Photocatalysed Addition of Alcohols to 5-Substituted 2,5-Dihydrofuran-2-ones: Novel Synthesis of (3'*R*)-2',3'-Dideoxy-3'-hydroxymethyl Nucleosides

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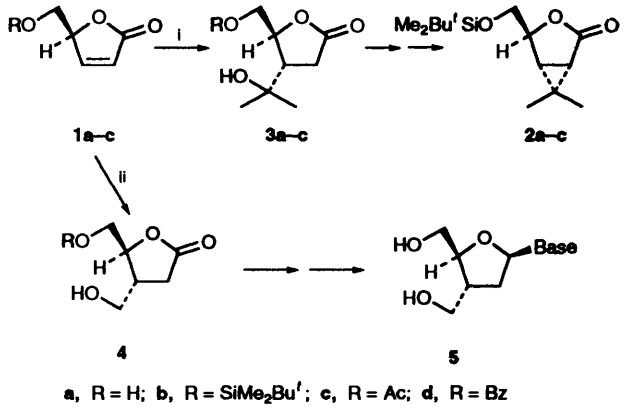
Methanol and propan-2-ol add in a regiospecific and highly stereocontrolled fashion to 5-substituted 2,5-dihydrofuran-2-ones (butenolides) under irradiation. The photoadducts with methanol have been converted into a number of (3'*R*)-2',3'-dideoxy-3'-hydroxymethyl nucleosides.

We recently reported[1,2] our preliminary results on the photocatalysed addition of alcohols to 5-substituted 2,5-dihydrofuran-2-ones **1** (Scheme 1). These additions were efficient, regiospecific and apparently face-selective. The adduct formed with propan-2-ol was converted into the known precursor **2** of *cis*-chrysanthemic acid[1] (Scheme 1), and this constitutes one of the most concise and stereo-efficient routes to this molecule. In this paper, we provide full details of both the photochemical methodology and a new route to the biologically interesting (3'*R*)-2',3'-dideoxy-3'-hydroxymethyl nucleosides.

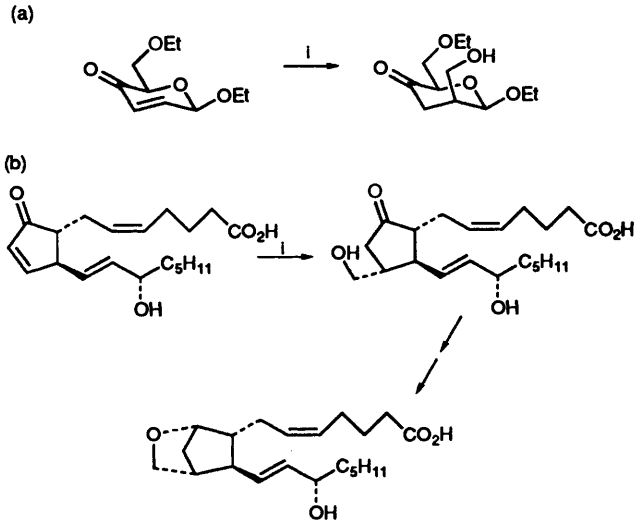


Scheme 1 *Reagents and conditions:* i, *hv*, Me_2CHOH; ii, $Ph_2C{=}O$, MeOH, *hv*

Results and Discussion

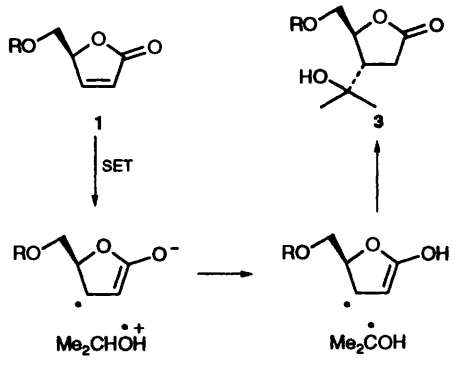
Photochemical Methodology.—At the commencement of this work, a literature survey revealed two major studies on the photocatalysed addition of alcohols to cycloalkenones. These were the work of Fraser-Reid *et al.*[3] on carbohydrate-derived α-enones (Scheme 2a) and the synthesis of a carbocyclic analogue of PGH_2 by Bundy[4] (Scheme 2b). In both instances the reactions were chemically sensitized using benzophenone, and proceeded with excellent regio- and stereo-selectivity. Fraser-Reid carried out further studies on the process[5] and concluded that the excited triplet state of benzophenone abstracted a hydrogen from methanol to yield the ketyl radical ($^{\bullet}CH_2OH$) which then participated in a conjugate addition reaction with the enone.

Our literature search did not reveal any studies on the photocatalysed addition of alcohols to cyclic unsaturated esters, and the studies summarized in Scheme 1 were therefore initiated. To our surprise (and delight) it was possible to effect addition of propan-2-ol to various derivatives of butenolide (**1**) by using a low-pressure mercury lamp without addition of benzophenone as sensitizer. The additions were completely regiospecific and apparently face-selective (we never isolated other stereoisomers), and they were also efficient (94% on the



Scheme 2 *Reagents and conditions:* i, MeOH, $Ph_2C{=}O$, *hv*

5 g scale for compound **3a**). It is likely that this reaction is initiated by a single-electron-transfer process (SET),[6] as shown in Scheme 3, though it then proceeds *via* radical chain reaction.



Scheme 3

Most remarkable was the stereoselectivity of the process. This was easily explained when a bulky protecting group was present as in substrate **1b**, but is more intriguing with the unprotected butenolide **1a**. We suggest that the solvent (propan-2-ol) is hydrogen bonded to the primary alcohol, thus rendering the upper face of the molecule more sterically hindered than the lower face. To assess the stereochemical purity of the adduct and the correctness of the spectral assignments, adduct **3a** was converted into the (*S*)-Mosher's ester[7] **6** (which exhibited discrete ^{13}C and ^{19}F signals in the respective NMR spectra), and into the crystalline benzoate ester **3d** for X-ray structural studies. The X-ray structure deter-

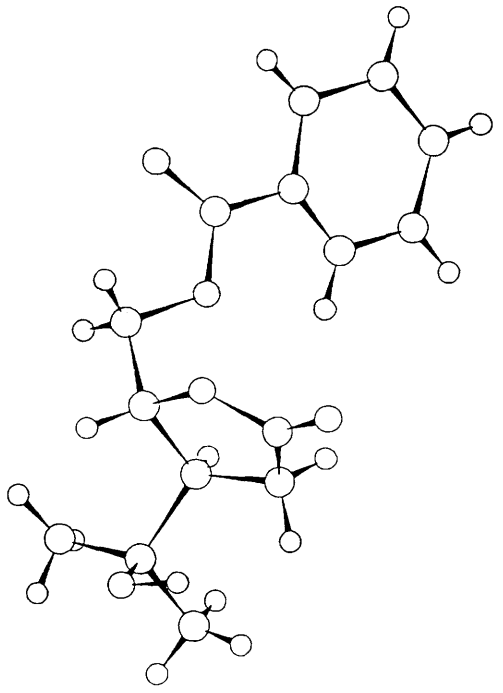


Fig. 1 The X-ray molecular structure of compound **3d**

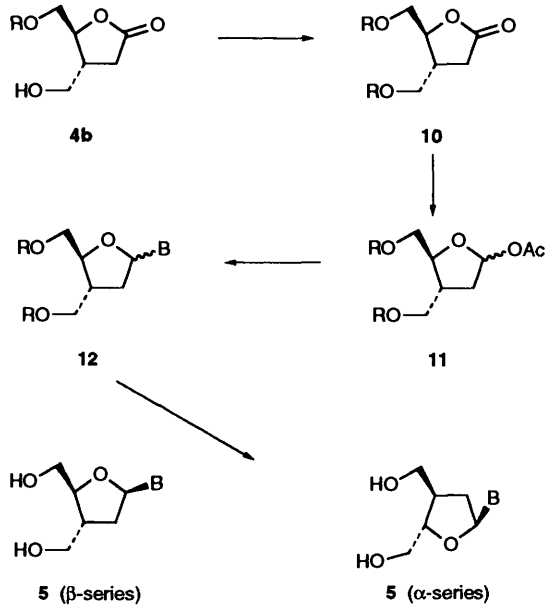
mination confirmed the relative stereochemical assignment predicted from the spectral studies, and the ORTEP representation is shown in Fig. 1.*

It proved impossible to add methanol to butenolides under the same conditions (the primary ketyl radical $^{\bullet}CH_2OH$ is certainly less stable than the tertiary radical $Me_2\dot{C}OH$), but after much experimentation we discovered that with one mole equivalent of benzophenone and a 500 W medium-pressure lamp (Pyrex vessel), it was possible to convert the butenolide **1b** into photoadduct **4b** in 60% yield. The photolysis time was a mere 4 h, and the reaction has been carried out routinely on the 30 gram scale. Around 75% of the benzophenone could be recovered unchanged, but variable amounts of benzopinacol **7** were also obtained, together with the not-unexpected adduct **8** (< 5% yield). No alternative regioisomers or stereoisomers of compound **4b** have been isolated.

