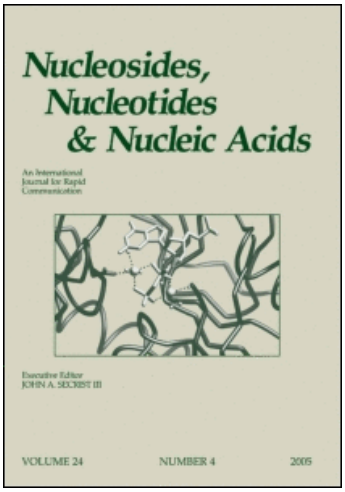


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Novel L-Series 2', 3'-Dideoxy-3'-Hydroxy-Methyl-Nucleosides and a Convenient Method for the Separation of Nucleosede Anomers

Jayne H. M. Gould[a]; John Mann[a]
[a] Department of Chemistry, Reading University, Reading, UK

To cite this Article Gould, Jayne H. M. and Mann, John(1997) 'Synthesis of Novel L-Series 2', 3'-Dideoxy-3'-Hydroxy-Methyl-Nucleosides and a Convenient Method for the Separation of Nucleosede Anomers', Nucleosides, Nucleotides and Nucleic Acids, 16: 1, 193 — 213
To link to this Article: DOI: 10.1080/07328319708002533
URL: http://dx.doi.org/10.1080/07328319708002533

NUCLEOSIDES & NUCLEOTIDES, 16(1&2), 193-213 (1997)

SYNTHESIS OF NOVEL L-SERIES 2',3'-DIDEOXY-3'-HYDROXY-METHYL-NUCLEOSIDES AND A CONVENIENT METHOD FOR THE SEPARATION OF NUCLEOSIDE ANOMERS

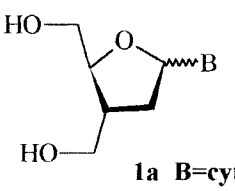
Jayne H.M.Gould and John Mann

Department of Chemistry, Reading University, Whiteknights, Reading RG6 6AD, UK.

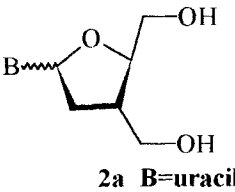
Abstract: Photoinduced addition of methanol to 5(R)-(*tert*-butyldimethylsilyloxymethyl) -2(5H)-furan-2-one (derived from L-gulono-1,4-lactone) provided the photoadduct 5(R)-(*tert*-butyldimethylsiloxymethyl)-4(S)-hydroxymethyl-tetrahydrofuran-2-one, which was converted into two L-series-2',3'-dideoxy-3'-hydroxymethyl-nucleosides. In addition, we describe a new method for the chromatographic separation of cytidine anomers using a N-2-(4-nitrophenyl)ethyl carbamate derivative.

Of the hundreds of D-series nucleosides that have been prepared and screened for anti-HIV activity, only AZT, ddC, ddI and d4T have proven clinical activity[1]. In their search for novel structures, researchers have begun to investigate the synthesis and biological properties of the corresponding L-series compounds and a number of these studies have now been published[2].

We have recently reported the synthesis and biological evaluation of a number of D-series 2',3'-dideoxy-3'-hydroxymethyl nucleosides **1**, of which the cytidine and 5-fluorocytidine analogues **1a** and **1b** were the most potent (against HIV, human cytomegalovirus and hepatitis B *in vitro*)[3]. In fact, the latter compound was subsequently prepared in gram quantities and evaluated *in vivo* against a mouse hepatatitis B model. These results suggested that the L-series 5-fluorocytidine analogue **2b** was an interesting target for synthesis.



1a B=cytosine
1b R=5-fluoro-C

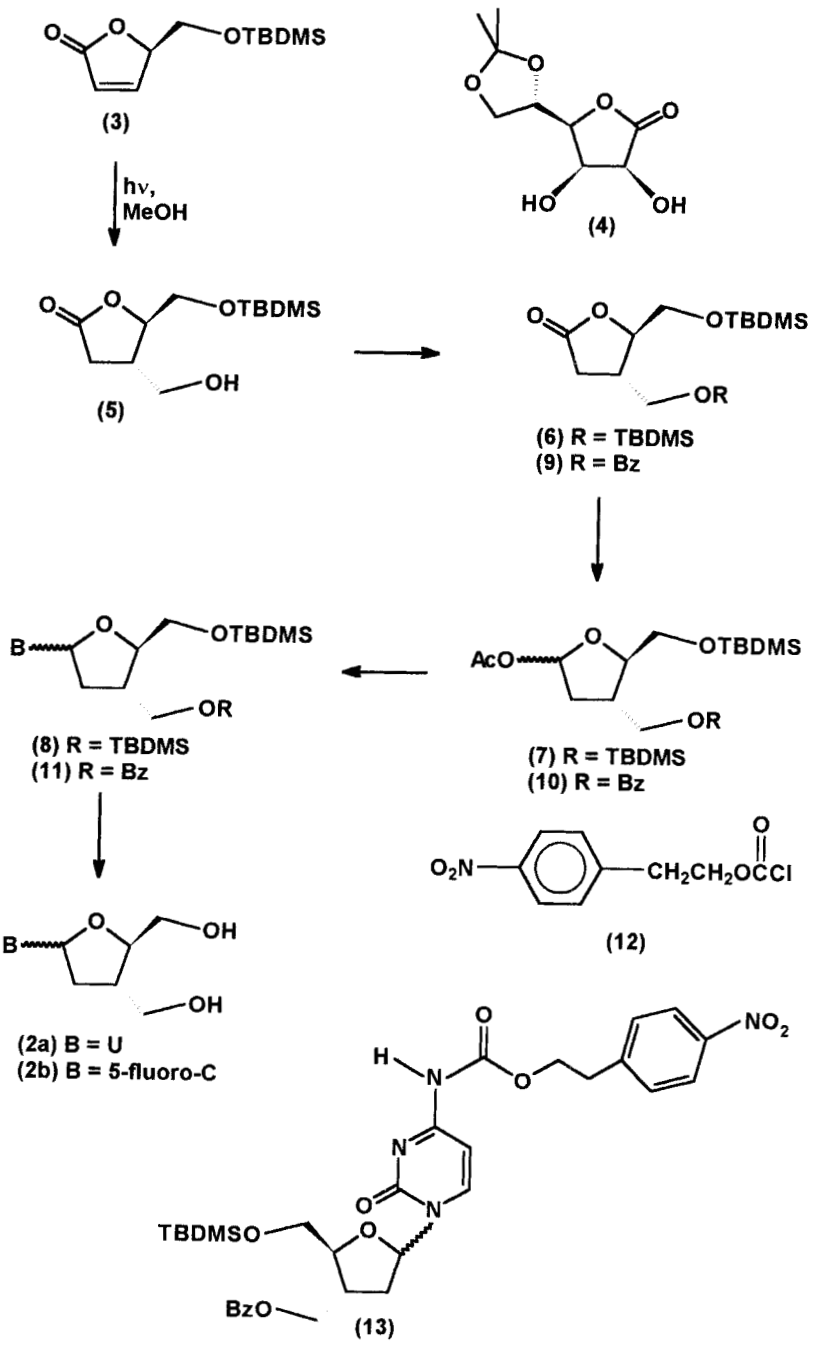


2a B=uracil
2b B=5-fluoro-C

Our initial approach (**Scheme 1**) used the route that we had developed for the large-scale synthesis mentioned above, though we now employed 5(R)-(*tert*-butyldimethylsiloxymethyl)-2(5H)-furan-2-one **3** in place of the corresponding 5(S)-enantiomer. The former is available in four steps from L-gulono-1,4-lactone[4] **4**, while the latter is prepared from D-mannitol[5], and the major advantage of the route shown in **Scheme 1** is that both L-series and D-series compounds are available using the same methodology but different chiral pool starting materials.

Photoinduced addition of methanol to **3** in the presence of benzophenone as a photosensitiser proceeded with the anticipated regio- and stereoselectivity[2] and in a reasonable yield (59%) to provide adduct **5**. Protection of the alcohol as its *tert*-butyldimethylsilyl ether **6**, followed by reduction of the lactone with DIBALH and acetylation of the resultant lactols produced the anomers **7** in an overall yield of 60% (for the three steps). Reaction of this mixture with $SnCl_4$ and *bis*-trimethylsilyluracil yielded the protected nucleosides **8** as a ca. 1:1 mixture of anomers. Deprotection with pTSA/MeOH provided the simple L-series nucleosides **2a**. These anomers were essentially impossible to separate by flash chromatography, and in an attempt to influence the stereoselectivity of nucleoside formation, we chose to use the benzoate **9** for the rest of our studies. We were encouraged by the work of Young[6] and Sugimura[7] who showed that a 3-substituent can influence the stereoselectivity of base attack even in the absence of a 2-substituent.

The benzoate was selectively reduced to the corresponding lactols using disiamyl borane[8] and then converted into the anomeric acetates **10** (overall yield 73% on the



Scheme 1

gram scale). Reaction of this mixture with *bis*-trimethylsilyl-5-fluorocytosine in the presence of trimethylsilyl iodide[9] yielded the protected nucleosides **11** (82%) with an anomeric ratio of 4:1 (β:α) (the relative stereochemistry was established through nOe experiments). At present we do not know the reason for this stereoselectivity, but suggest that interaction between the benzoyloxymethy group at C-3' and the developing carbocation at C-1' is favoured with TMSI, thus enhancing attack from the face opposite the benzoate group. Deprotection using 1% NaOH in MeOH followed by pTSA/MeOH provided the desired nucleosides **2b** (95% overall). The mixture of anomers (ca. 4:1 β:α) was tested *in vitro* against HIV1, but disappointingly there was no activity.

