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Note

1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-L-*erythro*-pentofuranose, a convenient precursor for the stereospecific synthesis of nucleoside analogues with the unnatural β-L-configuration

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Abstract

The title compound 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-L-*erythro*-pentofuranose (**5**), a useful precursor for the stereospecific synthesis of β-L-nucleoside analogues as potential antiviral agents, has been synthesised by a multi-step reaction sequence from L-xylose with a 38% overall yield. The preparation involved conversion of L-xylose to 1,2-*O*-isopropylidene-α-L-xylofuranose which, upon selective 5-O-benzoylation and subsequent radical deoxygenation, provided the protected 3-deoxy sugar derivative. Finally, cleavage of the acetonide group gave the resulting 5-*O*-benzoyl-3-deoxy-L-*erythro*-pentose which was acetylated to afford crystalline α,β-**5**.

Keywords: L-Xylose; 1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-L-*erythro*-pentofuranose; L-Nucleosides; Antiviral agents

1. Introduction

During recent years, there has been a growing interest in the synthesis and the biological evaluation of L-nucleoside analogues as potential antiviral drugs [1]. These investigations have led to the discovery of potent and selective agents against human immunodeficiency virus (HIV) and hepatitis B virus (HBV), such as 1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (3TC) [2] and 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (FTC) [3]. In connection with these efforts, our research group and others have reported the synthesis of β-L-2′,3′-dideoxy-5-fluorocytidine, which showed potent anti-HIV [4,5] and anti-HBV activity [6,7]. In addition to these findings, we have also described the synthesis and antiviral activity of various β-L-2′,3′-dideoxy and 2′,3′-didehydro-2′,3′-dideoxy purine nucleosides, and among them, β-L-2′,3′-didehydro-2′,3′-dideoxyadenosine exhibited significant activity against HIV and HBV in cell culture experiments [8,9]. Various methodologies have been used for the preparation of these β-L-pentofuranonucleoside derivatives. For our part, we

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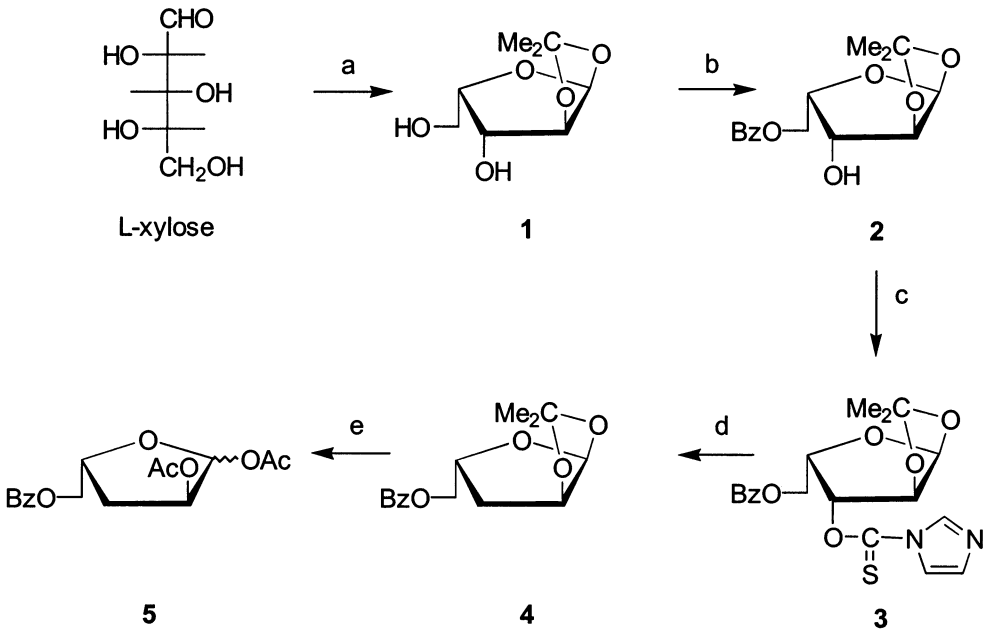

