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Note

The preparation of stable furanoid glycals by the method of Fischer and Zach

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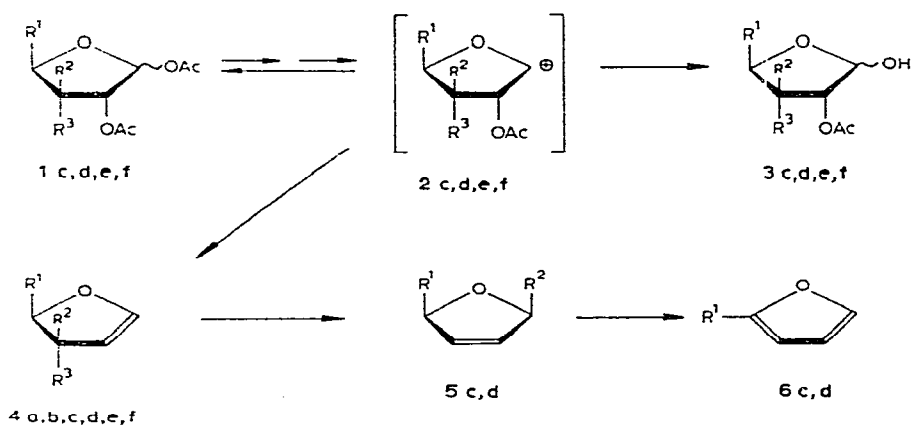
Modifications of the reaction discovered by Fischer and Zach[1], namely, the reduction of 2-*O*-acetyl-glycopyranosyl bromides with zinc in acetic acid, remain the only general methods of preparing pyranoid glycals[2]. Attempts[3] to apply such methods to the preparation of furanoid glycals failed because of their tendency to undergo allylic rearrangement reactions. Two furanoid glycals, namely, 1,4-anhydro-3,5-di-*O*-benzoyl-2-deoxy-D-*erythro*-pent-1-enitol (**4a**) and its 3,5-di-*O*-*p*-anisoyl analogue (**4b**) have been prepared by an alternative route[3,4], but their extreme sensitivity has prevented the synthetic exploitation of this class of compounds in a manner comparable to that of the versatile pyranoid glycals.



a $R^1 = CH_2OBz, R^2 = H, R^3 = OBz$
b $R^1 = CH_2OAn, R^2 = H, R^3 = OAn$ (An = *p*-anisoyl)
c $R^1 = CHOAc \cdot CH_2OAc, R^2 = OMe, R^3 = H$
d $R^1 = CH_2OBz, R^2 = OMe, R^3 = H$
e $R^1 = CH_2OBz, R^2 = H, R^3 = OMe$
f $R^1 = CH_2OAc, R^2 = H, R^3 = NHAc$

Allylic rearrangement and similar reactions in pyranoid glycals can be suppressed by the presence of a poor leaving-group at C-3, *e.g.*, the treatment of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol with hydrogen bromide in glacial acetic acid gives 4,6-di-*O*-acetyl-3-bromo-2,3-dideoxy-α-D-*arabino*-hexopyranose[5], whereas similar treatment of the 3-deoxy-3-ethoxycarbonylamino analogue gives 4,6-di-*O*-acetyl-2,3-dideoxy-3-ethoxycarbonylamino-D-arabinopyranosyl bromide[6]. This suggested to us that furanoid glycals containing, for example, a methoxyl or an acetamido group at C-3 might be less susceptible to allylic rearrangement and that a suitable modification of Fischer and Zach's method might be employed for the preparation of such compounds.

A series of 1,2-di-*O*-acetyl-D-furanosyl compounds, namely, 1,2,5,6-tetra-*O*-acetyl-3-*O*-methyl-α,β-D-glucofuranose[7] (**1c**), 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-*O*-methyl-α,β-D-xylofuranose[7] (**1d**), 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-*O*-methyl-α,β-D-ribofuranose[7] (**1e**), and 3-acetamido-1,2,5-tri-*O*-acetyl-3-deoxy-β-D-ribofuranose[8] (**1f**), was prepared and treated by a modification of Fischer and Zach's method for the preparation of glycals. After work-up, the products were isolated by chromatography and the results are listed in Table I. The compounds were readily identified by comparison with authentic samples or by their analytical and spectral properties.