Our inability to separate these mixtures, even given the favourable ratio of **2b**, encouraged us to explore the feasibility of separating N-protected cytidine derivatives. To this end we prepared the N-2(4--nitrophenyl)ethoxycarbonyl derivative of 5'-O-*tert*-butyldimethylsilyl-3'-benzyloxymethyl-D-cytidine. The requisite chloroformate **12** was prepared through reaction of phosgene and 2(4-nitrophenyl)ethanol[10] and this was then reacted with 5'-O-*tert*-butyldimethylsilyl-3'-benzoyloxymethylcytidine[3] to produce the desired carbamate **13** in 92% yield. The anomers (ca. 1:1) were now easily separable using silica and ethyl acetate (as elutant) to provide an excellent recovery of the pure anomers. Removal of the carbamate and benzoate groups could be accomplished using methanolic triethylamine at 40°C in near quantitative yield. The ease of protection and deprotection and the facility of the chromatographic separation on the gram scale, suggest that this methodology may have general utility, and we are exploring this possibility.

EXPERIMENTAL

Reagents and solvents were purified when necessary according to Perrin[11]. Flash column chromatography was performed using Crosfield Sorbsil C60 (32-63μm). The melting points were determined on an Electrothermal digital appartus without correction. IR

spectra were recorded on a Perkin Elmer 881 spectrometer as thin films or in solution. Mass spectra were recorded at the EPSRC Mass Spectrometry Centre at the University of Swansea on a VG Analytical ZAB-IF spectrometer. ^{1}H-NMR spectra were recorded on a Bruker WH250 spectrometer or on a Jeol FX400 instrument. ^{13}C spectra were recorded on the JEOL instrument. All compounds were pure by TLC in at least two systems and there were no spurious NMR signals.

(+)-5,6-O-*Isopropylidine*-L-*gulono*-1,4-*lactone*.

To a solution of L-gulono-1,4-lactone **4** (50.0 g, 0.28 mol) in dry DMF (450 cm^3) cooled to +10 °C, was added *p*-toluenesulphonic acid (0.41 g, 2.2 mmol) followed by isopropenyl methyl ether (26.3 cm^3, 0.37 mol), portionwise. The cooling bath was removed and the reaction mixture stirred at room temperature for 24 h. The solution was saturated with sodium carbonate decahydrate (50 g), and the suspension stirred vigorously for 2 h. The suspension was filtered through Celite, and the filtrate concentrated *in vacuo*. The residue was washed with 10% ethanol : 90% hexane (400 cm^3) to give the *title compound* as a white solid (46.0 g, 75%), R_f 0.38 (EtOAc); m.p. 165-166 °C (lit.[4] 165 °C); $[\alpha]_D^{23}$ +35.3 (*c* 1.26, MeOH) {lit.[4] $[\alpha]_D$ +36.3 (*c* 2.0, H_2O)}; ν_{max} (film)/cm^{-1} 3520 (OH), 3455 (OH) and 1770(C=O); δ_H(400 MHz; d_6-DMSO) 1.28 (3 H, s, Me), 1.33 (3 H, s, Me), 3.75 (1 H, dd, J_{gem} 8.6, $J_{6,5}$ 6.4, 6-H), 4.05 (1 H, dd, J_{gem} 8.6, $J_{6,5}$ 6.4, 6-H), 4.18-4.29 (3 H, m, 3,4,5-H), 4.41 (1 H, dd, $J_{2,OH}$ 7.3, $J_{2,3}$ 4.8, 2-H), 5.46 (1 H, d, $J_{OH,3}$ 4.4, OH) and 5.90 (1 H, d, $J_{OH,2}$ 7.3, OH) [Found: $(M+H)^+$, 219.0869. $C_9H_{15}O_6$ requires *M*, 219.0869].

S-*Glyceraldehyde acetonide*.

To a suspension of sodium metaperiodate (GPR, 90.30 g, 0.43 mol) in water (200 cm^3), cooled to 0 °C, was added aqueous sodium hydroxide (3 mol dm^{-3}, 143 cm^3, 0.43 mol), dropwise, until the final pH of the suspension was 5.5. During this time the temperature of the reaction was not allowed to exceed 7 °C. The cooling bath was removed and (+)-5,6-*O*-isopropylidine-L-gulono-1,4-lactone (45.90 g, 0.21 mol) was added in one portion. The thick suspension was stirred vigorously using an overhead stirrer, and the temperature of the reaction mixture was kept at 20-30 °C by occasional cooling with an

ice-water bath. The pH of the suspension was maintained at 5.5 during the course of the reaction by the addition of 15% aqueous Na_2CO_3 solution. The reaction mixture was stirred at room temperature for a further 30 min. and then saturated with NaCl (100 g) and filtered. The white solid was washed thoroughly with brine (2 x 100 cm^3), and the pH of the aqueous layer adjusted to 6.5-7.0 with 15% aqueous Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 cm^3) and the combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo* (not allowing the temperature of the water bath to exceed 30 °C), and the crude product obtained as a yellow oil was used without further purification (6.57 g, 24%), R_f 0.36 (Et_2O); ν_{max} (film)/cm^{-1} 1740(C=O), 1380, 1220 and 1070; δ_H(400 MHz; $CDCl_3$) 1.43 (3 H, s, Me), 1.49 (3 H, s, Me), 4.09-4.19 (2 H, m, 3-H); 4.38-4.41 (1 H, m, 2-H) and 9.72 (1 H, s, C*H*O).

***Methyl* (R)-(Z)- *and* -(E)-4,5-O-*Isopropylidene-pent-2-enoate*.**

To a solution of *S*-glyceraldehyde acetonide (6.55 g, 50.3 mmol) in MeOH (AnalaR 50 cm^3) at 0 °C was added (carbomethoxymethylene)triphenylphosphorane (17.7 g, 50.3 mmol), portionwise, and the mixture stirred for 1 h. The solvent was removed *in vacuo*, and the residue extracted with 30% Et_2O : 70% petroleum ether (3 x 30 cm^3) by heating at reflux. After cooling, the extract was filtered and the filtrate evaporated to dryness. Separation of the geometric isomers was achieved by flash chromatography (20% EtOAc : 80% hexane) to give the *title compound* (3.80 g, 41%) and the *trans* isomer (0.23 g, 2.5%), both as colourless oils.

***Cis* isomer:** R_f 0.53 (30% Et_2O : 70% petroleum ether); $[\alpha]_D^{26}$ -126.5 (*c* 1.5, $CHCl_3$) {lit.[4] $[\alpha]_D$ -118, (*c* 1.77, $CHCl_3$)}; ν_{max} (film)/cm^{-1} 1721 (C=O), 1649 (C=C), 1183 and 1058; δ_H(400 MHz; $CDCl_3$) 1.40 (3 H, s, Me), 1.45 (3 H, s, Me), 3.62 (1 H, dd, J_{gem} 8.4, $J_{4,5}$ 7.0, 5-H), 3.73 (3 H, s, OMe), 4.38 (1 H, dd, J_{gem} 8.4, $J_{4,5}$ 7.0, 5-H), 5.47-5.52 (1 H, m, 4-H), 5.86 (1 H, dd, $J_{2,3}$ 11.5, $J_{2,4}$ 1.7, 2-H) and 6.38 (1 H, dd, $J_{3,2}$ 11.5, $J_{3,4}$ 6.6, 3-H) [Found: $(M+H)^+$, 187.0968; C, 55.16; H, 7.48%. $C_9H_{15}O_4$ requires *M*, 187.0970; $C_9H_{14}O_4$ requires C, 55.06; H, 7.53%].

***Trans* isomer:** R_f 0.34 (30% Et_2O : 70% petroleum ether); $[\alpha]_D^{27}$ -44.5 (*c* 1.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 1720 (C=O), 1665 (C=C), 1439, 1372, 1252 and 1065; δ_H(400 MHz;

$CDCl_3$) 1.41 (3 H, s, Me), 1.45 (3 H, s, Me), 3.69 (1 H, dd, J_{gem} 8.1, $J_{5,4}$ 6.6, 5-H), 3.75 (3 H, s, OMe), 4.19 (1 H, dd, J_{gem} 8.1, $J_{5,4}$ 6.6, 5-H), 4.66-4.68 (1 H, m, 4-H), 6.11 (1 H, dd, $J_{2,3}$ 15.8, $J_{2,4}$ 1.5, 2-H) and 6.89 (1 H, dd, $J_{3,2}$ 15.8, $J_{3,4}$ 6.0, 3-H).

(R)-5-*Hydroxymethylfuran*-2(5H)-*one*.

