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An efficient route to per-*O*-acetylated hexofuranoses

Vincent Ferrières [a], Muriel Gelin [a], Rachel Boulch [a], Loïc Toupet [b], Daniel Plusquellec [a,*]

[a] *Laboratoire de Chimie Organique et des Substances Naturelles, associé au CNRS, Ecole Nationale Supérieure de Chimie de Rennes, avenue du Général Leclerc, F-35700 Rennes, France*

[b] *Groupe Matière Condensée et Matériaux, UMR CNRS 6626, Université de Rennes 1, avenue du Général Leclerc, F-35042 Rennes, France*

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Abstract

Anomeric mixtures of per-*O*-acetylated D-galacto-, D-gluco- and D-manno-furanose derivatives were prepared via the corresponding *n*-octyl hexofuranosides under mild acetolysis conditions. The crystal X-ray data of 1,2,3,5,6-penta-*O*-acetyl-α-D-mannofuranose corroborate the proposed structures.

Keywords: Per-*O*-acylated hexofuranoses; Acetolysis; Acetylation

1. Introduction

Per-*O*-acyl hexoses are important synthons in oligosaccharide synthesis [1]. Standard methods for acetylation of unprotected carbohydrates [2], as well as a variation introduced recently which uses *cis*-stannylene acetals [3], generally afford penta-*O*-protected compounds in the pyranoid form. Nevertheless, a 1,2,3,5,6-penta-*O*-acetyl-D-galactofuranose derivative was isolated by Hudson et al. [4] some decades ago in low yield through acetylation of the free sugar. More recently, the corresponding α- and β-perbenzoylated derivatives were synthesized from unprotected D-galactose by strictly controlling the temperature [5]. However, this direct approach is restricted to D-galactose, which shows appreciable proportions of the furanose forms in pyridine solution [6], and multistep sequences are required for the preparation of penta-*O*-acyl-D-gluco- and D-manno-furanoses.

As proposed by Ferrier and Haines [7], per-*O*-acylated D-glucofuranose derivatives are obtained from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose. This method could not be extended to D-galactose which provides the sterically more favoured 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose derivative. The second and more general strategy relies on the cyclization of aldose dithioacetals under kinetic control [8] in the presence of either mercuric salts [7,9] or strong acid [10]. Finally, acetolysis of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, in the presence of ferric chloride, afforded mixtures of pentaacetylated glucofuranoses and the corresponding pyranoses. Conversely, under similar conditions, the α anomer yielded almost exclusively the penta-*O*-acylated glucopyranose [11]. Surprisingly, and to the best of our knowledge, acetolysis of methyl hexofuranosides has been limited to compounds in the D-galactose series

* Corresponding author. Fax: +33-299-871364.

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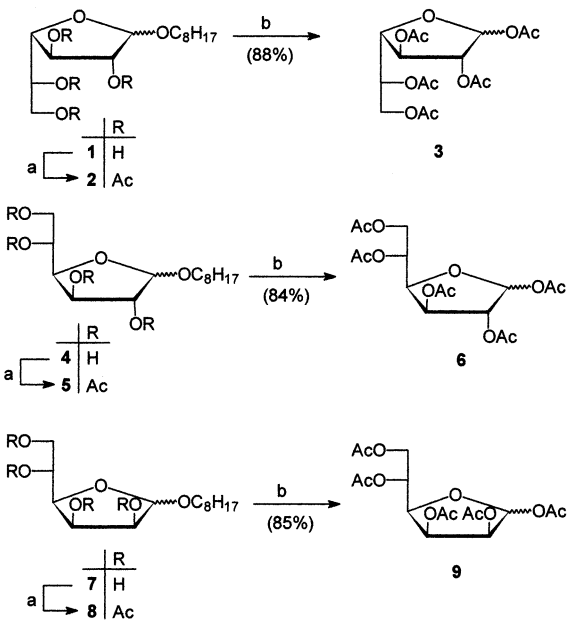
[12]. This may be related to the occurrence of D-galactofuranose residues in glycoconjugates found in some fungi, bacteria and archaebacteria [13] while gluco- or manno-furanose structures are uncommon. However, Agrocin 84, a natural antibiotic, contains a glucofuranose moiety whose anomeric configuration is still unknown [14].

As part of our ongoing interest in oligosaccharides and glycoconjugates containing alternate furanoid and pyranoid residues [15,16], we needed a general and efficient entry into penta-*O*-acyl hexofuranoses. In the present report, we show that *n*-octyl D-galacto-, D-gluco- and D-mannofuranosides can be readily converted into the desired penta-*O*-acetylated glycofuranoses **3**, **6** and **9**, respectively, by means of a convenient two-step procedure.

