Two synthetic routes to 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)-4′-thionucleosides

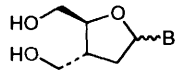
John Mann,*[a] Allen J. Tench,[a] Alexander C. Weymouth-Wilson,[a] Sue Shaw-Ponter[b] and Robert J. Young[b]

[a] *Department of Chemistry, Reading University, Whiteknights, Reading RG6 2AD, UK*

[b] *Department of Medicinal Chemistry, Wellcome Research Laboratories, Langley Court, Beckenham BR3 3BS, UK*

A number of 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)-4′-thionucleosides have been prepared from either (4*R*,5*S*)-4,5-bis(*tert*-butyldimethylsiloxymethyl)tetrahydrofuran-2-one or from (2*R*,3*R*)-1-benzyloxy-3-(benzyloxymethyl)hex-5-en-2-ol. The former was converted into methyl (3*R*,4*S*)-4-acetylsulfanyl-5-(*tert*-butyldimethylsiloxy)-3-(*tert*-butyldimethylsiloxymethyl)pentanoate and then into 1-*O*-acetyl-2,3-dideoxy-3-*C*-(*tert*-butyldimethylsiloxymethyl)-5-*O*-(*tert*-butyldimethylsilyl)-4-thio-D-*erythro*-pentofuranose prior to coupling with silylated pyrimidines. The second key intermediate was converted into (2*R*,3*R*)-1-benzyloxy-3-benzyloxymethyl-5,5-bis(benzylsulfanyl)pentan-2-ol and thence *via* the mesyl ester into 1-*S*-benzyl-5-*O*-benzyl-3-*C*-(benzyloxymethyl)-2,3-dideoxy-1,4-dithio-D-*erythro*-pentofuranose prior to coupling with silylated pyrimidines.

The quest for new antiviral agents is proceeding at an accelerating pace, not least because of the world-wide fear and alarm at the rapid spread of infections due to human immunodeficiency virus (HIV). We[1] and others[2] have recently shown that certain 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)nucleosides **1** have good *in vitro* activity against HIV and a number of other viruses, and this encouraged us to prepare the corresponding 4′-thionucleosides **2** for biological evaluation. In this paper we provide a full account of our work.



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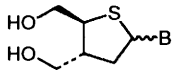
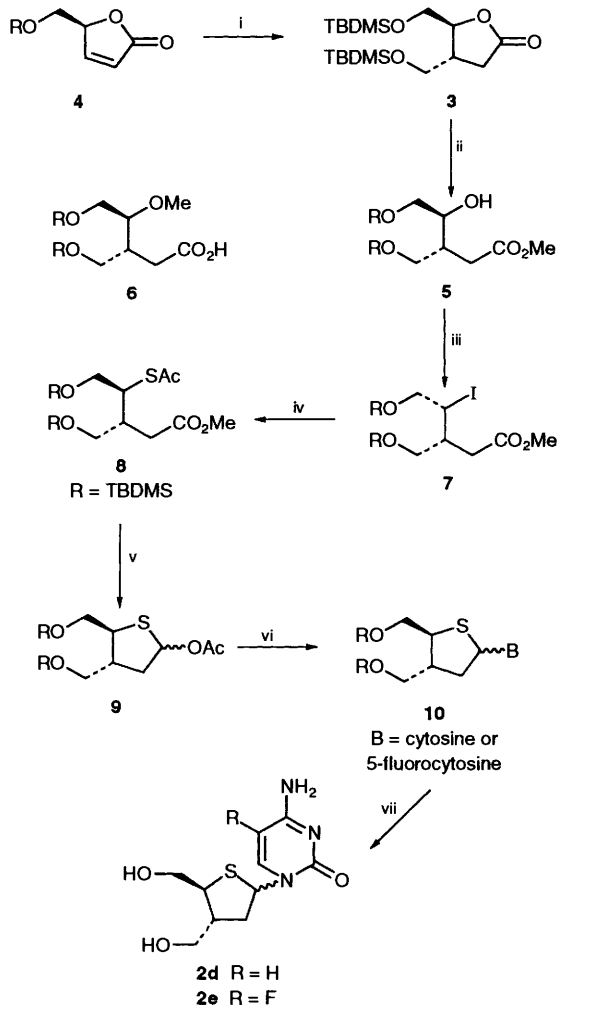