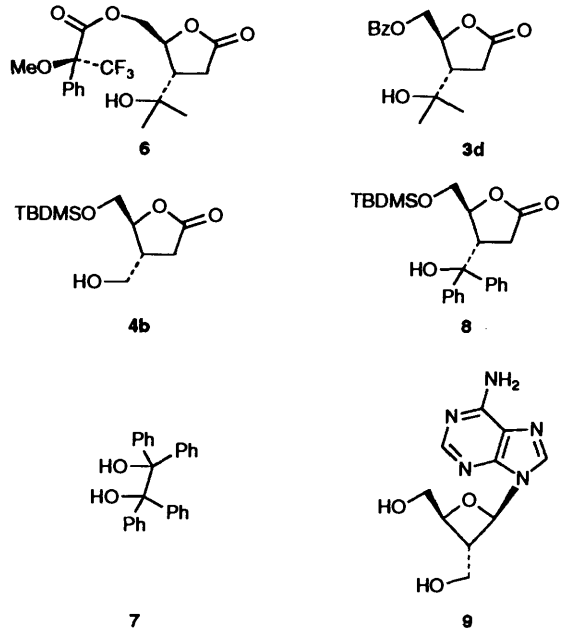
The mechanism of this photocatalysed reaction would appear to be analogous to that proposed by Fraser-Reid, and involves excitation of benzophenone to the triplet (*n*, π*) state with subsequent abstraction of a hydrogen atom from methanol and Michael addition of the resultant ketyl radical to the butenolide.

Nucleoside Synthesis.—With multigram quantities of adduct **4b** in hand, the synthesis of (3′*R*)-2′,3′-dideoxy-3′-hydroxymethyl nucleosides **5** could be attempted. These particular nucleosides are of interest because of their structural resemblance to the natural antiviral agent oxetanocin **9**,[8] and because both the β-anomer **5**β) and the α-anomer (**5**α) could conceivably act as substrates for viral enzymes (see Scheme 4).

Although a number of nucleosides of this type had been synthesized prior to our work,[9,10] all of the routes had employed



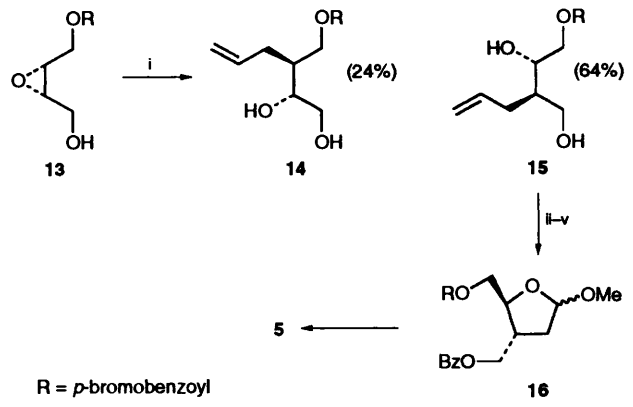
Scheme 4 R = $SiMe_2Bu^t$. **a**, B = cytosine; **b**, B = 5-fluorocytosine; **c**, B = uracil; **d**, B = 5-chlorouracil; **e**, B = thymine.



carbohydrates or other nucleosides as starting materials. As a result these routes were either lengthy (with much protection–deprotection chemistry) or did not allow the introduction of novel bases. During the course of our investigations, Svansson *et al.* reported a route[11] to these compounds that commenced with chiral epoxide **13** (Scheme 5). The problem with this route is that after cleavage of the epoxide with allylmagnesium bromide to the alkenes **14** and **15**, half of the product mixure (compound **14**) must be discarded before elaboration to the acetal **16**, and thence the nucleoside **5**.

Our synthesis (Scheme 4) proceeded uneventfully and involved formation of the bis-silyl ether **10**, reduction of the lactone with diisobutylaluminium hydride (DIBAL) and immediate formation of the anomeric acetates **11**. These were treated with the requisite pyrimidine base (as its bis-trimethylsilyl derivative) in the presence of either $EtAlCl_2$ or $SnCl_4$ to yield an anomeric mixture of the protected nucleosides **12**. As expected, there was no stereoselectivity observed, and in each instance a ~ 1:1 mixture of anomers was obtained. Finally,

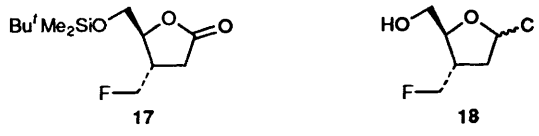
* We thank Dr. M. G. B. Drew for the X-ray structure determination. All data have been deposited but key features are listed below: $C_{15}H_{17}O_4$, M = 261.9, *F*(000) = 556, orthorhombic, *a* = 5.623(7), *b* = 11.371 (15), *c* = 22.594(21) Å, *V* = 1444.6 Å^3, D_c = 1.20 g cm^{-3}, D_m = 1.20 g cm^{-3}, *Z* = 4, λ = 0.7107 Å, μ = 0.93 cm^{-1}, space group $P2_12_12_1$.



Scheme 5 *Reagents:* i, allylmagnesium bromide; ii, BzCl, pyridine; iii, OsO_4, *N*-methylmorpholine oxide; iv, $NaIO_4$, THF–water; v, HCl, MeOH

removal of the silyl protecting group provided the desired nucleosides **5**.

A number of pyrimidines were employed, namely cytosine, 5-fluorocytosine, uracil, 5-chlorouracil and thymine, to produce the corresponding nucleosides **5a**–**5e**. In addition, the photoadduct **4b** was treated with (diethylamino)sulfur trifluoride (DAST) to produce the fluoromethyl compound **17** and thence the nucleoside analogue **18** by using the same chemistry as depicted in Scheme 4.



All of the compounds were screened for antiviral activity by Wellcome Research Laboratories and the results are shown in Table 1. The most active compound was **5a**, which possessed good levels of activity against all of the test viruses except influenza (data not shown). The fluoromethyl analogue **18** also exhibited a reasonable level of activity against HIV-1, but was inactive against the other viruses (data not shown). All compounds were tested as ~ 1:1 mixtures of the anomers.

Further studies on the synthesis of novel nucleosides will be reported in due course, and the utility of the photochemical methodology for the synthesis of other structures is also being vigorously pursued.

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 unless stated otherwise. 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 (at Reading) or on a Bruker WH400 instrument by the SERC NMR service at the University of Warwick. *J*-Values are in Hz. ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer. Flash chromatography was carried out using Sorbsil™ C60 silica gel (40–60 μm). Solvents were distilled from calcium hydride when required anhydrous, and light petroleum (LP) refers to the fraction with boiling range 40–60 °C.

The 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.

Table 1

Compound	HSV-1	HSV-2	VZV	HCMV	HIV-1
5a	9	16	20	7	1.2
5b	50	50	>40	>50	4.30
5c	>50	>50	>40	>100	>50
5d	>40	>50	>40	>100	>50
5e	>100	>100	>40	>100	>50

The data represent IC_{50} (μmol dm^{-3}) values. The viruses used were: HSV-1 and HSV-2 herpes simplex viruses; VZV varicella zoster virus; HCMV human cytomegalovirus; HIV-1 human immunodeficiency virus.

(4S,5S)-5-*Hydroxymethyl*-4-(1-*hydroxy*-1-*methylethyl*)*tetrahydrofuran*-2-*one* **3a**.—A solution of the butenolide **1a** (4.0 g, 35 mmol) in propan-2-ol (50 cm^3) was degassed with a steady stream of nitrogen, then was irradiated with two low-pressure lamps (254 nm) for 48 h. After removal of the solvent, the crystalline residue was recrystallized from ethyl acetate to give the title compound (5.72 g, 94%) as a crystalline solid, R_f 0.35 (EtOAc); m.p. 104 °C; $[\alpha]_D$ +25 (*c* 0.29, water); ν_{max}(KBr disc)/cm^{-1} 3420 (OH), 3360 (OH) and 1740 (C=O, lactone) cm^{-1}; δ_H[400 MHz; $(CD_3)_2SO$] 1.04 (3 H, s, Me), 1.07 (3 H, s, Me), 2.26 (1 H, m, 4-H), 2.39 (1 H, dd, J_{gem} 18.0, $J_{3,4}$ 5.5, 3-H), 2.57 (1 H, dd, $J_{3,4}$ 10, 3-H), 3.41 (1 H, ddd, J_{gem} 12, $J_{6,OH}$ 5.5, $J_{6,5}$ 4, 6-H),* 3.61 (1 H, ddd, $J_{6,5}$ 5.5, $J_{6,OH}$ 3, 6-H), 4.48 (1 H, dt overlapping, $J_{5,6}$ = $J_{5,4}$ 4, 5-H), 4.60 (1 H, s, OH) and 5.05 (1 H, t, $J_{OH,5}$ 5.5, OH); δ_C[100 MHz; $(CD_3)_2SO$] 26.67 (Me), 29.29 (Me), 30.61 (C-4), 45.94 (C-3), 63.37 (C-6),* [CMe_2C(OH)]; 81.97 (C-5) and 177.27 (C=O) (Found: C, 55.2; H, 8.2. Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10%).

(4R,5S)-5-(tert-*Butyldimethylsiloxy*)-4-(*hydroxymethyl*)-*tetrahydrofuran*-2-*one* **4b**.—The butenolide **1b** (29.5 g, 0.129 mol) with benzophenone (1 mol equiv.) was dissolved in methanol (AnalaR, 800 cm^3) and the solution was placed in a Pyrex vessel and degassed by passage of a steady stream of nitrogen for 1 h. The solution was irradiated by a medium-pressure mercury vapour 125 W (350 nm) lamp for 48 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography with gradient elution [eluent: LP–diethyl ether (1:1, v/v) to neat diethyl ether] to give the title compound **4b** (18.5 g, 59%), recovered benzophenone (18.3 g, 74%), benzopinacol (3.6 g) and the not-unexpected photoadduct **8** (1.56 g, 3%).

