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Note

Formation of a hexoseptanose by unusual rearrangements of a furanoid glycal

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During recent investigations on the scope of a new glycal synthesis[1], an unusual isomerisation of 3,6-anhydro-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose[2] (**1**) was observed; **1** was described previously as the sole product of base-promoted eliminations of 3,6-anhydro-5-deoxy-5-iodo-1,2-*O*-isopropylidene-β-L-idofuranose and 3,6-anhydro-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulfonyl-α-D-glucofuranose[2] (**4**). When 1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulfonyl-1,4:6,3-α-D-glucohexodialdodifuranos-α,β-6-yl chloride[3] (**2**) was treated with laminar Zn/Ag-graphite[1], the expected glycal **1** was found to be admixed with the isomeric 3,6-anhydro-5-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hex-4-enofuranose (**3**). Heating of this mixture in various solvents or, more rapidly, its treatment with potassium *tert*-butoxide in methyl sulfoxide at ambient temperature gave **3** exclusively, proving its unexpected thermodynamic and kinetic stability. This result coupled with a similar, but far less-stable carbohydrate-derived anti-Bredt-product[4], called for a re-examination of our earlier work[2].

In order to demonstrate whether **3** was generated directly or by isomerisation following the formation of glycal **1**, **4** was treated with an equimolar amount of potassium *tert*-butoxide in methyl sulfoxide at ambient temperature. Quenching of this reaction immediately after **4** had disappeared led only to **1** as a low-melting product, differing markedly from **3** in all physical properties. However, with excess of reagent under similar conditions, the rapid elimination reaction of **4** was followed immediately by isomerisation, giving **3** exclusively.

When a solution of **3** or **1** (the latter requiring significantly prolonged reaction time) in dichloromethane containing glacial acetic acid was stored at room temperature, a second, skeletal rearrangement occurred with the quantitative formation of **5**. This unprecedented reaction, which can be anticipated to be a

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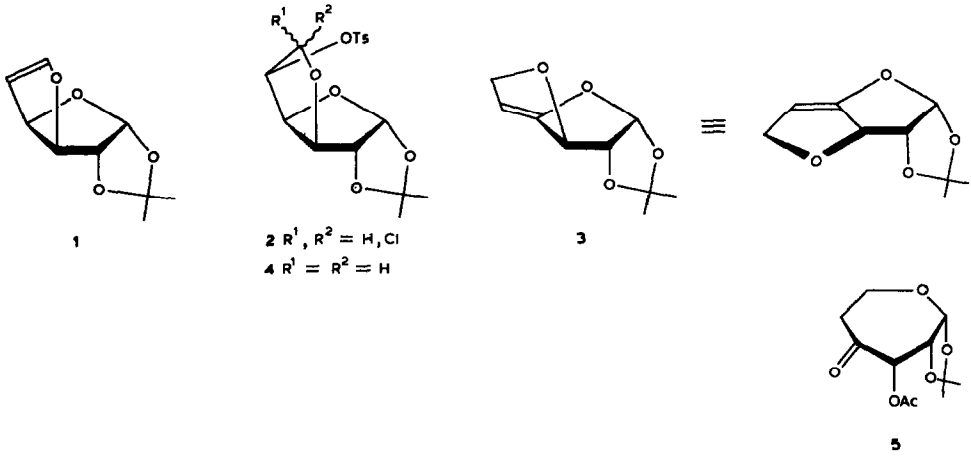


1 2 R^1, R^2 = H, Cl 3 5
4 R^1 = R^2 = H

prototropic rearrangement reaction of a furanoid glycal **1**, followed by a ring-expansion reaction of **3** as shown, called for a complete elucidation of the structure of **5**.

The 400-MHz ^{1}H-n.m.r. spectrum of **5** was too complex for determination of the proton coupling pattern, and 2D-homonuclear shift-correlation spectroscopy (COSY)[5] was applied (Fig. 1). By a pulse sequence $(T_R - \pi/2 - \tau - t_1 - \pi/2 - \tau - \text{FID})_{32}$, the ^{1}H–^{1}H-connectivities through vicinal couplings could be established and supported by homonuclear decoupling experiments. On irradiation of the doublet at δ 6.23, the triplet at δ 4.39 collapsed, which, in turn, on irradiation influenced both the resonances at δ 6.23 and 3.98. According to well established rules, the doublet at δ 6.23 was assigned to H-1, the triplet at δ 4.39, as a result of decoupling experiments and the COSY-spectrum, to H-2, and the third signal of this coupling pathway at δ 3.98 to H-3. The $J_{2,3}$ value of 2.7 Hz clearly indicated H-2,3 to be *cis*. D-Glucoseptanose derivatives[6] show $J_{2,3}$ values in the range of 7.0–8.9 Hz, whereas, for a D-alloseptanose of similiar conformation to **5**, a $J_{2,3}$ value of 2.0 Hz was reported[7], and there is little doubt about the correct configurational assignment to **5**.

