Stereoselective C-3 Substitution of 1,5-Anhydro-2-deoxy-2-formyl-3,4,6-tri-*O*-methylhex-1-enitols: Entry to *ribo* and *xylo* Series

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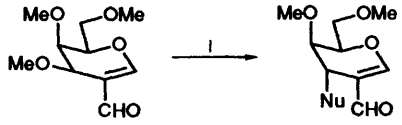
Reaction of 1,5-anhydro-2-deoxy-2-formyl-3,4,6-tri-*O*-methyl-D-*lyxo*-hex-1-enitol **1** and its *arabino* epimer **3** with various nucleophiles under Lewis acid catalysis led to stereoselective C-3 substitution.

The chemistry of glycals in general has received wide attention.[1] However, there are only a few reports on glycals with electron-withdrawing groups at C-2[2] despite their synthetic potential and added conformational interest.[3] The existence of scanty literature on this class of glycals may be due to the paucity of convenient methods for their preparation. Recently we reported a simple and expedient method for the synthesis of 1,5-anhydro-2-deoxy-2-formyl-3,4,6-tri-*O*-methyl-D-*lyxo*-hex-1-enitol **1** and its *arabino* epimer **3**[4] and observed some unusual reactivity with these compounds.[5]

Extension of this direct formylation[4] for the preparation of 2-formyl-*ribo* **4** and *xylo* **2** derivatives required the respective glycals which are not easily accessible.[6] In fact, reduction of hex-1-en-3-uloses has been reported to yield equatorial alcohols.[7] Normally, in glycals, inversion at 3-OH under Mitsunobu conditions[6f,8] and nucleophilic displacement at C-3[6f] lead only to the 2,3-unsaturated derivatives (by allylic rearrangement) and not to the desired axial product, excepting for the report of Vasella *et al.*[9] and the more recent one by Fraser-Reid *et al.*[10] In this communication we report a general route for a concise synthesis of 2-formyl-*ribo* and *xylo* derivatives involving the nucleophilic displacement of 3-OMe in 1,5-anhydro-2-deoxy-2-formyl-3,4,6-tri-*O*-methyl-D-*arabino*-hex-1-enitol **3** and the *lyxo* epimer **1** under Lewis acid catalysis.

Thus, the glycal **1** in benzene was treated with various nucleophiles under identical conditions with BF_3·Et_2O (see Experimental section) to afford the corresponding *xylo* derivatives **2** (Scheme 1, Table 1).



1

2a Nu = OMe
2b Nu = OEt
2c Nu = OBzl
2d Nu = SPh
2e Nu = OH

Scheme 1 *Reagents and conditions:* i, BF_3·Et_2O (1.2 equiv.), NuH, room temp.

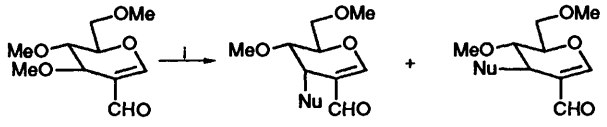
Application of this methodology to the *arabino* epimer **3** yielded both *ribo* **4** and *arabino* **5** derivatives, the former being major in all the cases. The stereoselectivity decreases in the order PhSH > $PhCH_2OH$ > MeOH. When benzyl alcohol and thiophenol (entries 2 and 3, Table 2) were used as nucleophiles the epimers could be separated and purified by preparative HPLC.† However, with methanol (entry 1, Table 2) the product was obtained as an inseparable mixture (Scheme 2, Table 2). The conformational aspects were studied and the

† Acetonitrile–water (40–60, v/v) and methanol–water (80–20, v/v) were used for the separation of epimers **4b**–**5b** and **4c**–**5c** respectively.

Table 1 Reaction of **1** with various nucleophiles

Entry	Product	Nu[a]	Reaction time/h	Yield (%)	$[\alpha]_D^{25}$ ($CHCl_3$)
1	**2a**	OMe	24	72	148.2 (*c*, 0.5)
2	**2b**	OEt	24	75	156.1 (*c*, 0.43)
3	**2c**	OBzl	12	78	196.5 (*c*, 1.1)
4	**2d**	SPh	8	80	136.9 (*c*, 1)
5	**2e**	OH	24	60	134.8 (*c*, 0.93)

[a] 1.2 Equiv. of each nucleophile was required; excess resulted in acetal formation except in the case of **2e**.