Data for compound **4b**: R_f 0.16 [Et_2O–LP (4:1, v/v)]; $[\alpha]_D$ +3.2 (*c* 2.0, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3430 (OH), 1760 (C=O), 1470 (C–O), 1410, 1380, 1258, 1121, 1020, 940, 875, 838 and 778; δ_H(400 MHz; $CDCl_3$) 0.04 (3 H, s, Me), 0.05 (3 H, s, Me), 0.86 (9 H, s, Bu^t), 2.29 (1 H, dd, J_{gem} 17.0, $J_{3,4}$ 4.6, 3-H), 2.63 (2 H, m, 4-H and OH), 2.69 (1 H, dd, $J_{3,4}$ 9.4, 3-H), 3.60 (1 H, dd, J_{gem} 10.5, $J_{CH,4}$ 6.6, CH_2OH), 3.66 (1 H, dd, $J_{CH,4}$ 5.2, CH_2OH), 3.72 (1 H, dd, J_{gem} 11.2, $J_{6,5}$ 2.9, 6-H), 3.83 (1 H, dd, $J_{6,5}$ 3.7, 6-H) and 4.39 (1 H, dt, $J_{5,6}$ 3.7, $J_{4,5}$ 3.2, 5-H); NOE (%); 4-H–3-H (no effect), 4-H–6-H (4.4), and 5-H–3-H (4.5); δ_C(100 MHz; $CDCl_3$) −5.76 (*CMe*), −5.69 (CMe), 18.21 (C-quart), 25.60 (C-Bu^t), 31.65 (C-3), 39.20 (C-4), 63.42 (C-5), 64.45 (CH_2OH), 80.45 (C-6) and 176.94 (C-2); *m/z* 43 (17%), 59 (22), 69 (100), 75 (95), 117 (43), 129 (51), 143 (44), 157 (12), 173 (5), 185 (22), 203 (18), 243 (3) and 261 (M^+ + 1) [Found: (M + NH_4)$^+$, 278.1788. $C_{12}H_{24}O_4Si$ requires M, 260.1444].

Data for compound **8**: R_f 0.27 [Et_2O–LP (4:1, v/v)];

* '6-H' refers to the ROCH_2 group attached to C-5, and 'C-6' to the corresponding carbon ROCH_2.

ν_{max}(thin film)/cm^{-1} 3433 (OH), 1765 (C=O) and 1484 (C=C); δ_H(400 MHz; $CDCl_3$) 0.09 (3 H, s, Me), 0.10 (3 H, s, Me), 0.89 (9 H, s, Bu^t), 1.62 (1 H, br, OH), 2.39 (1 H, m, 3-H), 2.68 (2 H, m, 3- and 4-H), 3.63 (1 H, dd, J_{gem} 11.5, $J_{6,5}$ 6.2, 6-H), 3.92 (1 H, dd, $J_{6,5}$ 3.5, 6-H), 4.40 (1 H, ddd, $J_{5,4}$ 6.4, $J_{5,6}$ 3.5, $J_{4,3}$ 8.9, 5-H) and 7.12–7.32 (10 H, m, Ph).

(4R,5S)-4,5-*Bis*-(tert-*butyldimethylsiloxymethyl*)*tetrahydrofuran-2-one* **10**.—To a solution of the alcohol **4b** (2.00 g, 0.0077 mol) in dichloromethane (DCM) (40 cm^3) with imidazole (0.72 g, 0.0092 mol) at 0 °C was added *tert*-butylchlorodimethylsilane (1.35 g, 0.0085 mol) portionwise and the mixture was stirred for 2 h. The reaction was quenched by the addition of water (50 cm^3). The aqueous layer was further washed with DCM (3 × 25 cm^3). The combined organic layers were washed successively with water (2 × 25 cm^3) and brine (2 × 25 cm^3) and then was dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography [LP–Et_2O (4:1 v/v)] to give the *title compound* **10** as crystals (2.48 g, 86%), m.p. 31.5 °C; ν_{max}($CHCl_3$)/cm^{-1} 1763 (C=O), 1471, 1389, 1366, 1255 and 1185; δ_H(250 MHz; $CDCl_3$) 0.05 (12 H, s, 2 × Me_2Si), 0.88 (18 H, s, 2 × Bu^t), 2.32 (1 H, dd, J_{gem} 15.8, $J_{3,4}$ 3.1, 3-H), 2.64 (1 H, m, 4-H), 2.67 (dd, $J_{3,4}$ 9.4, 3-H), 3.58 (1 H, dd, J_{gem} 10.7, $J_{6,4}$ 5.9, 6-H), 3.63 (1H, dd, $J_{6,4}$ 5.9, 6-H), 3.69 (2H, dd, J_{gem} 11.2, J 2.8, CH_2O), 3.89 (2H, dd, J 3.2, CH_2O) and 4.40 (1H, dt, $J_{4,3}$ 3.8, $J_{4,5}$ 3.2, 5-H); δ_C(62.9 MHz; $CDCl_3$) −5.5 (Me_2Si), 25.7 (Bu^t), 31.6 (C-3), 38.8 (C-4), 63.9 (C-6), 64.6 (CH_2O), 82.4 (C-5) and 176.7 (C-2) (Found: C, 57.7; H, 10.3. $C_{18}H_{38}O_4Si_2$ requires C, 57.70; H, 10.22%).

1-O-*Acetyl*-3-C-(tert-*butyldimethylsiloxymethyl*)-5-O-(tert-*butyldimethylsilyl*)-2,3-*dideoxy*-α-D- *and* -β-D-erythro-*pentofuranose* **11**.—To a solution of the lactone **10** (1.80 g, 0.0048 mol) in dry DCM at −78 °C was added DIBAL (5.3 cm^3, 1.1 mol equiv.) dropwise whilst the reaction temperature was maintained below −67 °C. The reaction mixture was stirred for 1 h, then was quenched by the addition of methanol (1 cm^3). The mixture was left to warm to room temperature and then ethyl acetate (7 cm^3) was added along with saturated aq. $NaHCO_3$ (1 cm^3) and the mixture was stirred for a further 2 h. Powdered Na_2SO_4 (5 g) was then added and the mixture was stirred for 1 h. The precipitate was removed by filtration through Celite and the solvent was removed under reduced pressure to give the expected lactol as an oil.

To a solution of the lactol (1.80 g, 0.0048 mol) in pyridine (10 cm^3) at 0 °C under nitrogen was added dropwise acetic anhydride (0.54 cm^3, 1.2 mol equiv.). The reaction mixture was stirred for 4 h, then was quenched by the addition of water (20 cm^3) followed by extraction with DCM (3 × 50 cm^3). The combined extracts were washed successively with water (2 × 20 cm^3) and brine (2 × 20 cm^3), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography [eluent: Et_2O–LP (1:5, v/v)] to give compound **11** (1.91 g, 95% overall) as an oily isomeric mixture. Samples of both isomers were obtained during purification. They displayed the following characteristics.

α-D-Isomer: R_f 0.42 [Et_2O–LP (1:5, v/v)]; $[\alpha]_D$ +49.1 (*c* 6.1, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1751 (C=O), 1473, 1362, 1256, 1193, 1107, 1005, 938, 777 and 665; δ_H(250 MHz; $CDCl_3$) 0.05 (6 H, s, 2 × Me), 0.07 (6 H, s, 2 × Me), 0.87 (9 H, s, Bu^t), 0.89 (9 H, s, Bu^t), 1.83 (1 H, dd, J_{gem} 13.2, $J_{2,3}$ 2.2, 2-H), 2.02 (3 H, s, Ac), 2.24 (1 H, dd, $J_{2,3}$ 4.5, 2-H), 2.35 (1 H, m, 3-H), 3.69 (4 H, m, Bu^tMe_2SiOCH_2), 4.08 (1 H, m, 4-H) and 6.34 (1 H, d, $J_{1,2}$ 6.4, 1-H); *m*/*z* 41 (4%), 57 (7), 73 (32), 95 (30), 115 (9), 143 (14), 169 (9), 187 (4), 227 (100), 301 (2), 315 (2) and 359 (38) [Found: (M − OAc)$^+$, 359.2438; requires M, 418.2557].

β-D-Isomer: R_f 0.37 [Et_2O–LP (1:5, v/v)]; $[\alpha]_D$ −23.4 (*c* 2.0, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1751 (C=O), 1473, 1390, 1376, 1252, 1180, 1006, 927, 815, 777 and 666; δ_H(250 MHz; $CDCl_3$) 0.05 (12 H, s, 2 × Me_2Si), 0.88 (18 H, s, 2 × Bu^t), 2.01 (3 H, s, Ac), 2.01–2.14 (2 H, m, 2-H), 2.39 (1 H, m, 3-H), 3.70 (4 H, m, 2 × Bu^tMe_2SiOCH_2), 3.92 (1 H, m, 4-H) and 6.24 (1 H, d, $J_{1,2}$ 6.4, 1-H); *m*/*z* 43 (16%), 57 (9), 73 (42), 95 (29), 117 (23), 143 (33), 169 (21), 187 (10), 209 (3), 227 (100), 301 (11), 315 (2) and 359 (41) [Found: (M − OAc)$^+$, 359.2438].

2-O,4-N-*Bis*(*trimethylsilyl*)*cytosine*.—A mixture of cytosine (0.37 g, 3.3 mmol), hexamethyldisilazane (HMDS) (2.5 cm^3), and a few crystals of $(NH_4)_2SO_4$ was refluxed for 1 h and then was cooled to room temperature before being concentrated under reduced pressure, and the residue was coevaporated three times with toluene to give the title compound as a powder, which was used without further purification.