A COSY-experiment, using a modified pulse-sequence with an additional pre-evolution and pre-acquisition delay with phase-cycling for quadrature detection in both dimensions[8], led to detection of the small ^5J couplings between H-1 and the isopropylidene methyl protons[9]. This group is thus located at positions 1 and 2. The complex multiplets at δ 4.1–4.35 and 2.4–2.5, exhibiting the coupling pattern of an AA'XX' system, were attributed to H-6,6' and H-5,5', respectively. Shifts and coupling constants of all protons of **5**, resulting from the analysis of a 400-MHz and a 2D-homonuclear *J*-resolved spectrum[10], were ascertained by a spectrum simulation using the PANIC-sequence (Table I).

^{13}C-N.m.r. spectroscopy, including a ^{13}C-n.m.r.-DEPT-sequence[11], revealed a carbonyl carbon (δ 212.89) and two methylene carbons in **5**, strongly indicating a

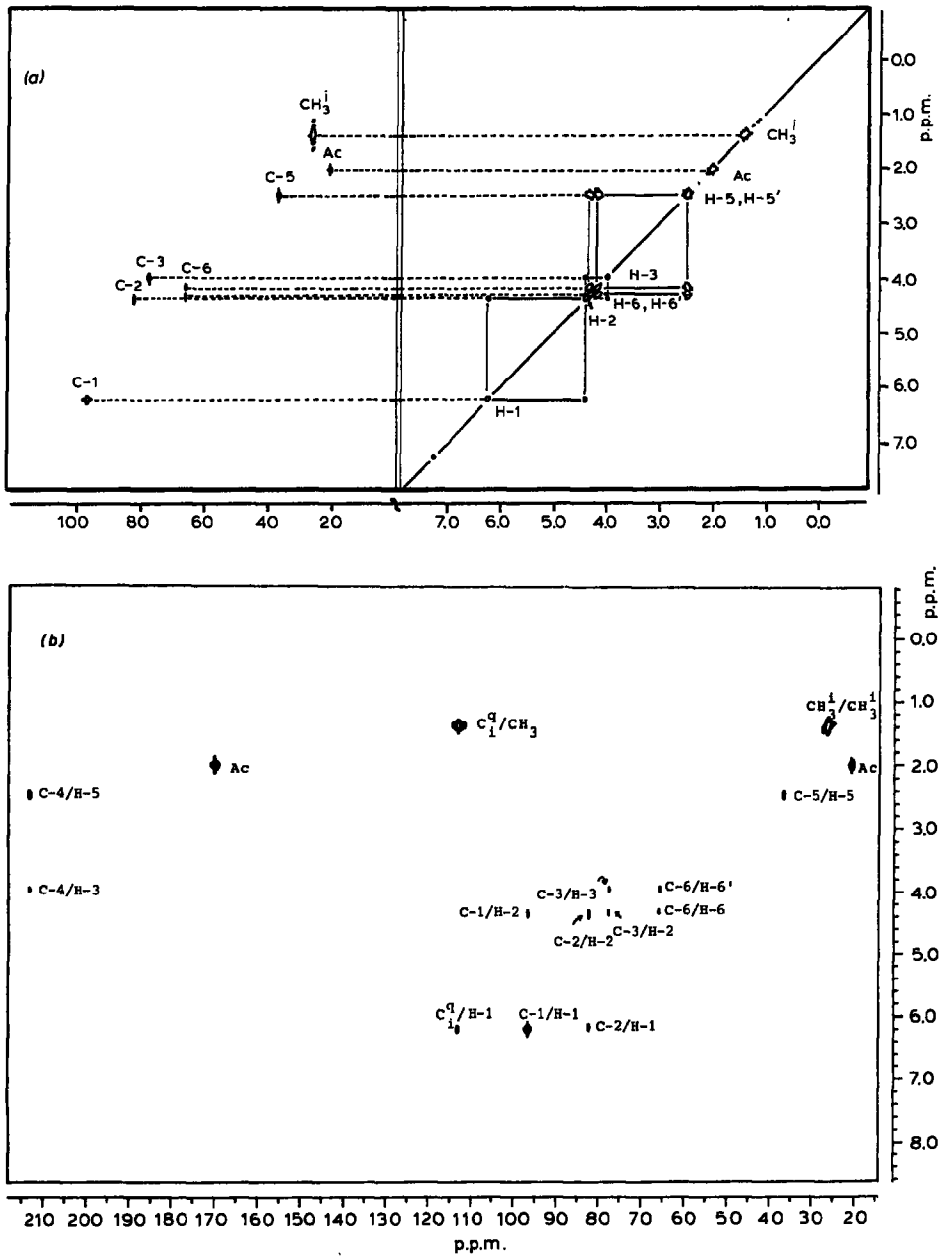


Fig. 1. (*a*) Combination of the COSY-spectrum (right) and the heteronuclear shift correlation (left) of **5**; (*b*) COLOC-spectrum of **5**; crosspeaks indicate heteronuclear coupling (indices or superscripts "i" stand for "of isopropylidene").

TABLE I

N.M.R. DATA (δ SCALE, J IN Hz) FOR **5**

Atom	δ	$^1J_{C,H}$	*Atom*	δ	J	
C-1	96.83	183.3	H-1	6.23	$J_{1,2}$	2.7
C-2	82.35	151.7	H-2	4.39	$J_{2,3}$	2.7
C-3	77.65	146.4	H-3	3.98	$J_{5,5'}$	7.8
C-4	212.89	—	H-5	2.46	$J_{5,6}$	8.1
C-5	36.89	133.7	H-5'	2.47	$J_{5',6}$	6.0
C-6	65.86	150.3	H-6	4.32	$J_{5,6'}$	7.6
			H-6'	4.17	$J_{5',6'}$	7.7
CH_3[a]	26.26		CH_3[a]	1.47	$J_{6,6'}$	9.1
CH_3[a]	26.65		CH_3[a]	1.51		
C_q[a]	113.24					
CH_3[b]	20.95		CH_3[b]	2.10		
CO[b]	170.11					

[a]CMe_2 group. [b]AcO-3.