2. Results and discussion

Octyl glycofuranosides **1**, **4** and **7** were synthesized from the corresponding unprotected carbohydrates according to the recently described procedure from this laboratory [17]. This methodology yields exclusively the kinetic hexofuranosides which are then used in the present work as key starting materials for the preparation of the required five-membered ring derivatives. Moreover, the octyl chain may be considered as an anomeric protecting group which possesses a sufficient hydrophobic character to allow an easy purification of the desired alkyl furanosides. Compounds **1**, **4**, **7** were next quantitatively acetylated under standard conditions and afforded acetylated glycosides **2**, **5** and **8**, respectively. Both conventional acetolysis of intermediate **2** (acetic anhydride, acetic acid and sulfuric acid) [18] or solvolysis in the presence of ferric chloride systematically afforded a complex mixture of acylated octyl galactofuranosides and pyranosides and per-*O*-acetylated galactofuranoses and pyranoses. These preliminary results underline the sensitivity of the furanoside intermediate **2** under such conditions. We therefore reasoned that dilution of the reaction mixture in an inert solvent should minimize the ring expansion during acetolysis process. After experimentation, we found that acetolysis occurred in dry dichloromethane in the presence of a slight excess of acetic anhydride (four equiv) and a catalytic amount of a Brönsted acid. While trifluoroacetic acid did not promote the reaction, sulfuric acid effectively catalyzed the acetolysis. Starting from the *galacto*-derivative **2** and using more than 0.4 equiv of acid resulted in the formation of the desired compound **3** (85% yield) but contaminated by the corresponding pyranose isomer (2–7%). However, treatment of **2** in the presence of 0.2 equiv of acid specifically gave the target peracetate **3** (Scheme 1). This product was easily purified by flash-chromatography and isolated in 88% yield as a mixture of α and β anomers (α/β = 1:4.9). Crystallization of the anomeric mixture from ethanol yielded the corresponding β anomer as a white powder. The application of this methodology to the glucofuranoside **4** afforded compound **6** [19] with a similar efficiency. No pyranose form was detected.

All structure assignments were ascertained by NMR spectroscopy (Tables 1 and 2) and are in good agreement with published data [20]. The 1,2-*trans* isomers **3β** and **6β** are characterized by a broad singlet for H-1 ($J_{1,2} < 1.0$ Hz) and by a low field signal for the anomeric carbon ($\delta \approx 99$ ppm), while larger



(a) Ac_2O, pyridine; (b) Ac_2O, H_2SO_4, CH_2Cl_2.

Scheme 1. Preparation of per-*O*-acetylated hexofuranoses **3**, **6** and **9** from the corresponding *n*-octyl D-glycofuranosides.

Table 1
^{1}H NMR (400 MHz) chemical shifts and coupling constants (^{1}H–^{1}H) for compounds **3**, **6** and **9**

Compound	δ (ppm), J (Hz)						
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6 ($J_{6,6'}$)	H-6′ ($J_{6',5}$)
3α	6.32 (4.6)	5.32 (7.3)	5.55 (6.2)	4.11–4.18 (6.2)	5.27 (6.2)	4.11–4.18 (12.0)	4.30 (4.0)
3β	6.19 (<1)	5.18 (2.0)	5.08 (5.4)	4.37 (4.0)	5.36 (6.9)	4.22 (11.9)	4.33 (4.1)
6α	6.46 (4.6)	5.21 (3.0)	5.55 (4.8)	4.51 (8.5)	5.24 (2.6)	4.10 (12.3)	4.57 (5.6)
6β ([20]b)	6.12 (<1)	5.11 (<1)	5.42 (4.8)	4.56 (9.1)	5.29 (2.5)	4.08 (12.4)	4.62 (5.0)
9α	6.24 (3.4)	5.38 (5.0)	5.62 (4.2)	4.49 (8.6)	5.29 (2.4)	4.10 (12.3)	4.59 (5.6)
9β	6.35 (4.8)	5.28 (5.0)	5.65 (4.7)	4.43 (9.2)	5.29 (2.4)	4.12 (12.3)	4.62 (nd)[a]

[a] nd, not determined.

$J_{1,2}$ values (i.e., 4.6 Hz) and upfield resonance for C-1 (δ 93–94 ppm) indicate a 1,2-*cis* relationship between H-1 and H-2 [21].