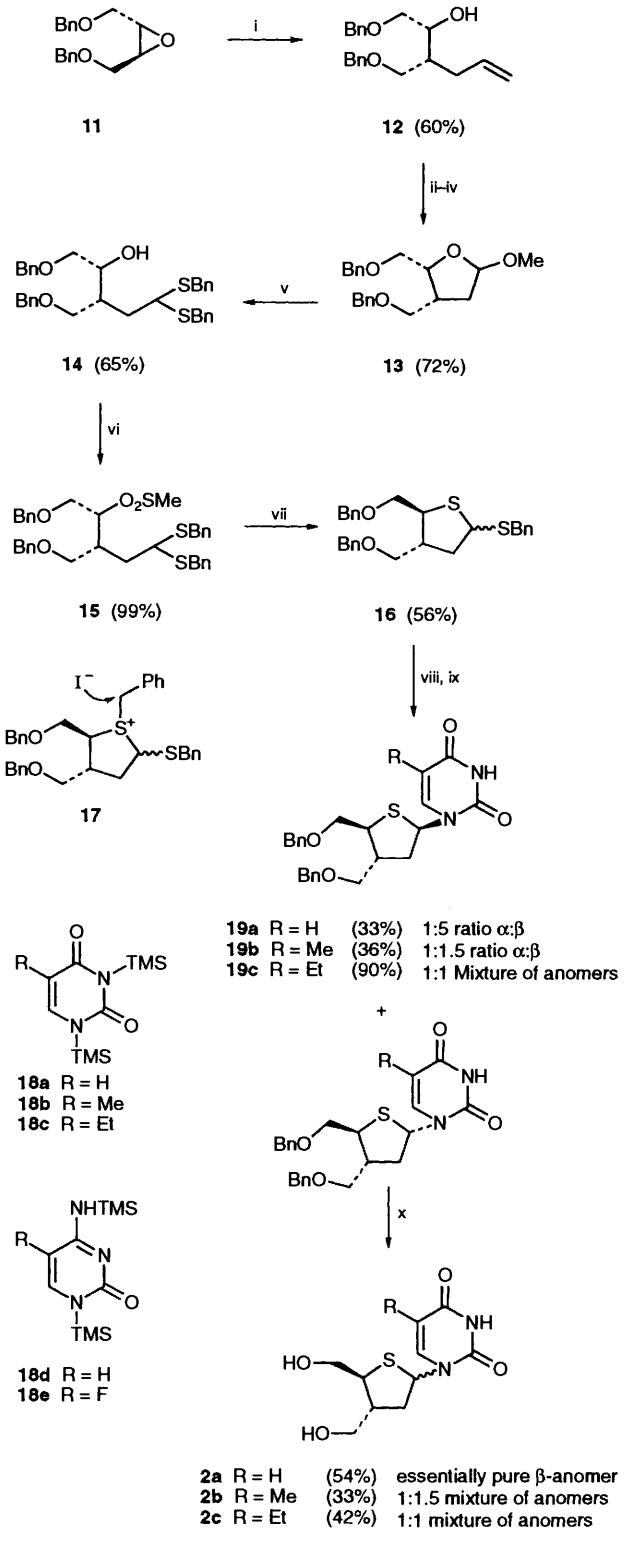
2a B = Uracil
b B = Thymine
c B = 5-Ethyluracil
d B = Cytosine
e B = 5-Fluorocytosine

A number of 4′-thionucleosides had been prepared prior to the commencement of our investigations, and these included 4′-thio derivatives of most of the natural 2′-deoxynucleosides as well as 4′-thio analogues of 3′-azido-3′-deoxythymidine (AZT), dideoxyinosine (ddI), dideoxycytidine (ddC) and (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU).[3] Several of these compounds had antiviral activity. Very recently (whilst we were awaiting the full results of biological evaluation) Samuelsson and co-workers have reported the synthesis of the same type of compounds **2** that we have prepared,[4] though their route to these compounds is different from ours.

Our first route (Scheme 1) employed the bis(*tert*-butyldimethylsiloxymethyl) ($TBDMSOCH_2$) derivative of butyrolactone (compound **3**) that we had previously prepared *via* the stereo- and regio-selective photocatalysed addition of methanol to the butenolide **4**. Reaction of compound **3** with sodium hydroxide in the presence of dimethyl sulfate provided a mixture of the desired ester **5** and the methyl ether **6** in variable ratios and yields. Conversion of the ester **5** into the unstable iodide **7** was achieved by using a mixture of iodine, triphenylphosphine and imidazole in dichloromethane (DCM)[5] (47% yield, 73% based on consumed alcohol). Reaction of this iodide with thioacetic acid in the presence of tetrabutylammonium hydroxide provided the thioacetate **8**, which was reduced with diisobutylaluminium hydride (DIBAL) and the resultant hemiacetal was trapped with acetic anhydride to yield



Scheme 1 *Reagents and conditions*: i, MeOH, *hν*; then TBDMSCl; ii, NaOH, Me_2SO_4; iii, I_2, PPh_3, imidazole; iv, AcSH, Bu_4N^+ OH^-; v, DIBAL; then Ac_2O; vi, $SnCl_4$; $(Me_3Si)_2$Base; vii, $MeC_6H_4SO_3H$, aq. MeOH



Scheme 2 *Reagents and conditions:* i, CH_2=$CHCH_2MgBr$, Et_2O, −50 °C; ii, OsO_4, NMMNO, aq. THF; iii, $NaIO_4$, aq. THF; iv, HCl, MeOH; v, $PhCH_2SH$, conc. HCl; vi, $MeSO_2Cl$, pyridine; vii, Et_3N, NaI, butan-2-one, reflux, 1 h; viii, $AcN(SiMe_3)_2$, MeCN; ix, NIS, MeCN, $CF_3SO_2OSiMe_3$, −78 °C, 1 h; x, BBr_3, DCM, −78 °C

the 1-*O*-acetyl-4-thio-D-*erythro*-pentofuranosides **9** (~ 1 : 1 ratio of anomers). Reaction of this anomeric mixture with a variety of silylated pyrimidines in the presence of tin tetrachloride in DCM at −78 °C provided the desired 4′-thionucleosides **10** as their bis(*tert*-butyldimethylsilyl) ethers. Many of the steps in this route were unreliable or low yielding, so a second route was developed and this is shown in Scheme 2.