TABLE I

Starting material	*Yields of products* (%)				
	Furan (**6**)	*Glycal* (**4**)	*2,3-Unsaturated compound* (**5**)	*Starting material* (**1**)	*Hydroxyl compound* (**3**)
1c	1	26	2	3	51
1d	2	20	5	5	48
1e		6		5	83
1f		3		18	29

The glycals, 5,6-di-*O*-acetyl-1,4-anhydro-2-deoxy-3-*O*-methyl-D-*arabino*-hex-1-enitol (**4c**) and 1,4-anhydro-5-*O*-benzoyl-2-deoxy-3-*O*-methyl-D-*threo*-pent-1-enitol (**4d**) were obtained in moderate yield, whereas 1,4-anhydro-5-*O*-benzoyl-2-deoxy-3-*O*-methyl-D-*erythro*-pent-1-enitol (**4e**) and 3-acetamido-5-*O*-acetyl-1,4-anhydro-2,3-dideoxy-D-*erythro*-pent-1-enitol (**4f**) were obtained only in very low yield. They all exhibited strong molecular ions in their mass spectra and strong vinyl-ether bands (~1620 cm^{-1}) in their i.r. spectra. Characteristic signals at τ 3.38 to 3.53 (H-1) and 4.68 to ~5.05 (H-2) in their n.m.r. spectra confirmed that they were furanoid glycals. They were stable on silica gel and in some cases could be distilled. They slowly decomposed when exposed to the atmosphere at room temperature; compound **4f** was considerably more stable than the other compounds, in this respect. When the compounds were stored under nitrogen at −5°, all the compounds were chromatographically homogeneous after a period of over six months.

These results show that the presence of a poor leaving-group at C-3 of 2-*O*-acetyl-glycofuranosyl bromides permits their conversion, by Fischer and Zach's method, into furanoid glycals, and that the stability of the compounds is increased. However, the formation of these glycals is not the predominant reaction.

The main product in each reaction was the free furanose derivative (**3**), which was readily identified by acetylation to give the corresponding starting-material (**1**). The formation of glycals by Fischer and Zach's method involves[10] the generation of the cationic species[9] **2**, which can either accept two electrons and lose an acetoxyl anion to form the glycal (**4**), or can combine with hydroxyl or acetoxyl anions to give the free aldose (**3**) or starting material (**1**). With the preparation of pyranoid glycals, the first reaction predominates, and glycals can be prepared in up to 80% yield. In the preparation of furanoid glycals, the other reactions clearly predominate. Variation of the reaction parameters, such as time and temperature, had little effect on the results.

The presence of trace amounts of the 2,3-unsaturated compounds (**5**) and the furan derivatives (**6**) suggests a possible decomposition path for the furanoid glycals (**4**). Compounds **5c** and **5d** probably arise from a 1,3-sigmatropic shift of the methoxyls of the parent glycals, whereas the furans (**6c**) and (**6d**) are produced by the decomposition[11] of **5c** and **5d**, respectively.

It is noteworthy that, while the yields of the furanoid glycals are low, considerable amounts of the starting materials and products that can be converted into the starting materials are recovered from the reaction mixtures. The preparation of stable glycals, by an alternative route, is being investigated.

EXPERIMENTAL

M.p.'s were determined on a hot-stage apparatus. I.r. spectra were measured with a Perkin–Elmer 257 spectrophotometer, and n.m.r. spectra were recorded on a Varian HA-100 instrument with tetramethylsilane as internal standard for $CDCl_3$ solutions. Mass spectra were determined with an A.E.I. MS-9 spectrometer by use of the direct-insertion technique. Each compound (~10 mmol) was treated and worked-up as described[9] for a similar compound. The mixtures obtained were chromatographed on silica gel (Merck GF_{254}). Where possible, small amounts of the compounds were distilled, under high vacuum, using a *kugelröhre*, for micro-analysis.

Reaction of **1c**. — Chromatography of the product mixture, with chloroform–ethyl acetate (5:1) as eluant, gave 2-(D-*glycero*-1,2-diacetoxyethyl)furan (**6c**, 1%) as an oil, identical (i.r., n.m.r., and mass spectra) with an authentic[12] sample. This was followed by the glycal (**4c**, 26%), which was obtained as a colourless oil, ν_{max}^{film} 1745 (CO) and 1615 cm^{-1} (C=C), *m/e* 244 (M^+). N.m.r. data: τ 3.44 (d, $J_{1,2}$ 3 Hz, H-1), 4.56 (m, H-5), 4.67 (dd, $J_{2,1}$ 3, $J_{2,3}$ 2, Hz, H-2), 5.36–5.86 (m, H-3,4,6,6'), 6.74 (s, OMe), and 7.94 and 7.96 (2 s, 2 AcO).

Anal. Calc. for $C_{11}H_{16}O_6$: C, 54.1; H, 6.6. Found: C, 53.9; H, 6.5.

Further elution gave methyl 5,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enofuranoside (**5c**, 2%) as a pale-yellow oil, ν_{max}^{film} 1740 cm^{-1} (CO), *m/e* 244 (M^+).

N.m.r. data: τ 3.78 and 4.04 (2 m, H-2,3), 4.26 (m, H-1), 4.81 (o, $J_{5,4}$ 5, $J_{5,6}$ 6, $J_{5,6'}$ 3 Hz, H-5), 5.08 (m, H-4), 5.59 (dd, $J_{6,6'}$ 12, $J_{6,5}$ 3 Hz, H-6), 5.79 (dd, $J_{6',6}$ 12, $J_{6',5}$ 6 Hz, H-6'), 6.51 (s, OMe), and 7.93 and 7.95 (2 s, 2 AcO).

