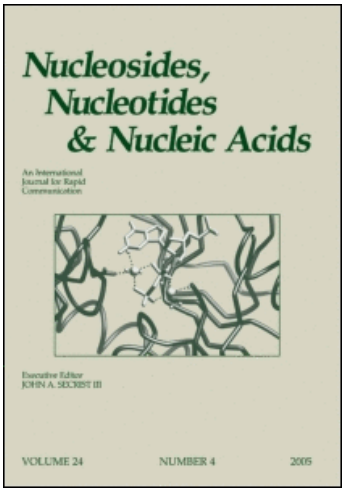


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# 1,3,5-Tri-O-acetyl-2-deoxy- α, β-D-*ERYTHRO*-Pentofuranose from 2-Deoxy-D-*ERYTHRO*-Pentose

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# 1,3,5-TRI-O-ACETYL-2-DEOXY-α,β-D-ERYTHRO-PENTOFURANOSE FROM 2-DEOXY-D-ERYTHRO-PENTOSE

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**ABSTRACT:** A convenient, high-yield synthesis of 1,3,5-tri-O-acetyl-2-deoxy-α,β-D-erythro-pentofuranose from 2-deoxy-D-erythro-pentose is described.

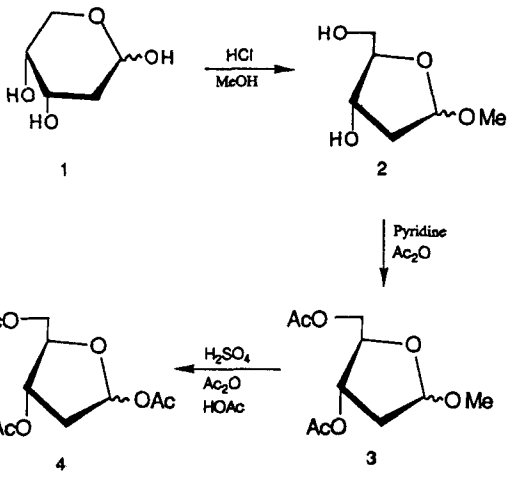


1,3,5-Tri-O-acetyl-2-deoxy-α,β-D-erythro-pentofuranose (4) has found extensive use in acid catalyzed fusion syntheses of 2'-deoxy-D-ribofuranosyl nucleosides[1] and should also be a convenient starting point for high yield Lewis acid catalyzed glycosylations of purines and pyrimidines which have been reported with a variety of ribose derivatives: 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose[2], 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride[3] and 1-O-acetyl-5-O-t-butyldimethylsilyl-2,3-dideoxy-D-pentofuranose[4]. The ready availability of 4 will therefore provide a useful intermediate in routes to 9-(2'-deoxy-β-D-erythro-pentofuranosyl)purines, which have become the focus of considerable interest as model DNA adducts[5] and anti-AIDS drugs[4,6] Currently, the only practical route to deoxyribose 4 is via acetylation and acetolysis of 2'-deoxyadenosine[1,7], a costly starting material of which less than half by weight is potentially convertible to the target sugar. A synthesis by direct acetylation of 2-deoxy-D-erythro-pentofuranose (1) would be highly desirable and has been reported for the pure β anomer[8]; however, the the product was obtained in only 2% yield after a two week period of crystallization. We report here an efficient route to 4 from 1 as starting material.

## RESULTS AND DISCUSSION

The following scheme was employed:

SCHEME




Although the Scheme is based on the straightforward strategy for the synthesis of 1,2,3,5-tetra-O-acetyl-β-D-ribose[9], direct application of the published procedure to derivatization of the deoxy sugar was not successful and several modifications are described below. $^1$H NMR spectra of compounds 2 - 4 were recorded at 400 MHz. The resolution of the high field $^1$H NMR spectra permitted the anomeric composition of the derivatization products to be definitively established.