The chiral epoxide **11**, available from diethyl (*S*,*S*)-tartrate in five steps,[6] was treated with allylmagnesium bromide at −50 °C to provide the expected alcohol **12** (60% on the 50 gram scale). Owing to the inherent C_2 symmetry of the epoxide, only one product was obtained in this reaction, and this is an advantage of our procedure over that of Samuelsson.[4] Oxidative cleavage of the double bond was achieved through the sequential use of osmium tetraoxide (catalytic) in conjunction with *N*-methylmorpholine *N*-oxide (NMMNO),[7] followed by sodium periodate in aq. tetrahydrofuran (THF). The resultant lactol was converted into its methyl glycoside **13** in methanolic HCl (72% isolated yield overall from **12**). The acyclic dibenzyl dithioacetal **14** was then produced by reaction of glycoside **13** with an excess of phenylmethanethiol in the presence of conc. HCl (65%) and this was converted into the mesyl ester **15** in essentially quantitative yield ($MeSO_2Cl$ and pyridine).

The key ring closure with inversion of configuration at C-4 (deoxyribose numbering) could now be attempted, and this was achieved through the use of sodium iodide and triethylamine in refluxing butan-2-one. Reaction was complete within 1 h and the desired 1-*S*-benzyl-5-*O*-benzyl-3-*C*-benzyloxymethyl-2,3-dideoxy-1,4-dithio-D-*erythro*-pentofuranose **16** was isolated (as a mixture of anomers) in an excellent yield of 93%. This conversion presumably proceeds *via* the intermediacy of sulfonium species **17**. All of these reactions have been carried out many times and on at least the 12 gram scale.

Coupling of thioglycoside **16** with bis-trimethylsilylated pyrimidines **18** was routinely carried out (on the 1 gram scale) using a mixture of *N*-iodosuccinimide (NIS) and trimethylsilyl triflate in dry acetonitrile at −78 °C—a modification of the procedure reported by Sugimura.[8] The dibenzylated nucleosides **19** were obtained (as ~ 1 : 1 anomeric mixtures) in yields ranging from 33% (**19a**) to 90% (**19c**). If the trimethylsilyl triflate was omitted from the reaction mixture, anomer ratios of up to 5 : 1 β : α were obtained, though the yields were generally reduced in comparison with the standard reaction conditions. It is not clear whether there is a genuine stereoselectivity under these conditions or whether the α-anomer is selectively degraded. Further studies are underway to clarify this interesting result and to establish factors that influence the yields. Finally, removal of the two benzyl groups was achieved through the use of boron tribromide in DCM at −78 °C to provide the desired nucleosides **2** as ~ 1 : 1 anomeric mixtures.

These compounds were assessed for antiviral activity against a number of viruses, but none showed any activity (or cell toxicity) up to a concentration of 100 micromolar. The viruses/cell lines included: HSV-1 (vero), HSV-2 (vero), VZV (MRC5), HCMV (MRC5), influenza A (MDCK), HIV-1 (HeLa CD4 and MT4) and HBV (HEP/G2/P5A).†

Experimental

IR spectra were recorded using a Perkin-Elmer 881 series double-beam spectrophotometer, and samples were run as thin films or in solution using NaCl plates. Low-resolution and accurate mass data were recorded on a VG Analytical ZAB-IF mass spectrometer by the SERC mass spectrometry service at the University of Swansea. ^{1}H NMR spectra were recorded on a Bruker WH250 spectrometer or on a JEOL FX400 instrument and *J* values are given in Hz. ^{13}C NMR spectra were recorded on the JEOL spectrometer. Flash chromatography was carried out using Sorbsil™ C60 silica gel (40–60 microns). TLC was carried out using 0.25 mm layers of silica gel on plastic sheets.

† *Abbreviations:* HSV-1, -2: herpes simplex virus 1, 2; VZV: varicella zoster virus; HCMV: human cytomegalovirus; HBV: hepatitis B virus.

Solvents were distilled from calcium hydride when required anhydrous, and light petroleum refers to the fraction with distillation range 40–60 °C.

Assignments of the NMR data for the separate anomers of nucleosides (where given) are in agreement with assignments for similar anomers in the literature. However, these assignments should be treated with some caution in the absence of nuclear Overhauser enhancement (NOE) and other confirmatory measurements.

(2*R*,3*R*)-1-Benzyloxy-3-(benzyloxymethyl)hex-5-en-2-ol 12

To a stirred solution of allylmagnesium bromide (1 mol dm^{-3} solution in diethyl ether; 400 cm^3, 400 mmol) cooled to −78 °C under nitrogen was added dropwise a solution of (2*S*,3*S*)-2,3-bis(benzyloxymethyl)oxirane (50.58 g, 178 mmol) in dry diethyl ether (300 cm^3). This gave a thick precipitate which dissolved to give a yellow solution. After 30 min, the mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with saturated aq. ammonium chloride. After separation of the organic and aqueous fractions, the aqueous fraction was extracted with one portion of diethyl ether (300 cm^3). The combined organic fractions were washed successively with sodium hydrogen carbonate (3 × 100 cm^3) and brine, and dried ($MgSO_4$). The mixture was evaporated to dryness to give a clear yellow oil, which was purified by column chromatography on silica gel and elution with 15% ethyl acetate–hexane to give the *title compound* (34.35 g, 60%) as an oil, R_f 0.36 (30% ethyl acetate–hexane); ν_{max}(thin film)/cm^{-1} 3477 (OH), 3065–2860, 699 and 737 (C–H stretch and bend), and 1641 (alkene C=C stretch); δ_H(400 MHz; $CDCl_3$) 1.89 (1 H, m, 3-H), 2.15–2.28 (2 H, m, 4-H_2), 3.00 (1 H, s, OH), 3.53–3.60 (4 H, m, 1-H_2 and BnOCH_2), 3.88 (1 H, m, 2-H), 4.45 (2 H, s, CH_2Ph), 4.53 (2 H, s, CH_2Ph), 5.00 (2 H, m, 6-H_2), 5.76 (1 H, m, 5-H) and 7.27–7.34 (10 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 33.04 (C-5), 40.35 (C-3), 70.09 (3-CH_2), 71.97 (C-1), 72.75–73.32 (2 × CH_2Ph, C-2), 116.59 (C-6), 127.6–138.08 (12 C-aromatic) and 136.51 (C-5) [Found: *m*/*z*, 326.18818 (M^+). $C_{21}H_{26}O_3$ requires *M*, 326.18828].