The last example is a priori less favoured. Indeed, we expected that the formation of the penta-*O*-acetyl-D-mannopyranose, resulting from the isomerisation of the furanose compounds to the thermodynamically more stable α-pyranose, should mainly occur as a result of: (i) considerable hindrance of the β-face; and (ii) a stronger anomeric effect in the mannopyranose derivatives than in other compounds [22]. Nevertheless, the reaction was successfully extended to compound **8** and the pentaacetyl mannofuranose **9** was isolated in 85% yield ($\alpha/\beta = 4.3{:}1$), using only 0.1 equiv of sulfuric acid. Moreover, crystallization from ethanol yielded one of the two anomers. While ^{1}H NMR data could not ascertain the configuration of the anomeric centre, the positive rotation (i.e., + 88°) allowed us to establish the α-configuration in accord with Hudson's rules [21,23]. This result was definitively corroborated by an X-ray diffraction analysis (Fig. 1, Table 3). Moreover, in the solid state, the small C-2–C-3–C-4–O-1 torsional angle (i.e., − 4°) and the positive value observed for the O-1–C-1–C-2–C-3 angle (i.e., + 29°) show that compound **9α** assumes a ^3E envelope conformation, slightly deformed into a twisted $^3T_2$ conformation. According to the coupling constants between H-1 and H-2, H-2 and H-3 and H-3 and H-4 (Table 1), the five-membered ring seems to adopt in solution an average conformation similar to that observed in the crystal but closer to the twisted form [21].

In conclusion, we have described a simple and quite general procedure for the synthesis of per-*O*-acetylated hexofuranoses in the *galacto*, *gluco* and *manno* series which could probably be extended to other hexoses.

Table 2
^{13}C NMR (100 MHz) chemical shifts (δ ppm) for compounds **3**, **6** and **9**

Compound	C-1	C-2	C-3	C-4	C-5	C-6
3α	93.0	75.2	73.3	79.0	70.3	62.1
3β	99.1	80.5	76.3	82.1	69.2	62.5
6α	93.8	76.3	73.8	76.5	67.7	62.6
6β	98.8	79.5	72.8	79.5	68.2	62.9
9α	98.2	75.3	70.2	77.3	67.9	62.5
9β	93.0	70.4	68.4	77.1	68.0	62.5

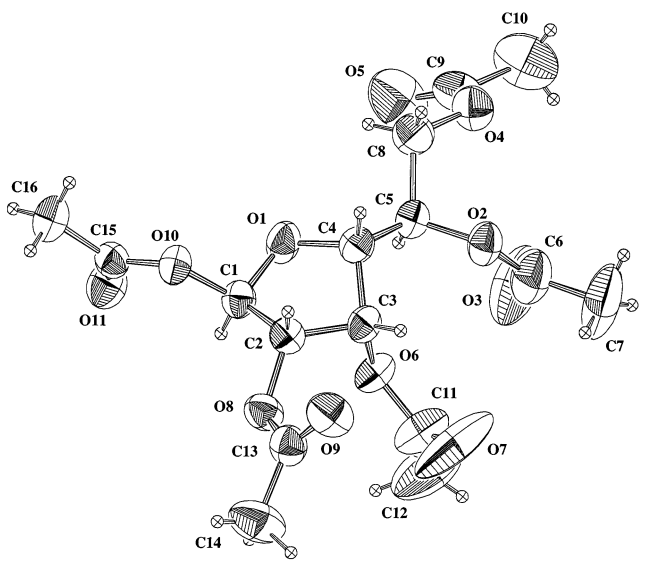


Fig. 1. ORTEP plot of the crystal structure of compound **9α**. Thermal ellipsoids are drawn at 50% probability.

Table 3
Crystal data and structure determination and refinement data for compound **9α**

Molecular formula	$C_{16}H_{22}O_{11}$
Molar mass (g)	390.35
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Z	4
a (Å)	8.210 (1)
b (Å)	10.200 (2)
c (Å)	23.416 (9)
V (Å^3)	1961 (1)
D_{calc} (g cm^{-3})	1.322
Crystal size (mm^3)	$0.24 \times 0.20 \times 0.16$
$F(000)$	824
μ (Mo-K$_\alpha$) (cm^{-1})	1.060
T (K)	294