To a solution of the *cis* alkene (4.18 g, 22.4 mmol) in MeOH (AnalaR 11 cm^3), was added 30% aqueous sulphuric acid (0.14 cm^3), and the solution stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (EtOAc) to give the butenolide as a white crystalline solid (2.31 g, 90%), R_f 0.44 (EtOAc); m.p. 42-43 °C (lit.[4] 37-39 °); $[\alpha]_D^{28}$ +140.1 (*c* 0.3, $CHCl_3$); {lit.[4] $[\alpha]_D$ +173 (*c* 0.2, H_2O)}; ν_{max}(mull)/cm^{-1} 3343 (br, OH), 1745(C=O) and 1607(C=C); δ_H(400 MHz; $CDCl_3$) 3.33 (1 H, s, OH), 3.80 (1 H, dd, J_{gem} 12.1, $J_{6,5}$ 5.1, 6-H), 4.00 (1 H, dd, J_{gem} 12.1, $J_{6,5}$ 3.7, 6-H), 5.17 (1 H, m, 5-H), 6.20 (1H, dd, $J_{3,4}$ 6.0, $J_{3,5}$ 2.0, 3-H) and 7.53 (1 H, dd, $J_{4,3}$ 6.0, $J_{4,5}$ 1.5, 4-H) (Found: C, 52.37; H, 5.31. $C_5H_6O_3$ requires: C, 52.63; H, 5.30%).

(R)-5-*(tert-Butyldimethylsiloxymethyl)*-(5H)-*furan*-2-*one* (3).

A solution of the butenolide, (2.29 g, 20.1 mmol) and imidazole (1.74 g, 26.3 mmol) in dry CH_2Cl_2 (50 cm^3) was cooled with an ice bath to 0 °C. *tert*-Butyldimethylsilyl chloride (3.63 g, 23.7 mmol) was added, the mixture was stirred for 15 min. at 0 °C and then for a further 20 min. at room temperature. The reaction was quenched by the addition of water (100 cm^3), and the phases separated. The aqueous layer was washed with CH_2Cl_2 (3 x 30 cm^3) and the combined organic solutions were washed with water (3 x 30 cm^3), brine (2 x 30 cm^3) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by flash chromatography (25% petroleum ether : 75% Et_2O) to give the protected butenolide **3** as a white crystalline solid (4.42g, 96%), R_f 0.5 (25% petroleum ether : 75% Et_2O); m.p. 35.5-36.5 °C (lit.[4] 31 °C); $[\alpha]_D^{26}$ +136.6 (*c* 0.9, $CHCl_3$); ν_{max}(mull)/cm^{-1} 1747 (C=O), 1605 (C=C) and 1473; δ_H (400 MHz; $CDCl_3$) 0.06 (3 H, s, Me), 0.07 (3 H, s, Me), 0.87 (9 H, s, ^tBu), 3.80 (1 H, dd, J_{gem} 10.8,

$J_{6,5}$ 5.3, 6-H), 3.94 (1 H, dd, J_{gem} 10.8, $J_{6,5}$ 4.6, 6-H), 5.03-5.06 (1 H, m, 5-H), 6.17 (1 H, dd, $J_{4,3}$ 5.7, $J_{4,5}$ 2.0, 4-H) and 7.50 (1 H, dd, $J_{3,4}$ 5.7, $J_{3,5}$ 1.7, 3-H) [Found: $(M+H)^+$, 229.1251; $C_{11}H_{21}O_3Si$ requires *M*, 229.1260].

(4S,5R)-5-(tert-*Butyldimethylsiloxymethyl)*-4-*(hydroxymethyl)*-tetrahydrofuran-2-one (5).

The protected butenolide **(3)** (4.39 g, 16.9 mmol) and benzophenone (1 equiv.) were dissolved in MeOH (AnalaR, 320 cm^3) and transferred to a pyrex photochemical reaction vessel. The solution was degassed by passage of a steady stream of nitrogen for 1 h, before irradiating with a medium pressure mercury vapour 500 W, 350 nm lamp for 4 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography with gradient elution (50-100% Et_2O : petroleum ether) to give the *title compound* **5** (2.45g, 9.94 mmol, 59%) as a yellow oil, recovered benzophenone (1.37g, 39%), and the photoadduct (4S,5R)-5-(*tert*-butyldimethylsiloxymethyl)-4-(diphenylhydroxymethyl)-tetrahydrofuran-2-one (0.34g, 6%).

Major product (5): R_f 0.16 (20% petroleum ether : 80% Et_2O); $[\alpha]_D^{26}$ -6.2 (*c* 0.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3451 (OH), 1760 (C=O), 1473 and 1368; δ_H (400 MHz; $CDCl_3$) 0.04 (3 H, s, Me), 0.05 (3 H, s, Me), 0.86 (9 H, s, ^{t}Bu), 2.23 (1 H, dd, J_{gem} 16.9, $J_{3,4}$ 4.8, 3-H), 2.56-2.60 (2 H, m, 4-H and OH), 2.65 (1 H, dd, J_{gem} 16.9, $J_{3,4}$ 9.3, 3-H), 3.56 (1 H, dd, J_{gem} 10.6, $J_{7,4}$ 7.0, 7-H), 3.63 (1 H, dd, J_{gem} 10.6, $J_{7,4}$ 5.1, 7-H), 3.69 (1 H, dd, J_{gem} 11.0, $J_{6,5}$ 2.9, 6-H), 3.77 (1 H, dd, J_{gem} 11.0, $J_{6,5}$ 4.0, 6-H) and 4.32 (1 H, dt, $J_{5,6}$ 4.0, $J_{4,5}$ 3.1, 5-H); δ_C(100 MHz; $CDCl_3$) -5.6 (Me), -5.5 (Me), 18.2 (CMe_3), 25.8 (CMe_3), 31.7 (C-3), 39.6 (C-4), 63.7 (C-7), 64.6 (C-6), 82.6 (C-5) and 176.5 (C=O) [Found: $(M+NH_4)^+$, 278.1768. $C_{12}H_{28}NO_4Si$ requires *M*, 278.1788].

Minor product: R_f 0.27 (20% petroleum ether : 80% Et_2O); ν_{max}(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, ^{t}Bu), 1.62 (1 H, br, OH), 2.39 (3 H, m, 2 x 3-H, 4-H), 3.63 (1 H, dd, J_{gem} 11.5, $J_{6,5}$ 6.2, 6-H), 3.92 (1 H, dd, J_{gem} 11.5, $J_{6,5}$ 3.5, 6-H), 4.40 (1 H, ddd, $J_{5,4}$ 8.9, $J_{5,6}$ 6.2, $J_{5,6}$ 3.5, 5-H) and 7.12-7.32 (10 H, m, Ar).

(4S,5R)-4,5-*Bis*-(tert-*Butyldimethylsiloxymethyl*)-*tetrahydrofuran*-2-*one* (6).

To a solution of the alcohol **(5)** (1.38 g, 5.3 mmol) in dry CH_2Cl_2 (30 cm^3) with imidazole (0.50 g, 6.3 mmol) at 0 °C, was added *tert*-butyldimethylsilyl chloride (0.93 g, 5.9 mmol), portionwise. The mixture was stirred for 2 h, before quenching with water (35 cm^3). The organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 20 cm^3). The combined organic extracts were washed with water (2 x 20 cm^3), brine (2 x 20 cm^3), and then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (20% Et_2O : 80% petroleum ether) to give the *title compound* **(6)** as colourless crystals (1.20 g, 60%), R_f 0.29 (20% Et_2O : 80% petroleum ether); m.p. 31-33 °C; ν_{max} (film)/cm^{-1} 1791 (C=O), 1462 and 1378; δ_H(400 MHz; $CDCl_3$) 0.0 (6 H, s, 2 x Me), 0.01 (3 H, s, Me), 0.02 (3 H, s, Me), 0.83 (18 H, s, 2 x ^{t}Bu), 2.25 (1 H, dd, J_{gem} 16.7, $J_{3,4}$ 3.8, 3-H), 2.52-2.58 (1 H, m, 4-H), 2.62 (1 H, dd, J_{gem} 16.7, $J_{3,4}$ 9.7, 3-H), 3.53 (1 H, dd, J_{gem} 10.1, $J_{7,4}$ 6.0, 7-H), 3.59 (1 H, dd, J_{gem} 10.1, $J_{7,4}$ 4.6, 7-H), 3.64 (1 H, dd, J_{gem} 11.4, $J_{6,5}$ 2.7, 6-H), 3.83 (1 H, dd, J_{gem} 11.4, $J_{6,5}$ 3.3, 6-H) and 4.34 (1 H, dt, $J_{5,4}$ 6.6, $J_{5,6}$ 3.3, 5-H); δ_C (100 MHz; $CDCl_3$) -5.6 (Me_2Si), 18.1 (Me_3C), 25.7 (Me_3C), 31.6 (C-3), 38.8 (C-4), 63.8 (C-7), 64.6 (C-6), 82.4 (C-5) and 176.9 (C-2).

1-O-*Acetyl*-3-C-(tert-*butyldimethylsiloxymethyl*)-5-O-(tert-*butyldimethylsilyl*)-2,3-*dideoxy*-α- L - *and* -β-L-erythro-*pentofuranose* (7).

To the lactone **(6)** (1.17 g, 3.0 mmol) in dry CH_2Cl_2 (20 cm^3) at -78 °C under an atmosphere of nitrogen was added DIBAL-H (1.0 mol dm^{-3} in toluene, 3.4 cm^3), dropwise, whilst maintaining the reaction mixture below -67 °C. The reaction was stirred for 1 h and then quenched by the addition of MeOH (0.6 cm^3). The reaction was left to warm to room temperature and then EtOAc (4.5 cm^3) was added, followed by saturated aqueous $NaHCO_3$ solution (0.6 cm^3), and the mixture stirred for a further 2 h. Powdered anhydrous Na_2SO_4 (3.2 g) was added and the mixture stirred for 1 h. The precipitate was removed by filtration through Celite, and the solvent removed *in vacuo* to give the lactol as a colourless oil, which was used without further purification.