Methyl 5-*O*-benzyl-3-*C*-(benzyloxymethyl-2,3-dideoxy-α/β-L-*threo*-pentofuranoside 13

To a solution of alcohol **12** (34 g, 104 mmol) and NMMNO (25.49 g, 187 mmol) in THF–water (3:1; 300 cm^3) under nitrogen at 0 °C was added osmium tetraoxide (26.44 cm^3, 2.1 mmol) as a 2.5% w/w solution in *tert*-butyl alcohol. After being stirred at this temperature for 30 min, and then at room temperature for 18 h the mixture was quenched with sodium hydrogen sulfite (10.55 g). After the mixture had been stirred for 15 min, THF was removed by evaporation and the residue was partitioned between ethyl acetate (200 cm^3) and 1 mol dm^{-3} hydrochloric acid (200 cm^3). The organic layer was washed with aq. sodium hydrogen carbonate (3 × 100 cm^3) dried ($MgSO_4$), and evaporated to yield the crude diol as a yellow oil.

The diol was dissolved in THF–water (3:1; 100 cm^3) and the solution was stirred with sodium periodate (40 g, 77.19 mmol) at room temperature for 30 min to give an unstable furanose. THF was removed by evaporation and the residue was partitioned between diethyl ether and saturated brine. After extraction of the aqueous layer with diethyl ether (2 × 100 cm^3), the combined organic fractions were filtered, dried ($MgSO_4$), and evaporated to leave a pale yellow oil. This was then treated with methanolic hydrogen chloride (0.05% w/w solution; 150 cm^3) to yield the furanoside. After the mixture had been stirred for 10 min, the solvent was removed by evaporation, the residue was dissolved in diethyl ether (50 cm^3), and the solution was washed with aq. sodium hydrogen carbonate (2 × 150 cm^3), dried ($MgSO_4$), and evaporated to dryness. The *pentofuranoside* **13** was purified by column chromatography on silica gel and elution with 35% ethyl acetate–hexane to yield an oil (29.75 g, 83.5%), R_f 0.36 (50% ethyl acetate–hexane); ν_{max}(thin film)/cm^{-1} 2906 and 2858 (OCH_2, OMe), 1455 (CH_2, Me) and 1104 (C–O); δ_H(400 MHz; $CDCl_3$) 1.91–1.96 (2 H, m, 2-H_2), 2.75–2.80 (1 H, m, 3-H), 3.35 (3 H, s, MeO), 3.4–3.7 (4 H, m, 5-H_2 and 3-CH_2), 4.33 (1 H, m, 4-H), 4.41–4.56 (4-H, m, PhCH_2O), 5.0–5.06 (1 H, m, 1-H) and 7.27–7.33 (10 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 36.13 and 36.25 (C-2), 39.03 and 40.04 (C-3), 54.82 and 55.20 (OMe), 69.56–78.13 (2 × CH_2Ph, 3-CH_2), 79.85 (C-4), 104.41 and 105.29 (C-1) and 127.51–138.28 (12 C-aromatic) [Found: *m*/*z*, 342.1829 (M^+), $C_{21}H_{26}O_4$ requires *M*, 342.1832].

(2*R*,3*R*)-1-Benzyloxy-3-benzyloxymethyl-5,5-bis(benzylsulfanyl)pentan-2-ol 14

To a stirred solution of the pentofuranoside **13** (29.75 g, 86.94 mmol) in phenylmethanethiol (23.5 g, 189 mmol) at 70 °C under nitrogen was added conc. hydrochloric acid (19.34 cm^3). After the mixture had been stirred for 5 h, distilled water (200 cm^3) was added and the mixture was extracted with diethyl ether (100 cm^3). The organic layer was washed with water (2 × 100 cm^3), dried ($MgSO_4$), and evaporated to dryness. The dibenzyl dithioacetal was purified by column chromatography on silica gel and elution with 20% ethyl acetate–hexane to yield the *dibenzyldithioacetal* **14** as an oil (33.53 g, 65%), R_f 0.16 (20% ethyl acetate–hexane); ν_{max}(thin film)/cm^{-1} 3488 (OH) and 1455 and 1496 (CH_2); δ_H(400 MHz; $CDCl_3$) 1.91–2.02 (2 H, m, 4-H_2), 2.79 (1 H, s, OH), 3.19–3.03 (1 H, m, 3-H), 3.36–3.41 (4 H, m, SCH_2Ph), 3.53 (1 H, m, 5-H), 3.63 (1 H, m, 2-H), 3.64–3.80 (4 H, m, 1-H_2 and 3-CH_2), 4.23 (2 H, m, CH_2Ph), 4.45 (2 H, m, CH_2Ph) and 7.16–7.33 (20 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 34.15–34.7 (2 × SCH_2Ph, C-3 and -4), 38.28 (C-2), 48.03 (C-5), 69.12 (3-CH_2), 71.49 (C-1), 72.59 and 73.18 (OCH_2Ph) and 126.89–138.26 (24 C-aromatic) [Found: *m*/*z*, 558.2265 (M^+). $C_{34}H_{38}O_3S_2$ requires *M*, 558.2264].