Scheme 1. (a) Ref. [11]; (b) BzCl, pyridine, 0 °C; (c) TCDI, $(CH_2Cl)_2$, reflux; (d) $(Me_3Si)_3SiH$, AIBN, toluene, reflux; (e) (i) 85% AcOH, H_2SO_4, 50 °C; (ii) Ac_2O, pyridine, 50 °C.

chose a stereospecific synthesis by direct condensation of a suitably protected L-sugar derivative and the purine or pyrimidine bases, followed by appropriate chemical modifications of the resulting nucleosides. As a starting sugar, we selected 1,2-di-*O*-acetyl-5-*O*-benzoyl - 3 - deoxy - L - *erythro* - pentofuranose (**5**) (Scheme 1). Although we have already cited the use of **5** in the literature [4,8,10], its preparation has never been published. In this work, we wish to report in detail the synthesis of this useful synthetic precursor.

2. Results and discussion

In order to prepare the target 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-L-*erythro*-pentofuranose (**5**), commercially available L-xylose was converted to 1,2-*O*-isopropylidene-α-L-xylofuranose (**1**), without purification of the intermediates and following a synthetic pathway previously reported by Gosselin et al. for the corresponding compounds in the D series [11]. Selective protection of the primary 5-hydroxy group was achieved by treatment of **1** with benzoyl chloride in anhydrous pyridine at 0 °C [12], resulting in **2** obtained as a crystalline solid in 74% yield after silica gel column chromatography. Compound **2** was then reacted with 1,1′-thiocarbonyldiimidazole (TCDI) in anhydrous 1,2-dichloroethane to give the corresponding 3-*O*-(imidazolylthiocarbonyl) derivative **3**, which was subsequently deoxygenated with tris(trimethylsilyl)-silane [13] in refluxing anhydrous toluene in the presence of α,α′-azobisisobutyronitrile (AIBN) to afford the 5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-L-*erythro*-pentofuranose (**4**) in 92% yield after purification on silica gel column. In our hands, the silicon hydride $[(CH_3)_3Si]_3SiH$ reagent proved to be an attractive alternative to tributyltin hydride for the radical deoxygenation of secondary alcohol [14,15]. Finally, acid-catalysed cleavage of the remaining acetonide group in aqueous 85% acetic acid with sulfuric acid gave 5-*O*-benzoyl-3-deoxy-L-*erythro*-pentose, which was not isolated, but treated in situ with acetic anhydride to afford 64% of crystalline α,β-**5**.

3. Experimental

General methods.—Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are

uncorrected. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz in Me_2SO-d_6 at ambient temperature with a Brüker DRX 400. Chemical shifts are given in δ values, Me_2SO-d_5 being set at δ_H 2.49 and δ_C 39.5 as a reference. Deuterium exchange and COSY experiments were performed in order to confirm proton assignments. Coupling constants, *J*, are reported in Hertz. 2D ^{1}H–^{13}C heteronuclear COSY were recorded for the attribution of ^{13}C signals. FAB mass spectra were recorded in the positive-ion mode on a Jeol SX 102. The matrix was 3-nitrobenzyl alcohol (NBA). Specific rotations were measured on a Perkin–Elmer model 241 spectropolarimeter (path length 1 cm), and are given in units of 10^{-1} cm^2 g^{-1}. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). Thin-layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 F_{254} (E. Merck, Art. 5554), visualisation of products being accomplished by UV absorbance followed by charring with 10% ethanolic H_2SO_4 and heating. Column chromatography was carried out on Silica Gel 60 (E. Merck, Art. 9385).

1,2-O-*Isopropylidene*-α-L-*xylofuranose* (**1**).—Compound **1** was prepared from L-xylose in 91% yield by the method reported in the literature [11].