To the lactol (1.17 g, 3.0 mmol) in pyridine (6.5 cm^3) at 0 °C under an atmosphere of

nitrogen was added acetic anhydride (1.1 cm^3, 3.7 mmol), dropwise. The reaction was stirred for 4 h, quenched by the addition of water (13 cm^3) and then extracted with CH_2Cl_2 (3 x 30 cm^3). The combined organic extracts were washed with water (2 x 20 cm^3), brine (2 x 20 cm^3) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by flash chromatography (15% Et_2O : 85% petroleum ether) to give an anomeric mixture of the acetate **(7)** as a colourless oil (0.75 g, 60% overall), in a ratio of α:β, 1:1.3 by ^{1}H-nmr, R_f 0.22 and 0.28 (15% Et_2O : 85% petroleum ether); ν_{max} (film)/cm^{-1} 1751 (C=O), 1474, 1464, 1362 and 1253; δ_H (400 MHz; $CDCl_3$) α-anomer 0.04 (6 H, s, 2 x Me), 0.05 (6 H, s, 2 x Me), 0.89 (18 H, s, 2 x ^{t}Bu), 1.81 (1 H, dd, J_{gem} 13.2, $J_{2,3}$ 3.7, 2-H), 2.02 (3 H, s, CO*Me*), 2.26 (1 H, dd, J_{gem} 13.2, $J_{2,3}$ 5.3, 2-H), 2.36-2.43 (1 H, m, 3-H), 3.60-3.75 (4 H, m, 2 x 5-H, 2 x 6-H), 3.87-3.92 (1 H, m, 4-H) and 6.22 (1 H, d, $J_{1,2}$ 4.8, 1-H), β-anomer 0.05 (6 H, s, 2 x Me), 0.06 (6 H, s, 2 x Me), 0.90 (18 H, s, 2 x ^{t}Bu), 1.85 (1 H, dd, J_{gem} 13.9, $J_{2,3}$ 3.3, 2-H), 2.03 (3 H, s, CO*Me*), 2.30 (1 H, dd, J_{gem} 13.9, $J_{2,3}$ 5.1, 2-H), 2.36-2.43 (1 H, m, 3-H), 3.60-3.75 (4 H, m, 2 x 5-H, 2 x 6-H), 4.01-4.04 (1 H, m, 4-H) and 6.26 (1 H, dd, $J_{1,2}$ 5.5, $J_{1,2}$ 1.1, 1-H); δ_C(100 MHz; $CDCl_3$) α-anomer -5.4 (MeSi), -5.3 (MeSi), 18.4 (Me_3C), 21.4 (CO*Me*), 25.9 (Me_3C), 35.0 (C-2), 41.5 (C-3), 64.8 (C-6), 64.9 (C-5), 83.6 (C-4), 99.5 (C-1) and 170.4 (C=O), β-anomer -5.5 (MeSi), -5.3 (MeSi), 18.3 (Me_3C), 21.5 (CO*Me*), 25.8 (Me_3C), 35.9 (C-2), 41.6 (C-3), 63.7 (C-6), 66.2 (C-5), 83.7 (C-4), 99.0 (C-1) and 170.4 (C=O) [Found: $(M\text{-}OAc)^+$, 359.2438. $C_{18}H_{39}O_3Si_2$ requires *M*, 359.2438].

2-O, 4-O-*Bis(trimethylsilyl)uracil*.

Uracil (0.22 g, 2 mmol) in bis(trimethylsilyl)acetamide (0.85 ml) was heated at reflux until the uracil had fully dissolved. The solvent was removed under reduced pressure, and the residue coevaporated with toluene (2 x 1.5 cm^3). The residue was used without further purification.

1-[3'-C-(tert-*Butyldimethylsiloxymethyl*)-5'-O-(tert-*butyldimethylsilyl*)-2',3'-*dideoxy*-α- *and* -β-L-erythro-*pentofuranosyl*] *uracil* (8).

To the acetate **(7)** (0.74 g, 1.8 mmol) with 2-O, 4-O-bis(trimethylsilyl)uracil in dry

MeCN (15 cm^3) under an atmosphere of nitrogen at 0 °C was added $SnCl_4$ (1.0 mol dm^{-3}, 1.8 cm^3), dropwise. The mixture was stirred overnight and allowed to warm to room temperature over this period. The reaction was quenched by pouring over a solution of MeCN and potassium sodium tartrate, which was stirred for 1 h. The precipitate was removed by filtering through Celite. The organic layer was washed with potassium sodium tartrate (3 x 20 cm^3), brine (2 x 20 cm^3) and then dried ($MgSO_4$). The solvent was removed and the residue purified by flash chromatography (3% MeOH : 97% CH_2Cl_2) to give the nucleoside **(8)** as a white amorphous solid (0.44 g, 52%), in a ratio of α:β, 1:1, by ^{1}H-nmr, R_f 0.42 (3% MeOH : 97%CH_2Cl_2); δ_H(400 MHz, $CDCl_3$) α-anomer 0.05 (6 H, s, 2 x Me), 0.07 (3 H, s, Me), 0.08 (3 H, s, Me), 0.88 (9 H, s, ^{t}Bu), 0.90 (9 H, s, ^{t}Bu), 1.84 (1 H, ddd, J_{gem} 13.0, $J_{2',3'}$ 8.4, $J_{2',1'}$ 6.6, 2'-H), 2.46-2.53 (1 H, m, 3'-H), 2.59 (1 H, ddd, J_{gem} 13.0, $J_{2',3'}$ 8.8, $J_{2',1'}$ 6.2, 2'-H), 3.60-3.69 (3 H, m, 5'-H, 2 x 6'-H), 3.79 (1 H, dd, J_{gem} 11.0, $J_{5',4'}$ 3.7, 5'-H), 4.17 (1 H, dt, $J_{4',3'}$ 7.3, $J_{4',5'}$ 3.7, 4'-H), 5.73 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.2, 5-H), 6.12 (1 H, t, $J_{1',2'}$ 6.2, 1'-H), 7.51 (1 H, d, $J_{6,5}$ 8.1, 6-H) and 8.38 (1 H, br, NH) β-anomer 0.05 (3 H, s, Me), 0.06 (3 H, s, Me), 0.10 (3 H, s, Me), 0.11 (3 H, s, Me), 0.89 (9 H, s, ^{t}Bu), 0.92 (9 H, s, ^{t}Bu), 2.05 (1 H, ddd, J_{gem} 15.4, $J_{2',3'}$ 8.1, $J_{2',1'}$ 3.8, 2'-H), 2.34 (1 H, ddd, J_{gem} 15.4, $J_{2',3'}$ 8.4, $J_{2',1'}$ 7.0, 2'-H), 2.47-2.52 (1 H, m, 3'-H), 3.60-3.69 (2 H, m, 2 x 6'-H), 3.73 (1 H, dd, J_{gem} 11.4, $J_{5',4'}$ 2.2, 5'-H), 3.99 (1 H, dt, $J_{4',3'}$ 7.3, $J_{4',5'}$ 2.2, 4'-H), 4.04 (1 H, dd, J_{gem} 11.4, $J_{5',4'}$ 2.2, 5'-H), 5.66 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.2, 5-H), 6.09 (1 H, dd, $J_{1',2'}$ 6.6, $J_{1',2'}$ 3.7, 1'-H), 8.11 (1 H, d, $J_{6,5}$ 8.1, 6-H) and 8.38 (1 H, br, NH) [Found: $(M-^tBu)^+$, 413.1930. $C_{18}H_{33}N_2O_5Si_2$ requires *M*, 413.1928].

1-[2',3'-*Dideoxy*-3'-C-(*hydroxymethyl*)-α- *and* -β-L-erythro-*pentofuranosyl*] *uracil* (2a).

To a solution of the protected nucleoside **(8)** (0.41 g, 0.9 mmol) in MeOH (AnalaR, 10 cm^3) and water (1.1 cm^3), was added *p*-toluenesulphonic acid monohydrate (0.38 g, 2.0 mmol) and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was neutralised by the addition of basic resins (IRA-93, 12.4 cm^3), stirred for a further 1 h and then filtered. The solvent was removed under reduced pressure, and the residue