(2*R*,3*R*)-1-Benzyloxy-3-benzyloxymethyl-5,5-bis(benzylsulfanyl)pentan-2-ylmethane sulfonate 15

To a solution of the alcohol **14** (12.641 g, 22.64 mmol) in dry pyridine (3.44 g, 43.51 mmol) at 0 °C was added methanesulfonyl chloride (5.21 g, 45.52 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for a further 4 h. The mixture was dissolved in ethyl acetate (100 cm^3), and the solution was washed with water (50 cm^3) and evaporated to dryness under highly reduced pressure to remove the solvent and all traces of pyridine. The crude mesyl ester was purified by column chromatography on silica gel and elution with 20% ethyl acetate–hexane. This gave pure mesyl ester **15** as an oil (14.263 g, 99%), R_f 0.5 (40% ethyl acetate–hexane); ν_{max}(thin film)/cm^{-1} 2858 and 2916 (CH, CH_2 stretch), 1360, 1175 (SO_2) and 1104 (C–O); δ_H(400 MHz; $CDCl_3$) 1.85 (2 H, t, J_{gem} 7.3, 4-H_2), 2.34 (1 H, m, 3-H), 2.91 (3 H, s, Me), 3.54–3.64 (5 H, m, 1-H_2, 3-CH_2 and 5-H), 3.7–3.8 (4 H, dd, SCH_2Ph), 4.17–4.28 (2 H, dd, J_{gem} 11.7, OCH_2Ph), 4.41–4.49 (2 H, dd, J_{gem} 11.7, OCH_2Ph) and 7.18–7.33 (20 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 33.2–35.18 (2 × SCH_2Ph, C-3 and -4), 38.9 (C-2), 48.36 (C-5), 68.02 (3-CH_2), 70.67 (C-1), 73.23–73.52 (OCH_2Ph), 83.40 ($MeSO_2$) and 127.25–138.5 (24 C-aromatic).

Benzyl-5-*O*-benzyl-3-*C*-benzyloxymethyl-2,3-dideoxy-1,4-dithio-D-*erythro*-pentofuranoside 16

The mesyl ester **15** (12.23 g, 19.22 mmol), triethylamine (2.78 g, 27.95 mmol) and sodium iodide (4.2 g, 27.95 mmol) were dissolved in butan-2-one (100 cm^3) and the solution was refluxed for 4 h. The reaction mixture was evaporated to dryness, the residue was dissolved in ethyl acetate (200 cm^3), and the solution was washed successively with cold 10% aq. citric acid (3 × 100 cm^3) and brine, dried ($MgSO_4$), and

evaporated to dryness. The crude product was purified by column chromatography on silica gel and elution with 20% ethyl acetate–hexane to give the *dithiopentofuranoside* **16** as a pale yellow oil (4.88 g, 56.4%) as a mixture of the α and β anomers; R_f 0.6 (40% ethyl acetate–hexane), 0.7 (EtOAc); ν_{max}(thin film)/cm^{-1} 3028, 3062 and 2856 (C–H stretch) and 1113 (C–O); δ_H(400 MHz; $CDCl_3$) 2.19–2.23 (2 H, m, 2-H_2), 2.65–2.70 (1 H, m, 3-H), 3.44–3.57 (4 H, m, 5-H_2 and 3-CH_2), 3.74–3.82 (3 H, m, 4-H and SCH_2Ph), 4.26 (1 H, t, $J_{1/2}$ 4.8, 1-H), 4.47–4.53 (4 H, m, OCH_2Ph) and 7.21–7.34 (15 H, m, ArH); δ_C(100 MHz; $CDCl_3$) 37.07 and 37.40 (SCH_2Ph), 41.06 and 41.26 (C-2), 45.24 and 46.84 (C-3), 50.62–51.24 (C-4), 71.43–75.11 (2 × PhCH_2O, C-5, C-6 and 3-CH_2) and 127.01–138.2 (18 C-aromatic) [Found: *m/z*, 450.1647 (M^+). $C_{27}H_{30}O_2S_2$ requires *M*, 450.1689].

1-(5′-*O*-Benzyl-3′-*C*-benzyloxymethyl-2′,3′-dideoxy-4′-thio-α/β-D-*erythro*-pentofuranosyl)uracil 19a