Sulfuric acid catalysis of the initial step (1 ---> 2) by the procedure of ref. [9] resulted in partial methylation accompanied by a significant amount of side reaction. Quantitative methylation of 1 was accomplished instead by HCl catalysis under conditions optimized for the formation of 2 as an intermediate in the synthetic route to a glycosyl chloride[10]. A mixture of anomers in a 1:1 ratio was confirmed in the $^1$H NMR spectrum of 2 by two methoxy methyl signals of equal area at 3.52 and 3.54 ppm and two signals of equal area resolved for H1: an apparent doublet at 5.24 ppm, $J_{1,2}$= 4.7 Hz and a doublet of doublets at 5.25 ppm, $J_{1,2}$= 5.6 Hz, $J_{1,2'}$= 2.0 Hz. The doublet is tentatively assigned to the α anomer by analogy to the appearance of the H1 signal of 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride as a doublet. Acetylation of 2 according to ref. [9] yielded the expected 1:1 anomeric mixture of 3,5-di-O-acetyl derivatives 3 cleanly and quantitatively, confirmed by $^1$H NMR spectrometry after removal of solvent under vacuum. Two methoxy methyl resonances of equal area appear at 3.48 and 3.53 ppm and four

acetyl methyl signals in a 1:2:1 ratio at 2.20, 2.21 (broad, unresolved) and 2.22 ppm. Two H1 signals of equal area are also resolved: an apparent doublet centered at 5.25 ppm, $J_{1,2}$= 5.3 Hz and a doublet of doublets centered at 5.27 ppm, $J_{1,2}$= 5.5 Hz, $J_{1,2'}$= 2.3 Hz. The doublet is tentatively assigned to the α anomer as explained above. Rotation of the mixture of anomers was $[\alpha]_D^{25}$ +20.0° (c 0.68, methanol).

Acetolysis of 3 catalyzed by sulfuric acid under conditions of ref. [9] caused charring of the sugar even with vigorous stirring and efficient cooling at 0° C, and only a trace amount of impure triacetyl derivative 4 could be isolated. Destruction of 4 was avoided by reducing the proportion of sulfuric acid by half and allowing the reaction mixture to stand for only 5 min rather than 2 h after completing the addition of sulfuric acid and removing the reaction from the ice bath. This interval appears to be critical: a shorter reaction time results in incomplete acetolysis of 3 while a longer time causes virtually complete destruction of the product. Acetolysis yields, after removal of solvent, a 1:1 mixture of anomers 4 with no side products by $^1$H NMR spectrometry. The 60 MHz $^1$H NMR spectrum of 4 from acetolysis of N-acetyl-3',5'-di-O-acetyl-2'-deoxyadenosine has been reported[1] but resolution was insufficient to determine whether the product was a mixture of anomers. In the 400 MHz $^1$H NMR spectrum of 4, six equal acetyl methyl signals are resolved at 2.11, 2.10, 2.09, 2.08, 2.07 and 2.06 ppm as expected for a mixture of anomers. Two H1 resonances of equal area are also well resolved, an apparent doublet centered at 6.30 ppm, $J_{1,2}$= 5.4 Hz, and a doublet of doublets centered at 6.38 ppm, $J_{1,2}$= 5.6 Hz, $J_{1,2'}$= 2.4 Hz. As discussed above, the doublet is assigned to the α anomer and the doublet of doublets to the β anomer. Rotation of the anomeric mixture, $[\alpha]_D^{25}$ +25.0° (c 0.69, methanol), was identical[1,7] to that reported for the product of acetolysis of N-acetyl-3',5'-di-O-acetyl-2'-deoxyadenosine. Since the 400 MHz $^1$H NMR spectrum unequivocally shows that the acetolysis of methyl riboside 3 yields a 1:1 mixture of anomers, the acetolysis of the deoxynucleoside must also give an anomeric mixture, rather than the pure α anomer as suggested[1]. Although 4 can be purified by distillation[7] at reduced pressure, the product obtained directly from the acetolysis of 3 is entirely suitable for use in glycosylation.

## EXPERIMENTAL

$^1$H NMR spectra were acquired on a Varian XL 400 at 400 MHz. Chemical shifts are given in parts per million (ppm) relative to TMS. Mass

spectrometry was performed on a VG 70-250SEQ mass spectrometer using a fast atom bombardment (FAB) source. All solvents were reagent grade. Pyridine was dried over KOH and distilled.

