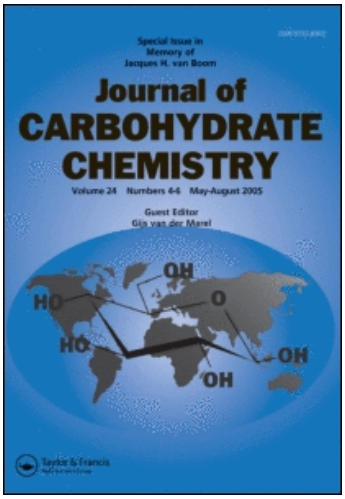

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From Pyranosuloses and Pyranosenuloses to Deoxy Hydroxyamino Sugars

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Communication

FROM PYRANOSULOSES AND PYRANOSENULOSES TO DEOXY HYDROXYAMINO SUGARS.[1,2]

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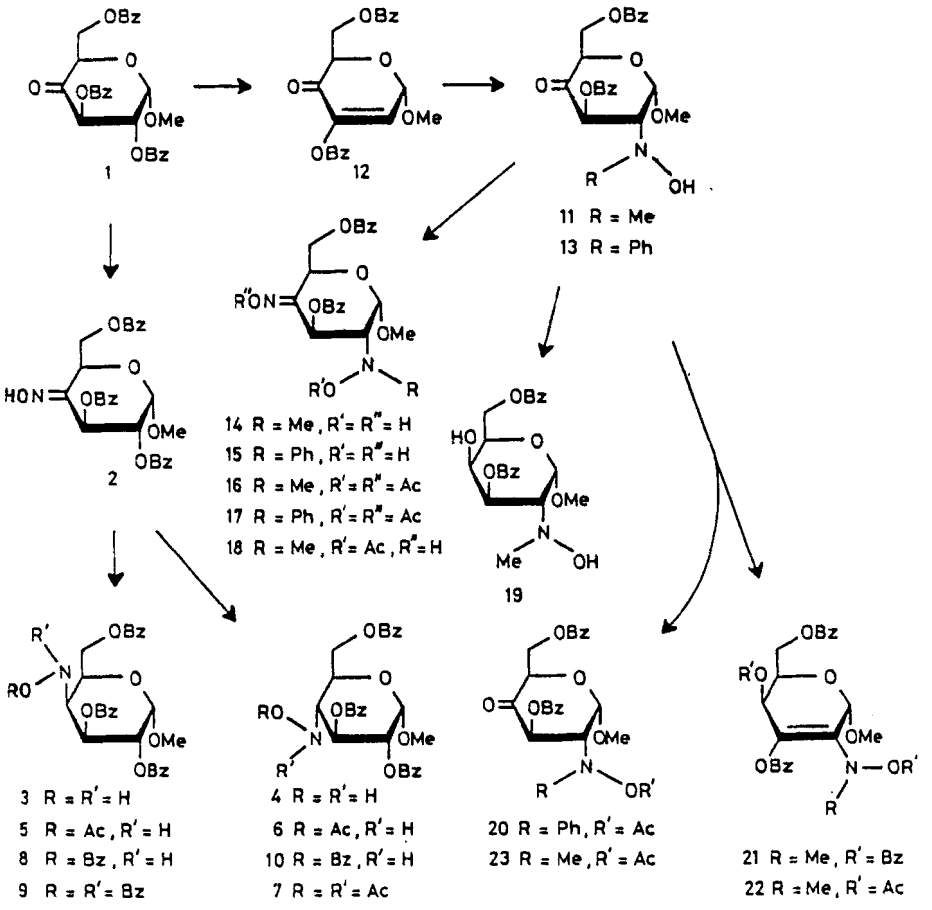
Deoxy hydroxyamino sugars represent a potentially useful series of sugar analogs owing mainly to the fact that they oxidize spontaneously to nitroxide free radicals to give spin-labeled sugar derivatives whose structure is very close to that of the parent sugar.[3] We describe herein two synthetic pathways toward these compounds, reduction of sugar oximes and conjugate addition to enolones derivatives, both in the pyranose series.

The ketosugar derivative **1**[4] was oximated to **2**[4,5] (80 %) then reduced ($NaBH_3CN$, MeOH, HCl) to a mixture (3:2) of **3** and **4** (total yield 85 %) (*Scheme 1*) which were separated by column chromatography. The configurations at C(4) were established by NMR, large (J(3.4) and J(4.5)) for the *gluco* derivative **4**, small couplings for the *galacto* derivative **3**. In the environment provided by the structures of **3** and **4** the nitrogen atom showed a low reactivity; for example, it was impossible to obtain nitrones by reacting either of these compounds with a variety of aldehydes (aliphatic, aromatic or sugar aldehydes). Upon acetylation (Ac_2O, pyridine), compounds **3** and **4** gave mostly the *O*-acetyl derivatives (**5**, 92 %) or **6** (47 %) respectively, accompanied by only a small amount of the diacetyl compound **7** (24 %). Upon benzoylation (BzCl, pyridine), the *galacto* derivative **8** (80 %) together with some **9** (14 %) was formed, whereas only the *O*-benzoyl derivative of **4** (**10**, 74 %) was isolated.