Uracil (416 mg, 3.75 mmol) and bis(trimethylsilyl)acetamide (2.6 cm^3, 10.51 mmol) were stirred in dry acetonitrile at room temperature under nitrogen until all the uracil had dissolved and reacted to form the bis(trimethylsilyl) derivative. The dithiopentofuranoside **16** (1.27 g, 2.82 mmol) and NIS (635 mg, 2.82 mmol) were added, causing the colour of the reaction mixture to change from colourless to bright red. After being stirred at room temperature under nitrogen for 2 h, the reaction mixture was quenched with cold 5% aq. sodium thiosulfate (50 cm^3). After evaporation of the acetonitrile, the residue was dissolved in ethyl acetate (50 cm^3), and the solution was washed with distilled water (2 × 30 cm^3), dried ($MgSO_4$), and evaporated to dryness. The crude nucleoside was purified by column chromatography on silica gel and elution with 50% ethyl acetate–hexane to give the product (410 mg, 33%) with a 1 : 5 ratio of α- to β-anomer. A second column produced a better separation to yield some pure β-anomer; R_f 0.51 (EtOAc); δ_H(400 MHz; $CDCl_3$) 2.23–2.34 (2 H, m, 2′-H_2), 2.58–2.66 (1 H, m, 3′-H), 3.45 (2 H, m, 3′-CH_2), 3.60 (1 H, m, 4′-H), 3.77–3.81 (2 H, m, 5′-H_2), 4.50 (2 H, s, PhCH_2O), 4.56 (2 H, s, PhCH_2O), 5.20–5.23 (1 H, dd, $J_{5,6}$ 5.9, 5-H β), 5.76 (1 H, dd, $J_{5,6}$ 5.8, 5-H α), 6.15 (1 H, dd, $J_{1',3'}$ 2.2, $J_{1',2'}$ 3.9, 1′-H β), 6.34–6.38 (1 H, dd, $J_{1',3'}$ 2.8, $J_{1',2'}$ 6.8, 1′-H α),7.76 (1 H, d, $J_{6,5}$ 8.06, 6-H α), 8.31 (1 H, d, $J_{6,5}$ 8.06, 6-H β), 9.19 (1 H, s, NH β) and 9.32 (s, NH α); δ_C(100 MHz; $CDCl_3$) 41.72 (C-2′), 43.07 (C-3′), 51.79 (C-4′), 63.32 (C-1′), 70.43 (3′-CH_2), 71.16 (C-5′), 73.15 (Ph-CH_2O), 73.59 (PhCH_2O), 101.31 (=C-5), 127–128 (=C-aromatics), 142.07 (=C-6), 150.54 (=C-2) and 163.03 (=C-4) [Found: *m/z*, 438.1692 (M^+). $C_{24}H_{26}N_2O_4S$ requires *M*, 438.1693].

1-(2′,3′-Dideoxy-3′-*C*-hydroxymethyl-4′-thio-β-D-*erythro*-pentofuranosyl)uracil 2a

To a solution of the benzyl-protected pentofuranosyl uridine β anomer **19a** (192 mg, 0.438 mmol) in dry DCM (2 cm^3) under argon at −78 °C was added boron tribromide (1 mol dm^{-3} solution in DCM; 2.19 cm^3, 2.19 mmol) dropwise. After the mixture had been stirred at −78 °C for 30 min, the reaction was quenched by the addition of methanol (1.45 cm^3). The acid reaction mixture was neutralised (*ca.* pH 7, pH paper) by the addition of pre-washed ion-exchange resin IRA 93 (OH-form). After filtration of the ion-exchange resin, the reaction mixture was evaporated to dryness, and the residue was purified by column chromatography on silica gel and eluted with 10% methanol–ethyl acetate to give the β-anomer as a crystalline solid (61 mg, 54%); R_f 0.15 (10% methanol–ethyl acetate); δ_H(400 MHz; $CDCl_3$) 2.29–2.36 (3 H, m, 2′-H_2 and 3′-H), 3.45 (1 H, m, 4′-H), 3.48–3.64 (2 H, m, 3′-CH_2), 3.75–3.87 (2 H, m, 5′-H_2), 5.70 (1 H, d, $J_{5,6}$ 8.06, 5-H), 6.12 (1 H, dd, $J_{1',2'}$ 4.4, $J_{1',3'}$ 1.5, 1′-H) and 8.40 (1 H, d, $J_{5,6}$ 8.06, 6-H); δ_C(100 MHz; $CDCl_3$) 41.5 (C-2′), 46.9 (C-3′), 55.03 (C-4′), 63.45 (3′-CH_2), 64.25 (C-1′), 64.76 (C-5′), 102.11 (C-5), 143.79 (C-6), 152.58 (C-2) and 166.26 (C-4).

1-(5′-*O*-Benzyl-3′-*C*-benzyloxymethyl-2′,3′-dideoxy-4′-thio-α/β-D-*erythro*-pentofuranosyl)-5-ethyluracil 19c