3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hexoseptanos-4-ulose structure. When a ^{13}C-n.m.r. spectrum of **5** was obtained under conditions of gated proton decoupling with switching off of the proton broad-band-decoupling irradiation immediately before the free-induction-decay was accumulated, it also indicated position 4 for the carbonyl group and contained all of the ^{1}H–^{13}C-couplings, whilst retaining most of the intensity enhancement associated with the n.O.e. The $J_{C\text{-}1,H\text{-}1}$ value of 183.3 Hz strongly supports the α-configuration. Since a 2D ^{1}H–^{13}C-heteronuclear shift correlation for small couplings[12] only allows

TABLE II

N.M.R. DATA (δ SCALE, J IN Hz) FOR **1** AND **3**

Atom	**1**	**3**	*Atom*	**1**	**3**
C-1	105.62[b]	111.67	H-1	5.84	5.97
C-2	85.01[c]	87.80[b]	H-2	4.71	4.68
C-3	85.14[c]	82.80[b]	H-3	4.86	5.01
C-4	87.74[c]	156.01	H-4	5.39	—
C-5	102.63[b]	97.88	H-5	5.20	4.92
C-6	150.48	77.40	H-6	6.46	4.56/4.77
CH_3[a]	27.21	27.86	$J_{1,2}$	3.9	5.2
CH_3[a]	27.92	28.38	$J_{2,3}$	—	3.3
C_q[a]	113.03	115.76	$J_{3,4}$	5.9	—
			$J_{4,5}$	2.7	—
			$J_{5,6(6')}$	2.7	2.7/1.4
			$J_{6,6'}$	—	11.2
			$J_{3,6(6')}$	—	3.6/4.9

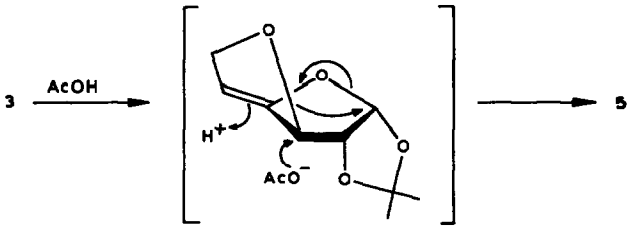
[a]CMe_2 group: δ 1.35 and 1.50 for CH_3 of **1**, and δ 1.47 and 1.54 for CH_3 of **3** ($^5J_{H\text{-}1,Me}$ 0.9 Hz). [b,c]Assignments may be reversed.

detection of $J_{C\text{-}4,H\text{-}3}$, a COLOC-pulse-sequence[13] was performed, clearly showing the couplings between C-4 and H-3,5,5'. The difference between these two experiments can be attributed to the different magnitudes of $^{n}J_{C,H}$ and $^{n}J_{H,H}$, influencing the intensity of the crosspeaks in the heteronuclear correlation experiment, whereas the COLOC-experiment is less difficult in selecting the experimental parameters.

