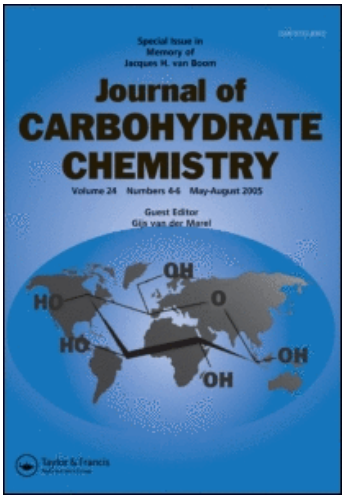

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ON THE CONVERSION OF ARABINO- AND RIBOFURANOSYL METHYL GLYCOSIDES TO THEIR 1-O-ACETYL DERIVATIVES

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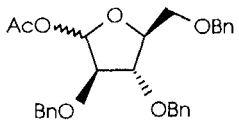
ABSTRACT

Improved conditions for the acetolysis of methyl 2,3,5-tri-*O*-benzyl-α-and β-L-arabinofuranosides and 2,3,5-tri-*O*-benzoyl-α-and β-L-ribofuranosides have been investigated. In the case of the arabinofuranosides, reproducible acetolysis conditions were obtained by substantially decreasing the amount of sulphuric acid with respect to acetic acid-acetic anhydride mixtures. With the ribofuranosides low temperature acetolysis for a short time resulted in good isolated yield of the β-1-*O*-acetyl anomer.

INTRODUCTION

The conversion of methyl glycosides to their 1-*O*-acetyl derivatives is a useful transformation in carbohydrate chemistry. The general protocol for this reaction involves treatment of the methyl glycosides with an acetylating reagent under strongly acidic conditions.[2] In our ongoing research program, we required an efficient and reproducible synthesis of 1-*O*-acetyl derivatives of 2,3,5-tri-*O*-benzyl-L-arabinofuranosyl **(1)** and 2,3,5-tri-*O*-benzoyl-ß-L-ribofuranosyl sugars **(2)**, respectively. However, for the above two cases, literature precedents proved to be problematic due to considerable charring of the sugar precursor during acetolysis leading to substantial decomposition and side reactions attributed, in part, to ring opening. We report herein efficient routes to **1** and **2** by modification of the acetolysis conditions of the corresponding methyl glycosides.



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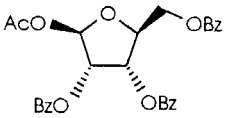

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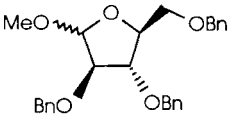
RESULTS AND DISCUSSION

Treatment of methyl 2,3,5-tri-*O*-benzyl-α-and-β-L-arabinofuranosides[3] **(3)** (3:1, ß:α) with acetic anhydride-glacial acetic acid mixtures (Ac_2O-HOAc) at room temperature in the presence of one equivalent of concentrated sulphuric acid (H_2SO_4) caused substantial decomposition of the sugar even upon cooling to 0 °C or allowing the reaction mixture to stand for short times. Considerable improvement in the yield of **1** was realized by the dropwise addition of a solution of HOAc containing 0.1 mL of H_2SO_4 to a solution of sugar in Ac_2O-HOAc. The reaction can be easily monitored by TLC (20% ethyl acetate in hexanes) and is usually completed after stirring at room temperature (< 1 h). Keeping the concentration of H_2SO_4 to a minimum, we steadily increased the amounts of HOAc and Ac_2O with respect to **3**, achieving an optimum yield of **1** at a molar ratio of 71:7.2:1, HOAc: Ac_2O: **3**. A weakly basic workup procedure afforded compound **1** as a pale yellowish syrup in excellent purity, suitable for glycosylation with nucleobases under strictly anhydrous reaction conditions without further purification.



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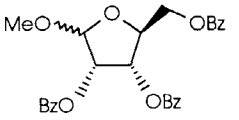
That the ratio of α to ß anomer in **1** reflected an equilibrium ratio was confirmed by separating the α-, $[\alpha]^{24}_D$ + 29°(*c* 1, chloroform), and the ß methyl glycosides of **3**, $[\alpha]^{24}_D$ -33° (c 1, chloroform) by chromatography on silica gel (15% ethyl acetate in hexanes) and subjecting each isomer to the acetolysis condition. In each case, the ratio of ß to α anomers was 3:1 identical to that obtained above.

Acetolysis of the ribofuranosyl derivative[4] **4** (3:1 ß: α mixture of anomers) according to the procedure reported for the 1-OH derivative[5] using Ac_2O - HOAc mixtures in excess H_2SO_4 afforded the desired product **2** in low yield contaminated with products arising from furanose ring opening whose general structure **5** was identified, after isolation from the reaction mixture, by ^1H NMR spectroscopy. Increasing the amount of Ac_2O and HOAc relative to H_2SO_4 resulted in an improvement in the yield of the isolated ß anomer from 21% to 36%, provided that the temperature was maintained at 0-5 °C for 15-24 h. As expected, at room temperature, the major product corresponded to compounds **5**. The highest yield of isolated **2** (54%) was obtained when the reaction was performed at -35 °C and allowed to warm up to -10 °C (molar ratios: 1:6.6:4.3:1.9, **4**: Ac_2O:HOAc:H_2SO_4).



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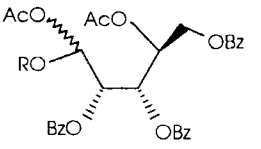

5 R = Me, Ac

Formation of acyclic sugars like **5** has been previously observed as by-products in the acetolysis of other sugars under either acidic conditions[6,7] or long reaction times.[8] In addition, the work-up procedure described in the experimental section minimizes the hydrolysis of the acetals **5** to the corresponding aldehyde derivatives.