1-[3′-C-(tert-*Butyldimethylsiloxymethyl*)-5′-O-(tert-*butyldimethylsilyl*)-2′,3′-*dideoxy*-α-D- *and* -β-D-erythro-*pentofuranosyl*]*cytosine* **12a**.—To a solution of 2-*O*,4-*N*-bis(trimethylsilyl)-cytosine and the acetate **11** (1.25 g, 3.0 mmol) in anhydrous DCM at 0 °C under nitrogen was added $EtAlCl_2$ (1.8 mol dm^{-3} in toluene; 1.67 cm^3, 1 mol equiv.) dropwise and the mixture was stirred for 1.5 h. The reaction mixture was poured over ice-cold DCM and $NaHSO_4$, which was then stirred for 30 min, then the mixture was filtered through a Celite pad and the pad was washed thoroughly with DCM. The organic layer was washed with aq. $NaHSO_4$ (2 × 50 cm^3), dried, then concentrated under reduced pressure. The product was purified by flash chromatography [eluent DCM–MeOH (10:1, v/v)] to give the *title compound* **12a** (1.04 g, 74%) as a foam which consisted of the α and β anomers in the ratio 1:1.1 by NMR spectroscopy; R_f 0.34 [DCM–MeOH (10:1, v/v)]; ν_{max}($CHCl_3$)/cm^{-1} 3330 (NH_2), 1648 and 1618; δ_H(220 MHz; $CDCl_3$), 0.05 (6 H, s, 2 × Me), 0.06 (12 H, s, 4 × Me), 0.09 (6 H, s, 2 × Me), 0.91 (18 H, s, 2 × Bu^t), 0.93 (18 H, s, 2 × Bu^t), 1.76 (1 H, m, 2′-H), 2.03 (1 H, m, 2′-H), 2.26–2.54 (3 H, m, 2′-H_2 and 3′-H), 2.67 (1 H, m, 3′-H), 3.56–4.12 (9 H, m, CH_2O, and 4′-H), 4.19 (1 H, m, 4′-H), 5.88 (1 H, d, $J_{5,6}$ 7.7, 5′-H), 6.01 (1 H, d, $J_{5',6'}$ 7.7, 5′-H), 6.14 (1 H, t, $J_{1',2'}$ 6.1, 1′-H), 6.19 (1 H, t, $J_{1',2'}$ 6.5, 1′-H), 7.40 (4 H, br, NH_2), 7.60 (1 H, d, $J_{6,5}$ 7.7, 6-H) and 8.12 (1 H, d, $J_{6,5}$ 7.7, 6-H) (Found: C, 56.1; H, 9.4; N, 8.85. $C_{22}H_{43}N_3O_4Si_2$ requires C, 56.28; H, 9.23; N, 8.94%).

1-[2′,3′-*Dideoxy*-3′-C-(*hydroxymethyl*)-α-D- *and* -β-D-erythro-*pentofuranosyl*]*cytosine* **5a**.—To a solution of compound **12a** (0.47 g, 1 mmol) in MeOH (10 cm^3)–water (1.1 cm^3) was added toluene-*p*-sulfonic acid (PTSA) monohydrate (0.40 g, 2 mol equiv.). After the mixture had been stirred at room temp. for 0.5 h, basic resin (IRA-90, 12 cm^3) was added and the solution was stirred for 0.5 h. The resins were removed by filtration, then the filtrate and washings were concentrated under reduced pressure and the product was purified by flash chromatography to give the title compound (0.23 g, 95%) as an amorphous foam. A small sample was further purified by semi-preparative HPLC (25 cm × 1 cm, HPLC column 10μ ODS; eluent 2% MeOH–98% water, with a flow rate of 1 cm^3 min^{-1}) to give the beta (10 mg) and alpha (9 mg) anomers.

α-D-*Isomer*: $[\alpha]_D$ −56.1 (*c* 0.1, water); λ_{max}(water)/nm 272 (ε 10800); δ_H[400 MHz; $(CD_3)_2SO$] 1.65 (1 H, ddd, J_{gem} 13.0, $J_{2',1'}$ 6.8, $J_{2',3'}$ 8.9, 2′-H), 2.23 (1 H, m, $J_{3',4'}$ 1.8, 3′-H), 2.39 (ddd, $J_{2',3'}$ 8.3, $J_{2',1'}$ 6.2, 2′-H), 3.34 (1 H, m, 5′-H), 3.41 (1 H, m, $J_{6',3'}$ 6.1, 6′-H), 3.42 (2 H, m, 6′-H), 3.52 (1 H, ddd, J_{gem} 11.4, $J_{5',4'}$ 6.1, $J_{5',OH}$ 5.6, 5′-H), 4.76 (1 H, t, $J_{OH,6'}$ 5.2, OH), 4.81 (1 H, t, $J_{OH,5'}$ 5.6, OH), 5.72 (1 H, d, $J_{5,6}$ 7.4, 5-H), 5.98 (1 H, t, $J_{1',2'}$ 6.5, 1′-H), 7.04–7.13 (2 H, m, NH_2) and 7.62 (1 H, d, $J_{6,5}$ 7.4, 6-H); *m*/*z* 112 (100%), 131 (15), 143 (2), 164 (4), 194 (4), 208 (3), 176 (30) and 242 (44) [Found: (M + 1)$^+$, 242.1142. $C_{10}H_{15}N_3O_4$ requires M, 241.1062].

β-D-*Isomer*: $[\alpha]_D$ +66 (*c* 0.1); λ_{max}(water)/nm 269 (ε 9215); δ_H[400 MHz; $(CD_3)_2SO$] 1.90 (1 H, ddd, J_{gem} 13.1, $J_{2',3'}$ 8.1, $J_{2',1'}$ 4.0, 2'-H), 2.14 (1 H, ddd, $J_{2',3'}$ 8.4, $J_{2',1'}$ 6.9, 2'-H), 2.22 (1 H, m, 3'-H), 3.40 (2 H, m, 6'-H), 3.52 (1 H, m, J_{gem} 12.6, $J_{5',4'}$ 5.3, 5'-H), 3.70 (1 H, m, $J_{5',4'}$ 2.8, 5'-H), 4.76 (1 H, m, OH), 5.00 (1 H, m, OH), 5.70 (1 H, d, $J_{5,6}$ 7.4, 5-H), 5.93 (1 H, t, $J_{1,2}$ 6.7, 1'-H), 7.10–7.24 (2 H, m, NH_2) and 7.97 (1 H, d, $J_{6,5}$ 7.4, 6-H); *m/z* 112 (100%), 131 (16), 143 (4), 164 (5), 176 (31), 194 (2), 208 (2) and 242 (45, $M^+ + 1$) [Found: $(M + 1)^+$, 242.1142; C, 46.9; H, 6.4; N, 15.95%. $C_{10}H_{15}N_3O_4$ requires M, 241.1063; $C_{10}H_{15}N_3O_4 \cdot 1H_2O$ requires C, 46.31; H, 6.56; N, 16.2%).

5-*Fluoro*-2-O,4-N-*bis*(*trimethylsilyl*)*cytosine*.—A solution of 5-fluorocytosine (0.372 g, 2.9 mmol) in bis(trimethylsilyl)-acetamide (3 cm^3) was refluxed until the cytosine had gone into solution. The solvent was removed under reduced pressure and the residue was coevaporated twice with toluene (2 × 5 cm^3). The residue was used without further purification.

1-[3'-C-(tert-*Butyldimethylsiloxymethyl*)-5'-O-(tert-*butyldimethylsilyl*)-2',3'-*dideoxy*-α-D- *and* -β-D-erythro-*pentofuranosyl*]-5-*fluorocytosine* **12b**.—The acetate **11** (1.00 g, 2.4 mmol) in admixture with 5-fluoro-2-*O*,4-*N*-bis(trimethylsilyl)cytosine in dry acetonitrile (20 cm^3) under nitrogen at 0 °C was treated with $SnCl_4$ (1 mol dm^{-3} in DCM; 2.4 cm^3, 1 mol equiv.). The reaction mixture was stirred overnight, then was quenched by being poured into saturated aq. potassium sodium tartrate (20 cm^3), and the mixture was stirred for 20 min. The precipitate was removed by filtration through a Celite pad, and the filtrate was washed successively with aq. potassium sodium tartrate (2 × 30 cm^3) and brine (2 × 20 cm^3), and then was dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography [MeOH–DCM (1:9, v/v)] to give the title compound **12b** (0.899 g, 77%) as an amorphous foam. It was impossible to separate the anomers by flash chromatography but the NMR spectrum showed a ratio for α:β of 1:1.2. R_f 0.52 [MeOH–DCM (1:9, v/v)]; ν_{max}(thin film)/cm^{-1} 3319 (NH_2), 3079 (NH_2), 1690 (C=O), 1684 (C=O), 1621 (NH) and 1512 (C=C); δ_H(400 MHz; $CDCl_3$) α-anomer 0.01 (6 H, s, Me), 0.02 (6 H, s, Me), 0.85 (9 H, s, Bu^t), 0.89 (9 H, s, Bu^t), 1.74 (1 H, ddd, J_{gem} 16.0, $J_{2',3'}$ 8.4, $J_{2',1'}$ 6.0, 2'-H), 2.38 (1 H, m, 3'-H), 2.70 (1 H, ddd, $J_{2',3'}$ 2.4, $J_{2',1'}$ 6.3, 2'-H), 3.51 (4 H, m, 5'- and 6'-H_2), 3.77 (1 H, dd, J_{gem} 11.0, $J_{5',4'}$ 4.0, 5'-H), 4.16 (1 H, dt, $J_{4',5'}$ 4.0, $J_{4',3'}$ 2.2, 4'-H), 6.00 (1H, t, $J_{1',2'}$ 6.7, 1'-H) and 7.64 (1 H, d, $J_{6,5F}$ 6.3, 6-H).