Reacting **1** with N-methylhydroxylamine gave **11** (60 %). As the transformation took place *via* an elimination to **12**[6] followed by a conjugate

SCHEME 1.



addition it was found more convenient to use **12** as a starting material which was converted to **11** in 80 % yield. In the same manner, **13** was obtained from **12** in 77 % yield. Both these conjugate additions were stereoselective, **11** and **13** bearing the α-D-*xylo* configuration as shown by their large $J(2,3)$ (12 and 11 Hz, respectively) and small $J(1,2)$ values (4 and 3.5 Hz, respectively). To help with the assignement of the ESR hyperfine coupling constants of the nitroxide formed from **11**, *vide infra*, this compound was deuterated at C(3).

Oximation of **11** and **13** led respectively to **14** (48 %) and **15** (87 %), di-*O*-acetylated to **16** (83 %) and **17** (91 %) respectively.

An attempted reduction of **16** gave only the partially de-*O*-acetylated compound **18** (27 %). The low reactivity towards reducing agents of compounds of this series bearing a sp^2 carbon atom at C(3) was confirmed by the poor yield (22 %) of **19** obtained by reduction ($NaBH_4$) of **11**.

The ESR data obtained from nitroxides derived from compounds **11**, 3-D-**11**, **14** and **19** are collected in *Table 1*, which shows hyperfine couplings involving the nitrogen atom, the methyl group and three ring protons, presumably H-C(1), H-C(2) and H-C(3). From the similarity, at room temperature, of the coupling constant values of these four nitroxides and from the deuteration experiment, the largest coupling could be assigned to H-C(2), the medium to H-C(3) and the smallest to H-C(1). It is known[7] that the most stable conformers of nitroxides are those in which the plane of the nitroxide group eclipses one of the bonds borne by the neighbouring carbon atom (*Scheme 2*).

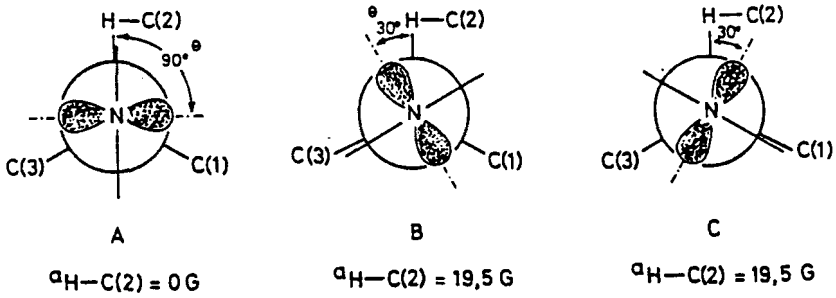
The validity of this assumption has been asserted using models where a methylene or a dialkoxyphosphonylmethylene group was fixed onto the nitroxide nitrogen atom.[7] The angular dependence of ESR hyperfine coupling constants of hydrogen atoms is well established[8] and expressed by $a(H) = 26 \cos \theta^2$ which gives for the three conformers A, B and C respectively 0, 19.5 and 19.5 G. From the experimental a(H-C(2)) value, the population p(A) of conformer A could be estimated (cf *Table 1*). At room temperature, this population was greater than 90% and, as expected, diminished when the temperature was increased, which

TABLE 1.

ESR Data (diglyme) of Nitroxide Free Radicals formed by Spontaneous Oxidation of some Deoxyhydroxyaminosugars.

Compounds	t (°C)	a_N	a_{Me}	a_{H-2}	p (A)	a_{H-3}	a_{H-1}	g
11	20	14.4	12.8	1.6	0.92	0.9	0.6	2.0061
3-D-**11**	30	14.4	12.7	1.75	0.91	0.7		
14	20	14.4	12.8	1.6	0.92	0.9	0.6	2.0063
	100	14.4	12.3	3	0.85	1	0	
19	20	14.4	12.8	1.6	0.92	0.9	0.6	2.0062
	80	14.4	12.8	2.3	0.89	0.9	0.6	

SCHEME 2.



confirmed the assignment of a(H-C(2)) to this coupling. For all compounds in *Table 1*, where an equatorial nitroxide group possesses one large equatorial neighbouring group, the preferred conformation is one where the nitroxide plane encompasses the H-C(2) bond. A typical case of the potential use of ESR for configurational assignment is encountered for the epimeric compounds **3** and **4**. The ESR spectra of their associated nitroxides differed significantly [a(H-4) 4.7 G for **3**, 2.1 G for **4**], the equatorial nitroxide group of **4**, flanked by two large equatorial groups, having a larger population of a periplanar conformer than in the case of **3** bearing an axial nitroxide group.

