (**20**). A solution of **19** (50 mg, 0.2 mmol) in pyridine (1 mL) and acetic anydride (1 mL) was left overnight at room temperature, and the solvents were removed by codistillation with toluene. Column chromatography (1:2 ethyl acetate–hexane) of the residue gave **20** (69 mg, 92%), as a syrup, $[\alpha]_D^{24}$ +34° (*c* 1.5); ν_{max}^{film} 1770, 1745, and 1730 cm^{-1} (C=O). E.i. mass spectrum: *m/z* 376 (0.05%, $[M^+ + 1]$), 330 (0.06), 316 (0.4), 287 (0.6), 270 (0.4), 258 (2), 242 (3), 228 (0.7), 215 (1), 198 (2), 182 (3), 168 (3), 150 (5), 140 (23), 128 (2), 122 (100), 114 (5), 101 (33), 94 (24), 85 (15), 80 (26), 70 (19), and 57 (19).

Anal. Calc. for $C_{17}H_{29}NO_8$ (375.42): C, 54.39; H, 7.79; N, 3.73. Found: C, 54.67; H, 7.79; N, 3.71.

Biochemical tests. — The inhibition of α-D-mannosidase[13], the precipitation of a concanavalin-A–glycogen complex[14], and the agglutination by concanavalin-A of rabbit red cells[15] were studied by classical methods.

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REFERENCES

1 J. M. J. Tronchet, E. Winter-Mihaly, F. Habashi, D. Schwarzenbach, U. Likic, and M. Geoffroy, *Helv. Chim. Acta*, 64 (1981) 610–616; J. M. J. Tronchet, R. Benhamza, N. Dolatshahi, M. Geoffroy, and H. Türler, *Nucelosides Nucleotides*, 7 (1988) 249–269.
2 J. M. J. Tronchet, E. Winter-Mihaly, J. Rupp, F. Barbalat-Rey, and M. Geoffroy, *Carbohydr. Res.*, 136 (1985) 375–390.
3 J. M. J. Tronchet, F. Habashi, J.-P. Fasel, G. Zosimo-Landolfo, F. Barbalat-Rey, and G. Moret, *Helv. Chim. Acta*, 69 (1986) 1332–1136; J. M. J. Tronchet, G. Zosimo-Landolfo, N. Bizzozero, D. Cabrini, F. Habashi, E. Jean, and M. Geoffroy, *J. Carbohydr. Chem.*, 7 (1988) 169–186.
4 J. M. J. Tronchet, R. Benhamza, G. Bernardinelli, and M. Geoffroy, *Tetrahedron Lett.*, 31 (1989) 531–534; J. M . J. Tronchet, N. Bizzozero, G. Bernardinelli, and M. Geoffroy, Carbohydr. Res., 200 (1990) 469–474.
5 B. Fraser-Reid, A. McLean, E. W. Usherwood, and M. Yunker, *Can. J. Chem.*, 48 (1970) 2877–2884.
6 H. Paulsen and W. Koebernick, *Chem. Ber.*, 110 (1977) 2127–2145; H. Paulsen, W. Koebernick, and H. Koebernick, *Tetrahedron Lett.*, (1976) 2297–2300; T. Sakakibara, T. Kawahara, and R. Sudoh, *Carbohydr. Res.*, 58 (1977) 39–46; J. Leboul, J. Cleophax, S. D. Gero, A. Rolland, and A. Forchioni, *Tetrahedron*, 33 (1977) 965–968; E. Jegon, J. Cleophax, J. Leboul, and S. D. Gero, *Carbohydr. Res.*, 45 (1975) 323–326; M. B. Yunker, D. E. Plaumann, and B. Fraser-Reid, *Can. J. Chem.*, 55 (1977) 4002–4009; B. Fraser-Reid, R. C. Anderson, D. R. Hicks, and D. L. Walker, *ibid.*, 55 (1977) 3986–3995.
7 B. Fraser-Reid, N. L. Holder, D. R. Hicks, and D. L. Walker, *Can. J. Chem.*, 55 (1977) 3978–3985.
8 J. M. J. Tronchet, N. Bizzozero, and M. Geoffroy, *Carbohydr. Res.*, 191 (1989) 138–143; J. M. J. Tronchet, N. Bizzozero, M. Koufaki, F. Habashi, and M. Geoffroy, *J. Chem. Res. (S)*, (1989) 334, (*M*) 2601–2609.
9 J. M. J. Tronchet, A. Ricca, F. Barbalat-Rey, and M. Geoffroy, *Carbohydr. Res.*, 214 (1991) 237–245.
10 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data*, Universities of York (England) and Louvain-la-Neuve (Belgium), 1987.
11 S. R. Hall and J. M. Stewart, *XTAL2.4 User's Manual*, Universities of Western Australia and Maryland, 1988.
12 M. Nardelli, *Acta Crystallogr., Sect.* C, 39 (1983) 1141–1142.
13 P. Lalegerie, G. Legler, and J. M. Yon, *Biochimie*, 64 (1982) 977–1000.
14 L. L. So and I. J. Goldstein, *J. Biol. Chem.*, 42 (1967) 1617–1622.
15 W. J. Herbert, in D. M. Weir (Ed.), *Handbook of Experimental Immunology*, Blackwell, New York, 1967, pp. 781–785.