purified by flash chromatography (10% MeOH : 30% EtOAc : 60% CH_2Cl_2) to give the *title compound* **(2a)** (0.2 g, 94%) as a white crystalline solid, in a ratio of α:β, 1:2, by 1H-nmr, R_f 0.34 (10% MeOH : 30% EtOAc : 60% CH_2Cl_2); m.p. 125-126 °C (MeOH); ν_{max} (mull)/cm^{-1} 3380 (br, OH), 3174 (br, NH), 1698 (C=O), 1660 (C=O), 1466, 1114 and 1018; δ_H(400 MHz; D_2O) α-anomer 1.89 (1 H, ddd, J_{gem} 13.6, $J_{2',3'}$ 9.5, $J_{2',1'}$ 7.0, 2'-H), 2.16-2.30 (1 H, m, 2'-H), 2.32-2.39 (1 H, m, 3'-H), 3.56 (1 H, dd, J_{gem} 12.5, $J_{6',5'}$ 5.5, 6'-H), 3.57-3.62 (2 H, m, 5'-H, 6'-H), 3.74 (1 H, dd, J_{gem} 12.5, $J_{5',4'}$ 2.9, 5'-H), 4.16 (1 H, dt, $J_{4',3'}$ 8.1, $J_{4',5'}$ 5.5, 4'-H), 5.79 (1 H, d, $J_{5,6}$ 8.1, 5-H), 6.04 (1 H, d, $J_{1',2'}$ 6.6, 1'-H) and 7.72 (1 H, d, $J_{6,5}$ 8.1, 6-H), β-anomer 2.16-2.30 (1 H, m, 2'-H), 2.32-2.39 (1 H, m, 3'-H), 2.59 (1 H, ddd, J_{gem} 16.1, $J_{2',3'}$ 8.4, $J_{2',1'}$ 6.2, 2'-H), 3.57-3.62 (2 H, m, 2 x 6'-H), 3.66 (1 H, dd, J_{gem} 12.6, $J_{5',4'}$ 5.3, 5'-H), 3.81 (1 H, dd, J_{gem} 12.6, $J_{5',4'}$ 2.9, 5'-H), 3.92 (1 H, dt, $J_{4',3'}$ 8.1, $J_{4',5'}$ 2.9, 4'-H), 5.77 (1 H, d, $J_{5,6}$ 8.1, 5-H), 6.01 (1 H, t, $J_{1',2'}$ 6.6, 1'-H) and 7.84 (1 H, d, $J_{6,5}$ 8.1, 6-H); δ_C(100.4 MHz, D_2O) α-anomer 35.8 (C-2'), 42.1 (C-3'), 62.5 (C-6'), 63.5 (C-5'), 84.5 (C-4'), 86.6 (C-1'), 102.7 (C-5), 142.8 (C-6), 152.4 (C=O) and 167.2 (C=O), β-anomer 35.4 (C-2'), 40.8 (C-3'), 62.7 (C-6'), 62.9 (C-5'), 84.8 (C-4'), 87.9 (C-1'), 102.5 (C-5), 142.9 (C-6), 152.5 (C=O) and 167.2 (C=O) [Found (FAB): $(M+Na)^+$, 265.0800; C, 49.36; H, 5.88; N, 11.11%. $C_{10}H_{14}N_2O_5Na$ requires *M*, 265.0800; $C_{10}H_{14}N_2O_5$ requires C, 49.58; H, 5.83; N, 11.56%].

(4S,5R)-5-(tert-*Butyldimethylsiloxymethyl*)-4-(*benzoyloxymethyl*)-*tetrahydrofuran-2-one* (9).

To a solution of the alcohol **(5)** (1.97 g, 7.6 mmol) in dry pyridine (40 cm^3) at 0 °C under nitrogen was added benzoyl chloride (0.99 cm^3, 8.3 mmol), dropwise. After stirring at 0 °C for 2 h, the reaction mixture was quenched by the addition of water (50 cm^3). The reaction mixture was washed with CH_2Cl_2 (3 x 50 cm^3), and the combined organic extracts were washed with aqueous HCl (2 mol dm^{-3}, 3 x 50 cm^3), saturated aqueous $NaHCO_3$ solution (3 x 50 cm^3) and then brine (2 x 50 cm^3). The organic phase was dried ($MgSO_4$), the solvent removed *in vacuo* and the residue was purified by flash

chromatography (30% EtOAc : 70% petroleum ether), to give the *title compound* **(9)** as a yellow oil (2.21 g, 80%), R_f 0.56 (30% EtOAc : 70% petroleum ether); $[\alpha]_D^{25}$ +2.6 (*c* 0.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 2931 (Ar), 2894, 2856, 1781 (C=O, lactone), 1723 (C=O, benzoate), 1602 (Ar), 1584, 1471, 1463, 1452, 1315, 1273, 1177 and 1119; δ_H(400 MHz, $CDCl_3$) 0.08 (6 H, s, 2 x Me), 0.89 (9 H, s, ^{t}Bu), 2.44 (1 H, dd, J_{gem} 17.6, $J_{3,4}$ 4.4, 3-H), 2.88 (1 H, dd, J_{gem} 17.6, $J_{3,4}$ 9.9, 3-H), 2.95-3.02 (1 H, m, 4-H), 3.77 (1 H, dd, J_{gem} 11.4, $J_{6,5}$ 2.6, 6-H), 3.93 (1 H, dd, J_{gem} 11.4, $J_{6,5}$ 2.9, 6-H), 4.34 (1 H, dd, J_{gem} 11.4, $J_{7,4}$ 6.0, 7-H), 4.41 (1 H, dd, J_{gem} 11.4, $J_{7,4}$ 5.1, 7-H), 4.48 (1 H, dd, $J_{5,4}$ 6.6, $J_{5,6}$ 2.9, 5-H), 7.46 (2 H, t, *J* 7.7, *m*-Ar), 7.59 (1 H, t, *J* 7.7, *p*-Ar) and 8.01 (2 H, d, *J* 8.2, *o*-Ar); δ_C(100.4 MHz, $CDCl_3$) -5.6 (Me), -5.5 (Me), 18.2 (CMe_3), 25.8 (CMe_3), 32.1 (C-3), 36.0 (C-4), 64.3 (C-6), 65.6 (C-7), 82.2 (C-5), 128.6 (Ar), 129.4 (C-quart, Ar), 129.6 (Ar), 133.4 (Ar), 166.3 (C=O, benzoate) and 176.1 (C=O) [Found: $(M+H)^+$, 365.1778; C, 62.41; H, 7.64%. $C_{19}H_{29}O_5Si$ requires *M*, 365.1784; $C_{19}H_{28}O_5Si$ requires C, 62.61; H 7.74%].

1-O-*Acetyl*-3-C-(*benzoyloxymethyl*)-5-O-(tert-*butyldimethylsilyl*)-2,3-*dideoxy*-α-L-*and*-β-L-erythro-*pentofuranose* (10).

A solution of 2-methyl-2-butene (2 mol dm^{-3} in THF, 33 cm^3) was added dropwise to a solution of borane-THF complex (1 mol dm^{-3} in THF, 33 cm^3) at -10 °C under nitrogen. After stirring at -5-0 °C for 6 h, a solution of the lactone **(9)** (2.16 g, 5.9 mmol) in dry THF (15 cm^3) was added dropwise, and the reaction mixture was stirred at room temperature for a further 18 h. The reaction mixture was cooled to 0 °C and the reaction quenched by the addition of water (2.0 cm^3). The ice-bath was removed and the mixture heated at reflux for 0.5 h. After cooling to 0 °C, aqueous 30% H_2O_2 (4.2 cm^3) was added dropwise, whilst adjusting the pH to 7-8 by the addition of aqueous NaOH (2 mol dm^{-3}). The mixture was concentrated under reduced pressure, and the residue extracted with CH_2Cl_2 (3 x 40 cm^3). The organic extracts were combined and dried ($MgSO_4$), before concentrating *in vacuo*.

The resulting oily mixture was not purified further but was dissolved in dry pyridine (15 cm^3), to which acetic anhydride (1.9 cm^3, 20.7 mmol) was added dropwise at 0 °C

under nitrogen. The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction was quenched by the addition of water (30 cm^3), followed by extraction with CH_2Cl_2 (3 x 40 cm^3). The combined organic extracts were washed with aqueous HCl (2 mol dm^{-3}, 3 x 40 cm^3), saturated aqueous $NaHCO_3$ solution (3 x 40 cm^3), brine (2 x 40 cm^3) and then dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue purified by flash chromatography (13% EtOAc : 87% petroleum ether) to give the acetate **(10)** as a colourless oil (1.76 g, 73%), in a ratio of α : β, 1:1.3 by ^{1}H-nmr. Partial isolation of the individual anomers was achieved for the purposes of characterisation.

α-anomer: R_f 0.51 (22% EtOAc : 78% petroleum ether); $[\alpha]_D^{28}$ -53.3 (*c* 0.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 2954 (Ar C-H), 2929, 2857, 1754 (C=O, acetate), 1724 (C=O, benzoate), 1604 (Ar), 1587, 1473, 1453, 1316, 1274 and 1115; δ_H (400 MHz, $CDCl_3$) 0.05 (6 H, s, 2 x Me), 0.88 (9 H, s, ^{t}Bu), 1.96 (1 H, dd, J_{gem} 13.9, $J_{2,3}$ 2.6, 2-H), 2.04 (3 H, s, OAc), 2.45 (1 H, ddd, J_{gem} 13.9, $J_{2,3}$ 9.9, $J_{2,1}$ 4.4, 2-H), 2.71-2.79 (1 H, m, 3-H), 3.70-3.78 (2 H, m, 2 x 5-H), 4.22 (1 H, dd, $J_{4,3}$ 8.8, $J_{4,5}$ 4.0, 4-H), 4.44 (2 H, d, $J_{6,5}$ 7.3, 2 x 6-H), 6.36 (1 H, d, $J_{1,2}$ 4.4, 1-H), 7.45 (2 H, t, *J* 7.3, *m*-Ar), 7.58 (1 H, t, *J* 7.3, *p*-Ar) and 8.06 (2 H, d, *J* 7.3, *o*-Ar); δ_C(100.4 MHz; $CDCl_3$) -5.5 (Me), -5.3 (Me), 18.3 (CMe_3), 21.4 ($COCH_3$), 25.9 (CMe_3), 35.3 (C-2), 38.2 (C-3), 64.5 (C-5), 66.4 (C-6), 83.5 (C-4), 99.2 (C-1), 128.4 (Ar), 129.6 (Ar), 130.0 (Ar), 133.1 (Ar), 166.4 (C=O, benzoate) and 170.3 (C=O, acetate) [Found: $(M\text{-}OAc)^+$, 349.1877. $C_{19}H_{29}O_4Si$ requires *M*, 349.1835].