β-Anomer 0.01 (3 H, s, Me), 0.02 (3 H, s, Me), 0.05 (3 H, s, Me), 0.05 (3 H, s, Me), 0.85 (9 H, s, Bu^t), 0.88 (9 H, s, Bu^t), 2.08 (1 H, ddd, J_{gem} 13.1, $J_{2',3'}$ 8.8, $J_{2',1'}$ 6.6, 2'-H), 2.34 (1H, dd, $J_{2',3'}$ 2.4, $J_{2',1'}$ 6.3, 2'-H), 2.42 (1 H, m, 3'-H), 3.51 (2 H, m, 6'-H_2), 3.73 (1 H, dd, J_{gem} 11.5, $J_{5',4'}$ 2.2, 5'-H), 3.97 (1 H, dt, $J_{4',5'}$ 2.0, $J_{4',3'}$ 7.8, 4'-H), 4.08 (1 H, dd, $J_{5',4'}$ 2.2, 5'-H), 6.00 (t, $J_{1',2'}$ 6.8, 1'-H) and 8.29 (1 H, d, $J_{6,5F}$ 6.5, 6-H).

1-[2',3'-*Dideoxy*-3'-C-(*hydroxymethyl*)-α-D- *and* -β-D-erythro-*pentofuranosyl*]-5-*fluorocytosine* **5b**.—To a solution of the protected nucleoside **12b** (45 mg, 0.92 mmol) in methanol (AnalaR, 12 cm^3)–water (1.1 cm^3) was added PTSA monohydrate (0.38 g, 2 mol equiv.) at room temperature. The mixture was stirred for 2 h, then was neutralized by the addition of a basic resin (IRA-90, 14 cm^3), and was then stirred for a further 20 min. The resin was removed by filtration, and the residue was thoroughly washed with methanol. Solvent was removed under reduced pressure, and the crude product was purified by flash chromatography [EtOAc–MeOH–DCM (1.5:2.5:6, v/v)] to give the title product (231 mg, 97%) as an amorphous solid, R_f 0.26 [EtOAc–MeOH–DCM (1.5:2.5:6, v/v)]; ν_{max}(thin film)/cm^{-1} 3270 (OH), 3200 (NH_2), 1678 (C=O), 1600 (C=C) and 1508; δ_H(400 MHz; D_2O) 1.82 (1 H, ddd, J_{gem} 13.6, $J_{2',3'}$ 9.1, $J_{2',1'}$ 6.5, 2'-Hα), 2.16 (1 H, ddd, J_{gem} 13.6, $J_{2',3'}$ 8.1, $J_{2',1'}$ 3.5, 2'-Hβ), 2.31 (3 H, m, 2'-Hβ and 3'-H_2), 2.32 (1 H, m, 2'-Hα), 3.59 (5 H, m, 6'-H_2 and 5'-Hα), 3.71 (1 H, dd, J_{gem} 12.7, $J_{5',4'}$ 5.0, 5'-Hβ), 3.76 (1 H, dd, J_{gem} 12.7, $J_{5',4'}$ 5.0, 5'-Hα), 3.87 (1 H, dd, $J_{5',4'}$ 2.8, 5'-Hβ), 3.94 (1 H, ddd, $J_{4',5'}$ 4.9, $J_{4',5'}$ 2.8, $J_{4',3'}$ 8.0, 4'-Hβ), 4.20 (1 H, ddd, $J_{4',5'}$ 5.5, $J_{4',5'}$ 2.8, $J_{4',3'}$ 8.0, 4'-Hα), 5.97 (dt, $J_{1',2'}$ 7.7, *J* 1.4, 1'-Hβ), 5.99 (1 H, m, 1'-Hα), 7.85 (1 H, d, $J_{6,F}$ 6.3, 6-Hα) and 8.04 (1 H, d, $J_{6,F}$ 6.5, 6-Hβ); *m/z* 45 (4%), 57 (100), 69 (60), 81 (13), 86 (25), 100 (43), 113 (4), 129 (92) and 152 (2) [Found: $(M + Na)^+$, 282.0870. $C_{10}H_{24}FN_2O_4$ requires M, 259.0968].

2-O,4-O-*Bis*(*trimethylsilyl*)*uracil*.—Uracil (3.83 g, 34 mmol) was refluxed in bis(trimethylsilyl)acetamide (15 cm^3) until the base went into solution. The mixture was cooled to room temperature and the solvent was removed under reduced pressure; the residue was coevaporated with toluene (2 × 25 cm^3), then was used without further purification.

3'-C-(tert-*Butyldimethylsiloxymethyl*)-1-[5'-O-(tert-*butyldimethylsilyl*)-2',3'-*dideoxy*-α-D- *and* -β-D-erythro-*pentofuranosyl*]*uracil* **12c**.—To a solution of the acetate **11** (13.0 g, 31 mmol) and 2-*O*,4-*O*-bis(trimethylsilyl)uracil in dry acetonitrile (250 cm^3) under nitrogen at 0 °C was added $SnCl_4$ (1.0 mol dm^{-3} in DCM; 31 cm^3, 1 mol equiv.) dropwise. The mixture was stirred overnight and allowed to warm to room temperature over this period. The reaction was quenched by pouring the mixture into a solution of acetonitrile and aq. potassium sodium tartrate, which was then stirred for 1 h. The precipitate was removed by filtration through a Celite pad. The organic layer was washed successively with aq. potassium sodium tartrate (3 × 30 cm^3) and brine (2 × 25 cm^3), then was dried ($MgSO_4$). The crude product was purified by flash chromatography [DCM–MeOH (30:1, v/v)] to give the *title compound* **12c** (8.35 g, 57%) as a crystalline solid (ratio of α:β 1:1.1, by NMR spectroscopy). R_f 0.46 [DCM–MeOH (30:1, v/v)]; ν_{max}(thin film)/cm^{-1} 3193 (NH), 3060 (NH), 1687 (C=O), 1550 (C=C) and 1191 (C–O); δ_H(400 MHz; $CDCl_3$) α-anomer 0.034 (3 H, s, Me), 0.044 (3 H, s, Me), 0.086 (3 H, s, Me), 0.091 (3 H, s, Me), 0.87 (9 H, s, Bu^t), 0.89 (9 H, s, Bu^t), 1.83 (1 H, ddd, J_{gem} 13.1, $J_{2',3'}$ 8.6, $J_{2',1'}$ 6.6, 2'-H), 2.48 (1 H, m, 3'-H), 2.59 (1 H, ddd, $J_{2',3'}$ 8.8, $J_{2',1'}$ 6.4, 2'-H), 3.58–3.67 (3 H, m, 5'-H and 6'-H_2), 3.72 (1 H, dd, J_{gem} 12.7, $J_{5',4'}$ 2.2, 5'-H), 3.97 (1 H, dt, $J_{4',5'}$ 2.2, $J_{4',3'}$ 7.3, 4'-H), 5.72 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,HN}$ 2.2, 5-H), 6.11 (1 H, t, $J_{1,2}$ 6.4, 1-H), 7.49 (1 H, d, $J_{6,5}$ 8.1, 6-H) and 8.81 (1 H, br, NH).

β-Anomer 0.031 (3 H, s, Me), 0.036 (3 H, s, Me), 0.076 (3 H, s, Me), 0.081 (3 H, s, Me), 0.88 (9 H, s, Bu^t), 0.90 (9 H, s, Bu^t), 2.03 (1 H, ddd, J_{gem} 15.2, $J_{2',3'}$ 8.1, $J_{2',1'}$ 3.8, 2'-H), 2.31 (1 H, ddd, $J_{2',3'}$ 8.4, $J_{2',1'}$ 6.8, 2'-H), 3.58–3.67 (2 H, m, 6'-H_2), 3.77 (1 H, dd, J_{gem} 15.2, $J_{5',4'}$ 3.7, 2'-H), 4.03 (1 H, dd, $J_{5',4'}$ 2.3, 5'-H), 4.10 [1 H, dt (overlapping), $J_{4',5'}$ 3.8, $J_{4',3'}$ 7.0, 4'-H], 5.65 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.2, 5-H), 6.1 (1 H, dd, $J_{1,2}$ 3.8, $J_{1,2'}$ 6.7, 1'-H), 8.09 (1 H, d, $J_{6,5}$ 8.1, 6-H) and 8.84 (1 H, br, NH); *m/z* 59 (3%), 73 (9), 90 (12), 113 (26), 130 (8), 143 (19), 169 (16), 185 (13), 227 (38), 281 (5), 301 (7), 359 (100), 376 (5), 413 (4) and 471 (14, $M^+ + 1$) [Found: $(M + 1)^+$, 471.2710. $C_{22}H_{42}N_2O_5Si_2$ requires M, 470.2632].