Methyl 2-deoxy-α,β-D-erythro-pentofuranoside (2). 2-Deoxy-D-erythro-pentose, 3.4 g (0.025 moles), was methylated according to the procedure of ref. [10]. The product was obtained as a colorless syrup after evacuating under an oil pump vacuum at 60°C to remove traces of methanol. The $^1$H NMR spectrum indicated complete conversion to a 1:1 mixture of methyl anomers and the entire product was carried on to the next step. $^1$H NMR (400 MHz, chloroform-d): δ 5.25, 5.24(1H total, dd, $J_{1,2}$= 5.6 Hz, $J_{1,2'}$= 2.0 Hz, [β anomer]; d, $J_{1,2}$= 4.7 Hz, [α anomer] H1); 4.32-4.29, 4.26-04.23, 4.18-4.16(2H total, m, H3, H4); 3.86-3.75(2H total, m, H5, H5'); 3.54, 3.52(3H, s:s::1:1, $OCH_3$); 2.39-2.38, 2.32-2.23, 2.16- 2.13(2H total, m, H2, H2').

Methyl 3,5-di-O-acetyl-2-deoxy-α,β-D-erythro-pentofuranoside (3). The acetylation was based on the procedure in ref. [9] for the triacetylation of methyl riboside. Compound 2 from the previous step was dissolved in 25 mL of dry pyridine, 10 mL acetic anhydride was added with cooling and the stoppered reaction allowed to stand 2 days at room temperature. The bulk of the solvents was removed on a rotary evaporator and the residue further evacuated on an oil pump at 60°C to remove traces of pyridine and acetic anhydride. The $^1$H NMR spectrum of the colorless syrup showed complete conversion to a 1:1 mixture of the methyl 3,5-di-O-acetyl anomers. $^1$H NMR (400 MHz, chloroform-d): δ 5.39-5.34, 5.20-5.17 (1H total, m, [α and β anomers] H3); 5.27, 5.25(1H total, dd, $J_{1,2}$= 5.4 Hz, $J_{1,2'}$= 2.2 Hz, [β anomer]); d, $J_{1,2}$= 5.3 Hz, [α anomer], H1); 4.50-4.21(6H total, m, H4, H5, H5'); 3.53, 3.48(6H, s:s::1:1, $OCH_3$); 2.57-2.48, 2.34-2.26, 2.18-2.12(4H total, m, H2, H2'); 2.20, 2.21, 2.22(12H total, s:bs:s::1:2:1, $OCOCH_3$). FAB mass spectrum (dithiothreitol/dithioerythritol matrix), m/z 233($MH^+$), 231($MH-H_2$), 201($MH - CH_3OH$); accurate mass of $MH^+$, obs. 233.1029; calcd. for $C_{10}H_{17}O_6$, 233.1025; $[\alpha]_D^{25}$ +20.0° (c 0.68, methanol).

1,3,5-Tri-O-acetyl-2-deoxy-α,β-D-erythro-pentofuranose (4). Compound 3, 1.36 g (0.0059 moles), was dissolved in 10 mL acetic acid and 2.5 mL acetic anhydride was added with cooling in an ice bath. Then, with continued cooling and stirring, 0.25 mL conc. sulfuric acid was added slowly dropwise. Upon completion of the addition, the reaction was removed from the ice bath and allowed to stand for 5 min, during which

time a greenish hue appeared. The reaction mixture was poured onto 100 mL crushed ice and extracted with 60 mL chloroform. The organic layer (pale yellow) was extracted with dist. $H_2O$, 2 x with saturated $NaHCO_3$, dried over anh. $Na_2SO_4$ and evaporated to give a yellowish syrup. The syrup was evacuated at 60°C on an oil pump to remove traces of solvent, yielding 1.42 g (93%) of 4. $^1H$ NMR (400 MHz, chloroform-d): $\delta$ 6.38, 6.30 (1H total, dd, $J_{1,2}$= 5.6 Hz, $J_{1,2'}$= 2.4 Hz, [β anomer]; d, $J_{1,2}$= 5.4 Hz, H1 [α anomer], H1); 5.22- 5.17, 5.12-5.09(2H total, m, H3); 4.40-4.39, 4.28-4.25, 4.17-4.13(6H total, m, H4, H5, H5'); 2.52-2.46, 2.34-2.27, 2.19, 2.15(4H total, m, H2, H2'); 2.11, 2.10, 2.09, 2.08, 2.07, 2.06(9H total, 6s, OCOC$\underline{H}_3$). FAB mass spectrum (dithiothreitol/dithioerythritol matrix): m/z 261($MH^+$), 201(MH - HOAc); $[\alpha]_D^{25}$+25.0° (c 0.69, methanol).

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