5-Ethyluracil (312 mg, 2.22 mmol) and bis(trimethylsilyl)acetamide (1.67 cm^3, 6.73 mmol) were stirred together in dry acetonitrile (30 cm^3) at room temperature under nitrogen until all the 5-ethyluracil had dissolved and reacted to form the trimethylsilyl complex. The dithiopentofuranoside (1.00 g, 2.22 mmol) was added and the mixture was cooled to −78 °C. NIS (500 mg, 2.22 mmol) and then trimethylsilyl triflate (0.43 cm^3, 2.22 mmol) were added, causing the colour of the reaction mixture to change from colourless to bright red. The reaction mixture was warmed to −18 °C, stirred for 3 h under nitrogen, and then quenched with cold 5% aq. sodium thiosulfate (50 cm^3). After evaporation of the acetonitrile, the residue was dissolved in ethyl acetate (50 cm^3), and the solution was washed with distilled water (2 × 30 cm^3), dried ($MgSO_4$), and evaporated to dryness. The crude nucleoside was purified by column chromatography on silica gel and elution with 40% ethyl acetate–hexane to give the nucleoside **19c** with a 1 : 1 ratio of α to β anomers as an oil (921 mg, 89%); R_f 0.46 (50% ethyl acetate–hexane); δ_H(400 MHz; $CDCl_3$)1.02 (t, *J* 7.33, Me α), 1.14 (t, *J* 7.33, Me β), 2.14–2.18 (m, 5-H_2 β), 2.29–2.38 (m, 5-H_2 α and 2′-H), 2.55–2.66 (1 H, m, 3′-H), 3.40–3.60 (3 H, m, 4′-H and 5′-H), 3.69–3.83 (2 H, m, 3′-CH_2), 4.48–4.62 (4 H, m, PhCH_2O), 6.21 (dd, $J_{1',2'}$ 6.23, 1′-H β), 6.39 (dd, $J_{1',2'a}$ 9.53, $J_{1',2'b}$ 6.97, 1′-H α), 7.25–7.36 (10 H, m, ArH), 7.50 (s, 6-H α), 8.01 (s, 6-H β), 8.86 (s, NH β) and 8.92 (s, NH α); δ_C(100 MHz; $CDCl_3$) 12.91 (Me α), 13.02 (Me β), 20.17 (5-CH_2 β), 20.30 (5-CH_2 α), 40.81 (C-2′ α), 41.35 (C-2′ β), 43.54 (C-3′ β), 45.66 (C-3′ α), 50.19 (C-4′ α), 51.59 (C-4′ β), 60.40 (C-1′ α), 62.95 (C-1′ β), 70.59–73.23 (C-5′ and 3′-CH_2), 116.02 (C-5 α), 117.35 (C-5 β), 127.39–128.42 (C-aromatics), 135.27 (C-6 β), 136.71 (C-6 α), 150.54 (C-2 α), 150.57 (C-2 β), 162.93 (C-4 β) and 163.17 (C-4 α) [Found: *m/z*, 466.1925 (M^+). $C_{26}H_{30}N_2O_4S$ requires M, 466.1928].

1-(2′,3′-Dideoxy-3′-*C*-hydroxymethyl-4′-thio-α/β-D-*erythro*-pentofuranosyl)-5-ethyluracil 2c

To a solution of the benzyl-protected pentofuranosyl 5-ethyluridine **19c** (904 mg, 2.01 mmol) in dry dichloromethane (17 cm^3) under argon at −78 °C was added dropwise boron tribromide (1 mol dm^{-3} solution in DCM; 5.00 cm^3, 5.00 mmol). After the mixture had been stirred at −78 °C for 30 min, the reaction was quenched by the addition of methanol (6.7 cm^3) and the mixture was stirred for a further 15 min. The acid reaction mixture was partially neutralised (to *ca.* pH 6, pH paper) by the careful addition of pyridine and was then evaporated to dryness. The residue was purified by column chromatography on silica gel and elution with 5% methanol–ethyl acetate to give compound **2c** as a hygroscopic foam (239 mg, 42%), R_f 0.5 (5% methanol–ethyl acetate); δ_H(400 MHz; $CDCl_3$) 1.20 (3 H, m, *J* 7.33, Me), 2.37–2.44 (4 H, m, 2′-H and 5-CH_2), 2.48–2.64 (1 H, m, 3′-H), 3.55–3.87 (3 H, m, 5′-H_2 and 4′-H), 3.87–3.98 (2 H, m, 3′-CH_2), 6.21 (dd, $J_{1'\beta,2'a}$ 5.49, $J_{1'\beta,2'b}$ 4.77, 1′-H β), 6.39 (dd, $J_{1'\alpha,2'a}$ 9.52, $J_{1'\alpha,2'b}$ 6.59, 1′-H α), 7.82 (s, 6-H α) and 8.30 (s, 6-H β); δ_C(100 MHz; $CDCl_3$) 13.41 (Me α), 13.63 (Me β), 21.13 (5-CH_2 β), 21.26 (5-CH_2 α), 41.19 (C-2′ α), 41.70 (C-2′ β), 46.70 (C-3′ β), 48.5 (C-3′ α), 54.76 (C-4′ α), 54.94 (C-4′ β), 61.45 (C-1′ α), 64.07 (C-1′ β), 63.15–65.75 (C-5′ and 3′-CH_2), 116.85 (C-5 β), 118.202 (C-5 α), 137.88 (C-6), 138.83 (C-aromatics), 152.49 (C-2 α), 152.53 (C-2 β), 165.55 (C-4 α) and 165.86 (C-4 β) [Found: *m/z*, 287.0660 (M^+). $C_{12}H_{18}N_2O_4S$ requires *M*, 287.0660].

The other nucleosides were prepared from thioglycoside **16** by this last method.

1-(2′,3′-Dideoxy-3′-*C*-hydroxymethyl-4′-thio-α/β-D-*erythro*-pentofuranosyl)thymine 2b

Compound **2b** (506 mg) was prepared in 12% overall yield from compound **16**. Ratio of anomers was 1:1.5 α:β; R_f 0.18 (5% methanol–ethyl acetate); δ_H(400 MHz; $CDCl_3$) 1.90 (d, $J_{CH3.6}$ 1.1, Me β), 1.92 (d, $J_{CH3.6}$ 1.1, Me α), 2.29–2.34 (2 H, m, 2′-H_2), 2.41–2.64 (1 H, m, 3′-H), 3.44–3.70 (3 H, m, 5′-H_2 and 4′-H), 3.71–3.89 (2 H, m, 3′-CH_2), 6.14 (dd, $J_{1'\beta.2'a}$ 6.04, $J_{1'\beta.2'b}$ 4.58, 1′-H β), 6.32 (dd, $J_{1'\alpha.2'a}$ 9.89, $J_{1'\alpha.2'b}$ 6.59, 1′-H α), 7.81 (d, $J_{CH3.6}$ 1.47, 6-H α) and 8.27 (t, $J_{CH3.6}$ 1.09, 6-H β), δ_C(100 MHz; $CDCl_3$) 12.51 (Me), 41.28 (C-2′ α), 41.43 (C-2′ β), 46.73 (C-3′ β), 49.0 (C-3′ α), 54.83 (C-4′ α), 54.93 (C-4′ β), 61.27 (C-1′ α), 63.89 (C-1′ β), 63.28–65.81 (C-5′ and 3′-CH_2), 110.99 (C-5′ β), 112.35 (C-5′ α), 138.5 (C-6), 139.45 (C-aromatic), 152.62 (C-2 α), 152.67 (C-2 β), 166.098 (C-4 α) and 166.35 (C-4 β) [Found: *m/z*, 273.0909 (M^+). $C_{11}H_{16}N_2O_4S$ requires *M*, 273.0910].