It appears that structural differences between compounds **3** and **4** require substantially varied conditions for acetolysis. However, in both cases, the amounts of Ac_2O and HOAc were significantly increased relative to H_2SO_4. Recently, Gold and Sangaiah reported on improved acetolysis of a 2'-deoxyribofuranosyl derivative by substantially decreasing the reaction time and the amount of H_2SO_4 in the reaction mixture.[9] We believe the above results provide the synthetic chemist with reproducible conditions to prepare 1-*O*-acetylfuranoside derivatives for subsequent manipulations.[10]

EXPERIMENTAL

General Methods. Melting points were determined with a Mel-Temp II melting point apparatus and were uncorrected. Specific rotations were measured on a Rudolph Autopol II polarimeter. TLC was performed on 0.20 mm thick Merck silica gel 60 F254. Components were located by spraying with 2% ceric sulphate in 2N sulphuric acid and heating with a hot gun until coloration took place. Flash column chromatography was performed on Merck silica gel particle size 0.04-0.063 mm (230-400 mesh) with the solvent systems specified. Evaporations were conducted *in vacuo*. The ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 NMR spectrometer. Chemical shifts are reported in ppm downfield from internal TMS.

1-*O*-Acetyl-2,3,5-Tri-*O*-Benzyl-α-and ß-L-Arabinofuranose (1). Methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside[3] (640 mg, 1.47 mmol) was dissolved in 5 mL of glacial acetic acid (87.3 mmol) and cooled in an ice bath. To this solution was added 1 mL of acetic anhydride (10.6 mmol) followed by a dropwise addition of a solution of 1 mL of glacial acetic acid (17.5 mmol) containing 0.1 mL of concd sulphuric acid. The reaction mixture was brought to room temperature and left for 1 h until all starting material had disappeared as shown by TLC (20% of ethyl acetate in hexanes). Crushed ice was used to quench the reaction and 10 mL of dichloroethane was added to dilute the reaction mixture which was then washed with saturated bicarbonate solution until the pH was close to neutral. Brine was then added, and the organic layer was filtered through anhydrous sodium sulphate. The filtrate was concentrated, azeotroped with toluene and put under vacuum, to

remove residual acetic acid, affording 605 mg (89%) of the title compound as a syrup consisting of a mixture of anomers, with no need for further purification; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 2.25 H), 2.12 (s, 0.75 H), 3.55 (m, 0.5H, H5), 3.62 (d, J=5 Hz, 1.5 H, H5), 3.98 (m, 1H, H3), 4.08 (d, J=2.5 Hz, 1H,H2), 4.21 (m, 1H, H4), 4.57 (m, 6H), 6.25 (s, 0.75H, HIß), 6.28 (d, J=2.5 Hz, 0.25H, HIα), 7.32 (m, 15H, ArH). An analytical sample was dried overnight.

Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.54; H, 6.61.

1-*O*-Acetyl-2,3,5-Tri-*O*-Benzoate-ß-L-Ribofuranose (2). Methyl 2,3,5-tri-*O*-benzoyl-α and ß-L-ribofuranoside[4] (65 g, 0.136 mol) was dissolved in a mixture of acetic acid (37 mL, 0.587 mol) and acetic anhydride (86 mL, 0.904 mol) at room temperature. The solution was cooled to -40 °C using an acetone-dry ice bath, and sulphuric acid (12 mL) was added dropwise, keeping the pot temperature between -35 °C and -25 °C. The clear solution was left to warm up and fine white crystals started to form after approximately 5 min. After an additional 10 min, the reaction was completed, and the thick suspension was poured onto ice (300 g) under vigorous stirring. The sticky precipitate was separated by filtration, carefully washed with water until neutral, recrystallized from ethanol (200 mL) and eventually washed with cold ethanol (100 mL) to leave a white fine powder (37.1 g, 54%): mp 138-139 °C, $[\alpha]^{20}_D$ -42.20° (*c* 1, chloroform). Literature values for the D-isomer[4] mp. 121-123 °C, $[\alpha]^{20}_D$ + 42.10° (*c* 1, chloroform). ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H, acetyl), 4.45-4.58 (m, 1H, H5), 4.72-4.85 (m, 2H, H4, H5), 5.71-5.92 (m, H, H3), 6.39 (s, 1H, H1), 7.25-8.09 (m, 15H, ArH). ^{13}C NMR ($CDCl_3$) δ 20.9, 63.7, 71.4, 75.0, 80.0, 98.4, 128.4, 128.5, 128.7, 128.8, 129.6, 129.8, 129.9, 133.2, 133.6, 133.7, 165.0, 165.3, 166.0, 169.0.

Anal. Calcd for $C_{28}H_{24}O_9$: C, 66.66; H, 4.80. Found: C, 66.80; H, 4.88.

TLC of the mother liquor with 9:1 dichloromethane-hexanes indicated the presence of a major component which was purified by concentrating the solution and subjecting it to chromatography on silica gel with 1:1 chloroform-hexanes. ^{1}H NMR spectral analysis indicated that the major component consisted of a mixture of acetals **5**. ^{1}H NMR ($CDCl_3$) δ 1.90-2.22 (4s, OAc, 6H), 3.38-3.57 (2s, OMe, 3H), 4.35-4.48 (m, 1H), 4.75-4.90 (m, 1H), 5.60-6.25 (m, 5H), 7.28-7.66 (m, 10H), 7.85-8.13 (m, 5H).

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