5-O-*Benzoyl*-*1,2*-O-*isopropylidene*-α-L-*xylofuranose* (**2**).—To a cooled (ice-bath) soln of **1** (57.5 g, 302 mmol) in anhyd pyridine (287 mL) was added benzoyl chloride (36.9 mL, 318 mmol) dropwise over a 30 min period with stirring. The mixture was stirred for a further 30 min at room temperature (rt) with the exclusion of moisture. Water (2 mL) was added and stirring was continued for 15 min. The mixture was then concd to a low volume, diluted with CH_2Cl_2 (400 mL), washed with satd aq $NaHCO_3$ (200 mL) and water (300 mL), dried (Na_2SO_4) and concd to dryness. The resulting residue was chromatographed on a column of silica gel with a stepwise gradient of MeOH (0–8%) in CH_2Cl_2 to afford **2**, which was crystallised from hexane (66 g, 74%): mp 78–80 °C, lit. 82–83 °C [16]; $[\alpha]_D^{20}$ + 16° (*c* 1.0, Me_2SO), $[\alpha]_D^{20}$ − 10.8° (*c* 0.37, $CHCl_3$), lit. − 12.14° (*c* 0.37, $CHCl_3$) [16]; ^{1}H NMR (Me_2SO-d_6): δ 8.0–7.5 (m, 5 H, Ar), 5.87 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.49 (d, 1 H, *J* 3.5 Hz, D_2O exchangeable, OH-3), 4.5–4.3 (m, 4 H, H-2, H-4, H-5a,b), 4.11 (br s, 1 H, H-3), 1.38 and 1.23 (2 s, each 3 H, CMe_2); ^{13}C NMR (Me_2SO-d_6): δ 166.5 (CO), 134.3, 130.3, 130.1, 129.6 (Ar–C), 111.6 (*C*Me_2), 105.4 (C-1), 85.8 (C-2), 79.0 (C-4), 74.6 (C-3), 64.0 (C-5), 27.5 (Me), 26.9, (Me). FAB-mass spectrum (NBA): positive mode *m/z* 295 $[M + H]^+$. Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.16. Found: C, 60.86; H, 6.27.

5-O-*Benzoyl*-*3*-O-*(imidazolylthiocarbonyl)*-*1,2*-O-*isopropylidene*-α-L-*xylofuranose* (**3**).—A soln of **2** (24.5 g, 83.5 mmol) and 1,1′-thiocarbonyldiimidazole (19.3 g, 108 mmol) in anhyd 1,2-dichloroethane (400 mL) was stirred and refluxed for 2 h under argon. After cooling to rt, the solvent was removed under reduced pressure. The residue was chromatographed on a column of silica gel with a stepwise gradient of EtOAc (0–14%) in CH_2Cl_2 to give **3** (32 g, 95%), which was crystallised from cyclohexane–EtOAc: mp 106–108 °C; $[\alpha]_D^{20}$ + 17.5° (*c* 1.2 Me_2SO); ^{1}H NMR ($CDCl_3$): δ 8.3 (m, 1 H, imidazole), 8.0–7.4 (m, 6 H, Ar and imidazole), 7.0 (m, 1 H, imidazole), 6.05 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 6.00 (d, 1 H, $J_{3,4}$ 2.9 Hz, H-3), 4.8–4.7 (m, 2 H, H-2, H-4), 4.60 (d, 2 H, $J_{5,4}$ 6.1 Hz, H-5a,b), 1.58 and 1.35 (s, 3 H, CMe_2). FAB-mass spectrum (NBA): positive mode *m/z* 405 $[M + H]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_6S$: C, 56.42; H, 4.98; N, 6.93; S, 7.93. Found: C, 56.48; H, 5.00; N, 6.89; S, 7.91.