1-(2′,3′-Dideoxy-3′-*C*-hydroxymethyl-4′-thio-α/β-D-*erythro*-pentofuranosyl)cytosine 2d

The nucleoside **2d** (108 mg) was obtained as an amorphous foam (79% from thioglycoside **16**). Separation of the anomers could not be achieved by flash chromatography; the NMR spectrum showed that the ratio of α/β anomers was 1:1.1; R_f 0.19 [EtOAc–DCM–MeOH (1.5:6:2.5)]; ν_{max}(thin film)/cm^{-1} 3320 (OH), 3200 (NH_2), 1640 (C=O), 1605 and 1495 (C=C), 1400 and 1090 (C–O); δ_H(400 MHz; $CDCl_3$) 1.97 (ddd, overlapping, J_{gem} 12.1, $J_{2'.1'}$ 9.4, $J_{2'.3'}$ 12.1, 2′-H α), 2.15–2.322 (4 H, m, 2′-H, 3′-H α and β), 2.57 (1 H, ddd, overlapping, $J_{2'.1'}$ 6.3, $J_{2'.3'}$ 6.3, 2′-H), 3.42 (dt, overlapping, $J_{4'.3'}$ 6.4, $J_{4'.5'}$ 4.6, 4′-H β), 3.52–3.71 (8 H, m, 4-H α, 5-H α and β, 6-H α and β, 3′-CH_2 α and β), 3.84 (dd, J_{gem} 11.3, $J_{5'.4'}$ 0.9, 5-H α), 3.86 (dd, J_{gem} 11.8, $J_{5.4}$ 2.5, 5-H β), 5.97 (1 H, d, $J_{5.6}$ 7.6, 5-H β), 6.01 (t, $J_{1'.2'}$ 5.3, 1′-H β), 6.02 (d, $J_{5.6}$ 7.6, 5-H α), 6.19 (1 H, dd, $J_{1'.2'}$ 6.5, $J_{1.2'}$ 9.4, 1′-H α), 8.01 (d, $J_{6.5}$ 7.6, 6-H α) and 8.19 (d, $J_{6.5}$ 7.6, 6-H β) [Found: *m/z*, 258.0912 ($M^+ + 1$). $C_{11}H_{16}N_3O_3S$ requires *m/z* 257.0915].

1-(2′,3′-Dideoxy-3′-*C*-hydroxymethyl-4′-thio-α/β-D-*erythro*-pentofuranosyl)-5-fluorocytosines 2e

The nucleoside **2e** was obtained as an amorphous foam (65% from compound **16**). Separation of the anomers could not be achieved by flash chromatography; the NMR spectrum showed that the ratio of α/β anomers was 1:1.1; R_f 0.26 [EtOAc–DCM–MeOH (1.5:6:2.5 v/v]; ν_{max}(thin film)/cm^{-1} 3376 (OH), 3210 (NH_2), 1680 (C=O), 1600 (C=C), 1533, 1505, 1295 and 1100 (C–O); δ_H(400 MHz; $CDCl_3$) 1.93 (overlapping, ddd, J_{gem} 13.0, $J_{2'.3'}$ 11.7, $J_{2'.1'}$ 9.37, 2′-H α), 2.33 (m, 2′-H, 2′-, 3′-H β and 3′-H α), 2.6 (1 H, ddd, overlapping, $J_{2'.1'}$ 6.0, $J_{2'.3'}$ 6.0, 2′-H), 3.43 (dt, overlapping, $J_{4'.3'}$ 8.0, $J_{4'.5'}$ 4.3, 4′-H β), 3.57 (dd, J_{gem} 10.9, $J_{6'.3'}$ 3.6, 6-H β), 3.55–3.74 (m, 4′-, 5′-H, 6′-H, 6′-H α and β), 3.75 (dd, J_{gem} 11.9, $J_{5'.4'}$ 6.1, 5′-H β), 3.85 (dd, J_{gem} 11.4, $J_{5'.4'}$ 4.1, 5′-H α), 3.87 (dd, $J_{5'.4'}$ 4.6, 5′-H β), 5.97 (1 H, dt, overlapping, $J_{1'.2'}$ 1.5, $J_{1'.2'}$ 5.2, 1′-H β), 6.18 (dt, overlapping, $J_{1'.2'}$ 6.7, $J_{1'.2'}$ 9.1, 1′-H α), 6.19 (dd, $J_{1'.2'}$ 6.5, $J_{1.2'}$ 9.4, 1′-H α), 8.17 (d, $J_{6.F}$ 6.6, 6-H α) and 8.39 (d, $J_{6.F}$ 6.8, 6-H β).

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