The unambiguous ^{13}C assignments, obtained from a "normal" 2D ^{1}H–^{13}C-heteronuclear shift-correlation experiment[14], accorded well with the results of the COLOC and the long-range hetero-correlation experiments. The ^{13}C- and ^{1}H-data are listed in Tables I and II.

Thus, 3,6-anhydro-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**1**) is invariably formed in either base-promoted eliminations, exemplified by **4**, or under the conditions of a new glycal synthesis[1]. Compound **1** irreversibly isomerises either thermally or, considerably faster, with strong base, to give **3**.

As unambiguously demonstrated by the n.m.r. analysis, both isomers **3** and **1** (by way of **3**) undergo an unusual skeletal rearrangement, giving the septanose derivative **5**. A tentative mechanism for this reaction is depicted in the annexed scheme.



EXPERIMENTAL

General. — Melting points are uncorrected (Tottoli), optical rotations were measured with a Perkin–Elmer 141 polarimeter, and n.m.r. spectra for solutions in $CDCl_3$ (internal Me_4Si) were recorded with Bruker WH-90, AC-250, and WM-400 instruments. T.l.c. was performed on silica gel (Merck, 5554).

*3,6-Anhydro-5-deoxy-1,2-*O*-isopropylidene-α-*D*-*xylo*-hex-5-enofuranose* (**1**). — To a solution of **4**[15] (3.5 g, 10 mmol) in anhydrous methyl sulfoxide (10 mL) was added potassium *tert*-butoxide (1.2 g, 10 mmol) in 5 portions with stirring at ambient temperature under argon. After 4–6 min, when **4** had been consumed, ether (250 mL) was added, the mixture was extracted twice with water, and the organic layer was dried and concentrated. Chromatography (toluene–ethyl acetate, 3:1) of the residue on a short column of silica gel yielded **1** (1.3 g, 71.3%), m.p. 29–31°, $[\alpha]_D^{20}$ +9.5° (*c* 3.4, chloroform).

Anal. Calc. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.61; H, 6.63.

When 1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulfonyl-1,4:6,3-α-D-glucohexo-

dialdodifuranos-α,β-6-yl chloride (0.8 g, 2.1 mmol) [obtained[3] from 1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulfonyl-1,4:6,3-α-D-hexodialdodifuranose[16] as an unstable oil (85%), the structure of which was confirmed by n.m.r. spectroscopy] in anhydrous tetrahydrofuran (5 mL) was added to a suspension of 4 mmol of Zn/Ag–graphite[1] (0.1 molar ratio) in tetrahydrofuran (15 mL) and the mixture was boiled under reflux for 4 h; the usual work-up[1] gave an inseparable, oily 4:1 mixture (0.24 g, 63%) of **3** and **1**. The physical data reported[2] for **1** are those for its isomer **3**.

*3,6-Anhydro-5-deoxy-1,2-O-isopropylidene-α-*D-erythro-*hex-4-enofuranose* (**3**). — A solution of **1** (0.9 g, 4.9 mmol) in anhydrous methyl sulfoxide (3 mL) containing potassium *tert*-butoxide (0.2 g, 1.8 mmol) was kept at ambient temperature for 20 min and then worked-up as described for **1**, to yield **3** (0.7 g, 77.4%), m.p. 77–78°, $[\alpha]_D^{20}$ +68° (*c* 1, chloroform).

Anal. Calc. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.62; H, 6.61.

Prolonged heating of the mixture of **1** and **3** in toluene, chloroform, or dichloromethane, or directly from **4** employing a 50% excess of potassium *tert*-butoxide as described above, also gave **3**.

*3-O-Acetyl-5-deoxy-1,2-O-isopropylidene-α-*D-erythro-*hexoseptanos-4-ulose* (**5**). — A solution of **3** (0.8 g, 4.3 mmol) in anhydrous dichloromethane (25 mL) containing glacial acetic acid (0.4 g, 6.64 mmol) was kept at ambient temperature until t.l.c. showed the complete disappearance of **3**. The solvents were evaporated under reduced pressure, and column chromatography (toluene–ethyl acetate, 15:1) of the residue then gave **5** (0.7 g, 66.7%), m.p. 80–82°, $[\alpha]_D^{20}$ +173° (*c* 1.3, chloroform), R_F 0.18 (*cf.* 0.42 for **3**).

Anal. Calc. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.31; H, 6.72.

Compound **5** was obtained from **1** under the same conditions but with a prolonged reaction time.

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