Upon acetylation (Ac_2O, pyridine), **13** gave **20** quantitatively, whereas its benzoylation (BzCl, pyridine) did not take place cleanly. The acylation of **11** took a very different course. Under standard conditions, its benzoylation (BzCl, pyridine) led to **21** (70%) and its acetylation (Ac_2O, pyridine) to **22** (80%). The reaction was stereospecific and the α-D-*threo* configuration of **21** and **22** was proved by NMR (small $J(4,5)$ value). In the absence of pyridine, the acetylation of **11** gave **23** (91%) whose standard acetylation led to a 4:1 mixture of **22** and **23**.

Compound **12** did not react with sterically hindered primary hydroxylamines like N-t-butylhydroxylamine, 2-hydroxyaminoadamantane or 2,3-bis (hydroxy-

SCHEME 3.

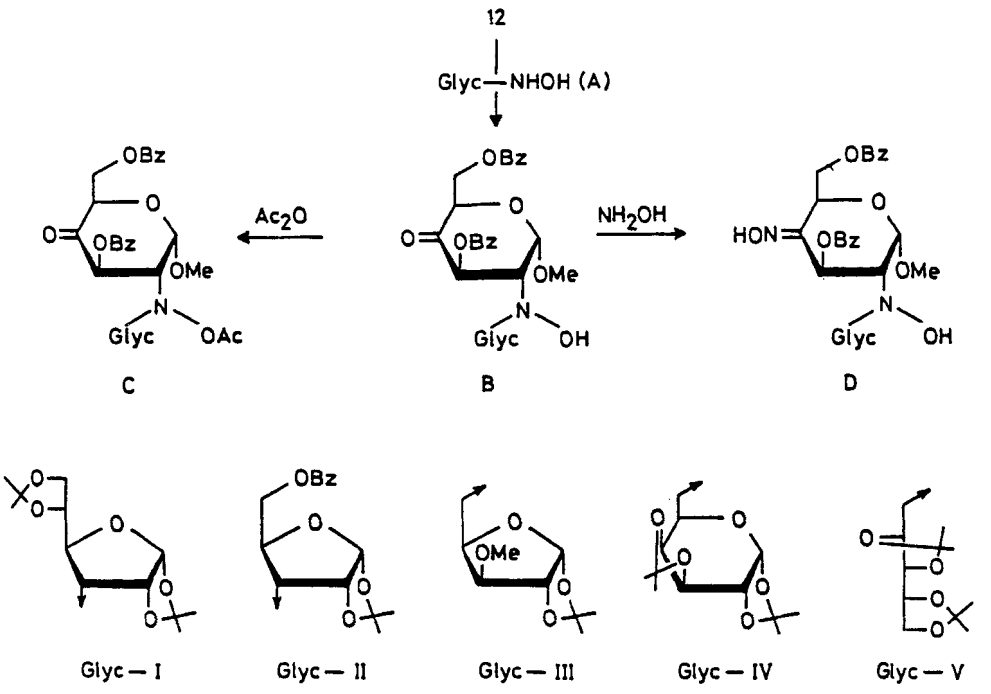


TABLE 2.

Blocked Disaccharides Analogs

	B			C			D		
Starting material (A)	Yield	$[\alpha]_D$(c,t°)[a][b]	m.p.	Yield	$[\alpha]_D$(c,t°)	m.p.	Yield	$[\alpha]_D$(c,t°)	m.p.
(Glyc-I)-NHOH[c]	64	+146.6(1.2,23)	67.1-68.2	85	+125(1,22)	75.5-76.9	95	+165.1(0.6,24)	98.7-101.0
(Glyc-II)-NHOH[c]	61	+136(1,23)	78.2-79.9	75	+133(0.9,22)	80.0-81.1	70	+142.9(1.1,22)	104.0-105.2
(Glyc-III)-NHOH[d]	45	+83(1.2,27)	75.4-76.4	93	+59(0.6,21)	70.5-71.4	59	+69.1(0.9,25)	99.5-101.0
(Glyc-IV)-NHOH[e]	73	+62.1(0.7,24)	81.5-82.4	83	+48.8(0.8,21)	140.1-141.2	80	+59.3(0.6,21)	183.7-185,7
(Glyc-V))-NHOH[f]	73	+109,8(1,22)	57.1-58.2	81	+96.3(1.1,21)	62.8-64.0	78	+104.5(1.3,22)	164.9-166.6

[a] temperature in °C. [b] in chloroform. [c] ref. 3,9 [d] ref.10 [e] ref.3 [f] This work.

amino)-2,3-dimethylbutane. On the contrary, the conjugate addition of deoxyhydroxyaminosugars on **12** provided a way to prepare analogs of blocked disaccharides of the general type **B** which could be oximated to **D** and acetylated to **C**. The examples of glycosyl groups used so far are represented in the Scheme 3 and the yields obtained as well as the melting points and rotatory powers of the compounds prepared collected in *Table 2.*

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