1-[2',3'-*Dideoxy*-3'-C-(*hydroxymethyl*)-α-D- *and* -β-D-erythro-*pentofuranosyl*]*uracil* **5c**.—To a solution of the protected nucleoside **12c** (8.00 g, 17 mmol) in methanol (AnalaR, 200 cm^3)–water (22 cm^3) was added PTSA monohydrate (3.4 g, 2 mol equiv.) and the solution was stirred for 2.5 h. The reaction mixture was neutralized by the addition of basic resin (IRA-90, 240 cm^3) and the mixture was stirred for 1 h before filtration. The solvent was removed under reduced pressure and the residue was purified by flash chromatography [MeOH–EtOAc–DCM (1:3:6)] to give the *title compound* **5c**

(3.86 g, 94%) as a crystalline solid, δ_H(400 MHz; D_2O) 1.92 (1 H, ddd, J_{gem} 13.5, $J_{2',3'}$ 9.5, $J_{2',1'}$ 6.8, 2'-Hα), 1.95–2.37 (2 H, m, 2'-Hα and -Hβ), 2.38–2.43 (2 H, m, 3'-Hα and -Hβ), 2.59 (1 H, ddd, J_{gem} 15.3, $J_{2',3'}$ 8.3, $J_{2',1'}$ 6.4, 2'-Hβ), 3.59 (1 H, dd, J_{gem} 12.5, $J_{6',4'}$ 5.5, 6'-Hα), 3.59–3.63 (4 H, m, 6'-Hβ, -Hβ, -Hα and 5'-Hα), 3.67 (1 H, dd, J_{gem} 12.6, $J_{5',4'}$ 5.2, 5'-Hβ), 3.77 (1 H, dd, J_{gem} 12.7, $J_{5',4'}$ 2.8, 5'-Hα), 3.83 (1 H, dd, $J_{5',4'}$ 2.9, 5'-Hα), 3.94 (1 H, dt, $J_{4',5'}$ 3.0, $J_{4',3'}$ 6.8, 4'-Hα), 4.18 (1 H, dt, $J_{4',5'}$ 5.2, $J_{4',3'}$ 7.3, 4'-Hβ), 5.80 (1 H, d, $J_{5,6}$ 8.1, 5-Hβ), 5.82 (1 H, d, $J_{5,6}$ 8.1, 5-Hα), 6.04 (1 H, t, $J_{1',2'}$ 6.6, 1'-Hβ), 6.05 (1 H, d, $J_{1',2'}$ 6.6, 1'-Hα), 7.75 (1 H, d, $J_{6,5}$ 8.1, 6-Hα) and 7.86 (1 H, d, $J_{6,5}$ 8.1, 6-Hβ); *m/z* 39 (3%), 58 (2), 69 (6), 81 (3), 99 (3), 113 (45), 131 (100), 148 (38) and 243 (9, $M^+ + 1$) [Found: $(M + 1)^+$, 243.099; C, 52.4; H, 8.2; N, requires M, 242.090; 5.5%. $C_{10}H_{14}N_2O_5$: C, 52.30; H, 8.18; N, 5.54%].

5-*Chloro*-2-O,3-*bis*(*trimethylsilyl*)*uracil*.—A mixture of uracil (0.88 g, 6 mmol) in bis(trimethylsilyl)acetamide (3 cm^3) was refluxed until the uracil went into solution. The mixture was cooled to room temperature and the solvent was removed under reduced pressure to give a residue, which was used without any further purification.

1-[3'-C-(tert-*Butyldimethylsiloxymethyl*)-5'-O-(tert-*butyldimethylsilyl*)-2',3'-*dideoxy*-α-D- *and* -β-D-erythro-*pentofuranosyl*]-5-*chlorouridine* **12d**.—To a mixutre of the acetate **11** (2.50 g, 6 mmol) with 5-chloro-bis(trimethylsilyl)uracil in dry acetonitrile (50 cm^3) under nitrogen at 0 °C was added $SnCl_4$ (1 mol dm^{-3} in DCM; 6.6 cm^3, 1.1 mol equiv.) dropwise and the mixture was stirred for 2 h. The reaction was quenched by pouring of the mixture into a solution of acetonitrile saturated with potassium sodium tartrate. The mixture was stirred for 20 min, then the precipitate was removed by filtration through a Celite pad; the organic layer was washed successively by aq. potassium sodium tartrate (2 × 50 cm^3) and brine (2 × 50 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography [DCM–MeOH (29:1, v/v)] to give the title compound **12d** (1.45 g, 48%) as an amorphous solid (ratio α:β, 1:4.3 by NMR spectroscopy); R_f 0.62 [DCM–MeOH, (29:1, v/v)]; ν_{max}(thin film)/cm^{-1} 3187 (NH), 3063 (NH), 1706 (C=O), 1463 (C=C) and 1137 (C–O); δ_H(400 MHz; $CDCl_3$) α-anomer 0.046 (3 H, s, Me), 0.086 (3 H, s, Me), 0.089 (3 H, s, Me), 0.113 (3 H, s, Me), 0.879 (9 H, s, Bu^t), 0.897 (9 H, s, Bu^t), 1.847 (1 H, ddd, J_{gem} 13.4, $J_{2',3'}$ 8.6, $J_{2',1'}$ 6.6, 2'-H), 2.334 (1 H, m, 3'-H), 2.33 (1 H, ddd, $J_{2',1'}$ 9.0, $J_{2',3'}$ 6.0, 2'-H), 3.60–3.87 (4 H, m, $J_{gem5',5'}$ 11.0, $J_{5',4'}$ 3.5, 5'- and 6'-H_2), 4.19 (1 H, dt, $J_{4',5'}$ 3.6, $J_{4',3'}$ 7.1, 4'-H), 6.06 (1 H, t, $J_{1',2'}$ 6.3, 1'-H), 7.65 (1 H, s, 6-H) and 8.62 (1 H, br, NH).

β-Anomer 0.046 (3 H, s, Me), 0.053 (3 H, s, Me), 0.122 (3 H, s, Me), 0.131 (3 H, s, Me), 0.885 (9 H, s, Bu^t), 0.926 (9 H, s, Bu^t), 2.009 (1 H, ddd, J_{gem} 11.6, $J_{2',3'}$ 8.4, $J_{2',1'}$ 5.1, 2'-H), 2.33 (1 H, dt, $J_{2',3'} = J_{2',1'}$ = 5.0, 2'-H), 3.60–3.77 [4 H, m, $J_{gem(5)}$ 11.6, $J_{5',4'}$ 3.5, 5'- and 6'-H_2], 4.05–4.22 (1 H, m, 4'-H), 6.06 (1 H, t, $J_{1',2'}$ 5.3, 1'-H), 8.14 (1 H, s, 6-H) and 8.62 (1 H, br, NH).

5-*Chloro*-1-[2',3'-*dideoxy*-3'-C-(*hydroxymethyl*)-α-D- *and* -β-D-erythro-*pentofuranosyl*]*uracil* **5d**.—To a solution of the protected nucleoside **12d** (1.0 g, 3.7 mmol) in AnalaR methanol (20 cm^3) containing water (2 cm^3) was added PTSA monohydrate. The reaction mixture was stirred for 2 h, then was neutralized by the addition of basic resin (IRA-90, 24 cm^3), and was stirred for a further 30 min. The resins were removed by filtration and the residue was washed with methanol; the solvent was removed under reduced pressure. The crude product was purified by flash chromatography [MeOH–EtOAc–DCM (1:3:6, v/v)] to give the *title product* **5d** (0.472 g, 86%) as an amorphous foam, R_f 0.16 [MeOH–EtOAc–DCM (1:3:6, v/v)]; ν_{max}(thin film)/cm^{-1} 3913 (OH), 1705 (C=O), 1462 (C=C) and 1274 (C–O); δ_H(400 MHz; D_2O) α-anomer 1.89 (1 H, ddd, J_{gem} 13.5, $J_{2',3'}$ 9.5, $J_{2',1'}$ 6.7, 2'-H), 3.84 (1 H, m, 3'-H), 2.61 (1 H, ddd, $J_{2',3'}$ 9.1, $J_{2',1'}$ 6.7, 2'-H), 3.58 (1 H, dd, J_{gem} 12.9, $J_{5',4'}$ 5.4, 5'-H), 3.61 (1 H, m, 6'-H), 3.76 (1 H, dd, $J_{5',4'}$ 2.8, 5'-H), 4.20 (1 H, m, $J_{4',3'}$ 10.8, $J_{4',5'}$ 2.7, 4'-H), 6.02 (1 H, t, $J_{1',2'}$ 3.1, 1'-H) and 8.02 (1 H, s, 6-H).

β-Anomer 2.23 (1 H, ddd, J_{gem} 13.8, $J_{2',3'}$ 3.4, $J_{2',1'}$ 9.5, 2'-H), 2.29 (1 H, ddd, $J_{2',3'}$ 9.1, $J_{2',1'}$ 6.7, 2'-H), 2.40 (1 H, m, 3'-H), 3.61 (2 H, m, 6'-H), 3.71 (1 H, dd, J_{gem} 12.7, $J_{5',4'}$ 5.0, 5'-H), 3.86 (1 H, dd, $J_{5',4'}$ 2.7, 5'-H), 3.94 (1 H, m, $J_{4',3'}$ 10.0, $J_{4',5'}$ 5.3, 4'-H), 6.00 (1 H, t, $J_{1',2'}$ 5.5, 1'-H) and 8.24 (1 H, s, 6-H) (Found: C, 41.4; H, 4.6. $C_{10}H_{13}ClN_2O_5$ requires C, 41.33; H, 4.51%).