3. Experimental

General methods.—Melting points were determined on a Reichert microscope and are uncorrected. TLC analyses were conducted on E. Merck 60 F_{254} Silica Gel non activated plates and compounds were revealed using a 5% solution of H_2SO_4 in EtOH followed by heating. For column chromatography, E. Merck 60H (5–40 μm) Silica Gel was used. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. ^{1}H, ^{13}C, HETCOR and COSY NMR spectra were recorded in $CDCl_3$ on a Bruker ARX 400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C analyses. Chemical shifts are given in δ units measured downfield from Me_4Si. The crystalline structure of **9α** was studied on an automatic diffractometer CAD4 Enraf–Nonius with graphite monochromatized Mo Kα radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max} = 54°$, scan $\omega/2\theta = 1$, $t_{max} = 60$ s, range *hkl*: *h* 0.10, *k* 0.13, *l* 0.29), intensity controls without appreciable decay (0.3%), gives 2471 reflections from which 1518 were independent with $I > 2.0\sigma(I)$. After Lorenz and polarization corrections, the structure was solved with SIR-92 which reveals the non hydrogen atoms of the structure. After anisotropic refinement, all the hydrogen atoms are found with a Fourier difference. The whole structure was refined by the full-matrix least-square techniques {use of F magnitude; x, y, z, βij for C and O atoms, x, y, z for H atoms; 311 variables and 1518 observations; $w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$} with the resulting $R = 0.045$, $R_w = 0.042$ and $S_w = 0.85$ (residual $\Delta\rho \leq 0.19$ e Å^{-3}). All the calculations were performed on a Silicon Graphics Indy computer with the MOLEN package (Enraf-Nonius, 1990). Microanalyses were performed by the 'Service de Microanalyse de l'ICSN' (Gif sur Yvette, France).

General method for acetylation and acetolysis.—To a solution of *n*-octyl glycofuranoside (4.00 g, 13.6 mmol) in dry pyridine (52 mL) Ac_2O (52 mL, 551.6 mmol) was added. The solution was stirred overnight at room temperature and concentrated under reduced pressure. The crude oil was then partitioned between EtOAc and 5% aq HCl. The organic layer was washed successively with the acidic solution, 5% aq $NaHCO_3$ and H_2O, dried ($MgSO_4$) and finally concentrated under reduced pressure. The HOAc traces were removed by co-distilling with MeOH at 50 °C/20 mmHg.

The crude peracetylated furanoside thus obtained was next dissolved in dry CH_2Cl_2, (10 mL/1 g) and Ac_2O and H_2SO_4 were successively added at room temperature. After stirring at the same temperature, the reaction was quenched by adding triethylamine and concentrated. The residue was finally purified by chromatography (3:2 petroleum ether–EtOAc). Major NMR data are reported in Tables 1 and 2.

1,2,3,5,6-Penta-O-*acetyl*-D-*galactofuranoses* (**3**).—The acetolysis step of **2** was performed in the presence of Ac_2O (1.3 mL, 13.7 mmol) and H_2SO_4 (37 μL, 0.7 mmol) for 16 h. Work-up gave an anomeric mixture (α/β = 1:4.9) of **3** (1.19 g, 88%): TLC (3:2 petroleum ether–EtOAc): $R_f = 0.3$. Crystallization from EtOH yielded exclusively the corresponding β-anomer as a white solid: $[\alpha]_D^{20}$ −41.5° (*c* 3.0, $CHCl_3$), lit. −41.9° (*c* 3.02, $CHCl_3$) [10]; mp 102–103 °C, lit. 98–99 °C [10].

1,2,3,5,6-Penta-O-*acetyl*-D-*glucofuranoses* (**6**).—The acetolysis step was performed from **5** as for the galacto-derivative and afforded an anomeric mixture (α/β = 1:2.8) of **6** (1.12 g, 84%) as a colorless oil: TLC (3:2 petroleum ether–EtOAc): $R_f = 0.3$.

1,2,3,5,6-Penta-O-acetyl-D-mannofuranoses (**9**).—The acetolysis step was performed from **8** in the presence of Ac_2O (2.6 mL, 27.4 mmol) and H_2SO_4 (18 μL, 0.3 mmol) for 18 h. Purification by column chromatography provided an anomeric mixture ($\alpha/\beta = 4.3:1$) of **9**: TLC (3:2 petroleum ether–EtOAc): $R_f = 0.3$. Crystallization from EtOH gave exclusively the corresponding α-anomer as white needles: $[\alpha]_D^{20}$ + 88° (*c* 1.0 $CHCl_3$); mp 84-85 °C (EtOH). Anal. Calcd for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.23; H, 5.71.

Supplementary material

Tables of atomic coordinates, bond lengths and bond angles have been deposited within the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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