β-anomer: R_f 0.46 (22% EtOAc : 78% petroleum ether); $[\alpha]_D^{30}$ +30.9 (*c* 0.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 2953 (Ar C-H), 2930, 2858, 1755 (C=O, acetate), 1724 (C=O, benzoate), 1603 (Ar), 1587, 1473, 1454, 1316, 1275 and 1115; δ_H (400 MHz, $CDCl_3$) 0.06 (3 H, s, Me), 0.07 (3 H, s, Me), 0.90 (9 H, s, ^{t}Bu), 2.04 (3 H, s, OAc), 2.09 (1 H, ddd, J_{gem} 13.4, $J_{2,3}$ 11.0, $J_{2,1}$ 4.8, 2-H), 2.26 (1 H, dd, J_{gem} 13.4, $J_{2,3}$ 7.3, 2-H), 2.74-2.84 (1 H, m, 3-H), 3.74 (1 H, dd, J_{gem} 10.6, $J_{5,4}$ 5.5, 5-H), 3.82 (1 H, dd, J_{gem} 10.6, $J_{5,4}$ 5.1, 5-H), 4.02-4.07 (1 H, m, 4-H), 4.37 (1 H, dd, J_{gem} 11.0, $J_{6,5}$ 6.2, 6-H), 4.44 (1 H, dd, J_{gem} 11.0, $J_{6,5}$ 5.7, 6-H), 6.31 (1 H, d, $J_{1,2}$ 4.8, 1-H), 7.45 (2 H, t, *J* 7.3, *m*-Ar), 7.58 (1 H, t, *J* 7.3, *p*-Ar) and 8.04 (2 H, d, *J* 7.3, *o*-Ar); δ_C(100.4 MHz; $CDCl_3$) -5.4 (2 x

Me), 18.4 (CMe_3), 21.4 ($COCH_3$), 25.9 (CMe_3), 36.4 (C-2), 38.6 (C-3), 65.3 (C-5), 65.5 (C-6), 83.7 (C-4), 98.5 (C-1), 128.5 (Ar), 129.6 (Ar), 129.8 (Ar), 133.2 (Ar), 166.3 (C=O, benzoate) and 170.2 (C=O, acetate).

***5-Fluoro*-2-O, 4-N-*bis(trimethylsilyl)cytosine*.**

5-Fluorocytosine (0.28 g, 2.16 mmol) in *bis*(trimethylsilyl)acetamide (2.4 ml) was heated at reflux until the cytosine had fully dissolved. The solvent was removed under reduced pressure, and the residue coevaporated with toluene (2 x 5 ml). The residue was used without further purification.

1-[3'-C-(*Benzoyloxymethyl*)-5'-O-(tert-*butyldimethylsilyl*)-2',3'-*dideoxy*-α-L- *and* -β-L-erythro-*pentofuranosyl*]-5-*fluorocytosine* (11).

To a solution of iodine (0.28 g, 1.10 mmol) in CH_2Cl_2 (2.2 cm^3) was added hexamethyldisilane (0.25 cm^3, 1.2 mmol). The mixture was heated at reflux at 70 °C for 1 h, after which time the purple colour had disappeared leaving a near colourless solution. The solution of trimethylsilyliodide (1 mol dm^{-3}) obtained was allowed to cool, and then used immediately.

To a solution of the acetate **(10)** (0.8 g, 1.96 mmol) in dry CH_2Cl_2 (15 cm^3) under an atmosphere of nitrogen was added *5*-fluoro-*2-O, 4-N*-bis(trimethylsilyl)cytosine (2.16 mmol), followed by trimethylsilyliodide (2.1 cm^3, 2.1 mmol), dropwise. The reaction mixture was stirred at room temperature for 2 h, and then quenched by the addition of water (4 cm^3). The organic layer was washed with saturated aqueous sodium thiosulphate solution (2 x 40 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (8% MeOH : 92% CH_2Cl_2) to give the nucleoside **(11)** as a white amorphous solid (0.77 g, 82%) in a ratio of α:β, 1:4 by ^{1}H-nmr, R_f 0.43 (10% MeOH : CH_2Cl_2); m.p. 78-79 °C ("softening"); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (br, NH_2), 3073 (br, NH_2), 2954 (Ar), 2929, 2858, 1723 (C=O, benzoate), 1682, 1620 (C=C), 1510, 1505, 1473, 1454, 1316, 1275 and 1122; δ_H(400 MHz; $CDCl_3$), integration values for the discrete anomers have not been given but were in the approximate ratio of 1:4 with respect to the signals for the discrete anomers, α-anomer 0.06 (s, Me), 0.07 (s, Me), 0.89 (s, ^{t}Bu), 1.88 (ddd, J_{gem} 13.6, $J_{2',3'}$ 8.1, $J_{2',1'}$ 5.9, 2'-H), 2.73-2.84 (m, 3'-H), 2.94 (ddd, J_{gem} 13.6, $J_{2',3'}$ 8.4, $J_{2',1'}$ 5.9, 2'-H), 3.74 (dd, J_{gem} 11.0,

$J_{5',4'}$ 4.0, 5'-H), 3.84 (dd, J_{gem} 11.0, $J_{5',4'}$ 3.7, 5'-H), 4.19-4.22 (m, 4'-H), 4.30-4.41 (m, 2 x 6'-H), 6.0 (td, $J_{1',2'}$ 5.9, $J_{1',3'}$ 4.4, 1'-H), 7.41 (t, J 7.3, Ar), 7.57 (t, J 7.3, Ar), 7.60 (d, $J_{6,F}$ 6.2, 6-H) and 7.97-8.02 (m, Ar), β-anomer 0.10 (s, Me), 0.11 (s, Me), 0.90 (s, ^{t}Bu), 2.34 (ddd, J_{gem} 13.9, $J_{2',3'}$ 7.7, $J_{2',1'}$ 2.6, 2'-H), 2.50 (ddd, J_{gem} 13.9, $J_{2',3'}$ 9.9, $J_{2',1'}$ 6.6, 2'-H), 2.73-2.84 (m, 3'-H), 3.81 (dd, J_{gem} 11.7, $J_{5',4'}$ 1.8, 5'-H), 4.0-4.03 (m, 4'-H), 4.13 (dd, J_{gem} 11.7, $J_{5',4'}$ 2.2, 5'-H), 4.30-4.41 (m, 2 x 6'-H), 6.08 (dd, $J_{1',2'}$ 4.4, $J_{1',3'}$ 1.8, 1'-H), 7.41 (t, J 7.3, Ar), 7.57 (t, J 7.3, Ar), 7.97-8.02 (m, Ar) and 8.29 (d, $J_{6,F}$ 6.2, 6-H); δ_C(100.4 MHz, $CDCl_3$) α-anomer -5.5 (2 x Me), 18.5 (*C*Me$_3$), 25.9 (C*Me*$_3$) 37.4 (C-2'), 39.2 (C-3'), 64.1 (C-5'), 64.6 (C-6'), 83.7 (C-4'), 87.8 (C-1'), 126.0 (d, $J_{6,F}$ 33, C-6), 128.6 (Ar), 129.7 (Ar), 133.4 (Ar), 136.2 (d, $J_{5,F}$ 239, C-5), 153.8 (C-4), 157.6 (C-2) and 166.3 (C=O, benzoate), β-anomer -5.5 (2 x Me), 18.5 (*C*Me$_3$), 26.0 (C*Me*$_3$) 35.7 (C-3'), 37.3 (C-2'), 62.6 (C-5'), 64.0 (C-6'), 84.3 (C-4'), 86.3 (C-1'), 126.2 (d, $J_{6,F}$ 33, C-6), 128.5 (Ar), 129.6 (Ar), 133.4 (Ar), 136.2 (d, $J_{5,F}$ 239, C-5), 153.8 (C-4), 157.5 (C-2) and 166.3 (C=O, benzoate) [Found: $(M+H)^+$, 478.2191; C, 57.24; H, 6.79; N, 8.81%. $C_{23}H_{33}FN_3O_5Si$ requires *M*, 478.2174; $C_{23}H_{32}FN_3O_5Si$ requires C, 57.84; H 6.75; N, 8.79%].

1-[3'-C-(*Hydroxymethyl*)-5'-O-(tert-*butyldimethylsilyl*)-2',3'-*dideoxy*-α-L- *and* -β-L-erythro-*pentofuranosyl*]-5-*fluorocytosine*.