2-O,4-O-*Bis*(*trimethylsilyl*)*thymine*.—A solution of thymine (0.33 g, 2.6 mmol) in HMDS (3 cm^3) was refluxed until all the base had gone into solution. The solvent was removed under reduced pressure after the solution had cooled to room temperature and the residue was coevaporated with toluene (3 × 10 cm^3).

1-[3'-C-(tert-*Butyldimethylsiloxymethyl*)-5'-O-(tert-*butyldimethylsilyl*)-2',3'-*dideoxy*-α-D- *and* -β-D-erythro-*pentofuranosyl*]*thymine* **12e**.—To a solution of the acetate **11** (1.00 g, 2.4 mmol) in dry acetonitrile with 2-*O*,4-*O*-bis(trimethylsilyl)thymine at 0 °C under nitrogen was added $SnCl_4$ (1 mol dm^{-3} in DCM; 2.4 cm^3, 1.0 mol equiv.) dropwise and the mixture was stirred for 2 h. The reaction mixture was quenched by being poured into an ice-cold solution of acetonitrile and potassium sodium tartrate, which was then stirred for 20 min. The precipitate was removed by filtration through Celite; the organic layer was further washed successively with aq. potassium sodium tartrate (2 × 50 cm^3) and brine (2 × 20 cm^3), then was dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [DCM–MeOH (3:97, v/v)] to give the *title compound* **12e** (0.877 g, 76%) as an amorphous foam. The anomers could not be separated by flash chromatography, and NMR spectroscopy showed a ratio for α:β of 1:1.1; R_f 0.43 [DCM–MeOH (3:97, v/v)]; ν_{max}(thin film)/cm^{-1} 3182 (NH), 3074 (NH), 1708 (C=O), 1457 (C=C) and 1267 (C–O); δ_H(400 MHz; $CDCl_3$) 0.033–0.097 (24 H, 8s, 4 × $SiMe_2$), 0.877–0.914 (36 H, 4s, 4 × Bu^t), 1.84 (1 H, m, 2-Hα), 1.91 (3 H, d, $J_{Me,6}$ 1.0, Meα), 1.92 (3 H, d, $J_{Me,6}$ 1.0, Meβ), 1.98 (1 H, ddd, J_{gem} 13.4, $J_{2',3'}$ 8.8, $J_{2',1'}$ 5.8, 2'-Hα), 2.26 (1 H, m, 2'-Hβ), 2.43–2.53 (4 H, m, 2'-Hβ, 2'-Hα, 3'-Hα and 3'-Hβ), 3.43–3.67 (5 H, m, 5-Hα, 6'-H_2, 6'-Hα and 6'-Hβ), 3.69 (1 H, dd, J_{gem} 11.3, $J_{5',4'}$ 2.8, 5'-Hα), 3.76 (1 H, dd, J_{gem} 11.0, $J_{5',4'}$ 3.7, 5'-Hβ), 3.96–4.18 (2 H, m, 4'-Hα and 5'-Hβ), 4.16 (1 H, dt, $J_{4',5'}$ 3.9, $J_{4',3'}$ 7.3, 4'-Hβ), 6.11 (2 H, m, 1'-Hα and 1'-Hβ), 7.22 (1 H, d, $J_{6,Me}$ 1.0, 6-H), 7.56 (1 H, d, $J_{6,Me}$ 1.0, 6-H), 8.64 (1 H, br, NH) and 8.67 (1 H, br, NH); *m/z* 73 (4%), 95 (11), 127 (19), 143 (13), 169 (7), 199 (5), 227 (61), 359 (100) and 485 (13, $M^+ + 1$) [Found: $(M + 1)^+$, 485.287. $C_{23}H_{44}N_2O_5Si_2$ requires M, 484.278].

1-[2',3'-*Dideoxy*-3'-C-(*hydroxymethyl*)-α-D- *and* -β-D-erythro-*pentofuranosyl*]*thymine* **5e**.—To a solution of the protected nucleoside **12e** (0.781 g, 1.6 mmol) in methanol (AnalaR, 17 cm^3) containing water (1.7 cm^3) was added PTSA monohydrate (0.61 g, 2 mol equiv.). The solution was stirred for 1.5 h, and this was followed by the addition of basic resin (IRA-90, 20 cm^3) and this mixture was stirred for a further 20 min. The resin was removed by filtration and the solvent was removed under reduced pressure and the crude product was purified by flash chromatography [MeOH–EtOAc–DCM (1:3:6, v/v)] to give the *title compound* **5e** (0.392 g, 95%) as a crystalline solid, ν_{max}(thin film)/cm^{-1} 3899 (OH), 1709 (C=O), 1453 (C=C) and 1165 (C–O); δ_H(400 MHz; D_2O) 1.82 (3 H, d, $J_{Me,6}$ 0.9, Me),

1.83 (1 H, d, $J_{Me,6}$ 0.9, Me), 1.89 (1 H, ddd, J_{gem} 15.9, $J_{2',3'}$ 9.9, $J_{2',1'}$ 7.3, 2'-Hα), 2.22 (2 H, m, 2'-Hβ), 2.41 (2 H, m, 3'-Hα and 3'-Hβ), 2.55 (1 H, ddd, $J_{2',3'}$ 6.3, $J_{2',1'}$ 8.1, 2'-Hβ), 3.56 (1 H, dd, J_{gem} 12.4, $J_{5',4'}$ 5.5, 5'-Hα), 3.6 (4 H, m, 6'-H_2α and 6'-H_2β), 3.67 (1 H, dd, J_{gem} 12.6, $J_{5',4'}$ 4.9, 5'-Hβ), 3.74 (1 H, dd, $J_{5',4'}$ 2.8, 5'-Hα), 3.83 (1 H, dd, $J_{5',4'}$ 2.8, 5'-Hβ), 3.91 (1 H, ddd, $J_{4',5'}$ 4.6, $J_{4',5'}$ 2.9, $J_{4',3'}$ 8.2, 4'-Hβ), 4.17 (1 H, ddd, $J_{4',5'}$ 5.4, $J_{4',5'}$ 3.2, $J_{4',3'}$ 8.4, 4'-Hα), 6.05 (1 H, t, $J_{1',2'}$ 6.4, 1'-Hβ), 6.07 (1 H, t, $J_{1',2'}$ 4.0, 1'-Hα), 7.53 (1 H, d, $J_{6,Me}$ 0.9, 6-Hα) and 7.68 (1 H, d, $J_{6,Me}$ 0.9, 6-Hβ) (Found: C, 49.2; H, 6.5; N, 11.7. $C_{10}H_{16}N_2O_5$ requires C, 49.17; H, 6.60; N, 11.46%).

(4S,5S)-5-(tert-*Butyldimethylsiloxymethyl*)-4-(*fluoromethyl*)-*tetrahydrofuran-2-one* **17**.—A solution of the alcohol **4b** (1.70 g, 6.5 mmol) in DCM (5 cm^3) was added to a solution of DAST (1 mol equiv.) in DCM (10 cm^3) at −78 °C under nitrogen. The solution was stirred overnight and the temperature was allowed to reach ambient. The reaction was quenched by the addition of ice–water (20 cm^3) and the mixture was neutralized by the addition of $NaHCO_3$. The organic layer was separated and the aqueous layer was further washed with DCM (3 × 50 cm^3). The combined organic layer was concentrated under reduced pressure, dried ($MgSO_4$) and purified by flash chromatography [Et_2O–LP (4:1, v/v)] to give the title compound **17** (0.82 g, 48%); R_f 0.48 [Et_2O–LP (4:1, v/v)]; ν_{max}(thin film)/cm^{-1} 1782 (C=O), 1472, 1420, 1362 and 1175; δ_H(250 MHz; $CDCl_3$) 0.08 (3 H, s, Me), 0.09 (3 H, s, Me), 0.90 (9 H, s, Bu^t), 2.36 (1 H, dd, J_{gem} 17.3, $J_{3,4}$ 4.6, 3-H), 2.73 (1 H, dd, $J_{3,4}$ 1.5, 3-H), 2.82 (1 H, m, 4-H), 3.72 (1 H, dd, J_{gem} 11.3, J 2.6, CH_2), 3.91 (1 H, dd, J 3.1, CH_2), 4.34 (1 H, ddd, J 46.9, J_{gem} 8.0, J 5.5, CH_2F), 4.44 (1 H, dt, $J_{5,4}$ 4.0, J 2.6, 5-H) and 4.53 (1 H, ddd, J 46.9, 5.5, CH_2F); δ_C(62.9 MHz; $CDCl_3$) −5.66 (Me), −5.45 (Me), 18.17 (C-quaternary), 25.73 (Bu^t), 30.73 (d, $J_{2,F}$ 10.4, C-2), 37.33 (d, $J_{3,F}$ 19.7, C-3), 64.27 (C-5), 81.06 (d, $J_{4,F}$ 4.89, C-4), 83.32 (d, $J_{6,F}$ 167.38, C-6) and 175.48 (C-1) (Found: C, 54.9; H, 8.8. $C_{12}H_{23}FO_3Si$ requires C, 54.94; H, 8.84%).