Anal. Calc. for $C_{11}H_{16}O_6$: M^+, 244.095. Found: M^+, 244.094.

Further elution gave the starting material (**1c**, 3%), and this was followed by 2,5,6-tri-*O*-acetyl-3-*O*-methyl-α,β-D-glucofuranose (**3c**, 51%) as a colourless syrup, ν_{max}^{film} 3460 (OH) and 1730 cm^{-1} (CO), *m/e* 303 ($M^+ - OH$), which was converted into starting material (**1c**) by acetylation.

Reaction of **1d**. — Chromatography of the product mixture, with chloroform–ethyl acetate (10:1) as eluant, gave furfuryl benzoate (**6d**, 2%) as an oil, identical (i.r., n.m.r., and mass spectra) with an authentic sample. This was followed by the glycal **4d** (20%), which was obtained as a colourless oil, ν_{max}^{film} 1720 (CO) and 1620 cm^{-1} (C=C), *m/e* 234 (M^+). N.m.r. data: τ 1.88–2.69 (m, C_6H_5), 3.38 (d, $J_{1,2}$ 3 Hz, H-1), 4.68 (dd, $J_{2,1}$ 3, $J_{2,3}$ 2 Hz, H-2), 5.09–5.60 (m, H-3,4,5,5') and 6.69 (s, OMe).

Anal. Calc. for $C_{13}H_{14}O_4$: C, 66.7; H, 6.0. Found: C, 66.9; H, 6.1.

Further elution gave methyl 5-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranoside (**5d**, 5%) as an oil (contaminated with a trace of **6d**), identical (n.m.r. spectrum) with an authentic[13] sample. This was followed by the starting material (**1d**, 5%). Further elution with chloroform–ethyl acetate (1:1) as eluant gave 2-*O*-acetyl-5-*O*-benzoyl-3-*O*-methyl-α,β-D-xylofuranose (**3d**, 48%) as a colourless syrup; ν_{max}^{film} 3440 (OH) and 1720 cm^{-1} (CO); *m/e* 311 ($M^+ + H$), 310 (M^+), and 293 ($M^+ - OH$); which was converted into starting material (**1d**) by acetylation.

Reaction of **1e**. — Chromatography of the product mixture with chloroform–ethyl acetate (10:1) as eluant gave the glycal (**4e**, 6%) as a colourless oil, ν_{max}^{film} 1730 (CO) and 1620 cm^{-1} (C=C), *m/e* 234 (M^+). N.m.r. data: τ 1.91–2.68 (m, C_6H_5), 3.39 (dd, $J_{1,2}$ 2, $J_{1,3}$ 1 Hz, H-1), 4.76 (dd, $J_{2,3}$ 5, $J_{2,1}$ 2 Hz, H-2), 5.29 (m, H-4), 5.47 (m, H-3), 5.61–5.66 (m, H-5,5') and 6.69 (s, OMe).

Anal. Calc. for $C_{13}H_{14}O_4$: C, 66.7; H, 6.0. Found: C, 66.8; H, 6.2.

Further elution gave the starting material (**1e**, 5%), and this was followed by 2-*O*-acetyl-5-*O*-benzoyl-3-*O*-methyl-α,β-D-ribofuranose (**3e**, 83%) as a colourless syrup; ν_{max}^{film} 3440 (OH) and 1720 cm^{-1} (CO); *m/e* 251 ($M^+ - CH_3CO_2$); which was acetylated to give starting material (**1e**).

Reaction of **1f**. — Chromatography of the reaction mixture, with ethyl acetate as eluant, gave the glycal (**4f**, 3%); $\nu_{max}^{CHCl_3}$ 3440 (NH), 1740 and 1680 (CO), and 1620 cm^{-1} (C=C); *m/e* 199 (M^+). N.m.r. data: τ 3.53 (dd, $J_{1,2}$ 3, $J_{1,3}$ 1 Hz, H-1,) 4.02 (broad s, disappears on addition of D_2O, NH), 5.02–5.21 (m, simplifies on addition of D_2O, H-3), 5.48–5.69 (m, H-4), 5.74–5.96 (m, H-5,5'), and 7.92 and 8.04 (2 s, NHAc and AcO).

Anal. Calc. for $C_{19}H_{13}NO_4$: M^+, 199.084; Found: M^+, 199.087.

Further elution gave the starting material (**1f**, 18%), and this was followed by 3-acetamido-2,5-di-*O*-acetyl-3-deoxy-α,β-D-ribofuranose (**3f**, 29%) as a colourless syrup, ν_{max}^{film} 3440 (NH and OH) and 1700 cm^{-1} (CO), which was acetylated to give an anomeric mixture of the starting material (**1f**).

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