A solution of 1% NaOH in MeOH (8.0 cm^3) was added to the fully protected nucleoside **(11)** (0.74g, 1.54 mmol), and the reaction mixture stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (10% MeOH : 90% CH_2Cl_2), to give the *title compound* as a white amorphous solid (0.53 g, 91%) in a ratio of α:β, 1:4 by ^{1}H-nmr, R_f 0.26 (10% MeOH : 90% CH_2Cl_2); m.p. 83-84 °C ("softening"); ν_{max} ($CHCl_3$)/cm^{-1} 3329 (br, NH_2, OH), 2927, 2857, 1678 (C=O), 1616 (C=C), 1509, 1257 and 1122; δ_H (400 MHz; CD_3OD), integration values for the discrete anomers have not been given but were in the approximate ratio of 1:4 with respect to the signals for the discrete anomers, α-anomer 0.10 (s, 2 x Me), 0.93 (s, ^{t}Bu), 1.81 (ddd, J_{gem} 13.2, $J_{2',3'}$ 8.4, $J_{2',1'}$ 6.2, 2'-H), 2.44-2.53 (m, 3'-H), 2.65 (ddd, J_{gem} 13.2, $J_{2',3'}$ 8.4, $J_{2',1'}$ 6.2, 2'-H), 3.58-3.60 (m, 2 x 6'-H), 3.71 (dd, J_{gem} 11.4, $J_{5',4'}$ 4.0, 5'-H), 3.84 (dd, J_{gem} 11.4, $J_{5',4'}$ 4.0, 5'-H), 4.21-4.24 (m, 4'-H), 6.03 (td, $J_{1',2'}$ 6.2,

$J_{1',3'}$ 1.5, 1'-H) and 7.88 (d, $J_{6,F}$ 6.6, 6-H), β-anomer 0.15 (s, Me), 0.16 (s, Me), 0.95 (s, ^{t}Bu), 2.12 (ddd, J_{gem} 13.6, $J_{2',3'}$ 7.7, $J_{2',1'}$ 3.3, 2'-H), 2.34 (ddd, J_{gem} 13.6, $J_{2',3'}$ 9.2, $J_{2',1'}$ 6.6, 2'-H), 2.44-2.53 (m, 3'-H), 3.58-3.60 (m, 2 x 6'-H), 3.85 (dd, J_{gem} 11.7, $J_{5',4'}$ 2.2, 5'-H), 3.96 (dt, $J_{4',3'}$ 7.7, $J_{4',5'}$ 2.2, 4'-H), 4.10 (dd, J_{gem} 11.7, $J_{5',4'}$ 2.2, 5'-H), 5.96 (dt, $J_{1',2'}$ 6.6, $J_{1',3'}$ 1.8, 1'-H) and 8.34 (d, $J_{6,F}$ 7.0, 6-H); δ_C(100.4 MHz; CD_3OD) α-anomer -5.3 (Me), 19.4 (CMe_3), 26.5 (CMe_3), 37.4 (C-2'), 43.4 (C-3'), 63.6 (C-6'), 66.3 (C-5'), 85.0 (C-4'), 89.0 (C-1'), 126.4 (d, $J_{6,F}$ 32, C-6), 132.3 (d, $J_{5,F}$ 270, C-5), 156.4 (C-4) and 159.5 (C=O), β-anomer -5.3 (Me), 19.4 (CMe_3), 26.5 (CMe_3), 38.0 (C-2'), 40.3 (C-3'), 63.0 (C-6'), 64.4 (C-5'), 85.8 (C-4'), 87.8 (C-1'), 126.8 (d, $J_{6,F}$ 33, C-6), 138.1 (d, $J_{5,F}$ 240, C-5), 156.4 (C-4) and 159.6 (C=O) [Found: $(M+H)^+$, 374.1884. $C_{16}H_{29}FN_3O_4Si$ requires *M*, 374.1911].

1-[2',3'-*Dideoxy*-3'-C-(*hydroxymethyl*)-α-L- *and* -β-L-erythro-*pentofuranosyl*]-5-*fluorocytosine* (2b).

To a solution of the mono protected nucleoside (0.20 g, 0.54 mmol) in MeOH (AnalaR, 6 cm^3) and H_2O (0.7 cm^3) was added *para*-toluenesulphonic acid monohydrate (0.12 g, 0.65 mmol), and the reaction mixture was stirred at room temperature for 2 h. After neutralising with basic resins (IRA-93, 4 cm^3), the mixture was stirred for a further 2 h and then filtered. The solvent was removed *in vacuo*, and the residue purified by flash chromatography (20% MeOH : 80% CH_2Cl_2) to give the fully deprotected nucleoside **(2b)** as a white amorphous solid (0.13 g, 95%), in a ratio of α:β, 1:4 by ^{1}H-nmr, R_f 0.35 (20% MeOH : 80% CH_2Cl_2); m.p. 85-86 °C ("softening"); ν_{max} (mull)/cm^{-1} 3327 (br), 3180 (br), 1679 (C=O), 1606 (C=C), 1505, 1340, 1287 and 1109; δ_H (400 MHz; CD_3OD), integration values for the discrete anomers have not been given but were in the approximate ratio of 1:4 with respect to the signals for the discrete anomers, α-anomer 1.83 (ddd, J_{gem} 13.3, $J_{2',3'}$ 9.1, $J_{2',1'}$ 6.5, 2'-H), 2.38-2.49 (m, 3'-H), 2.66 (ddd, J_{gem} 13.3, $J_{2',3'}$ 8.1, $J_{2',1'}$ 5.8, 2'-H), 3.57-3.65 (m, 2 x 6'-H), 3.73-3.78 (m, 5'-H), 3.91-3.96 (m, 5'-H), 4.21 (ddd, $J_{4',3'}$ 7.8, $J_{4',5'}$ 5.0, $J_{4',5'}$ 3.2, 4'-H), 6.02 (dd, $J_{1',2'}$ 6.5, $J_{1',3'}$ 1.5, 1'-H) and 7.91 (d, $J_{6,F}$ 6.6, 6-H), β-anomer 2.12 (ddd, J_{gem} 13.5, $J_{2',3'}$ 7.8, $J_{2',1'}$ 3.2, 2'-H), 2.33 (ddd, J_{gem} 13.5, $J_{2',3'}$ 9.4, $J_{2',1'}$ 6.7, 2'-H), 2.38-2.49 (m, 3'-H), 3.57-3.65 (m, 2 x 6'-H), 3.73-3.78 (m, 5'-H), 3.91-3.96 (m, 4',5'-H), 5.99 (dt, $J_{1',2'}$ 3.2, $J_{1',3'}$ 1.6, 1'-H) and 8.44

(d, $J_{6,F}$ 7.0, 6-H), δ_C(100.4 MHz; CD_3OD) α-anomer 37.3 (C-2'), 43.5 (C-3'), 63.2 (C-6'), 64.6 (C-5'), 85.3 (C-4'), 88.9 (C-1'), 126.3 (d, $J_{6,F}$ 32, C-6), 138.3 (d, $J_{5,F}$ 240, C-5), 156.5 (C-4) and 160.0 (C=O), β-anomer 37.6 (C-2'), 40.5 (C-3'), 62.7 (C-6'), 62.9 (C-5'), 85.8 (C-4'), 87.7 (C-1'), 127.2 (d, $J_{6,F}$ 35, C-6), 138.2 (d, $J_{5,F}$ 241, C-5), 156.5 (C-4) and 160.0 (C=O) [Found: M^+, 259.0991; C, 44.60; H, 5.48; N 15.39%. $C_{10}H_{14}FN_3O_4$ requires *M*, 259.0968; C, 46.33; H, 5.44; N, 16.20%].

2-(p-*Nitrophenyl*)*ethyl chloroformate* (12).

To a solution of phosgene in toluene (1.93 mol dm^{-3}, 12.4 cm^3, 24.0 mmol) cooled to 0 °C under nitrogen, was added a solution of 2-(*p*-nitrophenyl) ethanol (1.0 g, 6.0 mmol) in dry CH_2Cl_2 (3 cm^3) and dry toluene (1.5 cm^3), dropwise with stirring,. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 1 h, after which time the temperature was gradually raised to 50 °C over a period of 5 h. The solvents were removed by distillation, and the residue recrystallized from toluene to give the *title compound* (*) as pale yellow crystals (1.36 g, 98%), R_f 0.62 (66% Et_2O : 33% petroleum ether); m.p. 42-43 °C (Lit.* 42 °C); ν_{max} (mull)/cm^{-1} 1779 (C=O), 1603 (Ar), 1527 (C-NO_2), 1348 (C-NO_2) and 1141; δ_H(400 MHz, $CDCl_3$) 3.16 (2 H, t, $J_{3,2}$ 6.6, 3-H), 4.56 (2 H, t, $J_{2,3}$ 6.6, 2-H), 7.41 (2 H, d, $J_{o,m}$ 8.8, *o*-Ar) and 8.21 (2 H, d, $J_{o,m}$ 8.8, *m*-Ar); δ_C(100.4 MHz, $CDCl_3$) 34.5 (C-3), 70.9 (C-2), 124.0 (*m*-Ar), 129.8 (*o*-Ar), 140.7 (C-NO_2), 144.0 (C-quart, Ar) and 150.1 (C=O) [Found: $(M+H)^+$, 230.0225. $C_9H_9NO_4Cl$ requires *M*, 230.0220].

1-[3'-C-(*Benzoyloxymethyl*)-5'-O-(tert-*butyldimethylsilyl*)-2',3'-*dideoxy*-α-D- *and* -β-D-erythro-*pentofuranosyl*]-4-N-[2-(p-*nitrophenyl*)*ethoxycarbonyl*] *cytosine* (13).

To a solution of the nucleoside 5'-O-*tert*-butyldimethylsilyl-3'-benzoyloxymethyl-cytidine (0.84 g, 1.8 mmol) in dry pyridine (16 cm^3) under an atmosphere of nitrogen was added dimethylaminopyridine (0.08 g), followed by 2-(*p*-nitrophenyl)ethyl chloroformate (0.62 g, 2.7 mmol), and the reaction mixture stirred at room temperature overnight. The reaction was quenched by the addition of water (24 cm^3), and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 cm^3). The combined organic extracts were washed with aqueous HCl (2 mol dm^{-3}, 3 x 60 cm^3), saturated aqueous $NaHCO_3$

solution (3 x 60 cm^3) and brine (2 x 60 cm^3). The organic layer was dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was purified by flash chromatography (EtOAc) to give the fully protected nucleoside **(13)** as two separable anomers (1.08 g, 92% overall).