3 **4** **5**

4a, 5a Nu = OMe
4b, 5b Nu = OBzl
4c, 5c Nu = SPh

Scheme 2 *Reagents and conditions:* i, BF_3·Et_2O (1.2 equiv.), NuH, room temp.

structures assigned using ^1H and ^{13}C NMR spectroscopy. In the ^{13}C NMR spectrum of **2d** (entry 4, Table 1), the signal at δ 37 (C-3) confirms the regiochemistry. The axial stereochemistry of 3-SPh and the $^4H_5$ conformation of **2d** are confirmed by ^1H NMR coupling constants.‡ In the same way, the stereochemistry at the substitution site and the conformation are fixed for the rest of the compounds in this series.

In the ^{13}C NMR spectra of **4c** and **5c** (entry 3, Table 2), C-3 appears at δ 41 and 29 respectively proving the substitution site to be C-3. The configuration at C-3 is assigned by comparing the ^1H NMR spectra of the products with that of the starting material. In **5c** the splitting pattern of the ring protons is exactly similar to that of the starting material **3**, indicating it to be an *arabino* derivative. The similarity in the *J* values of **5c**§ and the parent *arabino* **3** showed that both exist in the 'inverted' $^5H_4$ (D) conformation[3] (Fig. 1) because of $A^{1,2}$ strain.[3] The conformation for **5a** and **5b** is also assigned in the same way. Analysis of the spectrum of **4c**¶ showed it to be the *ribo* derivative which exists in the 'normal' $^4H_5$ conformation (Fig. 1). The conformation for **4a** and **4b** is assigned similarly.

It is also interesting to note that in none of the cases studied, there seems to be any evidence for the formation of products

‡ **2d**: δ 3.5 (m, $J_{4,3}$ 2.6, $J_{4,5}$ 1.3 Hz, 4-H) and 4.2 (d, $J_{3,4}$ 2.6 Hz, 3-H). **1**: δ 4.4 (dd, $J_{3,4}$ 3.7, $J_{3,5}$ 1.1 Hz, 3-H); the conformation could not be precisely fixed from the *J* values.

§ **5c**: δ 4.1 (t, $J_{3,4}$ 2.6, $J_{3,5}$ 2.6 Hz, 3-H) and 3.67 (t, $J_{4,3}$ 2.6, $J_{4,5}$ 2.6 Hz, 4-H).

¶ **4c**: δ 4.56 (d, $J_{3,4}$ 4 Hz, 3-H) and 3.64 (dd, $J_{4,3}$ 4 Hz, $J_{4,5}$ 11 Hz, 4-H).

Table 2 Reaction of 3 with various nucleophiles

Entry	Products	Nu[a]	Reaction time/h	Yield (4:5)[b] (%)	$[\alpha]_D^{25}$ ($CHCl_3$) 4	5
1	**4a** and **5a**	OMe	24	70 (55:45)	141.9[c] (*c*, 0.42)	
2	**4b** and **5b**	OBzl	12	75 (60:40)	280.3 (*c*, 0.8)	125.9 (*c*, 0.42)
3	**4c** and **5c**	SPh	8	80 (80:20)	336.9 (*c*, 0.29)	114.8 (*c*, 0.77)

[a] 1.2 Equiv. of each nucleophile was required; excess resulted in acetal formation. [b] Ratio based on ^{1}H NMR and HPLC analyses. [c] Rotation reported for the mixture.

4 **5**

$^4H_5$ Conformation $^5H_4$ Conformation

Fig. 1

arising out of Ferrier rearrangement or Michael reaction. From the present study, it is clear that the introduction of a formyl group at C-2 has a marked effect on the reactivity and conformational behaviour of glycals.

This substitution reaction allows a convenient entry to 2-formyl-*ribo* and -*xylo* derivatives which can be useful as synthetic intermediates.[2c,d,6f] The selective introduction of diverse substituents at C-3 such as an axial hydroxy (entry 5, Table 1), formally 'deprotection with inversion' and an axial phenylthio group (entry 4, Table 1 and entry 3, Table 2), provides scope for further functionalisation at this centre.

Experimental

To a solution of hexenitol **1** (2 mmol) and nucleophile (2.4 mmol) in benzene (10 cm^3), BF_3·Et_2O (2.4 mmol) was added and the mixture stirred at room temp. for the appropriate period (Table 1). Work-up with aqueous $NaHCO_3$ yielded the corresponding *xylo* derivatives **2** which were purified by preparative HPLC (Shimadzu LC 8A) and analysed thoroughly by spectral and HRMS data. A similar procedure was followed in the corresponding *arabino* series **3** also.

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