1-O-*Acetyl*-5-O-(tert-*Butyldimethylsilyl*)-2,3-*dideoxy*-3-C-(*fluoromethyl*)-α-D- *and* -β-D-erythro-*pentofuranose*.—To a solution of the lactone **17** (0.40 g, 1.53 mmol) in anhydrous DCM (10 cm^3) under nitrogen at −78 °C was added DIBAL (1 mol dm^{-3} in DCM, 1.7 cm^3, 1.1 mol equiv.) over a period of 10 min. The reaction mixture was stirred for 3 h at −78 °C, then was quenched by the addition of ethyl acetate (5 cm^3) and saturated aq. $NaHCO_3$ (1 cm^3). The mixture was stirred for a further 30 min. Powdered Na_2SO_4 (5 g) was added with DCM (20 cm^3) and the mixture was stirred for 1 h. The precipitate was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure to give the lactol, which was used without further purification.

To a solution of the lactol (0.4 g, 1.52 mmol) in dry DCM with triethylamine (3 mol equiv.) under nitrogen at 0 °C was added acetic anhydride (1.1 mol equiv.) dropwise. The reaction mixture was stirred overnight, then was quenched by the addition of water (20 cm^3) and ethyl acetate (50 cm^3). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 cm^3); the combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography to give the acetate (0.33 g, 70% both steps). A pure sample of the β-isomer was obtained which showed the following characteristics: R_f 0.58 [Et_2O–LP (3:7, v/v)]; ν_{max}(thin film)/cm^{-1} 1750 (C=O, lactone), 1734 (C=O, ester), 1472, 1463, 1362 and 1253; δ_H(220 MHz; $CDCl_3$) 0.08 (3 H, s, Me), 0.09 (3 H, s, Me), 0.92 (9 H, s, Bu^t), 1.88 (1 H, dd, J_{gem} 13.3, $J_{2,3}$ 3.3, 2-H), 2.06 (3 H, s, Ac), 2.39 (1 H, m, 2-H), 2.68 (1 H, m, 3-H), 3.68 (1 H, dd, J_{gem} 11.0, $J_{5,4}$ 6.6, 5-H), 3.83 (1 H, dd, $J_{5,4}$ 4.4, 5-H), 4.14 (1 H, dt, $J_{4,3}$ 4.0, $J_{4,5}$ 6.6, 4-H), 4.42 (1 H, ddd, J_{gem} 8.0, $J_{6,F}$ 47.03, $J_{6,3}$ 5.5, 6-H), 4.64 (1 H, ddd, $J_{6,F}$ 47.03, $J_{6,3}$ 5.5, 6-H) and 6.38 (1 H, d, $J_{1,2}$ 6.0, 1-H).

1-[5-O-(tert-*Butyldimethylsilyl*)-2,3-*dideoxy*-3-C-(*fluoromethyl*)-α-D- *and* -β-D-erythro-*pentofuranosyl*]*cytosine*.— To a solution of 2-*O*,3-bis(trimethylsilyl)cytosine (1 mol equiv.) and the above acetate (0.3 g, 1 mmol) in anhydrous DCM (5 cm^3) at 0 °C under nitrogen was added dropwise $EtAlCl_2$ (1.8 mol dm^{-3} in toluene; 0.55 cm^3). The solution was stirred for 2 h prior to the addition of ice–water (20 cm^3), the organic layer was separated and the aqueous layer was washed with DCM (3 × 25 cm^3). The combined organic layer was washed successively with saturated aq. $NaHCO_3$ (2 × 10 cm^3) and brine (2 × 10 cm^3), dried ($MgSO_4$), then was concentrated under reduced pressure. The residue was purified by flash chromatography [MeOH–DCM (1:10, v/v)] to give the *title compound* (0.188 g, 76%) as an amorphous foam. The ratio of α:β anomers was 1:1.2 by NMR spectroscopy; R_f 0.30 [MeOH–DCM (1:10, v/v)]; ν_{max}(Nujol mull)/cm^{-1} 1640 (C=O), 1490, 1410, 1363, 1289, 1260, 1200, 1130, 1010, 840 and 782; δ_H(400 MHz; $CDCl_3$) 1.79 (1 H, ddd, J_{gem} 13.4, $J_{2',3'}$ 7.7, $J_{2',1'}$ 5.7, 2'-Hα), 2.12 (1 H, ddd, $J_{2',3'}$ 7.8, $J_{2',1'}$ 3.0, 2'-Hβ), 2.29 (1 H, ddd, $J_{2',3'}$ 10.0, $J_{2',1'}$ 6.8, 2'-H), 2.68 (1 H, m, 3'-Hα and 3'-Hβ), 2.72 (1 H, ddd, $J_{2',3'}$ 8.8, $J_{2',1'}$ 6.2, 2'-Hβ), 3.68 (1 H, d, J_{gem} 11.0, $J_{5',4'}$ 3.9, 5'-Hα), 3.75 (1 H, dd, $J_{5',4'}$ 2.1, 5'-Hα), 3.76 (1 H, dd, J_{gem} 11.4, $J_{5',4'}$ 1.8, 5'-Hβ), 3.97 (1 H, dt, $J_{4',5'}$ 2.4, $J_{4',3'}$ 8.1, 4'-Hβ), 4.03 (1 H, dd, $J_{5',4'}$ 2.5, 5'-Hβ), 4.18 [1 H, dt (overlapping), $J_{5',4'}$ 4.0, $J_{4',3'}$ 6.5, 4'-Hα], 4.26–4.55 (4 H, m, 6'-H, 6'-Hα, 6'-H and 6'-Hβ), 5.69 (1 H, d, $J_{5',6'}$ 7.4, 5'-Hβ), 5.85 (1 H, d, $J_{5,6}$ 7.5, 5-Hα), 6.03 (1 H, t, $J_{1',2'}$ 6.0, 1'-Hα), 6.05 (1 H, dd, $J_{1',2'}$ 3.0, $J_{1',2'}$ 6.6, 1'-Hβ), 7.47 (1 H, d, $J_{6,5}$ 7.4, 6-Hα) and 8.06 (1 H, d, $J_{6,5}$ 7.4, 6-Hβ); *m/z* 43 (84%), 59 (55), 67 (69), 77 (86), 95 (25), 112 (60), 157 (7), 168 (100), 189 (18), 255 (2), 300 (27) and 358 (17, $M^+ + 1$) [Found: $(M + 1)^+$, 358.1962. $C_{16}H_{28}FN_3O_3Si$ requires M, 357.1883).

1-[2',3'-*Dideoxy*-3'C-(*fluoromethyl*)-α-D- *and* -β-D-erythro-*pentofuranosyl*]*cytosine* **18**.—To a solution of the above protected nucleoside (170 mg, 0.48 mmol) in tetrahydrofuran (THF) (5 cm^3) under nitrogen was added tetrabutyl ammonium fluoride (TBAF) (0.152 cm^3) dropwise at room temperature. The mixture was stirred for 3 h, then was quenched by the addition of methanol (3 cm^3). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give the *title compound* **18** (111 mg, 90%) as an amorphous foam; ν_{max}(Nujol mull)/cm^{-1} 3334 (OH) 3157 (NH_2) 1720 (C=O), 1678 (C=O), 1538 (C=C), 1278 (C–O) and 1107 (C–O); δ_H[400 MHz; $(CD_3)_2SO$] 1.88 (1 H, ddd, J_{gem} 12.0, $J_{2',1'}$ 4.1, $J_{2',3'}$ 9.3, 2'-Hα), 2.23 (2 H, m, 2'-H and 2'-Hβ); 2.56 (1 H, ddd, $J_{2',1'}$ 6.6, $J_{2',3'}$ 10.4, 2'-H), 3.28–3.42 (4 H, br, OH), 3.45 (1 H, dd, J_{gem} 12.0, $J_{5',4'}$ 4.6, 5'-Hα), 3.57 (1 H, dd, $J_{5',4'}$ 3.5, 5'-Hα), 3.59 (1 H, dd, J_{gem} 12.2, $J_{5',4'}$ 3.2, 5'-Hβ), 3.75 (1 H, dd, $J_{5',4'}$ 3.2, 5'-Hβ), 3.98 (1 H, dt, $J_{4',5'}$ 3.0, $J_{4',3'}$ 8.3, 4'-Hβ), 4.17 [1 H, dt (overlapping), $J_{4',5'}$ 4.0, $J_{4',3'}$ 3.0, 4'-Hα]; 4.41–4.57 (4 H, m, 6'-H, 6'-Hα, 6'-H and 6'-Hβ), 5.93 (1 H, dd, $J_{1',2'}$ 3.3, $J_{1',2'}$ 6.6, 1'-Hβ), 5.96 (1 H, t, $J_{1',2'}$ 5.8, 1'-Hα), 6.08 (1 H, d, $J_{5,6}$ 7.6, 5-Hβ), 6.10 (1 H, d, $J_{5,6}$ 7.2, 5-Hα), 7.99 (1 H, d, $J_{6,5}$ 7.2, 6-Hα), 8.34 (1 H, d, $J_{6,5}$ 7.6, 6-Hβ), 8.48 (2 H, br, NH_2), 8.62 (2 H, br, NH_2); *m/z* 41 (71%), 56 (43), 69 (30), 83 (12), 95 (8), 100 (64), 111 (43), 133 (5), 142 (100), 186 (52), 224 (9, $M^+ - F$) and 244 (10, $M^+ + 1$) [Found: $(M + 1)^+$, 244.1097. $C_{10}H_{14}FN_3O_3$ requires M, 243.1016].

Acknowledgements

We thank Dr. Allen Miller of Wellcome Research for many helpful discussions and for organizing the biological testing, also Dr. Oliver Howarth for much help with the NMR spectra, and the Medical Research Council for a studentship from the AIDS Initiative.

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Paper 4/03469D
Received 8*th June* 1994
Accepted 18*th July* 1994