α-anomer : White powder (0.64 g, 54%), R_f 0.40 (EtOAc); m.p. 81-82 °C; $[\alpha]_D^{27}$ -56.6 (*c* 0.5, $CHCl_3$); ν_{max} (mull)/cm^{-1} 3323 (NH), 1748 (C=O, npeoc), 1722 (C=O, benzoate), 1651 (C=O, cytosine), 1619 (C=C), 1556, 1519 (C-NO_2), 1499, 1345 (C-NO_2), 1273, 1234, 1134, 1115 and 1063; δ_H(400 MHz, $CDCl_3$) 0.07 (3 H, s, Me), 0.08 (3 H, s, Me), 0.90 (9 H, s, ^{t}Bu), 1.92 (1 H, ddd, J_{gem} 13.9, $J_{2',3'}$ 8.1, $J_{2',1'}$ 5.9, 2'-H), 2.80-2.89 (1 H, m, 3'-H), 2.96-3.04 (1 H, m, 2'-H), 3.11 (2 H, t, *J* 6.6, CH_2-npeoc), 3.77 (1 H, dd, J_{gem} 11.0, $J_{5',4'}$ 4.0, 5'-H), 3.86 (1 H, dd, J_{gem} 11.0, $J_{5',4'}$ 3.5, 5'-H), 4.25-4.31 (3 H, m, 4'-H, 2 x 6'-H), 4.44 (2 H, t, *J* 6.6, CH_2-npeoc), 6.05 (1 H, t, $J_{1',2'}$ 5.9, 1'-H), 7.18 (1 H, d, $J_{5,6}$ 7.3, 5-H), 7.40 (2 H, d, *J* 8.8, Ar, npeoc), 7.43 (2 H, t, *J* 8.1, Ar), 7.57 (1 H, t, *J* 7.3, Ar), 7.94-7.99 (3 H, m, 2 x Ar, 6-H) and 8.18 (2 H, d, *J* 8.8, Ar, npeoc); δ_C(100.4 MHz, $CDCl_3$) -5.4 (Me), -5.3 (Me), 18.3 (CMe_3), 25.9 (CMe_3), 34.9 (CH_2-npeoc), 37.2 (C-2'), 39.2 (C-3'), 64.5 (C-5'), 65.0 (C-6'), 65.5 (CH_2-npeoc), 84.2 (C-4'), 88.6 (C-1'), 94.4 (C-5), 123.9 (Ar, npeoc), 128.5 (Ar), 129.6 (Ar), 129.8 (Ar, npeoc), 129.9 (C-quart), 133.3 (Ar), 143.1 (C-6), 144.9 (C-NO_2), 147.0 (C-quart), 152.1 (C-4), 154.8 (C=O, npeoc), 162.1 (C-2) and 166.2 (C=O, benzoate) [Found: $(M+Na-C_8H_8NO_3)^+$, 486.2061. $C_{24}H_{32}N_3O_6Si$ requies *M*, 486.2060].

β-anomer : White amorphous solid (0.44 g, 38%), R_f 0.30 (EtOAc); $[\alpha]_D^{27}$ +30.5 (*c* 0.7, $CHCl_3$); ν_{max} (mull)/cm^{-1} 1746 (C=O, npeoc), 1722 (C=O, benzoate), 1661 (C=O, cytosine), 1651, 1622 (C=C), 1563, 1557, 1520 (C-NO_2), 1346 (C-NO_2), 1270, 1191, 1108 and 1069; δ_H(400 MHz, $CDCl_3$) 0.09 (3 H, s, Me), 0.12 (3 H, s, Me), 0.92 (9 H, s, ^{t}Bu), 2.33-2.39 (1 H, m, 2'-H), 2.52-2.60 (1 H, m, 2'-H), 2.71-2.82 (1 H, m, 3'-H), 3.11 (2 H, t, *J* 6.6, CH_2-npeoc), 3.84 (1 H, dd, J_{gem} 11.7, $J_{5',4'}$ 1.8, 5'-H), 4.07-4.09 (1 H, m, 4'-H), 4.15 (1 H, dd, J_{gem} 11.7, $J_{5',4'}$ 2.2, 5'-H), 4.34 (1 H, dd, J_{gem} 11.4, $J_{6',3'}$ 5.9, 6'-H), 4.41 (1 H, dd, J_{gem} 11.4, $J_{6',3'}$ 5.5, 6'-H), 4.44 (2 H, t, *J* 6.6, CH_2-npeoc), 6.13 (1 H, dd, $J_{1',2'}$ 7.0, $J_{1',2'}$ 2.2, 1'-H), 7.12 (1 H, d, $J_{5,6}$ 7.0, 5-H), 7.40 (2 H, d, *J* 8.6, Ar-npeoc), 7.45 (2 H, t, *J* 7.7, Ar), 7.59 (1 H, t, *J* 7.7, Ar), 8.01 (2 H, d, *J* 8.4, Ar), 8.18 (2 H, d, *J* 8.6,

Ar-npeoc) and 8.56 (1 H, d, $J_{6,5}$ 7.0, 6-H); δ_C (100.4 MHz, $CDCl_3$) -5.5 (Me), -5.4 (Me), 18.4 (CMe_3), 25.9 (CMe_3), 35.0 (CH_2-npeoc), 35.4 (C-3'), 37.3 (C-2'), 62.3 (C-5'), 63.8 (C-6'), 65.5 (CH_2-npeoc), 84.7 (C-4'), 86.9 (C-1'), 93.9 (C-5), 123.9 (Ar-npeoc), 128.5 (Ar), 129.5 (C-quart), 129.6 (Ar), 129.8 (Ar-npeoc), 133.4 (Ar), 145.0 (C-6), 147.0 (C-quart), 152.3 (C-4), 155.0 (C=O, npeoc), 162.0 (C-2) and 166.2 (C=O, benzoate) *m/z* (FAB) 675 ($M+Na^+$, 42%), 371(14), 349(17), 306(11), 176(33), 133(7), 105(99), 89(18), 73(100) and 55(56).

ACKNOWLEDGEMENTS

Jayne Gould thanks the Medical Research Council for a grant from their AIDS Initiative; and we thank the EPSRC Mass Spectrometry Service at Swansea for numerous spectra.

REFERENCES

1. Excellent recent reviews on the subject of anti-HIV chemotherapy include: De Clercq, E. *J.Med.Chem.*. **1995**, *38*, 2491; Bochme, R.E., Borthwick, A.D. and Wyatt, P.G. *Ann.Rept.Med.Chem.*, **1995**, *30*, 139.
2. Kvarnstrom, I., Svansson, L., Svensson, C. and Svensson, S.C.T. *Nucleosides Nucleotides.* **1992**, *11*, 1367; Van Draanen and Koszalka, G.W. *Nucloesides Nucleotides*, **1994**, *13*, 1679; Lin, T-S., Luo, M-Z., Liu, M-C., Pai, S.B., Dutschman, G.E., and Cheng, Y-C. *J.Med.Chem.* **1994,** *37*, 798; Gosselin, G., Mathe, C., Bergogne, M-C., Aubertin, A-M., Kirn, A., Sommadossi, J-P., Schinazi, R., and Imbach, J-L. *Nucleosides Nucleotides.* **1995**, *14*, 611; Ma, T., Pai, S.B., Zhu, Y.L., Lin, J.S., Shanmuganathan, K., Du, J., Wang, C. Kim, H., Newton, M.G., Cheng, Y.C., and Chu, C.K. *J.Med. Chem.* **1996,** *39*, 2835; Lin, T-S., Luo, M-Z., Liu, M-C., Zhu, Y-L., Gullen, E., Dutschman, G.E. and Cheng, Y-C. *J.Med.Chem.* **1996**, *39*, 1757; Selwood, D.L., Carter, K., Young, R.J. and Jandu, K.S. *Biorg. Med. Chem.Lett.* **1996**, *6*, 991.
3. Mann, J. and Weymouth-Wilson, A.C. *J.Chem.Soc.Perkin Trans. I.* **1994**, 3141.
4. Hubschwerlen, C., Specklin, J-L. and Higelin, J. *Org.Synth.*, **1993**, *72*, 1.

5. Mann, J., Partlett, N.K. and Thomas, A. *J.Chem.Res.* **1987**, *S*, 369.

6. Young, R.J., Shaw-Ponter, S., Hardy, G.W., and Mills, G. *Tet.Lett.* **1994**, *35*, 8687.

7. Sugimura, H., Sujino, K. and Osumi, I. *Tet. Lett.*, **1992**, *33*, 2515.

8. Kohn, P. Lerner, L.M., Chan, A., Ginocchio, S.D. and Zitrin, C.A. *Carb.Res.*, **1968**, *7*, 21.

9. Tse, A. and Mansour, T.S.. *Tet.Lett.*, **1995**, *36*, 7807.

10. Himmelsbach, F., Schulz, B.S., Trichtinger, T., Charubala, R. and Pfleider, W. *Tetrahedron*, **1984**, *40*, 59.

11. Perrin, D.D. and Armarego, W.L.F. *Purification of Laboratory Chemicals*, Pergamon Press, 3rd. edition, Oxford, UK, 1988.

Received October 9, 1996
Accepted December 13, 1996