5-O-*Benzoyl*-*3*-*deoxy*-*1,2*-O-*isopropylidene*-α-L-erythro-*pentofuranose* (**4**).—To a soln of **3** (5.0 g, 12.4 mmol) in anhyd toluene were added successively tris(trimethylsilyl)silane (4.9 mL, 15.8 mmol) and α,α′-azobisisobutyronitrile (0.65 g, 4.0 mmol). The resulting soln was heated and stirred at 110 °C for 1 h under argon. After cooling to rt, the solvent was evaporated to dryness. Column chromatography of the residue on silica gel with a stepwise gradient of EtOAc (0–6%) in CH_2Cl_2 afforded **4** as an oil (3.17 g, 92%). Distillation under diminished pressure gave analytically pure **4**: bp 128–130 °C (0.06 mmHg); $[\alpha]_D^{20}$ + 10° (*c* 1.2, Me_2SO); ^{1}H NMR (Me_2SO-d_6): δ 8.0–7.5 (m, 5 H, Ar), 5.77 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1),

4.76 (t, 1 H, J 4.2 Hz, H-2), 4.45 (dd, $J_{5a,4}$ 2.9, $J_{5a,5b}$ 11.8 Hz, H-5a), 4.37 (m, 1 H, H-4), 4.25 (dd, 1 H, $J_{5b,4}$ 5.7 Hz, H-5b) 2.02 (dd, 1 H, $J_{3a,2}$ 4.4, $J_{3a,3b}$ 13.3 Hz, H-3a), 1.7 (m, 1 H, H-3b), 1.40 and 1.23 (2 s, each 3 H, CMe_2); ^{13}C NMR (Me_2SO-d_6): δ 166.4 (CO), 134.3, 130.3, 130.1, 129.7 (Ar–C), 111.2 (CMe_2), 106.0 (C-1), 80.6 (C-2), 76.2 (C-4), 66.0 (C-5), 35.3 (C-3), 27.4 (Me), 26.9 (Me). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.57; H, 6.62.

*1,2-Di-O-acetyl-5-O-benzoyl-3-deoxy-*L-erythro-*pentofuranose* (**5**).—A stirred soln of **4** (1.0 g, 3.60 mmol) and H_2SO_4 (0.04 mL, 0.75 mmol) in aq 85% AcOH (3.7 mL) was heated for 3 h at 50 °C. The mixture was concd under diminished pressure to half vol, then diluted with pyridine (3.7 mL). Acetic anhydride (4.6 mL, 48.7 mmol) was added dropwise with stirring at 50 °C, and stirring was continued for 30 min. After cooling to rt, the mixture was concd under diminished pressure, diluted with CH_2Cl_2 (100 mL), washed with aq 5% $NaHCO_3$ (2×50 mL), water (2×50 mL), dried (Na_2SO_4) and concd to dryness. Toluene was evaporated three times from the residue followed by $CHCl_3$ to give crude **5**. Chromatography on a column of silica gel with a stepwise gradient of EtOAc (0–6%) in CH_2Cl_2 gave pure **5** (0.75 g, 64%), which was crystallised as an anomeric α,β mixture from petroleum ether (boiling range 40–60 °C) –CH_2Cl_2: mp 54–56 °C; ^1H NMR (Me_2SO-d_6): δ 8.0–7.5 (m, 10 H, Ar), 6.28 (d, 0.17 H, $J_{1,2}$ 4.3 Hz, H-1α), 5.99 (s, 0.83 H, H-1β), 5.22 (m, 0.17 H, H-2α), 5.12 (m, 0.83 H, H-2β), 4.62 (m, 1 H, H-4), 4.5–4.2 (m, 2 H, H-5a,b), 2.3–2.1 (m, 2 H, H-3a,b), 2.05, 2.03, 2.02 (3s, 3 H, Ac), 1.84 (s, 3 H, Ac). FAB-mass spectrum (NBA): positive mode m/z 263 [M − AcOH]$^+$. Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.37; H, 5.74.

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